The University Of Sheffield.

SYNTHESIS OF PIPERIDINES USING ORGANOMETALLIC CHEMISTRY

A Dissertation Submitted for the Degree of Doctor of Philosophy

by:

MANSOUR A. S. ABDELSALAM

April 2013

For My Family

Contents

Acknowledgements 3
Abbreviations 4
Abstract 7
Chapter 1: Introduction 1
1.1 Introduction 1
1.1.1 Importance of 2,5-disubstituted piperidines 1
1.1.2 Importance of 2,6-disubstituted piperidines 2
1.2 Preparation of disubstituted piperidines 3
1.2.1 Preparation of 2,5-disubstituted piperidines 3
1.2.2 Preparation of indolizidines 8
1.2.3 Preparation of 2,6-disubstituted piperidines 11
1.2.4 Preparation of piperidines in the Jackson group 16
1.3 Organozinc reagents 19
1.4 Copper chemistry 21
1.5 Jackson group chemistry 26
1.6 Aims 28
Chapter 2: Synthesis of 2,5-disubstituted piperidines 30
2.1 Introduction 30
2.2 Results and discussion 31
2.2.1 Preparation of organoiodides 31
2.2.2 Investigation of pipecolate synthesis 35
2.2.3 Boc-protected piperidines 39
2.2.4 TFA-protected piperidines 43
2.2.5 Indolizidine synthesis 48
2.2.6 Hydrogenation of 5-methylenepiperidines 55
2.2.7 Hydrogenation of indolizidinone and oxazolidinone 78
2.2.8 Heck reactions 89
2.2.9 Hydrogenation of Heck reaction products 91

2.3 Conclusion 93
Chapter 3: Synthesis of 2,6-disubstituted piperidines 94
3.1 Introduction 94
3.2 Results and discussion 94
3.3 Conclusion 102
Chapter: 4 Experimental 103

Acknowledgements

I would like to thank my supervisor Professor Richard Jackson for his support and care during the study.

I also would like to say a big thank you to the rest of the Jackson Group for all their help and advice.

I would like to thank the Committee of Higher Education in Libya and the Libyan People's Bureau in London for the scholarship and generous support.

Abbreviations

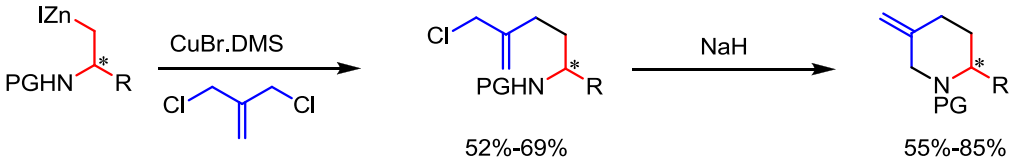
$[\alpha]^{20}_{D}$	Optical Rotation
Ac	Acetyl
acac	Acetylacetonyl
AIBN	Azo*bis*isobutyronitrile
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
c	Concentration
cat	Catalysis
d	Doublet
DCC	Dicyclohexylcarbodiimide
dd	Doublet of doublets
DMA	*N,N*-Dimethylacetamide
DMAP	*N,N*-4-Dimethylaminopyridine
DMF	*N, N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'-*bis*(Diphenylphosphino)ferrocene
dt	Doublet of triplets

ee	Enantiomeric excess
eq	Equivalents
GABA	γ-aminobutyric acid
GC	Gas Chromatography
HMPA	Hexamethylphosphoric acid triamide
^{i}Pr	Isopropyl
IR	Infrared
J	Coupling Constant
m	Multiplet
M	Metal
m/z	Mass/charge ratio
Me	Methyl
mp	Melting Point
Ms	Methanesulfonyl
NHS	N-Hydroxysuccinimide
NMR	Nuclear Magnetic Resonance
NPSP	N-Phenylselenophthalimide
Nu	Nucleophile
OTf	Trifluoromethanesulfonate
PG	Protecting group
Ph	Phenyl

Py	Pyridine
q	quartet
R	Alkyl group
RCM	Ring-Closing Metathesis
R_f	Retention Factor
s	Singlet
S_N2	Bimolecular nucleophilic substitution
TBDMS	*t*-Butyldimethylsilyl
TFA	Trifluoroacetyl
TFAA	Trifluoroacetic anhydride
TFE	Tetrafluoroethylene
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl
X	Halogen
Zn*	Activated zinc
δ	Chemical shift

Abstract

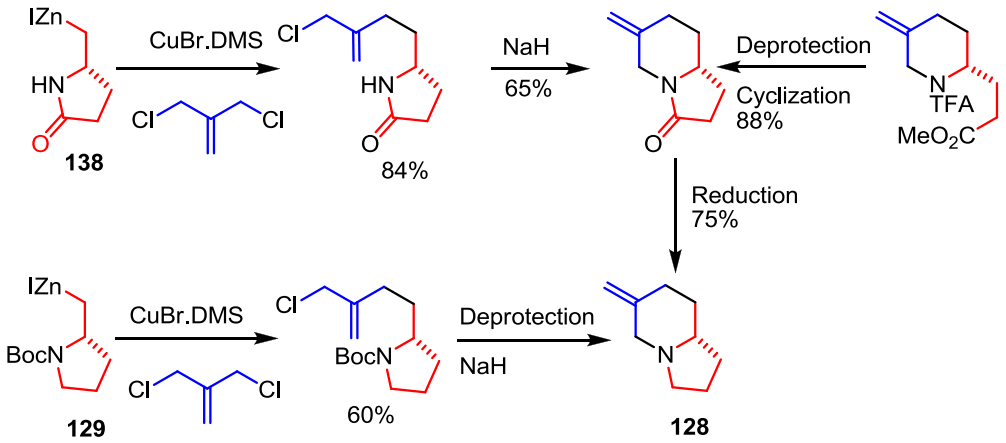
Reaction of a range of protected β-aminoalkyl zinc iodide with 3-chloro-2-(chloromethyl)prop-1-ene under copper catalysis, followed by cyclization using sodium hydride, gave enantiomerically enriched 5-methylene piperidines in good yields (55%-85%) (**Scheme A**).



R =Bn, ^{i}Pr, CO_2Me, CH_2CO_2Me and $CH_2CH_2CO_2Me$
PG = Boc and TFA

Scheme A: *Synthesis of 5-methylene-2-substituted piperidines*

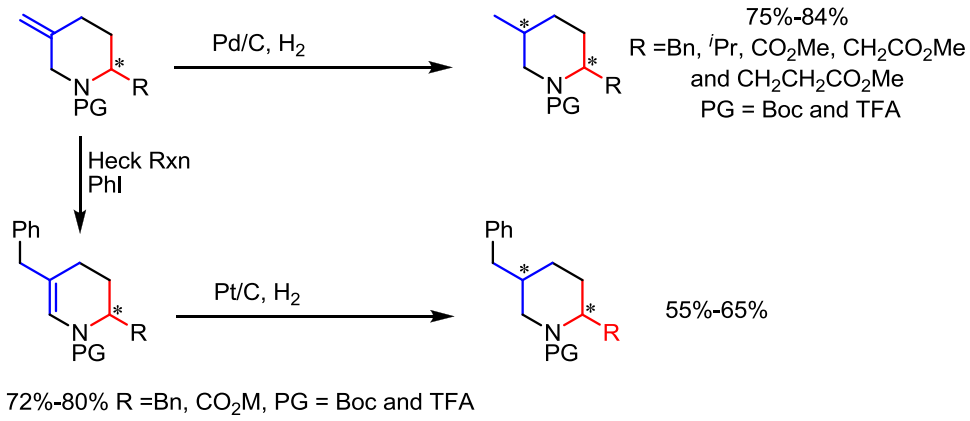
Application of this general method using the cyclic reagents **129** and **138**, followed by cyclization provided 6-methylene indolizidine **128** (**Scheme B**).



Scheme B: *Synthesis of 6-methyleneindolizidine*

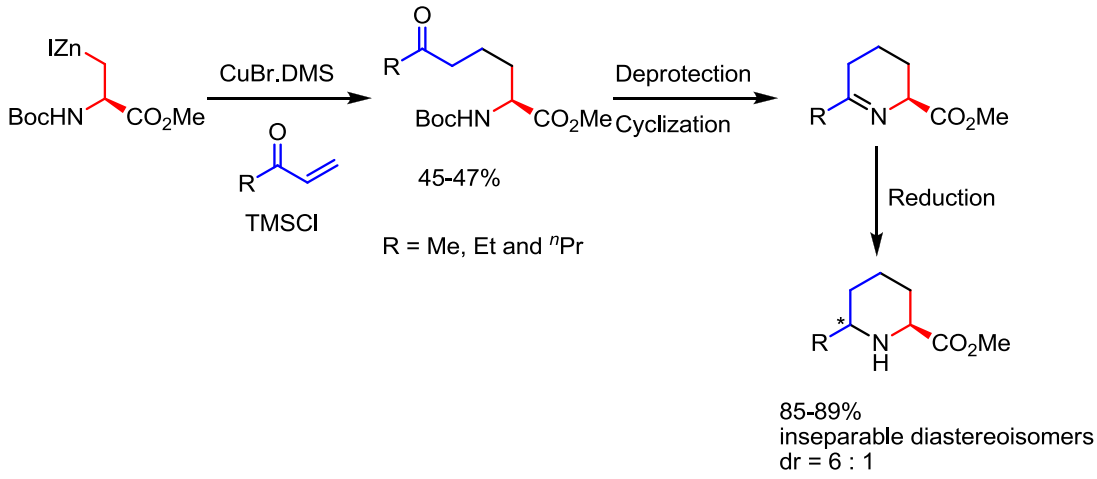
Hydrogenation of the previous piperidines (**Scheme A**) gave two separable diastereoisomeric 5-methyl-2-substituted piperidines: hydrogenation of substrates with a TFA-protecting group was more stereoselective than hydrogenation of the corresponding Boc-protecting

group derivatives. Heck reaction were carried out with these piperidines, and hydrogenation of the Heck products gave 2,5-disubstituted piperidines (**Scheme C**).



Scheme C: *Hydrogenation of piperidines and Heck products*

2,6-Disubstituted piperidines were formed by reductive cyclization of 6-oxoamino acid derivatives (**Scheme D**), prepared by conjugate addition of organozinc reagents derived from *L*-serine to enones. Stereoselective reduction of the intermediate imine produced two inseparable diastereoisomeric 2,6-disubstituted piperidines.



Scheme D: *Synthesis of pipecolic acid derivatives*

Chapter 1: Introduction

1.1 Introduction

Piperidine ring systems are important components of a number of natural products and pharmacologically and medically active substances, and have therefore been the subject of much synthetic effort.[1-3] This project will focus on short diastereoselective syntheses of a range of significant substituted piperidines, specifically 2,5 and 2,6-disubstituted piperidines.

1.1.1 Importance of 2,5-disubstituted piperidines

2,5-Disubstituted piperidines have been found to be useful for inhibiting γ-aminobutyric acid (GABA) uptake. For example, nipecotic acid derivatives **1** and **2** have been synthesized, and have shown reasonable activity as GABA uptake inhibitors. Other 2,5-disubstituted piperidines, for example compound **3a**, have been synthesized and studied biologically. The *cis*-isomer of compound **3a** was found to be more active than the *trans*-isomer for dopamine transport activity by a factor of 3. This activity could be increased further by replacing the fluorine atom with a cyano group (compound **3b**) (**Figure 1**).[4,5]

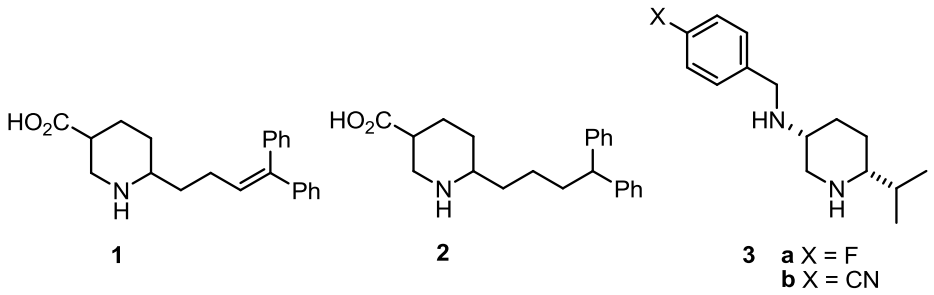


Figure 1

1.1.2 Importance of 2,6-disubstituted piperidines

The 2,6-disubstituted *N*-arylsulfonyl piperidines **4** have been reported to be γ-secretase inhibitors, used for the treatment of Alzheimer's disease (the *cis*-isomers **4** were more active than the *trans*-isomers). Introduction of a cyclopropyl ring, compound **5**, gave the most active γ-secretase inhibitors.[6-9] The *N*-sulfonamide **6** derived from *cis*-2,6-dimethylpiperidine, has been shown to inhibit acetylcholinesterase (**Figure 2**).[10]

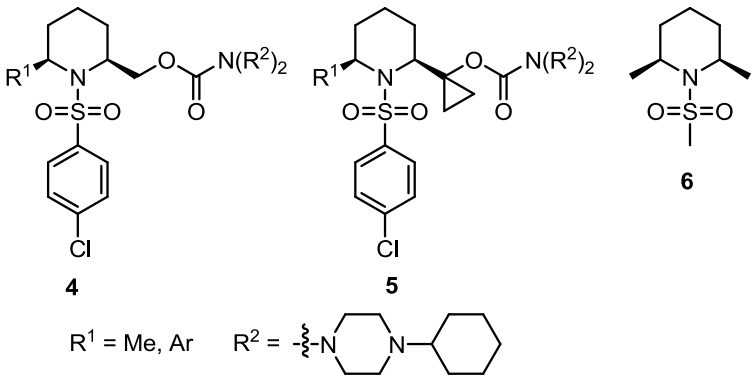


Figure 2

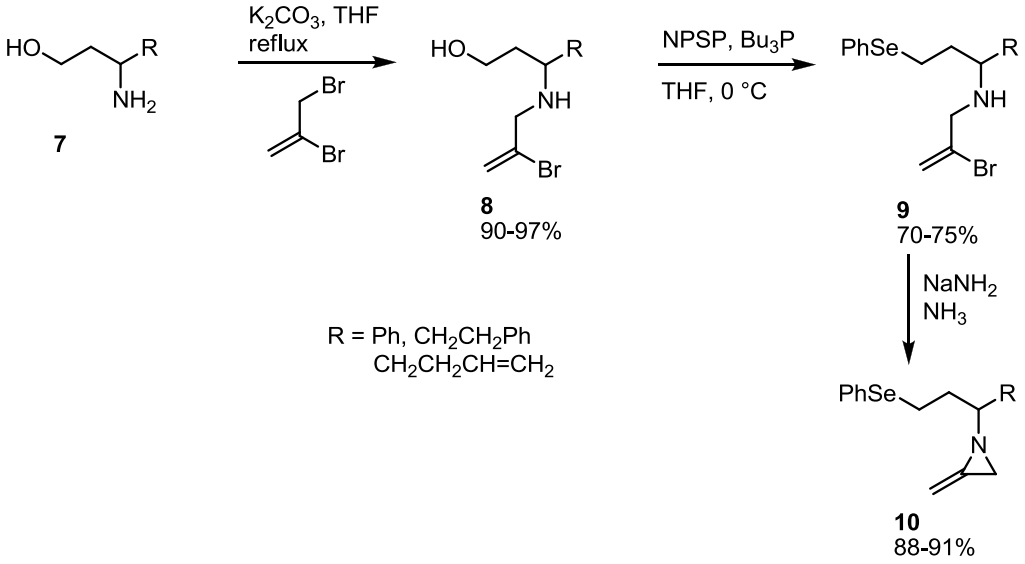
1.2 Preparation of disubstituted piperidines

There are a significant number of methods for the preparation of disubstituted piperidines. This section will summarize some of the most important methods for making 2,5 and 2,6-disubstituted piperidines using a cyclization strategy, rather than starting with the piperidine skeleton.[1-3,11,12]

1.2.1 Preparation of 2,5-disubstituted piperidines

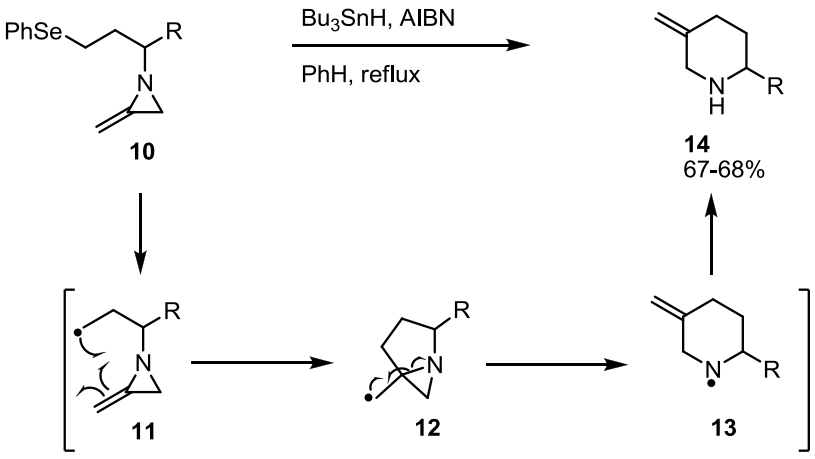
There have been a small number of synthetic methods reported for the preparation of 2-substituted-5-methylene piperidines, either as racemates or in enantiomerically pure form.

Shipman and co-workers reported radical 5-*exo* cyclization of 2-methylene-*N*-substituted aziridines containing a phenylselenide group to give 5-methylene piperidines.[13] The aziridines **10** were synthesized from the aminoalcohols **7** over three steps (**Scheme 1**).[14-16] Alkylation of compound **7** with 2,3-dibromopropene gave the alcohols **8**, and was followed by introduction of the phenylselenide group. Cyclization of compounds **9** with sodium amide gave the aziridines **10**.[17,18]



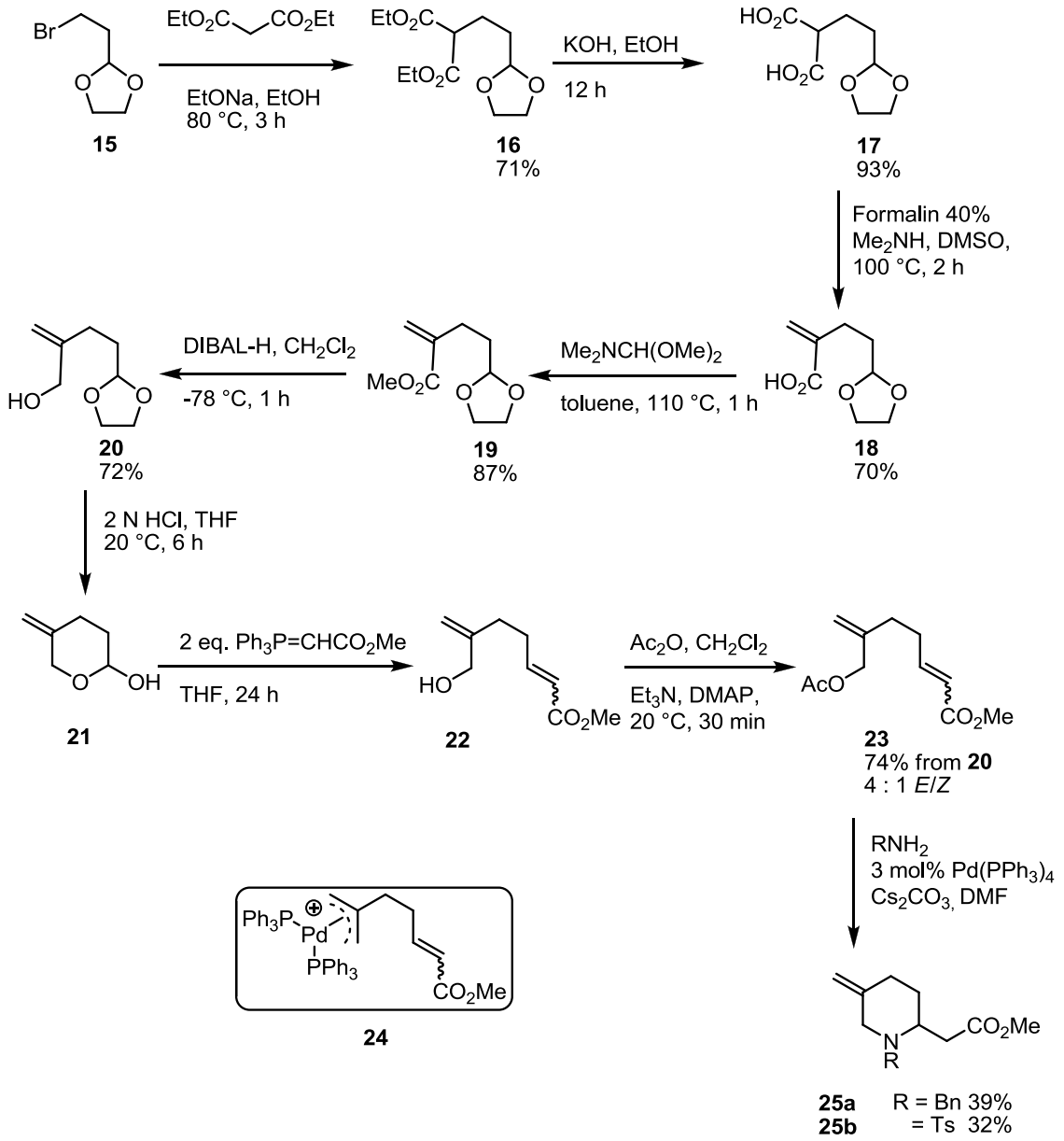
Scheme 1

The aziridines **10** underwent radical rearrangement upon treatment with *tri*-n-butyltin hydride and AIBN (**Scheme 2**).[19] This rearrangement proceeds *via* the aziridinylcarbinyl radical **11**, which undergoes a 5-*exo*-*trig* cyclization followed by ring opening of the aziridinylmethyl radical, releasing the ring strain present in compound **12** by breaking the C-N bond, giving the piperidines **14**.



Scheme 2

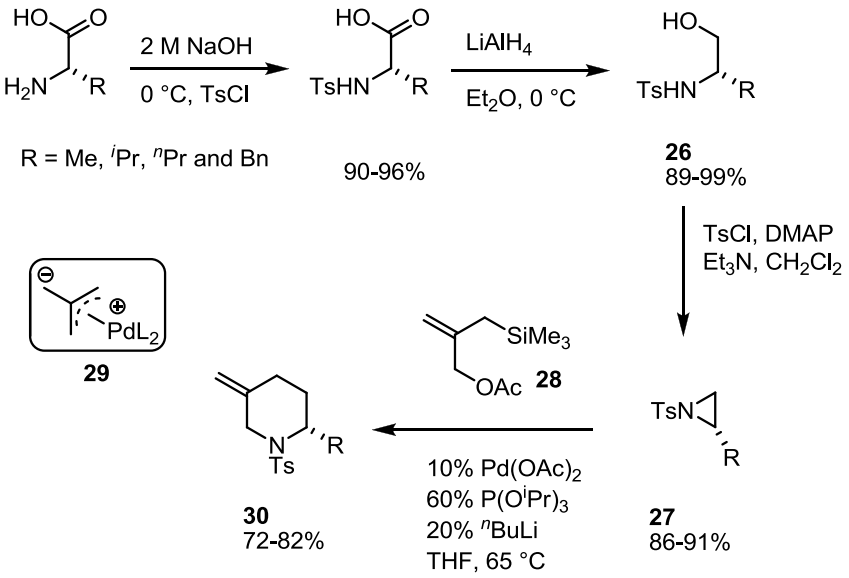
Desmaële and co-workers have disclosed an alternative route to 5-methylenepiperidines involving sequential palladium-catalyzed allylic amination and Michael addition (**Scheme 3**).[20,21] Reaction of commercially available bromo-acetal **15** with diethyl malonate in the presence of sodium ethoxide gave compound **16**, which underwent saponification to produce diacid **17**. A decarboxylative Mannich reaction gave **18** which was esterfied to give **19**. DIBAL-H reduction of the ester **19** and hydrolysis of the acetal group gave hemiacetal **21**, which on treatment with methyl (triphenylphosphoranylidene)acetate provided the unsaturated ester **22** which was acetylated to give unsaturated ester **23**.[22] Palladium-catalyzed reaction of benzylamine with compound **23** gave the piperidine **25a**, presumably via the η^3-allylpalladium complex **24**. A less nucleophilic amine (*p*-toluenesulfonamide) gave a lower yield.[23]



Scheme 3

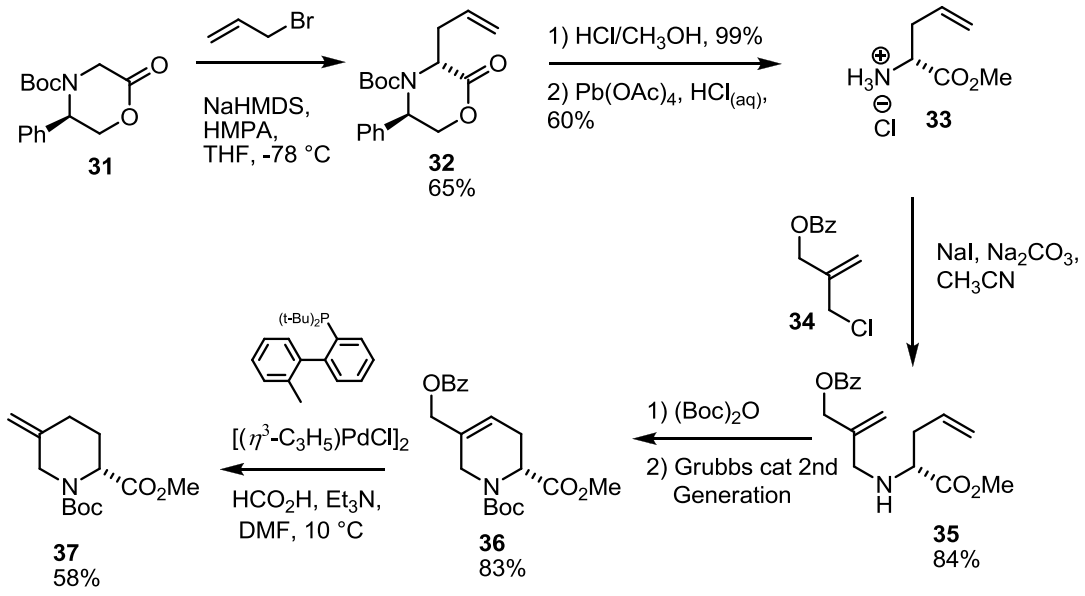
Ring opening of activated aziridines with palladium-trimethylenemethane (Pd-TMM) complex in a formal [3+3] cycloaddition has been reported by Bambal and Kemmitt.[24] Harrity and co-workers have applied this approach for the synthesis of functionalized piperidines.[25,26] The enantiomerically pure monosubstituted aziridine precursors **27** were prepared from the corresponding amino acids in three steps (**Scheme 4**).[27] The cycloaddition reaction of (Pd-TMM) complex **29**, prepared by heating 2-

[(trimethylsilyl)methyl]-2-prop-1-enyl acetate **28** with catalytic palladium, with monosubstituted aziridines **27** provided 5-methylene piperidines **30** in excellent yields.



Scheme 4

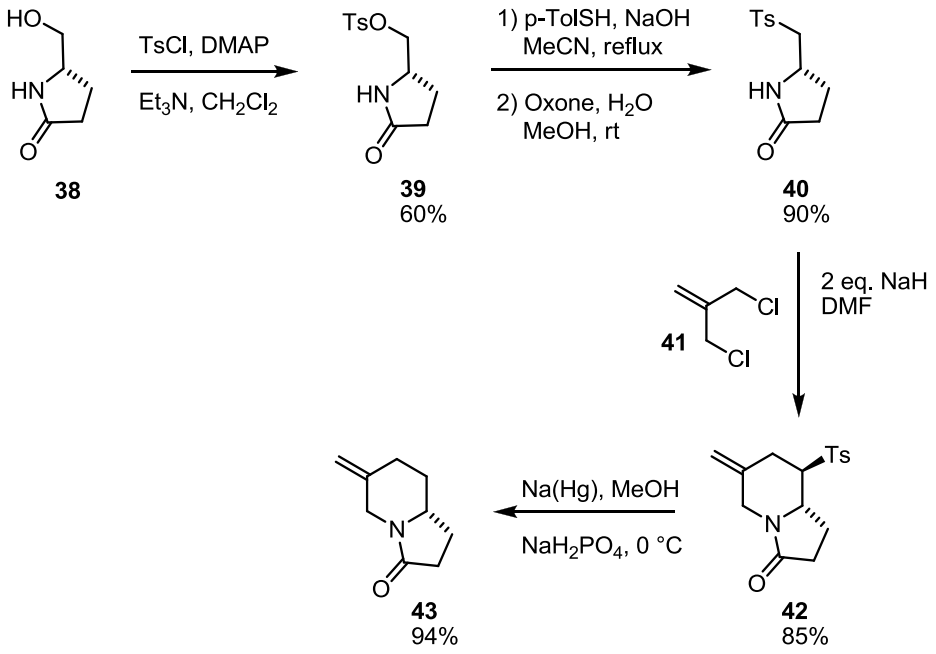
Sun and co-workers have synthesized 5-methylenepipecolate **37** through a sequence involving allylation, ring-closing metathesis and palladium-catalyzed formate reduction (**Scheme 5**).[28] Allylation of 5-phenylmorpholin-2-one **31** with allyl bromide furnished **32**. Acidic deprotection of the Boc group gave amine **33**, which underwent *N*-allylation with compound **34** to produce secondary amine **35**. Protection and ring closing metathesis (RCM) gave unsaturated pipecolate **36** in excellent yield. Regioselective palladium catalyzed formate reduction gave **37**.



Scheme 5

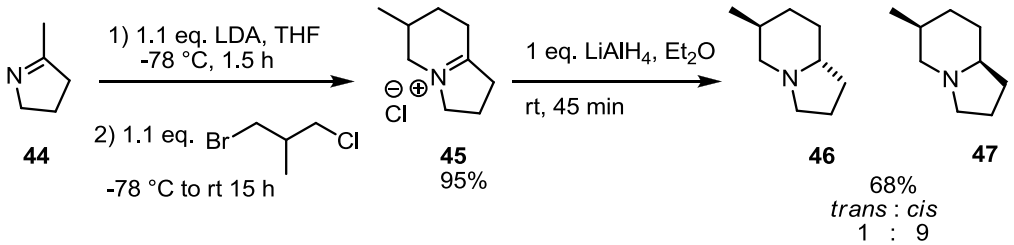
1.2.2 Preparation of indolizidines

Najera and co-workers have reported a synthetic approach to the related indolizidinone **43** (**Scheme 6**).[29,30] Treatment of (*S*)-pyroglutaminol **38** with *p*-toluenesulfonyl chloride under basic conditions afforded tosylate **39** which underwent nucleophilic displacement by *p*-methylthiophenol, followed by oxidation to give enantiomerically pure sulfone **40**. Subsequent addition of 2 eq. NaH and 3-chloro-2-(chloromethyl) propene **41** gave tosylindolizidine **42**, which was reduced to the indolizidinone **43.**



Scheme 6

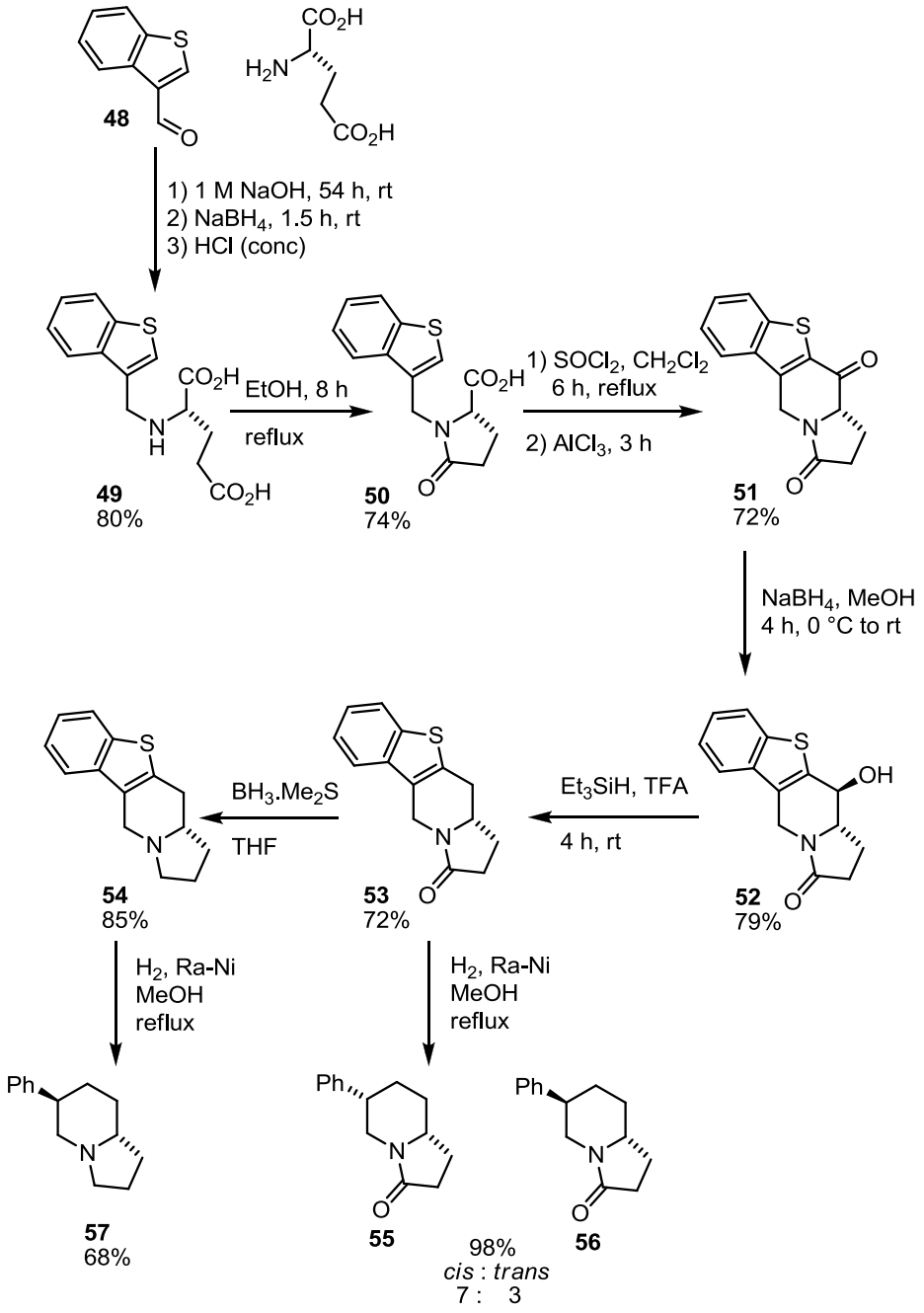
De Kimpe and co-workers developed a novel synthesis of indolizidines by dialkylating 2-methyl-1-pyrroline with a 1,3-dielectrophile (**Scheme 7**).[31] The pyrroline **44** was deprotonated by LDA and consecutive reaction with 1-bromo-3-chloro-2-methylpropane furnished the intermediate **45** as a stable salt, which was reduced with $LiAlH_4$ to give an inseparable mixture of the diastereoisomeric indolizidines **46** and **47** in a 1:9 *trans*:*cis* ratio.



Scheme 7

Daïch and co-workers have synthesized indolizidines using the reductive desulfurization of benzothienoindolizines (**Scheme 8**).[32] Preparation of (S)-*N*-benzothienylmethylglutamic acid **49** was achieved by reaction of aldehyde **48** with *L*-glutamic acid, forming a Schiff base, followed by reduction. Refluxing compound **49** in ethanol gave the γ-lactam **50**. The carboxylic acid was then transformed into an acid chloride, which underwent an intramolecular Friedel-Crafts reaction to give the expected tricyclic keto-lactam **51**. Reduction of the ketone provided *trans* alcohol **52** as a single diastereoisomer. The reduction of alcohol **52** was achieved using triethylsilane/trifluoroacetic acid furnishing lactam **53**. The use of $BH_3.Me_2S$ to reduce this lactam to compound **54** was successful.

Compounds **53** and **54** were each subjected to reduction with activated Ra-Ni in anhydrous methanol in the presence of hydrogen gas. Lactam **53** gave an inseparable mixture of the two diastereoisomers **55** and **56** in a 7:3 ratio *cis:trans*. Compound **57** was the only isomer observed when **54** was reduced under the same conditions.



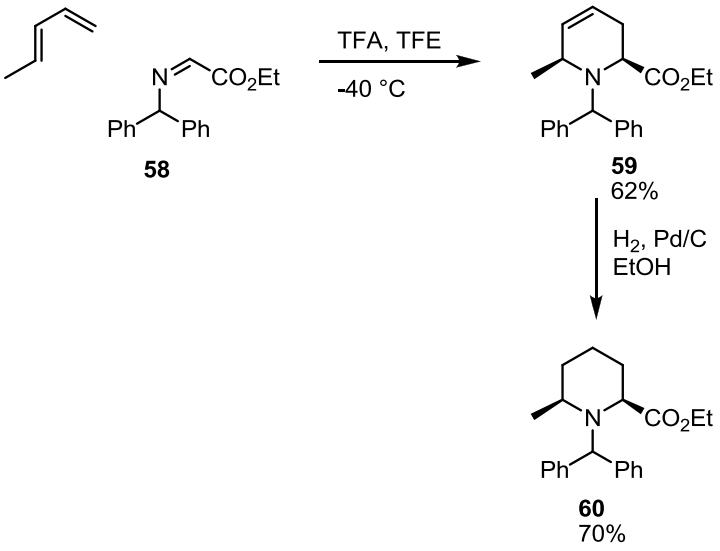
Scheme 8

1.2.3 Preparation of 2,6-disubstituted piperidines

Due to their potential biological activity, the synthesis of substituted derivatives of pipecolic acid has also received attention, and has been reviewed recently.[33-35] This potential for biological activity engaged our

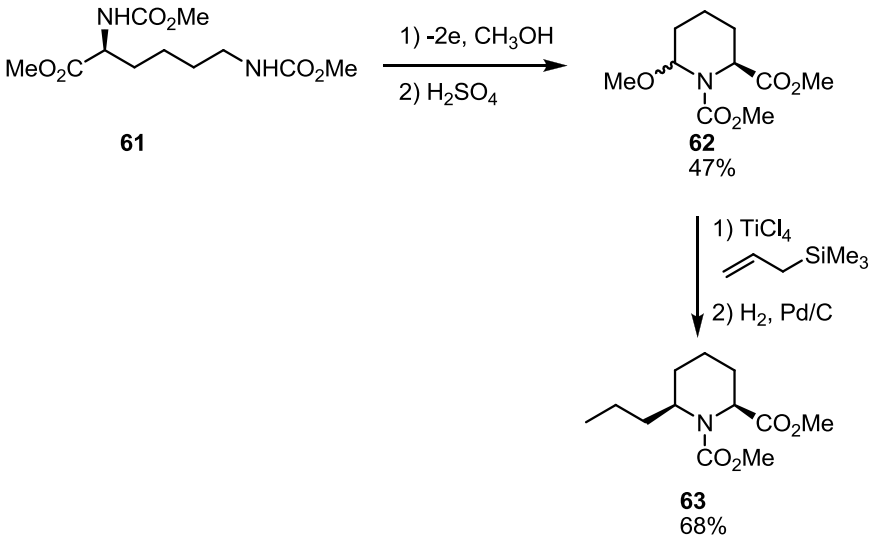
interest in the synthesis of pipecolates from amino acids and, due to the relatively small number of reports of structures bearing mono-substitution at the 6-position, we focused our efforts in this area. A number of routes to pipecolates substituted at the 6-position with saturated alkyl chains have been reported.

Bailey and co-workers described the aza-Diels-Alder reaction between imine **58** and 1,3-pentadiene (**Scheme 9**),[11,36,37] which led to the stereoselective formation of the *cis*-isomer of the unsaturated piperidine **59**, which in turn was reduced to piperidine **60.**



Scheme 9

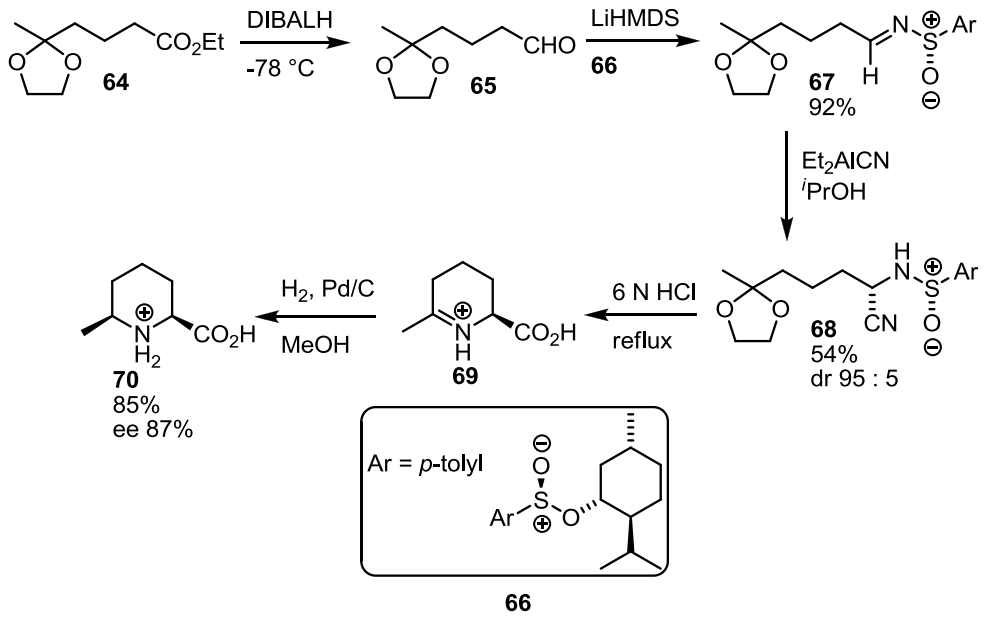
Shono and co-workers reported the anodic oxidation of compound **61** derived from L-lysine, which on treatment with acid gave the key intermediate **62** (**Scheme 10**).[38,39] Treatment of **62** with allyltrimethylsilane in the presence of $TiCl_4$, followed by hydrogenation, exclusively gave the *cis*-diastereoisomer **63**.



61 **62** 47% **63** 68%

Scheme 10

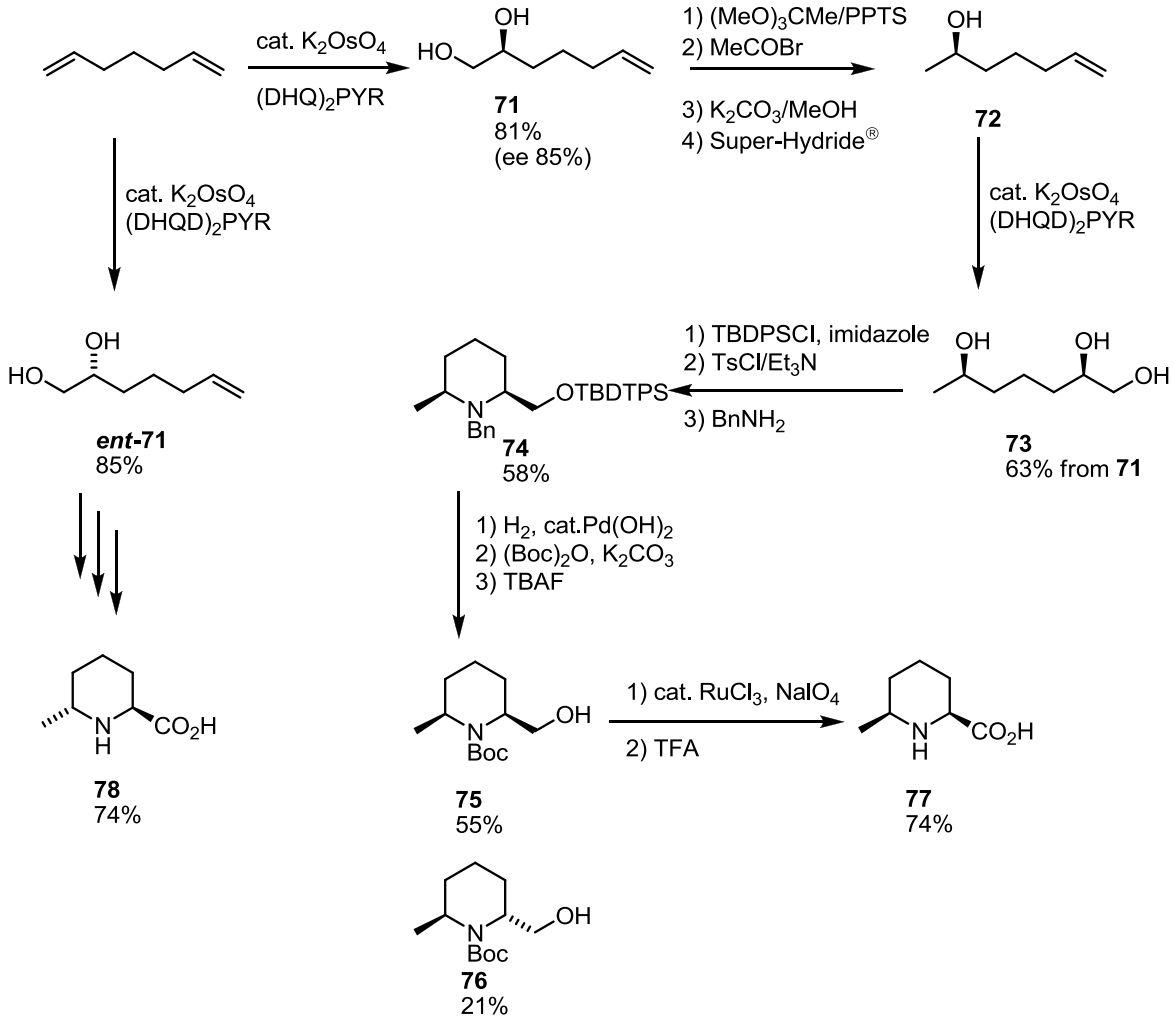
Davis and co-workers developed a method for synthesizing 6-oxoamino acids, which can be cyclized to give piperidines (**Scheme 11**).[40] The aldehyde **65** was prepared by reduction of the ester **64**. Treatment of commercially available (1*R*,2*S*,5*R*)-menthyl (*S*)-*p*-toluenesulfinate **66** with LiHMDS, followed by addition of the aldehyde **65**, gave the sulfinimine **67**. Introduction of the nitrile group in **67** was achieved using the reagent generated *in situ* from ^{i}PrOH and Et_2AlCN. Treatment of **68** with 6 N HCl resulted in removal of the sulfinyl group, hydrolysis of the nitrile to an acid, deprotection of the ketone, and finally cyclization. Hydrogenation of compound **69** occured as expected from the least hindered face to gave **70**.



Scheme 11

Takahata and Shimizu applied the Sharpless asymmetric dihydroxylation (AD) reaction to the synthesis of enantiomerically pure 6-methylpipecolic acid (**Scheme 12**).[41] Selective AD reaction of 1,6-heptadiene gave the 1,2-diol **71**, which was converted into the epoxide by the Sharpless one-pot procedure followed by reduction using Super-Hydride® as regioselective reducing reagent to give the alcohol **72**. A second $(DHQD)_2$-PYR ligand-derived AD reaction gave **73**, as well as a small amount of the C-2 epimer of **73**. The triol **73** was selectively monoprotected at the primary hydroxyl, followed by tosylation of both secondary alcohols. Double nucleophilic substitution reaction with benzylamine gave the enantiomerically enriched *cis*-piperidine **74**, contaminated with the *trans*-isomer. Deprotection of the benzyl group, Boc-protection, and desilylation furnished separable alcohols **75** and **76**. The last two steps to produce target compound **77** were an oxidation and a deprotection. The same procedure was followed

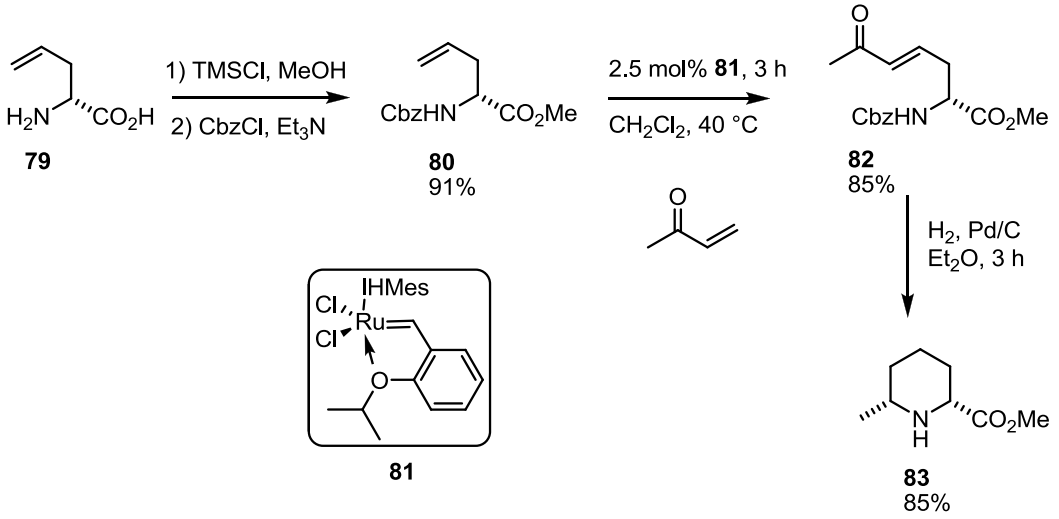
to synthesise the *trans*-isomer **78**, but the synthesis started with the $(DHQD)_2$-PYR ligand-derived (AD) reaction.



Scheme 12

Blechert and co-workers reported a short diastereoselective synthesis of 6-substituted pipecolates, applying a highly selective cross metathesis reaction followed by a domino reduction-cyclization reaction (**Scheme 13**).[42] Commercially available allylglycine **79** was converted into protected starting material **80.**[43] Cross metathesis of allylglycine derivative **80** with methyl vinyl ketone using the Hoveyda-Grubbs catalyst **81** affording the aminoenone **82**. Hydrogenation of compound **82** achieved three things:

hydrogenation of the double bond, deprotection of the amine, and cyclization to furnish *cis*-pipecolate **83**.

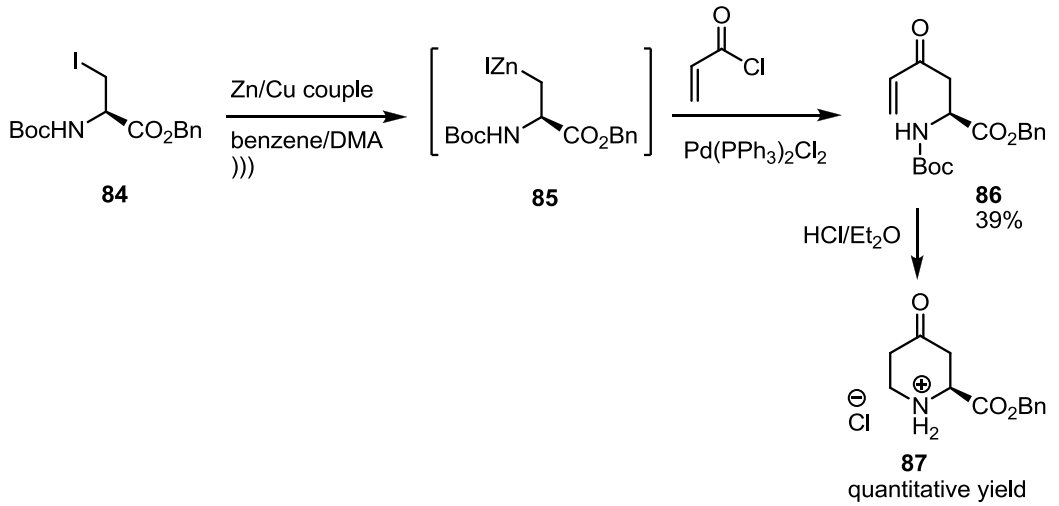


79 **80** 91% **81** **82** 85% **83** 85%

Scheme 13

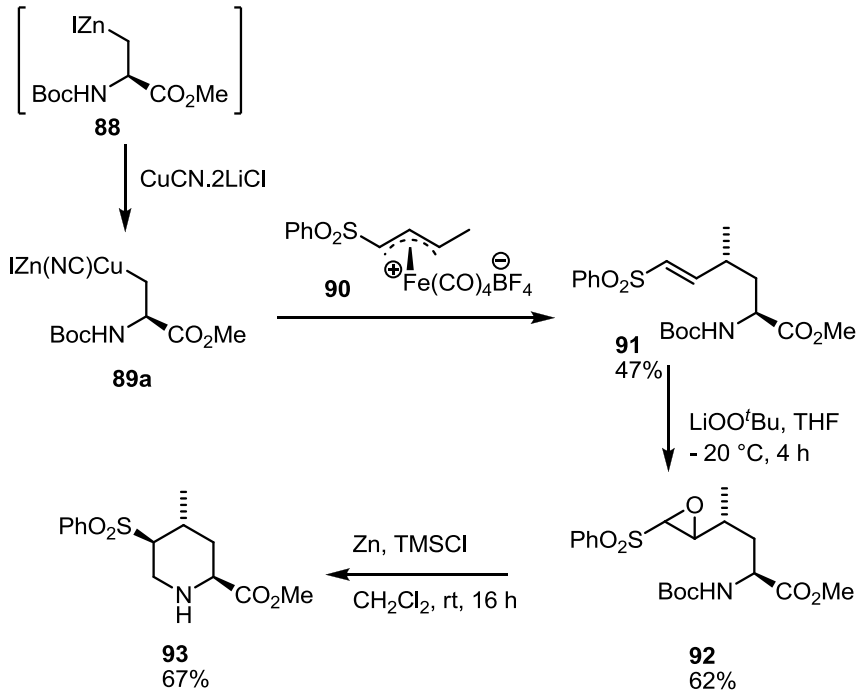
1.2.4 Preparation of piperidines in the Jackson group

Extensive work has been carried out to prepare enantiomerically pure substituted piperidine derivatives by using amino acids as chiral pool starting materials.[11,44] Some enantiomerically pure substituted piperidines have previously been prepared in the Jackson group using organozinc chemistry.[45] The Jackson group first reported the synthesis of piperidines derived from amino acids in 1994.[45,46] Cross coupling reaction of the serine-derived organozinc reagent **85** with propenoyl chloride gave 4-oxo amino acid **86** in a 39% yield, in a reaction catalyzed by $Pd(PPh_3)_2Cl_2$. The addition of HCl in diethyl ether furnished benzyl 4-oxopipecolate **87** in a quantitive yield (**Scheme 14**).[46]



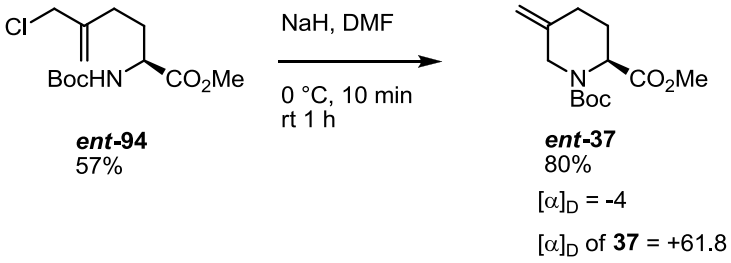
Scheme 14

In an approach to 4-methyl pipecolates, the zinc/copper reagent **89a** prepared from the corresponding zinc reagent **88** was treated with enantiomerically pure (η^3-allyl) iron tetracarbonyl salt **90** to give the adduct **91**. Addition of LiOO^{t}Bu gave the epoxide **92**, which gave 4-methylpiperidine **93** on treatment with Zn/TMSCl (**Scheme 15**).[47]



Scheme 15

In later unpublished work, Jackson and Gulati[48] developed a method to prepare 5-methylenepipecolates (**Scheme 16**). The allylic amino acid ***ent*-94** was cyclised by treatment with NaH to give the pipecolate ***ent*-37** in good yield. Unfortunately, it was demonstrated that the final step proceeded with racemisation; the observed specific rotation of ***ent*-37** was -4 compared to the value of +61.8 for **37** reported by Sun.[28]



***ent*-94**
57%

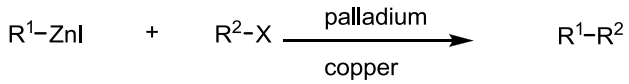
***ent*-37**
80%
$[\alpha]_D$ = -4
$[\alpha]_D$ of **37** = +61.8

Scheme 16

1.3 Organozinc reagents

Formation of carbon-carbon bonds is very important in the synthesis of natural products; organometallic compounds are significant tools to achieve this transformation.[49] The reactivity of organometallic compounds depends on the metal. Organolithium and organomagnesium reagents are very reactive reagents due to having highly polar bonds, due to their electronegativity (Li 1.53, Mg 1.27), in turn resulting in low chemoselectivity of these reagents. In contrast, the zinc-carbon bond is a less polar, covalent bond. Organozinc reagents have a lower reactivity and are more tolerant towards functional groups.

Transmetalation of the unreactive functionalized organozinc reagents to more reactive organometallic reagents, which can react with different organic electrophiles, is possible. Cross-coupling reactions of the organozinc reagents with a variety of electrophiles has been successfully achieved.[50-52] Negishi reported reaction of organozinc reagents with different electrophiles, aryl, heteroaryl and alkenyl halides in the presence of catalytic palladium (0).[53-56] In addition, organozinc reagents were transmetalated to copper reagents[57-60] (**Scheme 17**).



