Synthesis of Nitrogen Containing Heterocycles

A thesis submitted in partial fulfilment of the requirement
for the degree of Master of Science by Research

by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from September 2012 until January 2016, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

Alexander White

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Special thanks to Ian, Marta, Aileen, Kristina, Matt, David and Carole who have all been so much more than just colleagues throughout my time in Oxford and who I regard as great friends. Thank you all for looking out for me over the past few years both in and out of the lab. I've had many great times with you and I leave with lots of great memories, albeit some may be slightly hazy! I will miss you all.

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Abbreviations

The following abbreviations are used throughout this report.

$[\alpha]_D$	Specific rotation
Ac	Acyl
app	Apparent
aq	Aqueous
Boc	*tert*-butyloxycarbonyl
br	Broad
Bn	Benzyl
^{t}Bu	*Tertiary* Butyl
BuLi	Butyl lithium
c	Concentration
C	Celsius
CAN	Ceric Ammonium Nitrate
CBz	Carboxybenzyl
cm^{-1}	Wavenumber
COD	1,5-Cyclooactadiene
conc	Concentration
dd	Double doublet
ddd	Double double doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DIBAL-H	Diisobutylaluminium hydride
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
dt	Double triplet
δ_H	Proton (^{1}H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
ee	Enantiomeric excess
EI	Electron ionisation
eq	Equivalents
ESI	Electrospray ionisation
EtOAc	Ethyl acetate
FI	Field ionisation
FT	Fourier transform
g	Grams
GC	Gas Chromatography
h	Hours
HCl	Hydrochloric acid
HRMS	High resolution mass spectrometry
Hz	Hertz
i	Ipso
IR	Infra-red
IPA	Propan-2-ol
IUPAC	International Union of Pure and Applied Chemistry

J	Coupling constant
lit.	Literature
L	Litres
m	Meta
m	Multiplet
M	Molar
M^+	Molecular ion
$[M+H]^+$	Protonated molecular ion
$[M+Na]^+$	Sodiated molecular ion
Me	Methyl
MHz	Mega-hertz
min	Minutes
mL	Millilitres
mmol	Millimoles
mol	Moles
mp	Melting point
m/z	Mass to charge ratio
MS	Mass spectrometry
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
PCC	Pyridinium chlorochromate
Ph	Phenyl
PhCHO	Benzaldehyde
ppm	Parts per million
q	Quartet
quant	Quantitative
rt	Room temperature
s	Secondary
s	Singlet
satd	Saturated
tert	Tertiary
t	Triplet
T	Temperature
TBAF	Tetra-n-butylammonium fluoride
TEA	Triethylamine
Tf	Triflic
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TOF	Time-of-flight
UV	Ultra-violet
ν_{max}	Infra red absorption
v/v	Volume by volume

Chapter 1: Introduction

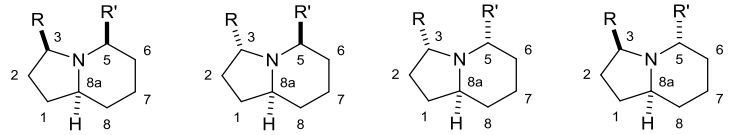
1.1 Discovery and Characterisation of 3,5-Disubstituted Indolizidines

Neotropical frogs characterised by their bright warning colourations[1] have been shown to possess an abundant array of toxic alkaloids which are stored in so called 'poison glands' of the skin and which act as a mechanism of chemical defence against both predators and microbial infection.[2] Extensive investigation, in independent studies by Daly[3] and Clark,[4] have shown that these alkaloids are in fact not produced directly by the frogs themselves. Clark showed that dendrobatid frogs bred in captivity (and fed on a controlled diet, excluding exposure to the alkaloids) did not possess the toxic alkaloids present in the skins of dendrobatid frogs caught in the wild. However, if these alkaloids were added into the diet of the captive bred frogs then they would rapidly accumulate and be detected in their skin extracts. Daly identified variation in the alkaloid composition from the skins of dendrobatid frogs sampled from different habitats and showed that these differences were linked to differences in the arthropod population in the different areas sampled. A large variety of alkaloids, normally based on pyrrolidine, piperidine, pyrrolizine, indolizidine, quinolizidine and decahydroquinoline scaffolds, are well known components of the venom of myricinine ants[5] which are known to constitute a major part of the diet of dendrobatid frogs native to Central and South America.[3] Of these, the most noteworthy are the 3,5-disubtstitued indolizidines.[6]

A 3,5-disubstituted indolizidine is a fused [4.3.0]-azabicyclic ring system with a nitrogen atom at the bridgehead position (position 4). The carbon atoms around the bicyclic skeleton are numbered according to IUPAC convection. This numbering system is used throughout this thesis.

To date, over 25 different 3,5-disubstituted indolizidines have been isolated from the skin extracts of dendrobatid frogs (Figure 1) and myricinime ants are undoubtedly the dietary source.[7] The 3,5-disubstitued indolizidines are named by a numerical designation, relating to their nominal molecular weight, followed by an identifying letter to distinguish between different structural isomers of the same molecular weight. The relative configuration at C(5) and C(8a) is assigned relative to the position of the hydrogen substituent at C(3).[8] In this

thesis, if the hydrogen at C(5) or C(8a) is on the same molecular face as the hydrogen at C(3) it will be designated *cis*- and if on the opposite face it is designated *trans*-.



(3,5-*cis*-, 3,8a-*cis*-) (3,5-*trans*-, 3,8a-*trans*-) (3,5-*cis*-, 3,8a-*trans*-) (3,5-*trans*-, 3,8a-*cis*-)

Indolizidine	3-substituent	5-substituent	Relative Configuration
167E	C_2H_5	CH_3	3,5-*cis*, 3,8a-*cis*
181A	C_2H_5	C_2H_5	unknown
195B	C_4H_9	CH_3	all four
211E	C_4H_9O	CH_3	3,5-*trans*, 3,8a-*trans*
221H	C_4H_7	C_3H_7	3,5-*trans*, 3,8a-*trans*
223AB	C_4H_9	C_3H_7	all four
223R	CH3	C_6H_{13}	unknown
223Z	C_2H_5	C_5H_{11}	unknown
237E	C_2H_5	C_5H_9O (OH)	unknown
239AB	C_4H_9	C_3H_7O	3,5-*trans*, 3,8a-*trans*
239CD	C_4H_9	C_3H_7	3,5-*trans*, 3,8a-*trans*
239E	C_2H_5	$C_5H_{11}O$	unknown
239Q	C_4H_9O	C_3H_7	3,5-*cis*, 3,8a-*cis*
247C	$(CH_2)_2CH=CH_2$	$(CH_2)_3CH=CH_2$	3,5-*trans*, 3,8a-*trans*
249A	C_4H_9	$(CH_2)_3CH=CH_2$	3,5-*cis*, 3,8a-*cis*
249R	C_6H_{11}	C_3H_7	unknown
253T	C_4H_9O	C_4H_9	unknown
265M	C_4H_9O	C_5H_9	unknown
271F	$(CH_2)_4CH=CH_2$	$(CH_2)_3CH\equiv CH$	3,5-*trans*, 3,8a-*trans*
275C	$(CH_2)_4CH=CH_2$	$(CH_2)_3CH=CH_2$	3,5-*cis*, 3,8a-*cis*

Figure 1. 3,5-Disubstituted indolizidines isolated from Dendrobatid frog skin extracts.

Due to the 3,5-disubstituted indolizidines being isolated as mixtures and only small quantities being available, separation of sufficient amounts of pure individual samples to allow for full characterisation by NMR spectroscopy is not always possible.[5] In these instances, a combination of GC, MS and vapour phase IR is used to allow for tentative structural assignment at the sub-microgram level. The EI mass spectra are normally dominated by cleavage of one or both of the C(3) or C(5)-substituents[9] and collision activated CI mass

spectra provide evidence as to which of the rings each substituent resides.[7] Analysis of the vapour phase FTIR spectra can be diagnostic of relative configuration, and has been used for the tentative assignment, of stereochemistry:[5] the (3,5-*cis*,3,8a-*cis*) isomers have a broad, complex Bohlmann band with a major absorption at 2791 cm^{-1}, the (3,5-*trans*,3,8a-*cis*) and (3,5-*trans*,3,8a-*trans*) isomers have weak Bohlmann bands at 2803 cm^{-1} and 2796 cm^{-1}, respectively, whilst the (3,5-*cis*,3,8a-*trans*) isomer has virtually no Bohlmann band.[7] The IR spectra of homologues with different length sidechains but the same relative configuration are virtually superimposable but these compounds are readily distinguished by GCMS.[9] Synthesis, and subsequent spectroscopic comparisons, are required to provide rigorous confirmation of structure and stereochemistry. As such, general synthetic procedures which allow for access to all diasteroisomers of 3,5-disubstituted indolizidines are desired.[5]

1.2 Literature Syntheses: Sequential Ring Formation

1.2.1 One Pot Deprotection-Cyclisation-Reduction Cascade

By far the most prevalent method for the synthesis of 3,5-disubstituted indolizidines in the literature is to start from either a 2,5-disubstituted pyrrolidine or 2,6-disubstituted piperidine which has a ketone functionality in one of the side chains and a protecting group on nitrogen which is readily removed by hydrogenolysis (typically *N*-Cbz or *N*-Bn). Deprotection of the nitrogen allows for reductive cyclisation, during which the *in situ* formed iminium is reduced to effect formation of the indolizidine core, with the substituents at both the C(3) and C(5) position. The diastereoselectivity is controlled by the two pre-existing stereocentres of the pyrrolidine or piperidine starting material. If the hydrogenolysis reaction is performed on a *trans*-2,5-disubstituted pyrrolidine **1** then the corresponding (3,5-*trans*,3,8a-*trans*)-indolizidine **2** is formed selectively. Hydrogenation of a *cis*-2,5-disubstituted pyrrolidine **3** results in selective formation of the (3,5-*cis*, 3,8a-*cis*) indolizidine **4**. The use of a *cis*-2,6-disubstituted piperidine **5** results in the selective formation of the (3,5-*cis*, 3,8a-*cis*)-indolizidine **6** (Figure 2). There are no examples in the literature which form a 3,5-disubstituted indolizidine by hydrogenolysis of a *trans*-2,6-disubstituted piperidine. This general strategy has been used to great effect, starting from *trans*-2,5-disubstituted pyrrolidines, by Kibayashi,[10] Lhommet,[11] Remuson[12] and Helmchen.[13] Craig,[14] Lesma,[15]

Wiest[16] and Livinghouse[17] all start from *cis*-2,5-disubstituted pyrrolidines, and Momose,[18] Solladie,[19] Somafi,[20] Harrity[21] and Reddy[22] start from *cis*-2,6-disubstituted piperidines.

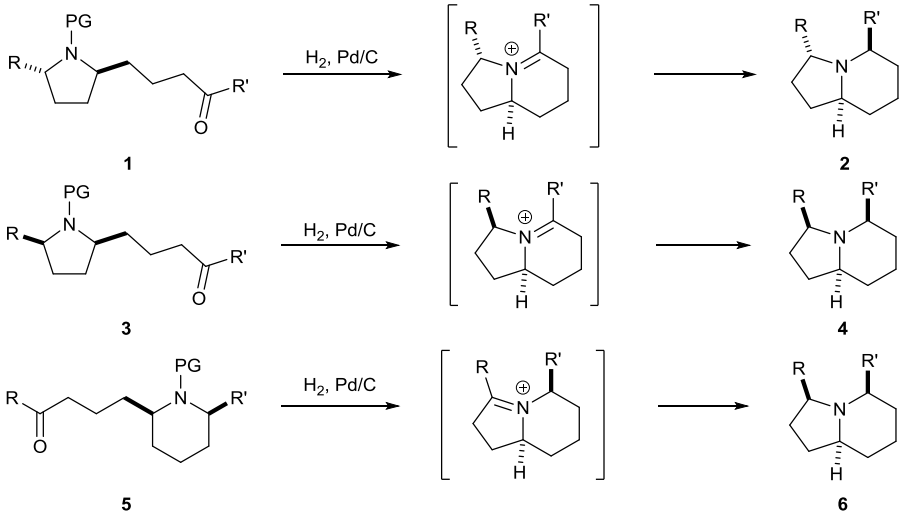
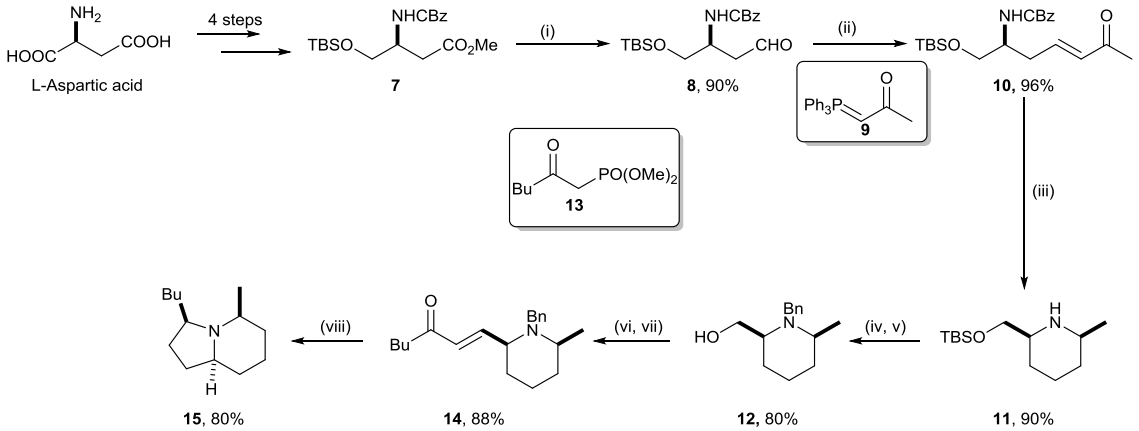


Figure 2. General strategy for the formation of 3,5-disubstituted indolizidines

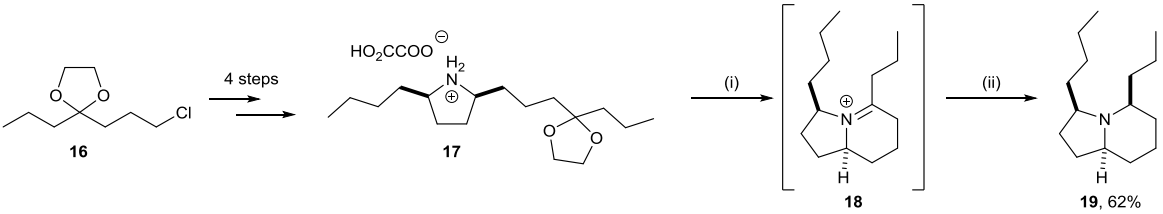
As a representative example of this approach, Reddy[22] forms the 2,6-*cis*-disubstituted piperidine **12** from L-aspartic acid. L-Aspartic acid was converted into **7** in four steps, which was then reduced to give aldehyde **8** upon treatment with DIBAL-H. Wittig olefination of **8** gave **10**, which was hydrogenated to give 2,6-*cis*-disubstituted piperidine **11**. Conversion of **11** into **14** was achieved by *N*-protection and *O*-deprotection to give **12** followed by oxidation and Horner-Wadswoth-Emmons reaction. Subjection of **14** to hydrogenation conditions formed the 3,5-*cis*-,3,8a-*cis*-3,5-disubstituted-indolizidine **15** as a single diasteroisomer (Scheme 1).



Scheme 1. *Reagents conditions: (*i) DIBAL-H, PhMe, −78 °C, 10 min; (ii) **9**, PhMe, 110 °C, 6 h; (iii) Pd/C, H_2 (1 atm), EtOH, rt, 12 h; (iv) BnBr, K_2CO_3, DMF, rt, 12 h; (v) HCl, EtOH, rt, 12 h; (vi) SO_3·py, CH_2Cl_2, DMSO, Et_3N, 0 °C, 30 min; (vii) **13**, $Ba(OH)_2·8H_2O$, THF/H_2O (20:1), 5 h; (viii) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 12 h.

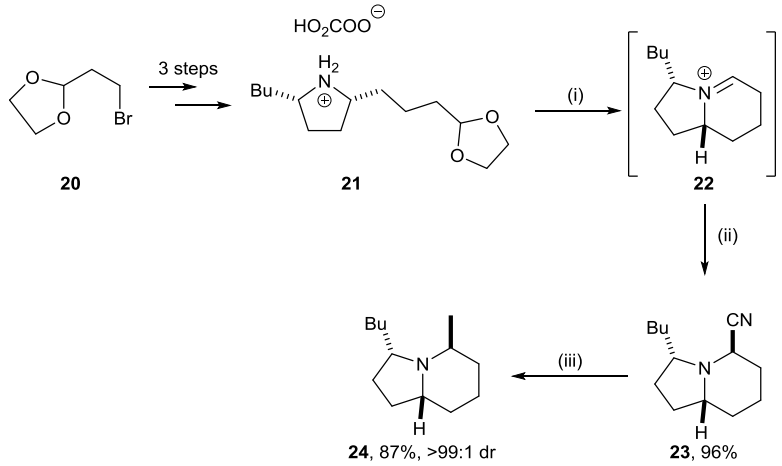
1.2.2 Iminium Formation then Reduction with Nucleophile

Nakagawa[23] starts his synthesis from **16** which is converted, in four steps, into the oxalate salt of the 2,5-disubstituted pyrrolidine **17**. Treatment of **17** with HCl revealed the ketone functionality and basification then led to formation of an iminium ion **18** which was reduced *in situ* by sodium cyanoborohydride to furnish the 3,5-disubstituted indolizidine **19** (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) HCl, THF, H_2O, rt, 12 h then KOH; (ii) $NaCNBH_3$, MeOH, THF, rt, 2.5 h.

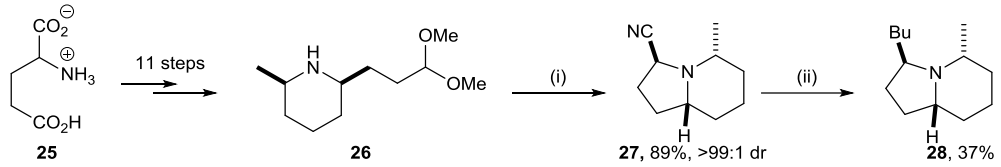
Stevens[24] started from bromoacetal **20** which was converted into the oxalate salt **21** in 3 steps. Subsequent acidic hydrolysis of **21** revealed the aldehyde functionality allowing for cyclisation to occur forming the tetrahydropyridinium salt **22** which was trapped by addition of KCN to give **23**. Treatment of **23** with MeMgBr provided the 3,5-disubstituted indolizidine **24** (Scheme 3).



Scheme 3. *Reagents and condtions*: (i) HCl, H_2O, rt; (ii) KCN, rt; (iii) MeMgBr, Et_2O, 0 °C.

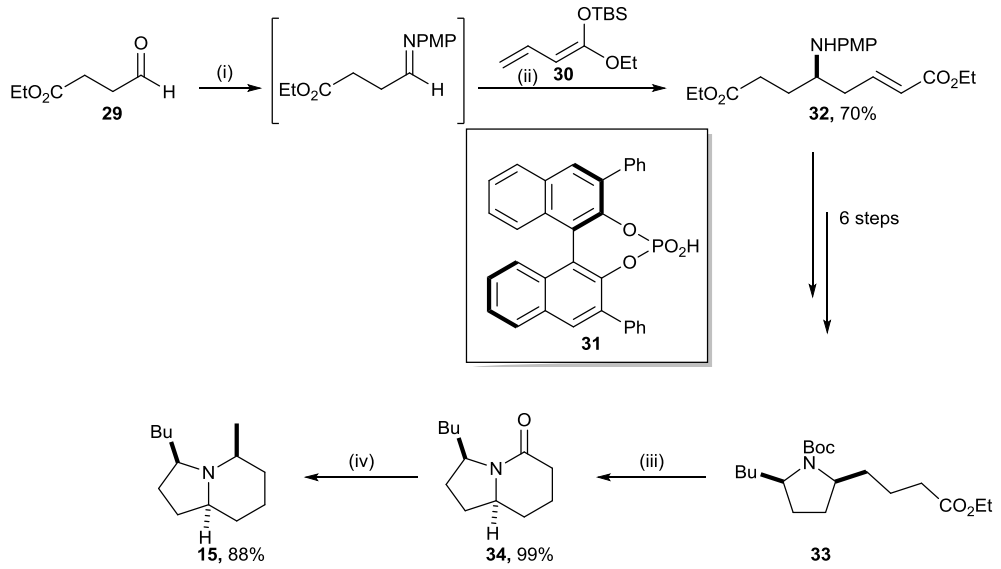
Angle[25] started from L-glutamic acid **25** and converted this into the 2,6-disubstituted piperidine **26** in an eleven step sequence. Treatment of **26** with acid triggered cyclisation, with KCN subsequently added to trap the iminium ion and form **27**. The synthesis was completed

by addition of butylmagnesium bromide which replaced the CN with a butyl group to give **28** (Scheme 4).



Scheme 4. *Reagents and conditions*: (i) KCN, 1 M aq HCl, rt, 16 h; (ii) BuMgBr, Et_2O, rt, 15 h.

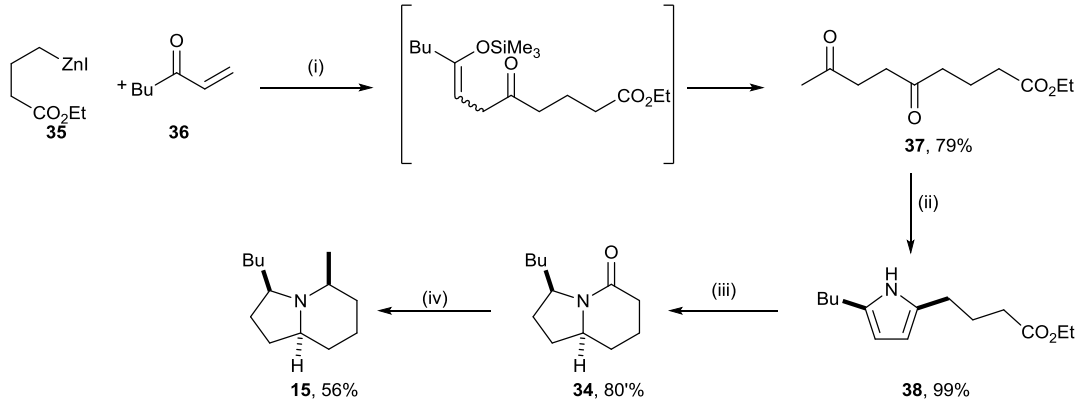
Schneider[26] initially performed a three component organocatalytic vinylogous Mukaiyama-Mannich reaction of aldehyde **29**, *para*-anisidine and vinylketene silyl acetal **30** to give access to **32**. A further six steps effected conversion of **32** into the *N*-Boc protected 2,5-disubstituted pyrrolidine **33**. Boc-deprotection with TFA followed by treatment with base formed the indolizidine core **34**, which has a carbonyl group at C(5). Installation of the required methyl group at C(5) was achieved by treatment of **34** with MeMgBr followed by acidification with glacial acetic acid to form an iminium ion *in situ*, which was reduced from the less hindered face by $NaBH_4$ to give **15** (Scheme 5).



Scheme 5. *Reagents and conditions*: (i) *para*-anisidine, THF, -50 °C, 30 min; (ii) **30**, **31**, -50 °C, 30 min; (iii) TFA, CH_2Cl_2, rt, 30 min then aq $NaHCO_3$, rt, 2 h; (iv) MeMgBr, THF, rt, 16 h then AcOH, $NaBH_4$, MeOH, rt, 1 h.

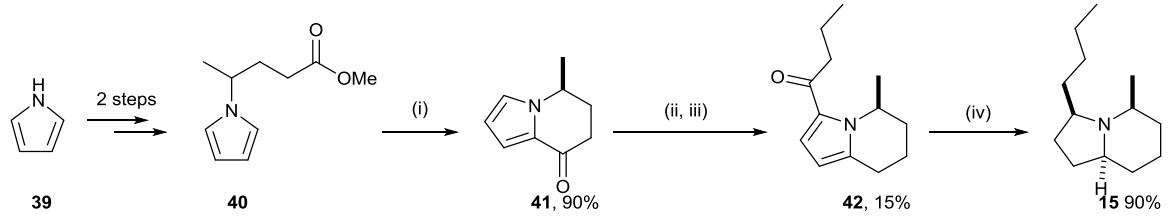
1.2.3 Reduction of Pyrrole/Pyridine

Orito[27] performed a one pot, four component reaction, based upon a palladium catalysed carbonylative 1,4-addition of an organozinc halide **35** to an α,β-enone **36** under a CO atmosphere, to form 1,4-diketone **37**. Aminocyclisation (Paal-Knorr) reaction of 1,4-diketone **37** with ammonium acetate then formed pyrrole **38**, which was hydrogenated in a *cis*-fashion to furnish the indolizidine core **34**. The C(5) position was subsequently functionalised by addition of Grignard reagent followed by acidification and borohydride reduction to give **15** (Scheme 6).



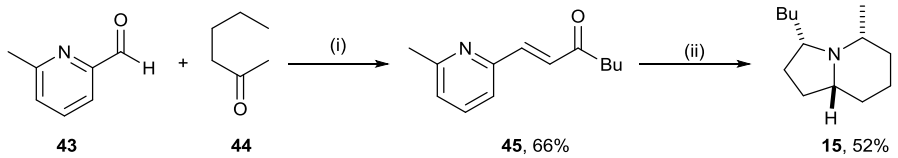
Scheme 6. *Reagents and conditions*: (i) CO (1 atm), $Pd(PPh_3)_4$, Me_3SiCl, LiCl, THF, 30 °C, 30 min then aq HCl; (ii) NH_4OAc, EtOH, rt, 24 h; (iii) PtO_2, H_2 (25 atm), AcOH, rt, 2 h then Me_3Al, CH_2Cl_2, 40 °C, 14 h; (iv) MeMgBr, THF, 67 °C, 5 h then AcOH, $NaBH_4$, MeOH, 0 °C, 2 h.

Smith[28] formed 3,5-disubstituted indolizidines by exploiting the nucleophilicity of the pyrrole unit **40**, initially synthesised from pyrrole **39** in two steps, to successfully annulate the six membered ring, giving access to **41**. Removal of the carbonyl at C(8) was achieved by treatment of **41** with $NaBH_3CN$ and zinc, subsequent reaction with butyryl chloride in the presence of silver triflate gave rise to **42**. Subsequent hydrogenation of **42** gave the 3,5-disubstituted indolizidine **15** (Scheme 7).



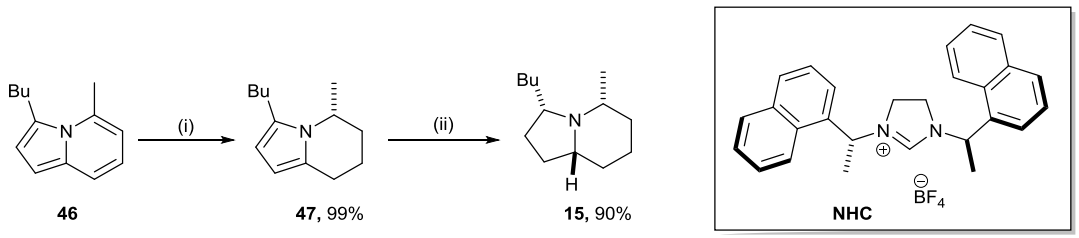
Scheme 7. *Reagents and conditions*: (i) BBr_3, CH_2Cl_2, 0 °C, 10 min; (ii) $NaBH_3CN$, ZnI_2, CH_2Cl_2, 45 °C, 6 h; (iii) Butytyl chloride, AgOTf, CH_2Cl_2, rt, 16 h; (iv) Pd/C, H_2 (3.7 atm), MeOH, cat H_2SO_4, rt, 10 h.

Mitton-Fry[29] formed **15** in two steps starting from a pyridine derivative **43**. An initial Claisen-Schmidt reaction of **43** with ketone **44** gave access to **45**. Hydrogenation of **45** removed the aromaticity of the pyridine ring and an intramolecular cyclisation furnished indolizidine **15** (Scheme 8).



Scheme 8. *Reagents and conditions*: (i) NaOH, H_2O, 100 °C, 45 min; (ii) Rh/C, H_2 (3 atm), MeOH/AcOH (3:1), 50 °C, 16 h.

Glorious[30] started from an indolizine derivative **46** and illustrated the ability to selectively hydrogenate to a pyrrole **47**, using a ruthenium catalyst with NHC ligands. The regioselectivity of the hydrogenation is due to the 5 membered ring having greater aromatic stabilisation compared to the six membered ring, resulting in the six membered ring being more amenable to hydrogenation. Subjection of the pyrrole **47** to more forcing hydrogenation conditions effected conversion to the 3,5-disubstituted indolizidine **15**, with the selectivity of the second hydrogenation step due to the platinum catalyst co-ordinating to the less hindered side (opposite to the methyl group) in order to reduce steric clash in the transition state (Scheme 9).

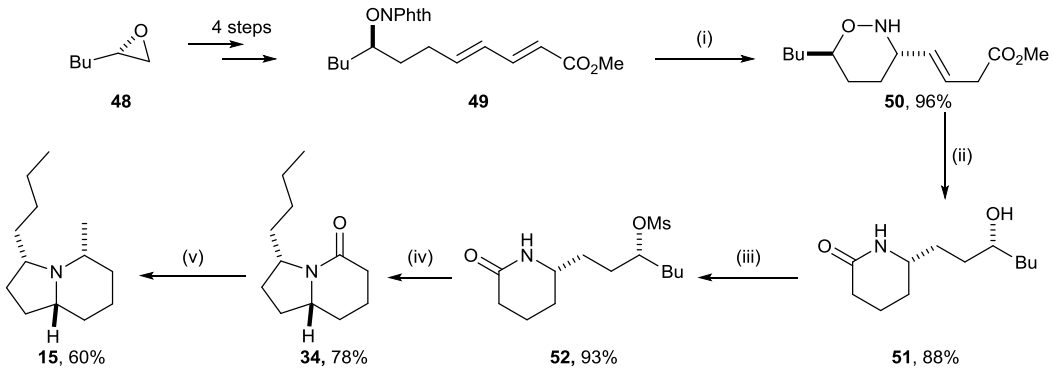


Scheme 9. *Reagents and conditions*: (i) [Ru(cod)(2-methylallyl)$_2$], **NHC**, KO^{t}Bu, H_2 (100 atm), rt, 24 h; (ii) PtO_2, AcOH, H_2 (20 atm), EtOH, rt, 16 h.

