

https://dspace.org/

Vinylogous sulfonamides in the total synthesis of indolizidine alkaloids from amphibians and ants

Winks, Susan

2010-09-08
http://hdl.handle.net/10539/8627

Downloaded from a DSpace repository. https://dspace.org/

VINYLOGOUS SULFONAMIDES IN THE TOTAL SYNTHESIS OF INDOLIZIDINE ALKALOIDS FROM AMPHIBIANS AND ANTS

Susan Winks

WitsETD

A thesis submitted to the Faculty of Science,
University of the Witwatersrand,
Johannesburg
in fulfilment of the requirements for the
Degree of Doctor of Philosophy.

January 2010

Declaration

I declare that the work presented in this thesis was carried out exclusively by me under the supervision of Professor J. P. Michael and Professor C. B. de Koning. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other university.

_____

15th day of January 2010.

WitsETD

Abstract

This thesis describes the application of vinylogous sulfonamides in a generalised synthetic protocol for the synthesis of indolizidine alkaloids, *viz.* monomorine I, 5-*epi*-monomorine I and the key precursor to indolizidine 209D. Chapter one puts the work into perspective with a review of the different classes of amphibian alkaloids, with specific emphasis on previous syntheses of indolizidine 209D and monomorine I. This is followed by a brief overview of previous synthetic strategies employed for alkaloid synthesis in the Wits laboratories and an introduction to vinylogous sulfonamides. Chapter 2 concludes with our aims and proposed strategies for the project.

The attempted total synthesis of (−)-indolizidine 209D is described in Chapter 3. The initial three steps to prepare *t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (**274**) proceeded well, but the fourth step, deprotecting the nitrogen, gave inconsistent results and hindered the completion of the synthesis. The free amine that we succeeded in isolating, *t*-butyl (3*R*)-3-aminononanoate (**275**), reacted with chlorobutyryl chloride to give us lactam, *t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)nonanoate (**277**) in addition to the unusual by-product *N*-(cyclopropanecarbonyl)cyclopropanecarboxamide (**327**). From the lactam (**277**) we successfully prepared the key intermediate, vinylogous sulfonamide *t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl} nonanoate (**280**). The vinylogous sulfonamide effectively facilitated a high-yielding cyclisation reaction to produce the bicyclic hexahydroindolizine (**282**). Unfortunately the failing debenzylation reaction prevented the completion of the synthesis as no more material was available.

The total syntheses of (±)-monomorine I and (±)-5-*epi*-monomorine I are described in Chapter 4. Notable intermediates include the enamide, ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (**293**), which we prepared from a condensation reaction between the ketoester (**292**) and the racemic amine (**291**). The diastereoselective reduction of the enamide (**293**) was optimised to give ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (**294**) as a 1:5 mixture of

WiSERD

isomers. After thionation, the two isomers were separable, (**295A**) was the intermediate for (±)-monomorine I and (**295B**) the intermediate for (±)-5-*epi*-monomorine I. Following the formation of the vinylogous sulfonamide, the key cyclisation step proceeded well for both the diastereomers to give the hexahydroindolizines (**298A**) and (**298B**). We obtained crystal structures of both hexahydroindolizines and were able to confirm the relative stereochemistry of the isomers. Defunctionalisation of the vinylogous sulfonamide included a stereoselective platinum-catalysed reduction of the alkene, followed by desulfonylation. Conditions were optimized and the synthesis was completed to give (±)-monomorine I in an overall yield of 3% and (±)-5-*epi*-monomorine I in an overall yield of 7%.

Approaches towards the enantioselective synthesis were explored but, unfortunately, we experienced difficulties with the debenzylation reaction required to produce the chiral amine (**291**). In the process of trying to circumvent this problem a side route involving monobenzylated analogues was investigated. While the side route produced some interesting products, we were unable to direct the synthetic path back towards enantiopure monomorine I.

The feasibility of extending this methodology to more complex alkaloids was briefly investigated. Initial experimentation involving allylated analogues of the ketoester (**292**) was investigated and was found to be incompatible with our reaction conditions.

WitsETD

In memory of my grandmother

Edna Robins

Sept 1927 – Aug 2009

WitsETD

Personal acknowledgements

Firstly, Professor J. P. Michael, thank you for giving me the freedom to explore organic chemistry and for nurturing my love of the subject. You were always there providing me with complete support, guidance and confidence.

In addition, I would like to thank my second supervisor, Professor C. B. de Koning, for many useful discussions and reminding me that there is more to life than chemistry.

I would also like to thank the other organic chemistry members of staff, Professor W. A. L. van Otterlo and Dr. S. Pelly for support and encouragement.

Richard Mampa, thank you for your endless patience and assistance with my many, many NMR samples, and thank you for taking the time to train and guide me in the use of the 300 MHz instrument.

I would like to express my sincere gratitude to Manuel Fernandes for constantly encouraging me to grow crystals, even when the majority of my products stubbornly remained as oils, and also, of course, for doing the crystallographic analyses when I did succeed. Thank you also to Andreas Lemmerer for crystallographic analyses.

A big thank you to Chris Perry, who is responsible for all the MD/SA results, and many fruitful discussions on stereoselectivity. Thank you also for proof-reading my thesis and supporting me through-out this project.

I would like to thank Tommy van der Merwe, Martin Brits and Marelize Ferreira for running low and high resolution mass spectrometry.

The Organic Group, past and present, thank you for all the fun and encouragement, especially to my lab mates, mentors and friends; Garreth, Sameshnee, Siyanda and Jeremy.

WiSETD

Acknowledgements for funding

Without all the funding I have received, this PhD would not have been possible. I would like to express my sincere appreciation to the Andrew Mellon Mentorship Programme for their substantial financial contribution, the University of the Witwatersrand for the Post Graduate Merit Award and the School of Chemistry for the Teaching Assistantship bursaries; I thoroughly enjoyed the classes I taught and the experience I gained from lecturing was invaluable.

The financial assistance of the National Research Foundation (NRF) towards this research is hereby acknowledged. Opinions expressed and conclusions arrived at are those of the author and are not necessarily to be attributed to the NRF.

WitsETD

CONTENTS

Chapter 1: An overview of amphibian alkaloids, and reported syntheses of indolizidine 209D and monomorine I.....1

1.1 Definition, occurrence and classification of alkaloids.....1

1.2 Indolizidine alkaloids in nature.....4

1.3 Major classes of “amphibian” alkaloids.....7

1.3.1 Steroidal alkaloids.....7

1.3.2 Monocyclic alkaloids.....8

1.3.3 Bicyclic alkaloids.....9

1.3.4 Tricyclic alkaloids.....15

1.3.5 Pyridine alkaloids.....17

1.3.6 Indole alkaloids.....17

1.4 Indolizidines of interest in this project.....18

1.4.1 Indolizidine 209D.....18

1.4.2 Monomorine I.....27

1.4.3 Tricyclic alkaloids.....52

Chapter 2: Background, aims and scope of this project.....56

2.1 The “Wits Approach” to indolizidine alkaloids 56

2.1.1 Introduction to the “Wits Approach”.....56

2.1.2 Preparation of enaminones.....57

2.1.3 Enaminones in action at Wits.....59

2.2 Vinylogous sulfonamides.....67

2.2.1 Preparation of vinylogous sulfonamides.....67

2.2.2 Uses of vinylogous sulfonamides.....68

2.3 Aims and proposed strategies of this project.....71

2.3.1 (−)-Indolizidine 209D.....71

2.3.2 Monomorine I and diastereomers.....74

2.3.3 Accessing tricyclic alkaloids.....79

2.3.4 Summary of aims.....83

WitsETD

Chapter 3: The attempted total synthesis of (−)-indolizidine 209D.....84
3.1 Introduction 84
3.2 Horner-Wadsworth-Emmons reaction; the Michael acceptor.....85
3.3 Davies methodology: Conjugate addition reaction.....87
3.4 Debenzylation reactions.....91
3.5 Formation of the lactam and cyclopropane by-products.....98
3.6 Thionation reactions.....107
3.7 Formation of the vinylogous sulfonamide.....111
3.8 Attempted deacetylation reactions.....116
3.9 Reduction to the alcohol.....116
3.10 Cyclisation reaction.....118
3.11 Conclusion.....122

Chapter 4: The total synthesis of monomorine I and 5-*epi*-monomorine I 123
4.1 Introduction 123
4.2 Preparation of the ketoester and amine precursor.....124
4.2.1 Preparation of the ketoester.....124
4.2.2 Preparation of the racemic amine 134
4.2.3 Davies' methodology: enantiopure amine.....139
4.3 Preparation of *N*,5-disubstituted pyrrolidin-2-ones.....148
4.3.1 Condensation reactions.....148
4.3.2 Attempted enzymatic resolution.....154
4.3.3 Diastereoselective reduction and optimization 156
4.4 Preparation and cyclisation of the vinylogous sulfonamide.....162
4.4.1 Thionation reaction and separation of diastereomers.....163
4.4.2 Condensation of thiolactam with β-ketosulfone 167
4.4.3 Deacetylation reactions.....172
4.4.4 Reduction of the ester.....172
4.4.5 Cyclisation reaction.....174
4.5 Completion of the synthesis.....179
4.5.1 Reduction of the vinylogous sulfonamide 179
4.5.2 Desulfonylation reaction.....183
4.6 Alternative approach via monobenzylated intermediates.....191

WitsETD

4.6.1 Condensation reaction....192
4.6.2 Stereoselective reduction....194
4.6.3 Thionation reaction and separation of diastereomers....196
4.6.4 Preparation of the vinylogous sulfonamide....198
4.6.5 Attempted debenzylations.... .201
4.7 Conclusion....204

Chapter 5: A model study for applying ring-closing metathesis in the synthesis of indolizidine-based alkaloids....205
5.1 Introduction 205
5.2 Preparation of allylic ketoesters....207
5.3 Attempted condensation reactions....210
5.4 Ring-closing metathesis reactions....214
5.5 Conclusion....216

Chapter 6: Summary, future prospects, and conclusion....217
6.1 Summary....217
6.1.1 Attempted total synthesis of (−)-indolizidine 209D....217
6.1.2 Total synthesis of (±)-monomorine I....219
6.1.3 Total synthesis of (±)-5-*epi*-monomorine I....221
6.1.4 Attempted enantioselective synthesis....222
6.1.5 Benzylated analogues....223
6.1.6 Model study for ring-closing metathesis....225
6.2 Future prospects....226
6.2.1 A new chiral auxiliary 227
6.2.2 Extending the reach of the Wits methodology....229
6.2.3 Partnering up with ring-closing metathesis 230
6.3 Conclusion....231

Chapter 7: Experimental procedures relating to chapter 3....232
7.1 General experimental procedures 232
7.1.1 Purification of solvents and reagents....232
7.1.2 Chromatography....232
7.1.3 Spectroscopic and physical data....232

WITSETD

7.1.4 Additional general procedures and terminology 234
7.1.5 Nomenclature and compound numbering.....234
7.2 Towards the total synthesis of enantiopure (−)-indolizidine 209D.....236
7.2.1 Horner-Wadsworth-Emmons reaction.....236
7.2.2 Conjugate addition reaction.....238
7.2.3 Debenzylation reactions.....239
7.2.4 Formation of the lactam and cyclopropane by-products.....246
7.2.5 Thionation reactions.....251
7.2.6 Formation of the vinylogous sulfonamide.....253
7.2.7 Reduction of the ester.....258
7.2.8 Cyclisation reaction.....259

Chapter 8: Experimental procedures relating to chapter 4.....261
8.1 The total synthesis of monomorine I and 5-*epi*-monomorine I.....261
8.1.1 Preparation of ethyl 4-oxooctanoate.....261
8.1.2 Preparation of ethyl 3-aminobutyrate.....270
8.1.3 Condensation reaction.....280
8.1.4 Stereoselective reduction of the exocyclic alkene.....284
8.1.5 Thionation reactions.....290
8.1.6 Formation of the vinylogous sulfonamide.....295
8.1.7 Reduction of the ester.....303
8.1.8 Cyclisation reaction.....306
8.1.9 Reduction of the vinylogous sulfonamide.....309
8.1.10 Desulfonylation.....312
8.2 Investigation of monobenzylated analogues.....316
8.2.1 (*R,E*)-5-Butylidene-1-(1-phenylethyl)pyrrolidin-2-one.....316
8.2.2 (*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidin-2-one.....317
8.2.3 (*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidine-2-thione.....320
8.2.4 (*R,E*)-2-Butyl-1-(1-phenylethyl)-5-(tosylmethylene)pyrrolidine....322
8.2.5 Attempted debenzylation reactions.....324

Chapter 9: Experimental procedures relating to chapter 5.....326
9.1. Preparation of allylic ketoesters.....326
9.1.1 Ethyl 4-allyl-4-hydroxyhept-6-enoate 327

WJSEED

9.1.2 Ethyl 4-oxohept-6-enoate 327
9.1.3 Ethyl (5*E*)-4-oxohept-5-enoate 327
9.2 Attempted condensation reactions.....329
9.2.1 (5*E*)-1-Allyl-5-butylidenepyrrolidin-2-one.....329
9.2.2 (5*E*)-1-But-3-enyl-5-butylidenepyrrolidin-2-one.....330
9.3 Ring-closing metathesis reactions.....331
9.3.1 (*E*)-5-Butylidene1-(prop-1-enyl)pyrrolidin-2-one.....331
9.3.2 Attempted RCM: (5*E*)-1-but-3-enyl-5-butylidenepyrrolidin-2-one.....332

References.....333

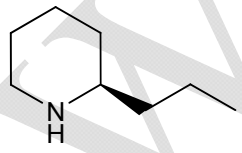
WitsETD

CHAPTER 1

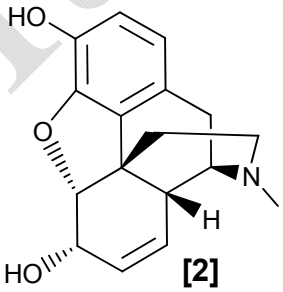
AN OVERVIEW OF AMPHIBIAN ALKALOIDS, AND REPORTED SYNTHESES OF INDOLIZIDINE 209D AND MONOMORINE I

1.1 Definition, occurrence and classification of alkaloids

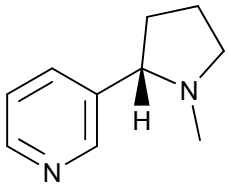
In 1819 an apothecary from Halle gave the name “alkaloids” to the “alkali-like” compounds purified from plant extracts. These “alkaloids” proved to be very diverse in origin and structure. One of their few similarities is that they are all biosynthesized from amino acids.[1] In the early days of alkaloid discovery, compounds such as coniine (**1**), morphine (**2**), nicotine (**3**) and the toxic molecule strychnine (**4**) from the seeds of the *Strychnos* plant were discovered. The poison used in the execution of Socrates, coniine, otherwise known as poison hemlock, was the first alkaloid to be synthesized by Ladenberg in 1886. The opium alkaloid morphine, whose name comes from Morpheus, the ancient Greek god of dreams, was first isolated in 1803, while its total synthesis only followed in 1952. Most alkaloids are toxic in large enough doses, but many, such as codeine (**5**), a morphine analogue widely used as a pain killer, have medicinal uses.[2]



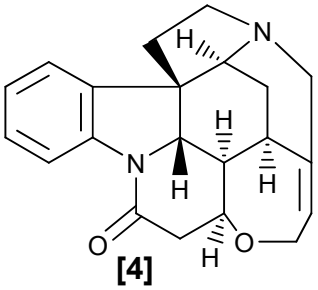
[1]