Scheme 17

Preparation of organozinc reagents by direct zinc insertion into the carbon-halogen bonds of poly-functional alkyl halides can be achieved using zinc

dust, provided prior activation to remove the oxide layer is carried out.[50,60-63]

Functionalised chiral organozinc reagents were synthesised from naturally occurring amino acids by the Jackson group.[45] A range of protected amino organoiodides derived from commercially available amino acids were converted into the corresponding organozinc reagents using a variety of zinc insertion methods (**Figure 3**).[64-68]

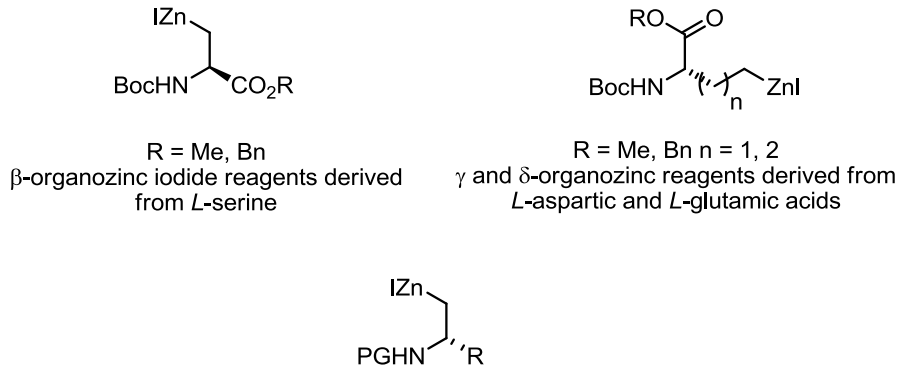


Figure 3

1.4 Copper chemistry

Organocopper compounds are amongst the most important source of carbon nucleophiles.[50,69] Organocopper(I) reagents can be generated *in situ* using catalytic copper(I) complex and organomagnesium, organozinc, or other organometallic reagent, or may be prepared as stoichiometric reagents. The organocopper(I) reagents are shown as RCu, R_2Cu^-, R_2CuLi and R_2CuZnX.[70]

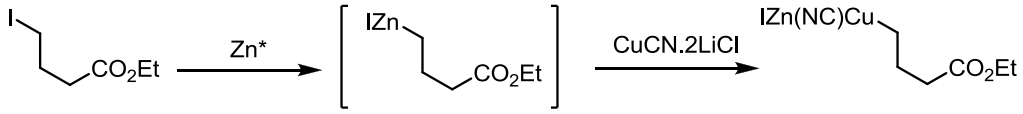
These reagents are very effective in a variety of reactions such as conjugate addition, carbocupration, alkylation, allylation, alkenylation, and acylation (**Scheme 18**).[71]

Scheme 18

Kharasch and Fields reported a conjugate addition reaction of a Grignard reagent to an *α*,*β*-unsaturated ketone in the presence of Cu(I) salt.[72] Gilman and co-workers reported in 1952 that the reaction of 1 eq of MeLi with copper formed a yellow precipitate and addition of another equivalent of MeLi gave a colourless solution. The latter type of reagent, formulated as R_2CuLi, is known as a Gilman reagent or Gilman cuprate.[73]

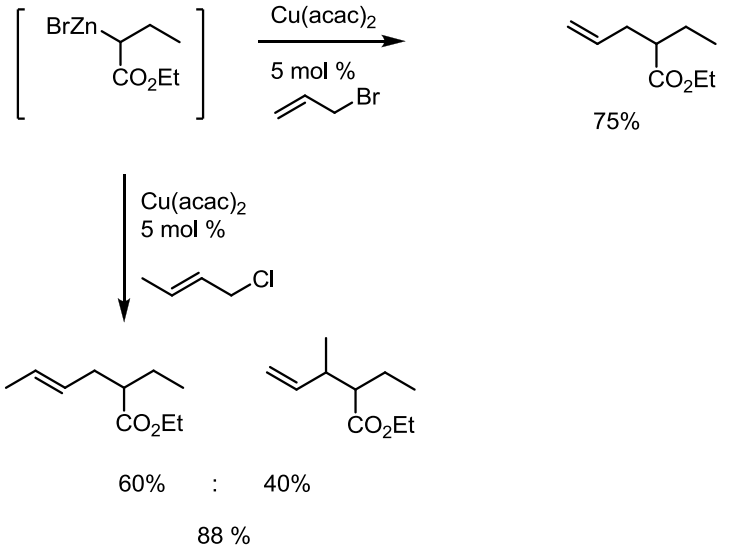
Costa and co-workers isolated phenyl copper(I) from the reaction of copper(I) bromide and phenyl lithium.[74] The synthetic chemistry of organocopper began to evolve rapidly since this report in 1966.[75]

Knochel and co-workers developed a method in which organozinc reagents were prepared by zinc insertion into carbon-halogen bonds, and subsequent conversion into cuprates *via* transmetallation with CuCN.2LiCl (**Scheme 19**).[76,77]



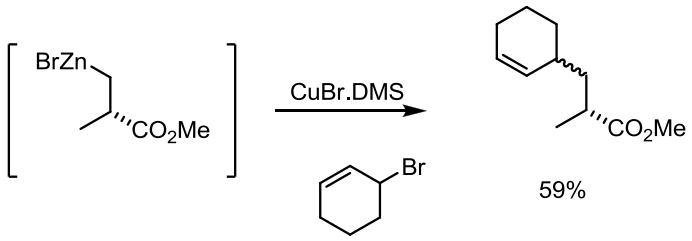
Scheme 19

In 1983 Gaudemar found that the reaction of Reformatsky reagents with allyl halides was catalyzed by the copper salt $Cu(acac)_2$. These reactions gave excellent yields, although S_N2/S_N2' selectivity was only modest (60% : 40%) (**Scheme 20**).[78]



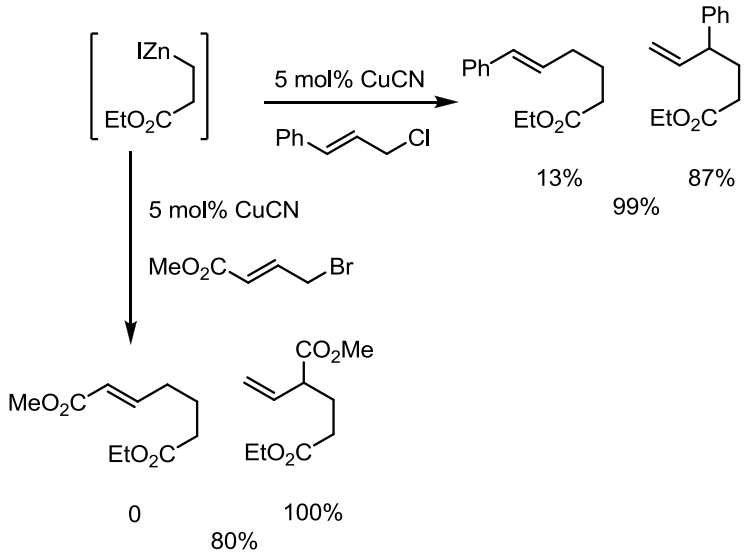
Scheme 20

In 1987 Nakamura and coworkers reported the allylation of chiral *β*-ester organozinc iodide with 3-bromocyclohexene under CuBr.DMS catalysis, providing two diastereoisomeric products (**Scheme 21**).[55]



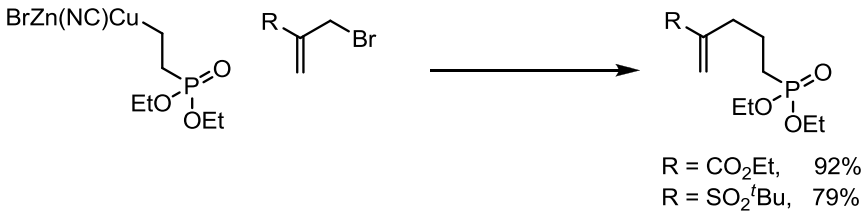
Scheme 21

Yoshida and co-workers carried out the reaction of *β* and *γ*-ester organozinc iodides with various allyl halides. These reactions were catalyzed by using CuCN, and generally resulted in gave the S_N2' products accompanied in some cases by the S_N2 products (**Scheme 22**).[60]



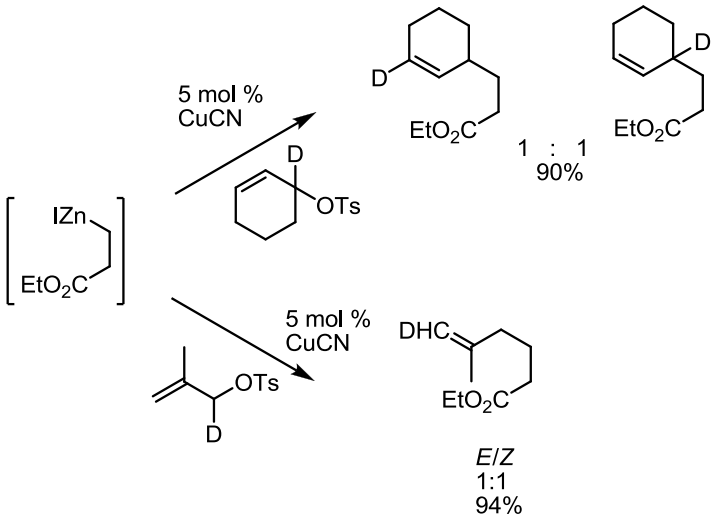
Scheme 22

Knochel and co-workers prepared a zinc/copper reagent containing a phosphonate group which reacted with allyl bromides to produce the corresponding terminal alkenes in high yields (**Scheme 23**).[79]



Scheme 23

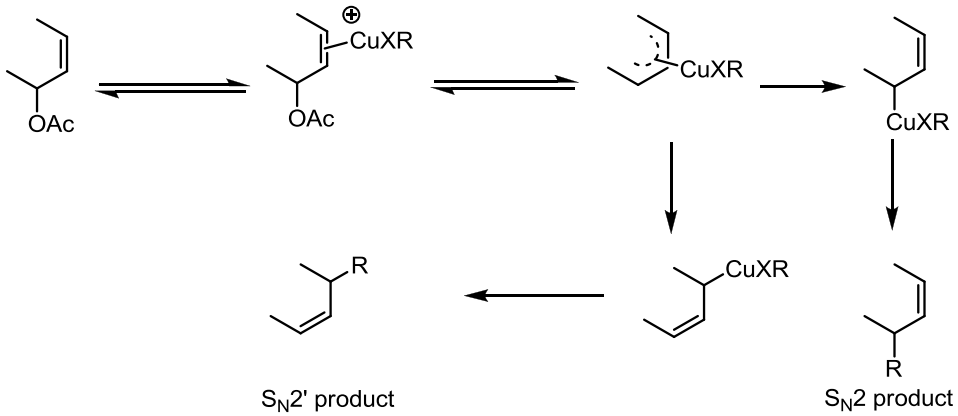
In order to distinguish between direct displacement of bromide S_N2, or attach at the double bond S_N2' labelled allylic halides were used. Yoshida and co-workers used a cyclic secondary allylic tosylate which they treated with an organozinc iodide under CuCN catalysis to furnish a mixture of formal S_N2 and S_N2' products. The S_N2' product obtained with a cyclic allylic tosylate whereas when an acyclic allylic tosylate was used, only the S_N2' product was obtained (**Scheme 24**).[60]



Scheme 24

Goering and Kantner have proposed a mechanism for the reaction of organocopper reagents with allylic acetate (**Scheme 25**). They propose that the copper coordinates to the alkene before the acetate group is lost

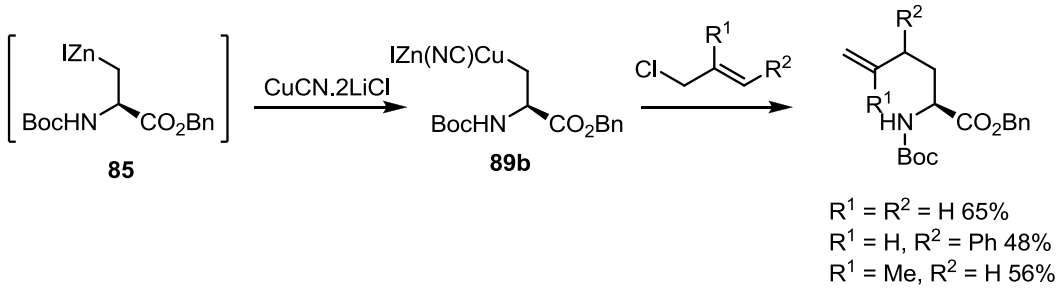
forming an allyl copper complex.The alkyl group could now attack at either the α or γ carbon giving rise to the S_N2 and S_N2' products.[80]



Scheme 25

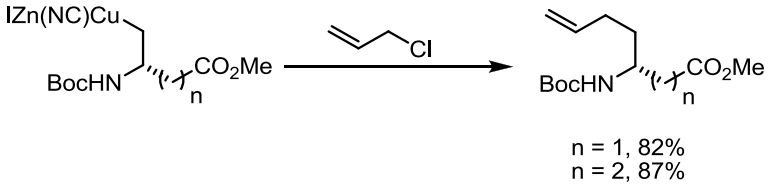
1.5 Jackson group chemistry

The first report of the use of the zinc/copper reagent **89b**, previously discussed on page 17, described its reaction with different allylic halides to give S_N2' products of protected unsaturated α-amino acids (**Scheme 26**).[81,82]



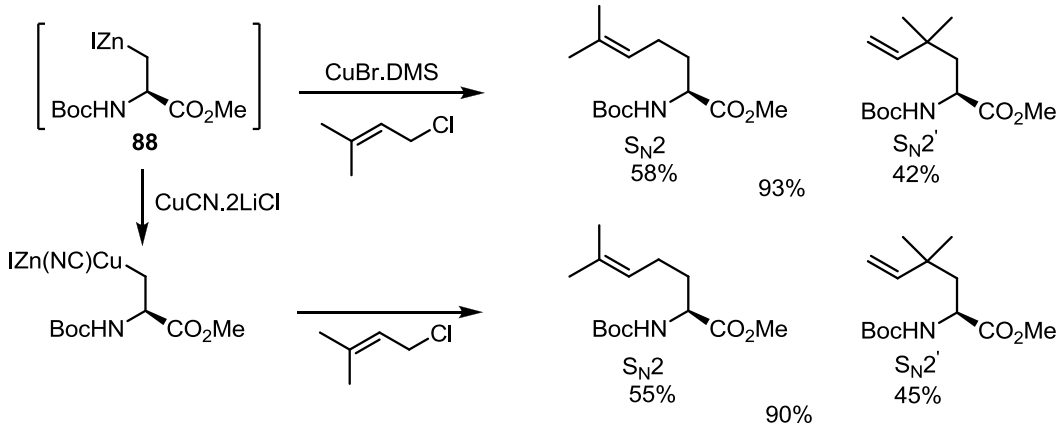
Scheme 26

Related zinc/copper reagents derived from *L*-aspartic and *L*-glutamic acids were reacted with allyl chloride to furnish unsaturated *β*- and *γ*-amino acid derivatives in good yields (**Scheme 27**).[83]



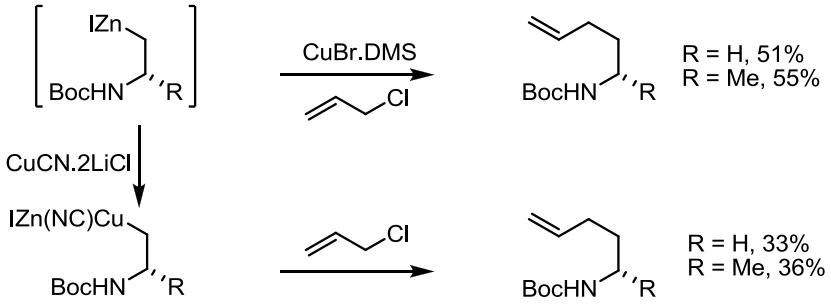
Scheme 27

The use of catalytic CuBr.DMS has been investigated as an alternative to using a stoichiometric amount of CuCN.2LiCl due to the latter's toxicity (**Scheme 28**). Allylation of *L*-serine-derived organozinc reagent with bulky allylic electrophiles in the presence of CuBr.DMS and CuCN.2LiCl provided nearly equal yields of a mixture of S_N2 and S_N2' products.[84]



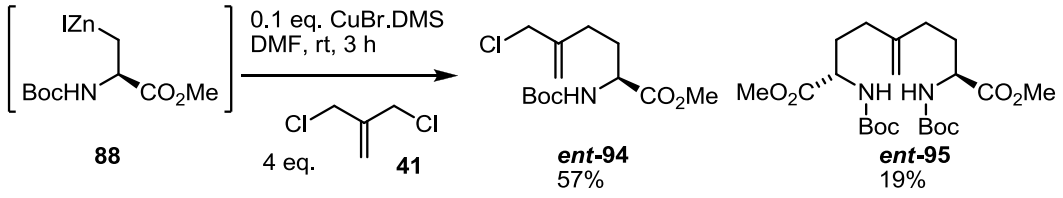
Scheme 28

However the use of catalytic CuBr.DMS generally gave higher yields of substitution products than those obtained with CuCN.2LiCl, especially for less stable β-amino organozinc reagents (**Scheme 29**).[66]



Scheme 29

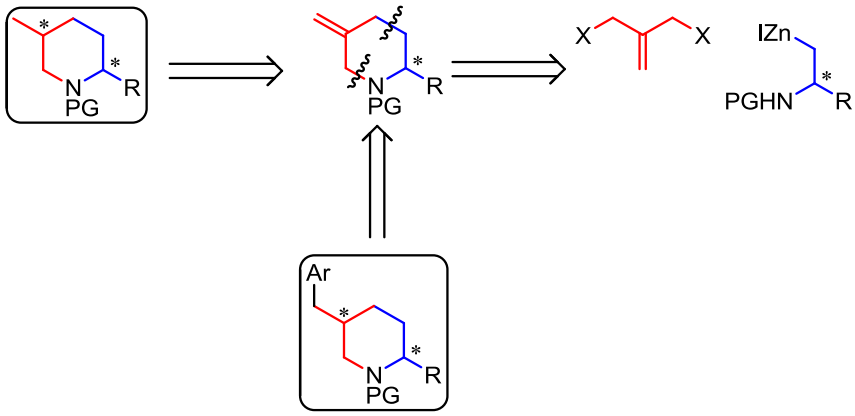
The precursor ***ent*-94** that was used in scheme 16 (page 18) was prepared by the CuBr.DMS catalysed allylation of the zinc reagent **88** using 3-chloro-2-(chloromethyl)prop-1-ene **41** (**Scheme 30**).[48] The product of the *bis*-allylation ***ent*-95** was also isolated.



Scheme 30

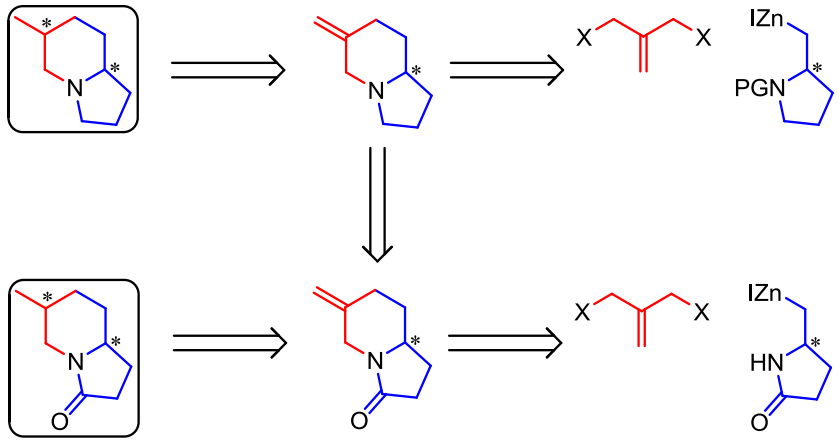
1.6 Aims

The main aim of the project was the extension of the approach to the synthesis of 2,5-disubstituted piperidines already developed within the Jackson group. 2,5-Disubstituted piperidines may be derived by hydrogenation of 5-methylenepiperidine. Alternatively we envisaged that Heck reaction of 5-methylenepiperidine, followed by hydrogenation, would lead to stereoselectively to the 5-benzyl piperidine (**Scheme 31**). The required 5-methylenepiperidine may be obtained from the organozinc reagents and allyl dihalide.



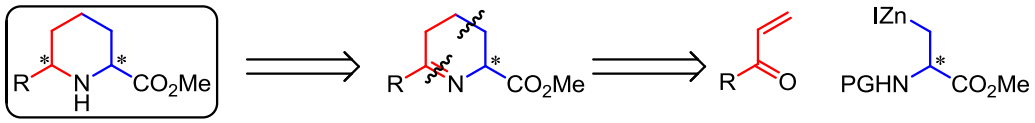
Scheme 31: *Retrosynthetic approach to 2,5-disubstituted piperidines*

The retrosynthetic plan can also be adapted to the synthesis of indolizidines and indolizidinones which may be accessed from hydrogenation of 6-methyleneindolizidine and 6-methyleneindolizidinone respectively (**Scheme 32**).



Scheme 32: *Retrosynthetic approach to indolizidines*

2,6-Disubstituted piperidines especially 6-substituted pipecolates will be targeted using a short retrosynthetic pathway (**Scheme 33**). Diastereoselective reduction of imines should lead to the pipecolate, which is potentially accessible from a range of enones and organozinc reagents.



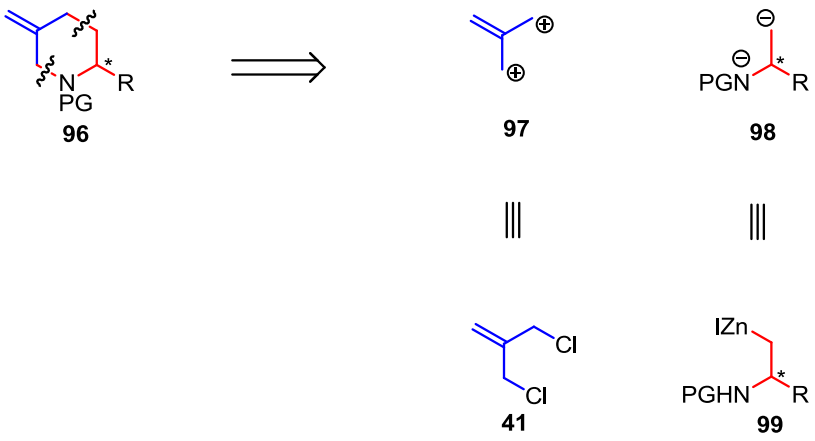
Scheme 33: *Retrosynthetic approach to 6-substituted pipecolates*

Chapter 2: Synthesis of 2,5-disubstituted piperidines

2.1 Introduction

Amino acids are an important chiral source of starting materials for the preparation of optically pure piperidines.[11,33,44] Amino acid derived organozinc iodides have been used to prepare protected 4-oxopipecolic acid,[46] 4-methylpipecolic acid derivatives[47] and 5-methylenepipecolic acid derivatives,[48] as mentioned in section (1.2.4).

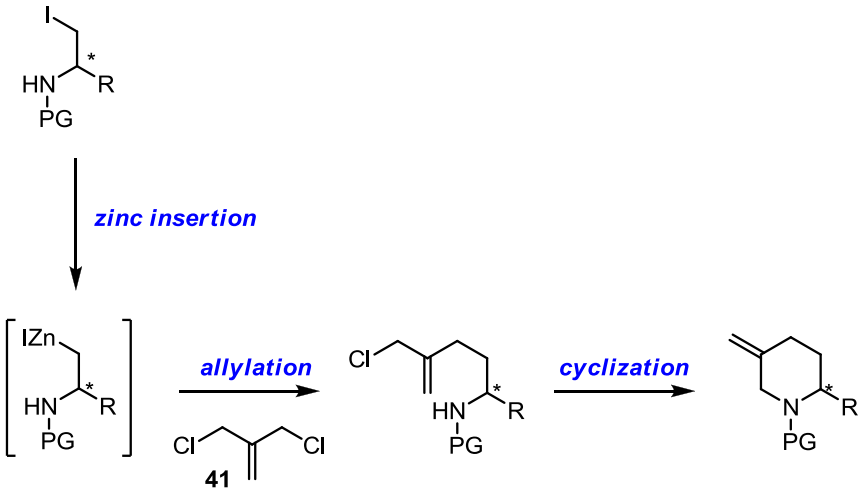
The planned approach to the 5-methylene piperidines **96**, precursors to 2,5-disubstituted piperidine derivatives, involves a [3+3] annulation reaction between 1,3-bifunctional electrophile **97** and 1,3-dianion **98**. Suitable synthetic equivalents were identified as 3-chloro-2-(chloromethyl)prop-1-ene **41** and a range of β-amino organozinc reagents **99** (**Scheme 34**).



Scheme 34: *Retrosynthetic approach to 5-methylene-2-disubstituted piperidines*

2.2 Results and discussion

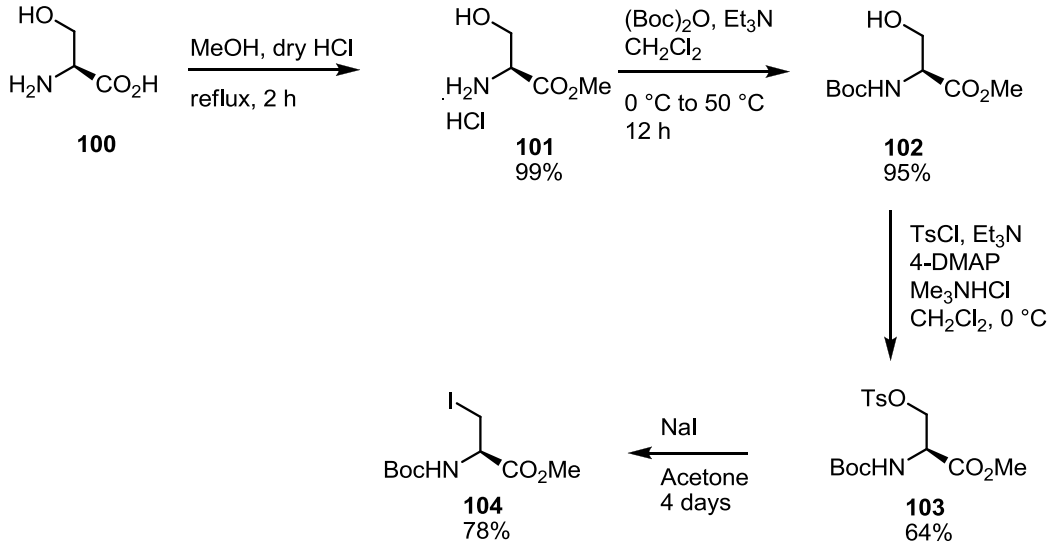
The initial aim was to develop a general synthesis for 5-methylene piperidines. The synthetic approach had been previously established for 5-methylene pipecolic acid derivatives,[48] and involved three steps; i) zinc insertion, ii) copper-catalyzed allylation with dichloride **41**, and finally iii) cyclization (**Scheme 35**).



Scheme 35

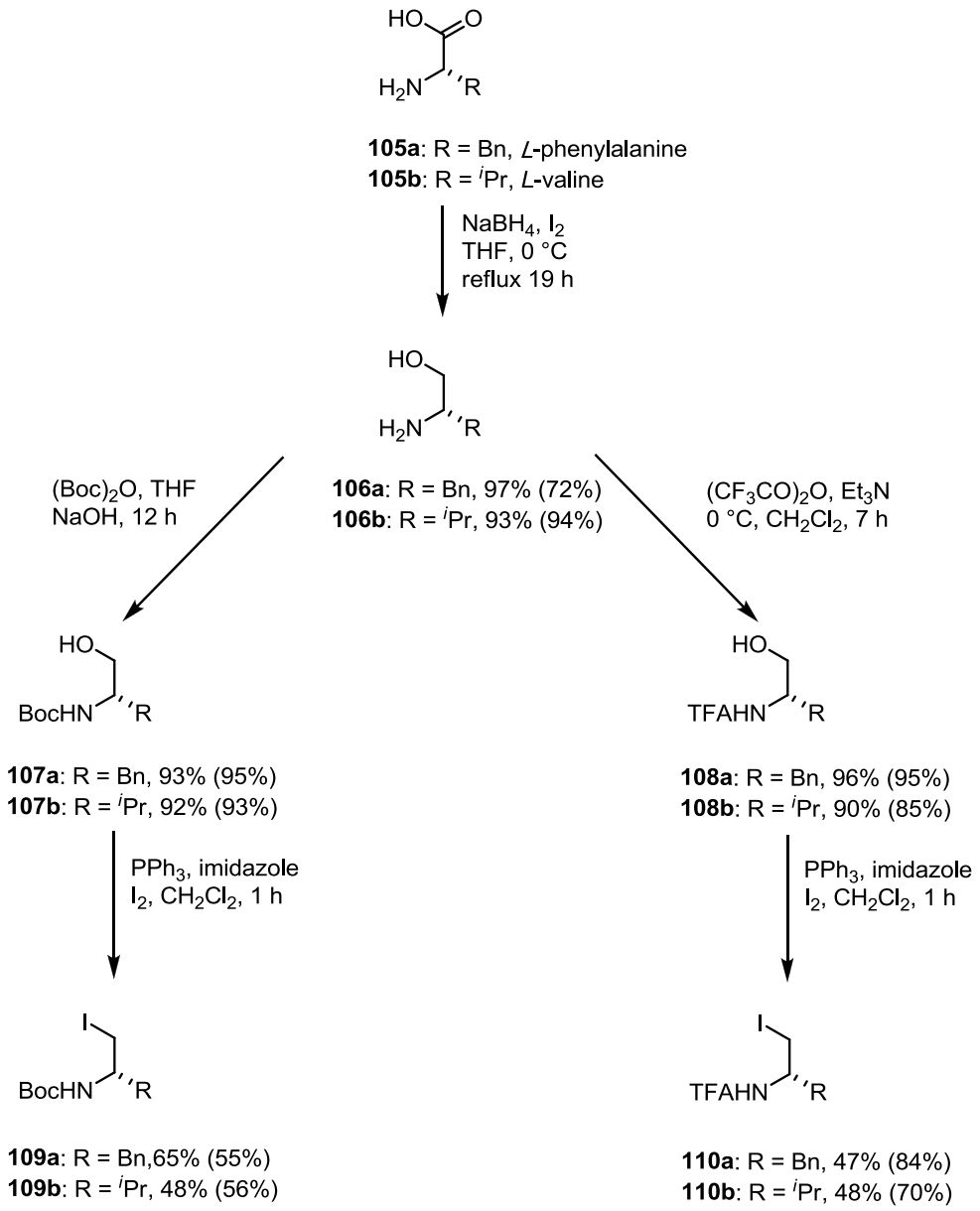
2.2.1 Preparation of organoiodides

The initial goal was the synthesis of a range of protected β-amino iodides. Protected *L*-iodoalanine was prepared from *L*-serine **100** in four steps using a literature procedure. This first involved protection of the carboxylic acid as methyl ester **101** and Boc-protection of the amine group to give **102**.[85] Following this, the alcohol was tosylated to give **103**, which was further reacted with sodium iodide to furnish the iodinated product, protected *L*-iodoalanine **104** (**Scheme 36**).[86] This procedure was also carried out with *D*-serine.



Scheme 36

The synthesis of the iodides **109a**, **109b**, **110a**, **110b** and ***ent*-109a** was carried out using the established procedures in the Jackson group.[87,88] The reduction of the carboxylic acid group of **105** to the alcohol was first carried out according to Meyers' procedure.[89,90] Two protection strategies were then considered. The reduced materials **106a** and **106b** were each Boc[87] and TFA[88,91] protected at the amine group to give compounds **107a**, **107b**, **108a** and **108b**. Iodides were prepared using the triphenylphosphine, iodine and imidazole method.[66,87] The iodide ***ent*-109a** was prepared by the same route (**Scheme 37**).[87,92]

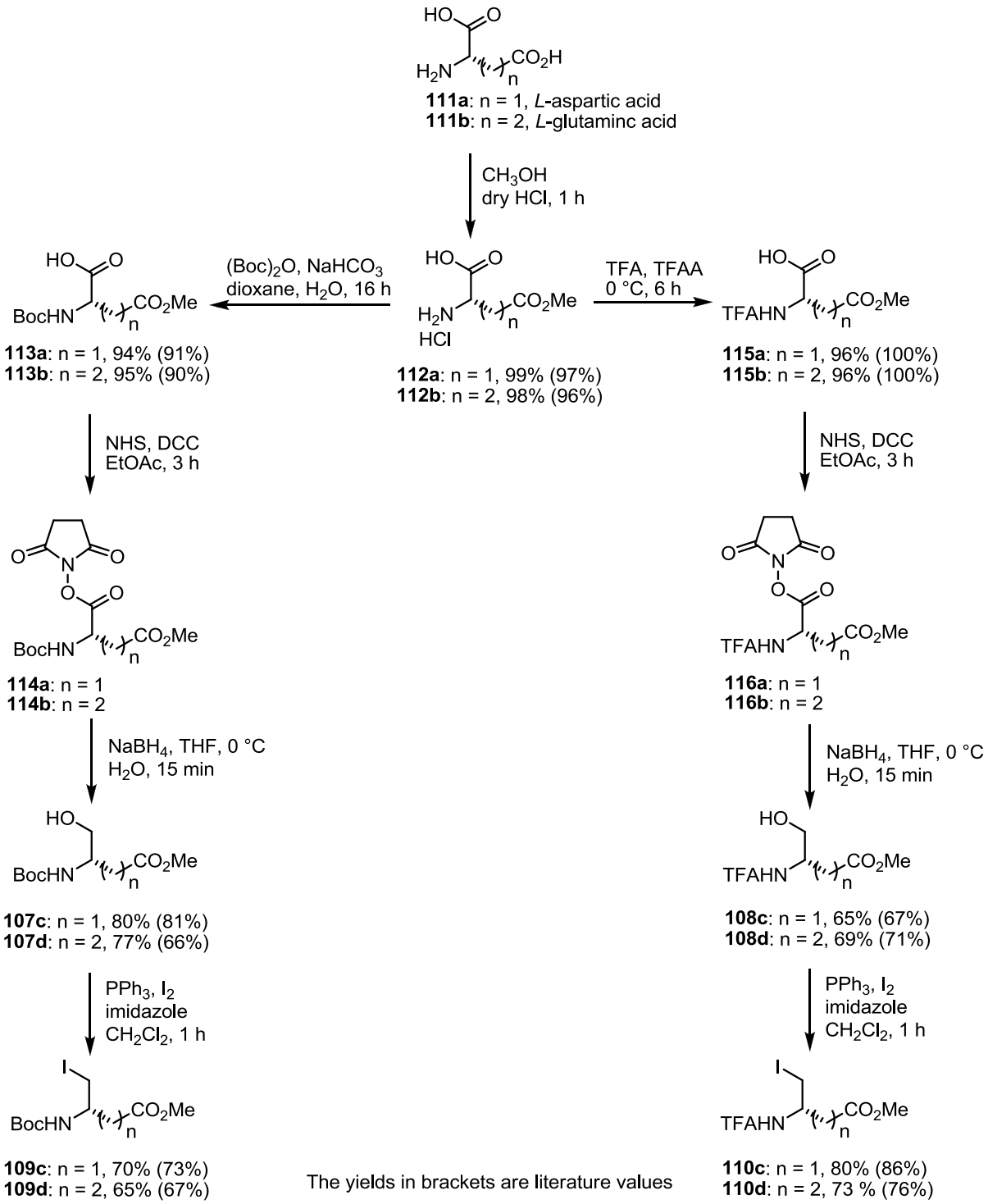


The yields in brackets are literature values

Scheme 37

Five steps were previously employed to synthesize organoiodides **109c** and **109d** by Dexter and co-workers[62,83] and organoiodides **110c** and **110d** have also been synthesised by Rilatt and co-workers[67] starting from *L*-aspartic **111a** and *L*-glutamic **111b** acid. After esterification of the carboxylic acids at the β and γ-position,[93,94] the amino groups were protected with Boc or TFA groups.[67,94,95] Reduction of the α-carboxylic

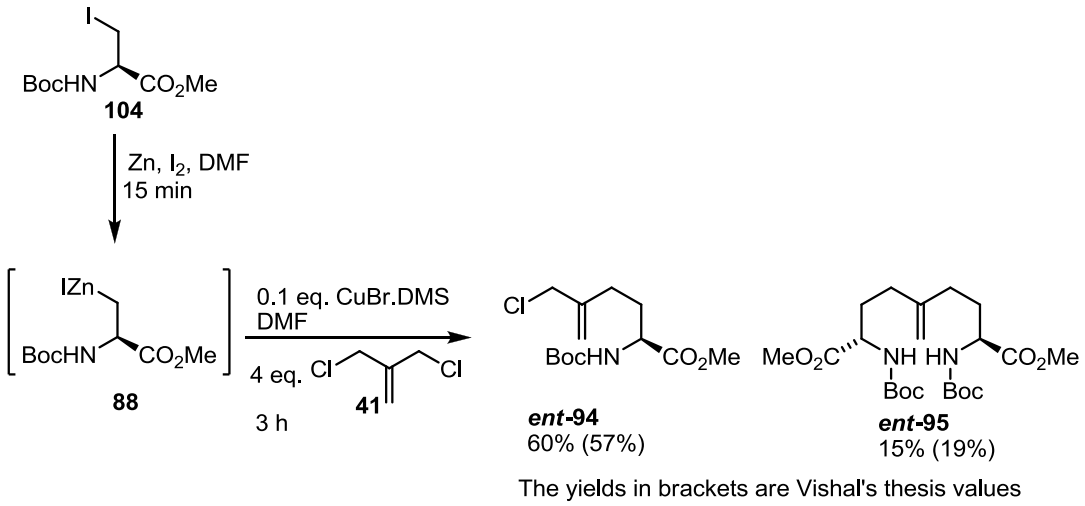
acid groups *via* the succinimide esters formed the corresponding alcohols,[96] which were iodinated using standard conditions to furnish the required iodides in good yields (**Scheme 38**).[97,98]



Scheme 38

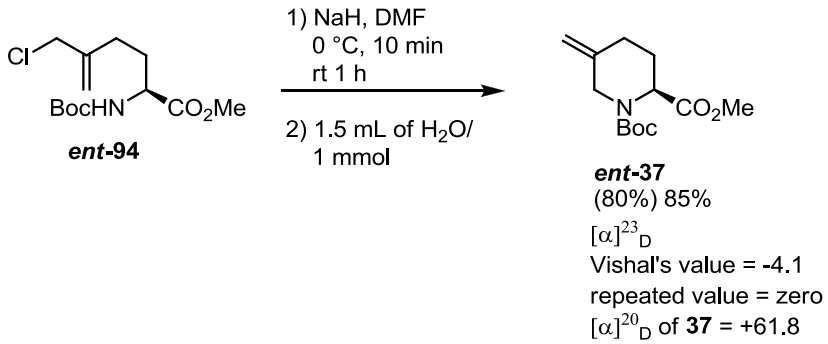
2.2.2 Investigation of pipecolate synthesis

The organozinc reagent derived from protected *L*-iodoalanine **104** was used in the copper-catalyzed allylation reaction with 1,3-dielectrophile **41** and gave unsaturated amino acid ***ent*-94** and *bis*-allylation product ***ent*-95** (**Scheme 39**).



Scheme 39

As already discussed, addition of NaH to a solution of unsaturated amino acid ***ent*-94** in dry DMF gave direct access to the protected pipecolate ***ent*-37** in a straightforward and efficient manner (**Scheme 40**). The specific rotation of the sample of ***ent*-37** was zero (*c* 2.5, $CHCl_3$) and -4.1 of the previous work within the Jackson group. The reported specific rotation of its enantiomer **37**, prepared by Sun and co-workers (section 1.2.1), was + 61.8 (*c* 1, $CHCl_3$).[28]



Scheme 40

Therefore, the pipecolate ***ent*-37** gave two signals by HPLC (Column: Chiralpak AD, mobile phase: 5% IPA in hexane, flow rate: 1 mL/min, retention time: 4.6 min one enantiomer, 5.6 min other enantiomer) (**Figure 4**). These signals indicate the presence of both enantiomers.

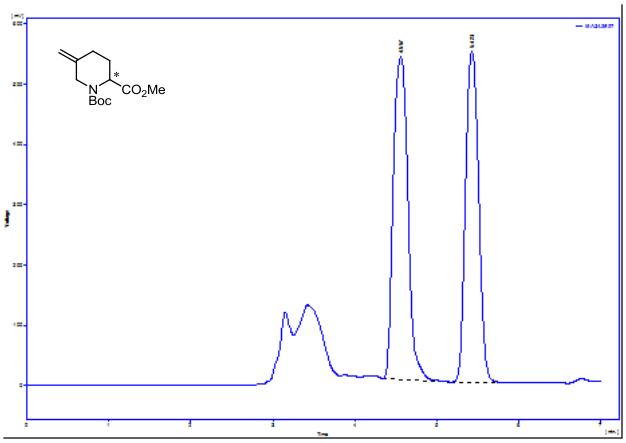
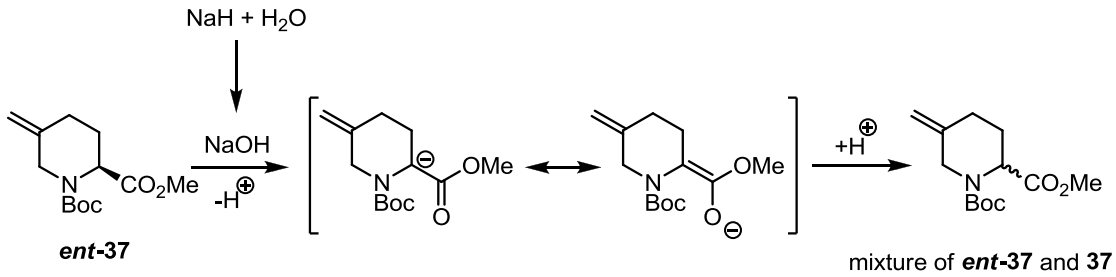


Figure 4: *HPLC of the pipecolate **ent-37** quenched by 1.5 mL of water*

It is possible that this is due to rapid racemisation during the workup caused by the formation of sodium hydroxide from the reaction of the sodium hydride with the water used to quench the reaction, which then has the ability to deprotonate the acidic α-proton (**Scheme 41**).



Scheme 41

Attempts to avoid the epimerization were made by modifying the work-up of the cyclization reaction. Different aqueous work-ups were investigated (**Table 1**). Increasing the quantity of water from 1.5 mL/ 1 mmol to 10 mL/ 1 mmol gave enantiomerically enriched pipecolate product ***ent*-37** (ee 94%), which was established using chiral HPLC techniques. Saturated ammonium chloride solution gave similar results. However, phosphate buffer solution (pH=7) can be used to improve the enantiomeric purity (ee 97%) (**Figures 5**, **6** and **7**).

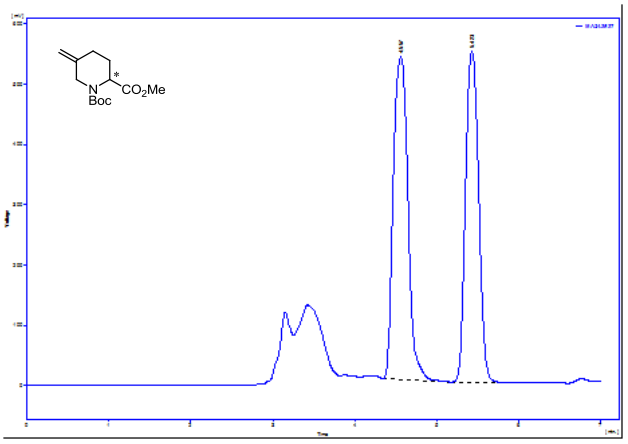


Figure 5: *HPLC of the pipecolate **ent-37** quenched by 1.5 mL of water*

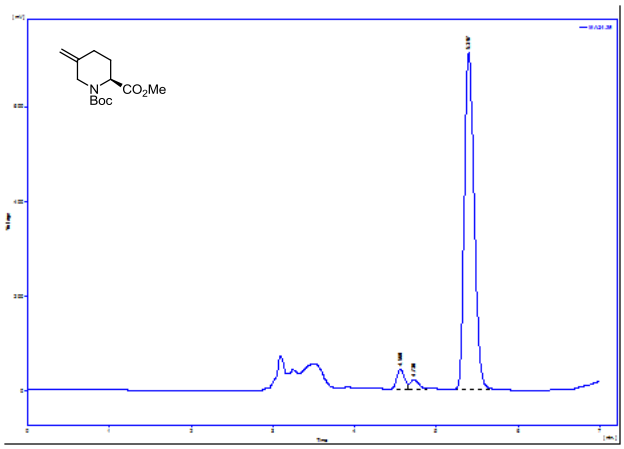


Figure 6: *HPLC of the pipecolate **ent-37** quenched by 10 mL of buffer phosphate*

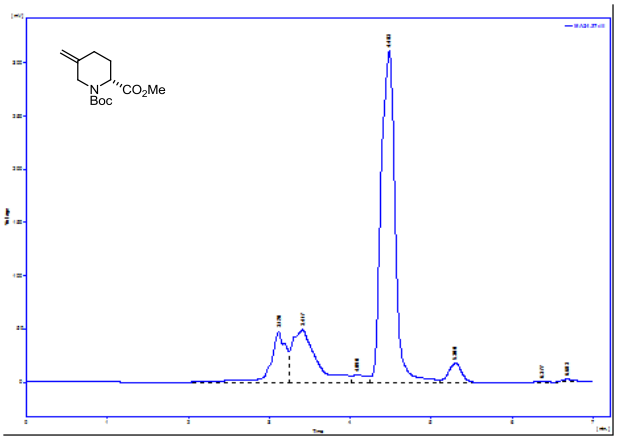


Figure 7: *HPLC of the pipecolate **37** quenched by 10 mL of buffer phosphate*

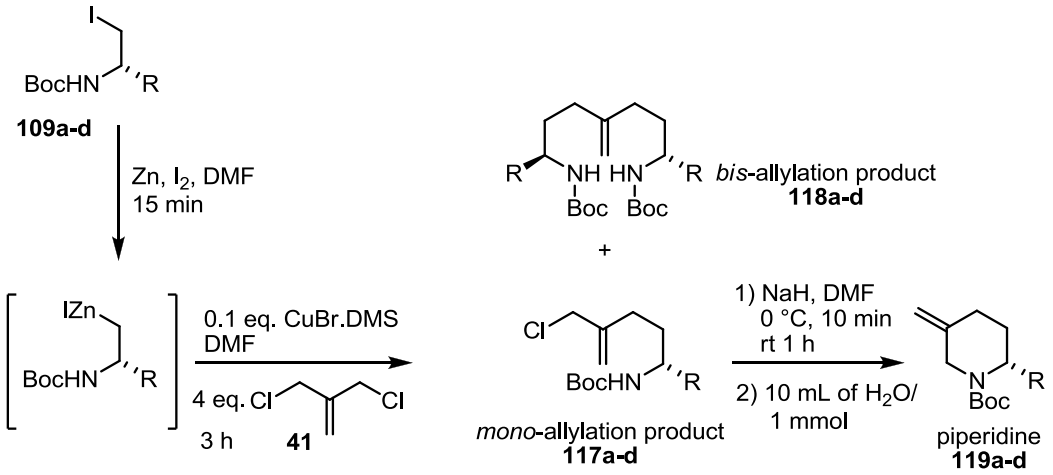
Table 1:

Different work-up	ee%	$[\alpha]^{17}_{D}$ *c* 1, $CHCl_3$
1 mL of water	0	0
10 mL of water	94	-57
10 mL of sat. Ammonium chloride	94	-57
10 mL of pH 7 phosphate buffer	97	-59

2.2.3 Boc-protected piperidines

Since the previous approach gave satisfactory results in the preparation of 5-methylene pipecolate from protected *L*-iodoalanine, attention turned to the use of other amino acids specifically *L*-phenylalanine, *L*-valine, *L*-aspartic acid and *L*-glutamic acid (**Schemes 37** and **38**)

The Boc-protected β-amino iodides (**109a**, **109b**, **109c** and **109d**) were each converted into the corresponding organozinc reagent which then underwent copper-catalyzed allylation reactions to give the corresponding *mono*-allylation products **117a**, **117b**, **117c** and **117d** in reasonable yields, with small amounts of the unwanted *bis*-allylation side products **118a**, **118b**, **118c** and **118d**. Addition of NaH to a solution of the allyl chlorides in dry DMF gave the piperidines **119a**, **119b**, **119c** and **119d** in good yields (**Scheme 42** and **table 2**).

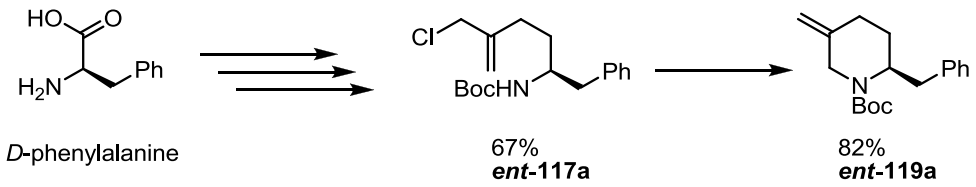


Scheme 42

Table 2:

RI	R	*mono*-allylation	%	*bis*-allylation	%	piperidine	%
109a	Bn	**117a**	69	**118a**	10	**119a**	85
109b	^{i}Pr	**117b**	59	**118b**	13	**119b**	72
109c	CH_2CO_2Me	**117c**	65	**118c**	10	**119c**	80
109d	$CH_2CH_2CO_2Me$	**117d**	60	**118d**	13	**119d**	80

Although there was no obvious mechanism for racemisation of these piperidines, it was decided to directly determine the ee for one example. So, ***ent*-119a** was therefore prepared starting from *D*-phenylalanine using the same approach (**Scheme 43**).



Scheme 43

The piperidines **119a** and ***ent*-119a** have equal and opposite specific rotations: -33.0 (*c* 1 in $CHCl_3$) for **119a** and +33.0 (*c* 1 in $CHCl_3$) for ***ent*-119a**. However, this was not enough evidence to prove that the two compounds **119a** and ***ent*-119a** were enantiomerically pure. Chiral gas chromatography was employed, which enabled separation of the enantiomers due to the difference in their retention times. A deliberately prepared mixture of compounds **119a** and ***ent*-119a** with a 2:1 ratio gave different retention times, 37.4 min for the **119a** and 39.2 min for ***ent*-119a** (**Figure 8**).

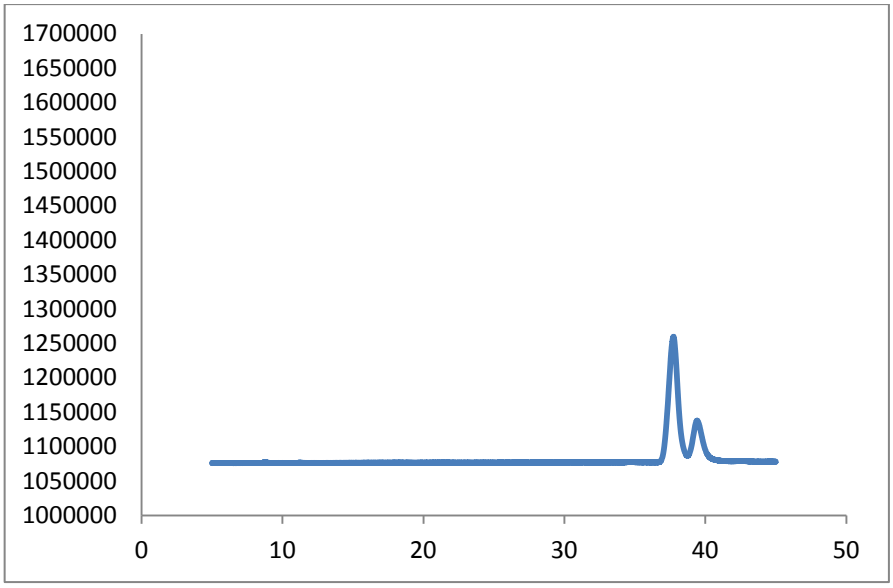


Figure 8: *GC of the mixture of the piperidines **119a** and **ent-119a** 2 : 1 ratio*

Injection of compound **119a** and ***ent*-119a** separately gave the enantiomeric purity of **119a** as 98% and ***ent*-119a** 99% (**Figures 9** and **10**).

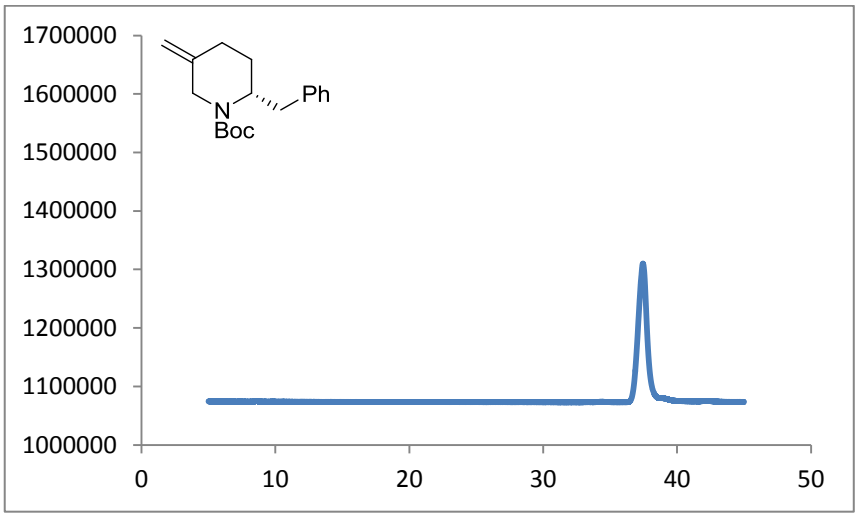


Figure 9: *GC of the piperidine **119a** quenched by 10 mL of water*

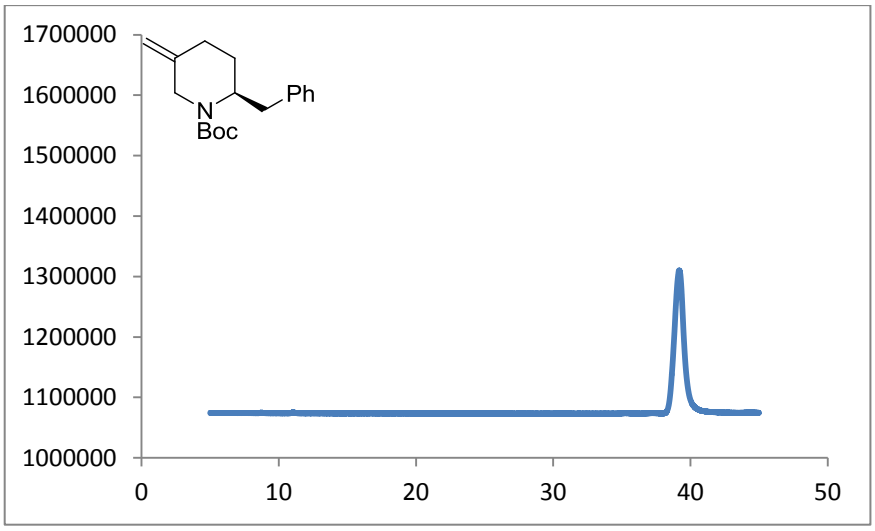


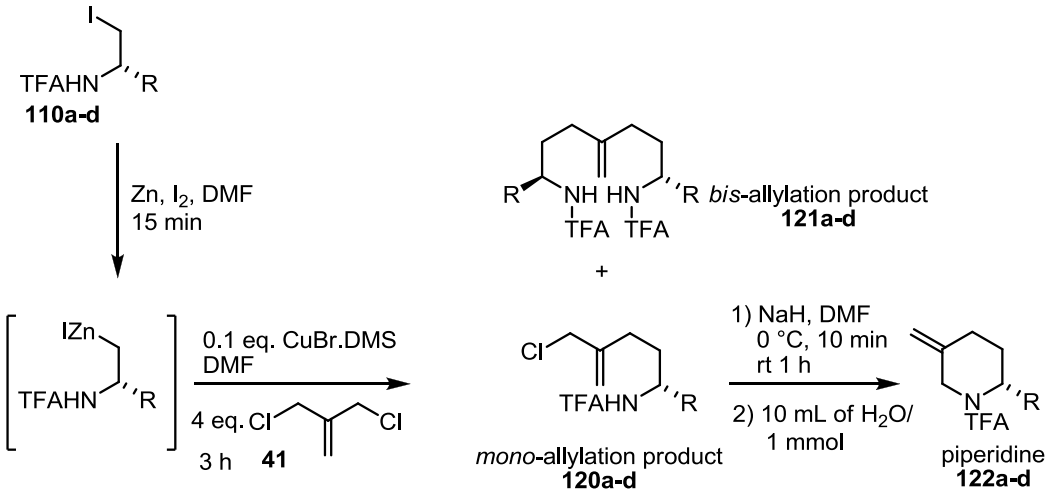
Figure 10: *GC of the piperidine **ent-119a** quenched by 10 mL of water*

We are therefore confident that the remaining 5-methylenepiperidines **119b-d** are also enantiomerically pure.

2.2.4 TFA-protected piperidines

Amino acid protecting groups have been generally categorized into two main classes: acid sensitive, for example, the Boc-protecting group and base sensitive, for instance, the TFA-protecting group, which can be introduced and removed easily. It was decided, following the success synthesising the Boc-protected piperidines, that the TFA analogues would also be investigated (**Schemes 37** and **38**).

The same approach used with the Boc-protected organoiodides was successfully followed with the TFA-protected organoiodides **110a**, **110b**, **110c** and **110d** giving the allylic chlorides **120a**, **120b**, **120c** and **120d** in reasonable yields. Cyclization using NaH/DMF provided the TFA-protected piperidines **122a**, **122b**, **122c** and **122d** (**Scheme 44** and **table 3**).



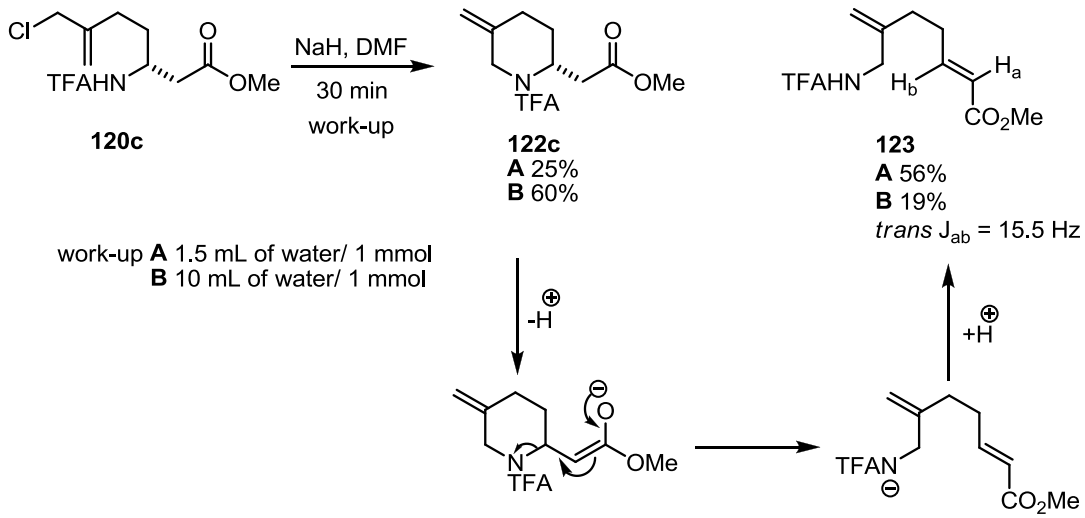
Scheme 44

Table 3:

RI	R	*mono*-allylation %		*bis*-allylation %		piperidine %	
110a	Bn	**120a**	60	**121a**	12	**122a**	58
110b	^{i}Pr	**120b**	60	**121b**	12	**122b**	55
110c	CH_2CO_2Me	**120c**	57	**121c**	12	**122c**	60 (25)[a]
110d	$CH_2CH_2CO_2Me$	**120d**	55	**121d**	21	**122d**	79

a 1.5 mL of water/ 1 mmol was used in the work-up

When the cyclization reaction using the TFA-protected derivative **120c**, derived from *L*-aspartic acid, was worked-up using less water (1.5 mL/ 1 mmol) the yield of the piperidine **122c** was much reduced (25%) and the major product was the diene **123** (56%). It is possible that the piperidine **122c** undergoes an E1cB reaction during the work-up. Increasing the amount of water to 10 mL/1 mmol improved the yield of the desired product **122c** to 60% and the yield of the diene **123** was reduced to 19% (**Scheme 45**).



Scheme 45

We had now successfully prepared a range of 5-methylene piperidines, and the final goal was the preparation of the TFA-protected piperidine **127** (**Figure 11**).

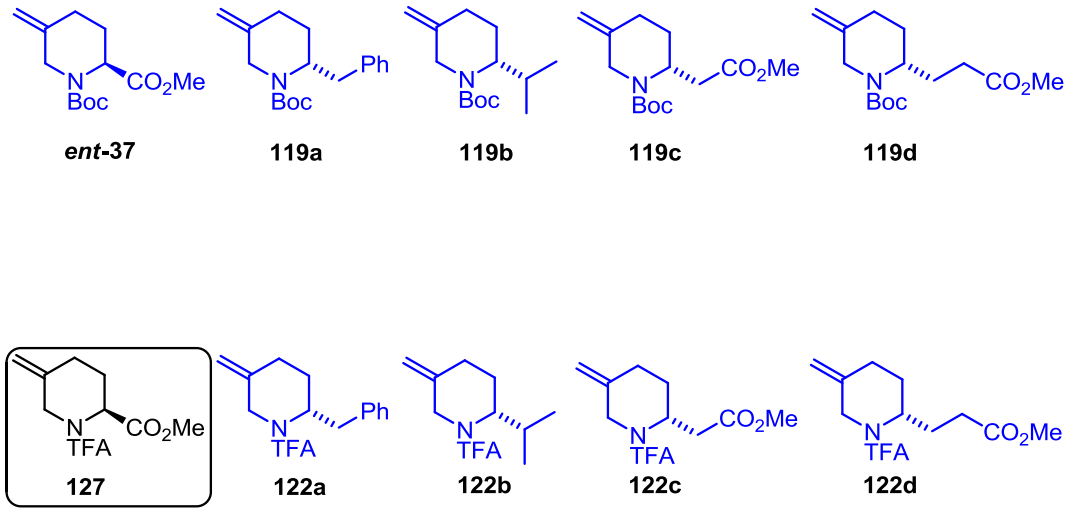
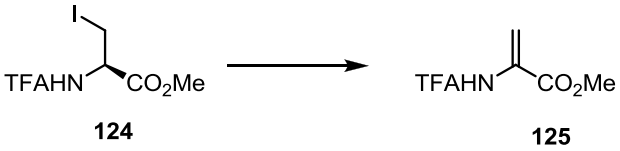


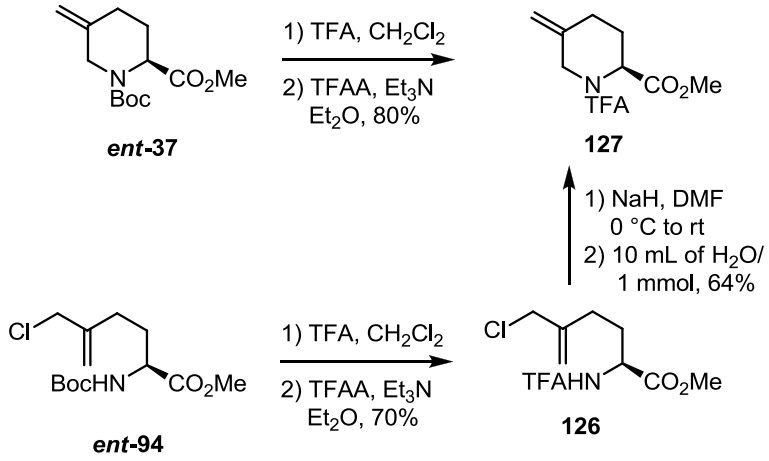
Figure 11

We did not explore the use of the TFA protected L-iodoalanine **124**, since previous work had shown that it was not especially stable, decomposing to give **125** (**Scheme 46**).