1.2.4 Alcohol Activation

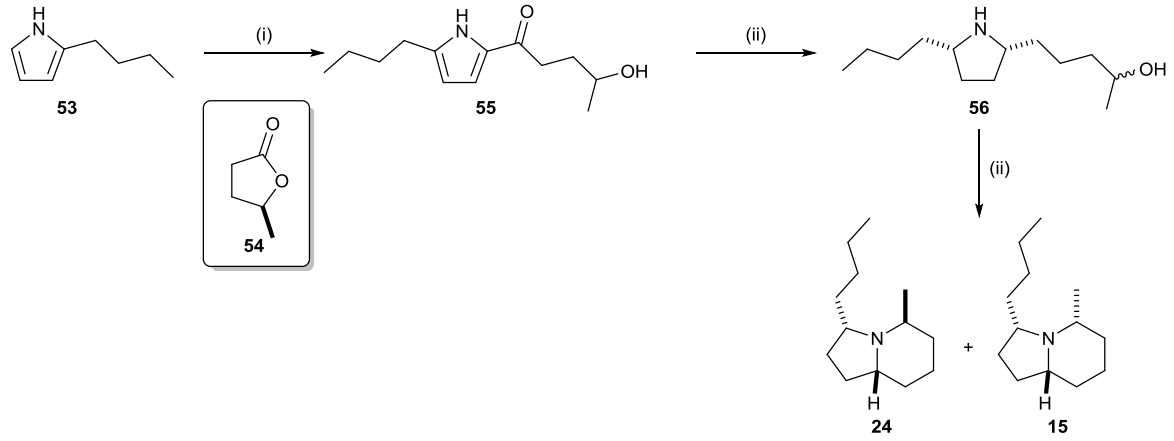
Bates[31] started from chiral epoxide **48** and converted this to **49** in four steps. Subsequent deprotection of **49** triggered concomitant intramolecular 1,6-conjugate addition to give access to **50**. A tandem hydrogenation-lactamisation reaction of **50** then gave **51**. The hydroxyl group of **51** was then converted into the corresponding mesylate **52** allowing for S_N2 chemistry to form the indolizidine core, which was triggered upon treatment of **52** with potassium *tert*-butoxide. After formation of the indolizidine core **34**, installation of the requisite methyl

group at C5 was achieved by treatment with MeMgBr followed by acidification and addition of $NaBH_4$ (Scheme 10).



Scheme 10. *Reagents and conditions*: (i) hydrazine hydrate, CH_2Cl_2, rt 10 h. (ii) Pt_2O, $CaCO_3$, MeOH, H_2 (1 atm), rt, 1 h; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; (iv) KO^{t}Bu, THF, rt, 1 h; (v) MeMgBr, THF, 67 °C, 5 h then AcOH, rt, 1 h then $NaBH_4$, 0 °C, 3 h.

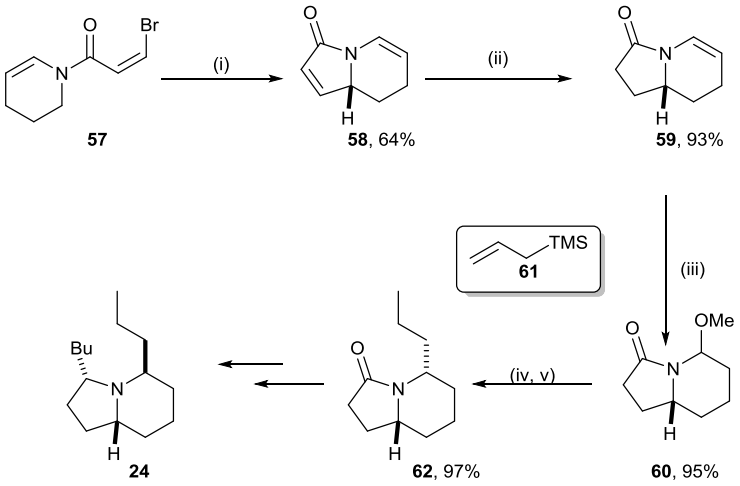
Sonnet[32] derived the indolizidine core from a 2,5-disubstituted pyrrolidine **56**, which has an alcohol on one of the side chains. Conversion of the hydroxyl group within **56** into a bromide allows for subsequent formation of the indolizidine cores **15** and **24** via an intramolecular S_N2 reaction. **56** was initially formed in two steps starting with a functionalization of 2-butylpyrrole **53** to give **55** followed by hydrogenation using platinum to destroy the aromaticity of the pyrrole ring (Scheme 11). Taber[33] employed the same principle for the formation of the indolizidine core but started from a 2,6-disubstituted piperidine and used the Appel reaction to form a chloride which underwent the S_N2 type reaction.



Scheme 11. *Reagents and conditions*: (i) MeMgBr, **54**; (ii) Pt_2O, H_2 (3.5 atm); (iii) $PPh_3 \cdot Br_2$ then Et_3N.

1.2.5 Heck Coupling

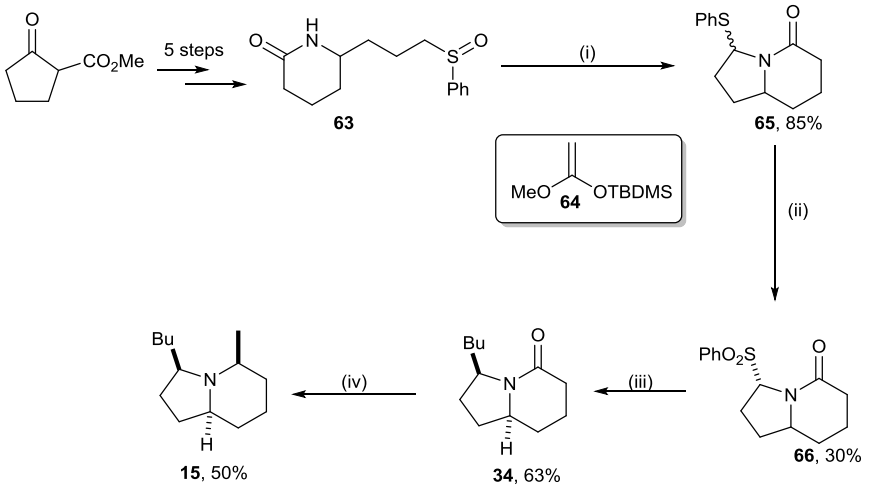
Sulikowski[34] utilised an intramolecular Heck reaction of enamide **57** to form **58**. Subsequent reduction with L-selectride formed lactam **59**, which was converted to enamine **60** by treatment with acidic methanol. Allylation of **60**, followed by hydrogenation, gave access to **62**, which was converted to **24** according to literature procedure (Scheme 12).



Scheme 12. *Reagents and conditions*: (i) Pd-(*R*)-BINAP, Ag_3PO_4, DMF, rt; (ii) L-Selectride, THF, 0 °C; (iii) TFA, MeOH, rt; (iv) **61**, $TiCl_4$, CH_2Cl_2, 0 °C (v) Pd/C, H_2 (1 atm), EtOH.

1.2.6 Pummerer Reaction

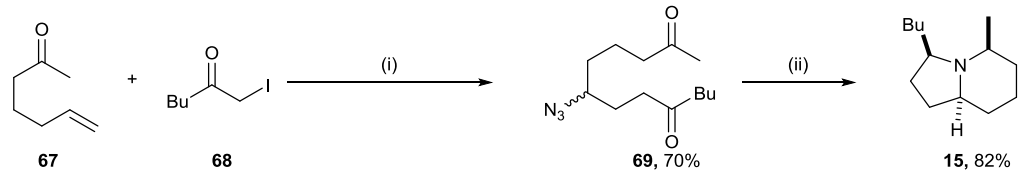
Kuhakarn[35] formed 3,5-disubstituted indolizidine **15** utilising a Pummerer cyclisation of the lactam sulfoxide **63** as a key step to form the bicyclic lactam **65**. Treatment of **65** with mCPBA was reported to give the sulfone **66** and subsequent reaction with BuMgCl in the presence of $ZnCl_2$ gave access to **34**, which was converted to the target **15** by initial treatment with MeMgBr followed by acidification and reduction with $NaBH_4$ (Scheme 13).



Scheme 13. *Reagents and conditions*: (i) **64**, ZnI_2, MeCN, rt, 24 h; (ii) *m*-CPBA, CH_2Cl_2, 0 °C, 16 h; (iii) BuMgCl, $ZnCl_2$, CH_2Cl_2, rt, 24 h; (iv) MeMgBr, THF, 67 °C, 5 h then AcOH, $NaBH_4$, 0 °C, 2 h.

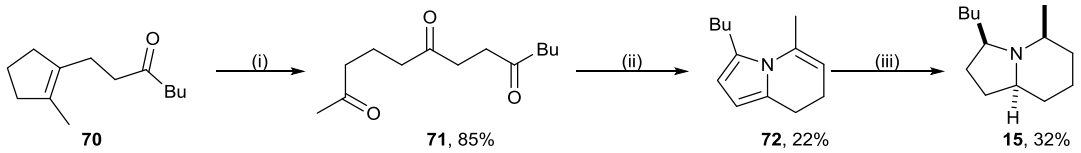
1.3 Literature Syntheses: Dual Ring Formation

Renaud[36] employed a radical carboazidation reaction of alkene **67** with α-iodoketone **68** to form an open chain azide precursor **69**, which on subjection to hydrogenation conditions, was reduced to the primary amine before undergoing two successive intramolecular reductive aminations to form the target compound **15** in one step (Scheme 14).



Scheme 14. *Reagents and conditions*: (i) $PySO_2N_3$, $(Bu_3Sn)_2$, $^tBuON{=}NO^tBu$, C_6H_6, 70 °C, 2.5 h; (ii) Pd/C, H_2 (30 atm), HCl, MeOH, rt, 96 h.

Mori[37] has also published a synthesis of **15**, utilising nitrogen fixation from the air. Ozonolysis of **70** was reported to give access to triketone **71**, which upon reflux in dry air with titanium tetrachloride, lithium and TMSCl formed the indolizine derivative **72**. Finally, hydrogenation of **72** using a rhodium catalyst gave the indolizidine product (Scheme 15).



Scheme 15. *Reagents and conditions*: (i) O_3, MeOH, −78 °C then DMS, rt, 1 h; (ii) Li, $TiCl_4$, TMSCl, CsF, THF, 67 °C, 34 h; (iii) Rh/Al_2O_3, H_2 (20 atm), EtOH, rt, 24 h.

1.4 Thesis Aims

The aim of this thesis was to develop a synthesis of 3,5-disubstituted indolizidines starting from an inexpensive and readily available starting material. The general synthetic route should be amenable to the synthesis of a large range of different 3,5-disubstituted indolizidines and their diastereoisomers. It was envisaged that this could be achieved by initially developing methodology for the diastereodivergent synthesis of *cis*- and *trans*- 2,5-disubstituted pyrrolidines (Figure 3).

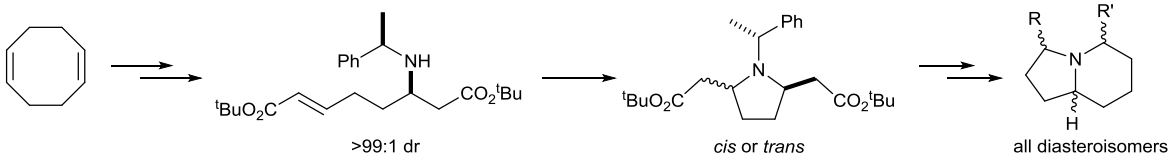


Figure 3. Thesis aims.

1.5 References

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Chapter 2: Synthesis of 2,5-Disubstituted Pyrrolidines

This chapter describes the synthesis of 2,5-*cis*- and 2,5-*trans*- disubstituted pyrrolidines starting from cyclooctadiene **73** via the diastereodivergent intramolecular aza-Michael reaction of **74** as the key step (Figure 4).

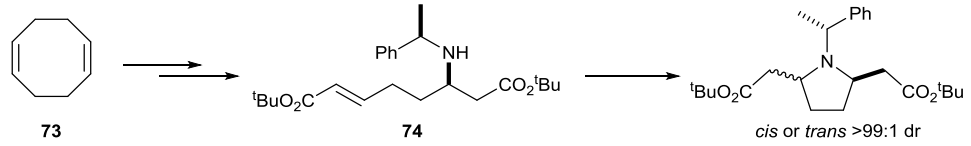
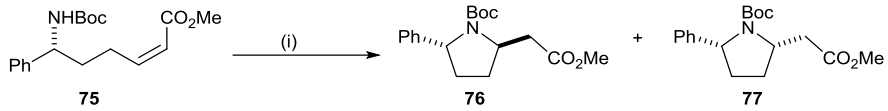


Figure 4. Synthesis of 2,5-disubstituted pyrrolidines from **73**.

2.1 Precedent for the Diastereodivergent Intramolecular Aza-Michael Reaction

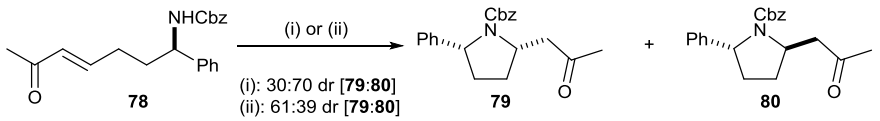
Helmchen[1] has studied the intramolecular aza-Michael reaction of substrate **75** and showed that the diastereoselectivity of the cyclisation can be changed by variation of the reaction time and temperature. For example, treatment of **75** with KO^{t}Bu at −78 °C resulted in only the *trans*-isomer **76** being formed, however, increasing the temperature to −60 °C resulted in the formation of an 84:16 mixture of **76**:**77** (Scheme 16).



Base	Solvent	Temp (°C)	Time (h)	*trans*:*cis*
Cs_2CO_3	^{t}BuOH	70	3	69:31
Cs_2CO_3	^{t}BuOH	40	8	75:25
KO^{t}Bu	THF	−60	0.25	84:16
KO^{t}Bu	THF	−78	0.5	100:0

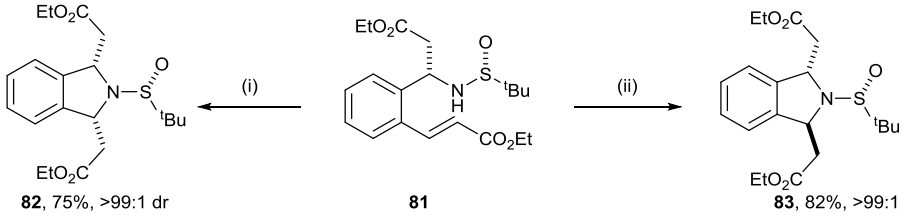
Scheme 16. *Reagents and conditions*: (i) see table.

Young[2] has shown that exposure of **78** to $(MeCN)_2PdCl_2$ effected cyclisation to the corresponding 2,5-disubstituted pyrrolidines **79** and **80**, with the *trans*-pyrrolidine **80** being formed with modest diastereoselectivity (70:30 dr). Reaction of **78** with TfOH effected cyclisation to yield the 2,5-disubstituted pyrrolidines **79** and **80** with 61:31 diastereoselectivity for the *cis* diastereoisomer **79** (Scheme 17).



Scheme 17. *Reagents and conditions*: (i) $(MeCN)_2PdCl_2$, CH_2Cl_2, rt, 5 h; (ii) TfOH, CH_2Cl_2, −20 °C, 5 h.

Fustero[3] has investigated the intramolecular aza-Michael reaction of *tert*-butylsulfinyl imine **81** to give the 1,3-disubsititued isoindoline **82** or **83** depending upon the choice of base. Treatment of **81** with TBAF afforded the *cis*- product **82** as a single diasteroisomer. Alternatively, when **81** was treated with DBU cyclisation occurred with complete diasteroselectivity to give the *trans*- isomer **83** (Scheme 18).



Scheme 18. *Reagents and conditions*: (i) TBAF, THF, rt, 30 min; (ii) DBU, THF, rt, 30 min.

2.2 First Proposed Route to *cis*- and *trans*-2,5-Disubstituted Pyrrolidines

It was proposed that *cis*- and *trans*- 2,5-disubstituted pyrrolidines **88** could be synthesised via a diastereodivergent cyclisation of a single common precursor **87**, which could be derived from a bis-α,β-unsaturated ester. The requisite bis-α,β-unsaturated ester **86** could be synthesised by utilising **73** as an inexpensive and readily available starting material. Exhaustive ozonolysis of **73** followed by reductive workup would furnish the intermediate dialdehyde **84** which could be trapped *in situ* by addition of a suitable ylide **85** to give the bis-α,β-unsaturated ester **86**. Subsequent conjugate addition with benzylamine would give access to the desired cyclisation precursor **87** which would subsequently cyclise, by way of an intramolecular aza-Michael reaction, to yield the *cis*- and *trans*- 2,5-disubstituted pyrrolidines (Figure 5).

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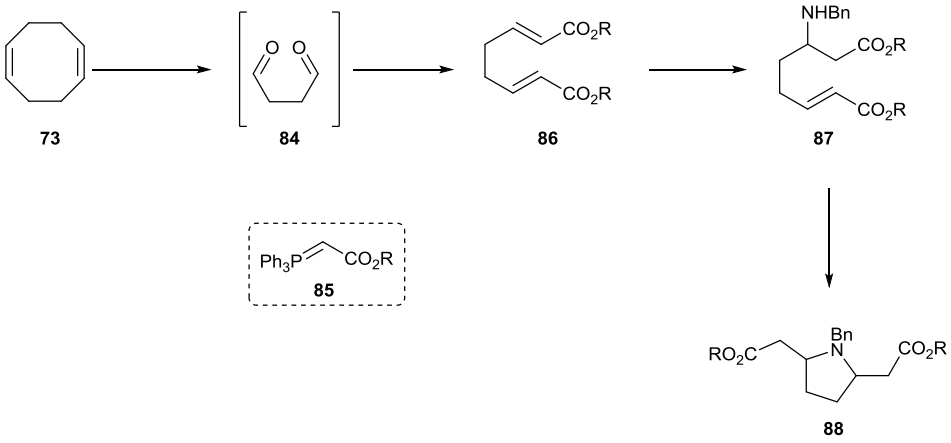
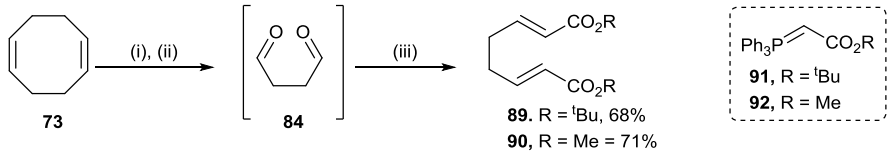


Figure 5. Proposed synthesis of 2,5-disubstituted pyrrolidines from **73**.

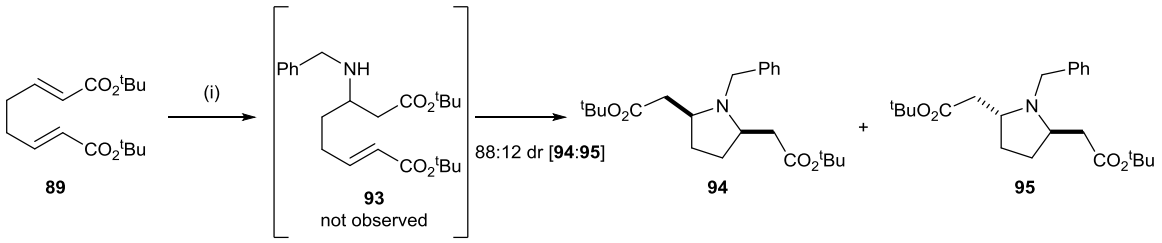
2.3 Disubstituted Pyrrolidine Synthesis

Bis-α,β-unsaturated esters **89** and **90** were synthesised from **73** via ozonolysis of both double bonds followed by reduction of the resulting ozonide with triphenylphosphine to give the intermediate dialdehyde **84**. Reaction of **84** with the requisite ylide, **91** or **92**, gave the *bis*-α,β-unsaturated esters **89** and **90** in 68 and 71% yield, respectively (Scheme 19).



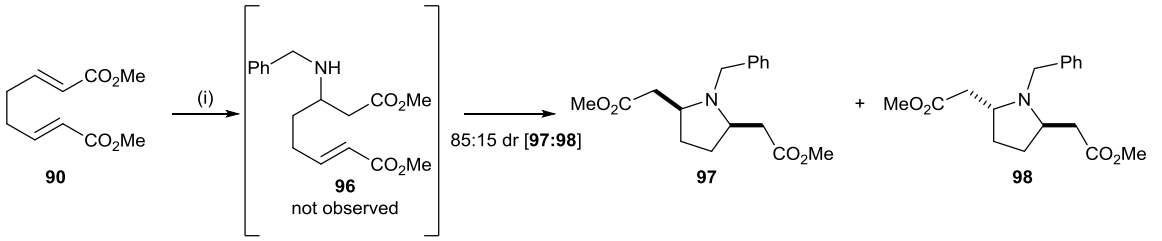
Scheme 19. *Reagents and conditions*: (i) O_3, CH_2Cl_2, −78 °C; (ii) PPh_3, rt, 1 h; (iii) **91** or **92**, rt, 16h.

Refluxing **89** with benzylamine for 48 h resulted in 80% conversion to pyrrolidines **94** and **95** in a *cis*:*trans* ratio of 88:12, respectively. Use of 10 eq of benzylamine resulted in full conversion after 16 h (75% conversion after 8 h), with an unchanged *cis*:*trans* ratio, however, separation of **94** and **95** by flash column chromatography proved unsuccessful. The intermediate **93** was never observed (Scheme 20).



Scheme 20. *Reagents and conditions*: (i) Benzylamine, EtOH, 78 °C, 16 h.

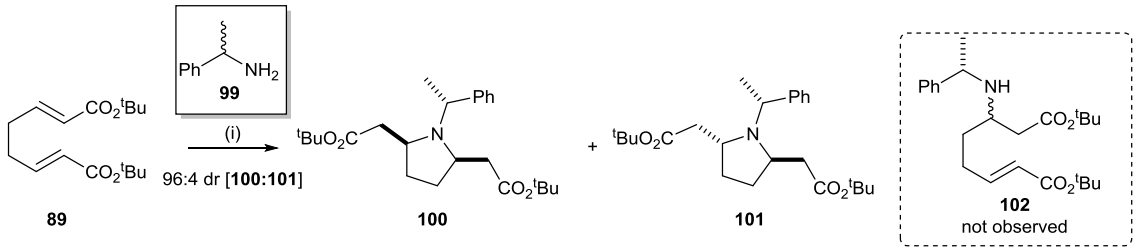
Reaction of **90** with 1 eq of benzylamine went to full conversion within 16 h, with **97** and **98** being formed in a ratio of 85:15, respectively. Reaction of **90** with 10 eq benzylamine went to full conversion in 4 h, with **97** and **98** again being formed in a ratio of 85:15, respectively, however, as in the case of reaction with **89**, **97** and **98** were inseparable by column chromatography. Again, the intermediate **96** was not observed (Scheme 21).



Scheme 21. *Reagents and conditions*: (i) Benzylamine, EtOH, 78 °C, 4 h.

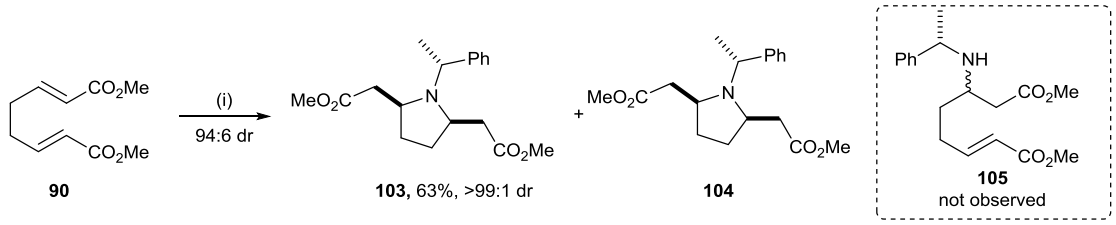
It was hypothesised that substituting the benzylamine for α-methylbenzylamine may allow the desired cyclisation precursor to be isolated, due to the increased steric hinderance by virtue of an α substituent on the benzyl group leading to a slower rate of cyclisation. This would also allow access to enantiopure *cis*- and *trans*- pyrrolidines, as both enantiomers of α-methylbenzylamine are available in enantiomerically pure form.

Refluxing equimolar amounts of racemic **99** and **89** in EtOH for 16 h resulted in only 14% conversion. When the reaction time was increased to 96 h, 80% conversion was observed, with a *cis*:*trans* ratio of 96:4 (**100**:**101**). The intermediate **102** was not observed (Scheme 22).



Scheme 22. *Reagents and conditions*: (i) **99**, EtOH, 78 °C, 96 h.

Reaction of **90** with 10 eq of **99** went to full conversion within 16 h, with **103** and **104** being formed in ratio of 94:6, respectively, resulting in **103** being isolated as a single diastereoisomer in 63% yield (Scheme 23). Again, however, the intermediate **105** was not observed. Acid wash of the crude reaction mixture (10% aq citric acid) followed by basification and re-extraction of the aqueous layer allowed for efficient recovery of the excess **99** (~90%). This was re-used in subsequent reactions, with identical results being obtained.



Scheme 23. *Reagents and conditions*: (i) **99**, EtOH, 78 °C, 16 h.

In summary, the desired cyclisation precursor **93**, **96**, **102** or **105**, could not be observed via the thermal addition of benzylamine or **99** to **89** or **90**. Whilst it is possible to access 2,5-disubstituted pyrrolidines in one step by the thermal addition of either benzylamine or **99** to either **89** or **90**, it is not possible to selectively form the *trans* isomer using this methodology. Although the isolated **103** is racemic, if the same reaction was performed with enantiopure **99** (both enantiomers are commercially available in >99% ee) identical cyclisation selectivities would be obtained and the products would be enantiopure.

2.4 Revised Synthetic Strategy

In an alternative strategy, it was proposed that the desired cyclisation precursor **74** could be derived from a β-amino ester **107**. The Davies diastereoselective lithium amide conjugate addition of enantiopure amines to α,β-unsaturated esters gives efficient access to β-amino esters with a high and predictable sense of diastereocontrol.[4] The prerequisite α,β-unsaturated ester **106** could be synthesised by utilising **73** as an inexpensive and readily available starting material. Selective ozonolysis of one of the double bonds of **73** followed by a reductive quench of the resulting ozonide would yield an intermediate dialdehyde which could be trapped *in situ* by addition of an ylide to yield a *bis*-α,β-unsaturated ester **106**. Lithium amide conjugate addition followed by an ozonolysis-Wittig reaction would give access to **107** which could be selectively mono-*N*-debenzylated using CAN to give the desired cyclisation precursor **74** (Figure 6**)**.

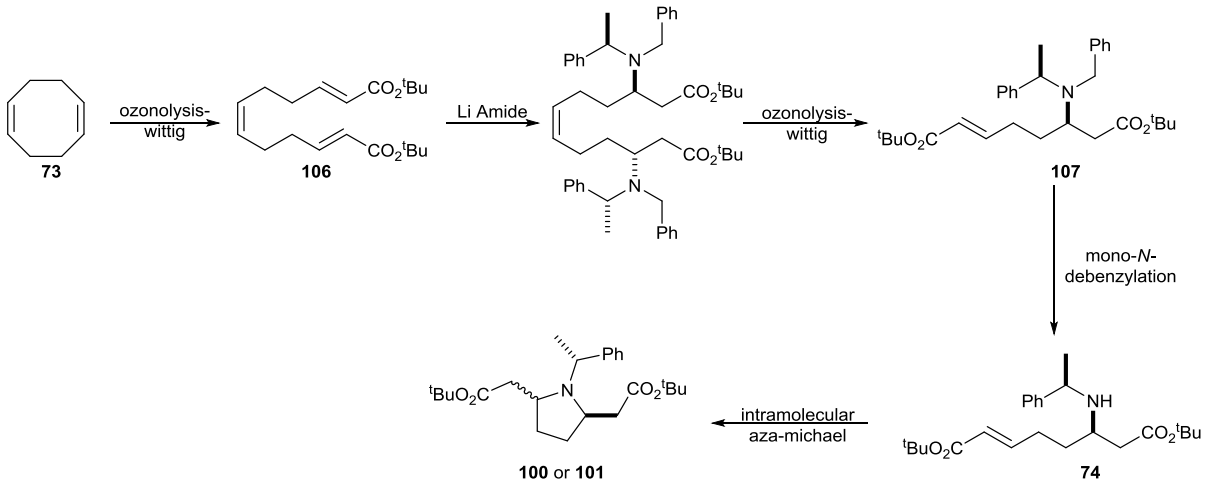


Figure 6. Revised strategy for the synthesis of 2,5-disubstituted pyrrolidines.

