The University Of Sheffield.

Enantiospecific Nitrogen Heterocycle Synthesis

A Dissertation Submitted for the Degree of Doctor of Philosophy

Akram N. M. Qaddo

Supervisor: Prof. Richard F.W. Jackson

The University of Sheffield

Department of Chemistry

November 2016

This thesis is dedicated to

my Parents, my Wife

and my Children

Contents

Declaration

This dissertation records the work carried out in the Department of Chemistry, University of Sheffield between January 2013 and November 2016, and is original except where acknowledged by reference. No portion of this work is being, nor has been, submitted for a degree, diploma or any other qualification at any other university.

Acknowledgements

First and foremost, I would like to thank Allah for helping, supporting and inspiring me to carry on this work.

There are many people I would like to extend my gratitude for their help, and support, while I have been undertaking my PhD.

I would like to express my special appreciation and sincerest gratitude to my supervisor Professor Richard Jackson, you have been a tremendous mentor for me. I would like to thank you for the opportunity to be a PhD student within your research group, and for encouraging me during my research. I also would like to thank you for supporting me through the difficult times of my PhD and also through the highs and lows in my personal life.

Over the past few years I have had the great pleasure to work with some fantastic people, some of whom are mentioned here: Mohamed Zreigh, Mansour Abdelsalam, Martyn Chilton, Phillip Reeve, Nabaz Salih, Liam Marshall and Mehul Makwana. Thank you all for making the group an enjoyable place to work, for your help, advice, suggestions and for your friendship. I would also like to thank all the masters students, for making the group a good and enjoyable environment in which to work.

Thanks also goes to all the technical staff, without whom it would not have been possible to complete this PhD. I would also like to thank professor Donald Craig from Imperial College of Science for personal communication.

I would never forget all the chats and beautiful moments I shared with my friends in Iraq and the United Kingdom. They were fundamental in supporting me in all stressful and difficult moments. I am extremely grateful to Bassam Mohammed Ali for his valuable guidance and loyal friendship. I would also like to thank all the people who helped me and supported me in my life.

A special thanks to my family. Words can not express how grateful I am to my father, my mother, my father-in-law and my mother-in law for all of the sacrifices that you have made on my behalf. Your prayers for me were what sustained me thus far. I would also like to thank to my brother Khaza'al and his family for their support and constant encouragement throughout my years of study. God bless my youngest brother Mohammed, and give him freedom again, keep him safe everywhere around the world, you are always with me. Thank you goes to my sisters too.

I would like to express my very profound gratitude to my beloved wife, for providing me with unconditional support and continuous encouragement throughout my life, throughout my study and through the process of researching and writing this thesis. I also wish to thank my beloved sons Mohammed and Hudhaifa and my darling daughters Rawnaq and Lyan for doing their best to understand a father who had to be confined to his study for such a long time. This accomplishment would not have been possible without their love, support and understanding.

Finally, but by no means least, I would like to thank the Higher Committee for Education Development in Iraq for the opportunity for the scholarship and generous support.

THANK YOU ALL

Abbreviations

$(Boc)_2O$	Di-*tert*-butyl dicarbonate
)))	Sonication
$[\alpha]^{23}_D$	Optical rotation
18-Crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
Ac	Acetyl
AIBN	Azobisisobutyronitrile
aq.	Aqueous
Ar	Aryl
atm	Atmosphere
ax	Axial
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Cat.	Catalysis
Cbz-OSu	*N*-(Benzyloxycarbonyloxy)succinimide
Cp	Cyclopentadienyl
CuBr.DMS	Copper(I) bromide dimethyl sulfide complex
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC	*N,N'*-Dicyclohexylcarbodiimide
DIBAL	Diisobutylaluminium hydride
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethyl sulfoxide
dr	Diastereoisomeric ratio
E	Electrophile
ee	Enantiomeric excess
eq	Equatorial
eq.	Equivalents
ES	Electrospray
Et	Ethyl
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOAc	Ethyl acetate
FGI	Functional group interconversion
h.	Hour
HPLC	High performance liquid chromatography
^{i}Bu	Isobutyl

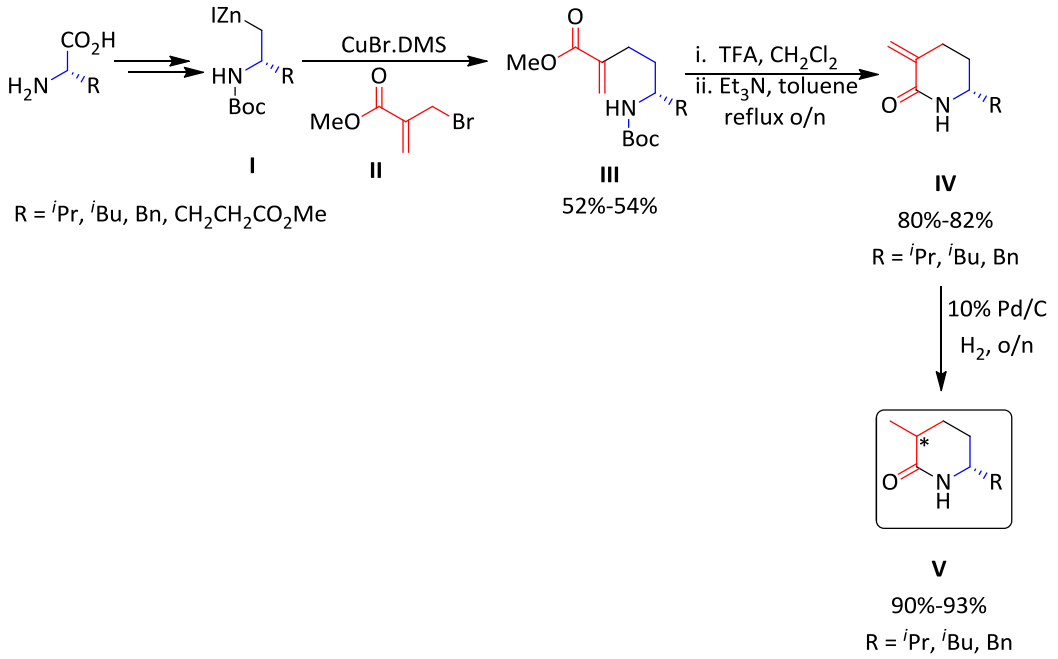
^{i}Pr	Isopropyl
^{i}PrOH	Isopropyl alcohol
IR	Infrared
J	Coupling constant
L	Ligand
LDA	Lithium diisopropylamide
Lit.	Literature
m.p.	Melting point
m/z	Mass/charge ratio
m-CPBA	3-Chloroperbenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MS	Mass spectrometry
NBS	*N*-Bromosuccinimide
^{n}Bu	*n*-Butyl
NHS	*N*-Hydroxysuccinimide
nm	Nanometre
NMO	*N*-Methylmorpholine N-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect

^{n}Pr	n-Propyl
Nu	Nucleophile
o/n	Overnight
OMs	Methanesulfonate
PG	Protecting group
Ph	Phenyl
PhF	9-phenylfluoren-9-yl
PMB	4-methoxybenzyl
PNA	Peptide nucleic acids
ppm	Parts per million
quant.	Quantitative
R	Alkyl
r.t.	Room temperature
Raney Ni	Raney nickel
Red-Al	Sodium bis(2-methoxyethoxy)aluminumhydride
R_f	Retention factor
SET	Single-electron transfer
S_N2	Bimolecular nucleophilic substitution
TBAF	Tetra-*n*-butylammonium fluoride
^{t}Bu	*tert*-Butyl
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl (para-toluenesulfonyl)
TsCl	4-Toluenesulfonyl chloride
TsOH	*p*-Toluenesulfonic acid
UV	Ultraviolet
X	Halogen (unless otherwise stated)
Zn*	Activated zinc
δ	Chemical shift

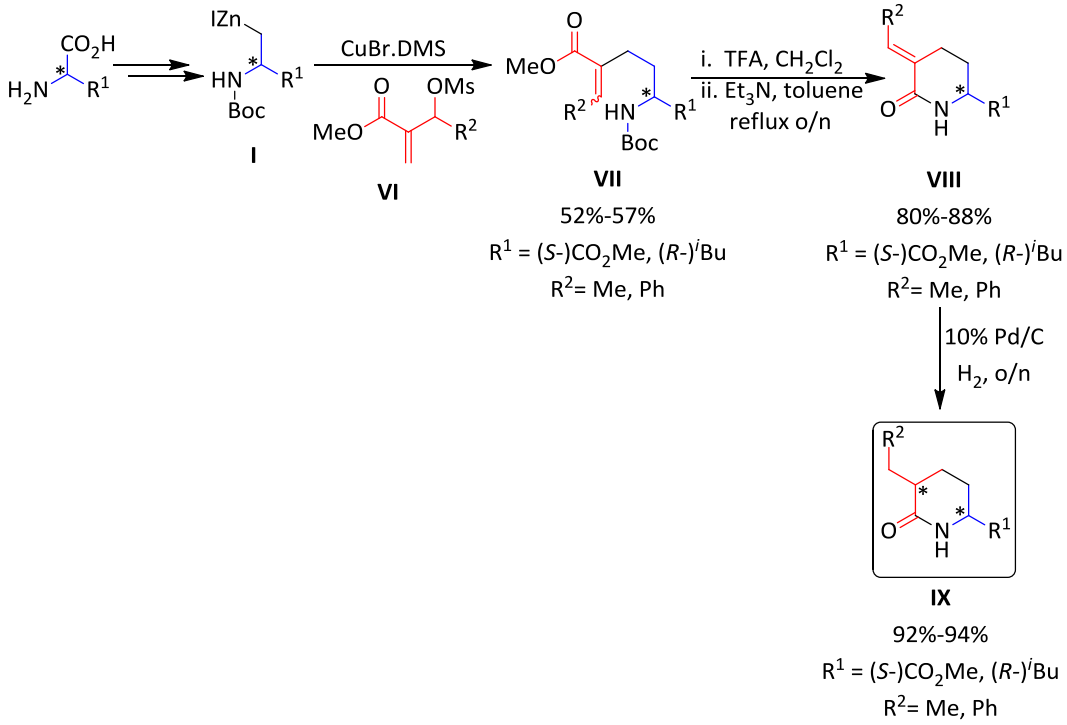
Abstract

A number of protected β-amino organozinc reagents **I** derived from enantiomerically pure α-amino acids, were allylated with methyl 2-(bromomethyl)prop-2-enoate **II** under copper catalysed conditions, to give a number of *N*-protected amino enoate substrates **III** in good yields. Deprotection and cyclisation under thermal conditions gave the lactams **IV**. Hydrogenation of the exo double bond gave separable 2-substituted-5-methyl piperidin-6-ones **V** in excellent yields (90%-93%) with varying diastereoselectivity, with a preference for *cis*-diastereoisomer in a range >19:1 to 2:1 (**Scheme A**).



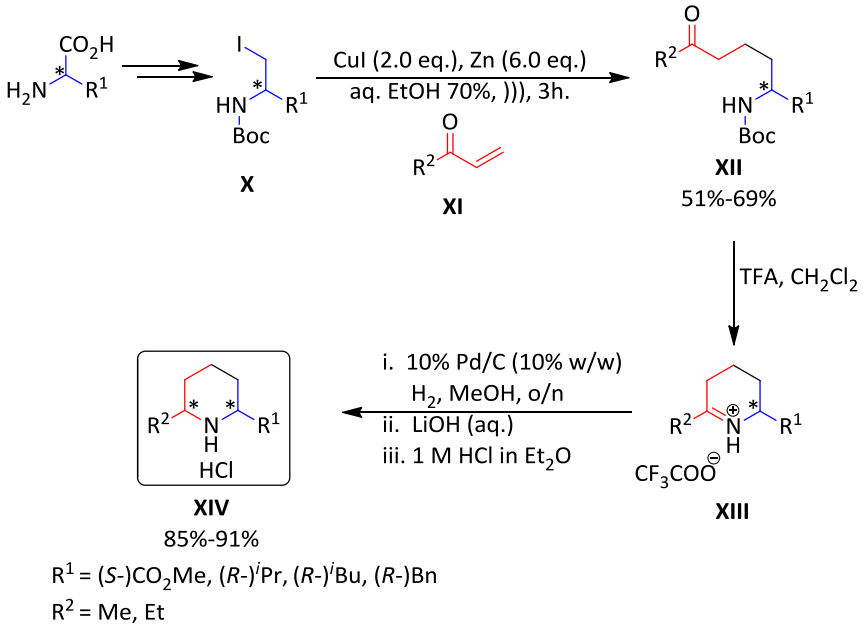
Scheme A

Extension of this general methodology to a range of mesylated electrophiles **VI**, followed by deprotection and cyclisation under thermal conditions gave the more substituted lactams **VIII**. Hydrogenation of the unsaturated lactams **VIII** gave 2,5-disubstituted piperidin-6-ones **IX** in excellent yields (92%-94%) (**Scheme B**) with varying diastereoselectivity.



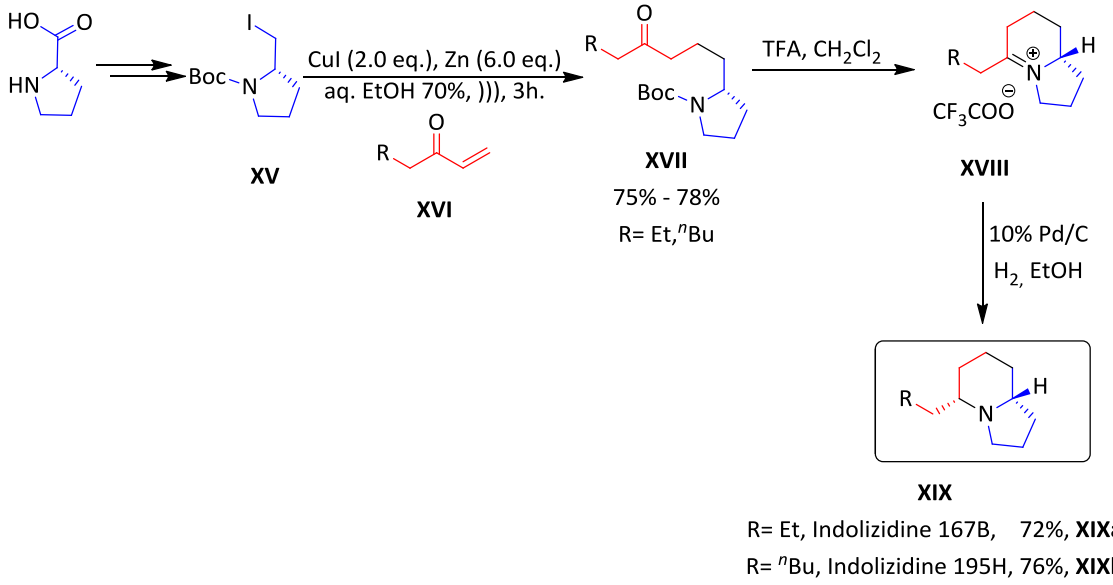
Scheme B

2,6-Disubstituted piperidines were synthesized by reductive cyclisation of 5-oxo amine derivatives **XII**, prepared by 1,4-free radical conjugate addition of a selection of alkyl iodides **X** to a range of enones **XI**. Stereoselective reductive amination of the iminium salts **XIII** was carried out using Pd/C (10% w/w) over hydrogen gas at ambient pressure and temperature and produced 2,6-disubstituted piperidines **XIV** exclusively as the *cis*-diastereoisomer, which were each converted to the corresponding hydrochloride salts (**Scheme C**).



Scheme C

(-)-Indolizidine 167B and (-)-indolizidine 195H were synthesized by 1,4-free radical conjugate addition of alkyl iodide **XV** derived from enantiomerically pure L-proline to a selection of enones **XVI**, followed by deprotection and cyclisation to the iminium salts **XVIII** in quantitative yields. Finally, stereoselective hydrogenation of iminium salts gave the natural products **XIXa** and **XIXb** in good yields of 72% and 76% respectively (**Scheme D**).



Scheme D

1. Introduction

1.1 Background

Both piperidines and indolizidines are found in a range of natural products. The stereoselective synthesis of substituted piperidines and indolizidines has attracted much attention.[1] Two groups of compounds within the piperidine family are the 2,5- and 2,6-disubstituted piperidines. Specific examples include Streptolutine, (-)-Hydroxysedamine, Scopolamine, Pinidine Slaframine, (-)-Indolizidine 167B, (-)-Indolizidine 195H and (-)-Indolizidine 209D (**Figure 1**).[2-6]

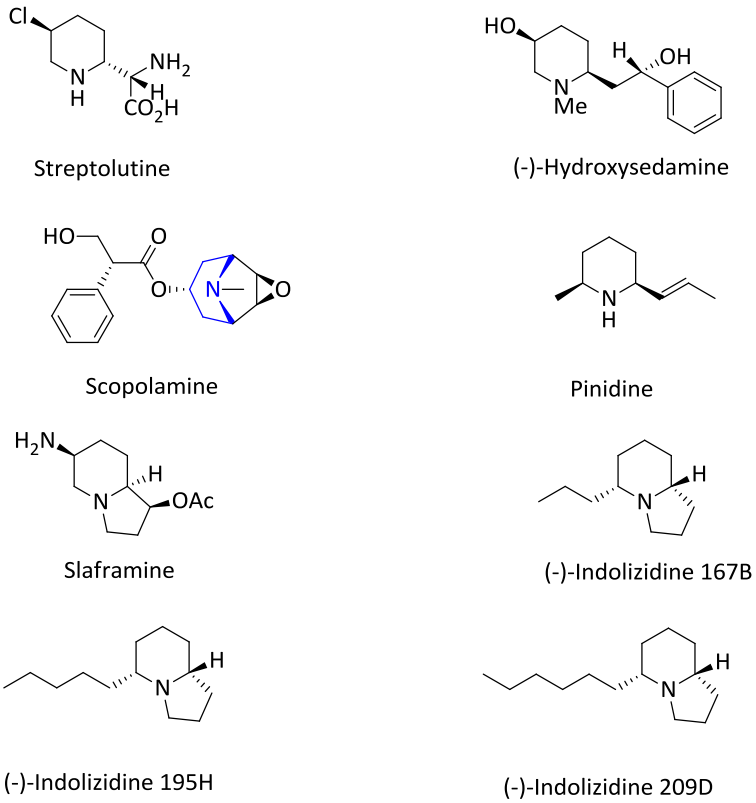
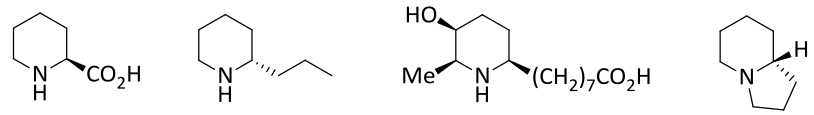


Figure 1

Moreover there are a large number of simple substituted piperidines and indolizidines that have potentially useful biological activity like pipecolic acid, coniine, carpamic acid and (-)-coniceine (**Figure 2**).[7-9]



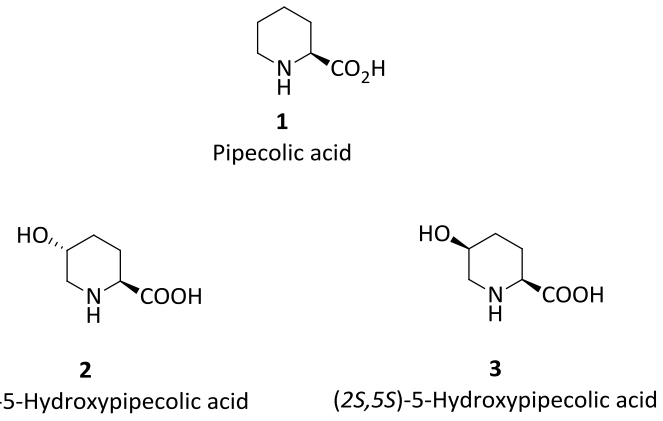
Pipecolic acid Coniine Carpamic acid (-)-Coniceine

Figure 2

This project will focus on diastereoselective synthesis of a range of disubstituted piperidines, particularly 2,5- and 2,6-disubstituted piperidines as well as the synthesis of (-)-indolizidine 167B and (-)-indolizidine 195H.

1.2 Importance of 2,5-Disubstituted Piperidines

The synthesis of 2,5-disubstituted piperidines has attracted attention because these compounds are widespread in natural products and in significant bioactive molecules.[10] For example, the stereoselective synthesis of pipecolic acid (piperidine-2-carboxylic acid) **1** and derivatives has received attention due to their powerful biological activities.[11,12] Examples include 5-hydroxy-substituted pipecolic acids **2** and **3** which have been used in the synthesis of novel chiral six-membered PNA (Peptide Nucleic Acid) analogues (**Figure 3**).[7,13]



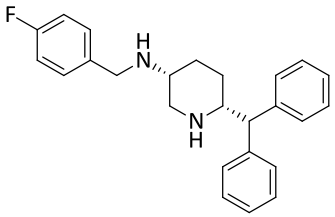
1
Pipecolic acid

2
(*2S,5R*)-5-Hydroxypipecolic acid

3
(*2S,5S*)-5-Hydroxypipecolic acid

Figure 3: Pipecolic acid and 5-hydroxypipecolic acid

Furthermore, the *cis*-2-diphenylmethyl-5-(4-fluorobenzylamino)-piperidine **4**, exhibited the most activity and selectivity for the dopamine transporter (**Figure 4**).[14]

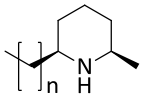


4
cis-2-Diphenylmethyl-5-(4-fluorobenzylamino)-piperidine

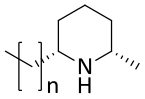
Figure 4

1.3 Importance of 2,6-Disubstituted Piperidines

2,6-Disubstituted piperidines with alkyl substituent groups occur extensively in a number of important pharmacologically active compounds.[15] Prior work in this area has concentrated on the diastereoselectivity in the synthesis of 2,6-disubstituted piperidines.[16,17] 2,6-*cis*-Disubstituted piperidines (isosolenopsins) have been extracted from the poison of fire ants of the genus *Solenopsis invicta*, and showed insecticidal, antibacterial, necrotic, cytotoxic, antifungal and anti-HIV properties (**Figure 5**).[18-20]



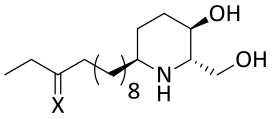
n = 8, (*2R,6S*)-Isosolenopsin
n = 10, (*2R,6S*)-Isosolenopsin A
n = 12, (*2R,6S*)-Isosolenopsin B
n = 14, (*2R,6S*)-Isosolenopsin C



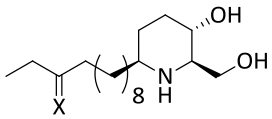
n = 8, (*2S,6R*)-Isosolenopsin
n = 10, (*2S,6R*)-Isosolenopsin A
n = 12, (*2S,6R*)-Isosolenopsin B
n = 14, (*2S,6R*)-Isosolenopsin C

Figure 5: Examples of isosolenopsins

Additionally, prosopinine, prosophylline and their deoxo analogues have shown antibiotic activity, anaesthetic and analgesic properties, and also exhibited central nervous system stimulating properties (**Figure 6**).[21]



X=O, (-)-Prosopinine
X=H_2, (-)-Deoxoprosopinine

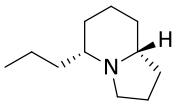


X=O, (+)-Prosophylline
X=H_2, (+)-Deoxoprosophyline

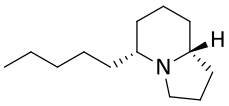
Figure 6

1.4 Importance of Indolizidines

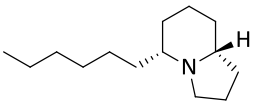
Indolizidine alkaloids are widely spread in natural products with a nitrogen-bridged bicyclic construction, found in anti-Alzheimer drugs and in compounds used for the treatment of infectious microorganisms.[22] For instance, indolizidines (-)-167B **5**, (-)-195H **6** and (-)-209D **7** were obtained from the skin secretions of neotropical frogs, which play a significant role as defensive agents due to their toxicity.[23] Moreover, indolizidines (-)-167B and (-)-209D are promising cardiotonic agents, and act as non-competitive blockers of neuromuscular transmission (**Figure 7**).[24,25]



5
(–)-Indolizidine 167B



6
(–)-Indolizidine 195H



7
(–)-Indolizidine 209D

Figure 7

1.5 Previous Syntheses of Disubstituted Piperidines

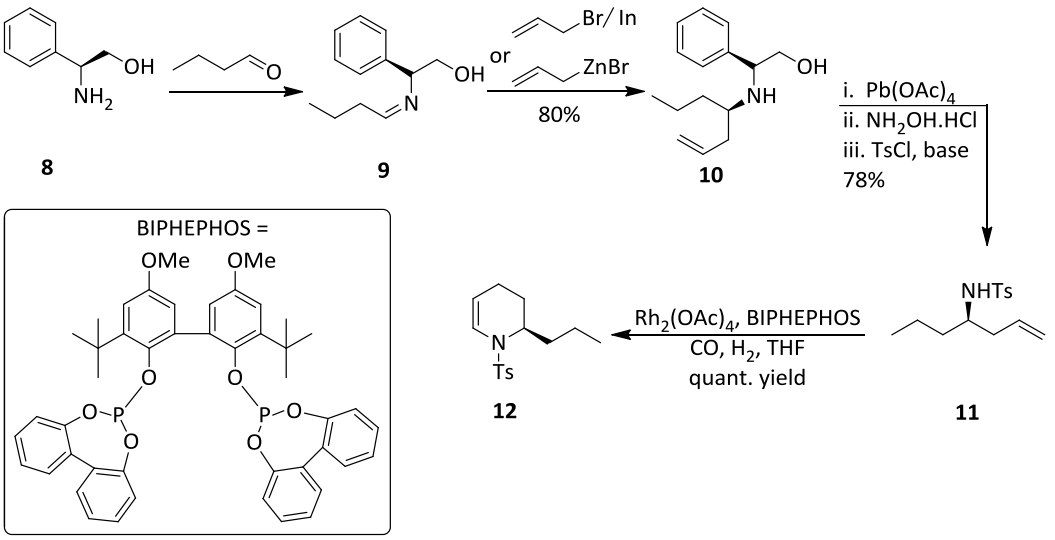
There are many approaches to the preparation of disubstituted piperidines. This section will summarize some of the common procedures for creating 2,5-disubstituted and 2,6-disubstituted piperidines employing a cyclisation strategy, rather than starting with the piperidine skeleton.

1.5.1 Preparation of 2,5-Disubstituted Piperidines

In this section a selection of previous methods for the synthesis of 2,5-disubstituted piperidines which are related to our target molecules will be reviewed.[4,8,15,26,27]

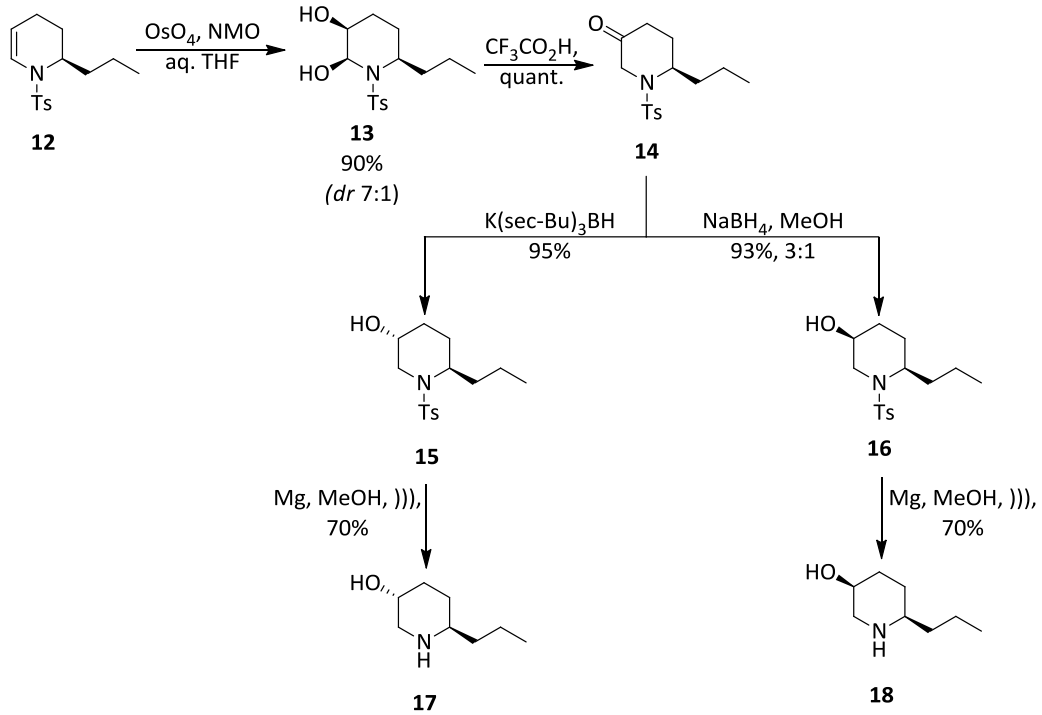
1.5.1.1 Tandem hydroformylation-condensation

Bates and co-workers synthesized pseudoconhydrine **17** and its epimer **18** using a tandem hydroformylation-condensation process.[28] This approach started through a sequence involving condensation of (*S*)-amino alcohol **8** with butanal, allylation with either allyl bromide and indium powder or allylzinc bromide.[29] Good diastereoselectivity for the allylation product **10** was obtained under carefully controlled conditions. Hydroformylation of **11** was achieved using rhodium acetate in THF under an atmosphere of CO and H_2 correspondingly to give the protected amino aldehyde, which underwent cyclisation to give **12 (Scheme 1).**



Scheme 1

Finally, treatment of compound **12** with osmium(VIII) tetroxide afforded *cis*-diol **13**, which was converted into the ketopiperidine **14**, followed by reduction with K-Selectride® to give the *trans*-alcohol and the protecting group was removed to furnish pseudoconhydrine **17.** Epi-pseudoconhydrine **18** was obtained by reduction of ketopiperidine **14** with sodium borohydride, followed by removal of the tosyl group **(Scheme 2).**

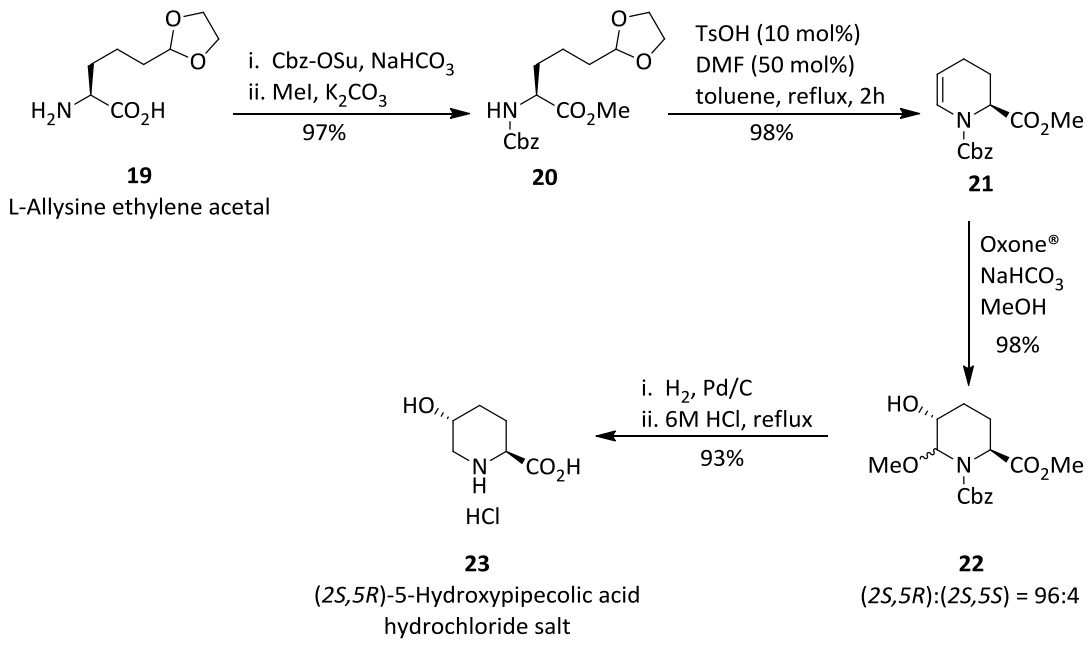


Scheme 2

1.5.1.2 Diastereoselective Synthesis of (*2S,5R*)-5-Hydroxypipecolic Acid

Blaauw and co-workers have described a diastereoselective synthetic approach to (*2S,5R*)-5-hydroxypipecolic acid **23** using a highly diastereoselective epoxidation reaction of an enantiomerically pure cyclic enamide intermediate.[30]

(*2S,5R*)-5-Hydroxypipecolic acid **23** was synthesized in six steps starting with *N*-protection of **19** with Cbz-OSu, followed by methylation of the carboxylic acid with MeI to obtain the protected amino acid **20**. This compound was treated with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene, promoting a cyclisation-elimination sequence leading to enamide **21**.[31] The key step in this route was the epoxidation of **21** which was performed in MeOH using Oxone® leading to the 5-hydroxypipecolic acid derivative **22** with the *trans*-isomer favoured (96:4 *dr*). The next step was deprotection of the amine, followed by hydrolysis of the methyl ester and precipitation from aqueous acetone, to give the desired natural product **23** as the corresponding HCl salt (**Scheme 3**).

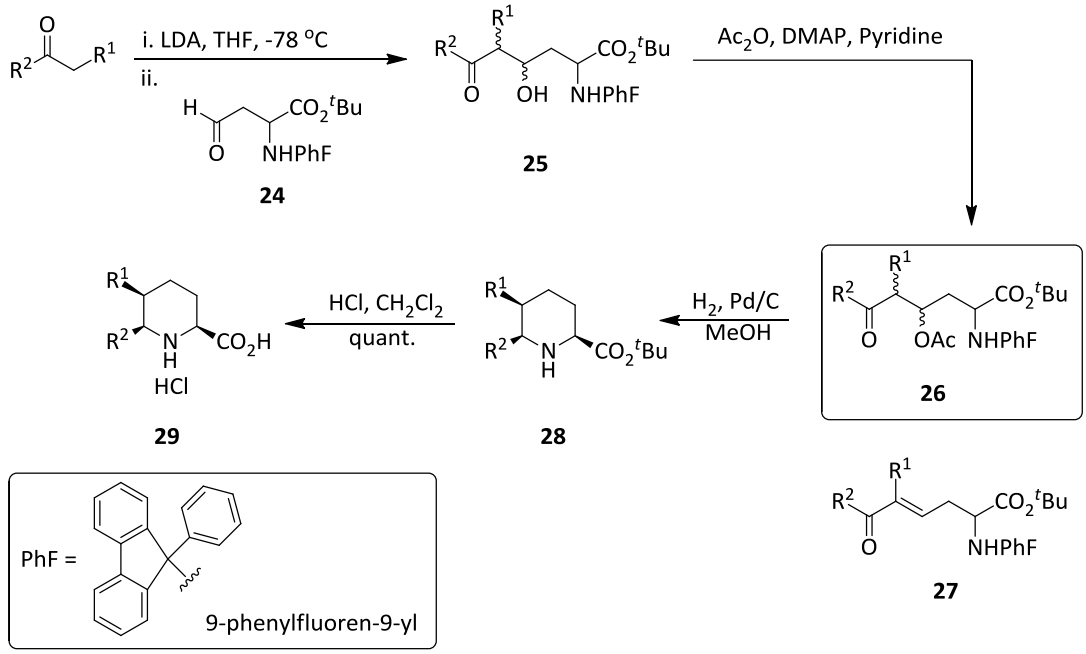


Scheme 3

1.5.1.3 Synthesis of 5,6-Dialkylpipecolic Acids

Lubell and Swarbrick have reported a diastereoselective synthetic approach to enantiopure 5,6-dialkylpipecolate derivatives involving sequential aldol condensation followed by cyclisation *via* a diastereoselective reductive amination.[32]

Reaction of lithium enolates of a number of ketones with aldehyde **24** gave the corresponding ε-oxo γ-hydroxy α-*N*-(PhF)amino esters **25** in a range of yields 40-81%. Conversion of the hydroxyl group to a better leaving group was achieved by treatment of the compounds **25** with acetic anhydride and DMAP in pyridine to give the desired acetates **26**, with α,β-unsaturated ketones **27** as a by-product. Diastereoselective reductive cyclisation of acetates **26** using Pd/C (10% w/w) gave (*2S,5S,6S*)-5,6-dialkylpipecolates **28** as a single diastereoisomer. Finally, the esters **28** were converted to the corresponding hydrochloride salts **29** by treatment with HCl in dichloromethane in quantitative yields (**Scheme 4** and **Table 1**).



Scheme 4

Table 1: Synthesis of 5,6-dialkylpipecolic acids

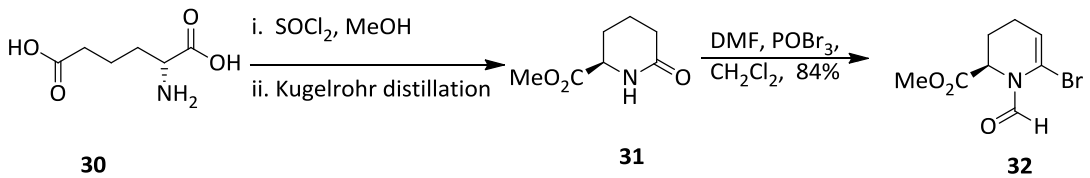
entry	Ketone	R^1	R^2	**25** (yield, %)	**26 (27)** (yield, %)	**28** (yield, %)
a	1,3-Diphenylacetone	Ph	$PhCH_2$	81	-	75
b	2,2-Dimethyl-3-pentanone	Me	^tBu	62	99	67
c	Cyclopentanone	$-(CH_2)_3-$		75	77 (15)	82
d	Cyclohexanone	$-(CH_2)_4-$		79	89 (6)	82
e	2-Nonanone	$^nC_6H_{13}$	Me	40	95	82

1.5.2 Preparation of 2,6-Disubstituted Piperidines

There have been a number of synthetic strategies developed for the preparation of 2,6-disubstituted piperidines, and some that give the products in an enantiomerically pure form.[7,16,33-35]

1.5.2.1 Sonogashira and Suzuki cross-coupling reactions

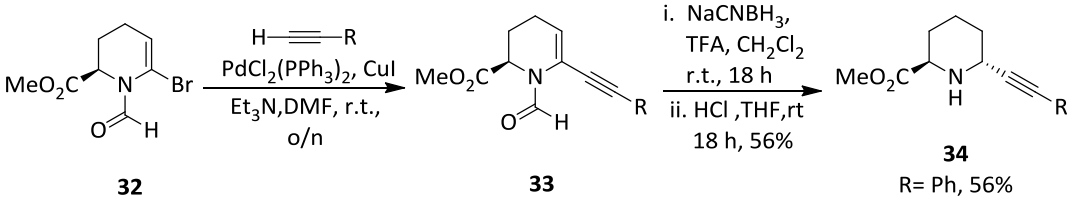
Sewald and Sadiq have developed an efficient route for the preparation of 6-substituted (*2R,6R*)-pipecolic acid derivatives. This route started by sequential esterification and lactamization of (*R*)-α-aminoadipic acid **30** to give 6-oxopipecolate **31**, followed by reacting with DMF and $POBr_3$ to give the bromo compound **32** (**Scheme 5**).[36]



30 **31** **32**

Scheme 5

Sonogashira cross-coupling reactions on the vinyl bromide **32** with terminal alkyne derivatives gave *N*-acyl substituted 2,3-dehydropiperidines **33** (**Scheme 6** and **Table 2**).



32 **33** **34**

R= Ph, 56%

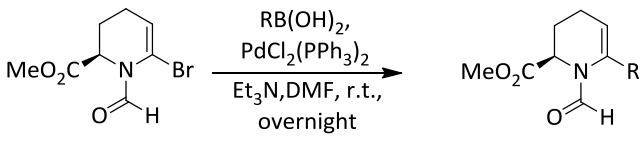
Scheme 6

Table 2:

alkyne	**33** (yield, %)	alkyne	**33** (yield, %)
≡—Ph	77	≡—△	74
≡—CO_2Et	72	≡—C_3H_7	75
≡—CH_2OH	68	≡—TMS	80

Finally, the compound **33** was reduced by $NaCNBH_3$ in the presence of trifluoroacetic acid, followed by cleavage of the *N*-formyl group under acidic conditions gave methyl (*2R,6R*)-6-(2-phenylethynyl)-piperidine-2-carboxylate **34**.

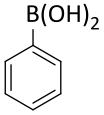
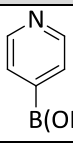
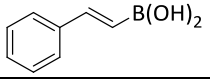
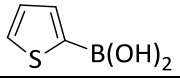
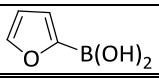
Suzuki cross-coupling reaction was accomplished between compound **32** and a range of boronic acids under mild conditions to give the corresponding 6-substituted (*R*)-pipecolates **35** in moderate yields (**Scheme 7** and **Table 3**).



32 **35**

Scheme 7

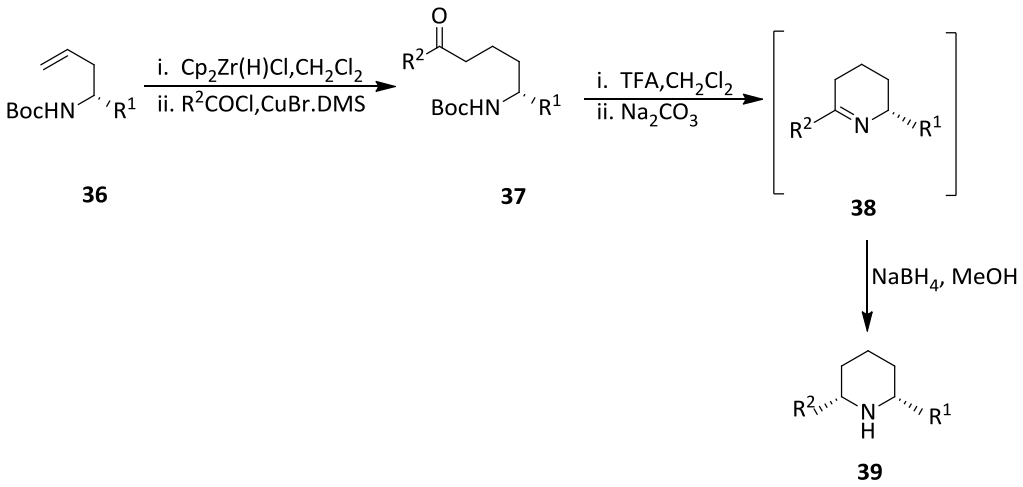
Table 3:

Boronic acid	**35** (yield, %)	Boronic acid	**35** (yield, %)
	72%		53%
	74%		48%
	66%	N/A	N/A

1.5.2.2 Hydrozirconation / transmetalation / acylation

Szymoniak and co-workers have described the preparation of 2,6-disubstituted piperidines using a hydrozirconation/acylation process.[6]

Preparation of protected amino ketones **37** was achieved by applying a hydrozirconation/acylation sequence on the enantiomerically pure *N*-Boc-protected 2-substituted homoallylic amines **36**, which used 2.0 equivalent of the Schwartz reagent. Treatment of compound **37** with trifluoroacetic acid in dichloromethane resulted in deprotection and cyclisation to the iminium salts. Treatment with base gave the free iminium intermediate **38**, which underwent reductive amination using sodium borohydride to give the 2,6-disubstituted piperidines **39** with diastereoselectivities typically >19:1 with R^1 = Ph, but much lower with other substituents (**Scheme 8** and **Table 4**).



36 **37** **38** **39**

Scheme 8

Table 4: Synthesis of Piperidines

entry	R^1	R^2	**37** (yield, %)	**39** (yield, %)	*dr*
a	Ph	Ph	70	77	>19:1
b	Ph	3-ClC_6H_4	50	87	>19:1
c	Ph	2-BrC_6H_4	56	81	>19:1
d	2-$OMeC_6H_4$	Ph	45	73	>19:1
e	Ph	Me	69	72	>19:1
f	Ph	*C*-C_3H_5	51	88	>19:1
g	Ph	^{i}Bu	72	73	>19:1
h	(*E*)-PhCH=CH	Ph	56	47	4:1
i	$(CH_2)_3$-OBn	*n*-C_6H_{13}	47	58	5.5:1

The diastereoselectivity in the reduction step presumably arises through an axial hydride addition to a half-chair-like conformation, particularly when the R^1 substituent occupies in a pseudo equatorial position (**Figure 8**).

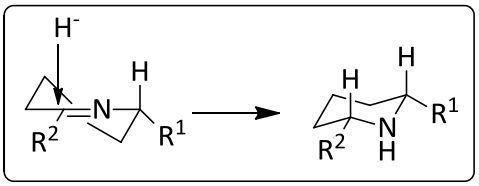
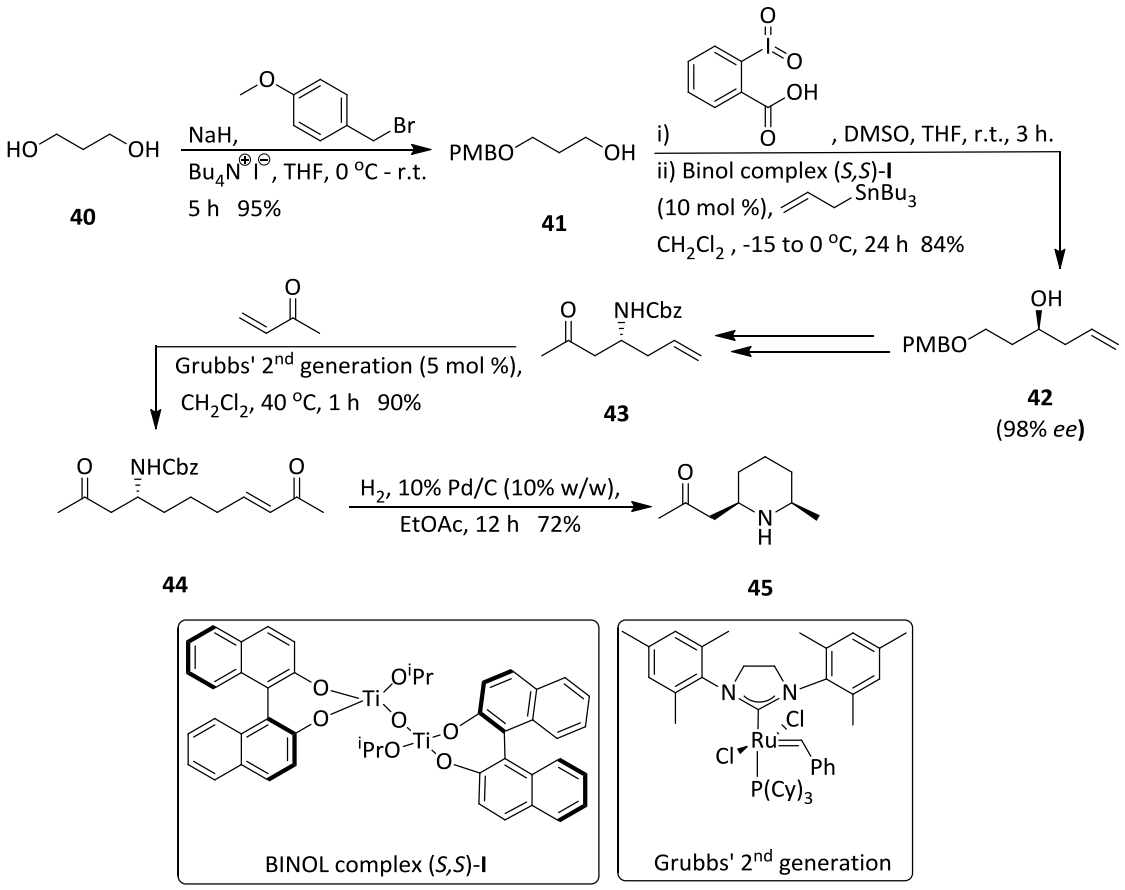


Figure 8: Proposed origin of the *cis*-selectivity

1.5.2.3 Maruoka asymmetric allylation / Grubbs' cross-metathesis / reductive cyclisation.

Babu and co-workers have synthesized enantiomerically pure (-)-pinidinone **45** by utilizing Maruoka asymmetric allylation and *Grubbs*' olefin cross-metathesis as key steps.[37] This approach started by selective protection of commercially available propane-1,3-diol **40**, followed by oxidation to the aldehyde and enantioselective Maruoka allylation using BINOL complex (*S,S*)-**I** gave the homoallylic protected alcohol **42** with excellent enantioselectivity (98% *ee*). After several steps, *Grubbs'* cross-metathesis was achieved between olefin precursor **43** and methyl vinyl ketone to obtain cyclisation substrate **44**. Treatment of compound **44** with Pd/C under hydrogen atmosphere, Cbz-deprotection, and diastereoselective reductive cyclisation sequence led to the final product **45** (**Scheme 9**).

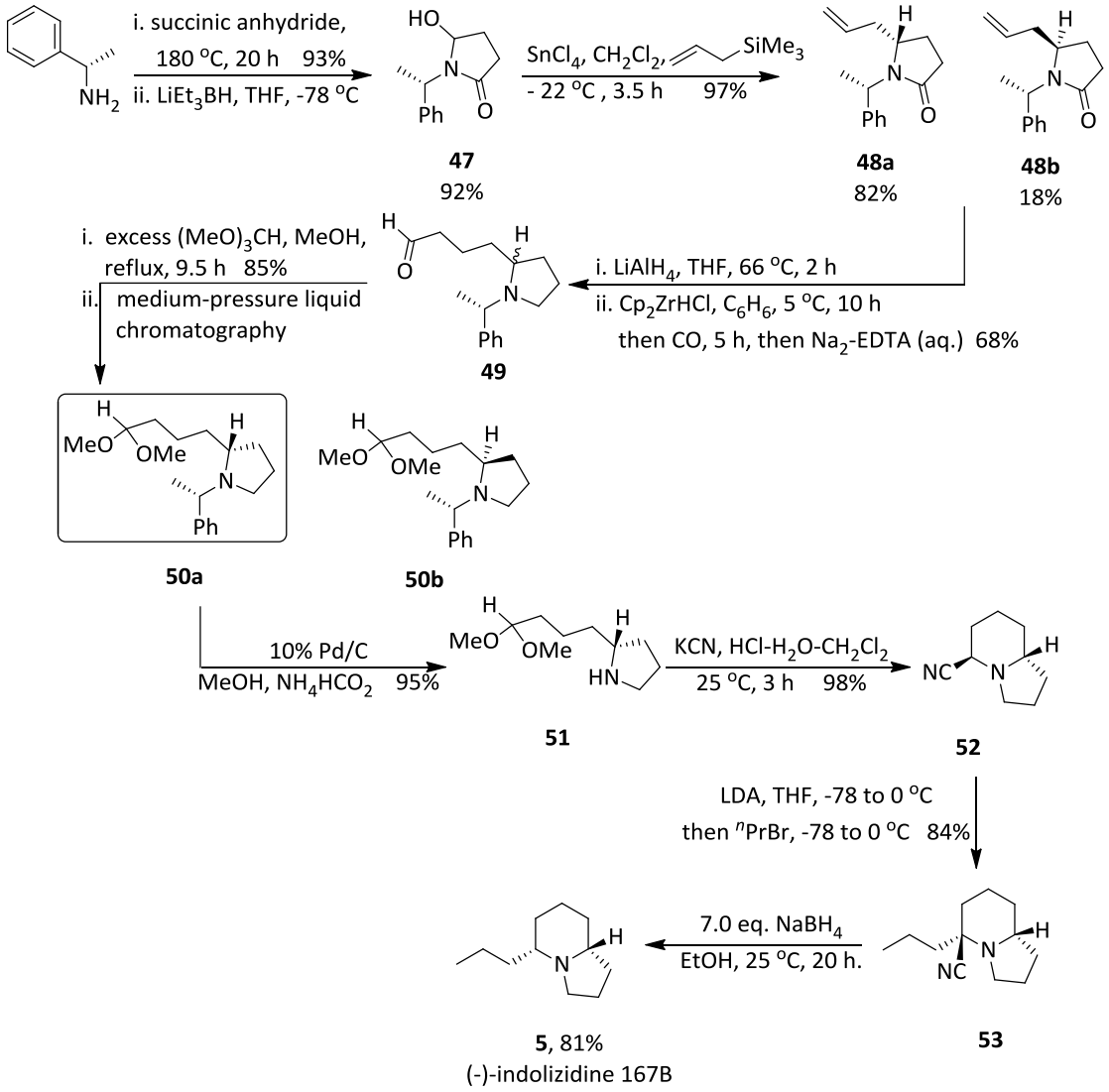


Scheme 9

1.5.3 Preparation of Indolizidines

There are many strategies for the preparation of indolizidines. This section will review the previous procedures to synthesize (-)-indolizidine 167B (**5**) and indolizidine 195H (**6**) which are our targets.

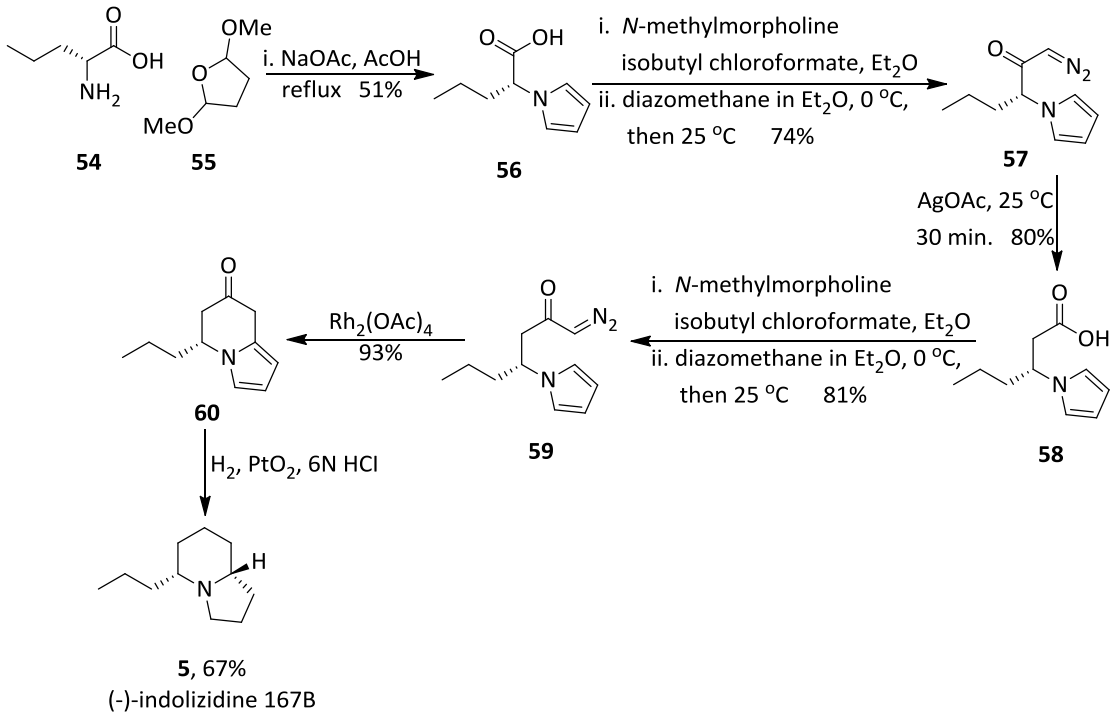
Polniaszek and Belmont described the first enantioselective synthesis of (-)-indolizidine alkaloid 167B (**5**) in ten steps and approximately 23% overall yield from (*S*)-(-)-α-phenethylamine.[38] Condensation of *(S)*-(-)-α-phenethylamine with succinic anhydride, followed by stereoselective reduction by lithium triethylborohydride gave stereoisomeric 95:5 of hydroxylactam **47**, which on treatment with allyltrimethylsilane in the presence of stannic chloride afforded inseparable epimeric mixture of **48a**:**48b**. The mixture of **48a** and **48b** was reduced with $LiAlH_4$, then hydrozirconation with Cp_2ZrHCl, followed by carbonylation gave a mixture of homologated aldehydes **49**. Treatment of aldehydes **49** with excess trimethyl orthoformate gave the corresponding dimethyl acetals **50a** and **50b**, which separated by medium-pressure liquid chromatography. The amino nitrile **52** was obtained by sequential removal of the phenethyl group from **50a**, followed by hydrolysis of the acetal **51** in the presence of hydrogen cyanide. Deprotonation of **52** by LDA and alkylation with propyl bromide gave alkylated amino nitriles **53**, which were reduced by sodium borohydride to give the desired product **5** (**Scheme 10**).



Scheme 10

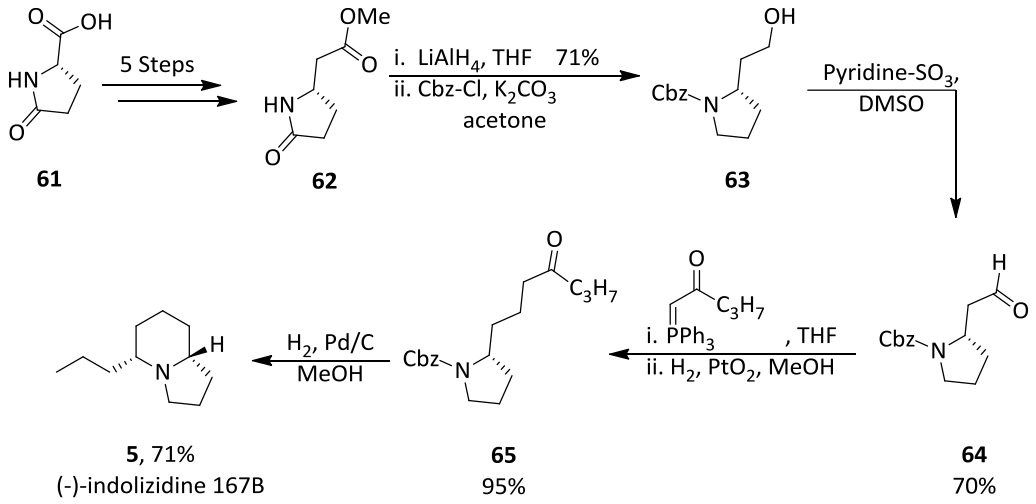
Jefford and co-workers have described the enantioselective synthesis of (-)-indolizidine 167B (**5**) in six steps in an overall yield of 15% starting from D-norvaline.[24] Condensation of D-norvaline **54** with 2,5-dimethoxytetrahydrofuran **55** gave 1-pyrrolylacetic acid **56,** which was converted to the α-diazo ketone **57**. Treatment of **57** with silver acetate afforded the acid **58**, which repetition of the diazomethane process gave the corresponding α-diazo ketone **59**. Decomposition of **59** by rhodium(II)acetate catalysis provided

the dihydroindolizinone **60**. Finally, **60** was subjected to hydrogenation using Adams's catalyst under acid conditions to give the desired product **5** in 67% yield (**Scheme 11**).



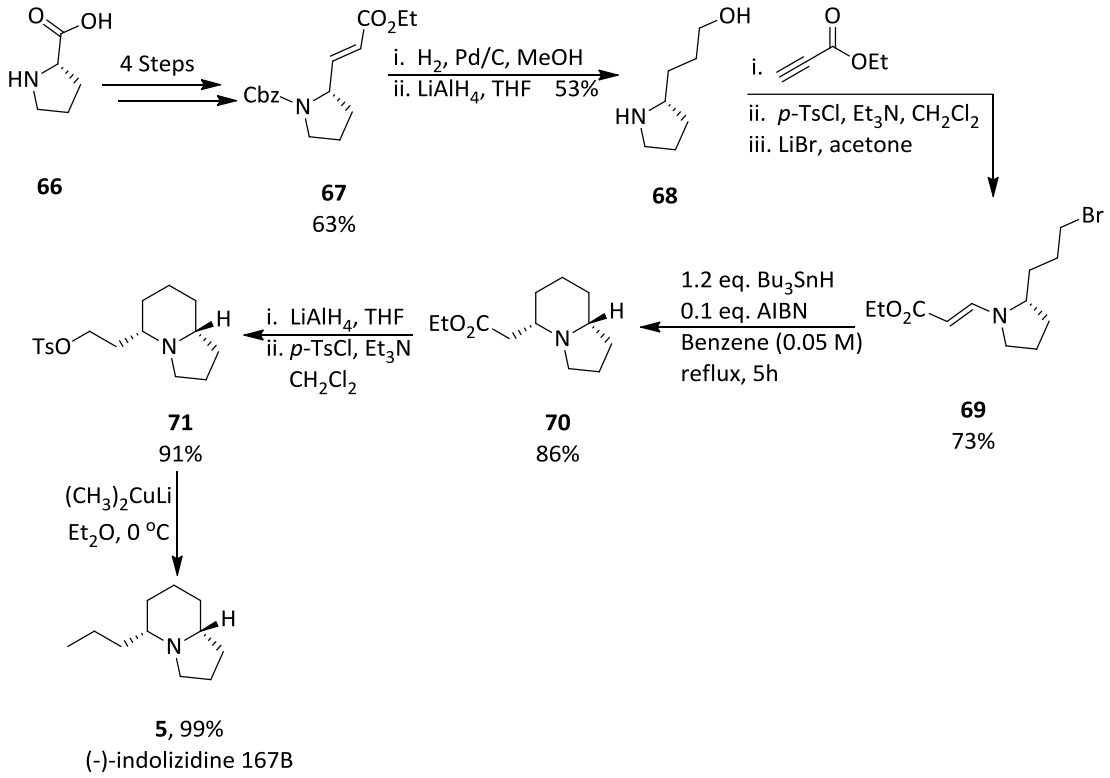
Scheme 11

Lhommet and co-workers have synthesized of (-)-indolizidine 167B (**5**) stereoselectively in eleven steps starting from (*S*)-pyroglutamic acid.[39] The lactam ester **62** was obtained from (*S*)-pyroglutamic acid **61** in five straightforward steps: esterification, reduction, tosylation, reaction with cyanide, then acidic methanolysis. Reduction of **62**, followed by amino group protection, gave amino alcohol **63**, which was converted to the corresponding aldehyde **64**. Wittig reaction on **64** gave the amino enone, then reduced to the corresponding saturated amino ketone **65** using Adams catalyst. Finally, sequential Cbz-deprotection, and diastereoselective reductive aminition gave the target **5** in 70% yield (**Scheme 12**).



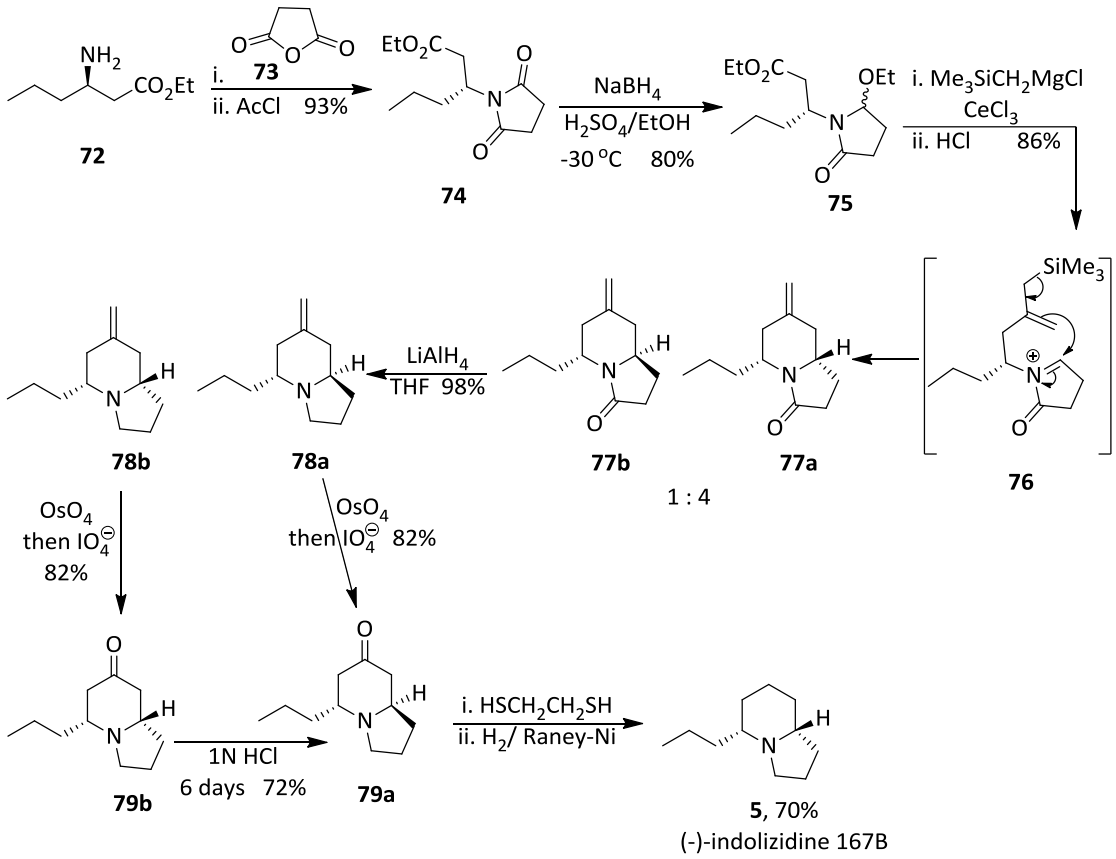
Scheme 12

Lee and co-workers have reported a stereoselective synthesis of (-)-indolizidine 167B (**5**) in twelve steps starting from (*S*)-proline.[40] The protected pyrrolidine acrylate **67** was obtained from (*S*)-proline **66** in four sequent steps (protection, borane reduction, oxidation, and Wittig reaction). Sequent hydrogenation and reduction of **67** was afforded **68**. *p*-Aminoacrylate **69** was obtained by reaction of **68** with ethyl propiolate, followed by conversion to the corresponding bromide. Treatment of **69** with Bu_3SnH/AIBN resulted in a radical itermediates to give **70**, which was reduced by $LiAlH_4$, followed by conversion to the corresponding tosylated alcohol **71**. The desired product **5** was obtained by treatment of **71** by lithium dimethylcuprate (**Scheme 13**).



Scheme 13

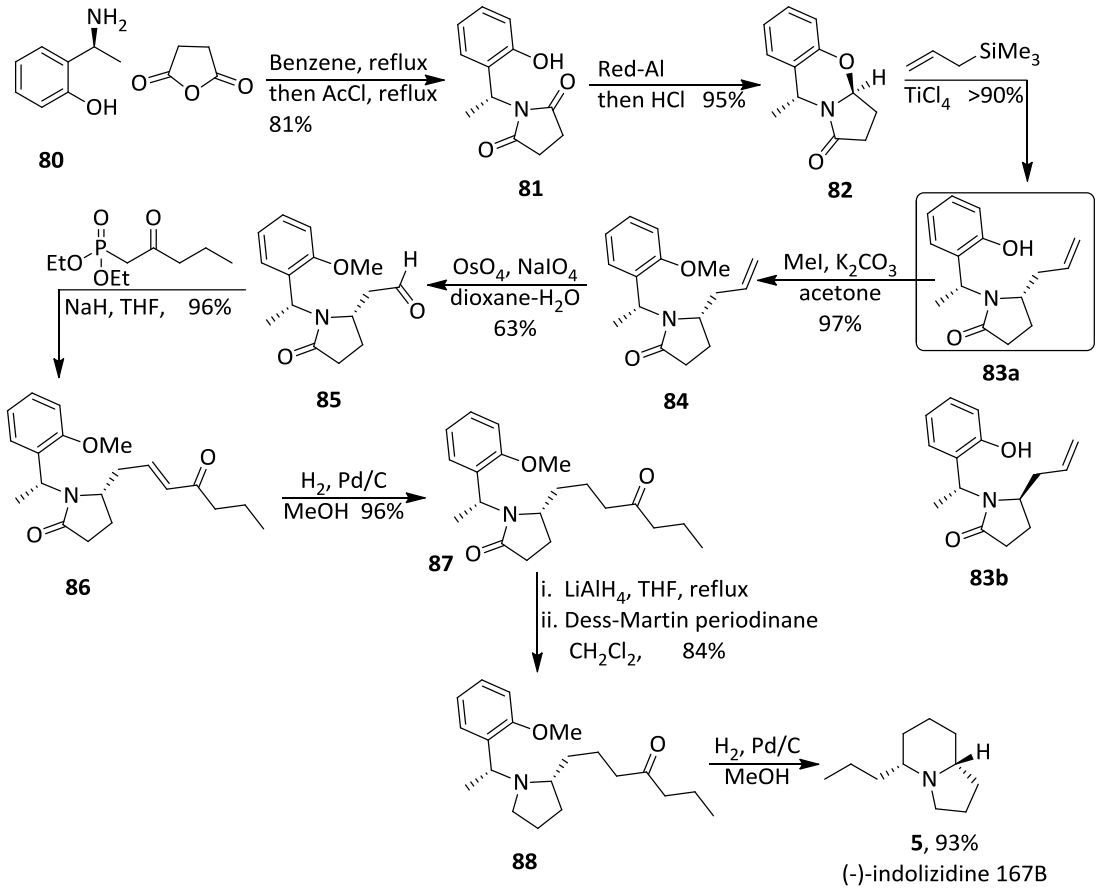
Remuson and co-workers have synthesized (-)-indolizidine 167B (**5**) stereoselectively in nine steps and an overall yield of 17% starting from (*3R*)-3-aminohexanoate **72**.[41] Ethyl (*3R*)-3-aminohexanoate **72** was condensed with succinic anhydride, followed by treatment with AcCl to yield imide **74**. The imide **74** was reduced by sodium borohydride to ethoxylactam **75**, then treated with trimethylsilylmethylmagnesium chloride in the presence of $CeCl_3$ to give a mixture of **77a** and **77b**. These isomers were reduced by $LiAlH_4$ to give two separable isomers **78a** and **78b**, which were each converted into the ketones **79a** and **79b**. Compound **79b** was converted to **79a** by refluxing with 1N HCl for six days. Finally, compound **79a** was converted into its dithiolane and sequential desulfurization using Raney nickel produced (-)-indolizidine 167B (**5**) in 70% yield respectively (**Scheme 14**).