Scheme 46

Therefore, Boc-deprotection and TFA-protection of Boc-protected pipecolate ***ent*-37** were carried out in good yield (80%).[99] Alternatively Boc deprotection of the unsaturated amino acid ***ent*-94** and TFA protection to **126** followed by cyclization also gave the desired product **127** (**Scheme 47**)



Scheme 47

All the protected piperidines showed rotamers in the NMR spectra, arising from restricted rotation of the N-C bond of the carbamate. At 25 °C, the TFA-protecting group has distinguishable separable peaks for each rotamer, but in the case of the Boc-protecting group, the peaks overlapped and were broad. In order to coalesce them into one signal, energy must be introduced using elevated temperatures to overcome the barrier to rotation (**Figure 12**).

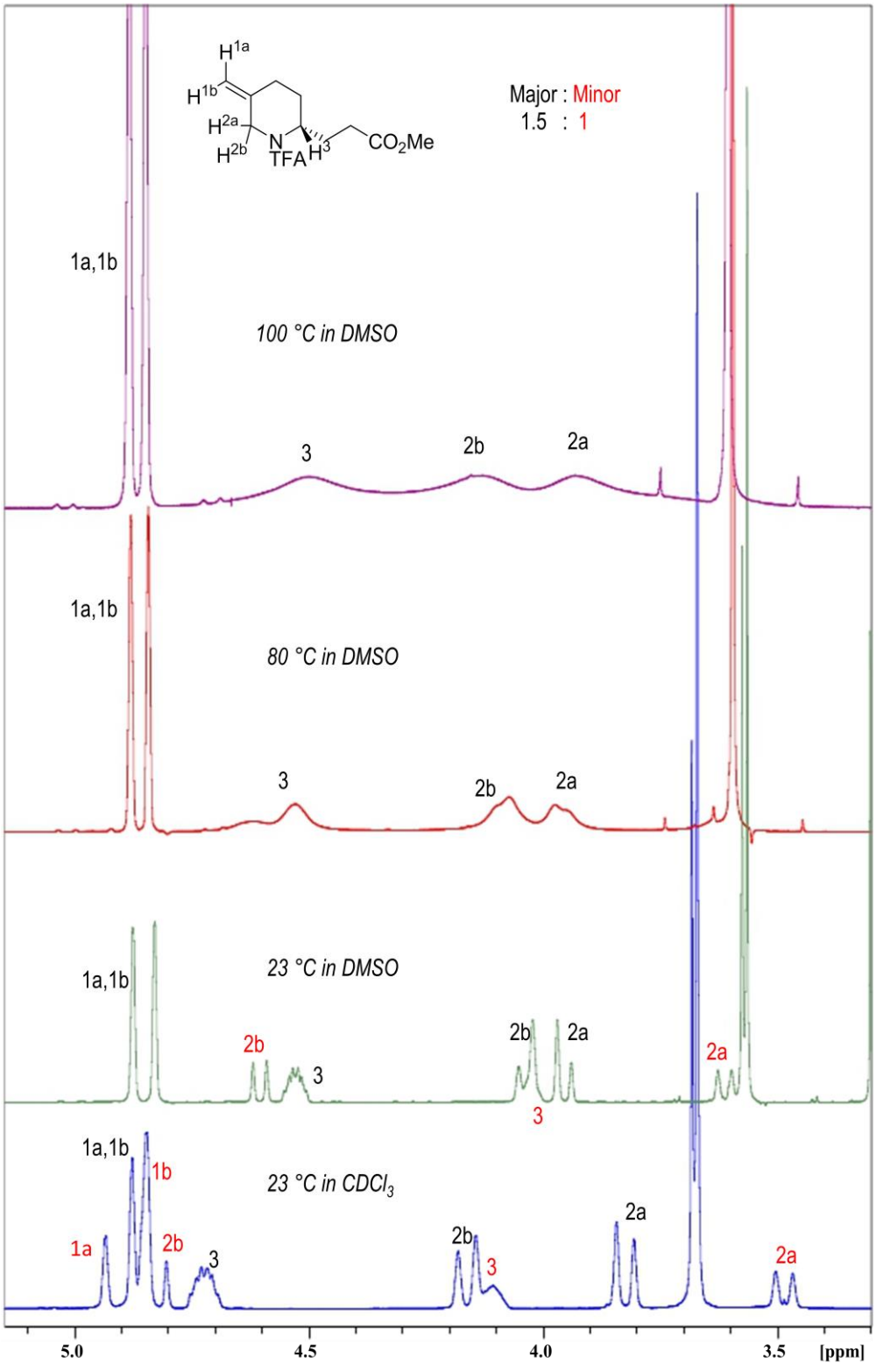
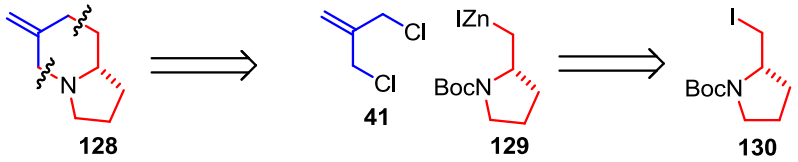


Figure 12: *H-NMR spectra of piperidine **122d** at different temperature*

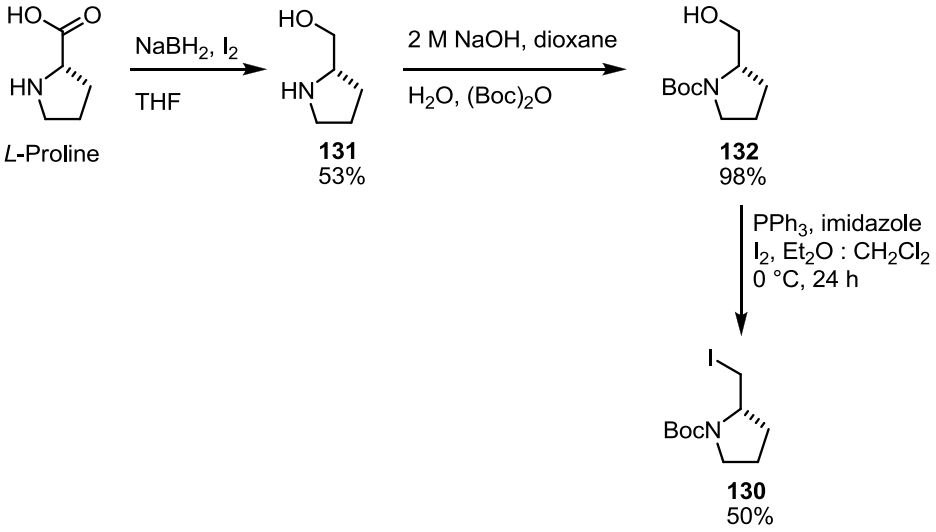
2.2.5 Indolizidine synthesis

The next target was the preparation of indolizidines, using the protected organozinc iodide **129** derived from *L*-proline (**Scheme 48**).



Scheme 48: *Retrosynthetic approach to 6-methylene indolizidine*

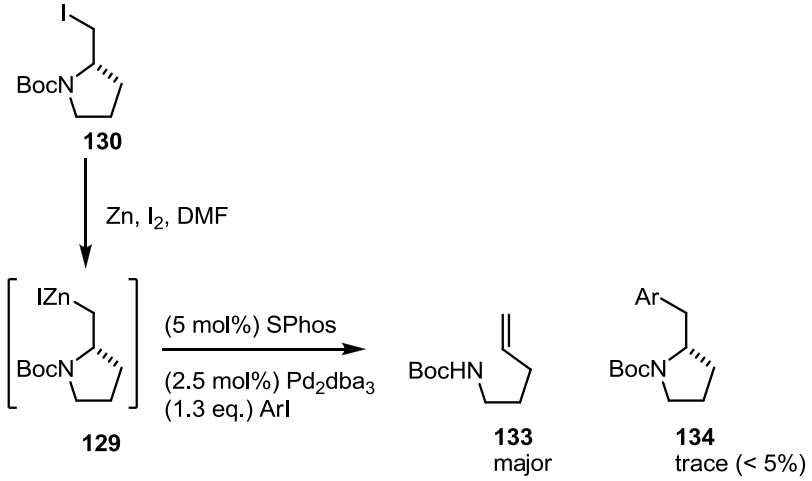
Reduction[89] of *L*-proline and subsequent Boc-protection[100] provided *N*-Boc *L*-prolinol **132** in an overall yield of 51%. Iodination[101] of the hydroxyl group of **132** to give iodide **130** was achieved in 50% yield using imidazole, I_2, and PPh_3 in ether (**Scheme 49**).



Scheme 49

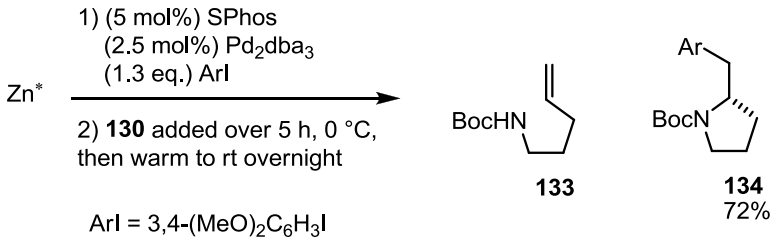
Conventional Negishi cross-coupling of the Boc-protected organozinc iodide derived from *L*-proline **130** with aryl halides to give protected 2-arylpyrrolidine **134** has been reported to be unsuccessful (**Scheme 50**).[68]

There are two reports of the rapid decomposition of organozinc reagent **129**, producing alkene **133**.[68,102]



Scheme 50

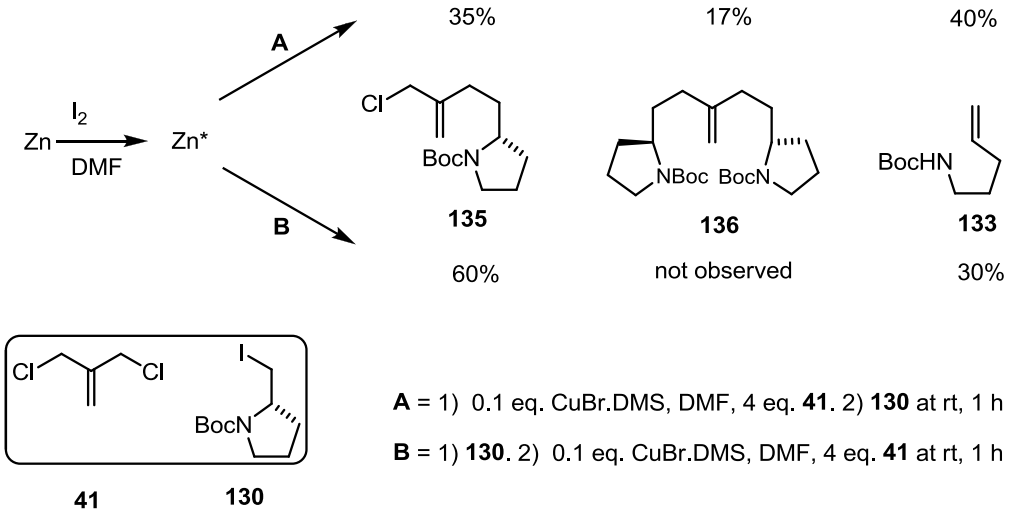
Therefore, the Jackson group explored the generation of the organozinc reagent **129** in the same pot as the catalyst and aryl iodide.[68] The organoiodide **130** was therefore added slowly to a mixture of activated zinc and aryl iodide in DMF at 0 °C with catalytic (2.5% mol) $Pd_2(dba)_3$ and (5% mol) SPhos (**Scheme 51**).



Scheme 51

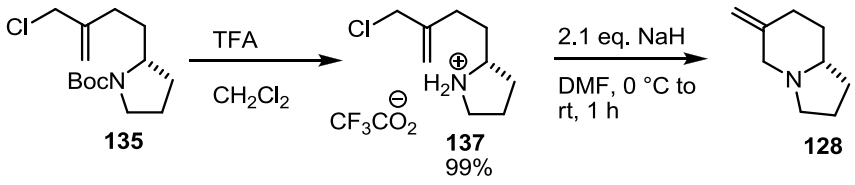
This *in situ* method was applied to the allylation reaction of the organoiodide **130**, giving the desired product **135** (35%), the double allylation product **136** (17%) and the elimination product **133** (40%) (Scheme **52**). However, reverting to the original procedure in which the

zinc reagent **129** was prepared first gave a much better outcome: the allylic chloride **135** was isolated in good yield (60%) and no *bis*-allylation product **136** was observed, although alkene **133** was isolated (30%). So the copper-catalysed allylation reaction is clearly faster than palladium cross-coupling.



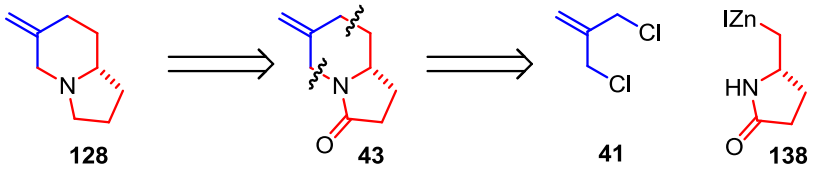
Scheme 52

The Boc-deprotection of **135** using TFA/CH_2Cl_2 gave **137**, which was cyclised by addition of NaH in DMF producing the indolizidine **128** which was difficult to purify. (**Scheme 53**).



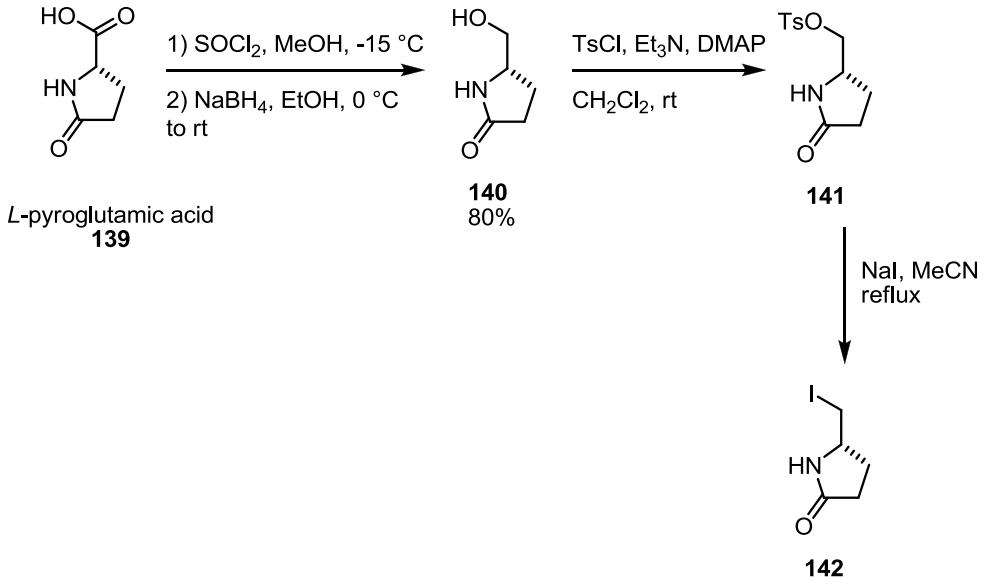
Scheme 53

The copper allylation reaction and cyclization approach can be applied to the organozinc reagent **138** to give the indolizidine **128**. This can be achieved by reduction of an indolizidinone **43** (**Scheme 54**).



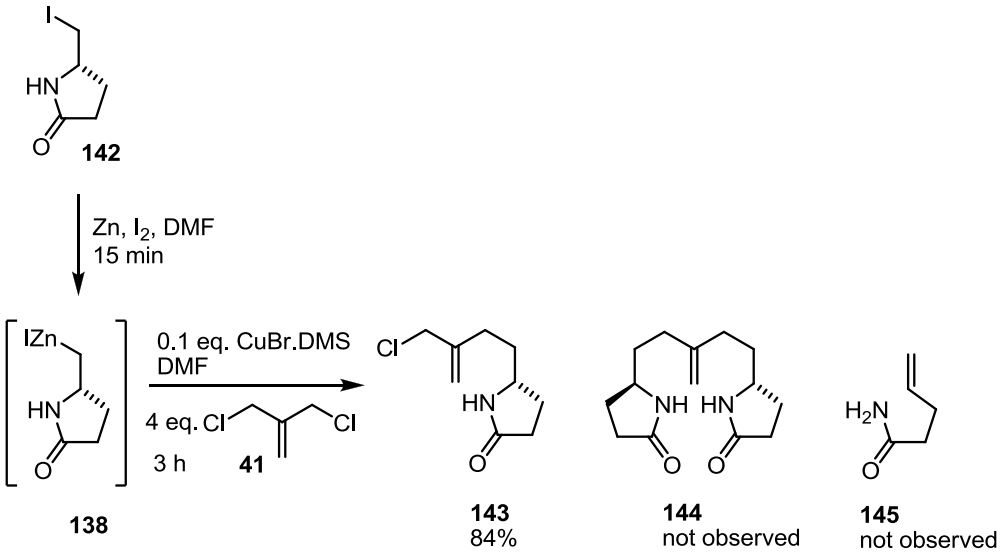
Scheme 54: *Alternative etrosynthetic approach to 6-methylene indolizidine*

The organoiodide **142** was formed over four steps starting from commercially available *L*-pyroglutamic acid **139**, which was converted into alcohol **140** by formation of methyl ester followed by reduction.[102,103] The alcohol **140** was converted into iodide[104] **142**, *via* the tosylate **141** (**Scheme 55**).[105,106]



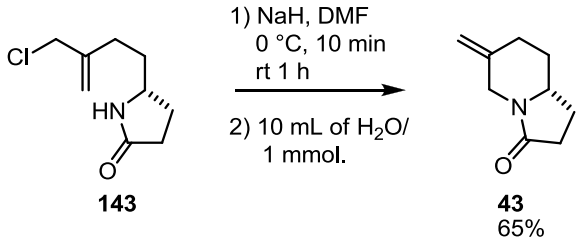
Scheme 55

Copper-catalysed allylation of the organozinc reagent **139** with **41** gave the allylic chloride **143** in excellent yield (84%). Interestingly, the *bis*-allylation product **144** and the eliminated product **145** were not observed, although the organozinc reagent **138** was prepared then transferred to the allyldichloride **41** (**Scheme 56**).



Scheme 56

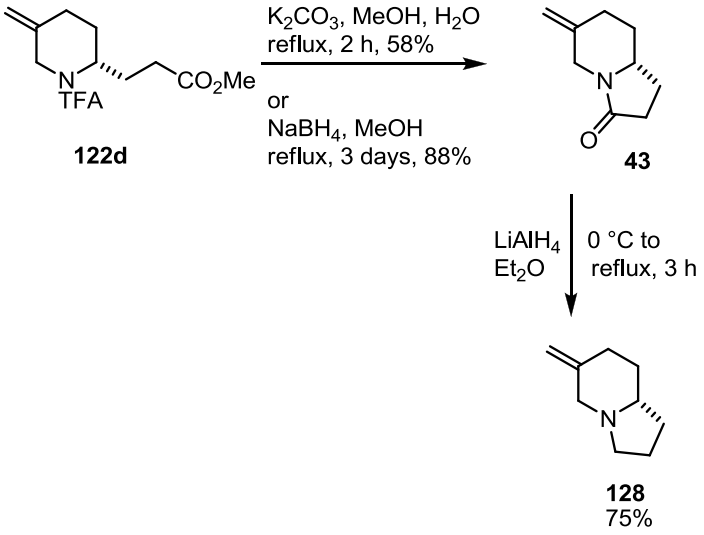
Cyclization of allylic chloride **143** gave the indolizidinone **43** in good yield (65%) (**Scheme 57**).



Scheme 57

We considered that the indolizidinone **43** (and the indolizidine **128**) could be simply accessed from the piperidine **122d** (**Scheme 58**), by TFA-deprotection followed by cyclization under basic conditions. Refluxing a mixture of the piperidine **122d** in methanol and water with potassium carbonate for 2 h gave the indolizidinone **43** (58%) while using sodium borohydride in methanol and refluxing for 3 days gave a higher yield (88%). Reduction of the lactam was accomplished smoothly using lithium

aluminium hydride in diethyl ether to the indolizidine **128** in good yield (75%).[107]



Scheme 58

Our next goal was to investigate the hydrogenation of the 5-methylene piperidines. The successful preparation of both monocyclic structures **119d** and **122d** and the bicyclic derivative **43**, would allows us to compare related structures. We considered that the oxazolidinone **147** would be an interesting bicyclic analogu of the pipecolates ***ent*-37** and **127** (**Figure 13**).

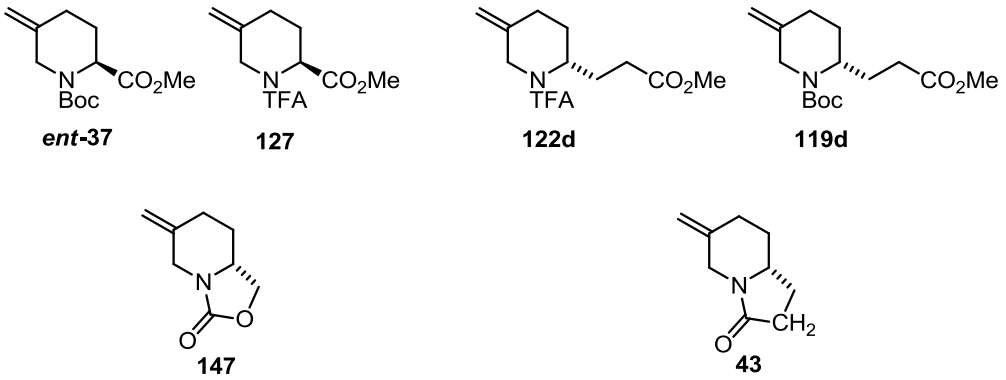
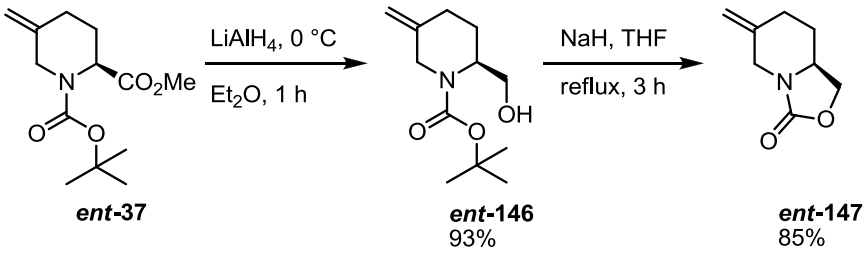


Figure 13

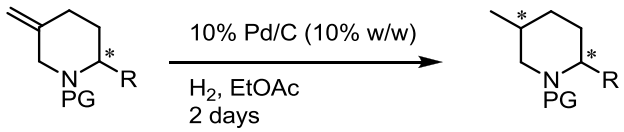
The oxazolidinone **147** and ***ent*-147** were prepared directly from the pipecolates **37** and ***ent*-37** (**Scheme 59**). The pipecolate ***ent*-37** was reduced using lithium aluminium hydride in diethyl ether to give an excellent yield 93% of ***ent*-146** without further purification, after the aqueous workup.[108] Cyclization using NaH gave the oxazolidinone ***ent*-147**. This procedure was also carried out with the pipecolate **37** to produce the oxazolidinone **147**.



Scheme 59

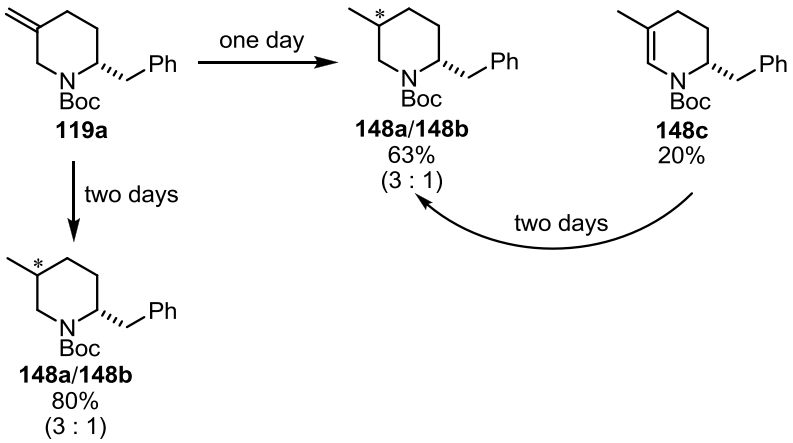
2.2.6 Hydrogenation of 5-methylenepiperidines

The method chosen for hydrogenation of the 5-methylenepiperidines used Pd/C as the catalyst, based on previous result in the group (**Scheme 60**).[48]



Scheme 60: *Hydrogenation of 5-methylenepiperidines*

Initial attempted hydrogenation of 5-methylenepiperidine **119a** using 10% Pd/C at 1 atm of hydrogen at room temperature gave a mixture of the hydrogenated piperidines **148a**/**148b** (3 : 1, according to the ^{1}H-NMR spectrum) and the *endo*-methylpiperidine **148c** (**Scheme 61**). The exocyclic double bond in **119a** was isomerised to the relatively stable cyclic enamine **148c**.[109] This suggests that the reaction time was not enough for achieving hydrogenation. When the reaction time was extended (from one day to two days) only the mixture of piperidines **148a**/**148b** (3 : 1) was isolated. Hydrogenation of **148c** under the latter conditions (two days) provided the same ratio (3 : 1). It is clear that the catalyst causes isomerisation of the alkene, and the similarity in the diastereoselectivity suggests that **148c** was an intermediate in the hydrogenation of **119a** to **148a**/**148b**.

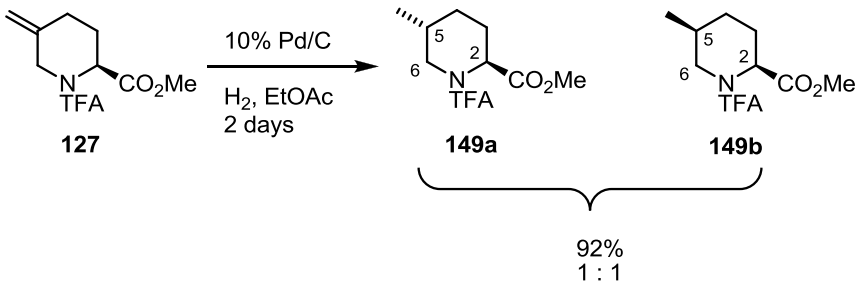


Scheme 61

2.2.6.1 Hydrogenation of TFA-protected piperidines

The TFA-protected piperidines **122a**, **122b**, **122c**, **122d** and **127** were each subjected to hydrogenation to furnish two separable diastereoisomers (except **122b**) in good yields. The cyclic enamines could be isolated in some cases when the hydrogenation reaction was stopped after one day.

The piperidine **127** was hydrogenated to give a 1:1 ratio of *trans* and *cis* isomers; the assignment will be considered in more detail below (**Scheme 62**).



Scheme 62

The hydrogenation produces two diastereoisomers **149a** and **149b**; one of them is *anti* across the ring, and another is *syn*. If we assume that the structure of the saturated ring can be considered as similar to a cyclohexane 'chair' conformation, this gives us two possible conformers for each of the products. **A**, **B** and **C**, **D** (**Figure 14**).

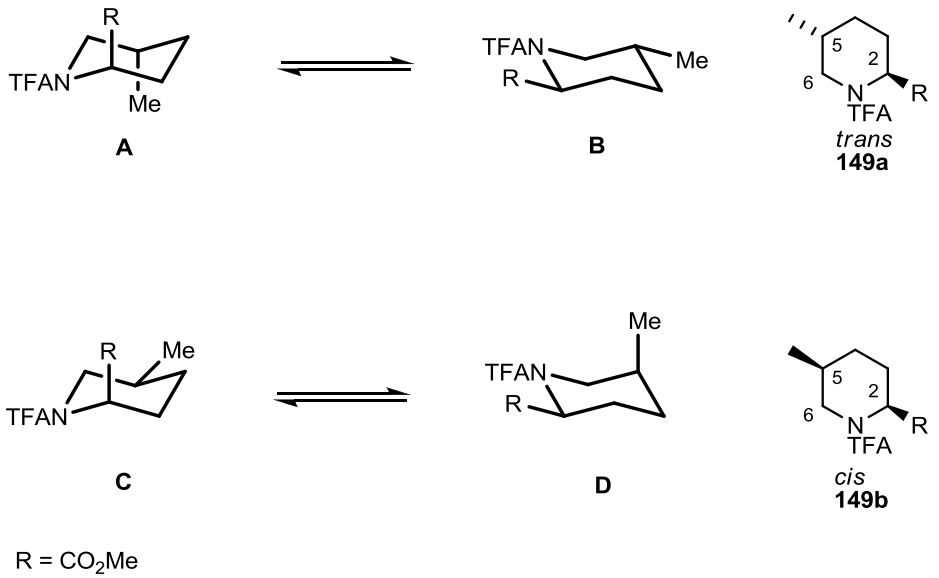


Figure 14: *Potential structural outcomes of hydrogenation of piperidine **127***

Looking at these possibilities, we can see that the C-2 and C-5 substituents may be in either an axial or equatorial position. With both substituents on the oppsite face of the ring, they can be arranged *either* **C-2_{ax}/C-5_{ax}** (**A**) *or* **C-2_{eq}/C-5_{eq}** (**B**). With the *syn* isomer, they can be arranged **C-2_{ax}/C-5_{eq}** (**C**) *or* **C-2_{eq}/C-5_{ax}** (**D**).

The Karplus equation tells us that the ^{3}J-coupling constants of aliphatic C-H signals are directly related to the dihedral angles between the hydrogens, with angles of 0° and 180° giving the largest values (~13-15 Hz), and 90° giving a value of approximately zero. The two diastereotopic

protons at C-6 and the α-protons at C-2 will play an important role in allowing us to determine the structure of all the hydrogenation products. Geminal protons also tend to have relatively large coupling constants of (~12-15 Hz). Thus, taking into account the coupling constants between the protons illustrated in figure **15** allows us to elucidate the stereochemistry of the structure with some certainty.

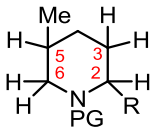


Figure 15

The isomer **149a** show clear rotameric behaviour, and two signals are observed for each proton of the isomer **149a**. The doublet of doublets (3.12 and 3.51 ppm for each rotamer) of one proton at C-6, the doublet (3.64 and 4.22 ppm for each rotamer) are for the other protons at C-6 as determined by $^{1}H/^{13}C$ correlation (**Figure 16**).

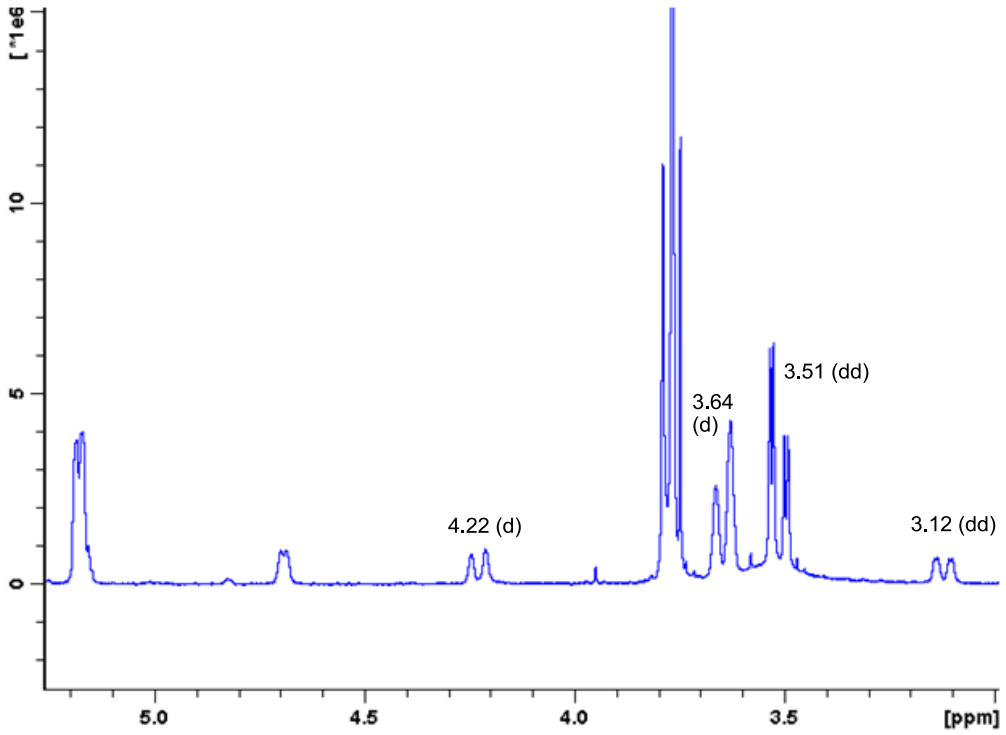


Figure 16: *partial ^{1}H-NMR spectrum of **149a***

Considering the signals of one proton at C-6 (3.12 and 3.51 ppm for each rotamer), which are a doublets of doublet (**Figure 17**), with large coupling constant (14.0 Hz for each rotamer) due to the geminal coupling and small coupling constant (3.5 Hz, and 3.0 Hz for each rotamer) with the equatorial proton at C-5.

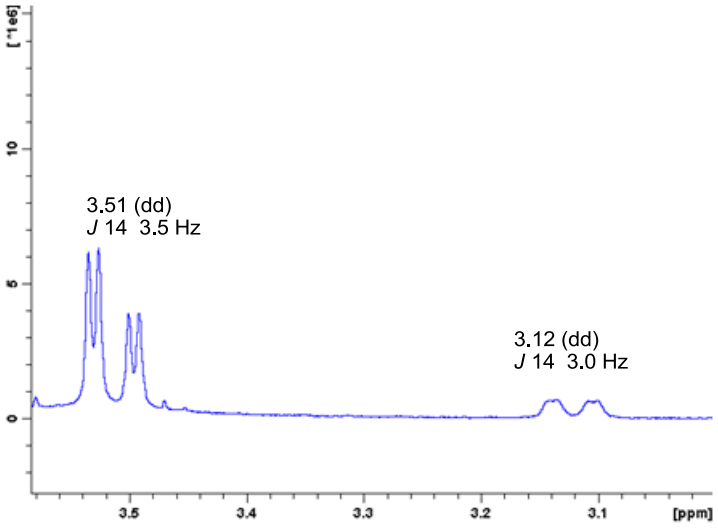


Figure 17

The other proton at C-6 is a doublet (3.64 and 4.22 ppm for each rotamer) with coupling constant (14.0 Hz) is a result of the geminal coupling (**Figure 18**).

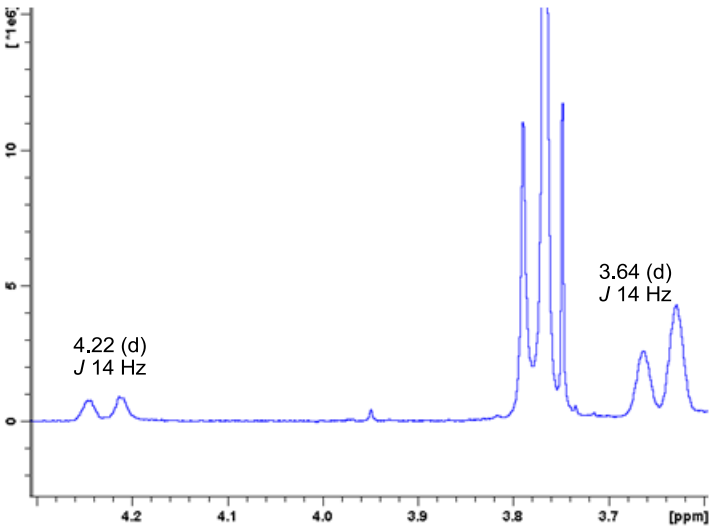


Figure 18

Since there is no evidence of a large axial/axial coupling for either proton at C-6 in each rotamer, the methyl group at C-5 must be axial (**Figure 19**).

We can delete **B** (**C-2$_{eq}$/C-5$_{eq}$**) and **C** (**C-2$_{ax}$/C-5$_{eq}$**) and keep **A** (**C-2$_{ax}$/C-5$_{ax}$**) if *trans*, or **D** (**C-2$_{eq}$/C-5$_{ax}$**) if *cis*.

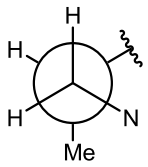


Figure 19

The α-proton at C-2 (4.68 and 5.17 ppm for each rotamer) is a doublet with a moderate coupling constants (5.5 and 6.5 Hz for each rotamer). Again, there is no evidence of a large diaxial coupling so the α-proton at C-2 must be equatorial (**Figure 20**).

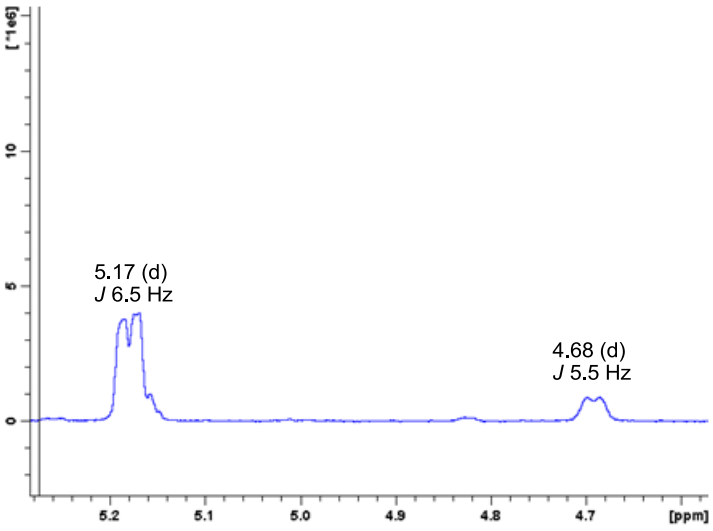


Figure 20

Thus, the α-proton must be at the equatorial position and the ester group at the axial position. 1,3 Allylic strain ($A^{1,3}$) may explain this observation.[110-112] (**Figure 21**).

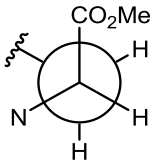
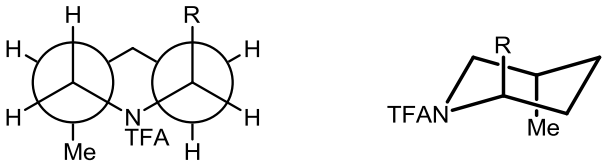


Figure 21

This analysis can eliminate the diequatorial isomer **D** (**C-2$_{eq}$/C-5$_{ax}$**) and suggests that we have the diaxial conformer **A** (**C-2$_{ax}$/C-5$_{ax}$**) of the *trans*-isomer **149a** (**Figure 22**).



A-conformer
R = CO_2Me

Figure 22

The other isomer **149b** also exhibits clear rotameric behavior for the protons at C-6 and α-proton (**Figure 23**).

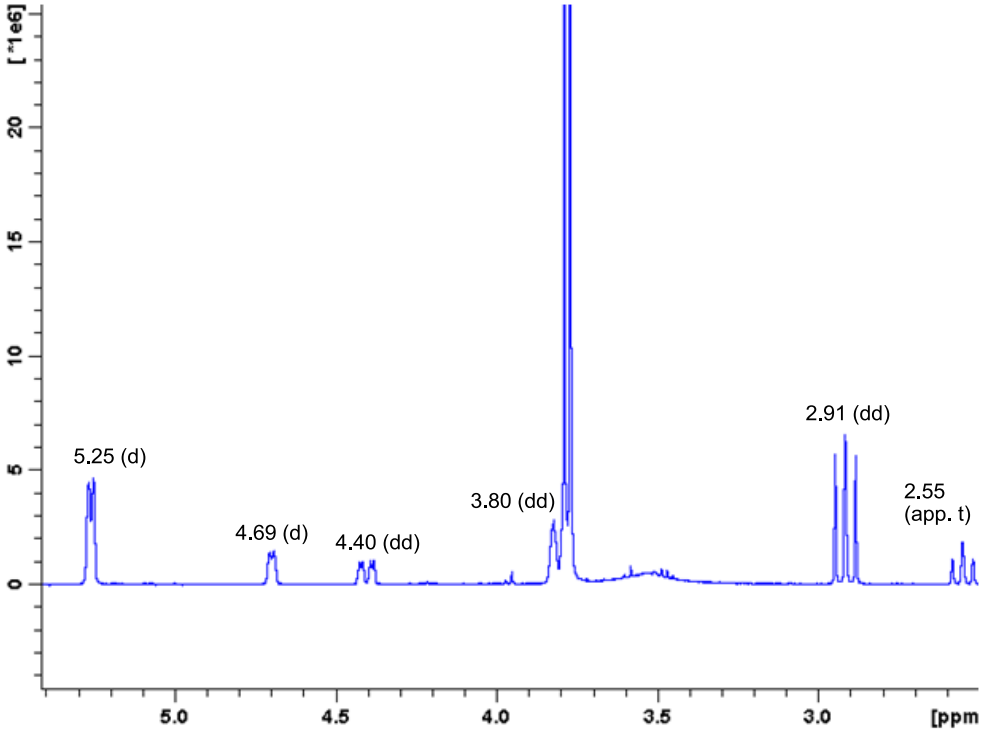


Figure 23: *partial ^{1}H-NMR spectrum of* ***149b***

The signals assigned to a proton at C-6 is a doublet of doublets (3.80 partly observed, and 4.40 ppm for each rotamer), arise from a geminal proton with large coupling constants (12.0 and 13.0 Hz for each rotamer) and small coupling constants (2.0 and 4.5 Hz for each rotamer) arise from the vicinal proton at C-5. The large values are a result of geminal coupling with the axial proton at C-6, and the smaller value indicative of a relatively small dihedral angle with the proton at C-5 (**Figure 24**).

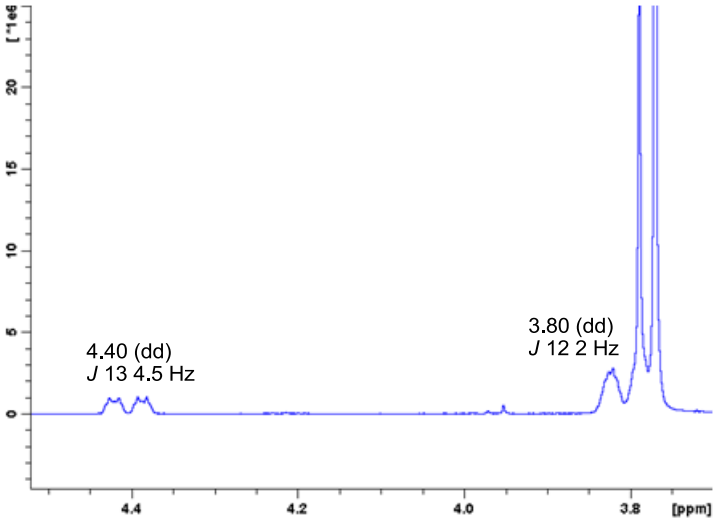


Figure 24

The apparent triplets (2.55 and 2.91 ppm for each rotamer) at C-6 (**Figure 25**), are actually two sets of doublet doublets with large coupling constants (14.0 and 14.0 Hz for each rotamer) due to geminal coupling and another large coupling constant (13.0 and 14.0 Hz for each rotamer) with the vicinal proton at C-5 (*anti* coupling constant). This allows us to assign the C-5 proton of the **149b** isomer as being in the axial position.

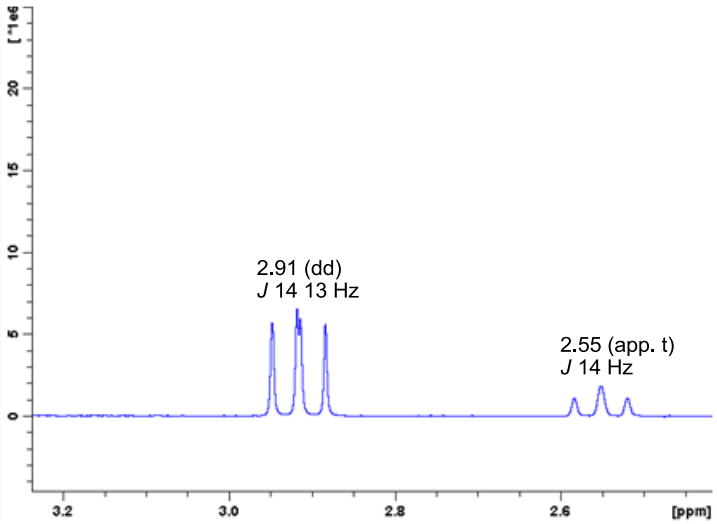


Figure 25

There is an indication of a large axial/axial coupling in both rotamers, so the methyl group at C-5 must be equatorial (**Figure 26**). We can keep **B** (**C-2$_{eq}$/C-5$_{eq}$**) and **C** (**C-2$_{ax}$/C-5$_{eq}$**).

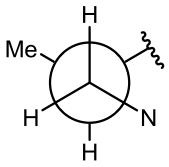


Figure 26

The α-proton is a doublet at (4.69 and 5.25 ppm for each rotamer), with moderate coupling constants (5.5 and 6.0 Hz for each rotamer). This coupling arises from the vicinal proton at C-3 (**Figure 27**).

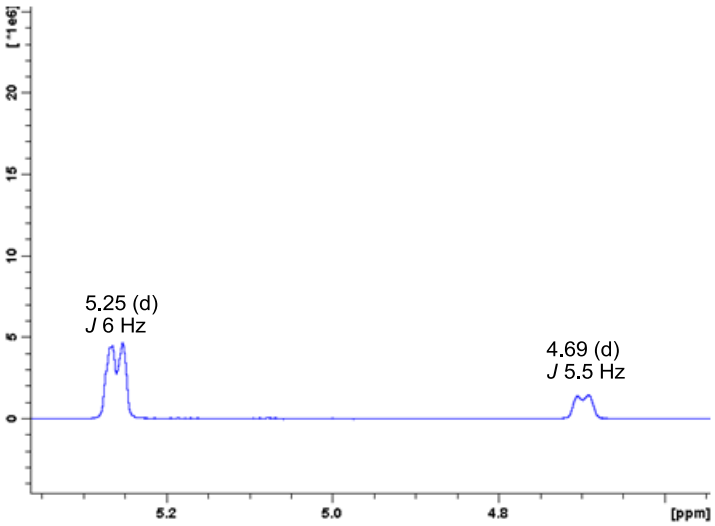


Figure 27

Therefore, there is no an indication of a large axial/axial coupling in either rotamer, so the ester group at C-2 must be axial (**Figure 28**).

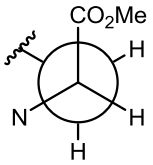
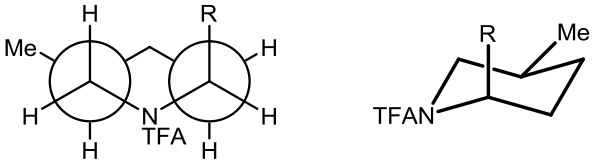


Figure 28

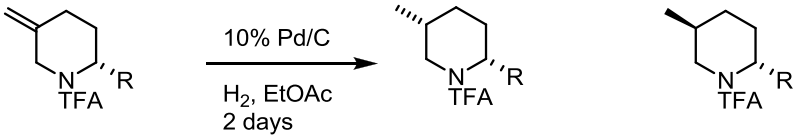
So we have conformation **C** of the *cis*-isomer **149b** (**Figure 29**).



C-conformer
R = CO_2Me

Figure 29

The next scheme **63** and table **4** summarise the hydrogenation outcome of the rest of the TFA-protected 5-methylene piperidines.



Scheme 63

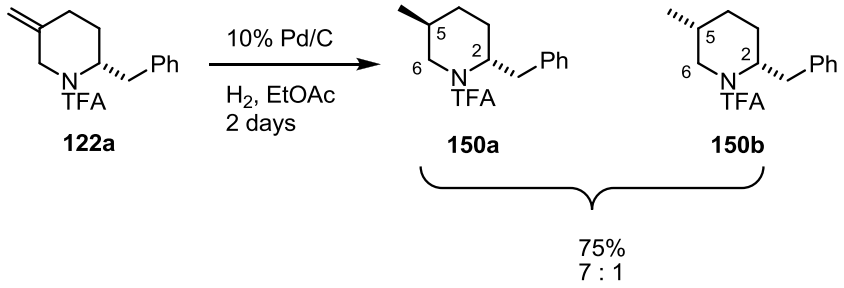
Table 4:

Substrate (R)	Piperidine	Combined yield %	Minor	Major
Bn	**122a**	75	1	7
^{i}Pr	**122b**	75	1	4
CH_2CO_2Me	**122c**	80	1	2.5
$CH_2CH_2CO_2Me$	**122d**	80	1	2.5

The ratio is determined by ^{1}H-NMR spectroscopy of the crude product

We will now discuss briefly the conformational analysis of the hydrogenation products of the piperidine **122a**.

The piperidine **122a** was subjected to hydrogenation which produced two separable diastereoisomers with significant diastereoselectivity (7 : 1) major : minor (**Scheme 64**).



Scheme 64

The ^{1}H-NMR spectra of two isomers **150a** and **150b** showed coupling between C-6/C-5 protons, and α-proton with benzylic and C-3 protons. The conformational investigation is summarized in the next figure (**Figure 30**).

The major isomer **150a** has a large (14.5 and 14.0 Hz for each rotamer) and a small (3.0 and 2.0 Hz for each rotamer) coupling constant at C-6, so there is no diaxial coupling, the methyl group must be axial. The α-proton has a small coupling constant (4.0 Hz), which suggests that the benzyl group must be axial.

The minor isomer **150b** has two large (14.0, 10.0 and 13.5, 12.5 Hz for each rotamer) coupling constants at C-6, so there is a diaxial coupling, the

methyl group must be equatorial. The benzyl group is axial as there is no diaxial coupling.

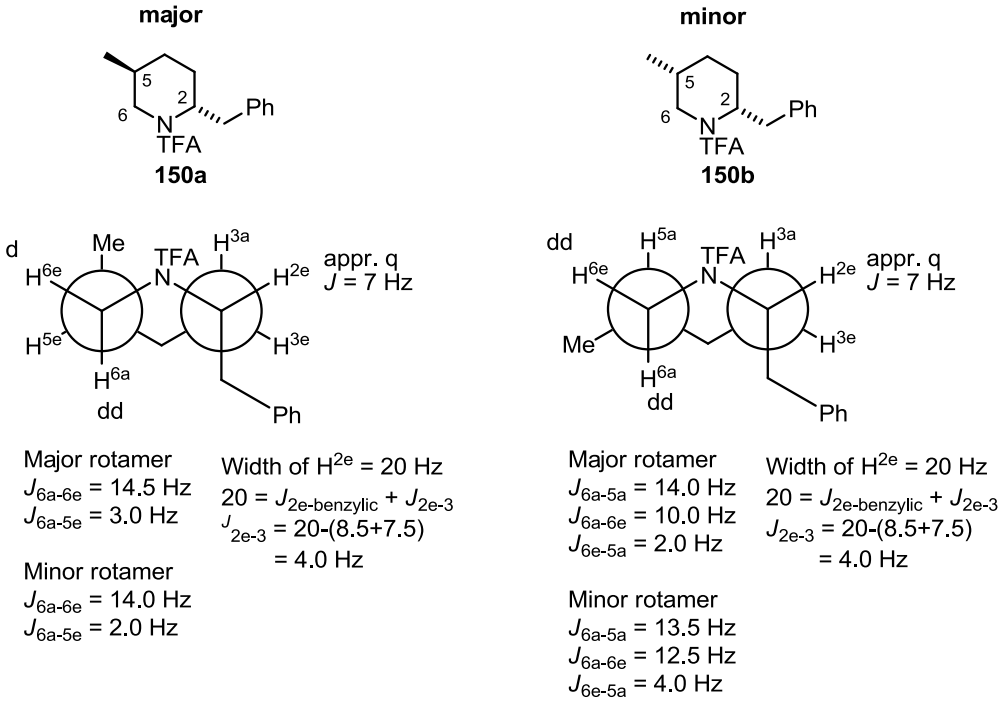


Figure 30

Table 5:

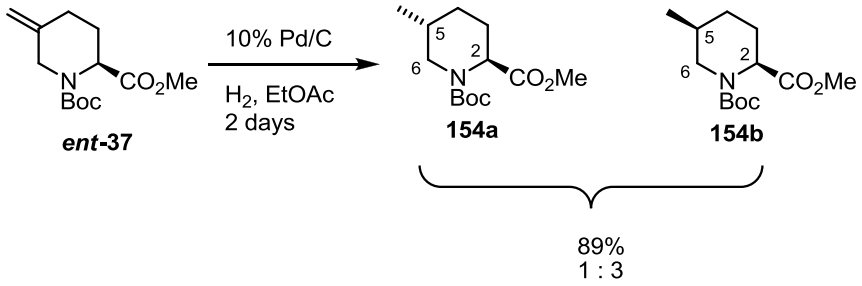
Substrate (R)	Piperidine	Combined yield %	*cis*	*trans*
Bn	**122a**	75	**150b**	**150a**
			1	7
^{i}Pr	**122b**	75	**151b**	**151a**
			1	4
CH_2CO_2Me	**122c**	80	**152b**	**152a**
			1	2.5
$CH_2CH_2CO_2Me$	**122d**	80	**153b**	**153a**
			1	2.5

The ratio is determined by ^{1}H-NMR spectroscopy of the crude product

2.2.6.2 Hydrogenation of Boc-protected piperidines

Hydrogenation of the Boc-protected piperidines **119a**, **119b**, **119c**, **1219d** and ***ent*-37** gave in each case two separable diastereoisomers (except for **119b**) in excellent yields.

The stereochemical assignment will be discussed in more detail for the hydrogenation of piperidine ***ent*-37**. The crude NMR spectrum of the hydrogenation of compound ***ent*-37** shows a (3 :1) ratio of major : minor stereoisomers (**Scheme 65**).



Scheme 65

As already discussed for the TFA-derivatives **149**, we need to consider two possible conformers for each stereoisomer. **A**, **B** and **C**, **D** (**Figure 31**).

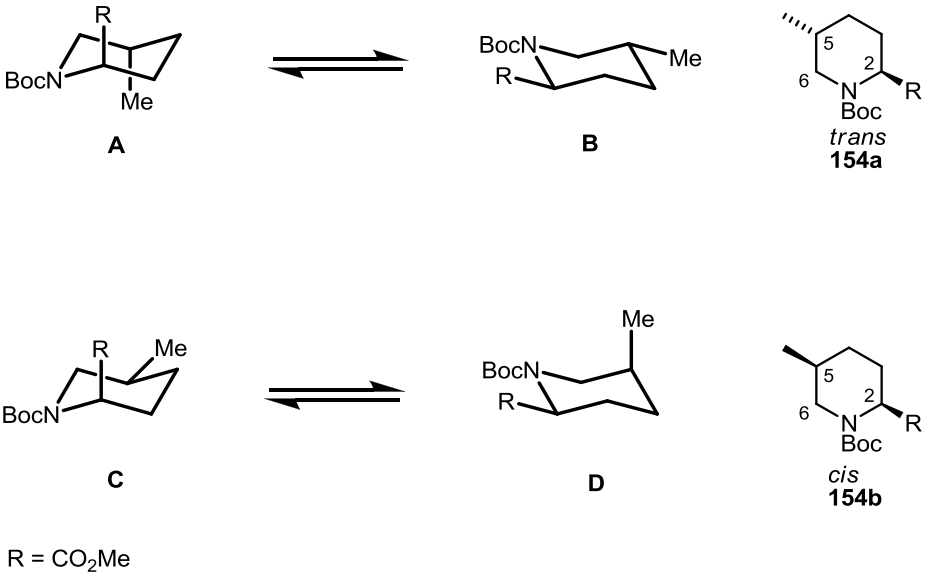


Figure 31: *Potential structural outcomes of hydrogenation of piperidine* ***ent-37***

The major isomer **154b** has a doublet of doublets (2.41 and 2.54 ppm for each rotamer) which have the same coupling constants, and a doublet of doublets (3.84 and 3.99 ppm), arising from the protons at C-6. They allow a determination of the local conformation. These two signals were identified as the C-6 protons by $^{1}H/^{13}C$ correlation.

The signal for the proton at C-6 (3.84 and 3.99 ppm) appears as a doublet of doublets with large (13.5 and 13.5 Hz for each rotamer) and small coupling constants (4.5 and 4.5 Hz for each rotamer) (**Figure 32**). The large values are a result of geminal coupling C-6, and the small values derived from a coupling with the vicinal proton at C-5.

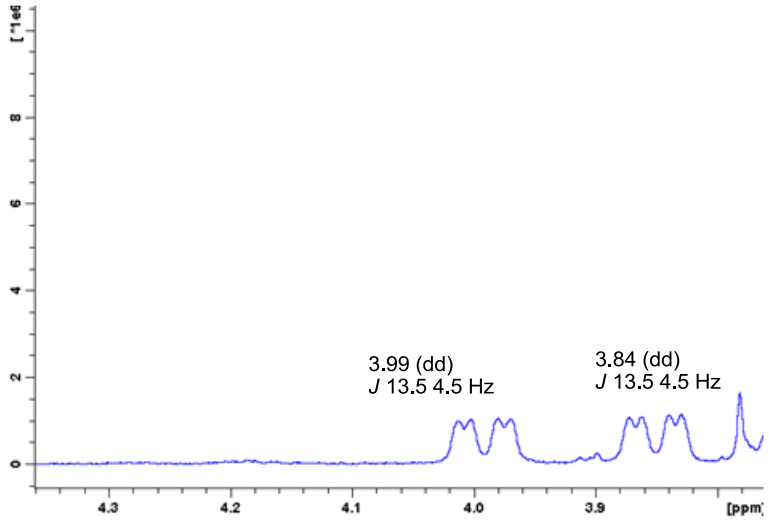


Figure 32

The signals for the other proton at C-6 (2.41 and 2.54 ppm for each rotamer) show a doublet of doublets and exhibits two large coupling constants (13.5 and 12.5 Hz for each rotamer) (**Figure 33**). The first value is a result of vicinal coupling with the proton at C-5 (diaxial coupling), and the second value arises from the geminal proton.

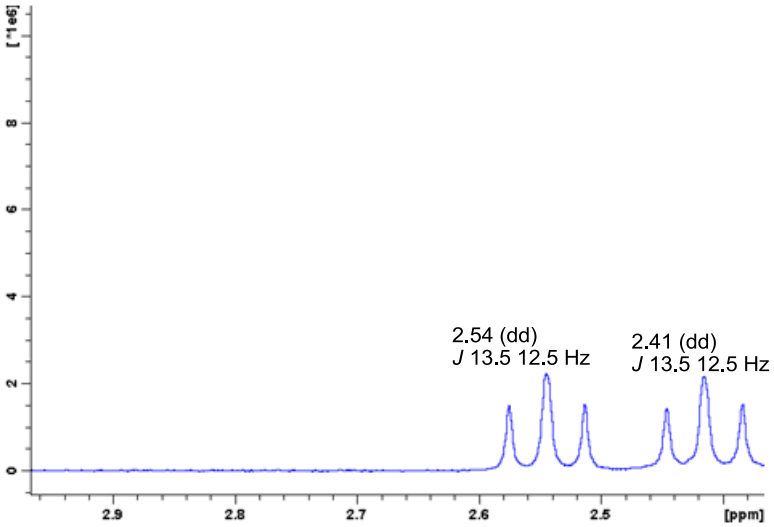


Figure 33

Consequently, this allows us to assign the methyl group at C-5 of the major isomer as being in the equatorial position (**Figure 34**).

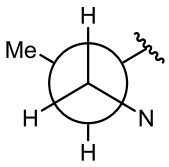


Figure 34

The signal for the α-proton at C-2 (4.71 and 4.89 ppm for each rotamer) is a doublet with a small coupling constant (5.5 Hz for each rotamer). This small values arising from the the proton at C-3, no diaxial coupling thus the ester group is axial (**Figure 35**).

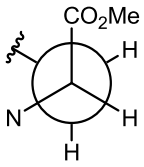
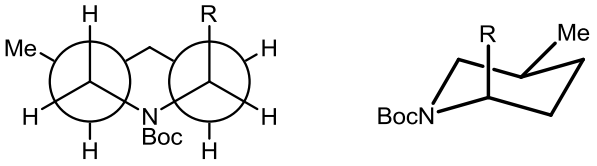


Figure 35

Through analysis of the NMR data, the compound exists in conformer **C** (**C-2$_{ax}$/C-5$_{eq}$**) of the *cis*-isomer **154b** (**Figure 36**).



C-conformer
R = CO_2Me

Figure 36

The minor isomer **154a** shows a doublet at (3.16 ppm) and a doublet at (3.60 ppm), arising from the protons at C-6 (**Figure 37**), again they allow a determination of the local conformation. These two signals were identified as the C-6 proton by $^{1}H/^{13}C$ correlation.