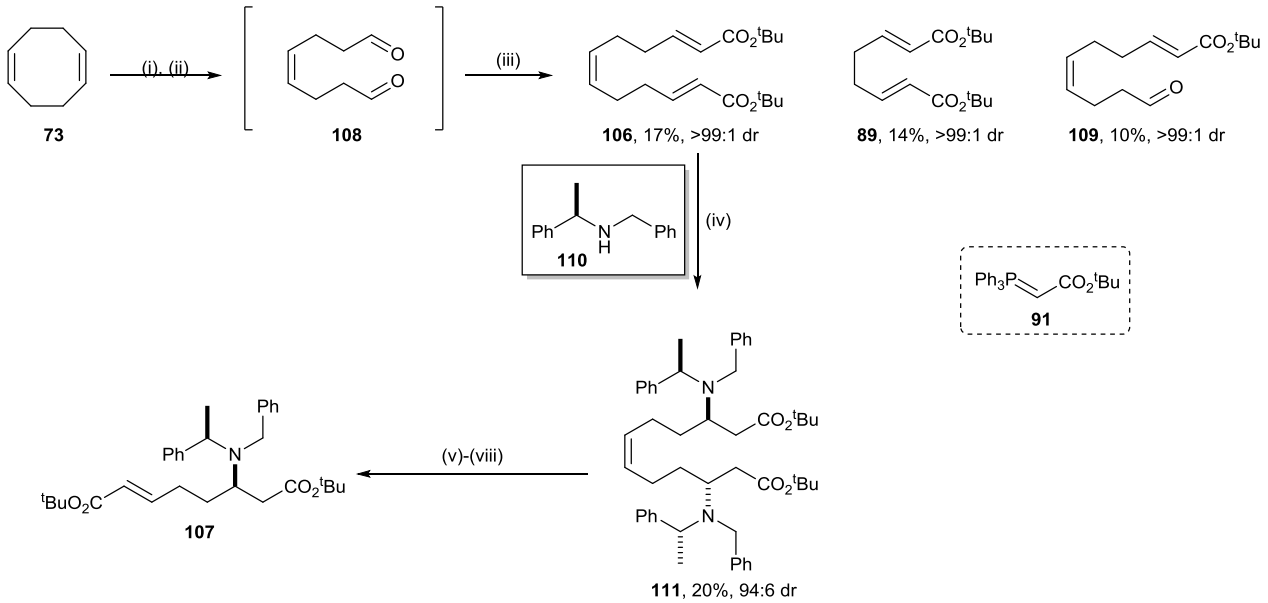
2.4.1 Preparation of 74

Selective ozonolysis of one of the double bonds in **73**, using a modification of the procedure reported by Li,[5] followed by reductive quench of the resulting mono-ozonide with triphenylphosphine gave an intermediate dialdehyde **108** which was trapped *in situ* by treatment with phosphonium ylide **91** to give a mixture of olefinic products from which the desired bis-α,β-unsaturated ester **106** was isolated in 17% yield and >99:1 dr, along with **89** and **109**, both of which are products derived from the initial exhaustive ozonolysis of **73** (i.e.

over reaction), and which were isolated in 14% and 10% yield, respectively. Due to overlapping peaks, in a complex ^{1}H NMR of the crude reaction mixture, reliable crude ratios for **89**:**106**:**109** could not be obtained.

(*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine **110** was synthesised by reductive amination of (*R*)-**99** with benzaldehyde. Conjugate addition of the lithium amide derived from **110** to **106** gave access to **111** in 20% yield and 94:6 dr, with the configuration of the newly formed stereogenic centres within the major product **111** assigned by reference to the well established transition state mnemonic for this class of reaction.[6]

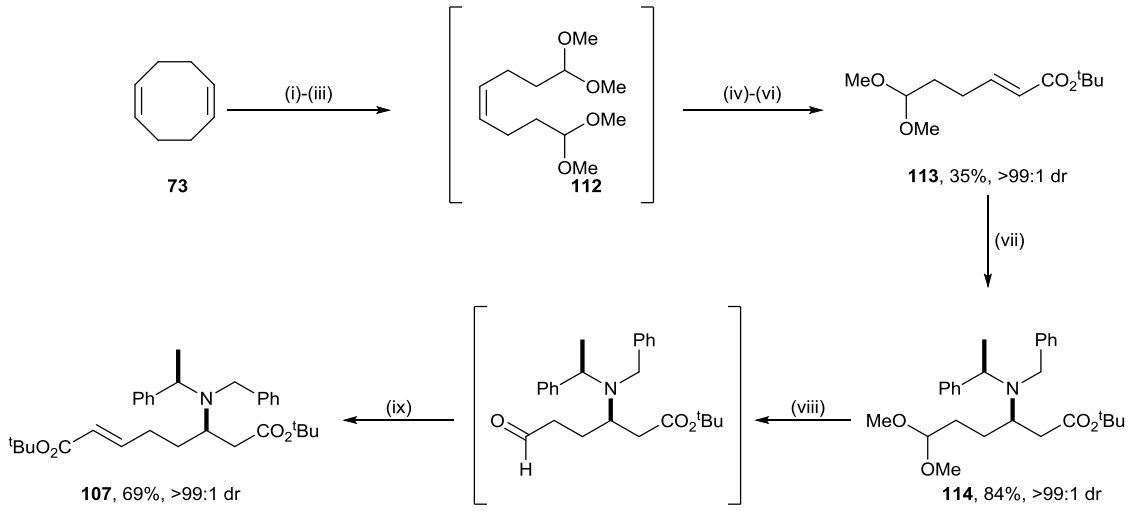
Treatment of **111** with ethereal HCl (to yield the HCl salt of **111** in order to prevent oxidation of the nitrogen upon ozonolysis) followed by ozonolysis and subsequent treatment with **91** gave a complex mixture of products, with the desired product **107** constituting <10% of the crude mixture, as deduced from comparison of the ^{1}H NMR spectrum of the crude reaction mixture with a subsequently synthesised pure sample of **107** (Scheme 24).



Scheme 24. *Reagents and conditions*: (i) O_3, CH_2Cl_2, −78 °C; (ii) PPh_3, rt, 1 h; (iii) **91**, CH_2Cl_2, rt, 16 h; (iv) **110**, BuLi, THF, −78 °C, 4 h; (v) HCl, Et_2O, rt, 5 min; (vi) O_3, CH_2Cl_2, −78 °C; (vii) PPh_3, rt, 1 h; (viii) **91**, CH_2Cl_2, rt, 16 h.

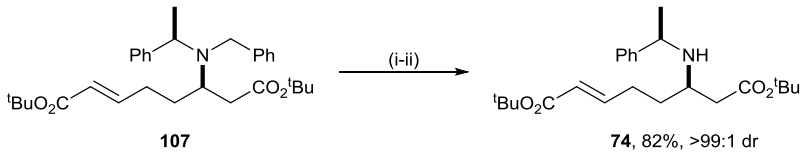
Consequently, an alternative route for the synthesis of **107** from **73** was investigated. Subjection of **73** to conditions reported by Li,[5] where selective ozonolysis of just one of the double bonds in **73** is performed in a 1:1 MeOH/CH_2Cl_2 mixture, followed by acidification with TsOH and a subsequent reduction by addition of DMS, gave access to the bis-acetal **112**.

A subsequent one-pot ozonolysis/Wittig reaction on the crude reaction mixture, utilising phosphonium ylide **91** gave access to **113** in 35% yield and >99:1 dr (from **73**). Conjugate addition of the lithium amide derived from **110** to α,β-unsaturated ester **113** gave access to **114** in 84% yield and >99:1 dr, with the configuration of the newly formed C(3)-stereogenic centre again assigned by reference to the established transition state mnemonic for this type of reaction.[6] Unmasking of the aldehyde functionality of **114** by acidic hydrolysis followed by a second highly (*E*)-selective Wittig reaction [93:7 (*E*):(*Z*) crude] with **91** furnished **107** in 69% yield and >99:1 dr (Scheme 25).



Scheme 25. *Reagents and conditions*: (i) O_3, MeOH/CH_2Cl_2 (1:1), −78 °C; (ii) TsOH·H_2O, rt, 2 h; (iii) Me_2S, rt, 16 h; (iv) O_3, CH_2Cl_2, −78 °C; (v) PPh_3, rt, 1 h; (vi) **91**, rt, 16 h; (vii) **110**, BuLi, THF, −78 °C, 2 h; (viii) HCl, acetone/H_2O (5:4), 56 °C, 1 h; (ix) **91**, CH_2Cl_2, rt, 24 h.

Treatment of **107** with CAN cleanly effected the desired mono *N*-debenzylation. However, purification by column chromatography proved problematic due to **107** cyclising on the silica gel, resulting in isolation of **74** in 51% yield and >99:1 dr along with pyrrolidine **100** (not present in the ^{1}H NMR of the crude reaction mixture) in 27% yield and 94:6 dr (*cis*:*trans*). Gratifyingly, stirring the crude reaction mixture in aqueous sodium bisulfite, followed by extraction with Et_2O, was effective in removing all the benzaldehyde by-product, yielding a pure sample of **74** in 82% yield and >99:1 dr (Scheme 26).



Scheme 26. *Reagents and conditions*: (i) CAN, MeCN/H_2O (5:1), rt, 2 h; (ii) aq sodium bisulphite, Et_2O, rt, 20 min.

2.4.2 Pyrrolidine Formation: Cyclisation of 74

There are three diastereoisomeric products (**100**, **101**, **115**) possible from the intramolecular aza-Michael reaction of **74** (Figure 7). However, as the configuration at C(2) has been pre-set by the lithium amide conjugate addition reaction and the configuration of the α-methylbenzyl group is fixed, it is predicted that only diastereoisomers **101** and **100** would be formed.

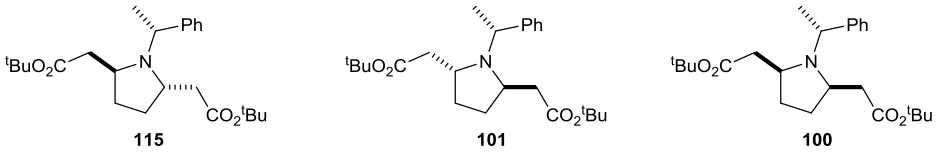
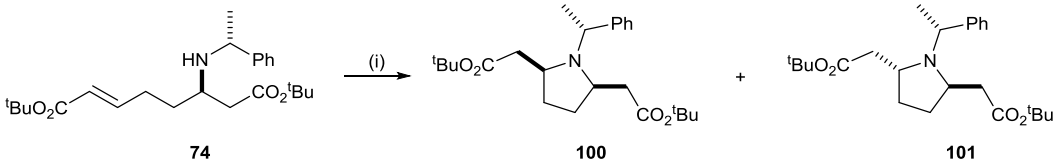


Figure 7. The three possible diastereoisomers from the intramolecular aza-Michael reaction of **74**.

A variety of different reaction conditions were screened for the key intramolecular aza-Michael reaction. Stirring **74** in MeOH under ambient conditions effected complete cyclisation with a high selectivity for the *cis*-2,5-disubstituted pyrrolidine **100**. The same result was obtained when **74** was heated in EtOH with 1 equiv of Et_3N, with **100** being isolated as a single diastereoisomer in 85% yield after column chromatography. When **74** was treated with BuLi at −78 °C a reversal in the diastereoselectivity was observed with the *trans* 2,5-disubsitiuted pyrrolidine **101** being preferentially formed in 80:20 dr (**101**:**100**) when the reaction had gone to full conversion. Upon separation by flash column chromatography, this gave access to **101** in 56% yield and >99:1 dr (Scheme 27).



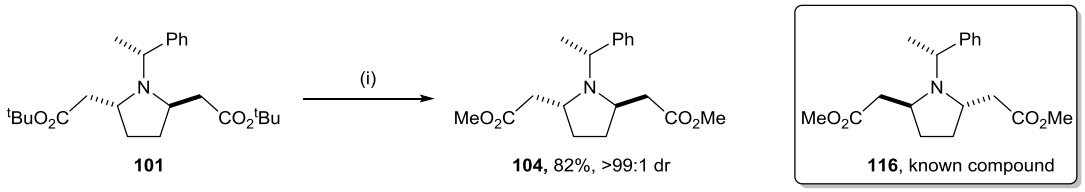
74 100 101

Reagents	Temperature (°C)	Time (h)	% Conversion	d.r. (100:101)	Isolated Product
MeOH	20	16	100	95:5	-
Et_3N, EtOH	78	16	100	95:5	**100**, 85%, >99:1 dr
BuLi, THF	−78	2	79	15:85	-
BuLi, THF	−78	4	100	20:80	**101**, 56%, >99:1 dr
BuLi, THF	−20	2	79	34:66	-

Scheme 27. *Reagents and conditions*: (i) See table.

Pyrrolidine **101** was assigned as a *trans* isomer due to the *trans* isomers possessing *pseudo*-C_2 symmetry meaning that the ^{1}H NMR spectrum of the *trans*- isomers show a reduced number of proton environments (compared to the *cis*-), e.g. the C(2)*H* and C(5)*H* are equivalent in the *trans*- isomer and appear as a single peak, unlike the *cis*- isomer **100** where two distinct peaks are observed. The observation of only one *trans* isomer in the ^{1}H NMR spectrum of all the crude reaction mixtures is consistent with the cyclisation proceeding via a classic Michael addition mechanism, with no epimerisation of the C(2)-stereogenic centre occurring.

To provide further evidence that the *trans*- isomer formed is **101** and not **115**, a sample of the isolated **101** was transesterified to the methyl ester analogue **104** (Scheme 28). Pyrrolidine **116**, the *bis*-methyl ester analogue of **115**, has been reported previously in the literature[7] and this is the opposite diastereoisomer to the one that would be obtained from transesterification of **101**. Comparison of the literature ^{1}H NMR data for **116** with the data obtained for the synthetic sample **104** showed significant differences between the spectra of the two compounds, and **116** was not observed in the ^{1}H NMR spectra of transesterified **101** (Table 1).



101 **104**, 82%, >99:1 dr **116**, known compound

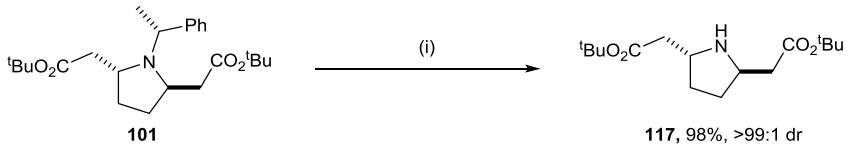
Scheme 28. *Reagents and conditions*: $SOCl_2$, MeOH, 68 °C, 2 h.

(1'*R*,2*S*,5*S*)-116	**(*R*,*R*,*R*)-104**
1.45, d, *J* 6.5	1.40, d, *J* 6.7
1.95, dd, *J* 14.5, 10.0	2.22, dd, *J* 14.7, 10.2
2.15, dd, *J* 14.5, 3.5	2.56, dd, *J* 14.7, 3.4
3.7, q, *J* 6.5	3.92, q, *J* 6.7

Table 1. ^{1}H NMR data for the diastereoisomers **116** and **104** (selected peaks only).

To fully confirm that **101** had been formed as a single diastereoisomer, the synthesis of an authentic sample of the opposite diasteroisomer **115** was pursued, as neither **101** nor **115** have been reported in the literature.

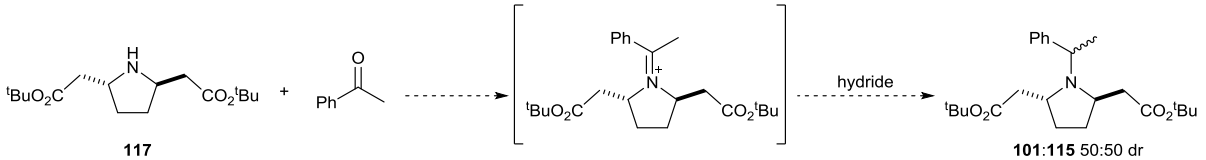
With **101** already synthesised, the simplest way to achieve this would be to remove the α-methylbenzyl group and then re-install it in a non-selective manner, to give a mixture of **101** and *ent*-**115**. Hydrogenolysis of **101** proceeded smoothly to give **117** in 98% yield (Scheme 29).



101 **117**, 98%, >99:1 dr

Scheme 29. *Reagents and conditions*: (i) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 16 h.

To re-install the α-methylbenzyl group it was envisaged that reaction of **117** with acetophenone would generate an intermediate iminium ion, which could be reduced, non-selectively, *in situ* with a hydride source to give a 50:50 mixture of **101** and **115** (Figure 8).



117 **101**:**115** 50:50 dr

Figure 8. Strategy for the synthesis of *ent*-**115**.

Refluxing **117** in ethanol followed by addition of sodium borohydride failed to effect the desired transformation, with only **117** and 1-phenylethanol (from the reduction of aectophenone) being observed in the ^{1}H NMR of the crude reaction mixture. Reaction of **117**

and acetophenone in 1,2-DCE with glacial acetic acid and sodium triacetoxyborohydride[8] gave returned starting material only. Likewise, reaction of **117** and acetophenone in CH_2Cl_2 with TMEDA and trichlorosilane[9] also gave returned starting material.

It was hypothesised that, due to the steric hindrance of **117**, formation of the iminium ion may be the problematic step. In order to try and promote iminium formation, **117** was mixed with benzaldehyde, instead of acetophenone, and MeMgBr subsequently added instead of a hydride source (Figure 9).

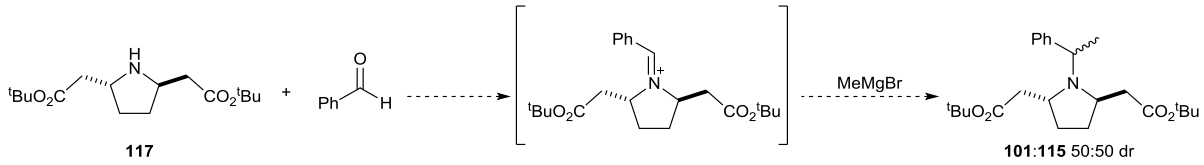
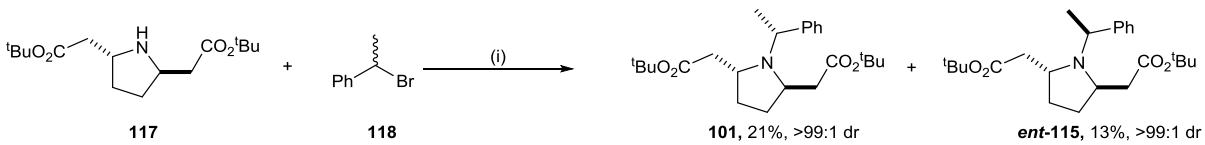


Figure 9. Revised strategy for the synthesis of *ent*-**115**.

Refluxing **117** and benzaldehyde in THF followed by addition of MeMgBr resulted in only **117** and 1-phenylethanol being observed in the ^{1}H NMR spectrum of the crude reaction mixture. The same result was obtained when the preformed TFA salt of **117** was mixed with benzaldehyde in toluene with 4 Å molecular sieves, followed by addition of MeMgBr.

Consequently an alternative strategy for the synthesis of *ent*-**115** was investigated, specifically the S_N2 reaction of **117** with (1-bromoethyl)benzene **118**. Initial reaction of an equimolar mixture of **117** and **118** in DMF (80 °C, 16 h) returned only starting material. However, running the reaction neat with 10 equivalents of **118** resulted in successful formation of a 50:50 mixture of **101** and **115**, which were separable by column chromatography (Scheme 30). Comparison of the ^{1}H NMR spectra of **101** and *ent*-**115** clearly showed significant differences in the two spectra (Table 2). Crucially, no *ent*-**115** was in the ^{1}H NMR spectrum of **101** formed from the original cyclisation.



Scheme 30. *Reagents and conditions*: (i) 50 °C, 16 h.

101	*ent*-**115**
1.39, 18H, s, 2 × C*Me*$_3$	1.31, 18H, s, 2 × C*Me*$_3$
1.41, 3H, d, *J* 6.8, C(α)*Me*	1.38, 3H, d, *J* 6.5, C(α)*Me*
1.56-1.67, 2H, m, C(3)H_A C(4)H_A	1.45-1.52, 2H, m, C(3)H_A C(4)H_A
1.98-2.06, 2H, m, C(3)H_B C(4)H_B	1.74-1.82, 2H, m, C(3)H_B C(4)H_B
3.37-3.44, 2H, m, C(2)*H* C(5)*H*	3.31-3.38, 2H, m, C(2)*H* C(5)*H*
3.89, 1H, q, *J* 6.8, C(α)*H*	3.63, 1H, q, *J* 6.5, C(α)*H*

Table 2: Comparison of the ^{1}H NMR data of **101** and *ent*-**115** (selected peaks only).

2.5 Selectivity of the Cyclisation of 74

When **74** was treated with BuLi at −20 °C, a reduced selectivity for **101** (66:34 **101**:**100**, compared with 80:20 when the reaction was perfomed at −78 °C- *vide supra*) was observed. This suggests that the cyclisation diastereoselectivity may be controlled by a fine interplay of thermodynamics *vs* kinetics, where **101** is the kinetic product and **100** is the thermodynamic product of the cyclisation.

If the *cis-trans* selectivity is controlled simply by thermodynamics-kinetics then stirring **101** in MeOH, or heating in EtOH with TEA, should effect conversion of pure **101** to a 5:95 mixture of **101**:**100**. However, subjection of diasteroisomerically pure **101** to both sets of conditions returned **101** in both cases. Likewise, subjection of various **101**:**100** mixtures to both sets of conditions failed to change the *cis*:*trans* ratio in all cases. The observation that it is not possible to interconvert **101** and **100** implies that the factors governing the cyclisation selectivity are more complicated than a simple kinetic-thermodynamic phenomenon.

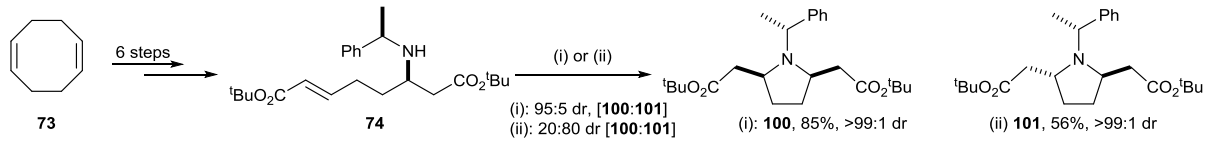
The differences in the cyclisation diastereoselectivity could potentially be explained by considering the (presumed) differences between the two mechanisms of cyclisation. Upon treatment of **74** with BuLi, *N*-deprotonation will occur followed by conjugate addition of the nitrogen anion and quenching of the resulting enolate upon work-up via proton transfer. The rate determining step in this process will be the conjugate addition and this will be most facile when the steric interactions within the cyclisation transition state are minimised. This is achieved by positioning the two ester group *trans*- relative to one another. Hence, the

cyclisation proceeds under kinetic control to give high diastereoselectivity for the *trans*-isomer.

When **74** is stirred in MeOH, initial *N*-deprotonation cannot occur. Consequently, during the conjugate addition the ring formation starts to occur with the N*H* proton still in place. Now, the rate determining step may be the proton transfer and not the conjugate addition. Consequently, although the cyclisation still proceeds under kinetic control, it is now highly selective for the *cis*- isomer.

2.6 Conclusion

The asymmetric syntheses of **100** and **101** have been completed in seven steps and in 14% and 10% overall yield, respectively, starting from **73**. The key step in the synthesis is the diastereodivergent cyclisation of **74**; refluxing **74** in EtOH with Et_3N gives high diastereoselectivity for the *cis*- pyrrolidine **100**, whilst treatment of **74** with BuLi at −78 °C gives high diastereoselectivity for the *trans*- pyrrolidine **101** (Scheme 31).



73 74

Scheme 31. *Reagents and conditions*: (i) Et_3N, EtOH, 78 °C, 16 h; (ii) BuLi, THF, −78 °C, 4 h.

2.7 References

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Chapter 3: Piperidine Synthesis

This chapter describes the attempted synthesis of 2,6-*cis*- and 2,6-*trans*- disubstituted piperdines **120** and **121**, starting from δ-valerolactone **118**, employing a diastereodivergent intramolecular aza-Michael reaction of **119** as the key step (Figure 10).

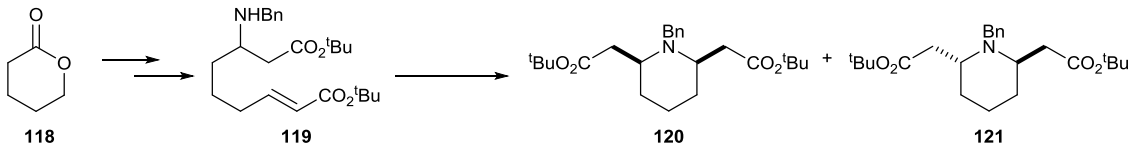


Figure 10. Strategy for the synthesis of 2,6-disubstituted piperidines.

Attempts to extend the scope of the Davies lithium amide conjugate addition methodology,[1] to allow for the synthesis of polysubstituted piperidines is also discussed (Figure 11).

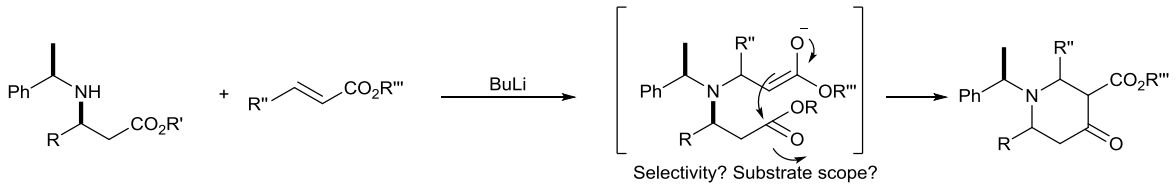


Figure 11. Strategy for the synthesis of polysubstituted piperidines.

3.1 Synthesis of 2,6-Disubstituted Piperidines

3.1.1 Synthetic Strategy

Following the ability to access both 2,5-*cis*- and 2,5-*trans*- disubstituted pyrrolidines **100** and **101** with high selectivity from a single common precursor (*vide* chapter two), it was hypothesised that it may be possible to access enantiopure 2,6-*cis*- and 2,6-*trans*- disubstituted piperdines via the same diasterodivergent cyclisation strategy from the homologous precursor **123**. Substrate **123** could be prepared from an analogous sequence of reactions starting with β-amino ester **122**, which can be initially be synthesised starting from δ-valerolactone **118** according to literature procedure[2] (Figure 12).

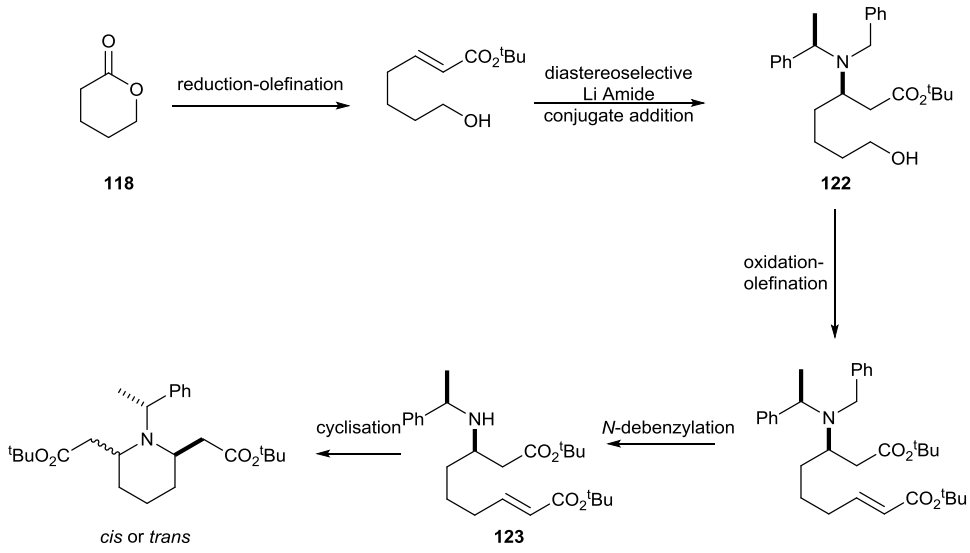
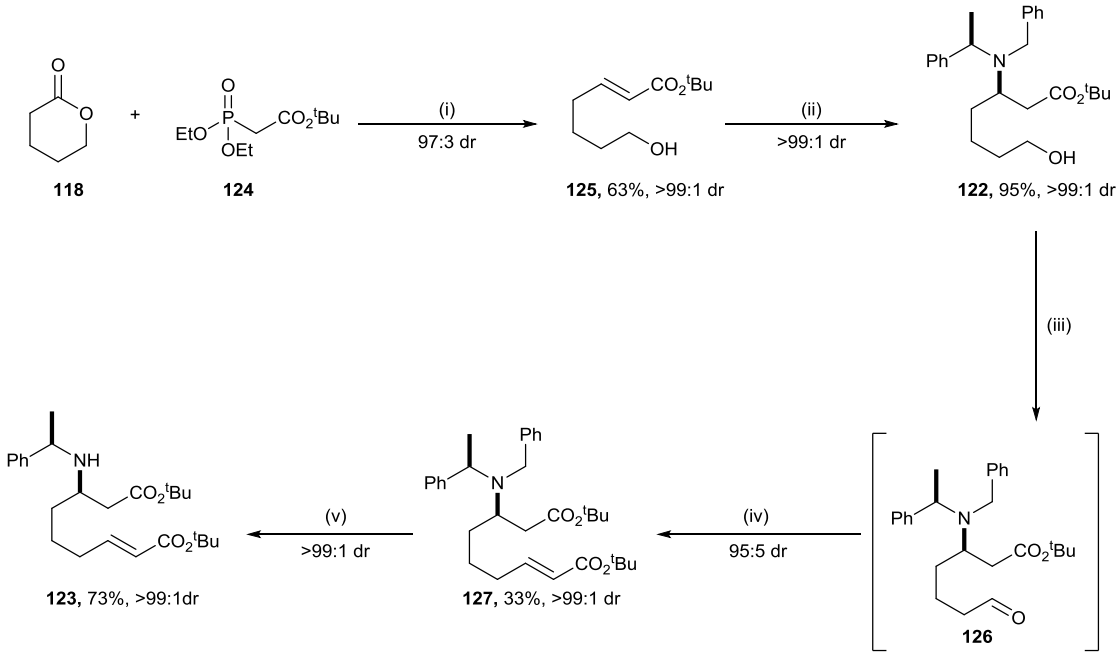


Figure 12. Proposed synthesis of 2,6-disubstituted piperidines.

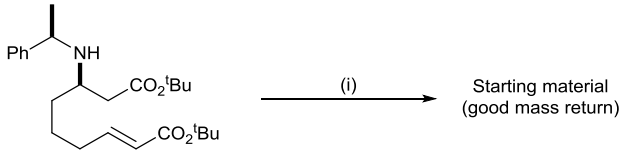
3.1.2 Synthesis and Cyclisation of 123

Reduction of **118** with DIBAL-H followed by addition of the anion of phosphonate ester **124**, which was pre-formed upon the addition of BuLi to **124**, afforded the α,β-unsaturated ester **125** in 63% yield and >99:1 dr. Conjugate addition of lithium amide derived from **110** to **125** gave **122** in 95% yield and >99:1 dr. Swern oxidation of **122**, under standard conditions,[3] gave access to the intermediate aldehyde **126** which was trapped *in situ* by the addition of stabilised ylide **91** to give **127** in 95:5 dr [(*E)*:(*Z)* crude]. Following purification, **127** was isolated as a single diastereoisomer in 33% yield (from **122**). Subsequent selective mono-*N*-debenzylation of **127**, upon treatment with CAN, afforded the desired cyclisation precursor **123** in 73% yield as a single diastereoisomer (Scheme 32).