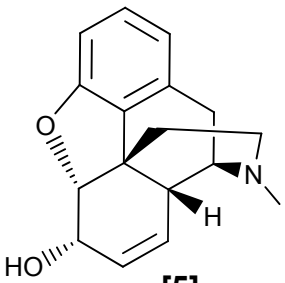
[2]



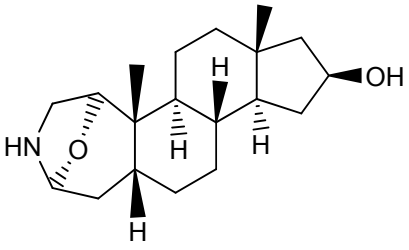
[3]



[4]



[5]

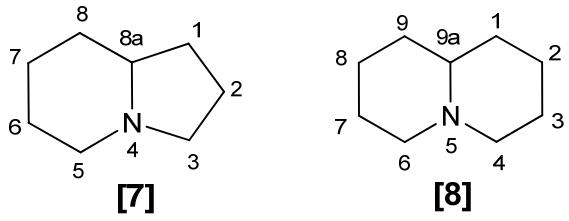


[6]

WitsETD

The definition of alkaloids has evolved with time, but they are generally accepted as nitrogen-containing secondary metabolites that are limited in Nature. One useful definition is Pelletier's "*An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms*".[3] This definition works for most alkaloids, but excludes the acyclic amines and amides. A more general and comprehensive definition is the recent IUPAC definition; "*An alkaloid is a basic nitrogen containing compound (mostly heterocyclic) occurring mostly in the plant kingdom (but not excluding those from animal origin). Amino acids, peptides, nucleotides, nucleic acids, amino sugars and antibiotics are not normally regarded as alkaloids. By extension, certain neutral compounds biogenetically related to basic alkaloids are included*".[4]

The first alkaloid isolated from an animal species was samandarine (**6**), isolated from the striking black and yellow European Fire Salamander in 1866.[5] Today there are over ten thousand known alkaloids, widely exemplified in Nature. Initially, these secondary metabolites were named according to the organism from which they were isolated, ending in "*-ine"* to indicate they were amines.[1, 2] Then they were classified according to structural features. Nowadays, the type of ring system is a key feature of the classification. One such class of alkaloids is the indolizidines (**7**), which are bicyclic compounds, with fused 6- and 5-membered rings and a bridgehead nitrogen. They are closely related to quinolizidines (**8**), which are analogous bicyclic structures with two fused 6-membered rings sharing a bridgehead nitrogen (Figure 1.1).[6] Indolizidines and quinolizidines form the structural basis for far more complicated fused polycyclic alkaloids and 25 to 30% of all known alkaloids incorporate either the fundamental indolizidine or quinolizidine structure.[6]



[7] **[8]**

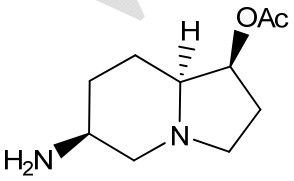
Figure 1.1: Indolizidine (**7**) and quinolizidine (**8**) structures with conventional numbering.

WISER

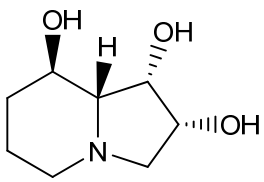
Indolizidines and quinolizidines occur widely in Nature, in bacteria, fungi, higher plants, invertebrates and vertebrates, both terrestrial and marine. A common ring system however, does not imply a common biogenetic pathway, and these apparent structural relationships are coincidental.[7]

Alkaloids exhibit a wide range of biological activities. In plants they usually exhibit allelochemical properties, that is to say they act as deterrents to herbivores, micro-organisms and even to other plants. In animals, alkaloids generally appear to be a chemical defence against predators or as a defence against protozoans, fungi and bacteria. Even when they are not highly toxic, the alkaloids are bitter tasting and noxious to predators. Most of the indolizidine alkaloids affect the nerves or muscles of buccal tissue.[8] Even so, many alkaloids have medicinal properties and have acted as scaffolds for drug development.

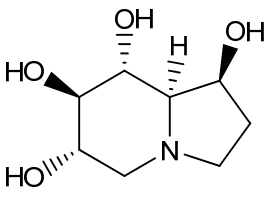
Extensive review articles on alkaloids have been published, especially the amphibian alkaloids and the "-izidine" alkaloids.[9 - 19] From these reviews it is clear that while there is a lot of interest in the isolation and synthesis of alkaloids, biosynthetic elucidation is sparse, and considering the obvious biological activity, pharmacological and biochemical research is virtually non-existent. The few alkaloids that have been well studied, such as slaframine (**9**), swainsonine (**10**) and castanospermine (**11**), are good indicators of the pharmaceutical potential of these molecules.[6]



[9]



[10]



[11]

WitsETD

1.2 Indolizidine alkaloids in Nature

Amphibian skin contains an array of biologically active compounds, including biogenic amines, peptides, proteins, steroidal butadienolides, cardenolides and alkaloids. It has been shown that secretions from the granular skin glands can serve to protect amphibians from predators due to noxious effects on buccal tissue.[8] Although the aposematic colouration of the frog skin warns predators of the toxins in the skin, to date there has been no correlation observed between the brightness of colouration, behaviour and toxicity in *Dendrobates pumilio*, a particularly varied and striking species of the frog.[20]

Before we can discuss "amphibian" alkaloids, it is important to understand that although many of these alkaloids were originally extracted from frog skin, they have subsequently been found to occur in other organisms such as arthropods and plants. In many cases, the reason a given alkaloid was originally detected in frogs is due to the relatively high concentration of that alkaloid in the frog's skin. These lipophilic alkaloids are extracted from the homogenized frog skins with methanol, followed by an acid/base partitioning.[17] The alkaloids are then typically characterised by GCMS, HPLC, FTIR and NMR spectroscopy. Sometimes chemical transformations such as hydrogenations, acetylations, boronations, methylations etc. are employed to assist in the identification of key functional groups.[17, 21] Flame ionization GC is used to quantitatively characterize mixtures of alkaloids.[17, 21] As technology has advanced, we are now able to detect and characterise alkaloids that previously went undetected due to the microgram quantities isolated.

As more "amphibian" alkaloids are detected in arthropods it has become increasingly obvious that there is a connection between them. In answer to this conundrum, John Daly proposed that the frogs in fact sequestered the alkaloids from arthropods through their diet. In 2000 a review by Daly *et al.*[22] showed that of the five hundred alkaloids known in frogs, twenty-two of them were also found in arthropods. There were an additional twenty-two alkaloids which had been detected in arthropods that at the time had not been detected in frogs. Despite the large number of alkaloids that had still not been detected in the

WitsETD

supposed dietary source, this discovery prompted dietary studies on the frogs. One of the studies revealed that when frogs are raised in captivity on a fruit fly diet, i.e. in the absence of dietary alkaloids, no alkaloids are detected in their skin. A further study showed that when certain species of frog were fed fruit flies dusted with alkaloid-containing powder, they accumulated those specific alkaloids in their skin. It was also demonstrated that environmental manipulations such as light and stress did not trigger alkaloid production in these frogs.[20] Another interesting observation from these studies indicated that while some frog species accumulate alkaloids with ease, other frog species cannot accumulate them at all, and that certain species accumulate certain alkaloids better than other species.[20]

Of the eighty genera of frog that have been examined, only seven genera contained alkaloids.[23] This reflects that only some species have the ability to transport and store the dietary alkaloids, thus it is a highly specialized and conserved biogenetic pathway. These alkaloids are so important to the frogs that they salvage skin alkaloids by ingesting their own shedded skin.[8] While many species of frog reject several arthropods as a food source due to their bite and sting, certain frog species have evolved modified sodium channels that no longer respond to the toxins such as batrachotoxin (**12**),[20] thus allowing them to eat the toxic arthropods. The dendrobatid frog species in particular have become known as the “ant specialists”, consuming toxic ants in higher proportions than they are present in the environment.[23, 24] Because of this, many alkaloids were originally detected only in dendrobatid anurans and hence became known as the “Dendrobatid alkaloids”. These alkaloids have subsequently been isolated from three other anuran families, including ranid frogs of the genus *Mantella*.[25]

In support of the dietary hypothesis, there is a large variation in alkaloid distribution within a particular species, but not within a given population. Thus there is a correlation between alkaloid distribution and environmental conditions/available food sources for a population.[26] Importantly, early studies of alkaloid distribution in frog skin are fairly consistent with later studies for a

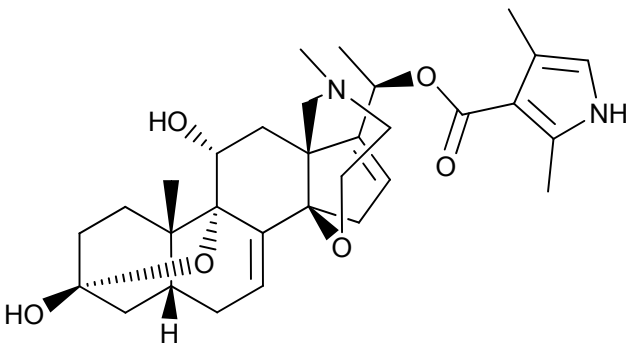
WITSETD

given population, allowing for the advancement of equipment and the superior detection of trace alkaloids.[26]

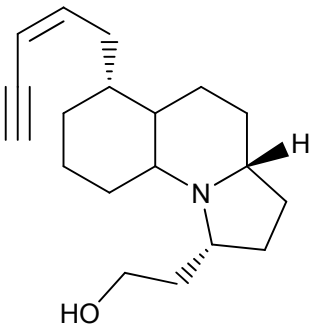
In ants, the distribution of alkaloids is caste specific.[23] For example, in certain *Solenopsis* species the queen ants contain the bicyclic indolizidines while the workers only contain the corresponding piperidines.[23] This invited the postulation that the piperidines found in the workers could be the precursors for the biosynthesis of the indolizidines. The functional significance of alkaloids for arthropods is largely unknown; for example the queen ants do not defend the colony, so why would their venom contain these 'deterrent' bicyclic alkaloids? The possible biological function of these alkaloids could be to protect eggs from microbial infection or to use them as a sex attractant.[23, 27] While there has been a study that indicated a possible taxonomic significance to the distribution of alkaloids in ants, the biosynthetic pathways to most of the alkaloids remain unknown. The pharmacological activity of these ant alkaloids still requires extensive investigation.[23, 27]

The limited biological studies on amphibian alkaloids have investigated the interaction of these alkaloids with the binding sites on nicotinic acetylcholine receptor channel (AChR) complex from the *Torpedo californica* electric organ.[28] For indolizidines and gephyrotoxins (e.g. gephyrotoxin 287C) (**13**) the hydrophobic interaction of side chains seems to be especially important, with longer, saturated chains interacting more favourably as more potent non-competitive blockers of the nicotinic receptor than shorter or unsaturated chains. The stereoconfiguration of these side-chains did not affect the results.[28] All the indolizidines and gephyrotoxins investigated acted as moderately active inhibitors. Presumably, artificially synthesized indolizidines with longer side chains would be even more potent and less sensitive to allosteric regulation by receptor agonists.[28]

WitsETD



[12]



[13]

1.3 Major classes of "amphibian" alkaloids

Originally two major groups of alkaloids were identified: The ones based on straight chains (class A) and the ones based on isoprene units (class B).[25] This classification is no longer used, and instead there are now twenty structural classes of alkaloids in amphibians, with over eight-hundred "amphibian" alkaloids known to date.[17] The conventional code given to any new alkaloids discovered consists of the nominal molecular weight and an identifying letter, both in bold face.[17] Owing to the occurrence of mixtures of stereoisomers in Nature, sometimes the prefixes *cis, trans, epi,* or *iso* are given to discriminate between two isomers.[a]

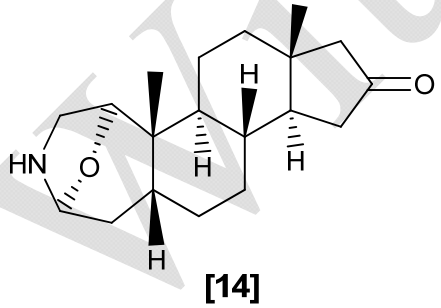
1.3.1 Steroidal alkaloids

There are two classes of amphibian alkaloids that can be classified as steroidal alkaloids; samandarines (**6** + **14**) and batrachotoxins (**12** + **15**). Samandarines were first isolated from Salamandridae *Salamandra*, the European fire salamander.[5] There is evidence that the salamanders synthesize samandarines from cholesterol. It forms the main component in parotid glands (20 mg/gland for the fire salamander, 5 mg/gland for the alpine salamander). Samandarine (**6**) is highly toxic, with an LD_{50} of 70 µg/mouse. This toxicity is likely due to potent local anaesthetic activity. Thus far nine structures that fit this class have been isolated.[17]

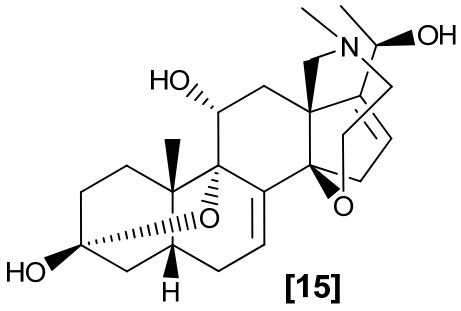
[a] *For clarity when reading this thesis, boldface numbers will only be used to refer to structures, not when referring to alkaloids classified by the conventional code.*

WitsETD

The second class of steroidal alkaloids are the batrachotoxins, isolated from Dendrobatidae *Phyllobates* in 1969. These are Western Colombian rain forest poison dart frogs. Only the three Colombian species of the five neotropical species of dendrobatid frogs (genus *Phyllobates*) have high levels of batrachotoxins and all of them have been used for poisoning blow darts. In contrast, the Central American species have very low levels of the toxins. Congeners of the batrachotoxins have been found in beetles of the species Melyridae *Choresine* and hence the beetles are the putative dietary source. The frogs that sequester the toxin have batrachotoxin resistant sodium channels and can therefore ingest the beetles with no ill effects. The batrachotoxins have also been found in the feathers and skin of passerine birds of Papua New Guinea. There have been no studies on the passerine birds to suggest biosynthesis or sequestering. There are three major alkaloids that fit into this class, and the most toxic frog, *Phyllobates terribilis*, has more than 1000 µg of batrachotoxin A (**15**) per frog skin, with a LD_{50} of 0.1 µg/mouse. *P. bicolor* and *P. aurotaenia* have 100 – 200 µg/skin. The mode of action of the toxin is by depolarisation of the nerve and muscle membranes by selective stabilization of sodium channels in an active, open form. These toxins have been widely used to research voltage dependent sodium channels.[17]



[14]



[15]

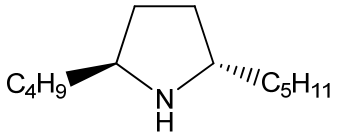
1.3.2 Monocyclic alkaloids

There are two classes of monocyclic alkaloids, the pyrrolidines, for example, (**16**), and the piperidines, for example (**17**) and (**18**). Pyrrolidines were identified as major alkaloids in *Dendrobates histrionicus* in 1986. They have been known in myrmicine ant venom since 1970 and studies have shown that pyrrolidine 197B (**16**) is sequestered poorly in an artificial environment. Ten pyrrolidines

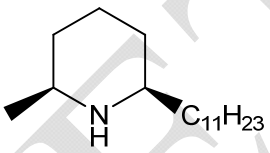
WitsETD

have been identified to date, nine of which are trace alkaloids. There has been no toxicity data reported. They act as non-competitive blockers of nicotinic receptors.[17]

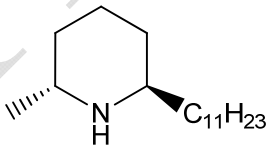
2,6-Disubstituted piperidines were first reported in the skin extracts of South American dendrobatid frogs in 1986. Twenty piperidines have since been reported. They have been known to occur in the venom of certain myrmicine ants since 1971 and they are relatively rare in dendrobatids and mantellids, occurring only in trace amounts.[29] Toxicity data has only been reported for the *cis* and *trans* piperidines from myrmicine ants – known as the solenopsins 253J (**17** + **18**) – which have proved toxic to mice and potent antifungals. They also act as non-competitive blockers of nicotinic receptors.[17]



[16]



[17]



[18]

1.3.3 Bicyclic alkaloids

There are several classes of alkaloids that are classified as bicyclics: Histrionicotoxins, pumiliotoxins, decahydroquinolines, pyrrolizidines, indolizidines, quinolizidines, lehmizidines and epiquinamides.