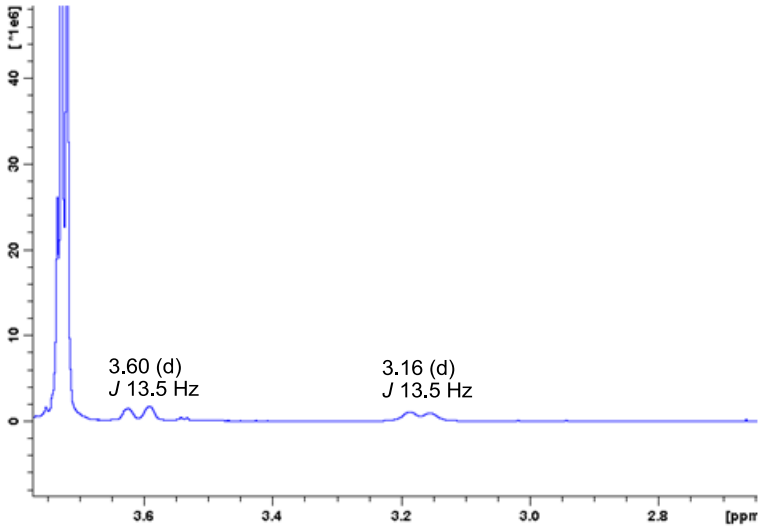


Figure 37

The signal for the proton at C-6 (3.60 ppm) appears as a doublet with a large coupling constant (13.5 Hz). This value is a result of geminal coupling with the axial proton at C-6, and no coupling with the proton at C-5.

The signal for the other proton at C-6 (3.16 ppm) appears as a doublet and exhibits a large coupling constant (13.5 Hz), which is a result of geminal coupling. This allows us to assign the methyl of the minor isomer as being in the axial position (**Figure 38**).

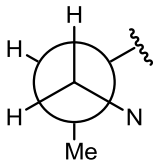


Figure 38

The α-proton of the minor isomer is broad. It will be based on the results obtained from the assignment of the α-proton of the major isomer, therefore the ester group is axial (**Figure 39**).

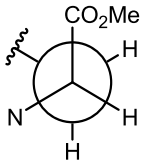
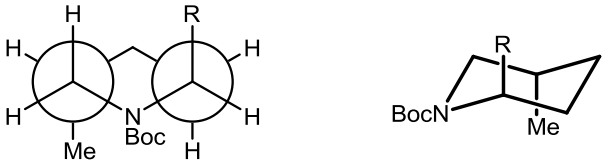


Figure 39

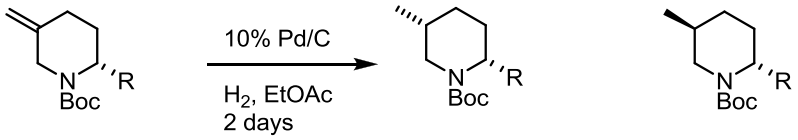
So, the conformational structure of the minor isomer **154a** is conformer **A** *trans*-isomer (diaxial) (**Figure 40**).



A-conformer
R = CO_2Me

Figure 40

Hydrogenation of the Boc-protected 5-methylene piperidines was summarised in Scheme **66** and Table **6**.



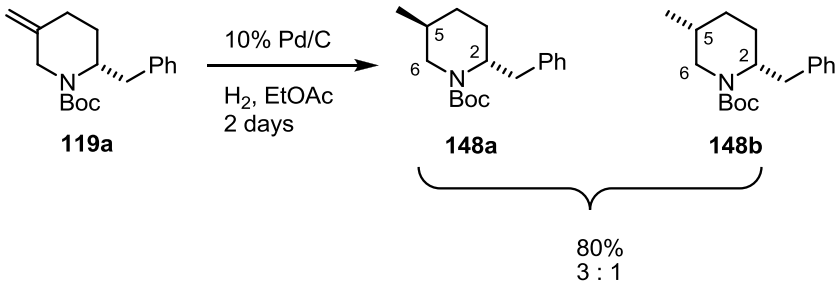
Scheme 66

Table 6:

Substrate (R)	Piperidine	Combined yield %	Minor	Major
Bn	**119a**	80	1	3
^{i}Pr	**119b**	78	1	1.5
CH_2CO_2Me	**119c**	83	1	1.5
$CH_2CH_2CO_2Me$	**119d**	84	1	1.5

The ratio is determined by ^{1}H-NMR spectroscopy of the crude product

Hydrogenation of piperidine **119a** gave two separable diastereoisomers (3 : 1) major : minor (**Scheme 67**).



Scheme 67

As before, the conformational structural analysis of the two isomers is summarized in the next figure (**Figure 41**).

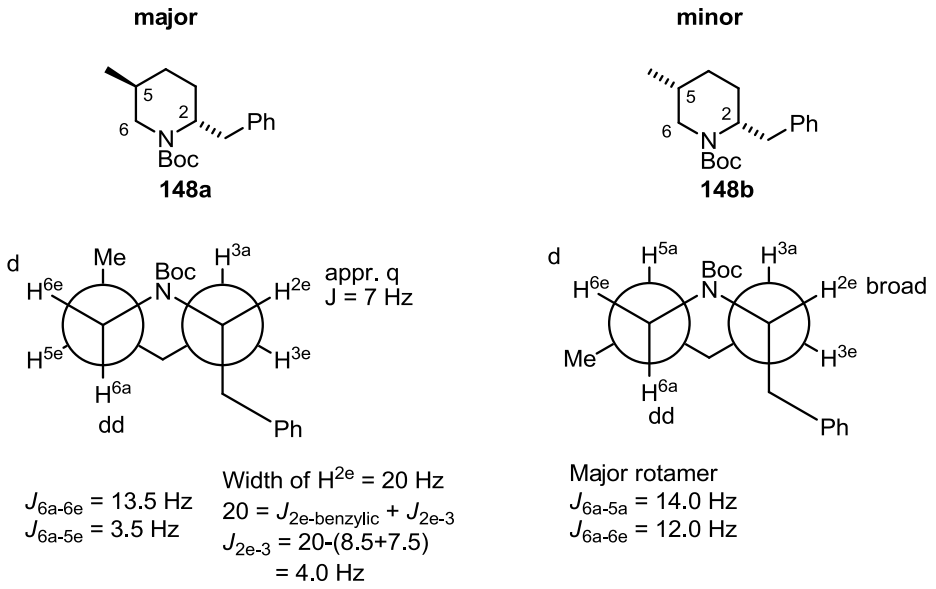


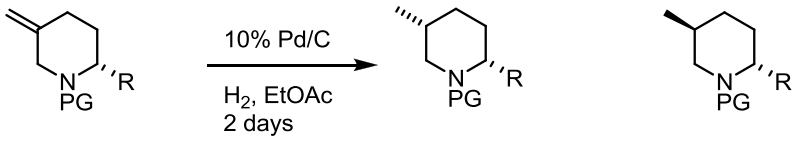
Figure 41

Table 7:

Substrate (R)	Piperidine	Combined yield %	*cis*	*trans*
Bn	**119a**	80	**148b**	**148a**
			1	3
^{i}Pr	**119b**	78	**155b**	**155a**
			1	1.5
CH_2CO_2Me	**119c**	83	**156b**	**156a**
			1	1.5
$CH_2CH_2CO_2Me$	**119d**	84	**157b**	**157a**
			1	1.5

The ratio is determined by ^{1}H-NMR spectroscopy of the crude product

The hydrogenation of all 5-methylenepiperidines is summarized in scheme **68** and table **8**.



Scheme 68

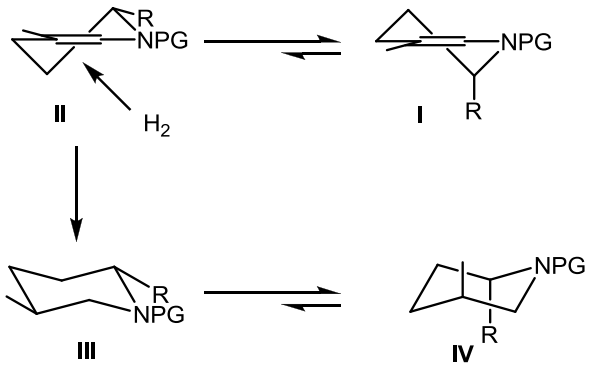
Table 8:

Substrate (R)	Piperidine	PG	Combined yield%	*cis*	*trans*
CO_2Me	***ent*-37**	Boc	89	3	1
	127	TFA	92	1	1
Bn	**119a**	Boc	80	1	3
	122a	TFA	75	1	7
^{i}Pr	**119b**	Boc	78	1	1.5
	122b	TFA	75	1	4
CH_2CO_2Me	**119c**	Boc	83	1	1.5
	122c	TFA	80	1	2.5
$CH_2CH_2CO_2Me$	**119d**	Boc	84	1	1.5
	122d	TFA	80	1	2.5

The ratio is determined by ^{1}H-NMR spectroscopy of the crude product

In most cases the *trans*-isomer is favoured, suggesting that hydrogen is preferentially delivered from below of half chair **II** which would have the R group in an equatorial position. This prouducs the diequatorial chair **III**

which may ring flip into a chair **IV** to avoid $A^{1,3}$ strain between the R group and the protecting group (PG) on nitrogen (Scheme **69**).

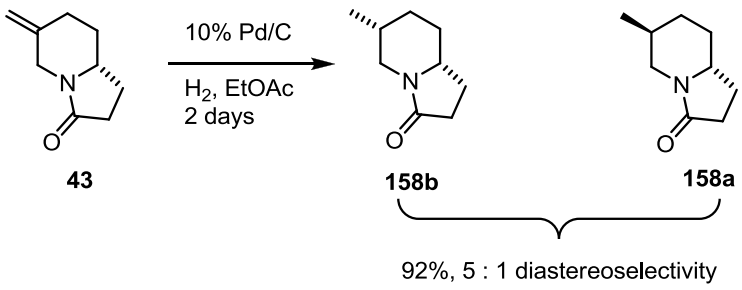


Scheme 69

2.2.7 Hydrogenation of indolizidinone and oxazolidinone

2.2.7.1 Hydrogenation of indolizidinone

Hydrogenation of the indolizidinone **43** furnished two inseparable diastereoisomers in excellent yield 92% with a moderate stereoselectivity (5:1) as determined using ^{1}H-NMR spectroscopy (**Scheme 70** and **figure 42**).



Scheme 70

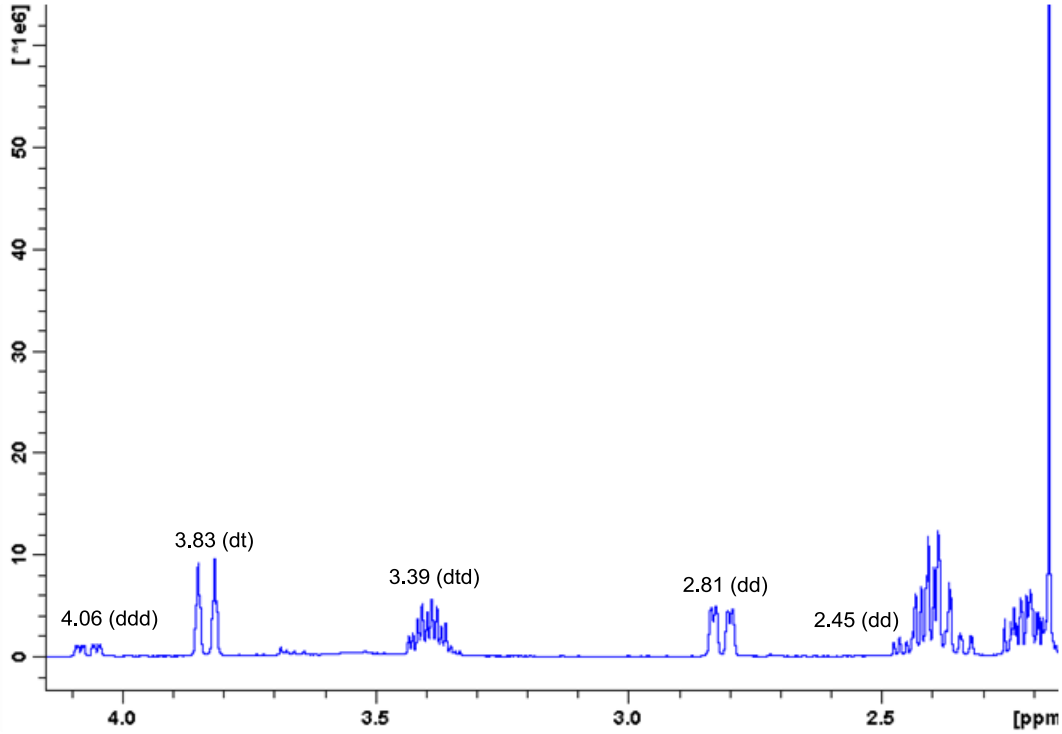


Figure 42: *partial ^{1}H-NMR spectrum of **158a/158b***

The configuration assignment of the major indolizidinone **158b** was made by ^{1}H-NMR spectroscopy. The two protons at C-5 were first identified using ^{1}H/^{13}C correlation, since these are important in determining the configuration at C-6. (**Figure 43**).

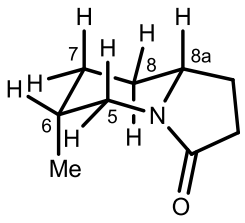


Figure 43

The signal for one of the protons at C-5 (3.83 ppm) of the major isomer **158b** appears as a doublet of triplets (**Figure 44**), with a large coupling to the geminal proton (13.0 Hz) and two small doublet coupling (1.5 Hz) to

the equatorial proton at C-6 and the equatorial proton at C-7 (W-coupling) respectively.

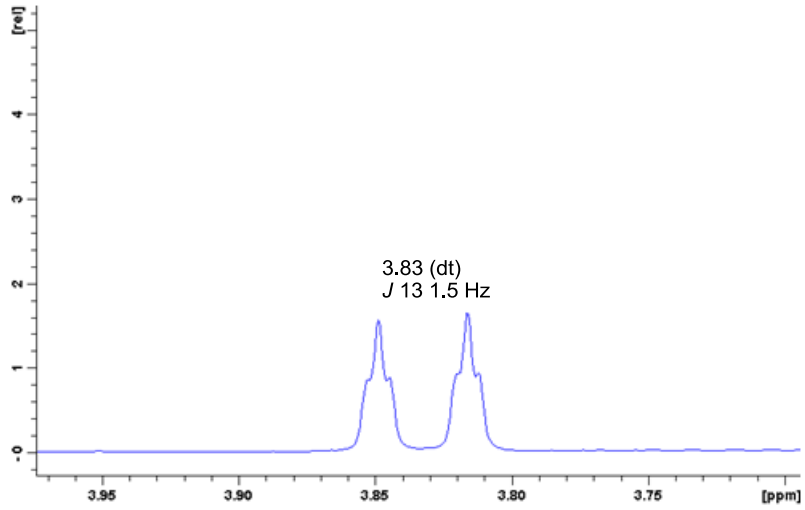


Figure 44

This means that the other proton at C-5 (2.81 ppm) is a doublet of doublets must be axial (**Figure 45**), shows a large geminal coupling (13.0 Hz) and a small coupling constant (4.0 Hz).

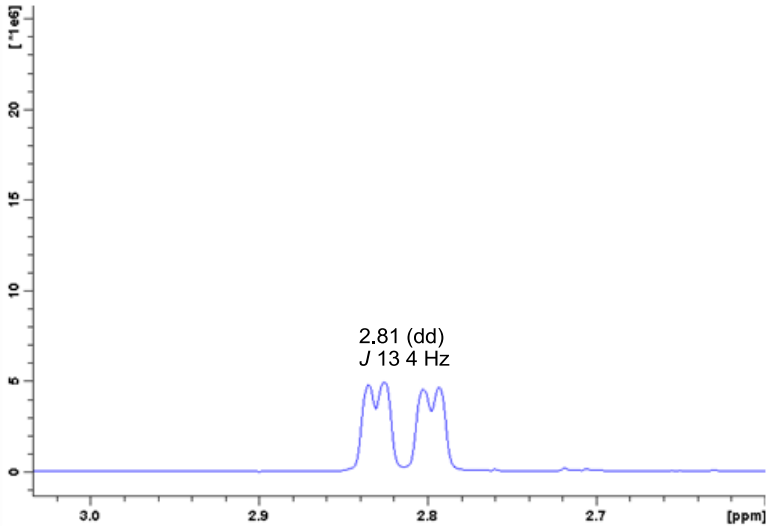


Figure 45

One large geminal coupling is present but no other large coupling, so the methyl at C-6 must be axial.

The appearance of a doublet of triplets of doublets for the proton at C-8a (3.39 ppm), the large doublet coupling constant (11.5 Hz) is generated from the axial proton at C-8 (diaxial coupling) and the triplet from the two protons at C-1 with a coupling constant (7.0 Hz), and the equatorial proton at C-8 gave a small coupling constant (3.0 Hz) (**Figure 46**).

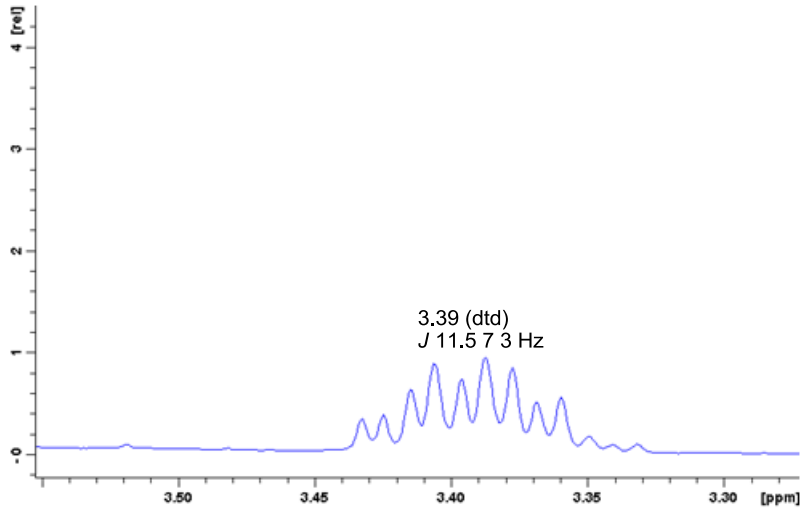


Figure 46

The distinguishable peaks of the minor indolizidinone **158a** are the protons at C-5 (2.45 and 4.06 ppm) but the proton at C-8a is not separated clearly in the spectrum (**Figure 47**).

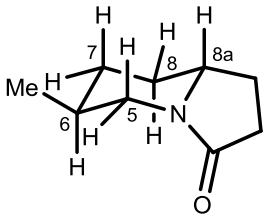


Figure 47

This proton at C-5 (4.06 ppm) is a doublet of doublets of doublets with a large (13.0 Hz), a medium (5.0 Hz) and small (2.0 Hz) coupling constants (**Figure 48**). The large value arises from the geminal proton, the medium value established from the vicinal axial proton at C-6, and the small value derived from the equatorial proton at C-7 (W-coupling).

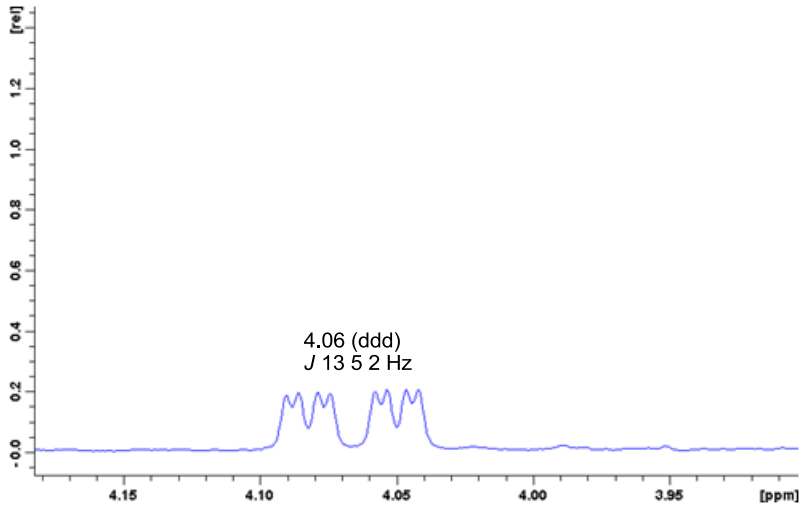


Figure 48

The other proton at C-5 (2.45 ppm) is a doublet of doublets with two large coupling constants (13.0 and 12.5 Hz), which are due to geminal and vicinal diaxial coupling (**Figure 49**). So the methyl group must be equatorial.

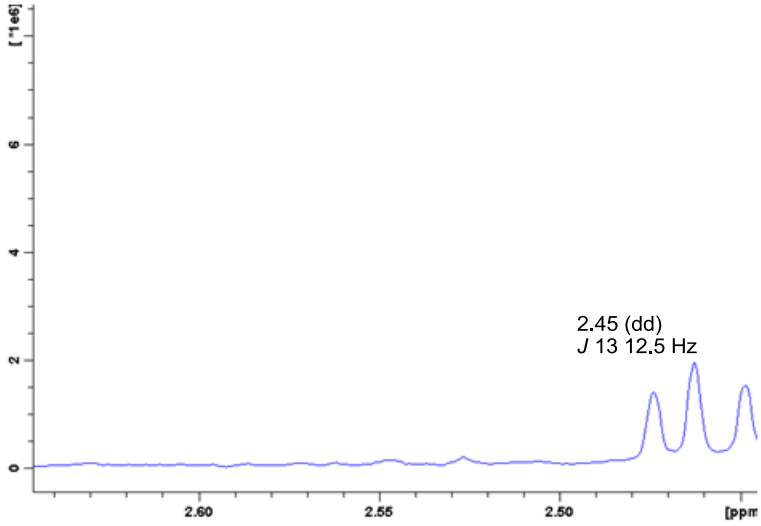
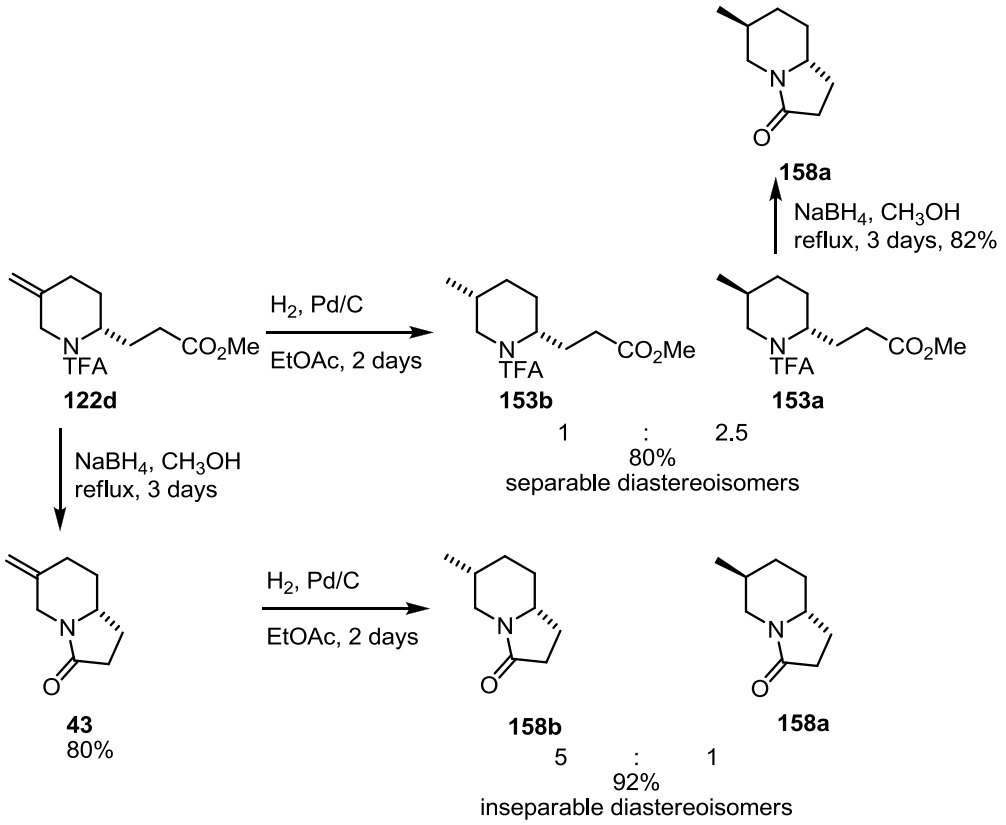


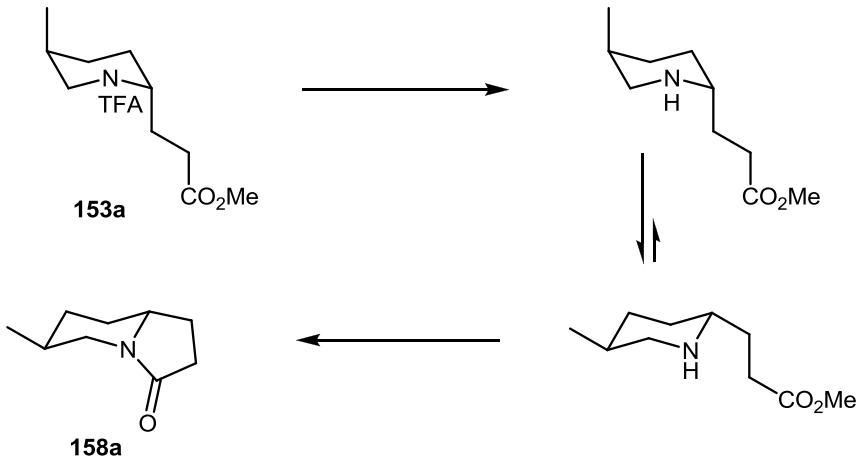
Figure 49

As already discussed, hydrogenation of the piperidine **122d** provided two separable diastereoisomers, *cis*-isomer **153b** (minor) and *trans*-isomer **153a** (major). The latter isomer was readily cyclised by utilizing the conditions employed for the preparation of the indolizidinone **43** to give the indolizidinone **159a** in excellent yield (82%) (**Scheme 71**). This compound had identical spectroscopic characterisations to the minor isomer from hydrogenation of **43**. This allows conformation of all earlier stereochemical assignments.



Scheme 71

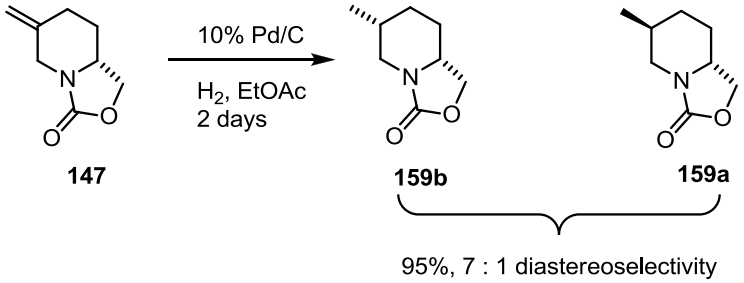
Formation of the indolizidinone **158a** occuried during TFA-deprotection of **153a**. Presumably rapid conversion of the diaxial conformer to the diequatorial conformer occurs (**Scheme 72**).



Scheme 72

2.2.7.2 Hydrogenation of oxazolidinone

The oxazolidinone **147** was also subjected to the previous hydrogenation conditions furnishing two inseparable diastereoisomers in excellent yield 95% (**Scheme 73**) with a stereoselectivity (7:1) major : minor measured according to ^{1}H-NMR spectroscopy (**Figure 50**).



Scheme 73

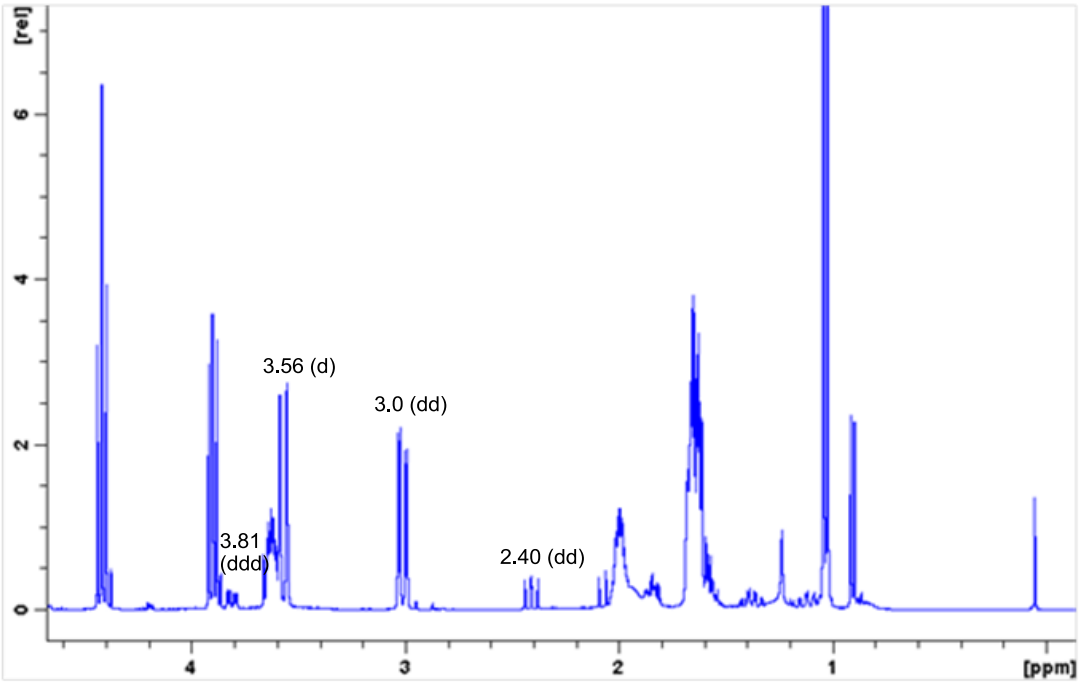


Figure 50: *partial ^{1}H-NMR spectrum of **159a/159b***

The stereochemical investigation of the products was by the protons at C-5 using ^{1}H/^{13}C correlation and ^{1}H-NMR spectroscopy (**Figure 51**). The

proton signal at C-5 of the major isomer **159b** (3.0 ppm) is a doublet of doublets with a large coupling constant (13.0 Hz) which is a result of the geminal coupling, and a small coupling constant (4.0 Hz) with the equatorial proton at C-6. The signal of the other proton (3.56 ppm) is a doublet with a large coupling constant (13.0 Hz) arising from the geminal proton (**Figure 52**). Since neither of the protons at C-5 show a record large coupling, the proton at C-6 must be equatorial.

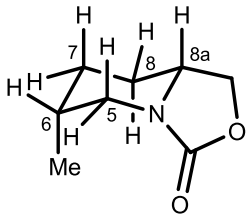


Figure 51

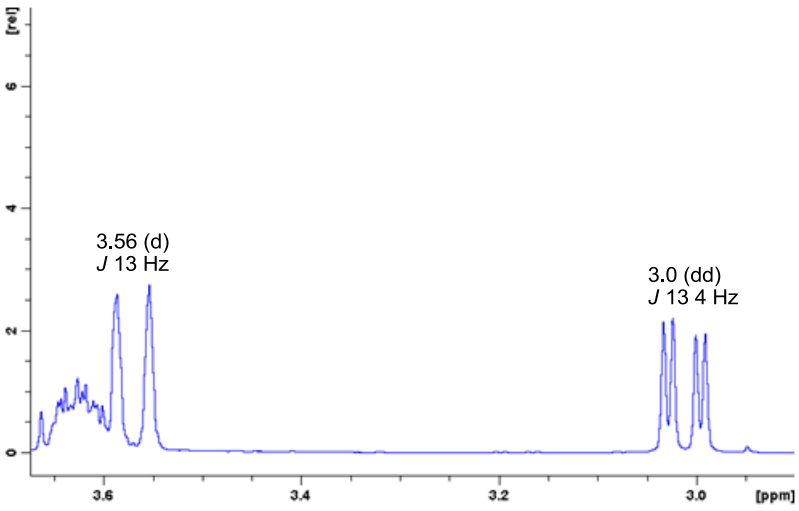


Figure 52

The minor isomer **159a**; the two protons at C-5 were also assigned (**Figure 53**). The doublet of doublets of the proton at C-5 (2.40 ppm) with two large coupling constants (13.0 Hz and 11.5 Hz) arising from the

equatorial geminal proton and the axial proton at C-6 (*anti*-coupling) respectively (**Figure 54**).

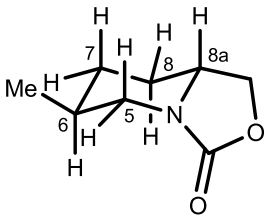


Figure 53

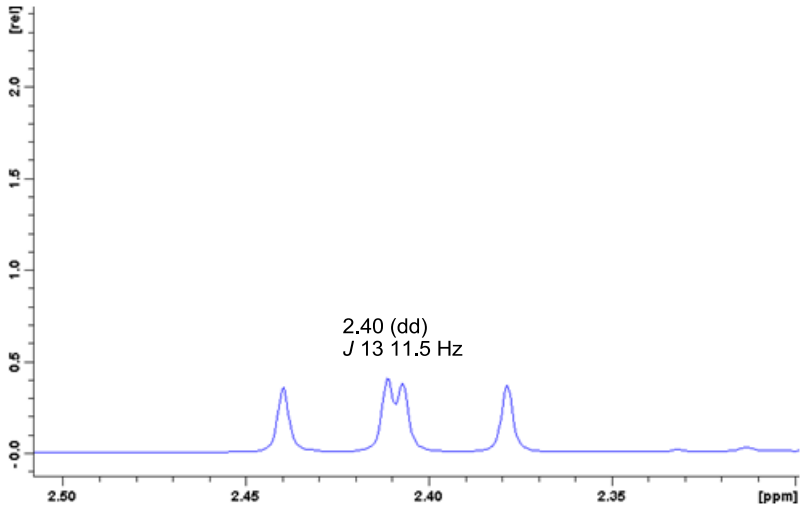


Figure 54

The other proton at C-5 (3.81 ppm) is a doublet of doublets of doublets with a large (13.0 Hz), medium (5.0 Hz), and small coupling constants (1.5 Hz) (**Figure 55**). The large value arises from the axial geminal proton, the medium value is a result of vicinal coupling with the axial proton at C-6, and the small value is due to long range coupling with the equatorial proton at C-7 (W-coupling).

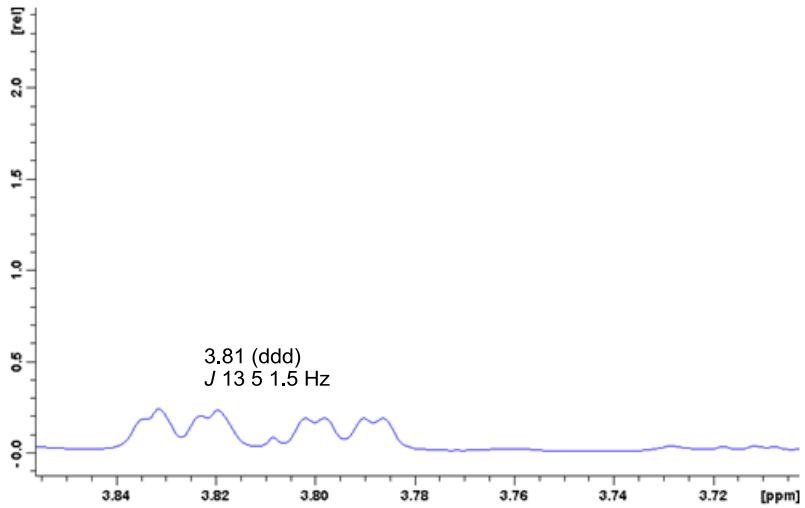
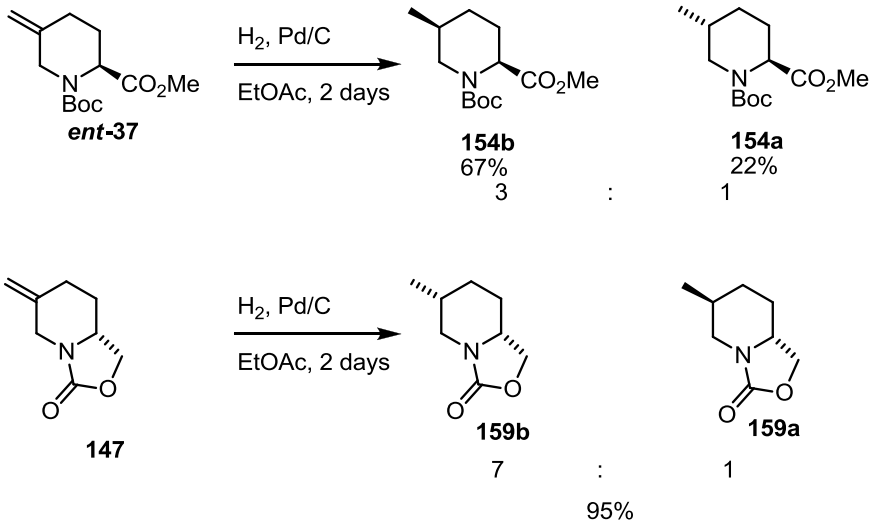


Figure 55

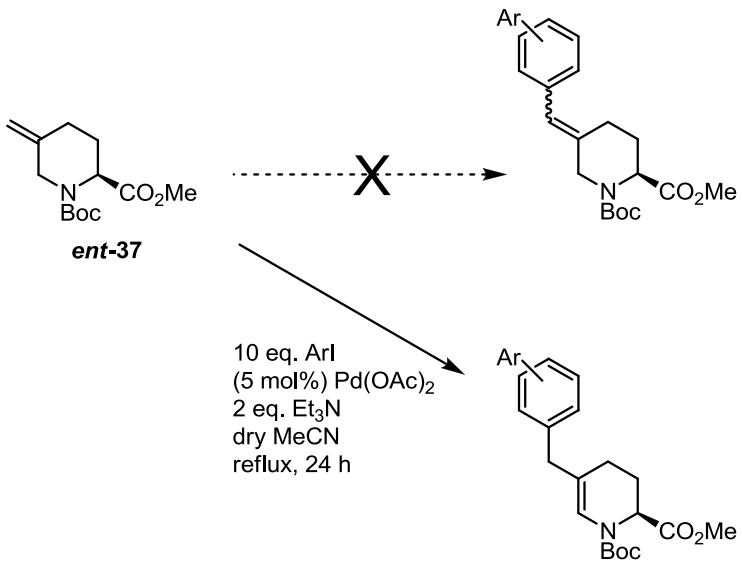
In conclusion, hydrogenation of pipecolate before and after cyclization showed a different diastereoselectivity. It was 3 : 1 *cis* : *trans* before cyclization and 7 : 1 after (**Scheme 74**).



Scheme 74

2.2.8 Heck reactions

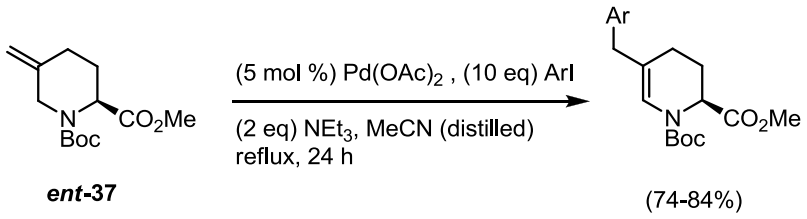
We next turned our attention to functionalization of 5-methylene piperidines, as a route to 2,5-disubstituted piperidines. Optimised Heck reaction conditions had been previously established using partially racemised piperidine ***ent*-37** (**Scheme 75)**.[48] The products were the corresponding endocyclic alkenes, rather than the initially expected exocyclic isomers. However, given the case of isomerisation of the exocyclic double bond during hydrogenation reactions this is not surprising.



Scheme 75

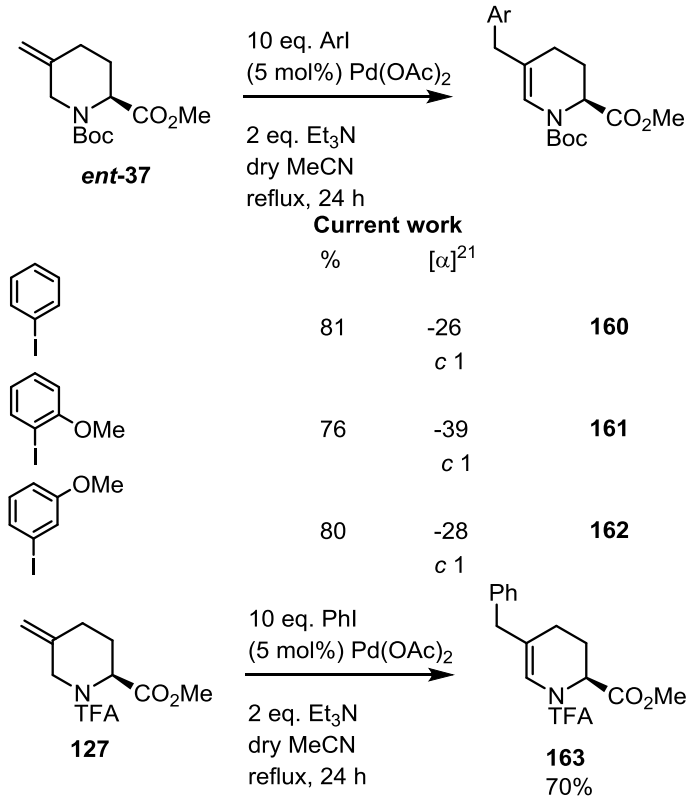
The conditions described by Kimura *et al*.[113] were utilized. A number of aryl iodide electrophiles furnished Heck products in low yields (25-40%). Optimisation of the previous Heck reaction conditions was carried out (**Scheme 76**). Using a large excess of aryl iodides relatively to pipecolate

***ent*-37** (from two to ten equivalents) and distilled acetonitrile gave good yields (70-76%).[48]



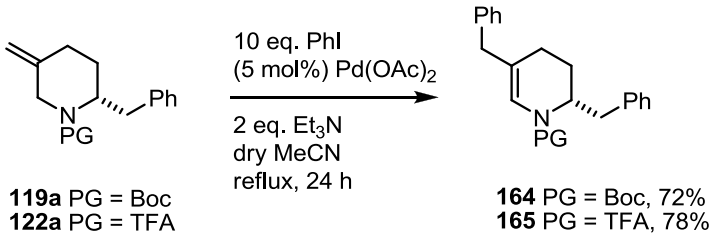
Scheme 76

The Heck conditions previously developed were used with the enantiomerically enriched 5-methylene pipecolate ***ent*-37**. The TFA-protected pipecolate **127** was also subjected to these conditions providing good yield 70% of compound **163** (**Scheme 77**).



Scheme 77

These Heck conditions were also successfully applied to the piperidines **119a** and **122a** to furnish the enamines **164** and **165** in comparable yields 72% and 78% respectively (**Scheme 78**).

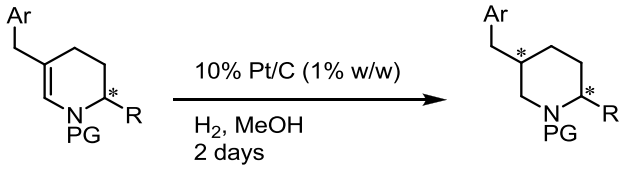


Scheme 78

2.2.9 Hydrogenation of Heck reaction products

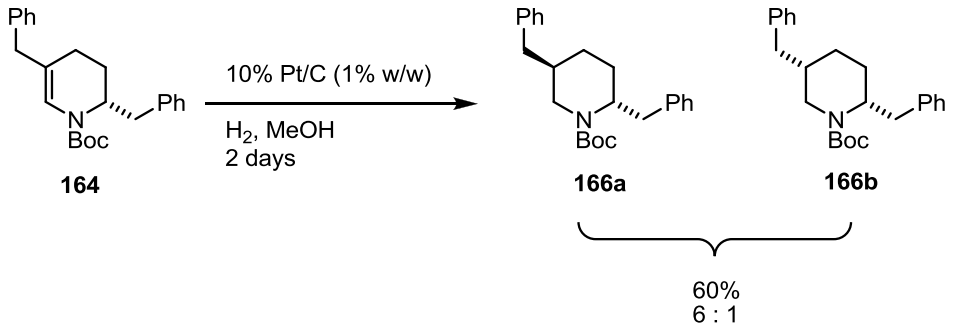
It had been reported previously that hydrogenation of the Heck products could be carried out using Pt/C (1% w/w) as catalyst.[48]

Application of these conditions to the Heck products (the 2,5-disubstituted piperidines) provided two inseparable diastereoisomers of the desired 2,5-disubstituted piperidines (**Scheme 79**)



Scheme 79

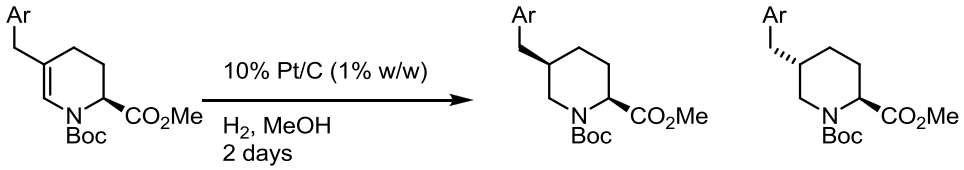
Hydrogenation of the Heck product **164** gave two diastereoisomers in good yield 60%, with 6 : 1 ratio and one diastereoisomer **166a** was isolated (**Scheme 80**).



164 **166a** **166b**

Scheme 80

Hydrogenation of the pipecolates **160**, **161** and **162** gave predominantly the *cis*-isomers with a diastereoisomeric ratio of ~4:1 in each case (**Scheme 81** and **table 9**).



Scheme 81

Table 9:

Heck products	Yield%	*trans*	*cis*
160	65	**167a**	**167b**
		1	4
161	55	**168a**	**168b**
		1	4
162	57	**169a**	**169b**
		1	4

The ratio is determined by ^{1}H-NMR spectroscopy

2.3 Conclusion

Initially, we examined using copper(I) mediated allylation and cyclisation methodology to the synthesis of enantiomerically pure 5-methylenepipecolate ***ent*-37** (**Schemes 39** and **40**).

Application this methodology with a range of β-amino organozinc reagents derived from different amino acids (*L*-phenylalanine, *L*-valine, *L*-aspartic and *L*-glutamic acids) and cyclic amino acids (*L*-proline and *L*-pyroglutamic acid), furnishing 2-substituted-5-methylenepiperidines (**Schemes 42** and **44**) and 6-methylene indolizidines respectively (**Schemes 53** and **57**).

Hydrogenation of these piperidines did not lead to the same levels of stereoselectivity as for the pipecolate ***ent*-37**, and a diastereoisomeric ratio of approximately 3:1, in preference of the *trans*-isomer was typically obtained (**Table 8**).

Subjecting some of the piperidines ***ent*-37**, **127**, **119a** and **122a** to developed Heck coupling conditions with aryl iodides provided access to a class of 2-substituted-5-benzylic-5,6-dehydropiperidines (**Schemes 77** and **78**).

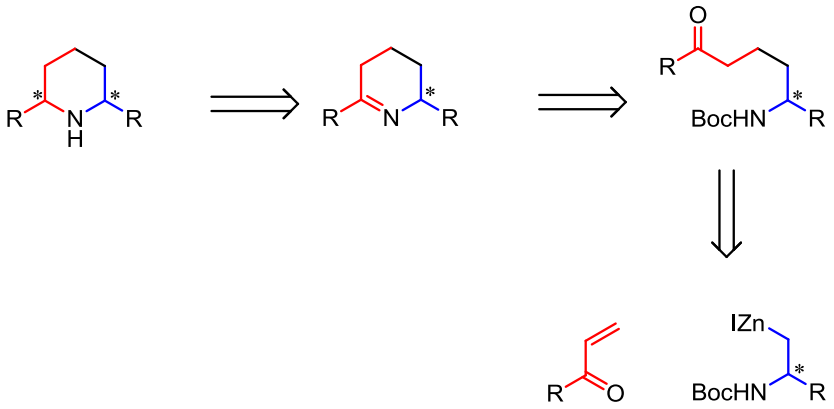
Finally, hydrogenation of these Heck coupling products proved to be a straightforward process to 2-substituted-5-benzylic piperidines in reasonable yields, and with diastereomeric ratios of approximately 4:1, in preference of the *cis*-isomer (**Schemes 80** and **81**).

Thus, we have successfully developed new routes to interesting and novel 2,5-disubstituted piperidines.

Chapter 3: Synthesis of 2,6-disubstituted piperidines

3.1 Introduction

Our retrosynthetic approach to the 2,6-disubstituted piperidines involved reduction of imines that might be made by cyclization of 6-oxo amino acids, in turn prepared by conjugate addition of β-amino organozinc reagents to enones (**Scheme 82**).

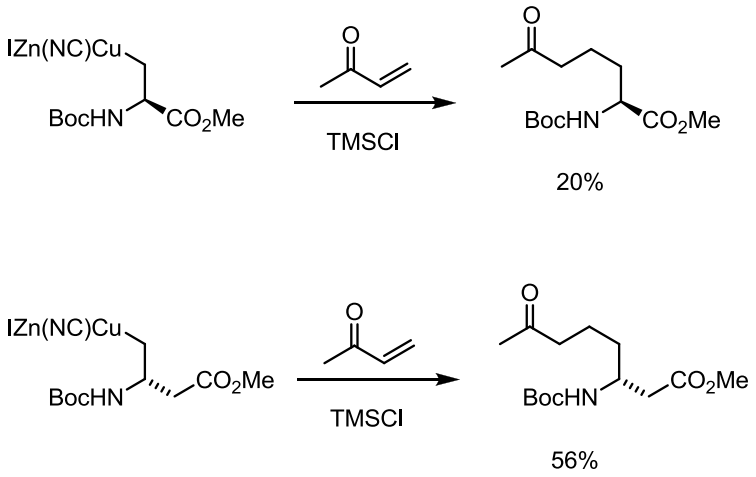


Scheme 82: *Retrosynthetic approach to 6-substituted pipecolate*

3.2 Results and discussion

The first goal was to develop a synthesis of 6-oxo amino acids via the conjugate addition of β-amino organozinc reagent to enones.

Previously in the Jackson group, the iodoalanine derived zinc/copper reagent (generated in THF) had been reacted in the presence of chlorotrimethylsilane, with methyl vinyl ketone to give the protected 6-oxo α-amino acid in low yield (20%).[82] However, zinc/copper reagent derived from *D*-aspartic acid (generated in DMF) gave a higher yield in a similar reaction (56%)[83] (**Scheme 83**).



Scheme 83

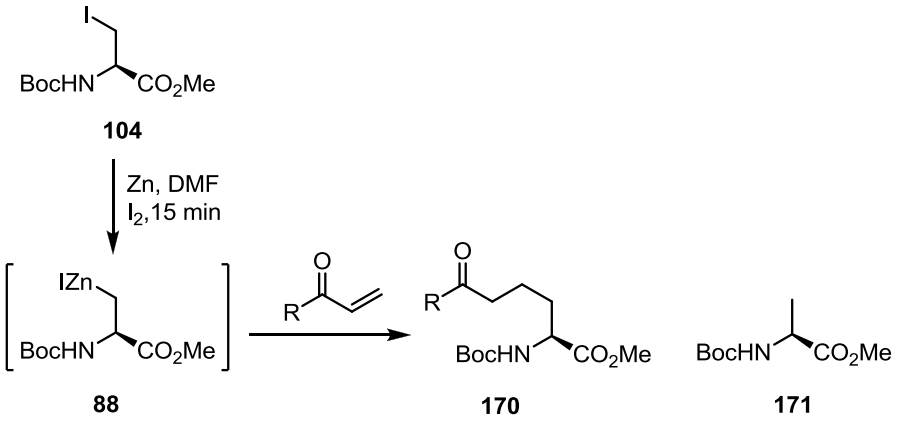
Copper catalyzed conjugate addition of *L*-iodoalanine **104** to methyl vinyl ketone was subjected to optimisation (**Scheme 84** and **table 10**):

Method **A**: using the allylation reaction recipe by addition of enone/TMSCl/DMF mixture to CuBr.DMS/DMF followed by addition of the organozinc reagent **88** derived from *L*-iodoalanine **49** at room temperature/overnight that gave 15% of Michael adduct **170a**, and the organozinc reagent was recovered as a protonated product **171**.

Method **B**: changing the addition order to addition of the organozinc reagent **88** to CuBr.DMS/DMF followed by addition of enone/TMSCl/DMF mixture at room temperature/overnight, increased the yield to 30%.

Method **C**: It is similar to the method **B**, but the addition was achieved in a water bath (5 °C) for 10 min and then the mixture was stirred at room temperature/overnight, which increased the yield to 47%.

Furthermore, some other enones ethyl vinyl ketone and propyl vinyl ketone were targeted to give **170b** and **170c**.



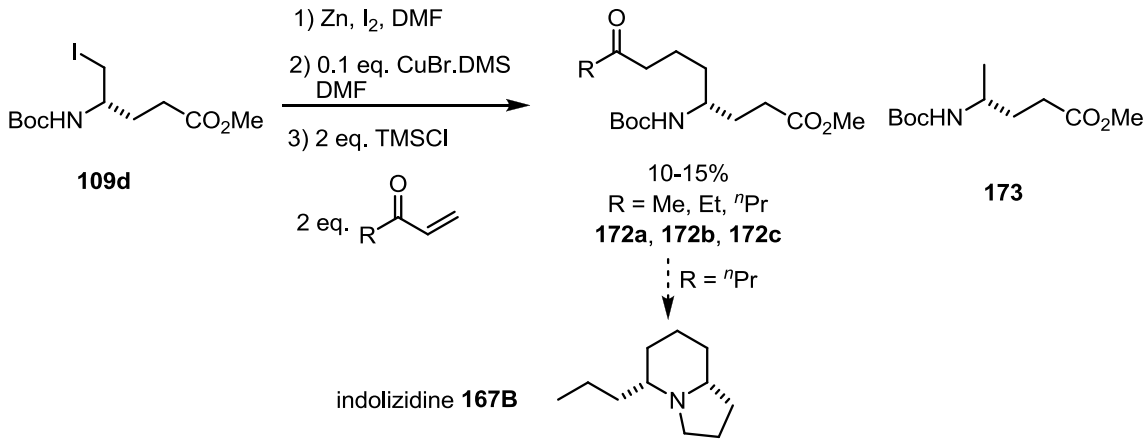
Method **A**: 1) 0.1 eq. CuBr.DMS/DMF 2) 2.0 eq. enone/2.0 eq. TMSCl/DMF 3) RZn**I** rt.
Method **B**: 1) 0.1 eq. CuBr.DMS/DMF 2) RZn**I** 3) 2.0 eq. enone/2.0 eq. TMSCl/DMF rt.
Method **C**: 1) 0.1 eq. CuBr.DMS/DMF 2) RZn**I** 3) 2.0 eq. enone/2.0 eq. TMSCl/DMF in water bath (5 °C).

Scheme 84

Table 10

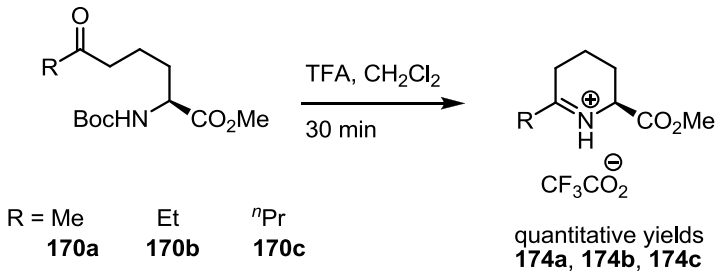
Enone	Method	Michael product	Yield %
Me	**A**	**170a**	15
Me	**B**	**170a**	30
Me	**C**	**170a**	47
Et	**C**	**170b**	45
^{n}Pr	**C**	**170c**	45

Unfortunately, disappointing yields (10-15%) of the desired Michael products **172a**, **172b** and **172c** were obtained by using the organozinc reagent derived from *D*-glutamic acid with the preceding enones. In each case the protonated products were observed **173** (**Scheme 85**). The compound **172c** was suggested to allow a very short synthesis of the alkaloid indolizidine**167B**.



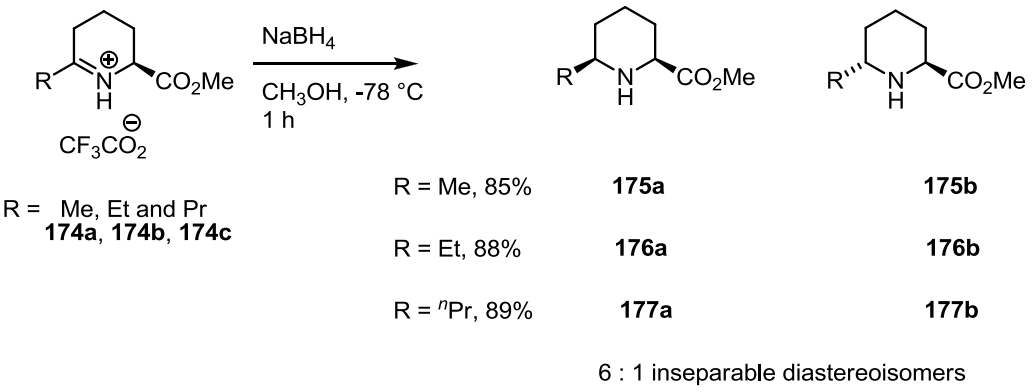
Scheme 85

Boc-deprotection/cyclization of the key intermediates **170a**, **170b** and **170c** was accomplished using TFA to give quantitative yields of the cyclic iminium salts **174a**, **174b** and **174c** (**Scheme 86**).



Scheme 86

At this point, stereoselective reduction of the iminium salts **174a**, **174b** and **174c** was straightforwardly achieved using sodium borohydride in methanol,[114] to give two inseparable diastereoisomers of the 6-substituted pipecolates in excellent yields (85-89%) with diastereoselectivity major : minor (6:1) (**Scheme 87**).



Scheme 87

If it is assumed that the saturated ring adopts a chair conformation. There are two possible conformers for each of the products, **A**, **B** and **C**, **D** (**Figure 56**).

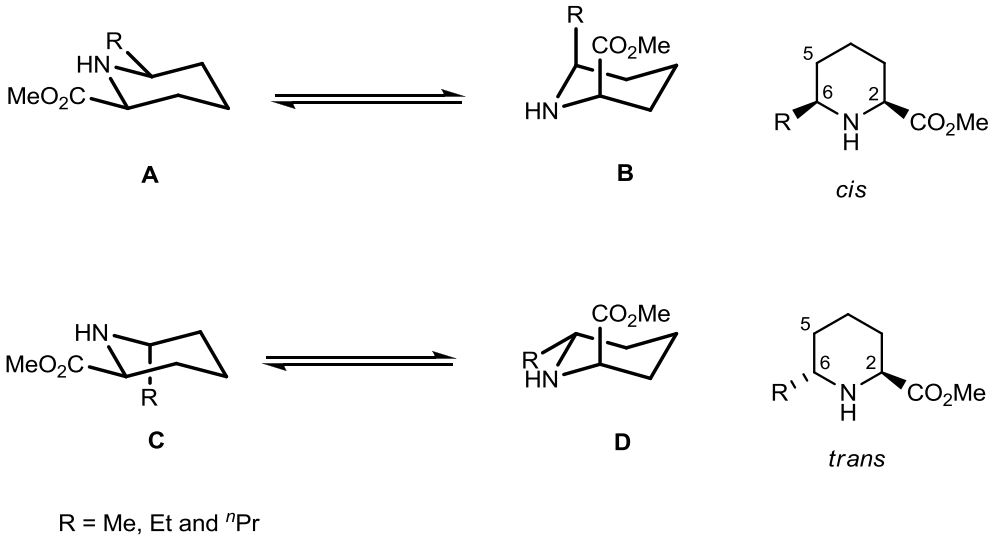


Figure 56

The stereochemical assignments of the major and minor isomers were determined using ^{1}H-NMR spectra. The signals for C-2 (3.38, 3.36 and 3.40 ppm) of the major isomers **175a**, **176a** and **177a** (R = Me, Et and ^{n}Pr respectively) are each a doublet of doublets with a large (11.5 Hz) and a small coupling constant (3.0 Hz) (**Figure 57**). The large values are a result of vicinal coupling with the axial protons at C-3 (diaxial coupling), which

establishes that ester group must be equatorial (**Figure 58**). So, conformers **B** and **D** can be deleted and keeping **A** and **C**.