Scheme 14

Kibayashi and co-workers have reported asymmetric synthesis route of (-)-indolizidine 167B (**5**) in ten steps starting from (*S*)-2-(1-aminoethyl)- phenol.[42] Condensation of (*S*)-2-(1-aminoethyl)-phenol **80** with succinic anhydride gave the imide **81**, which was reduced partially *via* Red-Al and treatment with acid resulted the *N*,*O*-acetal **82** as a single isomer. Allylation of **82** with allyltrimethylsilane gave the (*5S*)-allylated product **83a** in high yield and diastereoselectivity, and **83b** as a minor diastereomer. Methylation of **83a** gave the methoxy derivative **84**, followed by oxidative cleavage $OsO_4/NaIO_4$ afforded aldehyde **85**, which was converted into the (*E*)-enone **86** using a Horner–Wadsworth–Emmons reaction, which was then hydrogenated to **87**. Reduction of **87**, and Dess-Martin oxidation of the resulting amino alcohol gave

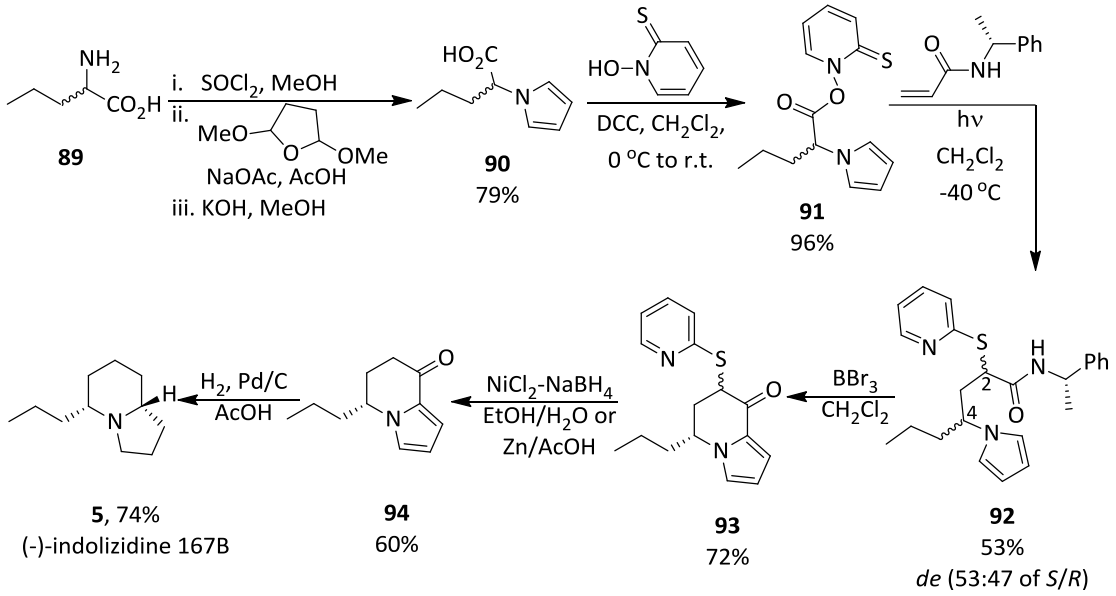
amino ketone **88**. Finally, sequential deprotection of the nitrogen protecting group, and intramolecular diastereoselective reductive amination gave the desired compound **5** in 93% yield as a single isomer (**Scheme 15**).



Scheme 15

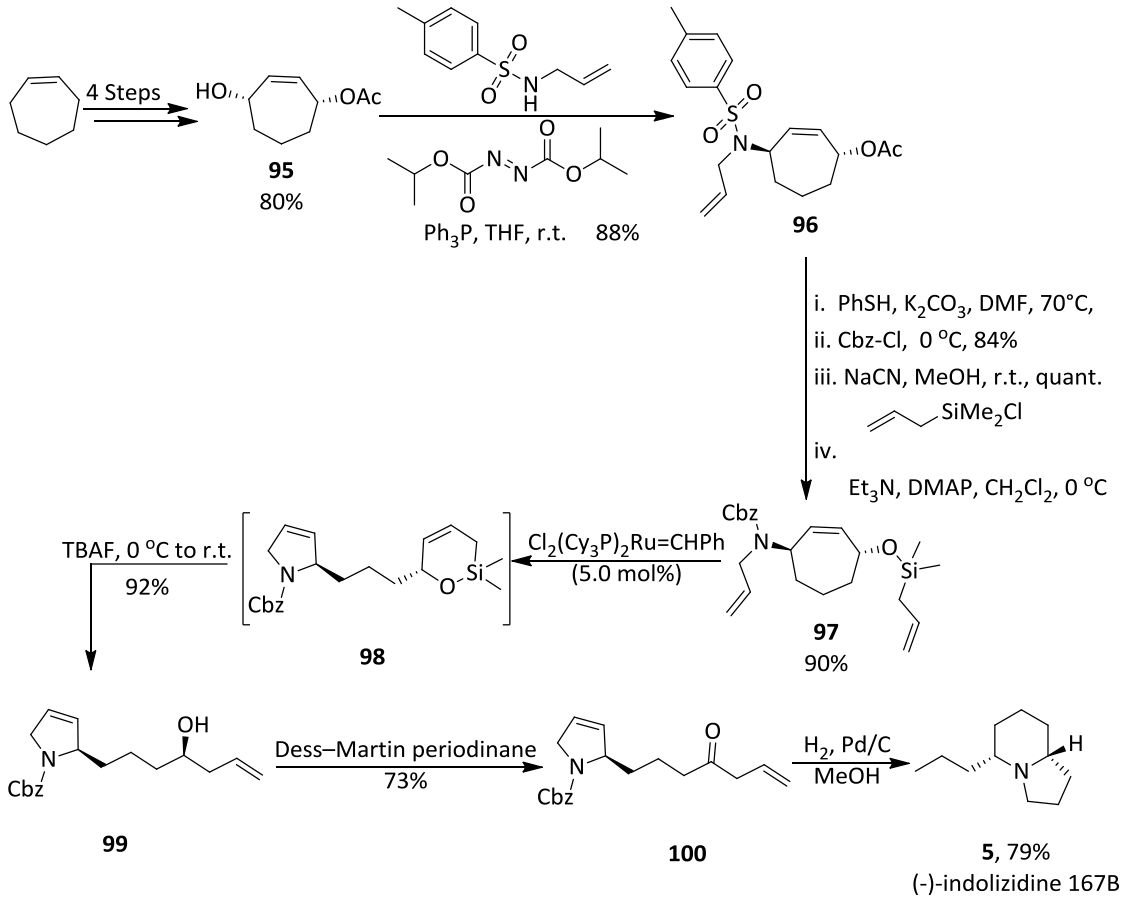
Pereira and Corvo have synthesized of (-)-indolizidine 167B (**5**) in eight steps from racemic norvaline using a stereoselective addition of a carbon radical onto an optically pure acrylamide.[43] Conversion of DL-norvaline **89** into a pyrrole carboxylic acid derivative **90**, was followed by formation of the *N*-hydroxy thiopyridone ester **91**. Irradiation of **91** at low temperature gave the corresponding carbon radical precursor, which added to (*S*)-*N*-(1-phenylethyl)acrylamide to produce **92** in 53% yield, with (*dr* 53:47 of *S*/*R* ratio). Removal of the chiral auxiliary and cyclisation occurred concomitantly by treatment of **92** with boron tribromide resulting in the cyclic ketone **93**, which was treated with 'nickel boride' to remove the thiopyridyl group to yield **94**.

The compound **94** was hydrogenated over palladium/carbon in acetic acid to furnish to the desired (-)-indolizidine 167B (**Scheme 16**).



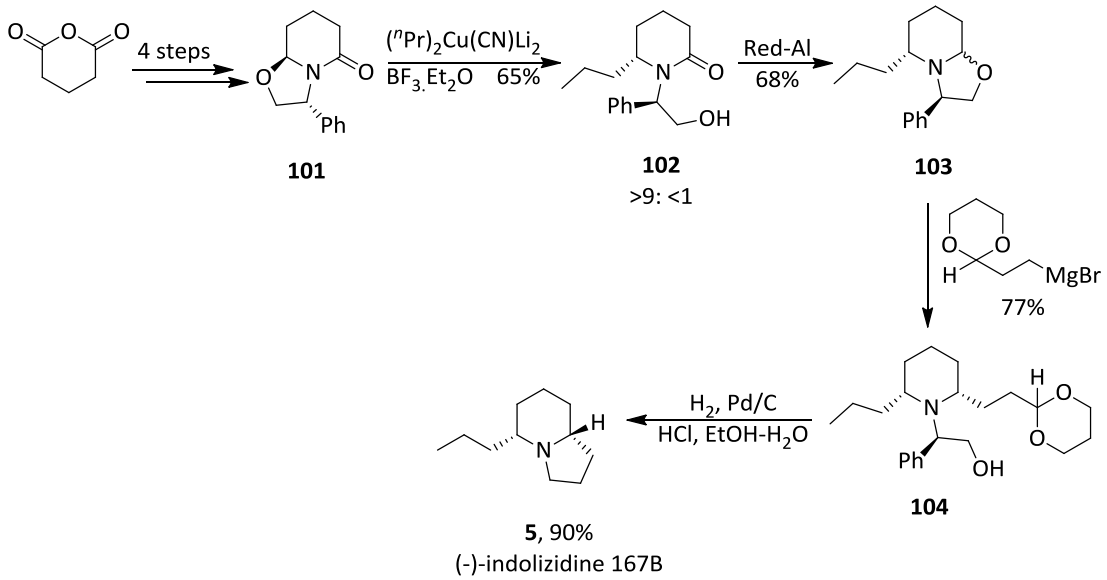
Scheme 16

Blechert and co-workers have reported enantioselective synthesis of (-)-indolizidine 167B (**5**) in eight steps and an overall yield of 35% starting from cycloheptenediol-monoacetate,[44] which was prepared from cycloheptene **95** in four steps. Mitsunobu reaction of **95** with *N*-nosyl-*N*-allylamine produced protected amine **96**, followed by a sequence of protecting group replacement by Cbz-group, O-deprotection and O-silylation. Ruthenium-catalysed tandem ring-rearrangement metathesis, followed by silyl ether cleavage of **97** gave amino alcohol **99**, which converted to the corresponding ketone **100** using Dess-Martin oxidation. Treatment of compound **100** with Pd/C under hydrogen atmosphere, Cbz-deprotection, and diastereoselective reductive aminition sequence leading to the enantiomerically pure desired compound **5** (**Scheme 17**).



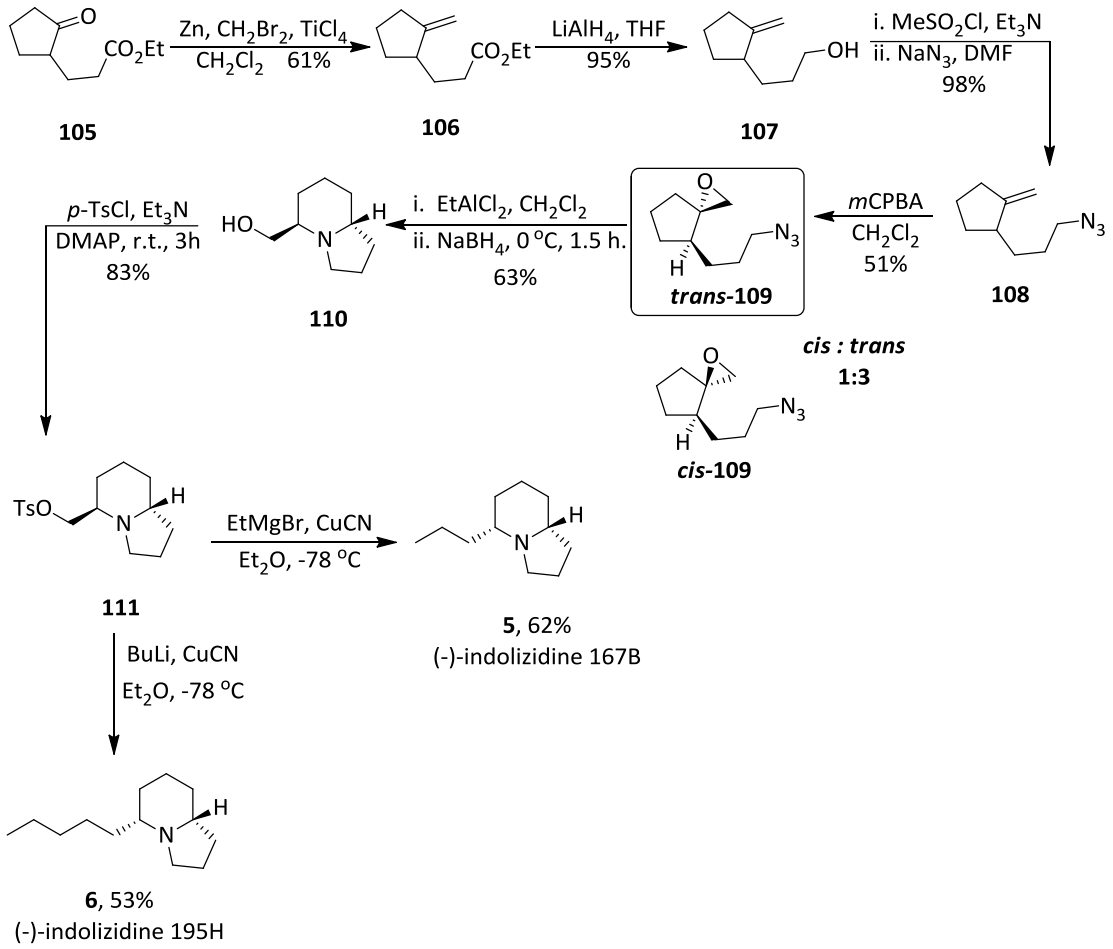
Scheme 17

Bosch and co-workers have disclosed an enantioselective synthesis of (-)-indolizidine 167B (**5**) in four steps starting from the bicyclic lactam **101**.[45] Itself prepared from glutaric anhydride in four steps. Treatment **101** with a cyanocuprate reagent in the presence of $BF_3.Et_2O$ gave **102**. Red-Al reduction of **102** gave the oxazolopiperidone **103**, which reacted with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane to produce **104.** Cleavage of the chiral auxiliary followed by diastereoselective hydrogenation using Pd/C (10% w/w) furnished the desired compound **5** (**Scheme 18**).



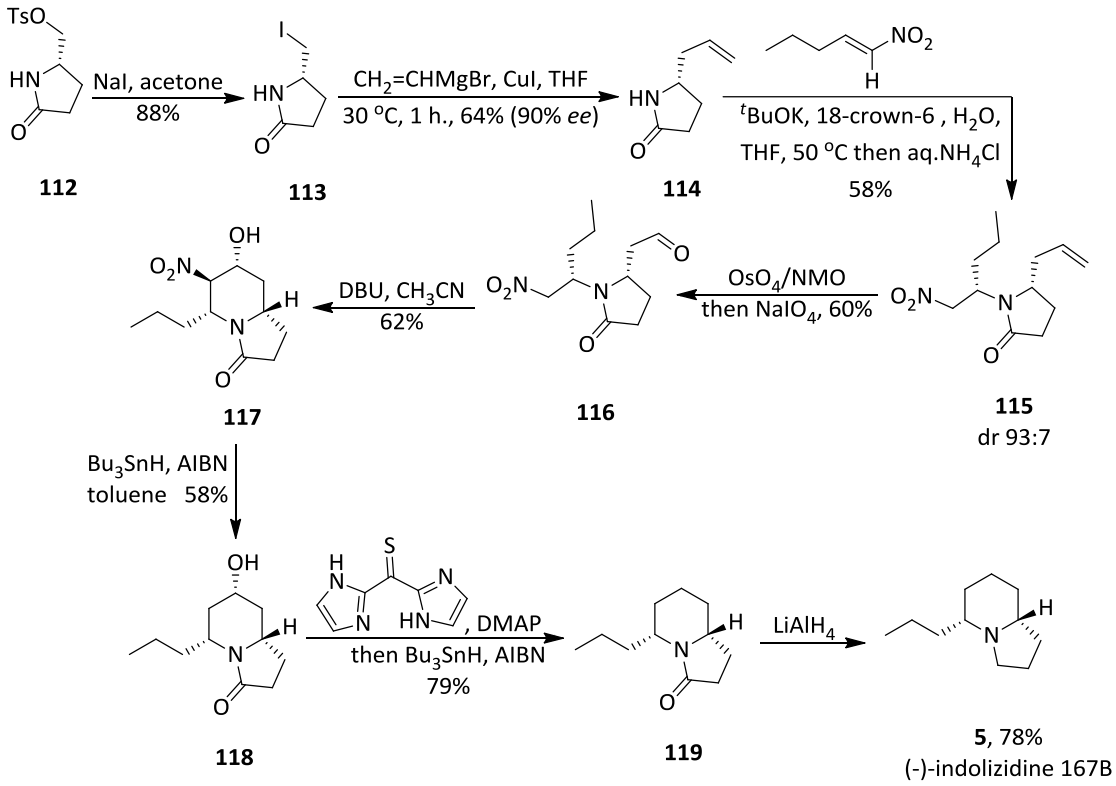
Scheme 18

Baskaran and Reddy developed a novel stereoselective synthesis of (-)-indolizidine 167B (**5**) and (-)-indolizidine 195H (**6**) in ten steps from the ketoester **105**.[46] Treatment **105** with neutral titanium carbene reagent derived from $Zn/TiCl_4/ CH_2Br_2$ gave the exocyclic olefin **106**, which was reduced by $LiAlH_4$ to give the corresponding alcohol **107**. The alcohol **107** was converted to azidoalkene **108**, which on reaction with *m*-CPBA gave the epoxyazide **109** as a separable racemic mixture of ***cis*** : ***trans*** (**1:3**) diastereoisomers. Treatment of the *trans*-epoxyazide **109** with Lewis acid ($EtAlCl_2$) followed by the addition of $NaBH_4$ gave the hydroxymethyl indolizidine **110**, which was converted into the corresponding tosylate **111**. Finally, copper catalysed reaction of **111** with EtMgBr at -78 °C, afforded enantiomerically pure desired compound (**5**). Treatment of the tosylate **111** with ^{n}BuLi in the presence of CuCN gave (-)-indolizidine 195H (**6**) in optically pure form (**Scheme 19**).



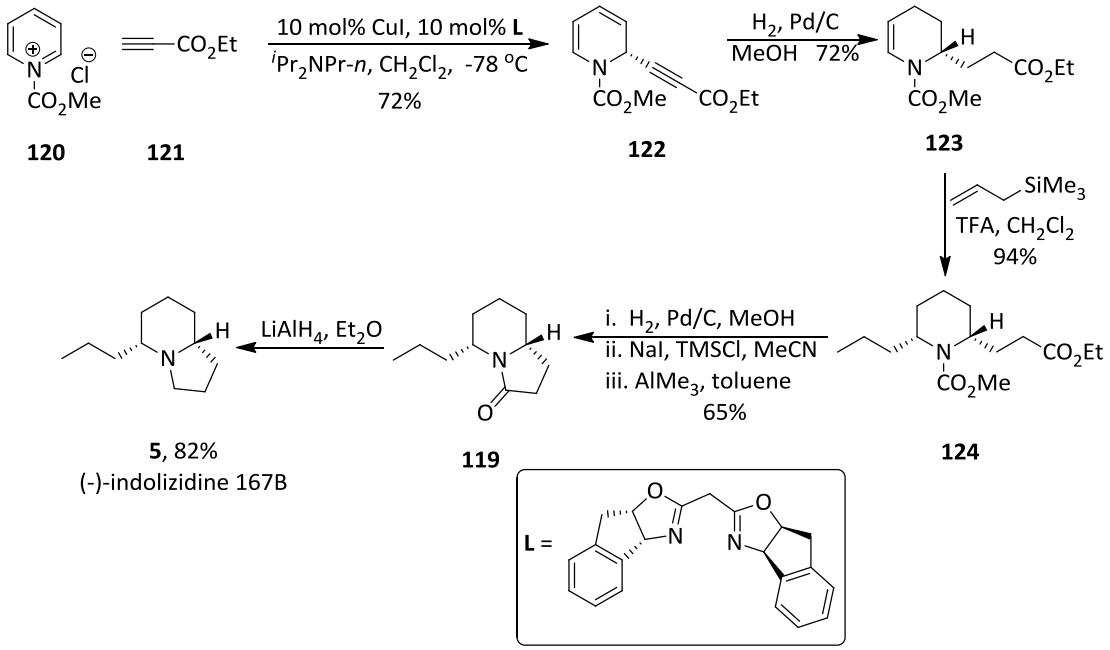
Scheme 19

Kamimura and co-workers have reported a stereoselective conjugate addition approach to synthesize of (-)-indolizidine 167B (**5**) in eight steps starting from the tosyloxymethylpyrrolidinone **112**.[47] Conversion to the 5-substituted pyrrolidinone **114** in two steps (iodination followed by Grignard reaction), followed by conjugate addition of **114** to (*E*)-1-nitropent-1-ene produced the corresponding nitroalkane **115** in high selectivity (*dr* 93:7). Treatment of **115** with OsO_4 and NMO then $NaIO_4$ gave aldehyde **116**, which underwent intramolecular nitroaldol reaction under basic conditions to give indolizidinone **117**. Sequential removal of the nitro and the hydroxyl groups gave **119**, which was reduced by $LiAlH_4$ to furnish to the desired compound **5** (**Scheme 20**).



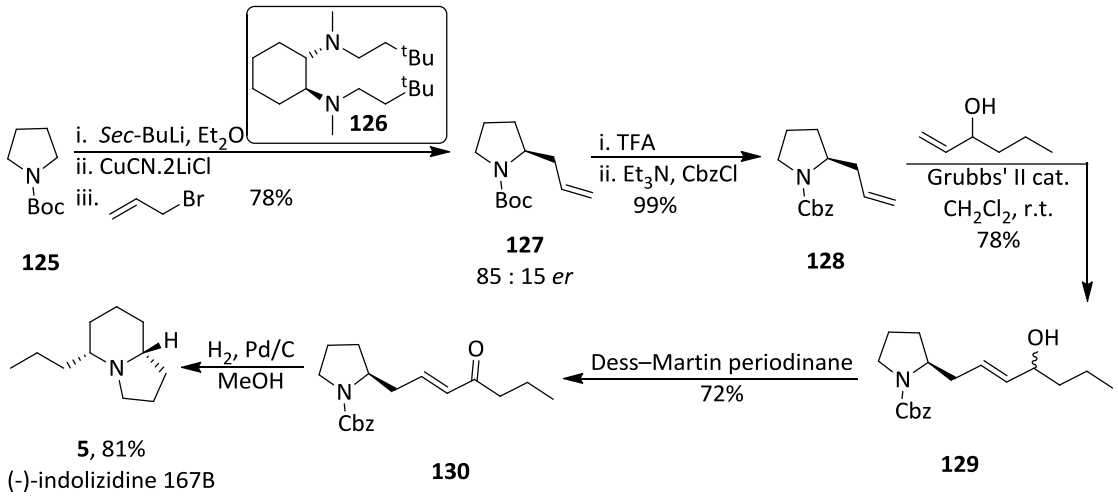
Scheme 20

Ma and co-workers developed an enantioselective approach to synthesize (-)-indolizidine 167B (**5**) in seven steps from the 1-acetylpyridinium salt **120**.[48] Reaction between **120** and **121** in the presence of the bis(oxazoline) ligand **L** and CuI gave dihydropyridine **122**, which was hydrogenated partially to afford tetrahydropyridine **123**. Allylation of **123** with allyltrimethylsilane produced **124** as the only stereoisomer. Hydrogenation, deprotection with TMSI and $AlMe_3$-mediated cyclisation gave lactam **119**, which was reduced by $LiAlH_4$ to furnish to the desired compound **5** (**Scheme 21**).



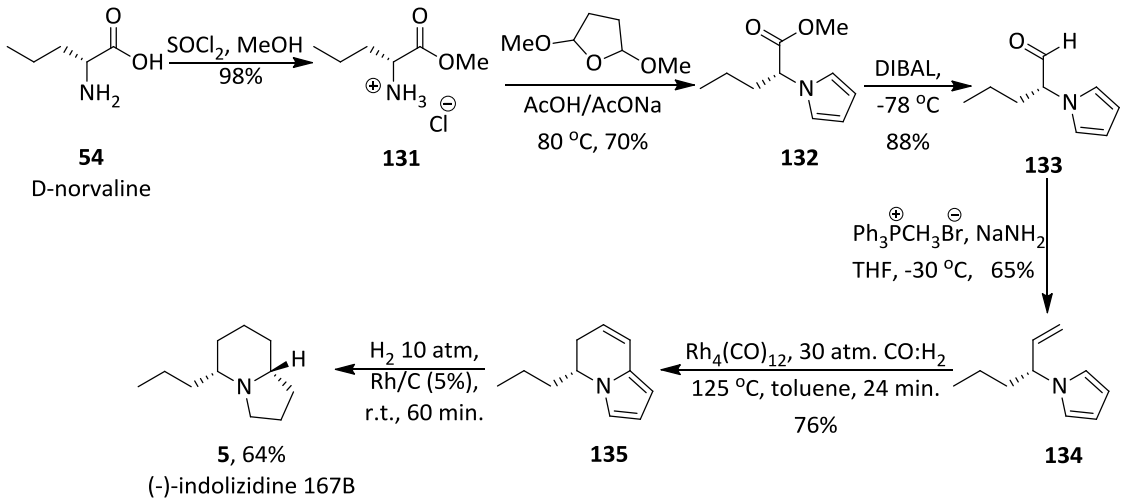
Scheme 21

Sanderson and co-workers have disclosed a synthetic route to prepare (-)-indolizidine 167B (**5**) in five steps and an overall yield of 35% starting from *N*-Boc pyrrolidine.[49] Enantioselective deprotonation of **125** by *sec*-BuLi/diamine (*S*,*S*) **126** and allylation in the presence of CuCN.2LiCl gave **127**. Exchange the *N*-protecting group to Cbz gave **128**, which was converted to **129** *via* olefin cross-metathesis, followed by Dess-Martin periodinane oxidation to give **130**. Treatment of compound **130** with Pd/C under a hydrogen atmosphere, Cbz-deprotection, and diastereoselective reductive aminition sequence lead to the desired compound **5** (**Scheme 22**).



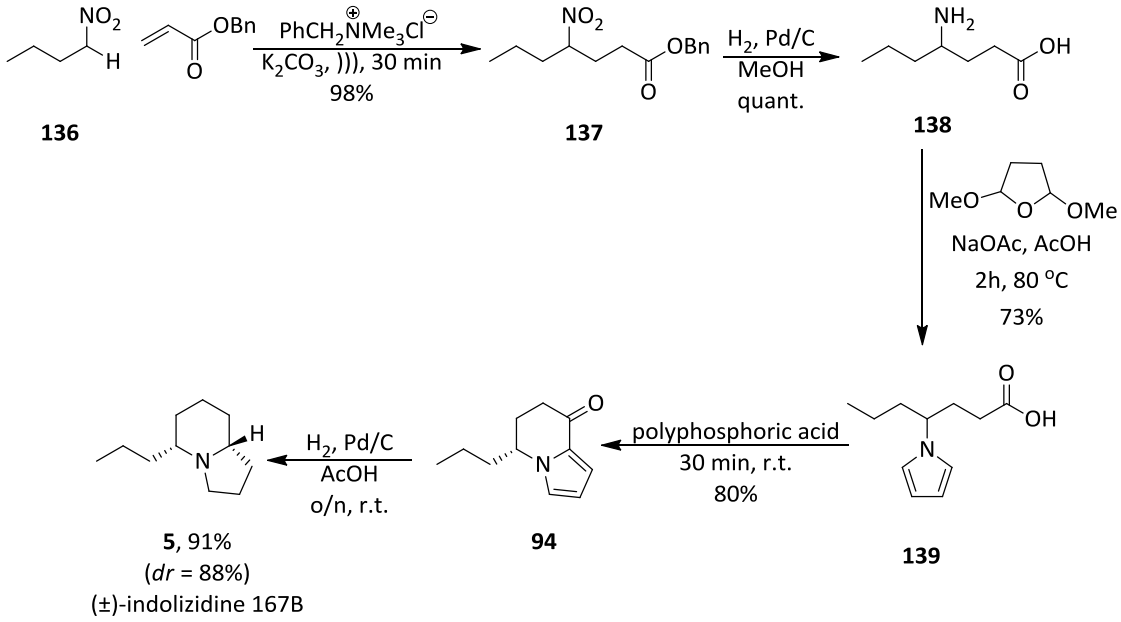
Scheme 22

Settambolo and co-workers developed an optically active synthesis of (-)-indolizidine 167B (**5**) in six steps from amino acid D-norvaline **54**.[25] Esterification of **54** and condensation with 2,5-dimethoxytetrahydrofuran gave pyrrole **132**, which was reduced to the corresponding aldehyde **133**. Wittig olefination of **133** gave *N*-protected amino alkene **134**, which underwent cyclisation under rhodium catalysed conditions gave **135**. Finally, compound **135** was subjected to hydrogenation reaction using rhodium on carbon as catalyst to give the desired product **5** in 64% yield (**Scheme 23**).



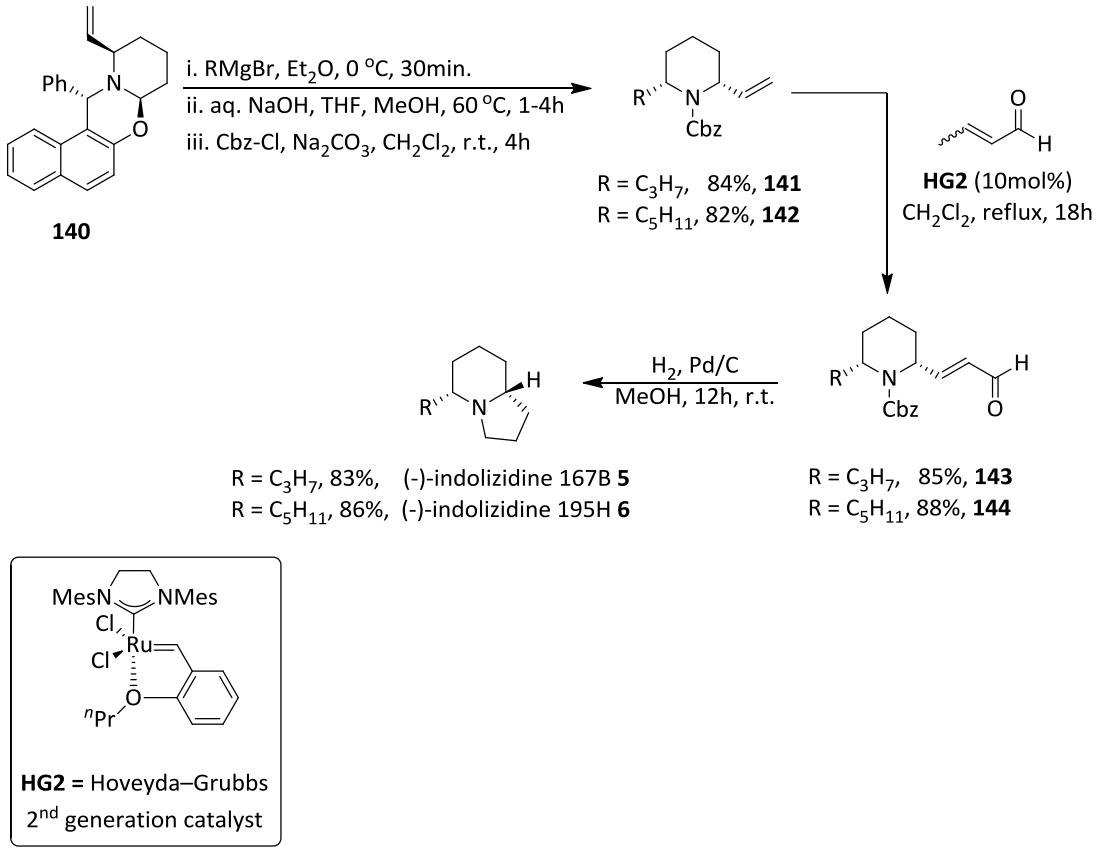
Scheme 23

Pellet-Rostaing and co-workers developed a synthetic approach to synthesize of (-)-indolizidine 167B (**5**) in five steps from 1-nitrobutane.[50] Conjugate addition of 1-nitrobutane to benzyl acrylate in the presence of benzyltrimethylammonium chloride under basic conditions gave nitro-ester **137**, which converted to **138** *via* reduction of the nitro group and removal of the benzyl ester. Treatment of **138** with dimethoxytetrahydrofuran and sodium acetate gave pyrrole derivative **139**, which underwent intramolecular Friedel-Crafts acylation in the presence of polyphosphoric acid to produce bicyclic adduct **94**. Eventually, diastereoselective hydrogenation of **94** using Pd/C (10% w/w) in acetic acid resulted the compound (±)**-5** in racemic form (*dr* 88%) (**Scheme 24**).



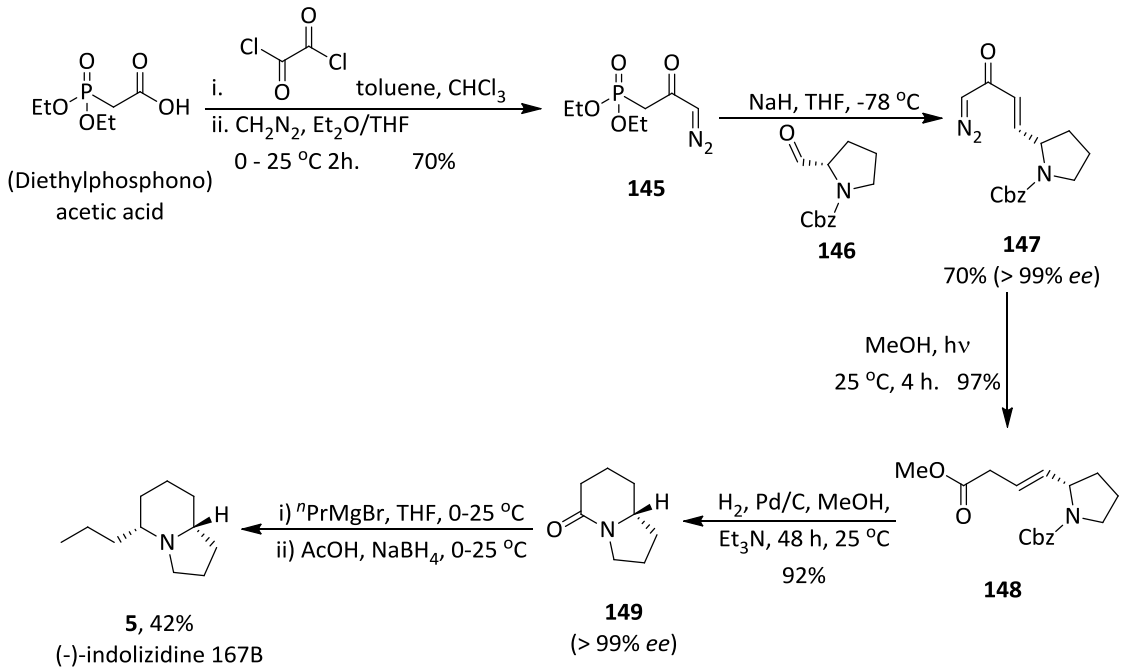
Scheme 24

Yuefei Hu and co-workers developed a stereoselective approach to the synthesis of (-)-indolizidine 167B (**5**) and (-)-indolizidine 195H (**6**) in five steps from the precursor **140**.[51] Treatment of **140** with Grignard reagents gave 2-vinyl-6-alkyl piperidines **141** and **142**, which were each converted to α,β-unsaturated aldehydes **143** and **144** by cross-metathesis reaction with but-2-enal in the presence of Hoveyda–Grubbs (**HG2**) catalyst. Finally, Treatment each compounds **143** and **144** with Pd/C under hydrogen atmosphere, Cbz-deprotection, and diastereoselective reductive amination sequence gave enantiomerically pure compounds **5** and **6** (**Scheme 25**).



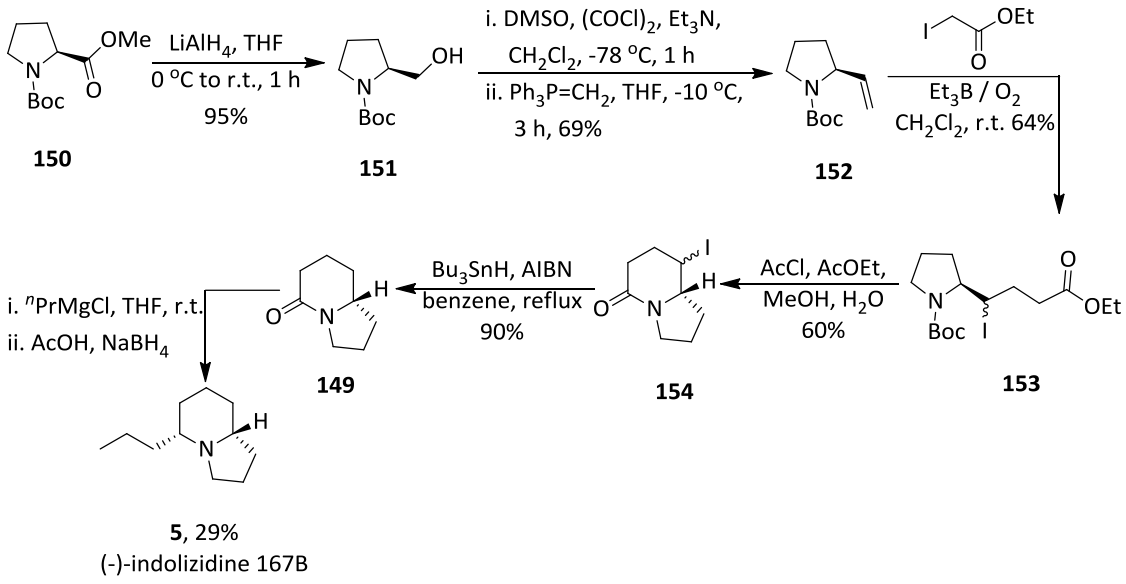
Scheme 25

Pinho and Burtoloso have reported a diastereoselective synthetic route to (-)-indolizidine alkaloid 167B (**5**) in five steps from aldehyde NCbz-pyrrolidine **146**.[52] Activation of (diethylphosphono)acetic acid with oxalyl chloride under dry conditions then reaction with diazomethane gave α,β-unsaturated diazoketone **145**, which treated with NCbz-pyrrolidine precursor to produce **146**. Irradiation of **147** in methanol gave the product **148**, followed by hydrogenation using Pd/C in the presence of Et_3N with concomitant Cbz-deprotection and diastereoselective reductive cyclisation gave the lactam **149**. Finally, treatment of lactam **149** with propylmagnesium bromide, followed by stereoselective reduction using $NaBH_4$ furnished to the enantiomerically pure compound **5** (**Scheme 26**).



Scheme 26

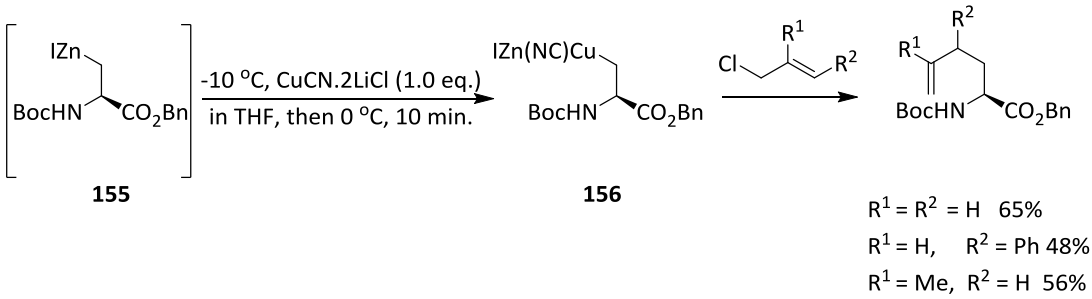
Cordero-Vargas and co-workers have described a synthetic route for (-)-indolizidine alkaloid 167B (**5**) in seven steps from *N*-Boc proline ester **150**.[53] Reduction of **150** with $LiAlH_4$ gave the corresponding alcohol **151**, which was converted to olefin **152** by Swern oxidation, followed by Wittig reaction. Treatment of **152** with ethyl iodoacetate in the presence of triethylborane gave **153**, which was converted to the iodo lactam **154**. Removal of iodine gave the bicyclic lactam **149**, which was treated with n-propylmagnesium chloride, followed by diastereoselective reduction using $NaBH_4$ which resulted in the desired copound **5** (**Scheme 27**).



Scheme 27

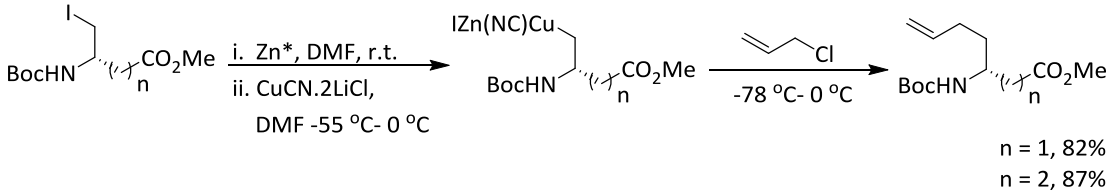
1.6 Jackson Group Chemistry

The Jackson group reported the use of a reactive zinc/copper reagent **156** prepared by treatment of the iodoalanine derived zinc reagent **155** with Knochel's soluble copper salt (CuCN.2LiCl). This zinc cuprate reagent **156** reacted efficiently with different allylic halides by an apparent S_N2' mechanism to provide a range of protected enantiomerically pure unsaturated α-amino acids (**Scheme 28**).[54,55]



Scheme 28: Synthesis of protected unsaturated α-amino acids

This methodology was extended to the synthesis of enantiomerically pure unsaturated β- and *γ*-amino acid derivatives using the reaction of zinc/copper reagents derived from L-aspartic and L-glutamic acids with allyl chloride to furnish allylated compounds in good yields (**Scheme 29**).[56]

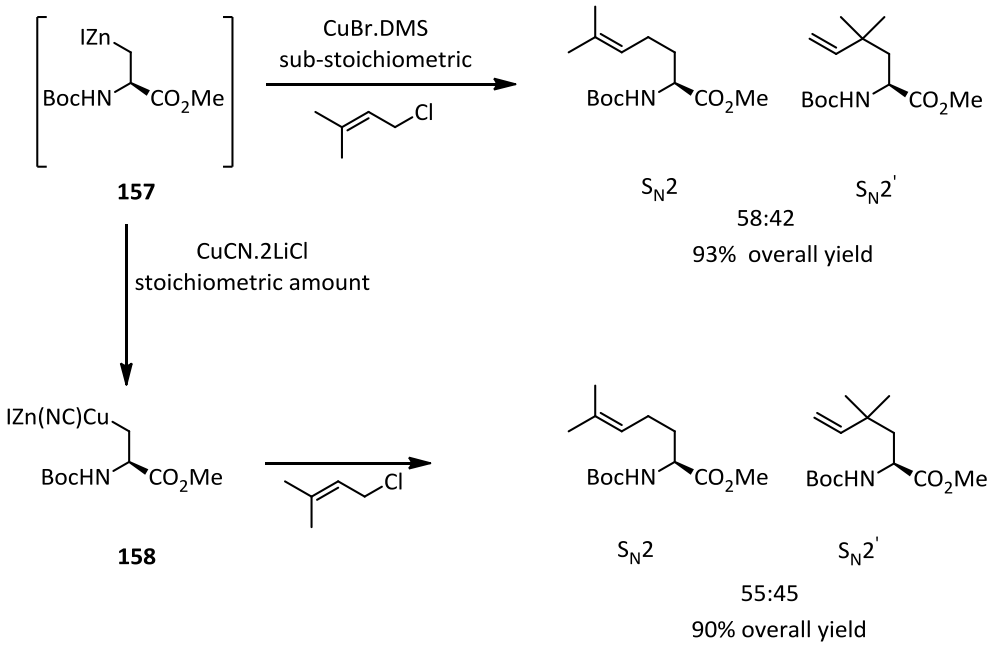


Scheme 29: Synthesis of unsaturated β- and γ-amino acid derivatives

They observed that the use of a polar aprotic solvent reduced β-elimination of the carbamate group in β-amino organozinc reagents. Moreover, the use of such solvents resulted in reliable formation of these zinc reagents and successful cross-coupling reactions under mild conditions.

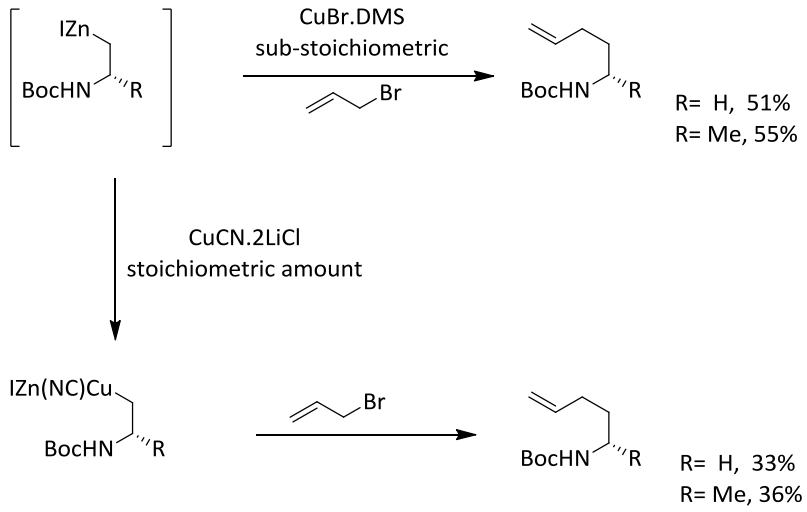
Although this procedure is reliable, the use of a stoichiometric amount of the toxic compound CuCN.2LiCl is a significant disadvantage. For this reason, the Jackson group investigated the use of sub-stoichiometric amounts of copper, specifically copper bromide dimethyl sulfide complex. Moreover, the work-up for reactions using catalytic amounts of copper is basically more straightforward and safer than using stoichiometric amount CuCN.2LiCl particularly in view of the need for special provisions for the disposal of aqueous cyanide waste.

Allylation of L-serine-derived organozinc reagent **157** with bulky allylic electrophiles in the presence of a catalytic CuBr.DMS and stoichiometric CuCN.2LiCl provided nearly equal yields of a mixture of S_N2 and S_N2' products (**Scheme 30**).[57]



Scheme 30: Allylic substitution of substituted electrophiles

They also observed the use of sub-stoichiometric CuBr.DMS in place of a stoichiometric amount of CuCN.2LiCl is more advantageous to improve the reactions for less stable β-amino organozinc reagents with a set of unsaturated electrophiles (**Scheme 31**).[58]



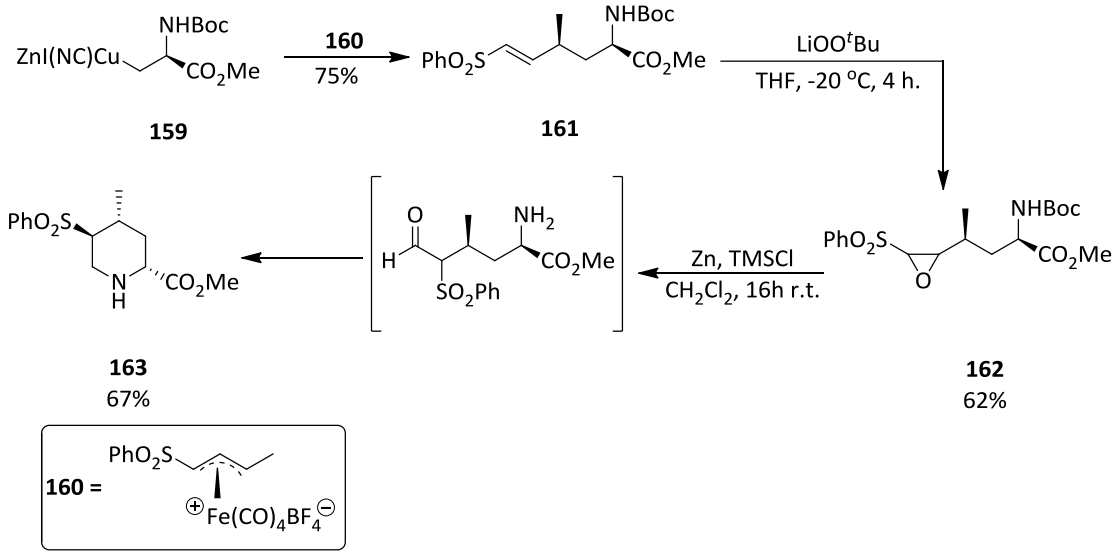
Scheme 31: Allylation of *L*-serine-derived organozinc reagent

The Jackson group has explored the use of the amino acid derived organozinc reagents in the synthesis of a variety of piperidines, which will now be discussed.

1.7 Preparation of Piperidines in the Jackson Group

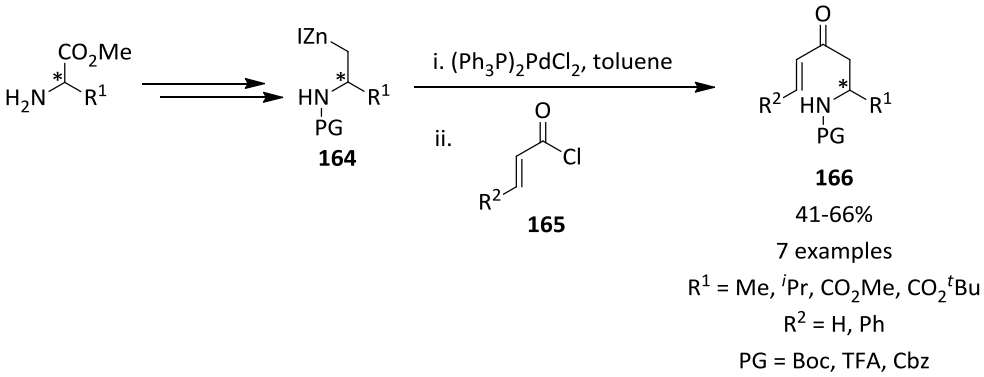
The synthesis of enantiomerically pure substituted piperidine derivatives has received considerable attention, and enantiomerically pure substituted piperidines have been synthesized in the Jackson group using organozinc chemistry.[59]

Jackson and Turner, reported the addition of the organozinc cuprate reagent **159** derived from L-serine to enantiomerically pure η^3-allyl iron complexes such as **160**. Epoxidation with lithium *tert*-butyl peroxide produced the corresponding oxirane, which was converted to the assumed intermediate aldehyde under Lewis acid catalysis. Finally, an intramolecular reductive amination mediated by zinc gave methyl (*4R*)-methyl-(*5S*)-(phenylsulfonyl)-(*2S*)-pipecolate **163** in a one pot reaction (**Scheme 32**).[60]



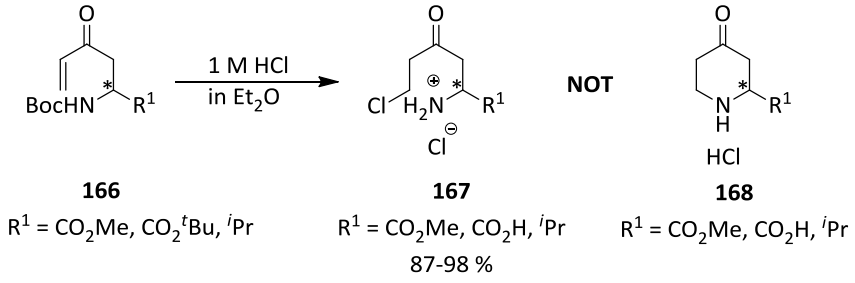
Scheme 32: Synthesis of methyl (*4R*)-methyl-(*5S*)-(phenylsulfonyl)-(*2R*)-pipecolate **163**

Recently, Chilton[61] has developed a synthesis of enantiomerically pure, methyl 4-oxo-L-pipecolate **168** using Negishi coupling. Treatment of a number of protected β-amino organozinc reagents **164** with α,β-unsaturated acid chlorides **165** under palladium catalysis afforded a number of amino enones **166** (**Scheme 33**).



Scheme 33

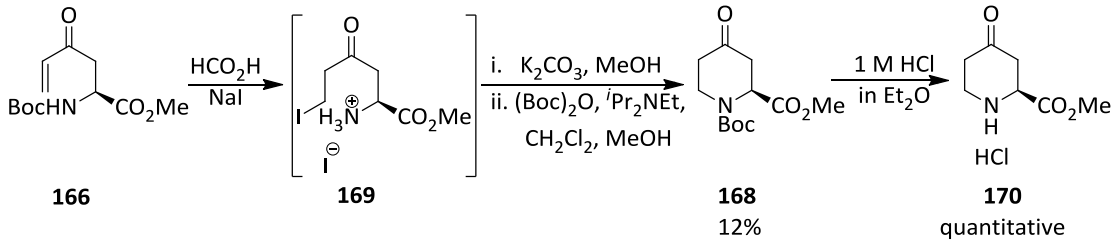
In order to synthesize 2-substituted-4-oxopiperidines, the literature cyclisation method using hydrogen chloride in diethyl ether was explored extensively.[62,63] However, treatment of a selection of protected amino enones **166** with HCl/Et_2O resulted in β-chloroketones **167** instead of the reported 4-oxopiperidinium salts **168** (**Scheme 34**).



Scheme 34

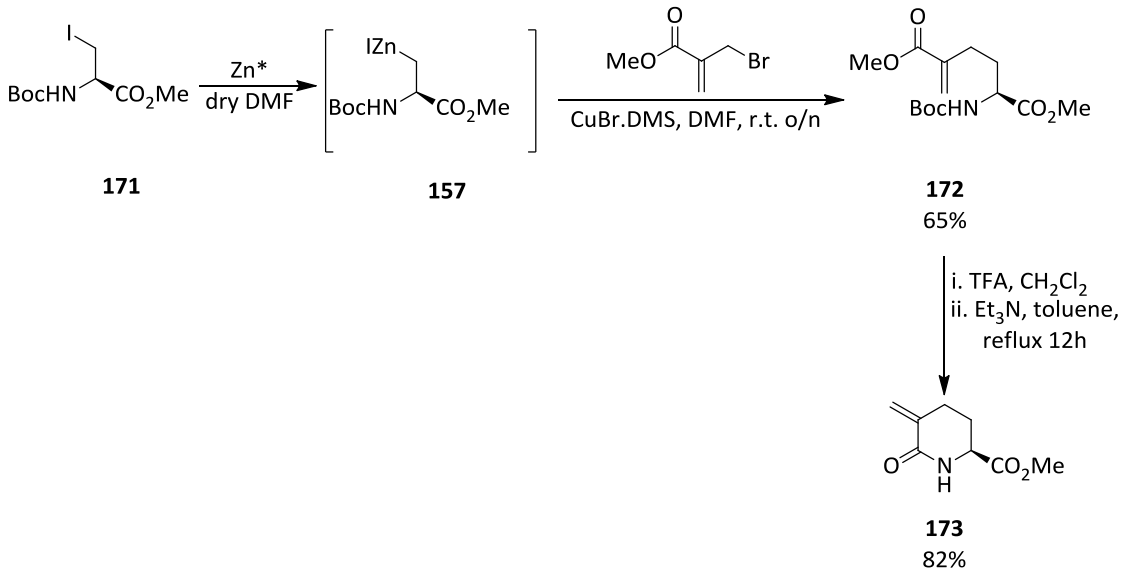
After extensive attempts, the cyclisation of amino enone **166** was accomplished through a sequence ordering Boc-deprotection, ring closure under basic conditions, and re-protection of the resulting amine to give Boc-protected

4-oxo-L-pipecolate **168** in low yield 12%. Finally, **168** was converted to the corresponding hydrochloride salt **170** (**Scheme 35**).



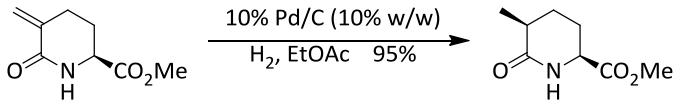
Scheme 35: Synthesis of 4-oxo-L-pipecolate **168**

Gulati[64] reported a route to prepare methyl 5-methylene-6-oxopiperidine-(*2S*)-carboxylate **173**. The allylation reaction of organozinc reagent **157** with methyl 2-(bromomethyl)prop-2-enoate proceeded smoothly to furnish di-ester **172** in moderate yield (65%). Subsequent deprotection and cyclisation afforded lactam **173** in good yield (82%) (**Scheme 36**).



Scheme 36: Synthesis of methyl 5-methylene-6-oxopiperidine-(*2S*)-carboxylate

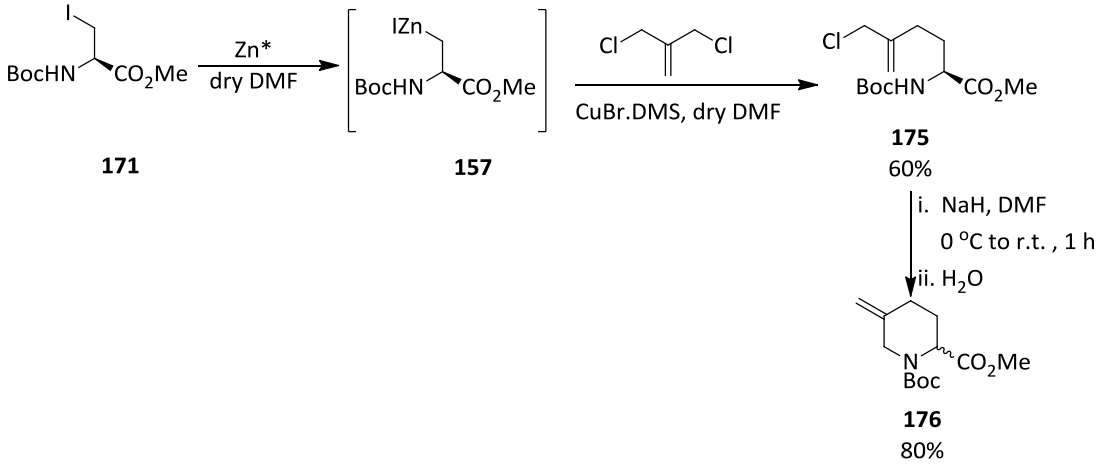
Hydrogenation of lactam **173** in the presence of Pd/C (10%w/w) as a catalyst gave methyl (*2S,5S*)-5-methyl-6-oxopiperidine-2-carboxylate **174** in a diastereoisomeric ratio of **>95:<5**, determined *via* chiral HPLC (**Scheme 37**).



173 **174**
>95 : <5 (*cis : trans*)

Scheme 37: Synthesis of methyl (*2S,5S*)-5-methyl-6-oxopiperidine-2-carboxylate

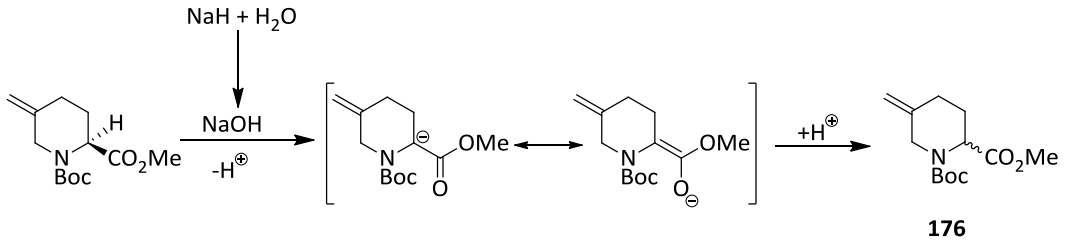
Gulati[64] then developed an approach to synthesize 5-methylenepipecolates **176**. The protected 5-methylene pipecolate **176** was obtained in a good yield by adding NaH to a solution of allylic amino acid **175** in dry DMF to induce the desired ring closure (**Scheme 38**).



171 **157** **175** 60% **176** 80%

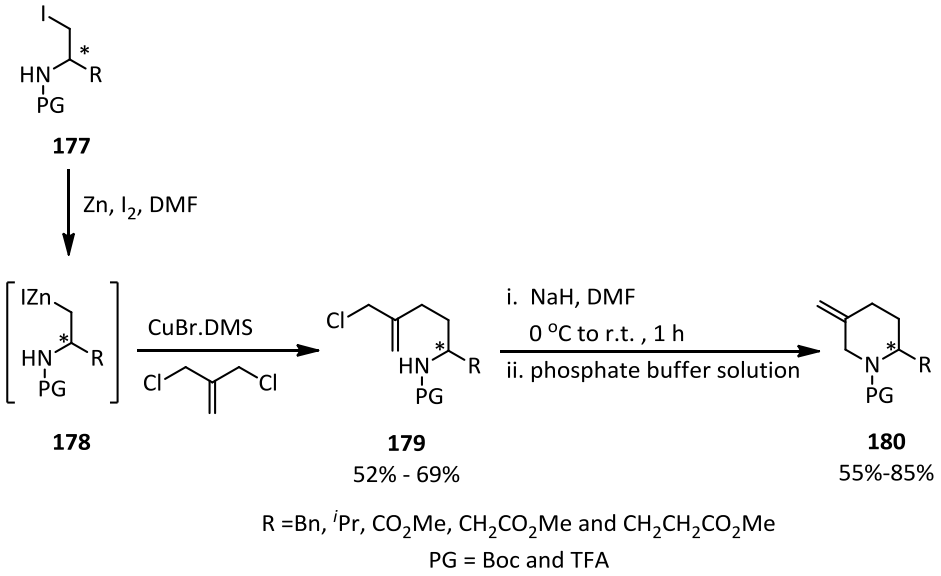
Scheme 38: Route to 5-methylene pipecolate

Unfortunately, the final product was found to be racemic. The racemisation probably occurs during the work-up of the reaction, as a result of the formation of sodium hydroxide when water is added, and which then has the ability to remove the acidic α-proton (**Scheme 39**).



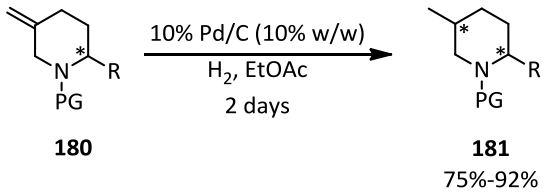
Scheme 39: Plausible racemisation of **176**

Subsequently, Abdelsalam described the synthesis of enantiomerically enriched 5-methylene piperidines **178** in good yields (55%-85%).[65] This route started with reaction of a variety of protected β-aminoalkyl zinc iodides **178** with 3-chloro-2-(chloromethyl)prop-1-ene under copper catalysed conditions, followed by cyclisation using sodium hydride. Eventually epimerization of compound **176** was avoided by modifying the work-up of the cyclisation reaction by using a phosphate buffer solution (pH = 7), rather than water, to obtain the enantiomerically pure pipecolate **180** (R = CO_2Me, *ee* 97%) (**Scheme 40**).



Scheme 40: Synthesis of enantiomerically pure 5-methylene piperidines **180**

5-Methylenepiperidines **180** were each subjected to hydrogenation to give two separable diastereoisomeric 5-methyl-2-substituted piperidines **181** (**Scheme 41** and **Table 5**).



Scheme 41: Synthesis of 5-methyl-2-substituted piperidines **181**

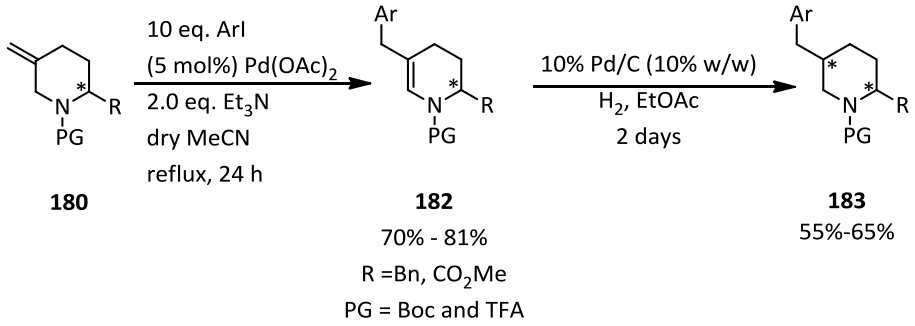
Table 5: 5-methyl-2-substituted piperidines

R	PG	**181** (Combined yield %)	*cis*	*trans*
CO_2Me	Boc	89	3	1
	TFA	92	1	1
Bn	Boc	80	1	3
	TFA	75	1	7
^{i}Pr	Boc	78	1	1.5
	TFA	75	1	4
CH_2CO_2Me	Boc	83	1	1.5
	TFA	80	1	2.5
$CH_2CH_2CO_2Me$	Boc	84	1	1.5
	TFA	80	1	2.5

Table 5 summarizes the hydrogenation products of all 5-methylenepiperidines, which shows that the *trans*-isomer is favoured in most cases with variety diastereomeric ratios.

Some of the 5-methylenepiperidines **180** were subjected to Heck reaction with aryl iodides, and led to the migration of the double bond into the ring to give the

product **182**. Finally, hydrogenation of the Heck products occurred smoothly to provide 2,5-disubstituted piperidines **183** in good yields (**Scheme 42** and **Table 6**).[65]



Scheme 42: Heck reaction

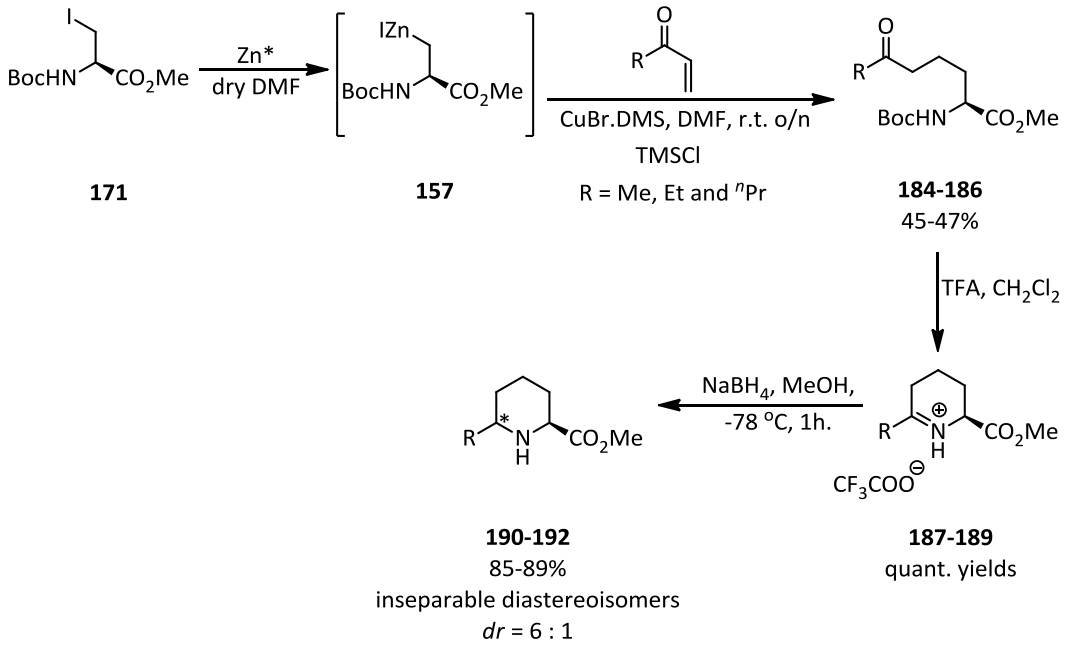
Table 6

R	Ar	PG	**182** (yield %)	**183** (Combined yield %)	*cis*	*trans*
CO_2Me	PhI	Boc	81	65	4	1
	o-OMe-Ph	Boc	76	55	4	1
	m-OMe-Ph	Boc	80	57	4	1
Bn	PhI	Boc	72	60	1	6
CO_2Me	PhI	TFA	70	N/A	N/A	N/A
Bn	PhI	TFA	78	N/A	N/A	N/A

Table 6 also summarizes the results from some hydrogenation of the Heck coupling products, which exhibits that the diastereomeric ratios of approximately **4:1** for the pipecolates, in preference of the *cis*-isomer.

Abdelsalam also reported the synthesis of 2,6-disubstituted piperidines **190-192**.[65] The conjugate addition of organozinc reagent **157** to a range of

enones produced 6-oxo amino acid derivatives **184-186**. Deprotection and cyclisation were achieved by treatment of **184-186** with trifluoroacetic acid in dichloromethane to form the iminium salts **187-189**, followed by stereoselective reduction using sodium borohydride in methanol to provide two inseparable diastereoisomeic 2,6-disubstituted piperidines **190-192** (**Scheme 43** and **Table 7**).



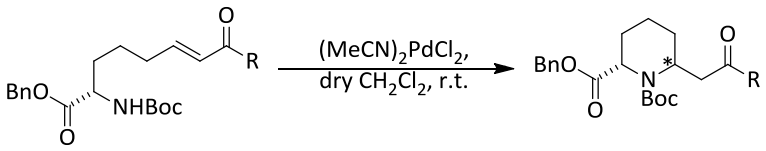
Scheme 43: Synthesis of 2,6-disubstituted piperidines **190-192**

Table 7

R	**184-186** (yield %)	**190-192** (Combined yield %)	*cis*	*trans*
Me	47	85	6	1
Et	45	88	6	1
^{n}Pr	45	89	6	1

The results from hydrogenation of the iminium salts **187-189** are summarized in **Table 7**, which shows that the diastereomeric ratios of approximately **6:1**, in preference of the *cis*-isomer. These results are consistent with the previous reaction results (**Table 4, page 12**),[6] which demonstrated that the carbomethoxy group (CO_2Me) behaves like an alkyl group.

Salih[66] has recently described the synthesis of a number of 2,6-disubstituted piperidines **194**. This approach involved the treatment of the enones **193** with $(MeCN)_2PdCl_2$, followed by cyclisation to give two separable diastereoisomeric 2,6-disubstituted piperidines **194** (**Scheme 44** and **Table 8**), albeit with poor diastereoselectivity.



193 **194** 60-92 %

Scheme 44

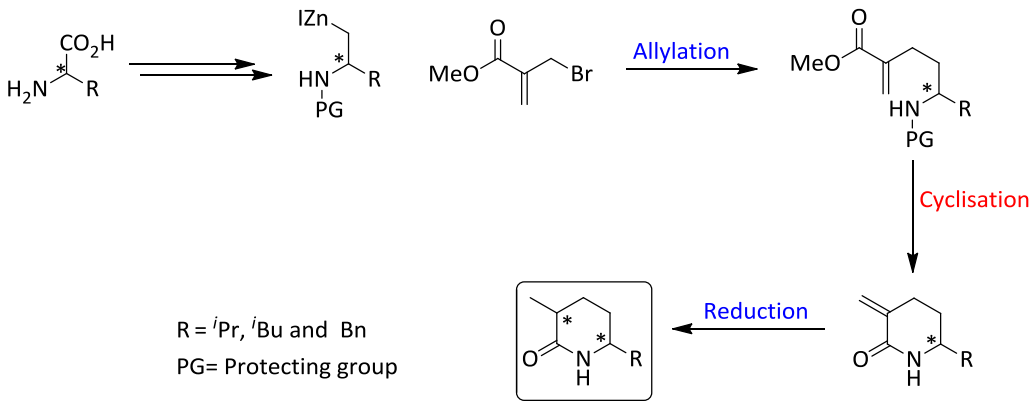
Table 8

R	Catalysis mol%	Time hour	**194** (Combined yield %)	*cis*	*trans*
CH_3	12	70	60	3	1
Et	12	19	92	2	1
^{n}Pr	22	12	64	1.6	1

1.8 Project Aims

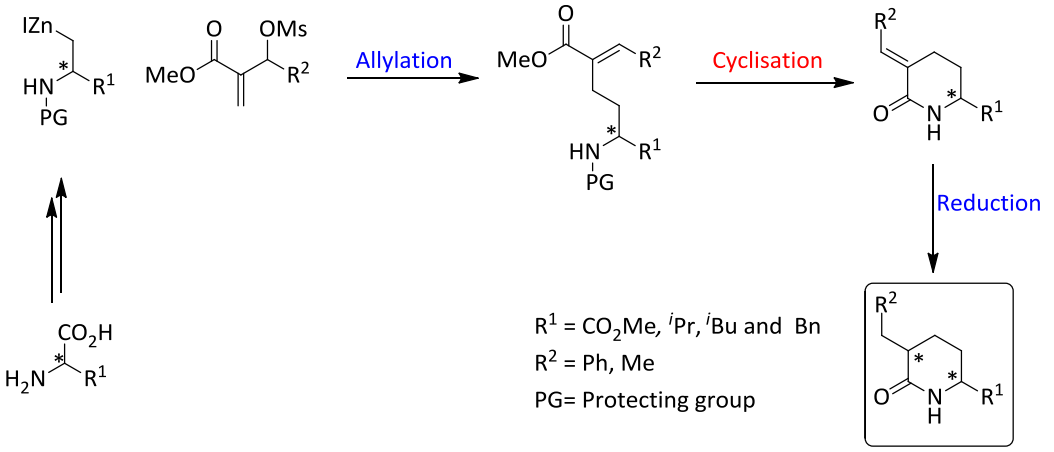
The initial aim of the project was to extend the approaches to the synthesis of enantiomerically pure 2,5-disubstituted and 2,6-disubstituted piperidines already developed within the Jackson group, using copper catalysed reactions between appropriate organozinc reagents and substituted allylic electrophiles.