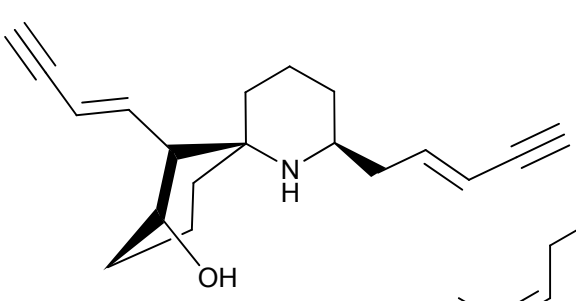
Histrionicotoxin 283A (**19**) was the first histrionicotoxin isolated from *Dendrobates histrionicus*, a South American, brightly coloured, extremely variable species of dendrobatid frog. The structure was first determined in 1971, and to date sixteen amphibian alkaloids fit into this class. A New World myrmicine ant is the putative dietary source. These alkaloids have been isolated in all neotropical frogs, at the high levels of up to 200 μg/frog. They exhibit low toxicity (even 1000 μg was not lethal to a mouse), but they are noxious and bitter and therefore act as predator deterrents. Biologically they function as non-competitive blockers of nicotinic receptor channels.[17]

WitsETD

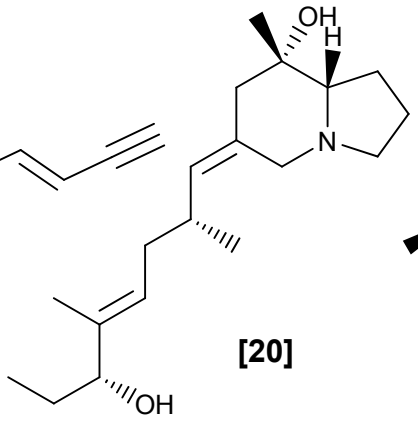
Pumiliotoxins were first isolated from *Dendrobates pumilio* in 1967. They were found as major alkaloids in this highly variable, brightly coloured, small Panamanian dendrobatid frog. The structures of pumiliotoxin A (**20**) and B (**21**) remained elusive until 1980, when X-ray crystallography revealed the structure of pumiliotoxin 251D (**22**); A and B were solved by analogy. Over thirty pumiliotoxins are known [with twenty of those being allopumiliotoxins (**23**)]. Many of the structures are tentative. These toxins are widely distributed in anurans from the neotropics, semi-temperate South America, Madagascar and Australia. They have been detected in formicine ants of two genera, as well as in oribatid mites – the putative dietary source for the ants.[24] Dendrobatid anurans have the pumiliotoxin 7-hydroxylase enzyme that has been shown to convert the dietary pumiliotoxin enantioselectively into the highly toxic allopumiliotoxin. This is the only known example in amphibians of a metabolically altered sequestered alkaloid. These alkaloids are prevalent in fairly large quantities, up to 200 µg/frog. They exhibit high toxicity with an LD_{50} of 50 µg/mouse for allopumiliotoxin and 7-fold less for pumiliotoxins. Biological studies have revealed marked cardiotonic activity by prolonging the open-time of voltage dependent sodium channels thereby triggering inositol triphosphate production in cardiac and neuronal preparations.[17]

The first decahydroquinoline was originally isolated along with the pumiliotoxins in *Dendrobates pumilio* and mistakenly named pumiliotoxin C (**24**). The real structure of decahydroquinoline *cis*-195A (**24**) was determined in 1969 by X-ray crystallography. Fifty alkaloids now belong to the 2,5-decahydroquinoline class and they are commonly found in neotropical dendrobatids, and rarely found in mantellid and bufonid anurans. The putative dietary source is the myrmicine ants.[22] These alkaloids occur in up to 50 µg/frog and exhibit low toxicity. The lethal dose for decahydroquinoline *cis*-195A is 250 µg/mouse. The mode of action is as a non-competitive blocker of nicotinic receptors.[17]

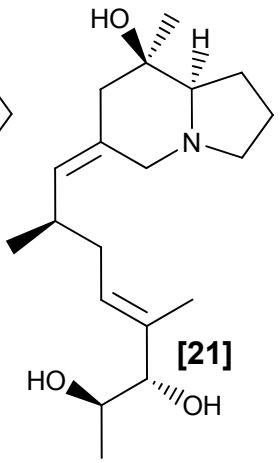
WitsETD



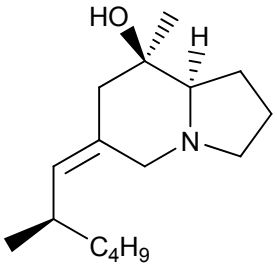
[19]



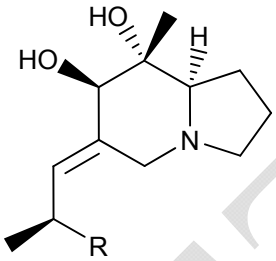
[20]



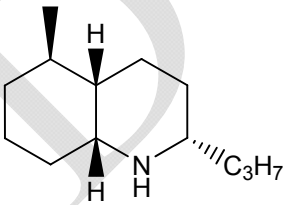
[21]



[22]



[23]



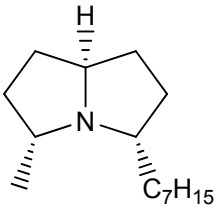
[24]

Pyrrolizidines such as pyrrolizidine 223H (**25**) have been known to occur in myrmicine ants since 1980 and were first reported in anurans in 1993.[21] There are about twenty-six alkaloids, including stereoisomers, in the 3,5-disubstituted pyrrolizidine class and both *cis* and *trans* isomers occur naturally. They are fairly common in trace amounts and myrmicine ants are definitely the dietary source.[22] No toxicity data has been reported.[17]

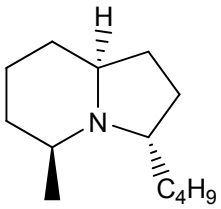
There are at least four classes of indolizidine alkaloids. The 3,5-disubstituted indolizidines were the first to be discovered in dendrobatid frogs. Indolizidine 195B (**26**) was isolated in 1986 from dendrobatid anurans, and reported as the diastereomer of the 5*Z*,9*Z* alkaloid monomorine I (**27**), isolated from myrmicine ants in 1973.[30] All four isomers (**26 – 29**) of monomorine I have been detected in anurans. In this class, at least thirty alkaloids, including stereoisomers, have been detected, and they occur randomly in dendrobatid, mantellid and bufonid anurans as minor or trace alkaloids. Myrmicine ants are undoubtedly the dietary source. Almost no toxicity data has been reported; the only tested 3,5-disubstutituted indolizidine is indolizidine 239CD (**30**) with an LD_{50} of

WiSETD

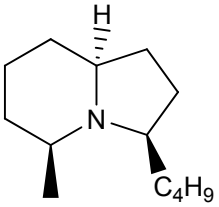
greater than 200 µg/ mouse. They act as non-competitive blockers of nicotinic receptors.[17]



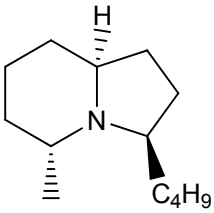
[25]



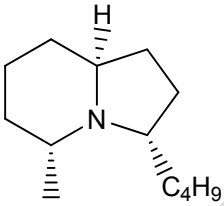
[26]



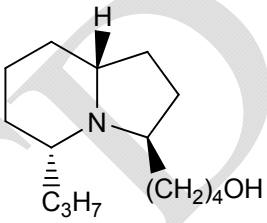
[27]



[28]



[29]



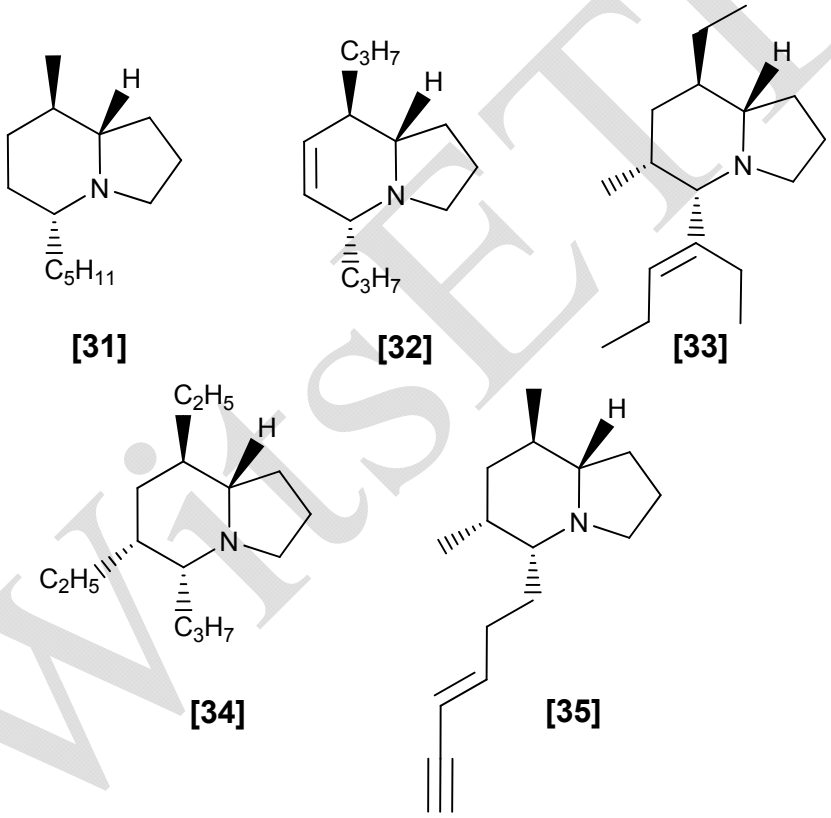
[30]

The second class of indolizidines are the 5,8-disubstituted indolizidines, which were first described in 1987. This is the largest class of alkaloids in anuran skins with more than eighty examples, including stereoisomers. They are common in dendrobatid and mantellid frogs and uncommon in bufonids. In most cases they occur as minor or trace alkaloids. One example is indolizidine 209B (**31**). The dietary source is not clear, but these alkaloids are present in leaf-litter arthropods, so the most likely sources are ants and oribatid mites.[24] There has been no toxicity data reported, but they are potent non-competitive blockers of nicotinic receptors.[17]

A new major class of the amphibian indolizidine alkaloids has been proposed: The 6,7-dehydro-5,8-disubstituted indolizidines, for example indolizidine 207E (**32**). Thirty alkaloids in this class have already been identified, all of which are minor or trace alkaloids in dendrobatid, bufonid and mantellid skin extracts. The putative dietary source is the myrmicine ant. As yet no toxicity data or biological activity data has been reported.[17]

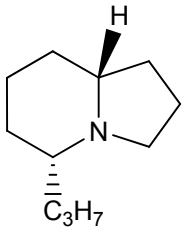
WJSETD

5,6,8-Trisubstituted indolizidines were first proposed in 1997, and already seventy alkaloids belonging to this class have been discovered. Most structures are still tentative. Indolizidine 249H (**33**), with a six carbon alkenyl chain, is the first and only example of a branched chain in the '*-izidines*' from an anuran skin extract. Indolizidines 223A (**34**) and 231B (**35**) occur in quantities up to 50 µg/frog, whereas the other alkaloids in this class occur as minor or trace alkaloids, hence the tentative structures. They are commonly found in mantellid species, but rarely found in bufonids. They have been detected in myrmicine ants and oribatid mites.[24] No toxicity data or biological activity data has been reported.[17]

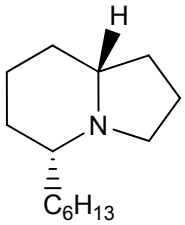


The structures proposed for the 5-monosubstituted indolizidines 167B (**36**) and 209D (**37**) were both tentative, and they are the only members of this class. They have since been proved to be pyrrolizidines and renamed as 167F (**38**) and 209K (**39**). It remains unclear as to whether this class of alkaloids exists in Nature. If these alkaloids do exist, they occur as trace components only and as a result they are difficult to characterise.[17]

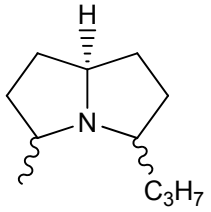
WISETD



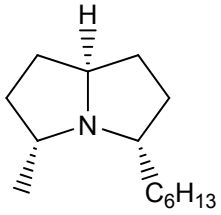
[36]



[37]



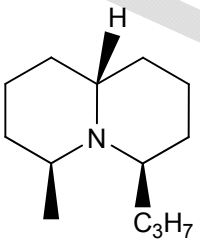
[38]



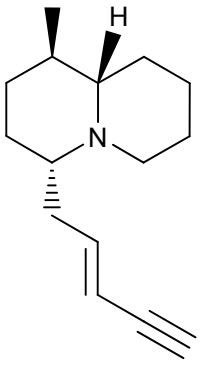
[39]

There are two classes of quinolizidines, the 4,6-disubstituted quinolizidines and the 1,4-disubstituted quinolizidines. Of the 4,6-disubstituted quinolizidines there are only six examples, and five of these structures are tentative. Quinolizidine 195C (**40**) is a minor or trace alkaloid in dendrobatid and mantellid frogs, and the others are rarely seen. Quinolizidine 195C is a major alkaloid in myrmicine ants, the confirmed dietary source. The frogs and ants both contain the same enantiomer of this alkaloid. No toxicity or biology has been reported.[17]

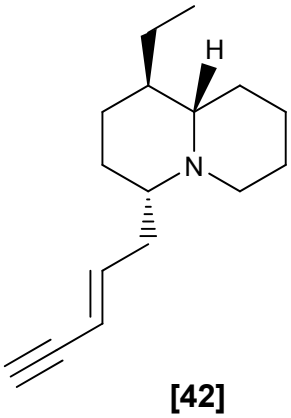
The 1,4-disubstituted quinolizidines were first recognized in 1996 and since then twenty structures have been isolated. Most of these structures are tentative. Quinolizidine 217A (**41**), 231A (**42**), and 233A (**43**) are common in certain species of mantellid frogs (up to 50 µg/frog) and they are also seen in dendrobatids. The other quinolizidines occur as trace alkaloids and are rare in Nature. As yet, none have been identified from bufonid frogs. The dietary source was recently identified as oribatid mites.[24] No toxicity data is available, but the alkaloids do act as non-competitive blockers of nicotinic receptors.[17]



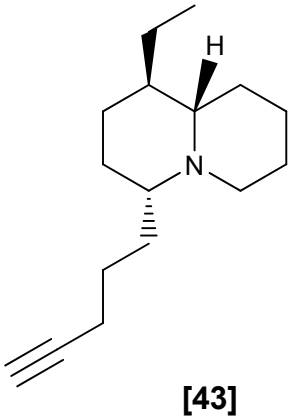
[40]



[41]



[42]