Scheme 32. *Reagents and conditions:* (i) BuLi, DIBAL-H, THF, −78 °C to rt, 16 h; (ii) **110**, BuLi, THF, −78 °C, 2 h; (iii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 20 min then Et_3N, −78 °C to rt, 1 h; (iv) **91**, rt, 16 h; (v) CAN, MeCN, H_2O, rt, 2 h.

A variety of different reaction conditions for the intramolecular aza-Michael addition of **123** was examined. Refluxing **123** with TEA in EtOH for 16 h (the conditions which effected full conversion and 95:5 *cis*:*trans* diastereoselectivity in the pyrrolidine series) returned only the starting material. Changing the reaction solvent to toluene, to allow for a higher reaction temperature, also failed to affect the desired cyclisation, with only the starting material being recovered. Treatment of **123** with BuLi at −78 °C (i.e. the conditions which effected full conversion and 80:20 *trans*:*cis* diastereoselectivity in the pyrrolidine series) also returned only the starting material. When the temperature was increased to 0 °C and the base changed to MeMgBr, cyclisation was still not observed. Refluxing **123** in toluene in the presence of NaH also failed to induce any reaction (Scheme 33).

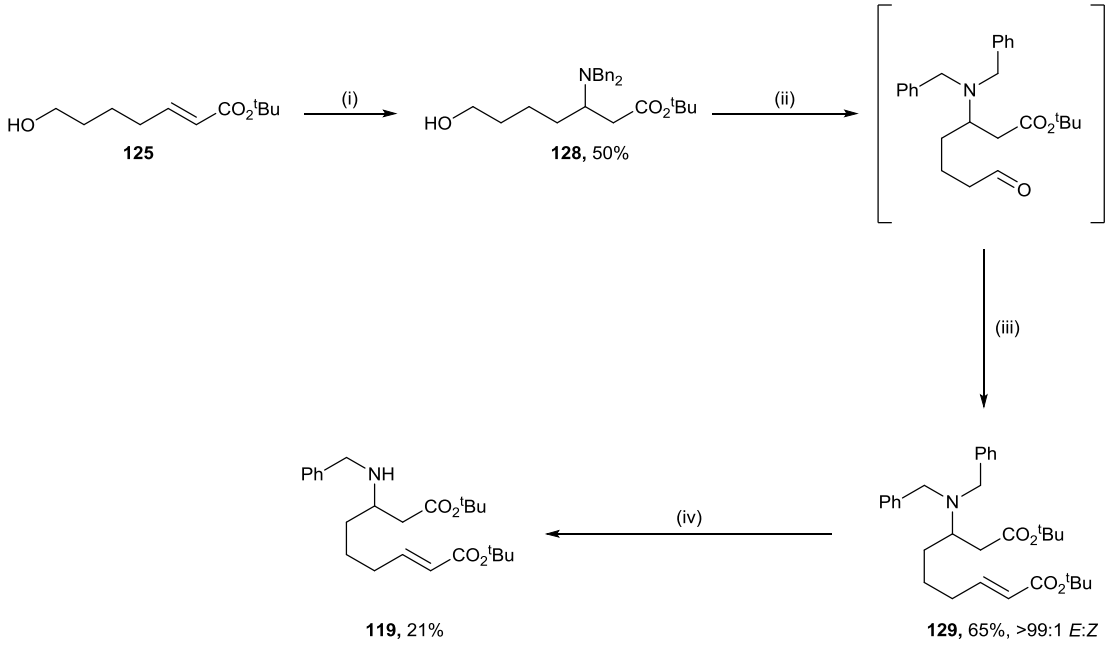


Base (1eq)	**Solvent**	**Temp (°C)**	**Time (h)**
TEA	EtOH	78	16
TEA	Toluene	110	16
BuLi	THF	−78	4
MeMgBr	THF	0	4
NaH	Toluene	110	16

Scheme 33. *Reagents and conditions:* (i) see table

3.1.3 Revised Strategy

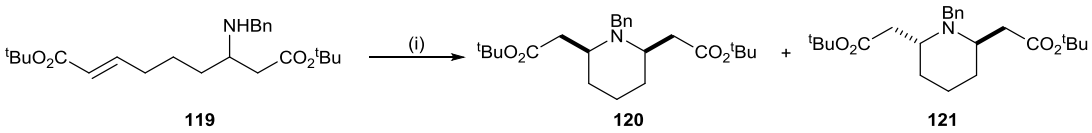
It was hypothesised that a reduction in steric bulk around the nitrogen atom may facilitate the cyclisation of **123**. To investigate this, the synthesis of an analogous cyclisation precursor **119**, which does not contain a α-branched *N*-benzyl group, was pursued. Conjugate addition of the lithium amide derived from deprotonation of dibenzylamine with BuLi to the previously synthesised α,β-unsaturated ester **125** gave access to racemic **128** in 50% yield. Application of the same, one pot, Swern oxidation – Wittig olefination procedure gave access to **129** in 65% yield and >99:1 dr [(*E*):(*Z*)]. Finally, mono-*N*-debenzylation of **129** was affected upon treatment with CAN, which gave access to the desired cyclisation precursor **119** in 21% yield (Scheme 34).



125 **128**, 50% **129**, 65%, >99:1 *E*:*Z* **119**, 21%

Scheme 34. *Reagents and conditions*: (i) Dibenzylamine, BuLi, THF, −78 °C, 2 h; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 20 min then Et_3N, −78 °C to rt, 1 h; (iii) **91**, rt, 16 h; (iv) CAN, MeCN/H_2O (5:1), rt, 2 h.

Stirring **119** in MeOH for 16 h at ambient temperature resulted in complete cyclisation, with the piperidine products **120** and **121** being formed in a 64:36 ratio respectively. When **119** was refluxed in EtOH with TEA complete cyclisation occurred, however, a reversal in the sense of diastereoselectivity was observed with **120** and **121** formed in a 33:67 ratio respectively. Treatment of **119** with BuLi at −78 °C resulted in only 30% conversion, with a **120**:**121** ratio of 40:60 being observed in the ^{1}H NMR spectrum of the crude reaction mixture. Treatment of **119** with MeMgBr at ambient temperature resulted in complete cyclisation, with **120** and **121** being formed in a 34:64 ratio respectively (Scheme 35).

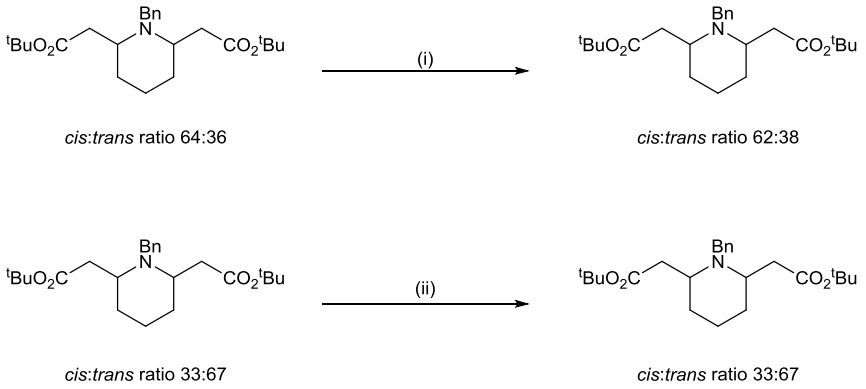


119 120 121

Base (1eq)	**Solvent**	**Temp (^oC)**	**Time (h)**	**Conversion (%)**	**120:121**
None	MeOH	20	16	100	64:36
TEA	EtOH	78	16	100	33:67
BuLi	THF	−78	2	30	40:60
MeMgBr	THF	20	4	100	34:64

Scheme 35. *Reagents and conditions*: (i) see table.

Due to the opposite sense of *cis*/*trans* diastereoselectivity observed during the cyclisation in MeOH, attempts were made to interconvert the mixtures by subjecting them to the opposing reaction conditions. However, this was unsuccessful with no change in *cis*/*trans* ratio being observed in either case (Scheme 36).



Scheme 36. *Reagents and conditions*: (i) Et_3N, EtOH, 78 °C, 72 h; (ii) MeOH, rt, 16 h.

Due to the inability to influence the *cis*/*trans* ratio and only achieving modest diastereoselectivity for the cyclisation no further work on the synthesis of 2,6-disubstituted piperidines was pursued.

3.2 Synthesis of Polysubstituted Piperidines

Since the initial seminal report by Davies,[4] the scope of the conjugate addition of enantiomerically pure lithium amides has been studied extensively.[1] It was postulated that upon treatment with BuLi, *N*-α-methylbenzyl protected β-amino esters **130** would undergo a highly selective conjugate addition to α,β-unsaturated esters **131**, which may cyclise *in situ* to yield a densely functionalised piperidine **132** (Figure 13). The starting *N*-α-methylbenzyl protected β-amino esters **130** could be readily synthesised according to literature procedure; [5]

involving the conjugate addition of the corresponding lithium amides to a variety of different α,β-unsaturated esters followed by subsequent mono-*N*-debenzylation upon treatment with CAN.

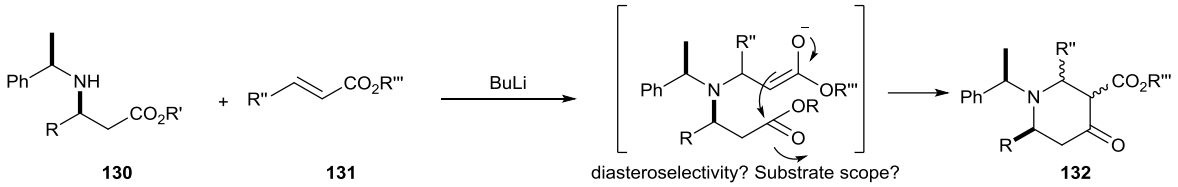
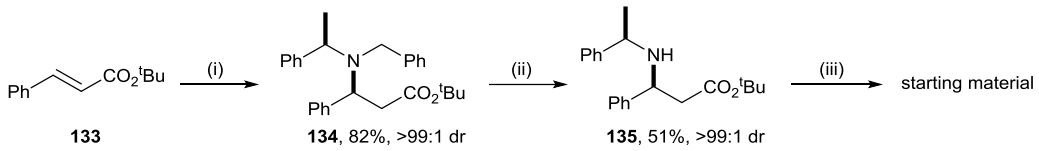


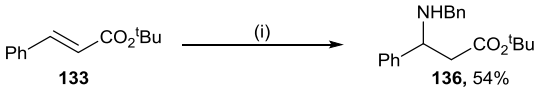
Figure 13. Proposed intermolecular conjugate addition to form polysubstituted piperidines

tert-Butyl cinnamate **133** was selected as a model α,β-unsaturated ester for use in these investigations. Wadsworth-Emmons reaction of benzaldehyde and phosphonate ester **124**, utilising MeMgBr as the base,[6] resulted in excellent diastereoselectivity (>99:1 dr *E*:*Z*) with the desired product **133** being isolated in 54% yield and >99:1 dr. Conjugate addition of the lithium amide derived from **110** to **133** gave **134** in 82% yield and >99:1 dr. Subsequent mono-*N*-debenzylation of **134** by treatment with CAN gave access to **135** in 51% yield and >99:1 dr. Addition of BuLi to a mixture of **135** and **133** in THF at −78 °C resulted in evidence of 1,2-addition of BuLi to **135** and no conjugate addition products being observed in the ^{1}H NMR of the crude reaction mixture. In order to eliminate any 1,2-addition ^{s}BuLi was used in preference to ^{n}BuLi. Unfortunately, attempted conjugate addition of the lithium anion of **135** to **133** at −78 °C returned only starting material (Scheme 37).



Scheme 37. *Reagents and conditions*: (i) **110**, BuLi, THF, −78 °C, 2 h; (ii) CAN, MeCN/H_2O (5:1), rt, 2 h; (iii) **133**, ^{s}BuLi, THF, −78 °C, 2 h.

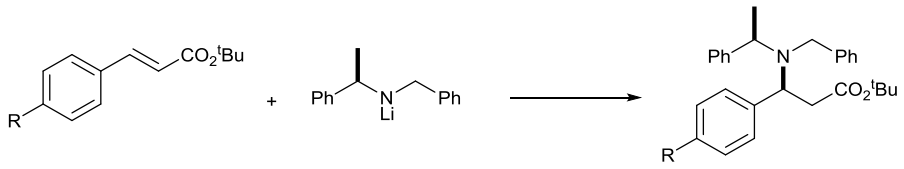
In order to increase the likelihood of the desired conjugate addition occurring, the two starting substrates were changed. The *N*-benzyl β-amino ester **136** was synthesised in one step upon conjugate addition of the lithium anion of benzylamine to **133**, which gave **136** in 54% yield (Scheme 38).



133 **136,** 54%

Scheme 38. *Reagents and conditions*: (i) Benzylamine, BuLi, THF, −78 °C, 2 h.

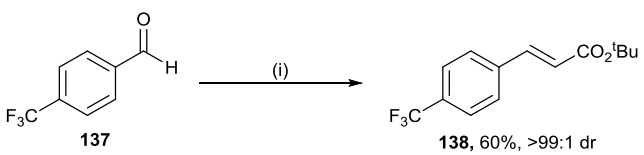
It has previously been shown[7] that altering the electrophilicity of the α,β-unsaturated ester, by installing electron donating or electron withdrawing groups at the *para* position of the aromatic ring, influences the rate of the lithium amide conjugate addition reaction. Specifically, the presence of a *p*-CF_3 group doubles the rate of reaction (Figure 14).



R	Rel. Rate
H	1
NMe_2	0.123
OMe	0.216
F	0.61
Br	1.1
Cl	1.08
OCF_3	1.48
CF_3	2.04
CN	2.63
NO_2	0.318

Figure 14. Effect of electron withdrawing and electron donating groups on the rate of conjugate addition.

Accordingly, α,β-unsaturated ester **138** was synthesised via a MeMgBr mediated Wadsworth-Emmons[6] reaction of commercially available **137** with **124**, which gave **138** in 60% yield and >99:1 dr (Scheme 39).

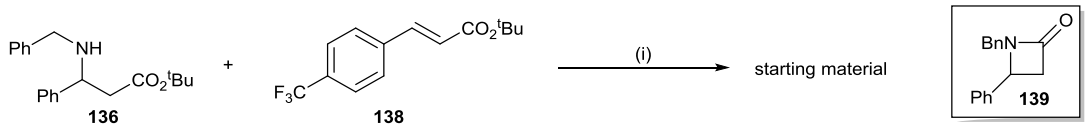


137 **138,** 60%, >99:1 dr

Scheme 39. *Reagents and conditions*: (i) **124**, MeMgBr, THF, −78 °C to rt, 16 h.

Additon of ^{s}BuLi to a mixture of **136** and **138** at −78 °C for 2 h resulted only in returned starting material. When the reaction was repeated at an increased temperature (−40 °C) still no reaction was observed. The effect of additives in the reaction mixture was next

investigated. Addition of an excess of 12-crown-4, prior to the addition of ^{s}BuLi, (to competitively chelate the lithium counter-ion) failed to effect the reaction with only the starting material being recovered, in good mass return. Although the aggregation state is known,[8] the reactive conformation of lithium amides in solution is unknown, however, it has been shown that the reactivity changes when a lithium salt is added.[9] Consequently, LiCl was added to the mixture of **136** and **138** prior to the addition of ^{s}BuLi to establish if its presence would induce any reaction, however, no reaction was observed. Changing the solvent from THF to Et_2O failed to effect the desired reaction, however, a small amount (<15% by ^{1}H NMR) of **136** was converted into the known[10] β-lactam **139** which was formed from intramolecular attack of the *N* atom on the ^{t}Bu ester. Separate treatment of the mixture of **136** and **138** with MeMgBr at −78 °C failed to induce any of the desired conjugate addition reaction (Scheme 40).

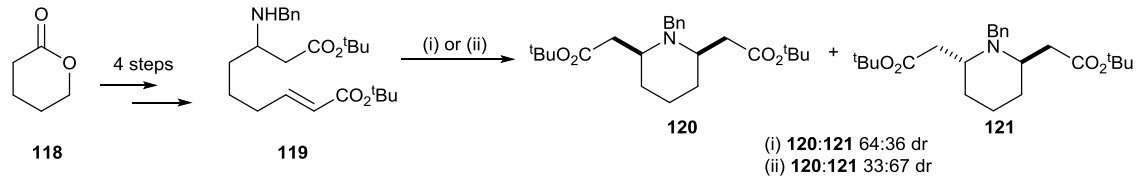


Base	Solvent	Additive	Temperature (°C)
^{s}BuLi	THF	none	−78
^{s}BuLi	THF	none	−40
^{s}BuLi	THF	12-crown-4	−78
^{s}BuLi	THF	LiCl	−78
^{s}BuLi	Et_2O	none	−20[a]
MeMgBr	THF	none	−78

Scheme 40. *Reagents and conditions*: (i) see table. [[a]15% of **136** had been converted to **139**]

3.3 Conclusion

The synthesis of 2,6-disubstituted piperidines **120** and **121** has been achieved in five steps starting from δ-valerolactone **118**. However, despite screening a range of cyclisation conditions, only modest *cis*:*trans* diastereoselectivities could be obtained (Scheme 41).



Scheme 41. *Reagents and conditions*: (i) MeOH, rt, 16 h; (ii) Et_3N, EtOH, 78 °C, 16 h.

Conjugate addition of secondary β-aminoesters **135** and **136** to α,β-unsaturated esters **133** and **138** respectively was unsuccessful under all conditions trialled.

3.4 References

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Chapter 4: Synthesis of 3,5-Disubstituted Indolizidines

This chapter describes the synthesis of the 3,5-disubstituted indolizidine scaffold **140**, starting from the previously synthesised 2,5-*cis*-disubstituted pyrrolidine **100**. The analogous reactions of the *trans*-diastereoisomer **101** to give **141** was also investigated. Subsequent conversion of **140** into the natural product monomorine **15** was undertaken (Figure 15).

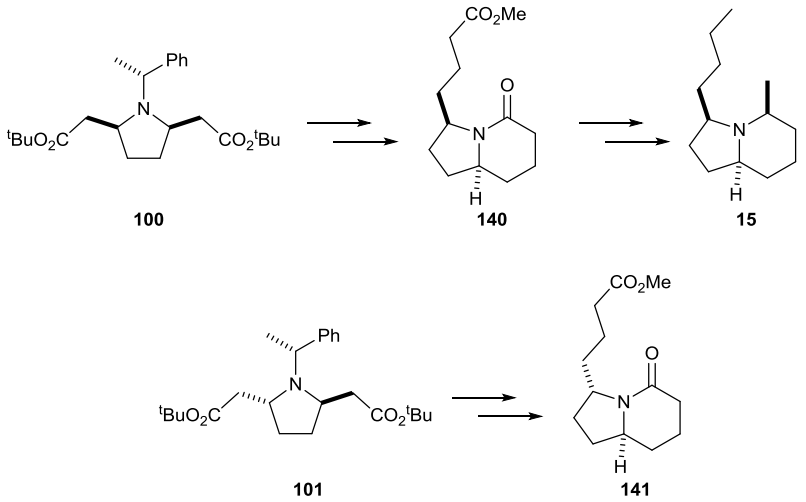


Figure 15. Proposed conversion of 2,5-disubstituted pyrrolidines **100** and **101** in to indolizidines.

4.1 Synthetic Strategy

Having previously developed an efficient, diastereoselective synthesis of 2,5-disubstituted pyrrolidines **100** and **101**, a general route for the conversion of both **100** and **101** into derivatives of 3,5-disubstituted indolizidines was pursued. Simultaneous homologation of both side chains within **142** would be achieved by conversion to dialdehyde **143** followed by olefination to yield **144**. Subsequent hydrogenation of **144** to reduce both olefins and cleave the *N*-α-methylbenzyl group to give **145**, followed by cyclisation *in situ* would generate the indolizidine core structure **146**. Chemoselective reduction of the methyl ester, whilst maintaining the integrity of the indolizidine core, would yield **147**. Removal of the hydroxyl group by conversion to the corresponding bromide followed by radical, homolytic cleavage of the carbon-bromine bond[1] would give **148**. Finally, conversion of the carbonyl group into an alkyl sidechain at C(5) would be achieved by addition of a Grignard reagent followed by acidification to generate an iminium ion *in situ*, which would be selectively reduced from one face using a hydride source[2] to yield the target **149** (Figure 16).

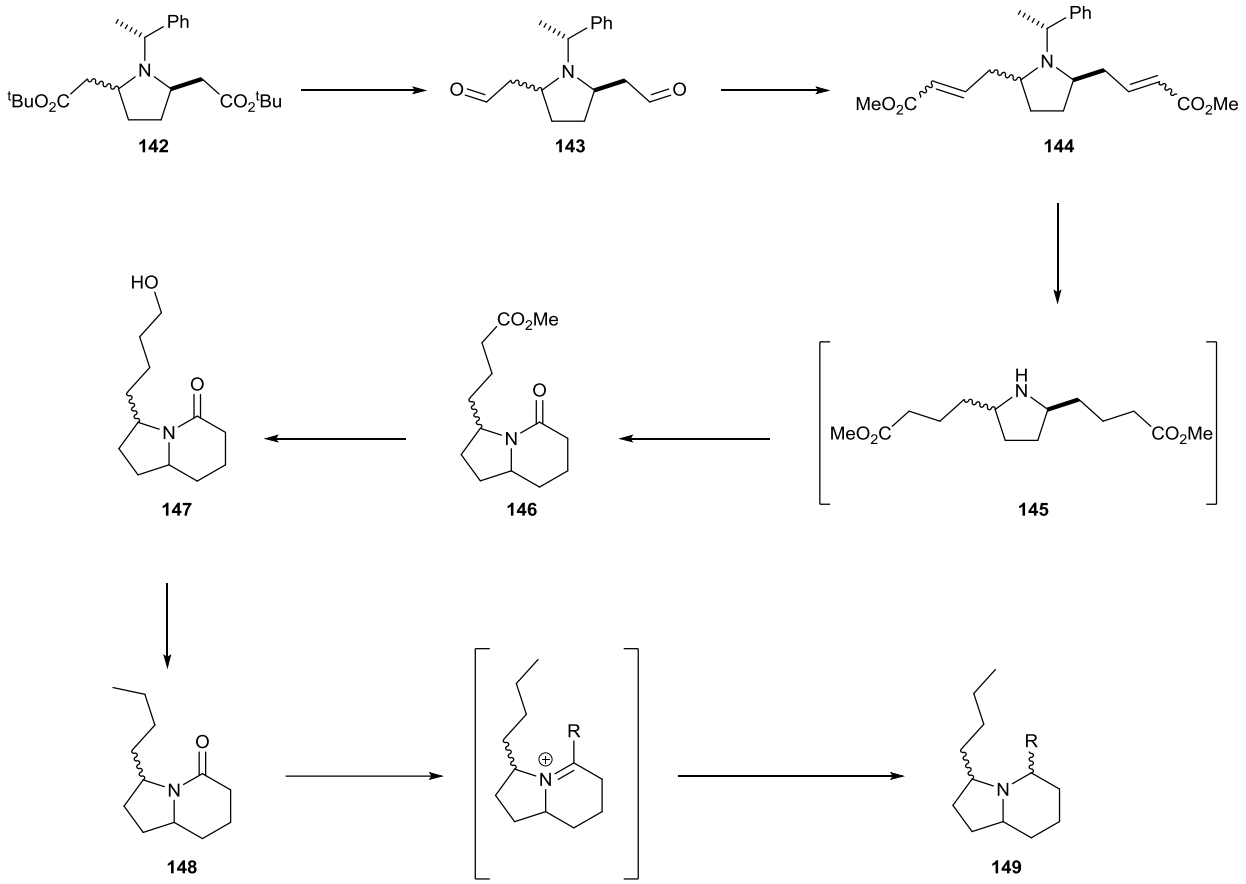
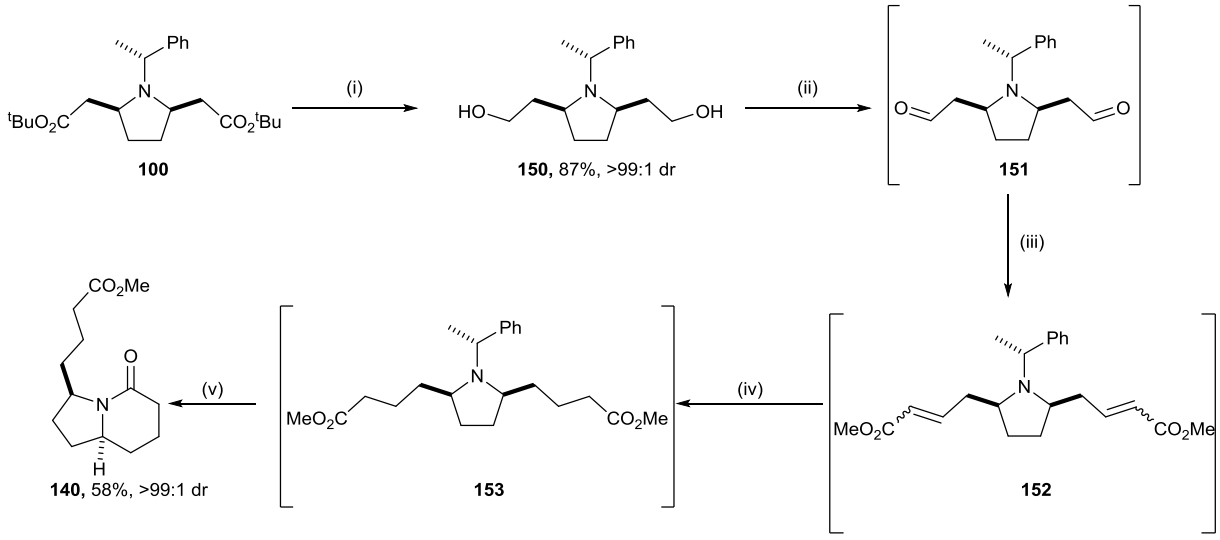


Figure 16. Proposed synthesis of 3,5-disubstituted indolizidines

4.2 Formation of the Indolizidine Core

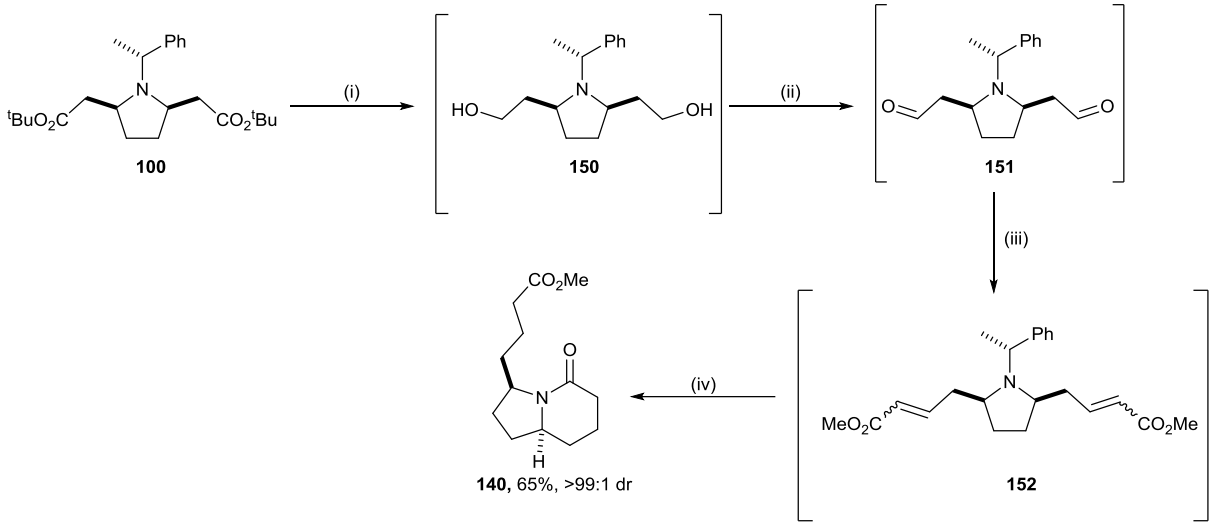
The *cis*-pyrrolidine **100** was first taken through the proposed synthetic sequence. Direct conversion of **100** to dialdehyde **151** by selective reduction with two equivalents of DIBAL-H resulted in a complex mixture of products with no characteristic aldehyde species being observed in the ^{1}H NMR of the crude reaction mixture. Consequently, pyrrolidine **100** was treated with $LiAlH_4$ to afford the diol **150** (>99:1 dr), which was isolated in 87% yield, as a single diasteroisomer, after column chromatography. Oxidation of **150**, by subjection to standard Swern oxidation conditions,[3] effected formation of the dialdehyde **151**, as observed by mass spectrometry ($[M+2MeOH]^+$). Attempts to workup the Swern oxidation and isolate the dialdehyde product proved unsuccessful resulting in a complex ^{1}H NMR spectrum, with no significant, characteristic aldehyde peak being observed. This was likely due to the instability and consequential decomposition of the β-amino aldehyde functionalities within **151**. Consequently, a one pot Swern-Wittig reaction was investigated whereby the intermediate dialdehyde **151** would be trapped *in situ* by addition of the stabilised ylide **92**. Swern oxidation of **150** to **151** followed by addition of **92** and stirring overnight at rt, followed by removal of the triphenylphosphine oxide and other by-products from the Swern-Wittig reaction by passing through a silica plug (eluent 30-40 °C petrol/Et_2O, 1:1), gave **152**

as a mixture of products. Overlapping peaks in the ^{1}H NMR spectrum of the crude reaction mixture precluded an accurate analysis of the diastereoisomeric purity of **152**. To verify that all the species were related as olefinic isomers, the mixture was subjected to mild hydrogenation conditions (Pd/C, 1 atm H_2), which reduced all of the olefins whilst leaving the *N*-α-methylbenzyl group in place, giving a single compound **153** in the ^{1}H NMR of the crude reaction mixture. This experiment illustrates that the isomeric mixture obtained from the Swern-Wittig reaction consisted of olefinic isomers only. Hydrogenolysis of **153** under more forcing conditions ($Pd(OH)_2$/C, 5 atm H_2) cleaved the α-methylbenzyl group, which subsequently underwent concomitant cyclisation to give **140** as a single diastereoisomer, and was isolated in 58% yield and >99:1 dr (Scheme 42).