To begin with, 2,5-disubstituted piperidines will be targeted starting from enantiomerically pure amino acids. The first step in the synthesis is the reaction of organozinc reagents with an appropriate allyl halide, followed by a cyclisation reaction. The reduction of the exo double bond stereoselectively would generate the target molecule and the second stereogenic centre (**Scheme 45**).



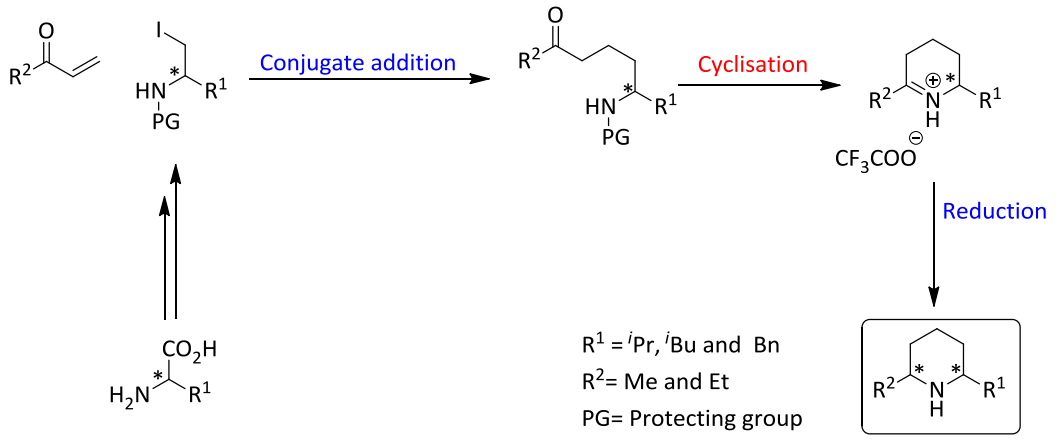
Scheme 45: Proposed synthesis of 2-disubstituted-5-methyl piperidines

A further extension for the synthesis of 2,5-disubstituted piperidines could utilize Baylis-Hillman adducts as electrophiles. This route will be an alternative to the use of the Heck reaction (**Scheme 42, page 41**) already developed within the Jackson group.[64,65] In a similar method to that mentioned previously, the reaction of organozinc reagents with allylic mesylates under copper-catalysis conditions will be explored. Deprotection followed by cyclisation should produce the lactam. Finally, the stereochemistry in the final products will be controlled through hydrogenation of the unsaturated lactam from the less hindered face (**Scheme 46**).



Scheme 46: Proposed synthesis of 2,5-disubstituted piperidines

We also aimed to extend the methodology for the synthesis of novel 2,6-disubstituted piperidines. The conjugate addition reaction of alkyl iodides derived from α-amino acids to suitable enones was explored in the Jackson group previously.[65] Our target is to extend this conjugate addition reaction scope, followed by deprotection and cyclisation to give iminium salts. Diastereoselective reduction of the iminium salts should lead to the desired products (**Scheme 47**).



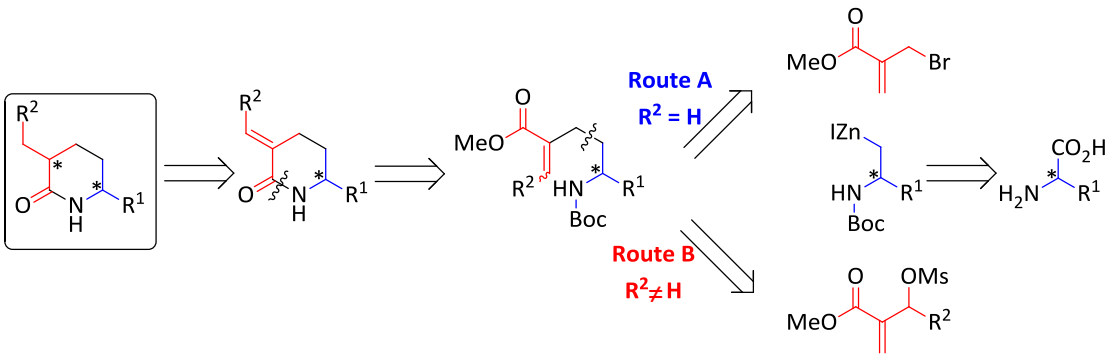
Scheme 47: Proposed synthesis of 2,6-disubstituted piperidines

2. Results and discussion

2.1 Synthesis of 2,5-disubstituted piperidin-6-ones

2.1.1 Introduction

Our approach to the synthesis of 2,5-disubstituted piperidin-6-ones involves copper-catalysed allylation of a range of organozinc reagents with an appropriate electrophiles (**Scheme 48**).



Scheme 48: Retrosynthetic approach to 2,5-disubstituted piperidin-6-ones

2-Substituted-5-methyl piperidin-6-ones, in which **R^2 is hydrogen** (**route A**) are potentially accessible from allylation of methyl 2-(bromomethyl)prop-2-enoate with a number of organozinc reagents under copper catalysed conditions, followed by deprotection and cyclisation. Hydrogenation of the exo double bond will generate the target molecule (**Scheme 48**).

2.1.2 Synthesis of starting materials

The essential intermediates required were the enantiomerically pure iodides **171** and **195-199** (**Figure 9**) derived from α-amino acid. All six precursor iodides have been previously synthesised, thus these syntheses were repeated starting from commercially available amino acids.

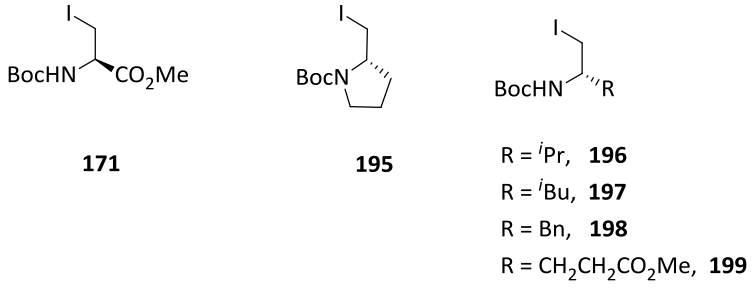
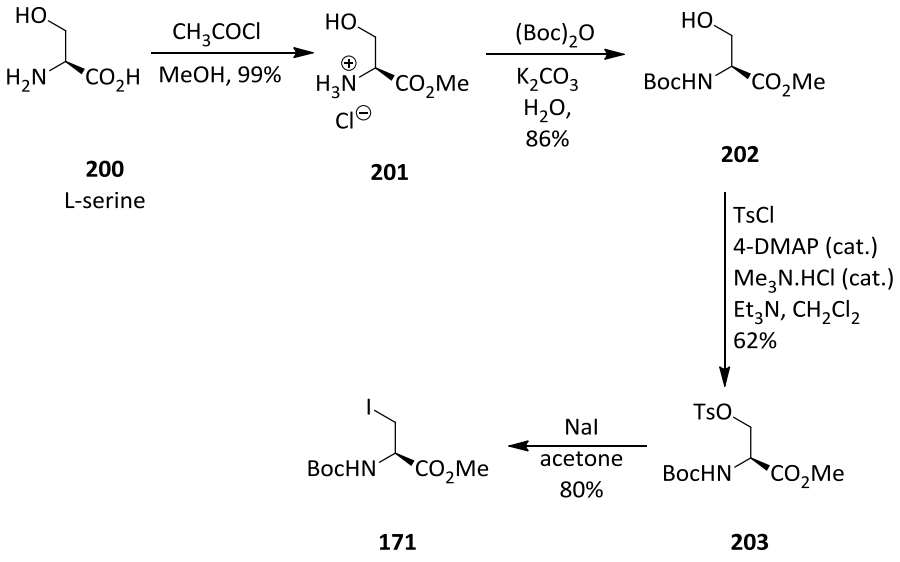


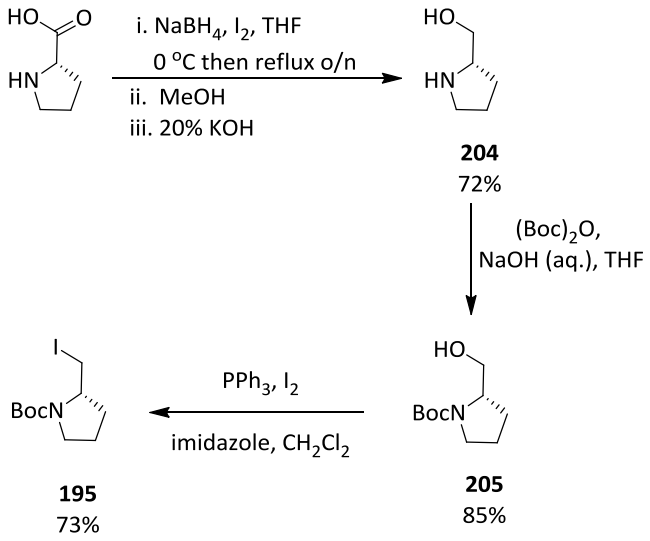
Figure 9: Key amino acid iodides **171** and **195-199**

N-(*tert*-Butoxycarbonyl)-L-iodoalanine methyl ester **171** can be synthesized from L-serine **200** in four steps using a literature procedure. Firstly, L-serine **200** was protected as L-methyl serinate hydrochloride **201**, using hydrochloric acid generated in situ by dropwise addition of acetyl chloride to methanol, followed by protection of N-H using *di*-*tert*-butyl dicarbonate in water, with potassium carbonate as the base, to give *N*-(*tert*-butoxycarbonyl)-L-serine methyl ester **202** in 86% crude yield.[67] Subsequently, the free hydroxyl group was converted into a tosylate to obtain *N*-(*tert*-butoxycarbonyl)-O-(p-toluenesulfonyl)-L-serine methyl ester **203**. Treatment with sodium iodide in a *pseudo*-Finkelstein reaction furnished *N*-(*tert*-butoxycarbonyl)-L-iodoalanine methyl ester **171** in 80% yield after purification by recrystallization (**Scheme 49**).

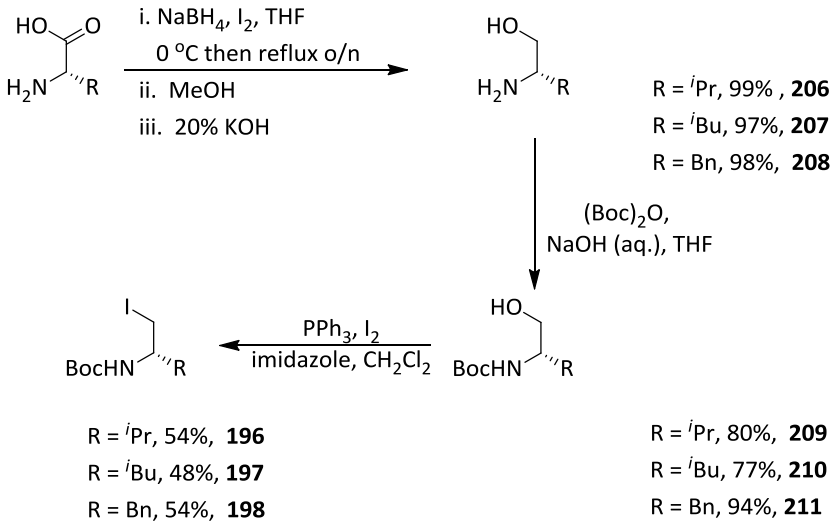


Scheme 49: Synthesis of *N*-(*tert*-butoxycarbonyl)-L-iodoalanine methyl ester

Generation of the iodides **195** and **196-198** was achieved according to the established procedures in the Jackson group.[68] The carboxylic acid group was reduced to the corresponding amino alcohols using $NaBH_4/I_2$, following Meyers' procedure,[69] to give **204** and **206-208**, respectively. The following step was Boc-protection of the crude aminoalcohols to yield *N*-Boc-amino alcohols **205** and **209-211**. Lastly, iodides were synthesized using iodine, triphenylphosphine and imidazole to give the target molecules **195** (**Scheme 50**) and **196-198** (**Scheme 51**).



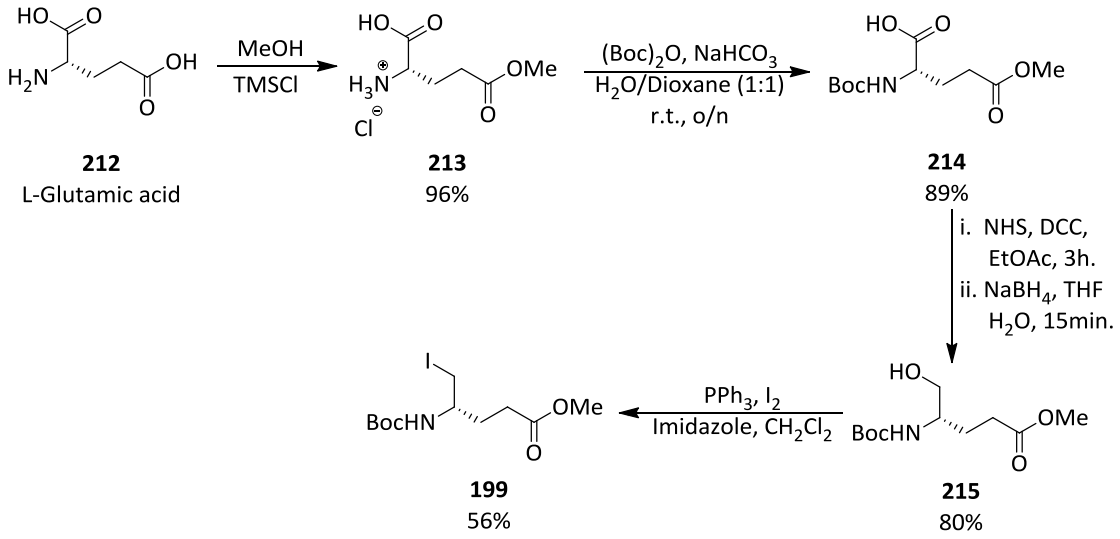
Scheme 50



Scheme 51: Synthesis of protected β-amino iodides

Methyl (*4S*)-4-((*tert*-butoxycarbonyl)amino)-5-iodopentanoate (199)

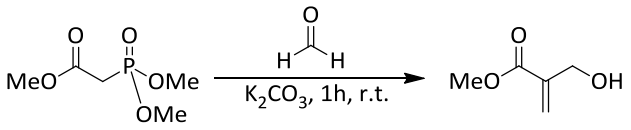
The synthesis of the iodide derived from L-glutamic acid **212** started with protection of the *γ*-carboxyl group by esterification to give **213** as reported by Vince and More.[70] Then the amino group was protected with a Boc group to produce *N*-Boc-L-glutamic acid-*γ*-methyl ester **214**.[56] Reduction of the α-carboxylic acid group was performed by activation of the α-carboxylic acid by *N*-hydroxysuccinimide/DCC to give the *N*-hydroxysuccinimide ester, which was reduced with sodium borohydride to the corresponding alcohol **215**. Finally, *N*-Boc-amino alcohol **215** was treated with iodine, triphenylphosphine and imidazole to yield **199** in 56% yield (**Scheme 52**).



Scheme 52: Synthesis of methyl (*4S*)-4-((*tert*-butoxycarbonyl)amino)-5-iodopentanoate **199**

Methyl 2-(bromomethyl)prop-2-enoate (218)

Methyl 2-(bromomethyl)prop-2-enoate **218** was synthesised from the commercially available phosphonate **216** using a Horner–Wadsworth–Emmons reaction to give methyl 2-(hydroxymethyl)prop-2-enoate **217** (**Scheme 53**).[71]

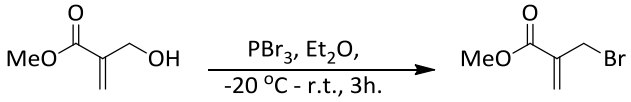


216 **217**

68%

Scheme 53: Synthesis of methyl 2-(hydroxymethyl)prop-2-enoate **217**

The crude alcohol **217** without further purification was treated with PBr_3 to give methyl 2-(bromomethyl)prop-2-enoate **218** (**Scheme 54**).[71]



217 **218**

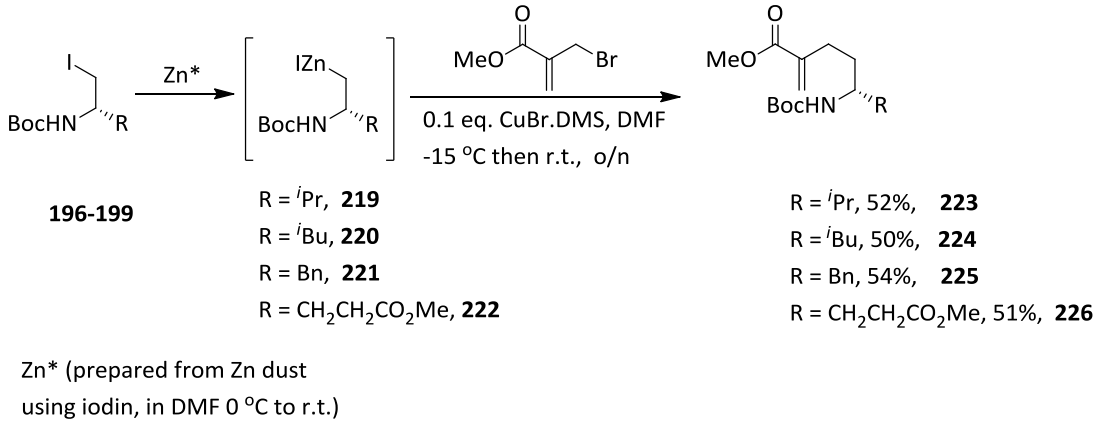
67%

Scheme 54: Synthesis of methyl 2-(bromomethyl)prop-2-enoate **218**

Finally, the compound **218** was purified by fractional distillation. The pure product was collected at b.p. 35-36 ^{o}C (1.3 mm Hg) as a colourless liquid in good yield (67%).[72]

2.1.3 Synthesis of *N*-protected amino enoate substrates (223-226)

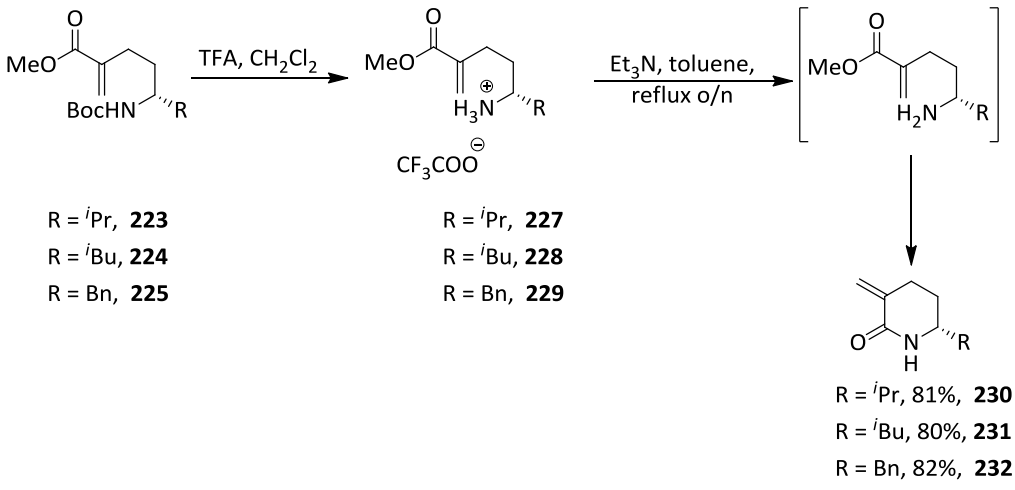
The iodides **196-199** were each separately converted into the corresponding zinc reagents **219-222**, which then reacted with an excess of methyl 2-(bromomethyl)prop-2-enoate **218** under copper catalysis to give the desired compounds **223-226** (**Scheme 55**).



Scheme 55: Synthesis of cyclisation substrates **223-226**

2.1.4 Synthesis of lactams (230-232)

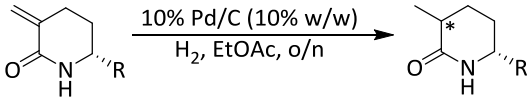
In the first step, deprotection of the amine using trifluoroacetic acid (TFA) in dichloromethane provided the trifluoroacetate salt **227-229** (**Scheme 56**). Then, a solution of the trifluoroacetate salts **227-229** in toluene were each separately heated at reflux in the presence of triethylamine under the conditions previously developed (**Scheme 36, Page 37**). Cyclisation is believed to occur *via* intramolecular addition of the free amine to the carbonyl group, providing lactams **230-232** in good yield 80-82% (**Scheme 56**).



Scheme 56: Synthesis of lactams **230-232**

2.1.5 Hydrogenation of unsaturated lactams

Finally, hydrogenation of the exo-cyclic methylene group of each of lactams **230-232** was performed using Pd/C (10% w/w) at ambient pressure and temperature in ethyl acetate as solvent (**Scheme 57**). This method was based on the previous work in the Jackson group[64] as well as Kroutil and co-workers hydrogenation procedure.[73] Hydrogenation of the exo double bond generated the target molecule favouring the *cis*-isomer (**Table 9**).



R = ^{i}Pr, **230**
R = ^{i}Bu, **231**
R = Bn, **232**

R= ^{i}Pr, 90%, **233a, 233b**
R= ^{i}Bu, 93%, **234**
R= Bn, 90%, **235a, 235b**

Scheme 57: Hydrogenation of lactams **230-232**

Table 9

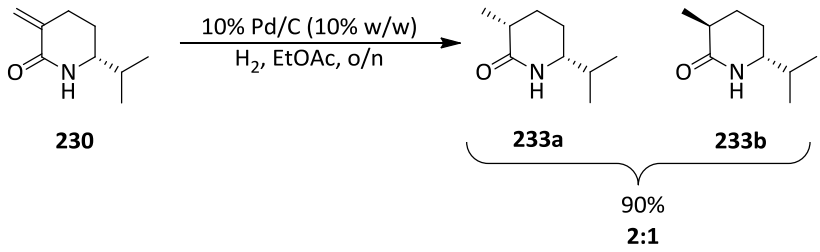
starting material	R	product	(yield, %)	Ratio [a]	
230	^{i}Pr	**233a, 233b**	90	2	1
231	^{i}Bu	**234**	93	>19 [b]	1
232	Bn	**235a, 235b**	90	3	1

a: Determined from ^{1}H NMR analysis of the crude reaction mixture.
b: The diastereoselectivity was estimated on the basis that only one isomer was evident.

2.1.6 Determination of configuration for the compounds 233a, 234, and 235b by X-ray diffraction:

Single crystal X-ray diffraction was used to establish the configuration of the major diastereoisomer (and therefore also of the minor diastereoisomer, since there are only two possibilities) for all saturated lactams (**Figures 10-12**).

The ^{1}H NMR analysis of the crude product for hydrogenation of **230** indicated the presence of two diastereoisomers in a **2:1** ratio (**Scheme 58**). These two diastereoisomers could not be separated by flash column chromatography, but were separated *via* preparative HPLC to give two products in 60% and 30% yields, consistent with the ^{1}H NMR of the crude product.



Scheme 58

The major diastereoisomer was obtained as a white crystalline solid and the structure was established by single-crystal X-ray diffraction analysis, which confirmed the ***cis*** relationship between the iso-propyl group on **C-2** and methyl group on **C-5** as illustrated in **Figure 10**, and established its structure as **233a.**

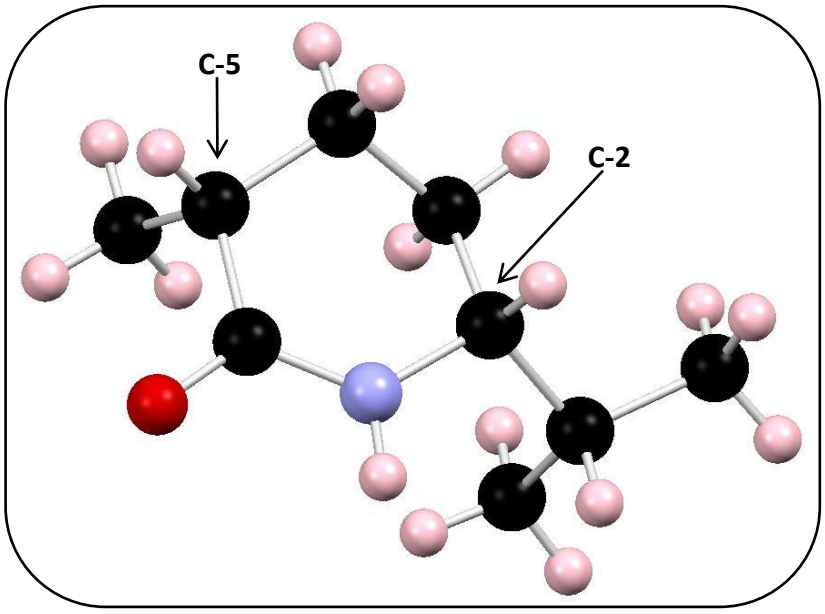
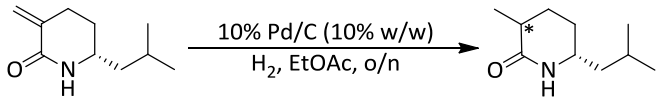


Figure 10: Crystal structure of the major product **233a** which confirms *cis*-configuration

The ^{1}H NMR analysis of the crude product for hydrogenation of **231** indicated that the reaction was highly diastereoselective (**>19:1**) (***cis*** : ***trans***) (**Scheme 59**). Purification by flash column chromatography gave the pure product **234** as a white crystalline solid.



231 **234** 93%

Scheme 59

The structure was determined by single-crystal X-ray diffraction analysis, which again confirmed the ***cis*** relationship between iso-butyl group on **C-2** and the methyl group on **C-5** as illustrated in **Figure 11**.

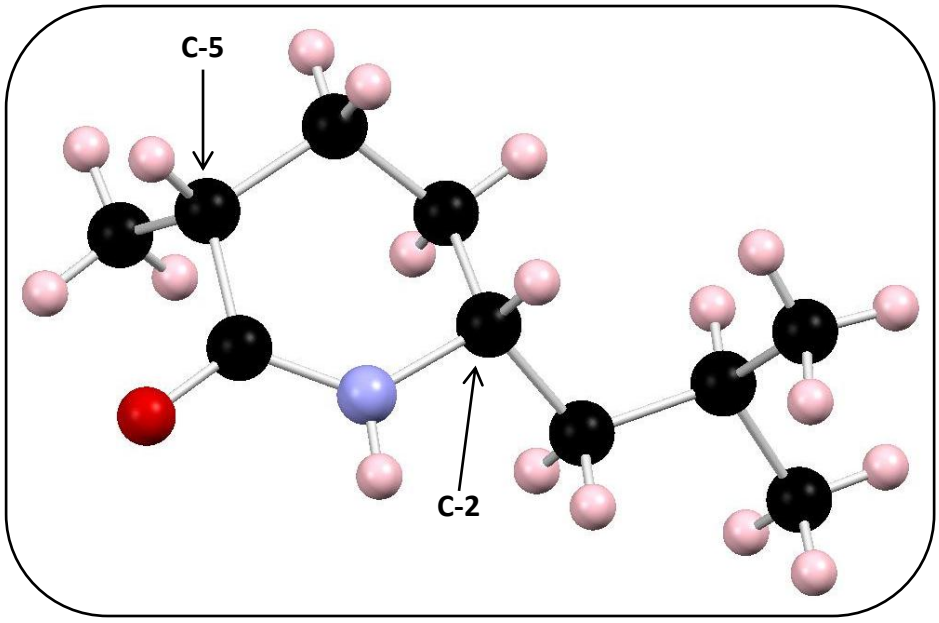
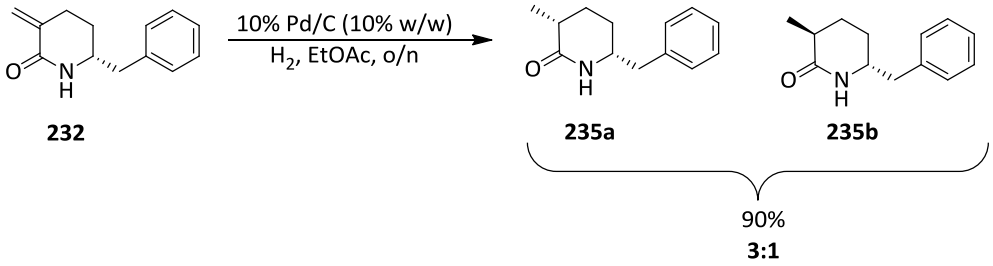


Figure 11: Crystal structure of the product **234** which confirms *cis*-configuration

The ^{1}H NMR analysis of the crude product for hydrogenation of **232** indicated the presence of two diastereoisomers in a **3:1** ratio (**Scheme 60**). Separation of the two diastereoisomers was performed successfully *via* flash column chromatography to give two products in 68% and 22% yields, consistent with the crude ^{1}H NMR spectroscopic data.



Scheme 60

The *minor* diastereoisomer **235b** was isolated as a white crystalline solid and the structure established by single-crystal X-ray diffraction analysis, which established the ***trans*** relationship between benzyl group on **C-2** and the methyl group on **C-5** as illustrated in **Figure 12**.

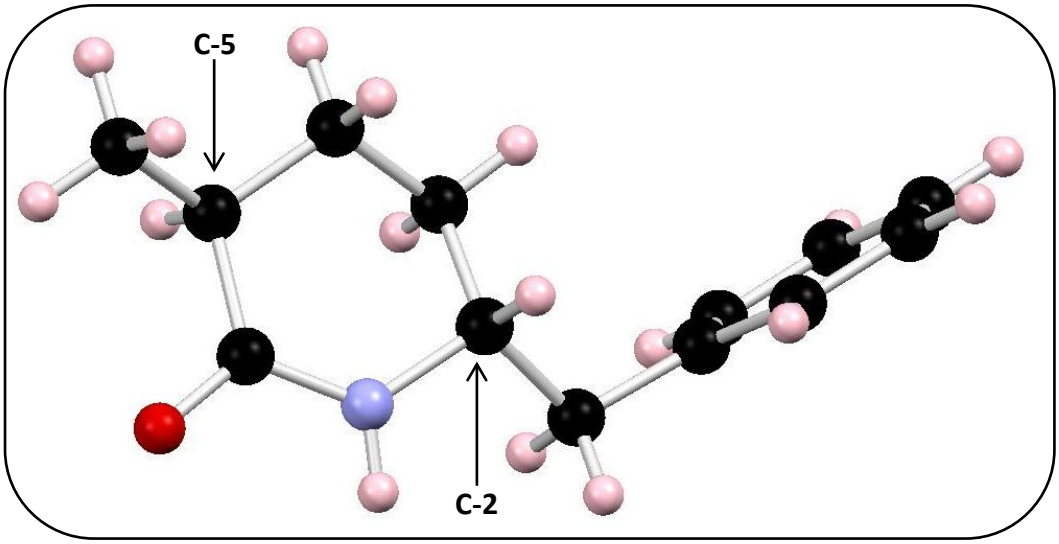


Figure 12: Crystal structure of the minor product **235b** which confirms *trans*-configuration

Having established the configuration of the three compounds **233a**, **234**, and **235b**, we now sought to establish their conformations in solution. We hoped that this would provide a basis for assigning the configuration of the remaining products using ^{1}H NMR alone. The ^{1}H NMR data for the *cis*-compounds **233a**, **234** and **235a** are shown in **Figure 13**, and for the *trans*-compounds **233b** and **235b** in **Figure 14**.

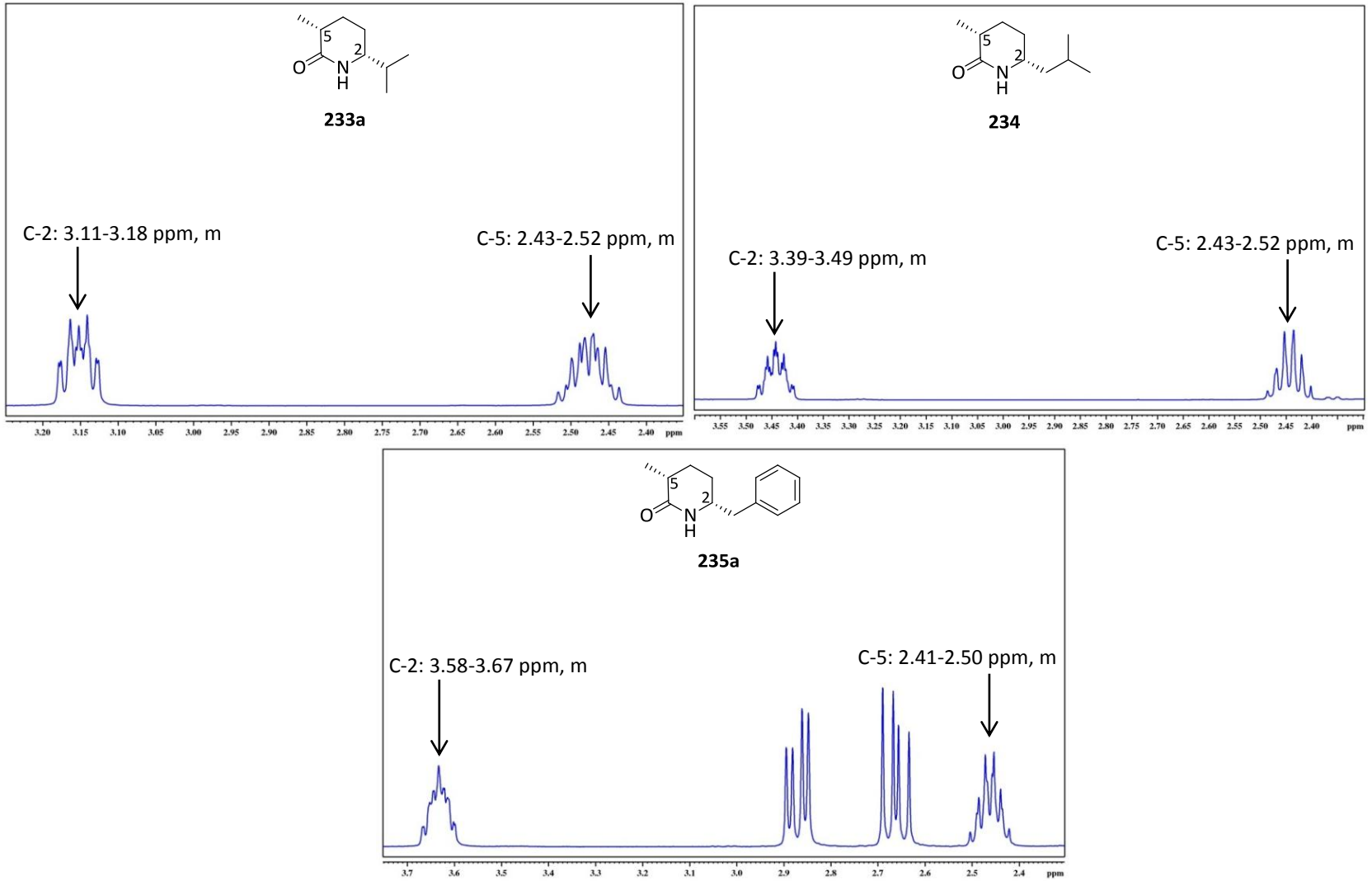
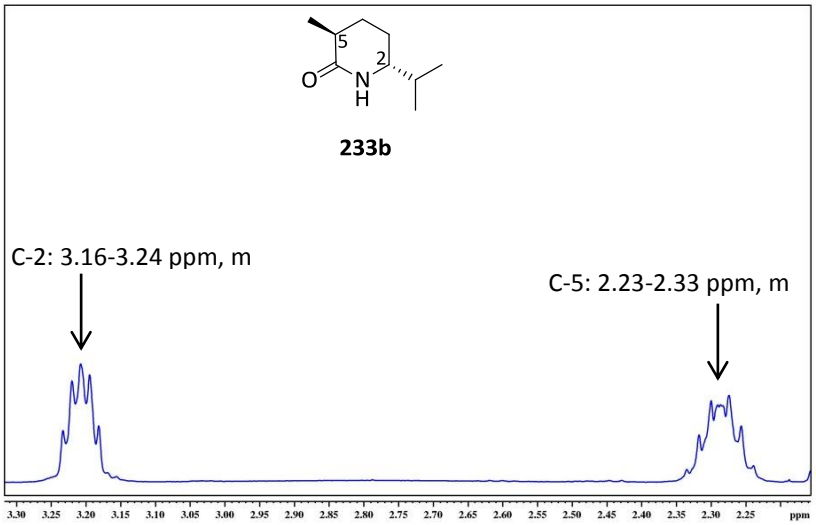


Figure 13: ^{1}H NMR signals of the protons at C-2 and C-5 for compounds **233a**, **234** and **235a**



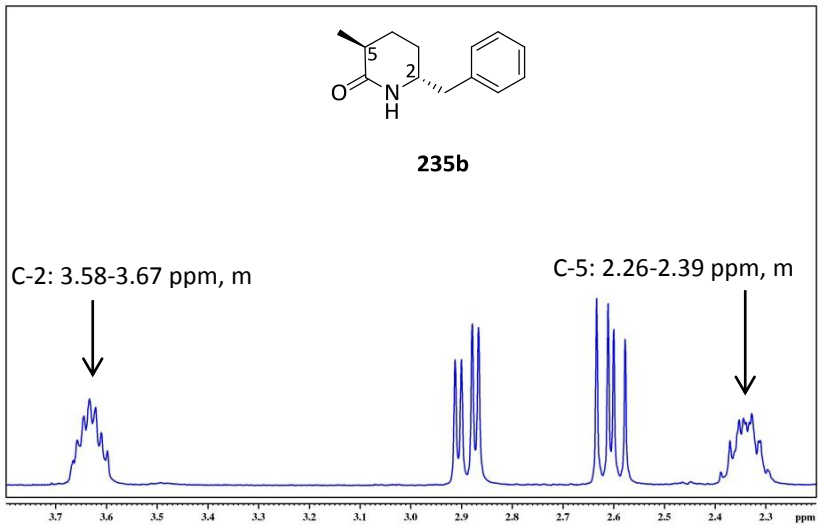
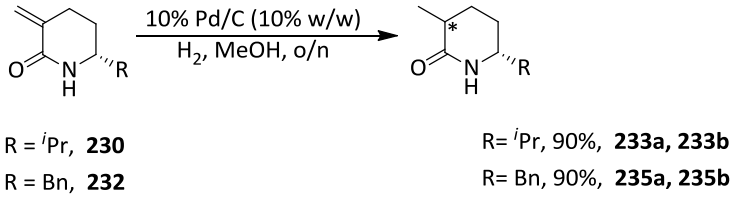


Figure 14: ^{1}H NMR signals of the protons at C-2 and C-5 for compounds **233b** and **235b**

2.1.7 Hydrogenation of selected substrates in methanol

We were intrigued by the variations in diastereoselectivity that were observed in the hydrogenation of the exocyclic methylene group. Since lactams are known to be both good hydrogen bond acceptors and donors, and could therefore potentially aggregate in solution, use of a more polar solvent could potentially disrupt aggregation. The hydrogenation reactions for the compounds **230** and **232** were therefore repeated in methanol (**Scheme 61** and **Table 10**).



Scheme 61: Hydrogenation of lactams **230** and **232** in methanol

Table 10

starting material	R	product	(yield, %)	solvent MeOH [a]		solvent EtOAc	
				cis	*trans*	*cis*	*trans*
230	^{i}Pr	**233a, 233b**	90	4	1	2	1
232	Bn	**235a, 235b**	90	10	1	3	1

a: Determined from ^{1}H NMR analysis of the crude reaction mixture.

Hydrogenation of unsaturated lactam **230** was carried out at a concentration of **0.2**M, under the same conditions described before. ^{1}H NMR analysis for the crude product indicated the presence of two diastereoisomers **233a** and **233b**, but in a ratio of **4:1** in favour of the *cis*-diastereoisomer. In further investigations, we carried out the hydrogenation of the same substrate using methanol at a

concentration **0.02**M. ^{1}H NMR analysis for the crude product indicated the presence of two diastereoisomers in the same **4:1** ratio in favour of the *cis*-diastereoisomer. It is evident that the solvent plays a role in the hydrogenation reaction, but concentration has no effect on the final outcome (**Figure 15** and **Table 10**).

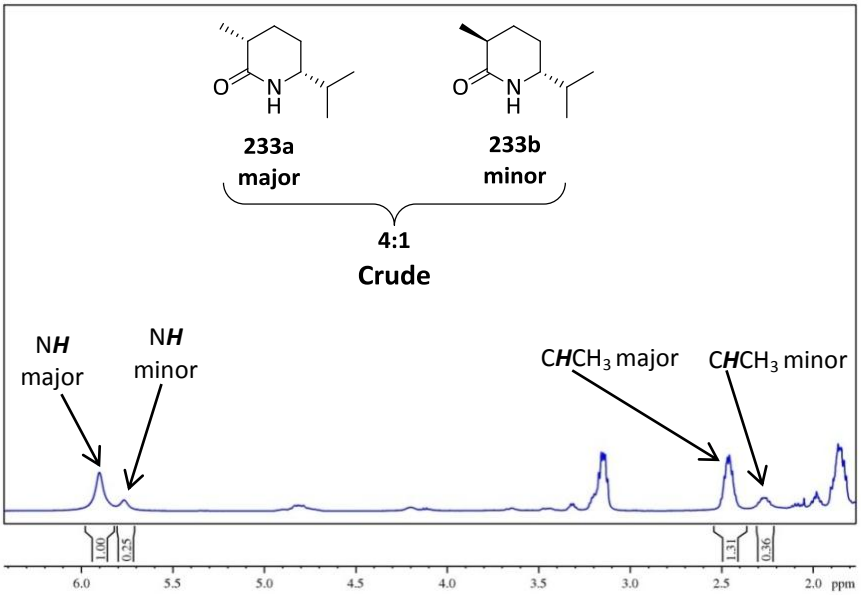


Figure 15: ^{1}H NMR for crude mixture of **233a** and **233b**, which carried out in MeOH

Hydrogenation of unsaturated lactam **232** using methanol at **0.2**M concentration gave a mixture of the two diastereoisomers **235a** and **235b** in a ratio of **10:1** in favour of the *cis*-diastereoisomer (**Figure 16** and **Table 10**).

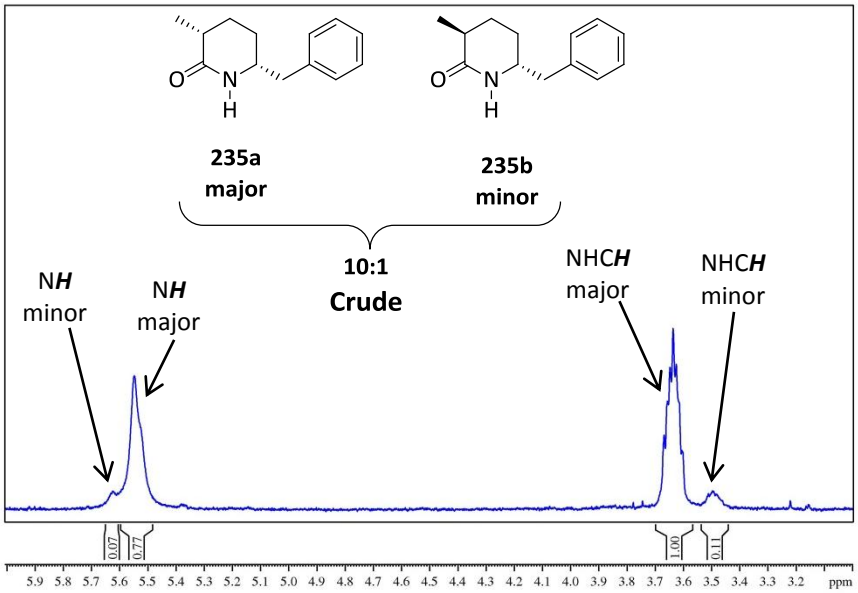


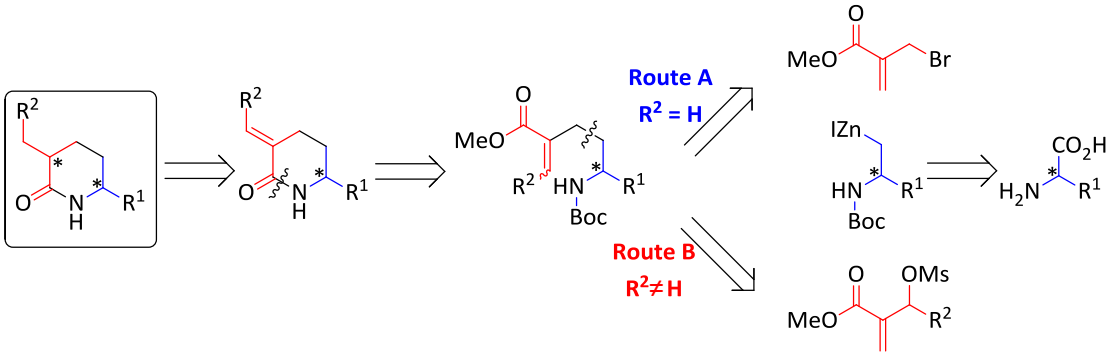
Figure 16: ^{1}H NMR for crude mixture of **235a** and **235b**, which carried out in MeOH

The most likely explanation for the increased stereoselectivity is the inhibition of formation hydrogen bond by methanol, leading to a higher concentration of unaggregated unsaturated lactam in solution.

2.2 Synthesis of 2,5-disubstituted piperidin-6-ones

2.2.1 Introduction

An adaptation of the approach already discussed, in which a more substituted electrophile was required, was the next target (**Scheme 48**).



Scheme 48: Retrosynthetic approach to 2,5-disubstituted piperidin-6-ones

2.2.2 Results and discussion

The initial aim was to develop the synthesis of 2,5-disubstituted piperidin-6-ones *via* copper-catalysed allylation of enantiomerically pure β-amino organozinc reagent with a number of mesylated electrophiles. We initially considered the synthesis of 5-ethyl and 5-benzyl 2-substituted piperidines (**Figure 17**).

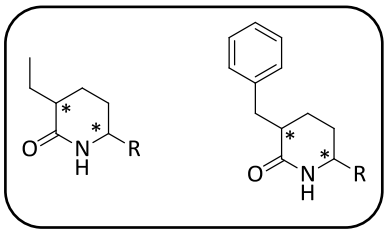
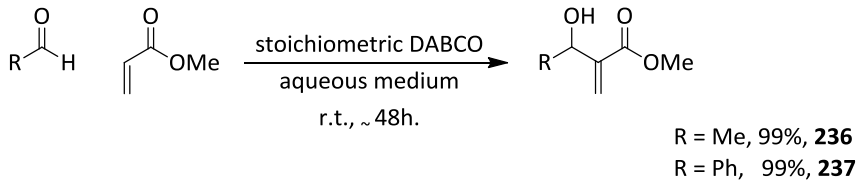


Figure 17

2.2.3 Baylis-Hillman reaction

In our planned route to 2,5-disubstituted piperidin-6-ones, we needed to synthesize potential electrophiles. We thought that the Morita-Baylis-Hillman reaction would be an appropriate method to explore.

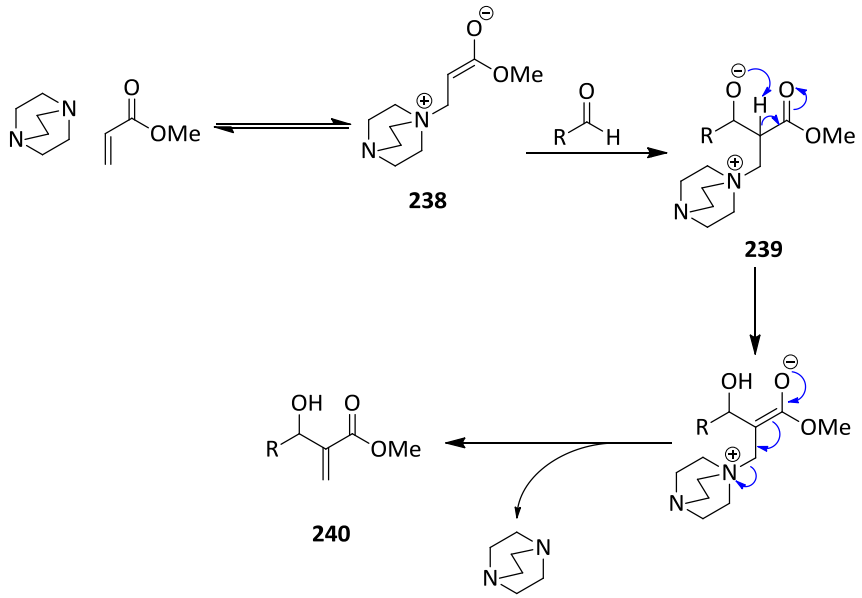
Although, the Morita-Baylis-Hillman reaction is versatile its application was initially hindered by low reaction yields and long reaction times. Hence, much effort has been devoted to overcoming these problems. For instance, using a stoichiometric amount of DABCO and performing the reaction in an aqueous medium was found to offer a substantially approved yield (**Scheme 62**).[74,75]



Scheme 62: Morita-Baylis-Hillman reaction reported by Gonzalez[75]

The mechanism of this reaction is believed to proceed in three steps **(Scheme 63)**:[74]

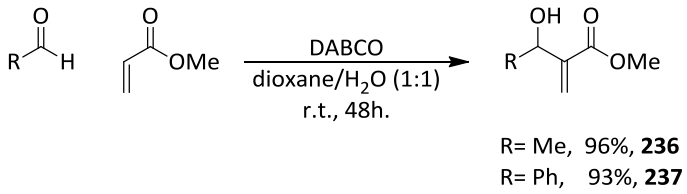
1. 1,4-addition of the catalyst to the Michael acceptor (methyl acrylate), gives the zwitterionic intermediate **238**.
2. This intermediate **238** adds to the aldehyde in an aldol-type reaction, which leads to a second zwitterionic intermediate **239**.
3. The Baylis-Hillman reaction product **240** is formed by subsequent β-elimination.



Scheme 63: Proposed mechanism for Morita-Baylis-Hillman reaction

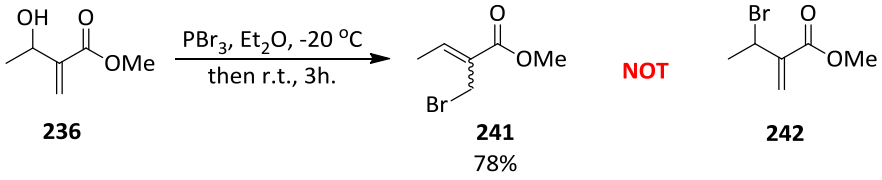
The mechanism is supported by the fact that polar solvents promote the reaction. Polar solvents such as water can stabilize the charged species through hydrogen-bonding and intermolecular charge-dipole interactions.

With this in mind, we successfully applied these optimized conditions to prepare **236** and **237** (**Scheme 64**).



Scheme 64: Synthsis of Baylis-Hillman adducts **236** and **237**

With these electrophiles in hand, we focused on converting the hydroxyl group into a good leaving group. Our first attempt involved bromination of the Baylis-Hillman adduct **236** using our previous conditions (**Scheme 54**, **page 50**). Treatment of **236** with PBr_3 under the same conditions for the compound **218**, gave the alkene **241** in which the double bond had isomerised, rather than the desired product **242** (**Scheme 65**).



236 **241** 78% **242**

Scheme 65: Bromination of the Baylis-Hillman adduct **236**

The ^{1}H NMR spectrum for the compound **241** shows a quartet for the proton at C-2 (7.07 ppm) with a coupling constant (7.0 Hz), which establishes that the double bond had isomerised (**Figure 18**).

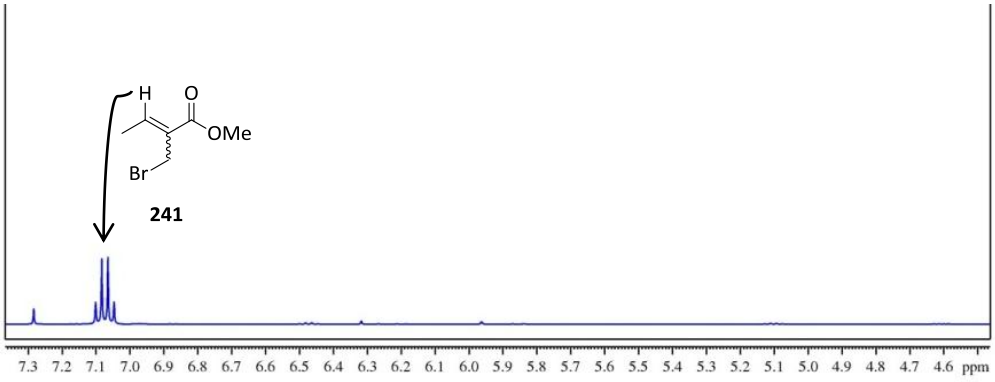
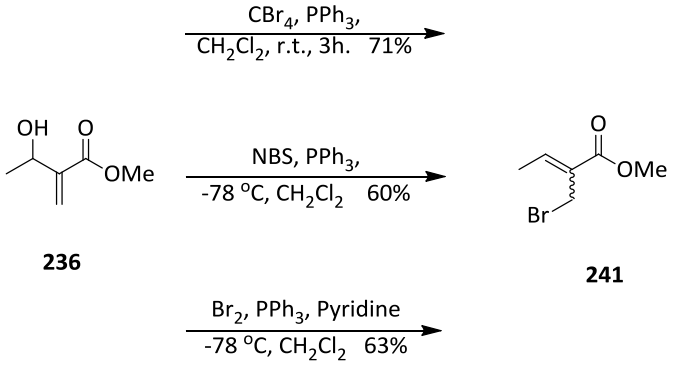


Figure 18

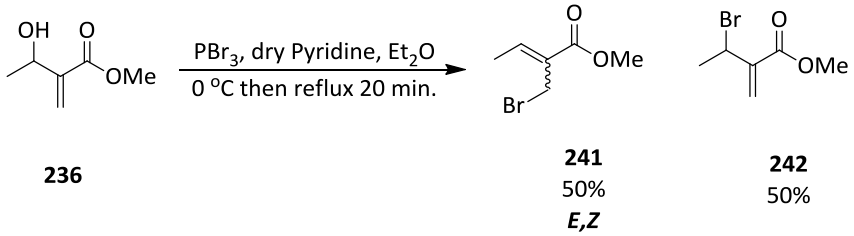
Use of a variety of alternative reagents all resulted in the same outcome (**Scheme 66**).



236 **241**

Scheme 66

Finally, we found a procedure using phosphorus tribromide in the presence of sub-stoichiometric amount of dry pyridine that gave a mixture (**1**:**1**) of the isomerised product **241** and desired product **242** (**Scheme 67** and **Figure 19**).[76]



236

241
50%
E,Z

242
50%

Scheme 67

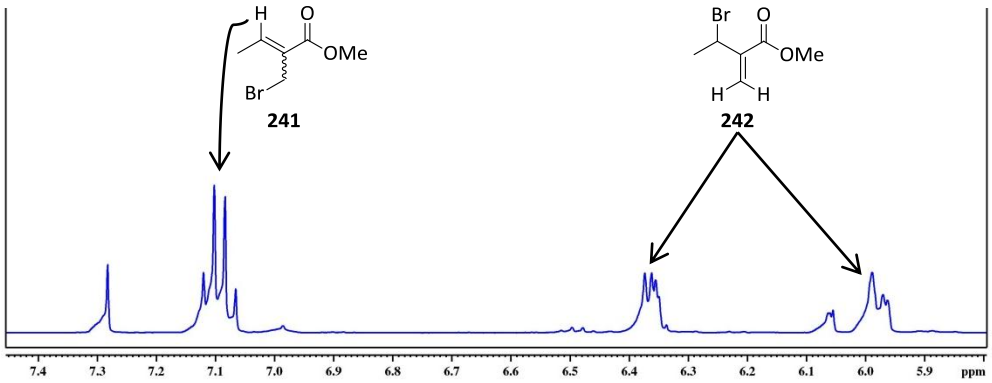
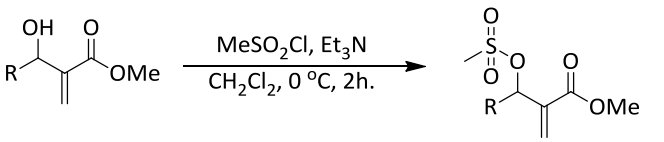


Figure 19: ^{1}H NMR spectrum for the crude mixture of compounds **241** and **242**

It is not clear whether the isomerised products arise by S_N2' substitution of the activated alcohol, or by isomerisation of the desired product.

We therefore explored an alternative method to convert the hydroxyl group of the adducts **236** and **237** into a good leaving group. We were delighted to find that treatment of the adducts with methanesulfonyl chloride and triethylamine gave the desired mesylates, with no evidence of double bond isomerisation (**Scheme 68**).

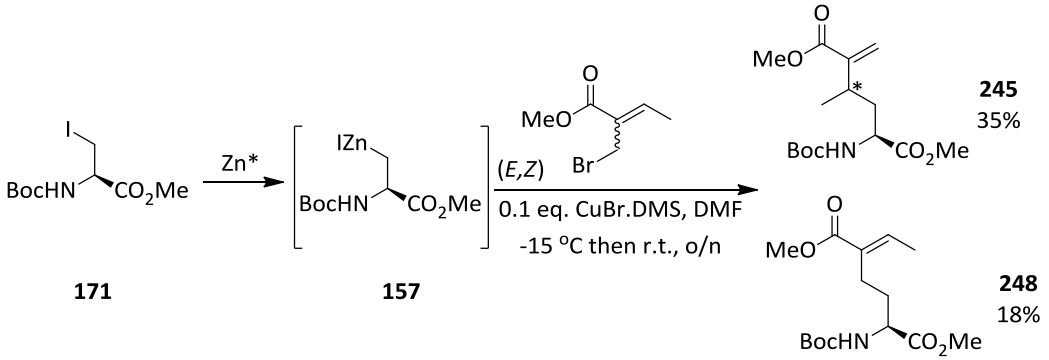


R= Me, **236**
R= Ph, **237**

R= Me, 65%, **243**
R= Ph, 60%, **244**

Scheme 68: Mesylation of the Baylis-Hillman adduct **236** and **237**

With mesylated electrophiles **243** and **244** in hand, attention turned to the key copper-catalysed allylation of a range of organozinc reagents. First of all, the allylation reaction between organozinc reagent **157** and (*E/Z*)methyl-2-(bromomethyl)but-2-enoate **241** was carried out under copper-catalysed conditions to give a mixture of compounds (53% overall yield). We attempted to separate these compounds by flash chromatography, which gave two inseparable diastereoisomers **245** as a major product as well as the desired allylated product **248** in low yield (18%) (**Scheme 69 and Figure 20**).



Scheme 69

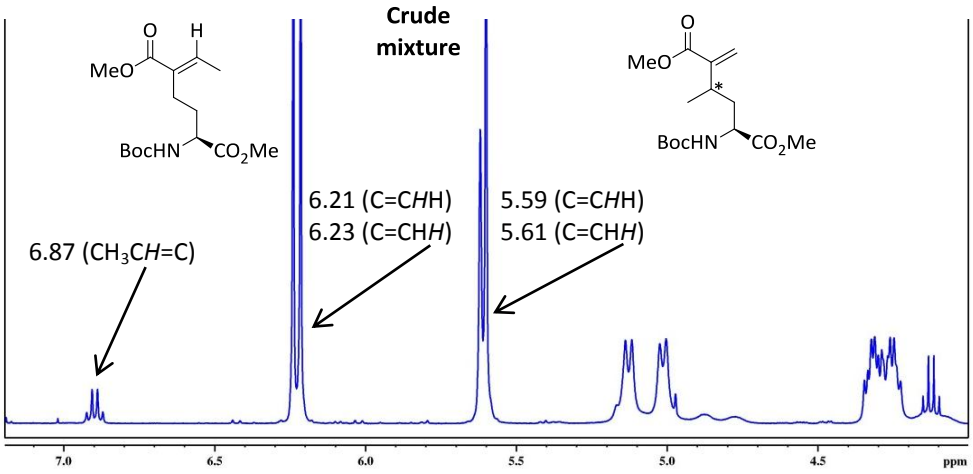


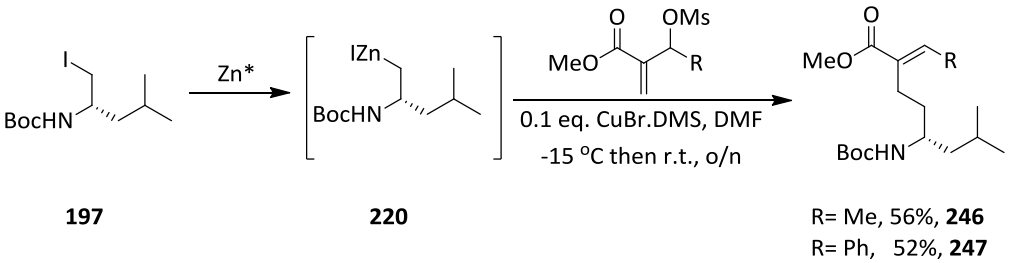
Figure 20: ^{1}H NMR spectrum for the crude mixture of compounds **245** and **248**

Since both the preparation and reaction of the allylic bromide **242** were problematic, attention turned to the mesylate substrates.

2.2.4 Synthesis *N*-protected amino enoate substrates (246-249)

The organozinc reagent derived from amino acid **197** was reacted with methyl 3-(methanesulfonyloxy)-2-methylidenebutanoate **243** and methyl 2-[(methanesulfonyloxy)(phenyl)methyl]prop-2-enoate **244** separately in the presence of sub-stoichiometric amounts of CuBr.DMS. This reaction gave the desired products **246** and **247** exclusively in moderate yields .

This allylation reaction was achieved by slowly adding a solution of iodide **197** in dry DMF to activated zinc in dry DMF under nitrogen atmosphere at 0°C. After the addition, the reaction mixture was stirred at room temperature until completion of zinc insertion. Thereafter, the organozinc reagent was added slowly to a solution of mesylated electrophile (4.0 equivalents) and CuBr.DMS (0.1 equivalent) in dry DMF at -15°C to room temperature. The reaction mixture was stirred overnight at room temperature to give the desired compound (**Scheme 70** and **Figure 21**).



Scheme 70

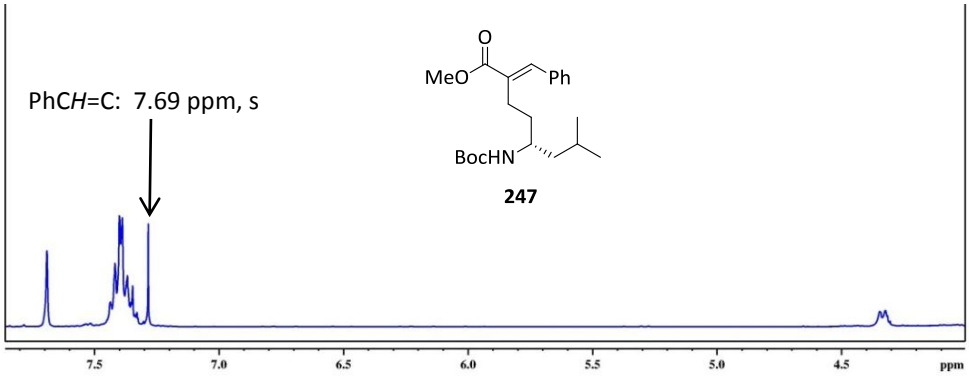
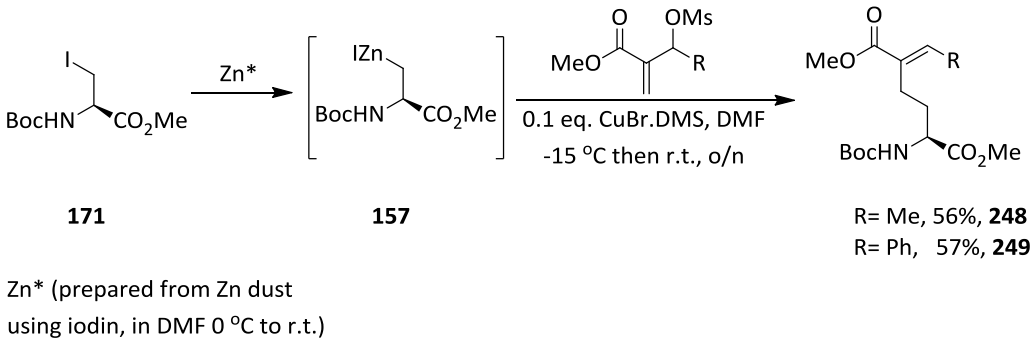


Figure 21: ^{1}H NMR spectrum for the compound **247**

In a similar way, the organozinc reagent derived from amino acid **171** was coupled with methyl 3-(methanesulfonyloxy)-2-methylidenebutanoate **243** and methyl 2-[(methanesulfonyloxy)(phenyl)methyl]prop-2-enoate **244** separately in the presence of sub-stoichiometric amounts of CuBr.DMS. This reaction also gave the desired products **248** and **249** exclusively in a moderate yields of 56% and 52% respectively (**Scheme 71** and **Figure 22**).



Scheme 71

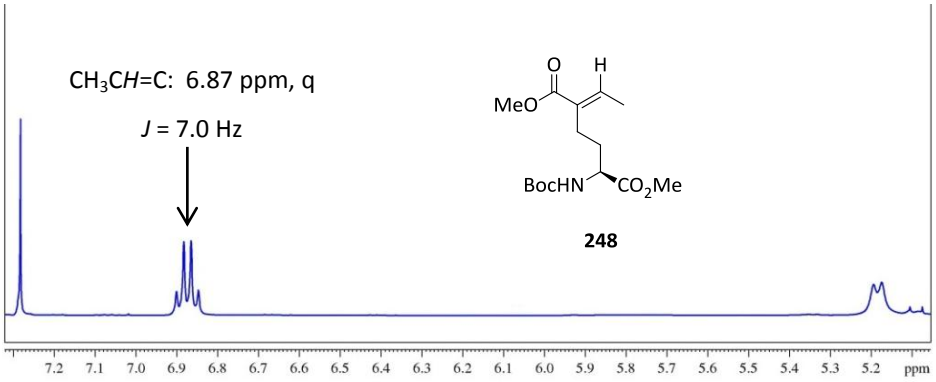


Figure 22: ^{1}H NMR spectrum for the compound **248**

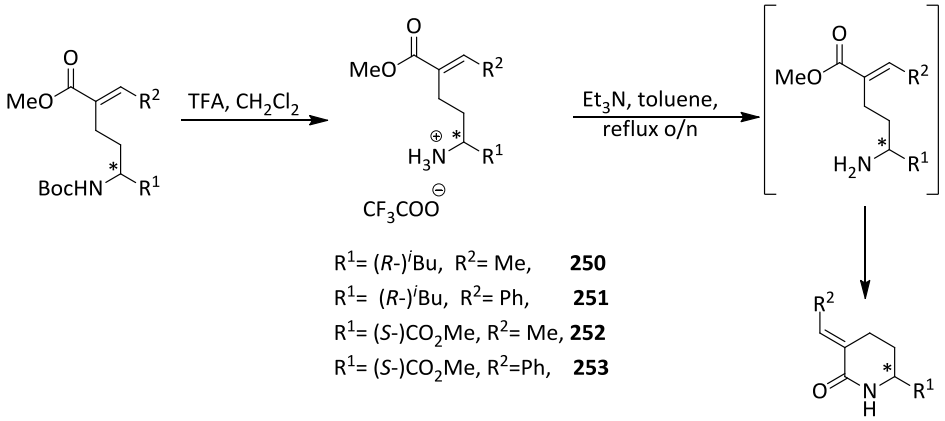
Table 11: Synthesis of cyclisation substrates **246-249**

compound	R^1	R^2	(yield, %)
246	(*R*-)^{i}Bu	Me	56
247	(*R*-)^{i}Bu	Ph	52
248	(*S*-)CO_2Me	Me	56
249	(*S*-)CO_2Me	Ph	57

At this stage we could not assign the configuration of the alkenes, but later studies using Nuclear Overhauser Effect Spectroscopy allowed us to determine that the double bond configuration was ***E***.

2.2.5 Synthesis of lactams (254-257)

Treatment of each of the four adducts **246-249** with TFA in dichloromethane resulted in formation of the trifluoroacetate salts **250-253**. Then, a solution of the trifluoroacetate salts **250-253** in toluene were each separately heated at reflux in the presence of triethylamine, which gave the lactams **254-257** in very good yields (**Scheme 72**).



R^1= (*R*-)^{i}Bu, R^2= Me, **250**
R^1= (*R*-)^{i}Bu, R^2= Ph, **251**
R^1= (*S*-)CO_2Me, R^2= Me, **252**
R^1= (*S*-)CO_2Me, R^2=Ph, **253**

R^1= (*R*-)^{i}Bu, R^2= Me, 83%, **254**
R^1= (*R*-)^{i}Bu, R^2= Ph, 86%, **255**
R^1= (*S*-)CO_2Me, R^2= Me, 88%, **256**
R^1= (*S*-)CO_2Me, R^2=Ph, 80%, **257**

Scheme 72: Synthesis of lactams **254-257**

The stereochemical assignment of alkene **256** was made using the nOe technique. Thus, irradiation of the $\mathbf{H^7}$ signal at 1.65 ppm in compound **256**, resulted in an enhancement of the protons $\mathbf{H^5}$ (**Figure 23**); irradiation of the proton $\mathbf{H^6}$ signal at 6.67 ppm showed no interaction with the protons at $\mathbf{H^5}$. Therefore, nOe suggests compound **256** is the *E*-alkene configuration, which in turn suggests that the precursore **248** is also *E*-configuration.