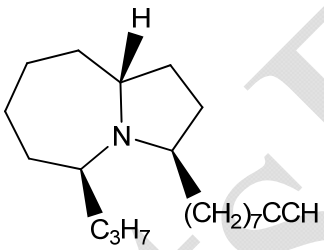


[43]

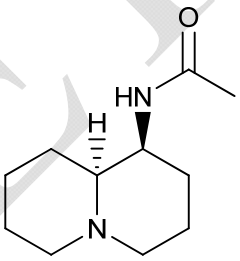
WISETD

Lehmizidines are a new and exciting class of bicyclic alkaloids that occur only in one species of Colombian dendrobatid frogs, *Dendrobates lehmanni*. The structure of lehmizidine 275A (**44**) was finally established in 2001, and since then the structures of nine other lehmizidines have been tentatively assigned. They are all minor alkaloids and they only occur in this montane species of Western Colombia. The putative dietary source is the myrmicine ant and no toxicity or biological data are available.[17]

The last class of the bicyclic alkaloids are the epiquinamides. Epiquinamide (**45**) was reported in 2003 as a trace alkaloid in the Ecuadorian dendrobatid frog *Epipedobates tricolor*. It is the only member of its class and it has only been detected in one extract of a dendrobatid frog. The dietary source is still unknown. Its' biological activity is as an agonist at the nicotinic receptor.[17]



[44]



[45]

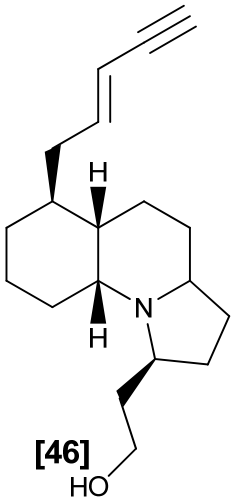
1.3.4 Tricyclic alkaloids

There are four classes of tricyclic alkaloids that have been found in frog skin extracts, namely gephyrotoxins, coccinelline tricyclics, cyclopentaquinolizidines and spiropyrrolizidines. The structure of gephyrotoxin 287C (**46**), isolated from *Dendrobates histrionicus*, was revealed in 1977 by X-ray crystallography. These alkaloids are rarely detected and occur as minor alkaloids. The putative dietary source is the myrmicine ant. They exhibit low toxicity with a lethal dose of greater than 500 µg/mouse and they act as non-competitive blockers of nicotinic receptors.[17]

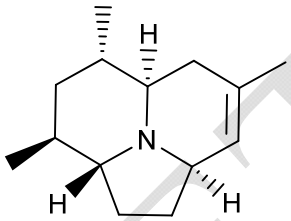
The coccinelline alkaloids have been known to occur in coccinellid beetles since 1971. They have been detected as a minor alkaloid in a Panamanian

WitsETD

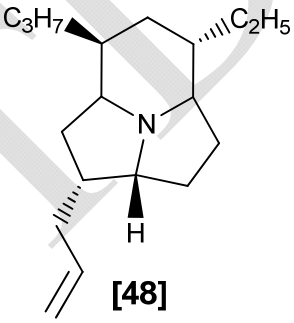
dendrobatid frog. Coccinelline 205B (**47**), 261C (**48**) and 263G (**49**) are indolizidine tricyclics. The coccinelline alkaloids have been found in dendrobatid, mantellid and bufonid anurans as minor or trace alkaloids. Precoccinelline 193C (**50**) was recently reported in oribatid mites and is the presumed dietary source for the coccinellid beetles. There is no toxicity data available. The unnatural enantiomer of 205B (**47**) is a potent and selective blocker for α-7 nicotinic receptors.[17]



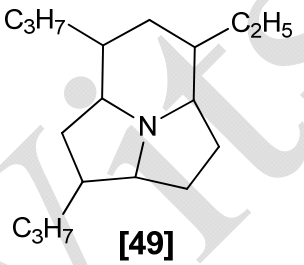
[46]



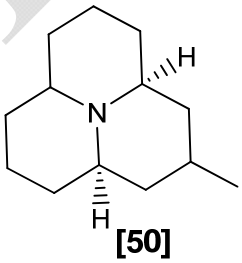
[47]



[48]



[49]

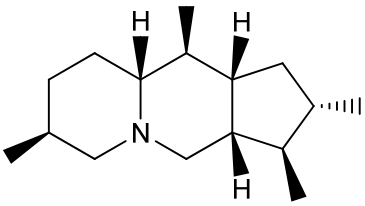


[50]

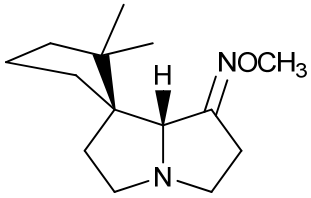
Cyclopentaquinolizidines were discovered in the 1970s in a tiny Colombian dendrobatid frog, *Minyobates bombetes*. The structure was only reported in 1992 and currently there are only ten alkaloids in this class, including cyclopentaquinolizidine 235H (**51**).[17]

Spiropyrrolizidines have been detected in both mantellid and bufonid frogs but are rarely seen in dendrobatids. There are nine alkaloids in this class and they have also been detected in millipedes. The siphonotid millipede is the putative dietary source for spiropyrrolizidine 236 (**52**). No toxicity data is available, but they are potent non-competitive blockers of the nicotinic receptor.[17]

WITHDRAWN



[51]



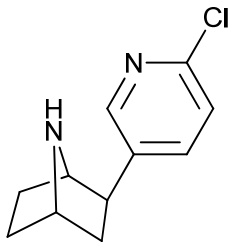
[52]

1.3.5 Pyridine alkaloids

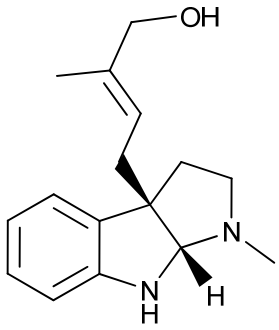
Epibatidine (**53**) is the main pyridine alkaloid that has been detected in frogs. It acts as a potent analgesic and it only occurs in certain South American frogs of the genus *Epipedobates*. It is presumed to be sequestered through a plant to arthropod to frog food chain. It is highly toxic with a lethal dose of 0.4 µg/mouse. Nicotine and other pyridine alkaloids found in plants have also been detected in anuran extracts.[17]

1.3.6 Indole alkaloids

Pseudophrynamines contain the indole skeleton and they were first detected in myobatrachid frogs in 1976 using an Ehrlich colour reaction for indoles. There are thirteen alkaloids in this class, including pseudophrynamine 258 (**54**), although some of the structures are tentative. These alkaloids are unique in that they are biosynthesized by the frogs and not sequestered through their diet. They have only been detected in myobatrachid frogs of the genus *Pseudophryne* and they are potent non-competitive blockers of the nicotinic receptor.[17]



[53]



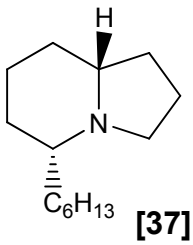
[54]

WISETD

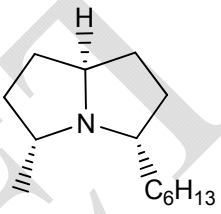
1.4 Indolizidines of interest in this project

1.4.1.1 Introduction to indolizidine 209D

The 5-monosubstituted indolizidine 209D (**37**) was the tentatively proposed structure of a natural product isolated from a dendrobatid frog and was one of the only two members of this class. It has since been shown that the real structure of this natural product is a pyrrolizidine and it has subsequently been renamed as 209K (**39**). It remains unclear as to whether this class of alkaloids does exist in Nature; however, indolizidine 209D has been the target alkaloid of many syntheses over the past thirty years and remains a popular choice for demonstrating the scope of new synthetic methodology.



[37]



[39]

Indolizidine 209D became the first target molecule of this project as a previous student at the University of the Witwatersrand had already performed extensive research into its total synthesis.[31] Repeating the experiments and optimising the reactions offered good experience with this type of chemistry and allowed for complete characterization of all the molecules in the synthesis for the purpose of publication.

1.4.1.2 Previous syntheses of indolizidine 209D

To date there have been at least twenty-five publications detailing the total synthesis of indolizidine 209D. Each of these publications uses a disconnection quite different from the one we chose to employ in our synthesis. Figure 1.2 shows the key cyclisation disconnections used by other research groups. Table 1.1 gives a detailed breakdown of which isomer was synthesized by which disconnection and the numbers in the columns are literature references to these publications.

WiSETD

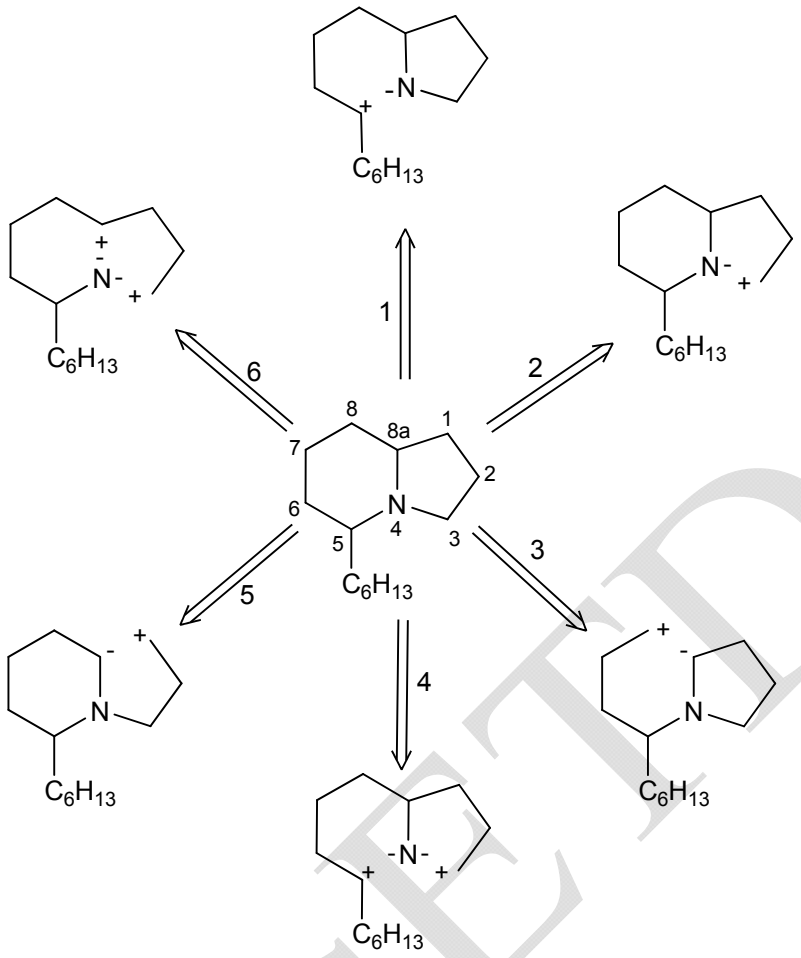


Figure 1.2: Cyclisation disconnections used in previous syntheses of indolizidine 209D.

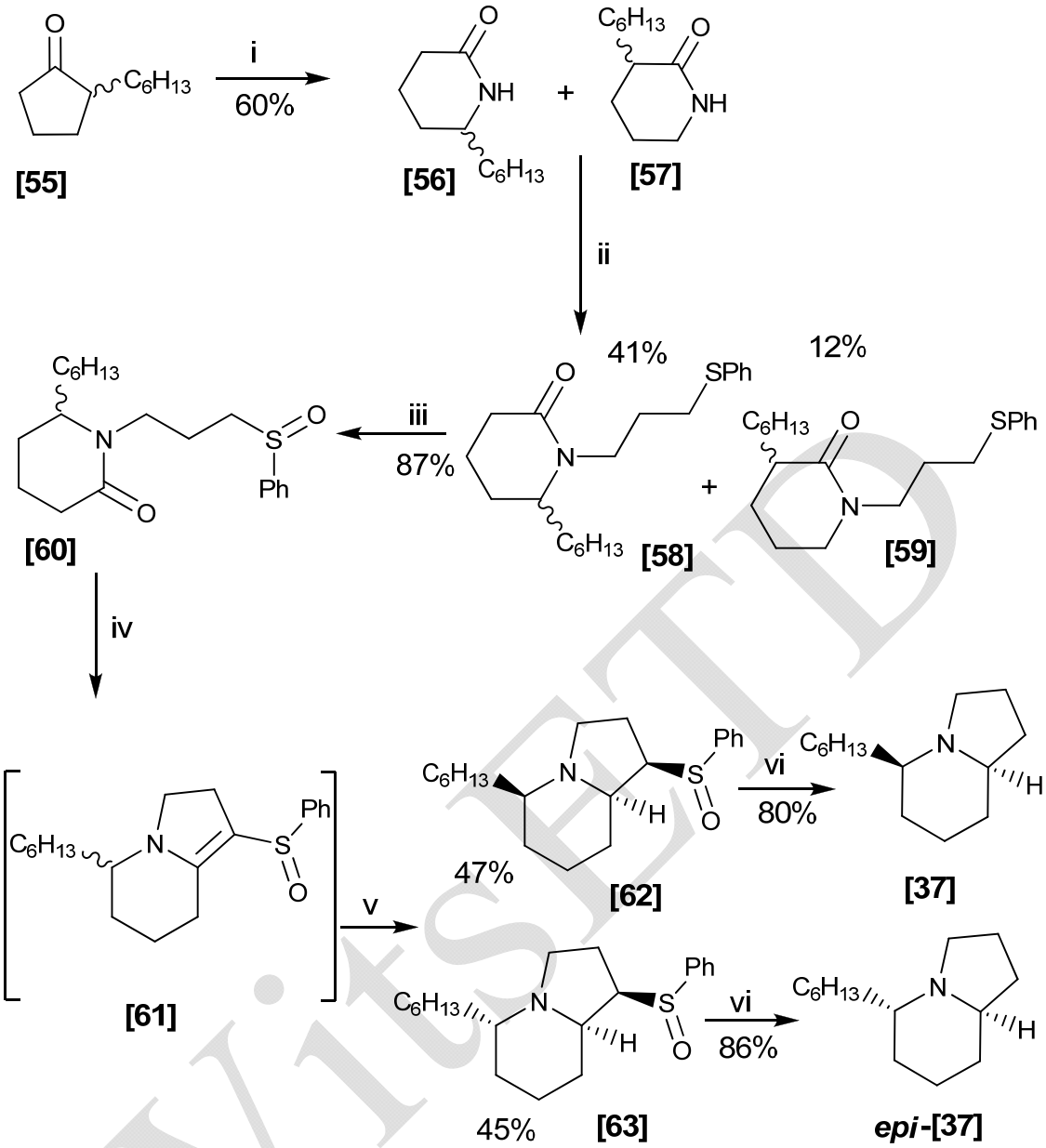
Disconnection	(+)-209D	(−)-209D	(±)-209D
1	32	32 - 36	37, 38
2	39, 40, (5-*epi*)-41	42	
3		43	44
4		45	
5	46, 47	48	49
6		50, 51	52
OTHER		53 - 56	44, 57

Table 1.1: Key disconnections in the synthesis of indolizidine 209D (literature references to the previous syntheses of indolizidine 209D are given in columns 2 – 4).