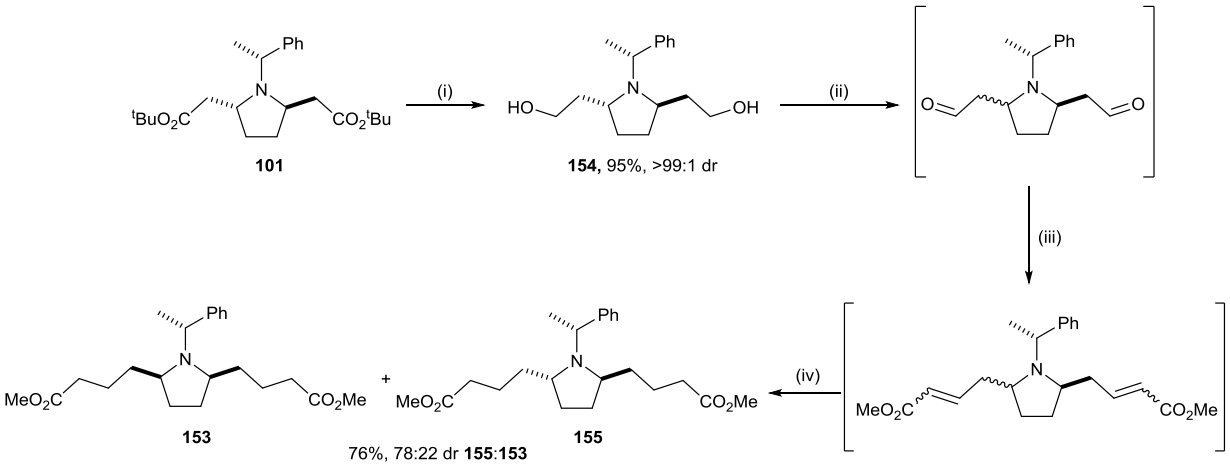
Scheme 42. *Reagents and conditions*: (i) $LiAlH_4$, THF, −78 °C to rt, 16 h; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 20 min then Et_3N, −78 °C to rt, 1 h; (iii) **92**, rt, 16 h; (iv) H_2 (1 atm), Pd/C, MeOH, rt, 4 h; (v) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h.

It was subsequently shown that the crude reaction product from the reduction of **100** with $LiAlH_4$ (quant. mass return) could be used in the subsequent Swern-Wittig reaction, without the need for further purification, to yield the same olefinic mixture **152**. Following removal of the by-products, direct subjection of the olefinic mixture **152** to the more forcing hydrogenation conditions (i.e. $Pd(OH)_2$/C, 5atm H_2, MeOH, 24h) resulted in hydrogenation of both double bonds and deprotection of the nitrogen, followed by concomitant cyclisation to give **140** as a single diastereoisomer (^{1}H NMR) which was subsequently isolated in 65% yield and >99:1 dr (Scheme 43).



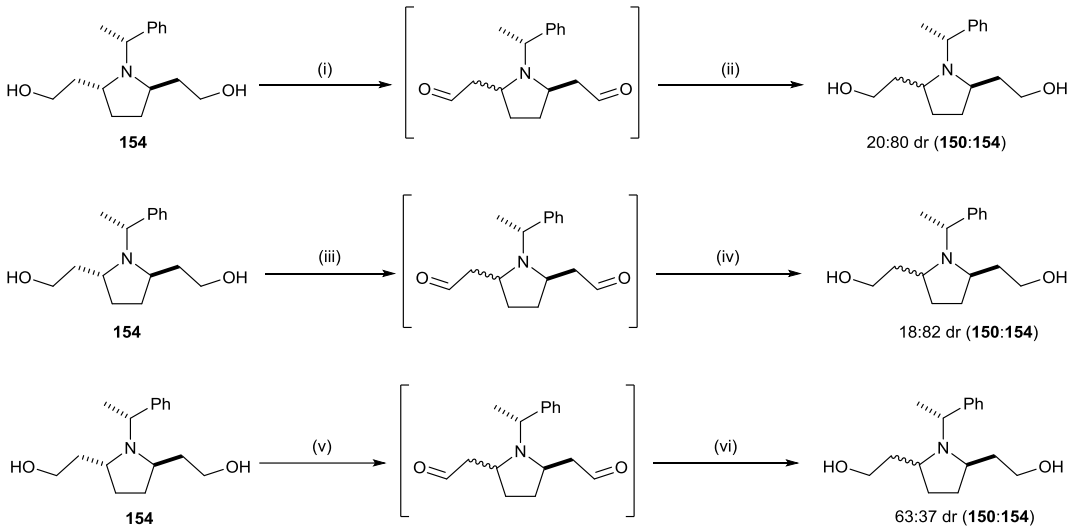
Scheme 43. *Reagents and conditions:* (i) $LiAlH_4$, THF, −78 °C to rt, 16 h; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 20 min then Et_3N, −78 °C to rt, 1 h; (iii) **92**, rt, 16 h; (iv) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h.

In order to obtain access to the opposite diastereoisomer of **141**, the *trans*-2,5-disubstituted pyrrolidine **101** was taken through the same series of reactions. Reduction of **101** (>99:1 dr) with $LiAlH_4$ formed diol **154** as a single diastereoisomer, a pure sample of which was isolated in 95% yield after column chromatography. Following Swern oxidation of **154**, isolation of the dialdehyde was again unsuccessful (although observation by mass spectrometry was again possible). However, addition of stabilised ylide **92** and stirring overnight at rt, followed by removal of the triphenylphosphine oxide and other by-products by passing through a silica plug (30-40 °C petrol/Et_2O 1:1), allowed the dialdehyde to be trapped *in situ* to give a mixture of products. Subjection of the product mixture to mild hydrogenation conditions (Pd/C, 1atm H_2, MeOH) reduced both of the olefins, whilst leaving the α-methylbenzyl group in place, to give an inseparable 78:22 mixture of **155** and **153** respectively. Comparison of the spectroscopic data for this mixture with those for the authentic sample of **153** clearly identified the minor diastereoisomer as **153** (Scheme 44).



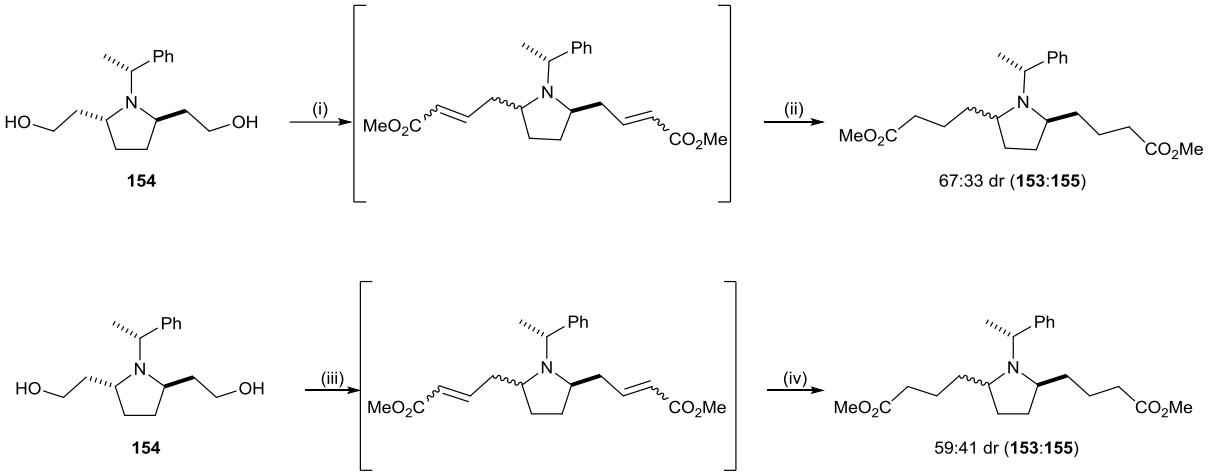
Scheme 44. *Reagents and conditions*: (i) $LiAlH_4$, THF, −78 °C to rt, 16 h; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 20 min then Et_3N, −78 °C to rt, 1 h; (iii) **92**, rt, 16 h; (iv) H_2 (1 atm), Pd/C, MeOH, rt, 4 h.

The results from the mild hydrogenation reaction suggest that epimerisation is occurring during the Swern-Wittig reaction. To investigate this hypothesis, and determine exactly which step was causing the epimerisation, each step was investigated systematically. As it had previously been shown that the dialdehyde could not be isolated, evidence of epimerisation in the Swern oxidation was assessed by addition of $NaBH_4$ (instead of yilde **92**) in order to reduce the dialdehyde back to the diol. The diol was then isolated and a crude *cis*:*trans* ratio determined by ^1H NMR spectrometry. The standard conditions used for the Swern oxidation involve addition of diol to premixed oxalyl chloride and DMSO in CH_2Cl_2, stirring at −78 °C for 20 min, followed by addition of Et_3N, stirring at −78 °C for 30 min then warming to rt (at which point the ylide is added). Subjection of **154** (>99:1 dr) to these conditions, adding $NaBH_4$ instead of ylide, resulted in a *cis*:*trans* ratio of 20:80 being obtained. This illustrates that, during the Swern oxidation, epimerisation from the *trans*- to the *cis*-isomer occurs. In order to determine which stage of the Swern oxidation was causing the epimerisation, two further experiments were undertaken. The first involved increasing the mixing time from 20 mins to 16 h between the addition of the diol and Et_3N whilst keeping other parameters constant. Following reduction back to the diol, this modification gave a *cis*:*trans* ratio of 18:82 indicating that epimerisation does not occur prior to the addition of Et_3N. When the oxidation-reduction experiment was run under standard conditions but left for 16 h instead of 30 mins post Et_3N addition and prior to addition of hydride a *cis*:*trans* ratio of 63:37 was obtained. This shows that it is the addition of Et_3N that is the origin of the epimerisation from the *trans*- to the *cis*-isomer (Scheme 45).



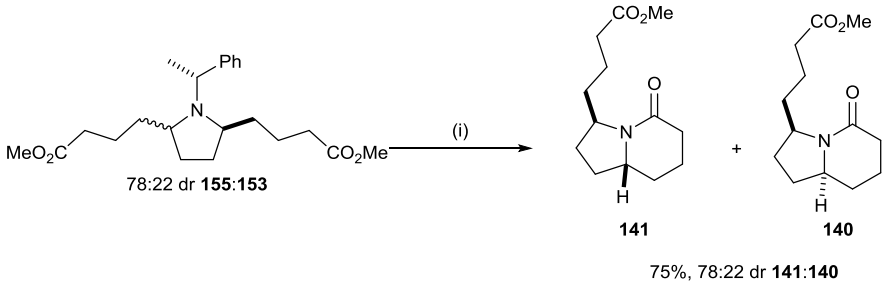
Scheme 45. *Reagents and conditions:* (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 20 min then Et_3N, −78 °C to rt, 1 h; (ii) $NaBH_4$, EtOH, rt, 3 h; (iii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 16 h then Et_3N, −78 °C to rt, 1 h; (iv) $NaBH_4$, EtOH, rt, 3 h; (v) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 20 min then Et_3N, −78 °C to rt, 16 h; (vi) $NaBH_4$, EtOH, rt, 3 h.

It was envisaged that having the ylide present prior to the formation of the dialdehyde would allow the ylide to react with the aldehyde before epimerisation could occur. Subjection of **154** to the conditions reported by Tilve,[4] whereby **154** and **92** are premixed in CH_2Cl_2 followed by addition of NaOAc and PCC and stirring the resulting mixture for 16 h at rt, did effect formation of the desired product. However, mild hydrogenation (Pd/C, H_2 1 atm) of the crude reaction mixture resulted in a 63:37 *cis*:*trans* ratio being observed. Subjecting **154** to the conditions reported by Barrett,[5] whereby **154** and **92** are premixed in 6:1 CH_2Cl_2:DMSO followed by sequential addition of PhCOOH and DMP and stirring at rt for 2 h, resulted in low mass return and a complex ^{1}H NMR spectrum. Hydrogenation (Pd/C, H_2 1 atm) of the crude reaction mixture resulted in a 59:41 mixture of **153** and **155** respectively (Scheme 46). Consequently, the Swern-Wittig reaction was retained as the optimal way of forming **155** from **154**.



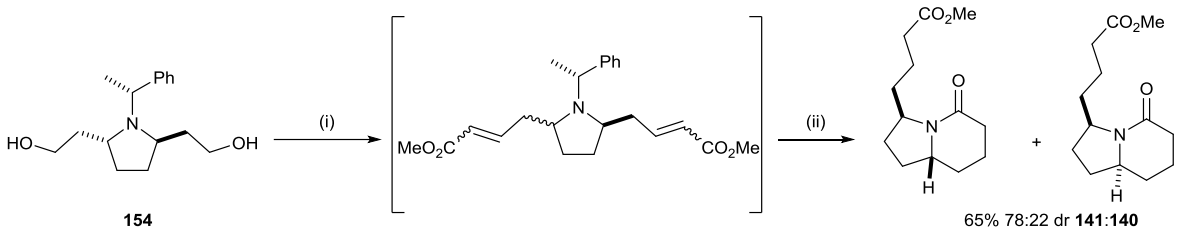
Scheme 46. *Reagents and conditions*: (i) PCC, NaOAc, **92**, CH_2Cl_2, rt, 16 h; (ii) H_2 (1 atm), Pd/C, MeOH, rt, 4 h; (iii) DMP, PhCOOH, **92**, CH_2Cl_2/DMSO (6:1), rt, 90 min; (iv) H_2 (1 atm), Pd/C, MeOH, rt, 2 h.

Subjection of the, inseparable, diastereoisomeric mixture (78:22 dr, **155**:**153**) to the more forcing hydrogenation conditions ($Pd(OH)_2$/C, 5 atm H_2) resulted in cleavage of the α-methylbenzyl group, followed by concomitant cyclisation to give **141** in 78:22 dr (comparison with the spectra for the authentic of **140** showed the minor diasteroisomer to be **140**). The diastereoisomers **140** and **141** were inseparable by column chromatography (Scheme 47).



Scheme 47. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 16 h.

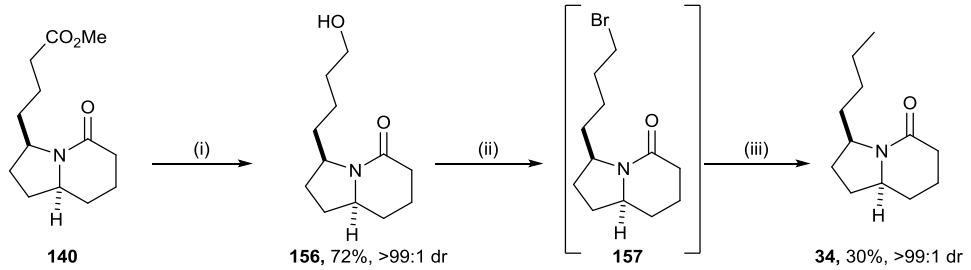
Direct subjection of the isomeric mixture from the Swern-Wittig reaction of **154** (the by-products from the reaction were removed by passing through a silica plug which was eluted with 1:1 petrol:Et_2O) to the more forcing hydrogenation conditions ($Pd(OH)_2$/C, 5atm H_2, MeOH, 24 h) removed both double bonds and deprotected the nitrogen, followed by concomitant cyclisation to give **141** in 78:22 dr. Comparison of the ^{1}H NMR spectrum of the crude reaction mixture with the pure sample of previously synthesised **140** clearly showed that the minor diastereoisomer was **140** (Scheme 48).



Scheme 48. *Reagents and conditions:* (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 20 min then Et_3N, −78 °C to rt, 1 h then **92**, rt, 16 h; (ii) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 16 h.

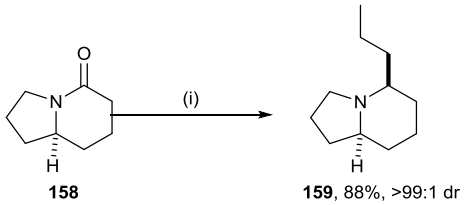
4.3 Formation of Monomorine

Conversion of **140** into the target 3,5-dialkylsubsituted indolizidines requires reduction of the methyl ester, removal of the resulting hydroxyl group and replacement of the carbonyl with an alkyl group at C(5). Thus, treatment of **140** with $LiBH_4$ reduced the methyl ester, whilst maintaining the integrity of the indolizidine core, to give **156** in 72% yield and >99:1 dr. Refluxing **156** with PBr_3 in 1,2-DCE effected conversion of the primary alcohol into the corresponding bromide **157**, which was subjected, as crude, to AIBN and $SnBu_3H$ in toluene to homolytically cleave the carbon-bromine bond and furnish **34** in 30% yield and >99:1 dr (Scheme 49).



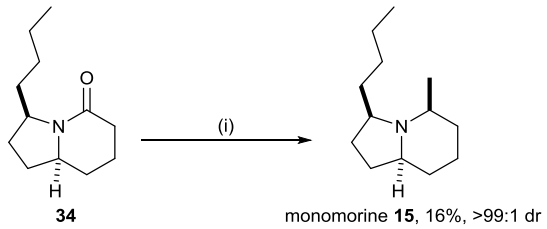
Scheme 49. *Reagents and conditions*: (i) $LiBH_4$, THF, rt, 6 h; (ii) PBr_3, 1,2-DCE, 84 °C, 3 h; (iii) AIBN, $SnBu_3H$, PhMe, 110 °C, 2 h.

There are several procedures in the literature for the conversion of the carbonyl group of a lactam into an alkyl substituent.[2,6] For example Schneider[2] performs a Grignard addition to the indolizidine **158** followed by an acid catalysed dehydration and a subsequent substrate controlled reduction of the *in situ* formed iminium to give **159** (Scheme 50).

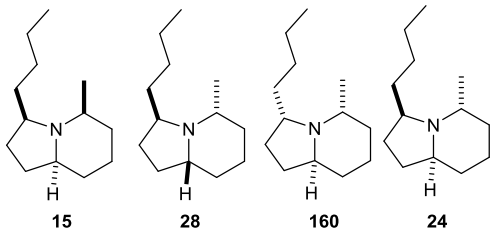


Scheme 50. *Reagents and conditions*: (i) PrMgCl, THF, rt, 16 h then AcOH, $NaBH_4$, 0 °C, 1 h.

Stirring **34** with MeMgBr at rt for 16 h followed by rapid addition of excess $NaBH_4$ and glacial AcOH effected full conversion of **34** to **15**, with **15** being formed as a single diastereoisomer (^{1}H NMR) and isolated in 16% yield (Scheme 51). The low yield for the isolated product was due to poor mass return from the column, with no other compounds being isolated. As **15** is originally derived from the 2,5-*cis*-disubstituted pyrrolidine **100**, **15** should be one of the 3,8a-*cis* diastereoisomers. Due to the selectivities observed in the literature for addition to the same iminium ion, it is predicted that the diastereoisomer formed will be monomorine and not 5-*epi*-monomorine. Comparison of the data obtained for the synthetic sample of **15** with the literature data for all four diasteroisomers showed a very close match to the data provided for monomorine **15**, and significant differences from the other known diastereoisomers **28**, **24** and **160** (Table 3).



Scheme 51. *Reagents and conditions*: (i) MeMgBr, THF, rt, 16 h then AcOH, $NaBH_4$, 0 °C, 1 h.



Synthetic 15 13C	15 13C	28 13C	160 13C	24 13C
14.2	14.1	14.3	14.2	7.4
22.8	22.8	20.5	19.1	14.3
22.9	22.8	23.1	20.6	19.8
24.9	24.8	24.8	23.1	23.5
29.5	29.3	25	27.1	28.4
29.8	29.7	26.4	27.1	28.4
30.3	30.3	29.3	28.7	30.1
30.8	30.8	30.1	29	32
35.7	35.8	32.4	29.2	33.1
39.6	39.7	34.6	36.2	33.2
60.4	60.2	52.1	49	47.2
63.0	62.8	58.9	55.5	55.4
67.3	67.1	59.1	60	58.7

Table 3. Comparison of ^{13}C NMR data for monomorine and its diastereoisomers.

4.4 Conclusion

Conversion of **100** and **101** into **140** and **141** respectively has been achieved in three steps. Subsequently **140** has been elaborated to the natural product monomorine **15** (Figure 17).

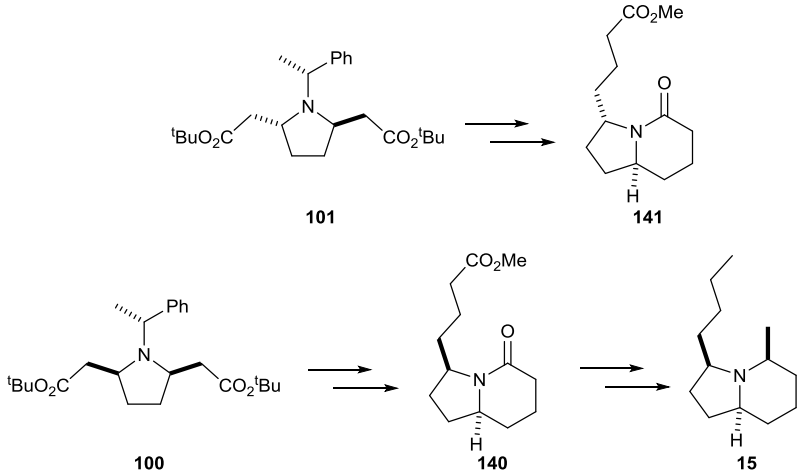


Figure 17. Synthesis of monomorine **15**.

4.5 Summary and Future Work

This thesis details the synthesis of *cis* and *trans* pyrrolidines **100** and **101** via a diastereodivergent cyclisation of **74**. The same high levels of diastereoselectivity for the

cyclisation are not observed in the analogous piperidine system. The *cis* and *trans* pyrrolidines were subsequently converted into indolizidines **140** and **141** respectively, utilising the same methodology in both cases. Subsequent elaboration of **140** to the natural product monomorine **15** was achieved. The general strategy employed for the synthesis of **15** from **73** should be amenable to the synthesis of a wide range of 3,5-disubstituted indolizidines. Future work should aim to improve the yields of the final two steps of the monomorine synthesis and synthesise its other diasteroisomers, as well as a library of different 3,5-disubstituted indolizidines, using the same synthetic strategy described. This will allow for the subsequent biological testing and evaluation of the compounds in order to ascertain if they are of medicinal or therapeutic benefit.

4.6 References

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(5) Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M. *J. Org. Chem.* **1997**, *62*, 9376.
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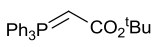
Chapter 5: Experimental

5.1 General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Organic layers were dried over $MgSO_4$ or Na_2SO_4. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm) or 1% aq $KMnO_4$. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[1] Water was purified by an Elix® UV-10 system. All other reagents were used as supplied without prior purification. Flash column chromatography was performed on Kieselgel 60 silica. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or on a diamond ATR module (ATR), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

5.2 Chapter 2 Experimental

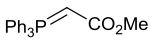
tert-Butyl (triphenylphosphoranylidene)acetate 91



PPh_3 (40.0 g, 150 mmol) was added to a stirred solution of *tert*-butyl bromoacetate (22.5 mL, 150 mmol) in EtOAc (200 mL) at rt and the resultant solution was stirred at rt for 16 h. The resultant suspension was filtered and the precipitate was washed with Et_2O (50 mL), then

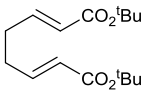
added portionwise to 2 M aq NaOH (200 mL) and the resultant suspension was stirred at rt for 10 min. The resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **91** as a white solid (49.7 g, 86%);[2] mp 152-154 °C; {lit.[2] 154-155 °C}; δ_H (400 MHz, $CDCl_3$) 1.25 (9H, br s, C*Me*$_3$), 2.71 (1H, br s, C(2)*H*), 7.40-7.71 (15H, m, *Ph*).

Methyl (triphenylphosphoranylidene)acetate 92



PPh_3 (40.0 g, 150 mmol) was added to a stirred solution of methyl bromoacetate (14.4 mL, 150 mmol) in EtOAc (200 mL) at rt and the resultant solution was stirred at rt for 16 h. The resultant suspension was filtered and the precipitate was washed with Et_2O (50 mL), then added portionwise to 2 M aq NaOH (200 mL) and the resultant suspension was stirred at rt for 10 min. The resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **92** as a white solid (43.9 g, 86%);[3] mp 167-169 °C; {lit.[3] 168-172 °C}; δ_H (400 MHz, $CDCl_3$) 2.93 (1H, br s, C(2)*H*), 3.55 (3H, br s, O*Me*), 7.45-7.73 (15H, m, *Ph*).

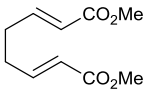
Di-*tert*-butyl (2*E*,6*E*)-octa-2,6-dienedioate 89



Ozone was bubbled through a stirred solution of **73** (1.13 mL, 9.26 mmol) in CH_2Cl_2 (5 mL) at −78 °C until the solution turned blue then degassed with oxygen for 5 min to remove any dissolved ozone. PPh_3 (3.64 g, 13.9 mmol) was added and the resultant solution was allowed to warm to rt and stirred for a further 1 h at rt. **91** (6.96 g, 18.5 mmol) was added portionwise and the resultant solution stirred at rt for 24 h then concentrated *in vacuo*. The residue was triturated with 30-40 °C petrol/Et_2O (v/v 1:1) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **89** as a white solid (4.73 g, 68%, >99:1 dr);[4] mp 64-65 °C; {lit.[4] 67-68 °C}; δ_H (400 MHz, $CDCl_3$)

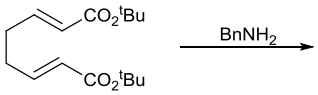
1.47 (18H, s, 2 × C*Me*$_3$), 2.32 (4H, t, *J* 3.3, C(4)*H*$_2$, C(5)*H*$_2$), 5.76 (2H, d, *J* 15.4, C(2)*H*, C(7)*H*), 6.77-6.87 (2H, m, C(3)*H*, C(6)*H*).

Dimethyl (2*E*,6*E*)-octa-2,6-dienedioate 90



Ozone was bubbled through a stirred solution of **73** (1.13 mL, 9.20 mmol) in CH_2Cl_2 (5 mL) at −78 °C until the solution turned blue then degassed with oxygen for 5 min to remove any dissolved ozone. PPh_3 (3.64 g, 13.9 mmol) was added and the resultant solution was allowed to warm to rt and stirred for a further 1 h at rt. **92** (6.19 g, 18.5 mmol) was added portionwise and the resultant solution stirred at rt for 24 h then concentrated *in vacuo*. The residue was triturated with 30-40 °C petrol/Et_2O (v/v 1:1) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **90** as a colourless oil (2.60 g, 71%, >99:1 dr);[5] δ_H (400 MHz, $CDCl_3$) 2.32-2.36 (4H, m, C(4)*H*$_2$, C(5)*H*$_2$), 3.68 (6H, s, 2 × O*Me*), 5.81 (2H, d, *J* 15.6, C(2)*H*, C(7)*H*), 6.83-6.93 (2H, m, C(3)*H*, C(6)*H*).

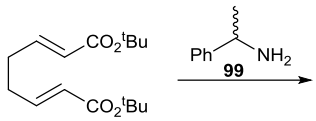
Addition of benzylamine to 89



Method A: Benzylamine (0.19 mL, 1.77 mmol) was added to a stirred solution of **89** (500 mg, 1.77 mmol) in EtOH (5 mL) and the resultant solution heated at 78 °C for 48 h then concentrated *in vacuo* to give a 88:12 mixture of **94**:**95**, respectively. Data for **94**: δ_H (400 MHz, $CDCl_3$) 1.43 (18H, s, 2 × C*Me*$_3$), 1.56-1.62 (2H, m, C(3)*H*$_A$, C(4)*H*$_A$), 1.90-1.98 (2H, m, C(3)*H*$_B$, C(4)*H*$_B$), 2.10 (2H, dd, *J* 14.5, 9.6, 2 × C*H*$_A$H$_B$CO$_2$^{t}Bu), 2.36 (2H, dd, *J* 14.5, 4.1, 2 × CH$_A$*H*$_B$CO$_2$^{t}Bu), 3.06-3.14 (2H, m, C(2)*H*, C(5)*H*), 3.79 (2H, s, C*H*$_2$Bn), 7.18-7.37 (5H, m, *Ph*).

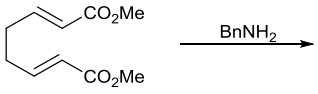
Method B: Benzylamine (1.93 mL, 17.7 mmol) was added to a stirred solution of **89** (500 mg, 1.77 mmol) in EtOH (5 mL) and the resultant solution heated at 78 °C for 16 h then concentrated *in vacuo* to give a 88:12 mixture of **94**:**95**, respectively.

Addition of 99 to 89



99 (0.23 mL, 1.77 mmol) was added to a stirred solution of **89** (500 mg, 1.77 mmol) in EtOH (5 mL) and the resultant solution heated at 78 °C for 96 h then concentrated *in vacuo* to give a 96:4 mixture of **100**:**101**, respectively. Data for **100**: δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.43 (3H, d, *J* 6.8, C(α)*Me*), 1.44 (9H, s, C*Me*$_3$), 1.50-1.60 (2H, m, C(3)H_A, C(4)H_A), 1.68-1.82 (2H, m, C(3)H_B, C(4)H_B), 1.96 (1H, dd, *J* 14.5, 9.2, CH_AH$_B$CO$_2$^{t}Bu), 2.02 (1H, dd, *J* 14.5, 4.4, CH$_A$$H_BCO_2$^{t}Bu), 2.21 (1H, dd, *J* 14.5, 9.2 CH_AH$_B$CO$_2$^{t}Bu), 2.44 (1H, dd, *J* 14.5, 4.4, CH$_A$$H_BCO_2$^{t}Bu), 3.30-3.37 (1H, m, C(2)*H*), 3.39-3.46 (1H, m, C(5)*H*), 3.99 (1H, q, *J* 6.8, C(α)*H*), 7.19-7.39 (5H, m, *Ph*).