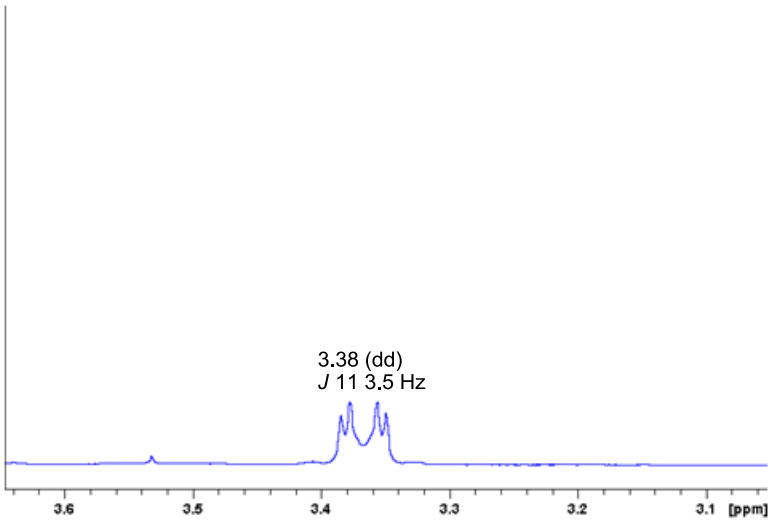


Figure 57

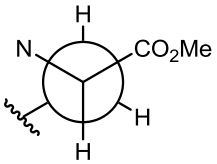


Figure 58

The signal of the major isomer **175a** at C-6 (2.67 ppm) is a doublet of quartets of doublets and exhibits a large (12.0 Hz) a medium (6.5 Hz) and small (2.5 Hz) coupling constants. The large value derives from the proton at C-5 (diaxial coupling), the medium value is a result of the methyl protons at C-6, and the small value arising from the other proton at C-5 (**Figure 59**).

The signal at C-6 (2.41 ppm) of **176a** and **177a** are doublet of triplets of doublets and also reveal a large (11.5 Hz) a medium (6.5 Hz) and a small (2.5 Hz) coupling constant. These values arising from the proton at C-5 (diaxial coupling), the methylene protons at C-6 and the other proton at C-5 respectively (**Figure 60**).

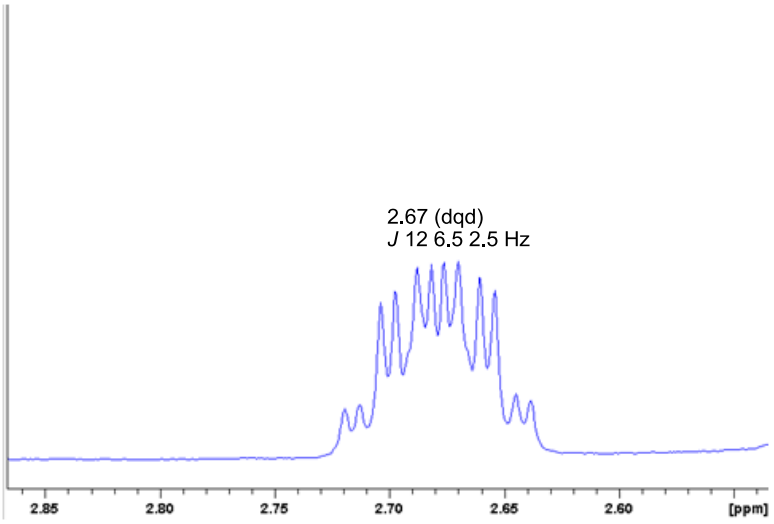


Figure 59

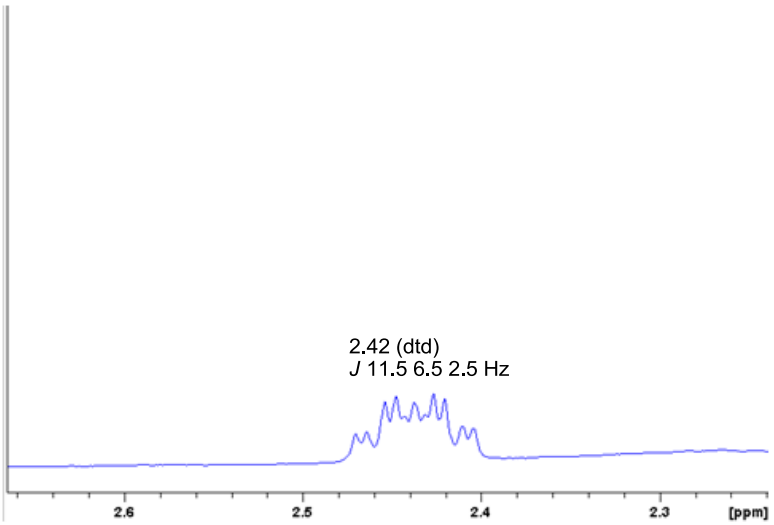


Figure 60

Thus, the proton at C-6 must be at the axial position and the alkyl groups (R = Me, Et and ^{n}Pr) at equatorial (**Figure 61**).

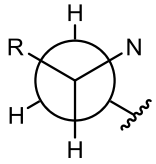


Figure 61

Thus, the *trans*-isomer **C** can be eliminated and suggests that the major isomer exists in the conformer **A** of the *cis*-isomers **175a**, **176a** and **177a** (**Figure 62**).

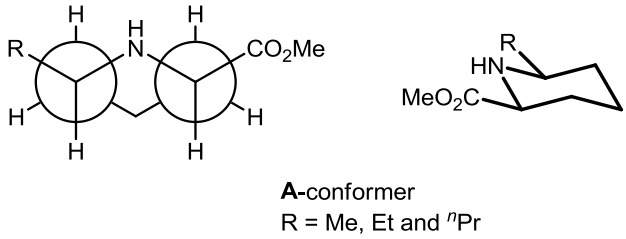


Figure 62

The signal of the minor isomers **175b**, **176b** and **177b** are multiplet coupling of the C-2 (3.75-3.83, 3.87-3.92 and 3.87-3.92 ppm respectively). If we look at the signals arising from the C-6 of the minor isomers **175b**, **177b** and **178b**, multiplet signals have been observed (2.91-3.0, 2.73-2.84 and 2.73-2.84) respectively.

3.3 Conclusion

We have explored the application of our copper(I) mediated conjugate addition methodology to the synthesis of 6-substituted pipecolic acid derivatives.

Copper-catalyzed conjugate addition of organozinc reagent derived from *L*-iodoalanine with a range of enones gave improved yields in comparison with using stoichiometric copper, followed by deprotection/cyclisation/ hydrogenation with diastereomeric ratios of approximately 6:1, in preference of the *cis*-isomer (**Schemes 83**, **85** and **86**).

Chapter: 4 Experimental

4.1 General

All moisture/air sensitive reactions were carried out under a nitrogen atmosphere in oven dried glassware. All reagents used were purchased from commercial sources or prepared and purified accordingly for literature procedure. All solvents used were HPLC grade or distilled. Petroleum ether refers to the fraction which boils in the range 40-60 °C. Dry DMF was distilled from calcium hydride and stored over 4 Å molecular sieves. Solvent evaporation under reduced pressure was performed using a Büchi rotary evaporator. Organic extracts were dried over $MgSO_4$. Purification by column chromatography was performed using silica gel for flash chromatography. Thin layer chromatography was performed using pre-coated plates, and compounds visualised by UV light (254 nm), ninhydrin solution (5% in MeOH).

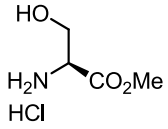
NMR spectra were recorded using Bruker AC 400 or Bruker DRX 500. The coupling constant is given in Hertz and are rounded to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 400 MHz.

Optical rotations were measured on a Perkin Elmer 241 automatic polarimeter at λ 589 nm (Na, D-line) with a path length of 1 dm at the room temperature and concentrations. The concentration is given in g/100ml. Infra-red spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer (**ν**max in cm^{-1}) as solutions (solvent stated in the text).

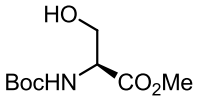
4.2 Starting materials

All starting materials were prepared from commercially available amino acids according to the literature method.

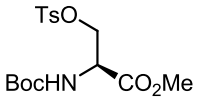
Methyl (2*S*)-2-amino-3-hydroxypropanoate hydrochloride (**101**)[85]



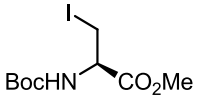
Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-hydroxypropanoate (**102**)[85]



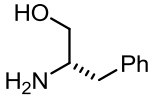
Methyl(2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-[(4methylbenzenesulfonyl) oxy]propanoate (**103**)[86]



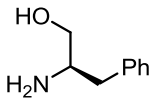
Methyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate (**104**)[86]



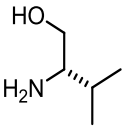
(2*S*)-2-Amino-3-phenylpropan-1-ol (**106a**)[89]



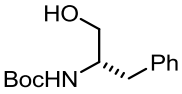
(2*R*)-2-Amino-3-phenylpropan-1-ol (***ent*-106a**)[89]



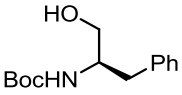
(2*S*)-2-Amino-3-methylbutan-1-ol (**106b**)[90]



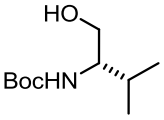
tert-Butyl N-[(2*S*)-1-hydroxy-3-phenylpropan-2-yl]carbamate (**107a**)[87]



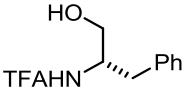
tert-Butyl N-[(2*R*)-1-hydroxy-3-phenylpropan-2-yl]carbamate (***ent*-107a**)[87]



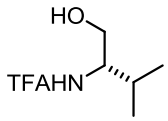
tert-Butyl N-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]carbamate (**107b**)[87]



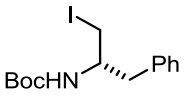
2,2,2-Trifluoro-N-[(2*S*)-1-hydroxy-3-phenylpropan-2-yl]acetamide (**108a**)[91]



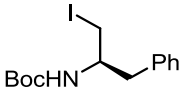
2,2,2-Trifluoro-N-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]acetamide (**108b**)[91]



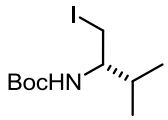
tert-Butyl N-[(2*S*)-1-iodo-3-phenylpropan-2-yl]carbamate (**109a**)[87]



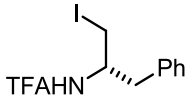
tert-Butyl N-[(2*R*)-1-iodo-3-phenylpropan-2-yl]carbamate (***ent*-109a**)[87]



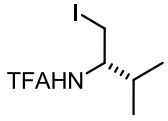
tert-Butyl N-[(2*S*)-1-iodo-3-methylbutan-2-yl]carbamate (**109b**)[87]



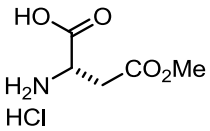
2,2,2-Trifluoro-N-[(2*S*)-1-iodo-3-phenylpropan-2-yl]acetamide (**110a**)[115]



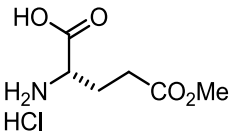
2,2,2-Trifluoro-N-[(2*S*)-1-iodo-3-methylbutan-2-yl]acetamide (**110b**)[115]



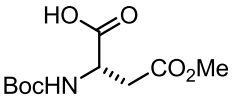
(2*S*)-2-Amino-4-methoxy-4-oxobutanoic acid hydrochloride (**112a**)[93]



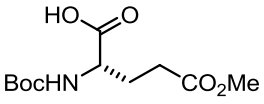
(2*S*)-2-Amino-5-methoxy-5-oxopentanoic acid hydrochloride (**112b**)[93]



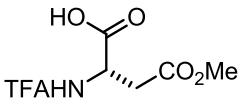
(2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-methoxy-4-oxobutanoic acid (**113a**)[96,116]



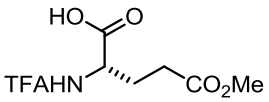
(2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-5-methoxy-5-oxopentanoic acid (**113b**)[116]



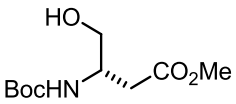
(2*S*)-4-Methoxy-4-oxo-2-(trifluoroacetamido)butanoic acid (**115a**)[67]



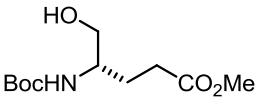
(2*S*)-5-Methoxy-5-oxo-2-(trifluoroacetamido)pentanoic acid (**115b**)[67]



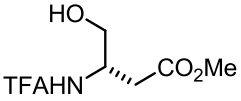
Methyl (3*S*)-3-{[(*tert*-butoxy)carbonyl]amino}-4-hydroxybutanoate (**107c**)[96]



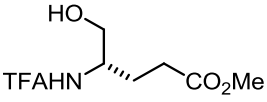
Methyl (4*S*)-4-{[(*tert*-butoxy)carbonyl]amino}-5-hydroxypentanoate (**107d**)[116]



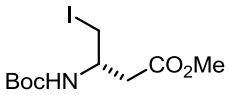
Methyl (3*S*)-4-hydroxy-3-(trifluoroacetamido)butanoate (**108c**)[67]



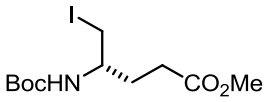
Methyl (4*S*)-5-hydroxy-4-(trifluoroacetamido)pentanoate (**108d**)[67]



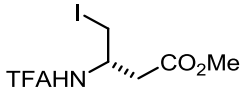
Methyl (3*S*)-3-{[(*tert*-butoxy)carbonyl]amino}-4-iodobutanoate (**109c**)[87]



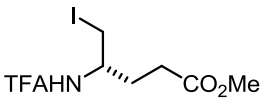
Methyl (4S)-4-{[(tert-butoxy)carbonyl]amino}-5-iodopentanoate (**109d**)[87]



Methyl (3*S*)-4-iodo-3-(trifluoroacetamido)butanoate (**110c**)[87]



Methyl (4*S*)-5-iodo-4-(trifluoroacetamido)pentanoate (**110d**)[87]



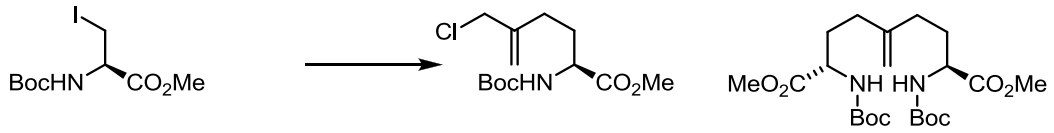
4.3 General Procedure A: Allylation reactions

A two-necked round bottomed flask, fitted with a three-way tap and rubber septum, was flame-dried, evacuated and backfilled with nitrogen three times. The flask was charged with a magnetic follower and zinc powder (2.0 mmol), and again evacuated and backfilled with nitrogen three times, with continuous stirring. Dry DMF (1 mL) was added *via* syringe, and the heterogeneous mixture stirred vigorously. Iodine (0.25 mmol) 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 min, until the solvent had become coluorless. The alkyl iodide (1.0 mmol) 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 min, before cessation of stirring. The solid zinc dust was allowed to settle before transferring the solution containing the zinc reagent into a new reaction vessel *via* syringe.

During the activation period, a separate two-necked round bottomed flask fitted with a three-way tap was flame-dried under vacuum, and backfilled with nitrogen three times. This flask was charged with a magnetic follower and CuBr.DMS (0.1 eq), and gently heated under vacuum until the CuBr.DMS changed appearance from a brown to light green powder. The flask was allowed to cool, before adding dry DMF (0.6 mL) and *3*-chloro-*2*-(chloromethyl)prop-1-ene (4.0 eq) *via* a syringe. The mixture was stirred at room temperature, at which point the organozinc reagent was added dropwise *via* syringe, and was stirred at room temperature for 3 h. The

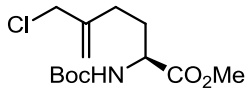
reaction mixture was transferred to a separatory funnel with (10 mL) ethyl acetate, and washed with a (5 mL) saturated sodium thiosulfate solution, (5 mL) water and (5 mL) brine. The organic layer was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica, using ethyl acetate in petroleum ether.

Reaction of methyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3 iodopropanoate (**104**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)



This reaction was done according to the general procedure **A** using (2.63 g, 8 mmol) of **104** to give ***ent*-94** (1.39 g, 60%) as a colourless oil and ***ent*-95** (539 mg, 15%) as a colourless oil.

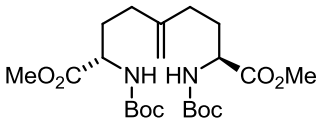
Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-5-(chloromethyl)hex-5-enoate (***ent*-94**)



R_f 0.25 (10% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 3356, 1740, 1702, 1502; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.42 (9 H, s, C($\mathbf{CH_3}$)$_3$), 1.71-1.79 (1 H, m, C$\mathbf{H_A}$CH$_B$), 1.96-2.10 (1 H, m, CH$_A$C$\mathbf{H_B}$), 2.22 (2 H, t, *J* 7.5 Hz, C$\mathbf{H_2}$C=CH$_2$), 3.73 (3 H, s, OC$\mathbf{H_3}$), 4.02 (2 H, s, C$\mathbf{H_2}$Cl), 4.30-4.36 (1 H, m, C**H**N), 4.97 (1 H, s, C$\mathbf{H_A}$CH$_B$=C), 5.1-5.21 (1 H, m, N**H**), 5.15 (1 H, s, CH$_A$C$\mathbf{H_B}$=C); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.2, 28.6, 30.5, 48.1, 52.3, 52.9, 80.1, 115.2, 143.7, 155.6 173.0; Found MH^+ 292.1323

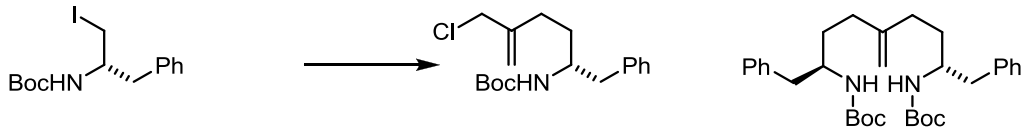
$C_{13}H_{23}NO_4{}^{35}Cl$ requires MH^+ 292.1316; $[\alpha]_D^{22}$ +20.5 (*c* 1.46 $CHCl_3$) (lit.[48] +20.5 (*c* 1.46 $CHCl_3$)).

1,9-Dimethyl(2*S*,8*S*)-2,8-*bis*({[(*tert*-butoxy)carbonyl]amino})-5-methyl idenenonanedioate (***ent*-95**)



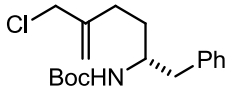
R_f 0.3 (20% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 2977, 1744, 1697, 1507; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.43 (18 H, s, 2C(C**H$_3$**)$_3$), 1.70-1.79 (2 H, m, 2C**H$_2$**), 1.91-1.99 (2 H, m, 2C**H$_2$**), 2.0-2.09 (4 H, m, 2C**H$_2$**C=CH_2), 3.73 (6 H, s, 2OC**H$_3$**), 4.27-4.34 (2 H, m, 2C**H**), 4.77 (2 H, s, C**H$_2$**=C), 4.96-5.09 (2 H, m, 2N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 27.3, 29.8, 30.6, 51.2, 52.1, 78.9, 109.5, 145.5, 154.5, 172.3; Found MH^+ 459.2689 $C_{22}H_{39}N_2O_8$ requires MH^+ 459.2706; $[\alpha]_D^{22}$ +24.9 (*c* 6.24 $CHCl_3$) (lit.[48] +24.1 (*c* 6.23, $CHCl_3$)).

Reaction of methyl *tert*-butyl N-[(2*S*)-1-iodo-3-phenylpropan-2-yl] carbamate (**109a**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)



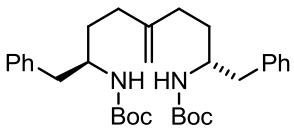
This reaction was done according to the general procedure **A** using (2.52 g, 7 mmol) of **109a** to give **117a** (1.56 g, 69%) as a white solid and **118a** (365 mg, 10%) as a white solid.

tert-Butyl N-[(2*R*)-5-(chloromethyl)-1-phenylhex-5-en-2-yl]carbamate (**117a**)



R_f 0.35 (10% ethyl acetate in petroleum ether); mp 62-63 °C; $\mathbf{\nu_{max}/cm^{-1}}$: 3299, 1695, 1603, 1556, 1158; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.42 (9 H, s, C(C$\mathbf{H_3}$)$_3$), 1.45-1.53 (1 H, m, C$\mathbf{H_A}$H$_B$CH$_2$C=CH$_2$), 1.68-1.75 (1 H, m, CH$_A$$\mathbf{H_B}CH_2$C=CH$_2$), 2.18-2.26 (1 H, m, C$\mathbf{H_A}H_B$C=CH$_2$), 2.27-2.32 (1 H, m, CH$_A$$\mathbf{H_B}$C=CH$_2$), 2.76-2.83 (2 H, m, C$\mathbf{H_2}$Ph), 3.80-3.89 (1 H, m, C**H**N), 3.99 (1 H, d *J* 12.0 Hz, C$\mathbf{H_A}$H$_B$Cl), 4.05 (1 H, d *J* 12.0 Hz, CH$_A$$\mathbf{H_B}$Cl), 4.35 (1 H, d *J* 8.0 Hz, N**H**), 4.94 (1 H, d *J* 1.0 Hz, C=C$\mathbf{H_A}$H$_B$), 5.13 (1 H, br, s, C=CH$_A$$\mathbf{H_B}$), 7.27 (5 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.3, 29.4, 31.9, 41.3, 48.2, 51.1, 79.2, 114.8, 126.3, 128.3, 129.4, 138.0, 144.4, 155.6; Found MH^+ 324.1743 $C_{18}H_{27}NO_2{}^{35}Cl$ requires MH^+ 324.1730; $[\alpha]_D^{22}$ +5 (*c* 1 in $CHCl_3$).

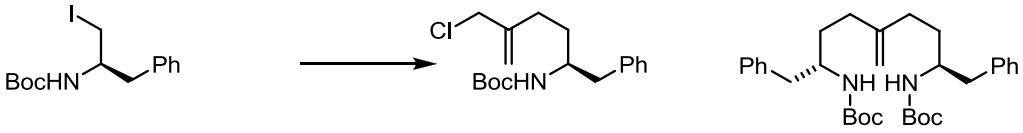
tert-Butyl N-[(2*R*,8*R*)-8-{[(*tert*-butoxy)carbonyl]amino}-5-methylidene 1,9-diphenylnonan-2-yl]carbamate (**118a**)



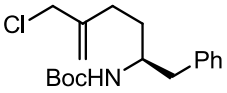
R_f 0.3 (20% ethyl acetate in petroleum ether); mp 138-140 °C; $\mathbf{\nu_{max}/cm^{-1}}$: 3294, 1695, 1610, 1556, 1152; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.42 (18 H, s, 2C(C$\mathbf{H_3}$)$_3$), 1.54-1.62 (4 H, m, 2C$\mathbf{H_2}$CH$_2$C=CH$_2$), 1.98-2.16 (4 H, m, 2C$\mathbf{H_2}$C=CH$_2$), 2.72-2.79 (4 H, m, 2C$\mathbf{H_2}$Ph), 3.77-3.88 (2 H, br, 2C**H**N), 4.34 (2 H, d *J* 8.5 Hz, 2N**H**), 4.69 (2 H, s, C=C$\mathbf{H_2}$), 7.25 (10 H, m, 2Ph);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.4, 32.2, 32.4, 41.4, 51.3, 79.0, 109.7, 126.3, 128.3, 129.5, 138.2, 148.2, 155.9; Found MH^+ 523.3536 $C_{32}H_{47}N_2O_4$ requires MH^+ 523.3536; $[\alpha]_D^{22}$ +7 (*c* 1 in $CHCl_3$).

Reaction of methyl *tert*-butyl N-[(2*R*)-1-iodo-3-phenylpropan-2-yl] carbamate (***ent*-109a**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)

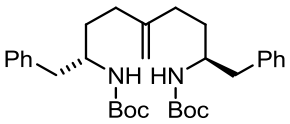


tert-Butyl N-[(2*S*)-5-(chloromethyl)-1-phenylhex-5-en-2-yl]carbamate (***ent*-117a**)



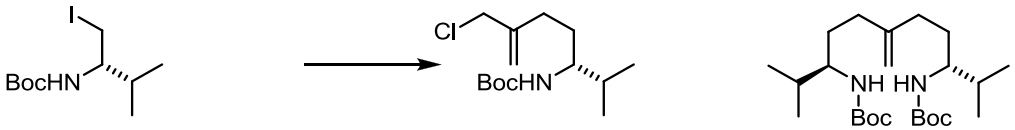
$[\alpha]_D^{22}$ -5 (*c* 1 in $CHCl_3$).

tert-Butyl N-[(2*S*,8*S*)-8-{[(*tert*-butoxy)carbonyl]amino}-5-methylidene 1,9-diphenylnonan-2-yl]carbamate (***ent*-118a**)



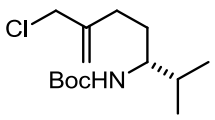
$[\alpha]_D^{22}$ -7 (*c* 1 in $CHCl_3$).

Reaction of *tert*-butyl N-[(2*S*)-1-iodo-3-methylbutan-2-yl]carbamate (**109b**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)



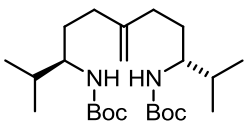
This reaction was done according to the general procedure **A** using (1.28 g, 4 mmol) of **109b** to give **117b** (616 mg, 59%) as a white solid and **118b** (114 mg, 13%) as a white solid.

tert-Butyl N-[(3*R*)-6-(chloromethyl)-2-methylhept-6-en-3-yl]carbamate (**117b**)



R_f 0.41 (5% ethyl acetate in petroleum ether); mp 44-45 °C; $\mathbf{\nu_{max}/cm^{-1}}$: 3300, 1676, 1535, 1171; $^{\mathbf{1}}$**H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.87 (3 H, d *J* 6.5 Hz, CHC$\mathbf{H_3}$CH$_3$), 0.91 (3 H, d *J* 6.5 Hz, CHCH$_3$C$\mathbf{H_3}$), 1.39-1.62 (1 H , m, C**H(**CH$_3$)$_2$)1.43 (9 H, s, C(C$\mathbf{H_3}$)$_3$), 1.62-1.72 (2 H, m, C$\mathbf{H_2}$C=CH$_2$), 2.12-2.19 (1 H, m, C$\mathbf{H_A}$H$_B$CHN), 2.21-2.28 (1 H, m, CH$_A$$\mathbf{H_B}$CHN), 3.40-3.47 (1 H, m, C**H**N), 4.03 (2 H, s, C$\mathbf{H_2}$Cl), 4.95 (1 H, d *J* 1.5 Hz, C=C$\mathbf{H_A}$H$_B$), 5.13 (1 H, br, s, C=CH$_A$$\mathbf{H_B}$); $^{\mathbf{13}}$**C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.5, 19.1, 28.4, 29.7, 30.5, 32.1, 48.4, 55.1, 78.9, 114.6, 144.8, 155.9; Found MH^+ 276.1737 $C_{14}H_{27}{}^{35}ClNO_2$ requires MH^+ 276.1730; $[\alpha]_D{}^{22}$ -5 (*c* 1 in $CHCl_3$).

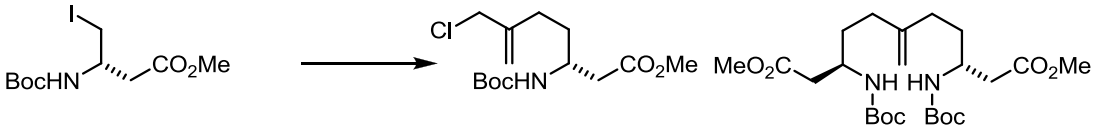
tert-Butyl N-[(3*R*,9*R*)-9-{[(*tert*-butoxy)carbonyl]amino}-2,10-dimethyl-6-methylideneundecan-3-yl]carbamate (**118b**)



R_f 0.4 (10% ethyl acetate in petroleum ether); mp 91-92 °C; $\mathbf{\nu_{max}/cm^{-1}}$: 2958, 1683, 1510, 1165; $^{\mathbf{1}}$**H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.86 (6 H, d *J*

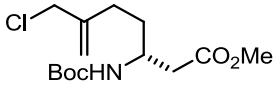
7.0 Hz, 2CHC**H$_3$**CH$_3$), 0.89 (6 H, d *J* 7.0 Hz, 2CHCH$_3$C**H$_3$**), 1.38-1.59 (2 H, m, 2C**H**(CH$_3$)$_2$), 1.43 (18 H, s, 2C(C**H$_3$**)$_3$), 1.57-1.62 (2 H, m, 2C**H$_A$**H$_B$C=CH$_2$), 1.68-1.75 (2 H, m, 2CH$_A$**H$_B$**C=CH$_2$), 1.99-2.11 (4 H, m, 2C**H$_2$**CHN), 3.40-2.49 (2 H, m, 2C**H**N), 4.30 (2 H, d, *J* 10.0 Hz, 2N**H**), 4.72 (2 H, s, C=C**H$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.6, 19.1, 28.4, 30.8, 32.2, 32.8, 55.4, 78.0, 109.0, 149.0, 156.3; Found MH^+ 427.3517 $C_{24}H_{47}N_2O_4$ requires MH^+ 427.3536; $[\alpha]_D^{22}$ -6 (*c* 1 in $CHCl_3$).

Reaction of methyl (3*S*)-3-{[(*tert*-butoxy)carbonyl]amino}-4-iodobutanoate (**109c**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)



This reaction was done according to the general procedure **A** using (1.37 g, 4 mmol) of **109c** to give **117c** (786 mg, 60%) as a colourless oil and **118c** (194 mg, 10%) as a white solid.

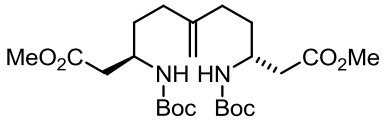
Methyl (3*R*)-3-{[(*tert*-butoxy)carbonyl]amino}-6-(chloromethyl)hept-6-enoate (**117c**)



R_f 0.34 (20% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 2977, 1736, 1690, 1505; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.42 (9 H, s, C(C**H$_3$**)$_3$), 1.68 (2 H, q *J* 7.5 Hz, C**H$_2$**CHN), 2.20-2.25 (2 H, m, C**H$_2$**C=CH$_2$), 2.51-2.57 (2 H, m, C**H$_2$**CO$_2$CH$_3$), 3.68 (3 H, s, CO$_2$C**H$_3$**), 3.88-3.92 (1 H, m, C**H**N), 4.03 (2 H, s, C**H$_2$**Cl), 4.96 (1 H, s, C=C**H$_A$**H$_B$), 4.93-5.1 (1 H, br, N**H**), 5.14

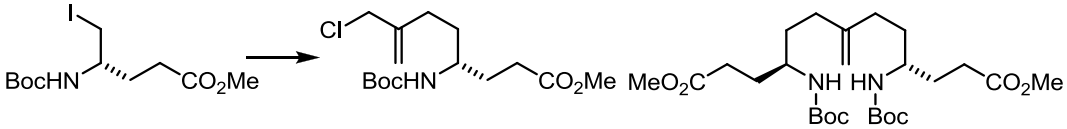
(1 H, s, C=CH_A**H_B**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.3, 29.5, 32.2, 39.0, 47.0, 48.2, 51.7, 79.5, 114.9, 144.1, 155.3, 172.0; Found MH^+ 306.1457 $C_{14}H_{25}{}^{35}ClNO_4$ requires MH^+ 306.1472; $[\alpha]_D{}^{20}$ +13.0 (*c* 1 in $CHCl_3$).

1,11-Dimethyl (3*R*,9*R*)-3,9-*bis*({[(*tert*-butoxy)carbonyl]amino})-6-methylideneundecanedioate (**118c**)



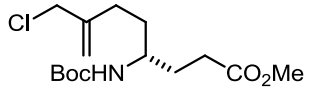
R_f 0.27 (20% ethyl acetate in petroleum ether); mp 54-55 °C; **ν_{max}/cm^{-1}**: 3332, 1737, 1707, 1681; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.42 (18 H, s, 2C(C**H_3**)**$_3$**), 1.59-1.65 (4 H, m, 2C**H_2**CHN), 2.0-2.17 (4 H, m, 2C**H_2**C=CH_2), 2.49-2.55 (4 H, m, 2C**H_2**CO_2CH_3), 3.67 (6 H, s, 2CO_2C**H_3**), 3.83-3.89 (2 H, m, 2C**H**N), 4.73 (2 H, s, C=C**H_2**), 4.96 (2 H, d *J* 9.0 Hz, 2N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.3, 32.4, 32.5, 39.1, 47.3, 51.6, 79.3, 109.9, 147.5, 155.3, 172.1; Found MH^+ 487.3018 $C_{24}H_{43}N_2O_8$ requires MH^+ 487.3019; $[\alpha]_D{}^{20}$ +15.0 (*c* 1 in $CHCl_3$).

Reaction of methyl (4S)-4-{[(tert-butoxy)carbonyl]amino}-5-iodopentanoate (**109d**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)



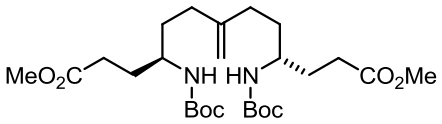
This reaction was done according to the general procedure **A** using (1.42 g, 4 mmol) of **109d** to give **117d** (764 mg, 60%) as a colourless oil and **118d** (266 mg, 13%) as a white solid.

Methyl (4*R*)-4-{[(*tert*-butoxy)carbonyl]amino}-7-(chloromethyl)oct-7-enoate (**117d**)



R_f 0.41 (10% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2948, 1735, 1686, 1518, 1164; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.45 (9 H, s, C(C**H$_3$**)$_3$), 1.58-1.65 (1 H, m, C**H$_A$**H$_B$CH$_2$CO$_2$CH$_3$), 1.68-1.73 (2 H, m, C**H$_2$**CHN), 1.87-1.95 (1 H, m, CH$_A$**H$_B$**CH$_2$CO$_2$CH$_3$), 2.18-2.25 (2 H, m, C**H$_2$**C=CH$_2$), 2.38 (2 H, t *J* 7.5 Hz, C**H$_2$**CO$_2$CH$_3$), 3.55-3.61 (1 H, m, C**H**N), 3.67 (3 H, s, CO$_2$C**H$_3$**), 4.03 (2 H, s, C**H$_2$**Cl), 4.31 (1 H, d *J* 9.0 Hz, N**H**) 4.96 (1 H, d *J* 1.0 Hz, C=C**H$_A$**H$_B$), 5.13 (1 H, br, s, C=CH$_A$**H$_B$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.3, 29.3, 30.4, 30.8, 33.6, 48.3, 50.0, 51.7, 79.2, 114.8, 144.4, 155.6, 174.0; Found MH^+ 320.1618 $C_{15}H_{27}{}^{35}ClNO_4$ requires MH^+ 320.1629; $[\alpha]_D{}^{22}$ -11 (*c* 1 in $CHCl_3$).

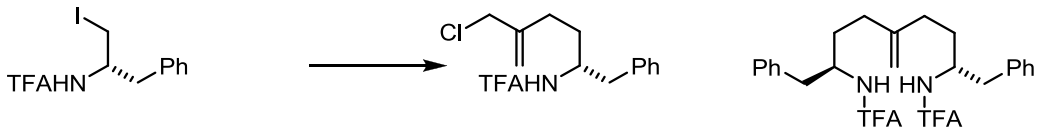
1,13-Dimethyl (4*R*,10*R*)-4,10-*bis*({[(*tert*-butoxy)carbonyl]amino})-7-methylidenetridecanedioate (**118d**)



R_f 0.28 (20% ethyl acetate in petroleum ether); mp 76-77 °C; $\mathbf{\nu_{max}/cm^{-1}}$: 2940, 1778, 1731, 1682, 1644, 1162; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.45 (18 H, s, 2C(C**H$_3$**)$_3$), 1.56-1.63 (2 H, m, 2C**H$_A$**H$_B$CH$_2$CO$_2$CH$_3$), 1.66-1.73 (4 H, m, 2C**H$_2$**CHN), 1.87-1.94 (2 H, m, 2CH$_A$**H$_B$**CH$_2$CO$_2$CH$_3$), 2.04 (4 H, t *J* 7.5 Hz, 2C**H$_2$**C=CH$_2$), 2.38 (4 H, t *J* 7.5 Hz, 2C**H$_2$**CO$_2$CH$_3$), 3.52-3.59

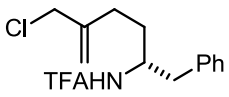
(2 H, m, 2C**H**N), 3.67 (6 H, s, 2CO_2C**H_3**), 4.31 (2 H, d *J* 9.5 Hz, 2N**H**), 4.72 (2 H, s, C=C**H_2**), **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.4, 30.6, 30.8, 32.3, 33.9, 50.2, 51.6, 77.3, 109.5, 148.5, 157.0, 174.5; Found MH^+ 515.3324 $C_{26}H_{47}N_2O_8$ requires MH^+ 515.3332; $[\alpha]_D^{22}$ -10 (*c* 1 in $CHCl_3$).

Reaction of 2,2,2-trifluoro-N-[(2*S*)-1-iodo-3-phenylpropan-2-yl]acetamide (**110a**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)



This reaction was done according to the general procedure **A** using (2.48 g, 7 mmol) of **110a** to give **120a** (1.32 g, 60%) as a white solid and **121a** (213 mg, 12%) as a white solid.

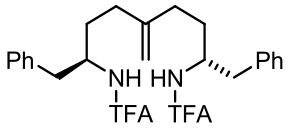
N-[(2*R*)-5-(Chloromethyl)-1-phenylhex-5-en-2-yl]-2,2,2-trifluoroacetamide (**120a**)



R_f 0.33 (10% ethyl acetate in petroleum ether); mp 58-59 °C; **ν_{max}/cm^{-1}**: 3296, 1694, 1644, 1555, 1161; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.64-1.69 (1 H, m, C**H_A**H_BCHN), 1.80-1.87 (1 H, m, CH_A**H_B**CHN), 2.21-2.29 (2 H, m, C**H_2**C=CH_2), 2.88-2.95 (2 H, m, C**H_2**Ph), 4.0 (1 H, d *J* 12.0 Hz, C**H_A**H_BCl), 4.05 (1 H, d *J* 12.0 Hz, CH_A**H_B**Cl), 4.20-4.29 (1 H, m, C**H**N), 4.97 (1 H, s, C=C**H_A**H_B), 5.18 (1 H, s, C=CH_A**H_B**), 6.13 (1 H, d *J* 8.0 Hz, N**H**), 7.25-7.34 (5 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 29.3,

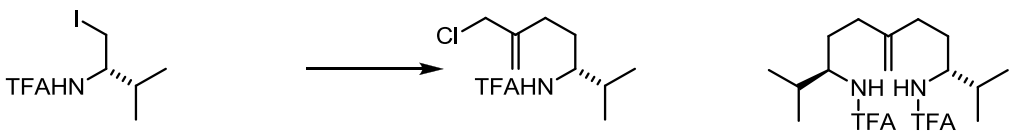
31.1, 40.2, 48.0, 50.9, 115.5, 115.8 (q *J* 293 Hz), 127.0, 128.6, 129.2, 136.3, 147.2, 157.2 (q *J* 38.0 Hz); Found MH^+ 320.1014 $C_{15}H_{18}NOF_3{}^{35}Cl$ requires MH^+ 320.1029; $[\alpha]_D{}^{22}$ +11 (*c* 1 in $CHCl_3$).

2,2,2-Trifluoro-N-[(2*R*,8*R*)-5-methylidene-1,9-diphenyl-8-(trifluoroacetamido)nonan-2-yl]acetamide (**121a**)



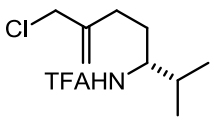
R_f 0.26 (10% ethyl acetate in petroleum ether); mp 153-155 °C; **ν_{max}/cm^{-1}**: 3298, 1696, 1455; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.52-1.67 (2 H, m, 2C**H_A**H_BCHN), 1.68-1.79 (2 H, m, 2CH_A**H_B**CHN), 2.05 (4 H, t *J* 7.5 Hz, 2C**H_2**C=CH_2), 2.83 (2 H, dd *J* 14.0 and 6.5 Hz, 2C**H_A**H_BPh), 2.90 (2 H, dd *J* 14.0 and 6.5 Hz, 2CH_A**H_B**Ph), 4.11-4.22 (2 H, m, 2C**H**N), 4.78 (2 H, s, C**H_2**=C), 6.15 (2 H, d *J* 9.0 Hz, 2N**H**), 7.14-7.20 (4 H, m, Ph), 7.24-7.37 (6 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 31.2, 31.9, 40.2, 50.8, 111.0, 115.8 (q *J* 290 Hz), 127.1, 128.7, 129.2, 136.5, 146.5, 157.2 (q *J* 38.0 Hz); Found MH^+ 515.2109. $C_{26}H_{29}N_2O_2F_6$ requires MH^+ 515.2133.; $[\alpha]_D{}^{22}$ +90 (*c* 1 in $CHCl_3$).

Reaction of 2,2,2-trifluoro-N-[(2*S*)-1-iodo-3-methylbutan-2-yl]acetamide (**110b**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)



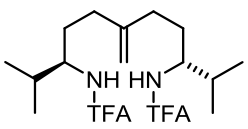
This reaction was done according to the general procedure **A** using (1.23 g, 4 mmol) of **110b** to give **120b** (647 mg, 60%) as a colourless oil and **121b** (100 mg, 12%) as a white solid.

N-[(3*R*)-6-(Chloromethyl)-2-methylhept-6-en-3-yl]-2,2,2-trifluoroacetamide (**120b**)



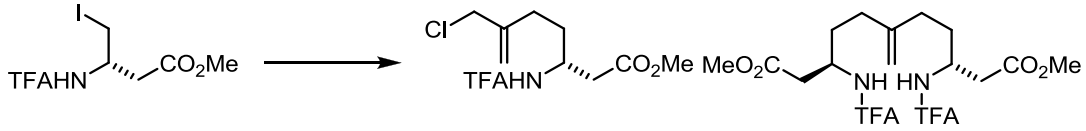
R_f 0.50 (5% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 3302, 1697, 1555, 1155; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.92 (3 H, d *J* 6.5 Hz, CHC**H$_3$**CH$_3$), 0.95 (3 H, d *J* 6.5 Hz, CHCH$_3$C**H$_3$**), 1.52-1.58 (1 H, m, C**H$_A$**H$_B$CHN), 1.75-1.81 (1 H, m, CH$_A$**H$_B$**CHN), 1.81-1.87 (1 H, m, C**H**(CH$_3$)$_2$), 2.18-2.25 (2 H, m, C**H$_2$**C=CH$_2$), 3.82-3.88 (1 H, m,C**H**N), 4.03 (2 H, s, C**H$_2$**Cl), 4.97 (1 H, d *J* 1.0 Hz, C=C**H$_A$**H$_B$), 5.16 (1 H, d *J* 1.0 Hz, C=CH$_A$**H$_B$**), 5.98 (1 H, d *J* 8.0 Hz, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.4, 19.1, 29.4, 29.7, 31.6, 48.1, 55.0, 115.3, 115.8 (q *J* 293 Hz), 143.8, 157.2 (q *J* 38.0 Hz); Found MH^+ 272.1019. $C_{11}H_{17}{}^{35}ClF_3NO$ requires MH^+ 272.1029; $[\alpha]_D^{22}$ -20 (*c* 1 in $CHCl_3$).

N-[(3*R*,9*R*)-2,10-Dimethyl-6-methylidene-9-(trifluoroacetamido)undecan-3-yl]-2,2,2-trifluoroacetamide (**121b**)



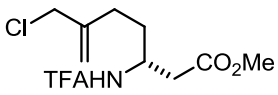
R_f 0.20 (5 % ethyl acetate in petroleum ether); mp 160-162 °C; $\mathbf{\nu_{max}/cm^{-1}}$: 3299, 1717, 1697.1556; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.91 (6 H, d *J* 6.5 Hz, 2CHC**H$_3$**CH_3), 0.94 (6 H, d *J* 6.5 Hz, 2CHCH_3C**H$_3$**), 1.48-1.55 (2 H, m, 2C**H$_A$**H_BCHN), 1.70-1.77 (2 H, m, 2CH_A**H$_B$**CHN), 1.81-1.88 (2 H, m, 2C**H**$(CH_3)_2$), 2.01 (4 H, t *J* 7.5 Hz, 2C**H$_2$**C=CH_2), 3.78-3.84 (2 H, m, 2C**H**N), 4.78 (2 H, s, C=C**H$_2$**), 6.07 (2 H, d *J* 9.5 Hz, 2N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.4, 19.1, 29.7, 31.6, 31.7, 55.0, 110.5, 115.3 (q *J* 294 Hz), 143.8, 157.2 (q *J* 39.0 Hz); Found MH^+ 419.2123. $C_{18}H_{29}F_6N_2O_2$ requires MH^+ 419.2133; $[\alpha]_D^{22}$ -26 (*c* 1 in $CHCl_3$).

Reaction of methyl (3*S*)-4-iodo-3-(trifluoroacetamido)butanoate (**110c**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)



This reaction was done according to the general procedure **A** using (1.35 g, 4 mmol) of **110c** to give **120c** (678 mg, 57%) as a colourless oil and **121c** (115 mg, 12%) as a white solid.

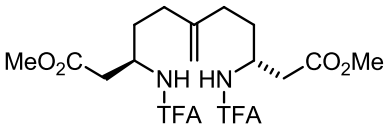
Methyl (3*R*)-6-(chloromethyl)-3-(trifluoroacetamido)hept-6-enoate (**120c**)



R_f 0.60 (30% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2931, 1702, 1555, 1438, 1154; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.77-1.82 (1 H, m, C**H$_A$**H_BCHN), 1.86-1.93 (1 H, m, CH_A**H$_B$**CHN), 2.18 (1 H, br d *J* 8.0 Hz, C**H$_A$**$H_B$$CO_2CH_3$), 2.28 (1 H, br d *J* 8.0 Hz, CH_A**H$_B$**CO_2CH_3), 2.65 (2 H, d *J*

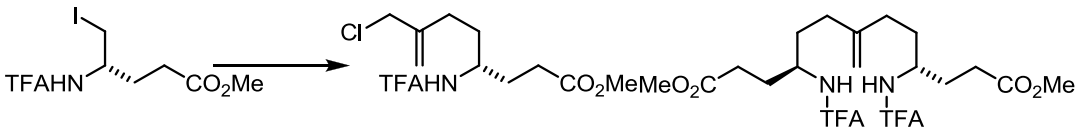
4.5 Hz, C**H$_2$**C=CH$_2$), 3.72 (3 H, s, CO$_2$C**H$_3$**), 4.03 (2 H, s, C**H$_2$**Cl), 4.26 (1 H, m, C**H**N), 4.98 (1 H, d *J* 1.0 Hz, C=C**H$_A$**H$_B$), 5.17 (1 H, br, s, C=CH$_A$**H$_B$**), 7.24-7.31 (1 H, br, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 29.3, 31.1, 37.1, 46.4, 48.0, 52.0, 115.5, 116.0 (q *J* 289 Hz) 143.3, 156.8 (q *J* 38.0 Hz), 171.8; Found MH^+ 302.0776 $C_{11}H_{16}{}^{35}ClF_3NO_3$ requires MH^+ 302.0771; $[\alpha]_D^{20}$ -1.0 (*c* 1 in $CHCl_3$).

1,11-Dimethyl(3*R*,9*R*)-6-methylidene-3,9-*bis*(trifluoroacetamido) undecanedioate (**121c**)



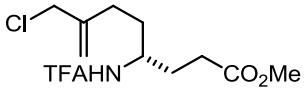
R_f 0.33 (30% ethyl acetate in petroleum ether); mp 85-86 °C; **ν_{max}/cm^{-1}**: 2927, 1728, 1699, 1647, 1557, 1146; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.66-1.73 (2 H, m, 2 C**H$_A$**H$_B$CHN), 1.75-1.84 (2 H, m, 2 CH$_A$**H$_B$**CHN), 2.05 (4 H, t *J* 7.5, 2C**H$_2$**CO$_2$CH$_3$), 2.60 (4 H, br, d *J* 5.0, 2C**H$_2$**C=CH$_2$), 3.72 (6 H, s, 2 CO$_2$C**H$_3$**), 4.13-4.21 (2 H, m, 2C**H**N), 4.85 (2 H, s, C=C**H$_2$**), 7.31 (2 H, d *J* 9.0 Hz, 2N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 31.2, 32.0, 37.1, 46.5, 52.0, 111.0, 115.9 (q, *J* 291 Hz), 145.8, 156.8 (q, *J* 38 Hz), 171.8; Found MH^+ 479.1610 $C_{18}H_{25}F_6N_2O_6$ requires MH^+ 479.1617; $[\alpha]_D^{22}$ -4.0 (*c* 1 in $CHCl_3$).

Reaction of methyl (4*S*)-5-iodo-4-(trifluoroacetamido)pentanoate (**110d**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)



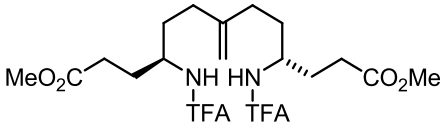
This reaction was done according to the general procedure **A** using (1.40 g, 4 mmol) of **110d** to give **120d** (694 mg, 55%) as a colourless oil and **121d** (212 mg, 21%) as a white solid.

Methyl (4*R*)-7-(chloromethyl)-4-(trifluoroacetamido)oct-7-enoate (**120d**)



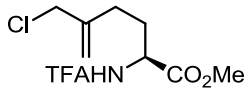
R_f 0.4 (20% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2953, 1700, 1555, 1152; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.43-1.49 (2 H, m, C**H$_2$**CHN), 1.80-1.87 (1 H, m, C**H$_A$**H$_B$CH$_2$CO$_2$CH$_3$), 1.92-1.97 (1 H, m, CH$_A$**H$_B$**CH$_2$CO$_2$CH$_3$), 2.22 (2 H, t *J* 8.0 Hz, C**H$_2$**C=CH$_2$), 2.32-2.39 (1 H, m, C**H$_A$**H$_B$CO$_2$CH$_3$), 2.41-2.48 (1 H, m, CH$_A$**H$_B$**CO$_2$CH$_3$), 3.67 (3 H, s, CO$_2$C**H$_3$**), 3.91-3.98 (1 H, m, C**H**N), 4.03 (2 H, s, C**H$_2$**Cl), 4.97 (1 H, s, C=C**H$_A$**H$_B$), 5.15 (1 H, s, C=CH$_A$**H$_B$**), 6.71 (1 H, d *J* 7.5 Hz, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.7, 29.0, 30.3, 32.3, 48.1, 50.1, 51.9, 114.4, 115.6 (q *J* 292 Hz), 143.6, 157.2 (q *J* 38 Hz), 174.1; Found MH$^+$ 316.0914 $C_{12}H_{18}F_3{}^{35}ClNO_3$ requires MH$^+$ 316.0927; $[\alpha]_D{}^{22}$ -1.0 (*c* 1 in $CHCl_3$).

1,13-Dimethyl (4*R*,10*R*)-7-methylidene-4,10-bis(trifluoroacetamido) tridecanedioate (**121d**)



R_f 0.24 (40% ethyl acetate in petroleum ether); mp 89-90 °C; $\mathbf{\nu_{max}/cm^{-1}}$: 2949, 1735, 1694, 1641, 1555, 1179; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.68 (4 H, q *J* 7.5 Hz, 2 C**H_2**CHN), 1.77-1.83 (2 H, m, 2 C**H_A**$H_B$$CH_2CO_2CH_3$), 1.91-1.99 (2 H, m, 2 CH_A**H_B**$CH_2CO_2CH_3$), 2.00-2.09 (4 H, m, 2 C**H_2**C=CH_2), 2.32-2.39 (2 H, m, 2 C**H_A**$H_B$$CO_2CH_3$), 2.41-2.49 (2 H, m, 2 CH_A**H_B**CO_2CH_3), 3.67 (6 H, s, 2 CO_2C**H_3**), 3.88-3.96 (2 H, m, 2C**H**N), 4.78 (2 H, s, C=C**H_2**), 6.84 (2 H, d *J* 8.0 Hz, 2N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.6, 30.3, 31.7, 32.2, 50.1, 51.9, 110.9, 115.6 (q *J* 292 Hz), 146.5, 157.2 (q *J* 37 Hz), 174.1; Found MH^+ 507.1931 $C_{20}H_{29}F_6N_2O_6$ requires MH^+ 507.1930; $[\alpha]_D^{22}$ -2.0 (*c* 1 in $CHCl_3$).

Methyl (2S)-5-(chloromethyl)-2-(trifluoroacetamido)hex-5-enoate (**126**)



Trifluoroacetic acid (1.5 g, 13.1 eq) was added dropwise to a stirred solution of methyl (2*S*)-2-{[(*tert*-butoxy) carbonyl] amino}-5 (chloromethyl)hex-5-enoate ***ent*-94** (70 mg, 0.24 mmol) in dichloromethane (13 mL), and stirred for 30 min. The exesse of trifluoroacetic acid and dichloromethane removed under reduced pressure. The residue was dissolved in diethylether (1 mL) followed by addition of

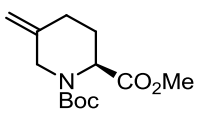
trifluoroacetic anhydride (80 mg, 0.38 eq) and stirring at room temperutre. Triethylamine (75 mg, 0.74 mmol) was added dropwise to the reaction mixture for 1 h. Ethyl acetate was added and after washing by ammonium chloride, the organic layer was then concentrated, and purified *via* flash chromatography on silica using an eluant gradient of 10% ethyl acetate in petroleum ether to give the title compound as a colourless oil (48 mg, 70%).

R_f 0.27 (10% ethyl acetate in petrolumether); $\mathbf{\nu_{max}/cm^{-1}}$: 3303, 2853, 1702, 1546; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.91-2.01 (1 H, m, C**H_A**H_BCHN), 2.10-2.16 (1 H, m, CH_A**H_B**CHN), 2.17-2.29 (2 H, m, C**H_2**C=CH_2), 3.81 (3 H, s, CO_2C**H_3**), 4.04 (2 H, s, C**H_2**Cl), 4.59-4.71 (1 H, m, C**H**N), 5.0 (1 H, s, C=C**H_A**H_B), 5.19 (1 H, s, C=CH_A**H_B**), 6.97 (1 H, d *J* 6.5 Hz, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.2, 29.7, 47.9, 52.2, 53.0, 115.8, 115.5 (q *J* 291 Hz), 143.0, 156.8 (q *J* 42 Hz), 171.1; Found MH^+ 288.0617 $C_{10}H_{14}NO_3F_3{}^{35}Cl$ requires MH^+ 288.0614; $[\alpha]_D^{21}$ +25 (*c* 4 in $CHCl_3$).

4.4 General Procedure B: Cyclization of allylic chlorides

A two-necked round-bottomed flask fitted with a rubber septum, three-way tap and magnetic follower was flame-dried under vacuum and backfilled with nitrogen three times. The flask was charged with allylic chloride (1.0 mmol) and dry DMF (0.8 mL). The mixture was stirred at room temperature until a colourless to pale yellow solution was obtained, at which point the flask was cooled to 0 °C. Sodium hydride (60 % dispersion in mineral oil, 1.2 eq) was added in one portion, and the reaction stirred at 0 °C for 10 min, before being allowed to warm to room temperature and stirred for 1 h. Phosphate buffer solution (pH 7) (10 mL) was carefully added to the vessel *via* syringe, and the reaction mixture was transferred to a separatory funnel using (10 mL) ethyl acetate. The aqueous layer was extracted further with (10 mL) ethyl acetate, and the combined organic layers washed with (5 mL) water and (5 mL) brine, dried over magnesium sulfate and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica, using ethyl acetate in petroleum ether.

1-*tert*-Butyl 2-methyl (2*S*)-5-methylidenepiperidine-1,2-dicarboxylate (***ent*-37**)

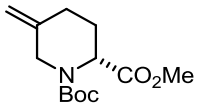


The title compound was synthesised according to the general procedure **B**, using methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-5-(chloromethyl)hex-

5-enoate ***ent*-94** (1.45 g, 5 mmol) as the starting material to give the title compound. The product was a colorless oil (1.1 g, 85%).

R_f 0.39 (10% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2930, 1743, 1694, 1448; **^{1}H NMR** (400 MHz, $CDCl_3$), exhibits strongly rotameric behaviour δ ppm: 1.40 (9 H, s, C(C**H$_3$**)$_3$), 1.45 (9 H, s, C(C**H$_3$**)$_3$), 1.68-1.84 (1 H, m, C**H$_A$**H$_B$CH), 1.97-2.10 (1 H, m, CH$_A$**H$_B$**CH), 2.15-2.30 (2 H, m, C**H$_2$**C=CH$_2$), 3.76-3.59 (1 H, m, C**H$_A$**H$_B$N), 3.72 (3 H, s, CO$_2$C**H$_3$**), 4.46-4.26 (1 H, m, CH$_A$**H$_B$**N), 4.98-4.69 (2 H, m, C=C**H$_2$**), 4.98-4.69 (1 H, m, C**H**N); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 27.2, 28.3, 28.9, 29.1, 46.8, 48.1, 52.1, 53.5, 54.2, 80.2, 109.9, 110.2, 141.5, 141.8, 155.1, 155.5, 172.2, 172.5; Found MH^+ 256.1539 $C_{13}H_{22}NO_4$ requires MH^+ 256.1549; $[\alpha]_D^{22}$ -59 (*c* 1 in $CHCl_3$).

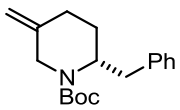
1-*tert*-Butyl 2-methyl (2*R*)-5-methylidenepiperidine-1,2-dicarboxylate (**37**)



The title compound was synthesised according to the general procedure **B**, using methyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-5-(chloromethyl)hex-5-enoate **94** (583 mg, 2 mmol) as the starting material to give the title compound. The product was a colourless oil (413 mg, 81%).

$[\alpha]_D^{22}$ 57 (*c* 1 in $CHCl_3$).

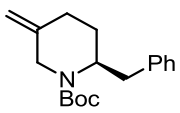
tert-Butyl (2*R*)-2-benzyl-5-methylidenepiperidine-1-carboxylate (**119a**)



The title compound was synthesised according to the general procedure **B**, using *tert*-butyl N-[(2*R*)-5-(chloromethyl)-1-phenylhex-5-en-2-yl]carbamate **117a** (1.61 g, 5 mmol) as the starting material to give the title compound. The product was a colorless oil (1.22 g, 85%).

R_f 0.31 (5% ethyl acetate in petroleum ether); $\mathbf{v_{max}/cm^{-1}}$: 1740, 1692, 1448; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.45 (9 H, s, C(C**H$_3$**)$_3$), 1.66-1.73 (2 H, m, C**H$_2$**$CH_2C{=}CH_2$), 2.30 (1 H, dt, *J* 4.0 and 14.5 Hz, C**H$_A$**$H_BC{=}CH_2$), 2.47-2.53 (1 H, m, CH_A**H$_B$**$C{=}CH_2$), 2.88-2.94 (1 H, m, C**H$_A$**H_BPh), 3.05 (1 H, dd, *J* 7.5 and 3.5 Hz, CH_A**H$_B$**Ph), 3.67 (1 H, d, *J* 14.5 Hz, C**H$_A$**H_BN), 4.47-4.55 (1 H, br, C**H**N), 4.47-4.55 (1 H, br, CH_A**H$_B$**N), 4.85 (1 H, s, C=C**H$_A$**H_B), 4.95 (1 H, s, C=CH_A**H$_B$**), 7.31-7.42 (5 H, m, Ph); **^{13}C NMR** (500 MHz, $CDCl_3$) δ ppm: 27.5, 28.3, 29.6, 36.5, 45.0, 52.3, 79.3, 109.4, 126.2, 128.3, 128.9, 138.9, 142.8, 154.6; Found MH^+ 288.1967. $C_{18}H_{26}NO_2$ requires MH^+ 288.1964.; $[\alpha]_D^{22}$ -33.0 (*c* 1 in $CHCl_3$), **GC**: Chiraldex-PM, H_2 at 1.4 mL/ min, 140 °C, retention time: 37.7 min, ee 98%.

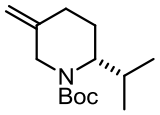
tert-Butyl (2*S*)-2-benzyl-5-methylidenepiperidine-1-carboxylate (***ent*-119a**)



The title compound was synthesised according to the general procedure **B**, using *tert*-butyl N-[(2*S*)-5-(chloromethyl)-1-phenylhex-5-en-2-yl]carbamate ***ent*-117a** (323.8 mg, 1 mmol) as the starting material to the title compound. The product was as colorless oil. $[\alpha]_D^{22}$ +34.0 (*c* 1 in

$CHCl_3$), **GC**: Chiraldex-PM, H_2 at 1.4 mL/ min, 140 °C, retention time: 39.5 min, ee 99%.

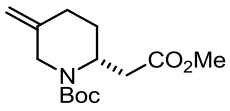
tert-Butyl (2*R*)-5-methylidene-2-(propan-2-yl)piperidine-1-carboxylate (**119b**)



The title compound was synthesised according to the general procedure **B**, using *tert*-butyl N-[(3*R*)-6-(chloromethyl)-2-methylhept-6-en-3-yl]carbamate **117b** (551.6 mg, 2 mmol) as the starting material to give the title compound. The product was a colourless oil (344 mg, 72%).