The C_{8a} –C_1 disconnection approach

Pohmakotr *et al.*[49] used disconnection 5 (see Figure 1.2 and Table 1.1) to synthesize the indolizidine skeleton. Synthesis of the δ-lactam (**56**) was achieved in 60% yield by the Beckmann rearrangement of 2-hexylcyclopentanone (**55**) using sodium hydroxide and tosyl chloride (see Scheme 1.1). This reaction gave an inseparable mixture of lactams (**56**) and (**57**) in a 4:1 ratio. This mixture was treated with 1-bromo-3-phenylsulfonylpropane and sodium hydride to give sulfides (**58**) and (**59**) in 41% and 12% yield respectively. Sulfide (**58**) was separated from sulfide (**59**) and was oxidized in the presence of sodium periodate to give sulfoxide (**60**) in 87% yield. The key step in this synthesis was the cyclisation step which was promoted by deprotonating the α-position of the sulfoxide. This allowed ring closure onto the lactam carbonyl to give indolizidine (**61**). Due to the instability of (**61**) it was used without purification to give the reduced product (**62**) and its diastereomer (**63**) in 47% and 45% yield respectively, over the two steps. Initial desulfurization attempts using a sodium amalgam or Raney nickel proved unsuccessful, and finally the synthesis was completed by removing the sulfoxide group with nickel boride to give racemic indolizidine 209D (**37**) and its epimer in 80% and 86% yield respectively. The total synthesis of racemic 209D was achieved in six steps with an overall yield of 8%.

WitsETD

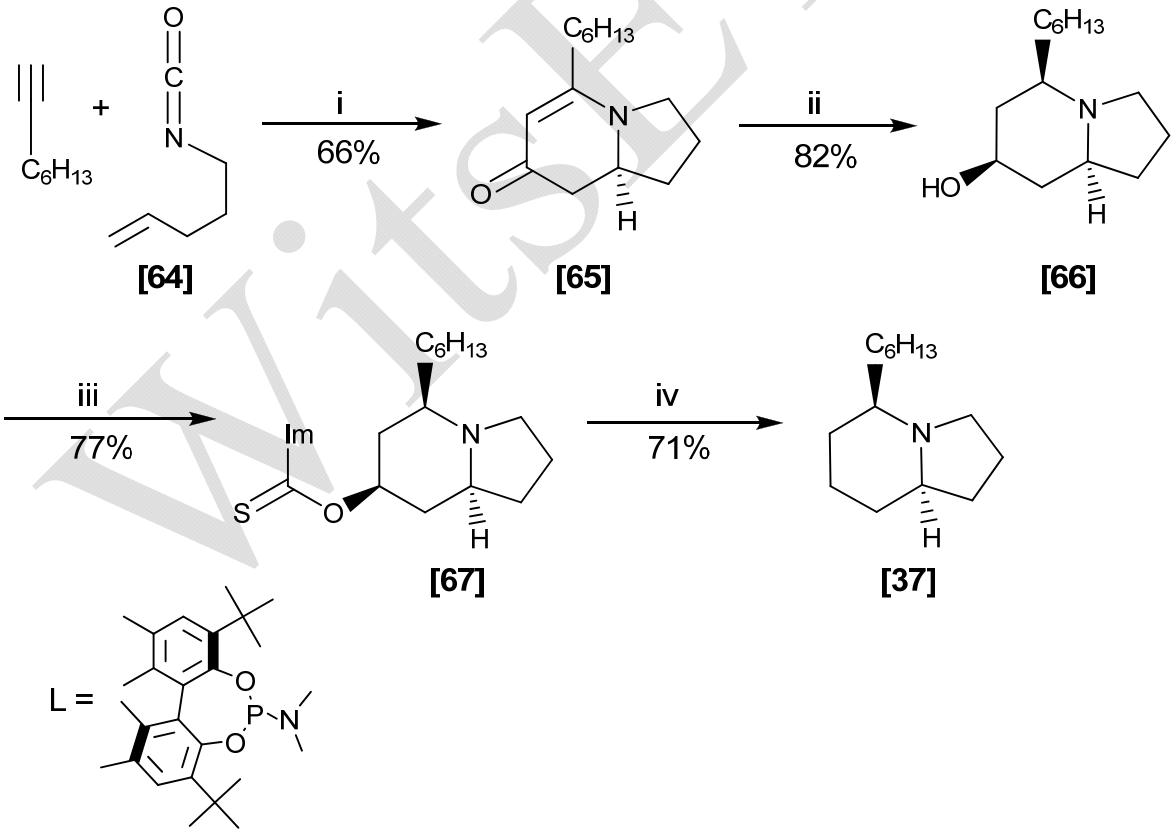


Scheme 1.1: Total synthesis of indolizidine 209D by Pohmakotr and co-workers.[49] *Reagents and conditions: i) a) $NH_2OH.HCl$, EtOH; b) TsCl, NaOH, acetone, RT, overnight; ii) NaH, DMF, $PhS(CH_2)_3Br$, 0°C, to RT, overnight; iii) $NaIO_4$, MeOH, H_2O, 0°C, to RT, overnight; iv) LiHMDS, THF, -78°C, to RT, overnight; v) $NaBH_4$, MeOH, 0°C, to RT overnight; vi) $NiCl_2.6H_2O/NaBH_4$, MeOH/THF (3:1), 0°C, to RT, 2 hr.*

WitsETD

Alternative disconnections

Yu *et al.*[53] developed an efficient catalyst system that promotes cycloadditions between terminal alkyl alkynes and alkenyl isocyanates involving a carbonyl migration process. This technology was the key step in their synthesis of indolizidine 209D (**37**) (see Scheme 1.2). The [2+2+2] cycloaddition of an alkenyl isocyanate (**64**) and a terminal hexyl alkyne was attempted with various catalyst systems. The catalyst that gave the highest conversion and enantiomeric excess produced indolizidine (**65**) as the principal product in a yield of 66% and an *ee* of 91%. Vinylogous amide (**65**) readily underwent diastereoselective reduction in the presence of hydrogen and palladium to give compound (**66**) as a single diastereomer in 82% yield. The Barton-McCombie protocol for deoxygenation via (**67**) was employed to give (−)-indolizidine 209D (**37**) in 55% yield. Starting from the alkyne, the total synthesis was achieved in four steps with an overall yield of 30%.

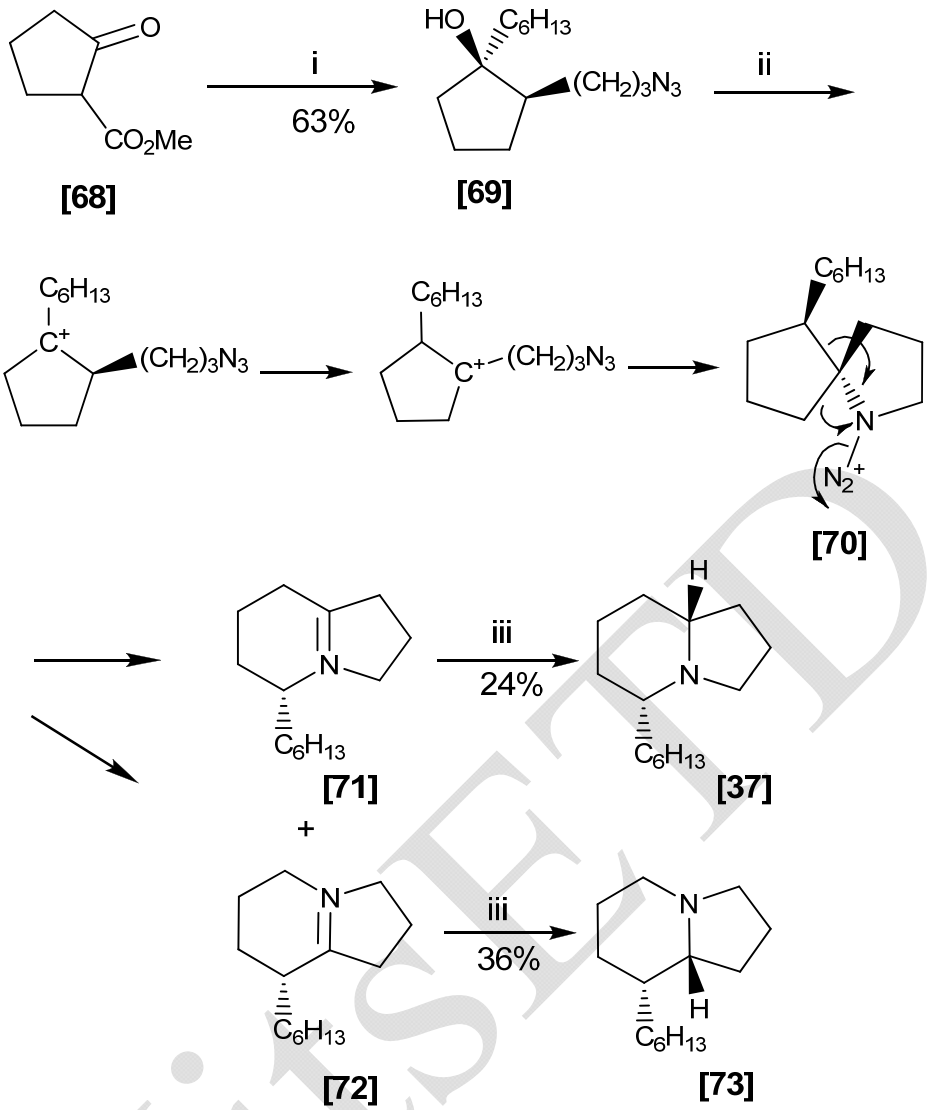


Scheme 1.2: Total synthesis of indolizidine 209D by Yu and co-workers.[53] *Reagents and conditions: i) 2.5 mol% $[Rh(C_2H_4)_2Cl]_2$, 5.0 mol% L-CH_2OTIPS, PhMe, 110°C, 12 hr.; ii) Pd-C, MeOH, H_2, (1 atm.); iii) $(imidazole)_2CS$, DMAP, neat, 50°C; iv) AIBN, Bu_3SnH, PhMe, 100°C.*

WitsETD

Pearson *et al*.[54, 55] employed an approach that utilizes intramolecular Schmidt reactions of azides with carbocations (see Scheme 1.3). Starting from known β-ketoester (**68**) alkylation with chloropropyl iodide at the α-position, followed by azide formation and a second alkylation at the ketone with n-hexyl magnesium bromide and cerium chloride gave alcohol (**69**) in 30% yield over the three steps. Alcohol (**69**) was dehydroxylated to generate a carbocation which rearranged rapidly by means of a 1,2 hydride shift to give a second carbocation that underwent intramolecular cyclisation onto the azide to produce the spirocyclic aminodiazonium ion (**70**). Migration of the adjacent bonds formed iminium ions (**71**) and (**72**). Reaction with sodium borohydride produced indolizidine 209D in 24% [from (**69**)] and its structural isomer (**73**) in 36% yield [from (**69**)]. The total synthesis took five steps and produced indolizidine 209D in 7.2% yield.

WitsETD

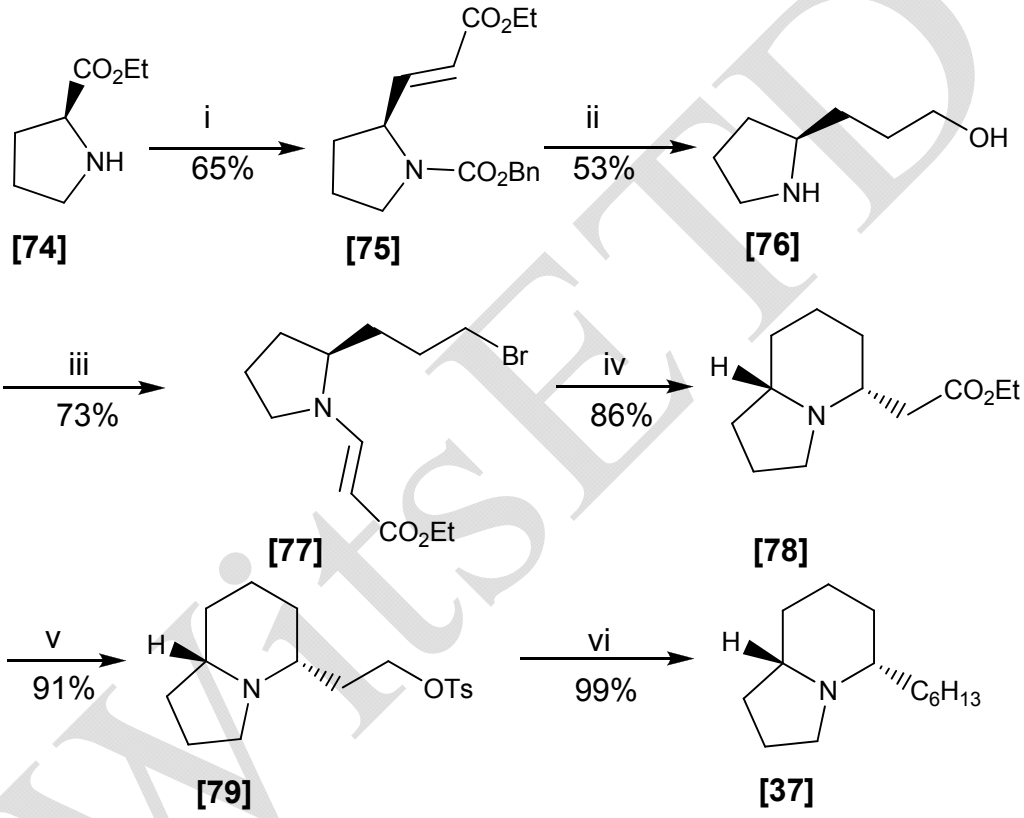


Scheme 1.3: Total synthesis of indolizidine 209D by Pearson and co-workers.[54] *Reagents and conditions: i) a)* t-*BuOK, Cl(CH$_2$)$_3$I; b) HBr, NaN$_3$; c)* n-*hexyl MgBr, CeCl$_3$, THF, 1 hr.; ii) TfOH, benzene; iii) NaBH$_4$.*

Lee and Li[55] started from *S*-proline ester (**74**) (see Scheme 1.4) which they protected with Cbz, followed by a borane reduction to the corresponding aldehyde and transformation to pyrrolidine acrylate (**75**) by a Horner-Emmons reaction in 65% yield for the three steps. Pyrrolidine (**75**) was hydrogenated and the ester was reduced with lithium aluminium hydride to give alcohol (**76**) in 53% yield over the two steps. The alcohol (**76**) was treated with ethyl propiolate and brominated to give the key intermediate β-amino acrylate (**77**) in 73% yield over the two steps. The radical derived from the primary bromide of (**77**) underwent intramolecular conjugate addition to the β-amino acrylate to form the indolizidine skeleton as a single stereoisomer (**78**) in 86% yield. Reduction of

WiSER

the ester (**78**) followed by activation of the resulting alcohol with a tosyl group gave indolizidine (**79**) in 91% yield over the two steps. The final step, homologation of the alkyl side chain with an appropriate dialkylcuprate, gave indolizidine 209D (**37**) in 99% yield. This route serves as a general route to 5-monosubstituted indolizidine alkaloids and the use of a different dialkylcuprate in the final step gave access to indolizidine 167B as well. The total synthesis was achieved in eleven steps and produced indolizidine 209D in an overall yield of 19%.