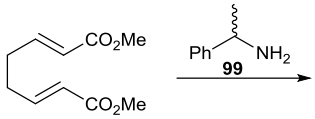
Addition of benzylamine to 90



Method A: Benzylamine (0.28 mL, 2.53 mmol) was added to a stirred solution of **90** (500 mg, 2.53 mmol) in EtOH (5 mL) and the resultant solution heated at 78 °C for 16 h then concentrated *in vacuo* to give a 85:15 mixture of **97**:**98** respectively. Data for **97**: δ_H (400 MHz, $CDCl_3$) 1.46-1.52 (2H, m, C(3)H_A, C(4)H_A), 1.84-1.94 (2H, m, C(3)H_B, C(4)H_B), 2.14 (2H, dd, *J* 15.2, 8.9, 2 × CH_AH$_B$CO$_2$^{t}Bu), 2.33 (2H, dd, *J* 15.2, 4.3, 2 × CH$_A$$H_BCO_2$^{t}Bu), 3.04-3.13 (2H, m, C(2)*H*, C(5)*H*), 3.54 (6H, s, 2 × O*Me*), 3.70 (2H, s, CH_2Bn), 7.13-7.24 (5H, m, *Ph*).

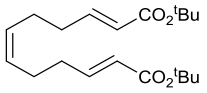
Method B: Benzylamine (2.75 mL, 25.3 mmol) was added to a stirred solution of **90** (500 mg, 2.53 mmol) in EtOH (5 mL) and the resultant solution heated at 78 °C for 4 h then concentrated *in vacuo* to give a 85:15 mixture of **97**:**98**, respectively.

Addition of 99 to 90



99 (3.21 mL, 25.3 mmol) was added to a stirred solution of **90** (500 mg, 2.53 mmol) in EtOH (5 mL) and the resultant solution heated at 78 °C for 16 h then concentrated *in vacuo* to give a 94:6 mixture of **103**:**104**, respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **103** as a colourless oil (808 mg, 63%, >99:1 dr);[6] δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.0, C(α)*Me*), 1.42-1.53 (2H, m, C(3)H_A, C(4)H_A), 1.64-1.81 (2H, m, C(3)H_B, C(4)H_B), 1.99-2.03 (2H, m, CH_AH$_B$CO$_2$Me, CH$_A$$H_BCO_2$Me), 2.24 (1H, dd, *J* 14.9, 8.9, CH_AH$_B$CO$_2$Me), 2.43 (1H, dd, *J* 14.9, 4.6, CH$_A$$H_BCO_2$Me), 3.28-3.36 (1H, m, C(2)*H*), 3.37-3.44 (1H, m, C(5)*H*), 3.51 (3H, s, O*Me*), 3.58 (3H, s, O*Me*), 3.89 (1H, q, *J* 7.0, C(α)*H*), 7.12-7.30 (5H, m, *Ph*).

Di-*tert*-butyl (2*E*,6*Z*,10*E*)-dodeca-2,6,10-trienedioate 106

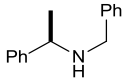


Ozone was bubbled through a stirred solution of **73** (1.00 g, 9.20 mmol) in CH_2Cl_2 (20 mL) at −78 °C for 15 min[1] then degassed with oxygen for 5 min to remove any dissolved ozone. PPh_3 (3.64 g, 13.9 mmol) was added and the resultant solution was allowed to warm to rt and stirred for a further 1 h at rt. **91** (6.96 g, 18.5 mmol) was added portionwise and the resultant solution stirred at rt for 24 h then concentrated *in vacuo*. The residue was triturated with 30-40 °C petrol/Et_2O (v/v 1:1). The precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **106** as a colourless oil (500 mg, 17%, >99:1 dr); ν_{max} (film) 2978 (C–H), 1711 (C=O), 1653 (C=C); δ_H (400 MHz, $CDCl_3$) 1.46 (18H, s, 2 × CMe_3), 2.10-2.25 (8H, m, C(4)H_2, C(5)H_2, C(8)H_2, C(9)H_2), 5.36-5.41 (2H, m, C(6)*H*, C(7)*H*), 5.74 (2H, d, *J* 15.7, C(2)*H*, C(11)*H*), 6.83 (2H, dt, *J* 15.7, 6.6, C(3)*H*, C(10)*H*); δ_C (100 MHz, $CDCl_3$) 25.8 (*C*(4), *C*(9)), 28.2 (2 × CMe_3) 31.9 (*C*(5), *C*(8)), 80.0 (2 × *C*Me$_3$), 123.4 (*C*(2), *C*(11)), 129.2 (*C*(6),

[1] Ozonolysis of **73** (1.00 g, 9.20 mmol) in CH_2Cl_2 (20 mL) at −78 °C required 30 min for the solution to turn blue, i.e. complete ozonolysis of both C=C bonds.

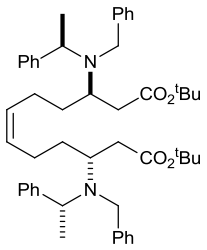
C(7)), 147.0 (*C*(3), *C*(10)), 165.9 (*C*(1), *C*(12)); *m/z* (ESI$^+$) 759 ([M+Na]$^+$, 100%); HRMS (TOF MS EI$^+$) $C_{24}H_{38}NO_4^+$ {[M–(2 × O^{t}Bu)]$^+$} requires 190.0994; found 190.0930. Further elution gave **89** (350 mg, 14%, >99:1 dr); Further elution gave **109** as a colourless oil (220 mg, 10%, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 2.16-2.25 (4H, m, C(4)*H*$_2$, C(5)*H*$_2$), 2.29-2.39 (2H, m, C(8)*H*$_2$), 2.45-2.52 (2H, m, C(9)*H*$_2$), 5.32-5.44 (2H, m, C(6)*H*, C(7)*H*), 5.74 (1H, d, *J* 15.7, C(2)*H*), 6.75-6.86 (1H, m, C(3)*H*), 9.75 (1H, app s, C(10)*H*); δ_C (100 MHz, $CDCl_3$) 20.0 (*C*(8)), 25.6 (*C*(5)), 28.1 (C*Me*$_3$), 31.8 (*C*(6)), 43.6 (*C*(9)), 80.1 (*C*Me$_3$), 123.5 (*C*(2)), 128.4 (*C*(6)), 129.6 (*C*(7)), 146.9 (*C*(3)), 165.9 (*C*(1)), 201.9 (*C*(10)).

(*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine 110



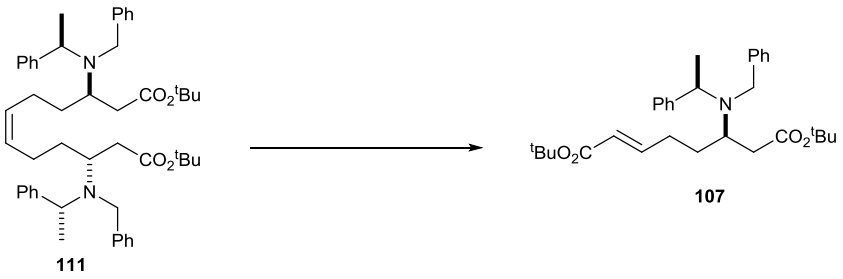
Benzaldehyde (41.7 mL, 400 mmol) was added to a stirred solution of (*R*)-**99** (53.2 mL, 400 mmol) in EtOH (400 mL) and the resultant solution was heated at reflux for 3 h, then allowed to cool to rt and then cooled to 0 °C. $NaBH_4$ (15.7 g, 400 mmol) was added portionwise, maintaining the reaction temperature below 15 °C and the resultant suspension was stirred for 48 h at rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (300 mL) and H_2O (300 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was slowly added to a stirred mixture of Et_2O (200 mL) and 10 M aq HCl (50 mL), to give a white precipitate which was isolated by filtration and recrystallised (CH_2Cl_2/pentane) to give (*R*)-**110**·HCl as a white solid (68.0 g, 68%). The free amine was then regenerated quantitatively as required by treatment with 2 M aq NaOH followed by extraction into CH_2Cl_2. The combined organic extracts were then dried and concentrated *in vacuo* to give (*R*)-**110** as a colourless oil;[7] $[\alpha]_D^{25}$ +48.3 (*c* 1.0 in $CHCl_3$); {lit.[7] $[\alpha]_D^{25}$ +46.4 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.6, C(α)*Me*), 1.83 (1H, br s, N*H*), 3.62 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 3.75 (1H, d, *J* 14.9, NCH$_A$*H*$_B$Ph), 3.86 (1H, q, *J* 6.6, C(α)*H*), 7.25-7.43 (10H, m, *Ph*).

Di-*tert*-butyl(*R*,*R*,*R*,*R*,*Z*)-3,10-bis-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dodec-6-enedioate 111



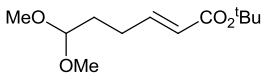
BuLi (2.5 M in hexanes, 3.80 mL, 9.50 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**110** (2.00 g, 9.50 mmol) in THF (10 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. A solution of **106** (1.00 g, 3.00 mmol) in THF (2 mL) at −78 °C was added dropwise via cannula, and the resultant solution was stirred at −78 °C for a further 4 h. Satd aq NH_4Cl (10 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **111** as a colourless oil (452 mg, 20%, 94:6 dr); $[\alpha]_D^{20}$ +36.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2973 (C–H), 1723 (C=O), 1654 (C=C); δ_H (400 MHz, $CDCl_3$) 1.28 (6H, d, *J* 7.1, 2 × C(α)*Me*), 1.32 (18H, s, 2 × C*Me*$_3$), 1.38-1.51 (4H, m, C(4)*H*$_2$, C(9)*H*$_2$), 1.75-1.82 (4H, m, C(5)*H*$_2$, C(8)*H*$_2$), 1.99-2.11 (2H, m, C(2)*H*$_A$, C(11)*H*$_A$), 2.21-2.34 (2H, m, C(2)*H*$_B$, C(11)*H*$_B$), 3.24-3.35 (2H, m, C(3)*H*, C(10)*H*), 3.41 (2H, d, *J* 14.8, 2 × NC*H*$_A$CH$_B$Ph), 3.71 (2H, d, *J* 14.8, 2 × NCH$_A$C*H*$_B$Ph), 3.75 (2H, q, *J* 7.1, 2 × C(α)H), 5.25 (2H, t, *J* 4.7, C(6)*H*, C(7)*H*), 7.11-7.38 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.2 (2 × C(α)*Me*), 24.9 (*C*(2), *C*(11)), 28.0 (2 × C*Me*$_3$), 33.5 (*C*(4), *C*(9)), 37.9 (*C*(5), *C*(8)), 50.1 (2 × *C*H$_2$Ph), 53.5 (*C*(3), *C*(10)), 58.0 (2 × *C*(α)), 80.0 (2 × *C*Me$_3$), 126.6, 127.0 (*p-Ph*), 128.0, 128.1, 128.2, 128.3 (*o,m-Ph*), 129.0 (*C*(6), *C*(7)), 141.7, 142.7 (*i-Ph*), 172.1 (*C*(1), *C*(12)); *m/z* (ESI$^+$) 760 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{50}H_{67}N_2O_4^+$ ([M+H]$^+$) requires 759.5101; found 759.5110.

Ozonolysis/Wittig of 111



HCl (2 M in Et_2O, 1 mL, 2 mmol) was added dropwise to **111** (1.00 g, 1.30 mmol) at rt and the resultant mixture was stirred for 5 min then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and cooled to −78 °C. Ozone was bubbled through the solution until the solution turned blue then oxygen was bubbled through for 10 min to remove dissolved ozone. PPh_3 (517 mg, 2.00 mmol) was added and the resultant solution was allowed to warm to rt and stirred for a further 1 h. **91** (990 mg, 2.60 mmol) was then added portionwise and the resultant solution stirred at rt for 16 h then concentrated *in vacuo.* The residue was triturated in Et_2O (20 mL) and filtered. The liquors were concentrated *in vacuo* to give a complex mixture of products consisting of <10% of **107**.

***tert*-Butyl (*E*)-6,6-dimethoxyhex-2-enoate 113**



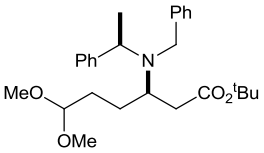
Step 1: **73** (11.3 mL, 93.0 mmol) was added to MeOH/CH_2Cl_2 (200 mL, v/v 1:1) and the resultant solution was cooled to −78 °C. Ozone was bubbled through the solution for 2.5 h[2] then oxygen was bubbled through the solution for 10 min, to remove dissolved ozone. $TsOH{\cdot}H_2O$ (1.30 g, 7.00 mmol) was added and the resultant mixture was stirred for 2 h whilst warming to rt. Me_2S (10.0 mL, 135 mmol) was then added and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in satd aq $NaHCO_3$ (100 mL) and extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **112** as a colourless oil which was used without further purification (17.5 g);[8] δ_H (400 MHz, $CDCl_3$) 1.50-1.56 (4H, m, C(3)H_2, C(6)H_2), 1.95-

[2] Ozonolysis of a solution of **73** (1 g, 9.20 mmol) in MeOH/CH_2Cl_2 (20 mL, v/v 1:1) at −78 °C took 30 min to turn blue.

2.04 (4H, m, C(2)H_2, C(7)H_2), 3.20 (12H, s, 4 × O*Me*), 4.25 (2H, t, *J* 5.8, C(4)*H*, C(5)*H*), 5.27 (2H, t, *J* 5.5, C(1)*H*, C(8)*H*).

Step 2: **112** (17.5 g, 75.4 mmol) was dissolved in CH_2Cl_2 (200 mL) and the resultant solution was cooled to −78 °C. Ozone was bubbled through the solution until the solution turned blue, then oxygen was bubbled through the solution for 10 min, to remove dissolved ozone. PPh_3 (29.6 g, 113 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred for a further 1 h. **91** (56.7 g, 150 mmol) was added portionwise and the resultant solution was stirred at rt for 16 h then concentrated *in vacuo*. The residue was triturated in Et_2O (100 mL) and filtered. The liquors were concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave **113** as a colourless oil (12.2 g, 35%, >99:1 dr); ν_{max} (film) 2978 (C–H), 1712 (C=O), 1654 (C=C); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 1.71-1.77 (2H, m, C(5)H_2), 2.19-2.27 (2H, m, C(4)H_2), 3.32 (6H, s, C(O*Me*)$_2$), 4.37 (1H, t, *J* 5.7 C(6)*H*), 5.76 (1H, d, *J* 15.7, C(2)*H*), 6.85 (1H, dt, *J* 15.7, 6.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.1 (*C*(4)), 28.1 (*CMe*$_3$), 30.1 (*C*(5)), 52.8 (C(O*Me*)$_2$), 80.1 (*C*Me$_3$), 103.6 (*C*(6)), 126.4 (*C*(2)), 146.8 (*C*(3)), 166.0 (*C*(1)); *m/z* (ESI$^+$) 759 ([M+Na]$^+$, 100%); HRMS (TOF MS EI$^+$) $C_8H_{13}NO_4^+$ ([M–^{t}Bu]$^+$) requires 173.0814; found 173.0835.

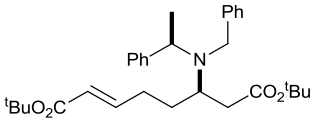
***tert*-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6,6-dimethoxyhexanoate 114**



BuLi (2.5 M in hexanes, 21.3 mL, 53.0 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**110** (11.2 g, 53.0 mmol) in THF (120 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. A solution of **113** (7.65 g, 33.0 mmol) in THF (20 mL) was then added dropwise via cannula and the resultant solution was stirred for a further 2 h at −78 °C. Satd aq NH_4Cl (50 mL) was then added and the resultant mixture allowed to warm to rt. CH_2Cl_2 (200 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **114** as a colourless oil (12.3 g, 84%, >99:1 dr); $[\alpha]_D^{20}$ +6.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2974 (C–H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.9, C(α)*Me*), 1.32 (9H, s, C*Me*$_3$), 1.34-1.45 (2H, m, C(4)H_2), 1.53-1.57 (1H, m, C(5)H_A), 1.74-

1.79 (1H, m, C(2)H_A), 1.80-1.83 (1H, m, C(2)H_B), 1.86-1.94 (1H, m, C(5)H_B), 3.20 (3H, s, O*Me*), 3.22 (3H, s, O*Me*), 3.23-3.27 (1H, m, C(3)*H*), 3.41 (1H, d, *J* 14.9, NC$H_A$$H_B$Ph), 3.68-3.77 (2H, m, C(α)*H*, NCH_AH_BPh), 4.19 (1H, t, *J* 5.9, C(6)*H*), 7.14-7.19 (2H, m, *Ph*), 7.21-7.29 (6H, m, *Ph*), 7.34-7.38 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 28.1 (CMe_3), 28.3 (*C*(4)), 30.1 (*C*(5)), 37.6 (*C*(2)), 50.1 (CH_2Ph), 52.5, 52.7 (O*Me*), 53.7 (*C*(3)), 58.1 (*C*(α)), 80.1 (CMe_3), 104.5 (*C*(6)), 126.6, 127.0 (*p-Ph*), 127.9, 128.0, 128.2, 128.3 (*o,m-Ph*), 141.7, 142.8 (*i-Ph*), 172.1 (*C*(1)); *m/z* (ESI^+) 442 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{39}NNaO_4^+$ ($[M+H]^+$) requires 464.2761; found 464.2771.

Di-*tert*-butyl (*R,R,E*)-6-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-2-enedioate 107

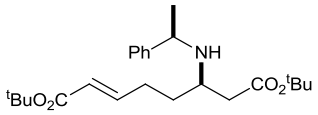


Step 1: HCl (2 mL, conc) was added to a stirred solution of **114** (10.0 g, 23.0 mmol) in acetone/H_2O (90 mL, v/v 5:4) and the resultant mixture was heated at reflux for 1 h, then allowed to cool to rt. H_2O (30 mL) was then added and the resultant mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (200 mL), H_2O (150 mL) and brine (150 mL), then dried and concentrated *in vacuo* to give *tert*-butyl (*R,R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-oxohexanoate as a pale yellow oil which was used without further purification (8.70 g);[9] $[\alpha]_D^{20}$ +10.5 (*c* 1.0 in $CHCl_3$); {lit.[9] for enantiomer $[\alpha]_D^{23}$ −6.6 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.1, C(α)*Me*), 1.41 (9H, s, CMe_3), 1.65-1.73 (2H, m, C(4)H_2), 1.81-1.93 (2H, m, C(2)H_2), 2.54-2.65 (1H, m, C(5)H_A), 2.71-2.81 (1H, m, C(5)H_B), 3.30-3.39 (1H, m, C(3)*H*), 3.50 (1H, d, *J* 14.9, C$H_A$$H_B$Ph), 3.78 (1H, d, *J* 14.9, CH_AH_BPh), 3.83 (1H, q, *J* 7.1, C(α)*H*), 7.23-7.44 (10H, m, *Ph*), 9.75 (1H, app s, C(6)*H*).

Step 2: **91** (7.20 g, 19.0 mmol) was added to a stirred solution of *tert*-butyl (*R,R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-oxohexanoate (7.50 g, 19.0 mmol) in CH_2Cl_2 (75 mL) at rt and the resultant solution was stirred at rt for 18 h then concentrated *in vacuo*. The residue was triturated with 30-40 °C petrol/Et_2O (v/v 1:1). The precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **107** as a colourless oil (6.74 g, 69%, >99:1 dr); $[\alpha]_D^{20}$ −14.9 (*c*

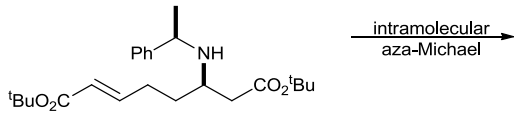
1.0 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1714 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.0, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 1.49 (9H, s, C*Me*$_3$), 1.52-1.65 (2H, m, C(4)*H*$_2$), 1.83-1.96 (2H, m, C(2)*H*$_2$), 2.23 (1H, dt, *J* 8.8, 6.7, C(5)*H*$_A$), 2.50-2.61 (1H, m, C(5)*H*$_B$), 3.29-3.37 (1H, m, C(3)*H*), 3.50 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 3.77 (1H, d, *J* 14.9, NCH$_A$*H*$_B$Ph), 3.82 (1H, q, *J* 7.0, C(α)*H*), 5.72 (1H, d, *J* 15.7, C(7)*H*), 6.85 (1H, dt, *J* 15.7, 6.7, C(6)*H*), 7.22-7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 28.0 (C*Me*$_3$), 28.1 (C*Me*$_3$), 29.7 (*C*(5)), 31.9 (*C*(4)), 37.5 (*C*(2)), 50.1 (N*C*H$_2$Ph), 53.4 (*C*(3)), 58.1 (*C*(α)), 79.9 (*C*Me$_3$), 80.2 (*C*Me$_3$), 122.9 (*C*(7)), 126.7, 127.1 (*p-Ph*), 127.9, 128.1, 128.2, 128.4 (*o,m-Ph*), 141.5, 142.5 (*i-Ph*), 148.0 (*C*(6)), 166.1, 171.9 (*C*(1), *C*(8)); *m/z* (ESI$^+$) 494 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{44}NO_4^+$ ([M+H]$^+$) requires 494.3247; found 494.3265.

Di-*tert*-butyl (*R,R,E*)-6-[*N*-(α-methylbenzyl)amino]oct-2-enedioate 74



CAN (11.7 g, 21.0 mmol) was added portionwise to a stirred solution of **107** (5.00 g, 10.1 mmol, >99:1 dr) in MeCN/H_2O (120 mL, v/v 5:1) at rt and the resultant solution was stirred at rt for 2 h. Satd aq $NaHCO_3$ (75 mL) was then added and the resultant mixture was stirred for 30 min. The aqueous layer was then extracted with CH_2Cl_2 (2 × 150 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was added to 2 M aq sodium bisulphite (50 mL) and the resultant mixture was stirred at rt for 20 min then extracted with Et_2O (3 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **74** as a pale yellow oil (3.35 g, 82%, >99:1 dr); $[\alpha]_D^{20}$ −5.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2982 (C–H), 1708 (C=O), 1655 (C=C); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.43 (9H, s, C*Me*$_3$), 1.58 (1H, br s, N*H*), 1.72 (3H, d, *J* 6.8, C(α)*Me*), 1.79-1.89 (2H, m, C(4)*H*$_2$), 2.09-2.23 (2H, m, C(5)*H*$_2$), 2.62 (1H, dd, *J* 16.4, 7.6, C(2)*H*$_A$), 2.84 (1H, dd, *J* 16.4, 4.7, C(2)*H*$_B$), 3.12-3.20 (1H, m, C(3)*H*), 4.40 (1H, q, *J* 6.8, C(α)*H*), 5.55 (1H, d, *J* 15.7, C(7)*H*), 6.55 (1H, dt, *J* 15.7, 6.8, C(6)*H*), 7.34-7.46 (3H, m, *Ph*), 7.51-7.57 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 27.4 (*C*(5)), 28.0 (C*Me*$_3$), 28.1 (C*Me*$_3$), 31.0 (*C*(4)), 36.7 (*C*(2)), 53.0 (*C*(3)), 57.5 (*C*(α)), 80.1 (*C*Me$_3$), 82.2 (*C*Me$_3$), 124.3 (*C*(7)), 127.7 (*p-Ph*), 129.0, 129.5 (*o,m-Ph*), 136.7 (*i-Ph*), 144.9 (*C*(6)), 165.4, 169.5 (*C*(1), *C*(8)); *m/z* (ESI$^+$) 404 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{38}NO_4^+$ ([M+H]$^+$) requires 404.2975; found 404.2784.

Attempted intramolecular aza-Michael of 74

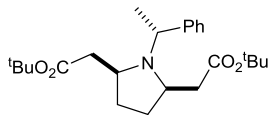


Method A: **74** (100 mg, 0.25 mmol) was dissolved in MeOH (2 mL) and the resultant solution heated at reflux for 4 h then allowed to cool to rt and concentrated *in vacuo* to give a 95:5 mixture of **100**:**101**, respectively.

Method B: BuLi (2.5 M in hexanes, 0.10 mL, 0.25 mmol) was added dropwise via syringe to a stirred solution of **74** (100 mg, 0.25 mmol) in THF (2 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo* to give a 21:12:67 mixture of **74**:**100**:**101**, respectively.

Method C: BuLi (2.5 M in hexanes, 0.10 mL, 0.25 mmol) was added dropwise via syringe to a stirred solution of **74** (100 mg, 0.25 mmol) in THF (2 mL) at −20 °C, and the resultant mixture was stirred at −20 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo* to give a 21:27:52 mixture of **74**:**100**:**101**, respectively.

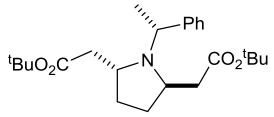
Di-*tert*-butyl (2*S*,5*R*,*αR*)-[(*N*-α-methylbenzyl)pyrrolidine-2,5-diyl]diacetate 100



Et_3N (0.04 mL, 0.27 mmol) was added to a stirred solution of **74** (100 mg, 0.25 mmol) in EtOH (2 mL) and the resultant solution was heated at reflux for 16 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in Et_2O (2 mL) and washed with H_2O (1 mL), then dried and concentrated *in vacuo* to give a 93:7 mixture of **100**:**101**, respectively . Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **100** as a colourless oil (85 mg, 85%, >99:1 dr);[10] $[\alpha]_D^{20}$ −1.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.43 (3H, d, *J* 6.8, C(α)*Me*), 1.44

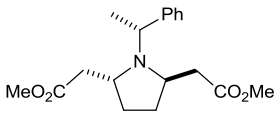
(9H, s, C*Me*$_3$), 1.50-1.60 (2H, m, C(3)*H*$_A$, C(4)*H*$_A$), 1.68-1.82 (2H, m, C(3)*H*$_B$, C(4)*H*$_B$), 1.96 (1H, dd, *J* 14.5, 9.2, C*H*$_A$H$_B$CO$_2$^{t}Bu), 2.02 (1H, dd, *J* 14.5, 4.4, CH$_A$*H*$_B$CO$_2$^{t}Bu), 2.21 (1H, dd, *J* 14.5, 9.2 C*H*$_A$H$_B$CO$_2$^{t}Bu), 2.44 (1H, dd, *J* 14.5, 4.4, CH$_A$*H*$_B$CO$_2$^{t}Bu), 3.30-3.37 (1H, m, C(2)*H*), 3.39-3.46 (1H, m, C(5)*H*), 3.99 (1H, q, *J* 6.8, C(α)*H*), 7.19-7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 28.1 (2 × C*Me*$_3$), 30.0, 30.4 (*C*(3), *C*(4)), 40.0, 43.5 (*C*H$_2$CO$_2$^{t}Bu), 56.9, 58.3 (*C*(2), *C*(5)), 57.9 (*C*(α)), 79.9, 80.1 (2 × *C*Me$_3$), 126.8 (*p-Ph*), 127.9, 128.0 (*o,m-Ph*), 143.5 (*i-Ph*), 171.9 (2 × *C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 404 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{38}NO_4^+$ ([M+H]$^+$) requires 404.2795; found 404.2777.

Di-*tert*-butyl (*R,R,R*)-[(*N*-α-methylbenzyl)pyrrolidine-2,5-diyl]diacetate 101



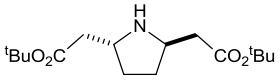
BuLi (2.5 M in hexanes, 0.10 mL, 0.25 mmol) was added dropwise via syringe to a stirred solution of **74** (100 mg, 0.25 mmol) in THF (2 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 4 h. Satd aq NH_4Cl (2 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo* to give a 20:80 mixture of **100:101**, respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **101** as a colourless oil (56 mg, 56%, >99:1 dr); $[\alpha]_D^{20}$ +32.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2976 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (18H, s, 2 × C*Me*$_3$), 1.41 (3H, d, *J* 6.8, C(α)*Me*), 1.56-1.67 (2H, m, C(3)*H*$_A$, C(4)*H*$_A$), 1.98-2.06 (2H, m, C(3)*H*$_B$, C(4)*H*$_B$), 2.10 (2H, dd, *J* 14.2, 10.4, 2 × C*H*$_A$H$_B$CO$_2$^{t}Bu), 2.48 (2H, dd, *J* 14.2, 3.3, 2 × CH$_A$*H*$_B$CO$_2$^{t}Bu), 3.37-3.44 (2H, m, C(2)*H*, C(5)*H*), 3.89 (1H, q, *J* 6.8, C(α)*H*), 7.21 (1H, d, *J* 7.1, *p-Ph*), 7.29 (2H, d, *J* 7.8, *o-Ph*), 7.35 (2H, dd, *J* 7.8, 7.1, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 24.5 (C(α)*Me*), 28.1 (2 × C*Me*$_3$), 28.6 (C(3), C(4)), 40.4 (2 × *C*H$_2$CO$_2$^{t}Bu), 57.2 (*C*(2), *C*(5)), 58.1 (*C*(α)), 80.1 (2 × *C*Me$_3$), 126.6 (*p-Ph*), 126.9 (*m-Ph*), 128.3 (*o-Ph*), 146.1 (*i-Ph*), 172.0 (2 × *C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 404 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{38}NO_4^+$ ([M+H]$^+$) requires 404.2795; found 404.2784.

Dimethyl (*R*,*R*,*R*)-[(*N*-α-methylbenzyl)pyrrolidine-2,5-diyl]diacetate 104



$SOCl_2$ (0.13 mL, 1.7 mmol) was added dropwise to a stirred solution of **101** (70 mg, 0.17 mmol, >99:1) in MeOH (1 mL) at 0 °C and the reaction mixture was then stirred at 67 °C for 2 h. The resultant solution was concentrated *in vacuo*, then dissolved in CH_2Cl_2 (5 mL) and washed with satd aq $NaHCO_3$ (3 × 5 mL). The organic extract was then dried and concentrated *in vacuo* to give **104** as a yellow oil (45 mg, 82%, >99:1 dr); $[\alpha]_D^{25}$ +36.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2953 (C–H), 1730 (C=O), 1151 (C–O); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.6, C(α)*Me*), 1.49-1.55 (2H, m, C(3)H_A, C(4)H_A), 1.93-2.01 (2H, m, C(3)H_B, C(4)H_B), 2.16 (2H, dd, *J* 14.7, 10.2, 2 × CH_AH$_B$CO$_2$Me), 2.49 (2H, dd, *J* 14.7, 3.4, 2 × CH$_A$$H_BCO_2$Me), 3.37-3.44 (2H, m, C(2)*H*, C(5)*H*), 3.52 (6H, s, 2 × O*Me*), 3.84 (1H, q, *J* 6.6, C(α)*H*), 7.11-7.30 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.8 (C(α)*Me*), 28.9 (*C*(3), *C*(4)), 39.0 (2 × *C*H$_2$CO$_2$Me), 51.4 (2 × O*Me*), 56.9 (*C*(2), *C*(5)), 58.2 (*C*(α)), 126.8 (*p-Ph*), 126.9, 128.4, (*o,m-Ph*), 145.9 (*i-Ph*), 172.9 (*C*O$_2$Me); *m/z* (ESI$^+$) 320 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{26}NO_4^+$ [M+H]$^+$ requires 320.1856; found 320.1850.