R_f 0.35 (5% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 1689, 1454; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.86 (3 H, d *J* 6.5 Hz, CHC**H_3**CH_3), 0.95 (3 H, d *J* 6.5 Hz, $CHCH_3C$**H_3**), 1.43 (9 H, s, $C(C$**H_3**$)_3$), 1.57-1.66 (1 H, m, C**H_A**H_BCHN), 1.77-1.83 (1 H, m, CH_A**H_B**CHN), 1.98-2.1 (1 H, m, C**H**CH_3CH_3), 2.14 (1 H, dt *J* 14.0 and 4.0 Hz, C**H_A**H_BC=CH_2), 2.28 (1 H, t *J* 14.0 Hz, CH_A**H_B**C=CH_2), 3.35 (1 H, d *J* 15.0 Hz, C**H_A**H_BN), 3.71-3.80 (1 H, br, C**H**N), 4.36-4.44 (1 H, br, CH_A**H_B**N), 4.70 (1 H, s, C=C**H_A**H_B), 4.77 (1 H, s, C=CH_A**H_B**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm: 19.4, 19.8, 26.7, 27.8, 28.4, 29.6, 45.0, 56.7, 79.2, 108.8, 143.3, 155.1; Found MH^+ 240.1960 $C_{14}H_{26}NO_2$ requires MH^+ 240.1960; $[\alpha]_D^{22}$ -17.0 (*c* 1 in $CHCl_3$).

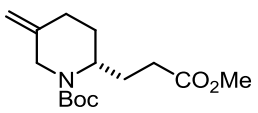
tert-Butyl(2*R*)-2-(2-methoxy-2-oxoethyl)-5-methylidenepiperidine-1-carboxylate (**119c**)



The title compound was synthesised according to the general procedure **B**, using methyl (3*R*)-3-{[(*tert*-butoxy)carbonyl]amino}-6-(chloromethyl)hept-6-enoate **117c** (611.5 mg, 2 mmol) as the starting material to give the title compound. The product was a colorless oil (431 mg, 80%).

R_f 0.51 (20% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2973, 1737, 1689, 1403, 1159; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.43 (9 H, s, C(C**H$_3$**)$_3$), 1.61-1.69 (1 H, m, C**H$_A$**H$_B$CHN), 1.74-1.79 (1 H, m, CH$_A$**H$_B$**CHN), 2.21-2.28 (2 H, m, C**H$_2$**C=CH$_2$), 2.54 (1 H, dd *J* 14.0 and 8.0 Hz, C**H$_A$**H$_B$CO$_2$CH$_3$), 2.65 (1 H, dd *J* 14.0 and 7.0 Hz, CH$_A$**H$_B$**CO$_2$CH$_3$), 3.47 (1 H, d *J* 15.0 Hz, C**H$_A$**H$_B$N), 3.66 (3 H, s, CO$_2$C**H$_3$**), 4.30-4.39 (1 H, br, CH$_A$**H$_B$**N), 4.61-4.71 (1 H, br, C**H**N), 4.75 (1 H, s, C=C**H$_A$**H$_B$), 4.82 (1 H, s, C=CH$_A$**H$_B$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm: 27.4, 28.2, 28.3, 28.7, 35.5, 47.9, 51.7, 79.8, 109.7, 142.2, 154.4, 171.6; Found MH^+ 270.1693 $C_{14}H_{24}NO_4$ requires MH^+ 270.1705; $[\alpha]_D^{22}$ +3.0 (*c* 1 in $CHCl_3$).

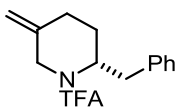
tert-Butyl(2*R*)-2-(3-methoxy-3-oxopropyl)-5-methylidenepiperidine-1-carboxylate (**119d**)



The title compound was synthesised according to the general procedure B, using methyl (4*R*)-4-{[(*tert*-butoxy)carbonyl]amino}-7-(chloromethyl)oct-7-enoate **117d** (639.5 mg, 2 mmol) as the starting material to give the title compound.The product was a colorless oil (453 mg, 80%).

R_f 0.55 (20% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2930, 1737, 1687, 1409, 1153; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.44 (9 H, s, C(C$\mathbf{H_3}$)$_3$), 1.58-1.66 (1 H, m, C$\mathbf{H_A}$H$_B$CH$_2$CO$_2$CH$_3$), 1.70-1.77 (1 H, m, CH$_A$$\mathbf{H_B}CH_2CO_2CH_3$), 2.03-2.11 (1 H, m, CH$_A$$\mathbf{H_B}CH_2$C=CH), 2.15-2.22 (1 H, m, C$\mathbf{H_A}$H$_B$C=CH$_2$), 2.31-2.39 (1 H, m, CH$_A$$\mathbf{H_B}$C=CH$_2$), 2.31-2.39 (2 H, m, C$\mathbf{H_2}CO_2CH_3$), 3.40 (1 H, d *J* 15.0 Hz, C$\mathbf{H_A}$H$_B$N), 3.67 (3 H, s, CO$_2$C$\mathbf{H_3}$), 4.20-2.28 (1 H, br, C**H**N), 4.31-4.39 (1 H, br, CH$_A$$\mathbf{H_B}$N), 4.67-4.75 (1 H, s, C=C$\mathbf{H_A}$H$_B$), 4.80 (1 H, s, C=CH$_A$$\mathbf{H_B}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm: 25.1, 27.7, 28.3, 30.3, 30.9, 49.8, 51.5, 68.1, 79.6, 109.3, 142.8, 154.8, 173.7; Found MH^+ 284.1760 $C_{15}H_{26}NO_4$ requires MH^+ 284.1862; $[\alpha]_D^{22}$ +20 (*c* 1 in $CHCl_3$).

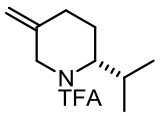
1-[(2*R*)-2-Benzyl-5-methylidenepiperidin-1-yl]-2,2,2-trifluoroethan-1-one (**122a**)



The title compound was synthesised according to the general procedure **B**, using N-[(2*R*)-5-(chloromethyl)-1-phenylhex-5-en-2-yl]-2,2,2-trifluoroacetamide **120a** (1.6 g, 5 mmol) as the starting material to give the title compound. The product was as colourless crystal (850 mg, 60%).

R_f 0.45 (5% ethyl acetate in petroleum ether); mp 181-183 °C; **ν_{max}/cm^{-1}**: 2937, 1675, 1451, 1272, 1186; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour (1.3 : 1), **major rotamer** δ ppm: 1.66-1.74 (2 H, m, C**H_2**CHN), 2.28-2.36 (1 H, m, C**H_A**H_BC=CH_2), 2.51-2.59 (1 H, m, CH_A**H_B**C=CH_2), 2.94-3.1 (2 H, m, C**H_2**Ph), 3.89 (1 H, d *J* 15.0 Hz, C**H_A**H_BN), 4.22 (1 H, d *J* 15.0 Hz, CH_A**H_B**N), 4.85-4.93 (1 H, m, C**H**N), 4.89 (1 H, s, C=C**H_A**H_B), 4.92 (1 H, s, C=CH_A**H_B**), 7.25-7.33 (5 H, m, Ph); **minor rotamer** δ ppm: 1.66-1.74 (2 H, m, C**H_2**CHN), 2.28-2.36 (1 H, m, C**H_A**H_BC=CH_2), 2.51-2.59 (1 H, m, CH_A**H_B**C=CH_2), 2.94-3.1 (2 H, m, C**H_2**Ph), 3.18 (1 H, dd *J* 14.0 and 10.0 Hz, CH_A**H_B**Ph), 3.69 (1 H, d *J* 14.5 Hz, C**H_A**H_BN), 4.27-4.35 (1 H, m, C**H**N), 4.91 (1 H, m, CH_A**H_B**N), 4.91 (1 H, m, C=C**H_A**H_B), 5.0 (1 H, s, C=CH_A**H_B**), 7.25-7.33 (5 H, m, Ph); **^{1}H NMR at 353 K** (500 MHz, d_6-DMSO) δ ppm: 1.60-1.69 (1 H, m, C**H_A**H_BCHN), 1.70-1.80 (1 H, m, CH_A**H_B**CH_2N), 2.21-2.29 (1 H, m, C**H_A**H_BC=CH_2), 2.55-2.63 (1 H, m, CH_A**H_B**C=CH_2), 2.95-3.1 (2 H, m , C**H_2**Ph), 4.0-4.1 (2 H, m, C**H_2**N), 4.68-4.76 (1 H, m, C**H**N), 4.87 (1 H, s, C=C**H_A**H_B), 4.91 (1 H, s, C=CH_A**H_B**), 7.25-7.33 (5 H, m, Ph); **^{13}C NMR** (125 MHz, $CDCl_3$) **major rotamer** δ ppm: 26.6, 27.2, 35.9, 54.8, 57.6, 112.1, 116.7 (q *J* 292 Hz), 126.8, 128.6, 129.0, 137.2, 140.7, 155.8 (q *J* 38.0 Hz), **minor rotamer** δ ppm: 26.6, 27.4, 36.6, 45.0, 52.0, 111.2, 116.7 (q *J* 292 Hz), 127.0, 128.2, 129.1, 136.1, 140.3, 155.8 (q *J* 38.0 Hz), Found MH^+ 284.1249 $C_{15}H_{17}F_3NO$ requires MH^+ 284.1262; $[\alpha]_D^{22}$ -31.0 (*c* 1 in $CHCl_3$).

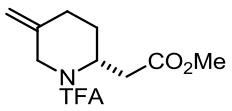
2,2,2-Trifluoro-1-[(2*R*)-5-methylidene-2-(propan-2-yl)piperidin-1-yl]ethan-1-one (**122b**)



The title compound was synthesised according to the general procedure **B**, using (*R*)- N-[(3*R*)-6-(chloromethyl)-2-methylhept-6-en-3-yl]-2,2,2-trifluoroacetamide **120b** (543.5 mg, 2 mmol) as the starting material to give the title compound. The product was a colourless oil (258 mg, 55%). R_f 0.76 (5% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 1687, 1447, 1188; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour (2 : 1), **major rotamer** δ ppm: 0.87 (3 H, d *J* 6.5 Hz, CHC$\mathbf{H_3}$$CH_3$), 1.0 (3 H, d *J* 6.5 Hz, $CHCH_3C\mathbf{H_3}$), 1.59-1.74 (1 H, m, C**H**CH_3CH_3), 1.90-2.05 (1 H, m, C$\mathbf{H_A}H_BCHN$), 2.13-2.22 (1 H, m, $CH_A\mathbf{H_B}CHN$), 2.22-2.31 (1 H, m, C$\mathbf{H_A}H_BC{=}CH_2$), 2.32-2.48 (1 H, m, $CH_A\mathbf{H_B}C{=}CH_2$), 3.74 (1 H, d *J* 15.0 Hz, C$\mathbf{H_A}H_BN$), 4.17 (1 H, d *J* 15.0 Hz, $CH_A\mathbf{H_B}N$), 4.25-4.33 (1 H, m, C**H**N), 4.80-4.84 (m, 1 H, C$\mathbf{H_A}H_B{=}C$), 4.84-4.87 (m, 1 H, $CH_A\mathbf{H_B}{=}C$); **minor rotamer** δ ppm: 0.87 (3 H, d *J* 6.5 Hz, CHC$\mathbf{H_3}$$CH_3$), 1.0 (3 H, d *J* 6.5 Hz, $CHCH_3C\mathbf{H_3}$), 1.59-1.74 (1 H, m, C**H**CH_3CH_3), 1.90-2.05 (1 H, m, C$\mathbf{H_A}H_BCHN$), 2.13-2.22 (1 H, m, $CH_A\mathbf{H_B}CHN$), 2.22-2.31 (1 H, m, C$\mathbf{H_A}H_BC{=}CH_2$), 2.32-2.48 (1 H, m $CH_A\mathbf{H_B}C{=}CH_2$), 3.41 (1 H, d *J* 15.0 Hz, C$\mathbf{H_A}H_BN$), 3.52-3.60 (1 H, m, C**H**N), 4.80-4.84 (1 H, m, $CH_A\mathbf{H_B}N$), 4.84-4.87 (1 H, m, C$\mathbf{H_A}H_B{=}C$), 4.91 (1 H, d *J* 1.5 Hz, $CH_A\mathbf{H_B}{=}C$); **^{13}C NMR** (100 MHz, $CDCl_3$) **major rotamer** δ ppm: 18.8, 19.4, 26.0, 26.2, 27.5, 44.9, 56.5, 110.8, 121.3 (q *J* 290 Hz), 140.6 156.1 (q *J* 38.0 Hz); **minor**

rotamer δ ppm: 18.8, 19.8, 27.5, 27.9, 28.0, 47.4, 59.5, 111.8, 121.3 (q *J* 290 Hz), 141.1, 156.1 (q *J* 38.0 Hz); Found MH^+ 236.1255 $C_{11}H_{17}F_3NO$ requires MH^+ 236.1262; $[\alpha]_D^{19}$ -15.4 (*c* 4.67 in $CHCl_3$).

Methyl 2-[(2*R*)-5-methylidene-1(trifluoroacetyl)piperidin-2-yl]acetate (**122c**)

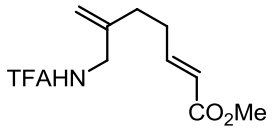


The title compound was synthesised according to the general procedure **B**, using methyl (3*R*)-6-(chloromethyl)-3-(trifluoroacetamido)hept-6-enoate **120c** (620 mg, 2 mmol) as the starting material to give the title compound. The product was as colourless oil (326 mg, 60%).

R_f 0.52 (20% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 1736, 1682, 1438, 1269; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour (1.5 : 1), **major rotamer** δ ppm: 1.81-1.89 (2 H, m, C**H$_2$**CHN), 2.30-2.41 (2 H, m, C**H$_2$**C=CH_2), 2.64 (1 H, dd *J* 15.0 and 7.5 Hz, C**H$_A$**$H_B$$CO_2CH_3$), 2.74 (1 H, dd *J* 15.0 and 7.5 Hz, CH_A**H$_B$**CO_2CH_3) 3.66 (3 H, s, CO_2C**H$_3$**), 3.87 (1 H, d *J* 15.0 Hz, C**H$_A$**H_BN), 4.20 (1 H, d *J* 15.0 Hz, CH_A**H$_B$**N), 4.87 (1 H, s, C=C**H$_A$**H_B), 4.90 (1 H, s, C=CH_A**H$_B$**), 4.97-5.1 (1 H, m, C**H**N); **minor rotamer** δ ppm: 1.81-1.89 (2 H, m, C**H$_2$**CHN), 2.30-2.41 (2 H, m, C**H$_2$**C=CH_2), 2.70 (1 H, dd *J* 15.0 and 7.5 Hz, C**H$_A$**$H_B$$CO_2CH_3$), 2.88 (1 H, dd *J* 15.0 and 7.5 Hz, CH_A**H$_B$**CO_2CH_3), 3.48 (1 H, d *J* 15.0 Hz, C**H$_A$**H_BN), 3.70 (3 H, s, CO_2C**H$_3$**), 4.57-4.63 (1 H, m, C**H**N), 4.83 (1 H, d *J* 15.0 Hz, CH_A**H$_B$**N), 4.87 (1 H, s, C=C**H$_A$**H_B), 4.95 (1 H, s, C=CH_A**H$_B$**); **^{1}H NMR at 353 K** (125 MHz, d_6-DMSO) δ ppm: 1.69-1.81 (2 H, m, C**H$_2$**CHN), 2.20-2.32 (1 H, m, C**H$_A$**H_BC=CH_2), 2.41-2.52 (1 H, m, CH_A**H$_B$**C=CH_2), 2.80

(2 H, m, C**H$_2$**CO$_2$CH$_3$), 4.60 (3 H, s, CO$_2$C**H$_3$**), 3.94-4.10 (1 H, m, C**H$_A$**H$_B$N), 4.11-4.22 (1 H, m, CH$_A$**H$_B$**N), 4.85 (1 H, s, C=C**H$_A$**H$_B$), 4.90 (1 H, s, C=CH$_A$**H$_B$**); **^{13}C NMR** (125 MHz, CDCl$_3$) **major rotamer** δ ppm: 27.9, 34.7, 47.14, 47.18, 47.8, 51.9, 111.5, 116.5 (q *J* 288 Hz), 140.1, 157.2 (q *J* 40 Hz), 170.6; **minor rotamer** δ ppm: 27.1, 29.4, 35.4, 44.9, 49.8, 52.1, 112.4, 116.6 (q *J* 288 Hz), 139.7, 157.2 (q *J* 40 Hz), 170.6; Found MH$^+$ 266.1006 $C_{11}H_{15}F_3NO_3$ requires MH$^+$ 266.1004; $[\alpha]_D^{22}$ +5 (*c* 1 in CHCl$_3$).

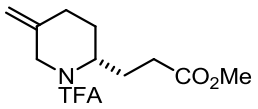
Methyl (2*E*)-6-[(trifluoroacetamido)methyl]hepta-2,6-dienoate (**123**)



The title compound is obtained as a by-product at preparing the previous compound as a colorless crystal (82 mg, 15%).

R_f 0.32 (20% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 3293, 1697, 1653, 1555, 1435; **^{1}H NMR** (400 MHz, CDCl$_3$) δ ppm: 2.19 (2 H, t *J* 7.5 Hz, C**H$_2$**C=CH$_2$), 2.39 (2 H, qd *J* 7.5 and 1.5 Hz, C**H$_2$**CH=CHCO$_2$CH$_3$), 3.71 (3 H, s, CO$_2$C**H$_3$**), 3.93 (2 H, d *J* 6.0 Hz, C**H$_2$**NH), 4.97 (2 H, d *J* 7.0 Hz, C=C**H$_2$**), 5.84 (1 H, dt *J* 15.5 and 1.5 Hz, C**H**=CHCO$_2$CH$_3$), 6.48-6.55 (1 H, br, N**H**), 6.95 (1 H, dt *J* 15.5 and 7.0 Hz, CH=C**H**CO$_2$CH$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ ppm: 29.8, 32.0, 44.0, 51.4, 112.7, 114.0 (q *J* 80 Hz), 121.7, 142.3, 147.6, 157.2 (q *J* 40 Hz), 166.8; Found MH$^+$ 266.1012 $C_{11}H_{15}F_3NO_3$ requires MH$^+$ 266.1004.

Methyl 3-[(2*R*)-5-methylidene-1-(trifluoroacetyl)piperidin-2-yl]propanoate (**122d**)

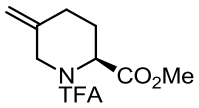


The title compound was synthesised according to the general procedure **B**, using methyl (4*R*)-7-(chloromethyl)-4-(trifluoroacetamido)oct-7-enoate **120d** (637 mg, 2 mmol) as the starting material to give the title compound. The product was a colourless oil (446 mg, 79%).

R_f 0.38 (20% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2926, 1736, 1681, 1438, 1364, 1178; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour (1.5 : 1), **major rotamer** δ ppm: 1.77-1.91 (2 H, m, C**H$_2$**CHN), 1.77-1.91 (2 H, m, C**H$_2$**$CH_2CO_2CH_3$), 2.25-2.40 (2 H, m, C**H$_2$**CO_2CH_3), 2.25-2.40 (2 H, m, C**H$_2$**$C{=}CH_2$), 3.67 (3 H, s, CO_2C**H$_3$**), 3.82 (1 H, d *J* 15.0 Hz, C**H$_A$**H_BN), 4.16 (1 H, d *J* 15.0 Hz, CH_A**H$_B$**N), 4.72 (1 H, m, C**H**N), 4.86 (1 H, s, C=C**H$_A$**H_B), 4.90 (1 H, s, C=CH_A**H$_B$**); **minor rotamer** δ ppm: 1.77-1.91 (2 H, m, C**H$_2$**CH_2N), 1.77-1.91 (2 H, m, C**H$_2$**$CH_2CO_2CH_3$), 2.25-2.40 (2 H, m, C**H$_2$**CO_2CH_3), 2.25-2.40 (2 H, m, C**H$_2$**$C{=}CH_2$), 3.48 (1 H, d *J* 15.0 Hz, C**H$_A$**H_BN), 3.68 (3 H, s, CO_2C**H$_3$**), 4.10 (1 H, m, C**H**N), 4.81 (1 H, d *J* 15.0 Hz, CH_A**H$_B$**N), 4.86 (1 H, s, C=C**H$_A$**H_B), 4.93 (1 H, s, C=CH_A**H$_B$**); **^{1}H NMR at 353 K** (125 MHz, d_6-DMSO) δ ppm: 1.63-1.76 (2 H, m, C**H$_2$**CHN), 1.90-2.1 (2 H, m, C**H$_2$**$CH_2CO_2CH_3$), 2.22-2.40 (2 H, m, C**H$_2$**$C{=}CH_2$), 2.43-2.55 (2 H, m, C**H$_2$**CO_2CH_3), 3.59 (3 H, s, CO_2C**H$_3$**), 3.90-3.99 (1 H, m, C**H$_A$**H_BN), 4.0-4.13 (1 H, m, CH_A**H$_B$**N), 4.84 (1 H, s, C=C**H$_A$**H_B), 4.87 (1 H, s, C=CH_A**H$_B$**); **^{13}C NMR** (125 MHz, $CDCl_3$)

major rotamer δ ppm: 27.5, 28.5, 34.9, 47.2, 47.3, 47.8, 52.0, 111.6, 116.0 (q *J* 290 Hz), 140.6, 157.9 (q *J* 41 Hz), 170.9; **minor rotamer** δ ppm: 27.2, 28.2, 29.6, 35.8, 45.0, 49.8, 52.3, 112.4, 116.0 (q *J* 290 Hz), 139.7, 157.9 (q *J* 41 Hz), 170.6; Found MH^+ 280.1154 $C_{12}H_{17}F_3NO_3$ requires MH^+ 280.1161; $[\alpha]_D^{22}$ +48 (*c* 1.0 in $CHCl_3$).

Methyl (2*S*)-5-methylidene-1-(trifluoroacetyl)piperidine-2-carboxylate (**127**)



The title compound was synthesised according to the general procedure **B**, using methyl (2*S*)-5-(chloromethyl)-2-(trifluoroacetamido)hex-5-enoate **126** (72 mg, 0.25 mmol) as the starting material to give the title compound. The product was as colourless oil (40 mg, 64%).

Alternatively, trifluoroacetic acid acid (12.4 g, 110.5 mmol) was added dropwise to the stirred solution of 1-*tert*-butyl 2-methyl (2*S*)-5-methylidenepiperidine-1,2-dicarboxylate ***ent*-37** (562 mg, 2.2 mmol) in dichloromethane (100 mL), and the reaction mixture stirred for a further 20 min. At this time, the solvent and excess trifluoroacetic acid were removed under reduced pressure. The residue was dissolved in diethyl ether (4 mL), and adding triethylamine (467 mg, 4.62 mmol), then trifluoroacetic anhydride (508 mg, 2.42 mmol, 1.1 eq) was added dropwise. The mixture was stirred for 1 h, and washed with 1 M hydrochloric acid the organic layer was concentrated and column chromatography using 10% ethyl

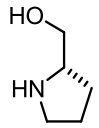
acetate in petroleum ether to produce the title compound as a colourless oil (441 mg, 80%).

R_f 0.35 (10% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 2959, 1743, 1691, 1442; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour (3 : 1), **major rotamer** δ ppm: 1.77-1.91 (1 H, m, C**H_A**H_BCHN), 2.11-2.25 (1 H, m, C**H_A**H_BC=CH_2), 2.37-2.46 (1 H, m, CH_A**H_B**CHN), 2.37-2.46 (1 H, m, CH_A**H_B**C=CH_2), 3.78 (3 H, s, CO_2C**H_3**), 3.99 (1 H, d *J* 14.5 Hz, C**H_A**H_BN), 4.29 (1 H, d *J* 14.5 Hz, CH_A**H_B**N), 4.88 (1 H, d *J* 1.5 Hz, C=C**H_A**H_B), 4.92 (1 H, d *J* 1.5 Hz, C=CH_A**H_B**), 5.25 (1 H, dd *J* 6.5 and 3.0 Hz, C**H**N); **minor rotamer** δ ppm: 1.77-1.91 (1 H, m, C**H_A**H_BCHN), 2.11-2.25 (1 H, m, C**H_A**H_BC=CH_2), 2.37-2.46 (1 H, m, CH_A**H_B**CHN), 2.37-2.46 (1 H, m, CH_A**H_B**C=CH_2), 3.65 (1 H, d *J* 15.5 Hz, C**H_A**H_BN), 3.79 (3 H, s, CO_2C**H_3**), 5.25 (1 H, m, C**H**N) 4.79 (1 H, d *J* 15.5 Hz, CH_A**H_B**N), 4.88 (1 H, d *J* 1.5 Hz, C=C**H_A**H_B), 4.95 (1 H, d *J* 1.5 Hz, C=CH_A**H_B**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm **major rotamer**: 26.7, 28.9, 47.1, 52.7, 53.3, 112.0, 116.3 (q *J* 279 Hz), 139.2, 156.5 (q *J* 27 Hz), 170.0; **minor rotamer**: 28.0, 28.9, 49.2, 52.9, 55.5, 112.4, 116.3 (q *J* 279 Hz), 139.4, 156.5 (q *J* 27 Hz), 170.0; Found MH^+ 252.0839 $C_{10}H_{13}F_3NO_3$ requires MH^+ 252.0848; $[\alpha]_D^{19}$ -39.0 (*c* 1 in $CHCl_3$).

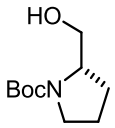
4.5 Indolizidine Synthesis

tert-Butyl (2*S*)-2-(iodomethyl)pyrrolidine-1-carboxylate **130** and (5*S*)-5-(iodomethyl)pyrrolidin-2-one **142** were prepared according to the literature method.

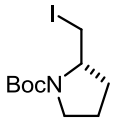
(2*S*)-Pyrrolidin-2-ylmethanol (**131**)[89]



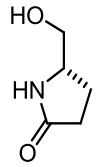
tert-Butyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**132**)[100]



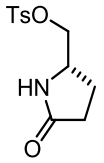
tert-Butyl (2*S*)-2-(iodomethyl)pyrrolidine-1-carboxylate (**130**)[101]



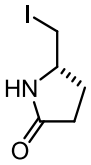
(5*S*)-5-(Hydroxymethyl)pyrrolidin-2-one (**140**)[102]



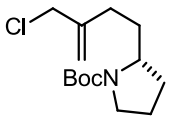
[(2*S*)-5-Oxopyrrolidin-2-yl]methyl 4-methylbenzene-1-sulfonate (**141**)[102]



(5*S*)-5-(Iodomethyl)pyrrolidin-2-one (**142**)[102]



tert-Butyl (2*R*)-2-[3-(chloromethyl)but-3-en-1-yl]pyrrolidine-1-carboxylate (**135**)



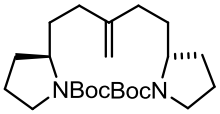
A two-necked round bottom flask, fitted with a three-way tap and rubber septum, was flame-dried, evacuated and back-filled with nitrogen three times. The flask was charged with a magnetic follower and zinc powder (390 mg, 6 mmol, 2.0 eq), and again evacuated and back-filled with nitrogen three times, with continuous stirring. Dry DMF (3 mL) was added *via* syringe, and the heterogeneous mixture stirred vigorously. Iodine (195 mg, 0.75 mmol) 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 mins, until the solvent had become colourless.. During the 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 (60 mg, 0.3 mmol, 0.1 eq), and gently heated under vacuum until the CuBr.DMS changed appearance from a brown to light green powder. The flask was allowed to cool, before adding dry DMF (2.4 mL) and *3*-chloro-2-(chloromethyl)prop-1-ene **41** (1.2 mL, 12 mmol, 4.0 eq) *via* syringe. The mixture was stirred at room temperature, at which point the (*S*)-*tert*-butyl 2-(iodomethyl)pyrrolidine-1-carboxylate **130** (933 mg, 3 mmol) was added by rapid removal of the three-way tap under a stream of nitrogen to the activated zinc and the allyl dichloride and CuBr.DMS mixture was added *via* syringe quickly, and was stirred at room temperature for 1 h. The reaction mixture was transferred to a separatory funnel with (30 mL) ethyl acetate, and washed with (15 mL) saturated sodium thiosulfate solution, (15 mL) water and (15 mL) brine. The organic layer was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica, using 10% diethylether in petroleum ether to provide the title compound as colourless oil (491 mg, 60%).

R_f 0.35 (10% diethyl ether in petroleum ether); **ν_{max}/cm^{-1}**: 1686, 1652, 1478; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.45 (9 H, s, C(C**H$_3$**)$_3$), 1.60-1.71 (2 H, m, C**H$_2$**CH$_2$N), 1.74-2.01 (2 H, m, C**H$_2$**CH), 1.74-2.01 (2 H, m, C**H$_2$**CH), 2.05-2.27 (2 H, m, C**H$_2$**C=CH$_2$), 3.26-3.44 (2 H, m, C**H$_2$**N), 3.69-3.82 (1 H, br, C**H**N), 4.06 (2 H, s, C**H$_2$**Cl), 4.97 (1 H, s, C=C**H$_A$**H$_B$), 5.11 (1 H, s, C=CH$_A$**H$_B$**); **^{13}C NMR** (125 MHz, $CDCl_3$) **major rotamer** δ ppm: 23.1, 28.4, 29.7, 30.9, 32.2, 46.3, 48.3, 56.8, 79.0, 114.4, 144.7, 154.6; Found

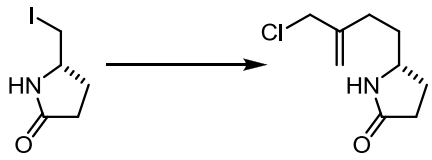
MH^+ 274.1584 $C_{14}H_{25}{}^{35}ClNO_2$ requires MH^+ 274.1574; $[\alpha]_D{}^{21}$ -31 (*c* 1.0 in $CHCl_3$).

tert-Butyl (2*R*)-2-{5-[(2*R*)-1-[(*tert*-butoxy)carbonyl]pyrrolidin-2-yl]-3-methylidenepentyl}pyrrolidine-1-carboxylate (**136**)



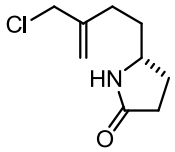
R_f 0.15 (10% diethyl ether in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2971, 1692, 1393 **^{1}H NMR** (400 MHz, $CDCl_3$) δ-ppm: 1.45 (18 H, s, 2C($C\mathbf{H_3})_3$), 1.52-1.69 (4 H, m, 2 $C\mathbf{H_2}CH_2$), 1.52-1.69 (4 H, m, 2 $CH_2C\mathbf{H_2}$), 1.73-1.95 (4 H, m, 2 $C\mathbf{H_2}CH$), 1.95-2.07 (4 H, m, 2 $C\mathbf{H_2}C{=}CH_2$), 3.21-3.47 (4 H, m, 2 $C\mathbf{H_2}N$), 3.64-3.86 (2 H, br, 2 C**H**N), 4.72 (2 H, s, $C\mathbf{H_2}{=}C$); **^{13}C NMR** (125 MHz, $CDCl_3$): 28.5, 29.6, 30.3, 32.8, 46.2, 56.8, 57.0, 78.9, 108.9, 148.9, 154.6; Found MH^+ 423.3209 $C_{24}H_{43}N_2O_4$ requires MH^+ 423.3223; $[\alpha]_D{}^{24}$ -45 (*c* 1.33 in $CHCl_3$).

Reaction of (5*S*)-5-iodomethyl)pyrrolidin-2-one (**142**) with 3-chloro-2-(chloromethyl) prop-1-ene (**41**)



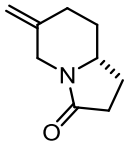
This reaction was done according to the general procedure **A** using (112 mg, 0.5 mmol) of **142** to give **143** (78 mg, 84%) as a white solid.

(5*R*)-5-[3-(Chloromethyl)but-3-en-1-yl]pyrrolidin-2-one (**143**)



R_f 0.16 (ethyl acetate); mp 62-64 °C; $\mathbf{\nu_{max}/cm^{-1}}$: 3219, 2931, 1690, 1444; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.61-1.82 (2 H, m, C**H_2**CH_2CO), 2.14-2.26 (2 H, m, C**H_2**C=CH_2), 2.14-2.26 (2 H, m, C**H_2**CHN), 2.27-2.41 (2 H, m, C**H_2**CO), 3.65-3.73 (1 H, m, C**H**N), 4.04 (2 H, s, C**H_2**Cl), 4.99 (1 H, s, C**H_A**H_B=C), 5.16 (1 H, s, CH_A**H_B**=C), 6.40-6.25 (1 H, br, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 27.2, 29.3, 30.0, 34.4, 48.1, 54.0, 115.2, 143.9, 178.1; Found MH^+ 188.0833 $C_9H_{15}{}^{35}ClNO$ requires MH^+ 188.0842; $[\alpha]_D{}^{24}$ +8.6 (*c* 2.33 in $CHCl_3$).

(8a*R*)-6-Methylidene-octahydroindolizin-3-one (**43**)



Potassium carbonate (830 mg, 6.0 mmol) was added to methyl 3-[(2*R*)-5-methylidene-1-(trifluoroacetyl)piperidin-2-yl] propanoate **122d** (320 mg, 1.15 mmol) in methanol (45 mL) and water (2.5 mL), the reaction was heated at reflux for 2 h, The residue was purified by flash chromatography on silica, using 80% ethyl acetate in petroleum ether to yield the title compound as a colourless oil (147 mg, 58%).

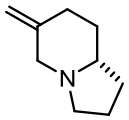
Alternative, sodium borohydride (102 mg, 2.7 mmol, 3.0 eq) was added to methyl 3-[(2*R*)-5-methylidene-1-(trifluoroacetyl)piperidin-2-yl] propanoate

122d (250 mg, 0.9 mmol) in methanol (9 mL), the reaction was heated at reflux for 3 days. Removing the methanol on rotary vapour and The residue was dissolved in (15 mL) ethyl acetate, washing by (10 mL) water and (10 mL) brine, the organic layer was concentrated to produce the title compound as colourless oil (117 mg, 88%).

Alternative method, the title compound was synthesised according to the general procedure **B**, using (5*R*)-5-[3-(chloromethyl)but-3-en-1-yl]pyrrolidin-2-one **143** (56 mg, 0.3 mmol) as the starting material to give the title compound. The product was a colourless oil (29 mg, 65%).

R_f 0.47 (ethyl acetate); **ν_{max}/cm^{-1}**: 1666, 1453, 1420; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.26 (1 H, qd *J* 12.5 and 4.0 Hz, C**H$_A$**H$_B$CH), 1.52-1.65 (1 H, m, CH$_A$**H$_B$**CH), 1.96 (1 H, dq *J* 13.0 and 3.5 Hz, C**H$_A$**H$_B$CH$_2$CO), 2.13-2.27 (1 H, m, CH$_A$**H$_B$**CH$_2$CO), 2.13-2.27 (1 H, m, C**H$_A$**H$_B$C=CH$_2$), 2.33-2.47 (1 H, m, CH$_A$**H$_B$**C=CH$_2$), 2.33-2.47 (2 H, m, C**H$_2$**CO), 3.30 (1 H, d *J* 14.5 Hz, C**H$_A$**H$_B$N), 3.48-3.58 (1 H, m, C**H**N), 4.49 (1 H, d *J* 14.5 Hz, CH$_A$**H$_B$**N), 4.80 (1 H, d *J* 2.0 Hz, C**H$_A$**H$_B$=C), 4.88 (1 H, d *J* 2.0 Hz, CH$_A$**H$_B$**=C); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 24.9, 30.6, 32.2, 34.0, 46.1, 56.7, 110.9, 140.8, 173.3; Found MH^+ 151.0994 $C_9H_{13}NO$ requires MH^+ 151.0997; $[\alpha]_D^{19}$ -38 (*c* 1.0 in $CHCl_3$).

(8a*R*)-6-Methylidene-octahydroindolizine (**128**)



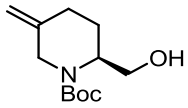
Trifluoroacetic acid (9.6 g, 85.5 mmol) was added dropwise to the stirred solution of (*R*)-*tert*-butyl 2-(3-(chloromethyl)but-3-enyl)pyrrolidine-1-carboxylate **135** (468 mg, 1.7 mmol) in dichloromethane (80 mL), and the reaction mixture stirred for a further 20 min. At this time, the solvent and excess trifluoroacetic acid was removed under reduced to produce a brown oil (655 mg, 2.39 mmol). The flask was flame-dried under vacuum and back-filled with nitrogen three times, dry DMF (2.5 mL) was added. The mixture was stirred at room temperature at which point the flask was cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 235 mg, 2.1 eq) was added in one portion, and the reaction stirred at 0 °C for 10 min, before being allowed to warm to room temperature and stirred for 1 h. Water (20 mL) was carefully added to the vessel *via* syringe, and the reaction mixture was transferred to a separatory funnel using ethyl acetate. The aqueous layer was extracted further with ethyl acetate, and the combined organic layers washed with water and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure.

Alternative, lithium aluminium hydride (43 mg, 1.13 mmol) was added to a solution of (8a*R*)-6-methylidene-octahydroindolizin-3-one **43** (45 mg, 0.3 mmol) in (2 mL) of ether at 0 °C under nitrogen. The resulting suspension was refluxed for 3 h, and cooled to 0 °C, and water (0.04 mL), 15% sodium hydroxide (0.04 mL), water (0.128 mL) were sequentially added.

The resulting suspension was stirred for 20 min, filtered through Celite, and concentrated to produce the title compound as colourless oil (30 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.64-1.76 (2 H, m, C**H_2**), 1.78-1.97 (5 H, m), 2.01-2.18 (2 H, m, C**H_2**N), 2.34-2.41 (1 H, m), 2.63 (1 H, d *J* 12.0 Hz, C**H_A**H_BN), 3.00-3.12 (1 H, m, C**H**N), 3.49 (1 H, d *J* 12.0 Hz, CH_A**H_B**N),

tert-Butyl (2*S*)-2-(hydroxymethyl)-5-methylidenepiperidine-1 carboxylate (***ent*-146**)[108]

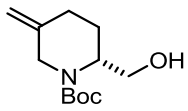


Lithium aluminium hydride (25 mg, 0.65 mmol, 0.75 eq) was added to stirred solution of 1-*tert*-butyl 2-methyl (2*S*)-5-methylidenepiperidine-1,2-dicarboxylate ***ent*-37** (223 mg, 0.87 mmol) in diethyl ether (2 mL) at 0 °C for 10 min then 1 h at room tempurture under nitrogen. Water (10 mL) was carefully added to quench the reaction and the reaction mixture was transferred to a separatory funnel using (15 mL) ethyl acetate and washing by (10 mL) brine, dried over magnesium sulfate and the solvent removed under reduced pressure to give the title compound as a colourless oil (183 mg, 93%) without any further purification.

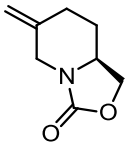
R_f 0.17 (50% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 3446 (br), 2976, 1697;); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.45 (9 H, s, C(C**H_3**)**$_3$**), 1.65-1.82 (2 H, m, C**H_2**CHN), 2.15-2.33 (2 H, m, C**H_2**C=CH_2), 3.56 (1 H, d *J* 15.0 Hz, C**H_A**H_BN), 3.66 (1 H, d *J* 15.0 Hz, CH_A**H_B**N), 3.79 (1 H, t *J* 10.5 Hz, O**H**), 4.21-4.36 (2 H, m, C**H_2**OH), 4.76 (1 H, s, C=C**H_A**H_B), 4.83 (1 H,

s, C=CH_A**H_B**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 25.5, 27.9, 28.4, 46.0, 52.9, 62.6, 80.1, 109.5, 142.5, 172.0; Found MH^+ 228.1600 $C_{12}H_{22}NO_3$ requires MH^+ 228.1600; $[\alpha]_D^{19}$ -12 (*c* 1.0 in $CHCl_3$).

tert-Butyl (2*R*)-2-(hydroxymethyl)-5-methylidenepiperidine-1 carboxylate (**146**)[108]



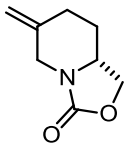
(8a*S*)-6-Methylidene-hexahydro-1H-[1,3]oxazolo[3,4-a]pyridin-3-one (***ent*-147**)



Sodium hydride (60 % dispersion in mineral oil, 20 mg, 1 eq) was added to stirred solution of *tert*-butyl (2*S*)-2-(hydroxymethyl)-5-methylidenepiperidine-1 carboxylate (112 mg, 0.5 mmol) in (2 mL) of tetrahydrofuran at 0 °C for 10 min and then at room tempurter for 2 h. Water was carefully added and the reaction mixture was transferred to a separatory funnel using ethyl acetate. The aqueous layer was extracted further with ethyl acetate, and the combined organic layers washed with water and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica, using 50% ethyl acetate in petroleum ether to produce the title compound as a colourless oil (65 mg, 85%).

R_f 0.28 (50% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 2924, 1745, 1421; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.44-1.56 (1 H, m, C**H_A**H_BCHN), 1.92-1.99 (1 H, m, CH_A**H_B**CHN), 2.17-2.28 (1 H, m, C**H_A**H_BC=CH_2), 2.47-2.54 (1 H, m, CH_A**H_B**C=CH_2), 3.54 (1 H, dd *J* 14.5 and 1.5 Hz, C**H_A**H_BN), 3.76-3.85 (1 H, m, C**H**N), 3.92 (1 H, dd *J* 9.0 and 6.0 Hz, C**H_A**H_BO), 4.28 (1 H, dd *J* 14.5 and 1.0 Hz, CH_A**H_B**N), 4.45 (1 H, dd *J* 9.0 and 8.5 Hz, CH_A**H_B**O), 4.86-4.89 (1 H, m, C=C**H_A**H_B), 4.93-4.96 (1 H, m, C=CH_A**H_B**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ-ppm: 31.2, 31.5, 47.2, 54.0, 57.7, 116.7, 139.8, 179.1; Found MH^+ 154.0873 $C_8H_{12}NO_2$ requires MH^+ 154.0868; $[\alpha]_D^{19}$ -10 (*c* 1.0 in $CHCl_3$).

(8a*R*)-6-Methylidene-hexahydro-1H-[1,3]oxazolo[3,4-a]pyridin-3-one (***ent*-147**)

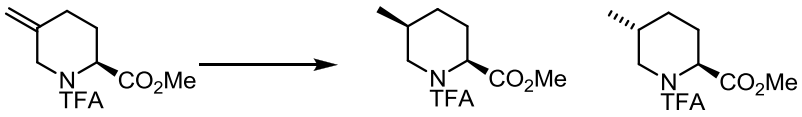


The spectroscopic data is the same as **147**, Found MH^+ 154.0877 $C_8H_{12}NO_2$ requires MH^+ 154.091; $[\alpha]_D^{19}$ 12 (*c* 1.0 in $CHCl_3$).

4.6 General procedure C: Reduction of 5-methylenepiperidines

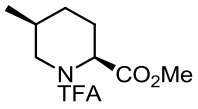
A two-necked round bottomed flask, fitted with a rubber septum, three-way tap and magnetic follower was flame-dried under vacuum and back-filled with nitrogen three times. Palladium on carbon (10% w/w, 0.1 eq) was added to the flask, which was again evacuated and back-filled with nitrogen three times. Piperidine (1 eq) was added to the flask as a solution in ethyl acetate (20 mL), and then a balloon of hydrogen was attached to the three-way tap. The flask was evacuated until the reaction mixture began to boil, and then back-filled with hydrogen. This procedure was repeated three more times, and the reaction stirred at room temperature for overnight. At this time, the mixture was filtered through Celite® and the solvent removed from the filtrate under reduced pressure. The residue was purified by flash chromatography.

Hydrogenation of methyl 2-[(2*R*)-5-methylidene-1(trifluoroacetyl)piperidin-2-yl] acetate **127**



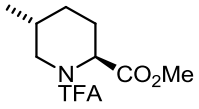
This reaction was done according to the general procedure **C** using (251 mg, 1 mmol) of **127** to give **149b** and **149a** each as colourless oil. Chromatography gave **149b** (50 mg, 20%), a mixed fraction of **149b** and **149a** (113 mg, 45%) and **149a** (70 mg, 28%). The ratio of *trans* : *cis* (1 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

Methyl (2*S*,5*S*)-5-methyl-1-(trifluoroacetyl)piperidine-2-carboxylate (**149b**)



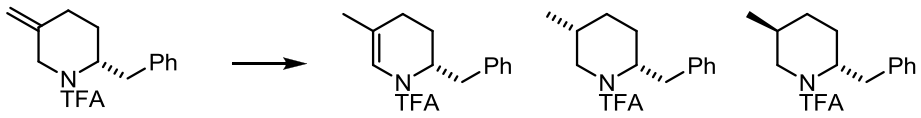
R_f 0.53 (20% diethyl ether in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2958, 1747, 1696, 1450; **^{1}H NMR** (400 MHz, $CDCl_3$) Exhibits strongly rotameric behaviour, **major rotamer** δ-ppm: 0.93 (3 H, d *J* 3.5 Hz, CHC**H$_3$**), 0.99-1.13 (1 H, m, C**H**CH_3), 1.75-1.68 (1 H, m, C**H$_A$**H_BCHN), 1.72-1.80 (2 H, m, C**H$_2$**$CHCH_3$), 2.31-2.40 (1 H, m, CH_A**H$_B$**CHN), 2.91 (1 H, dd *J* 14.0 and 12.0 Hz, C**H$_{A(ax)}$**$CH_{B(eq)}$N), 3.76 (3 H, s, CO_2C**H$_3$**), 3.80 (1 H, dd *J* 12.0 and 4.5 Hz, $CH_{A(ax)}$**H$_{B(eq)}$**N), 5.25 (1 H, d *J* 6.0 Hz, C**H$_{(eq)}$**N), **minor rotamer** δ-ppm: 0.92 (3 H, d *J* 3.5 Hz, CHC**H$_3$**), 0.99-1.13 (1 H, m, C**H**CH_3), 1.75-1.68 (1 H, m, C**H$_A$**H_BCHN), 1.72-1.80 (2 H, m, C**H$_2$**$CHCH_3$), 2.31-2.40 (1 H, m, CH_A**H$_B$**CHN), 2.55 (1 H, dd *J* 14.0 and 13.0 Hz, C**H$_{A(ax)}$**$CH_{B(eq)}$N), 3.78 (3 H, s, CO_2C**H$_3$**), 4.40 (1 H, dd *J* 13.0 and 2.0 Hz, $CH_{A(ax)}$**H$_{B(eq)}$**N), 4.69 (1 H, d *J* 5.5 Hz, C**H$_{(eq)}$**N); **^{13}C NMR** (500 MHz, $CDCl_3$) **major rotamer** δ-ppm: 19.0, 26.3, 29.4, 31.1, 50.0, 52.6, 116.1 (q *J* 280 Hz), 156.7 (q *J* 38 Hz), 170.0; **minor rotamer** δ-ppm: 18.8, 27.5, 29.3, 30.9, 47.5, 52.8, 116.1 (q *J* 280 Hz), 156.7 (q *J* 38 Hz), 170.1; Found MH^+ 254.1002. $C_{10}H_{15}F_3NO_3$ requires MH^+ 254.1004.; $[\alpha]_D^{19}$ -45 (*c* 0.67 in $CHCl_3$).

Methyl (2*S*,5*R*)-5-methyl-1-(trifluoroacetyl)piperidine-2-carboxylate (**149a**)



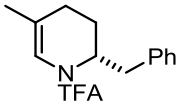
R_f 0.48 (20% diethyl ether in petroleum ether); **ν_{max}/cm^{-1}**: 2959, 1746, 1693, 1452; **^{1}H NMR** (400 MHz, $CDCl_3$) Exhibits strongly rotameric behaviour, **major rotamer** δ-ppm: 1.03 (3 H, d *J* 7.0 Hz, CHC**H$_3$**), 1.44-1.55 (1 H, m, C**H**CH$_3$), 1.54-1.73 (2 H, m, C**H$_2$**CHCH$_3$), 1.92-2.09 (1 H, m, C**H$_A$**H$_B$CHN), 2.11-2.21 (1 H, m, CH$_A$**H$_B$**CHN), 3.51 (1 H, dd *J* 14.0 and 3.5 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.64 (1 H, d *J* 14.0 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 3.76 (3 H, s, CHC**H$_3$**), 5.17 (1 H, d *J* 6.5 Hz, C**H$_{(eq)}$**N), **minor rotamer** δ-ppm: 1.0 (3 H, d *J* 7.5 Hz, CHC**H$_3$**), 1.44-1.55 (1 H, m, C**H**CH$_3$), 1.54-1.73 (2 H, m, C**H$_2$**CHCH$_3$), 1.92-2.09 (1 H, m, C**H$_A$**H$_B$CHN), 2.11-2.21 (1 H, m, CH$_A$**H$_B$**CHN), 3.12 (1 H, dd *J* 14.0 and 3.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.78 (3 H, s, CHC**H$_3$**), 4.22 (1 H, d *J* 14.0 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 4.68 (1 H, d *J* 5.5 Hz, C**H$_{(eq)}$**N); **^{13}C NMR** (500 MHz, $CDCl_3$) **major rotamer** δ-ppm: 15.8, 21.8, 26.7, 30.9, 48.5, 53.5, 117.3 (q, *J* 281 Hz), 157.6 (q *J* 39 Hz), 170.2; **minor rotamer** δ-ppm: 18.8, 22.9, 26.5, 30.3, 46.1, 52.8, 117.1 (q *J* 281 Hz), 157.6 (q *J* 39 Hz), 170.6; Found MH^+ 254.0999. $C_{10}H_{15}F_3NO_3$ requires MH^+ 254.1004.; $[\alpha]_D^{19}$ -52.5 (*c* 1.33 in $CHCl_3$).

Hydrogenation of 1-[(2*R*)-2-Benzyl-5-methylidenepiperidin-1-yl]-2,2,2-trifluoroethan-1-one **122a**



This reaction was done according to the general procedure **C** using (283 mg, 1 mmol) of **122a** to give **150c, 150b** and **150a** each as colourless oil. Chromatography gave **150c** (42 mg, 15%), **150b** (27 mg, 10%) a mixed fraction of **150b** and **150a** (100 mg, 35%) and **150a** (70 mg, 25%). The ratio of *trans* : *cis* (7 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

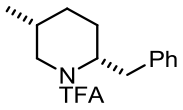
1-[(2*R*)-2-Benzyl-5-methyl-1,2,3,4-tetrahydropyridin-1-yl]-2,2,2-trifluoroethan-1-one (**150c**)



R_f 0.58 (10% diethyl ether in petrolum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 1916, 1667, 1426; **^{1}H NMR** (500 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 1.55-1.80 (2 H, m, C**H$_2$**CHN), 1.81 (3 H, s, C**H$_3$**), 1.90-2.06 (1 H, m, C**H$_A$**H$_B$C=C), 2.22-2.34 (1 H, m, CH$_A$**H$_B$**C=C), 2.70 (1 H, dd *J* 13.5 and 10.0 Hz, C**H$_A$**H$_B$Ph), 2.88 (1 H, dd *J* 13.5 and 6.0 Hz, C**H$_A$**H$_B$Ph), 4.75-4.83 (1 H, m, C**H**N), 6.48 (1 H, s, C**H**=C), 7.18-7.38 (5 H, m, Ph); **minor rotamer** δ ppm: 1.55-1.80 (2 H, m, C**H$_2$**CHN), 1.81 (3 H, s, C**H$_3$**), 1.90-2.06 (1 H, m, C**H$_A$**H$_B$C=C), 2.22-2.34 (1 H, m, CH$_A$**H$_B$**C=C), 2.70 (1 H, dd *J* 13.5 and 10.0 Hz, C**H$_A$**H$_B$Ph), 2.88 (1 H, dd *J* 13.5 and 6.0 Hz,

$CH_A\mathbf{H_B}Ph$), 4.28-4.36 (1 H, m, C**H**N), 6.88 (1 H, s, C**H**=C), 7.18-7.38 (5 H, m, Ph); **^{13}C NMR** ($CDCl_3$) **major rotamer** δ ppm: 21.1, 22.1, 23.3, 35.8, 51.0, 115.4, 116.1 (q *J* 288 Hz), 116.6, 126.9, 128.7, 129.2, 137.5, 157.1 (q *J* 39 Hz); **minor rotamer** δ ppm: 20.9, 22.6, 23.4, 37.0, 53.2, 116.1 (q *J* 288 Hz), 118.5, 120.4, 126.7, 128.5, 129.0, 141.1, 157.1 (q *J* 39 Hz); Found MH^+ 284.1265 $C_{15}H_{17}F_3NO$ requires MH^+ 284.1262; $[\alpha]_D^{19}$ +45 (*c* 2.67 in $CHCl_3$).

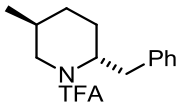
1-[(2*R*,5*R*)-2-Benzyl-5-methylpiperidin-1-yl]-2,2,2-trifluoroethan-1-one (**150b**)



R_f 0.46 (10% diethyl ether in petrolum ether); **ν_{max}/cm^{-1}**: 2931, 1685, 1196; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 1.0 (3 H, d *J* 6.5 Hz, C**H_3**CH), 1.41-1.75 (2 H, m, C**H_2**CHN), 1.41-1.75 (2 H, m, C**H_2**$CHCH_3$), 1.41-1.75 (1 H, m, CH_3C**H**), 2.85-2.96 (2 H, m, C**H_2**Ph), 3.09 (1 H, dd *J* 14.0 and 10.0 Hz, C**$H_{A(ax)}$**$H_{B(eq)}$N), 3.72 (1 H, dd *J* 14.0 and 2.0 Hz, $CH_{A(ax)}$**$H_{B(eq)}$**N), 4.0 (1 H, appr.q *J* 7.0 Hz, C**$H_{(eq)}$**N), 7.17-7.4 (5 H, m, Ph); **minor rotamer** δ ppm: 1.03 (3 H, d *J* 6.5 Hz, C**H_3**CH), 1.41-1.75 (2 H, m, C**H_2**CHN), 1.41-1.75 (2 H, m, C**H_2**$CHCH_3$), 1.41-1.75 (1 H, m, CH_3C**H**), 2.64 (1 H, dd *J* 13.5 and 12.5 Hz, C**$H_{A(ax)}$**$H_{B(eq)}$N), 2.85-2.96 (2 H, m, C**H_2**Ph), 4.18-4.26 (1 H, m, C**$H_{(eq)}$**N), 4.44 (1 H, dd *J* 12.5 and 4.0 Hz, $CH_{A(ax)}$**$H_{B(eq)}$**N), 7.17-7.4 (5 H, m, Ph); **^{13}C NMR** ($CDCl_3$) **major rotamer** δ ppm: 19.0, 26.1,

27.3, 31.3, 35.5, 45.2, 51.0, 126.6, 128.5, 129.0, 137.5, 116.1 (q *J* 288 Hz), 157.1 (q *J* 39 Hz); **minor rotamer** δ ppm: 19.2, 26.6, 27.6, 31.9, 36.5, 47.9, 54.6, 126.9, 128.7, 129.1, 137.5, 116.1 (q *J* 288 Hz), 157.1 (q *J* 39 Hz); Found MH^+ 286.1424 $C_{15}H_{19}F_3NO$ requires MH^+ 286.1419; $[\alpha]_D^{19}$ -37 (*c* 2.67 in $CHCl_3$).

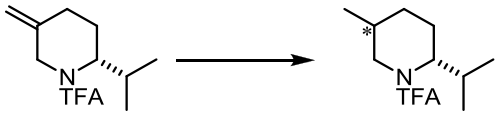
1-[(2*R*,5*S*)-2-Benzyl-5-methylpiperidin-1-yl]-2,2,2-trifluoroethan-1-one (**150a**)



R_f 0.37 (10% diethyl ether in petrolum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2940, 1683, 1194; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 1.03 (3 H, d *J* 7.0 Hz, C**H$_3$**CH), 1.37-1.53 (1 H, m, C**H$_A$**H$_B$CHN), 1.37-1.53 (1 H, m, C**H$_A$**H$_B$CHCH$_3$), 1.75-1.88 (1 H, m, CH$_A$**H$_B$**CHCH$_3$), 1.97-2.12 (1 H, m, CH$_A$**H$_B$**CHN), 2.11-2.21 (1 H, m, CH$_3$C**H**), 2.89-2.95 (2 H, m, C**H$_2$**Ph), 3.50 (1 H, dd *J* 14.5 and 3.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.59 (1 H, d *J* 14.5 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 4.85 (1 H, appr.q *J* 7.0 Hz, C**H$_{(eq)}$**N), 7.15-7.37 (5 H, m, Ph); **minor rotamer** δ ppm: 1.04 (3 H, d *J* 7.0 Hz, C**H$_3$**CH), 1.37-1.53 (1 H, m, C**H$_A$**H$_B$CHN), 1.37-1.53 (1 H, m, C**H$_A$**H$_B$CHCH$_3$), 1.75-1.88 (1 H, m, CH$_A$**H$_B$**CHCH$_3$), 1.97-2.12 (1 H, m, CH$_A$**H$_B$**CHN), 2.11-2.21 (1 H, m, CH$_3$C**H**), 2.89-2.95 (2 H, m, C**H$_2$**Ph), 3.24 (1 H, dd *J* 14.0 and 2.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 4.17-4.26 (1 H, m, C**H$_{(eq)}$**N), 4.32 (1 H, d *J* 14.0 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 7.15-7.37 (5 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) **major rotamer** δ ppm: 16.1, 20.8, 24.6, 27.6, 35.7,

46.2, 52.0, 116.4 (q *J* 288 Hz), 126.6, 128.5, 129.1, 137.5, 157.1 (q *J* 39 Hz); **minor rotamer** δ ppm: 15.9, 21.0, 24.3, 27.8, 36.6, 43.5, 55.2, 116.4 (q *J* 288 Hz), 126.9, 128.7, 129.2, 137.5, 157.1 (q *J* 39 Hz); Found MH^+ 286.1413 $C_{15}H_{19}F_3NO$ requires MH^+ 286.1419; $[\alpha]_D^{19}$ -33.3 (*c* 4.5 in $CHCl_3$).

Hydrogenation of 2,2,2-Trifluoro-1-[(2R)-5-methylidene-2-(propan-2-yl)piperidin-1-yl]ethan-1-one **122b**

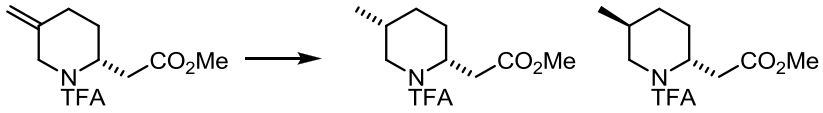


This reaction was done according to the general procedure **C** using (102 mg, 0.43 mmol) of **122b** to give **151b** and **151a** each as colourless oil. Chromatography gave two an inseparable mixture of **151b** and **151a** (76 mg, 75%). The ratio of *trans* : *cis* (4 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

^{1}H NMR (500 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major diastereoisomer** δ ppm: 0.81 and 0.83 (3 H, d *J* 7.0 Hz, C**H$_3$**CH for each rotamer), 0.96 and 0.97 (3 H, d *J* 7.0 Hz, CHC**H$_3$**CH_3 for each rotamer), 1.0 and 1.05 (3 H, d *J* 7.0 Hz, $CHCH_3$C**H$_3$** for each rotamer), 1.34-1.41 (1 H, m, C**H$_A$**H_BCHN), 1.65-1.70 (1 H, m, CH_A**H$_B$**CHN), 1.75-1.90 (2 H, m, C**H$_2$**$CHCH_3$), 1.95-2.0 and 2.0-2.10 (1 H, m, C**H$_3$**CH for each rotamer), 2.10-2.20 and 2.20-2.30 (1 H, m, C**H**CH_3CH_3 for each rotamer), 2.95 and 3.32 (1 H, dd *J* 13.5 and 3.5 Hz, 14.0 and 4.0 Hz, C**H$_{A(ax)}$**$H_{B(eq)}$N for each rotamer), 3.47 and 4.25 (1 H, m, C**H**N for each rotamer), 3.53 and 4.21 (1

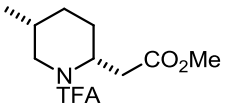
H, d *J* 13.5 Hz, 14.0 Hz, $CH_{A(ax)}\mathbf{H_{B(eq)}}N$ for each rotamer); **minor diastereoisomer**: 2.36 and 2.70 (1 H, dd *J* 13.5 and 13.5 Hz, and 14.0 and 11.5 Hz, $C\mathbf{H_{A(ax)}}H_{B(eq)}N$ for each rotamer), 3.65 and 4.31 (1 H, d *J* 13.5 Hz, and 14.0 Hz, $CH_{A(ax)}\mathbf{H_{B(eq)}}N$ for each rotamer); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm: 16.1, 18.6, 19.7, 20.0, 20.1, 21.5, 24.7, 25.6, 27.6, 28.0, 43.5, 46.1, 56.6, 59.9, 117.1 (q *J* 288 Hz), 158.0 (q *J* 40 Hz).