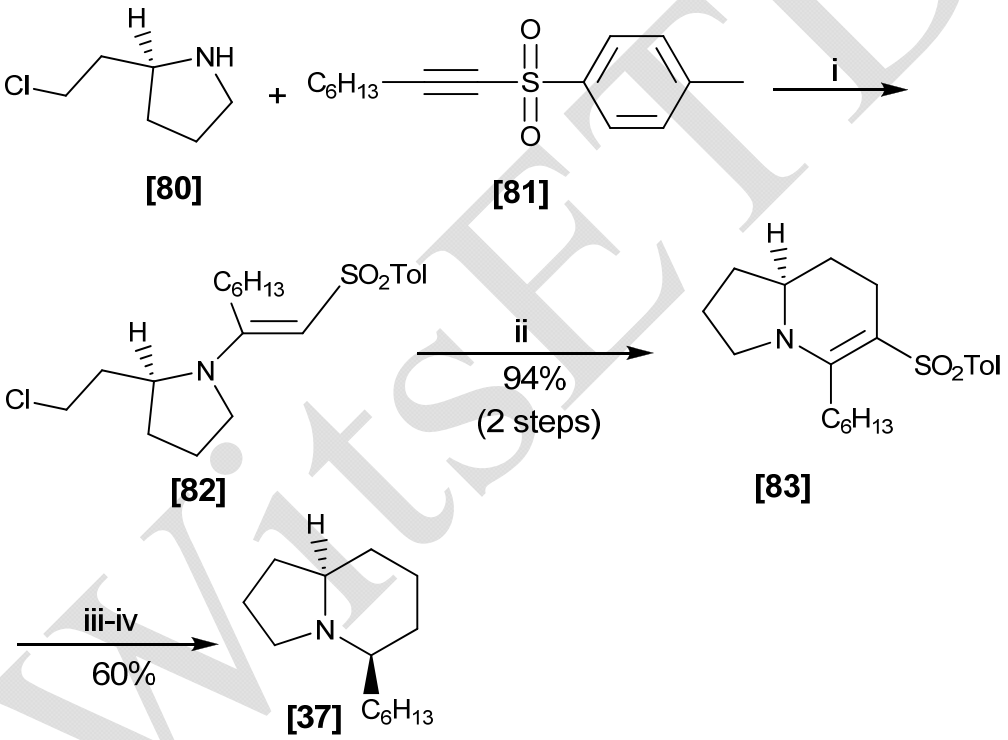


Scheme 1.4: Total synthesis of indolizidine 209D by Lee and co-workers.[55] *Reagents and conditions: i) a) $ClCO_2Bn$, NaOH; b) BH_3.DMS, THF; c) Py.SO_3, Et_3N, DMSO, Ph_3PCHCO_2Et; ii) a) H_2, $Pd(OH)_2$, MeOH; b) $LiAlH_4$, THF; iii) a) $HCCCO_2Et$, p-TsCl, Et_3N, CH_2Cl_2; b) LiBr, acetone; iv) Bu_3SnH, AIBN, benzene, reflux, 5 hr.; v) a) $LiAlH_4$, THF; b) p-TsCl, Et_3N, CH_2Cl_2; vi) $(C_6H_{13})_2CuLi$, ether, 0°C.*

The synthetic strategy employed by Back and Nakajima[56] is of particular interest to us as it utilizes vinylogous sulfonamides (see Chapter 2, Section 2.2.2). Their synthesis relies on the coupling reaction of proline-derived chloroamine (**80**) and an alkynyl sulfone (**81**) (see Scheme 1.5). The acetylenic group is activated by the electron withdrawing sulfone allowing it to participate

WitsETD

in conjugate additions to give β-substituted vinyl sulfones (vinylogous sulfonamides). These can then be deprotonated at the α-position due to the anion stabilization of the sulfone and then reacted with electrophiles. The products can easily be desulfonylated by exposure to Birch reduction conditions. Chloroamine (**80**) was coupled with alkynyl sulfone (**81**) to give the vinylogous sulfonamide (**82**). In the presence of base (**82**) underwent intramolecular cyclisation to give indolizidine (**83**) in an efficient 94% yield over the two steps. Stereoselective reduction of the conjugated double bond followed by cleavage of the sulfone with sodium in ammonia gave indolizidine 209D (**37**) in a respectable yield of 60%.



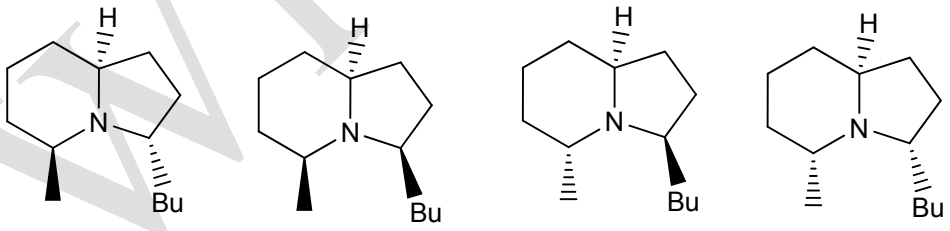
Scheme 1.5: Total synthesis of indolizidine 209D by Back and Nakajima.[56] *Reagents and conditions: i) THF, reflux; ii) LDA, THF, -78°C; iii) $NaBH_3CN$, MeOH; iv) Na, NH_3 liq.*

This completes the brief overview of published syntheses of indolizidine 209D. Several of the additional publications follow analogous synthetic strategies to those detailed in section 1.4.2.2. Chapter 2 describes how our proposed synthesis differs from previously published syntheses and how we exploited novel methodology in an attempt to achieve the total synthesis of 209D.

WitsETD

1.4.2.1 Introduction to monomorine I

The second target natural product of this project was monomorine I (**27**), and its total synthesis formed the bulk of the original research conducted during this project. Monomorine I (**27)** has frequently been used as a target molecule to illustrate the applicability of new synthetic methodology. It is the natural target molecule for any new methodology developed for the synthesis of 3,5-disubstituted indolizidines as it is appropriately simple and has served as a target for many research groups. It thus allows for easy comparison between the different methods available. Monomorine I (**27**) was first detected in the pheromone trail of the myrmicine ant, *Monomorium pharaonis,* in 1973. Monomorine I was isolated from *Monomorium pharaonis* along with alkaloids monomorine II – VI (**84** – **88**), all in the scent trail mix (see Figure 1.3).[30, 58] Monomorene was also isolated and its structure was revealed as a bicyclic saturated hydrocarbon.[58] Monomorine (**27**) was the first indolizidine derivative discovered in the animal kingdom.[30, 59] It originates in the abdominal gland and is found both in the poison gland, the Dufour's gland and in sting excretions.[59] Five years later, one of its diastereoisomers was discovered in a frog skin extract and became known as indolizidine 195B (**26**) after its molecular weight and chronology of discovery.[17] Subsequently all four diastereomers of 3-butyl-5-methylindolizidine (**26 – 29**) have been detected in frog skin extracts.[21]



[26] **[27]** **[28]** **[29]**

WISETD

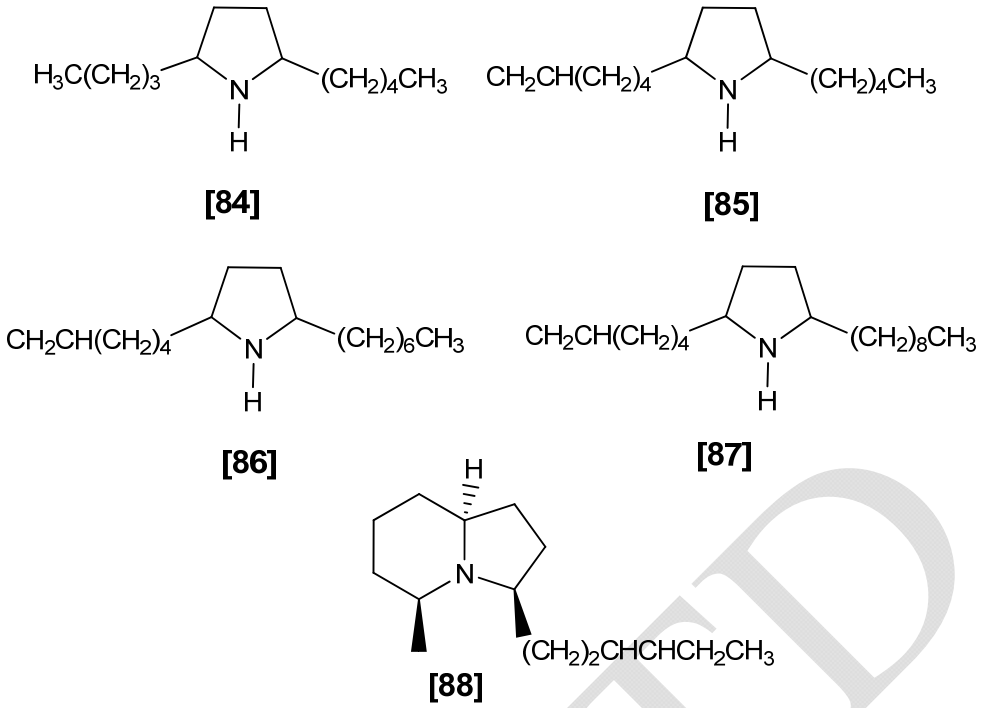


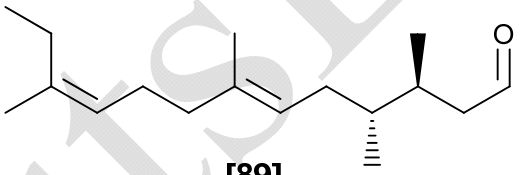
Figure 1.3: Monomorine II – VI (**84 – 88**), isolated from the *Monomorium pharaonis* scent trail mix.

The Pharaoh ant, *Monomorium pharaonis* is a tiny, red-brown ant that is 2 – 3 mm in size and small enough to penetrate bandages and sterile packaging. Originally a tropical species, it has now become a domestic pest in non-tropical countries in both North America and Western Europe, and the ants are attracted to heated buildings, particularly hospitals, bakeries and households.[29, 58] Their attraction to wound exudates, beds soiled with urine and baby slobber, combined with their ability to carry pathogenic bacteria causes them to transmit disease.[29, 30, 58] Their well concealed nests and multi-queened colonies that thrive in small wall spaces have eluded most insecticides.[60] There is a need to detect and control infestations at an early stage or it becomes almost impossible to route out the queens and the nests.[60]

A famous infestation of the Biological Laboratories of Harvard University during the 1960s and 1970s was finally exterminated after discovering that the worker ants had carried radioactive chemicals from culture dishes to the surrounding walls (coincidently this inspired the science-fiction novel “Spirals” by William Patrick).[60] Shortly thereafter the Dutch Ministry of Public Health and Environmental Hygiene commissioned research into trail pheromones as a

WITSETD

potential means to control the ant population.[59] It had been noted that trail-following behaviour was common in both the queens and the workers and it was hypothesized that the trail pheromones could be used to trap the ants and thus exterminate them.[59] It was demonstrated that a crude hexane extract of homogenized ants could induce trail-following behaviour in the ants. Monomorine I (**27**) was one of the components in the ant-trail mix. Studies revealed that the trail following activity is both concentration dependent and synergistic.[29] The term pheromone is no longer a valid term for a single molecule, as it is often refers to a mixture of compounds that creates the 'pheromone' effect.[59] This is definitely the case for monomorine I (**27**) as the mutually synergizing mixtures of alkaloids are far more active than the individual compounds.[29, 59, 61] Dual or multiple functions are suspected for most of these alkaloids, as sex attractants, insect repellents, trail markers, antimicrobials etc.[58] The most active component of the trail pheromones is in fact faranal (**89**), a sesquiterpenoid also found in the Dufour's gland, with as little as 1 picogram giving a positive trail following result.[62, 63]



[89]

Monomorine I (**27**) seems to play a role both as a trail marker, a repellent and in allomone defence.[59] It has been demonstrated as a repellent against ants when combined with 2,5-dialkylpyrrolidines.[61] Interestingly, it is only the 5*Z*,9*Z* isomer of 3-butyl-5-methylindolizidine that has both attractant and arrestant (causing aggregation) activities in feeding studies with *M. pharaonis*.[61]

Monomorine I (**27**) has three stereogenic centres, and therefore could exist as one of eight stereoisomers. The nitrogen atom is an sp^3 hybridized centre, however the atomic inversion energy is easily overcome. In most indolizidines the *trans*-fused ring junction is dominant at equilibrium. Bohlmann determined that if two or more α hydrogen atoms were *anti*-periplanar to the lone pair on the nitrogen then bands would be observed in the *infra*-red spectrum in the

WitsETD

region of 2790 cm^{-1}. Therefore the presence or absence of these bands could be used to determine the favoured ring junction configuration. In fact, a single hydrogen atom *anti*-periplanar to the nitrogen lone pair also gives a band in the IR spectra, but it is often obscured by methylene signals.[4] In addition, the coupling constants and chemical shift in the ^{1}H-NMR spectra could be used to determine the conformation of the molecule.[4]

Initially the favoured chair conformer was expected for monomorine I, but the spectroscopic evidence accumulated accommodates the *trans*-fused boat conformer as illustrated in Figure 1.4. NMR spectral evidence supports this conformation as long-distance *cis*-coupling of the hydrogen atoms shown in Figure 1.4 is also observed.[1, 4]

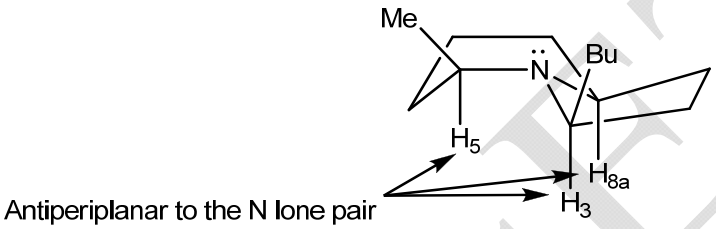
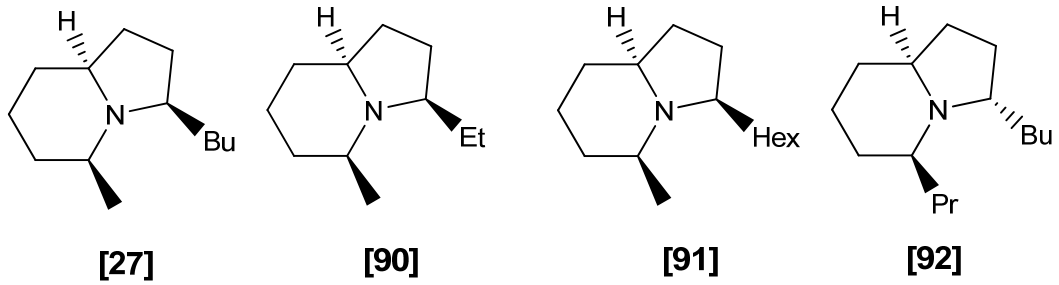


Figure 1.4: The preferred, *trans*-fused boat conformation of monomorine I.

The *trans*-fused indolizidine ring shows a single, weak, Bohlmann band due to the *cis*-relationship of H-5 and H-8a at approximately 2790 cm^{-1}.[2] This allows assignment of the relative configuration, but not the absolute configuration. The relative configuration of monomorine I (**27**) was elucidated by NMR spectral comparison of the natural compound to the four major diasteromers. The absolute configuration of monomorine I (**27**) has been established as 3*R*,5*S*,9*S* and that of indolizidine 195B (**26**) as 3*S*,5*S*,9*S*.[4] Many differing stereoselective syntheses have been attempted with varying degrees of success.

Structurally similar alkaloids to those found in the Pharaoh ant were discovered in dendrobatid frog species in 1986.[3] Several of these 3,5-disubstituted indolizidine alkaloids are shown below (see Figure 1.5) (**27** + **90 – 92**). These provide additional synthetic targets for the methodology outlined in this project.

WisETD



[27] **[90]** **[91]** **[92]**

Figure 1.5: Monomorine I (**27**) and structurally related indolizidines (**90 – 92**).

1.4.2.2 Previous syntheses of monomorine I

During the development of methodology for synthesizing monomorine I (**27**), all four diastereomers have been synthesized. As all four diastereomers are natural products all these syntheses have value and application in natural product chemistry. The many different synthetic routes have varying degrees of stereoselectivity and in the different syntheses, different enantiomers have been favoured as the final product. When comparing the approaches adopted by different research groups working on monomorine I and its diastereomers, and 3,5-disubstituted indolizidines in general, the key difference shows up in the cyclisation step (Figure 1.6 and Table 1.2), and although monomorine I has already been synthesised many times, the methodology envisaged in this project will provide a novel cyclisation strategy to 3,5-disubstituted indolizidines.