Di-*tert*-butyl (*R*,*R*)-pyrrolidine-2,5-diyl]diacetate 117



$Pd(OH)_2$/C (20 mg, 20 wt%) was added to a stirred solution of **101** (100 mg, 0.25 mmol, >99:1 dr) in degassed MeOH (1 mL) and the resultant suspension was stirred at rt for 16 h under H_2 (5 atm). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to give **117** as a colourless oil (72 mg, 98%, >99:1 dr); $[\alpha]_D^{25}$ −10.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2973 (C–H), 1723 (C=O), 1149 (C–O); δ_H (400 MHz, $CDCl_3$) 1.32-1.36 (2H, m, C(3)H_A, C(4)H_A), 1.37 (18H, s, 2 × CMe_3), 1.89-1.97 (2H, m, C(3)H_B, C(4)H_B), 2.25-2.29 (4H, m, 2 × CH_2CO$_2$^{t}Bu), 3.44-3.52 (2H, m, C(2)*H*, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 28.8 (2 × CMe_3), 31.1 (*C*(3), *C*(4)), 40.3 (2 × *C*H$_2$CO$_2$^{t}Bu), 53.9 (*C*(2), *C*(5)), 172.0 (2 × *C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 300 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{30}NO_4^+$ [M+H]$^+$ requires 300.2169; found 300.2170.

Attempts to form 115

Method A: Acetophenone (40 mg, 0.33 mmol) was added to a stirred solution of **117** (100 mg, 0.33 mmol) in EtOH (1 mL) and the resultant solution was heated at reflux for 2 h then cooled to 0 °C. $NaBH_4$ (13 mg, 0.33 mmol) was added and the resultant solution was allowed to warm to rt then stirred for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (2 mL) and H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give starting material **117** and 1-phenylethanol.

Method B: Acetophenone (17 mg, 0.14 mmol) was added to a stirred solution of **117** (50 mg, 0.17 mmol) at rt. TMEDA (0.02 mL, 0.14 mmol) was added and the resultant solution stirred at rt for 30 mins. Trichlorosilane (0.03 mL, 0.28 mmol) was added and the resultant mixture was stirred for 36 h at rt. Satd aq $NaHCO_3$ (1 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give starting material **117** only.

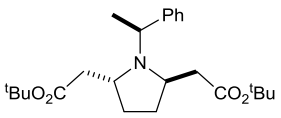
Method C: Acetophenone (20 mg, 0.17 mmol) was added to a stirred solution of **117** (50 mg, 0.17 mmol) in 1,2-DCE (1 mL) at rt. $Na(OAc)_3BH$ (53 mg, 0.25 mmol) was added, then glacial AcOH (0.01 mL) and the resultant mixture was stirred for 24 h at rt. 1 M aq NaOH (1 mL) was added, the aqueous layer was extracted with Et_2O (2 × 2 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give starting material **117** only.

Method D: Benzaldehyde (0.01 mL, 0.10 mmol) was added to a stirred solution of **117** (30 mg, 0.10 mmol) in THF (1 mL) at rt and the resultant solution heated at reflux for 6 h then cooled to 0 °C. MeMgBr (3 M in Et_2O, 0.07 mL, 0.20 mmol) was added dropwise and the resultant mixture was stirred for 16 h whilst warming to rt then concentrated *in vacuo*. The residue was partitioned between satd aq NH_4Cl (1 mL) and CH_2Cl_2 (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give starting material **117** and 1-phenylethanol.

Method E: TFA (23 mg, 0.20 mmol) was added to a stirred solution of **117** (50 mg, 0.17 mmol) in Et_2O (0.5 mL) at rt and the resultant mixture was concentrated *in vacuo*. The residue was added to a stirred solution of benzaldehyde (18 mg, 0.17 mL) in PhMe (1 mL) with 4Å molecular sieves and the resultant mixture stirred for 16 h at rt then cooled to 0 °C. MeMgBr (3 M in Et_2O, 0.11 mL, 0.33 mmol) was added dropwise and the resultant mixture stirred for

4 h at 0 °C. Satd aq NH_4Cl (1 mL) was added. The aqueous layer was extracted with Et_2O (2 × 2 mL) and the combined organic extracts were washed with brine (3 mL) then dried and concentrated *in vacuo* to give starting material **117** and 1-phenylethanol.

Di-*tert*-butyl (2*R*,5*R*,α*S*)-[(*N*-α-methylbenzyl)pyrrolidine-2,5-diyl]diacetate 115

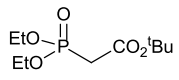


Method A: (1-bromoethyl)benzene **118** (0.02 mL, 0.17 mmol) was added to a stirred solution of **117** (100 mg, 0.33 mmol, >99:1 dr) in DMF (1 mL) at rt and the resultant solution was stirred at 80 °C for 16 h then cooled to rt. The reaction mixture was diluted with EtOAc (2 mL) then washed sequentially with H_2O (2 mL) and brine (2 mL). The organic extract was then dried and concentrated *in vacuo* to give starting material only.

Method B: A mixture of **117** (100 mg, 0.33 mmol, >99:1 dr) and **118** (0.55 mL, 3.30 mmol) was heated at 50 °C for 16 h, then allowed to cool to rt and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **101** as a colourless oil (28 mg, 21%, >99:1 dr). Further elution gave **115** as a colourless oil (17 mg, 13%, >99:1 dr); $[\alpha]_D^{25}$ +4.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2977 (C–H), 1730 (C=O), 1149 (C–O); δ_H (400 MHz, $CDCl_3$) 1.31 (18H, s, C*Me*$_3$), 1.38 (3H, d, *J* 6.5, C(α)*Me*), 1.45-1.52 (2H, m, C(3)H_A, C(4)H_A), 1.74-1.82 (2H, m, C(3)H_B, C(4)H_B), 1.90-2.02 (4H, m, 2 × CH_2CO_2^{t}Bu), 3.31-3.38 (2H, m, C(2)*H*, C(5)*H*), 3.63 (1H, q, *J* 6.5, C(α)*H*), 7.14-7.29 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(α)*Me*), 28.1 (2 × C*Me*$_3$), 28.5 (*C*(3), *C*(4)), 57.4 (*C*(2), *C*(5)), 58.5 (*C*(α)), 80.1 (2 × *C*Me$_3$), 127.3 (*p-Ph*), 128.1, 128.3, (*o,m-Ph*), 145.1 (*i-Ph*), 147.7 (2 × *C*O_2^{t}Bu)); *m/z* (ESI$^+$) 404 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{38}NO_4^+$ [M+H]$^+$ requires 404.2795; found 404.2799.

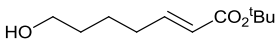
5.3 Chapter 3 Experimental

tert-Butyl (diethylphosphono)acetate 124



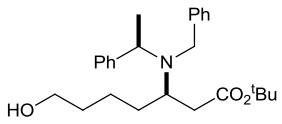
tert-Butyl bromoacetate (37.9 mL, 256 mmol) was added to $P(OEt)_3$ (44.0 mL, 256 mmol) at rt and the resultant mixture was stirred at rt for 16 h, then heated at 35 °C for 16 h, then concentrated *in vacuo* to give **124** as a colourless oil (64.0 g, quant);[11] δ_H (400 MHz, $CDCl_3$) 1.32 (6H, t, *J* 7.1, $P(OCH_2CH_3)_2$), 1.44 (9H, s, CMe_3), 2.85 (2H, d, *J* 21.5, PCH_2), 4.09-4.18 (4H, m, $P(OCH_2CH_3)_2$).

tert-Butyl (*E*)-7-hydroxyhept-2-enoate 125



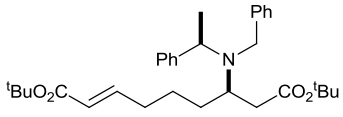
BuLi (2.5 M in hexanes, 8.90 mL, 20.0 mmol) was added dropwise to a stirred solution of **124** (5.54 g, 20.0 mmol) in THF (15 mL) at −78 ºC. The resultant solution was stirred for 30 min at −78 °C and then a solution of δ-valerolactone **118** (1.85 mL, 20.0 mmol) in THF (5 mL) at −78 °C and DIBAL-H (1.0 M in PhMe, 20.0 mL, 20.0 mmol) were added sequentially. The resultant mixture was allowed to warm to rt over 16 h, then satd aq sodium potassium tartrate (50 mL) was added, and the resultant mixture was allowed to stir at rt for a further 1 h. The mixture was then partitioned between EtOAc (200 mL) and 0.5 M aq HCl (100 mL). The organic layer was washed with satd aq K_2CO_3 (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give **125** in 97:3 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:2) gave **125** as a yellow oil (2.50 g, 63%, >99:1 dr);[12] δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, CMe_3), 1.50-1.63 (4H, m, C(5)H_2, C(6)H_2), 2.15 (1H, br s, O*H*), 2.17-2.23 (2H, app dq, *J* 7.0, 1.5, C(4)H_2), 3.63 (2H, t, *J* 6.1, C(7)H_2), 5.74 (1H, d, *J* 15.8, C(2)*H*), 6.84 (1H, dt, *J* 15.8, 7.0, C(3)*H*).

tert-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-hydroxyheptanoate 122



BuLi (2.5 M in hexanes, 15.0 mL, 37.5 mmol) was added dropwise via syringe to a stirred solution of **110** (7.95 g, 37.5 mmol) in THF (50 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. A solution of **125** (2.50 g, 12.5 mmol) in THF (25 mL) at −78 °C was added dropwise via cannula, and the resultant solution was stirred at −78 °C for a further 2 h. Satd aq NH_4Cl (30 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **122** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 10:1) gave **122** as a yellow oil (4.90 g, 95%, >99:1 dr);[9] $[\alpha]_D^{25}$ +11.2 (*c* 1.0 in $CHCl_3$); {lit.[9] for enantiomer $[\alpha]_D^{25}$ −12.8 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 7.0, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 1.47-1.56 (4H, m, C(5)*H*$_2$, C(6)*H*$_2$), 1.57-1.73 (2H, m, C(4)*H*$_2$), 1.91 (1H, dd, *J* 14.7, 9.5, C(2)*H*$_A$), 2.00 (1H, dd, *J* 14.7, 3.4, C(2)*H*$_B$), 3.30-3.37 (1H, m, C(3)*H*), 3.52 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ph), 3.61-3.66 (2H, m, C(7)*H*$_2$), 3.82 (1H, d, *J* 15.2, NCH$_A$*H*$_B$Ph), 3.84 (1H, q, *J* 7.0, C(α)*H*), 7.25-7.48 (10H, m, *Ph*).

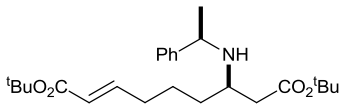
Di-_tert_-butyl (*R*,*R*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-non-7-enedioate 127



DMSO (3.40 mL, 47.6 mmol) was added dropwise to a stirred solution of oxalyl chloride (2.00 mL, 23.8 mmol) in CH_2Cl_2 (125 mL) at −78 °C and the resultant solution was stirred at −78 °C for 20 min. A solution of **122** (4.90 g, 11.9 mmol, >99:1 dr) in CH_2Cl_2 (125 mL) was added dropwise via cannula, and the resultant solution was stirred at −78 °C for 20 min. Et_3N (9.90 mL, 71.4 mmol) was added dropwise via syringe and the resultant solution was stirred at −78 °C for 30 min then allowed to warm to rt. **91** (4.47 g, 11.9 mmol) was added portionwise and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was triturated with Et_2O (50 mL) and filtered. The filtrate was washed sequentially with satd aq $NaHCO_3$ (40 mL) and brine (40 mL), then concentrated *in vacuo* to give **127** in 95:5 dr. Purification via flash column chromatography (eluent 30-40 °C

petrol/Et_2O, 10:1) gave **127** as a colourless oil (2.00 g, 33%, >99:1 dr); $[\alpha]_D^{25}$ +0.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1714 (C=O), 1652 (C=C), 1145 (C–O); δ_H (400 MHz, $CDCl_3$) 1.29-1.35 (3H, m, C(4)H_A, C(5)H_2), 1.36 (3H, d, *J* 7.0, C(α)*Me*), 1.42 (9H, s, CMe_3), 1.47-1.50 (1H, m, C(4)H_B), 1.52 (9H, s, CMe_3), 1.89 (1H, dd, *J* 14.7, 9.6, C(2)H_A), 1.98 (1H, dd, *J* 14.7, 3.1, C(2)H_B), 2.07-2.15 (2H, m, C(6)H_2), 3.30-3.37 (1H, m, C(3)*H*), 3.51 (1H, d, *J* 15.0, CH_AH$_B$Ph), 3.82 (1H, d, *J* 15.0, CH$_A$$H_B$Ph), 3.84 (1H, q, *J* 7.0, C(α)*H*), 5.76 (1H, d, *J* 15.6, C(8)*H*), 6.88 (1H, dt, *J* 15.6, 6.9, C(7)*H*), 7.25-7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.7 (C(α)*Me*), 25.4 (*C*(5)), 28.1, 28.2 (2 × CMe_3), 31.9 (*C*(4)), 33.0 (*C*(6)), 37.5 (*C*(2)), 50.1 (*C*H_2Ph), 53.5 (*C*(3)), 58.4 (*C*(α)), 80.0, 80.1 (2 × *C*Me_3), 123.1 (*C*(8)), 126.7, 127.1 (2 × *p-Ph*), 127.9, 128.1, 128.2, 128.4 (2 × *o,m-Ph*), 141.8, 142.9 (2 × *i-Ph*), 148.0 (*C*(7)), 166.2, 172.1 (*C*(1), *C*(9)); *m/z* (ESI^+) 508 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{46}NO_4^+$ $[M+H]^+$ requires 508.3421; found 508.3420.

Di-*tert*-butyl (*R,R,E*)-3-[*N*-(α-methylbenzyl)amino]-non-7-enedioate 123



CAN (4.50 g, 8.30 mmol) was added to a stirred solution of **127** (2.00 g, 3.90 mmol, >99:1 dr) in MeCN/H_2O (48 mL, v/v 5:1) at rt and the resultant mixture was stirred at rt for 2 h. Satd aq $NaHCO_3$ (30 mL) was then added and the resultant mixture stirred for 30 min at rt. The aqueous layer was then extracted with EtOAc (2 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **123** as a colourless oil (1.20 g, 73%, >99:1 dr); $[\alpha]_D^{25}$ +7.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2976 (C–H), 1713 (C=O), 1652 (C=C), 1150 (C–O); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.4, C(α)*Me*), 1.36-1.45 (4H, m, C(4)H_2, C(5)H_2), 1.47 (9H, s, CMe_3), 1.50 (9H, s, CMe_3), 2.00-2.06 (2H, m, C(6)H_2), 2.30 (1H, dd, *J* 14.3, 5.1, C(2)H_A), 2.39 (1H, dd, *J* 14.3, 5.8, C(2)H_B), 2.66-2.74 (1H, m, C(3)*H*), 3.91 (1H, q, *J* 6.4, C(α)*H*), 5.69 (1H, d, *J* 15.6, C(8)*H*), 6.80 (1H, dt, *J* 15.6, 6.8, C(7)*H*), 7.22-7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.4 (C(α)*Me*), 25.1 (*C*(5)), 28.2 (2 × CMe_3), 31.9 (*C*(4)), 34.8 (*C*(6)), 39.4 (*C*(2)), 51.9 (*C*(3)), 55.1 (*C*(α)), 80.0, 80.4 (2 × *C*Me_3), 123.1 (*C*(8)), 126.8 (*p-Ph*), 126.9, 128.4, (*o,m-Ph*), 145.9 (*i-Ph*), 147.7 (*C*(7)), 166.1, 171.7 (*C*(1), *C*(9)); *m/z* (ESI^+) 418 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{40}NO_4^+$ $[M+H]^+$ requires 418.2952; found 418.2955.

Attempts at intramolecular aza-Michael of 123

Method A: Et_3N (0.03 mL, 0.24 mmol) was added to a stirred solution of **123** (100 mg, 0.24 mmol) in EtOH (2 mL) and the resultant solution was heated at reflux for 16 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in Et_2O (2 mL) and washed with H_2O (1 mL), then dried and concentrated *in vacuo* to give starting material **123** only.

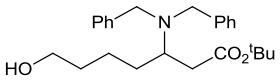
Method B: Et_3N (0.03 mL, 0.24 mmol) was added to a stirred solution of **123** (100 mg, 0.24 mmol) in PhMe (2 mL) and the resultant solution was heated at reflux for 16 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in Et_2O (2 mL) and washed with H_2O (1 mL), then dried and concentrated *in vacuo* to give starting material **123** only.

Method C: BuLi (2.5 M in hexanes, 0.10 mL, 0.24 mmol) was added dropwise via syringe to a stirred solution of **123** (100 mg, 0.24 mmol) in THF (2 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 4 h. Satd aq NH_4Cl (2 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo* to give starting material **123** only.

Method D: NaH (60% dispersion in mineral oil, 10 mg, 0.24 mmol) was added to a stirred solution of **123** (100 mg, 0.24 mmol) in PhMe (2 mL) and the resultant solution was heated at reflux for 16 h, then allowed to cool to rt. Satd aq NH_4Cl (2 mL) was then added and the layers were separated. The organic layer was dried and concentrated *in vacuo* to give starting material **123** only.

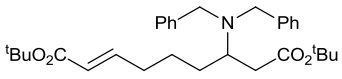
Method E: MeMgBr (3 M in Et_2O, 0.08 mL, 0.24 mmol) was added dropwise via syringe to a stirred solution of **123** (100 mg, 0.24 mmol) in THF (2 mL) at 0 °C, and the resultant solution was allowed to warm to rt and then stirred for 4 h. MeOH (2 mL) was then added dropwise via syringe and the resultant solution was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with brine (5 mL), then dried and concentrated *in vacuo* to give starting material **123** only.

tert-Butyl (*RS*)-3-(*N*,*N*-dibenzylamino)-7-hydroxyheptanoate 128



BuLi (2.5 M in hexanes, 12.0 mL, 30.0 mmol) was added dropwise via syringe to a stirred solution of dibenzylamine (5.76 mL, 30.0 mmol) in THF (20 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. A solution of **125** (2.00 g, 10.0 mmol) in THF (10 mL) at −78 °C was added dropwise via cannula, and the resultant solution was stirred at −78 °C for a further 2 h. Satd aq NH_4Cl (20 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (50 mL), satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 1:1) gave **128** as a colourless oil (2.00 g, 50%); ν_{max} (film) 2933 (C–H), 1721 (C=O), 1149 (C–O); δ_H (400 MHz, $CDCl_3$) 1.31-1.41 (4H, m, C(5)H_2, C(6)H_2), 1.47 (9H, s, CMe_3), 1.62-1.72 (2H, m, C(4)H_2), 2.15 (1H, dd, *J* 13.7, 8.9, C(2)H_A), 2.69 (1H, dd, *J* 13.7, 4.6, C(2)H_B), 3.06-3.14 (1H, m, C(3)*H*), 3.41 (2H, d, *J* 13.4, N(CH_AH_BPh)$_2$), 3.57-3.58 (2H, m, C(7)H_2), 3.73 (2H, d, *J* 13.4, N(CH_AH_BPh)$_2$), 7.23-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.4 (*C*(5)), 28.1 (CMe_3), 31.0 (*C*(4)), 32.3 (*C*(6)), 36.0 (*C*(2)), 53.6 (N(*C*H$_2$Ph)$_2$), 55.0 (*C*(3)), 62.9 (*C*(7)), 80.3 (*C*Me$_3$), 126.9 (*p-Ph*), 128.2, 129.1, (*o,m-Ph*), 140.0 (*i-Ph*), 172.5 (*C*(1)); *m/z* (ESI$^+$) 398 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{36}NO_3^+$ [M+H]$^+$ requires 398.2690; found 398.2695.

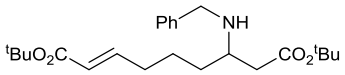
Di-_tert_-butyl (*RS*,*E*)-3-(*N*,*N*-dibenzylamino)non-7-enedioate 129



DMSO (1.42 mL, 20.0 mmol) was added to a stirred solution of oxalyl chloride (0.85 mL, 10.0 mmol) in CH_2Cl_2 (60 mL) at −78 °C and the resultant solution was stirred at −78 °C for 20 min. A solution of **128** (2.00 g, 5.0 mmol) in CH_2Cl_2 (60 mL) was added dropwise via cannula, and the resultant solution was stirred at −78 °C for 20 min. Triethylamine (4.20 mL, 30.0 mmol) was added dropwise via syringe and the resultant solution was stirred at −78 °C for 30 min then allowed to warm to rt. **91** (1.90 g, 5 mmol) was added portionwise and the resultant solution was stirred at rt for 16 h then concentrated *in vacuo*. The residue was

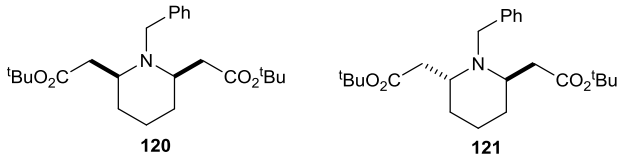
triturated with Et_2O (30 mL) and filtered. The filtrate was washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **129** as a colourless oil (1.60 g, 65%); ν_{max} (film) 2977 (C–H), 1714 (C=O), 1147 (C–O); δ_H (400 MHz, $CDCl_3$) 1.28-1.38 (2H, m, C(5)H_2), 1.46 (9H, s, CMe_3), 1.52 (9H, s, CMe_3), 1.58-1.72 (2H, m, C(4)H_2), 1.90-1.99 (2H, m, C(6)H_2), 2.13 (1H, dd, *J* 13.4, 9.0, C(2)H_A), 2.71 (1H, dd, *J* 13.4, 4.5, C(2)H_B), 3.05-3.14 (1H, m, C(3)*H*), 3.39 (1H, d, *J* 13.6, CH_AH$_B$Ph), 3.74 (1H, d, *J* 13.6, CH$_A$$H_B$Ph), 5.67 (1H, d, *J* 15.8, C(8)*H*), 6.80 (1H, dt, *J* 15.8, 7.0, C(7)*H*), 7.24-7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.8 (*C*(5)), 28.1, 28.2 (2 × CMe_3), 30.0 (*C*(4)), 31.5 (*C*(6)), 35.7 (*C*(2)), 53.5 (2 × *C*H$_2$Ph), 54.7 (*C*(3)), 80.0, 80.3 (2 × *C*Me$_3$), 123.1 (*C*(8)), 127.0 (2 × *p-Ph*), 128.2, 129.1 (2 × *o,m-Ph*), 139.8 (2 × *i-Ph*), 147.9 (*C*(7)), 166.2, 172.3 (*C*(1), *C*(9)); *m/z* (ESI^+) 494 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{44}NO_4^+$ $[M+H]^+$ requires 494.365; found 494.3259.

Di-*tert*-butyl (*RS,E*)-3-(*N*-benzylamino)non-7-enedioate 119



CAN (3.50 g, 6.40 mmol) was added to a stirred solution of **129** (1.50 g, 3.00 mmol, >99:1 dr) in MeCN/H_2O (36 mL, v/v 5:1) at rt and the resultant mixture was stirred at rt for 2 h. Satd aq $NaHCO_3$ (30 mL) was then added and the resultant mixture stirred at rt for 30 min. The aqueous layer was then extracted with EtOAc (2 × 75 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **119** as a colourless oil (200 mg, 21%); ν_{max} (film) 2974 (C–H), 1715 (C=O), 1148 (C–O); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, CMe_3), 1.40 (9H, s, CMe_3), 1.41-1.50 (4H, m, C(4)H_2, C(5)H_2), 2.05-2.12 (2H, m, C(6)H_2), 2.28-2.32 (2H, m, C(2)H_2), 2.87-2.94 (1H, m, C(3)*H*), 3.70 (2H, ABq, NCH_2Ph), 5.65 (1H, d, *J* 15.6, C(8)*H*), 6.76 (1H, dt, *J* 15.6, 7.0, C(7)*H*), 7.13-7.28 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.9 (*C*(5)), 28.1, 28.2 (2 × CMe_3), 29.9 (*C*(4)), 32.1 (*C*(6)), 36.3 (*C*(2)), 52.9 (*C*H$_2$Ph), 54.4 (*C*(3)), 80.1, 80.2 (2 × *C*Me$_3$), 123.1 (*C*(8)), 126.9 (*p-Ph*), 128.3, 128.9 (*o,m-Ph*), 141.2 (*i-Ph*), 147.8 (*C*(7)), 166.3, 172.1 (*C*(1), *C*(9)); *m/z* (ESI^+) 404 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{38}NO_4^+$ $[M+H]^+$ requires 404.2795; found 404.2789.

(*R*,*R*,*R*) and (2*R*,5*S*,*αR*)-*N*-(1)-benzyl-2,5-bis-(2′-*tert*-butoxy-2′-oxoethyl)piperidine 120 and 121



Method A: Et_3N (0.03 mL, 0.25 mmol) was added to a stirred solution of **119** (100 mg, 0.25 mmol) in EtOH (1 mL) and the resultant solution was heated at reflux for 16 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in Et_2O (5 mL) and washed with H_2O (5 mL), then dried and concentrated *in vacuo* to give a 33:67 mixture of **120** and **121**, respectively. Data for **121**: δ_H (400 MHz, $CDCl_3$) 1.33 (9H, s, 2 × C*Me*$_3$), 1.35-1.38 (2H, m, C(4)*H*$_2$), 1.54-1.59 (4H, m, C(3)*H*$_2$, C(5)*H*$_2$), 2.24 (2H, dd, *J* 14.3, 8.5, 2 × C*H*$_A$H$_B$CO$_2$^{t}Bu), 2.42 (2H, dd, *J* 14.3, 5.2, 2 × CH$_A$*H*$_B$CO$_2$^{t}Bu), 3.10-3.18 (2H, m, C(2)*H*, C(6)*H*), 3.67 (2H, ABq *J* 15.3, C*H*$_2$Ph), 7.09-7.27 (5H, m, Ph).

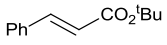
Method B: BuLi (2.5 M in hexanes, 0.10 mL, 0.25 mmol) was added dropwise via syringe to a stirred solution of **119** (100 mg, 0.25 mmol) in THF (1 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (1 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 40:60 mixture of **120** and **121**, respectively.

Method C: MeMgBr (3 M in Et_2O, 0.08 mL, 0.25 mmol) was added dropwise via syringe to a stirred solution of **119** (100 mg, 0.25 mmol) in THF (1 mL) at 0 °C, and the resultant mixture was allowed to warm to rt then stirred for 4 h. MeOH (1 mL) was then added dropwise via syringe and the resultant solution was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL), washed with brine (5 mL), then dried and concentrated *in vacuo* to give a 34:64 mixture of **120** and **121**, respectively.

Method D: **119** (100 mg, 0.25 mmol) was added to MeOH (1 mL) and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo* give a 64:36 mixture of **120** and **121**, respectively. Data for **120**: δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, 2 × C*Me*$_3$), 1.34-1.41 (2H, m, C(4)*H*$_2$), 1.53-1.59 (4H, m, C(3)*H*$_2$, C(5)*H*$_2$), 2.00 (2H, dd, *J* 14.4, 9.9, 2 × C*H*$_A$H$_B$CO$_2$^{t}Bu),

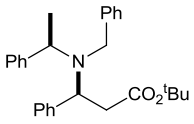
2.39 (2H, dd, *J* 14.4, 3.4, 2 × $CH_AH_BCO_2{}^tBu$), 3.02-3.09 (2H, m, C(2)*H*, C(6)*H*), 3.41 (2H, s, CH_2Ph), 7.11-7.30 (5H, m, Ph).

tert-Butyl cinnamate 133



MeMgBr (3.0 M in Et_2O, 27.0 mL, 81.0 mmol) was added dropwise via syringe to a stirred solution of **124** (20.0 g, 80.0 mmol) in THF (200 mL) at rt and the resultant solution was stirred at rt for 15 min. A solution of benzaldehyde (8.90 mL, 88.0 mmol) in THF (50 mL) was added via cannula and the resultant mixture was heated at 67 °C for 16 h and then allowed to cool to rt. Satd aq NH_4Cl (300 mL) was added and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (400 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 20:1) gave **133** as pale yellow oil (8.55 g, 54%, >99:1 dr);[13] δ_H (400 MHz, $CDCl_3$) 1.55 (9H, s, C*Me*$_3$), 6.38 (1H, d, *J* 16.0, C(2)*H*), 7.36-7.41 (3H, m, *Ph*), 7.49-7.54 (2H, m, *Ph*), 7.60 (1H, d, *J* 16.0, C(3)*H*).

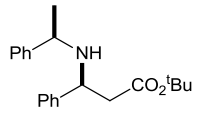
tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 134



BuLi (2.5 M in hexanes, 25.0 mL, 62.5 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**110** (13.2 g, 62.0 mmol) in THF (100 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. A solution of **133** (8.00 g, 39.0 mmol) in THF (50 mL) at −78 °C was added dropwise via cannula, and the resultant solution was stirred at −78 °C for a further 2 h. Satd aq NH_4Cl (50 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give **134** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **134** as a colourless oil (13.4 g, 82%, >99:1 dr);[14] $[\alpha]_D^{20}$ +5.7 (*c* 1.0 in $CHCl_3$); {lit.[14] $[\alpha]_D^{23}$ +4.1 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, C*Me*$_3$), 1.27 (3H, d, *J*

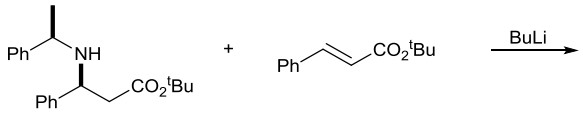
6.8, C(α)*Me*), 2.46-2.58 (2H, m, C(2)H_2), 3.69 (2H, ABq, *J* 14.9, NCH_2Ph), 4.00 (1H, q, *J* 6.8, C(α)*H*), 4.40 (1H, dd, *J* 9.9, 5.3, C(3)*H*), 7.15-7.45 (15H, m, *Ph*).