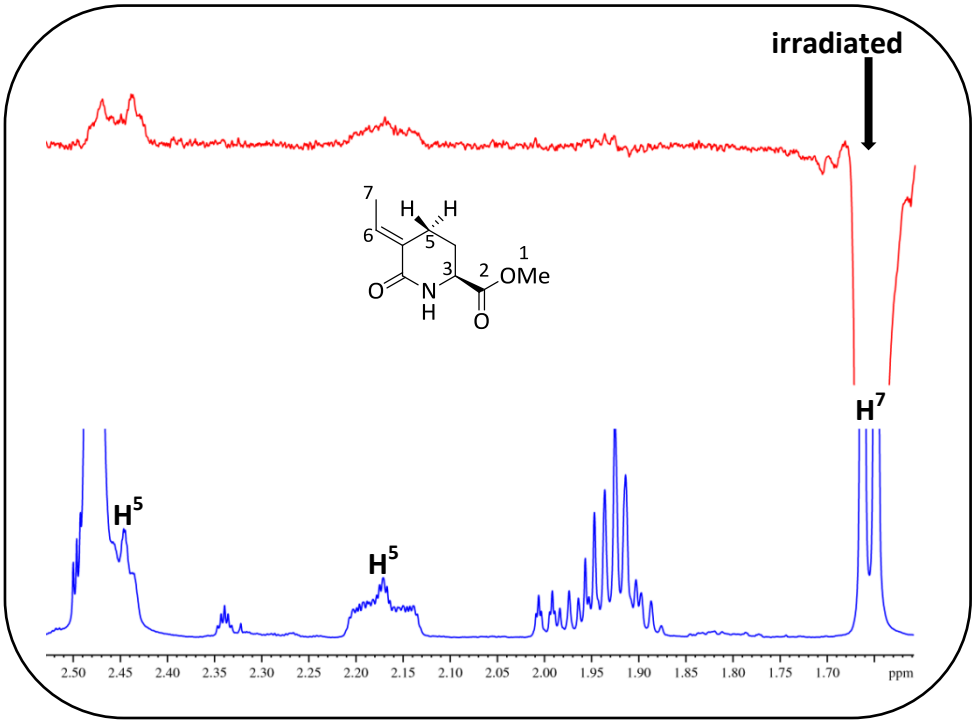
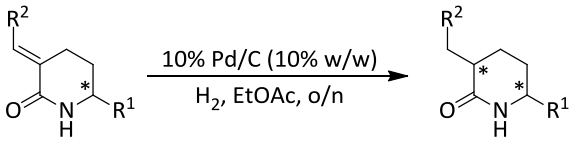


Figure 23: nOe spectrum for the compound **256** on irradiation of the H^7

2.2.6 Hydrogenation of unsaturated lactams

Hydrogenation of the exo-cyclic methylene group of each of lactams **254-257** was performed using Pd/C (10% w/w) at ambient pressure and temperature in ethyl acetate as solvent (**Scheme 73)**. The hydrogenation reaction proceeded in excellent yields (92-94%), generating the second stereogenic centre with varying stereoselectivity (**Table 12**).



R^1= (*R*-)^{i}Bu, R^2= Me, 83%, **254**
R^1= (*R*-)^{i}Bu, R^2= Ph, 86%, **255**
R^1= (*S*-)CO_2Me, R^2= Me, 88%, **256**
R^1= (*S*-)CO_2Me, R^2=Ph, 80%, **257**

R^1= (*R*-)^{i}Bu, R^2= Me, 94%, **258a, 258b**
R^1= (*R*-)^{i}Bu, R^2= Ph, 94%, **259a, 259b**
R^1= (*S*-)CO_2Me, R^2= Me, 94%, **260**
R^1= (*S*-)CO_2Me, R^2=Ph, 92%, **261a, 261b**

Scheme 73: Hydrogenation of lactams **254-257**

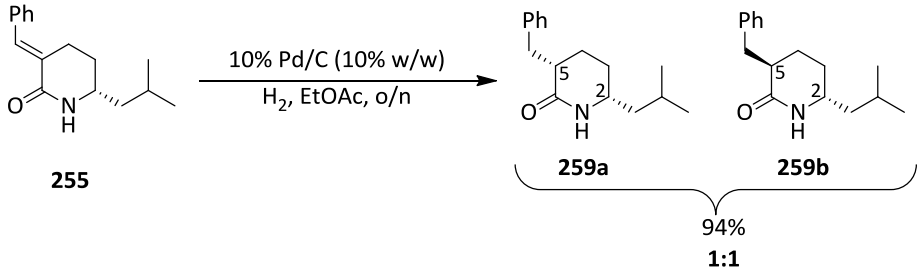
Table 12

starting material	R^1	R^2	product	(yield, %)	Ratio [a]	
254	(*R*-)^{i}Bu	Me	**258a, 258b**	94	5	1
255	(*R*-)^{i}Bu	Ph	**259a, 259b**	94	1	1
256	(*S*-)CO_2Me	Me	**260**	94	>19 [b]	1
257	(*S*-)CO_2Me	Ph	**261a, 261b**	92	2	1

a: Determined from ^{1}H NMR analysis of the crude reaction mixture.
b: The diastereoselectivity was estimated on the basis that only one isomer was evident.

2.2.7 Determination of configuration for the compound 259b by X-ray diffraction:

Hydrogenation of the exo-cyclic methylene group in lactam **255** gave the product as a yellow oil in excellent yield (94%) (**Scheme 74**). ^{1}H NMR analysis for the crude product indicated the presence of two diastereoisomers **259a** and **259b** in a **1:1** ratio.



Scheme 74

Separation of the two diastereoisomers was performed successfully by preparative HPLC, and each isomer was isolated in 47% yield, confirming the conclusion from the crude NMR.

One of these diastereoisomers **259b** was isolated as a white crystalline solid, and the structure determined by single-crystal X-ray diffraction analysis, which established the ***trans*** relationship between the iso-butyl group on **C-2** and the benzyl group on **C-5** as illustrated in **Figure 24**.

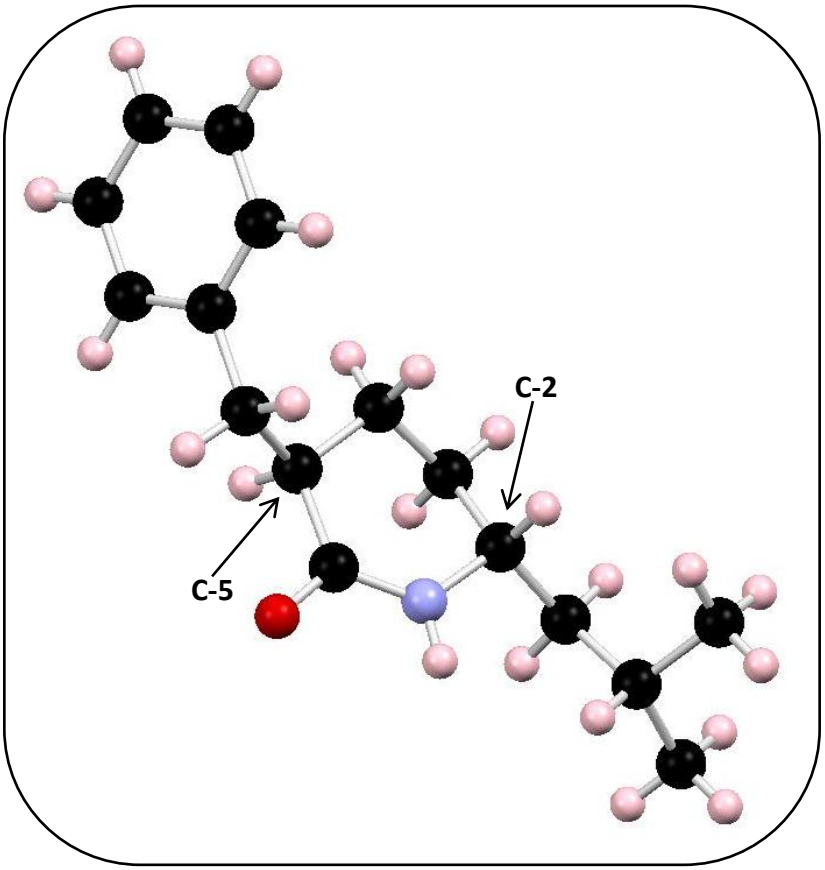


Figure 24: Crystal structure of the product **259b** which confirms *trans*-configuration

2.2.8 Determination of configuration by 1H NMR:

- **Compound 259b**

The ^{1}H NMR spectrum for the compound **259b**, (which we know is the *trans*-diastereoisomer) illustrated in **Figure 25**.

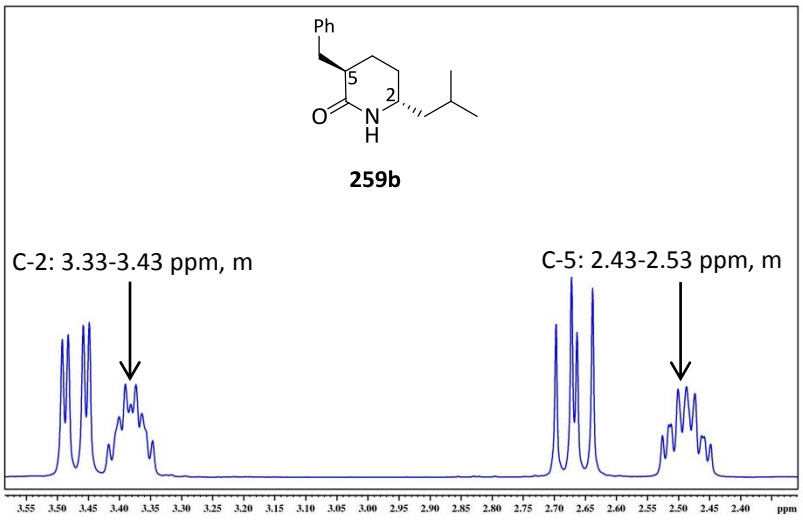


Figure 25: ^{1}H NMR signals of the protons at C-2 and C-5 for the compound **259b**

Having established the configuration of the compound **259b**, we attempted to establish its conformation in solution. We hope that this would provide a basis for assigning the configuration of the remaining products using ^{1}H NMR alone.

- **Compound 259a**

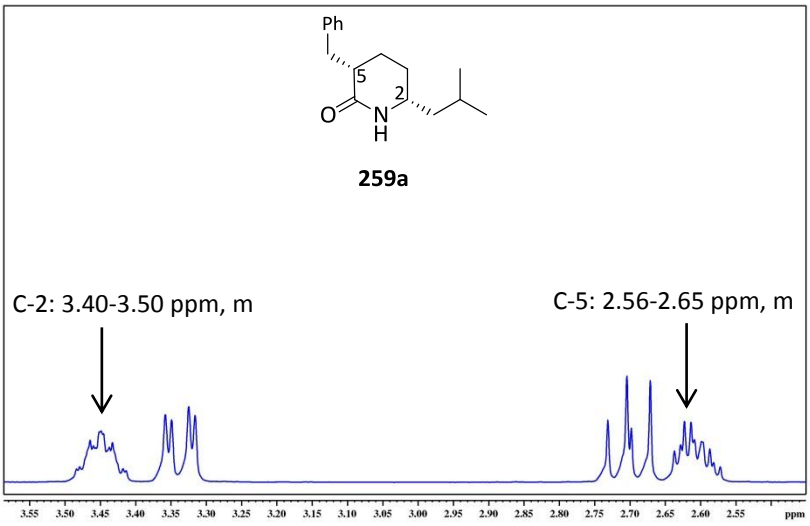
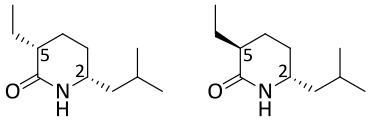


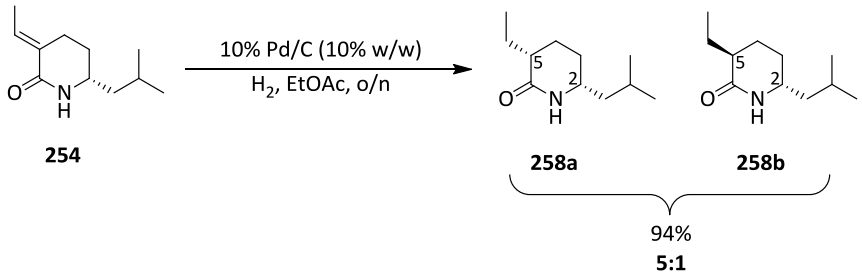
Figure 26: ^{1}H NMR signals of the protons at C-2 and C-5 for the compound **259a**

- **Compounds 258a and 258b**



258a **258b**

Hydrogenation of the exo-cyclic methylene group in lactam **254** gave the product as a yellow oil in excellent yield (94%) (**Scheme 76**). ^{1}H NMR analysis for the crude product indicated the presence of two diastereoisomers **258a** and **258b** in a **5:1** ratio, although we were not able to ascertain which particular isomer was formed at this stage. These two diastereoisomers could not be separated by flash column chromatography, but were separated successfully *via* preparative HPLC, to give two products in 79% and 15% yields, consistent with the crude ^{1}H NMR.



Scheme 75

The structure of compound **234** is closely related to compound **258a**. Since the configuration of compound **234** was established by X-ray crystallography as the *cis*-isomer, it was thought the stereochemistry of **234** would be analogous. Moreover, the ^{1}H NMR spectra for both compounds are closely comparable (**Figure 27**). Therefore, the configuration of **258a** was assigned as *cis*-isomer by comparison with compound **234**.

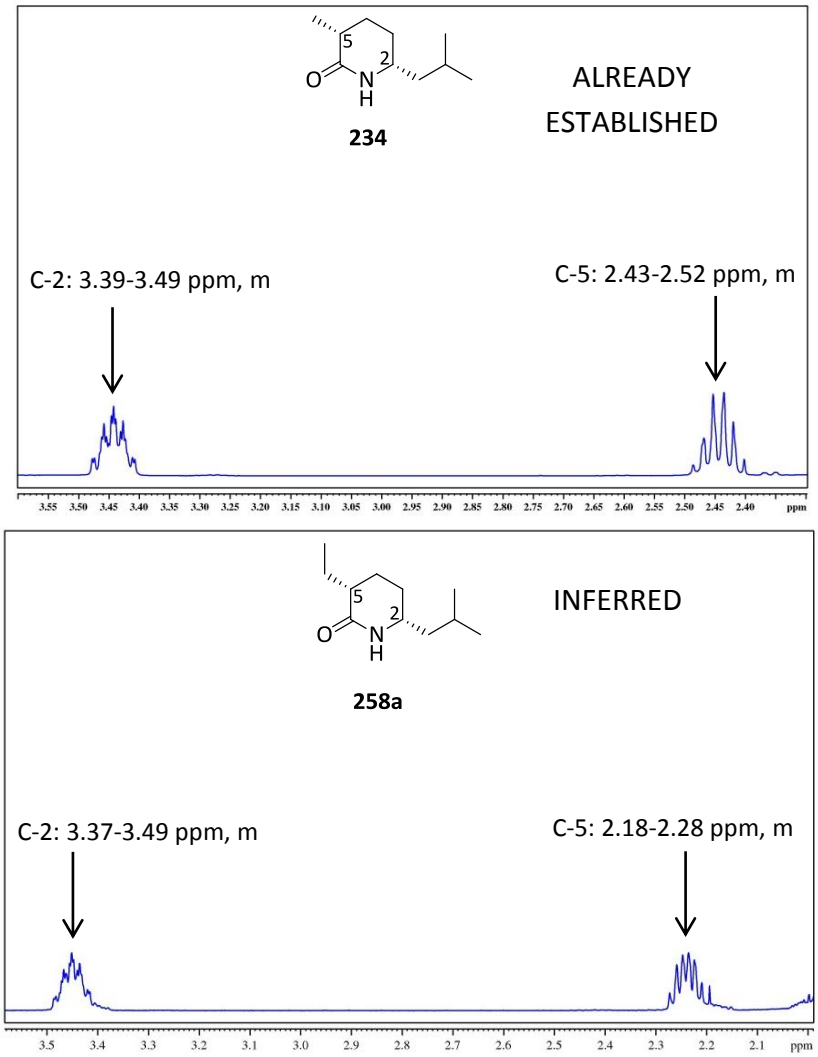


Figure 27: Comparison of the ^{1}H NMR signals of the protons at C-2 and C-5 for the compounds **234** and **258a**

The minor diastereoisomer **258b** must therefore be *trans*-isomer. The ^{1}H NMR spectrum for the minor diastereoisomer **258b** shows a multiplet for the proton at C-2 (2.36-2.50 ppm), and the signal for the proton at C-5 (2.13-2.29 ppm) is also a multiplet (**Figure 28**). Since it was not possible to determine straightforwardly the magnitude of the coupling constants for the protons at C-2 and C-5 we can not assign the conformation directly.

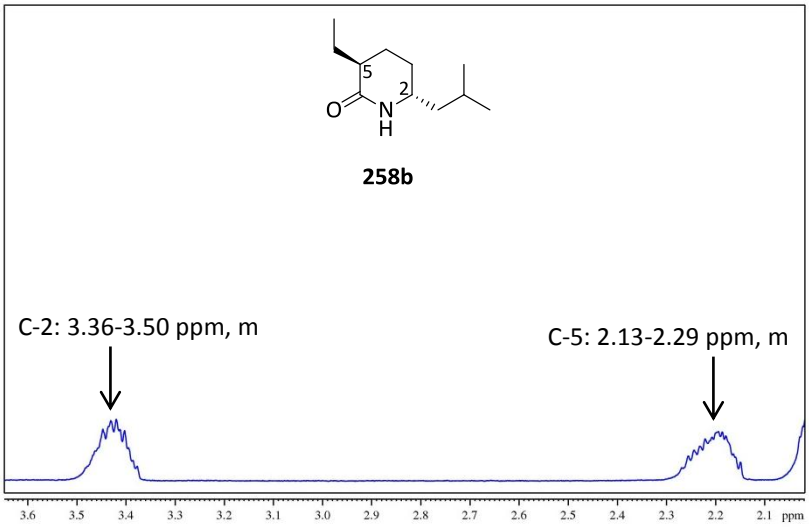
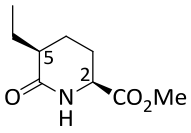
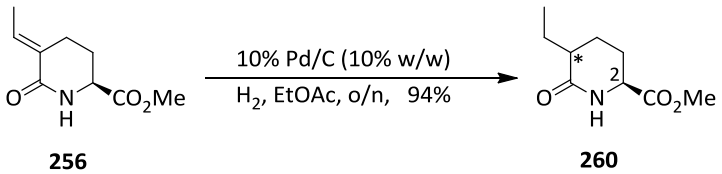


Figure 28: ^{1}H NMR signals of the protons at C-2 and C-5 for the compound **258b**

- **Compound 260**



The exo-cyclic methylene group in lactam **256** underwent hydrogenation to give the product in excellent yield (94%) (**Scheme 75**). ^{1}H NMR analysis of the crude product indicated the presence of one diastereoisomer **260** (**Figure 29**). The pure product **260** was obtained as a white solid, The diastereoselectivity was estimated as **>19:1** (***cis*** : ***trans***) from ^{1}H NMR analysis of the crude reaction mixture on the basis that only one isomer was evident.



Scheme 76

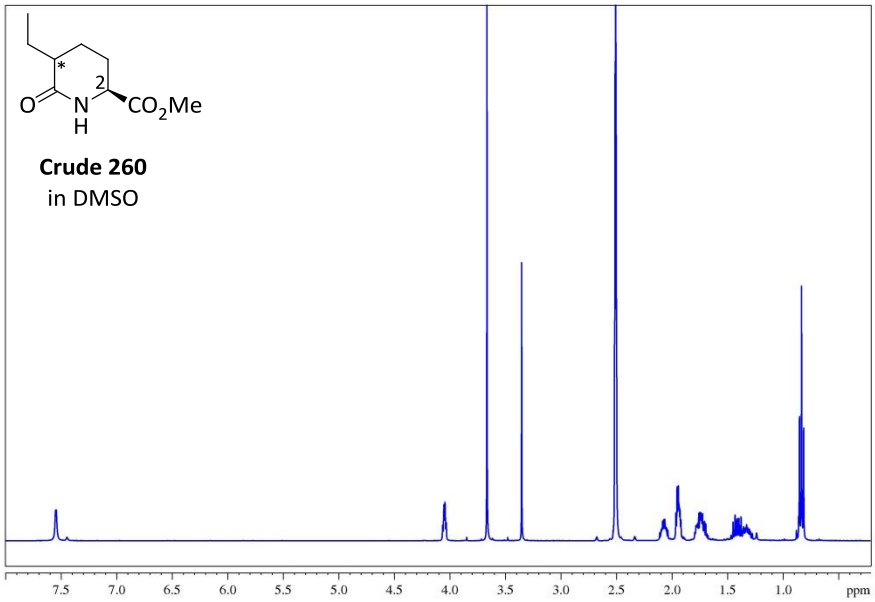


Figure 29: ^{1}H NMR spectrum for the crude compound **260**

The ^{1}H NMR spectrum shows a doublet of doublets (apparent quartet) for the proton at C-2 (4.04 ppm), with a large (12.5 Hz) and a small (4.0 Hz) coupling constants. The large value is an outcome of vicinal coupling with the axial proton at C-3 (diaxial coupling), the medium value arises from the equatorial proton at C-3 (**Figure 30**). This establishes that the proton at C-2 must be in the pseudo-axial position and ester group therefore must be pseudo-equatorial.

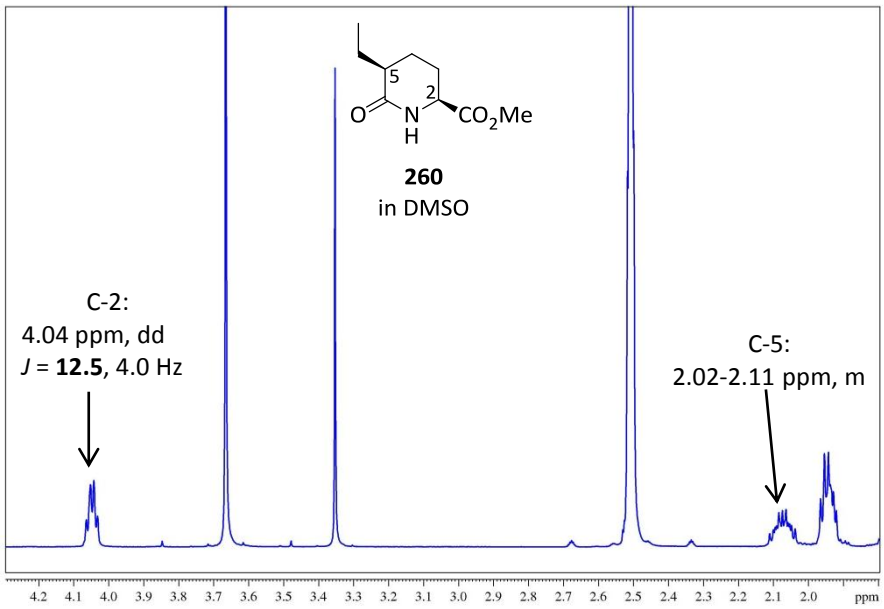
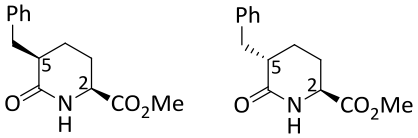


Figure 30: ^{1}H NMR signals of the protons at C-2 and C-5 for the compound **260**

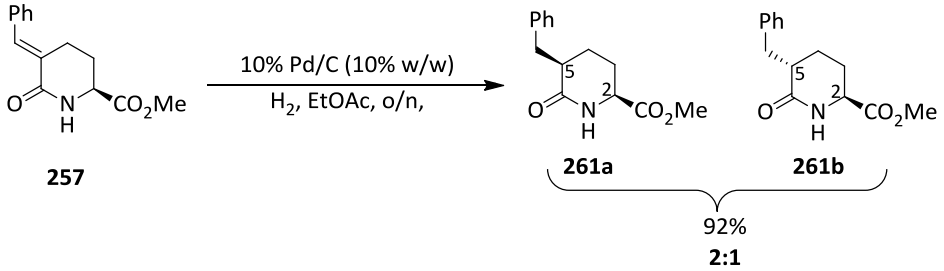
The signal for the proton at C-5 (2.02-2.11 ppm) is a multiplet (**Figure 30**). Since it was not possible to determine straightforwardly the magnitude of the coupling constant for the proton at C-5 we can not assign the conformation directly. However, if we compare the signal for C-5 in **Figure 30**, with that for C-5 in **Figure 28**, it seems reasonable to propose that the ethyl group in **260** is pseudo-axial. These results are consistent with the previous results within the Jackson group (**Scheme 37, page 38**).[64]

- **Compounds 261a and 261b**



261a **261b**

Application of the hydrogenation conditions to lactam **257** gave the product as a yellow oil in excellent yield (92%) (**Scheme 77**). ^{1}H NMR analysis for the crude product indicated the presence of two diastereoisomers **261a** and **261b** in a **2:1** ratio, though we were not able to ascertain which particular isomer was the major isomer at this stage. Attempts to separate the diastereoisomers by flash column chromatography and preparative HPLC were not successful.



257 **261a** **261b**

Scheme 77

The ^{1}H NMR spectrum for the major diastereoisomer **261a** shows a doublet of doublets for the proton at C-2 (3.42 ppm), with a large (13.0 Hz) and a small (3.5 Hz) coupling constant. The large value arises from vicinal coupling with the

axial proton at C-3 (diaxial coupling), the medium value derives from the equatorial proton at C-3 (**Figure 31**). This establishes that the proton at C-2 must be in the pseudo-axial position and ester group therefore must be pseudo-equatorial.

The ^{1}H NMR spectrum for the minor diastereoisomer **261b** similarly shows a doublet of doublets for the proton at C-2 (4.03 ppm), with a large (10.5 Hz) and a small (4.5 Hz) coupling constant. The large value arises from the proton at C-3 (diaxial coupling), the medium value derives from the equatorial proton at C-3 (**Figure 31**). This establishes that the proton at C-2 must also be pseudo-axial and the ester group therefore pseudo-equatorial. The signal for the proton at C-5 in both isomers is an overlapping multiplet, so no conclusion can be drawn.

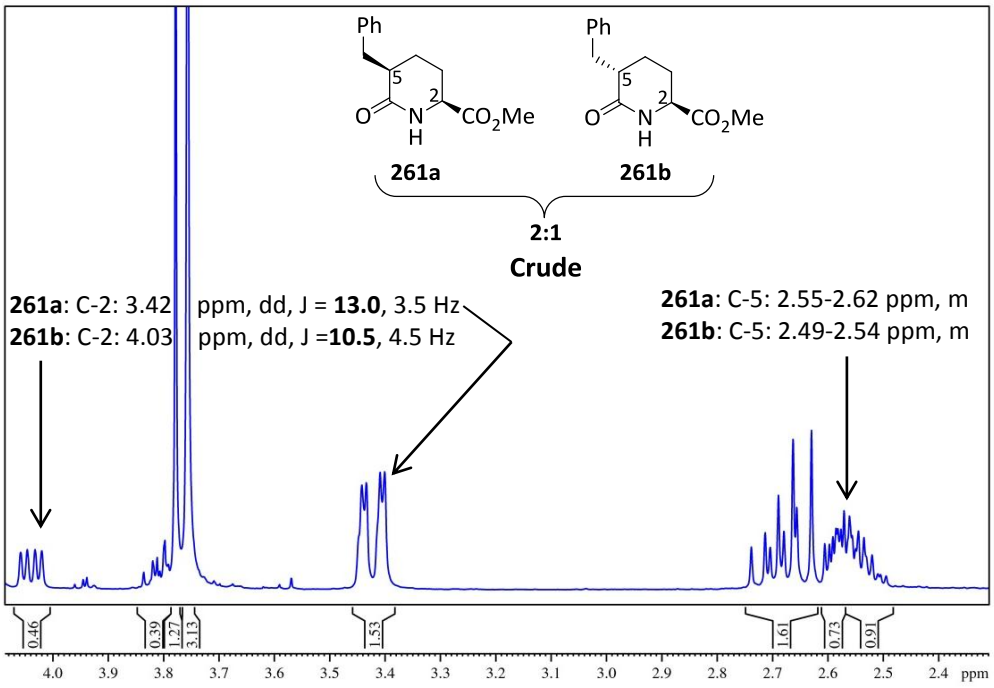


Figure 31: ^{1}H NMR signals of the protons at C-2 and C-5 for the crude mixture of compounds **261a** and **261b**

The ^{1}H NMR data for the *cis*-compounds **258a, 259a** and **260** are summarized in **Figure 32**, and for the *trans*-compounds **258a** and **259a** in **Figure 33**.

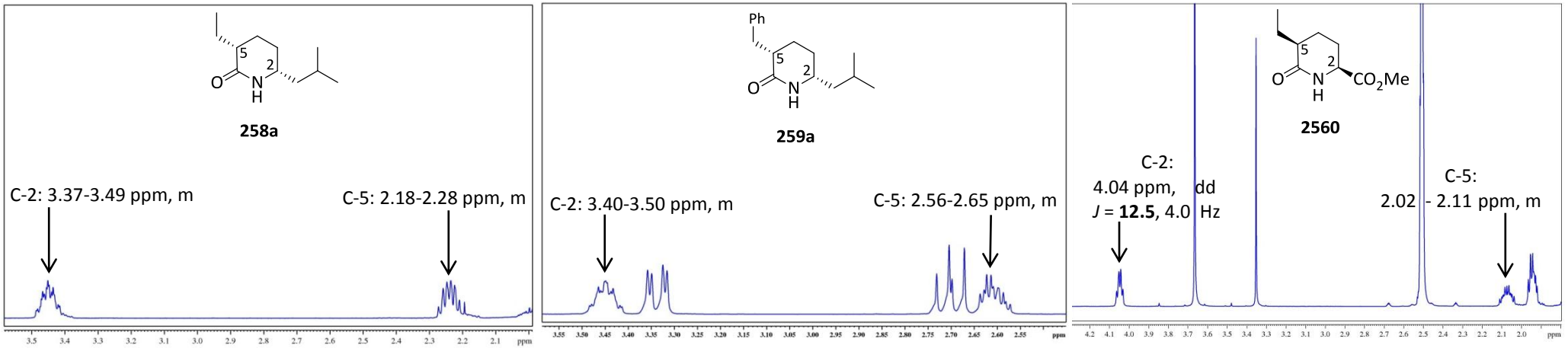


Figure 32: ^{1}H NMR signals of the protons at C-2 and C-5 for compounds **258a, 259a** and **260**

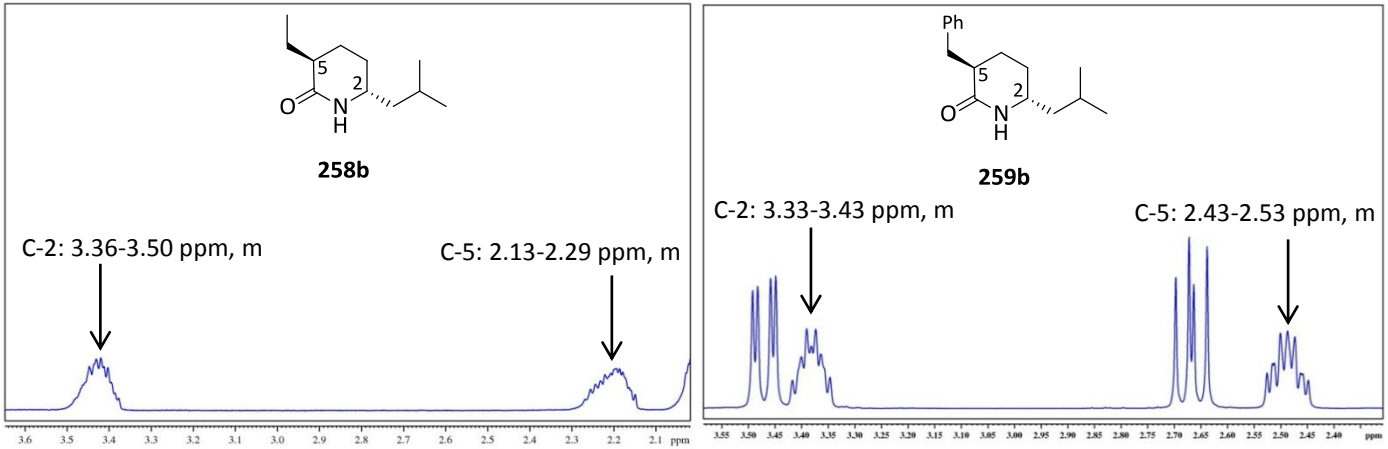
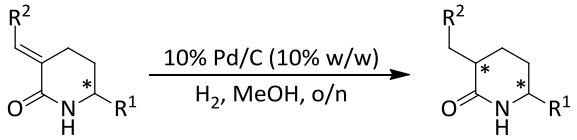


Figure 33: ^{1}H NMR signals of the protons at C-2 and C-5 for compounds **258b** and **259b**

2.2.9 Hydrogenation of selected substrates in methanol

In order to explore the effect of solvent, the hydrogenation reactions for the compounds **254**, **255** and **257** were therefore repeated in methanol (**Scheme 78** and **Table 13**).



R^1= (*R*-)^{i}Bu, R^2= Me, **254**
R^1= (*R*-)^{i}Bu, R^2= Ph, **255**
R^1= (*S*-)CO_2Me, R^2=Ph, **257**

R^1= (*R*-)^{i}Bu, R^2= Me, 94%, **258a, 258b**
R^1= (*R*-)^{i}Bu, R^2= Ph, 94%, **259a, 259b**
R^1= (*S*-)CO_2Me, R^2=Ph, 92%, **261a, 261b**

Scheme 78: Hydrogenation of lactams **254**, **255** and **257** in methanol

Table 13

starting material	R^1	R^2	product	yield, %	solvent MeOH [a]		solvent EtOAc	
					cis	*trans*	*cis*	*trans*
254	(*R*-)^{i}Bu	Me	**258a, 258b**	94	>19 [b]	1	5	1
255	(*R*-)^{i}Bu	Ph	**259a, 259b**	94	1	1	1	1
257	(*S*-)CO_2Me	Ph	**261a, 261b**	92	2	1	2	1

a: Determined from ^{1}H NMR analysis of the crude reaction mixture.
b: The diastereoselectivity was estimated on the basis that only one isomer was evident.

Hydrogenation of unsaturated lactams **254** was carried out using methanol as solvent at **0.2**M concentration to give the product as a yellow oil in excellent yield (94%). ^{1}H NMR analysis of the crude product indicated the presence of one diastereoisomer exclusively, which was assigned as the *cis*-isomer by comparison with the known isomer **258a** (**Figure 34** and **Table 13**).

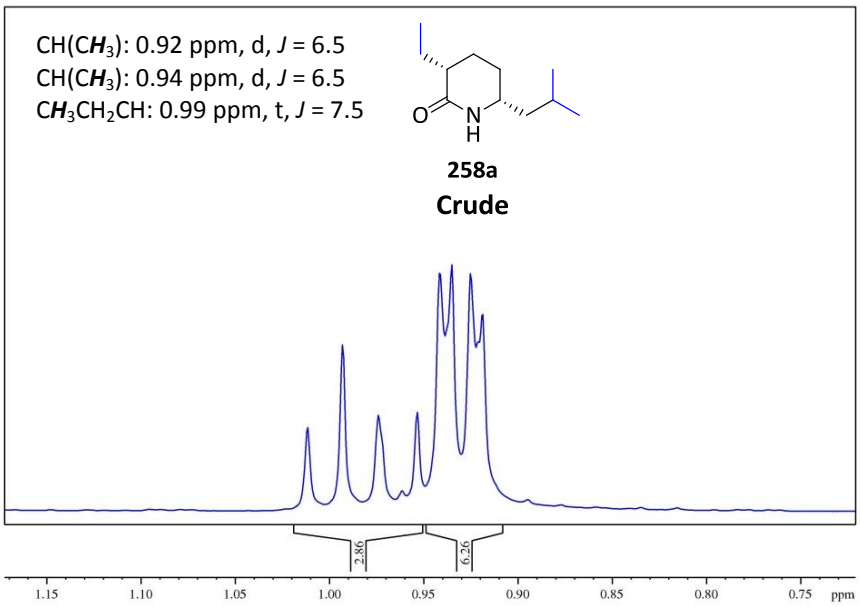


Figure 34*: :* ^{1}H NMR signals of methyl group protons in compound **258a**

Hydrogenation of unsaturated lactam **255** was carried out using methanol as solvent at **0.2**M concentration to give the product as a yellow oil in excellent yield (94%). The ^{1}H NMR analysis for the crude product indicated the presence of two diastereoisomers **259a** and **259b**, in a ratio of **1:1** (***cis*** : ***trans***), identical to that reported previously (**Figure 35** and **Table 13**).

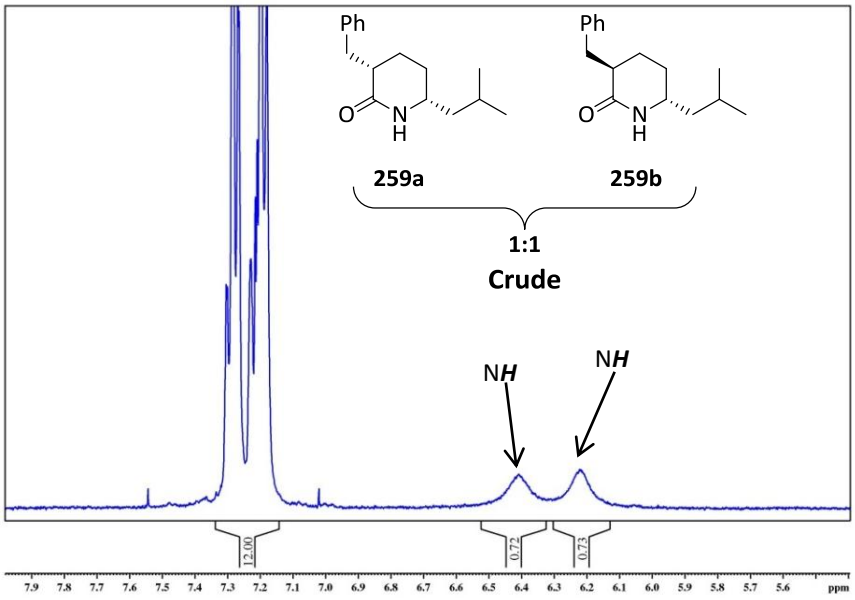


Figure 35: ^{1}H NMR spectrum for the crude mixture **259a** and **259b**

Finally, the lactam **257** underwent hydrogenation using methanol as solvent at **0.2**M concentration to give the product as a yellow oil in excellent yield (92%). The ^{1}H NMR analysis for the crude product indicated the presence of two diastereoisomers **261a** and **261b**, in a **2:1** ratio, which is the same as reported previously (**Figure 36** and **Table 13**).

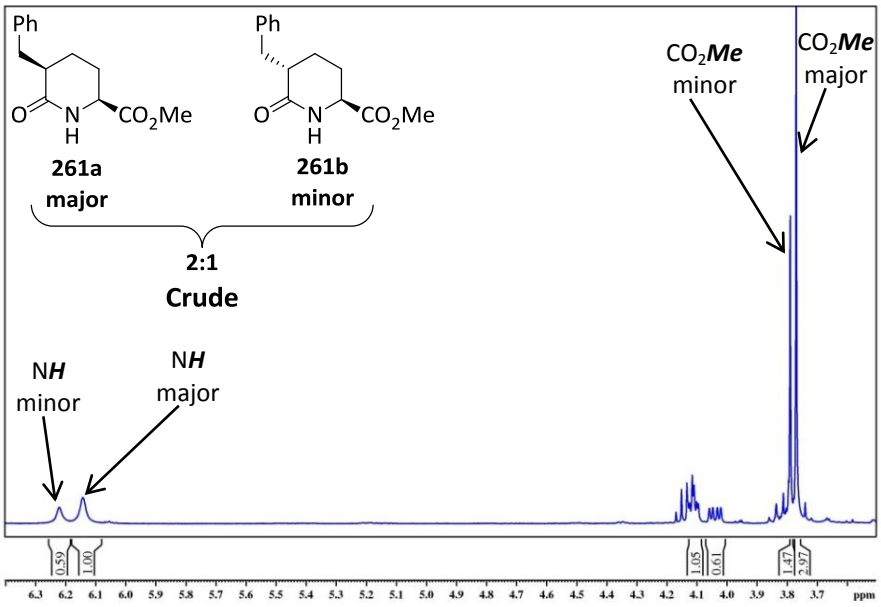


Figure 36: ^{1}H NMR spectrum for the crude mixture **261a** and **261b**

Our results are difficult to explain, but it is clear that in some cases the use of protic solvent can significantly improve stereoselectivity.

2.3 Conclusion

We have developed a new synthetic approaches for the synthesis of 2,5-disubstituted piperidin-6-ones.

Organozinc reagents derived from enantiomerically pure amino acids (specifically L-serine, L-valine, L-leucine, and L-phenyl alanine), can be extended *via* copper-catalysed allylation. The stereo centre can then carried forward to form *N*-protected amino enoate precursors with the (*R*) configuration.

Allylation proceeds in moderate yields when using methyl 2-(bromomethyl)acrylate **218**. However, more substituted methyl 2-(bromomethyl)acrylate resulted in a mixture of allylated products due to competing mechanisms. Whereas, substituted mesylated electrophiles does not have this problem and proceeds to form the desired outcome. Cyclisation of the allylation products by acid then base treatment gives the unsaturated lactams in excellent yields (80-88%).

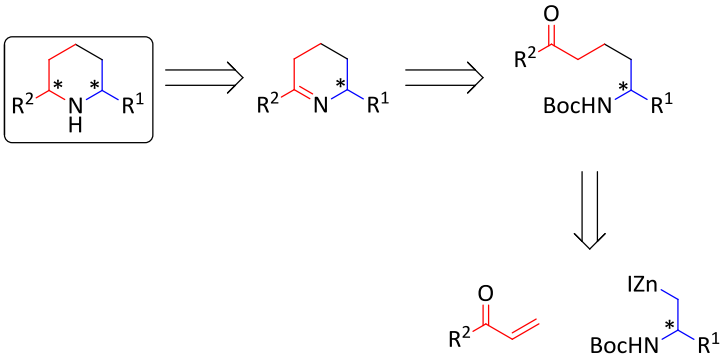
Subsequent hydrogenation of the unsaturated lactams proceeded in excellent yields (90-94%), though stereoselectivity varied depending on solvent. The ***cis*-isomer** was favoured by over two fold using methanol over ethyl acetate. Our best rational for this observation is methanol competes as a hydrogen bond donor, and breaks up dimers formed which helps stereocontrol, but it is unclear why and how.

In the other hand, there seem to be no solvent effect when a benzyl group is on the C-5 position, or when a methyl ester and iso-butyl groups on C-2 position (these two groups also seem to improve diastereoselectivity). It is unclear as to why this occurs, but perhaps steric and intramolecular H-bonding which hinders dimerisation is to blame.

2.4 Synthesis of 2,6-disubstituted piperidines

2.4.1 Introduction

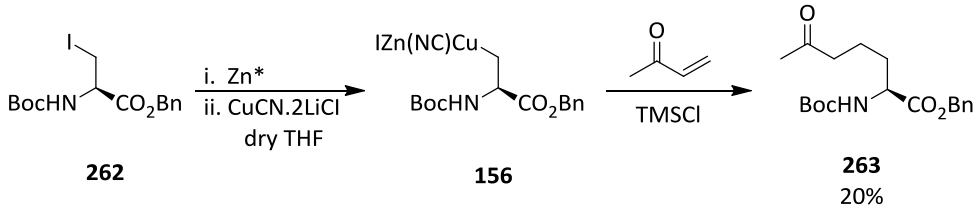
Our initial approach to the synthesis of 5-oxo amine, precursors to 2,6-disubstituted piperidine derivatives, was to involve copper catalyzed conjugate addition of β-amino organozinc reagents to a range of α,β-unsaturated ketones. Deprotection, followed by reductive amination, should lead to the target 2,6-disubstituted piperidines (**Scheme 79**).



Scheme 79: Retrosynthetic approach to 2,6-disubstituted piperidines

2.4.2 Results and discussion

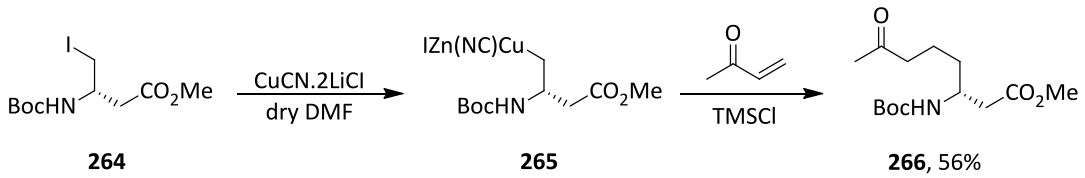
In prior work within the Jackson group, it had been shown that reaction of the L-serine derived zinc/copper reagent **156** with methyl vinyl ketone, in the presence of chlorotrimethylsilane, gave the protected 6-oxo α-amino acid **263**, albeit in low yield (20%) (**Scheme 80**).[55]



262 **156** **263** 20%

Scheme 80: Synthesis of 6-oxo α-amino acid **263**

In a similar manner, aspartic acid-derived organozinc reagent **265** (generated in DMF) reacted with methyl vinyl ketone, also in the presence of TMSCl, to give the conjugate addition product **266** in higher yield (56%) (**Scheme 81**).[56]

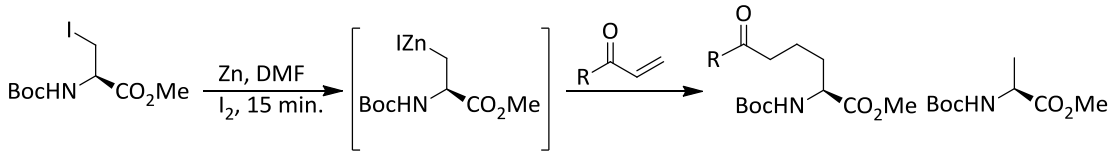


264 **265** **266**, 56%

Scheme 81: Synthesis of compound **266**

The enhancement in the yield of the conjugate addition product was attributed to the use of a polar aprotic solvent, due to the minimization of β-elimination of the carbamate group from the organozinc reagent which occurs more readily in THF.

Subsequently, Abdelsalam attempted to optimise the reaction using catalytic amounts of copper (**Scheme 82** and **Table 14**). Organozinc reagent **157** (1.0 eq.) in dry DMF was added to CuBr.DMS (0.1 eq.)/DMF, followed by addition of a mixture of enone (2.0 eq.) and freshly distilled TMSCl (2.0 eq.) in dry DMF (0.5 mL) at 5°C stirred for 10 min, then stirred overnight at room temperature.



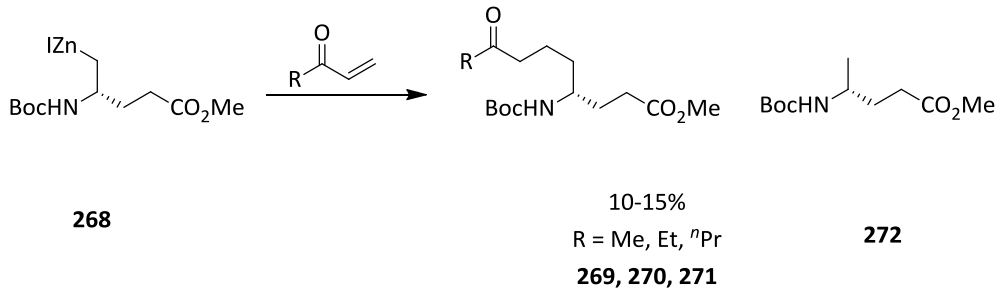
171 **157** **184-186** **267**

Scheme 82

Table 14

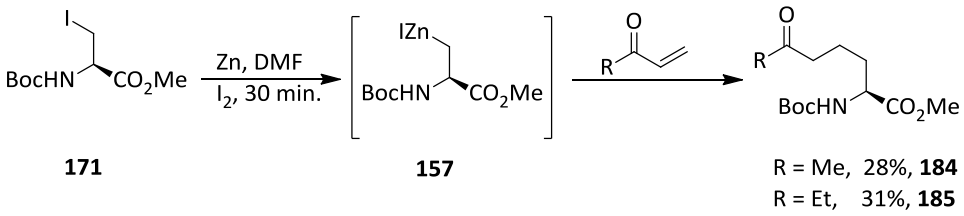
Enone	Michael product	Yield %
Me	**184**	47
Et	**185**	45
^{n}Pr	**186**	45

Copper catalysed reaction of the organozinc reagent **268** derived from D-glutamic acid under the same conditions (**Table 14**) gave disappointing yields (10-15%) of the desired products **269**, **270** and **271**. In each case the protonated product was the major product **272** (**Scheme 83**).



Scheme 83

The first step was to reproduce the reaction reported by Abdelsalam. Repetition of the conjugate addition reaction gave the products **184** and **185** but in lower yields (**Scheme 84**).

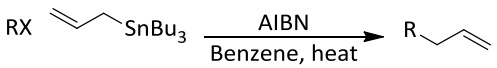


Scheme 84: Synthesis of compounds **184** and **185**

Despite extensive efforts to reproduce Abdelsalam's yields, unfortunately all yields obtained were significantly lower. Since our efforts to carry out the key conjugate addition reaction *via* organometallic intermediates had only been partially successful, it seemed appropriate to consider other ways in which the key conjugate addition reaction could be carried out. Our attention therefore turned to the possibility of using a radical process.

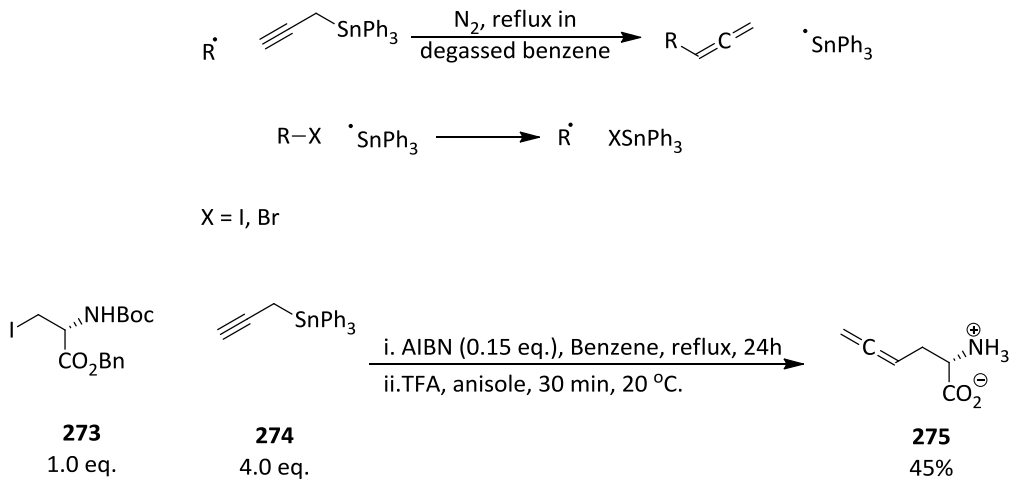
2.4.3 Radical conjugate addition reaction

Free radical reactions have been widely used in the synthesis of natural products as a simple method for C-C bond formation. For example, radical allylation can be achieved successfully either using thermal or photochemical procedures (**Scheme 85**).[77]



Scheme 85: Free radical allylation

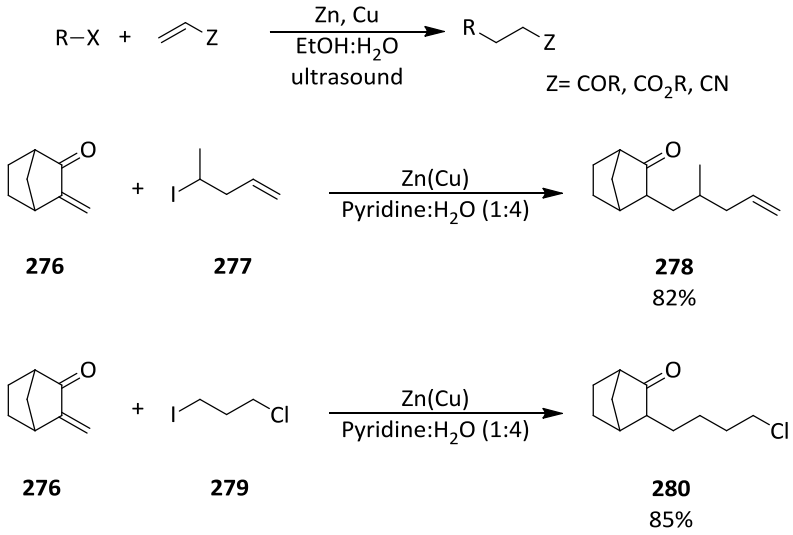
The synthesis of unusual naturally occurring amino-acid **275** was achieved by treatment of protected 3-iodo-L-alanine **273** with triphenylprop-2-ynylstannane **274** in the presence a catalytic amount of AIBN (0.15 eq.), followed by deprotection, to give the desired product in modest yield (**Scheme 86**).[78]



Scheme 86: Allene transfer by free radical reaction

The 1,4-conjugate addition reaction is an important reaction in organic synthesis. The conjugate addition of free radicals to electron deficient olefins in the presence of zinc/copper couple, under aqueous conditions can be an extremely efficient synthetic protocol.[79,80] One of the most important procedures to accomplish radical conjugate addition in aqueous media under sonochemical conditions was discovered by Luche *et al*. in 1986.[81-83] Ultrasonically induced free

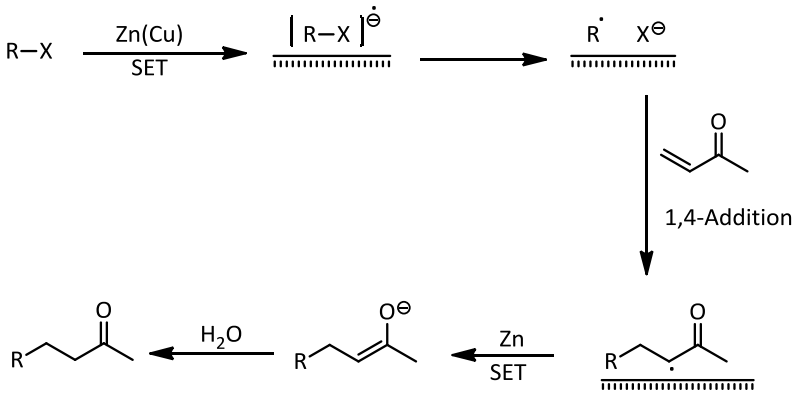
radical conjugate addition of alkyl halides in the presence of zinc-copper mediate to α,β-unsaturated carbonyl compounds under aqueous conditions afforded the 1,4-addition products in very good yields (**Scheme 87**).



Scheme 87: Luche's conjugate addition

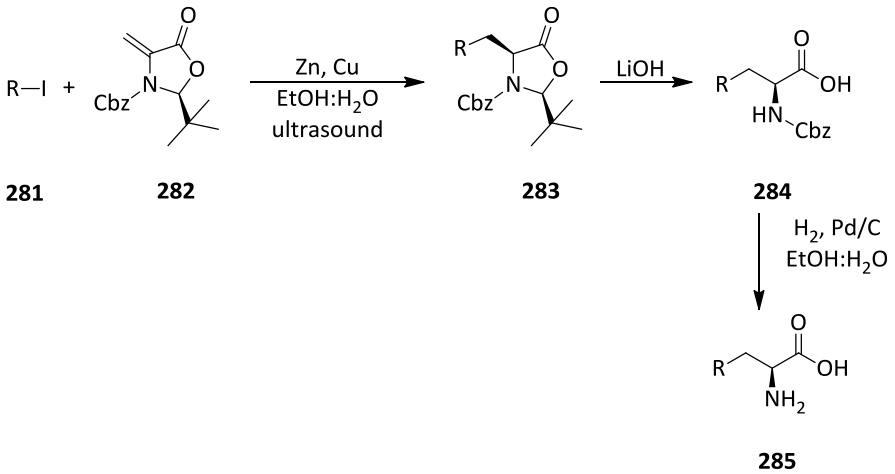
The reaction is believed to proceed by a free radical mechanism summarized in **Scheme 88**:[84]

1. In the first step a single-electron transfer (SET) occurs from the metal surface to the carbon-halogen bond.
2. Carbon-halogen bond breaks to produce an adsorbed free radical.
3. 1,4-radical addition to the α,β-unsaturated system occurs.
4. Additional single-electron transfer (SET) occurs from the metal surface, which generates an enolate.
5. Finally, the enolate is protonated by the solvent.



Scheme 88: Proposed mechanism for the zinc-copper conjugate addition

Subsequently Sarandeses[85] has applied Luche's conjugate addition to develop a short synthetic route to enantiopure natural and unnatural α-amino acids, in high yields under aqueous conditions at room temperature. The essential point of the synthesis is the conjugate addition of alkyl radicals derived from iodides induced by ultrasonic waves to the chiral methyleneoxazolidinone **283** in aqueous media which occurred with high diastereoselectivity (>98% *de*) (**Scheme 89** and **Table 15**).

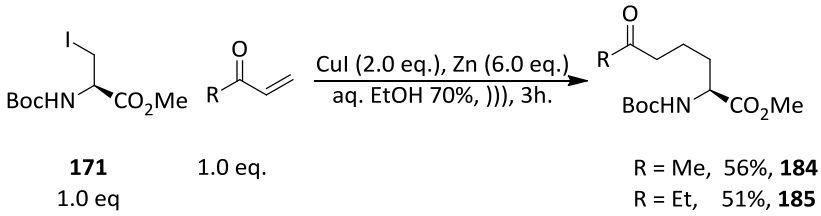


Scheme 89: Synthesis of enantiopure natural and unnatural α-amino acids

Table 15: Preparation of compounds **283** and **285**

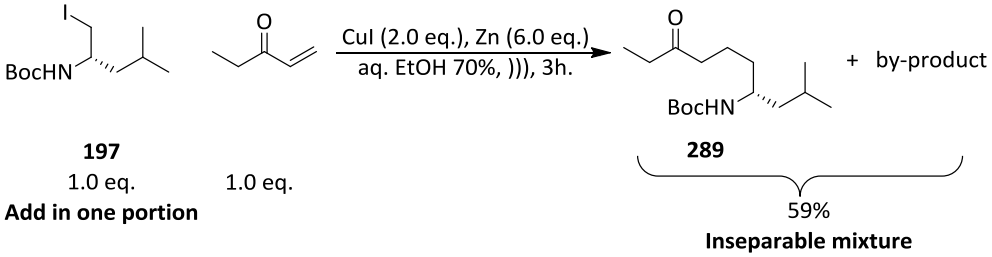
entry	R^1	**283** (yield, %)	**285** (yield, %)
a	^{i}Pr	76	93
b	$^{n}C_5H_{11}$	96	94
c	cyclohexyl	98	74
d	$(CH_2)_3CO_2H$	60	100
e	$(CH_2)_3CO_2Me$	99	N/A
f	$(CH_2)_{12}OH$	96	N/A

These products encouraged us to apply free radical conjugate addition reaction to our target. The reaction of iodide **171** with methyl vinyl ketone and ethyl vinyl ketone was carried out using an ultrasonic cleaning bath as a source of ultrasound at room temperature. After three hours of sonication it was found (judged by TLC) that iodide **171** had been consumed, and encouraging yields of each of the products of conjugate addition were obtained (**Scheme 90**).



Scheme 90: Synthesis of compounds **184** and **185**

In order to identify the best conditions, we decided to investigate the reaction between iodide **197** and 1-penten-3-one. Initial attempts were carried out according to Sarandeses' procedure.[84,85] In our preliminary experiments, we examined the addition of cuprous iodide (2.0 eq.) and zinc dust (6.0 eq.) to a solution of ethyl vinyl ketone in aqueous ethanol 70%, followed by the addition of protected iodide **197** (1.0 eq.) in one portion to this mixture as shown in **Scheme 91**. The reaction mixture was continuously sonicated using an ultrasonic cleaning bath until no starting material remained.



Scheme 91: Synthesis of compound **289**

^{1}H NMR analysis for the crude product **289** showed the desired product signals, as well as a number of additional signals in the alkene region at (5.19 ppm, dd), (5.34 ppm, dd), (6.03 ppm, dd), which are characteristic signals for a terminal vinyl group (**Figure 37**).

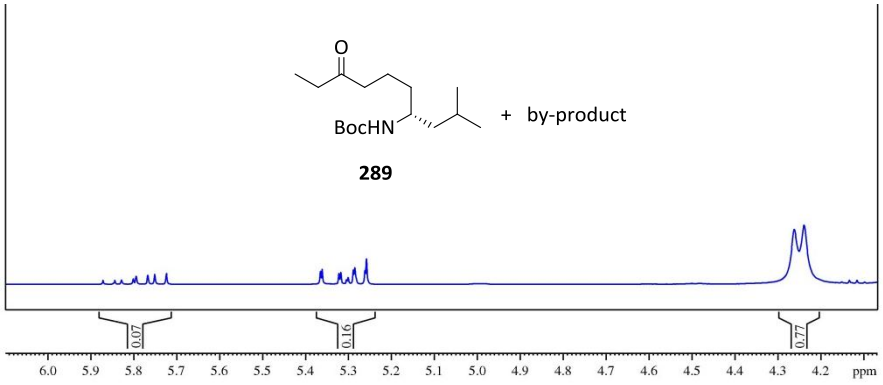
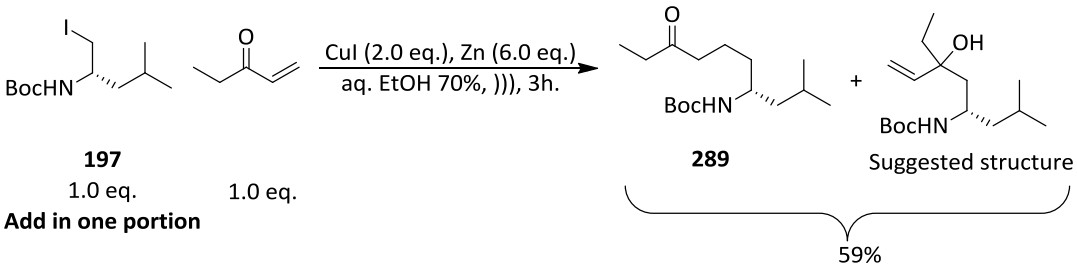


Figure 37

It was thought that the by-product could have resulted from competing nucleophilic addition to the carbonyl group in a Barbier type process (**Scheme 92**). This competition comes from the addition of alkyl iodide (1.0 equivalent) in one portion to the enone in the reaction mixture, which may evaporate during the reaction time due to its low boiling point (38.0 ^{o}C).

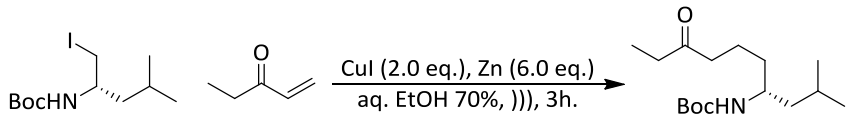


Scheme 92

However, optimization studies established that the best conditions under which to perform this reaction was by addition of a solution of the alkyl iodide in ethanol using a syringe over 30-45 minutes to a dilute solution of two equivalents of the enone.

As described in the literature,[86] the reaction flask and second empty flask were placed in the ultrasonic cleaning bath above the transducers. The positions of both flasks were altered until a standing wave was achieved (**Figure 38**).

Finally, these optimized conditions were combined to provide optimum conditions for the free radical conjugate addition reaction (**Scheme 93, Figures 38** and **39**).



197
1.0 eq.

2.0 eq.

289
57%

Optimized conditions: 2.0 eq. of enone in aq. EtOH 70%, 2.0 eq. of CuI, 6.0 eq. of Zn dust, 1.0 eq. of alkyl iodide dissolved in aq. EtOH 70% added *via* syringe over 30-45 min.

Scheme 93: Optimization of reaction conjugate addition

Figure 38: Optimum conditions for the ultrasonic cleaning, with a perfectly smooth water surface

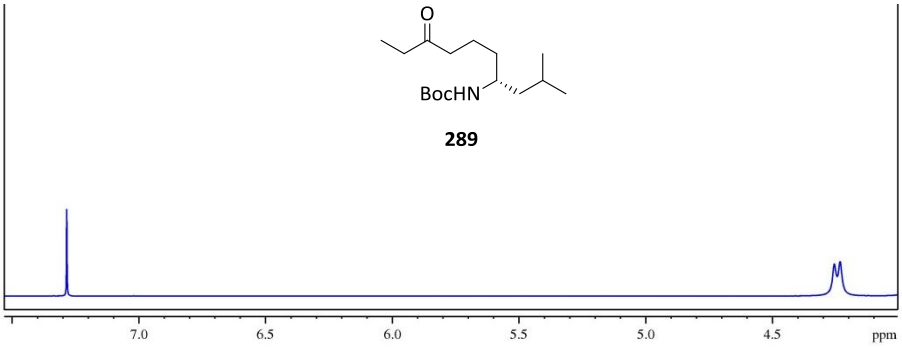
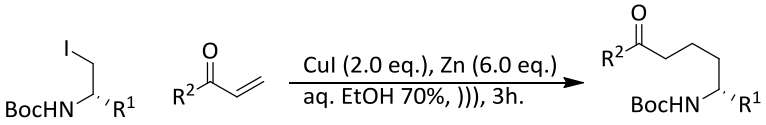


Figure 39

Our attention then turned to exploring the scope of this conjugate addition of a range of free radicals derived from chiral functionalized alkyl iodides to different enones. The reaction proved to be reliable and general (**Scheme 94** and **Table 16**).



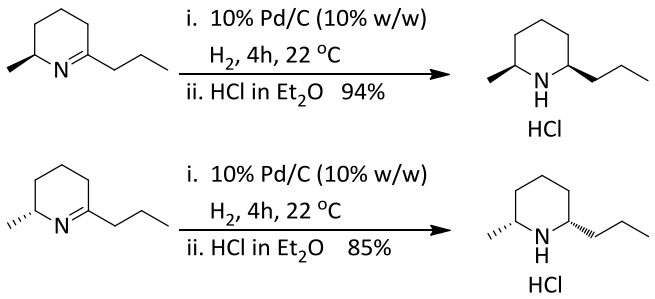
Scheme 94: Synthesis of 5-oxo amines

Table 16: Synthesis of 5-oxo amines **184-185, 286-292**

5-oxo amine	R^1	R^2	(yield, %)
184	(*S*-)CO_2Me	Me	56
185	(*S*-)CO_2Me	Et	51
286	(*R*-)^{i}Pr	Me	60
287	(*R*-)^{i}Pr	Et	61
288	(*R*-)^{i}Bu	Me	59
289	(*R*-)^{i}Bu	Et	57
290	(*R*-)Bn	Me	63
291	(*R*-)Bn	Et	69
292	(*R*-)$CH_2CH_2CO_2Me$	^{n}Pr	63

With efficient access to a range of 5-oxo amines, attention now turned to deprotection, and reductive amination to give our target 2,6-disubstituted piperidines. Given the previous results from Abdelsalam (**Scheme 43, Table 7,**

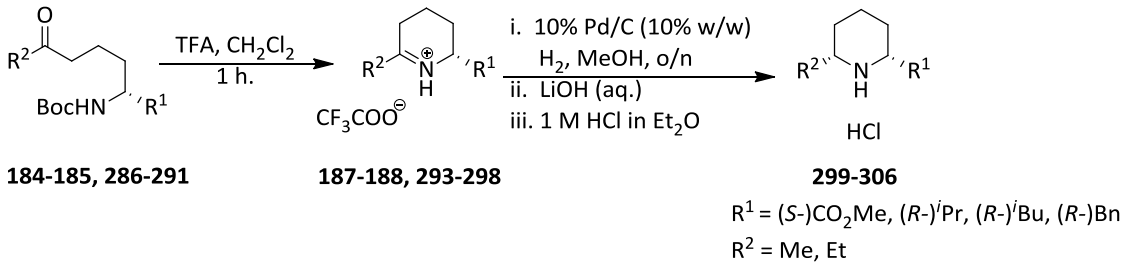
Page 42),[65] which established that reduction of the cyclic iminium salts with $NaBH_4$/MeOH resulted in moderate diastereoselectivity (~ **6:1**, ***cis*** : ***trans***), we decided to investigate alternative reducing agents. Given the encouraging precedent from Kroutil and co-workers in the synthesis of 2,6-disubstituted piperidines with excellent stereoselectivity (>99% *de*) using H_2 in the presence of Pd/C (10% w/w) (**Scheme 95**),[73] we decided to explore catalytic hydrogenation.



Scheme 95: Kroutil and co-workers hydrogenation

2.4.4 Deprotection and Hydrogenation

Treatment of each of the protected 5-oxo amines with TFA in dichloromethane resulted in deprotection and cyclisation to give the iminium salts in quantitative yields. These cyclic iminium salts were each subjected to hydrogenation without further purification. The hydrogenation was carried out using Pd/C (10% w/w) at ambient pressure and temperature in methanol, to give the desired 2,6-disubstituted piperidines in excellent yields (85-91%) (**Scheme 96**, **Table 17**).



184-185, 286-291 **187-188, 293-298** **299-306**

R^1 = (*S*-)CO_2Me, (*R*-)^{i}Pr, (*R*-)^{i}Bu, (*R*-)Bn

R^2 = Me, Et

Scheme 96: Synthesis of 2,6-disubstituted piperidines **299-306**

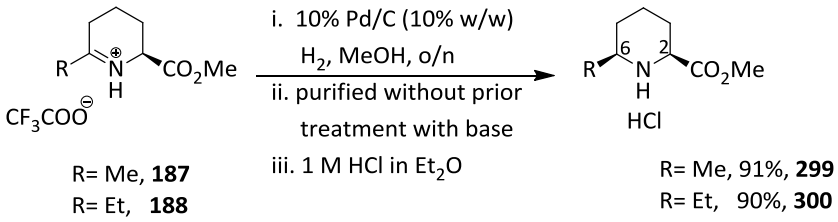
Table 17: Synthesis of 2,6-disubstituted piperidines **299-306**

starting material	R^1	R^2	product	(yield, %)	*dr* [a]
187	(*S*-)CO_2Me	Me	**299**	91	>19:1
188	(*S*-)CO_2Me	Et	**300**	90	>19:1
293	(*R*-)^{i}Pr	Me	**301**	91	>19:1
294	(*R*-)^{i}Pr	Et	**302**	89	>19:1
295	(*R*-)^{i}Bu	Me	**303**	88	>19:1
296	(*R*-)^{i}Bu	Et	**304**	85	>19:1
297	(*R*-)Bn	Me	**305**	89	>19:1
298	(*R*-)Bn	Et	**306**	88	>19:1

a: Determined from ^{1}H NMR analysis of the crude reaction mixture.