The first successful synthesis of monomorine I was performed by Ritter *et al.*[30] in 1973. But it was only when Oliver and Sonnet[64] synthesized all the diastereomers of monomorine I in 1974, making use of stereoselective reactions, that the relative stereochemistry of monomorine I was established. The first synthesis to give exclusively (+)-monomorine I was performed by Yamazaki and Kibayashi[65] in 1988 and it incorporated disconnection 1 (see Figure 1.6) as the key disconnection. This was also the first disconnection that led to the successful synthesis of indolizidine 195B.[7] Table 1.2 shows which disconnections from Figure 1.6 were used for the total synthesis of (+)-monomorine I, (−)-monomorine I and (±)-monomorine I.

WISER

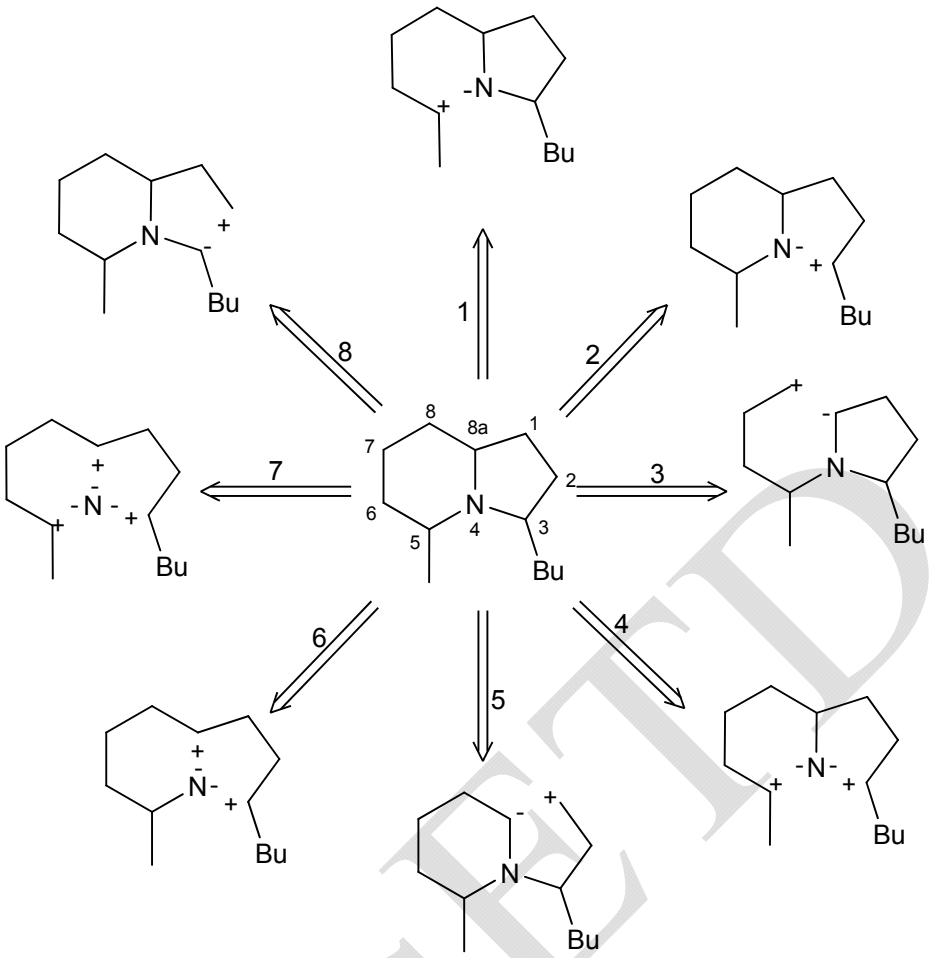


Figure 1.6: Cyclisation disconnections used in previous syntheses of monomorine I.

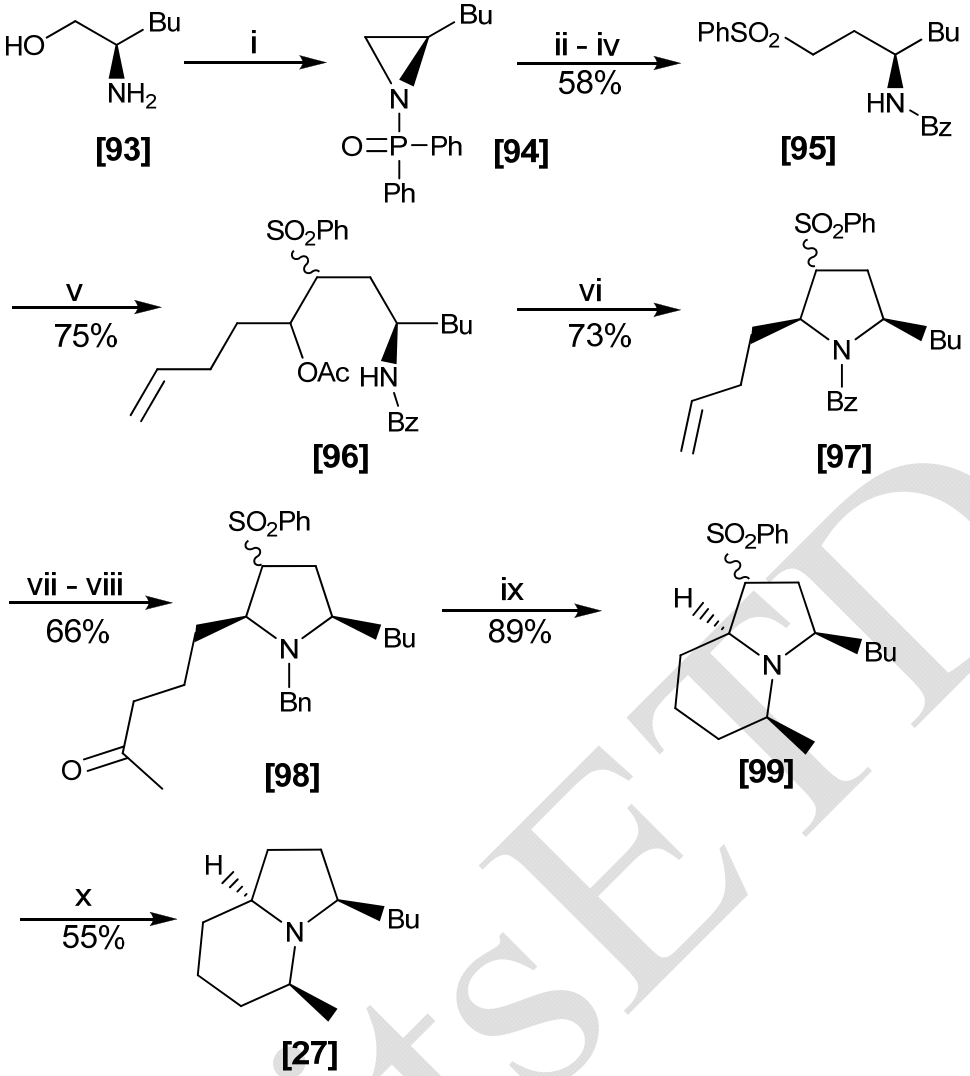
Disconnection	(+)-monomorine	(−)-monomorine	(±)-monomorine
1	65 - 76	77	64, 78 - 83
2	73, 84 - 90	91, 92	93 - 101
3		102 - 104	105 - 107
4	108 - 110		
5			111
6			112
7			113
8	114		
195B	19, 66, 84, 115, 116	117 - 120	101

Table 1.2: Key disconnections in the synthesis of monomorine I (literature references to the previous syntheses of monomorine I are given in columns 2 – 4).

Disconnection 1: The C_5 - N disconnection approach

Berry and Craig[67] prepared (+)-monomorine I in eleven steps starting from chirally pure D-norleucine (see Scheme 1.6). A key feature of their synthesis was the highly stereoselective ring closure, via a 5-*endo-trig* cyclisation. Enantiopure aziridine (**94**) was prepared in two steps from D-norleucine via amino alcohol (**93**) and then exposed to anion ring opening by methyl phenyl sulfone at the less substituted carbon. The resulting amine was dephosphonylated and reprotected with a benzoyl group to give (**95**) in 58% yield over the three steps. Compound (**95**) was deprotonated with a strong base and condensed with hex-5-enal. The resulting alkoxy anion was trapped by acetylation to give (**96**) in 75% yield. Treatment of (**96**) with base resulted in a one-pot elimination of acetic acid and a 5-*endo-trig* cyclisation to give (**97**) in 73% yield. Pyrrolidine (**97**) was formed as a single diastereomer as confirmed by X-ray diffraction. Reduction of the benzoyl group followed by a modified Wacker oxidation gave (**98**) in 66% yield. Debenzylation of pyrrolidine (**98**) resulted in spontaneous reductive amination to give indolizidine (**99**) as a single isomer. Desulfonylation using sodium naphthalenide gave the resulting (+)-monomorine I (**27**) in a 10% overall yield for the eleven steps.

WitsETD



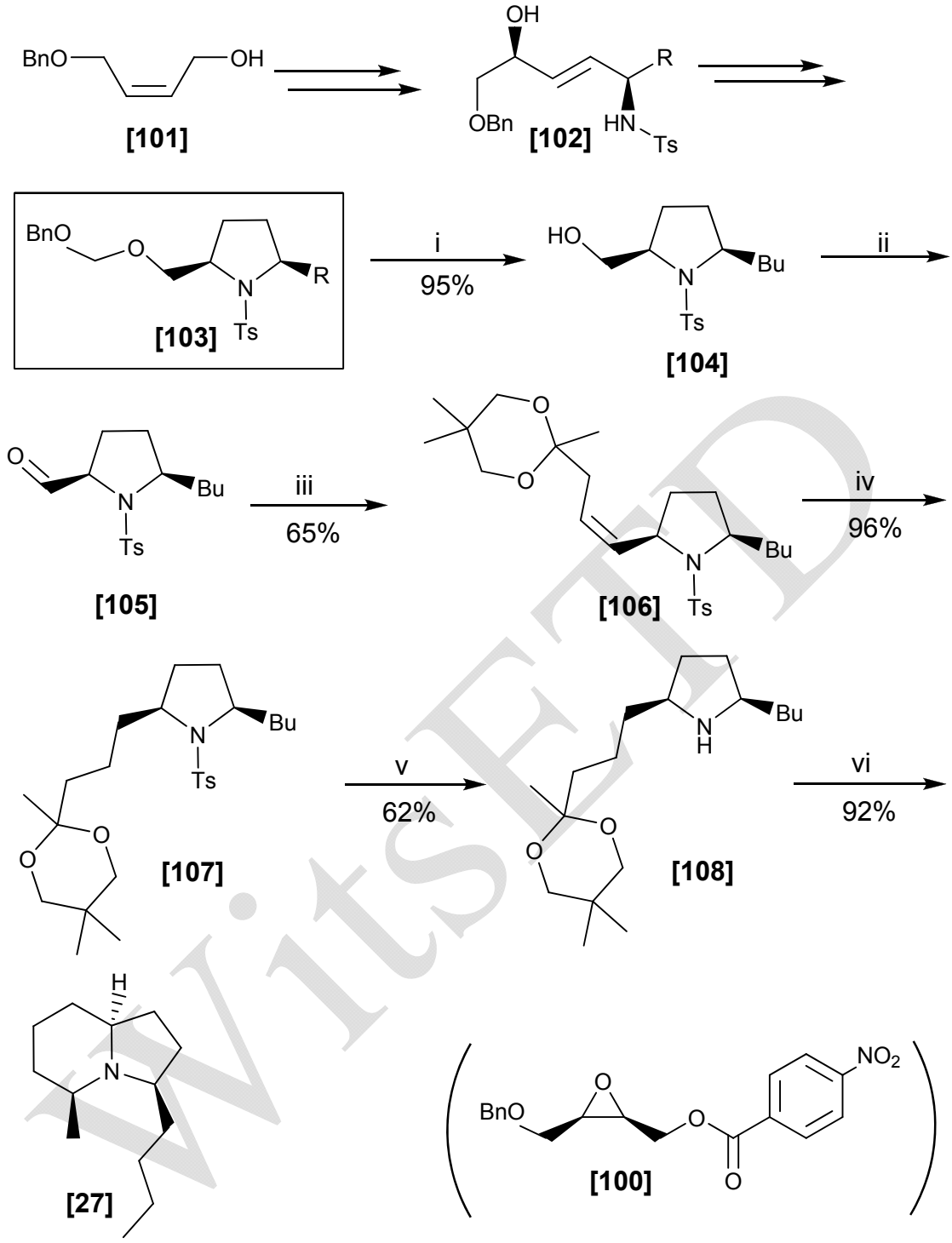
Scheme 1.6: Total synthesis of monomorine I by Berry and Craig.[67] *Reagents and conditions: i) a) $Ph_2P(O)Cl$ (2.1 eq.), Et_3N (3 eq.), THF, 0°C → RT, 12 hrs.; b) excess NaH, RT, 1 – 2 weeks; ii) $PhSO_2Me$ (1 eq.), BuLi (1 eq.) 3:1 THF-$Me_2N(CH_2)_2NMe_2$, -78°C → RT, 12 hrs.; iii) $BF_3.OEt_2$ (10 eq.) 1:1 CH_2Cl_2-MeOH, RT, 12 hrs.; iv) BzCl (1.2 eq.), pyridine (1.1 eq.), CH_2Cl_2, RT, 12 hrs, work up with $Me_2N(CH_2)_3NH_2$; v) BuLi (2.1 eq.) 3:1 THF-$Me_2N(CH_2)_2NMe_2$, -78°C, add hex-5-enal (1.3 eq.) -78°C, 40 min., then add Ac_2O (5 eq.), -78°C → RT, 12 hrs.; vi) Bu^tOK (2.1 eq.), Bu^tOH (10 eq.), in THF, RT, 12 hrs.; vii) DIBAL-H (4 eq.), CH_2Cl_2, -78°C → RT, 2 hrs.; viii) $Hg(OAc)_2$ (1.05 eq.), 3:1 THF-H_2O, $PdCl_2$ (0.6 eq.), $CuCl_2$ (3 eq.), RT, 1.5 hrs.; ix) 10% Pd-C, cyclohexa-1,4-diene (15 eq.), MeOH, reflux, 4 hrs.; x) $Na^+C_{10}H_8^-$ (3.5 eq.), THF, RT, 5 min.*

Riesinger, Bäckvall and co-worker[70] employed a general approach to indolizidine alkaloids using an easily prepared, common chiral intermediate (**103**) in their synthesis of (+)-monomorine I (see Scheme 1.7). The stereochemistry was introduced either by using Sharpless epoxidation methodology on molecule (**101**) via (**102**) or by purchasing the commercially available chiral epoxide (**100**). Their key step was a novel Wittig coupling with a

SUBMITTED

ketone-protected phosphonium salt. Pyrrolidine (**103**) was subjected to a debenzylation to give (**104**) in 95% yield. Compound (**104**) was oxidized to the corresponding aldehyde (**105**), ready for the Wittig reaction. Wittig coupling gave (**106**) in 65% yield over the two steps. The double bond was reduced using platinum dioxide and the tosyl group was removed using dissolving metal conditions. Compounds (**107**) and (**108**) were obtained in 96% and 62% yields respectively. The final step was the cyclisation reaction which took place under acidic conditions to cleave the ketal and under one atmosphere of hydrogen pressure with activated palladium on carbon to reduce out the resulting imine and afford (+)-monomorine I (**27**) as it hydrochloride salt in 92% yield. The overall yield from the commercially available epoxide (**100**) was 12%.