Hydrogenation of methyl 2-[(2*R*)-5-methylidene-1(trifluoroacetyl)piperidin-2-yl] acetate **122c**



This reaction was done according to the general procedure **C** using (267 mg, 1 mmol) of **122c** to give **152b** and **152a** each as colourless oil. Chromatography gave **152b** (428 mg, 18%), a mixed fraction of **152b** and **152a** (112 mg, 42%) and **152a** (53 mg, 20%). The ratio of *trans* : *cis* (2.5 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

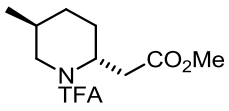
Methyl 2-[(2*R*,5*R*)-5-methyl-1-(trifluoroacetyl)piperidin-2-yl]acetate (**152b**)



R_f 0.38 (15% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 2928, 1742, 1656; **^{1}H NMR** (500 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 0.96 (3 H, d *J* 4.0 Hz, $C\mathbf{H_3}CH$), 1.19-1.37 (2 H, m, $C\mathbf{H_2}CHCH_3$), 1.53-1.66 (1 H, m, $C\mathbf{H}CH_3$), 1.67-1.80 (2 H, m, $C\mathbf{H_2}CHN$),

2.56 (1 H, dd *J* 15.0 and 8.0 Hz, C**H$_A$**H$_B$CO$_2$CH$_3$), 2.65 (1 H, dd *J* 15.0 and 7.5 Hz, CH$_A$**H$_B$**CO$_2$CH$_3$), 2.79 (1 H, dd *J* 15.0 and 12.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.65 (3 H, s, CO$_2$C**H$_3$**), 3.70 (1 H, d *J* 12.0 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 5.1 (1 H, m C**H$_{(eq)}$**N), **minor rotamer** δ ppm: 0.94 (3 H, d *J* 4.0 Hz, C**H$_3$**CH), 1.19-1.37 (2 H, m, C**H$_2$**CHCH$_3$), 1.53-1.66 (1 H, m, C**H**CH$_3$), 1.67-1.80 (2 H, m, C**H$_2$**CHN), 2.41 (1 H, dd *J* 15.0 and 12.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 2.56 (1 H, dd *J* 15.0 and 8.0 Hz, C**H$_A$**H$_B$CO$_2$CH$_3$), 2.83 (1 H, dd *J* 15.0 and 6.5 Hz, CH$_A$**H$_B$**CO$_2$CH$_3$), 3.69 (3 H, s, CO$_2$C**H$_3$**), 4.37 (1 H, dd *J* 12.0 and 4.0 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 4.51-4.60 (1 H, m C**H**N); **^{13}C NMR** (100 MHz, CDCl$_3$) **major rotamer** δ ppm: 18.9, 27.3, 27.8, 31.1, 34.4, 46.7, 47.7, 51.9, 116.1 (q *J* 285 Hz), 157.0 (q *J* 39 Hz), 173.3, **minor rotamer** δ ppm: 19.2, 27.5, 27.9, 31.8, 35.3, 46.9, 47.8, 52.3, 116.1 (q *J* 285 Hz), 157.0 (q *J* 39 Hz), 173.3, Found MH$^+$ 268.1157 $C_{11}H_{17}F_3NO_3$ requires MH$^+$ 268.1161; $[\alpha]_D^{22}$ -40 (*c* 1.0 in CHCl$_3$).

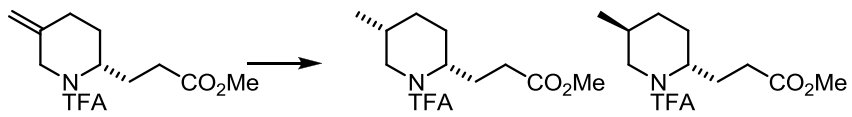
Methyl 2-[(2*R*,5*S*)-5-methyl-1-(trifluoroacetyl)piperidin-2-yl]acetate (**152a**)



R$_f$ 0.33 (15% ethyl acetate in petrplum ether); **ν_{max}/cm^{-1}**: 2946, 1737, 1681, 1454; **^{1}H NMR** (500 MHz, CDCl$_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 1.03 (3 H, d *J* 7.5 Hz, C**H$_3$**CH), 1.40-1.50 (1 H, m, C**H$_A$**H$_B$CHCH$_3$), 1.50-1.55 (1 H, m C**H$_A$**H$_B$CHN), 1.83-1.95 (1 H, m, CH$_A$**H$_B$**CHCH$_3$), 1.95-2.05 (1 H, m, CH$_A$**H$_B$**CHN), 2.05-2.15 (1 H, m, CH$_3$C**H**), 2.60 (1 H, dd *J* 14.5 and 8.0 Hz, C**H$_A$**H$_B$CO$_2$CH$_3$), 2.73 (1 H, dd *J*

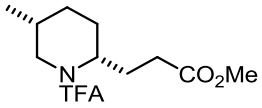
14.5 and 8.0 Hz, $CH_A\mathbf{H_B}CO_2CH_3$), 3.45 (1 H, dd *J* 14.0 and 3.5 Hz, $C\mathbf{H_{A(ax)}}H_{B(eq)}N$), 3.57 (1 H, d *J* 14.0 Hz, $CH_{A(ax)}\mathbf{H_{B(eq)}}N$), 3.67 (3 H, s, $CO_2C\mathbf{H_3}$), 5.05 (1 H, q *J* 6.5 Hz, $C\mathbf{H_{(eq)}}N$); **minor rotamer** δ ppm: 1.03 (3 H, d *J* 7.5 Hz, $C\mathbf{H_3}CH$), 1.40-1.50 (1 H, m, $C\mathbf{H_A}H_BCHCH_3$), 1.50-1.55 (1 H, m $C\mathbf{H_A}H_BCHN$), 1.83-1.95 (1 H, m, $CH_A\mathbf{H_B}CHCH_3$), 1.95-2.05 (1 H, m, $CH_A\mathbf{H_B}CHN$), 2.05-2.15 (1 H, m, $CH_3C\mathbf{H}$), 2.63 (1 H, dd *J* 15.5 and 8.0 Hz, $C\mathbf{H_A}H_BCO_2CH_3$), 2.88 (1 H, dd *J* 15.5 and 9.0 Hz, $CH_A\mathbf{H_B}CO_2CH_3$), 3.02 (1 H, dd *J* 14.0 and 2.5 Hz, $C\mathbf{H_{A(ax)}}H_{B(eq)}N$), 3.71 (3 H, s, $CO_2C\mathbf{H_3}$), 4.26 (1 H, d *J* 14.0 Hz, $CH_{A(ax)}\mathbf{H_{B(eq)}}N$), 4.57-4.6 (1 H, m, C**H**N); **^{1}H NMR at 303 K** (500 MHz, $CDCl_3$) δ ppm: 1.04 (3 H, d *J* 7.0 Hz, $C\mathbf{H_3}CH$), 1.44 (1 H, d *J* 10.0 Hz, $C\mathbf{H_A}H_BCHCH_3$), 1.57 (1 H, d *J* 15.5 Hz, $C\mathbf{H_A}H_BCHN$), 1.85-1.97 (1 H, m, $CH_A\mathbf{H_B}CHCH_3$), 1.97-2.16 (1 H, m, $CH_A\mathbf{H_B}CHN$), 1.97-2.16 (1 H, m, $CH_3C\mathbf{H}$), 2.52-2.79 (2 H, m, $C\mathbf{H_2}CO_2CH_3$), 3.52 (1 H, d *J* 4.5 Hz, $C\mathbf{H_{A(ax)}}H_{B(eq)}N$), 3.69 (3 H, s, $CO_2C\mathbf{H_3}$), 4.43 (1 H, d *J* 16.0 Hz, $CH_{A(ax)}\mathbf{H_{B(eq)}}N$), 4.87-5.13 (1 H, m, C**H**N); **^{13}C NMR** (100 MHz, $CDCl_3$) **major rotamer** δ ppm: 16.1, 24.8, 27.5, 34.6, 46.3, 48.0, 51.9, 116.5 (q *J* 288 Hz), 140.1, 157.2 (q *J* 40 Hz), 170.6; **minor rotamer** δ ppm: 15.7, 24.3, 27.5, 35.4, 43.5, 48.0, 51.9, 116.6 (q *J* 288 Hz), 139.7, 157.2 (q *J* 40 Hz), 170.6; Found MH^+ 268.1157 $C_{11}H_{17}F_3NO_3$ requires MH^+ 268.1161; $[\alpha]_D^{22}$ +20 (*c* 1.0 in $CHCl_3$).

Hydrogenation of methyl 3-[(2*R*)-5-methylidene-1-(trifluoroacetyl)piperidin-2-yl]propanoate **122d**



This reaction was done according to the general procedure **C** using (279 mg, 1 mmol) of **122d** to give **153b** and **153a** each as colourless oil. Chromatography gave **153b** (47 mg, 17%), a mixed fraction of **153b** and **153a** (106 mg, 38%) and **153a** (70 mg, 25%). The ratio of *trans* : *cis* (2.5 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

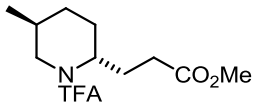
Methyl 3-[(2*R*,5*R*)-5-methyl-1-(trifluoroacetyl)piperidin-2-yl]propanoate (**153b**)



R_f 0.35 (30% diethyl ether in petroleum ether); **ν_{max}/cm^{-1}**: 2953, 1739, 1684; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 0.94 (3 H, d *J* 5.5 Hz, C**H$_3$**CH), 1.21-1.39 (2 H, m, CH_3CHC**H$_2$**), 1.60-1.65 (1 H, m, CH_3C**H**), 1.70-1.85 (2 H, m, C**H$_2$**CHN), 1.84-1.99 (1 H, m, C**H$_A$**$H_B$$CH_2CO_2CH_3$), 2.08-2.21 (1 H, m, CH_A**H$_B$**$CH_2CO_2CH_3$), 2.21-2.39 (2 H, m, C**H$_2$**CO_2CH_3), 3.79 (1 H, dd *J* 12.5 and 11.5 Hz, C**H$_{A(ax)}$**$H_{B(eq)}$N), 3.64 (1 H, dd *J* 12.5 and 2.0 Hz, $CH_{A(ax)}$**H$_{B(eq)}$**N), 3.66 (3 H, s, CO_2C**H$_3$**), 4.62-4.75 (1 H, m, C**H**N); **minor rotamer** δ ppm: 0.93 (3 H, d *J* 5.5 Hz, C**H$_3$**CH), 1.21-1.39 (2 H, m, C**H$_2$**$CHCH_3$), 1.60-1.65 (1 H, m, CH_3C**H**), 1.70-1.85 (2 H, m, C**H$_2$**CHN), 1.84-1.99 (1 H, m, C**H$_A$**$H_B$$CH_2CO_2CH_3$), 2.08-2.21 (1 H, m, CH_A**H$_B$**$CH_2CO_2CH_3$), 2.21-2.39 (2 H, m, C**H$_2$**CO_2CH_3), 2.54 (1 H, dd *J* 14.5 and 13.0 Hz, C**H$_{A(ax)}$**$H_{(eq)}$N), 3.67 (3 H, s, CO_2C**H$_3$**), 4.31 (1 H, dd *J* 13.0 and 4.0 Hz, $CH_{A(ax)}$**H$_{B(eq)}$**N), 3.99-4.08 (1 H, m, C**H**N); **^{13}C NMR** (100 MHz,

$CDCl_3$) **major rotamer** δ ppm: 15.5, 22.9, 25.4, 27.9, 28.3, 30.3, 48.9, 51.7, 52.8, 116.6 (q *J* 291 Hz), 157.2 (q *J* 40 Hz), 173.3; **minor rotamer** δ ppm: 15.7, 23.1, 26.2, 28.0, 28.9, 31.3, 44.5, 51.8, 52.2, 116.6 (q *J* 291 Hz), 157.2 (q *J* 40 Hz), 173.3; Found MH^+ 282.1328 $C_{12}H_{19}F_3NO_3$ requires MH^+ 282.1317; $[\alpha]_D^{22}$ +51 (*c* 1.0 in $CHCl_3$).

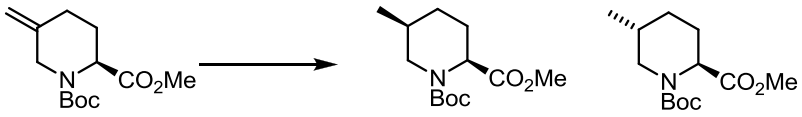
Methyl 3-[(2*R*,5*S*)-5-methyl-1-(trifluoroacetyl)piperidin-2-yl]propanoate (**153a**)



R_f 0.29 (30% diethyl ether in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2946, 1736, 1678, 1439, 1365; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 1.00 (3 H, d *J* 7.0 Hz, C**H$_3$**CH), 1.35-1.42 (1 H, m, C**H$_A$**H$_B$CH$_2$CO$_2$CH$_3$), 1.42-1.52 (1 H, m, CH$_2$CH$_A$**H$_B$**CH), 1.74-1.86 (1 H, m C**H$_A$**H$_B$CHN), 1.86-2.10 (1 H, m, CH$_A$**H$_B$**CHN), 1.86-2.10 (2 H, m, C**H$_2$**CO$_2$CH$_3$), 1.86-2.10 (1 H, m, CH$_3$C**H**), 2.13-2.38 (2 H, m, C**H$_2$**CO$_2$CH$_3$), 3.40 (1 H, dd *J* 14.0 and 3.5 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.53 (1 H, d *J* 14.0 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 3.66 (3 H, s, CO$_2$C**H$_3$**), 4.64-4.73 (1 H, m, C**H**N); **minor rotamer** δ ppm: 1.00 (3 H, d *J* 7.0 Hz, C**H$_3$**CH), 1.35-1.42 (1 H, m, C**H$_A$**H$_B$CHCH$_3$), 1.42-1.52 (1 H, m, CH$_A$**H$_B$**CHCH$_3$), 1.74-1.86 (1 H, m CHNC**H$_A$**H$_B$), 1.86-2.10 (1 H, m, CHNCH$_A$**H$_B$**), 1.86-2.10 (2 H, m, C**H$_2$**CH$_2$CO$_2$CH$_3$), 1.86-2.10 (1 H, m, CH$_3$C**H**), 2.13-2.38 (2 H, m, C**H$_2$**CO$_2$CH$_3$), 3.03 (1 H, dd *J* 14.0 and 2.50 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.67 (3 H, s, CO$_2$C**H$_3$**), 3.99-4.07 (1 H, m, C**H**N), 4.21 (1 H, d *J* 14.0 Hz,

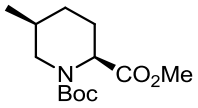
$CH_{A(ax)}\mathbf{H_{B(eq)}}N$); **^{13}C NMR** (100 MHz, $CDCl_3$) **major rotamer** δ ppm: 15.8, 19.2, 22.9, 24.6, 27.5, 29.7, 45.6, 50.0, 51.7, 116.1 (q *J* 290 Hz), 157.2 (q *J* 40 Hz), 173.4, **minor rotamer** δ ppm: 16.1, 20.1, 23.7, 24.7, 27.9, 30.3, 42.8, 50.3, 52.7, 116.1 (q *J* 290 Hz), 157.2 (q *J* 40 Hz), 173.4; Found MH^+ 282.1328 $C_{12}H_{19}F_3NO_3$ requires MH^+ 282.1317; $[\alpha]_D^{22}$ +44 (*c* 1.0 in $CHCl_3$).

Hydrogenation of 1-*tert*-Butyl 2-methyl (2*S*)-5-methylidenepiperidine-1,2-dicarboxylate ***ent*-37**



This reaction was done according to the general procedure **C** using (255 mg, 1 mmol) of ***ent*-37** to give **154b** and **154a** each as colourless oil. Chromatography gave **154b** (79 mg, 31%), a mixed fraction of **154b** and **154a** (120 mg, 47%) and **154a** (43 mg, 17%). The ratio of *cis* : *trans* (3 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

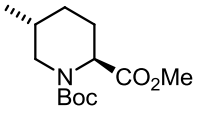
1-*tert*-Butyl 2-methyl (2*S*,5*S*)-5-methylpiperidine-1,2-dicarboxylate (**154b**)



R_f 0.45 (25% diethyl ether in petroleum ether); **ν_{max}/cm^{-1}**: 1745, 1702, 1393; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **first rotamer** δ-ppm: 0.87 (3 H, d *J* 3.0 Hz, C**H$_3$**CH), 1.43 (9 H, s, C(C**H$_3$**)$_3$), 1.55-1.76 (2 H, m, C**H$_2$**CHN), 1.77-1.96 (2 H, m, C**H$_2$**CH), 2.16-2.27 (1 H, m, CH_3C**H**), 2.41 (1 H, dd *J* 13.5 and 12.5 Hz, C**H$_{A(ax)}$**$H_{B(eq)}$N), 3.71 (3 H, s, CO_2C**H$_3$**), 3.84 (1 H, dd *J* 12.5 and 4.5 Hz, $CH_{A(ax)}$**H$_{B(eq)}$**N), 4.72 (1 H, d *J* 5.5 Hz, C**H$_{(eq)}$**N); **second rotamer** δ-ppm: 0.85 (3 H, d *J* 3.0

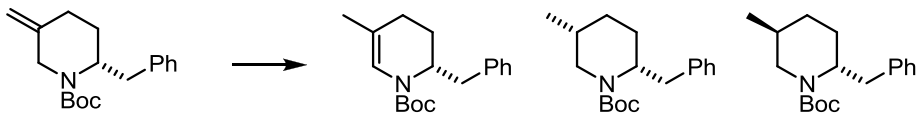
Hz, C**H**$_3$CH), 1.44 (9 H, s, C(C**H**$_3$)$_3$), 1.55-1.76 (2 H, m, C**H**$_2$CHN), 1.77-1.96 (2 H, m, C**H**$_2$CH), 2.16-2.27 (1 H, m, CH$_3$C**H**), 2.54 (1 H, dd *J* 13.5 and 12.5 Hz, C**H**$_{A(ax)}$H$_{B(eq)}$N), 3.73 (3 H, s, CO$_2$C**H**$_3$), 3.99 (1 H, dd *J* 12.5 and 4.5 Hz, CH$_{A(ax)}$**H**$_{B(eq)}$N), 4.0 (1 H, d *J* 5.5 Hz, C**H**$_{(eq)}$N); **^{13}C NMR** (400 MHz, CDCl$_3$) **first rotamer** δ ppm: 19.1, 26.7, 28.2, 29.4, 30.4, 47.9, 52.0, 81.9, 157.3; **second rotamer** δ ppm: 19.1, 26.5, 28.3, 29.6, 30.6, 48.9, 53.1, 81.9, 157.3; Found MH$^+$ 258.1696. $C_{13}H_{24}NO_4$ requires MH$^+$ 258.1705.; $[\alpha]_D^{21}$ -25 (*c* 2.0 in CHCl$_3$).

1-*tert*-Butyl 2-methyl (2*S*,5*R*)-5-methylpiperidine-1,2-dicarboxylate (**154a**)



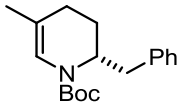
R$_f$ 0.41 (25% diethyl ether in petroleum ether); **ν_{max}/cm^{-1}**: 1750, 1703, 1363; **^{1}H NMR** (400 MHz, CDCl$_3$) δ-ppm: 0.98 (3 H, d *J* 7.0 Hz, C**H**$_3$CH), 1.45 (9 H, s, C(C**H**$_3$)$_3$), 1.50-1.63 (2 H, m, C**H**$_2$CHN), 1.80-1.91 (1 H, m, CH$_3$C**H**), 1.91-1.99 (2 H, m, C**H**$_2$CH), 3.16 (1 H, d *J* 13.5 Hz, C**H**$_{A(ax)}$H$_{B(eq)}$N), 3.60 (1 H, d *J* 13.5 Hz, CH$_{A(ax)}$**H**$_{B(eq)}$N), 3.72 (3 H, s, CO$_2$C**H**$_3$), 4.58-4.87 (1 H, br, C**H**$_{(eq)}$N); Found MH$^+$ 258.1698. $C_{13}H_{24}NO_4$ requires MH$^+$ 258.1705.; $[\alpha]_D^{21}$ -5 (*c* 2.0 in CHCl$_3$).

Hydrogenation of *tert*-butyl (2*R*)-2-benzyl-5-methylidenepiperidine-1-carboxylate (**119a**)



This reaction was done according to the general procedure **C** using (286 mg, 1 mmol) of **119a** to give **148c, 148b** and **148a** each as colourless oil. Chromatography gave **148c** (28 mg, 10%), **148b** (28 mg, 10%) a mixed fraction of **148b** and **148a** (156 mg, 55%) and **148a** (42 mg, 15%). The ratio of *trans* : *cis* (3 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

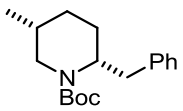
tert-Butyl (2*R*)-2-benzyl-5-methyl-1,2,3,4-tetrahydropyridine-1-carboxylate (**148c**)



R_f 0.53 (10% diethyl ether in petroleum ether), $\mathbf{\nu_{max}/cm^{-1}}$: 2920, 1693, 1453, 1393, 1365; **^{1}H NMR** (500 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 1.35 (9 H, s, C(C**H$_3$**)$_3$), 1.53-1.62 (1 H, m, C**H$_A$**H$_B$CHN), 1.64-1.69 (1 H, m, CH$_A$**H$_B$**CHN), 1.71 (3 H, s, C**H$_3$**), 1.76-1.87 (1 H, m, C**H$_A$**H$_B$C=CH), 2.08-2.20 (1 H, m, CH$_A$**H$_B$**C=CH), 2.56-2.59 (1 H, m, C**H$_A$**H$_B$Ph), 2.80 (1 H, dd *J* 12.5, 6.0 Hz, CH$_A$**H$_B$**Ph), 4.26-4.32 (1 H, m, C**H**N), 6.67 (1 H, s, C**H**=C), 7.03-7.14 (5 H, m, Ph); **minor rotamer** δ ppm: 1.44 (9 H, s, C(C**H$_3$**)$_3$), 1.53-1.62 (1 H, m, C**H$_A$**H$_B$CHN), 1.64-1.69 (1 H, m, CH$_A$**H$_B$**CHN), 1.71 (3 H, s, C**H$_3$**), 1.76-1.87 (1 H, m, C**H$_A$**H$_B$C=CH), 2.08-2.20 (1 H, m, CH$_A$**H$_B$**C=CH), 2.56-2.59 (1 H, m, C**H$_A$**H$_B$Ph), 2.80 (1 H, dd *J* 12.5 and 6.0 Hz, CH$_A$**H$_B$**Ph), 4.41-4.48 (1 H, m, C**H**N), 6.50 (1 H, s, C**H**=C), 7.12-7.25 (5 H, m, Ph); **^{1}H NMR at 373 K** (500 MHz, d_6-DMSO) δ ppm: 1.34 (9 H, s, C(C**H$_3$**)$_3$), 1.54-1.63 (1 H, m,

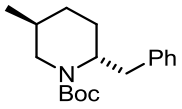
C**H$_A$**H$_B$CHN), 1.65-1.68 (1 H, m, CH$_A$**H$_B$**CHN), 1.69 (3 H, s, C**H$_3$**), 1.81 (1 H, dd *J* 18.0 and 6.0 Hz, C**H$_A$**H$_B$C=CH), 2.11-2.22 (1 H, m, CH$_A$**H$_B$**C=CH), 2.61 (1 H, dd *J* 13.5 and 8.5 Hz, C**H$_A$**H$_B$Ph), 2.71 (1 H, dd *J* 13.5 and 7.0 Hz, CH$_A$**H$_B$**Ph), 4.27-4.35 (1 H, m, C**H**N), 6.52 (1 H, s, C**H**=C), 7.13-7.30 (5 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) **major rotamer** δ ppm: 20.9, 22.6, 23.1, 28.1, 36.5, 50.4, 80.0, 113, 118.6, 126.2, 128.2, 129.3, 149.0, 156; **minor rotamer** δ ppm: 20.9, 22.9, 23.6, 28.3, 37.1, 51.7, 80.0, 114.0, 119.0, 126.2, 128.4, 129.3, 149.5, 156.0; Found MH$^+$ 288.1952 $C_{18}H_{26}NO_2$ requires MH$^+$ 288.1964; $[\alpha]_D^{24}$ +7 (*c* 1.0 in $CHCl_3$).

tert-Butyl (2*R*,5*R*)-2-benzyl-5-methylpiperidine-1-carboxylate (**148b**)



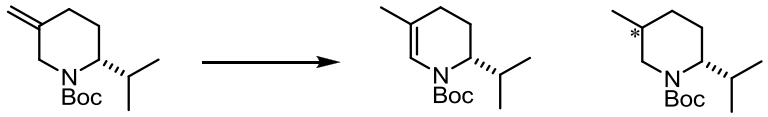
R$_f$ 0.33 (10% diethyl ether in petroleum ether); **ν_{max}/cm^{-1}**: 2927, 1689, 1158; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.95 (3 H, d *J* 6.5 Hz, C**H$_3$**CH), 1.23-1.45 (2 H, m, C**H$_2$**CHN), 1.23-1.45 (2 H, m, C**H$_2$**CHCH$_3$), 1.58-1.62 (1 H, m, CH$_3$C**H**), 2.51 (1 H, dd *J* 14.0 and 12.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 2.65-2.77 (1 H, m, C**H$_A$**H$_B$Ph), 2.77-2.94 (1 H, m, CH$_A$**H$_B$**Ph), 4.08 (1 H, d *J* 12.0 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 4.31-4.42 (1 H, br, C**H$_{(eq)}$**N), 7.15-7.35 (5 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.1, 19.3, 27.8, 28.2, 31.2, 46.1, 65.8, 72.3, 79.1, 126.1, 128.3, 129.2, 136.2, 157.1; Found MH$^+$ 290.2125 $C_{18}H_{28}NO_2$ requires MH$^+$ 290.2120; $[\alpha]_D^{19}$ -30 (*c* 1.67 in $CHCl_3$).

tert-Butyl (2*R*,5*S*)-2-benzyl-5-methylpiperidine-1-carboxylate (**148a**)



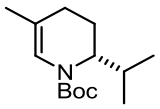
R_f 0.26 (10% diethyl ether in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2933, 1688, 1172; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.01 (3 H, d *J* 7.0 Hz, C$\mathbf{H_3}$CH), 1.30-1.39 (1 H, m, C$\mathbf{H_A}$$H_B$CHN), 1.36 (9 H, s, C(C$\mathbf{H_3}$)$_3$), 1.59-1.62 (1 H, m, C$\mathbf{H_A}$$H_BCHCH_3$), 1.72-1.84 (1 H, m, C$H_A$$\mathbf{H_B}$CHN), 1.86-1.99 (1 H, m, C$H_A$$\mathbf{H_B}CHCH_3$), 1.86-1.99 (1 H, m, C$H_3$C**H**), 2.78 (1 H, dd *J* 13.0 and 8.5 Hz, C$\mathbf{H_A}$$H_B$Ph), 2.92 (1 H, dd *J* 13.0 and 7.5 Hz, C$H_A$$\mathbf{H_B}$Ph), 3.14 (1 H, dd *J* 13.5 and 3.5 Hz, C$\mathbf{H_{A(ax)}}$$H_{B(eq)}$N), 3.78 (1 H, d *J* 13.5 Hz, C$H_{A(ax)}$$\mathbf{H_{B(eq)}}$N), 4.35 (1 H, appr.q *J* 7.5 Hz, C$\mathbf{H_{(eq)}}$N), 7.16-7.32 (5 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 16.6, 21.8, 25.0, 27.7, 28.3, 36.3, 43.9, 52.3, 78.9, 126.0, 128.3, 129.2, 139.3, 155.5; Found MH^+ 290.2132 $C_{18}H_{28}NO_2$ requires MH^+ 290.2120; $[\alpha]_D^{19}$ -32.9 (*c* 4.25 in $CHCl_3$).

Hydrogenation of *tert*-butyl (2*R*)-5-methylidene-2-(propan-2-yl)piperidine-1-carboxylate **119b**



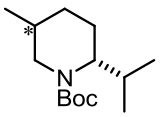
This reaction was done according to the general procedure **C** using (167 mg, 0.69 mmol) of **119b** to give **155c**, **155b** and **155a** each as colourless oil. Chromatography gave **155c** (15 mg, 9%), and two inseparable **155b** and **155a** (129 mg, 78%). The ratio of *trans* : *cis* (1.5 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

tert-Butyl (2*R*)-5-methyl-2-(propan-2-yl)-1,2,3,4-tetrahydropyridine-1carboxylate (**155c**)



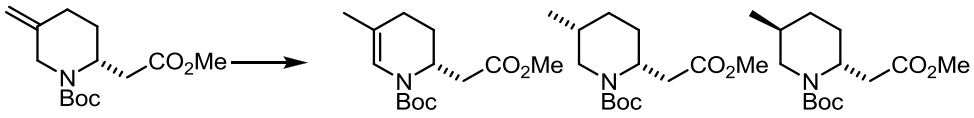
R_f 0.47 (2.5% diethyl ether in petroleum ether) $\mathbf{\nu_{max}/cm^{-1}}$: 2965, 1695, 1455, 1395, 1365, 1155; **^{1}H NMR** (500 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **first rotamer** δ ppm: 0.84 (3 H, d *J* 6.0 Hz, CHC**H$_3$**CH$_3$), 0.97 (3 H, d *J* 6.0 Hz, CHCH$_3$C**H$_3$**), 1.47 (9 H, s, C(C**H$_3$**)$_3$), 1.62-1.66 (1 H, m, C**H**CH$_3$CH$_3$), 1.64 (3 H, s, C**H$_3$**), 1.77 (2 H, dd *J* 17.0 and 5.5 Hz C**H$_2$**CHN), 1.89-2.02 (2 H, m, C**H$_2$**C=CH), 3.90 (1 H, d *J* 10.0 Hz, C**H**N), 6.43 (1 H, s, C**H**=C), **second rotamer** δ ppm: 0.84 (3 H, d *J* 6.0 Hz, CHC**H$_3$**CH$_3$), 0.97 (3 H, d *J* 6.0 Hz, CHCH$_3$C**H$_3$**), 1.47 (9 H, s, C(C**H$_3$**)$_3$), 1.62-1.66 (1 H, m, C**H**CH$_3$CH$_3$), 1.64 (3 H, s, C**H$_3$**), 1.77 (2 H, dd *J* 17.0 and 5.5 Hz, C**H$_2$**CHN), 1.89-2.02 (2 H, m, C**H$_2$**C=CH), 3.74 (1 H, d *J* 10.0 Hz, C**H**N), 6.59 (1 H, s, C**H**=C); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm **first rotamer**: 19.2, 19.7, 20.8, 23.0, 23.3, 28.3, 54.6, 79.9, 114.4, 119.2, 152.2, **second rotamer**: 19.2, 19.3, 19.7, 23.3, 23.5, 27.7, 56.0, 79.9, 115.4, 118.0, 157.0; Found MH^+ 240.1960. $C_{14}H_{26}NO_2$ requires MH^+ 240.1964.; $[\alpha]_D^{24}$ +156 (*c* 1.0 in $CHCl_3$).

tert-Butyl (2*R*)-5-methyl-2-(propan-2-yl)piperidine-1-carboxylate (**155b**/**155a**)



R_f 0.35 (2.5% diethyl ether in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$) **major diastereoisomer** δ ppm: 0.82 (6 H, d *J* 7.0 Hz, (C**H$_3$**)$_2$CH), 0.87 (3 H, d *J* 6.5 Hz, C**H$_3$**CH), 1.24 (1 H, m, C**H$_A$**H$_B$CHCH$_3$), 1.43 (9 H, s, (C**H$_3$**)$_3$), 1.50 (1 H, m, CH$_A$**H$_B$**CHCH$_3$), 1.70-1.76 (2 H, m, C**H$_2$**CHN), 1.78-1.82 (1 H, m, C**H**(CH$_3$)$_2$), 2.03-2.09 (1 H, m, C**H**CH$_3$), 2.89 (1 H, dd *J* 13.5 and 3.5 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.73 (1 H, d *J* 13.5 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 3.80-3.83 (1 H, m, C**H**N); **minor diastereoisomer**: 0.8 (6 H, d *J* 6.5 Hz, (C**H$_3$**)$_2$CH), 0.97 (3 H, d *J* 7.0 Hz, C**H$_3$**CH), 1.10-1.18 (1 H, m, C**H$_A$**H$_B$CHCH$_3$), 1.43 (9 H, s, (C**H$_3$**)$_3$), 1.45-1.51 (1 H, m, CH$_A$**H$_B$**CHCH$_3$), 1.70-1.76 (2 H, m, C**H$_2$**CHN), 1.78-1.82 (1 H, m, C**H**(CH$_3$)$_2$), 2.03-2.09 (1 H, m, C**H**CH$_3$), 3.65 (1 H, dd *J* 11.5 and 4.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.71-3.73 (1 H, m, CH$_{A(ax)}$**H$_{B(eq)}$**N), 3.98-4.03 (1 H, m, C**H**N); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm: 16.6, 18.9, 19.2, 19.4, 20.0, 20.2, 20.5, 25.2, 25.9, 26.0, 26.3, 27.8, 27.9, 28.4, 31.1, 31.4, 44.0, 45.3, 46.7, 55.4, 56.8, 78.7, 78.9, 155.2, 155.9; Found MH$^+$ 242.2131 $C_{14}H_{28}NO_2$ requires MH$^+$ 242.2120.

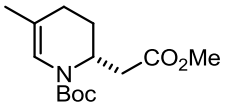
Hydrogenation of *tert*-butyl (2*R*)-2-(2-methoxy-2-oxoethyl)-5-methylidene piperidine-1-carboxylate **119c**



This reaction was done according to the general procedure **C** using (269 mg, 1 mmol) of **119c** to give **156c**, **156b** and **156a** each as colourless oil. Chromatography gave **156c** (26 mg, 10%), **156b** (47 mg, 15%) a mixed fraction of **156b** and **156a** (133 mg, 49%) and **156a** (51 mg, 19%). The

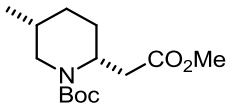
ratio of *trans* : *cis* (1.5 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

tert-Butyl (2*R*)-2-(2-methoxy-2-oxoethyl)-5-methyl-1,2,3,4 tetrahydropyridine-1-carboxylate (**156c**)



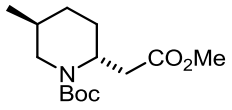
R_f 0.57 (30% diethyl ether in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 1740, 1698, 1680; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 1.18 (3 H, s, C**H$_3$**C=CH), 1.47 (9 H, s, C(C**H$_3$**)$_3$), 1.75-1.83 (2 H, m, CH_3CC**H$_2$**), 1.85-1.92 (1 H, m, C**H$_A$**H$_B$CHN), 1.97-2.10 (1 H, m, CH_A**H$_B$**CHN), 2.51 (1 H, dd *J* 13.5 and 7.0 Hz, C**H$_A$**H$_B$CO$_2$CH$_3$), 2.36 (1 H, dd *J* 13.5 and 8.5 Hz, CH_A**H$_B$**CO$_2$CH$_3$), 3.66 (3 H, s, CO$_2$C**H$_3$**), 4.64-4.72 (1 H, m, C**H**N), 6.43 (1 H, s, C=C**H**N); **minor rotamer** δ ppm: 1.25 (3 H, s, C**H$_3$**C=CH), 1.47 (9 H, s, C(C**H$_3$**)$_3$), 1.75-1.83 (2 H, m, CH_3CC**H$_2$**), 1.85-1.92 (1 H, m, C**H$_A$**H$_B$CHN), 1.97-2.10 (1 H, m, CH_A**H$_B$**CHN), 2.39-2.47 (2 H, m, C**H$_2$**CO$_2$CH$_3$), 3.68 (3 H, s, CO$_2$C**H$_3$**), 4.51-4.60 (1 H, m, C**H**N), 6.58 (1 H, s, C=C**H**N); **^{13}C NMR** (100 MHz, $CDCl_3$) **major rotamer** δ ppm: 21.2, 23.1, 24.6, 28.3, 35.7, 46.2, 51.8, 80.6, 114.1, 119.6, 152.5, 168.6; **minor rotamer** δ ppm: 21.0, 24.4, 24.6, 28.9, 36.3, 46.2, 52.7, 80.6, 114.1, 119.6, 152.5, 168.6; Found MH^+ 270.1711 $C_{14}H_{24}NO_4$ requires MH^+ 270.1705; $[\alpha]_D^{21}$ +50 (*c* 1.0 in $CHCl_3$).

tert-Butyl (2*R*,5*R*)-2-(2-methoxy-2-oxoethyl)-5-methylpiperidine-1-carboxylate (**156b**)



R_f 0.50 (30% diethyl ether in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 1740, 1693, 1435; ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.88 (3 H, d *J* 6.5 Hz, C$\mathbf{H_3}$CH), 1.08-1.33 (2 H, m, C$\mathbf{H_2}$CHCH$_3$), 1.40-1.44 (1 H, m, C$\mathbf{H_A}$H$_B$CHN), 1.44 (9 H, s, C(C$\mathbf{H_3}$)$_3$), 1.54-1.62 (1 H, m, CH$_A$$\mathbf{H_B}$CHN), 1.63-1.71 (1 H, m, CH$_3$C$\mathbf{H}$), 2.47 (1 H, dd *J* 14.5 and 8.0 Hz, C$\mathbf{H_A}$H$_B$CO$_2$CH$_3$), 2.56 (1 H, dd *J* 14.5 and 7.5 Hz, CH$_A$$\mathbf{H_B}CO_2CH_3$), 3.65 (3 H, s, CO$_2C\mathbf{H_3}$), 3.77 (1 H, d *J* 12.0 Hz, C$\mathbf{H_{A(ax)}}$H$_{B(eq)}$N), 4.01 (1 H, d *J* 12.0 Hz, CH$_{A(ax)}$$\mathbf{H_{B(eq)}}$N), 3.60-4.73 (1 H, m, C$\mathbf{H}$N); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.4, 19.2, 25.2, 27.7, 28.4, 32.1, 44.6, 49.1, 51.6, 81.9, 151.2, 173.4; Found MH^+ 272.1853 $C_{14}H_{26}NO_4$ requires MH^+ 272.1862.

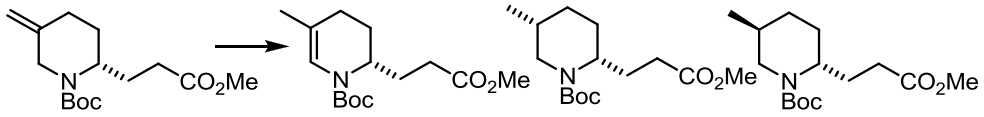
tert-Butyl (2*R*,5*S*)-2-(2-methoxy-2-oxoethyl)-5-methylpiperidine-1-carboxylate (**156a**)



R_f 0.44 (30% diethyl ether in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 1740, 1691, 1414; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.97 (3 H, d *J* 7.0 Hz, C$\mathbf{H_3}$CH), 1.27-1.39 (2 H, m, C$\mathbf{H_2}$CHCH$_3$), 1.44 (9 H, s, (C$\mathbf{H_3}$)$_3$), 1.70-1.82 (2 H, m, C$\mathbf{H_2}$CHN), 1.82-1.96 (1 H, m, C$\mathbf{H}$CH$_3$), 2.51 (1 H, dd *J* 14.0 and 8.0 Hz, C$\mathbf{H_A}$H$_B$CO$_2$CH$_3$), 2.62 (1 H, dd *J* 14.0 and 7.5 Hz, CH$_A$$\mathbf{H_B}CO_2CH_3$), 3.02 (1

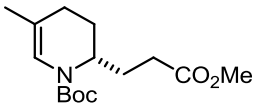
H, dd *J* 13.5 and 3.5 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.65 (3 H, s, CO$_2$C**H$_3$**), 3.67 (1 H, d *J* 13.5 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 4.64 (1 H, q *J* 7.0 Hz, C**H**N); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 16.6, 23.1, 25.1, 27.6, 28.4, 35.5, 44.3, 48.1, 51.6, 79.4, 152.3, 171.8; Found MH^+ 272.1854 $C_{14}H_{26}NO_4$ requires MH^+ 272.1862; $[\alpha]_D^{21}$ +30 (*c* 1.0 in $CHCl_3$).

Hydrogenation of *tert*-butyl (2*R*)-2-(3-methoxy-3-oxopropyl)-5 methylidene piperidine-1-carboxylate **119d**



This reaction was done according to the general procedure **C** using (283 mg, 1 mmol) of **119d** to give **157c**, **157b** and **157a** each as colourless oil. Chromatography gave **157c** (28 mg, 10%), **157b** (45 mg, 16%) a mixed fraction of **157b** and **157a** (133 mg, 47%) and **157a** (60 mg, 21%). The ratio of *trans* : *cis* (1.5 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

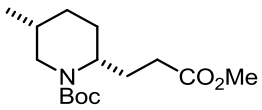
tert-Butyl (2*R*)-2-(3-methoxy-3-oxopropyl)-5-methyl-1,2,3,4-tetrahydropyridine-1-carboxylate (**157c**)



R_f 0.55 (30% diethyl ether in petrolum ether); **ν_{max}/cm^{-1}**: 2943, 1742, 1696, 1397; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **first rotamer** δ ppm: 1.24 (3 H, s, C**H$_3$**C=CH), 1.47 (9 H, s, C(C**H$_3$**)$_3$),

1.57-1.63 (2 H, m, C**H$_2$**C=CH), 1.72-1.81 (1 H, m, C**H$_A$**H$_B$CH$_2$CO$_2$CH$_3$), 1.81-1.87 (1 H, m, CH$_A$**H$_B$**CH$_2$CO$_2$CH$_3$), 1.95-2.10 (1 H, m, C**H$_A$**H$_B$CHN), 2.23-2.45 (1 H, m, CH$_A$**H$_B$**CHN), 2.23-2.45 (2 H, m, C**H$_2$**CO$_2$CH$_3$), 3.66 (3 H, s, CO$_2$C**H$_3$**), 4.25-4.34 (1 H, m, C**H**N), 6.40 (1 H, s, C=C**H**N); **second rotamer** δ ppm: 1.24 (3 H, s, C**H$_3$**C=CH), 1.47 (9 H, s, C(C**H$_3$**)$_3$), 1.57-1.63 (2 H, m, C**H$_2$**C=CH), 1.72-1.81 (1 H, m, C**H$_A$**H$_B$CH$_2$CO$_2$CH$_3$), 1.81-1.87 (1 H, m, CH$_A$**H$_B$**CH$_2$CO$_2$CH$_3$), 1.95-2.10 (1 H, m, C**H$_A$**H$_B$CHN), 2.23-2.45 (1 H, m, CH$_A$**H$_B$**CHN), 2.23-2.45 (2 H, m, C**H$_2$**CO$_2$CH$_3$), 3.67 (3 H, s, CO$_2$C**H$_3$**), 4.13-4.21 (1 H, m, C**H**N), 6.55 (1 H, s, C=C**H**N); **^{13}C NMR** (100 MHz, CDCl$_3$) **first rotamer** δ ppm: 20.9, 22.9, 25.3, 28.3, 29.7, 31.0, 48.1, 51.5, 80.4, 113.1, 118.5, 152.3, 168.1; **second rotamer** δ ppm: 20.9, 23.1, 24.9, 28.9, 29.9, 31.2, 49.2, 51.8, 80.4, 113.7, 118.9, 152.3, 168.1; Found MH$^+$ 284.1852 $C_{15}H_{26}NO_4$ requires MH$^+$ 284.1862; $[\alpha]_D^{21}$ +20 (*c* 1.0 in CHCl$_3$).

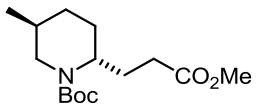
tert-Butyl (2*R*,5*R*)-2-(3-methoxy-3-oxopropyl)-5-methylpiperidine-1-carboxylate (**157b**)



R$_f$ 0.49 (30% diethyl ether in petroleum ether); **ν_{max}/cm^{-1}**: 2936, 1740, 1689 **^{1}H NMR** (400 MHz, CDCl$_3$) δ ppm: 0.86 (3 H, d *J* 7.0 Hz, C**H$_3$**CH), 1.14-1.34 (2 H, m, C**H$_2$**CHCH$_3$), 1.44 (9 H, s, (C**H$_3$**)$_3$), 1.51-1.73 (2 H, m, C**H$_2$**), 1.96-2.11 (1 H, m, CH$_3$C**H**), 2.20-2.42 (2 H, m, C**H$_2$**CO$_2$CH$_3$), 2.20-2.42 (2 H, m, C**H$_2$**CHN), 3.66 (3 H, s, CO$_2$C**H$_3$**), 3.78 (1 H, d *J* 13.0 Hz,

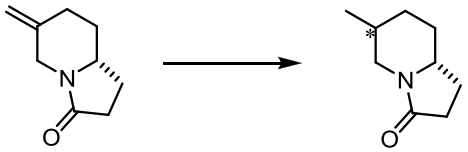
C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.99 (1 H, d *J* 13.0 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 4.13-4.21 (1 H, br, C**H**N); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 17.9, 19.2, 25.0, 26.8, 28.4, 29.4, 30.9, 31.7, 48.1, 51.5, 80.2, 155.2, 178.0; Found MH^+ 286.2007 $C_{15}H_{28}NO_4$ requires MH^+ 286.2018; $[\alpha]_D^{21}$ +30 (*c* 0.67 in $CHCl_3$).

tert-Butyl (2*R*,5*S*)-2-(3-methoxy-3-oxopropyl)-5-methylpiperidine-1-carboxylate (**157a**)



R_f 0.42 (30% diethyl ether in petrolum ether); **ν_{max}/cm^{-1}**: 2940, 1746, 1689; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.96 (3 H, d *J* 7.0 Hz, C**H$_3$**CH), 1.23-1.34 (2 H, m, C**H$_2$**CHCH$_3$), 1.43 (9 H, s, (C**H$_3$**)$_3$), 1.60-1.70 (2 H, m, C**H$_2$**CHN), 1.74-1.91 (1 H, m, C**H**CH$_3$), 1.74-1.91 (1 H, m, C**H$_A$**H$_B$CHN), 2.02-2.16 (1 H, m, CH$_A$**H$_B$**CHN), 2.20-2.35 (2 H, m, C**H$_2$**CO$_2$CH$_3$), 2.95 (1 H, dd *J* 13.5 and 3.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.69 (1 H, d *J* 13.5, CH$_{A(ax)}$**H$_{B(eq)}$**N), 3.65 (3 H, s, CO$_2$C**H$_3$**), 4.17- 4.27 (1 H, m, C**H**N); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 16.3, 23.4, 25.1, 25.2, 27.8, 28.4, 30.9, 43.6, 49.9, 51.5, 79.1, 155.2, 178.0; Found MH^+ 286.2005 $C_{15}H_{28}NO_4$ requires MH^+ 286.2018; $[\alpha]_D^{21}$ +30 (*c* 1.0 in $CHCl_3$).

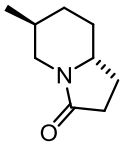
Hydrogenation of (8a*R*)-6-methylidene-octahydroindolizin-3-one **43**



This reaction was done according to the general procedure **C** using (22 mg, 0.15 mmol) of **43** to give **158b** and **158a** each as colourless oil. Chromatography gave an in separable **158b** and **158a** (56 mg, 92%). The ratio of *trans* : *cis* (1 : 5) determined by ^{1}H-NMR spectroscopy of the crude product.

R_f 0.11 (90% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 2929, 1681, 1423; ***cis*-diastereoisomer 159b ^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.96 (3 H, d *J* 7.5 Hz, C**H$_3$**CH), 1.37-1.52 (2 H, m, C**H$_2$**CHN), 1.54-1.72 (2 H, m, C**H$_2$**CHCH$_3$), 1.54-1.72 (1 H, m, C**H$_A$**H$_B$CH$_2$CO), 1.95-2.10 (1 H, m, CH$_3$C**H**), 2.14-2.26 (1 H, m, CH$_A$**H$_B$**CH$_2$CO), 2.31-2.44 (2 H, m, C**H$_2$**CO), 2.81 (1 H, dd *J* 13.0 and 4.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.39 (1 H, dtd *J* 11.5, 7.0 and 3.0 Hz, C**H**N), 3.83 (1 H, ddd *J* 13.0, 1.5 and 1.5 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 16.3, 25.3, 26.6, 27.8, 29.4, 30.3, 45.5, 57.5, 164.0; ***trans*-diastereoisomer 159a ^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.91 (3 H, d *J* 7.0 Hz, C**H$_3$**CH), 1.04-1.23 (2 H, m, C**H$_2$**CHCH$_3$), 1.54-1.72 (1 H, m, C**H$_A$**H$_B$CH$_2$CO), 1.77-1.91 (2 H, m, C**H$_2$**CHN), 1.59-2.10 (1 H, m, CH$_3$C**H**), 2.14-2.26 (1 H, m, CH$_A$**H$_B$**CH$_2$CO), 2.31-2.44 (1 H, m, C**H$_A$**H$_B$N), 3.32-3.44 (1 H, m, C**H**N), 4.06 (1 H, ddd *J* 13.0, 5.0 and 2.0 Hz, CH$_A$**H$_B$**N); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 18.9, 24.9, 30.5, 30.6, 32.5, 33.4, 47.0, 56.9, 166.5; Found MH^+ 154.1232 $C_9H_{16}NO$ requires MH^+ 154.1232.

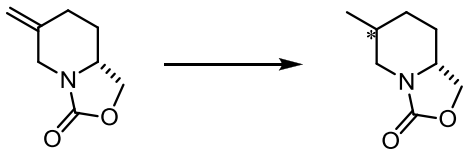
(6*S*,8a*R*)-6-Methyl-octahydroindolizin-3-one (**158a**)



Sodium borohydride (18 mg, 0.69 mmol, 3.0 eq) was added to methyl 3-[(2*R*,5*S*)-5-methyl-1-(trifluoroacetyl)piperidin-2-yl]propanoate **153a** (67 mg, 0.23 mmol) in methanol (3 mL), the reaction was heated at reflux for 3 days. Removing the methanol on rotary vapour and The residue was dissolved in (5 mL) ethyl acetate, washing by (3 mL) water and (3 mL) brine, the organic layer was concentrated to produce the title compound as colorless oil (60 mg, 90%).

ν_{max}/cm^{-1}: 1682, 1442; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.78-0.89 (1 H, m, C**H$_A$**H$_B$CHN), 0.9 (3 H, d *J* 7.0 Hz, C**H$_3$**CH), 1.03-1.26 (1 H, m, CH$_A$**H$_B$**CHN), 1.03-1.26 (2 H, m, COCH$_2$C**H$_2$**CHN), 1.40-1.52 (1 H, m, C**H**CH$_3$), 1.52-1.61 (1 H, m, C**H$_A$**H$_B$CHCH$_3$), 1.76-1.90 (2 H, m, C**H$_2$**CO), 2.13-2.23 (1 H, m, CH$_A$**H$_B$**CHCH$_3$), 2.41 (1 H, dd *J* 13.0 and 12.5 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.41 (1 H, ddd *J* 11.5, 7.0 and 3.5 Hz, C**H**N), 4.05 (1 H, ddd *J* 13.0, 5.0 and 2.0 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 18.9, 29.7, 30.5, 31.9, 32.5, 46.9, 56.8, 173.3; Found MH$^+$ 154.1229. $C_9H_{16}NO$ requires MH$^+$ 154.1232; $[\alpha]_D^{22}$ +5 (*c* 4.0 in $CHCl_3$).

Hydrogenation of (8a*R*)-6-methylidene-hexahydro-1H-[1,3]oxazolo[3,4-a]pyridin-3-one **147**



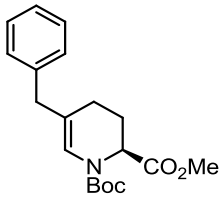
This reaction was done according to the general procedure **C** using (22 mg, 0.15 mmol) of **147** to give **159b** and **159a** each as colourless oil. Chromatography gave an in separable **159b** and **159a** (22 mg, 95%). The ratio of *trans* : *cis* (1 : 7) determined by ^{1}H-NMR spectroscopy of the crude product.

R_f 0.35 (70% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 2929, 1747, 1425; ***cis*-diastereoisomer 160b ^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.03 (3 H, d *J* 7.5 Hz, C**H$_3$**CH), 1.53-1.70 (2 H, m, C**H$_2$**CHCH$_3$), 1.53-1.70 (2 H, m, C**H$_2$**CHN), 1.89-2.06 (1 H, m, CH$_3$C**H**), 3.0 (1 H, dd *J* 13.0 and 4.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.56 (1 H, d *J* 13.0 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 3.59-3.65 (1 H, m, C**H**N), 3.90 (1 H, dd *J* 8.5 and 7.5 Hz, C**H$_A$**H$_B$O), 4.42 (1 H, d *J* 8.5 Hz, CH$_A$**H$_B$**O) ***trans*-diastereoisomer 159a** 0.90 (3 H, d *J* 7 Hz, C**H$_3$**CH), 1.53-1.70 (2 H, m, C**H$_2$**CHCH$_3$), 1.53-1.70 (2 H, m, C**H$_2$**CHN), 1.78-1.89 (1 H, m, CH$_3$C**H**), 2.4 (1 H, dd *J* 13.0 and 11.5 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.59-3.65 (1 H, m, C**H**N), 3.81 (1 H, ddd *J* 13.0, 5.0 and 1.5 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 3.88 (1 H, dd *J* 8.5 and 7 Hz, C**H$_A$**H$_B$O), 4.39 (1 H, dd *J* 8.5 and zero, CH$_A$**H$_B$**O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 16.3, 18.7, 25.0, 26.6, 28.3, 30.3, 30.6, 31.5, 46.5, 54.1, 54.6, 68.0, 68.3, 157.9, 160.0; Found MH$^+$ 156.1022. $C_8H_{14}NO_2$ requires MH$^+$ 156.1025.

4.7 General procedure D: Heck Reaction

A 10 mL one-necked round bottomed flask, reflux condenser, magnetic stirrer bar, and three-way tap, was flame dried under vacuum and back-filled with nitrogen three times. The flask was then charged with $Pd(OAc)_2$ (10.8 mg, 0.05 mmol, 0.05 eq), and an aryl iodide (9.5 mmol, 10 eq) and back-filled with nitrogen. Methylene piperidine (1.0 mmol), triethylamine (2.5 mmol, 2.5 eq) and acetonitrile (7.5 mL) were then added to the flask *via* syringe, and the reaction mixture was stirred at reflux for 20 h. The flask was then removed from the heat source and allowed to cool to room temperature, and transferring the reaction mixture into a single necked round bottom flask using methanol, and removal of the solvent under reduced pressure. Flash chromatography on silica, using an eluant gradient of ethyl acetate in petroleum ether.

1-*tert*-Butyl 2-methyl (2*S*)-5-benzyl-1,2,3,4-tetrahydropyridine-1,2-dicarboxylate (**160**)

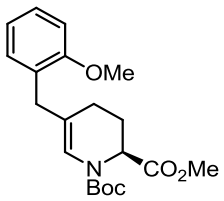


The title compound was synthesised according to the general procedure **D**, using 1-*tert*-butyl 2-methyl (2*S*)-5-methylidenepiperidine-1,2-dicarboxylate ***ent*-37** (255 mg, 1 mmol) as the starting material to give the title compound (268 mg, 81%) as a colourless oil.

R_f 0.5 (10% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 1747, 1701, 1672, 1475, 1452; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric

behaviour, **first rotamer** δ ppm: 1.48 (9 H, s, C(C**H$_3$**)$_3$), 1.75-1.93 (2 H, m, C**H$_2$**C=CH), 1.75-1.93 (1 H, m, C**H$_A$**H$_B$CHN), 2.22-2.35 (1 H, m, CH$_A$**H$_B$**CHN), 3.31 (2 H, s,C**H$_2$**Ph), 3.72 (3 H, s, CO$_2$C**H$_3$**), 4.70-4.75 (1 m, C**H**N), 6.74 (1 H, s, C**H**=C), 7.16-7.24 (3 H, m, Ph), 7.24-7.34 (2 H, m, Ph); **second rotamer** δ ppm: 1.53 (9 H, s, C(C**H$_3$**)$_3$), 1.75-1.93 (2 H, m, C**H$_2$**C=CH), 1.75-1.93 (1 H, m, C**H$_A$**H$_B$CHN), 2.22-2.35 (1 H, m, CH$_A$**H$_B$**CHN), 3.31 (2 H, s ,C**H$_2$**Ph), 3.73 (3 H, s, CO$_2$C**H$_3$**), 4.87-4.91 (1 m, C**H**N), 6.93 (1 H, s, C**H**=C), 7.16-7.24 (3 H, m, Ph), 7.24-7.34 (2 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm **first rotamer**: 21.3, 23.6, 28.2, 41.4, 52.1, 52.7, 81.1, 115.8, 120.8, 126.0, 128.2, 128.6, 139.7, 152.4, 171.7, **second rotamer**: 21.7, 23.9, 28.3, 41.5, 25.2, 53.9, 81.3, 116.4, 121.4, 126.1, 128.5, 128.6, 139.7, 152.9, 172.2; Found MH^+ 332.1860 $C_{19}H_{26}NO_4$ requires MH^+ 332.1862; $[\alpha]_D^{21}$ -26 (*c* 1.0 in $CHCl_3$).

1-*tert*-Butyl 2-methyl (2*S*)-5-[(2-methoxyphenyl)methyl]-1,2,3,4 tetrahydropyridine -1,2-dicarboxylate (**161**)

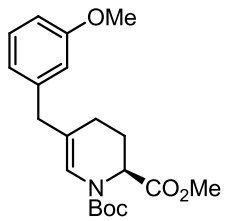


The title compound was synthesised according to the general procedure **D**, using 1-*tert*-butyl 2-methyl (2*S*)-5-methylidenepiperidine-1,2-dicarboxylate ***ent*-37** (255 mg, 1 mmol) as the starting material to give the title compound (273 mg, 76%) as a colourless oil.

R_f (10% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 1751, 1698, 1588, 1586, 1492, 1456; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric

behaviour, **first rotamer** δ ppm: 1.45 (9 H, s, C(C**H$_3$**)$_3$), 1.79-1.91 (2 H, m, C**H$_2$**C=CH), 1.79-1.91 (1 H, m, C**H$_A$**H$_B$CHN), 2.19-2.35 (1 H, m, CH$_A$**H$_B$**CHN), 3.25-3.35 (2 H, m, C**H$_2$**Ar), 3.70 (3 H, s, OC**H$_3$**), 3.80 (3 H, s, CO$_2$C**H$_3$**), 4.67-4.72 (1 H, m, C**H**N), 6.69 (1 H, s, C**H**=C), 6.80-6.87 (3 H, m, Ar), 7.09 (1 H, dd *J* 7.5 and 1.5 Hz, Ar), 7.13-7.21 (1 H, m, Ar); **second rotamer** δ ppm: 1.49 (9 H, s, C(C**H$_3$**)$_3$), 1.79-1.91 (2 H, m, C**H$_2$**C=CH), 1.79-1.91 (1 H, m, C**H$_A$**H$_B$CHN), 2.19-2.35 (1 H, m, CH$_A$**H$_B$**CHN), 3.25-3.35 (2 H, m, C**H$_2$**Ar), 3.71 (3 H, s, OC**H$_3$**), 3.81 (3 H, s, CO$_2$C**H$_3$**), 4.84-4.88 (1 H, m, C**H**N), 6.80-6.87 (3 H, m, Ar), 6.88 (1 H, s, C**H**=C), 7.09 (1 H, dd *J* 7.5 and 1.5 Hz, Ar), 7.13-7.21 (1 H, m, Ar); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm **first rotamer**: 21.6, 23.7, 28.2, 34.3, 52.1, 52.7, 55.3, 80.9, 110.3, 115.4, 120.4, 121.3, 127.1, 128.2, 129.5, 152.3, 157.5, 171.7; **second rotamer:** 21.9, 24.0, 28.3, 34.4, 52.2, 52.7, 53.9, 81.1, 110.3, 116.2, 120.7, 127.2, 128.2, 129.7, 141.1, 152.5, 157.5, 172.1; Found MH^+ 362.1958 $C_{20}H_{28}NO_5$ requires MH^+ 362.1967; $[\alpha]_D^{21}$ -39 (*c* 1.0 in $CHCl_3$).

1-*tert*-Butyl 2-methyl (2*S*)-5-[(3-methoxyphenyl)methyl]-1,2,3,4-tetrahydropyridine-1,2-dicarboxylate (**162**)

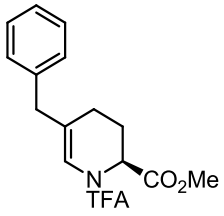


The title compound was synthesised according to the general procedure **D**, using 1-*tert*-butyl 2-methyl (2*S*)-5-methylidenepiperidine-1,2-

dicarboxylate ***ent*-37** (255 mg, 1 mmol) as the starting material to give the title compound (288 mg, 80%) as a colourless oil.