Since low molecular weight piperidines are volatile, the products of reductive amination were converted to the free amine by treatment with an aqueous solution of LiOH, followed by conversion to the HCl salt using HCl in Et_2O. The resulting crude hydrochloride salts were purified by flash column chromatography on silica, using methanol in dichloromethane as eluent to give 2,6-disubstituted piperidine hydrochloride salts (**Scheme 96** and **Table 17**). The diastereoselectivity was estimated as **>19:1** (***cis*** : ***trans***) from ^{1}H NMR analysis of the crude reaction mixture on the basis that only one isomer was evident.

However, in the case of compounds **299** and **300** (R^1 = CO_2Me), the purification process resulted in the isolation of two diastereoisomeric products as determined by ^{1}H NMR analysis (**Figure 40**). In order to attempt to prevent the presumed epimerization, the crude products of **299** and **300** were each purified *via* flash column chromatography without prior treatment with base. The free amine products were each converted to the corresponding hydrochloride salts by treatment with HCl in Et_2O to give the desired compounds (**Scheme 97**). The ^{1}H NMR analysis now showed the presence of only one diastereoisomer in each case (**Figures 40** and **41**).



Scheme 97: Optimized conditions for the synthesis of **299** and **300**

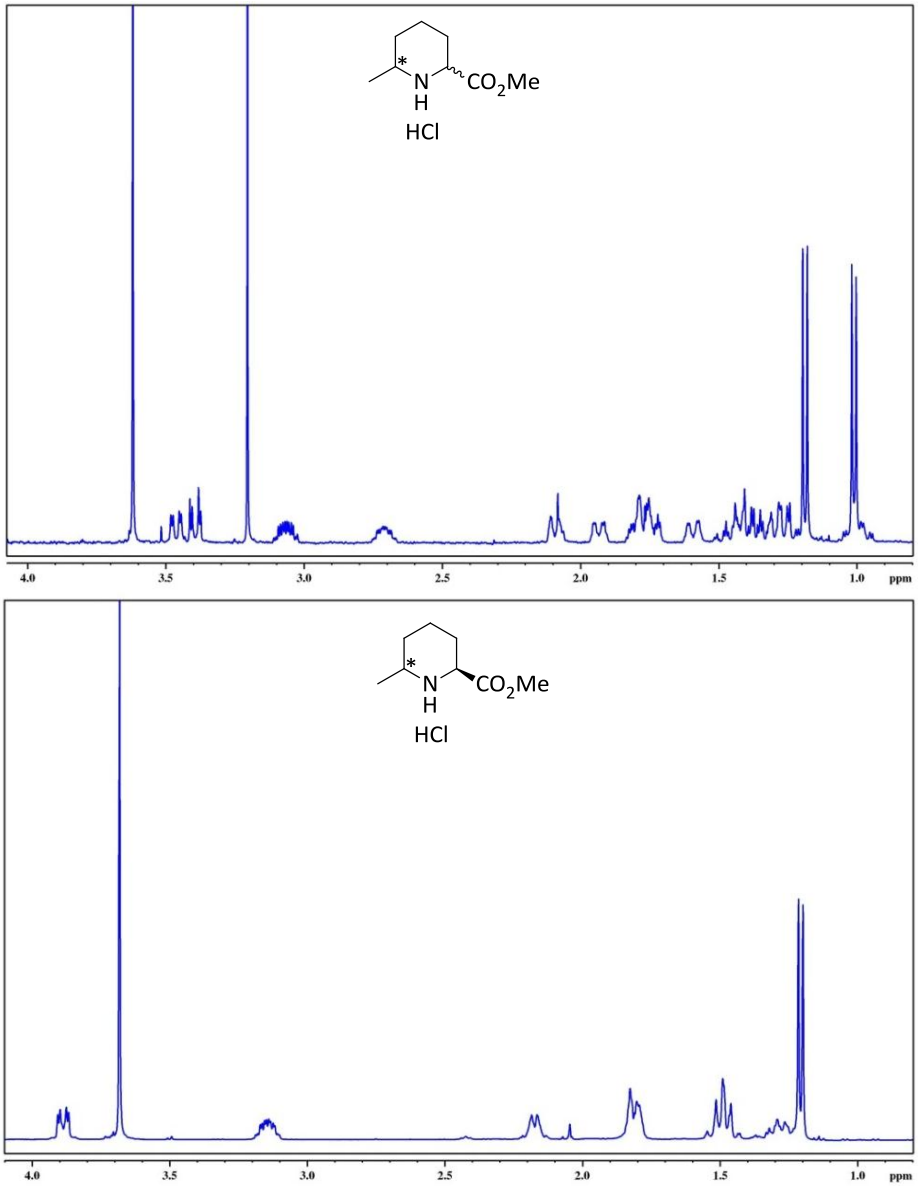


Figure 40: ^{1}H NMR spectrum for the compound **299** after purification

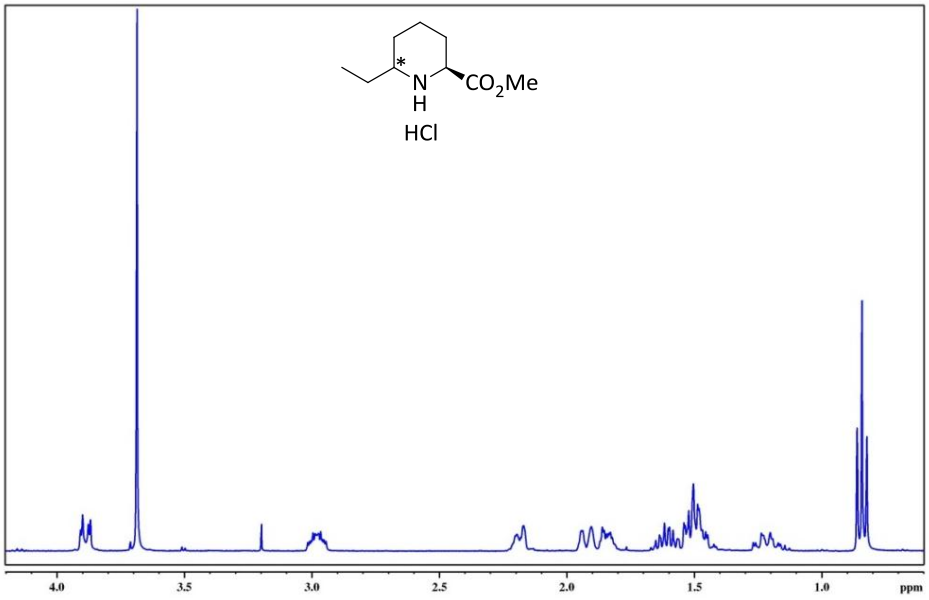


Figure 41: ^{1}H NMR spectrum for the compound **300** without base treatment

2.4.5 Determination of configuration for the compounds 301, 302, and 304 by X-ray diffraction:

The stereochemistry of the compounds **301**, **302** and **304** was established unambiguously by single crystal X-ray diffraction, which established that these compounds are all *cis*-diastereoisomers. In each case, the substituents at **C-2** and **C-6** were (unsurprisingly) equatorial (**Figures 42-44**).

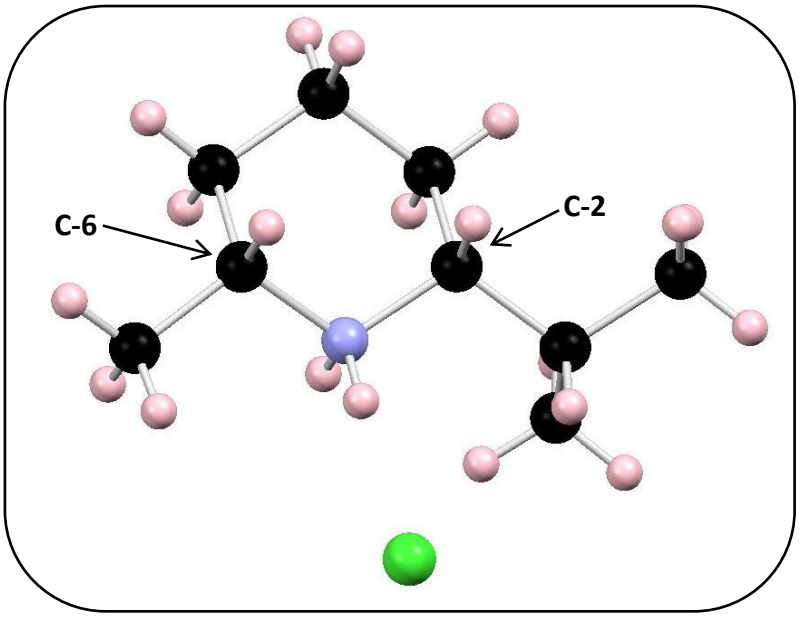


Figure 42: Crystal structure of the product **301** which confirms *cis*-configuration

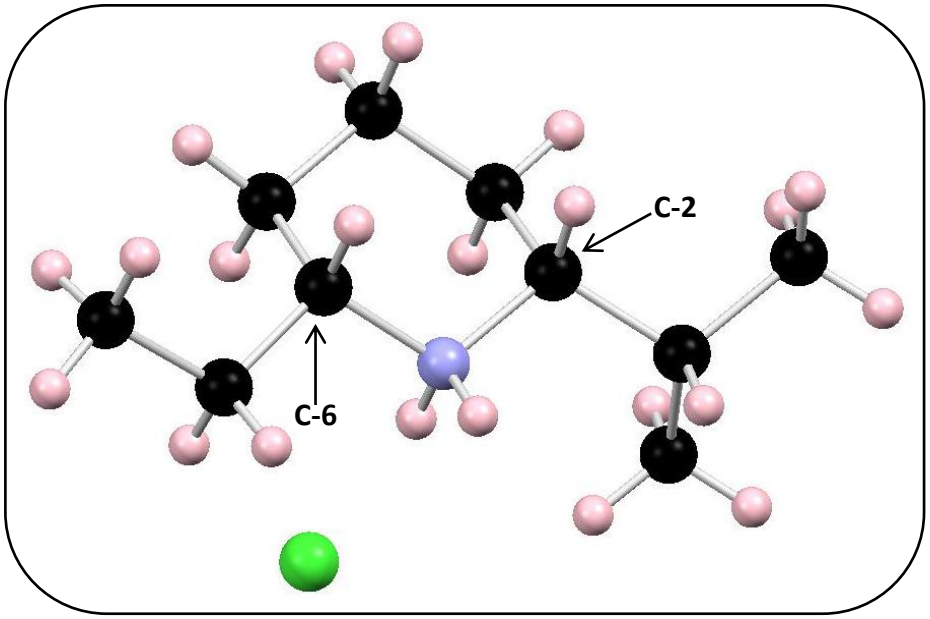


Figure 43: Crystal structure of the product **302** which confirms *cis*-configuration

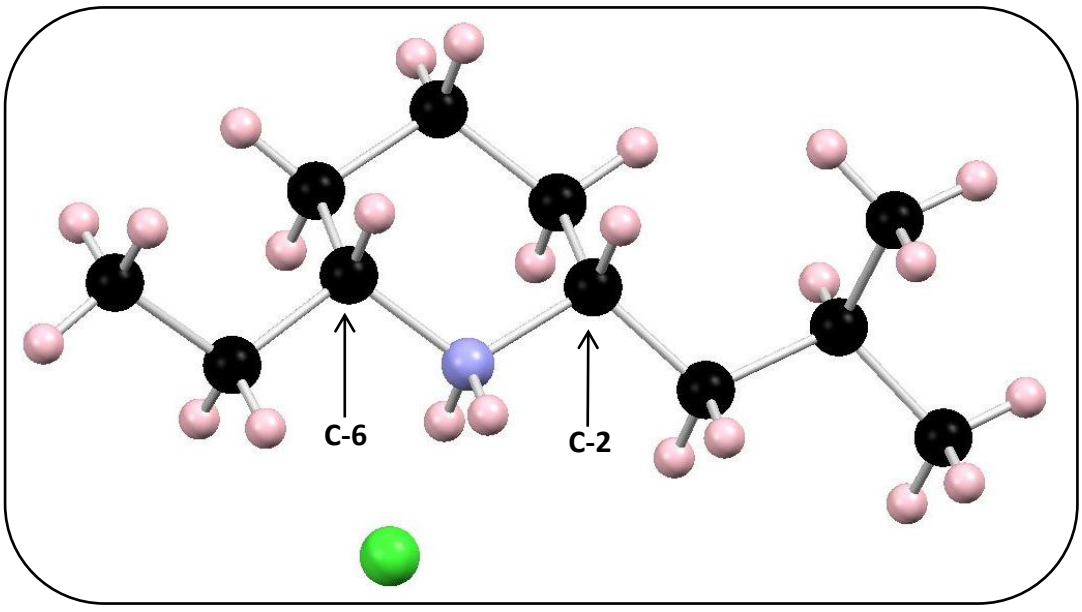


Figure 44: Crystal structure of the product **304** which confirms *cis*-configuration

Having established the configuration of the three compounds **301**, **302** and **304**, we wondered now how to establish their conformation in solution.

2.4.6 Determination of conformation for the compounds 301, 302, and 304 by ^{1}H NMR:

The **C-2** and **C-6** substituents can exist in either an axial or an equatorial position. With both substituents on the same face of the ring (***cis*-isomer**), they can be arranged *either* **C-2 eq/C-6 eq** (**Conformer A**) with diaxial protons in **C-2** and **C-6**, which gives largest *J*-values (~11-15 Hz) (diaxial coupling). O*r* **C-2 ax/C-6 ax** (**Conformer B**) (**Figure 45**).

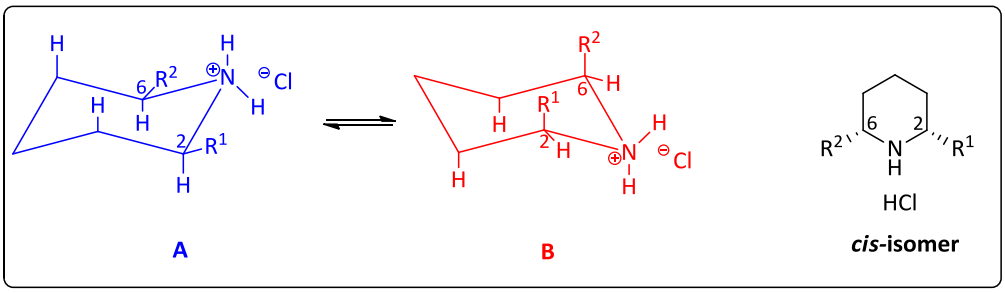
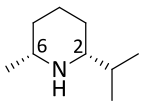


Figure 45

The multiplicities and coupling constants for all products were determined using Bruker TopSpin™ 3.2.

- **Compound 301**



301

The ^{1}H NMR spectrum for the compound **301** shows a doublet of doublets of doublets for the proton at C-2 (2.81 ppm), with a large (12.0 Hz), as well as medium (5.5 Hz) and small (3.0 Hz) coupling constants. The large value arises from vicinal coupling with the axial proton at C-3 (diaxial coupling), the medium value is a consequence of coupling to the iso-propyl proton at C-2, and the small value derives from the equatorial proton at C-3 (**Figure 46**). The *J* values suggests the proton at C-2 must be in the axial position and the iso-propyl group therefore equatorial (**Figure 45**).

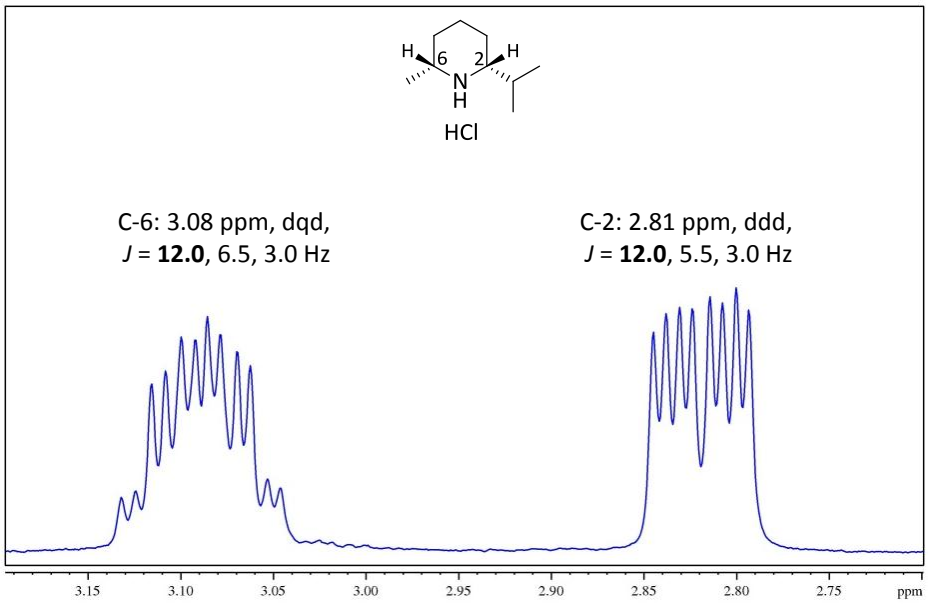
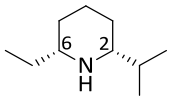


Figure 46: ^{1}H NMR signals of the protons at C-2 and C-6 for the compound **301**

The signal for the proton at C-6 (3.08 ppm) is a doublet of quartet of doublets and displays a large (12.0 Hz), a medium (6.5 Hz) and a small (3.0 Hz) coupling constants. The large value comes from the interaction between the proton at C-6 and the axial proton at C-5 (diaxial coupling), the medium value is due to the methyl protons at C-6, and the small value derives from the equatorial proton at C-5 (**Figure 46**), which establishes that the proton at C-6 is in the axial position and the methyl group must be equatorial (**Conformer A, Figure 45**). This establishes that the solution state conformation is the same as that found in the solid state. Spectroscopic data closely matched those reported previously by Kroutil and co-workers for its enantiomer.[73]

➢ **Compound 302**



HCl

302

The ^{1}H NMR spectrum for the compound **302** shows a multiplet for the proton at C-2 (2.80-2.87 ppm), and the signal for the proton at C-6 (2.87-2.95 ppm) is also a multiplet (**Figure 47**). However, we were expected to see a doublet of doublets of doublets for the proton at C-2, there is a similarity between the relative shape and relative chemical shifts for the signals of C-2/C-6 with that for C-2/C-6 in **Figure 46**. Therefore, the protons at C-2 and C-6 are in the axial position, and the iso-propyl group and ethyl group are equatorial (which is favoured) (**Conformer A, Figure 45**). This establishes that the solution state conformation is the same as that found in the solid state.

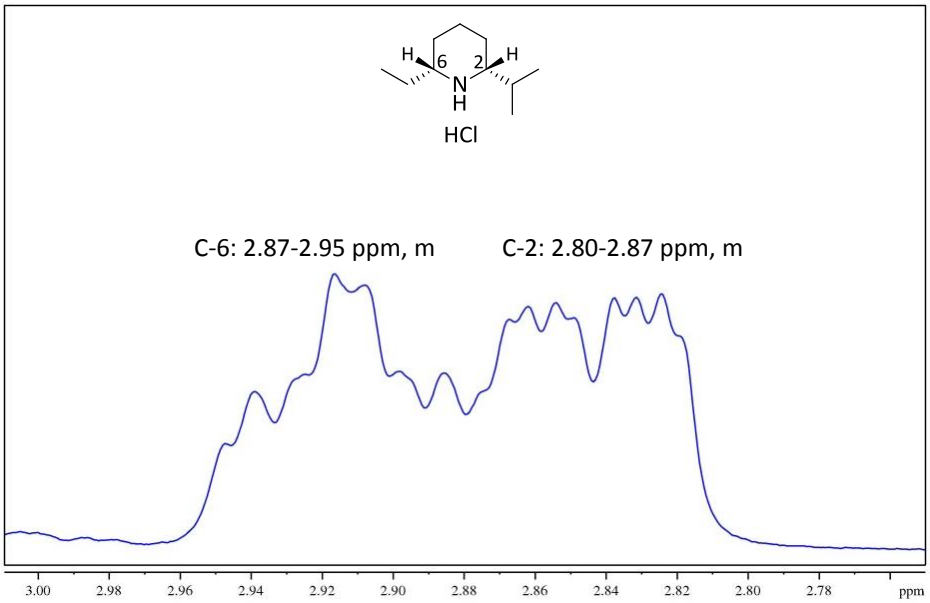
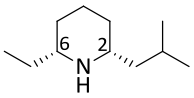


Figure 47: ^{1}H NMR signals of the protons at C-2 and C-6 for the compound **302**

- **Compound 304**



304

In compound **304**, C-2 and C-6 are each connected to a methylene group. Hence, it is difficult to distinguish between them in the ^{1}H NMR spectrum. The signals for the proton at C-2 and the proton at C-6 are similar, which is consistent with a similar environment for these protons.

The signals for the both protons at C-2 and C-6 (2.84-2.94 and 2.98-3.09 ppm) are multiplet respectively (**Figure 48**). Since the configuration of compound **304** was established by X-ray crystallography as the *cis*-isomer, it was thought the stereochemistry at C-2/C-6 are the same. The comparison between the relative chemical shifts for the signals of C-2/C-6 and that for C-2/C-6 in **Figure 46** and **Figure 47**, these show a reasonable similarity. Therefore, the protons at C-2 and C-6 must be in the axial positions, the iso-butyl and ethyl groups equatorial (which is favoured) (**Conformer A, Figure 45**). This establishes that the solution state conformation is the same as that found in the solid state.

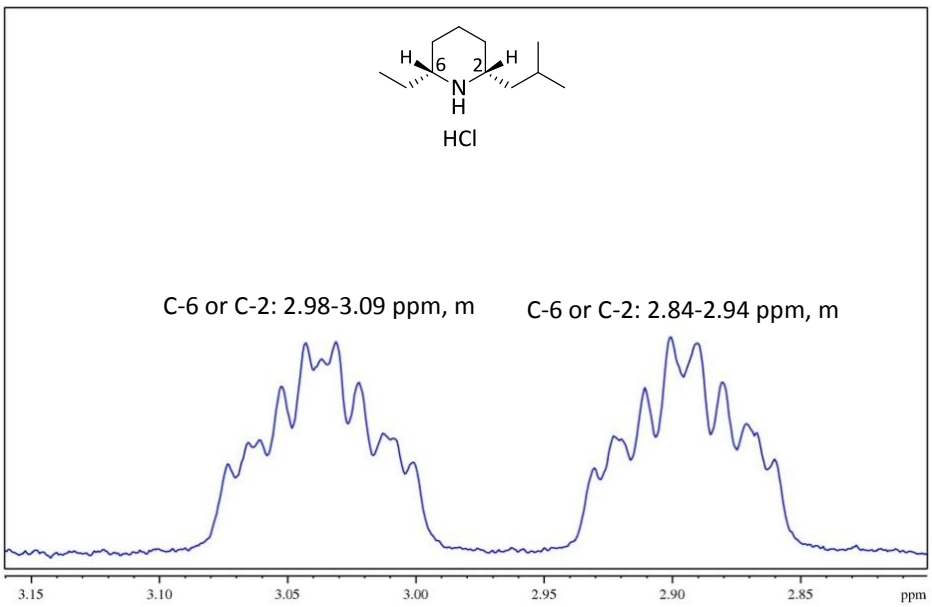
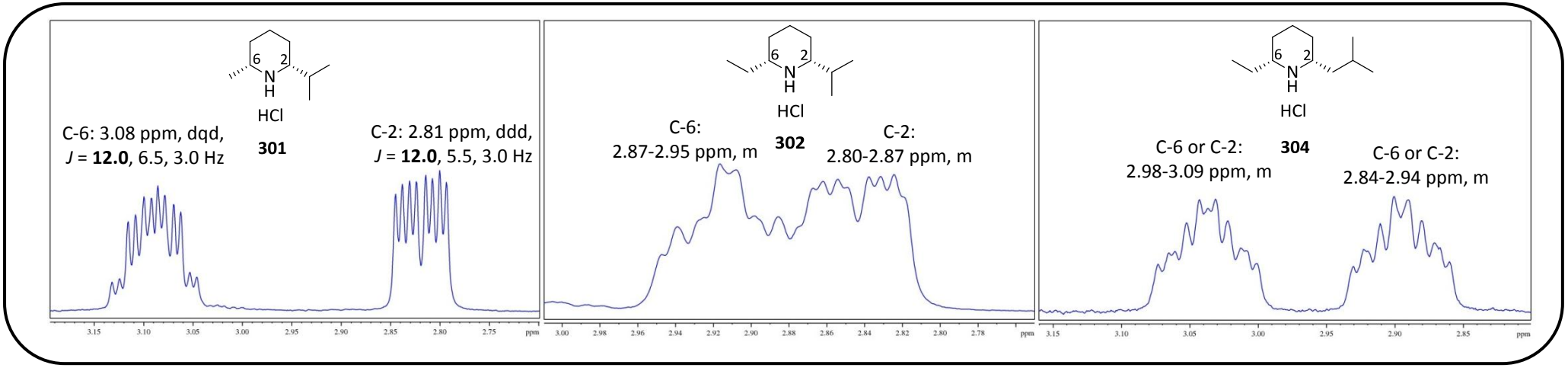


Figure 48: ^{1}H NMR signals of the protons at C-2 and C-6 for the compound **304**

Having established that each of the compounds **301**, **302** and **304** adopts the same conformation in solution as in the solid state, this provides a basis for assigning the configuration of the remaining products using ^{1}H NMR alone.

The ^{1}H NMR data for the compounds **301**, **302** and **304** are summarized in **Figure 49**.



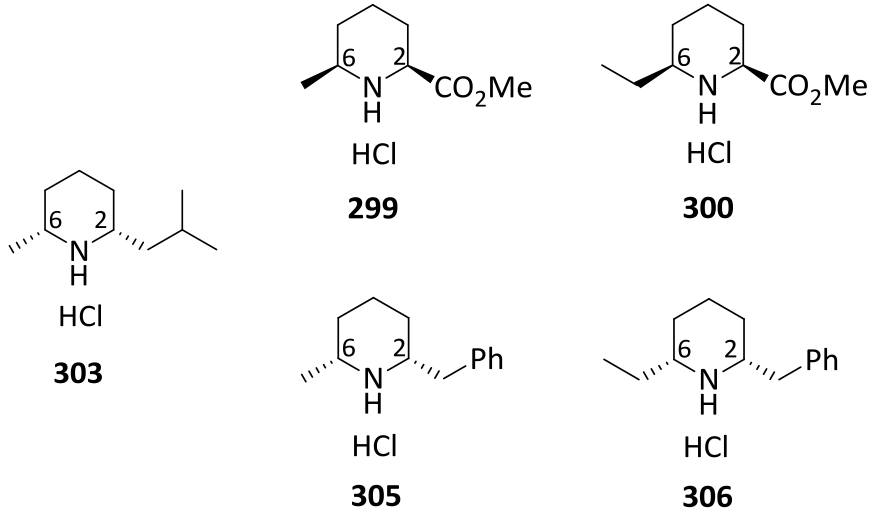
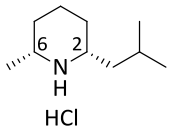


Figure 49: 2,6-disubstituted piperidines **299-306**

- **Compound 303**



303

The ^{1}H NMR spectrum shows a multiplet for the protons at C-2 and C-6 (2.98-3.11 ppm) (**Figure 50**). Attempts were made to separate the overlapping peaks by running the ^{1}H NMR in deuterated methanol and deuterated dimethyl sulphoxide. However, the signals still overlapped, regardless of the solvent used.

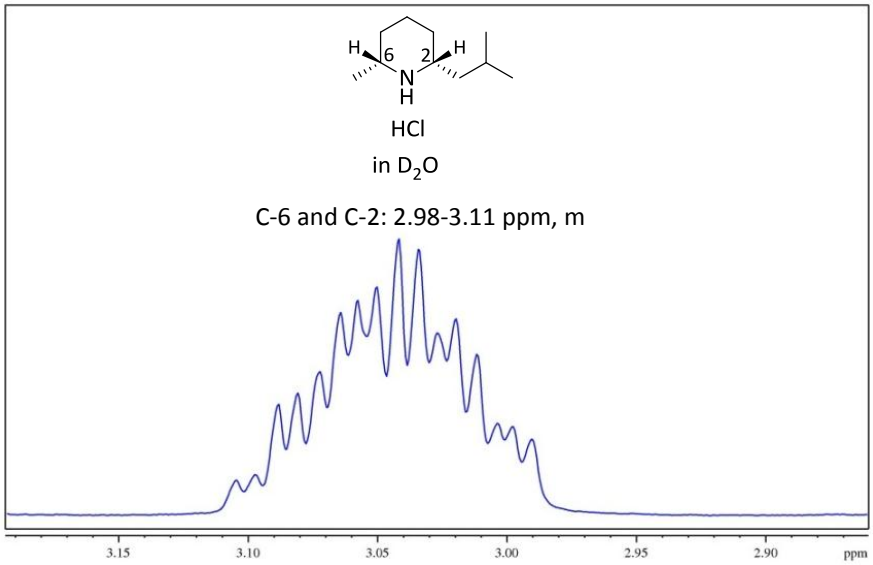
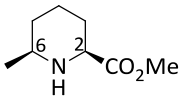


Figure 50: ^{1}H NMR signals of the protons at C-2 and C-6 for the compound **303**

The structure of compound **303** is closely related to compound **304**. Since the configuration of compound **304** was established by X-ray crystallography to be the *cis*-isomer and its conformation in solution also was established as **Conformer A, Figure 45**, it was thought the stereochemical outcome of **304** would be analogous. Moreover, the ^{1}H NMR spectra for both compounds are closely comparable by combination of C-6 from **301** and C-2/C-6 from **304**. Therefore, the protons at C-2 and C-6 is in the axial position, and the iso-butyl group and methyl group are equatorial (**Conformer A, Figure 45**). Spectroscopic data closely matched those reported previously by Molander and co-workers, who established the absolute configuration of the corresponding picrate salt for enantiomer **303** by single-crystal X-ray diffraction analysis.[87]

- **Compound 299**



299

The ^{1}H NMR spectrum for the compound **299** shows a doublet of doublets for the proton at C-2 (3.88 ppm), with a large (12.0 Hz) and a small (3.0 Hz) coupling constant (**Figure 51**). The large value arises from vicinal coupling with the axial proton at C-3 (diaxial coupling), which establishes that the proton at C-2 must be in the axial position and ester group therefore must be equatorial (**Figure 45**).

The signal for the proton at C-6 (3.09-3.19 ppm) is a multiplet (**Figure 51**). The comparison between relative shape and relative chemical shift for the proton at C-6 with that for C-6 in **Figure 46**, allowed us to assign the stereochemistry. Therefore, the proton at C-6 is axial and the methyl group equatorial (**Conformer A, Figure 45**).

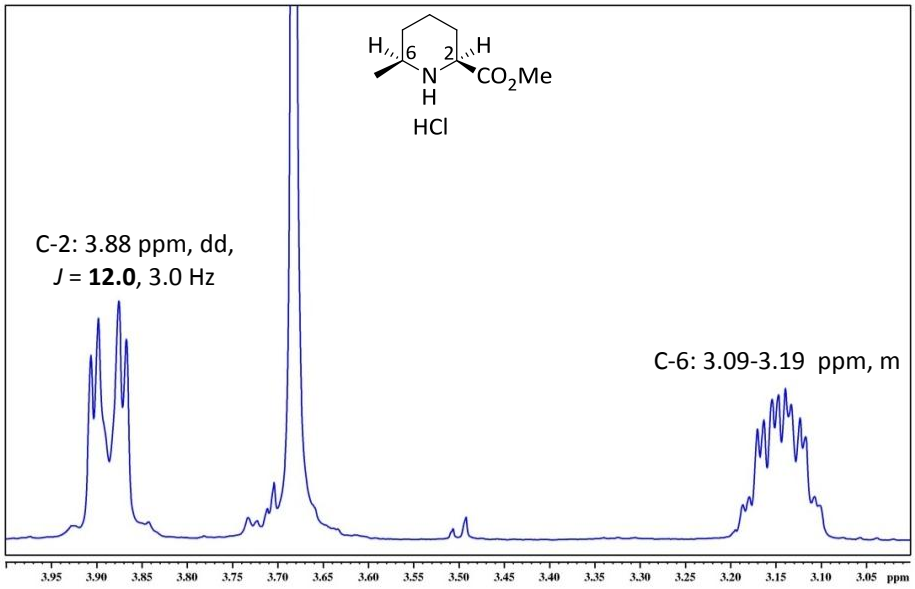
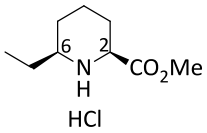


Figure 51: ^{1}H NMR signals of the protons at C-2 and C-6 for the compound **299**

- **Compound 300**



300

The ^{1}H NMR spectrum for the compound **300** shows a doublet of doublets for the proton at C-2 (3.88 ppm), with a large (12.0 Hz) and a small (3.0 Hz) coupling constant (**Figure 52**). The large value is an outcome of vicinal coupling with the axial proton at C-3 (diaxial coupling), which establishes that the proton at C-2 must be in the axial position and ester group therefore must be equatorial (**Figure 45**).

The signal for the proton at C-6 (2.92-3.02 ppm) is a multiplet (**Figure 52**). The stereochemistry was assigned by comparison the relative shape and relative chemical shift for the proton at C-6 with that for C-2/C-6 in **Figure 48**. Therefore, the proton at C-6 must be in the axial position and the ethyl group equatorial (**Conformer A, Figure 45**).

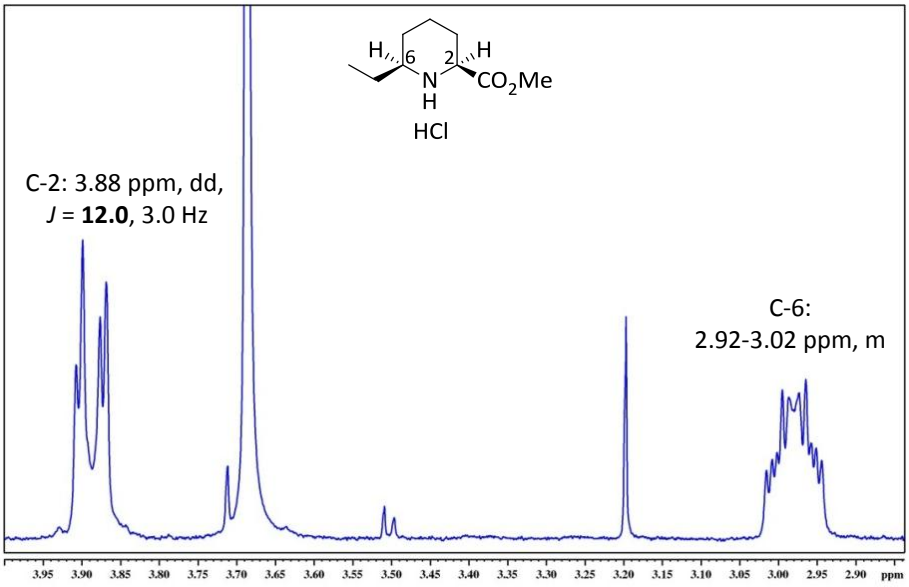
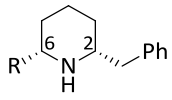


Figure 52: ^{1}H NMR signals of the protons at C-2 and C-6 for the compound **300**

- **Compounds 305 and 306**



HCl

R= Me, **305**
R= Et, **306**

The final task was to establish the relative configuration of compounds **305** and **306**. The free amine *trans*-isomer of **305** has been reported in the literature. [88]

In order to assign the stereochemistry of **305**, we converted it from hydrochloride salt form to the free amine by treatment with base, and compared its ^{13}C NMR data with *trans*-isomer which was previously reported by Craig and co-workers.[88] The ^{13}C NMR data are given in **Table 18**.

Table 18

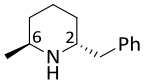
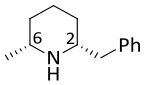
Craig's results 		**Our results** 
^{13}C NMR (75 MHz, $CDCl_3$) δ		**^{13}C NMR (100 MHz, $CDCl_3$) δ**
19.6		22.9
21.0		24.8
30.3		32.2
32.7		34.1
40.3		43.8
45.9		52.4
52.7		58.5
126.1		126.1
128.5		128.4
129.1		129.2
139.8		139.3

Table 18 shows that the ^{13}C NMR data of our compound is different from Craig's results (*trans*-isomer),[88] which suggests we have different diastereoisomer (*cis*-isomer).

The ^{1}H NMR spectrum for the compound **305** showed a multiplet for the proton at C-2 (3.12-3.22 ppm), and the signal for the proton at C-6 (2.93-3.04) is also a multiplet (**Figure 53**). Since the stereochemistry at C-2 was established as (*R*) from starting material and we know that the compound **305** is *cis*-isomer. Therefore, the stereochemistry was assigned by comparison the relative shape and relative chemical shift for the protons at C-2/C-6 with that for C-2/C-6 in **Figure 46**. Thence, the proton at C-6 must be in the axial position and the methyl group equatorial (**Conformer A, Figure 45**).

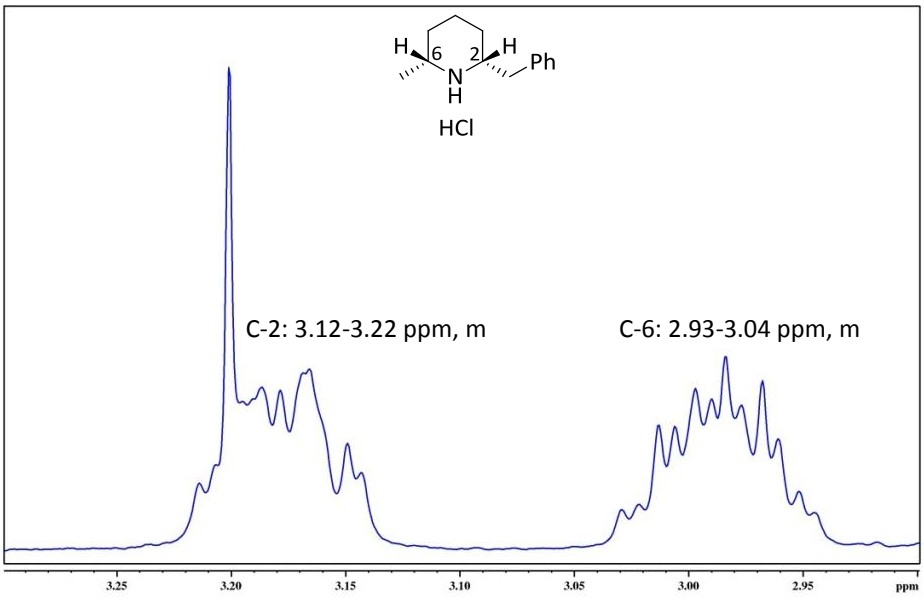


Figure 53: ^{1}H NMR signals of the protons at C-2 and C-6 for the compound **305**

The ^{1}H NMR spectrum for the compound **306** showed a multiplet for the proton at C-2 (3.14-3.25 ppm), and the signal for the proton at C-6 (2.80-2.85 ppm) is also a multiplet (**Figure 54**). The structure of compound **306** is closely related to compound **305**, since the conformation in solution of compound **305** was established as **Conformer A, Figure 45**, it was thought the stereochemical outcome of **305** would be analogous. Moreover, if we compare the relative shape and relative chemical shift for the protons at C-2/C-6 with that for C-2/C-6 in **Figure 53**, they show a reasonable similarity. Therefore, the protons at C-2 and C-6 must be in the axial positions, the benzyl and ethyl groups equatorial (which is favoured) (**Conformer A, Figure 45**).

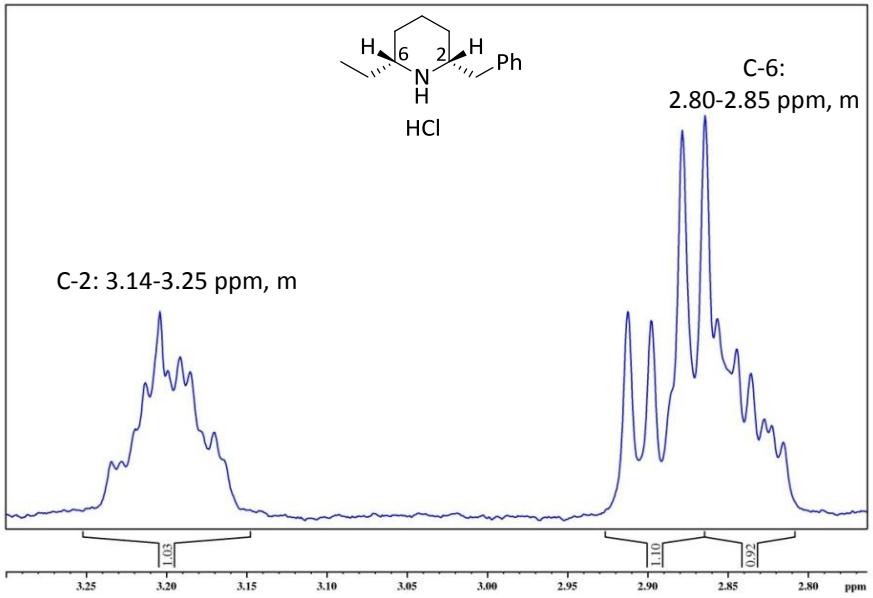


Figure 54: ^{1}H NMR signals of the protons at C-2 and C-6 for the compound **306**

The ^{1}H NMR data for the compounds **299**-**306** are summarized in **Figure 55**.

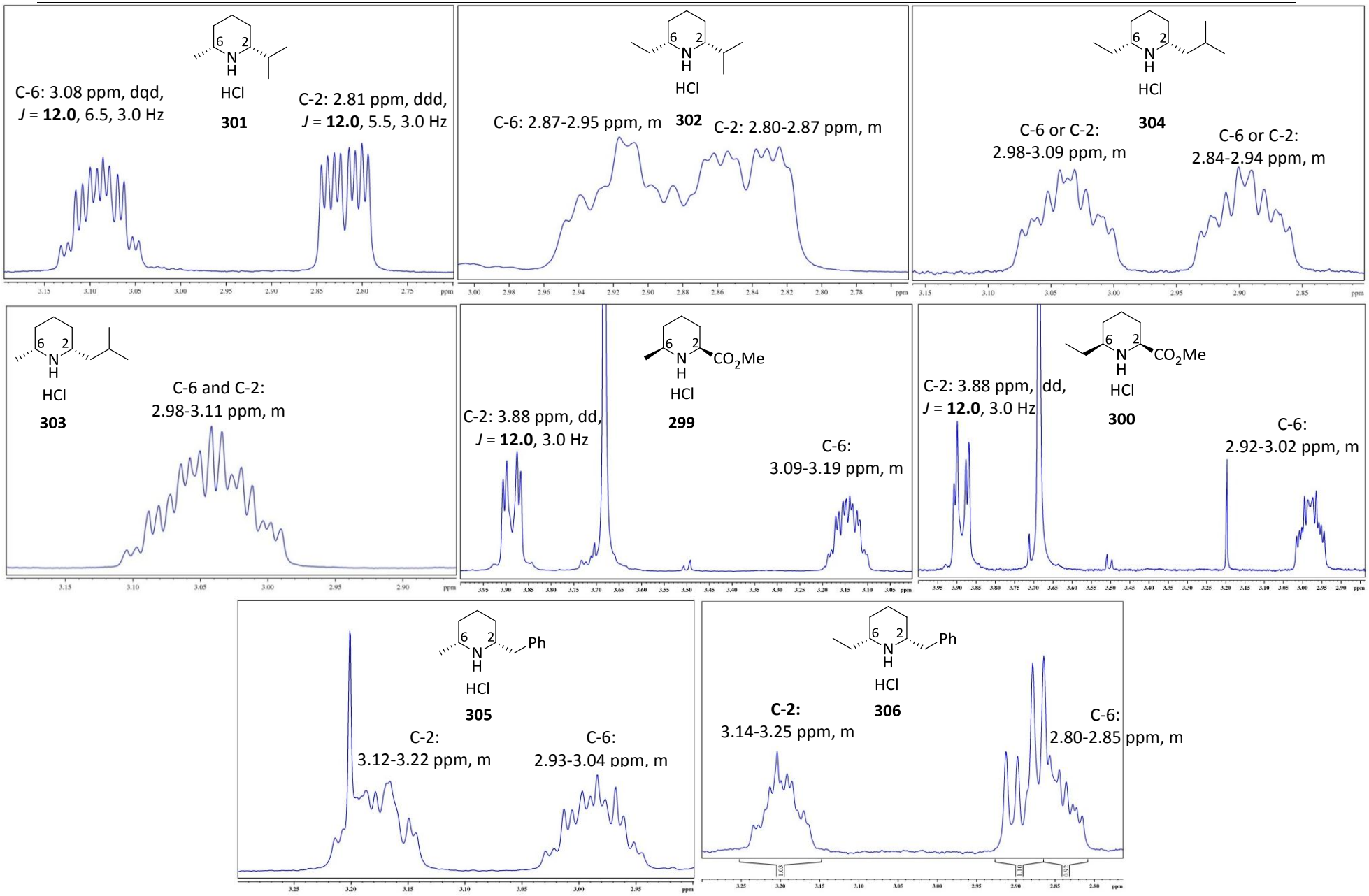


Figure 55: 2,6-disubstituted piperidines **299-306**

2.5 Conclusion

In conclusion, we have developed a straightforward and diastereoselective approach for the synthesis of ***cis***-2,6-disubstituted piperidines.

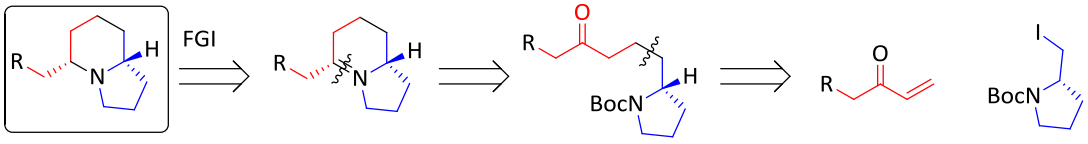
Using a range of β-amino alkyl iodides derived from amino acids, 1,4-free radical conjugate addition methodology allows access to 5-oxo amines in useful yields (**Scheme 94 and Table 16**).

Deprotection of 5-oxo amine precursors to yield the iminium salts, followed by diastereoselective reductive amination gave *cis*-2,6-disubstituted piperidines in excellent yields and with diastereomeric ratio **>19:1** (***cis : trans***) (**Scheme 96** and **Table 17**).

2.6 Synthesis of indolizidines

2.6.1 Introduction

Given the successful synthesis of *cis*-2,6-disubstituted piperidines, we considered that the approach could be extended to the synthesis of indolizidines, particularly (-)-indolizidine 167B (**5**) and (-)-indolizidine 195H (**6**). Our retrosynthetic analysis is shown below (**Scheme 98**).

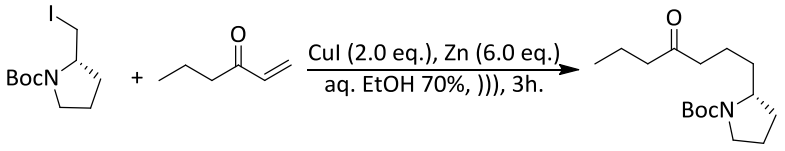


5, R= Et, (-)-Indolizidine 167B.
6, R= ^{n}Bu, (-)-Indolizidine 195H.

Scheme 98: Retrosynthetic approach to (-)-indolizidine 167B and (-)-indolizidine 195H

2.6.2 Results and discussion

Alkyl iodide **195** derived from enantiomerically pure L-proline[89] was subjected to the free radical conjugate addition conditions with 1-hexen-3-one **307** and gave the expected compound **308** in good yield (75%) (**Scheme 99**).



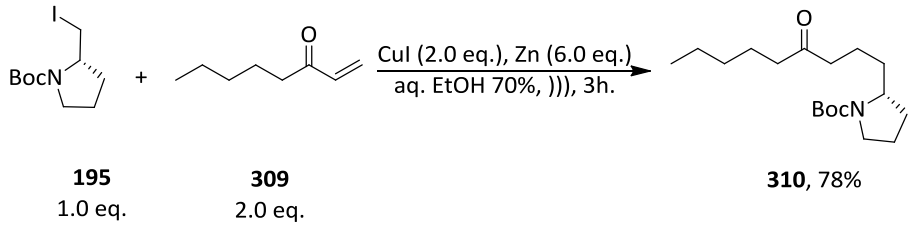
195
1.0 eq.

307
2.0 eq.

308, 75%

Scheme 99: Synthesis of compound **308**

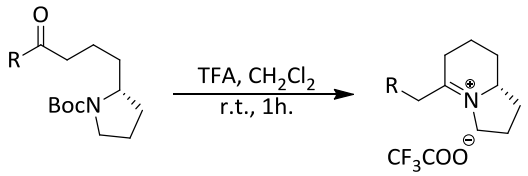
Similarly, treatment of the iodide **195** with 1-octen-3-one **309** under the same conditions gave the desired product **310** in very good yield (78%) (**Scheme 100**).



195 1.0 eq. **309** 2.0 eq. **310**, 78%

Scheme 100: Synthesis of compound **310**

Treatment of each protected amino ketones **308** and **310** with TFA in dichloromethane resulted in deprotection and cyclisation to the iminium salts **311** and **312** in quantitative yields (**Scheme 101**).



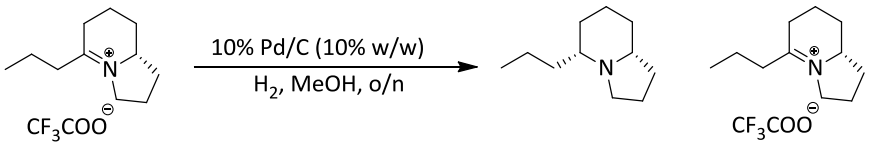
R= Et, **308**
R= ^{n}Bu, **310**

R= Et, **311**
R= ^{n}Bu, **312**

Scheme 101

2.6.3 (-)-Indolizidine 167B and (-)-Indolizidine 195H

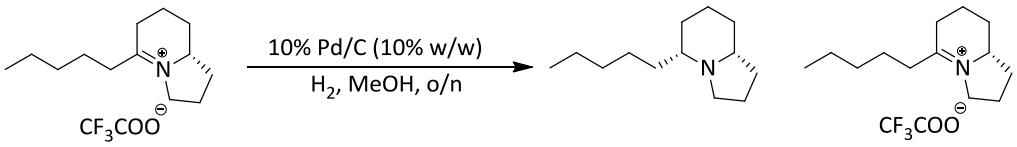
The stereoselective hydrogenation of cyclic iminium trifluoroacetate salts **311** and **312** was expected to provide the desired indolizidines. With this in mind, the hydrogenation of iminium salt **311** was carried out using Pd/C (10% w/w) at ambient pressure and temperature in methanol for one day (**Scheme 102**). The ^{1}H NMR spectrum of the crude product showed the expected compound **5** as well as some starting material.



311 **5** Trace amount

Scheme 102

Hydrogenation of compound **312** gave a similar result under the same conditions (**Scheme 103**). According to the ^{1}H NMR spectrum of the crude product, the expected compound was formed and starting material was also observed in a trace amount.

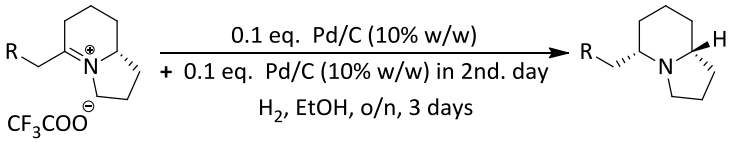


312 **6** Trace amount

Scheme 103

It was thought that the incomplete hydrogenation reaction could be because the reaction time was not long enough. Thus, we left the hydrogenation reaction for an extended time (2-3) days. However, the unwanted signals remained in the ^{1}H NMR spectra for both substrates. The most likely explanation was poisoning of the catalyst. So, more catalyst was added to the reaction mixture in the second day. After three days, the ^{1}H NMR spectra still showed the unwanted signals for both molecules.

Finally, we considered that the choice of solvent might be important, we noticed that both starting materials dissolved in ethanol better than in methanol. Hydrogenation of iminium salts **311** and **312** was carried out using Pd/C (10% w/w) at ambient pressure and temperature in ethanol for three days, adding more catalyst to each reaction mixture on the second day. This gave the desired products **5** and **6** respectively without starting material(**Scheme 104**).



R= Et, **311**
R= ^{n}Bu, **312**

R= Et, (-)-Indolizidine 167B, **5**, 72%
R= ^{n}Bu, (-)-Indolizidine 195H, **6**, 76%

Scheme 104: Synthesis of compounds **5** and **6**

The ^{1}H NMR spectra of the crude products now showed the formation of the desired compounds and complete consumption of starting materials (**Figures 56 and 59**).

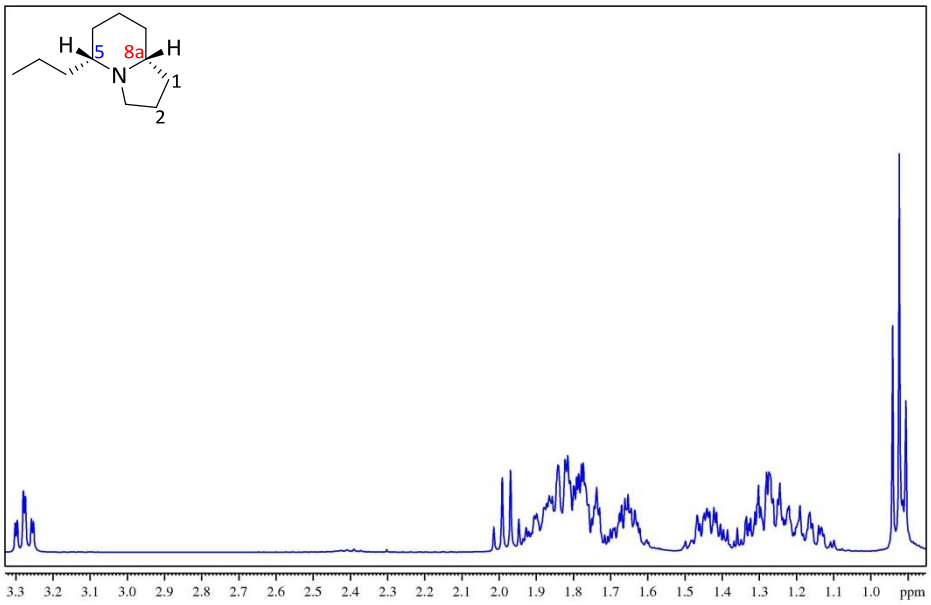


Figure 56: ^{1}H NMR spectrum for (-)-Indolizidine 167B

Physical and spectroscopic data of compound **5** were closely matched those reported in the literature (**Figures 57** and **58**).[46,48] The ^{1}H NMR spectrum shows a doublet of triplet for the methine proton (3.27 ppm), and an apparent quartet for the proton (NC*H*^{n}Pr) (1.97 ppm). The value of the optical rotation for the pure compound **5** $[\alpha]^{25}_{D}$ -98.0, (*c* 1.0, CH_2Cl_2) agreed with the literature (lit. $[\alpha]^{25}_{D}$ -98.0, (*c* 1.0, CH_2Cl_2).[52] We established that the absolute configuration of our products is (5*R,8aR*) (**Table 19**).

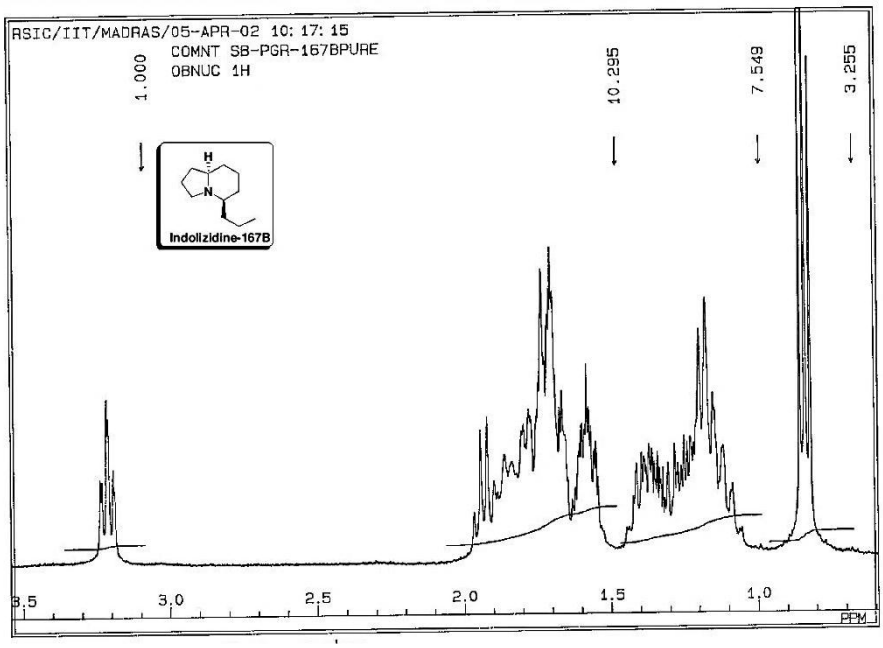


Figure 57: Expanded 1H NMR Spectrum of (-)-Indolizidine 167B [46]

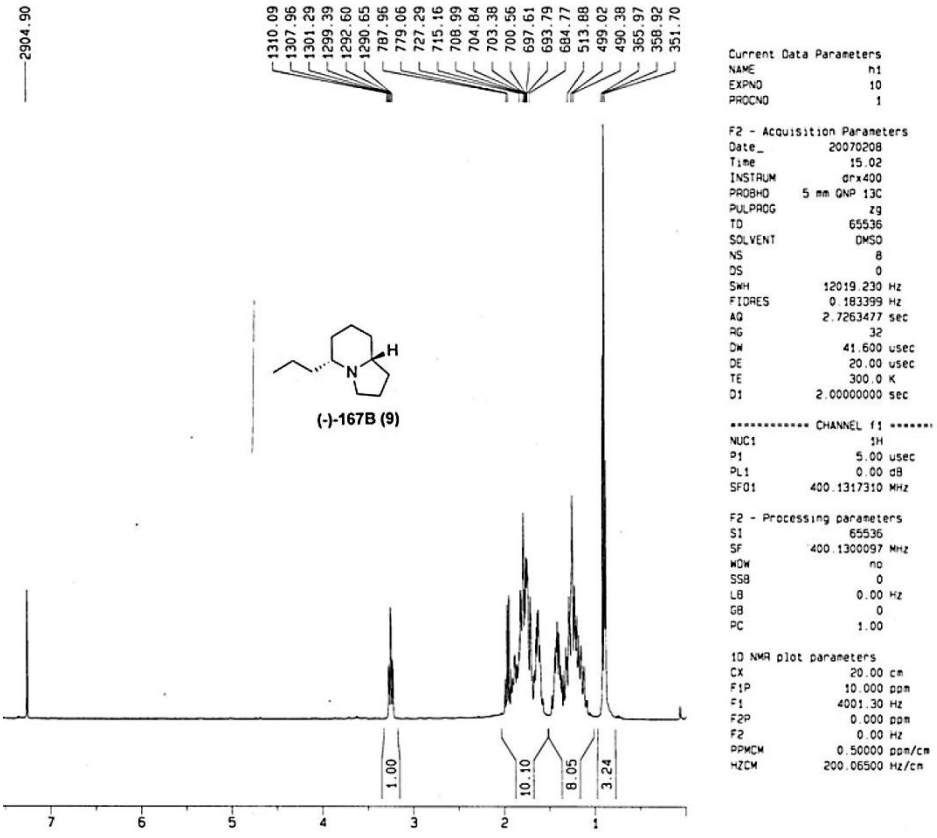
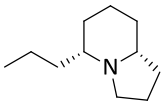


Figure 58: ^{1}H NMR spectrum for (-)-Indolizidine 167B [48]



(5*R*,8a*R*)-5-propyloctahydroindolizine
Chemical Formula: $C_{11}H_{21}N$

Table 19

J. Org. Chem. ***2004***, 69, 3093-3101[46]	*J. Am. Chem. Soc.* ***2007***, 129, 9300-9301[48]	**Our results**
^{1}H NMR (400 MHz, CDCl3) δ	**^{1}H NMR (500 MHz, CDCl3) δ**	**^{1}H NMR (400 MHz, CDCl3) δ**
0.91 (3H, t, *J* = 7.1, C*H*$_3$)	0.90 (3H, t, *J* = 7.1, C*H*$_3$)	0.92 (3H, t, *J* = 7.0, C*H*$_3$)
1.14-1.49 (7H, m, C*H*$_2$)	1.50-1.06 (8H, m, C*H*$_2$)	1.11-1.47 (7H, m, C*H*$_2$)
1.62-1.92 (9H, m, C*H*$_2$)	1.88-1.52 (8H, m, C*H*$_2$)	1.60-1.88 (9H, m, C*H*$_2$)
1.99 (1H, q, *J* = 9.0)	1.95 (1H, t, *J* = 8.9)	1.97 (1H, app. q, *J* = 9.0)
3.28 (1H, dt, *J* = 8.8, 2.4)	3.25 (1H, dt, *J* = 8.8, 2.2)	3.27 (1H, dt, *J* = 9.0, 2.0)
^{13}C NMR (100 MHz, $CDCl_3$) δ	**^{13}C NMR (125 MHz, $CDCl_3$) δ**	**^{13}C NMR (100 MHz, $CDCl_3$) δ**
14.4	14.5	14.5
19.0	19.1	19.4
20.3	20.4	20.4
24.6	24.7	24.7
30.4	30.6	30.5
30.7	30.9	30.8
30.9	31.0	31.0
36.8	36.9	36.9
51.4	51.6	51.5
63.7	63.7	63.7
65.0	65.0	65.0
$[\alpha]_D^{26}$ = -83.5 (*c* 1.3, CH_2Cl_2)	$[\alpha]_D^{23}$= -102.8 (*c* 0.88,CH_2Cl_2)	$[\alpha]_D^{25}$ = -98.0 (*c* 1.0, CH_2Cl_2)

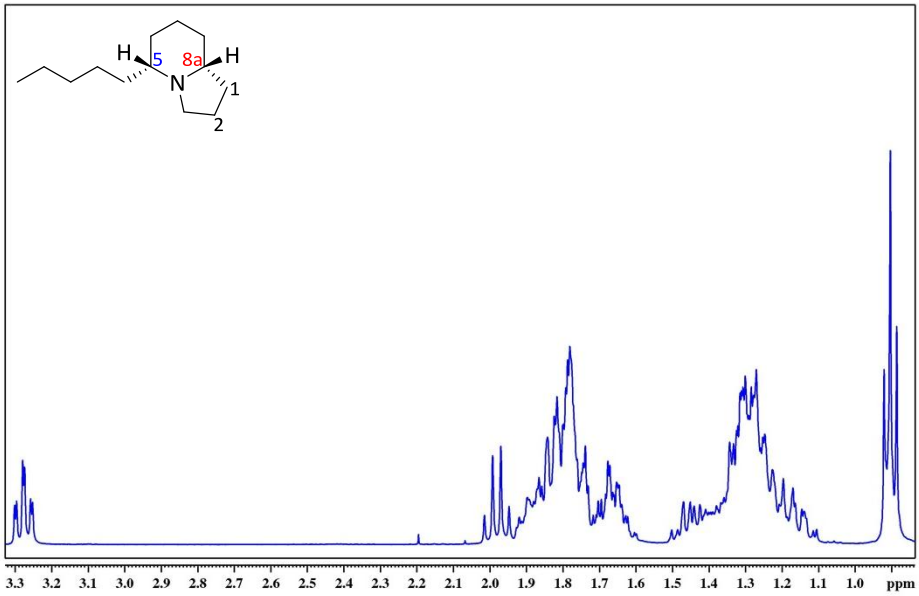


Figure 59: ^{1}H NMR spectrum for (-)-Indolizidine 195H

Physical and spectral data of compound **6** were identical with those reported previously (**Figure 60**).[51] The ^{1}H NMR spectrum again shows a doublet of triplet for the methine proton (3.27 ppm), and an apparent quartet for the proton (NC*H*^{n}Pentyl) (1.98 ppm). The value of the optical rotation for the pure compound **6** $[\alpha]^{26}_{D}$ -95.0, (*c* 1.0, CH_2Cl_2) was in accordance with the reported data (lit. $[\alpha]^{23}_{D}$ -95.6, (*c* 1.1, CH_2Cl_2).[51] We established that the absolute configuration of our products is (5*R,8aR*) (**Table 20**).

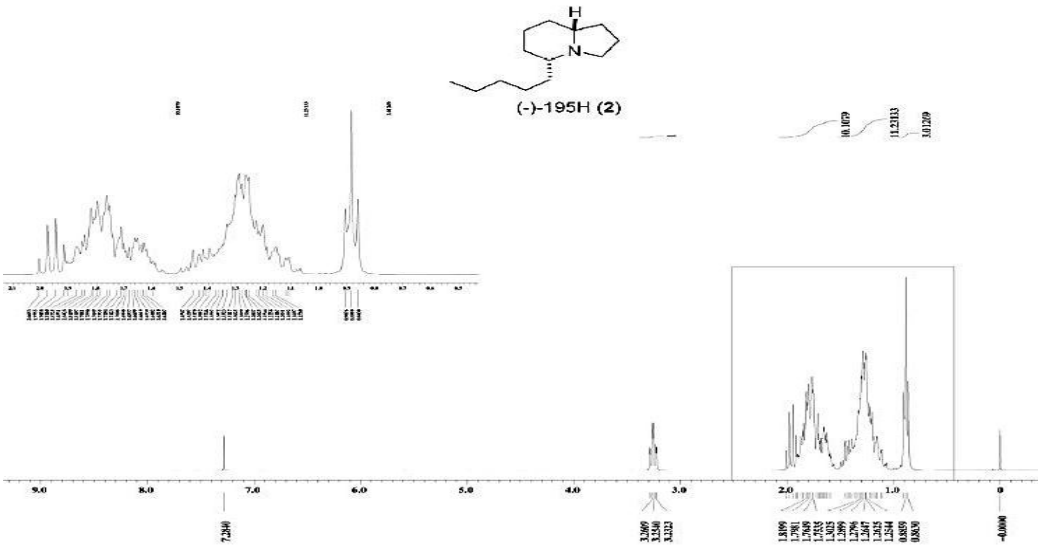
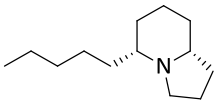


Figure 60: ^{1}H NMR spectrum for (-)-Indolizidine 195H [51]



(5*R*,8a*R*)-5-pentyloctahydroindolizine

Chemical Formula: $C_{13}H_{25}N$

Table 20

J. Org. Chem. ***2004***, 69, 3093-3101 [46]	*Org. Biomol. Chem.* ***2010***, *8, 1899–1904* [51]	**Our results**
^{1}H NMR (400 MHz, $CDCl_3$) δ	**^{1}H NMR (400 MHz, CDCl3) δ**	**^{1}H NMR (400 MHz, $CDCl_3$) δ**
0.88 (3H, t, *J* = 6.8, C*H*$_3$)	0.89 3H, t, *J* = 6.8, C*H*$_3$)	0.90 (3H, t, *J* = 7.0, C*H*$_3$)
1.11-1.50 (11H, m, C*H*$_2$)	1.05-1.95 (20H, m, C*H*$_2$)	1.09-1.51 (11H, m, C*H*$_2$)
1.61-1.92 (9H, m, C*H*$_2$)	1.97 (1H, q, *J* = 8.8)	1.63-1.88 (9H, m, C*H*$_2$)
1.98 (1H, q, *J* = 8.8)	3.25 (1H, dt, *J* = 8.6, 2.1)	1.98 (1H, app. q, *J* = 9.0)
3.27 (1H, dt, *J* = 8.8, 2.0)		3.27 (1H, dt, *J* = 9.0, 2.0)
^{13}C NMR (100 MHz, $CDCl_3$) δ	**^{13}C NMR (100 MHz, $CDCl_3$) δ**	**^{13}C NMR (100 MHz, $CDCl_3$) δ**
14.0	14.0	14.1
20.4	20.4	20.4
22.6	22.6	22.6
24.7	24.7	24.7
25.5	25.5	25.5
30.5	30.5	30.5
30.8	30.8	30.8
30.9	31.0	31.0
32.3	32.3	32.3
34.6	34.6	34.5
51.5	51.5	51.5
63.9	63.9	63.9
65.0	65.0	65.0
	$[\alpha]_D^{23}$= -95.6 (c 1.1, CH_2Cl_2)	$[\alpha]_D^{26}$= -95.0 (c 1.0, CH_2Cl_2)

2.7 Conclusion

In conclusion, we have developed a new and efficient protocol for the diastereoselective synthesis of indolizidines, particularly (-)-indolizidine 167B (**5**) and (-)-indolizidine 195H (**6**).

We have extended the application of 1,4-free radical conjugate addition methodology, using β-amino alkyl iodides derived from cyclic amino acid L-proline to prepare protected amino ketones **308** and **310** (**Schemes 99** and **100**).

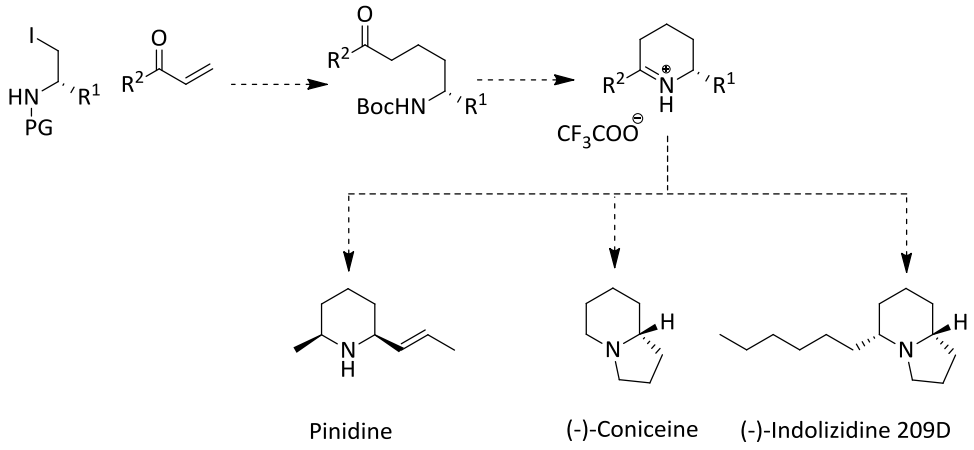
Deprotection of protected amino ketones **308** and **310** gave iminium salts, followed by diastereoselective reduction to give the target molecules as a single diastereoisomer, (-)-indolizidine 167B (**5**) and (-)-indolizidine 195H (**6**) (**Schemes 101** and **104**) in good yields.

It is worth mentioning that the numerous approaches in the literature have reported the asymmetric total synthesis of (-)-indolizidine 167B have involved more steps (5-14 steps) from commercially available materials. We were able to synthesize (-)-indolizidine 167B and (-)-indolizidine 195H in the shortest routes known to-date without the need for chiral auxiliaries and using commonly available starting materials (**Tables 19** and **20**).