***tert*-Butyl (3*S*,α*R*)-3-[*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 135**



CAN (8.34 g, 15.2 mmol) was added to a stirred solution of **134** (3.00 g, 7.20 mmol, >99:1 dr) in MeCN/H_2O (90 mL, v/v 5:1) at rt and the resultant mixture was stirred at rt for 2 h. Satd aq $NaHCO_3$ (75 mL) was then added and the resultant mixture stirred for 30 min at rt. The aqueous layer was then extracted with EtOAc (2 × 75 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **135** as a colourless oil (1.20 g, 51%, >99:1 dr);[15] $[\alpha]_D^{20}$ +14.7 (*c* 1.0 in $CHCl_3$); {lit.[15] for enantiomer $[\alpha]_D^{22}$ −15.8 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.5, C(α)*Me*), 1.29 (9H, s, CMe_3), 1.81 (1H, br s, N*H*), 2.48 (1H, dd, *J* 14.7, 6.4, C(2)H_A), 2.56 (1H, dd, *J* 14.7, 7.9, C(2)H_B), 3.58 (1H, q, *J* 6.5, C(α)*H*), 4.08 (1H, dd, *J* 7.9, 6.4, C(3)*H*), 7.09-7.31 (10H, m, *Ph*).

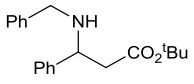
Attempted Intermolecular Conjugate Addition of 135 and 133



135 **133**

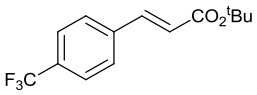
133 (100 mg, 0.49 mmol) was added to a stirred solution of **135** (254 mg, 0.61 mmol) in THF (3 mL) and the resultant solution cooled to −78 °C. ^{s}BuLi (1.4 M in cyclohexane, 0.44 ml, 0.61 mmol) was added dropwise via syringe and the resultant solution stirred at −78 °C for 2 h. Satd aq NH_4Cl (3 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give starting material only.

tert-Butyl (*RS*)-3-[*N*-(benzylamino)]-3-phenylpropanoate 136



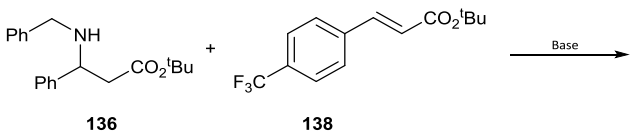
BuLi (2.5 M in hexanes, 50.0 mL, 125 mmol) was added dropwise via syringe to a stirred solution of benzylamine (13.6 mL, 125 mmol) in THF (150 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. A solution of **133** (15.0 g, 74.0 mmol) in THF (50 mL) at −78 °C was added dropwise via cannula, and the reaction mixture was stirred at −78 °C for a further 2 h. Satd aq NH_4Cl (100 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **136** as a yellow oil (12.0 g, 54%);[16] δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 2.15 (1H, br s, N*H*), 2.57 (1H, dd, *J* 15.2, 6.4, C(2)*H*$_A$), 2.68 (1H, dd, *J* 15.2, 8.7, C(2)*H*$_B$), 3.57 (1H, d, *J* 13.1, NC*H*$_A$H$_B$Ph), 3.67 (1H, d, *J* 13.1, NCH$_A$*H*$_B$Ph), 4.08 (1H, dd, *J* 8.7, 6.4, C(3)*H*), 7.22-7.42 (10H, m, *Ph*).

tert-Butyl (*E*)-4-(trifluoromethyl)phenylpropan-2-oate 138



MeMgBr (3.0 M in Et_2O, 3.48 mL, 10.4 mmol) was added dropwise via syringe to a stirred solution of **124** (2.63 g, 10.5 mmol) in THF (25 mL) at rt and the resultant mixture was stirred at rt for 15 min. A solution of **137** (1.57 mL, 11.5 mmol) in THF (5 mL) was added via cannula and the resultant mixture was heated at 67 °C for 16 h and then allowed to cool to rt. Satd aq NH_4Cl (30 mL) was then added and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 10:1) gave **138** as a colourless oil (1.70 g, 60%, >99:1 dr);[17] δ_H (400 MHz, $CDCl_3$) 1.55 (9H, s, C*Me*$_3$), 6.46 (1H, d, *J* 16.1, C(2)*H*), 7.58-7.67 (5H, m, C(3)*H*, *Ph*).

Attempted Intermolecular Conjugate Addition of 136 and 138



Method A: **138** (250 mg, 0.90 mmol) was added to a stirred solution of **136** (457 mg, 1.50 mmol) in THF (5 mL) and the resultant solution was cooled to −78 °C. ^{s}BuLi (1.4 M in cyclohexane, 1.05 mL, 1.50 mmol) was added dropwise via syringe and the resultant solution stirred at −78 °C for 2 h. Satd aq NH_4Cl (5 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give starting material only.

Method B: **138** (250 mg, 0.90 mmol) was added to a stirred solution of **136** (457 mg, 1.50 mmol) in THF (5 mL) and the resultant solution was cooled to −78 °C. ^{s}BuLi (1.4 M in cyclohexane, 1.05 mL, 1.50 mmol) was added dropwise via syringe and the resultant solution was warmed to −40 °C and stirred at −40 °C for 2 h. Satd aq NH_4Cl (5 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give starting material only.

Method C: **138** (200 mg, 0.74 mmol) was added to a stirred solution of **136** (366 mg, 1.20 mmol) and 12-crown-4 (0.12 mL, 1.20 mmol) in THF (5 mL) and the resultant solution was cooled to −78 °C. ^{s}BuLi (1.4 M in cyclohexane, 0.84 mL, 1.20 mmol) was added dropwise via syringe and the resultant solution stirred at −78 °C for 2 h. Satd aq NH_4Cl (5 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give starting material only.

Method D: **138** (109 mg, 0.40 mmol) was added to a stirred solution of **136** (200 mg, 0.64 mmol) and LiCl (33 mg, 0.80 mmol) in THF (5 mL) and the resultant mixture was cooled to −78 °C. ^{s}BuLi (1.4 M in cyclohexane, 0.46 mL, 0.64 mmol) was added dropwise via syringe and the resultant mixture stirred at −78 °C for 2 h. Satd aq NH_4Cl (5 mL) was then added and

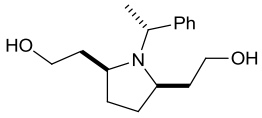
the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give starting material only.

Method E: **138** (200 mg, 0.74 mmol) was added to a stirred solution of **136** (366 mg, 1.18 mmol) in Et_2O (5 mL) and the resultant solution was cooled to −20 °C. ^{s}BuLi (1.4 M in cyclohexane, 0.84 mL, 1.18 mmol) was added dropwise via syringe and the resultant solution stirred at −20 °C for 2 h. Satd aq NH_4Cl (5 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give a 39:52:9 mixture of **138**:**136**:**139**, respectively. Data for **139**: δ_H (400 MHz, $CDCl_3$) 2.90 (1H, dd, *J* 14.7, 2.2, C(3)H_AH_B), 3.36 (1H, dd, *J* 14.7, 5.2, C(3)H_AH_B), 3.77 (1H, d, *J* 14.9, NCH_AH_BPh), 4.41 (1H, dd, *J* 5.2, 2.2, C(4)*H*), 4.82 (1H, d, *J* 14.9, NCH_ACH_BPh), 7.12-7.41 (10H, m, *Ph*).

Method F: **138** (60 mg, 0.22 mmol) was added to a stirred solution of **136** (110 mg, 0.35 mmol) in THF (2 mL) and the resultant solution was cooled to −78 °C. MeMgBr (3.0 M in Et_2O, 0.12 mL, 0.35 mmol) was added dropwise via syringe and the resultant solution stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were washed with brine (5 mL), then dried and concentrated *in vacuo* to give starting material only.

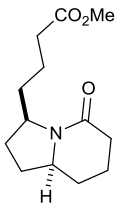
5.4 Chapter 4 Experimental

(2*R*,5*S*,*αR*)-*N*-(1)-(α-methylbenzyl)-2,5-bis-(2′-hydroxyethyl)pyrrolidine 150



$LiAlH_4$ (1.0 M in THF, 6.90 mL, 6.90 mmol) was added dropwise via syringe to a stirred solution of **100** (700 mg, 1.70 mmol, >99:1 dr) in THF (7 mL) at −78 °C and the resultant solution was allowed to warm to rt over 16 h. 1 M aq NaOH (1 mL) was then added and the resultant suspension was refluxed for 1 h. The mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo* to give **150** as a colourless oil (395 mg, 87%, >99:1 dr); $[\alpha]_D^{25}$ −5.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3323 (O–H), 2937 (C–H), 2871 (C–H), 1054 (C–N); δ_H (400 MHz, $CDCl_3$) 1.52 (3H, d, *J* 6.9, C(α)*Me*), 1.55-1.90 (8H, m, C(3)H_2, C(4)H_2, 2 × C(1′)H_2), 3.28-3.38 (2H, m, C(2)*H*, C(5)*H*), 3.56-3.64 (2H, m, 2 × C(2′)H_A), 3.67-3.78 (2H, m, 2 × C(2′)H_B), 3.95 (1H, q, *J* 6.9, C(α)*H*), 7.26-7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4 (C(α)*Me*), 29.6, 30.2 (*C*(3), *C*(4)), 37.0, 37.5 (*C*(1′)), 59.8, 60.1 (*C*(2), *C*(5)), 60.8, 60.9 (*C*(2′)), 61.3 (*C*(α)), 127.5 (*p-Ph*), 128.4, 128.9 (*o,m-Ph*), 142.8 (*i-Ph*); *m/z* (ESI^+) 264 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{26}NO_2^+$ ($[M+H]^+$) requires 264.1964; found 264.1973.

(*RS*,*RS*)-3-(4′-methoxy-4′-oxobutyl)-5-oxo-indolizidine 140



Method A: DMSO (0.22 mL, 3.05 mmol) was added dropwise via syringe to a stirred solution of oxalyl chloride (0.13 mL, 1.50 mmol) in CH_2Cl_2 (1 mL) at −78 °C and the resultant solution was stirred at −78 °C for 20 min. A solution of **150** (100 mg, 0.38 mmol, >99:1 dr) in CH_2Cl_2 (1 mL) was added dropwise via syringe, and the resultant solution was stirred at −78 °C for 20 min. Et_3N (0.64 mL, 4.55 mmol) was added dropwise via syringe and the resultant solution was stirred at −78 °C for 30 min then allowed to warm to rt. **92** (254 mg, 0.75 mmol) was added and the resultant solution stirred at rt for 16 h then concentrated *in vacuo*. The

residue was passed through a short plug of silica (eluent 30-40 °C petrol/Et_2O, 1:1) and the filtrate concentrated *in vacuo* to give **152** (125 mg).

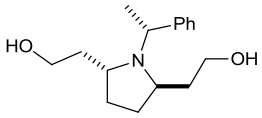
152 (125 mg) was dissolved in MeOH (1 mL) and Pd/C (25 mg, 20 wt%) was added. The resultant suspension was stirred at rt for 4 h under H_2 (balloon). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to give **153** as a colourless oil (112 mg, 79%, >99:1 dr). Data for **153**: δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 7.0, C(α)*Me*), 1.42-1.78 (12H, m, C(3)H_2, C(4)H_2, 2 × C(1')H_2, 2 × C(2')H_2), 2.13-2.18 (2H, m, 2 × C(3')H_A), 2.24-2.30 (2H, m, 2 × C(3')H_B), 2.86-2.93 (1H, m, C(2)*H*), 2.94-3.00 (1H, m, C(5)*H*), 3.65 (3H, s, O*Me*), 3.68 (3H, s, O*Me*), 3.92 (1H, q, *J* 7.0, C(α)*H*), 7.27-7.38 (5H, m, *Ph*).

153 (112 mg, 0.30 mmol) was dissolved in MeOH (1 mL) and $Pd(OH)_2$/C (22.4 mg, 20 wt%) was added. The resultant suspension was stirred at rt for 24 h under H_2 (5 atm). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave **140** as a colourless oil (53 mg, 58%, >99:1 dr); ν_{max} (film) 2949 (C–H), 1736 (C=O), 1634 (C=O), 1452 (C–H); δ_H (400 MHz, $CDCl_3$) 1.14-2.36 (16H, m, C(1)H_2, C(2)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(1′)H_2, C(2′)H_2, C(3′)H_2), 3.25-3.34 (1H, m, C(3)*H*), 3.59 (3H, s, O*Me*), 3.85-3.93 (1H, m, C(8a)*H*); δ_C (100 MHz, $CDCl_3$) 21.1, 21.9, 27.5, 29.2, 31.0, 31.4, 32.1, 33.8 (*C*(1), *C*(2), *C*(6), *C*(7), *C*(8), *C*(1′), *C*(2′), *C*(3′)), 51.5 (*C*(3)), 56.8 (*C*(8a)), 60.0 (O*Me*), 169.5 (*C*(5)), 174.0 (*C*(4′)); *m/z* (ESI^+) 240 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{22}NO_3^+$ ($[M+H]^+$) requires 240.1600; found 240.1598.

Method B: DMSO (0.22 mL, 3.05 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.13 mL, 1.50 mmol,) in CH_2Cl_2 (1 mL) at −78 °C and the resultant solution was stirred at −78 °C for 20 min. A solution of **150** (100 mg, 0.38 mmol, >99:1 dr) in CH_2Cl_2 (1 mL) was added dropwise via syringe, and the resultant solution was stirred at −78 °C for 20 min. Et_3N (0.64 mL, 4.55 mmol) was added dropwise via syringe and the resultant solution was stirred at −78 °C for 30 min then allowed to warm to rt. **92** (254 mg, 0.75 mmol) was added and the resultant solution stirred at rt for 16 h then concentrated *in vacuo*. The residue was passed through a short plug of silica (eluent 30-40 °C petrol/Et_2O, 1:1) and the filtrate concentrated *in vacuo* to give **152** (132 mg).

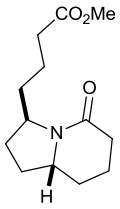
152 (132 mg) was dissolved in MeOH (1 mL) and $Pd(OH)_2/C$ (26 mg, 20 wt%) was added. The resultant suspension was stirred at rt for 24 h under H_2 (5 atm). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave **140** as a colourless oil (59 mg, 65%, >99:1 dr).

(*R*,*R*,*R*)-*N*-(1)-(α-methylbenzyl)-2,5-bis-(2′-hydroxyethyl)pyrrolidine 154



$LiAlH_4$ (1.0 M in THF, 10.0 mL, 10.0 mmol) was added dropwise via syringe to a stirred solution of **101** (1.00 g, 2.50 mmol, >99:1 dr) in THF (10 mL) at −78 °C and the resultant solution was allowed to warm to rt over 16 h. 1 M aq NaOH (1.5 mL) was then added and the resultant suspension was refluxed for 1 h. The mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo* to give **154** as a colourless oil (620 mg, 95%, >99:1 dr); $[\alpha]_D^{25}$ +8.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3341 (O–H), 2961 (C–H), 2874 (C–H), 1054 (C–N); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.7, C(α)*Me*), 1.50-1.57 (2H, m, C(3)H_A, C(4)H_A), 1.58-1.69 (4H, m, 2 × C(1′)H_2), 1.92-2.02 (2H, C(3)H_B, C(4)H_B), 3.13-3.22 (2H, m, C(2)*H*, C(5)*H*), 3.30-3.39 (2H, m, 2 × C(2′)H_A), 3.55-3.64 (2H, m, 2 × C(2′)H_B), 3.83 (1H, q, *J* 6.7, C(α)*H*), 7.09-7.26 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.2 (C(α)*Me*), 29.5 (*C*(3), *C*(4)), 33.0 (*C*(1′)), 58.9 (*C*(2), *C*(5)), 59.0 (*C*(2′)), 60.6 (*C*(α)), 126.9 (*p-Ph*), 127.1, 128.5 (*o,m-Ph*), 145.1 (*i-Ph*); *m/z* (ESI^+) 264 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{26}NO_2^+$ ($[M+H]^+$) requires 264.1964; found 264.1958.

(3*R*,8a*S*)- 3-(4′-methoxy-4′-oxobutyl)-5-oxo-indolizidine 141



Method A: DMSO (0.22 mL, 3.05 mmol) was added dropwise via syringe to a stirred solution of oxalyl chloride (0.13 mL, 1.50 mmol) in CH_2Cl_2 (1 mL) at −78 °C and the resultant

solution was stirred at −78 °C for 20 min. A solution of **154** (100 mg, 0.38 mmol, >99:1 dr) in CH_2Cl_2 (1 mL) was added dropwise via syringe, and the resultant solution was stirred at −78 °C for 20 min. Et_3N (0.64 mL, 4.55 mmol) was added dropwise via syringe and the resultant solution was stirred at −78 °C for 30 min then allowed to warm to rt. **92** (254 mg, 0.75 mmol) was added and the resultant solution stirred at rt for 16 h then concentrated *in vacuo*. The residue was passed through a short plug of silica (eluent 30-40 °C petrol/Et_2O, 1:1) and the filtrate concentrated *in vacuo*.

The residue (123 mg) was dissolved in MeOH (2 mL) and Pd/C (24 mg, 20 wt%) was added. The resultant suspension was stirred at rt for 4 h under H_2 (balloon). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to give a 80:20 mixture of **155:153**, respectively, as a colourless oil (108 mg, 76%). Data for **155**: δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.7, C(α)*Me*), 1.38-1.67 (12H, m, C(3)H_2, C(4)H_2, 2 × C(1')H_2, 2 × C(2')H_2), 2.13-2.33 (4H, m, 2 × C(3')H_2), 2.91-2.99 (2H, m, C(2)*H*, C(5)*H*), 3.66 (6H, s, 2 × O*Me*), 3.95 (1H, q, *J* 6.7, C(α)*H*), 7.27-7.39 (5H, m, *Ph*).

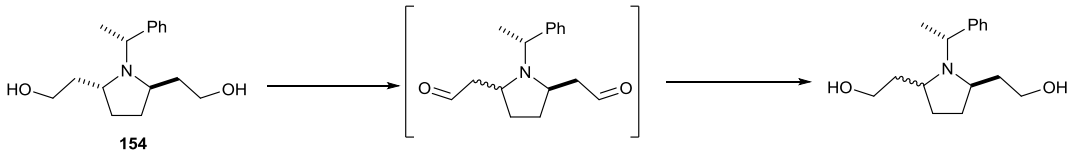
155 (108 mg, 0.29 mmol) was dissolved in MeOH (1 mL) and $Pd(OH)_2$/C (21 mg, 20 wt%) was added. The resultant suspension was stirred at rt for 24 h under H_2 (5 atm). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave a 78:22 mixture of **141:140**, respectively, as a colourless oil (52 mg, 57%). Data for **141**: δ_H (400 MHz, $CDCl_3$) 1.09-2.43 (16H, m, C(1)H_2, C(2)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(1′)H_2, C(2′)H_2), C(3′)H_2), 3.26-3.39 (1H, m, C(3)*H*), 3.59 (3H, s, O*Me*), 3.98-4.08 (1H, m, C(8a)*H*); δ_C (100 MHz, $CDCl_3$) 20.8, 20.9, 28.6, 29.4, 31.7, 33.0, 33.8, 33.9 (*C*(1), *C*(2), *C*(6), *C*(7), *C*(8), *C*(1′), *C*(2′), *C*(3′)), 51.5 (*C*(3)), 56.7 (*C*(8a)), 58.8 (O*Me*), 168.3 (*C*(5)), 174.0 (*C*(4′)).

Method B: DMSO (0.22 mL, 3.05 mmol) was added dropwise via syringe to a stirred solution of oxalyl chloride (0.13 mL, 1.50 mmol) in CH_2Cl_2 (4 mL) at −78 °C and the resultant solution was stirred at −78 °C for 20 min. A solution of **154** (100 mg, 0.38 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) was added dropwise via syringe, and the resultant solution was stirred at −78 °C for 20 min. Et_3N (0.64 mL, 4.55 mmol) was added dropwise via syringe and the resultant solution was stirred at −78 °C for 30 min then allowed to warm to rt. **92** (780 mg, 2.27 mmol) was added and the resultant solution stirred at rt for 16 h then concentrated *in vacuo*. The

residue was passed through a short plug of silica (eluent 1:1 petrol/Et_2O) and the filtrate concentrated *in vacuo*.

The residue (127 mg) was dissolved in MeOH (1 mL) and $Pd(OH)_2/C$ (25 mg, 20 wt%) was added. The resultant suspension was stirred at rt for 24 h under H_2 (5 atm). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave a 78:22 mixture of **141:140**, respectively, as a colourless oil (59 mg, 65%).

Oxidation-reduction experiments



Method A: DMSO (0.22 mL, 3.00 mmol) was added dropwise via syringe to a stirred solution of oxalyl chloride (0.13 mL, 1.50 mmol) in CH_2Cl_2 (5 mL) at −78 °C and the resultant solution was stirred at −78 °C for 20 min. A solution of **154** (100 mg, 0.38 mmol, >99:1 dr) in CH_2Cl_2 (5 mL) was added dropwise via syringe, and the resultant solution was stirred at −78 °C for 20 min. Et_3N (0.65 mL, 4.50 mmol) was added dropwise via syringe and the resultant solution was stirred at −78 °C for 30 min then allowed to warm to rt. Anhydrous Et_2O (3 mL) was added and the reaction mixture was then filtered and concentrated *in vacuo*. The residue was dissolved in EtOH (2 mL) at rt then cooled to 0 °C. $NaBH_4$ (29 mg, 0.76 mmol) was added and the resultant mixture was stirred for 3 h whilst warming to rt then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 80:20 mixture of **154**:**150**, respectively.

Method B: DMSO (0.22 mL, 3.00 mmol) was added dropwise via syringe to a stirred solution of oxalyl chloride (0.13 mL, 1.50 mmol) in CH_2Cl_2 (5 mL) at −78 °C and the resultant solution was stirred at −78 °C for 20 min. A solution of **154** (100 mg, 0.38 mmol, >99:1 dr) in CH_2Cl_2 (5 mL) was added dropwise via syringe, and the resultant solution was stirred at −78 °C for 16 h. Et_3N (0.65 mL, 4.50 mmol) was added dropwise via syringe and the resultant solution was stirred at −78 °C for 30 min then allowed to warm to rt. Anhydrous Et_2O (3 mL) was added and the reaction mixture was then filtered and concentrated *in vacuo*. The residue

was dissolved in EtOH (2 mL) at rt then cooled to 0 °C. $NaBH_4$ (29 mg, 0.76 mmol) was added and the resultant mixture was stirred for 3 h whilst warming to rt then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 82:18 mixture of **154**:**150**, respectively.

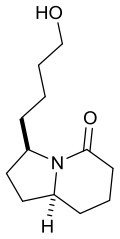
Method C: DMSO (0.22 mL, 3.00 mmol) was added dropwise via syringe to a stirred solution of oxalyl chloride (0.13 mL, 1.50 mmol) in CH_2Cl_2 (5 mL) at −78 °C and the resultant solution was stirred at −78 °C for 20 min. A solution of **154** (100 mg, 0.38 mmol, >99:1 dr) in CH_2Cl_2 (5 mL) was added dropwise via synringe, and the resultant solution was stirred at −78 °C for 20 mins. Triethylamine (0.65 mL, 4.50 mmol) was added dropwise via syringe and the resultant solution was stirred at −78 °C for 16 h then allowed to warm to rt. Anhydrous Et_2O (3 mL) was added and the reaction mixture was then filtered and concentrated *in vacuo*. The residue was dissolved in EtOH (2 mL) at rt then cooled to 0 °C. $NaBH_4$ (29 mg, 0.76 mmol) was added and the resultant mixture was stirred for 3 h whilst warming to rt then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 37:63 mixture of **154**:**150**, respectively.

Oxidation-olefination with 154 and 92 premixed

Method A: **154** (200 mg, 0.76 mmol, >99:1 dr) and **92** (508 mg, 1.50 mmol) were added to a stirred solution of PCC (492 mg, 2.28 mmol) and NaOAc (187 mg, 2.28 mmol) in CH_2Cl_2 (10 mL) at rt and the resultant solution was stirred at rt for 16 h. Et_2O (10 mL) was added and the reaction mixture was then filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. The residue was dissolved in degassed MeOH (2 mL). $Pd(OH)_2/C$ (30 mg) was added and the resultant mixture stirred under H_2 (balloon) at rt for 4 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to give a 67:33 mixture of **153**:**155**, respectively.

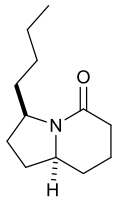
Method B: **92** (1.02 g, 3.1 mmol) was added to a stirred solution of **154** (200 mg, 0.76 mmol, >99:1 dr) and $PhCO_2H$ (371 mg, 3.1 mmol) in CH_2Cl_2:DMSO (7 mL, v/v 6:1) at rt. DMP (773 mg, 1.80 mmol) was added and the resultant mixture was stirred at rt for 90 mins. Satd aq $NaHCO_3$ (5 mL) was added, then Et_2O (3 mL) then solid $NaHCO_3$ (100 mg) and the resultant mixture stirred at rt for 20 min then filtered and the organic layer was dried and concentrated *in vacuo*. The residue was dissolved in degassed MeOH (2 mL). $Pd(OH)_2/C$ (30 mg) was added and the resultant mixture stirred under H_2 (balloon) at rt for 4 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to give a 59:41 mixture of **153**:**155**, respectively.

(*RS*,*RS*)-3-(4′-hydroxybutyl)-5-oxo-indolizidine 156



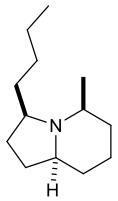
$LiBH_4$ (4.0 M in THF, 0.22 mL, 0.88 mmol) was added dropwise via syringe to a stirred solution of **140** (100 mg, 0.44 mmol, >99:1 dr) in THF (1 mL) at 0 °C and the resultant solution was allowed to warm to rt over 6 h. Satd aq NH_4Cl (1 mL) was then added followed by CH_2Cl_2 (3 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 3 mL) and the combined organic extracts were washed with brine (5 mL), dried and concentrated *in vacuo* to give **156** as a colourless oil (64 mg, 72%, >99:1 dr); ν_{max} (film) 3383 (O–H), 2932 (C–H), 2861 (C–H), 1618 (C=O); δ_H (400 MHz, $CDCl_3$) 0.98-2.46 (16H, m, C(1)H_2, C(2)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(1′)H_2, C(2′)H_2, C(3′)H_2), 3.26-3.35 (1H, m, C(3)*H*), 3.57 (2H, t, *J* 6.4, C(4′)H_2), 3.86-3.94 (1H, m, C(8a)*H*); δ_C (100 MHz, $CDCl_3$) 21.1, 22.7, 27.7, 29.3, 31.0, 31.3, 32.2, 32.3 (*C*(1), *C*(2), *C*(6), *C*(7), *C*(8), *C*(1′), *C*(2′), *C*(3′)), 57.2 (*C*(3)), 60.1 (*C*(8a)), 62.3 (*C*(4′)), 169.8 (*C*(5)); *m/z* (ESI^+) 212 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{12}H_{22}NO_2^+$ ($[M+H]^+$) requires 212.1645; found 212.1643.

(*RS*,*RS*)-3-(4′-butyl)-5-oxo-indolizidine 34



PBr_3 (0.54 mL, 5.69 mmol) was added dropwise to a stirred solution of **156** (200 mg, 0.95 mmol) in 1,2-DCE (5.61 mL) and the resultant solution heated at reflux for 3 h then cooled to 0 °C. Satd aq $NaHCO_3$ (5 mL) was added, the resulting solution extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. AIBN (62 mg, 0.38 mmol) and Bu_3SnH (0.28 mL, 1.04 mmol) were added to the residue in degassed toluene (6.8 mL) at rt and the resultant solution was heated at reflux for 2 h then concentrated *in vacuo*. Purification via flash column chromatography (eluent 100% TBME) gave **34** as a colourless oil (55 mg, 30%, >99:1 dr);[18] δ_H (400 MHz, $CDCl_3$) 0.82 (3H, t, *J* 7.3, C(3')*Me*), 1.09-1.28 (6H, m, C(1')H_2, C(2')H_2, C(3')H_2), 1.46-1.73 (4H, m, C(7)H_2, C(8)H_2), 1.80-1.99 (4H, m, C(1)H_2, C(2)H_2), 2.21-2.28 (2H, m, C(6)H_2), 3.25-3.34 (1H, m, C(3)*H*), 3.85-3.92 (1H, m, C(8a)*H*).

Monomorine 15



MeMgBr (3M in Et_2O, 0.26 mL, 1.3 mmol) was added dropwise to a stirred solution of **34** (50 mg, 0.26 mmol) in THF at 0 °C and the resulting solution was stirred for 16 h whilst being allowed to warm to rt. The mixture was cooled to 0 °C then $NaBH_4$ (29 mg, 0.77 mmol) and glacial acetic acid (1.5 mL) were added and the resulting solution stirred for 1 h whilst being allowed to warm to rt. 2 M aq NaOH (5 mL) was added and the resulting solution extracted with CH_2Cl_2 (5 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 9:1) gave **15** as a colourless oil (8 mg, 16%, >99:1 dr);[19] δ_H (400 MHz, $CDCl_3$) 0.82 (3H, t, J 7.0, C(3')*Me*), 1.07 (3H, d, *J* 6.1, C(5)*Me*), 1.17-1.70 (16H, m, C(1)H_2, C(2)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(1')H_2, C(2')H_2, C(3')H_2), 1.98-2.05 (1H, m, C(3)*H*), 2.12-2.19 (1H, m, C(5)*H*), 2.36-2.45 (1H, m, C(8a)*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (C(3')*Me*), 22.8, 22.9, 24.9, 29.5, 29.8, 30.3,

30.8, 35.7, 39.6 (*C*(1), *C*(2), C(5)*Me*, *C*(6), *C*(7), *C*(8), *C*(1'), *C*(2'), *C*(3')), 60.4 (*C*(3)), 63.0 (*C*(5)), 67.3 (*C*(8a)).

5.5 References

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