R_f 0.25 (10% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 1749, 1701, 1672, 1597, 1584, 1486; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **first rotamer** δ ppm: 1.46 (9 H, s, C(C$\mathbf{H_3}$)$_3$), 1.72-1.91 (2 H, m, C$\mathbf{H_2}$C=CH), 1.72-1.91 (1 H, m, C$\mathbf{H_A}$H$_B$CHN), 2.19-2.32 (1 H, m, CH$_A$$\mathbf{H_B}$CHN), 3.22-3.32 (2 H, m, C$\mathbf{H_2}$Ar), 3.70 (3 H, s, OC$\mathbf{H_3}$), 3.78 (3 H, s, CO_2C$\mathbf{H_3}$), 4.67-4.72 (1 H, m, C**H**N), 6.70-6.67 (3 H, m, Ar), 6.77 (1 H, s, C**H**=C), 7.14-7.22 (1 H, m, Ar); **second rotamer** δ ppm: 1.51 (9 H, s, C(C$\mathbf{H_3}$)$_3$), 1.72-1.91 (2 H, m, C$\mathbf{H_2}$C=CH), 1.72-1.91 (1 H, m, C$\mathbf{H_A}$H$_B$CHN), 2.19-2.32 (1 H, m, CH$_A$$\mathbf{H_B}$CHN), 3.22-3.32 (2 H, m, C$\mathbf{H_2}$Ar), 3.71 (3 H, s, OC$\mathbf{H_3}$), 3.79 (3 H, s, CO_2C$\mathbf{H_3}$), 4.85-4.90 (1 H, m, C**H**N), 6.70-6.67 (3 H, m, Ar), 6.91 (1 H, s, C**H**=C), 7.14-7.22 (1 H, m, Ar); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm **first rotamer**: 21.3, 23.6, 28.2, 41.4, 52.1, 52.7, 55.1, 81.1, 111.3, 114.1, 115.5, 120.9, 121.1, 129.1, 141.4, 152.4, 159.7, 171.6; **second rotamer**: 21.6, 23.9, 28.3, 41.5, 52.2, 53.9, 55.1, 81.3, 111.5, 114.3, 116.2, 121.0, 121.5, 129.2, 141.5, 152.7, 160.1, 172.0; Found MH^+ 362.1958 $C_{20}H_{28}NO_5$ requires MH^+ 362.1967; $[\alpha]_D^{21}$ -28 (*c* 1.0 in $CHCl_3$).

Methyl(2*S*)-5-benzyl-1-(trifluoroacetyl)-1,2,3,4-tetrahydropyridine-2 carboxylate (**163**)

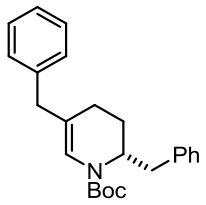


The title compound was prepared according to the general procedure **D**, using (*S*)-methyl 5-methylene-1-(2,2,2-trifluoroacetyl)piperidine-2-carboxylate **127** (292 mg, 1.16 mmol) as the starting material to give the title compound (265 mg, 70%) as a colorless oil.

R_f 0.4 (10% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 2320, 1748, 1697, 1495; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 1.85-2.03 (2 H, m, C$\mathbf{H_2}$C=CH_2), 1.85-2.03 (1 H, m, C$\mathbf{H_A}$$H_B$CH), 2.38-2.49 (1 H, m, C$H_A$$\mathbf{H_B}$CH), 3.34 (2 H, s, C$\mathbf{H_2}$Ph), 3.75 (3 H, s, $CO_2C\mathbf{H_3}$), 5.14-5.20 (1 H, br, C**H**N), 6.66 (1 H, s, C=C**H**N), 7.12-7.38 (5 H, m, Ph); **minor rotamer** δ ppm: 1.85-2.03 (2 H, m, C$\mathbf{H_2}$C=CH_2), 1.85-2.03 (1 H, m, C$\mathbf{H_A}$$H_B$CH), 2.38-2.49 (1 H, m, C$H_A$$\mathbf{H_B}$CH), 3.38 (2 H, s, C$\mathbf{H_2}$Ph), 3.75 (3 H, s, $CO_2C\mathbf{H_3}$), 4.84-4.88 (1 H, br, C**H**N), 6.45 (1 H, s, C=C**H**N), 7.12-7.38 (5 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm **major rotamer**: 21.8, 23.0, 30.1, 41.4, 52.9, 116.2 (q *J* 219 Hz), 118.7, 123.3, 126.5, 128.5, 128.6, 138.1, 154.8 (q *J* 41 Hz), 169.4; **minor rotamer**: 22.1, 24.1, 41.5, 52.9, 54.6, 116.2 (q *J* 219 Hz), 118.7, 125.0, 126.6, 128.5, 128.6, 138.5, 154.8 (q *J* 41 Hz), 169.7; Found

MH^+ 328.1174 $C_{16}H_{17}F_3NO_3$ requires MH^+ 328.1161; $[\alpha]_D^{24}$ -45 (*c* 2.0 in $CHCl_3$).

tert-Butyl (2*R*)-2,5-dibenzyl-1,2,3,4-tetrahydropyridine-1-carboxylate (**164**)

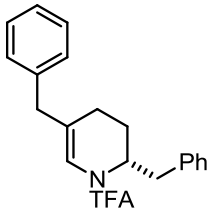


The title compound was synthesised according to the general procedure **D**, using *tert*-butyl (2*R*)-2-benzyl-5-methylidenepiperidine-1-carboxylate **119a** (287 mg, 1 mmol) as the starting material to give the title compound (261 mg, 72%) as a colourless oil.

R_f 0.71 (5% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 1694, 1600, 1476, 1453, 1395, 1366, 1347, 1322; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 1.41 (9 H, s, C(C**H$_3$**)$_3$), 1.55-1.73 (2 H, m, C**H$_2$**CH), 1.74-1.87 (1 H, m, C**H$_A$**H$_B$C=CH), 1.98-2.12 (1 H, m, CH$_A$**H$_B$**C=CH), 2.53-2.65 (1 H, m, CHC**H$_A$**H$_B$Ph), 2.79-2.91 (1 H, m, CHCH$_A$**H$_B$**Ph), 3.31-3.43 (2 H, s, C**H$_2$**Ph), 4.30-4.38 (1 H, m, C**H**N), 6.91 (1 H, s, C**H**=C), 7.15-730 (10 H, m, 2 Ph); **minor rotamer**: 1.49 (9 H, s, C(C**H$_3$**)$_3$), 1.55-1.73 (2 H, m, C**H$_2$**CH), 1.74-1.87 (1 H, m, C**H$_A$**H$_B$C=CH), 1.98-2.12 (1 H, m, CH$_A$**H$_B$**C=CH), 2.53-2.65 (1 H, m, CHC**H$_A$**H$_B$Ph), 2.79-2.91 (1 H, m, CHCH$_A$**H$_B$**Ph), 3.31-3.43 (2 H, s, C**H$_2$**Ph), 4.47-4.53 (1 H, m, C**H**N), 6.69 (1 H, s, C**H**=C), 7.15-7.30 (10 H, m, 2 Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm **major rotamer**: 20.6, 23.5, 28.2, 36.6, 41.9, 50.6, 80.3, 116.8, 117.1, 120.2, 126.1, 127.1, 128.3,

128.6, 128.7, 129.3, 138.9, 152.7; **minor rotamer**: 20.8, 22.7, 28.3, 37.2, 41.9, 42.3, 51.9, 81.5, 116.8, 117.1, 126.1, 127.1, 128.3, 128.6, 128.7, 129.3, 140.6, 152.7; Found MH^+ 364.2276 $C_{24}H_{30}NO_2$ requires MH^+ 364.2277; $[\alpha]_D^{19}$ +12 (*c* 1.0 in $CHCl_3$).

1-[(2*R*)-2,5-Dibenzyl-1,2,3,4-tetrahydropyridin-1-yl]-2,2,2-trifluoroethan-1-one (**165**)



The title compound was synthesised according to the general procedure **D**, using 1-[(2*R*)-2-Benzyl-5-methylidenepiperidin-1-yl]-2,2,2-trifluoroethan-1-one **122a** (283. mg, 1 mmol) as the starting material to give the title compound (280 mg, 78%) as a colourless oil.

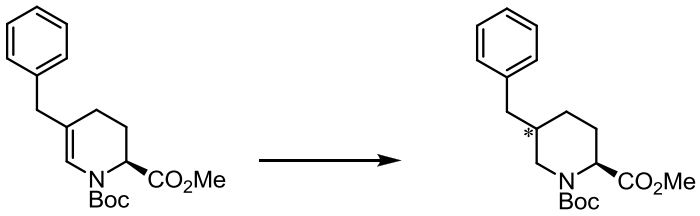
R_f 0.57 (5% diethyl ether in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 1685, 1602, 1494, 1453, 1424, 1228, 1191, 1136; **^{1}H NMR** (400 MHz, $CDCl_3$) exhibits strongly rotameric behaviour, **major rotamer** δ ppm: 1.63-1.83 (2 H, m, C**H$_2$**CH), 1.95 (1 H, dd *J* 18.0 and 6.0 Hz, C**H$_A$**H$_B$C=CH), 2.08-2.23 (1 H, m, CH$_A$**H$_B$**C=CH), 2.66 (1 H, dd *J* 13.5 and 9.5 Hz, CHC**H$_A$**H$_B$Ph), 2.88 (1 H, dd *J* 13.5 and 6.0 Hz, CHCH$_A$**H$_B$**Ph), 3.41 (2 H, s, C**H$_2$**Ph), 4.76-4.83 (1 H, m, C**H**N), 6.60 (1 H, s, C=C**H**), 7.20-7.40 (10 H, m, 10 Ph); **minor rotamer**: 1.63-1.83 (2 H, m, C**H$_2$**CH), 1.95 (1 H, dd *J* 18.0 and 6.0 Hz, C**H$_A$**H$_B$C=CH), 2.08-2.23 (1 H, m, CH$_A$**H$_B$**C=CH), 2.66 (1 H, dd *J* 13.5 and

9.5 Hz, CHC**H$_A$**H$_B$Ph), 2.88 (1 H, dd *J* 13.5 and 6.0 Hz, CHCH$_A$**H$_B$**Ph), 3.46 (2 H, d *J* 5.0 Hz, C**H$_2$**Ph), 4.30-4.38 (1 H, m, C**H**N), 7.09 (1 H, s, C=C**H**), 7.20-7.40 (10 H, m, 2 Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm **major rotamer**: 21.2, 22.1, 35.8, 41.8, 51.2, 115.0 (q *J* 90 Hz), 118.0, 123.7, 125.3, 126.6, 126.7, 128.5, 128.7, 129.0, 129.2, 137.3, 157.9 (q *J* 50 Hz), **minor rotamer**: 21.2, 22.5, 37.0, 41.8, 53.4, 115.0 (q *J* 90 Hz), 118.4, 123.6, 124.6, 126.7, 126.6, 126.7, 128.6, 128.7, 129.2, 138.5, 157.9 (q *J* 50 Hz); Found MH^+ 360.1580 $C_{21}H_{21}F_3NO$ requires MH^+ 360.1575; $[\alpha]_D^{19}$ +77 (*c* 1.0 in $CHCl_3$).

4.8 General procedure E: Hydrogenation of Heck reaction products

A two-necked round-bottomed flask, equipped with a rubber septum, three-way tap and magnetic follower, was flame-dried under vacuum and back-filled with nitrogen three times. The flask was charged with platinum supported on activated carbon (1% w/w, 0.1 eq), and then evacuated and back-filled with nitrogen three times. A solution of the Heck reaction product (1.0 mmol) in methanol (17 mL) was added to the flask *via* syringe, and the reaction mixture stirred vigorously. A balloon of hydrogen was fitted to the three-way tap, and the reaction vessel evacuated until the solvent began to boil, at which point it was back-filled with hydrogen, and this process was repeated three times. The reaction mixture was stirred vigorously at room temperature for 48 h, then filtered through celite using methanol. The solvent was then removed from the filtrate under reduced pressure and the residue purified *via* flash chromatography on silica.

Hydrogenation of 1-*tert*-butyl 2-methyl (2*S*)-5-benzyl-1,2,3,4-tetrahydropyridine-1,2-dicarboxylate **160**

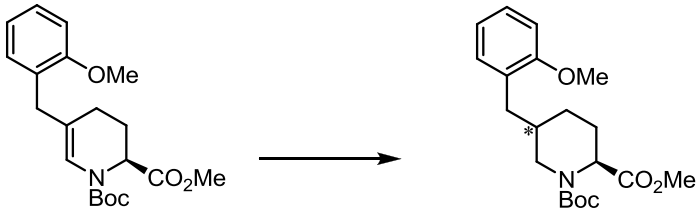


This reaction was done according to the general procedure **E** using (130 mg, 0.39 mmol) of **160** to give **167b** and **167a** as inseparable

diastereoisomers (84 mg, 65%) as a colourless oil. The ratio of *cis* : *trans* (4 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

R_f 0.45 (15% diethyl ether in petroleum ether), $\mathbf{\nu_{max}/cm^{-1}}$: 2930, 1744, 1698, 1392; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.78-1.10 (1 H, m), 1.44 (9 H, s, C(C$\mathbf{H_3}$)$_\mathbf{3}$), 1.98-1.79 (3 H, m), 2.17-2.29 (1 H, m, C$\mathbf{H_A}$H$_B$CHN), 2.38-2.47 (1 H, m, CH$_A$$\mathbf{H_B}$CHN), 2.51-2.62 (2 H, m, C$\mathbf{H_2}$Ph), 2.67 (1 H of major isomer of one rotamer, app. t *J* 12.5 Hz, C$\mathbf{H_A}$H$_B$N), 2.77 (1 H of minor isomer of one rotamer, dd *J* 14.0 and 8.5 Hz, C$\mathbf{H_A}$H$_B$N), 3.12 (1 H of minor isomer of other rotamer, dd *J* 13.0 and 4.0 Hz, C$\mathbf{H_A}$H$_B$N), 3.75 (3 H, s, CO$_2$C$\mathbf{H_3}$), 3.77 (3 H, s, CO$_2$C$\mathbf{H_3}$), 3.89 (1 H of minor isomer of one rotamer, d *J* 4.5 Hz, CH$_A$$\mathbf{H_B}$N), 3.93 (1 H of major isomer of one rotamer, dd *J* 14.0 and 4.0 Hz, CH$_A$$\mathbf{H_B}$N), 4.03 (1 H of minor isomer of other rotamer, d *J* 4.5 Hz, CH$_A$$\mathbf{H_B}$N), 4.08 (1 H of major rotamer of other rotamer, dd *J* 13.0 and 4.0 Hz, CH$_A$$\mathbf{H_B}$N), 4.74 (1 H of major isomer of one rotamer, d *J* 5.0 Hz, C**H**N), 4.86 (1 H of minor isomer of one rotamer, d *J* 6.5 Hz, C**H**N), 4.92 (1 H of major isomer of other rotamer, d *J* 5.0 Hz, C**H**N), 5.10 (1 H of minor isomer of other rotamer, d *J* 6.5 Hz, C**H**N), 7.11-7.33 (5 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) *many signals was observed due to rotameric behaviour, and the presence of diastereoisomers* δ ppm: 26.6, 26.7, 27.1, 27.3, 28.3, 31.2, 35.4, 37.4, 37.6, 40.5, 40.7, 46.5, 47.5, 52.0, 53.4, 54.6, 80.0, 128.2, 128.9, 129.0, 139.6, 155.4, 155.5, 172.3, 172.8; Found MH^+ 334.2023. $C_{19}H_{28}NO_4$ requires MH^+ 334.2018.

Hydrogenation of 1-*tert*-butyl 2-methyl (2*S*)-5-[(2-methoxyphenyl)methyl]-1,2,3,4 tetrahydropyridine -1,2-dicarboxylate **161**

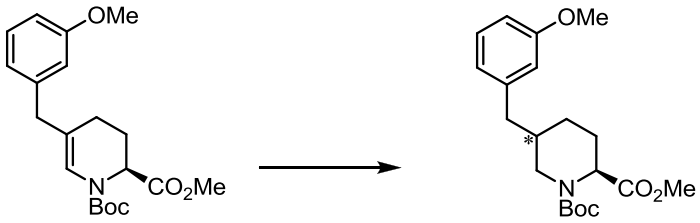


This reaction was done according to the general procedure **E** using (141 mg, 0.39 mmol) of **161** to give **168b** and **168a** as inseparable diastereoisomers (78 mg, 55%) as a colourless oil. The ratio of *cis* : *trans* (4 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

R_f 0.28 (25% diethyl ether in petroleum ether), $\mathbf{\nu_{max}/cm^{-1}}$: 2930, 1741, 1690, 1493; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.8-1.01 (2 H, m, C$\mathbf{H_2}$CH), 1.41 (9 H of major isomer, s, C(C$\mathbf{H_3}$)$_3$), 1.46 (9 H of minor isomer, s, C(C$\mathbf{H_3}$)$_3$), 1.55-1.80 (1 H, m, C**H**CH_2Ph), 2.15-2.25 (1 H, m, C$\mathbf{H_A}H_B$CHN), 2.37-2.46 (1 H, m, C$H_A\mathbf{H_B}$CHN), 2.48-2.57 (2 H, m, C$\mathbf{H_2}$Ph), 2.65 (1 H of major isomer of one rotamer, app. t *J* 12.5 Hz, C$\mathbf{H_A}H_B$N), 3.07 (1 H of minor isomer of one rotamer, dd *J* 13.5 and 4.0 Hz, C$\mathbf{H_A}H_B$N), 3.26-3.30 (1 H of major isomer of other rotamer, m, C$\mathbf{H_A}H_B$N), 3.71 (3 H of minor isomer, s, CO_2C$\mathbf{H_3}$), 3.72 (3 H of major isomer of one rotamer, s, CO_2C$\mathbf{H_3}$), 3.74 (3 H of major isomer of other rotamer, s, CO_2C$\mathbf{H_3}$), 3.78 (3 H of major isomer of one rotamer, s, OC$\mathbf{H_3}$), 3.79 (3 H of minor isomer, s, CO_2C$\mathbf{H_3}$), 3.81 (3 H of major isomer of other rotamer, s, CO_2C$\mathbf{H_3}$), 3.88 (1 H of major isomer of one rotamer, dd *J* 13.5 and 4.0 Hz, C$H_A\mathbf{H_B}$N), 4.03 (1 H of major isomer of other rotamer, dd *J* 13.5 and 4.5 Hz, C$H_A\mathbf{H_B}$N), 4.70 (1 H of major isomer of one rotamer, d *J* 5.0 Hz, C**H**N), 4.88 (1 H of

major isomer of other rotamer, d *J* 5.0 Hz, C**H**N), 4.91 (1 H of minor isomer, d *J* 6.0 Hz, C**H**N), 6.79-6.90 (2 H, m, Ph), 7.02-7.08 (1 H, m, Ph), 7.13-7.21 (1 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) *many signals was observed due to rotameric behaviour, and the presence of diastereoisomers* δ ppm: 26.6, 26.7, 27.2, 27.5, 28.3, 34.6, 34.9, 35.8, 36.2, 46.7, 47.7, 52.0, 53.5, 54.6, 55.2, 79.9, 110.2, 120.2, 127.3, 130.6, 130.8, 157.7, 175.3; Found MH^+ 364.2115. $C_{20}H_{30}NO_5$ requires MH^+ 364.2124.

Hydrogenation of 1-*tert*-butyl 2-methyl (2*S*)-5-[(3-methoxyphenyl)methyl]-1,2,3,4-tetrahydropyridine-1,2-dicarboxylate **162**

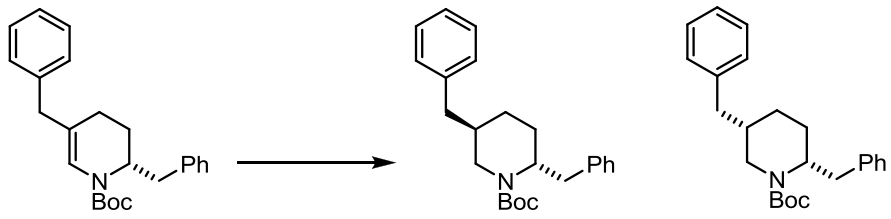


This reaction was done according to the general procedure **E** using (141 mg, 0.39 mmol) of **162** to give **169b** and **169a** as inseparable diastereoisomers (81 mg, 57%) as a colourless oil. The ratio of *cis* : *trans* (4 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

R_f 0.3 (25% diethyl ether in petroleum ether), **ν_{max}/cm^{-1}**: 2928, 1745, 1697, 1499; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.81-1.02 (2 H, m, C**H_2**CH), 1.41 (9 H of major isomer, s, C(C**H_3**)$_3$), 1.42 (9 H of minor isomer, s, C(C**H_3**)$_3$), 1.56-1.75 (1 H, m, C**H**CH_2Ph), 2.15-2.26 (1 H, m, C**H_A**H_BCHN), 2.33-2.41 (1 H, m, CH_A**H_B**CHN), 2.47-2.59 (2 H, m, C**H_2**Ph), 2.65 (1 H of major isomer of one rotamer, app. t *J* 12.5 Hz, C**H_A**H_BN), 3.08 (1 H of minor

isomer of one rotamer, dd *J* 14.0 and 4.0 Hz, C**H**$_A$H$_B$N), 3.26-3.30 (1 H of major isomer of other rotamer, m, C**H**$_A$H$_B$N), 3.68 (3 H of minor isomer, s, CO_2C**H**$_3$), 3.70 (3 H of major isomer of one rotamer, s, CO_2C**H**$_3$), 3.73 (3 H of major isomer of other rotamer, s, CO_2C**H**$_3$), 3.75 (3 H of major isomer of one rotamer, s, OC**H**$_3$), 3.80 (3 H of minor isomer, s, CO_2C**H**$_3$), 3.82 (3 H of major isomer of other rotamer, s, CO_2C**H**$_3$), 3.91 (1 H of major isomer of one rotamer, dd *J* 13.0 and 4.0 Hz, CH$_A$**H**$_B$N), 4.05 (1 H of major isomer of other rotamer, dd *J* 13.0 and 3.5 Hz, CH$_A$**H**$_B$N), 4.72 (1 H of major isomer of one rotamer, d *J* 6.0 Hz, C**H**N), 4.83 (1 H of major isomer of other rotamer, d *J* 6.0 Hz, C**H**N), 4.90 (1 H of minor isomer, d *J* 6.0 Hz, C**H**N), 6.64-6.78 (2 H, m, Ph), 6.86-6.96 (1 H, m, Ph), 7.14-7.22 (1 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) *many signals was observed due to rotameric behaviour, and the presence of diastereoisomers* δ ppm: 26.7, 27.3, 28.3, 37.3, 37.5, 40.5, 46.5, 47.5, 52.0, 53.4, 54.5, 55.1, 77.3, 111.32, 114.7, 121.4, 129.2, 131.8, 157.7, 175.3; Found MH^+ 364.2134. $C_{20}H_{30}NO_5$ requires MH^+ 364.2124.

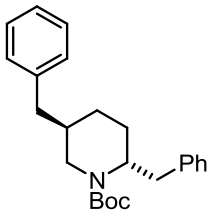
Hydrogenation of *tert*-butyl (2*R*)-2,5-dibenzyl-1,2,3,4-tetrahydropyridine-1-carboxylate **164**



This reaction was done according to the general procedure **E** using (120 mg, 0.33 mmol) of **164** to give **166a** and **166b** as partly separable

diastereoisomers (81 mg, 57%) as a colourless oil. The separated yield of **166a** (29 mg, 24%). The ratio of *trans* : *cis* (6 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

tert-Butyl (2*R*,5*R*)-2,5-dibenzylpiperidine-1-carboxylate (**166a**)



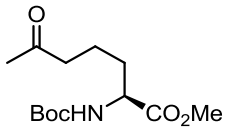
ν_{max}/cm^{-1}: 2928, 1686, 1414; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.24-1.38 (1 H, m, C**H$_A$**H$_B$CH), 1.41-1.50 (1 H, m, CH$_A$**H$_B$**CH), 1.78-1.89 (2 H, m, C**H$_2$**CHN), 1.95-2.04 (1 H, m, C**H**CH$_2$Ph), 2.60 (1 H, dd *J* 13.0 and 7.0 Hz, C**H$_A$**H$_B$Ph), 2.73-2.84 (2 H, m, C**H$_2$**Ph), 2.93 (1 H dd *J* 13.0 7.5 Hz, CH$_A$**H$_B$**Ph), 3.08 (1 H, dd *J* 13.5 and 4.0 Hz, C**H$_{A(ax)}$**H$_{B(eq)}$N), 3.90 (1 H, d *J* 13.5 Hz, CH$_{A(ax)}$**H$_{B(eq)}$**N), 4.44-4.54 (1 H, m, C**H**N), 7.17-7.24 (5 H, m, Ph), 7.26-7.33 (5 H, m, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 28.4, 29.7, 35.5, 36.9, 52.1, 61.1, 79.2, 125.8, 126.1, 128.2, 128.3, 129.2, 129.3, 139.1, 141.0, 157.2; Found MH^+ 366.2415. $C_{24}H_{32}NO_2$ requires MH^+ 366.2433; $[\alpha]_D^{23}$ -12 (*c* 1.67 in $CHCl_3$).

4.9 General procedure F: Conjugate addition

A two-necked round bottomed 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 (2.0 eq), and again evacuated and back-filled with nitrogen three times, with continuous stirring. Dry DMF (1 mL) was added *via* syringe, and the heterogeneous mixture stirred vigorously. Iodine (0.25 mmol) was added by rapid removal and replacement of the three-way tap under nitrogen, turning the solvent yellow. The mixture was stirred for 1-2 min, until the solvent had become colourless. The alkyl iodide (1.0 mmol) was added by rapid removal of the three-way tap under a stream of nitrogen. The mixture was stirred, and an exothermic was observed. The mixture was stirred for a further 45 min, before cessation of stirring. The solid zinc dust was allowed to settle before transferring the reagent into a new reaction vessel *via* syringe. During the 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), and gently heated under vacuum until the CuBr.DMS changed appearance from a brown to light green powder. The flask was allowed to cool, before adding dry DMF (0.5 mL) and the organozinc iodide was transferred to the previous flask. A mixture of distilled trimethylsilyl chloride (2.0 eq), DMF (0.5 mL) and an enone (2.0 eq) in a vial was added dropwise *via* syringe on water bath for 10 min and then at room temperature overnight. A (10 mL) ammonium

chloride was added to the reaction for 30 min and the reaction mixture was transferred to a separatory funnel with (15 mL) ethyl acetate, and washed with (10 mL) water and (10 mL) brine. The organic layer was dried over magnesium sulfate, filtered, and the solvent removed at reduced pressure. The residue was purified by flash chromatography on silica, using ethyl acetate in petroleum ether.

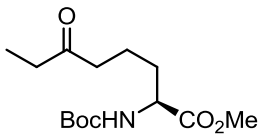
Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-6-oxoheptanoate (**170a**)



The title compound was synthesised according to the general procedure **F** using methyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate **104** (658 mg, 2 mmol) and methyl vinyl ketone (280 mg, 4 mmol, 2 eq) to give the title compound as colourless oil (257 mg, 47%).

R_f 0.35 (30% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 3313, 1730, 1705, 1515; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.43 (9 H, s, C(C**H$_3$**)$_3$), 1.41-1.45 (2 H, m, C**H$_2$**CH$_2$CO), 1.41-1.45 (1 H, m, C**H$_A$**H$_B$CHN), 1.77-1.81 (1 H, m, CH$_A$**H$_B$**CHN), 2.13 (3 H, s, C**H$_3$**CO), 2.45-2.48 (2 H, m, C**H$_2$**CO), 3.73 (3 H, s, CO$_2$C**H$_3$**), 4.27-4.31 (1 H, m, C**H**N), 5.05 (1 H, d *J* 8.0 Hz, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 19.3, 28.3, 29.9, 32.0, 42.7, 52.3, 53.0, 80.0, 155.2, 173.0; Found MH^+ 247.1644. $C_{13}H_{24}NO_5$ requires MH^+ 274.1654.; $[\alpha]_D^{17}$ +81 (*c* 1.0 in $CHCl_3$).

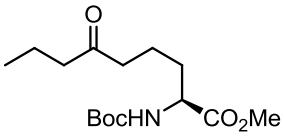
Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-6-oxooctanoate (**170b**)



The title compound was synthesised according to the general procedure **F** using methyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate **104** (658 mg, 2 mmol) and ethyl vinyl ketone (336 mg, 4 mmol, 2 eq) to give the title compound as colorless oil (258 mg, 45%).

R_f 0.39 (30% ethyl acetate in petroleum ether); $\mathbf{\nu_{max}/cm^{-1}}$: 3304, 1726, 1709, 1520; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.03 (3 H, t *J* 7.5 Hz, C**H$_3$**CH$_2$), (9 H, s, C(C**H$_3$**)$_3$), 1.56-1.67 (2 H, m, C**H$_2$**CH$_2$CO), 1.56-1.67 (1 H, m, C**H$_A$**H$_B$CHN), 1.70-1.83 (1 H, m, CH$_A$**H$_B$**CHN), 2.39 (2 H, q *J* 7.5 Hz, CH$_3$C**H$_2$**CO), 2.44 (2 H, t *J* 7.0 Hz, CH$_2$C**H$_2$**CO), 3.72 (3 H, s, CO$_2$C**H$_3$**), 4.23-4.33 (1 H, m, C**H**N), 5.05 (1 H, d *J* 8.0 Hz, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 7.7, 19.4, 28.3, 32.0, 35.9, 41.3, 52.3, 53.0, 79.0, 155.4, 173.1, 210.0; Found MH^+ 288.1811. $C_{14}H_{26}NO_5$ requires MH^+ 288.1811.; $[\alpha]_D^{21}$ +20 (*c* 1.0 in $CHCl_3$).

Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-6-oxononanoate (**170c**)

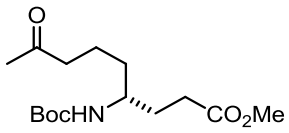


The title compound was synthesised according to the general procedure **F** using methyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate **104**

(658 mg, 2 mmol) and propyl vinyl ketone (392 mg, 4 mmol, 2 eq) to give the title compound as colorless oil (269 mg, 45%).

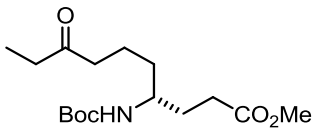
R_f 0.35 (30% ethyl acetate in petroleum ether); **ν_{max}/cm^{-1}**: 2956, 1730, 1709, 1512; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.89 (3 H, t *J* 7.5 Hz, C**H$_3$**CH_2), 1.43 (9 H, s, C(C**H$_3$**)$_3$), 1.52-1.66 (2 H, m, C**H$_2$**CH_2CO), 1.52-1.66 (2 H, m, C**H$_2$**CH_2CO), 1.56-1.67 (1 H, m, C**H$_A$**H_BCHN), 1.72-1.84 (1 H, m, CH_A**H$_B$**CHN), 2.35 (2 H, t *J* 7.0 Hz, CH_3CH_2C**H$_2$**CO), 2.39 (2 H, t *J* 7.0 Hz, CH_2C**H$_2$**CO), 3.73 (3 H, s, CO_2C**H$_3$**), 4.23-4.34 (1 H, m, C**H**N), 5.05 (1 H, d *J* 8.0 Hz, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 13.7, 17.2, 19.3, 28.3, 32.0, 41.7, 44.7, 52.3, 53.1, 80.1, 151.7, 173.4, 208.2; Found MH^+ 302.1975. $C_{15}H_{28}NO_5$ requires MH^+ 274.1654.; $[\alpha]_D^{23}$ +10 (*c* 1.0 in $CHCl_3$).

Methyl 4-{[(*tert*-butoxy)carbonyl]amino}-8-oxononanoate (**172a**)



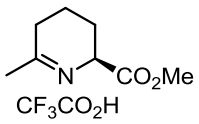
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.32-1.50 (2 H, m, C**H$_2$**CH_2CO), 1.42 (9 H, s, C(C**H$_3$**)$_3$), 1.52-1.69 (2 H, m, C**H$_2$**CH), 1.52-1.69 (1 H, m, C**H$_A$**H_BCH), 1.77-1.89 (1 H, m, CH_A**H$_B$**CH), 2.12 (3 H, s, C**H$_3$**CO), 2.37 (2 H, t *J* 3.5 Hz, C**H$_2$**CO), 2.40-2.54 (2 H, m, C**H$_2$**CO_2CH_3), 3.49-3.62 (1 H, m, C**H**N), 3.66 (3 H, s, CO_2C**H$_3$**), 4.30 (1 H, d *J* 9.5 Hz, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 19.8, 28.3, 29.9, 30.5, 30.8, 35.2, 43.5, 49.9, 51.8, 79.3, 155.7, 173.9, 181.4.

Methyl 4-{[(*tert*-butoxy)carbonyl]amino}-8-oxodecanoate (**172b**)



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.09 (3 H, m, C**H$_3$**CH_2), 1.32-1.50 (2 H, m, C**H$_2$**CH_2CO), 1.42 (9 H, s, $C(C$**H$_3$**$)_3$), 1.53-1.71 (2 H, m, C**H$_2$**CH), 1.53-1.71 (1 H, m, C**H$_A$**H_BCH), 1.76-1.89 (1 H, m, CH_A**H$_B$**CH), 2.31-2.49 (2 H, m, C**H$_2$**CO), 2.31-2.49 (2 H, m, C**H$_2$**CO), 2.31-2.49 (2 H, m, C**H$_2$**CO_2CH_3), 3.49-3.61 (1 H, m, C**H**N), 3.66 (3 H, s, CO_2C**H$_3$**), 4.30 (1 H, d *J* 9.5 Hz, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 19.9, 28.3, 29.9, 30.8, 32.3, 35.2, 35.9, 43.5, 49.9, 51.6, 79.3, 155.7, 173.8, 181.2.

Trifluoroacetic acid methyl (2*S*)-6-methyl-2,3,4,5-tetrahydropyridine-2 carboxylate (**174a**)

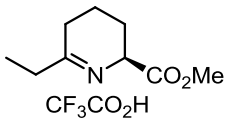


Trifluoroacetic acid (4.4 g, 39.2 mmol) was added dropwise to the stirred solution of methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-6-oxoheptanoate **170a** (218 mg, 0.8 mmol) in dichloromethane (40 mL), and the reaction mixture stirred for a further 20 min. At this time, the solvent and excess trifluoroacetic acid was removed under reduced to produce the title compound as brown oil.

ν_{max}/cm^{-1}: 1748, 1666, 1519,1438; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.78-1.98 (2 H, m, C**H$_2$**CH_2), 2.09-2.25 (2 H, m, C**H$_2$**CH), 2.57 (3 H, s,

C**H$_3$**C=N), 2.81 (2 H, t *J* 6.0 Hz, C**H$_2$**C=N), 3.81 (3 H, s, CO_2C**H$_3$**), 4.68 (1 H, td *J* 5.5 and 1.5 Hz, C**H**N), 11.60-11.75 (1 H, br, N**H**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 15.2, 22.4, 24.9, 31.8, 53.6, 56.4, 115.5 (q *J* 288 Hz), 160.6 (q *J* 40 Hz), 167.7, 191.8; Found MH^+ 156.1023. $C_8H_{14}NO_2$ requires MH^+ 156.1025.

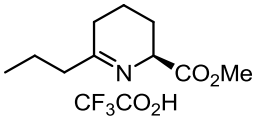
Trifluoroacetic acid methyl (2*S*)-6-ethyl-2,3,4,5-tetrahydropyridine-2-carboxylate (**174b**)



Trifluoroacetic acid (4.4 g, 39.2 mmol) was added dropwise to the stirred solution of methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-6-oxooctanoate **170b** (230 mg, 0.8 mmol) in dichloromethane (40 mL), and the reaction mixture stirred for a further 20 min. At this time, the solvent and excess trifluoroacetic acid was removed under reduced to produce the title compound as brown oil.

ν_{max}/cm^{-1}: 2961, 1747, 1664, 1439; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.32 (3 H, t *J* 7.5 Hz, C**H$_3$**CH_2), 1.77-1.88 (1 H, m, C**H$_A$**H_BCH), 1.88-1.99 (1 H, m, CH_A**H$_B$**CH), 2.14-2.21 (2 H, m, C**H$_2$**CH_2CH), 2.75-2.92 (2 H, m, C**H$_2$**C=N), 2.75-2.92 (2 H, m, C**H$_2$**CH_3), 3.81 (3 H, s, CO_2C**H$_3$**), 4.71 (1 H, t *J* 5.0 Hz, C**H**N); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 9.9, 14.9, 22.6, 29.3, 31.7, 53.4, 56.2, 117.9 (q *J* 286 Hz), 160.7 (q *J* 38.5 Hz), 167.9, 195.8; Found MH^+ 170.1185. $C_9H_{16}NO_2$ requires MH^+ 170.1181.; $[\alpha]_D^{23}$ +36 (*c* 1.0 in $CHCl_3$).

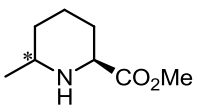
Trifluoroacetic acid methyl (2*S*)-6-propyl-2,3,4,5-tetrahydropyridine-2-carboxylate (**174c**)



Trifluoroacetic acid (4.4 g, 39.2 mmol) was added dropwise to the stirred solution of methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-6-oxononanoate **170c** (239 mg, 0.8 mmol) in dichloromethane (40 mL), and the reaction mixture stirred for a further 20 min. At this time, the solvent and excess trifluoroacetic acid was removed under reduced to produce the title compound as brown oil.

ν_{max}/cm^{-1}: 2969, 1750, 1660, 1450; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.03 (3 H, t *J* 7.5 Hz, C**H$_3$**CH_2), 1.69-1.87 (1 H, m, C**H$_A$**H_BCH), 1.69-1.87 (2 H, m, CH_3C**H$_2$**), 1.88-1.99 (1 H, m, CH_A**H$_B$**CH), 2.12-2.23 (2 H, m, C**H$_2$**CH_2CH), 2.69-2.84 (2 H, m, C**H$_2$**C=N), 2.69-2.84 (2 H, m, C**H$_2$**CH_2CH_3), 3.81 (3 H, s, CO_2C**H$_3$**), 4.73 (1 H, t *J* 5.0 Hz, C**H**N); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 13.2, 15.0, 20.2, 22.6, 29.7, 39.9, 53.6, 56.2, 114.0 (q *J* 300 Hz), 160.7 (q *J* 60 Hz), 167.9, 194.5; Found MH^+ 184.1335. $C_{10}H_{18}NO_2$ requires MH^+ 184.1338.; $[\alpha]_D^{23}$ +50 (*c* 1.0 in $CHCl_3$).

Methyl (2*S*)-6-methylpiperidine-2-carboxylate (**175a**/**175b**)

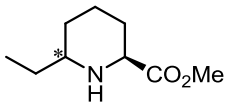


Sodium borohydride (8.19 mg, 0.2 mmol, 1.0 eq) was added to a stirred solution of trifluoroacetic acid methyl (2*S*)-6-methyl-2,3,4,5-tetrahydropyridine-2 carboxylate **174a** (53.8 mg, 0.2 mmol, 1.0 eq) in methanol (8.5 mL) at -78 °C. The mixture was stirred for 1 h at -78 °C, and the reaction was quenched by addition of acetone (0.04 mL). After concentration, the resulting oil was dissolved in chloroform and methanol (10:1) (10 mL), washed with saturated ammonium sulfate solution, and dried over magnesium sulfate and concentrated on rotary evaporator to provide the title compound as colorless oil (27 mg, 85%).[114] The ratio of *cis* : *trans* (6 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

ν_{max}/cm^{-1}: 2973, 1711; ***cis*** **diastereoisomer 175a**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.12 (3 H, d *J* 6.5 Hz, C**H$_3$**CH), 1.0-1.15 (1 H, m, C**H$_A$**H$_B$CHCH$_3$), 1.32-1.49 (2 H, m, C**H$_2$**CH$_2$CH), 1.72-1.83 (1 H, m, CH$_A$**H$_B$**CHCH$_3$), 1.83-1.91 (1 H, m, C**H$_A$**H$_B$CHN), 1.96-2.02 (1 H, m, CH$_A$**H$_B$**CHN), 2.12-2.50 (1 H, br, N**H**), 2.67 (1 H, dqd *J* 12.0, 6.5 and 2.5 Hz, CH$_3$C**H**), 3.38 (1 H, dd *J* 11.5 and 3.0 Hz, NHC**H$_{(ax)}$**CO$_2$CH$_3$), 3.71 (3 H, s, CO$_2$C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ-ppm: 23.1, 28.2, 29.7, 31.2, 52.0, 58.0, 59.9, 173.8. ***trans*** **diastereoisomer 175b**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.15 (3 H, d *J* 6.5 Hz, C**H$_3$**CH), 1.0-1.15 (1 H, m, C**H$_A$**H$_B$CHCH$_3$), 1.32-1.49 (2 H, m, C**H$_2$**CH$_2$CH), 1.72-1.83 (1 H, m, CH$_A$**H$_B$**CHCH$_3$), 1.83-1.91 (1 H, m, C**H$_A$**H$_B$CHN), 1.96-2.02 (1 H, m, CH$_A$**H$_B$**CHN), 2.12-2.50 (1 H, br, N**H**), 2.91-3.0 (1 H, m, CH$_3$C**H**), 3.73 (3 H, s, CO$_2$C**H$_3$**), 3.75-3.83 (1 H, m, NHC**H$_{(ax)}$**CO$_2$CH$_3$); **^{13}C NMR** (100 MHz,

$CDCl_3$) δ ppm: 23.1, 23.7, 26.4, 28.2, 29.3, 29.7, 31.2, 46.0, 52.0, 55.1, 57.2, 58.0, 59.9, 167.6, 173.8. Found MH^+ 158.1183. $C_8H_{16}NO_2$ requires MH^+ 158.1181.

Methyl (2S)-6-ethylpiperidine-2-carboxylate (**176a**/**176b**)

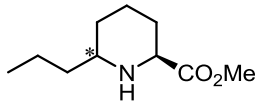


Sodium borohydride (8.19 mg, 0.2 mmol, 1.0 eq) was added to a stirred solution of trifluoroacetic acid methyl (2S)-6-ethyl-2,3,4,5-tetrahydropyridine-2-carboxylate **174b** (56 mg, 0.2 mmol, 1.0 eq) in methanol (8.5 mL) at -78 °C. The mixture was stirred for 1 h at -78 °C, and the reaction was quenched by addition of acetone (0.04 mL). After concentration, the resulting oil was dissolved in chloroform and methanol (10:1) (10 mL), washed with saturated ammonium sulfate solution, and dried over magnesium sulfate and concentrated on rotary evaporator to provide the title compound as colorless oil (30 mg, 88%). The ratio of *cis* : *trans* (6 : 1) determined by ^{1}H-NMR spectroscopy of the crude product.

ν_{max}/cm^{-1}: 3008, 2949, 1797, 1795, 1388, 1382; ***cis*** **diastereoisomer 176a**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.92 (3 H, t *J* 7.5 Hz, C**H$_3$**CH_2), 0.97-1.09 (1 H, m, C**H$_{A(eq)}$**H_BCHCH_2CH_3), 1.36-1.51 (2 H, m, C**H$_2$**CH_2CH), 1.36-1.51 (2 H, m, C**H$_2$**CH_3), 1.68 (1 H, d *J* 11.0 Hz, CH_A**H$_{B(ax)}$**CHCH_2CH_3), 1.83-1.91 (1 H, m, C**H$_{A(eq)}$**H_BCHN), 2.00-2.09 (1 H, m, CH_A**H$_{B(ax)}$**CHN), 2.17-2.27 (1 H, br, N**H**), 2.43 (1 H, dtd *J* 11.5 6.5 and 2.5 Hz, CH_3CH_2C**H$_{(ax)}$**), 3.36 (1 H, dd *J* 11.5 and 3.0 Hz,

NHC**H$_{(ax)}$**CO_2CH_3), 3.71 (3 H, s, CO_2C**H$_3$**); ***trans*** **diastereoisomer 176b**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ-ppm: 0.91 (3 H, t *J* 7.5 Hz, C**H$_3$**CH_2), 0.97-1.09 (1 H, m, C**H$_A$**$H_B$$CHCH_2CH_3$), 1.36-1.51 (2 H, m, C**H$_2$**CH_2CH), 1.36-1.51 (2 H, m, C**H$_2$**CH_3), 1.68 (1 H, m, CH_A**H$_B$**$CHCH_2CH_3$), 1.83-1.91 (1 H, m, C**H$_A$**$H_B$$CHN$), 2.00-2.09 (1 H, m, CH_A**H$_B$**CHN), 2.17-2.27 (1 H, br, N**H**), 2.73-2.84 (1 H, br, CH_3CH_2C**H**), 3.75 (3 H, s, CO_2C**H$_3$**), 3.87-3.92 (1 H, br, NHC**H**CO_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ-ppm: 10.0, 10.3, 20.9, 26.4, 29.2, 29.7, 31.2, 46.0, 51.9, 55.1, 57.2, 58.0, 59.3, 167.6, 173.6; Found MH^+ 172.1330. $C_9H_{18}NO_2$ requires MH^+ 172.1338.

Methyl (2*S*)-6-propylpiperidine-2-carboxylate (**177a**/**177b**)



Sodium borohydride (8.19 mg, 0.2 mmol, 1.0 eq) was added to a stirred solution of trifluoroacetic acid methyl (2S)-6-propyl-2,3,4,5-tetrahydropyridine-2-carboxylate **174c** (59 mg, 0.2 mmol, 1.0 eq) in methanol (8.5 mL) at -78 °C. The mixture was stirred for 1 h at -78 °C, and the reaction was quenched by addition of acetone (0.04 mL). After concentration, the resulting oil was dissolved in chloroform and methanol (10:1) (10 mL), washed with saturated ammonium sulfate solution, and dried over magnesium sulfate and concentrated on rotary evaporator to provide the title compound as colorless oil (28 mg, 89%). The ratio of *cis* : *trans* (6 : 1) determined by ^{1}H-NMR spectroscopy of the crude product. **ν_{max}/cm^{-1}**: 2958, 1740; ***cis*** **diastereoisomer 177a**: **^{1}H NMR** (400 MHz,

$CDCl_3$) δ ppm: 0.85-.91 (2 H, m, $CH_3C\mathbf{H_2}CH_2$), 0.91 (3 H, t *J* 7.5 Hz, $C\mathbf{H_3}CH_2$), 1.0-1.13 (1 H, m, $C\mathbf{H_{A(eq)}}H_BCHCH_2CH_2CH_3$), 1.29-1.49 (2 H, m, $C\mathbf{H_2}CH_2CH$), 1.29-1.49 (2 H, m, $C\mathbf{H_2}CH_2CH_3$), 1.62 (1 H, d *J* 13.0 Hz, $CH_A\mathbf{H_{B(ax)}}CHCH_2CH_2CH_3$), 1.83-1.91 (1 H, m, $C\mathbf{H_{A(eq)}}H_BCHN$), 1.97-2.05 (1 H, m, $CH_A\mathbf{H_{B(ax)}}CHN$), 2.17-2.27 (1 H, br, N**H**), 2.54 (1 H, dtd *J* 11.5 6.5 and 2.5 Hz, $CH_3CH_2CH_2C\mathbf{H_{(ax)}}$), 3.40 (1 H, dd *J* 11.5 and 3.0 Hz, $NHC\mathbf{H_{(ax)}}CO_2CH_3$), 3.71 (3 H, s, $CO_2C\mathbf{H_3}$); ***trans*** **diastereoisomer 177b**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.85-.91 (2 H, m, $CH_3C\mathbf{H_2}CH_2$), 0.91 (3 H, t *J* 7.5 Hz, $C\mathbf{H_3}CH_2$), 1.0-1.13 (1 H, m, $C\mathbf{H_A}H_BCHCH_2CH_3$), 1.29-1.49 (2 H, m, $C\mathbf{H_2}CH_2CH$), 1.29-1.49 (2 H, m, $C\mathbf{H_2}CH_2CH_3$), 1.58-1.64 (1 H, m, $CH_A\mathbf{H_B}CHCH_2CH_2CH_3$), 1.83-1.91 (1 H, m, $C\mathbf{H_A}H_BCHN$), 1.97-2.05 (1 H, m, $CH_A\mathbf{H_B}CHN$), 2.17-2.27 (1 H, br, N**H**), 2.73-2.84 (1 H, br, $CH_3CH_2CH_2C\mathbf{H}$), 3.76 (3 H, s, $CO_2C\mathbf{H_3}$), 3.87-3.92 (1 H, br, $NHC\mathbf{H}CO_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 14.1, 14.2, 18.9, 19.0, 24.1, 24.2, 28.9, 29.7, 31.2, 31.3, 38.6, 38.7, 52.0, 52.1, 56.3, 59.1, 59.2, 177.5, 179.8; Found MH^+ 186.1487. $C_{10}H_{20}NO_2$ requires MH^+ 186.1494.

5: References

(1) Weintraub, P. M.; Sabol, J. S.; Kane, J. A.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.

(2) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.

(3) Laschat *Synthesis* **2000**, *13*, 33.

(4) Hoesl, C. E.; Hofner, G.; Wanner, K. T. *Tetrahedron* **2004**, *60*, 307.

(5) Dutta, A. K.; Davis, M. C.; Reith, M. E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2337.

(6) Pissarnitski, D. A.; Asberom, T.; Bara, T. A.; Buevich, A. V.; Clader, J. W.; Greenlee, W. J.; Guzik, H. S.; Josien, H. B.; Li, W.; McEwan, M.; McKittrick, B. A.; Nechuta, T. L.; Parker, E. M.; Sinning, L.; Smith, E. M.; Song, L. X.; Vaccaro, H. A.; Voigt, J. H.; Zhang, L.; Zhang, Q.; Zhao, Z. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 57.

(7) Asberom, T.; Zhao, Z.; Bara, T. A.; Clader, J. W.; Greenlee, W. J.; Hyde, L. A.; Josien, H. B.; Li, W.; McPhail, A. T.; Nomeir, A. A.; Parker, E. M.; Rajagopalan, M.; Song, L.; Wong, G. T.; Zhang, L.; Zhang, Q.; Pissarnitski, D. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 511.

(8) Josien, H.; Bara, T.; Rajagopalan, M.; Asberom, T.; Cladera, J. W.; Favreau, L.; Greenlee, W. J.; Hyde, L. A.; Nomeir, A. A.; Parker, E. M.; Pissarnitski, D. A.; Song, L. X.; Wong, G. T.; Zhang, L. L.; Zhang, Q.; Zhao, Z. Q. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5330.

(9) McBriar, M. D.; Clader, J. W.; Chu, I.; Del Vecchio, R. A.; Favreau, L.; Greenlee, W. J.; Hyde, L. A.; Nomeir, A. A.; Parker, E. M.; Pissarnitski, D. A.; Song, L. X.; Zhang, L. L.; Zhao, Z. Q. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 215.

(10) Girisha, H. R.; Chandra, J.; Boppana, S.; Malviya, M.; Sadashiva, C. T.; Rangappa, K. S. *Eur. J. Med. Chem.* **2009**, *44*, 4057.

(11) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chemical Communications* **1998**, 633.

(12) Kallstrom, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601.

(13) Prevost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383.

(14) Pollard, C. B.; Parcell, R. F. *J. Am. Chem. Soc.* **1951**, *73*, 2925.

(15) Bottini, A. T.; Roberts, J. D. *J. Am. Chem. Soc.* **1957**, *79*, 1462.

(16) Ince, J.; Ross, T. M.; Shipman, M.; Slawin, A. M. Z. *Tetrahedron* **1996**, *52*, 7037.

(17) Gensler, W. J.; Koehler, W. R. *J. Org. Chem.* **1962**, *27*, 2754.

(18) Weiler, L. *J. Amer. Chem. Soc.* **1970**, *92*, 6702.

(19) Prevost, N.; Shipman, M. *Tetrahedron* **2002**, *58*, 7165.

(20) Desmaele, D.; Louvet, J.-M. *Tetrahedron Lett.* **1994**, *35*, 2549.

(21) Le, D. M. A.; Desmaele, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933.

(22) Jousse, C.; Mainguy, D.; Desmaele, D. *Tetrahedron Lett.* **1998**, *39*, 1349.

(23) Jousse-Karinthi, C.; Zouhiri, F.; Mahuteau, J.; Desmaele, D. *Tetrahedron* **2003**, *59*, 2093.

(24) Bambal, R. B.; Kemmitt, R. D. W. *J. Organomet. Chem.* **1989**, *362*, C18.

(25) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286.

(26) Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2005**, *7*, 2993.

(27) Berry, M. B.; Craig, D. *Synlett* **1992**, 41.

(28) Sun, C. S.; Lin, Y. S.; Hou, D. R. *J. Org. Chem.* **2008**, *73*, 6877.

(29) Caturla, F.; Najera, C. *Tetrahedron Lett.* **1997**, *38*, 3789.

(30) Costa, A.; Najera, C.; Sansano, J. M. *Tetrahedron: Asymmetry* **2001**, *12*, 2205.

(31) Tehrani, K. A.; D'Hooghe, M.; De, K. N. *Tetrahedron* **2003**, *59*, 3099.

(32) Safar, P.; Zuziova, J.; Bobosikova, M.; Marchalin, S.; Pronayova, N.; Comesse, S.; Daich, A. *Tetrahedron: Asymmetry* **2009**, *20*, 2137.

(33) Couty, F. *Amino Acids* **1999**, *16*, 297.

(34) Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101.

(35) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379.

(36) Bailey, P. D.; Smith, P. D.; Morgan, K. M.; Rosair, G. M. *Tetrahedron Lett.* **2002**, *43*, 1071.

(37) Bailey, P. D.; Smith, P. D.; Pederson, F.; Clegg, W.; Rosair, G. M.; Teat, S. J. *Tetrahedron Lett.* **2002**, *43*, 1067.

(38) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590.

(39) Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118.

(40) Davis, F. A.; Zhang, H. M.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759.

(41) Takahata, H.; Shimizu, M. *Amino Acids* **2003**, *24*, 267.

(42) Gebauer, J.; Dewi, P.; Blechert, S. *Tetrahedron Lett.* **2005**, *46*, 43.

(43) Caplan, J. F.; Sutherland, A.; Vederas, J. C. *Journal of the Chemical Society-Perkin Transactions 1* **2001**, 2217.

(44) Sardina *Chemical Reviews* **1996**, *96*, 48.

(45) Rilatt, I.; Caggiano, L.; Jackson, R. F. W. *Synlett* **2005**, 2701.

(46) Jackson, R. F. W.; Graham, L. J.; Rettie, A. B. *Tetrahedron Lett.* **1994**, *35*, 4417.

(47) Jackson, R. F. W.; Turner, D.; Block, M. H. *Synlett* **1997**, 789.

(48) Gulati, V. *Thesis* **2008**.

(49) Knochel, P.; Diene, C. *C. R. Chim.* **2011**, *14*, 842.

(50) Knochel, P.; Singer, R. D. *Chemical Reviews* **1993**, *93*, 2117.

(51) Erdik, E. *Tetrahedron* **1992**, *48*, 9577.

(52) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.

(53) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298.

(54) Negishi, E.; Matsushita, H.; Kobayashi, M.; Rand, C. L. *Tetrahedron Lett.* **1983**, *24*, 3823.

(55) Nakamura, E.; Sekiya, K.; Kuwajima, I. *Tetrahedron Lett.* **1987**, *28*, 337.

(56) Negishi, E.-i.; Wang, G.; Rao, H.; Xu, Z. *J. Org. Chem.* **2010**, *75*, 3151.

(57) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368.

(58) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056.

(59) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 4431.

(60) Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4418.

(61) Erdik, E. *Tetrahedron* **1987**, *43*, 2203.

(62) Dexter, C. S.; Jackson, R. F. W. *Chemical Communications* **1998**, 75.

(63) Rieke, R. D.; Uhm, S. J.; Hudnall, P. M. *J. Chem. Soc., Chem. Commun.* **1973**, 269.

(64) Jackson, R. F. W.; Wythes, M. J.; Wood, A. *Tetrahedron Lett.* **1989**, *30*, 5941.

(65) Jackson, R. F. W.; Moore, R. J.; Dexter, C. S.; Elliott, J.; Mowbray, C. E. *J. Org. Chem.* **1998**, *63*, 7875.

(66) Hunter, C.; Jackson, R. F. W.; Rami, H. K. *Journal of the Chemical Society-Perkin Transactions 1* **2001**, 1349.

(67) Rilatt, I.; Jackson, R. F. W. *J. Org. Chem.* **2008**, *73*, 8694.

(68) Massah, A. R.; Ross, A. J.; Jackson, R. F. W. *J. Org. Chem.* **2010**, *75*, 8275.

(69) Breit, B.; Schmidt, Y. *Chemical Reviews* **2008**, *108*, 2928.

(70) Yoshikai, N.; Nakamura, E. *Chemical Reviews* **2012**, *112*, 2339.

(71) Lipshutz, B. H.; Sengupta, S. *Org. React. (N. Y.)* **1992**, *41*, 135.

(72) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316.

(73) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630.

(74) Costa, G.; Camus, A.; Gatti, L.; Marsich, N. *J. Organomet. Chem.* **1966**, *5*, 568.

(75) House, H. O. *Current Contents/Physical Chemical & Earth Sciences* **1981**, 16.

(76) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(77) Knochel, P.; Rozema, M. J.; Tucker, C. E.; Retherford, C.; Furlong, M.; Rao, S. A. *Pure Appl. Chem.* **1992**, *64*, 361.

(78) Gaudemar, M. *Tetrahedron Lett.* **1983**, *24*, 2749.

(79) Retherford, C.; Chou, T. S.; Schelkun, R. M.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 1833.

(80) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422.

(81) Dunn, M. J.; Jackson, R. F. W. *J. Chem. Soc., Chem. Commun.* **1992**, 319.

(82) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210.

(83) Dexter, C. S.; Jackson, R. F. W.; Elliott, J. *J. Org. Chem.* **1999**, *64*, 7579.

(84) Deboves, H. J. C.; Grabowska, U.; Rizzo, A.; Jackson, R. F. W. *Journal of the Chemical Society-Perkin Transactions 1* **2000**, 4284.

(85) Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64.

(86) Jackson, R. F. W.; Perez-Gonzalez, M. *Org. Synth.* **2005**, *81*, 77.

(87) Hunter, C.; Jackson, R. F. W.; Rami, H. K. *Journal of the Chemical Society-Perkin Transactions 1* **2000**, 219.

(88) Goddard, C. M. L.; Massah, A. R.; Jackson, R. F. W. *Tetrahedron* **2010**, *66*, 9175.

(89) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.

(90) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568.

(91) Wiktelius, D.; Luthman, K. *Org. Biomol. Chem.* **2007**, *5*, 603.

(92) Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473.

(93) More, S. S.; Vince, R. *J. Med. Chem.* **2009**, *52*, 4650.

(94) Katritzky, A. R.; Tao, H.; Jiang, R.; Suzuki, K.; Kirichenko, K. *J. Org. Chem.* **2007**, *72*, 407.

(95) More, S. S.; Vince, R. *J. Med. Chem.* **2009**, *52*, 4650.

(96) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167.

(97) Hjelmgaard, T.; Tanner, D. *Org. Biomol. Chem.* **2006**, *4*, 1796.

(98) Jackson, R. F. W.; Moore, R. J.; Dexter, C. S.; Elliot, J.; Mowbray, C. E. *J. Org. Chem.* **1998**, *63*, 7875.

(99) Schenck, H. A.; Lenkowski, P. W.; Choudhury-Mukherjee, I.; Ko, S.-H.; Stables, J. P.; Patel, M. K.; Brown, M. L. *Bioorg. Med. Chem.* **2004**, *12*, 979.

(100) Slaitas, A.; Yeheskiely, E. *Eur. J. Org. Chem.* **2002**, 2391.

(101) Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621.

(102) Hjelmgaard, T.; Tanner, D. *Org. Biomol. Chem.* **2006**, *4*, 1796.

(103) Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353.

(104) Provot, O.; Celerier, J. P.; Petit, H.; Lhommet, G. *J. Org. Chem.* **1992**, *57*, 2163.

(105) Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.

(106) Nakagawa, Y.; Matsumoto, K.; Tomioka, K. *Tetrahedron* **2000**, *56*, 2857.

(107) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549.

(108) Akireddy, S. R.; Mazurov, A.; Yohannes, D.; Miao, L.; Speake, J. D.; Targacept, Inc., USA . 2010, p 57pp.

(109) Martinez, S. J.; Joule, J. A. *Tetrahedron* **1978**, *34*, 3027.

(110) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(111) Chow, Y. L.; Colon, C. J.; Tam, J. N. S. *Can. J. Chem.* **1968**, *46*, 2821.

(112) Quick, J.; Mondello, C.; Humora, M.; Brennan, T. *J. Org. Chem.* **1978**, *43*, 2705.

(113) Kimura, J.; Takada, Y.; Inayoshi, T.; Nakao, Y.; Goetz, G.; Yoshida, W. Y.; Scheuer, P. J. *J. Org. Chem.* **2002**, *67*, 1760.

(114) Ishida, A.; Jujii, H.; Nakamura, T.; Oh-Ishi, T.; Aoe, K.; Nishibata, Y.; Kinumaki, A. *Chem. Pharm. Bull.* **1986**, *34*, 1994.

(115) Goddard, C. M. L.; Massah, A. R.; Jackson, R. F. W. *Tetrahedron* **2010**, *66*, 9175.

(116) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167.