3. Future Work

Possible work in this area in the future would be the investigation of the different hydrogenation protocols, and to study the effect of solvents on the stereoselectivity. Further work would be reducing 2,5-disubstituted piperidin-6-one precursors to fully saturated 2,5-disubstituted piperidines.

Other 2,6-disubstituted piperidines such as pinidine, pipecolic acid and its derivatives may be accessible by the 1,4-free radical conjugate addition methodology. Moreover, (-)-coniceine might be synthesized by conjugate addition of alkyl iodide **195** to 2-propenal, although this reaction seems to be challenging. A possible further potential application for this methodology could be the synthesis of some important indolizidine alkaloids like (-)-indolizidine 209D (**Scheme 105**); the required non-1-en-3-one has been prepared previously by Ballini and Giantomassi in five steps starting from heptanal. [90]



Scheme 105

4. Experimental

4.1 General experimental

All moisture/air sensitive reactions were performed in dry solvents under a nitrogen atmosphere in flame dried glassware. All reactions were carried out with stirring using a magnetic stirrer bar. All solvents used were HPLC grade and were purchased from Sigma-Aldrich or Fisher Scientific. All dry solvents were obtained from the in-house Grubbs dry solvent system. All reagents used were purchased from suppliers without further purification. Organic extracts were dried over $MgSO_4$ or Na_2SO_4. Dropwise additions were achieved using a dropping funnel, or two-piece syringes fitted with a needle. Solvent evaporation under reduced pressure was accomplished using a Büchi rotary evaporator connected to a pump. Petroleum ether refers to the fraction which boils in the range 40-60 °C.

Purification was carried out using flash chromatography apparatus and pressurised air on silica gel 60 gel purchased from BDH, Davisil or Fluorochem. Thin layer chromatography was performed using pre-coated silica plates (0.2mm, Merck DC-alufolien Kieselgel 60 F254). TLC plates were visualised with UV irradiation (254 nm), ninhydrin solution (5% in MeOH) or $KMnO_4$ (aqueous solution made basic with NaOH).

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 400 or Av III 400 or Bruker DRX 500 spectrometer at room temperature. Chemical shifts were measured relative to residual solvent and are expressed in parts per million (δ). Coupling constants (*J*) are given in Hertz and the measured values are rounded to the nearest 0.5 Hertz. The multiplicities and coupling constant were determined using Bruker TopSpin™ 3.2. The multiplicities are defined as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad,

app. = apparent, ddd = doublet of doublet of doublets, dt = doublet of triplets of doublets, dqd = doublet of quartets of doublets. High-resolution mass spectra were recorded using a MicroMass LCT operating in electrospray (ES). Infra-red spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer. Melting points were determined using a Linkam HFS91 heating stage, used in conjunction with a TC92 controller and are uncorrected. Optical rotations were recorded on a Perkin Elmer 241 automatic polarimeter at λ 589 nm (Na, D-line).

4.2 General Procedure A: Reduction of amino acids

A 500 mL two-necked round bottom flask, fitted with a magnetic follower, a reflux condenser, and an addition funnel equipped with a three-way tap on top, was flame-dried, evacuated and back-filled with nitrogen. Sodium borohydride (6.92 g, 183 mmol, 2.4 eq.) and amino acid (76.0 mmol, 1.0 eq.) were added to dry THF (200 mL). The resulting reaction mixture was cooled to 0 ^{o}C in an ice bath. A solution of Iodine (19.3 g, 76.0 mmol, 1.0 eq.) dissolved in dry THF (50 mL) was added dropwise to the suspension over 1 hour, and hydrogen gas evolution vigorously was observed. After addition of iodine, the solution was heated at reflux overnight. After cooling to room temperature, MeOH (60 mL) was added cautiously until the mixture became clear. Gas evolution was observed while the MeOH was added. The solvent was removed under reduced pressure leaving a white paste, which was dissolved by addition of 20% aqueous KOH (150 mL). This solution was stirred at room temperature for 4 h, thereafter extracted with dichloromethane (3 x 150 mL). Extra water and brine were added to avoid formation of an emulsion. The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield the crude amino alcohol.[69]

4.3 General Procedure B: Boc-Protection of amino alcohols

The crude amino alcohol (65.0 mmol, 1.0 eq.) was dissolved in THF (160 mL). Subsequently, 1 M NaOH (70 mL) was added, followed di-tert-butyl dicarbonate $(Boc)_2O$ (14.2 g, 65.0 mmol, 1.0 eq.). The resulting reaction mixture was stirred at room temperature overnight before the solvent was removed under reduced pressure. The solution was acidified to pH 2 with 2M HCl. A colourless oil formed on top of the aqueous solution. The mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the protected aminoalcohol as a colourless oil which was used without further purification.[68]

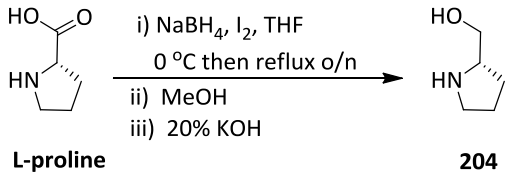
4.4 General Procedure C: Iodination of protected amino alcohols

A two-necked round bottom flask, charged with a magnetic follower fitted with a three-way tap and rubber septum, was flame-dried, evacuated and back-filled with nitrogen. Triphenylphosphine (5.24 g, 20.0 mmol, 1.0 eq.) and imidazole (1.36 g, 20.0 mmol, 1.0 eq.) were dissolved in dry dichloromethane (300 mL) with stirring under nitrogen to give a colourless solution. Thereafter, solid iodine (5.58 g, 22.0 mmol, 1.1 eq.) was added slowly, resulting in a brown solution. After about 30 minutes a solution of Boc-protected amino alcohol (20.0 mmol, 1.0 eq.) in dry dichloromethane (75 mL) was also added to the reaction mixture. This suspension was stirred in the dark (by covering the flask with aluminium foil) at room temperature until starting materials were consumed (judged by TLC 2 : 1, petroleum ether:ethyl acetate). The solvent was removed under reduced pressure to yield a brown slurry, which was dissolved in

the minimum volume of CH_2Cl_2 and filtered through a short column of silica gel eluting with Et_2O. The solvent was evaporated under reduced pressure to give the crude product as a brown oil. Purification was performed by gradient flash chromatography on silica, using ethyl acetate in petroleum ether as eluent to yield the pure iodide, which was stored under nitrogen atmosphere in the dark at -20 ^{o}C.[68]

4.5 Synthesis of Starting materials

(*2S*)-Pyrrolidin-2-ylmethanol (204)

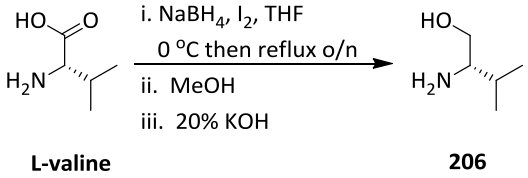


L-proline **204**

This reaction was done according to the general procedure **A** using (8.74 g, 76.0 mmol, 1.0 eq.) of L-proline to yield (*2S*)-pyrrolidin-2-ylmethanol **204** as a pale yellow oil (5.53 g, 72% crude yield), which was used without further purification: $[\alpha]^{26}_{D}$ +28.0, (*c* 0.5, MeOH) (lit. $[\alpha]^{25}_{D}$ +28.4, (*c* 0.5, MeOH)[91]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.28-1.46 (1H, m, NHCHCH*H*CH_2), 1.62-2.02 (3H, m, NHCHC*H*HC*H*$_2$), 2.76-3.02 (2H, m, NHC*H*$_2$), 3.19-3.31 (1H, m, NHC*H*), 3.32-3.40 (1H, m, CH*H*OH), 3.49-3.63 (1H, m, C*H*HOH), 3.64-3.83 (2H, m, O*H* + N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 24.9 (NHCH$_2$*C*H$_2$), 26.9 (NHCH*C*H$_2$), 45.5 (NH*C*H$_2$), 62.6 (NH*C*H), 68.7 (*C*H$_2$OH).

These characterisation data are in accordance with the literature values.[91,92]

(*2S*)-2-Amino-3-methylbutan-1-ol (206)



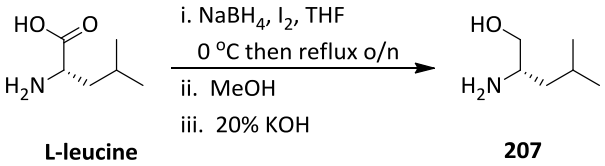
L-valine **206**

This reaction was accomplished according to the general procedure **A** using (8.9 g, 76.0 mmol, 1.0 eq.) of L-valine to yield (*2S*)-2-amino-3-methylbutan-1-ol **206** as a colourless oil (7.75 g, 99% crude yield), which was used without further

purification: $[\alpha]^{23}_{D}$ +16.0, (*c* 1.0, EtOH) (lit. $[\alpha]^{20}_{D}$ +17.0, (*c* 1.0, EtOH)[69]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.89 (3H, d, *J* = 7.0, CH(C*H*$_3$)(CH$_3$)), 0.91 (3H, d, *J* = 7.0, CH(CH$_3$)(C*H*$_3$)), 1.52-1.63 (1H, m, C*H*(CH$_3$)$_2$), 2.54 (4H, br. s, N*H*$_2$C*H*CH$_2$*OH*), 3.30 (1H, dd, *J* = 10.5, 8.5, C*H*HOH), 3.63 (1H, dd, *J* = 10.5, 4.0, CH*H*OH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.8 (*C*H$_3$), 19.4 (*C*H$_3$), 27.3 (*C*H(CH$_3$)$_2$), 58.4 (NH*C*H), 64.5 (*C*H$_2$OH).

These characterisation data are in accordance with the literature values.[93]

(*2S*)-2-Amino-4-methylpentan-1-ol (207)

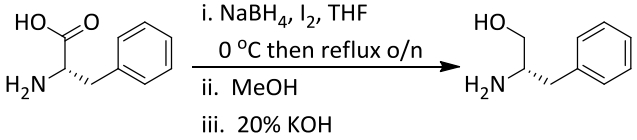


L-leucine **207**

This reaction was done according to the general procedure **A** using (9.95 g, 76.0 mmol, 1.0 eq.) of L-leucine to yield crude (*2S*)-2-amino-4-methylpentan-1-ol **207** as a colourless oil (8.62 g, 97% crude yield), which was used without further purification: $[\alpha]^{25}_{D}$ +6.0, (*c* 1.0, EtOH) (lit. $[\alpha]^{20}_{D}$ +4.9, (*c* 1.23, EtOH)[94]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.92 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 0.95 (3H, d, *J* = 6.5, CH(CH$_3$)(C*H*$_3$)), 1.18-1.28 (2H, m, CHC*H*$_2$CH), 1.68-1.76 (1H, m, C*H*(CH$_3$)$_2$), 1.81 (3H, br. s, N*H*$_2$CHCH$_2$O*H*), 2.88-2.97 (1H, m, NH$_2$C*H*CH$_2$), 3.24 (1H, dd, *J* = 10.0, 8.0, C*H*HOH), 3.59 (1H, dd, *J* = 10.5, 4.0, CH*H*OH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 22.3 (*C*H$_3$), 23.3 (*C*H$_3$), 24.6 (*C*H(CH$_3$)$_2$), 43.8 (CH*C*H$_2$CH), 50.6 (NH*C*H), 67.1 (*C*H$_2$OH).

These characterisation data are in accordance with the literature values.[94]

(*2S*)-2-Amino-3-phenylpropan-1-ol (208)

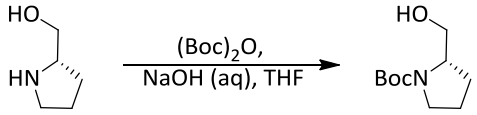


L-phenylalanine **207**

This reaction was achieved according to the general procedure **A** using (12.54 g, 76.0 mmol, 1.0 eq.) crude of L-phenylalanine to give (*2S*)-2-amino-3-phenylpropan-1-ol **208** as colourless solid (10.7 g, 93% crude yield) which was used without further purification: m.p. 92-94 ^{o}C (lit. 90-92 ^{o}C)[69]; $[\alpha]^{23}_{D}$ -23.0, (*c* 1.0, EtOH) (lit. $[\alpha]^{20}_{D}$ -24.0, (*c* 1.0, EtOH)[69]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 2.84 (2H, dd, *J* = 13.5, 5.5, C*H*$_2$Ph), 3.15-3.23 (1H, m, NHC*H*), 3.43 (2H, dd, *J* = 13.0, 5.5, C*H*HOH), 3.68 (1H, dd, *J* = 11.0, 4.0, CH*H*OH), 4.15 (1H, br. s, N*H*), 5.32 (1H, br. s, O*H*), 7.21–7.31 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 35.5 (*C*H_2Ph), 54.4 (NH*C*H), 64.9 (*C*H_2OH), 126.6 (Ar*C*H), 126.9 (Ar*C*H), 129.2 (Ar*C*H), 137.8 (Ar quat.C).

These characterisation data are in accordance with the literature values.[69]

tert-Butyl (*2S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (205)



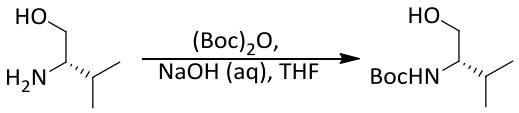
204 **205**

This reaction was performed according to the general procedure **B** using (6.56 g, 65.0 mmol, 1.0 eq.) crude of (*2S*)-pyrrolidin-2-ylmethanol **204** to give *tert*-butyl (*2S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate **205** as a colourless oil (11.0 g, 85% crude yield), which was used without further purification: $[\alpha]^{26}_{D}$ -46.0,

(*c* 1.0, MeOH) (lit. $[\alpha]^{25}_{D}$ -45.7, (*c* 1.0, MeOH)[95]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.47 (9H, s, $C(CH_3)_3$), 1.69-2.16 (4H, m, $NCHCH_2CH_2$), 2.82-3.39 (2H, m, NCH_2), 3.40-3.67 (2H, m, CH_2OH), 3.90-4.04 (NC*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 23.5 (NCH_2CH_2), 24.0 ($NCHCH_2$), 28.4 ($C(CH_3)_3$), 47.5 (NCH_2), 64.4 (N*C*H), 67.7 (CH_2OH), 80.2 ($C(CH_3)_3$), 153.4 (*C*O).

These characterisation data are in accordance with the literature values.[95]

tert-Butyl *N*-[(*2S*)-1-hydroxy-3-methylbutan-2-yl]carbamate (209)

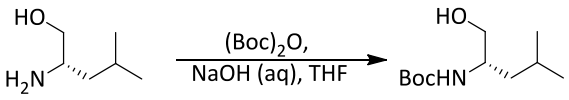


206 **209**

This reaction was performed according to the general procedure **B** using (6.7 g, 65.0 mmol, 1.0 eq.) crude of **206** to give *tert*-butyl *N*-[(*2S*)-1-hydroxy-3-methylbutan-2-yl]carbamate **209** as a colourless oil (10.57 g, 80% crude yield), which was used without further purification: $[\alpha]^{23}_{D}$ -15.2, (*c* 1.0, MeOH) (lit. $[\alpha]^{25}_{D}$ -16.7, (*c* 1.0, MeOH)[96]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.91 (3H, d, *J* = 7.0, $CH(CH_3)(CH_3)$), 0.94 (3H, d, *J* = 7.0, $CH(CH_3)(CH_3)$), 1.43 (9H, s, $C(CH_3)_3$), 1.79-1.87 (1H, m, $CH(CH_3)_2$), 3.02 (1H, br. s, CH_2OH), 3.37-3.45 (1H, m, NHC*H*), 3.58 (1H, dd, *J* = 11.0, 6.0, C*H*HOH), 3.64-3.68 (1H, dd, *J* = 11.0, 3.5, CH*H*OH), 4.82-4.84 (1H, d, *J* = 8.0, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 18.4 (CH_3), 19.5 (CH_3), 28.3 ($C(CH_3)_3$), 29.2 ($CH(CH_3)_2$), 57.9 (NH*C*H), 63.7 (CH_2OH), 79.4 ($C(CH_3)_3$), 156.8 (*C*O).

These characterisation data are in accordance with the literature values.[95,96]

tert-Butyl *N*-[(*2S*)-1-hydroxy-4-methylpentan-2-yl]carbamate (210)

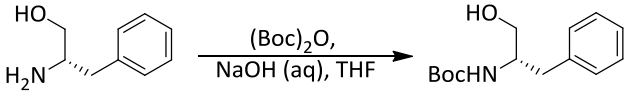


207 **210**

This reaction was accomplished according to the general procedure **B** using (7.6 g, 65.0 mmol, 1.0 eq.) crude of **207** to give *tert*-butyl *N*-[(*2S*)-1-hydroxy-4-methylpentan-2-yl]carbamate **210** as a colourless oil (10.86 g, 77% crude yield), which was used without further purification: $[\alpha]^{23}_{D}$ -22.0, (*c* 1.0, MeOH) (lit. $[\alpha]^{25}_{D}$ -23.2 , (*c* 1.0, MeOH)[95]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.91 (3H, d, *J* = 7.0, CH(C*H*$_3$)(CH$_3$)), 0.94 (3H, d, *J* = 7.0, CH(CH$_3$)(C*H*$_3$)), 1.30-1.33 (2H, m, CHC*H*$_2$CH), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.60-1.71 (1H, m, C*H*(CH$_3$)$_2$), 2.91 (1H, br. s, O*H*), 3.47-3.58 (1H, m, NHC*H*), 3.49 (1H, dd, *J* = 11.0, 6.0, C*H*HOH), 3.64 (1H, dd, *J* = 11.0, 3.0, CH*H*OH), 4.68 (1H, d, *J* = 6.5, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 22.2 (*C*H$_3$), 23.0 (*C*H$_3$), 24.8 (*C*H(CH$_3$)$_2$), 28.3 (C(*C*H$_3$)$_3$), 40.5 (CH*C*H$_2$CH), 51.0 (NH*C*H), 66.6 (*C*H$_2$OH), 77.3 (*C*(CH$_3$)$_3$), 156.7 (*C*O).

These characterisation data are in accordance with the literature values.[95]

tert-Butyl *N*-[(*2S*)-1-hydroxy-3-phenylpropan-2-yl]carbamate (211)



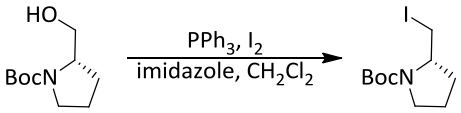
208 **211**

This reaction was done according to the general procedure **B** using (9.82 g, 65.0 mmol, 1.0 eq.) crude of **208** to yield *tert*-butyl *N*-[(*2S*)-1-hydroxy-3-phenylpropan-2-yl]carbamate **211** as a white solid powder (14.69 g, 90% crude yield), which was used without further purification: m.p.= 92-93 ^{o}C,

(lit. 95-97 ^{o}C)[97]; $[\alpha]^{22}_{D}$ -18.0, (*c* 1.0, $CHCl_3$), (Lit. $[\alpha]^{26}_{D}$ -19.5, (*c* 1.0, $CHCl_3$)[97]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.41 (9H, s, $C(CH_3)_3$), 2.84 (2H, d, *J* = 7.0, CH_2Ph), 3.53 (1H, dd, *J* = 11.0, 5.0, CHHOH), 3.64 (1H, dd, *J* = 11.0, 4.0, CHHOH), 3.70-4.01 (1H, m, NHCH), 3.87 (1H, br. s, OH), 4.91 (1H, d, *J* = 5.0, NH), 7.21–7.31 (5H, m, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 27.3 ($C(CH_3)_3$), 37.4 (CH_2Ph), 53.6 (NHCH), 63.7 (CH_2OH), 79.4 ($C(CH_3)_3$), 126.3 (ArCH), 128.4 (ArCH), 129.3 (ArCH), 138.0 (Ar quat.C), 156.1 (CO).

These characterisation data are in accordance with the literature values.[97]

tert-Butyl (*2S*)-2-(iodomethyl)pyrrolidine-1-carboxylate (195)

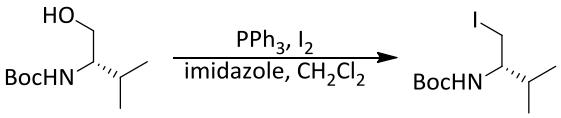


205 **195**

This reaction was accomplished according to the general procedure **C** using (4.0 g, 20.0 mmol, 1.0 eq.) of **205** to give *tert*-butyl (*2S*)-2-(iodomethyl)pyrrolidine-1-carboxylate **195**, which was purified *via* flash column chromatography, using a gradient of 5:95 EtOAc : petroleum ether to 20:80 EtOAc : petroleum ether (4.5 g, 73%) as a pale yellow solid. : m.p. 34-35 ^{o}C (lit. 34-40 ^{o}C)[89]; R_f 0.36 (10:90 EtOAc/petroleum ether); $[\alpha]^{26}_{D}$ -32.0, (*c* 1.0, $CHCl_3$) (lit. $[\alpha]^{22}_{D}$ -31.0, (*c* 1.06, $CHCl_3$)[89]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.46 (9H, s, $C(CH_3)_3$), 1.72-2.15 (4H, m, $NCHCH_2CH_2$), 3.06-3.56 (4H, m, NCH_2 + CH_2OH), 3.78-4.03 (1H, m, NCH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 10.7 (CH_2I), 22.8 (NCH_2CH_2), 23.4 ($NCHCH_2$), 28.4 ($C(CH_3)_3$), 47.5 (NCH_2), 66.9 (NCH), 79.6 ($C(CH_3)_3$), 153.4 (CO).

These characterisation data are in accordance with the literature values.[89]

tert-Butyl *N*-[(*2S*)-1-iodo-3-methylbutan-2-yl]carbamate (196)

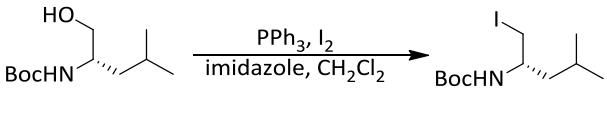


209 **196**

This reaction was accomplished according to the general procedure **C** using (4.0 g, 20.0 mmol, 1.0 eq.) of **209** to give *tert*-butyl *N*-[(*2S*)-1-iodo-3-methylbutan-2-yl]carbamate **196**, which was purified *via* flash column chromatography, using a gradient of 5:95 EtOAc : petroleum ether to 20:80 EtOAc : petroleum ether (3.32 g, 54%) as a pale yellow solid. : m.p. 50-52 ^{o}C (lit. 49-51 ^{o}C)[68], R_f 0.35 (10:90 EtOAc/petroleum ether); $[\alpha]^{23}_{D}$ -16.0, (*c* 1.8, $CHCl_3$) (lit. $[\alpha]^{21}_{D}$ -18.1, (*c* 1.75, $CHCl_3$)[68]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.94 (3H, d, *J* = 7.0, CH(C*H*$_3$)(CH$_3$)), 0.98 (3H, d, *J* = 7.0, CH(CH$_3$)(C*H*$_3$)), 1.47 (9H, s, C(C*H*$_3$)$_3$), 1.72-1.84 (1H, m, C*H*(CH$_3$)$_2$), 3.09-3.15 (1H, m, NHC*H*), 3.35 (1H, dd, *J* = 10.0, 4.0, C*H*HI), 3.43 (1H, dd, *J* = 10.0, 4.0, CH*H*I), 4.59 (1H, d, *J* = 8.5, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 13.3 (*C*H$_2$), 18.2 (*C*H$_3$), 19.3 (*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 32.3 (*C*H(CH$_3$)$_2$), 55.4 (NH*C*H), 79.5 (*C*(CH$_3$)$_3$), 155.3 (*C*O).

These characterisation data are in accordance with the literature values.[68]

tert-Butyl *N*-[(*2S*)-1-iodo-4-methylpentan-2-yl]carbamate (197)



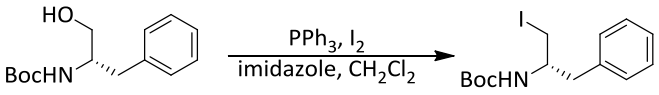
210 **197**

This reaction was done according to the general procedure **C** using (4.34 g, 20.0 mmol, 1.0 eq.) of **210** to yield *tert*-butyl *N*-[(*2S*)-1-iodo-4-methylpentan-2-yl]carbamate **197**, which was purified *via* flash column chromatography, using a gradient of 5:95 EtOAc : petroleum ether to 20:80 EtOAc : petroleum ether

(3.13 g, 48%) as a yellow solid. : m.p. 54-56 °C, (lit. 55-56 °C)[98]; R_f 0.42 (10:90 EtOAc/petroleum ether); $[\alpha]^{22}_D$ -28.0, (*c* 2.0, $CHCl_3$) (lit. $[\alpha]^{25}_D$ -29.9, (*c* 2.31, $CHCl_3$)[98]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.94 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 0.96 (3H, d, *J* = 6.5, CH(CH$_3$)(C*H*$_3$)), 1.35 (2H, m, CHC*H*$_2$CH), 1.46 (9H, s, C(C*H*$_3$)$_3$), 1.65 (1H, m, C*H*(CH$_3$)$_2$), 3.37-3.34 (1H, m, NHC*H*), 3.29 (1H, dd, *J* = 10.0, 3.0, C*H*HI), 3.47 (1H, dd, *J* = 10.0, 4.0, CH*H*I), 4.54 (1H, d, *J* = 7.5, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 15.9 (CH_2), 22.4 (*C*H$_3$), 22.6 (*C*H$_3$), 24.7 (*C*H(CH$_3$)$_2$), 28.3 (C(*C*H$_3$)$_3$), 44.2 (CH*C*H$_2$CH), 47.8 (NH*C*H), 79.6 (*C*(CH$_3$)$_3$), 155.1 (*C*O).

These characterisation data are in accordance with the literature values.[98]

tert-Butyl *N*-[(*2S*)-1-iodo-3-phenylpropan-2-yl]carbamate (198)

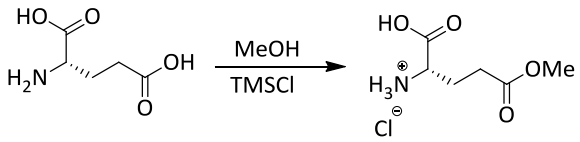


211 **198**

This reaction was performed according to the general procedure **C** using (5.0 g, 20.0 mmol, 1.0 eq.) of **211** to give *tert*-butyl *N*-[(*2S*)-1-iodo-3-phenylpropan-2-yl]carbamate **198**, which was purified *via* flash column chromatography, using a gradient of 5:95 EtOAc : petroleum ether to 20:80 EtOAc : petroleum ether (3.87 g, 54%) as a pale yellow solid. : m.p. 120-121 °C (lit. 118 °C)[68]; R_f 0.32 (10:90 EtOAc/petroleum ether); $[\alpha]^{23}_D$ +18.0, (*c* 1.0, $CHCl_3$) (lit. $[\alpha]^{26}_D$ +18.8, (*c* 1.0, $CHCl_3$)[68]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.45 (9H, s, C(C*H*$_3$)$_3$), 2.78 (2H, dd, *J* = 13.5, 8.0, C*H*$_2$Ph), 2.92 (2H, dd, *J* = 13.5, 5.5, C*H*$_2$Ph), 3.17 (1H, dd, *J* = 10.0, 4.0, C*H*HI), 3.41 (1H, dd, *J* = 10.0, 4.0, CH*H*I), 3.56-3.66 (1H, m, C*H*NH), 4.71 (1H, d, *J* = 7.5, N*H*), 7.24–7.34 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 14.0 (*C*H$_2$I), 27.4 (C(*C*H$_3$)$_3$), 40.6 (*C*H$_2$Ph), 51.2 (NH*C*H), 85.1 (*C*(CH$_3$)$_3$), 126.8 (ArCH), 128.6 (ArCH), 129.2 (ArCH), 137.0 (Ar quat.C), 154.8 (*C*O).

These characterisation data are in accordance with the literature values.[68]

(*1S*)-1-Carboxy-4-methoxy-4-oxobutan-1-aminium chloride (213)

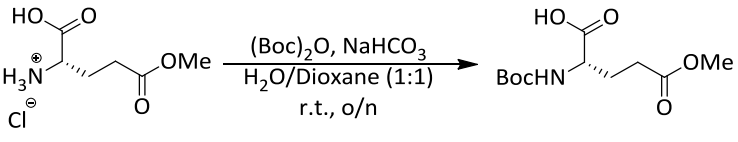


212 **213**

To a suspension of L-glutamic acid **212** (7.36 g, 50.0 mmol) in dry methanol (150 mL) under nitrogen was added chlorotrimethylsilane dropwise (11.95 g, 110 mmol) over 10 min at room temperature. The clear solution obtained was stirred at room temperature for 15 min. The solvent was removed under reduced pressure and dried under high vacuum. The crude product was recrystallized from hot methanol to yield (*1S*)-1-carboxy-4-methoxy-4-oxobutan-1-aminium chloride **213** as a white solid (7.7 g, 96% crude yield)), which was used without further purification: m.p. 183-184 ^{o}C (dec.) (lit. 182 ^{o}C (dec.))[70]; $[\alpha]^{23}_{D}$ +28.0, (*c* 2.0, 6M HCl) (lit. $[\alpha]^{23}_{D}$ +29.2, *c* 2.0, 6M HCl)[70]; **^{1}H NMR** (400 MHz, D_2O) δ ppm: 2.05-2.21 (2H, m, CHC*H*$_2$), 2.53 (2H, t, *J* = 7.5, C*H*$_2$COOCH$_3$), 3.60 (3H, s, COOC*H*$_3$), 3.98 (1H, t, *J* = 7.0, NHC*H*); **^{13}C NMR** (100 MHz, D_2O) δ ppm: 24.8 (CH*C*H$_2$), 29.4 (*C*H$_2$CO$_2$Me), 52.2 (CO$_2$*C*H$_3$), 52.4 (NH*C*H*)*, 171.7 (*C*O$_2$Me), 175.0 (*C*O$_2$H).

These characterisation data are in accordance with the literature values.[70]

(*2S*)-2-((*tert*-Butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid (214)



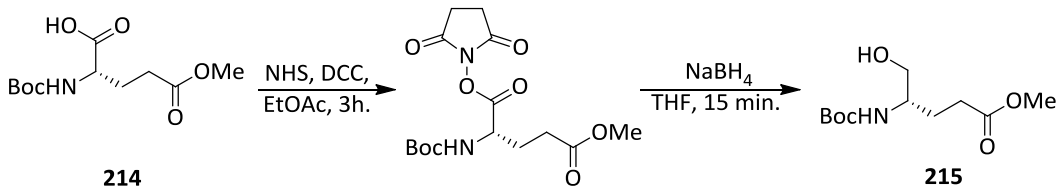
213 **214**

The crude of (*1S*)-1-carboxy-4-methoxy-4-oxobutan-1-aminium chloride **213** (18.4 g, 114 mmol) was dissolved in water (300 mL). Subsequently, 1,4-dioxane (300 mL) was added to the solution and stirred for 5 min at 0 ^{o}C. Boc_2O (31 mL, 137 mmol) and $NaHCO_3$ (24 g, 285 mmol) were added to the solution and stirred

at room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in 10% aqueous $NaHCO_3$ (75 mL), and washed with diethyl ether (75 mL). The aqueous layer was neutralized to pH 4 with 2M HCl. The mixture was extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield (*2S*)-2-((*tert*-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid **214** as a colourless oil (26.4 g, 89% crude yield), which was used without further purification: $[\alpha]^{24}_D$ +15.0, (*c* 1.5, $CHCl_3$) (lit. $[\alpha]^{20}_D$ +16.5, (*c* 1.4, $CHCl_3$)[70]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.96-2.04 (1H, m, NHCHC*H*H), 2.18-2.29 (1H, m, NHCHCH*H*), 2.37-2.54 (2H, m, C*H*$_2$CO$_2$Me), 3.69 (s, 3H, COOC*H*$_3$), 4.20-4.41 (1H, m, NHC*H*), 5.27 (1H, d, *J* = 8.0, N*H*), 10.86 (1H, br. s, COO*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 27.4 (CH*C*H$_2$), 27.6 (*C*H$_2$CO$_2$Me), 28.3 (C(*C*H$_3$)$_3$), 51.8 (CO$_2$*C*H$_3$), 52.7 (NH*C*H), 80.3 (*C*(CH$_3$)$_3$), 155.6 (NH*C*O), 173.5 (*C*O$_2$Me), 176.2 (*C*O$_2$H). Rotamers are seen in **^{1}H NMR** and **^{13}C NMR**.

These characterisation data are in accordance with the literature values.[70]

Methyl (*4S*)-4-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanoate (215)



214 **215**

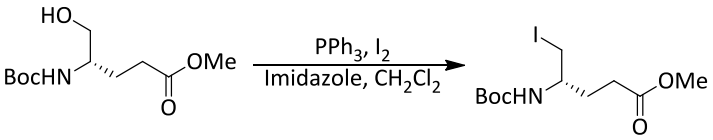
(*2S*)-2-((*tert*-Butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid **214** (13 g, 49.6 mmol) and *N*-hydroxysuccinimide (6.3 g, 54.4 mmol) were dissolved in ethyl acetate (40 mL), and stirred at 0 ^oC under nitrogen. *N,N'*-Dicyclohexylcarbodiimide (11.24 g, 54.4 mmol) was added to the solution in one

portion to give a white suspension. The mixture was warmed to room temperature and was stirred for 3 h. The reaction mixture was then filtered to remove the solid by-product. The filtrate was washed with aqueous $NaHCO_3$, and brine respectively. Thereafter dried $MgSO_4$, and the solvent was removed under reduced pressure to yield a crude succinimide ester as a white solid (17.1 g, 98%). This product was used directly, without further purification.

To a solution of succinimide ester (4.16 g, 10.0 mmol) in THF (30 mL) was added $NaBH_4$, (4.16 g, 10.0 mmol) at 0 ^oC. Then EtOH (15 mL) was added slowly. The resulting suspension was stirred for 20 min at 0 ^oC. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and stirred for 10 min. The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to give an oily residue. This product was purified by recrystallization (Et_2O / hexane) to yield methyl (*4S*)-4-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanoate **215** as a white solid (2.3 g, 80%).: m.p.= 42-45 ^oC, (lit. m.p.= 40.5-41.5 ^oC)[99], $[\alpha]^{24}_D$ -13.0, (*c* 1.0, $CHCl_3$) (lit. $[\alpha]^{23}_D$ -13.2, (*c* 1.0, $CHCl_3$)[99] ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.39 (9H, s, C(C*H*$_3$)$_3$), 1.48-1.58 (2H, m, CHC*H*$_2$CH$_2$), 2.32-2.42 (2H, m, C*H*$_2$CO$_2$CH$_3$), 3.10-3.20 (1H, m, C*H*HOH), 3.33-3.46 (1H, m, CH*H*OH), 3.50-3.59 (1H, m, NHC*H*), 3.63 (3H, s, COOC*H*$_3$), 5.22 (1H, d, *J* = 8.0, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 24.6 (CH*C*H$_2$), 25.4 (*C*H$_2$CO$_2$Me), 28.3 (C(*C*H$_3$)$_3$), 51.7 (CO$_2$*C*H$_3$), 55.7 (NH*C*H), 64.8 (*C*H$_2$OH*)*, 79.3 (*C*(CH$_3$)$_3$), 156.1 (NH*C*O), 174.1 (*C*O$_2$Me).

These characterisation data are in accordance with the literature values.[99]

Methyl (*4S*)-4-((*tert*-butoxycarbonyl)amino)-5-iodopentanoate (199)

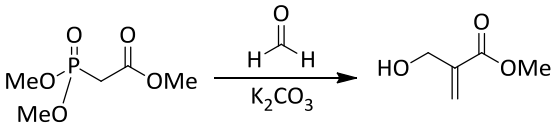


215 **199**

This reaction was performed according to the general procedure **C** using (4 g, 16.2 mmol, 1.0 eq.) of methyl (*4S*)-4-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanoate **215** to provide methyl (*4S*)-4-((*tert*-butoxycarbonyl)amino)-5-iodopentanoate **199**, which was purified *via* flash column chromatography, using a gradient of 5:95 EtOAc : petroleum ether to 20:80 EtOAc : petroleum ether (2.9 g, 50%) as a yellow solid. : m.p.= 87-89 ^{o}C (lit. mp= 92-93 ^{o}C)[56]; R_f 0.40 (10:90 EtOAc/petroleum ether); $[\alpha]^{24}_{D}$ -16.2, (*c* 1.5, CH_2Cl_2) (lit. $[\alpha]^{20}_{D}$ -15.6, (*c* 1.38, CH_2Cl_2)[56]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.46 (9H, s, C(C*H*$_3$)$_3$), 1.78-1.97 (2H, m, NHCHC*H*$_2$), 2.35-2.48 (2H, m, C*H*$_2$CO$_2$Me), 3.28-3.35 (1H, m, NHC*H*), 3.40-3.49 (2H, m, C*H*$_2$I), 3.70 (3H, s, COOC*H*$_3$), 4.66 (1H, d, *J* = 8.0, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 14.0 (*C*H$_2$I), 28.3 (CH*C*H$_2$), 30.3 (*C*H$_2$CO$_2$Me), 30.4 (C(*C*H$_3$)$_3$), 49.5 (CO$_2$*C*H$_3$), 51.8 (NH*C*H), 79.8 (*C*(CH$_3$)$_3$), 155.0 (NH*C*O), 173.4 (*C*O$_2$Me).

These characterisation data are in accordance with the literature values.[56]

Methyl 2-(hydroxymethyl)prop-2-enoate (217)



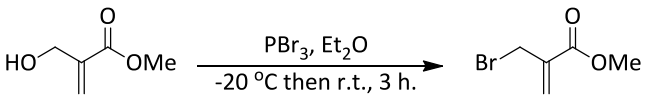
216 **217**

A mixture of trimethyl phosphonoacetate **216** (27.31 g, 150 mmol) and formaldehyde (35% aqueous solution) (17.7 g, 590 mmol) was placed in a round

bottomed flask and stirred at room temperature. A saturated aqueous solution of potassium carbonate (33.17 g, 240 mmol) was added dropwise to the flask over 30 min, The reaction temperature was keep below 35 ^{o}C by stirring in an ice bath. After addition, the reaction mixture was warmed to room temperature and stirred for further 1 h. This was transferred to a separatory funnel and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, the solvent was removed under reduced pressure. The product was methyl 2-(hydroxymethyl)prop-2-enoate **217** as a colourless oil (10.78 g, 66%) which is used without further purification. : **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 2.65 (1H, br. s, O*H*), 3.76 (3H, s, CO_2CH_3), 4.31 (2H, s, $CH_2C{=}CH_2$), 5.84 (1H, s, C=C*H*H), 6.25 (1H, s, 1H, s, C=CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 51.7 (CO_2CH_3), 61.6 (CH_2OH), 125.0 ($C{=}CH_2$), 139.6 ($C{=}CH_2$), 166.6 (*C*O).

These characterisation data are in accordance with the literature values. [71]

Methyl 2-(bromomethyl)prop-2-enoate (218)



217 **218**

A round-bottomed flask was charged with a magnetic follower and a solution of methyl 2-(hydroxymethyl)prop-2-enoate **217** (5.80 g, 50.0 mmol) in Et_2O (100 mL). phosphorus tribromide (5.42 g, 1.88 mL, 20.0 mmol) was added dropwise to the reaction mixture at -20 ^{o}C. The resulting mixture was allowed to warm to room temperature and stirred for 3h. Subsequently, the solution was cooled to 0 ^{o}C, and water (50 mL) was added slowly. The mixture was extracted with hexane (3 x 50 mL), the combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure to give the crude of methyl 2-(bromomethyl)prop-2-enoate **218**. Finally, the crude product was purified by

fractional distillation under reduced pressure (1.3 mm Hg) using an oil bath at 50-55 ^{o}C, the pure product was collected at b.p. 35-36°C as a colourless liquid in good yield (6 g, 67%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 3.82 (3H, s, CO_2CH_3), 4.18 (2H, s, $CH_2C{=}CH_2$), 5.96 (1H, s, C=CHH), 6.34 (1H, s, C=CHH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 29.3 (CH_2Br), 52.3 (CO_2CH_3), 129.2 ($C{=}CH_2$), 137.2 ($C{=}CH_2$), 165.3 (CO).

These characterisation data are in accordance with the literature values. [71,72]

4.5 General Procedure D: Preparation of organozinc iodides - zinc activation using iodine.

A two-necked round bottom flask, fitted with a three-way tap and rubber septum, was flame-dried, evacuated and back-filled with nitrogen three times. The flask was charged with a magnetic follower and zinc dust (2.0 eq. relative to alkyl iodide), and again evacuated and back-filled with nitrogen three times, with continuous stirring. Dry DMF (1 mL / mmol of alkyl iodide) was added *via* syringe, and the heterogeneous mixture stirred vigorously. Iodine (~2 mol% relative to alkyl iodide) was added by rapid removal and replacement of the three-way tap under a stream of nitrogen, turning the solvent yellow. The mixture was stirred for 1-2 minutes, until the solvent had become colourless. The alkyl iodide (1.0 mmol, 1.0 eq.) was added by rapid removal of the three-way tap under a stream of nitrogen. The mixture was stirred and an exotherm was observed. The mixture was stirred for a further 30-45 minutes, before cessation of stirring. The solid zinc dust was allowed to settle before transferring the reagent into a new reaction vessel *via* syringe.

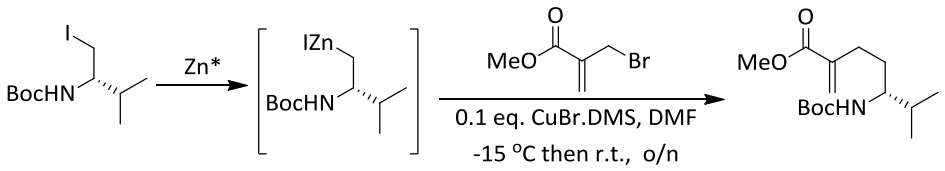
4.6 General Procedure E: Allylation reactions

During the zinc activation period, a separate two-necked round bottomed flask fitted with a three-way tap was flame-dried under vacuum, and back-filled with nitrogen three times. This flask was charged with a magnetic follower and CuBr.DMS (0.1 eq. relative to alkyl iodide), and gently heated under vacuum until the CuBr.DMS changed appearance from a brown or white powder to light green powder. The flask was allowed to cool, before adding dry DMF (0.6 mL /1.0 mmol) and the electrophile (4.0 eq.) *via* a syringe. The mixture was stirred at room temperature, then cooled to -15 ^{o}C before adding the supernatant of the zinc

reagent carefully *via* syringe. The reaction mixture became yellow and then dark brown. After complete addition, the cooling bath was removed and stirring was continued overnight at room temperature.

Ethyl acetate (15 mL) was added to the reaction mixture and stirring was continued for 15 min. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 1M $Na_2S_2O_3$ solution (5 mL), water (5 mL), and brine (5 mL) respectively, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified by gradient flash chromatography on silica, using ethyl acetate in petroleum ether as eluent.

Methyl (*5R*)-5-([(*tert*-butoxy)carbonyl]amino)-6-methyl-2-methylideneheptanoate (223)

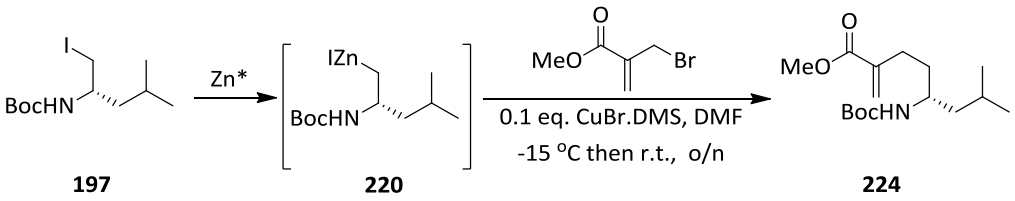


196 **219** **223**

Organozinc reagent **219** was synthesised according to the general procedure **D**, using *tert*-butyl *N*-[(*2S*)-1-iodo-3-methylbutan-2-yl]carbamate **196** (940 mg, 3.0 mmol). The allylation reaction between **219** and methyl 2-(bromomethyl)prop-2-enoate **218** was performed according to the general procedure **E**. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **223** (440 mg, 52%) as a colourless oil. : R_f 0.23 (20:80 EtOAc/petroleum ether); $[\alpha]^{23}_D$ -4.0, (*c* 1.0, $CHCl_3$); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 3456 (N-H), 3014 (=C-H), 2971 (C-H), 1747 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.85 (3H, d, *J* = 7.0, CH(C*H*$_3$)(CH$_3$)), 0.95 (3H, d, *J* = 7.0, CH(CH$_3$)(C*H*$_3$)), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.60-1.68 (1H, m, C*H*(CH$_3$)$_2$), 1.70-1.79 (2H, m, CH$_2$=CC*H*$_2$), 2.23-2.33 (1H, m,CH$_2$C*H*HCH), 2.37-2.46 (1H, m, CH$_2$CH*H*CH),

3.40-3.50 (1H, m, NHC*H*), 3.75 (3H, s, CO_2CH_3), 4.36 (1H, d, *J* = 10.0, N*H*), 5.60 (1H, s, C=C*H*H), 6.15 (1H, s, C=CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.5 (CH_3), 19.00 (CH_3), 28.3 ($C(CH_3)_3$), 29.0 (CH_2CH_2C=), 31.4 ($CHCH_2$), 32.2 ($CH(CH_3)_2$), 51.7 (CO_2CH_3), 55.0 (NHCH), 78.6 ($C(CH_3)_3$), 125.3 (C=CH_2), 140.0 (C=CH_2), 155.9 (NHCO), 167.4 (CO_2Me); ***m/z*** (ES+): 286.2018 (MH^+, 100%, $C_{15}H_{28}NO_4$ requires 286.2014).

Methyl (*5R*)-5-([(*tert*-butoxy)carbonyl]amino)-7-methyl-2-methylideneoctanoate (224)

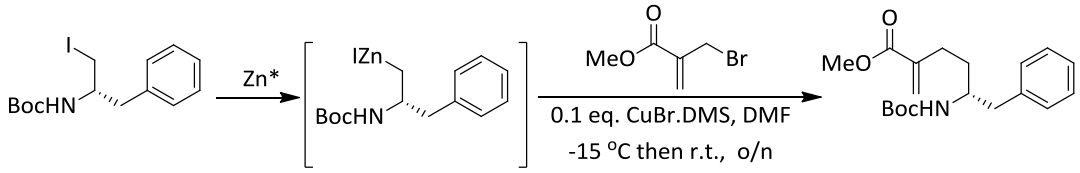


197 **220** **224**

Organozinc reagent **220** was prepared according to the general procedure **D**, using *tert*-butyl *N*-[(*2S*)-1-iodo-4-methylpentan-2-yl]carbamate **197** (980 mg, 3.0 mmol). The allylation reaction between **220** and methyl 2-(bromomethyl)prop-2-enoate **218** was accomplished according to the general procedure **E**. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **224** (450 mg, 50%) as a colourless oil. : R_f 0.22 (20:80 EtOAc/petroleum ether); $[\alpha]^{23}_D$ -12.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3462 (N-H), 3009 (=C-H), 2989 (C-H), 1707 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.89 (3H, d, *J* = 6.5, $CH(CH_3)(CH_3)$), 0.92 (3H, d, *J* = 6.5, $CH(CH_3)(CH_3)$), 1.21-1.33 (2H, m, $CHCH_2CH$), 1.44 (9H, s, $C(CH_3)_3$), 1.49-1.53 (1H, m, $CH(CH_3)_2$), 1.59-1.68 (m, 2H, CH_2CH_2=C), 2.26-2.34 (1H, m,$CHCHHCH_2$), 2.36-2.44 (1H, m, $CHCHHCH_2$), 3.62-3.72 (1H, m, NHC*H*), 3.75 (3H, s, CO_2CH_3), 4.26 (1H, d, *J* = 10.5, N*H*), 5.59 (1H, s, C=C*H*H), 6.15 (1H, s, C=CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 22.2 (CH_3), 23.0 (CH_3), 24.8 ($CH(CH_3)_2$), 28.3 ($C(CH_3)_3$),

30.8 (CH_2CH_2C=), 34.8 ($CHCH_2CH_2$), 48.4 ($CHCH_2CH$), 51.7 (CO_2CH_3), 51.8 (NH*C*H), 78.8 ($C(CH_3)_3$), 126.0 (C=CH_2), 140.1 (*C*=CH_2), 166.1 (NH*C*O), 167.5 (CO_2Me); ***m/z*** (ES+): 300.2170 (MH^+, 100%, $C_{16}H_{30}NO_4$ requires 300.2175).

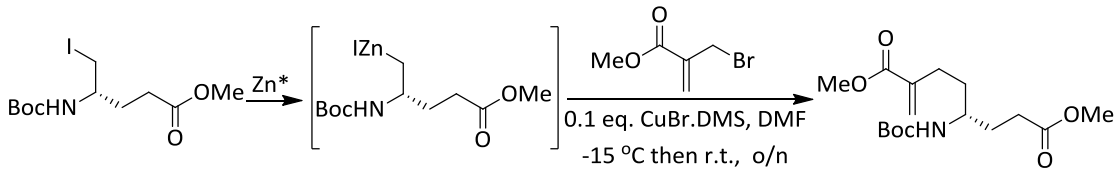
Methyl (*5R*)-5-([(*tert*-butoxy)carbonyl]amino)-2-methylidene-6-phenylhexanoate(225)



198 **221** **225**

Organozinc reagent **221** was synthesized according to the general procedure **D**, using *tert*-butyl *N*-[(*2S*)-1-iodo-3-phenylpropan-2-yl]carbamate **198** (1.08 g, 3.0 mmol). The allylation reaction between **221** and methyl 2-(bromomethyl)prop-2-enoate **218** was done according to the general procedure **E**. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **225** (538 mg, 54%) as a white solid. : R_f 0.29 (20:80 EtOAc/petroleum ether); $[\alpha]^{23}_D$ +7.0, (*c* 1.0, $CHCl_3$); m.p.= 52-53 ^oC; **ν_{max}(ATR)/cm^{-1}**: 3467 (N-H), 3362 (=C-H), 3014 (C-H), 1747 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.42 (9H, s, C(CH_3)$_3$), 1.46-1.51 (1H, m, CHC*H*HCH_2), 1.65-1.73 (1H, m, CHCH*H*CH_2), 2.27-2.37 (1H, m, CHC*H*HPh), 2.41-2.48 (1H, m, CHCH*H*Ph), 2.74-2.85 (2H, m, =CCH_2CH_2), 3.74 (3H, s, CO_2CH_3), 3.81-3.90 (1H, m, C*H*NH), 4.41 (1H, d, *J* = 8.5, N*H*), 5.54 (1H, s, C=C*H*H), 6.15 (s, 1H, C=CH*H*), 7.18-7.31 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.3 ($C(CH_3)_3$), 28.6 (CH_2CH_2C), 32.9 ($CHCH_2CH_2$), 41.5 ($CHCH_2$Ph), 51.2 (CO_2CH_3), 51.8 (NH*C*H), 79.1 ($C(CH_3)_3$), 125.4 (C=CH_2), 126.3 (ArCH), 128.3 (ArCH), 129.5 (ArCH), 138.0 (Ar quat.C), 139.7 (*C*=CH_2), 155.4 (NH*C*O), 167.5 (CO_2Me); ***m/z*** (ES+): 334.2018 (MH^+, 100%, $C_{19}H_{28}NO_4$ requires 334.2030).

1,8-Dimethyl (*5R*)-5-([(*tert*-butoxy)carbonyl]amino)-2-methylideneoctanedioate (226)



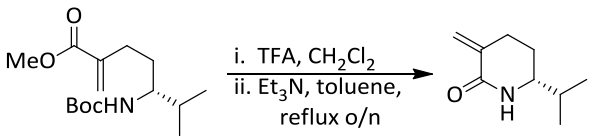
199 **222** **226**

Organozinc reagent **222** was synthesized according to the general procedure **D**, using methyl (*4S*)-*4*-((*tert*-butoxycarbonyl)amino)-5-iodopentanoate **199** (357 mg, 1.0 mmol). The allylation reaction between **222** and methyl 2-(bromomethyl)prop-2-enoate **218** was achieved according to the general procedure **E**. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **226** (167 mg, 51%) as a colourless oil. : R_f 0.23 (20:80 EtOAc/petroleum ether); $[\alpha]^{24}_D$ -10.0, (*c* 1.0, $CHCl_3$); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 3376 (N-H), 2986 (=C-H), 2951 (C-H), 1714 (C=O ester), 1692 (C=O amide); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.43 (9H, s, C(C*H*$_3$)$_3$), 1.60-1.70 (2H, m, C*H*$_2$CH$_2$CO$_2$Me), 1.82-1.90 (2H, m, C*H*$_2$CH$_2$C=CH$_2$), 2.27-2.40 (4H, m, C*H*$_2$CO$_2$Me + C*H*$_2$C=CH$_2$), 3.60 (1H, m, NHC*H*), 3.67 (3H, s, CH$_2$CO$_2$C*H*$_3$), 3.75 (3H, s, CH$_2$=CCO$_2$C*H*$_3$), 4.36 (1H, d, *J* = 9.5, N*H*), 5.58 (1H, s, C=C*H*H), 6.16 (1H, s, C=CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.3 (C(*C*H$_3$)$_3$), 28.5 (*C*H$_2$CH$_2$CO$_2$Me), 30.6 (*C*H$_2$CO$_2$Me), 30.7 (*C*H$_2$CH$_2$C=), 34.5 (CH$_2$*C*H$_2$C=), 49.9 (NH*C*H), 51.6 (CO$_2$*C*H$_3$ or CO$_2$*C*H$_3$), 51.8 (CO$_2$*C*H$_3$ or CO$_2$*C*H$_3$), 79.1 (*C*(CH$_3$)$_3$), 125.4 (C=*C*H$_2$), 139.7 (*C*=CH$_2$), 155.6 (NH*C*O), 167.4 (*C*O$_2$Me), 174.0 (*C*O$_2$Me); ***m/z*** (ES+): 330.1917 (MH$^+$, 100%, $C_{16}H_{28}NO_6$ requires 330.1931).

4.7 General Procedure F: Cyclisation reactions

A round bottomed flask, equipped with a magnetic follower, was charged with a cyclisation substrate (1.0 mmol, 1.0 eq.) dissolved in dichloromethane (30 mL). Trifluoroacetic acid (5.7 g, 3.72 mL, 50.0 mmol) was added dropwise to the stirred solution at room temperature, and the reaction mixture was stirred for 15 minutes. The solvent and excess trifluoroacetic acid were then removed under reduced pressure in a fume cupboard. Afterwards, the residue was dissolved in toluene (30 mL). Triethylamine (203 mg, 276 mL, 2.0 mmol, 1.0 eq.) was added to the reaction mixture, and the solution was heated at reflux overnight. The solvent was evacuated under reduced pressure to give an amber oil. Purification was performed by gradient flash chromatography on silica, using methanol in ethyl acetate as eluent, to give the desired cyclisation compound.

(*6R*)-3-Methylidene-6-(propan-2-yl)piperidin-2-one (230)

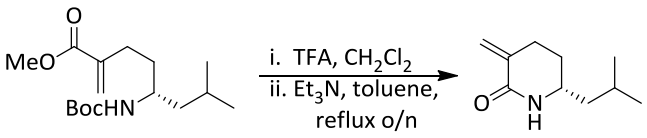


223 **230**

This reaction was performed according to the general procedure **F** using (0.285 g, 1.0 mmol, 1.0 eq.) of methyl (*5R*)-5-((*tert*-butoxy)carbonyl)amino)-6-methyl-2-methylideneheptanoate **223** to yield (*6R*)-3-methylidene-6-(propan-2-yl)piperidin-2-one **230**, which was purified *via* flash column chromatography, using an eluent gradient of 0.5% methanol in ethyl acetate to 10% methanol in ethyl acetate (0.32 g, 81%) as a brown oil. : R_f 0.32 (5:95 MeOH/EtOAc); $[\alpha]^{23}_D$ -16.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3467 (N-H), 3201 (=C-H), 3018 (C-H), 1740 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.93 (3H, d, *J* = 7.0, CH(C*H*$_3$)(CH$_3$)),

0.96 (3H, d, *J* = 7.0, CH(CH_3)(CH_3)), 1.48-1.58 (1H, m, C=CC*H*HCH_2), 1.86-1.93 (1H, m, C=CCH*H*CH_2), 1.66-1.76 (1H, m, C*H*(CH_3)(CH_3)), 2.40-2.50 (1H, m, CHC*H*HCH_2), 2.65-2.71 (1H, m, CHCH*H*CH_2), 3.24-3.32 (1H, m, NHC*H*), 5.33 (1H, s, C=C*H*H), 6.0 (1H, br. s, N*H*), 6.20 (1H, s, C=CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.7 (CH*C*H_3), 18.1 (CH*C*H_3), 25.2 (CH*C*H_2CH_2), 28.6 (CH_2*C*H_2), 32.5 (*C*H(CH_3)$_2$), 58.9 (NH*C*H), 121.6 (C=*C*H_2), 137.3 (*C*=CH_2), 166.1 (NH*C*O); ***m/z*** (ES+): 154.1237 (MH^+, 100%, $C_9H_{16}NO$ requires 154.1232).

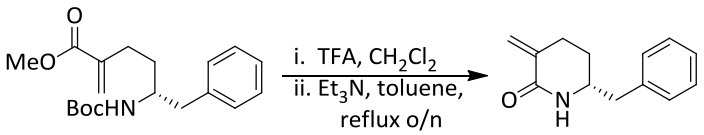
(*6R*)-3-Methylidene-6-(2-methylpropyl)piperidin-2-one (231)



224 **231**

This reaction was performed according to the general procedure **F** using (0.3 g, 1.0 mmol, 1.0 eq.) of methyl (*5R*)-5-((*tert*-butoxy)carbonyl)amino)-7-methyl-2-methylideneoctanoate **224** to yield (*6R*)-3-methylidene-6-(2-methylpropyl)piperidin-2-one **231**, which was purified *via* flash column chromatography, using an eluent gradient of 0.5% methanol in ethyl acetate to 10% methanol in ethyl acetate (0.13 g, 80%) as a brown oil. : R_f 0.36 (5:95 MeOH/EtOAc); $[\alpha]^{23}_D$ -22.0, (*c* 1.0, $CHCl_3$); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 3467 (N-H), 3187 (=C-H), 3018 (C-H), 1758 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.94 (6H, d, *J* = 6.5, CH(CH_3)$_2$), 1.30-1.46 (2H, m, CHCH_2CH), 1.47-1.57 (1H, m, CHCH*H*CH_2), 1.66-1.76 (m, 1H, C*H*(CH_3)(CH_3)), 1.94-2.00 (1H, m, CHCH*H*CH_2), 2.44-2.54 (1H, m, C=CC*H*HCH_2), 2.65-2.71 (1H, tt, *J* = 15.5, 4.5, C=CCH*H*CH_2), 3.50-3.58 (1H, m, NHC*H*), 5.36 (1H, s, C=C*H*H), 6.10 (1H, br. s, N*H*), 6.24 (1H, s, C=CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 22.3 (CH*C*H_3), 22.7 (CH*C*H_3), 24.2 (*C*H(CH_3)$_2$), 28.3 (CH*C*H_2CH_2), 29.2 (CH_2*C*H_2), 45.6 (CH*C*H_2CH), 51.3 (NH*C*H), 122.3 (C=*C*H_2), 133.9 (*C*=CH_2), 166.8 (NH*C*O); ***m/z*** (ES+): 168.1388 (MH^+, 100%, $C_{10}H_{18}NO$ requires 168.1392).

(*6R*)-6-Benzyl-3-methylidenepiperidin-2-one (232)



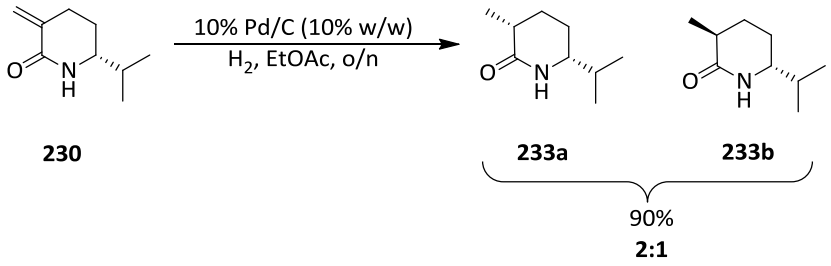
225 **232**

This reaction was done according to the general procedure **F** using (0.33 g, 1.0 mmol, 1.0 eq.) of methyl (*5R*)-5-((*tert*-butoxy)carbonyl)amino-2-methylidene-6-phenylhexanoate **225** to yield (*6R*)-6-benzyl-3-methylidenepiperidin-2-one **232**, which was purified *via* flash column chromatography, using an eluent gradient of 0.5% methanol in ethyl acetate to 10% methanol in ethyl acetate (0.16 g, 82%) as a white solid. : m.p.= 113-115 ^{o}C; R_f 0.36 (5:95 MeOH/EtOAc); $[\alpha]^{23}_{D}$ -96.0, (*c* 0.5, $CHCl_3$); $\mathbf{\nu_{max}}$(ATR)**/cm^{-1}**: 3463 (N-H), 3183 (=C-H), 3015 (C-H), 1742 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.56-1.66 (1H, m, CHC*H*HCH$_2$), 2.0-2.07 (1H, m, CHCH*H*CH$_2$), 2.45-2.54 (1H, m, CHC*H*HPh), 2.64-2.74 (2H, m, =CC*H*$_2$CH$_2$), 2.88-2.93 (1H, dd, *J* = 13.5, 5.5, CHCH*H*Ph), 3.73 (1H, m, NHC*H*), 5.36 (1H, s, C=C*H*H), 5.74 (1H, br. s, N*H*), 6.22 (s, 1H, C=CH*H*), 7.2–7.31 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.5 (CH*C*H$_2$CH$_2$), 29.3 (CH$_2$*C*H$_2$), 43.1 (CH*C*H$_2$Ph), 54.5 (NH*C*H), 122.2 (C=*C*H$_2$), 127.1 (ArCH), 128.9 (ArCH), 129.1 (ArCH), 136.6 (Ar quat.C), 137.0 (*C*=CH$_2$), 165.4 (NH*C*O); ***m/z*** (ES+): 202.1232 (MH$^+$, 100%, $C_{13}H_{16}NO$ requires 202.1226).

4.8 General procedure G: Hydrogenation reactions

A two-necked round bottomed flask, charged with a magnetic follower fitted with a three-way tap and rubber septum, was flame-dried, evacuated and back-filled with nitrogen three times. The flask was charged with palladium on carbon 10% w/w (10 mol%, 0.1 eq.), and the flask evacuated and backfilled with nitrogen three times again. A solution of cyclisation product (1.0 mmol, 1.0 eq.) in a variety of solvents (10 mL), was added to the flask *via* syringe, after that a balloon of hydrogen fitted to the three-way tap. The flask was evacuated until the solvent began to boil, then back-filled with hydrogen, and this process repeated three more times. The reaction mixture was stirred at room temperature for overnight. At which time the mixture was filtered through Celite®, and the solvent removed from the filtrate under reduced pressure. The residue was purified by flash column chromatography.

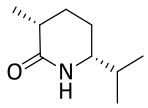
Hydrogenation of (*6R*)-3-methylidene-6-(propan-2-yl)piperidin-2-one



This reaction was performed according to the general procedure **G** using (153 mg, 1.0 mmol, 1.0 eq.) of (*6R*)-3-methylidene-6-(propan-2-yl)piperidin-2-one **230** to yield a crude mixture (139 mg, 90% overall yield). ^{1}H NMR spectroscopy for the crude product demonstrated the presence of two diastereoisomers. The purification and separation were achieved *via* preparative HPLC (XBridge Prep OBD C18 5µm 19 mmid x 250 mm), using 30:70

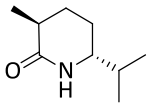
acetonitrile/water, at a flow rate of 17 mL/min and UV detection at 210 nm, room temperature. The HPLC analysis indicated that the first diastereoisomer had a retention time of 7.5 minute, which was identified as a major diastereoisomer **233a** (92 mg, 60%) as a white crystalline solid, and the second diastereoisomer had a retention time of 8.6 minute, which was identified as a minor diastereoisomer **233b** (46 mg, 30%) as a yellow oil. The configuration of the major diastereoisomer was established as a *cis*-diastereoisomer by X-ray crystallography (**Figure 10**).

(*3R,6R*)-3-Methyl-6-(propan-2-yl)piperidin-2-one (233a)



(**major diastereoisomer**) m.p.= 74-75 ^{o}C; R_f 0.39 (5:95 MeOH/EtOAc); $[\alpha]^{23}_{D}$ +27.0, (c 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3470 (N-H), 2958 (C-H), 1743 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.90 (3H, d, *J* = 7.0, CH(C*H*$_3$)(CH$_3$)), 0.93 (3H, d, *J*= 7.0, CH(CH$_3$)(C*H*$_3$)), 1.2 (3H, d, *J*= 7.5, CHC*H*$_3$), 1.52-1.72 (4H, m, CHC*H*$_2$C*H*$_2$CH), 1.80-1.89 (1H, m, C*H*(CH$_3$)(CH$_3$)), 2.43-2.52 (1H, m, C*H*CH$_3$), 3.11-3.18 (1H, m, NHC*H*), 6.01 (1H, br. s, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.9 (CH*C*H$_3$), 18.0 (CH*C*H$_3$), 18.1 (CH*C*H$_3$), 21.2 (CH*C*H$_2$CH$_2$), 26.8 (CH$_2$*C*H$_2$), 32.7 (*C*H(CH$_3$)$_2$), 35.0 (*C*HCH$_3$), 58.4 (NH*C*H), 176.3 (NH*C*O); ***m/z*** (ES+): 156.1388 (MH$^+$, 100%, $C_9H_{18}NO$ requires 156.1382).

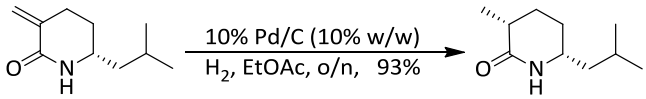
(*3S,6R*)-3-Methyl-6-(propan-2-yl)piperidin-2-one (233b)



(**minor diastereoisomer**) R_f 0.26 (5:95 MeOH/EtOAc); $[\alpha]^{23}_{D}$ +10.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3276 (N-H), 2969 (C-H), 1640 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$)

δ ppm: 0.92 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 0.94 (3H, d, *J* = 6.5, CH(CH$_3$)(C*H*$_3$)), 1.25 (3H, d, *J*= 7.0, CHC*H*$_3$), 1.40-1.47 (2H, m, NHCHC*H*$_2$), 1.61-1.69 (1H, m, CH$_3$CHC*H*H), 1.82-1.89 (1H, m, C*H*(CH$_3$)(CH$_3$)), 1.97-2.05 (1H, m, CH$_3$CHCH*H*), 2.23-2.33 (1H, m, C*H*CH$_3$), 3.16-3.24 (1H, m, NHC*H*), 5.71 (1H, br. s, N*H*); **^{13}C NMR** (100 MHz, CDCl$_3$) δ ppm: 16.9 (CH*C*H$_3$), 17.7 (CH*C*H$_3$), 17.8 (CH*C*H$_3$), 25.3 (CH*C*H$_2$CH$_2$), 29.2 (CH$_2$*C*H$_2$), 33.0 (*C*H(CH$_3$)$_2$), 36.2 (*C*HCH$_3$), 59.3 (NH*C*H), 175.8 (NH*C*O); ***m/z*** (ES+): 156.1388 (MH$^+$, 100%, $C_9H_{18}NO$ requires 156.1390).

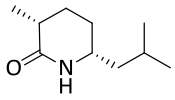
Hydrogenation of (*6R*)-3-Methylidene-6-(2-methylpropyl)piperidin-2-one



231 **234**

This reaction was carried out according to the general procedure **G** using (167 mg, 1.0 mmol, 1.0 eq.) of (*6R*)-3-methylidene-6-(2-methylpropyl)piperidin-2-one **231** to give one diastereoisomer **234,** which was confirmed by ^{1}H NMR spectroscopy for the crude product. The residue was purified by flash column chromatography on silica gel using an eluent gradient of 0.5% methanol in ethyl acetate to 10% methanol in ethyl acetate gave (157 mg, 93%) as a white crystalline solid. The pure product was identified by X-ray crystallography as a *cis*-diastereoisomer (**Figure 11**).

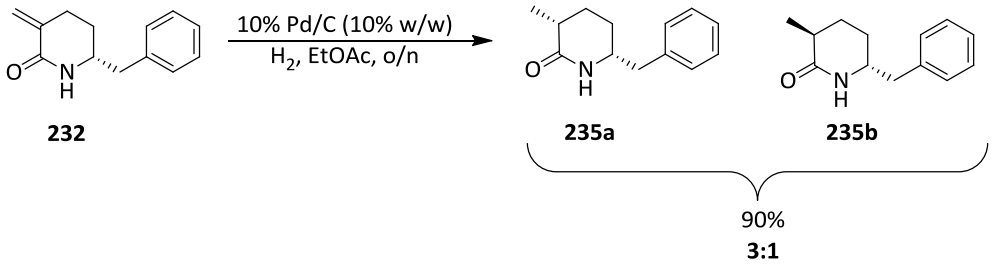
(*3R,6R*)-3-Methyl-6-(2-methylpropyl)piperidin-2-one (234)



m.p.= 57-59 ^{o}C; R_f 0.2 (5:95 MeOH/EtOAc); $[\alpha]^{23}_D$ -11.0, (*c* 1.0, CHCl$_3$); **ν_{max}(ATR)/cm^{-1}**: 3420 (N-H), 2992 (C-H), 1661 (C=O); **^{1}H NMR** (400 MHz, CDCl$_3$) δ ppm: 0.91 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 0.93 (3H, d, *J* = 6.5, CH(CH$_3$)(C*H*$_3$)),

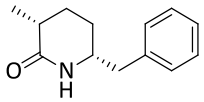
1.21-1.23 (3H, d, *J* = 7.5, CHCH_3), 1.27-1.42 (2H, m, CHCH_2CH), 1.47-1.56 (1H, m, NHCHC*H*HCH$_2$), 1.58-1.73 (2H, m, CH_2CHCH$_3$), 1.77-1.84 (m, 1H, C*H*(CH$_3$)$_2$), 1.85-1.93 (1H, m, NHCHCH*H*CH$_2$), 2.43-2.52 (1H, m, C*H*CH$_3$), 3.39-3.49 (1H, m, NHC*H*), 5.79 (1H, br. s, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.9 (CH*C*H$_3$), 22.2 (CH*C*H$_3$), 22.8 (CH*C*H$_3$), 24.3 (*C*H(CH$_3$)$_2$), 25.8 (CH*C*H$_2$CH$_2$), 26.6 (CH$_2$*C*H$_2$), 35.2 (*C*HCH$_3$), 45.9 (CH*C*H$_2$CH), 50.6(NH*C*H), 175.8 (NH*C*O); ***m/z*** (ES+): 170.1545 (MH$^+$, 100%, $C_{10}H_{20}NO$ requires 170.1546).

Hydrogenation of (*6R*)-6-benzyl-3-methylidenepiperidin-2-one



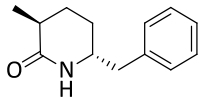
This reaction was done according to the general procedure **G** using (201 mg, 1.0 mmol, 1.0 eq.) of (*6R*)-6-benzyl-3-methylidenepiperidin-2-one **232** to yield a crude mixture **235A** and **235B** (182 mg, 90% overall yield). ^{1}H NMR spectroscopy for the crude product demonstrated two diastereoisomers. The purification and separation was achieved by flash column chromatography on silica gel, using 10% chloroform in ethyl acetate affording the major diastereoisomer (137 mg, 68%) as a white solid, and the minor diastereoisomer (45 mg, 22%) as a white crystalline solid. The configuration of the minor diastereoisomer was established as a *trans*-diastereoisomer by X-ray crystallography (**Figure 12**).

(*3R,6R*)-6-Benzyl-3-methylpiperidin-2-one (235a)



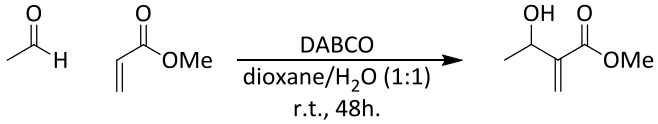
(major diastereoisomer) m.p.= 127-129 ^{o}C; R_f 0.29 (10:90 EtOAc/chloroform); $[\alpha]^{23}_{D}$ -81.0, (*c* 1.0, $CHCl_3$); ν_{max}(ATR)**/cm^{-1}**: 3206 (N-H), 2931 (C-H), 1666 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.27 (3H, d, *J* = 7.5, CHC*H*$_3$), 1.60-1.72 (2H, m, CHC*H*$_2$CH$_2$), 1.83-1.95 (2H, m, C*H*$_2$CHCH$_3$), 2.41-2.50 (1H, m, C*H*CH$_3$), 2.66 (1H, dd, *J* = 13.5, 9.0, CHC*H*HPh), 2.87 (1H, dd, *J* = 13.5, 5.5, CHCH*H*Ph), 3.58-3.67 (1H, m, NHC*H*), 5.61 (1H, br. s, N*H*), 7.17–7.36 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 18.0 (CH*C*H$_3$), 25.4 (CH*C*H$_2$CH$_2$), 26.6 (CH$_2$*C*H$_2$), 35.3 (*C*HCH$_3$), 43.3 (CH*C*H$_2$Ph), 54.1 (NH*C*H), 127.0 (ArCH), 128.8 (ArCH), 129.1 (ArCH), 136.9 (Ar quat.C), 175.6 (NH*C*O); ***m/z*** (ES+): 204.1388 (MH$^+$, 100%, $C_{13}H_{18}NO$ requires 204.1395).

(*3S,6R*)-6-Benzyl-3-methylpiperidin-2-one (235b)



(**minor diastereoisomer**) m.p.= 112-114 ^{o}C; R_f 0.5 (10:90 EtOAc/chloroform); $[\alpha]^{23}_{D}$ -61.0, (*c* 1.0, $CHCl_3$); ν_{max}(ATR)**/cm^{-1}**: 3240 (N-H), 2928 (C-H), 1675 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.23 (3H, d, *J* = 7.0, CHC*H*$_3$), 1.46-1.53 (2H, m, CHC*H*$_2$CH$_2$), 1.98-2.03 (2H, m, C*H*$_2$CHCH$_3$), 2.26-2.39 (1H, m, C*H*CH$_3$), 2.57-2.63 (1H, dd, *J* = 13.5, 9.0, CHC*H*HPh), 2.86-2.91 (1H, dd, *J* = 13.5, 5.0, CHCH*H*Ph), 3.58-3.67 (1H, m, NHC*H*), 5.52 (1H, br. s, N*H*), 7.17-7.36 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.0 (CH*C*H$_3$), 29.1 (CH*C*H$_2$CH$_2$), 29.3 (CH$_2$*C*H$_2$), 36.2 (*C*HCH$_3$), 43.6 (CH*C*H$_2$Ph), 54.9 (NH*C*H), 127.0 (ArCH), 128.9 (ArCH), 129.1 (ArCH), 136.8 (Ar quat.C), 175.1 (NH*C*O); ***m/z*** (ES+): 204.1388 (MH$^+$, 100%, $C_{13}H_{18}NO$ requires 204.1391).

Methyl 3-hydroxy-2-methylidenebutanoate (236)

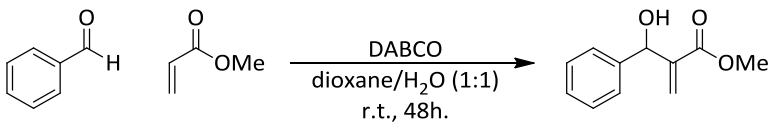


236

1,4-Diazabicyclo[2.2.2]octan (DABCO) (1.12 g, 10.0 mmol, 1.0 eq.) was added to a solution of acetaldehyde (0.44 g, 10.0 mmol, 1.0 eq.) in dioxane/water (1:1) (0.1 mL/1.0 mmol) and methyl acrylate (2.58 g, 30.0 mmol, 3.0 eq.). The reaction mixture was stirred at room temperature for 48 h. Upon completion, water (50 mL) was added and the mixture was extracted with dichloromethane (3 × 75 mL) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give the title compound **236** (1.25 g, 96%) as a colourless liquid which was used without further purification. : **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.30 (3H, d, *J* = 6.5, C*H*$_3$CH), 3.10 (1H, br. s, CH_3CHO*H*), 3.72 (3H, s, CO_2CH_3), 4.57 (1H, q, *J* = 6.5, CH_3C*H*OH), 5.80 (1H, s, C=C*H*H), 6.16 (1H, s, C=CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 22.2 (*C*H_3), 51.8 (CO_2CH_3), 66.6 (*C*HOH), 123.9 (C=*C*H_2), 143.7 (*C*=CH_2), 167.0 (*C*O_2Me); ***m/z*** (ES+): 153.0523 (MNa^+, 100%, $C_6H_{10}O_3Na$ requires 153.0528).

These characterisation data are in accordance with the literature values.[74,75]

Methyl 2-[hydroxy(phenyl)methyl]prop-2-enoate (237)



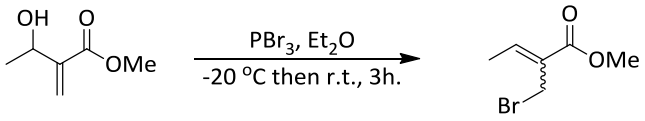
237

1,4-Diazabicyclo[2.2.2]octan (DABCO) (1.12 g, 10.0 mmol, 1.0 eq.) was added to a solution of benzaldehyde (1.06 g, 10.0 mmol, 1.0 eq.) in dioxane/water (1:1) (0.1 mL/1.0 mmol) and methyl acrylate (2.58 g, 30.0 mmol, 3.0 eq.). The reaction mixture was stirred at room temperature for 48h. Upon completion,

water (50 mL) was added and the mixture was extracted with dichloromethane (3 × 75 mL) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give the title compound **237** (1.78 g, 93%) as a colourless liquid which was used without further purification. : **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 3.39-3.52 (1H, br. s, PhCHO*H*), 3.70 (3H, s, CO_2CH_3), 5.55 (1H, s, PhC*H*OH), 5.88 (1H, s, C=C*H*H), 6.34 (1H, s, C=CH*H*), 7.26-7.38 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 51.8 (CO_2CH_3), 72.5 (*C*HOH), 125.4 (C=CH_2), 126.8 (ArCH), 127.7 (ArCH), 128.3 (ArCH), 141.6 (Ar quat.C), 142.3 (*C*=CH_2), 166.6 (*C*O_2Me); ***m/z*** (ES+): 215.0681 (MNa^+, 100%, $C_{11}H_{12}O_3Na$ requires 215.0684).

These characterisation data are in accordance with the literature values.[74,75]

Methyl (*E/Z*)-2-(bromomethyl)but-2-enoate (241)

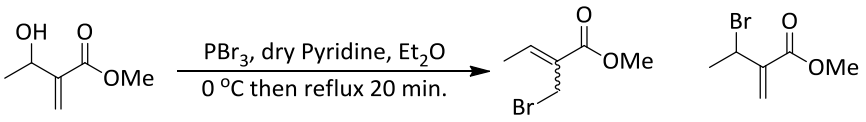


236 **241**

A round-bottomed flask, was charged with a magnetic follower and a solution of methyl 2-(hydroxymethyl)prop-2-enoate **236** (6.5 g, 50.0 mmol) in Et_2O (100 mL). phosphorus tribromide (5.42 g, 1.88 mL, 20.0 mmol) was added dropwise to the reaction mixture at -20 °C. The resulting mixture was allowed to warm to room temperature and stirred for 3h. Subsequently, The solution was cooled to 0 °C, and water (50 mL) was added carefully. The mixture was extracted with hexane (3 x 50 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude of methyl (*E/Z*)-2-(bromomethyl)but-2-enoate **241**, which purified by flash chromatography on silica, using an eluent gradient of 5% ethyl acetate in chloroform to 20% ethyl acetate in chloroform to give the title compound (7.5 g, 78%) as a yellow liquid

with pungent smell. : R_f 0.38 (10:90 EtOAc/chloroform); ν_{max}(ATR)/cm^{-1}: 3001 (C-H), 2956 (C-H), 1713 (C=O), 1647 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.91 (3H, d, *J* = 7.0, C*H*$_3$CH=C), 3.78 (3H, s, CO_2CH_3), 4.23 (2H, s, BrC*H*$_2$), 7.07 (1H, q, *J* = 7.0, CH$_3$C*H*=C); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 14.5 (*C*H$_3$CH=), 24.0 (Br*C*H$_2$), 51.1 (CO_2CH_3), 130.2 (=*C*CO$_2$Me), 143.4 (CH$_3$*C*H=), 166.0 (*C*O$_2$Me); ***m/z*** (ES+): 192.9864 (MH^+, 100%, $C_6H_{10}O_2{}^{79}Br$ requires 192.9867), 194.9844 (MH^+, 100%, $C_6H_{10}O_2{}^{81}Br$).

Methyl 3-bromo-2-methylidenebutanoate (242)[76]



236

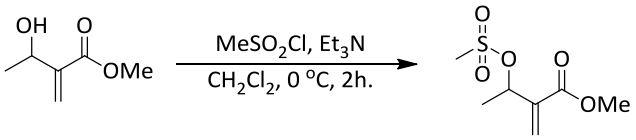
241
50%
E,Z

242
50%

A round-bottomed flask, was charged with a magnetic follower and a solution of methyl 3-hydroxy-2-methylidenebutanoate **236** (1.17 g, 9.0 mmol, 1.0 eq.) in dry Et_2O (50 mL) and dry pyridine (72 mg, 0.9 mmol, 0.1 eq.). Phosphorus tribromide (1.29 g, 4.8 mmol, 1.9 eq.) in dry Et_2O (5 mL) was added to the reaction mixture over 15 minutes at 0 °C. The reaction mixture was heated to reflux for 20 min. After cooling the mixture was poured onto ice, organic layer was separated and washed water (5 mL), saturated sodium carbonate solution (5 mL), water (5 mL) respectively, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude mixture of compounds. The separation was performed by flash chromatography on silica, using an eluent gradient of 5% ethyl acetate in chloroform to 20% ethyl acetate in chloroform, to give the title compound **242** (860 mg, 50%) as a pale yellow to colourless liquid. : R_f 0.26 (10:90 EtOAc/chloroform). : ν_{max}(ATR)/cm^{-1}: 2988(C-H), 2955 (C-H), 1717 (C=O), 1633 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.52 (3H, d, *J* = 6.0, C*H*$_3$CHBr), 3.78 (3H, s, CO_2CH_3), 5.36-5.46 (H, m, CH$_3$C*H*Br), 5.98 (1H, s, C=CH*H*), 6.36 (1H, s,

C=C*H*H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 22.5 (*C*H_3CHBr), 52.06 (CH_3*C*HBr), 52.08 (CO_2*C*H_3), 125.9 (C=*C*H_2), 140.7 (*C*=CH_2), 165.4 (*C*O_2Me); ***m/z*** (ES+): 192.9864 (MH^+, 100%, $C_6H_{10}O_2{}^{79}Br$ requires 192.9864), 194.9840 (MH^+, 100%, $C_6H_{10}O_2{}^{81}Br$), and methyl (*E/Z*)-2-(bromomethyl)but-2-enoate **241** (860 mg, 50%) as yellow liquid with pungent smell. : R_f 0.38 (10:90 EtOAc/chloroform).

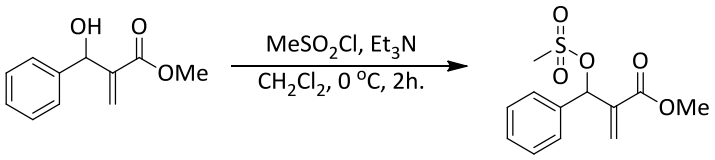
Methyl 3-(methanesulfonyloxy)-2-methylidenebutanoate (243)



236 **243**

A round-bottomed flask, was charged with a magnetic follower and a solution of methyl 3-hydroxy-2-methylidenebutanoate **236** (1.3 g, 10.0 mmol, 1.0 eq.) in CH_2Cl_2 (50 mL). Methanesulfonyl chloride (2.3 g, 1.55 mL, 20.0 mmol, 2.0 eq.) and triethylamine (2.0 g, 2.75 mL, 20.0 mmol, 2.0 eq.) were added to the reaction mixture at 0 ^oC respectively. After stirring for 2h, the resulting mixture was allowed to warm up to room temperature. The mixture was washed with water (30 mL) and the organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure to yield the crude of methyl 3-(methanesulfonyloxy)-2-methylidenebutanoate **243** (1.3 g, 65%) as a colourless liquid which was used without further purification. : $\mathbf{\nu_{max}}$(ATR)**/cm^{-1}**: 3016 (C-H), 2934 (C-H), 1716 (C=O), 1616 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.60 (3H, d, *J* = 6.5, C*H*$_3$CH), 3.04 (3H, s, SO_2CH_3), 3.81 (3H, s, CO_2CH_3), 5.59 (1H, q, *J* = 6.5, CH_3C*H*), 6.05 (1H, s, C=C*H*H), 6.44 (1H, s, C=CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 16.4 (*C*H_3), 38.5 (SO_2*C*H_3), 54.0 (CO_2*C*H_3), 66.9 (*C*HOMs), 127.2 (C=*C*H_2), 139.1 (*C*=*C*H_2), 165.2 (*C*O_2Me); ***m/z*** (ES+): 209.0484 (MH^+, 100%, $C_7H_{13}O_5S$ requires 209.0474).

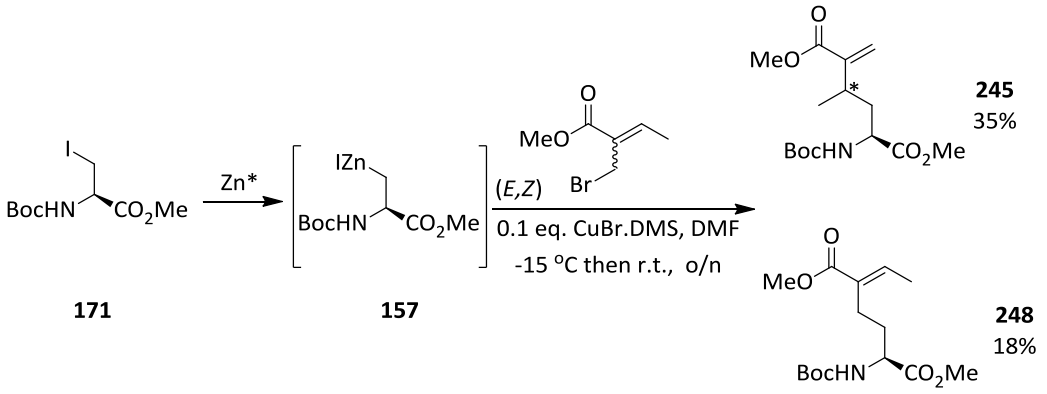
Methyl 2-[(methanesulfonyloxy)(phenyl)methyl]prop-2-enoate (244)



237 **244**

A round-bottomed flask, was charged with a magnetic follower and a solution of methyl 2-[hydroxy(phenyl)methyl]prop-2-enoate **237** (1.92 g, 10.0 mmol, 1.0 eq.) in dichloromethane (50 mL). Methanesulfonyl chloride (2.3 g, 1.55 mL, 20.0 mmol, 2.0 eq.) and triethylamine (2.0 g, 2.75 mL, 20.0 mmol, 2.0 eq.) were added to the reaction mixture at 0 ^{o}C respectively. After stirring for 2h, the resulting mixture was allowed to warm up to room temperature. The mixture was washed with water (30 mL) and the organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude of methyl 2-[(methanesulfonyloxy)(phenyl)methyl]prop-2-enoate **244** (1.62 g, 60%) as a colourless liquid which was used without further purification. : $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 2932 (C-H), 1716 (C=O), 1616 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 3.12 (3H, s, C*H*$_3$SO$_2$), 3.71 (3H, s, CO$_2$C*H*$_3$), 5.99 (1H, s, PhC*H*), 6.44 (1H, s, C=C*H*H), 6.49 (1H, s, C=CH*H*), 7.35-7.42 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 39.1 (SO$_2$*C*H$_3$), 53.5 (CO$_2$*C*H$_3$), 67.0 (*C*HOMs), 127.7 (C=*C*H$_2$), 128.8 (ArCH), 129.3 (ArCH), 129.7 (ArCH), 138.1 (Ar quat.C), 152.4 (*C*=CH$_2$), 164.9 (*C*O$_2$Me); ***m/z*** (ES+): 293.0460 (MNa$^+$, 100%, $C_{12}H_{14}O_5NaS$ requires 293.0464).

1,6-Dimethyl (*5S*)-5-([(*tert*-butoxy)carbonyl]amino)-3-methyl-2-methylidenehexanedioate (245)

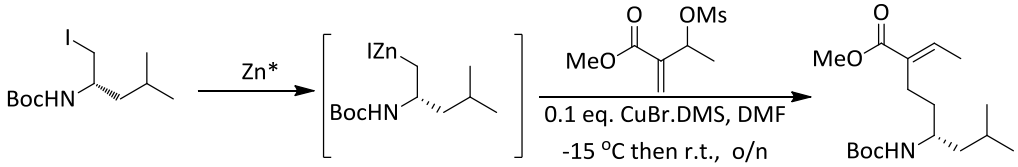


171 157

Organozinc reagent **157** was synthesised according to the general procedure **D**, using methyl (*2R*)-2-([(*tert*-butoxy)carbonyl]amino)-3-iodopropanoate **171** (987 mg, 3.0 mmol). The allylation reaction between **157** and methyl-2-(bromomethyl)but-2-enoate **241** was performed according to the general procedure **E** to give a mixture of compounds (500 mg, 53% overall yield). ^{1}H NMR spectroscopy for the crude product showed three compounds. The separation was done by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **245** (334 mg, 35%) as a yellow oil. (**two inseparable diastereoisomers**) : R_f 0.36 (20:80 EtOAc/petroleum ether); **ν_{max}(ATR)/cm^{-1}**: 3373 (N-H), 2977 (C-H), 1718 (C=O), 1627 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm : 1.14 (3H, d, *J* = 7.0, C*H*$_3$CHC=), 1.16 (3H, d, *J* = 7.0, C*H*$_3$CHC=), 1.42 (9H, s, C(C*H*$_3$)$_3$), 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.59-1.88 (4H, m, 2NHCHC*H*$_2$), 2.78-2.88 (2H, m, 2CH$_3$C*H*C=), 3.70 (3H, s, CHCO$_2$C*H*$_3$), 3.73 (3H, s, CHCO$_2$C*H*$_3$), 3.75 (3H, s, =CCO$_2$C*H*$_3$), 3.76 (3H, s, =CCO$_2$C*H*$_3$), 4.22-4.36 (2H, m, 2NHC*H*), 5.01 (1H, d, *J* = 8.5, N*H*), 5.12 (1H, d, *J* = 8.5, N*H*), 5.59 (1H, s, C=C*H*H), 5.61 (1H, s, C=CH*H*), 6.21 (1H, s, C=C*H*H), 6.23 (1H, s, C=CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 19.0 & 20.5 (*C*H$_3$CH), 28.2 (C(*C*H$_3$)$_3$), 31.4 & 31.9 (CH$_3$*C*H), 38.5 & 38.6 (NHCH*C*H$_2$), 51.7 & 52.1 (CO$_2$*C*H$_3$), 51.8 & 52.2 (=CCO$_2$*C*H$_3$), 51.6 & 51.9 (NH*C*H), 79.7 & 79.8 (*C*(CH$_3$)$_3$), 123.9 & 124.1 (C=*C*H$_2$), 143.9 & 144.4 (*C*=CH$_2$), 155.1 & 155.5 (NH*C*O),

167.2 & 167.3 (=C*C*O_2Me or CH*C*O_2Me), 173.1 & 173.4 (=C*C*O_2Me or CH*C*O_2Me); ***m/z*** (ES+): 316.1760 (MH^+, 100%, $C_{15}H_{26}NO_6$ requires 316.1764) and 1,6-Dimethyl (*2S,5E*)-2-([(*tert*-butoxy)carbonyl]amino)-5-ethylidenehexanedioate **248** (166 mg, 18%) as a pale yellow oil. : R_f 0.31 (20:80 EtOAc/petroleum ether).

Methyl (*2E,5R*)-5-([(*tert*-butoxy)carbonyl]amino)-2-ethylidene-7-methyloctanoate (246)

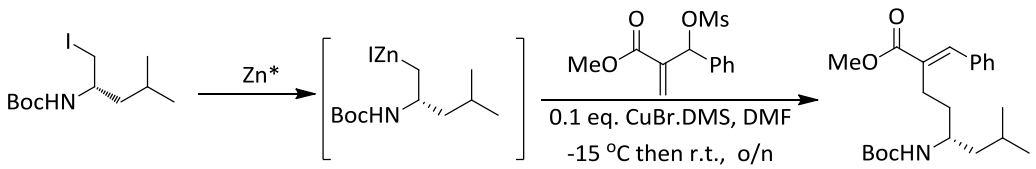


197 **220** **246**

Organozinc reagent **220** was synthesised according to the general procedure **D**, using *tert*-butyl *N*-[(*2S*)-1-iodo-4-methylpentan-2-yl]carbamate **197** (981 mg, 3.0 mmol). The allylation reaction between **220** and methyl 3-(methanesulfonyloxy)-2-methylidenebutanoate **243** was performed according to the general procedure **E**. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **246** (525 mg, 56%) as a yellow solid. : m.p.= 46-48 °C; R_f 0.29 (20:80 EtOAc/petroleum ether); $[\alpha]^{25}_D$ -13.0, (*c* 1.0, $CHCl_3$); $\mathbf{\nu_{max}}$(ATR)**/cm^{-1}**: 3350 (N-H), 2957 (C-H), 1715 (C=O), 1519 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.91 (3H, d, *J* = 6.0, CH(C*H*$_3$)(CH$_3$)), 0.93 (3H, d, *J* = 6.0, CH(CH$_3$)(C*H*$_3$)), 1.23-1.32 (2H, m, CHC*H*$_2$CH), 1.34-1.42(1H, m, C*H*(CH$_3$)$_2$), 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.53-1.61 (1H, m, NHCHC*H*H), 1.62-1.68 (1H, m, NHCHCH*H*), 1.81 (3H, d, *J* = 7.0, C*H*$_3$CH=), 2.30-2.40 (2H, m, CH$_2$C*H*$_2$C=), 3.59-3.68 (1H, m, NHC*H*), 3.74 (3H, s, CO$_2$C*H*$_3$), 4.32 (1H, d, *J* = 9.0, N*H*), 6.86 (1H, q, *J* = 7.0, CH$_3$C*H*=C); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 14.1 (*C*H$_3$CH=), 22.4 (CH*C*H$_3$), 22.8 (CH$_2$*C*H$_2$C=), 23.0 (CH*C*H$_3$), 24.9 (CH(*C*H$_3$)$_2$), 28.4 (C(*C*H$_3$)$_3$), 34.8 (NHCH*C*H$_2$CH$_2$), 44.8 (CH*C*H$_2$CH), 48.9 (NH*C*H), 51.6 (CO$_2$*C*H$_3$), 78.8 (*C*(CH$_3$)$_3$), 132.7 (C=*C*HCH$_3$),

137.7 (*C*=CHCH$_3$), 155.6 (NH*C*O), 168.1 (*C*O$_2$Me); ***m/z*** (ES+): 314.2331 (MH$^+$, 100%, $C_{17}H_{32}NO_4$ requires 314.2338).

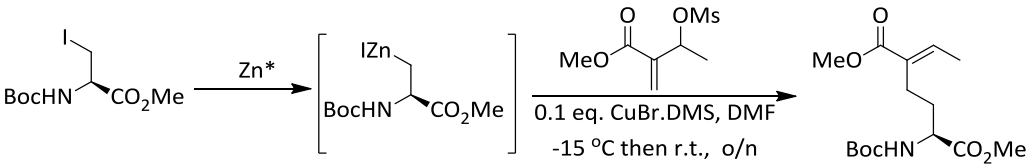
Methyl (*2E,5R*)-5-([(*tert*-butoxy)carbonyl]amino)-7-methyl-2-(phenylmethylidene)octanoate (247)



197 **220** **247**

Organozinc reagent **220** was synthesised according to the general procedure **D**, using *tert*-butyl *N*-[(*2S*)-1-iodo-4-methylpentan-2-yl]carbamate **197** (654 mg, 2.0 mmol). The allylation reaction between **220** and methyl 2-[(methanesulfonyloxy)(phenyl)methyl]prop-2-enoate **244** was performed according to the general procedure **E**. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **247** (390 mg, 52%) as a yellow solid. : m.p.= 43-45 °C; R_f 0.24 (20:80 EtOAc/petroleum ether); $[\alpha]^{23}_D$ -25.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3365 (N-H), 2980 (C-H), 1706 (C=O), 1524 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.92 (6H, d, *J* = 7.5, CH(C*H*$_3$)$_2$), 1.23-1.34 (2H, m, CHC*H*$_2$CH), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.52-1.61 (1H, m, NHCHC*H*H), 1.63-1.71 (1H, m, C*H*(CH$_3$)$_2$), 1.72-1.82 (1H, m, NHCHCH*H*), 2.48-2.62 (m, 2H, CH$_2$C*H*$_2$C=), 3.66-3.75 (1H, m, NHC*H*), 3.83 (3H, s, CO$_2$C*H*$_3$), 4.33 (1H, d, *J* = 9.0, N*H*), 7.35-7.45 (5H, m, Ar*H*), 7.69 (1H, s, PhC*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 22.4 (CH*C*H$_3$), 22.9 (CH*C*H$_3$), 24.0 (*C*H$_2$C=), 24.9 (*C*H(CH$_3$)$_2$), 28.4 (C(*C*H$_3$)$_3$), 35.1 (NHCH*C*H$_2$CH$_2$), 44.6 (CH*C*H$_2$CH), 49.1 (NH*C*H), 52.0 (CO$_2$*C*H$_3$), 78.8 (*C*(CH$_3$)$_3$), 128.4 (C=*C*HPh), 128.5 (ArCH), 129.1 (ArCH), 132.8 (ArCH), 135.5 (Ar quat.C), 139.3 (*C*=CHPh), 155.6 (NH*C*O), 168.7 (*C*O$_2$Me); ***m/z*** (ES+): 376.2488 (MH$^+$, 100%, $C_{22}H_{34}NO_4$ requires 376.2494).

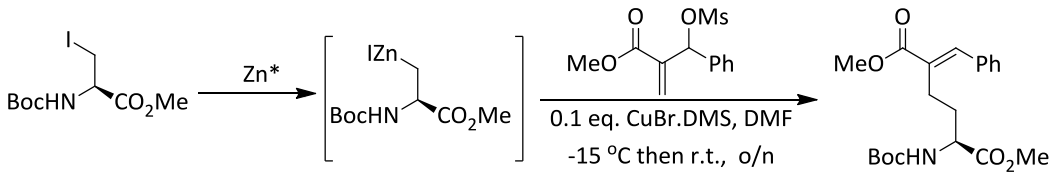
1,6-Dimethyl (*2S,5E*)-2-([(*tert*-butoxy)carbonyl]amino)-5-ethylidenehexanedioate (248)



171 **157** **248**

Organozinc reagent **157** was synthesised according to the general procedure **D**, using methyl (*2R*)-2-([(*tert*-butoxy)carbonyl]amino)-3-iodopropanoate **171** (987 mg, 3.0 mmol). The allylation reaction between **157** and methyl 3-(methanesulfonyloxy)-2-methylidenebutanoate **243** was performed according to the general procedure **E**. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **248** (530 mg, 56%) as a pale yellow oil. : R_f 0.31 (20:80 EtOAc/petroleum ether); $[\alpha]^{25}_D$ +23.0, (*c* 1.0, $CHCl_3$); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 3367 (N-H), 2978 (C-H), 1712 (C=O), 1649 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.43 (9H, s, C(C*H*$_3$)$_3$), 1.66-1.75 (1H, m, CHC*H*HCH$_2$), 1.78 (3H, d, *J* = 7.0, C*H*$_3$CH=C), 1.86-1.98 (1H, m, CHCH*H*CH$_2$), 2.30-2.39 (2H, m, CH$_2$C*H*$_2$C=), 3.70 (3H, s, CHCO$_2$C*H*$_3$), 3.72 (3H, s, =CCO$_2$C*H*$_3$), 4.22-4.30 (1H, m, NHC*H*), 5.18 (1H, d, *J* = 8.0, N*H*), 6.87 (1H, q, *J* = 7.0, CH$_3$C*H*=C); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 14.1 (*C*H$_3$CH), 22.2 (CH$_2$*C*H$_2$C=), 28.2 (C(*C*H$_3$)$_3$), 31.3 (CH*C*H$_2$), 51.6 (CO$_2$*C*H$_3$), 52.2 (=CCO$_2$*C*H$_3$), 53.2 (NH*C*H), 79.8 (*C*(CH$_3$)$_3$), 131.5 (C=*C*HCH$_3$), 138.7 (*C*=CHCH$_3$), 155.4 (NH*C*O), 167.7 (=C*C*O$_2$Me or CH*C*O$_2$Me), 173.1 (=C*C*O$_2$Me or CH*C*O$_2$Me); ***m/z*** (ES+): 316.1760 (MH$^+$, 100%, $C_{15}H_{26}NO_6$ requires 316.1747).

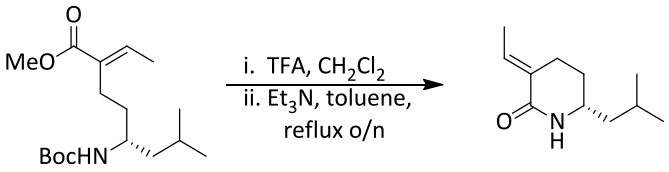
1,6-Dimethyl (*2S,5E*)-2-([(*tert*-butoxy)carbonyl]amino)-5-(phenylmethylidene)hexanedioate (249)



171 **157** **249**

Organozinc reagent **157** was synthesised according to the general procedure **D**, using methyl (*2R*)-2-([(*tert*-butoxy)carbonyl]amino)-3-iodopropanoate **171** (658 mg, 2.0 mmol). The allylation reaction between **157** and methyl 2-[(methanesulfonyloxy)(phenyl)methyl]prop-2-enoate **244** was performed according to the general procedure **E**. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **249** (430 mg, 57%) as a pale yellow oil. : R_f 0.26 (20:80 EtOAc/petroleum ether); $[\alpha]^{25}_D$ +29.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3374 (N-H), 2977 (C-H), 1712 (C=O), 1630 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.87-1.97 (1H, m, CHC*H*HCH$_2$), 2.05-2.16 (1H, m, CHCH*H*CH$_2$), 2.49-2.66 (2H, m, CH$_2$C*H*$_2$C=), 3.73 (3H, s, CHCO$_2$C*H*$_3$), 3.83 (3H, s, =CCO$_2$C*H*$_3$), 4.32-4.41 (1H, m, NHC*H*), 5.17 (1H, d, *J* = 8.0, N*H*), 7.31-7.44 (5H, m, Ar*H*), 7.73 (1H, s, PhC*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 23.4 (CH$_2$*C*H$_2$C=), 28.2 (C(*C*H$_3$)$_3$), 31.5 (CH*C*H$_2$), 52.0 (CO$_2$*C*H$_3$), 52.2 (CO$_2$*C*H$_3$), 53.3 (NH*C*H), 79.8 (*C*(CH$_3$)$_3$), 126.6 (C=*C*HPh), 128.5 (ArCH), 129.0 (ArCH), 131.5 (ArCH), 135.2 (Ar quat.C), 140.2 (*C*=CHPh), 155.5 (NH*C*O), 168.3 (=C*C*O$_2$Me or CH*C*O$_2$Me), 172.8 (=C*C*O$_2$Me or CH*C*O$_2$Me); ***m/z*** (ES+): 378.1917 (MH$^+$, 100%, $C_{20}H_{28}NO_6$ requires 378.1915).

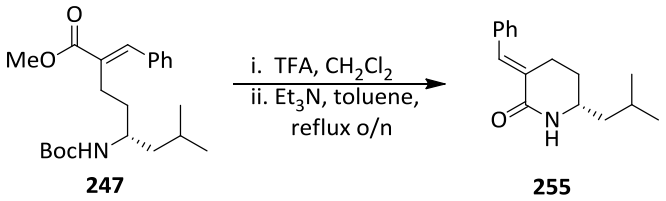
(*3E,6R*)-3-Ethylidene-6-(2-methylpropyl)piperidin-2-one (254)



246 **254**

This reaction was performed according to the general procedure **F** using (626 mg, 2.0 mmol, 2.0 eq.) of methyl (*2E,5R*)-5-([(*tert*-butoxy)carbonyl]amino)-2-ethylidene-7-methyloctanoate **246** to yield (*3E,6R*)-3-ethylidene-6-(2-methylpropyl)piperidin-2-one **254**, which was purified *via* flash column chromatography, using an eluent gradient of 0.5% methanol in ethyl acetate to 10% methanol in ethyl acetate (300 mg, 83%) as a brown solid. : m.p.= 76-78 ^{o}C; R_f 0.40 (5:95 MeOH/EtOAc); $[\alpha]^{25}_{D}$ -42.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3179 (N-H), 2952 (C-H), 1623 (C=O amide); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.93 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 0.95 (3H, d, *J* = 6.5, CH(CH$_3$)(C*H*$_3$)), 1.25-1.38 (2H, m, CHC*H*$_2$CH), 1.39-1.52 (1H, m, NHCHC*H*H), 1.77 (3H, d, *J* = 7.5, C*H*$_3$CH), 1.90-2.01 (1H, m, C*H*(CH$_3$)$_2$), 2.22-2.63 (1H, m, CH$_2$C*H*HC=), 2.65-2.73 (1H, m, CH$_2$CH*H*C=), 3.43-3.54 (1H, m, NHC*H*), 5.71 (1H, br. s, N*H*), 6.90-7.00 (1H, m, CH$_3$C*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 13.5 (*C*H$_3$CH=), 22.4 (CH*C*H$_3$), 22.90 (CH*C*H$_3$), 22.95 (=C*C*H$_2$CH$_2$), 24.3 (*C*H(CH$_3$)$_2$), 28.9 (CH*C*H$_2$CH$_2$), 45.5 (NHCH*C*H$_2$CH), 50.3 (NH*C*H), 129.0 (C=*C*HCH$_3$), 133.9 (*C*=CHCH$_3$), 166.3 (NH*C*O); ***m/z*** (ES+): 182.1545 (MH$^+$, 100%, $C_{11}H_{20}NO$ requires 182.1547).

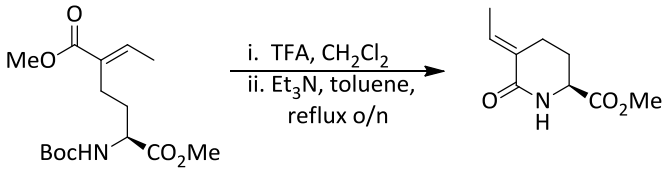
(*3E,6R*)-6-(2-Methylpropyl)-3-(phenylmethylidene)piperidin-2-one (255)



247 **255**

This reaction was performed according to the general procedure **F** using (750 mg, 2.0 mmol, 2.0 eq.) of methyl (*2E,5R*)-5-([(*tert*-butoxy)carbonyl]amino)-7-methyl-2-(phenylmethylidene)octanoate **247** to yield (*3E,6R*)-6-(2-methylpropyl)-3-phenylmethylidene)piperidin-2-one **255** which was purified *via* flash column chromatography, using an eluent gradient of 0.5% methanol in ethyl acetate to 10% methanol in ethyl acetate (420 mg, 86%) as a pale brown solid.: m.p.= 130-132 ^{o}C; R_f 0.38 (5:95 MeOH/EtOAc); $[\alpha]^{24}_{D}$ +10.0, (*c* 1.0, MeOH); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 3353 (N-H), 2958 (C-H), 1652 (C=O amide); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.86 (3H, d, *J* = 6.0, CH(C*H*$_3$)(CH$_3$)), 0.88 (3H, d, *J* = 6.0, CH(CH$_3$)(C*H*$_3$)), 1.20-1.29 (1H, m, C*H*(CH$_3$)$_2$), 1.30-1.48 (2H, m, CHC*H*$_2$CH), 1.66-1.80 (1H, m, NHCHC*H*H), 1.83-1.91 (1H, m, NHCHCH*H*), 2.56-2.70 (1H, m, CH$_2$C*H*HC=), 2.77-2.87 (1H, m, CH$_2$CH*H*C=), 3.42-3.50 (1H, m, NHC*H*), 7.33 (1H, br. s, N*H*), 7.38-7.58 (5H, m, Ar*H*), 7.76 (1H, s, PhC*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 22.8 (CH*C*H$_3$), 23.4 (CH*C*H$_3$), 24.1 (*C*H(CH$_3$)$_2$), 24.7 (=C*C*H$_2$CH$_2$), 28.5 (NHCH*C*H$_2$CH$_2$), 45.1 (CH*C*H$_2$CH), 49.8 (NH*C*H), 128.4 (C=*C*HPh), 128.8 (ArCH), 130.1 (ArCH), 131.0 (ArCH), 133.6 (Ar quat.C), 136.0 (*C*=CHPh), 165.1 (NH*C*O); ***m/z*** (ES+): 244.1701 (MH^{+}, 100%, $C_{16}H_{22}NO$ requires 244.1711).

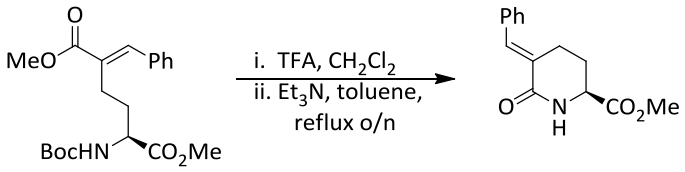
Methyl (*2S,5E*)-5-ethylidene-6-oxopiperidine-2-carboxylate (256)



248 **256**

This reaction was performed according to the general procedure **F** using (316 mg, 1.0 mmol, 1.0 eq.) of 1,6-dimethyl (*2S,5E*)-2-([(*tert*-butoxy)carbonyl]amino)-5-ethylidenehexanedioate **248** to yield methyl (*2S,5E*)-5-ethylidene-6-oxopiperidine-2-carboxylate **256**, which was purified *via* flash column chromatography, using an eluent gradient of 0.5% methanol in ethyl acetate to 10% methanol in ethyl acetate (162 mg, 88%) as a thick brown oil. : R_f 0.38 (5:95 MeOH/EtOAc); $[\alpha]^{23}_{D}$ +9.0, (*c* 1.0, MeOH); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 3399 (N-H), 2958 (C-H), 1682 (C=O ester), 1636 (C=O amide); **^{1}H NMR** (400 MHz, DMSO) δ ppm: 1.65 (3H, d, *J* = 7.0, C*H*$_3$CH=), 1.86-1.97 (2H, m, NHCHC*H*$_2$), 2.12-2.21 (1H, m, CH$_2$C*H*HC=), 2.42-2.45 (1H, m, CH$_2$CH*H*C=), 3.64 (3H, s, CHCO$_2$C*H*$_3$), 4.07-4.12 (1H, m, NHC*H*), 6.63-6.70 (1H, m, CH$_3$C*H*=), 7.62 (1H, br. s, N*H*); **^{13}C NMR** (100 MHz, DMSO) δ ppm: 13.5 (*C*H$_3$CH), 21.6 (CH$_2$*C*H$_2$C), 25.4 (CH*C*H$_2$CH$_2$), 52.6 (CO$_2$*C*H$_3$), 53.6 (NH*C*H), 129.5 (CH$_3$*C*H), 133.0 (*C*=CHCH$_3$), 164.5 (NH*C*O), 173.0 (*C*O$_2$Me); ***m/z*** (ES+): 184.0974 (MH$^+$, 100%, $C_9H_{14}NO_3$ requires 184.0970).

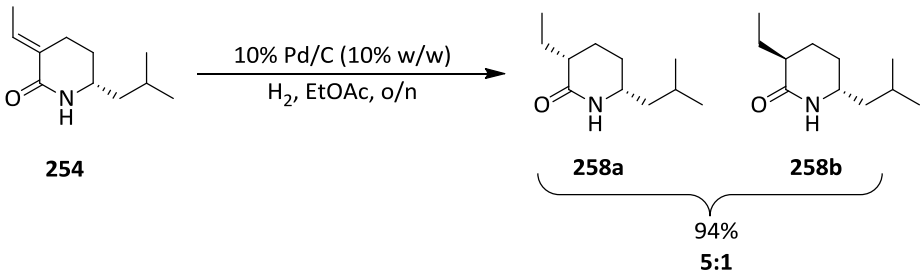
Methyl (*2S,5E*)-6-oxo-5-(phenylmethylidene)piperidine-2-carboxylate (257)



249 **257**

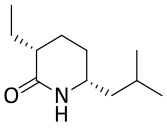
This reaction was performed according to the general procedure **F** using (378 mg, 1.0 mmol, 1.0 eq.) of 1,6-dimethyl (*2S,5E*)-2-([(*tert*-butoxy)carbonyl]amino)-5-(phenylmethylidene)hexanedioate **249** to yield methyl (*2S,5E*)-6-oxo-5-(phenylmethylidene)piperidine-2-carboxylate **257**, which was purified *via* flash column chromatography, using an eluent gradient of 0.5% methanol in ethyl acetate to 10% methanol in ethyl acetate (197 g, 80%) as a thick brown oil. : R_f 0.40 (5:95 MeOH/EtOAc); $[\alpha]^{23}_{D}$ -15.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3213 (N-H), 2956 (C-H), 1741 (C=O ester), 1659 (C=O amide); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.88-2.00 (1H, m, NHCHC*H*H), 2.26-2.37 (1H, m, NHCHCH*H*), 2.73-2.86 (1H, m, CH_2CHHC=), 2.93-3.04 (1H, m, CH_2CHHC=), 3.83 (3H, s, $CHCO_2CH_3$), 4.20-4.29 (1H, m, NHC*H*), 6.46 (1H, br. s, N*H*), 7.31-7.47 (5H, m, Ar*H*), 7.87 (1H, s, PhC*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 24.8 (CH_2CH_2C), 25.9 ($CHCH_2CH_2$), 52.8 (CO_2CH_3), 54.2 (NH*C*H), 127.7 (C=*C*HPh), 128.42 (ArCH), 128.45 (ArCH), 129.8 (ArCH), 135.4 (Ar quat.C), 136.9 (*C*=CHPh), 165.5 (NH*C*O), 171.2 (CO_2Me); ***m/z*** (ES+): 246.1130 (MH^+, 100%, $C_{14}H_{16}NO_3$ requires 246.1140).

Hydrogenation of (*3E,6R*)-3-ethylidene-6-(2-methylpropyl)piperidin-2-one



This reaction was carried out according to the general procedure **G** using (181 mg, 1.0 mmol, 1.0 eq.) of (*3E,6R*)-3-ethylidene-6-(2-methylpropyl)piperidin-2-one **254** to yield a crude mixture **258a** and **258b** (170 mg, 94% overall yield). ^{1}H NMR spectroscopy for the crude product showed the presence of two diastereoisomers. The purification and separation were achieved by preparative HPLC (XBridge Prep OBD C18 5µm 19 mmid x 250 mm), using 30:70 acetonitrile/water, at a flow rate of 17 mL/min and UV detection at 210 nm, room temperature. The HPLC analysis indicated that the first diastereoisomer had a retention time of 18.3 minute, which was identified as a major diastereoisomer **258a** (142 mg, 79%) as a white solid, and the second diastereoisomer had a retention time of 20.8 minute, which was identified as a minor diastereoisomer **258b** (28 mg, 15%) as a white solid.

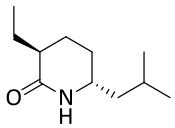
(*3R,6R*)-3-Ethyl-6-(2-methylpropyl)piperidin-2-one (258a)



(**major diastereoisomer**) m.p.= 59-60 ^{o}C; $[\alpha]^{25}_{D}$ -26.0, (*c* 0.5, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3199 (N-H), 2957 (C-H), 1652 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.92 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 0.94 CH(CH$_3$)(C*H*$_3$)), 0.99 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$CH), 1.25-1.41 (2H, m, NHCHC*H*$_2$), 1.46-1.75 (2H, m, CHC*H*$_2$CH), 1.62-1.71 (2H, m, NHCHCH$_2$C*H*$_2$), 1.77-1.86 (2H, m, CH$_3$C*H*$_2$), 1.89-1.96 (1H, m, C*H*(CH$_3$)$_2$),

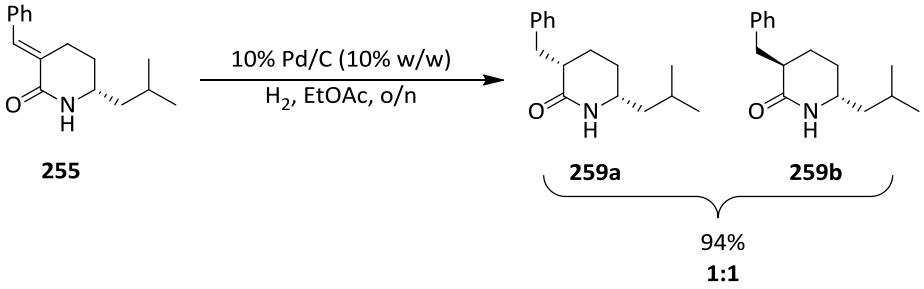
2.18-2.28 (1H, m, CH_3CH_2CH), 3.37-3.49 (1H, m, NHC*H*), 5.69 (1H, br. s, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 11.8 (CH_3CH), 22.2 ($CH(CH_3)_2$), 22.8 ($CH(CH_3)_2$), 22.9 ($NHCHCH_2CH_2$), 24.3 (CH_3CH), 24.7 ($NHCHCH_2CH_2$), 25.8 ($CH(CH_3)_2$), 41.9 ($NHCHCH_2CH$), 50.5 (CH_3CHCH_2), 51.3 (NHCH), 175.3 (NHCO); ***m/z*** (ES+): 184.1701 (MH^+, 100%, $C_{11}H_{22}NO$ requires 184.1705).

(*3S,6R*)-3-ethyl-6-(2-methylpropyl)piperidin-2-one (258b)



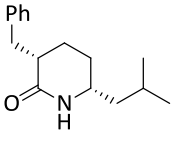
(**minor diastereoisomer**) m.p.= 88-90 ^{o}C; $[\alpha]^{25}_{D}$ +8.0, (*c* 0.5, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3201 (N-H), 2962 (C-H), 1650 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.93 (3H, d, *J* = 6.5, $CH(CH_3)(CH_3)$), 0.94 (3H, d, *J* = 6.5, $CH(CH_3)(CH_3)$), 0.99 (3H, t, *J* = 8.0, CH_3CH_2CH), 1.31-1.37 (2H, m, $NHCHCH_2$), 1.45-1.62 (2H, m, $CHCH_2CH$), 1.65-1.75 (2H, m, $NHCHCH_2CH_2$), 1.76-1.88 (1H, m, $CH(CH_3)_2$), 1.90-2.06 (2H, m, CH_3CH_2), 2.13-2.29 (1H, m, CH_3CH_2CH), 3.36-3.50 (1H, m, NHC*H*), 5.60 (1H, br. s, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 11.0 (CH_3CH), 22.2 ($CH(CH_3)_2$), 22.8 ($CH(CH_3)_2$), 24.1 (CH_3CH), 24.2 ($NHCHCH_2CH_2$), 25.4 ($NHCHCH_2CH_2$), 29.3 ($NHCHCH_2CH$), 42.2 ($CH(CH_3)_2$), 46.3 (CH_3CHCH_2), 51.3 (NHCH), 174.6 (NHCO); ***m/z*** (ES+): 184.1701 (MH^+, 100%, $C_{11}H_{22}NO$ requires 184.1708).

Hydrogenation of (*3E,6R*)-6-(2-methylpropyl)-3-(phenylmethylidene)piperidin-2-one



This reaction was done according to the general procedure **G** using (243 mg, 1.0 mmol, 1.0 eq.) of (*3E,6R*)-6-(2-methylpropyl)-3-(phenylmethylidene)piperidin-2-one **255** to yield a crude mixture (233 mg, 94% overall yield). ^{1}H NMR spectroscopy for the crude product showed two diastereoisomers. The purification and separation were achieved by preparative HPLC (XBridge Prep OBD C18 5µm 19 mmid x 250 mm), using 35:65 acetonitrile/water, at a flow rate of 17 mL/min and UV detection at 210 nm, room temperature. The HPLC analysis indicated that the first diastereoisomer had a retention time of 16.3 minute, which was identified as a ***cis***-diastereoisomer **259a** (116 mg, 47%) as a white crystalline solid, and the second diastereoisomer had a retention time of 18.5 minute, which was identified as a ***trans***-diastereoisomer **259b** (116 mg, 47%) as a white crystalline solid. The configuration of **259b** was determined as *trans*-isomer by X-ray crystallography (**Figure 24**).

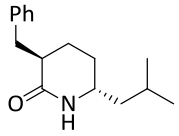
(*3S,6R*)-3-benzyl-6-(2-methylpropyl)piperidin-2-one (259a)



m.p.= 93-94 ^{o}C; $[\alpha]^{25}_{D}$ -78.0, (*c* 1.0, $CHCl_3$); ν_{max}(ATR)**/cm^{-1}**: 3196 (N-H), 2941 (C-H), 1655 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.92 (6H, d, *J* = 6.5,

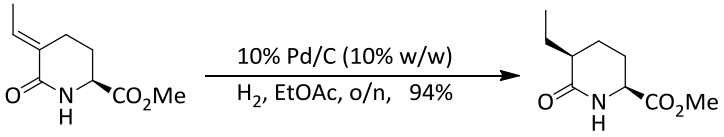
CH(CH_3)$_2$), 1.21-1.31 (1H, m, NHCHC*H*H), 1.32-1.40 (1H, m, NHCHCH*H*), 1.43-1.54 (1H, m, C*H*(CH$_3$)$_2$), 1.55-1.65 (2H, m, CHCH_2CH), 1.66-1.70 (1H, m, NHCHCH$_2$C*H*H), 1.71-1.81 (1H, m, NHCHCH$_2$CH*H*), 2.56-2.65 (1H, m, PhCH$_2$C*H*), 2.70 (1H, dd, *J* = 13.0, 10.5, PhC*H*HCH), 3.34 (1H, dd, *J* = 13.0, 3.5, PhCH*H*CH), 3.40-3.50 (1H, m, NHC*H*), 5.77 (1H, br. s, N*H*), 7.21-7.35 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, CDCl$_3$) δ ppm: 22.1 (CH*C*H$_3$), 22.3 (NHCHCH$_2$*C*H$_2$), 22.8 (CH*C*H$_3$), 24.3 (*C*H(CH$_3$)$_2$), 25.7 (NHCH*C*H$_2$CH$_2$), 37.5 (Ph*C*H$_2$), 42.2 (PhCH$_2$*C*H), 45.8 (NHCH*C*H$_2$CH), 50.4 (NH*C*H), 126.2 (ArCH), 128.4 (ArCH), 129.2 (ArCH), 139.7 (Ar quat.C), 174.4 (NH*C*O); ***m/z*** (ES+): 246.1858 (MH$^+$, 100%, $C_{16}H_{24}NO$ requires 246.1863).

(*3R,6R*)-3-benzyl-6-(2-methylpropyl)piperidin-2-one (259b)



m.p.= 110-111 ^{o}C; [α]$^{25}_{D}$ +24.0, (*c* 0.5, CHCl$_3$); **ν_{max}**(ATR)**/cm^{-1}**: 3280 (N-H), 2949 (C-H), 1653 (C=O); **^{1}H NMR** (400 MHz, CDCl$_3$) δ ppm: 0.91 (6H, d, *J* =7.0, CH(CH_3)$_2$), 1.21-1.46 (4H, m, (NHCHCH_2) + (CHCH_2CH)), 1.60-1.72 (1H, m, C*H*(CH$_3$)$_2$), 1.73-1.82 (1H, m, NHCHCH$_2$C*H*H), 1.83-1.93 (1H, m, NHCHCH$_2$CH*H*), 2.43-2.53 (1H, m, PhCH$_2$C*H*), 2.66 (1H, dd, *J* = 13.5, 10.0, PhC*H*HCH), 3.33-3.43 (1H, m, NHC*H*), 3.47 (1H, dd, *J* = 13.5, 4.0, PhCH*H*CH), 5.74 (1H, br. s, N*H*), 7.22-7.34 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, CDCl$_3$) δ ppm: 22.2 (CH*C*H$_3$), 22.8 (CH*C*H$_3$), 24.1 (*C*H(CH$_3$)$_2$), 25.6 (NHCHCH$_2$*C*H$_2$), 29.2 (NHCH*C*H$_2$CH$_2$), 37.3 (Ph*C*H$_2$), 42.9 (PhCH$_2$*C*H), 46.3 (NHCH*C*H$_2$CH), 51.4 (NH*C*H), 126.1 (ArCH), 128.3 (ArCH), 129.3 (ArCH), 139.9 (Ar quat.C), 173.8 (NH*C*O); ***m/z*** (ES+): 246.1858 (MH$^+$, 100%, $C_{16}H_{24}NO$ requires 246.1858).

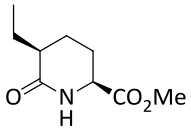
Hydrogenation of methyl (*2S,5E*)-5-ethylidene-6-oxopiperidine-2-carboxylate



256 **260**

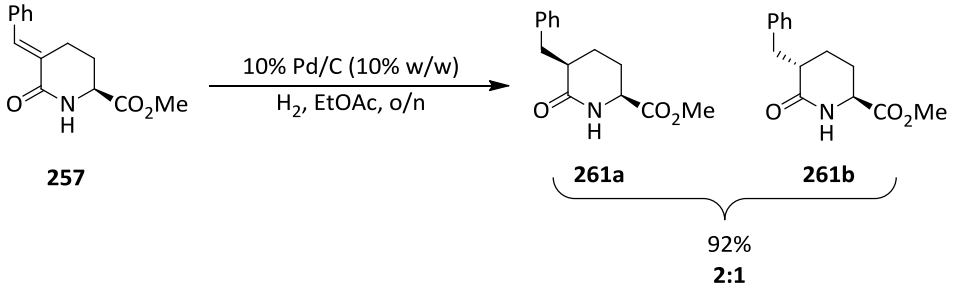
This reaction was performed according to the general procedure **G** using (183 mg, 1.0 mmol, 1.0 eq.) of methyl (*2S,5E*)-5-ethylidene-6-oxopiperidine-2-carboxylate **256** to give the crude of methyl (*2S,5S*)-5-ethyl-6-oxopiperidine-2-carboxylate **260**. ^{1}H NMR spectroscopy for the crude product represented only one diastereoisomer. The residue was purified by flash column chromatography on silica gel, using an eluent gradient of 0.5% methanol in ethyl acetate to 10% methanol in ethyl acetate gave (172 mg, 94%) as a white solid.

Methyl (*2S,5S*)-5-ethyl-6-oxopiperidine-2-carboxylate (260)



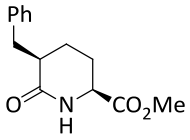
m.p.= 54-56 ^{o}C; R_f 0.37 (5:95 MeOH/EtOAc); $[\alpha]^{23}_{D}$ +40.0, (*c* 1.0, MeOH); **ν_{max}(ATR)/cm^{-1}**: 3207 (N-H), 2955 (C-H), 1739 (C=O ester), 1660 (C=O amide); **^{1}H NMR** (400 MHz, DMSO) δ ppm: 0.83 (3H, d, *J* = 7.5, C*H*$_3$CH), 1.26-1.45 (2H, m, NHCHC*H*$_2$), 1.66-1.80 (2H, m, NHCHCH$_2$C*H*$_2$), 1.90-1.98 (2H, m, CH$_3$C*H*$_2$CH), 2.02-2.11 (1H, m, CH$_3$CH$_2$C*H*), 3.66 (3H, s, CO$_2$C*H*$_3$), 4.04 (1H, dd, *J* = 12.5, 4.0, NHC*H*), 7.54 (1H, br. s, N*H*); **^{13}C NMR** (100 MHz, DMSO) δ ppm: 11.2 (*C*H$_3$CH), 23.0 (CH$_3$*C*H$_2$CH or NHCH*C*H$_2$), 24.0 (NHCH*C*H$_2$ or CH$_3$*C*H$_2$CH), 24.7 (COCH*C*H$_2$), 41.6 (CH$_3$CH$_2$*C*H), 52.5 (CO$_2$*C*H$_3$), 54.0 (NH*C*H), 172.9 (NH*C*O), 173.5 (*C*O$_2$Me); ***m/z*** (ES+): 186.1130 (MH$^+$, 100%, $C_9H_{16}NO_3$ requires 186.1136).

Hydrogenation of methyl (*2S,5E*)-6-oxo-5-(phenylmethylidene)piperidine-2-carboxylate



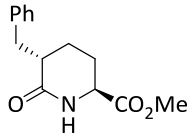
This reaction was performed according to the general procedure **G** using (245 mg, 1.0 mmol, 1.0 eq.) of methyl (*2S,5E*)-6-oxo-5-(phenylmethylidene)piperidine-2-carboxylate **257** to give a mixture of inseparable two diastereoisomers **261a** and **261b** (yield 227 mg, 92% overall yield) as a pale yellow oil. The ratio of ***cis : trans*** (**2** : **1**) determined by ^{1}H NMR spectroscopy of the crude product.

Methyl (*2S,5R*)-5-benzyl-6-oxopiperidine-2-carboxylate (261a)



ν_{max}(ATR)/cm^{-1}: 3244 (N-H), 2953 (C-H), 1744 (C=O ester), 1662 (C=O amide); **(major diastereoisomer)**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.61-1.70 (2H, m, C*H*$_2$CHNH), 2.00-2.06 (2H, m, C*H*$_2$CHCH$_2$Ph), 2.55-2.62 (1H, m, PhCH$_2$C*H*), 2.66 (1H, dd, *J* = 13.0, 10.5, CHC*H*HPh), 2.70 (1H, dd, *J* = 13.0, 10.0, CHCH*H*Ph), 3.76 (3H, s, CO$_2$C*H*$_3$), 3.42 (1H, dd, *J* = 13.0, 3.5, NHC*H*CO$_2$Me), 6.14 (1H, br. s, N*H*), 7.18-7.25 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 23.0 (NHCHCH$_2$*C*H$_2$), 23.7 (NHCH*C*H$_2$CH$_2$), 37.1 (Ph*C*H$_2$), 42.3 (PhCH$_2$*C*H), 52.6 (CO$_2$*C*H$_3$), 54.5 (NH*C*H), 126.3 (ArCH), 128.4 (ArCH), 129.2 (ArCH), 139.4 (Ar quat.C), 171.9 (NH*C*O), 173.7 (*C*O$_2$Me); ***m/z*** (ES+): 248.1287 (MH$^+$, 100%, $C_{14}H_{18}NO_3$ requires 248.1277).

Methyl (*2S,5S*)-5-benzyl-6-oxopiperidine-2-carboxylate (261b)

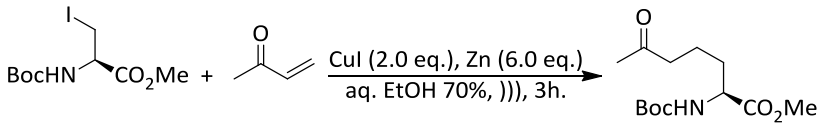


(minor diastereoisomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.47-1.57 (2H, m, C*H*$_2$CHNH), 1.70-1.76 (2H, m, C*H*$_2$CHCH$_2$Ph), 2.49-2.54 (1H, m, PhCH$_2$C*H*), 2.66 (1H, dd, *J* = 13.0, 10.5, CHC*H*HPh), 2.70 (1H, dd, *J* = 13.0, 10.0, CHCH*H*Ph), 3.78 (3H, s, CO$_2$C*H*$_3$), 4.03 (1H, dd, *J* = 10.5, 4.5, NHC*H*CO$_2$Me), 6.22 (1H, br. s, N*H*), 7.26-7.33 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 24.9 (NHCHCH$_2$*C*H$_2$), 25.1 (NHCH*C*H$_2$CH$_2$), 37.2 (Ph*C*H$_2$), 42.5 (PhCH$_2$*C*H), 52.7 (CO$_2$*C*H$_3$), 54.9 (NH*C*H), 126.3 (ArCH), 128.4 (ArCH), 129.2 (ArCH), 139.4 (Ar quat.C), 171.4 (NH*C*O), 173.0 (*C*O$_2$Me); ***m/z*** (ES+): 248.1287 (MH^+, 100%, %, $C_{14}H_{18}NO_3$ requires 248.1277).

4.9 General Procedure H: Conjugate addition

Copper(I)iodide (381 mg, 2.0 mmol, 2.0 eq. relative to alkyl iodide) and Zn dust (392 mg, 6.0 mmol, 6.0 eq. relative to alkyl iodide) were added to a solution of an enone (2.0 mmol, 2.0 eq.) in aqueous ethanol 70% (5 mL). Alkyl iodide (1.0 mmol, 1.0 eq.) was dissolved in aqueous ethanol 70% (10 mL) and added dropwise over 45 minutes, the sonication was continued until all starting materials were consumed. The reaction mixture was diluted with Et_2O (10 mL), and sonicated for further 10 minutes. After this, the mixture was filtered through Celite®, the solid precipitate was washed with ethyl acetate (100 mL) and the solvent removed from the filtrate under reduced pressure. The residue was purified by gradient flash chromatography on silica, using ethyl acetate in petroleum ether as eluent.

Methyl (*2S*)-2-([(*tert*-butoxy)carbonyl]amino)-6-oxoheptanoate (184)

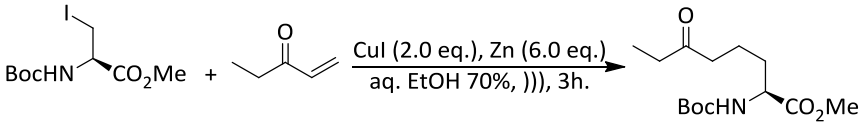


171 **184**

The title compound was synthesised according to the general procedure **H**, using methyl (*2R*)-2-([(*tert*-butoxy)carbonyl]amino)-3-iodopropanoate **171** (987 mg, 3.0 mmol, 1.0 eq.) and methyl vinyl ketone (630 mg, 9.0 mmol, 3.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **184** (366 mg, 56%) as a pale yellow oil.: R_f 0.24 (20:80 EtOAc/petroleum ether); $[\alpha]^{24}_D$ +82.0, (*c* 1.0, $CHCl_3$) (lit. $[\alpha]^{17}_D$ +81.0 , (*c* 1.0, $CHCl_3$)[65]; $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 3368 (N-H), 2978 (C-H), 1730 (C=O ketone), 1718 (C=O ester); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm:

1.42 (9H, s, C(CH_3)$_3$), 1.50-1.84 (4H, m, CHCH_2CH_2CH$_2$), 2.12 (3H, s, CH_3CO), 2.38-2.54 (2H, m, COCH_2), 3.72 (3H, s, CO$_2$CH_3), 4.04-4.34 (1H, m, NHC*H*), 5.12 (1H, d, *J* = 8.0, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 19.3 (CH$_2$*C*H$_2$CH$_2$), 28.1 (C(*C*H$_3$)$_3$), 29.7 (CH$_2$CO*C*H$_3$ or NHCH*C*H$_2$), 31.6 (CH$_2$CO*C*H$_3$ or NHCH*C*H$_2$), 42.5 (CH$_3$CO*C*H$_2$), 52.1 (CO$_2$*C*H$_3$), 53.0 (NH*C*H), 79.5 (*C*(CH$_3$)$_3$), 155.3 (NH*C*O), 173.0 (NHCH*C*O$_2$Me), 208.1 CH$_2$*C*OCH$_3$); ***m/z*** (ES+): 296.1474 (MNa$^+$, 100%, $C_{13}H_{23}NO_5Na$ requires 296.1480).

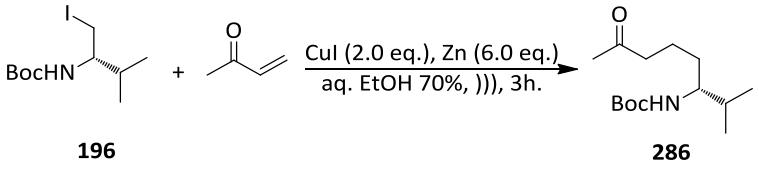
Methyl (*2S*)-2-([(*tert*-butoxy)carbonyl]amino)-6-oxooctanoate (185)



171 **185**

The title compound was synthesised according to the general procedure **H**, using methyl (*2R*)-2-([(*tert*-butoxy)carbonyl]amino)-3-iodopropanoate **171** (987 mg, 3.0 mmol, 1.0 eq.) and ethyl vinyl ketone (505 mg, 6.0 mmol, 2.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **185** (440 mg, 51%) as a pale yellow oil.: R_f 0.30 (20:80 EtOAc/petroleum ether); $[\alpha]^{24}_D$ +21.0, (*c* 1.0, $CHCl_3$) (lit. $[\alpha]^{21}_D$ +20.0, (*c* 1.0, $CHCl_3$)[65]; **ν_{max}(ATR)/cm^{-1}**: 3383 (N-H), 2981 (C-H), 1725 (C=O ketone), 1709 (C=O ester); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.04 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$CO), 1.43 (9H, s, C(C*H*$_3$)$_3$), 1.51-1.86 (4H, m, CHC*H*$_2$C*H*$_2$CH$_2$), 2.37-2.52 (4H, m, C*H*$_2$COC*H*$_2$), 3.73 (3H, s, CO$_2$C*H*$_3$), 4.14-4.36 (1H, m, NHC*H*), 5.10 (1H, d, *J* = 8.0, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 7.7 (*C*H$_3$CH$_2$CO), 19.4 (CH$_2$*C*H$_2$CH$_2$), 28.3 (C(*C*H$_3$)$_3$), 32.0 (CH*C*H$_2$CH$_2$), 35.9 (CH$_3$*C*H$_2$CO), 41.3 (CH$_3$CH$_2$CO*C*H$_2$), 52.3 (CO$_2$*C*H$_3$), 53.1 (NH*C*H), 79.9 (*C*(CH$_3$)$_3$), 155.4 (NH*C*O), 173.1 (NHCH*C*O$_2$Me), 210.9 CH$_2$*C*OCH$_3$); ***m/z*** (ES+): 310.1630 (MNa$^+$, 100%, $C_{14}H_{25}NO_5Na$ requires 310.1633).

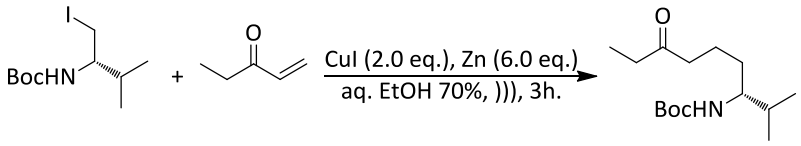
tert-Butyl *N*-[(*3R*)-2-methyl-7-oxooctan-3-yl]carbamate (286)



196 **286**

The title compound was accomplished according to the general procedure **H**, using *tert*-butyl *N*-[(*2S*)-1-iodo-3-methylbutan-2-yl]carbamate **196** (939 mg, 3.0 mmol, 1.0 eq.) and methyl vinyl ketone (630 mg, 9.0 mmol, 3.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **286** (463 mg, 60%) as a white crystalline solid. : R_f 0.34 (20:80 EtOAc/petroleum ether); m.p.= 45-46 ^{o}C; $[\alpha]^{23}_{D}$ +4.5, (*c* 1.0, $CHCl_3$); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 3359 (N-H), 2952 (C-H), 1681 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.87 (3H, d, *J* = 7.0, $CH(CH_3)(CH_3)$), 0.90 (3H, d, *J* = 7.0, $CH(CH_3)(CH_3)$), 1.20-1.35 (1H, m, $CH(CH_3)_2$), 1.45 (9H, s, $C(CH_3)_3$), 1.51-1.78 (4H, m, $CHCH_2CH_2CH_2$), 2.15 (3H, s, CH_3CO), 2.37-2.58 (2H, m, CH_3COCH_2), 3.38-3.49 (1H, m, NHC*H*), 4.32 (1H, d, *J* = 10.0, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.6 ($COCH_2CH_2$), 19.1 ($CHCH_3$), 20.3 ($CHCH_3$), 28.4 ($C(CH_3)_3$), 29.9 (CH_3CO), 31.7 ($CHCH_2$), 32.1 ($CH(CH_3)_2$), 43.2 ($COCH_2CH_2$), 55.0 (NH*C*H), 78.9 ($C(CH_3)_3$), 156.0 (NH*C*O), 209.0 (CH_2COCH_2); ***m/z*** (ES+): 280.1889 (MNa^+, 100%, $C_{14}H_{27}NO_3Na$ requires 280.1884).

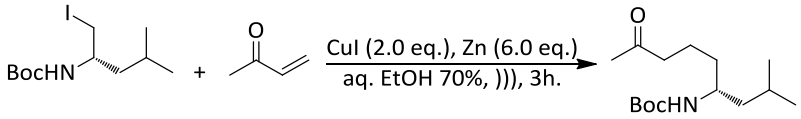
tert-Butyl N-[(*3R*)-2-methyl-7-oxononan-3-yl]carbamate (287)



196 **287**

The title compound was prepared according to the general procedure **H**, using *tert*-butyl *N*-[(*2S*)-1-iodo-3-methylbutan-2-yl]carbamate **196** (939 mg, 3.0 mmol, 1.0 eq.) and ethyl vinyl ketone (505 mg, 6.0 mmol, 2.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **287** (496 mg, 61%) as a white crystalline solid. : R_f 0.32 (20:80 EtOAc/petroleum ether); m.p.= 50-52 ^{o}C; $[\alpha]^{23}_{D}$ +13.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3368 (N-H), 2978 (C-H), 1718 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.87 (3H, d, *J* = 7.0, CH(C*H*$_3$)(CH$_3$)), 0.90 (3H, d, *J* = 7.0, CH(CH$_3$)(C*H*$_3$)), 1.06 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$CO), 1.21-1.34 (1H, m, C*H*(CH$_3$)$_2$), 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.50-1.78 (4H, m, CHC*H*$_2$C*H*$_2$CH$_2$), 2.34-2.56 (4H, m, C*H*$_2$COC*H*$_2$), 3.38-3.50 (1H, m, NHC*H*), 4.31 (1H, d, *J* = 10.0, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 7.8 (*C*H$_3$CH$_2$CO), 17.6 (COCH$_2$*C*H$_2$), 19.1 (CH*C*H$_3$), 20.4 (CH*C*H$_3$), 28.4 (C(*C*H$_3$)$_3$), 31.8 (CH*C*H$_2$), 32.0 (*C*H(CH$_3$)$_2$), 35.9 (CH$_3$*C*H$_2$CO), 41.8 (CO*C*H$_2$CH$_2$), 55.0 (NH*C*H), 78.8 (*C*(CH$_3$)$_3$), 156.0 (NH*C*O), 211.6 (CH$_2$*C*OCH$_2$); ***m/z*** (ES+): 272.2226 (MH$^+$, 100%, $C_{15}H_{30}NO_3$ requires 272.2237).

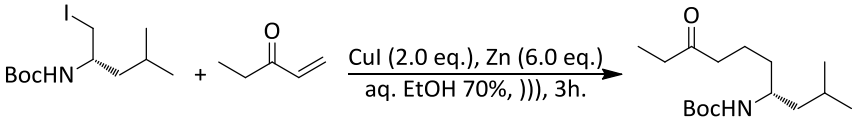
tert-Butyl *N*-[(*4R*)-2-methyl-8-oxononan-4-yl]carbamate (288)



197 **288**

The title compound was synthesised according to the general procedure **H**, using *tert*-butyl *N*-[(*2S*)-1-iodo-4-methylpentan-2-yl]carbamate **197** (981 mg, 3.0 mmol, 1.0 eq.) and methyl vinyl ketone (630 mg, 9.0 mmol, 3.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **288** (480 mg, 59%) as a colourless oil.: R_f 0.32 (20:80 EtOAc/petroleum ether); $[\alpha]^{23}_D$ -10.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3352 (N-H), 2959 (C-H), 1684 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.89 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 0.91 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 1.20-1.27 (2H, m, CHC*H*$_2$CH), 1.28-1.37 (1H, m, C*H*(CH$_3$)$_2$), 1.42 (9H, s, C(C*H*$_3$)$_3$), 1.49-1.72 (4H, m, CHC*H*$_2$C*H*$_2$CH$_2$), 2.13 (3H, s, C*H*$_3$CO), 2.35-2.56 (2H, m, CH$_3$COC*H*$_2$), 3.56-3.69 (1H, m, NHC*H*), 4.25 (1H, d, *J* = 9.0, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 19.7 (COCH$_2$*C*H$_2$), 22.1 (CH*C*H$_3$), 23.0 (CH*C*H$_3$), 24.7 (*C*H(CH$_3$)$_2$), 28.3 (C(*C*H$_3$)$_3$), 29.7 (*C*H$_3$CO), 35.2 (CH*C*H$_2$), 43.1 (CO*C*H$_2$CH$_2$), 44.7 (CH*C*H$_2$CH), 48.1 (NH*C*H), 78.6 (*C*(CH$_3$)$_3$), 155.6 (NH*C*O), 208.9 (CH$_3$*C*OCH$_2$); ***m/z*** (ES+): 294.2045 (MNa$^+$, 100%, $C_{15}H_{29}NO_3Na$ requires 294.2057).

tert-Butyl *N*-[(*4R*)-2-methyl-8-oxodecan-4-yl]carbamate (289)

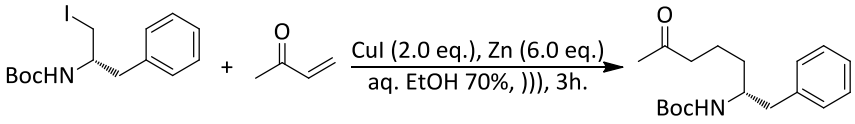


197 **289**

The title compound was accomplished according to the general procedure **H**, using *tert*-butyl *N*-[(*2S*)-1-iodo-4-methylpentan-2-yl]carbamate **197** (981 mg,

3.0 mmol, 1.0 eq.) and ethyl vinyl ketone (505 mg, 6.0 mmol, 2.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **289** (484 mg, 57%) as a white solid. : R_f 0.34 (20:80 EtOAc/petroleum ether); m.p.= 59-60 ^{o}C; $[\alpha]^{23}_{D}$ -9.0, (*c* 1.0, $CHCl_3$); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 3348 (N-H), 2941 (C-H), 1681 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.89 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 0.91 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 1.05 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$CO), 1.16-1.28 (2H, m, CHC*H*$_2$CH), 1.29-1.37(1H, m, C*H*(CH$_3$)$_2$), 1.43 (9H, s, C(C*H*$_3$)$_3$), 1.47-1.75 (4H, m, CHC*H*$_2$C*H*$_2$CH$_2$), 2.34-2.53 (4H, m, C*H*$_2$COC*H*$_2$), 3.56-3.69 (1H, m, NHC*H*), 4.24 (1H, d, *J* = 9.0, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 19.7 (*C*H$_3$CH$_2$CO), 22.1 (COCH$_2$*C*H$_2$), 23.0 (CH(*C*H$_3$)$_2$), 34.7 (*C*H(CH$_3$)$_2$), 28.3 (C(*C*H$_3$)$_3$), 29.7 (CH*C*H$_2$CH$_2$), 35.2 (CH$_3$*C*H$_2$CO), 43.1 (CO*C*H$_2$CH$_2$), 44.7 (CH*C*H$_2$CH), 48.1 (NH*C*H), 78.6 (*C*(CH$_3$)$_3$), 155.6 (NH*C*O), 208.9 (CH$_2$*C*OCH$_2$); ***m/z*** (ES+): 286.2382 (MH$^+$, 100%, $C_{16}H_{32}NO_3$ requires 286.2382).

tert-Butyl *N*-[(*2R*)-6-oxo-1-phenylheptan-2-yl]carbamate (290)

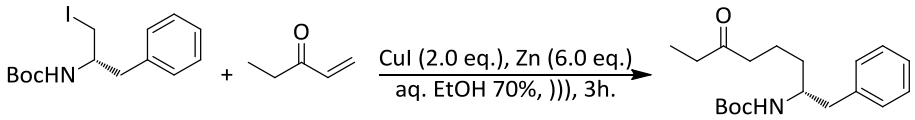


198 **290**

The title compound was prepared according to the general procedure **H**, using *tert*-butyl *N*-[(*2S*)-1-iodo-3-phenylpropan-2-yl]carbamate **198** (722 mg, 2.0 mmol, 1.0 eq.) and methyl vinyl ketone (420 mg, 6.0 mmol, 2.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **290** (384 mg, 63%) as a white solid. : R_f 0.34 (20:80 EtOAc/petroleum ether); m.p.= 54-55 ^{o}C; $[\alpha]^{24}_{D}$ +2.7, (*c* 1.5, $CHCl_3$); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 3327 (N-H), 2916 (C-H), 1684 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$)

δ ppm: 1.41 (9H, s, C(CH_3)$_3$), 1.43-1.77 (4H, m, CHCH_2CH_2CH$_2$), 2.12 (3H, s, CH_3CO), 2.33-2.53 (2H, m, CHCH_2Ph), 2.67-2.85 (2H, m, COCH_2), 3.74-3.88 (1H, m, NHC*H*), 4.40 (1H, d, *J* = 9.0, N*H*), 7.11-7.36 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 20.0 (COCH$_2$*C*H$_2$), 28.3 (C(*C*H$_3$)$_3$), 29.9 (*C*H$_3$CO), 33.3 (CH*C*H$_2$), 41.4 (CH*C*H$_2$Ph), 43.1 (CO*C*H$_2$CH$_2$), 51.2 (NH*C*H), 79.1 (*C*(CH$_3$)$_3$), 126.3 (ArCH), 128.3 (ArCH), 129.4 (ArCH), 138.1 (Ar quat.C), 155.5 (NH*C*O), 208.8 (CH$_3$*C*OCH$_2$); ***m/z*** (ES+): 328.1889 (MNa$^+$, 100%, $C_{18}H_{27}NO_3Na$ requires 328.1882).

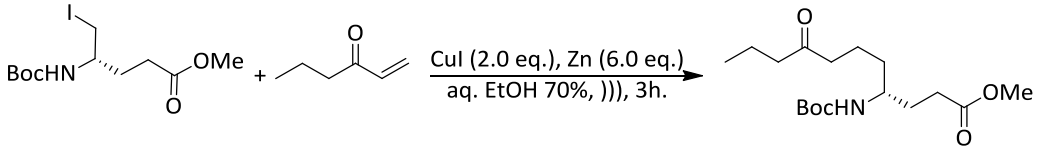
tert-Butyl N-[(*2R*)-6-oxo-1-phenyloctan-2-yl]carbamate (291)



198 **291**

The title compound was prepared according to the general procedure **H**, using *tert*-butyl *N*-[(*2S*)-1-iodo-3-phenylpropan-2-yl]carbamate **198** (722 mg, 2.0 mmol, 1.0 eq.) and ethyl vinyl ketone (336 mg, 4.0 mmol, 2.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **291** (441 mg, 69%) as a white solid. : R_f 0.36 (20:80 EtOAc/petroleum ether); m.p.= 54-56 ^oC; $[\alpha]^{23}_D$ +8.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3348 (N-H), 2941 (C-H), 1681 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.04 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$CO), 1.41 (9H, s, C(C*H*$_3$)$_3$), 1.47-1.89 (4H, m, CHC*H*$_2$C*H*$_2$CH$_2$), 2.30-2.53 (4H, m, C*H*$_2$COC*H*$_2$), 2.55-2.88 (2H, m, CHC*H*$_2$Ph), 3.55-3.89 (1H, m, NHC*H*), 4.39 (1H, d, *J* = 9.0, N*H*), 7.09-7.38 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 7.8 (*C*H$_3$CH$_2$CO), 20.1 (COCH$_2$*C*H$_2$), 28.3 (C(*C*H$_3$)$_3$), 33.4 (CH*C*H$_2$), 35.9 (CH$_3$*C*H$_2$CO), 41.4 (CH*C*H$_2$Ph), 41.7 (CO*C*H$_2$CH$_2$), 51.2 (NH*C*H), 78.0 (*C*(CH$_3$)$_3$), 126.2 (ArCH), 128.3 (ArCH), 129.4 (ArCH), 138.1 (Ar quat.C), 155.5 (NH*C*O), 211.5 (CH$_3$CH$_2$*C*OCH$_2$); ***m/z*** (ES+): 320.2226 (MH$^+$, 100%, $C_{19}H_{30}NO_3$ requires 320.2227).

Methyl (*4R*)-4-([(*tert*-butoxy)carbonyl]amino)-8-oxoundecanoate (292)



199 **292**

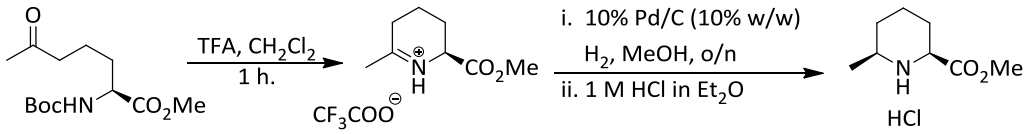
The title compound was synthesised according to the general procedure **H**, using methyl (*4S*)-4-([(*tert*-butoxy)carbonyl]amino)-5-iodopentanoate **199** (1.071 g, 3.0 mmol, 1.0 eq.) and hex-1-en-3-one (588 mg, 6.0 mmol, 2.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **291** (622 mg, 63%) as a pale yellow solid. : m.p.= 63-65 ^{o}C; R_f 0.26 (20:80 EtOAc/petroleum ether); $[\alpha]^{26}_{D}$ +3.0, (*c* 1.0, $CHCl_3$); **ν_{max}(ATR)/cm^{-1}**: 3341 (N-H), 2948 (C-H), 1735 (C=O ketone), 1706 (C=O ester), 1677(C=O amide); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.92 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$), 1.25-1.40 (1H, m, NHCHC*H*H), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.52-1.71 (6H, m, NHCHC*H*$_2$C*H*$_2$ + CH$_3$C*H*$_2$), 1.79-1.91 1H, m, NHCHCH*H*), 2.30-2.55 (6H, m, C*H*$_2$COC*H*$_2$ + C*H*$_2$CO$_2$Me), 3.44-3.64 (1H, m, NHC*H*), 3.68 (3H, s, CO$_2$C*H*$_3$), 4.32 (1H, d, *J* = 9.0, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 13.7 (*C*H$_3$CH$_2$), 17.3 (CH$_3$*C*H$_2$), 19.8 (COCH$_2$*C*H$_2$), 28.3 (*C*(CH3)3), 30.5 (NHCH*C*H$_2$), 30.8 (*C*H$_2$CO$_2$Me), 35.0 (COCH$_2$CH$_2$*C*H$_2$), 42.1 (*C*H$_2$CO(CH$_2$)$_2$CH$_3$), 44.7 (CO*C*H$_2$CH$_2$CH$_3$), 49.9 (CO$_2$*C*H$_3$), 51.6 (NH*C*H), 79.1 (*C*(CH$_3$)$_3$), 155.7 (N*C*O), 174.0 (*C*OCH$_3$), 211.0 (CH$_2$*C*OCH$_2$); ***m/z*** (ES+): 352.2100 (MNa^{+}, 100%, $C_{17}H_{31}NO_5Na$ requires 352.2096).

4.10 General Procedure I: 2,6-Disubstituted piperidine preparation

A round-bottomed flask was charged with a magnetic follower and a solution of 5-oxo amine precursors (1.0 mmol, 1.0 eq.) in dichloromethane (40 mL). Trifluoroacetic acid (5.7 g, 3.83 mL, 50.0 mmol, 50.0 eq.) was added dropwise to this reaction mixture at room temperature and stirred for a further 1h. At this time, the solvent and excess trifluoroacetic acid was removed under reduced pressure to produce a brown oil. This residue was subjected without purification to the hydrogenation reaction.

A two-necked round bottomed flask, charged with a magnetic follower fitted with a three-way tap and rubber septum, was flame-dried, evacuated and back-filled with nitrogen three times. The flask was charged with palladium on carbon 10% w/w (10 mol%, 0.1 eq.), and the flask evacuated and backfilled with nitrogen three times again. A solution of cyclic iminium salt in methanol (10 mL) was added to the flask *via* syringe, after that a balloon of hydrogen was fitted to the three-way tap. The flask was evacuated until the solvent began to boil, then back-filled with hydrogen, and this process repeated three more times. The reaction mixture was stirred at room temperature until all starting material consumed. At which time the mixture was filtered through a small plug of Celite®, followed by base work-up using diluted solution of LiOH, extracted with ethyl acetate (3 × 50 mL), the combined organic extracts were dried over $MgSO_4$, filtered and cooled to 0 ^{o}C. 1M HCl in Et_2O solution (~5.0 eq. relative to 5-oxo amine) was added dropwise. The solvent was removed under reduced pressure to give the crude solid hydrochloride salt, which was purified by flash column chromatography on silica, using methanol in dichloromethane as eluent.

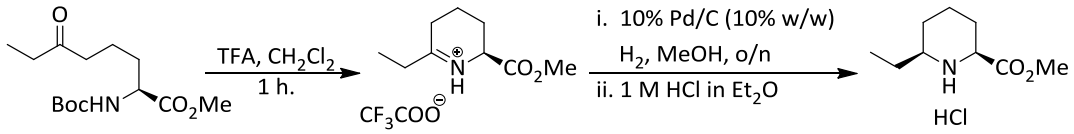
Methyl (*2S,6S*)-6-methylpiperidine-2-carboxylate hydrochloride(299)



184 **187** **299**

A round-bottomed flask was charged with a magnetic follower and a solution of methyl (*2S*)-2-([(*tert*-butoxy)carbonyl]amino)-6-oxoheptanoate **184** (273 mg, 1.0 mmol, 1.0 eq.) in dichloromethane (40 mL). Trifluoroacetic acid (5.7 g, 3.83 mL, 50.0 mmol, 50.0 eq.) was added dropwise to this reaction mixture at room temperature and stirred for a further 1h. At this time, the solvent and excess trifluoroacetic acid was removed under reduced pressure to produce brown oil compound. This sediment was subjected without purification to the hydrogenation reaction according to the general procedure **G**. After full conversion of the starting material, the solution was filtrated thorough a small plug of Celite®, ^{1}H NMR spectroscopy for the crude product represented only one isomer. The residue was purified by flash chromatography on silica gel using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether. The pure compound solution was cooled to 0 ^{o}C. 1M HCl in Et_2O solution was added dropwise (~5.0 eq. relative to 6-oxo amine), the solvent was removed under reduced pressure gave the title compound **299** (176 mg, 91%) as a yellow solid. : m.p.= 231-233 ^{o}C; R_f 0.29 (30:70 EtOAc/petroleum ether); $[\alpha]^{23}_{D}$ -35.0, (*c* 1.0, MeOH); **ν_{max}(ATR)/cm^{-1}**: 2943 (C-H stretching), 1746 (C=O), 1428 (C-H bending); **^{1}H NMR** (400 MHz, D_2O) δ ppm: 1.20 (3H, d, *J* = 6.5, C*H*$_3$CH), 1.24-1.39 (1H, m, CH_3CHCHH), 1.41-1.57 (2H, m, $CH_2CH_2CH_2$), 1.75-1.89 (2H, m, CH_3CO_2CHCHH + CH_3CHCHH), 2.17 (1H, d, *J* = 7.5, CH_3CO_2CHCHH), 3.09-3.19 (1H, m, CH_3CH), 3.68 (3H, s, CO_2CH_3), 3.88 (1H, dd, *J* = 12.0, 3.0, CH_3CH); **^{13}C NMR** (100 MHz, D_2O) δ ppm: 18.3 (CH_3CH), 21.6 ($CH_2CH_2CH_2$), 25.1 (CH_2), 29.3 (CH_2), 53.3 (CO_2CH_3), 53.4 (*C*HNHCH or CHNH*C*H), 57.2 (*C*HNHCH or CHNH*C*H), 170.1 (CO_2CH_3); ***m/z*** (ES+): 158.1176 (MH^+, 100%, $C_8H_{16}NO_2$ requires 158.1173).

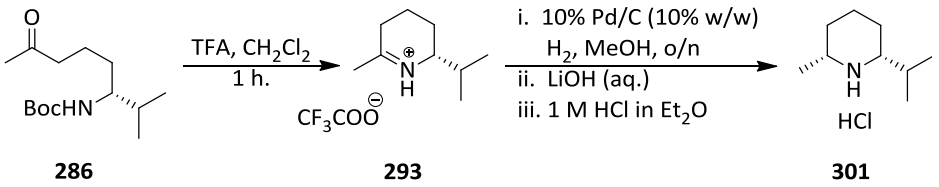
Methyl (*2S,6S*)-6-ethylpiperidine-2-carboxylate hydrochloride (300)



185 **188** **300**

A round-bottomed flask, was charged with a magnetic follower and a solution of methyl (*2S*)-2-([(*tert*-butoxy)carbonyl]amino)-6-oxooctanoate **185** (287 mg, 1.0 mmol, 1.0 eq.) in dichloromethane (40 mL). Trifluoroacetic acid (5.7 g, 3.83 mL, 50.0 mmol, 50.0 eq.) was added dropwise to this reaction mixture at room temperature and stirred for a further 1h. At this time, the solvent and excess trifluoroacetic acid was removed under reduced pressure to produce brown oil compound. This sediment was subjected without purification to the hydrogenation reaction according to the general procedure **G**. After full conversion of the starting material, the solution was filtrated thorough a small plug of Celite®, ^{1}H NMR spectroscopy for the crude product represented only one isomer. The residue was purified by flash chromatography on silica gel using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether. The pure compound solution was cooled to 0 ^{o}C. 1M HCl in Et_2O solution was added dropwise (~5.0 eq. relative to 6-oxo amine), the solvent was removed under reduced pressure gave the title compound **300** (186 mg, 90%) as a pale yellow solid. : m.p.= 234-236 ^{o}C; R_f 0.26 (30:70 EtOAc/petroleum ether); $[\alpha]^{23}_{D}$ -36.0, (*c* 1.0, MeOH); $\mathbf{\nu_{max}}$(ATR)**/cm^{-1}**: 2913 (C-H stretching), 1750 (C=O), 1431 (C-H bending); **^{1}H NMR** (400 MHz, D_2O) δ ppm: 0.84 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$CH), 1.12-1.28 (1H, m, CH$_3$C*H*HCH), 1.44-1.54 (3H, m, CH$_2$C*H*$_2$CH$_2$ + CH$_3$CH*H*CH), 1.55-1.65 (1H, m, CH$_3$CH$_2$CHC*H*H), 1.78-1.87 (1H, m, CH$_3$CH$_2$CHCH*H*), 1.88-1.96 (1H, m, CH$_3$CO$_2$CHC*H*H), 2.12-2.23 (1H, m, CH$_3$CO$_2$CHCH*H*), 2.92-3.02 (1H, m, CH$_3$CH$_2$C*H*), 3.68 (3H, s, CO$_2$C*H*$_3$*),* 3.88 (1H, dd, *J* = 12.0, 3.0, C*H*CO$_2$Me); **^{13}C NMR** (100 MHz, D_2O) δ ppm: 8.7 (*C*H$_3$CH$_2$CH), 21.5 (*C*H$_2$), 25.5 (*C*H$_2$), 26.1 (*C*H$_2$), 26.8 (*C*H$_2$), 53.4 (CO$_2$*C*H$_3$), 57.4 (*C*HNHCH or CHNH*C*H), 58.6 (*C*HNHCH or CHNH*C*H), 170.0 (*C*O$_2$CH$_3$); ***m/z*** (ES+): 172.1332 (MH^{+}, 100%, $C_9H_{18}NO_2$ requires 172.1329).

(*2R,6R*)-2-(Propan-2-yl)-6-methylpiperidine hydrochloride (301)

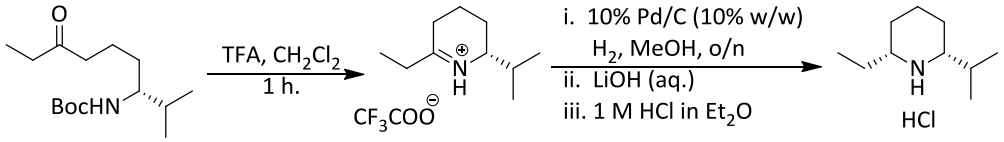


286 **293** **301**

The title compound was carried out according to the general procedure **I**, using *tert*-butyl *N*-[(*3R*)-2-methyl-7-oxooctan-3-yl]carbamate **286** (257 mg, 1.0 mmol, 1.0 eq.) to give the title compound. ^{1}H NMR spectroscopy for the crude product represented only one isomer, which was purified by flash chromatography on silica gel using 10% methanol in dichloromethane to give the title compound **301** (161 mg, 91%) as a white crystalline solid. : m.p.= 243-245 ^{o}C; R_f 0.26 (10:90 methanol/dichloromethane); $[\alpha]^{25}_{D}$ -30.0, (*c* 1.0, MeOH); **ν_{max}(ATR)/cm^{-1}**: 2947 (C-H stretching), 1457 (C-H bend); **^{1}H NMR** (400 MHz, D_2O) δ ppm: 0.82 (3H, d, *J* = 7.0, CH(C*H*$_3$)(CH$_3$)), 0.85 (3H, d, *J* = 7.0, CH(CH$_3$)(C*H*$_3$)), 1.16 (3H, d, *J* = 7.5, C*H*$_3$CH), 1.18-1.29 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.29-1.41 (1H, m, C*H*(CH$_3$)$_2$), 1.69-1.87 (4H, m, C*H*$_2$CH$_2$C*H*$_2$), 2.81 (1H, ddd, *J* = 12.0, 5.5, 3.0, NHC*H*CH), 3.08 (1H, dqd, *J* = 12.0, 6.5, 3.0, NHC*H*CH$_3$); **^{13}C NMR** (100 MHz, D_2O) δ ppm: 16.6 (CH$_2$*C*H$_2$CH$_2$), 18.0 (*C*H$_3$CH), 18.4 (*C*H$_3$CH), 22.0 (*C*H$_3$CHNH), 23.9 (CHCH*C*H$_2$), 30.0 (*C*H(CH$_3$)$_2$) or *C*H$_2$CHCH$_3$), 30.7 (*C*H(CH$_3$)$_2$) or *C*H$_2$CHCH$_3$) or *C*H$_2$CHCH$_3$), 54.4 (CH$_3$*C*H), 63.2 (*C*HCH(CH$_3$)$_2$); ***m/z*** (ES+): 142.1590 (MH$^+$, 100%, $C_9H_{20}N$ requires 142.1587).

The pure product was identified by X-ray crystallography as a *cis*-diastereoisomer (**Figure 42**). Spectroscopic data closely matched those reported previously by Kroutil for its enantiomer.[73]

(*2R,6R*)-2-(Propan-2-yl)-6-ethylpiperidine hydrochloride (302)

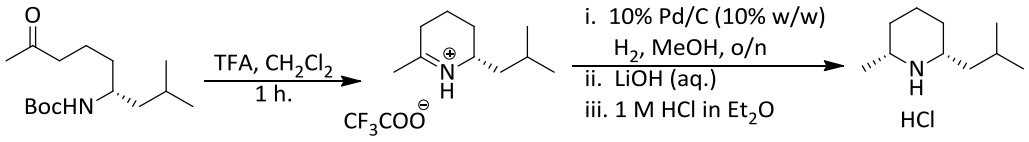


287 **294** **302**

The title compound was synthesized according to the general procedure **I**, using *tert*-butyl *N*-[(*3R*)-2-methyl-7-oxononan-3-yl]carbamate **287** (271 mg, 1.0 mmol, 1.0 eq.) to afford the title compound. ^{1}H NMR spectroscopy for the crude product represented only one isomer, which was purified by flash chromatography on silica gel using 10% methanol in dichloromethane gave the title compound **302** (170 mg, 89%) as a white crystalline solid. : m.p.= 236-238 ^{o}C; R_f 0.26 (10:90 methanol/dichloromethane); $[\alpha]^{25}_{D}$ -35.0, (*c* 1.0, MeOH); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 2947 (C-H stretching), 1459 (C-H bend); **^{1}H NMR** (400 MHz, D_2O) δ ppm: 0.81 (3H, d, *J* = 7.0, CH(C*H*$_3$)(CH$_3$)), 0.82 (3H, d, *J* = 7.0, CH(CH$_3$)(C*H*$_3$)), 0.85 (3H, t, *J* = 6.0, C*H*$_3$CH$_2$CH), 1.09-1.28 (2H, m, CH$_3$C*H*$_2$CHNH), 1.29-1.48 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.52-1.68 (1H, m, C*H*(CH$_3$)$_2$), 1.72-1.98 (4H, m, C*H*$_2$CH$_2$C*H*$_2$), 2.80-2.87 (1H, m, NHC*H*CH), 2.87-2.95 (1H, m, NHC*H*CH$_2$CH$_3$); **^{13}C NMR** (100 MHz, D_2O) δ ppm: 8.9 (*C*H$_3$CH$_2$CH), 16.4 (*C*H$_3$CH), 18.1 (*C*H$_3$CH), 21.9 (CH$_2$*C*H$_2$CH$_2$), 24.0 (CH$_3$*C*H$_2$), 26.2 (CH$_2$CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$CH$_2$), 27.2 (CH$_2$CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$CH$_2$), 30.6 (*C*H(CH$_3$)$_2$), 59.9 (*C*HNHCH or CHNH*C*H), 63.4 (*C*HNHCH or CHNH*C*H); ***m/z*** (ES+): 156.1747 (MH^{+}, 100%, $C_{10}H_{22}N$ requires 156.1742).

The pure product was identified by X-ray crystallography as a *cis*-diastereoisomer (**Figure 43**).

(*2R,6R*)-2-(2-Methylpropyl)-6-methylpiperidine hydrochloride (303)

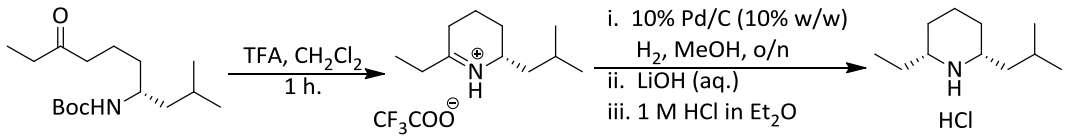


288 **295** **303**

The title compound was accomplished according to the general procedure **I**, using *tert*-butyl *N*-[(*4R*)-2-methyl-8-oxononan-4-yl]carbamate **288** (271 mg, 1.0 mmol, 1.0 eq.) to afford the title compound. ^{1}H NMR spectroscopy for the crude product represented one isomer only. The residue was purified by flash chromatography on silica gel using 10% methanol in dichloromethane gave the title compound **303** (168 mg, 88%) as a white solid. : m.p.= 247-249 ^{o}C; R_f 0.28 (10:90 methanol/dichloromethane); $[\alpha]^{25}_{D}$ -28.0, (*c* 1.0, MeOH); **ν_{max}(ATR)/cm^{-1}**: 2944 (C-H stretching), 1449 (C-H bend); **^{1}H NMR** (400 MHz, D_2O) δ ppm: 0.75 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 0.78 (3H, d, *J* = 6.5, CH(CH$_3$)(C*H*$_3$)), 1.15 (3H, d, *J* = 6.5, C*H*$_3$CH), 1.17-1.47 (4H, m, CHC*H*$_2$CH + CH$_2$C*H*$_2$CH$_2$), 1.53-1.65 (1H, m, C*H*(CH$_3$)$_2$), 1.67-1.95 (4H, m, C*H*$_2$CH$_2$C*H*$_2$), 2.98-3.11 (2H, m, NHC*H*CH$_2$ + NHC*H*CH$_3$); **^{13}C NMR** (100 MHz, D_2O) δ ppm: 18.6 (CH$_2$*C*H$_2$CH$_2$), 20.7 (*C*H$_3$CH), 21.8 (CH(*C*H$_3$)$_2$), 22.2 (CH(*C*H$_3$)$_2$), 23.4 (*C*H(CH$_3$)$_2$), 27.7 (CH*C*H$_2$CH$_2$ or CH$_3$CH*C*H$_2$), 30.1 (CH*C*H$_2$CH$_2$ or CH$_3$CH*C*H$_2$), 42.3 (CH*C*H$_2$CH), 53.4 (NH*C*HCH$_2$ or NH*C*HCH$_3$), 55.7 (NH*C*HCH$_2$ or NH*C*HCH$_3$); ***m/z*** (ES+): 156.1747 (MH^{+}, 100%, $C_{10}H_{22}N$ requires 156.1745).

Spectroscopic data closely matched those reported previously for its enantiomer.[73,87]

(*2R,6R*)-2-(2-Methylpropyl)-6-ethylpiperidine hydrochloride (304)

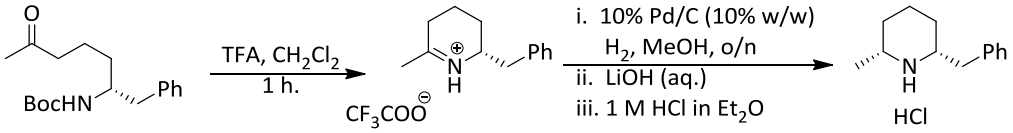


289 **296** **304**

The title compound was accomplished according to the general procedure **I**, using *tert*-butyl *N*-[(*4R*)-2-methyl-8-oxodecan-4-yl]carbamate **289** (285 mg, 1.0 mmol, 1.0 eq.) to give the title compound. ^{1}H NMR spectroscopy for the crude product represented only one isomer. The residue was purified by flash chromatography on silica gel using 10% methanol in dichloromethane to give the title compound **304** (174 mg, 85%) as a white crystalline solid. : m.p.= 233-235 ^{o}C; R_f 0.24 (10:90 methanol/dichloromethane); $[\alpha]^{25}_{D}$ -26.0, (*c* 1.0, MeOH); **ν_{max}(ATR)/cm^{-1}**: 2963 (C-H stretching), 1472 (C-H bend); **^{1}H NMR** (400 MHz, D_2O) δ ppm: 0.74 (3H, d, *J* = 6.5, CH(C*H*$_3$)(CH$_3$)), 0.78 (3H, d, *J* = 6.5, CH(CH$_3$)(C*H*$_3$)), 0.82 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$CH), 1.22-1.37 (2H, m, CHC*H*$_2$CH), 1.42-1.66 (4H, m, C*H*$_2$CH$_2$C*H*$_2$), 1.71-1.85 (2H, m, CH$_3$C*H*$_2$), 1.90-2.00 (1H, m, C*H*(CH$_3$)$_2$), 2.02-2.15 (2H, m, CH$_2$C*H*$_2$CH$_2$), 2.84-2.94 (1H, m, NHC*H*CH$_2$ or NHC*H*CH$_2$CH$_3$), 2.98-3.09 (1H, m, NHC*H*CH$_2$CH$_3$ or NHC*H*CH$_2$); **^{13}C NMR** (100 MHz, D_2O) δ ppm: 8.7 (*C*H$_3$CH$_2$CH), 20.5 (CH$_2$*C*H$_2$CH$_2$), 21.7 (*C*H$_3$CH), 22.4 (*C*H$_3$CH), 23.5 (*C*H(CH$_3$)$_2$), 26.3 (CH$_3$*C*H$_2$), 27.3 (CH$_2$CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$CH$_2$), 27.9 (CH$_2$CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$CH$_2$), 42.2 (CH*C*H$_2$CH), 56.0 (*C*HNHCH or CHNH*C*H), 58.9 (*C*HNHCH or CHNH*C*H); ***m/z*** (ES+): 170.1936 (MH^{+}, 100%, $C_{11}H_{24}N$ requires 170.1938).

The pure product was identified by X-ray crystallography as a *cis*-diastereoisomer (**Figure 44**).

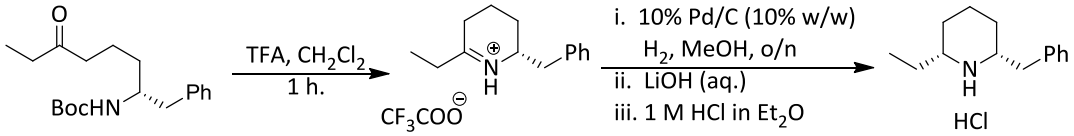
(*2R,6R*)-2-Benzyl-6-methylpiperidine hydrochloride (305)



290 **297** **305**

The title compound was achieved according to the general procedure **I**, using *tert*-butyl *N*-[(*2R*)-6-oxo-1-phenylheptan-2-yl]carbamate **290** (305 mg, 1.0 mmol, 1.0 eq.) to give the title compound. ^{1}H NMR spectroscopy for the crude product represented only one isomer. The residue was purified by flash chromatography on silica gel using 10% methanol in dichloromethane to give the title compound **305** (200 mg, 89%) as a pale yellow solid. : m.p.= 244-246 ^{o}C; R_f 0.26 (10:90 methanol/dichloromethane); $[\alpha]^{25}_{D}$ -34.0, (*c* 1.0, MeOH); **ν_{max}(ATR)/cm^{-1}**: 2918 (C-H stretching), 1465 (C-H bend); **^{1}H NMR** (400 MHz, D_2O) δ ppm: 1.10 (3H, t, *J* = 6.5, C*H*$_3$CH), 1.15-1.81 (6H, m, CHC*H*$_2$C*H*$_2$C*H*$_2$CH), 2.74 (1H, dd, *J* = 13.5, 8.0, CHC*H*HPh), 2.82 (1H, dd, *J* = 13.5, 6.5, CHCH*H*Ph), 2.93-3.04 (1H, m, NHC*H*CH$_3$), 3.12-3.22 (1H, m, NHC*H*CH$_2$Ph), 7.10-7.32 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, D_2O) δ ppm: 18.7 (*C*H$_3$CH), 21.9 (CH$_2$*C*H$_2$CH$_2$), 27.7 (CH$_2$CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$CH$_2$), 30.1 (CH$_2$CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$CH$_2$), 39.6 (CH*C*H$_2$Ph), 53.7 (*C*HCH$_2$Ph or *C*HCH$_3$), 58.3 (*C*HCH$_3$ or *C*HCH$_2$Ph), 127.3 (ArCH), 128.9 (ArCH), 129.4 (ArCH), 135.9 (Ar quat.C); ***m/z*** (ES+): 190.1590 (MH$^+$, 100%, $C_{13}H_{20}N$ requires 190.1586).

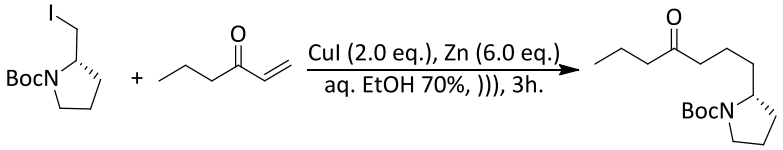
(*2R,6R*)-2-Benzyl-6-ethylpiperidine hydrochloride (306)



291 **298** **306**

The title compound was achieved according to the general procedure **I**, using *tert*-butyl *N*-[(*2R*)-6-oxo-1-phenyloctan-2-yl]carbamate **291** (319 mg, 1.0 mmol, 1.0 eq.) to afford the title compound. ^{1}H NMR spectroscopy for the crude product represented only one isomer. The residue was purified by flash chromatography on silica gel using 10% methanol in dichloromethane gave the title compound **306** (211 mg, 88%) as a pale yellow solid. : m.p.= 254-256 ^{o}C; R_f 0.26 (10:90 methanol/dichloromethane); $[\alpha]^{25}_{D}$ -36.0, (*c* 1.0, MeOH); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 2923 (C-H stretching), 1455 (C-H bend); **^{1}H NMR** (400 MHz, D_2O) δ ppm: 0.80 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$CH), 1.08-1.93 (8H, m, CHC*H*$_2$C*H*$_2$C*H*$_2$CH + CH$_3$C*H*$_2$), 2.71 (1H, dd, *J* = 13.5, 8.5, CHC*H*HPh), 2.80-2.85 (1H, m, NHC*H*CH$_2$CH$_3$), 2.89 (1H, dd, *J* = 13.5, 6.0, CHCH*H*Ph), 3.14-3.25 (1H, m, NHC*H*CH$_2$Ph), 7.12-7.31 (5H, m, Ar*H*); **^{13}C NMR** (100 MHz, D_2O) δ ppm: 8.7 (*C*H$_3$CH$_2$CH), 21.7 (CH$_2$*C*H$_2$CH$_2$), 26.4 (CH$_3$*C*H$_2$), 27.4 (CH$_2$CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$CH$_2$), 27.8 (CH$_2$CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$CH$_2$), 39.5 (CH*C*H$_2$Ph), 58.5 (*C*HCH$_2$Ph), 59.1 (*C*HCH$_2$CH$_3$), 127.3 (ArCH), 128.9 (ArCH), 129.4 (ArCH), 135.8 (Ar quat.C); ***m/z*** (ES+): 204.1747 (MH$^+$, 100%, $C_{14}H_{22}N$ requires 204.1744).

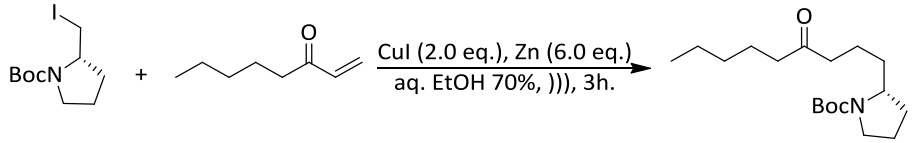
tert-Butyl (*2R*)-2-(4-oxoheptyl)pyrrolidine-1-carboxylate (308)



195 **307** **308**

The title compound was synthesised according to the general procedure **H**, using *tert*-butyl (*2S*)-2-(iodomethyl)pyrrolidine-1-carboxylate **195** (933 mg, 3.0 mmol, 1.0 eq.) and hex-1-en-3-one **307** (588 mg, 6.0 mmol, 2.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **308** (637 mg, 75%) as a yellow oil.: R_f 0.24 (20:80 EtOAc/petroleum ether); $[\alpha]^{26}_D$ -42.0, (*c* 1.0, $CHCl_3$); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 2965 (N-H), 2933 (C-H), 1688 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.91 (3H, t, *J* = 7.5, CH_3CH_2), 1.24-1.35 (1H, m, NCH_2CH_2CHH), 1.46 (9H, s, $C(CH_3)_3$), 1.50-1.62 (4H, m, $NCHCH_2CH_2$), 1.64-1.70 (1H, m, NCH_2CH_2CHH), 1.73-2.16 (4H, m, CH_3CH_2 + NCH_2CH_2), 2.30-2.51 (4H, m, CH_2COCH_2), 3.22-3.42 (2H, m, NCH_2), 3.65-3.79 (1H, m, NCH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 13.7 (CH_3CH_2), 17.2 (CH_3CH_2), 20.4 ($NCHCH_2CH_2$), 23.4 (NCH_2CH_2), 28.4 ($C(CH_3)_3$), 30.1 ($NCHCH_2$), 33.9 ($NCHCH_2$), 42.6 ($CH_2CO(CH_2)_2CH_3$), 44.7 ($COCH_2CH_2CH_3$), 46.2 (NCH_2), 57.0 (NCH), 78.9 ($C(CH_3)_3$), 154.6 (NCO), 211.1 (CH_2COCH_2); ***m/z*** (ES+): 306.2040 (MNa^+, 100%, $C_{16}H_{29}NO_3Na$ requires 306.2044).

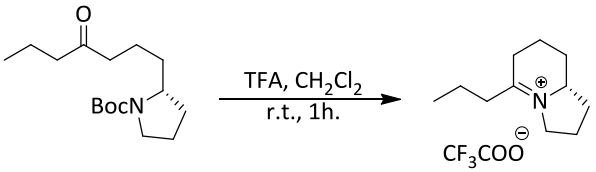
tert-Butyl (*2R*)-2-(4-oxoheptyl)pyrrolidine-1-carboxylate (310)



195 **309** **310**

The title compound was synthesised according to the general procedure **H**, using *tert*-butyl (*2S*)-2-(iodomethyl)pyrrolidine-1-carboxylate **195** (933 mg, 3.0 mmol, 1.0 eq.) and oct-1-en-3-one **309** (757 mg, 6.0 mmol, 2.0 eq.) to give the title compound. The residue was purified by flash chromatography on silica, using an eluent gradient of 10% ethyl acetate in petroleum ether to 40% ethyl acetate in petroleum ether, to give the title compound **310** (728 mg, 78%) as a pale yellow oil.: R_f 0.26 (20:80 EtOAc/petroleum ether); $[\alpha]^{26}_{D}$ -37.0, (*c* 1.0, $CHCl_3$); $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 2961 (N-H), 2929 (C-H), 1745 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.86 (3H, t, *J* = 7.0, C*H*$_3$CH$_2$), 1.16-1.34 (5H, m, NCH$_2$CH$_2$C*H*H + CH$_3$C*H*$_2$C*H*$_2$), 1.43 (9H, s, C(C*H*$_3$)$_3$), 1.47-1.60 (4H, m, NCHC*H*$_2$C*H*$_2$), 1.61-1.70 (1H, m, NCH$_2$CH$_2$CH*H*), 1.72-1.98 (4H, m, CH$_3$CH$_2$CH$_2$C*H*$_2$ + NCH$_2$C*H*$_2$), 2.28-2.57 (4H, m, C*H*$_2$COC*H*$_2$), 3.22-3.39 (2H, m, NC*H*$_2$), 3.60-3.76 (1H, m, NC*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 13.8 (*C*H$_3$CH$_2$), 20.4 (NCHCH$_2$*C*H$_2$), 22.4 (CH$_3$*C*H$_2$), 23.4 (NCH$_2$*C*H$_2$), 23.5 (CH$_3$CH$_2$CH$_2$*C*H$_2$), 27.7 (CH$_3$CH$_2$*C*H$_2$), 28.4 (C(*C*H$_3$)$_3$), 28.5 (NCH*C*H$_2$), 31.3 (NCH*C*H$_2$), 42.5 (*C*H$_2$CO(CH$_2$)$_4$CH$_3$), 42.7 (CO*C*H$_2$(CH$_2$)$_3$CH$_3$), 46.2 (N*C*H$_2$), 56.9 (N*C*H), 78.9 (*C*(CH$_3$)$_3$), 154.6 (N*C*O), 211.2 (CH$_2$*C*OCH$_2$); ***m/z*** (ES+): 312.2533 (MH^+, 100%, $C_{18}H_{34}NO_3$ requires 312.2533).

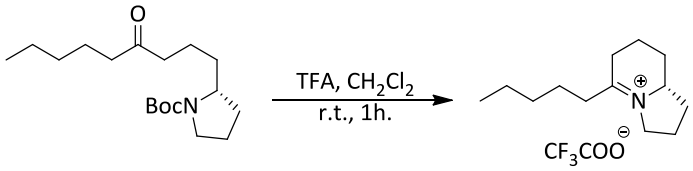
(*8aR*)-5-Propyl-2,3,6,7,8,8a-hexahydro-1H-4λ^5-indolizin-4-ylium trifluoroacetate (311)



308 **311**

Trifluoroacetic acid (5.7 g, 3.83 mL, 50.0 mmol, 50.0 eq.) was added dropwise to the stirred solution of *tert*-butyl (*2R*)-2-(4-oxoheptyl)pyrrolidine-1-carboxylate **308** (283 mg, 1.0 mmol, 1.0 eq.) in dichloromethane (40 mL), and the reaction mixture stirred for a further 1 h. At this time, the solvent and excess trifluoroacetic acid was removed under reduced pressure to produce the title compound **311** as brown oil.: $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 2972 (C-H), 2890 (C-H), 1222 (C-H bend); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.04 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$), 1.62-1.87 (4H, m, NCH$_2$C*H*$_2$ + NCHC*H*$_2$), 1.97-2.13 (2H, m, NCHC*H*$_2$), 2.16-2.44 (4H, m, CH$_3$C*H*$_2$ + N=CCH$_2$C*H*$_2$), 2.55-3.01 (4H, m, N=CC*H*$_2$+ N=CC*H*$_2$), 3.70-3.86 (1H, m, NC*H*), 3.91-4.14 (2H, m, NC*H*$_2$), 11.7 (1H, br. s, CF_3COOH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 13.8 (*C*H$_3$CH$_2$), 17.4 (CH$_3$*C*H$_2$), 18.6 (N=CCH$_2$*C*H$_2$), 21.5 (NCH*C*H$_2$), 25.6 (NCH*C*H$_2$), 30.8 (NCH$_2$*C*H$_2$), 31.1 (N=C*C*H$_2$), 38.6 (CH$_3$CH$_2$*C*H$_2$), 53.0 (N*C*H$_2$), 65.1 (N*C*H), 188.6 (N=*C*); ***m/z*** (ES+): 166.1590 (M^+, 100%, $C_{11}H_{20}N^+$ requires 166.1589).

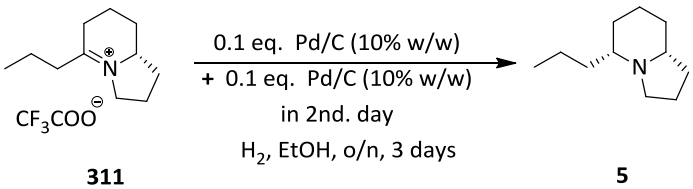
(*8aR*)-5-Pentyl-2,3,6,7,8,8a-hexahydro-1H-4λ^5-indolizin-4-ylium trifluoroacetate (312)



310 **312**

Trifluoroacetic acid (5.7 g, 3.83 mL, 50.0 mmol, 50.0 eq.) was added dropwise to the stirred solution of *tert*-butyl (*2R*)-2-(4-oxoheptyl)pyrrolidine-1-carboxylate **310** (311 mg, 1.0 mmol, 1.0 eq.) in dichloromethane (40 mL), and the reaction mixture stirred for a further 1 h. At this time, the solvent and excess trifluoroacetic acid was removed under reduced pressure to produce the title compound as **312** brown oil.: $\boldsymbol{\nu_{max}}$(ATR)**/cm^{-1}**: 2963 (C-H stretching), 1411 (C-H bend); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.9 (3H, t, *J* = 7.5, C*H*$_3$CH$_2$), 1.20-2.34 (14H, m, 7 C*H*$_2$), 2.36-3.01 (4H, m, N=CCH$_2$C*H*$_2$), 3.62-4.15 (3H, m, NC*H* + NC*H*$_2$), 10.8 (1H, br. s, CF_3COOH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 13.8 (*C*H$_3$CH$_2$), 17.4 (CH$_3$*C*H$_2$), 21.5 (N=CCH$_2$*C*H$_2$), 24.2 (NCH*C*H$_2$), 24.7 (NCH*C*H$_2$), 26.1 (*C*H$_2$), 30.9 (*C*H$_2$), 31.1 (*C*H$_2$), 31.4 (*C*H$_2$), 36.6 (NCH*C*H$_2$), 52.9 (N*C*H$_2$), 65.1 (N*C*H), 188.8 (N=*C*); ***m/z*** (ES+): 194.1903 (M^+, 100%, $C_{13}H_{24}N^+$ requires 194.1900).

(*5R,8aR*)-5-Propyl-octahydroindolizine (5)

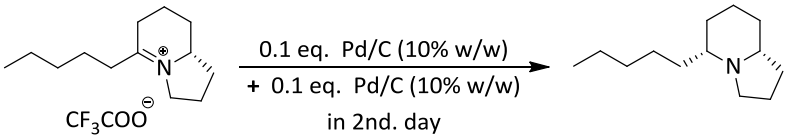


311 **5**

The title compound was synthesised according to the general procedure **G**, using (*8aR*)-5-propyl-2,3,6,7,8,8a-hexahydro-1H-4λ^5-indolizin-4-ylium trifluoroacetate **311**. The residue was purified by flash chromatography on silica gel (**deactivated with Et$_3$N**), using an eluent gradient of 5% ethyl acetate in petroleum ether to 10% ethyl acetate in petroleum ether, to give the title compound **5** (120 mg, 72%

over two steps) as a yellow oil. : R_f 0.22 (10:90 EtOAc/petroleum ether); $[\alpha]^{25}_D$ -98.0, (*c* 1.0, CH_2Cl_2) (lit. $[\alpha]^{25}_D$ -98.0, (*c* 1.0, CH_2Cl_2)[52]; **ν_{max}(ATR)/cm^{-1}**: 2958, 2923, 2849, 1710, 1456, 1379, 1276, 1262; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.92 (3H, t, *J* = 7.0, C*H*$_3$CH$_2$), 1.11-1.47 (7H, m, C*H*$_2$), 1.60-1.88 (9H, m, C*H*$_2$), 1.97 (1H, app. q, *J* = 9.0, NC*H*^{n}Pr), 3.27 (1H, dt, *J* = 9.0, 2.0, NC*H*CH$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 14.5 (*C*H$_3$CH$_2$), 19.4 (CH$_3$*C*H$_2$), 20.4 (*C*H$_2$), 24.7 (*C*H$_2$), 30.5 (*C*H$_2$), 30.8 (*C*H$_2$), 31.0 (*C*H$_2$), 36.9 (*C*H$_2$), 51.5 (N*C*H$_2$), 63.7 (N*C*H$_2$), 65.0 (N*C*H); ***m/z*** (ES+): 168.1747 (MH^+, 100%, $C_{11}H_{22}N$ requires 168.1744).

(*5R,8aR*)-5-Pentyl-octahydroindolizine (6)



The title compound was synthesised according to the general procedure **G**, using (*8aR*)-5-pentyl-2,3,6,7,8,8a-hexahydro-1H-4λ^5-indolizin-4-ylium trifluoroacetate **312**. The residue was purified by flash chromatography on silica gel (**deactivated with Et$_3$N**), using an eluent gradient of 5% ethyl acetate in petroleum ether to 10% ethyl acetate in petroleum ether, to give the title compound **6** (148 mg, 76% over two steps) as a yellow oil. : R_f 0.24 (10:90 EtOAc/petroleum ether); $[\alpha]^{26}_D$ -95.0, (*c* 1.0, CH_2Cl_2) (lit. $[\alpha]^{23}_D$ -95.6, (*c* 1.1, CH_2Cl_2)[51] ; **ν_{max}(ATR)/cm^{-1}**: 2954, 2929, 2857, 1717, 1459, 1380, 1129; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.90 (3H, t, *J* = 7.0, C*H*$_3$CH$_2$), 1.09-1.51 (11H, m, C*H*$_2$), 1.63-1.88 (9H, m, C*H*$_2$), 1.98 (1H, app. q, *J* = 9.0, NC*H*^{n}Pentyl), 3.27 (1H, dt, *J* = 9.0, 2.0, NC*H*CH$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 14.1 (*C*H$_3$CH$_2$), 20.4 (CH$_3$*C*H$_2$), 22.6 (*C*H$_2$), 24.7 (*C*H$_2$), 25.5 (*C*H$_2$), 30.5 (*C*H$_2$), 30.8 (*C*H$_2$), 31.0 (*C*H$_2$), 32.3 (*C*H$_2$), 34.5 (*C*H$_2$), 51.5 (N*C*H$_2$), 63.9 (N*C*H$_2$), 65.0 (N*C*H); ***m/z*** (ES+): 196.2060 (MH^+, 100%, $C_{13}H_{26}N$ requires 196.2057).

5. References

(1) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.
(2) Ibebeke-Bomangwa, W.; Hootele, C. *Tetrahedron* **1987**, *43*, 935.
(3) Gardiner, R. A.; Rinehart, K. L., Jr.; Snyder, J. J.; Broquist, H. P. *J. Amer. Chem. Soc.* **1968**, *90*, 5639.
(4) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.
(5) Aniszewski, T. *Elsevier* **2007**.
(6) Coia, N.; Mokhtari, N.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2011**, *13*, 6292.
(7) Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101.
(8) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun. (Cambridge)* **1998**, 633.
(9) Costa, A.; Najera, C.; Sansano, J. M. *Tetrahedron: Asymmetry* **2001**, *12*, 2205.
(10) Dockner, M.; Sasaki, N. A.; Riche, C.; Potier, P. *Liebigs Ann./Recl.* **1997**, 1267.
(11) Occhiato, E. G.; Scarpi, D.; Guarna, A. *Eur. J. Org. Chem.* **2008**, 524.
(12) Alegret, C.; Santacana, F.; Riera, A. *J. Org. Chem.* **2007**, *72*, 7688.
(13) Scarpi, D.; Bartali, L.; Casini, A.; Occhiato, E. G. *Eur. J. Org. Chem.* **2013**, *2013*, 1306.
(14) Dutta, A. K.; Davis, M. C.; Reith, M. E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2337.
(15) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.
(16) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379.
(17) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957.
(18) Leclerq, S.; Thirionet, I.; Broeders, F.; Daloze, D.; van der Meer, R.; Braekman, J. C. *Tetrahedron* **1994**, *50*, 8465.
(19) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949.
(20) Yi, G. B.; McClendon, D.; Desaiah, D.; Goddard, J.; Lister, A.; Moffitt, J.; Vander Meer, R. K.; Deshazo, R.; Lee, K. S.; Rockhold, R. W. *Int. J. Toxicol.* **2003**, *22*, 81.
(21) Jha, V.; Kauloorkar, S. V.; Kumar, P. *Eur. J. Org. Chem.* **2014**, *2014*, 4897.
(22) Li, Y.-J.; Hou, C.-C.; Chang, K.-C. *Eur. J. Org. Chem.* **2015**, *2015*, 1659.
(23) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549.
(24) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513.
(25) Guazzelli, G.; Lazzaroni, R.; Settambolo, R. *Beilstein J. Org. Chem.* **2008**, *4*, No. 2.
(26) Prevost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383.
(27) Sun, C.-S.; Lin, Y.-S.; Hou, D.-R. *J. Org. Chem.* **2008**, *73*, 6877.
(28) Bates, R. W.; Sivarajan, K.; Straub, B. F. *J. Org. Chem.* **2011**, *76*, 6844.
(29) Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1542.
(30) Botman, P. N. M.; Dommerholt, F. J.; de Gelder, R.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2004**, *6*, 4941.
(31) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5043.
(32) Swarbrick, M. E.; Lubell, W. D. *Chirality* **2000**, *12*, 366.
(33) Couty, F. *Amino Acids* **1999**, *16*, 297.
(34) Bailey, P. D.; Smith, P. D.; Morgan, K. M.; Rosair, G. M. *Tetrahedron Lett.* **2002**, *43*, 1071.
(35) Davis, F. A.; Zhang, H.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759.
(36) Sadiq, A.; Sewald, N. *Org. Lett.* **2013**, *15*, 2720.
(37) Shankaraiah, G.; Vijaya Kumar, T.; Venkateswara Reddy, G.; Madhusudana Rao, J.; Suresh Babu, K. *Helv. Chim. Acta* **2013**, *96*, 990.

(38) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688.
(39) Fleurant, A.; Celerier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1992**, *3*, 695.
(40) Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett.* **1996**, *37*, 1445.
(41) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C.; Canet, I. *Tetrahedron Lett.* **1999**, *40*, 1661.
(42) Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 465.
(43) Corvo, M. C.; Pereira, M. M. A. *Tetrahedron Lett.* **2002**, *43*, 455.
(44) Zaminer, J.; Stapper, C.; Blechert, S. *Tetrahedron Lett.* **2002**, *43*, 6739.
(45) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919.
(46) Reddy, P. G.; Baskaran, S. *J. Org. Chem.* **2004**, *69*, 3093.
(47) Kamimura, A.; Nagata, Y.; Kadowaki, A.; Uchida, K.; Uno, H. *Tetrahedron* **2007**, *63*, 11856.
(48) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300.
(49) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.
(50) Gracia, S.; Jerpan, R.; Pellet-Rostaing, S.; Popowycz, F.; Lemaire, M. *Tetrahedron Lett.* **2010**, *51*, 6290.
(51) Liu, H.; Su, D.; Cheng, G.; Xu, J.; Wang, X.; Hu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1899.
(52) Pinho, V. D.; Burtoloso, A. C. B. *Tetrahedron Lett.* **2012**, *53*, 876.
(53) Morales-Chamorro, M.; Meza-Gonzalez, J.; Cordero-Vargas, A. *Tetrahedron Lett.* **2015**, *56*, 4892.
(54) Dunn, M. J.; Jackson, R. F. W. *J. Chem. Soc., Chem. Commun.* **1992**, 319.
(55) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210.
(56) Dexter, C. S.; Jackson, R. F. W.; Elliott, J. *J. Org. Chem.* **1999**, *64*, 7579.
(57) Deboves, H. J. C.; Grabowska, U.; Rizzo, A.; Jackson, R. F. W. *Perkin 1* **2000**, 4284.
(58) Hunter, C.; Jackson, R. F. W.; Rami, H. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1349.
(59) Rilatt, I.; Caggiano, L.; Jackson, R. F. W. *Synlett* **2005**, 2701.
(60) Jackson, R. F. W.; Turner, D.; Block, M. H. *Synlett* **1997**, 789.
(61) Chilton, M. L., The University of Sheffield, 2015.
(62) Jackson, R. F. W.; Graham, L. J.; Rettie, A. B. *Tetrahedron Lett.* **1994**, *35*, 4417.
(63) Muehlemann, C.; Hartmann, P.; Obrecht, J.-P. *Org. Synth.* **1993**, *71*, 200.
(64) Gulati, V., The University of Sheffield, 2008.
(65) Abdelsalam, M. A. S., The University of Sheffield, 2013.
(66) Salih, N. A., The University of Sheffield, 2015.
(67) Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64.
(68) Hunter, C.; Jackson, R. F. W.; Rami, H. K. *Perkin 1* **2000**, 219.
(69) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568.
(70) More, S. S.; Vince, R. *J. Med. Chem.* **2009**, *52*, 4650.
(71) Borrell, J. I.; Teixido, J.; Martinez-Teipel, B.; Matallana, J. L.; Copete, M. T.; Llimargas, A.; Garcia, E. *J. Med. Chem.* **1998**, *41*, 3539.
(72) Cassady, J. M.; Howie, G. A.; Robinson, J. M.; Stamos, I. K. *Org. Synth.* **1983**, *61*, 77.
(73) Simon, R. C.; Grischek, B.; Zepeck, F.; Steinreiber, A.; Belaj, F.; Kroutil, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 6713.
(74) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413.
(75) Latorre, A.; Saez, J. A.; Rodriguez, S.; Gonzalez, F. V. *Tetrahedron* **2014**, *70*, 97.

(76) Celmer, W. D.; Solomons, I. A. *J. Am. Chem. Soc.* **1953**, *75*, 3430.
(77) Clive, D. L. J.; Paul, C. C.; Wang, Z. *J. Org. Chem.* **1997**, *62*, 7028.
(78) Baldwin, J. E.; Adlington, R. M.; Basak, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1284.
(79) Blanchard, P.; El Kortbi, M. S.; Fourrey, J. L.; Robert-Gero, M. *Tetrahedron Lett.* **1992**, *33*, 3319.
(80) Jose Maria, E.; Da Silva, A. D.; Fourrey, J.-L.; Machado, A. S.; Robert-Gero, M. *Tetrahedron Lett.* **1994**, *35*, 3301.
(81) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149.
(82) Luche, J. L.; Allavena, C. *Tetrahedron Lett.* **1988**, *29*, 5369.
(83) Luche, J. L.; Allavena, C.; Petrier, C.; Dupuy, C. *Tetrahedron Lett.* **1988**, *29*, 5373.
(84) Suarez, R. M.; Sestelo, J. P.; Sarandeses, L. A. *Chem. - Eur. J.* **2003**, *9*, 4179.
(85) Suarez, R. M.; Perez Sestelo, J.; Sarandeses, L. A. *Org. Biomol. Chem.* **2004**, *2*, 3584.
(86) Knochel, P.; Joned, P.; Editors *Organozinc Reagents: A Practical Approach*; Oxford Univ Press, 1999.
(87) Molander, G. A.; Dowdy, E. D.; Pack, S. K. *J. Org. Chem.* **2001**, *66*, 4344.
(88) Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett* **1998**, 58.
(89) Massah, A. R.; Ross, A. J.; Jackson, R. F. W. *J. Org. Chem.* **2010**, *75*, 8275.
(90) Ballini, R.; Giantomassi, G. *Tetrahedron* **1995**, *51*, 4173.
(91) Maerkl, G.; Merkl, B. *Tetrahedron Lett.* **1981**, *22*, 4459.
(92) Katarzynska, J.; Mazur, A.; Bilska, M.; Adamek, E.; Zimecki, M.; Jankowski, S.; Zabrocki, J. *J. Pept. Sci.* **2008**, *14*, 1283.
(93) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489.
(94) Poindexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* **1977**, 3527.
(95) Jadhav, S. V.; Bandyopadhyay, A.; Benke, S. N.; Mali, S. M.; Gopi, H. N. *Org. Biomol. Chem.* **2011**, *9*, 4182.
(96) Huo, S. *Org. Lett.* **2003**, *5*, 423.
(97) Kumar, G. D. K.; Baskaran, S. *J. Org. Chem.* **2005**, *70*, 4520.
(98) Soderman, S. C.; Schwan, A. L. *Org. Lett.* **2011**, *13*, 4192.
(99) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167.

6. Appendix

Crystal structure data

Table 1: Crystal data and structure refinement for the compound 233a.

Empirical formula	$C_9 H_{16} N O$	
Formula weight	154.23	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.2274(2) Å	α= 90°.
	b = 7.9564(2) Å	β= 90°.
	c = 17.7883(5) Å	γ = 90°.
Volume	881.37(4) $Å^3$	
Z	4	
Density (calculated)	1.162 Mg/m^3	
Absorption coefficient	0.588 mm^{-1}	
F(000)	340	
Crystal size	0.210 x 0.120 x 0.120 mm^3	
Theta range for data collection	4.972 to 71.462°.	
Index ranges	-7<=h<=6, -9<=k<=9, -21<=l<=17	
Reflections collected	6201	
Independent reflections	1596 [R(int) = 0.0317]	
Completeness to theta = 67.000°	97.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.87 and 0.67	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1596 / 0 / 103	
Goodness-of-fit on F^2	1.019	
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0838	
R indices (all data)	R1 = 0.0457, wR2 = 0.0897	
Absolute structure parameter	0.16(15)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.153 and -0.178 $e.Å^{-3}$	

Table 2: Crystal data and structure refinement for the compound 234.

Empirical formula	C_{10} H_{19} N O	
Formula weight	169.26	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 5.4799(9) Å	α= 90°.
	b = 22.168(4) Å	β= 102.517(2)°.
	c = 8.7394(15) Å	γ = 90°.
Volume	1036.4(3) $Å^3$	
Z	4	
Density (calculated)	1.085 Mg/m^3	
Absorption coefficient	0.069 mm^{-1}	
F(000)	376	
Crystal size	0.320 x 0.210 x 0.180 mm^3	
Theta range for data collection	1.837 to 27.663°.	
Index ranges	-7<=h<=7, -28<=k<=28, -11<=l<=11	
Reflections collected	18642	
Independent reflections	4821 [R(int) = 0.0387]	
Completeness to theta = 25.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.991 and 0.876	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4821 / 1 / 223	
Goodness-of-fit on F^2	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0410, wR2 = 0.0984	
R indices (all data)	R1 = 0.0484, wR2 = 0.1041	
Absolute structure parameter	?	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.238 and -0.189 $e.Å^{-3}$	

Table 3: Crystal data and structure refinement for the compound 235b.

Empirical formula	C_{13} H_{17} N O	
Formula weight	203.27	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 5.2549(2) Å	α= 90°.
	b = 18.9734(8) Å	β= 90°.
	c = 22.8900(9) Å	γ = 90°.
Volume	2282.21(16) $Å^3$	
Z	8	
Density (calculated)	1.183 Mg/m^3	
Absorption coefficient	0.581 mm^{-1}	
F(000)	880	
Crystal size	0.210 x 0.110 x 0.110 mm^3	
Theta range for data collection	3.025 to 75.801°.	
Index ranges	-6<=h<=5, -22<=k<=19, -28<=l<=27	
Reflections collected	15557	
Independent reflections	4568 [R(int) = 0.1108]	
Completeness to theta = 72.500°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.87 and 0.65	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4568 / 0 / 273	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0829, wR2 = 0.1419	
R indices (all data)	R1 = 0.1546, wR2 = 0.1674	
Absolute structure parameter	0.2(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.255 and -0.274 $e.Å^{-3}$	

Table 4: Crystal data and structure refinement for the compound 259b.

Empirical formula	$C_{16} H_{23} N O$
Formula weight	245.35
Temperature	173(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.44380(10) Å α= 90°. b = 10.1327(2) Å β=93.5540(10)°. c = 26.0105(6) Å γ = 90°.
Volume	1431.99(5) $Å^3$
Z	4
Density (calculated)	1.138 Mg/m^3
Absorption coefficient	0.539 mm^{-1}
F(000)	536
Crystal size	0.24 x 0.11 x 0.08 mm^3
Theta range for data collection	3.405 to 66.748°.
Index ranges	-6<=h<=5, -12<=k<=12, -30<=l<=30
Reflections collected	18423
Independent reflections	5010 [R(int) = 0.0233]
Completeness to theta = 66.748°	99.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5010 / 1 / 329
Goodness-of-fit on F^2	1.129
Final R indices [I>2sigma(I)]	R1 = 0.0330, wR2 = 0.0801
R indices (all data)	R1 = 0.0351, wR2 = 0.0852
Absolute structure parameter	0.06(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.149 and -0.206 $e.Å^{-3}$

Table 5: Crystal data and structure refinement for the compound 301.

Empirical formula	$C_9 H_{20} Cl N$	
Formula weight	177.71	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 8.0295(3) Å	α= 90°.
	b = 7.5358(3) Å	β= 108.535(3)°.
	c = 9.0564(4) Å	γ = 90°.
Volume	519.57(4) $Å^3$	
Z	2	
Density (calculated)	1.136 Mg/m^3	
Absorption coefficient	2.785 mm^{-1}	
F(000)	196	
Crystal size	0.320 x 0.120 x 0.120 mm^3	
Theta range for data collection	5.812 to 66.516°.	
Index ranges	-9<=h<=9, -8<=k<=7, -10<=l<=10	
Reflections collected	4427	
Independent reflections	1632 [R(int) = 0.0344]	
Completeness to theta = 66.516°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.86 and 0.54	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1632 / 1 / 104	
Goodness-of-fit on F^2	1.013	
Final R indices [I>2sigma(I)]	R1 = 0.0292, wR2 = 0.0707	
R indices (all data)	R1 = 0.0324, wR2 = 0.0726	
Absolute structure parameter	0.07(2)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.207 and -0.223 $e.Å^{-3}$	

Table 6: Crystal data and structure refinement for the compound 302.

Empirical formula	$C_{10}H_{22}ClN$	
Formula weight	191.73	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 8.6666(11) Å	α= 90°.
	b = 7.4639(8) Å	β= 107.276(6)°.
	c = 9.1796(11) Å	γ = 90°.
Volume	567.01(12) $Å^3$	
Z	2	
Density (calculated)	1.123 Mg/m^3	
Absorption coefficient	0.291 mm^{-1}	
F(000)	212	
Crystal size	0.27 x 0.12 x 0.05 mm^3	
Theta range for data collection	2.839 to 27.518°.	
Index ranges	-11<=h<=10, -9<=k<=9, -11<=l<=11	
Reflections collected	8706	
Independent reflections	2549 [R(int) = 0.0378]	
Completeness to theta = 25.242°	99.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2549 / 1 / 112	
Goodness-of-fit on F^2	1.064	
Final R indices [I>2sigma(I)]	R1 = 0.0326, wR2 = 0.0638	
R indices (all data)	R1 = 0.0396, wR2 = 0.0669	
Absolute structure parameter	-0.01(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.188 and -0.182 e.$Å^{-3}$	

Table 7: Crystal data and structure refinement for the compound 304.

Empirical formula	C_{11} H_{24} Cl N	
Formula weight	205.76	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.2368(3) Å	α= 90°.
	b = 8.4177(4) Å	β= 90°.
	c = 20.7326(9) Å	α = 90°.
Volume	1262.97(10) $Å^3$	
Z	4	
Density (calculated)	1.082 Mg/m^3	
Absorption coefficient	2.349 mm^{-1}	
F(000)	456	
Crystal size	0.270 x 0.040 x 0.040 mm^3	
Theta range for data collection	4.265 to 66.622°.	
Index ranges	-8<=h<=8, -10<=k<=10, -24<=l<=24	
Reflections collected	8450	
Independent reflections	2193 [R(int) = 0.0392]	
Completeness to theta = 66.622°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.5913	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2193 / 0 / 122	
Goodness-of-fit on F^2	1.078	
Final R indices [I>2sigma(I)]	R1 = 0.0283, wR2 = 0.0635	
R indices (all data)	R1 = 0.0317, wR2 = 0.0653	
Absolute structure parameter	0.03(2)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.148 and -0.199 $e.Å^{-3}$	