WitsETD

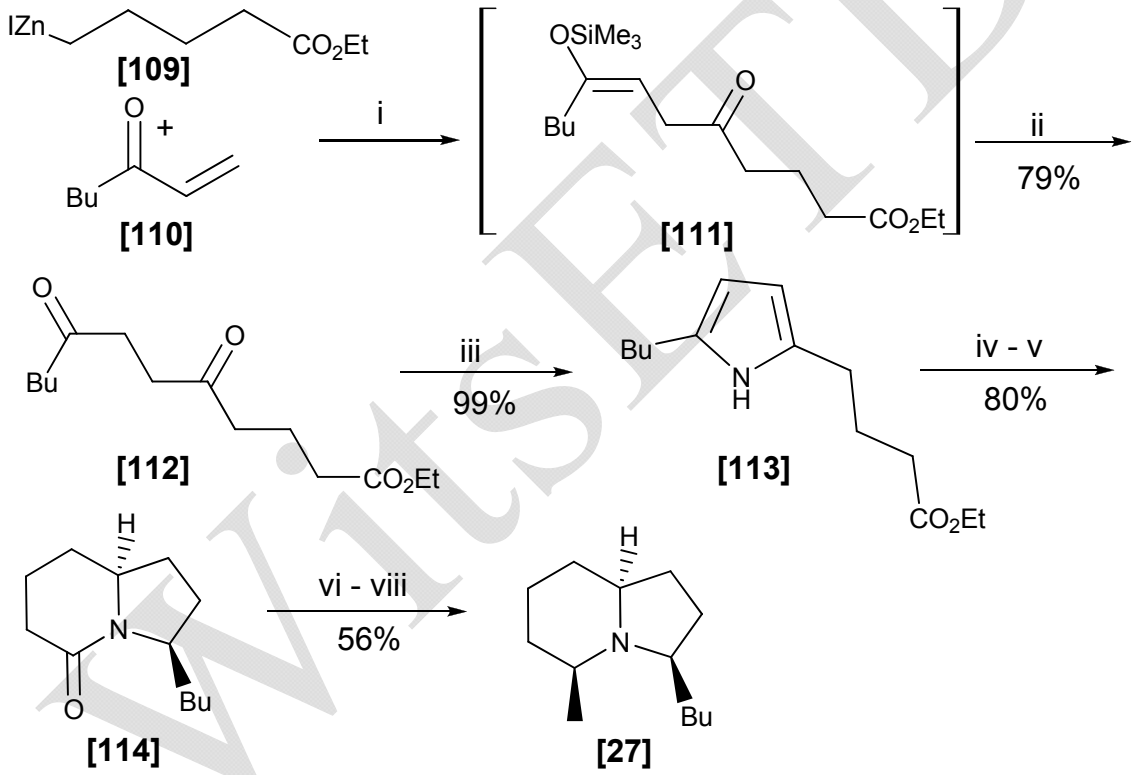


Scheme 1.7: Total synthesis of monomorine I by Riesinger and co-workers.[70] *Reagents and conditions: i) Pd-C, H_2, MeOH; ii) pyridine-SO_3, DMSO, Et_3N, CH_2Cl_2; iii) $Br^-Ph_3P^+(CH_2)_2C(OCH_2C(CH_3)_2CH_2O)CH_3$, Bu^tOK, THF, -78°C; iv) PtO_2, H_2, EtOH; v) Na/NH_3, EtOH, −78°C → RT; vi) 10% Pd-C, H_2, HCl (1.0 M), MeOH.*

Yuguchi, Tokuda and Orito[82] used a synthetic route with the novel feature of a one-pot, four component coupling reaction, palladium catalysed and mediated by an organozinc reagent under a carbon monoxide atmosphere (see Scheme

WitsETD

1.8). 1,4-Diketone (**112**) was prepared by this reaction from organozinc reagent (**109**) and the Michael acceptor (**110**) in 79% yield via intermediate (**111**). The diketone (**112**) was then subjected to a Paal-Knorr reaction with ammonium acetate to give pyrrole (**113**) in 99% yield. Catalytic hydrogenation of pyrrole (**113**) followed by a trimethylaluminium-mediated cyclisation gave indolizidine (**114**) in 80% yield over the two steps. The final steps introduced the methyl group via a Grignard reaction and mild reduction of the resulting alcohol with sodium borohydride. This gave racemic monomorine I (**27**) as a single diastereomer in 56% yield over the three steps. Thus monomorine I was synthesized in a total of eight steps with an overall yield of 35%.



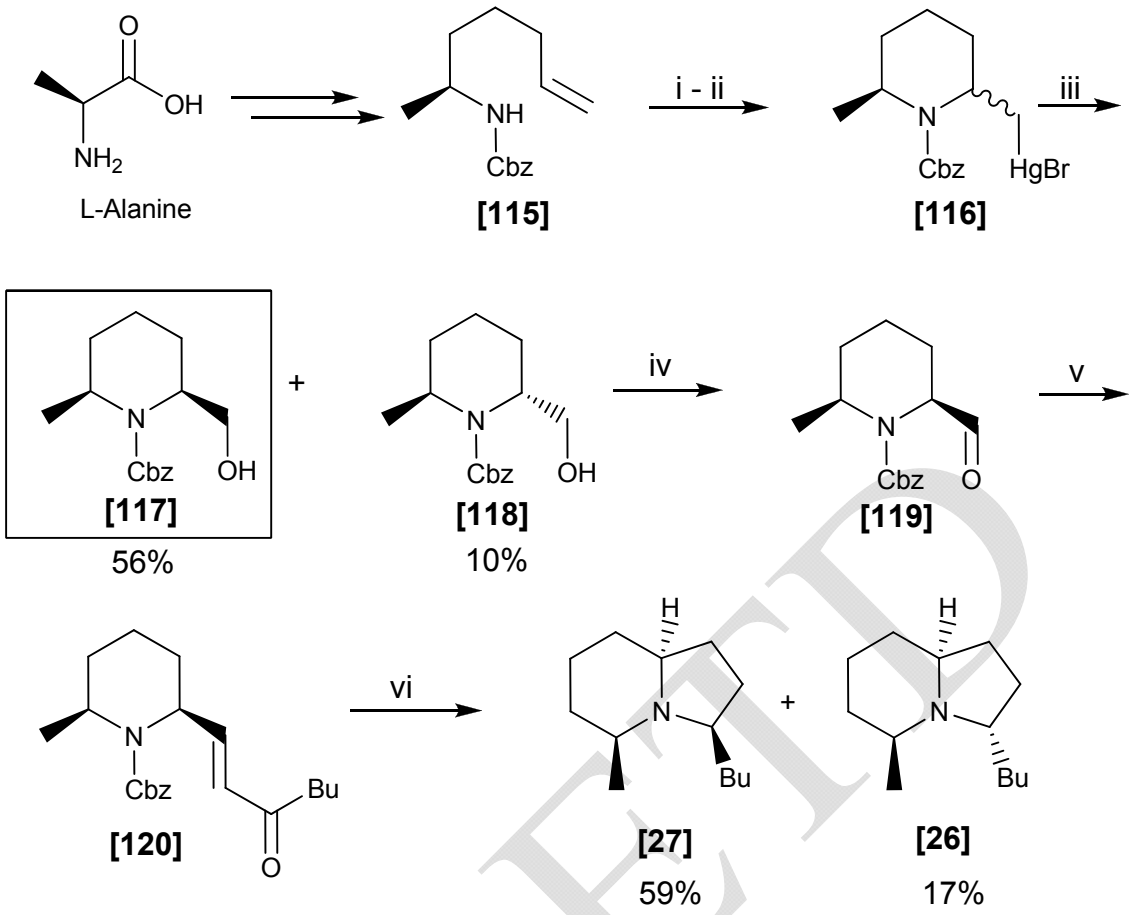
Scheme 1.8: Total synthesis of monomorine I by Yuguchi and co-workers.[82] *Reagents and conditions: i) CO (1 atm.), $Pd(PPh_3)_4$, Me_3SiCl, LiCl; ii) H_3O^+; iii) NH_4OAc, EtOH; iv) H_2 (25 atm.), PtO_2, AcOH; v) Me_3Al, CH_2Cl_2; vi) MeMgBr, THF; vii) AcOH; viii) $NaBH_4$.*

WitsETD

Disconnection 2: The C_3 - N disconnection approach

The presence of 2,6-disubstituted piperidines in ants together with the absence of the 2,5 dialkyl pyrrolidines suggests that the biogenetic pathway forms the 6-membered ring prior to the 5-membered ring. Takahata and Momose[84] chose to follow this "biomimetic" model (see Scheme 1.9). Starting with readily available enantiopure L-alanine, amine (**115**) was prepared. Intramolecular amidomercuration using mercury trifluoroacetate followed by sodium bromide gave piperidine (**116**). Oxidative demercuration with sodium borohydride gave a 5.6:1 *cis* : *trans* mixture of piperidine alcohols (**117**) and (**118**). These diastereomers were separated by column chromatography to give the desired *cis* isomer in 56% yield from amine (**115**). Swern oxidation of the *cis*-piperidine alcohol (**117**) gave the aldehyde (**119**), which was the enantiomerically pure intermediate for the synthesis of several methyl substituted ant indolizidines. Chain homologation by Horner-Emmons reaction gave an (8:1) *E:Z* mixture of the unsaturated enone (**120**). Exposure of enone (**120**) to hydrogen in the presence of Pearlman's catalyst reduced out the double bond, deprotected the nitrogen and allowed the subsequent cyclisation reaction to occur. Finally, the resulting iminium moiety was stereoselectively reduced to give the desired (+)-monomorine I (**27**) in 59% yield, along with its C-3 epimer (**26**) (indolizidine 195B) in 17% yield.

WitsETD



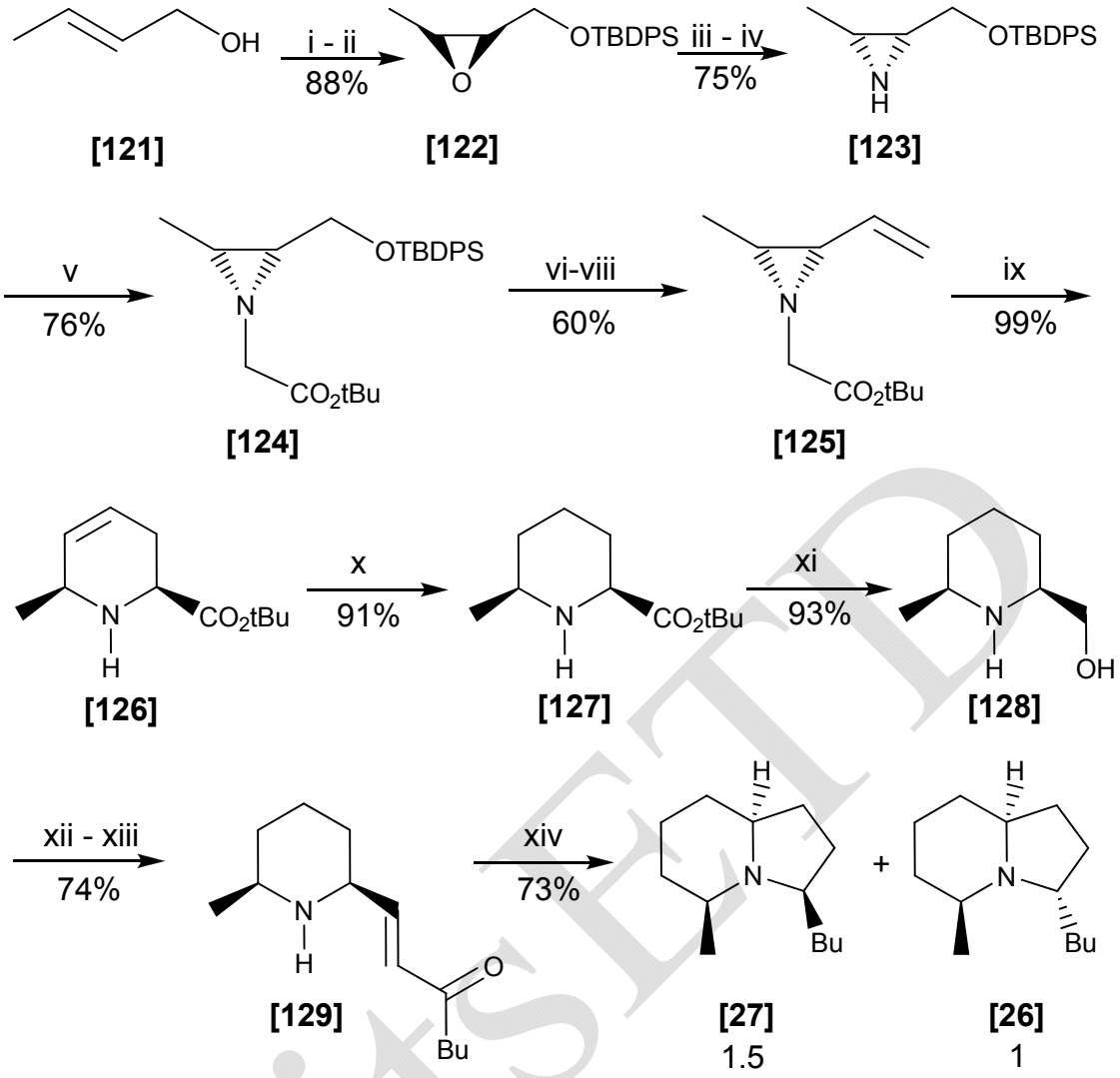
Scheme 1.9: Total synthesis of monomorine I by Takahata and co-workers.[84] *Reagents and conditions: i) $Hg(OCOCF_3)_2$, CH_3NO_2; ii) NaBr, $NaHCO_3$; iii) O_2, $NaBH_4$, DMF; iv) $(COCl)_2$, DMSO, Et_3N; v) $(H_3CO)_2POCH_2CO(CH_2)_3CH_3$, NaH, THF; vi) H_2, $Pd(OH)_2$, MeOH.*

Somfai *et al.*[97] began their synthesis with the protection of alcohol (**121**) followed by epoxidation to give epoxide (**122**) in 88% yield over the two steps (see Scheme 1.10). The epoxide was then converted into aziridine (**123**) in 75% yield by reaction with sodium azide followed by treatment with triphenylphosphine. Aziridine (**123**) was alkylated with *t*-butyl bromoacetate under basic conditions to give compound (**124**) in 76% yield. The silyl group was removed under standard conditions to give a free alcohol which underwent Swern oxidation and Wittig olefination to give the key intermediate vinyl aziridine (**125**) in 60% yield over the three steps. The key step in this synthesis converted vinyl aziridine (**125**) into 2,6-disubstituted piperidine (**126**) via an aza-[2-3]-Wittig rearrangement in the presence of lithium di-isopropylamide in an efficient 99% yield. This reaction gave exclusively the *cis* isomer. Hydrogenation of piperidine (**126**) using 5% palladium on carbon gave poor

WISETD

yields, rather, 5% rhodium-on-carbon was employed to give (**127**) in an excellent 91% yield. Reduction of the *t*-butyl ester gave alcohol (**128**) in 93% yield. This was followed by a Swern oxidation and a Horner-Emmons reaction which gave enone (**129**), almost exclusively as the *Z* isomer, in a reasonable yield of 74%. The final step was reduction of the alkene followed by stereoselective cyclisation by reductive amination in the presence of 5% palladium on carbon. This gave racemic monomorine I (**27**) and racemic indolizidine 195B (**26**) in a 1.5:1 ratio in a combined yield of 73%. In total the synthesis took fourteen steps and gave an overall yield of 8% for (±)-monomorine I (**27**) and 5.4% for (±)-indolizidine 195B (**26**).

WitsETD

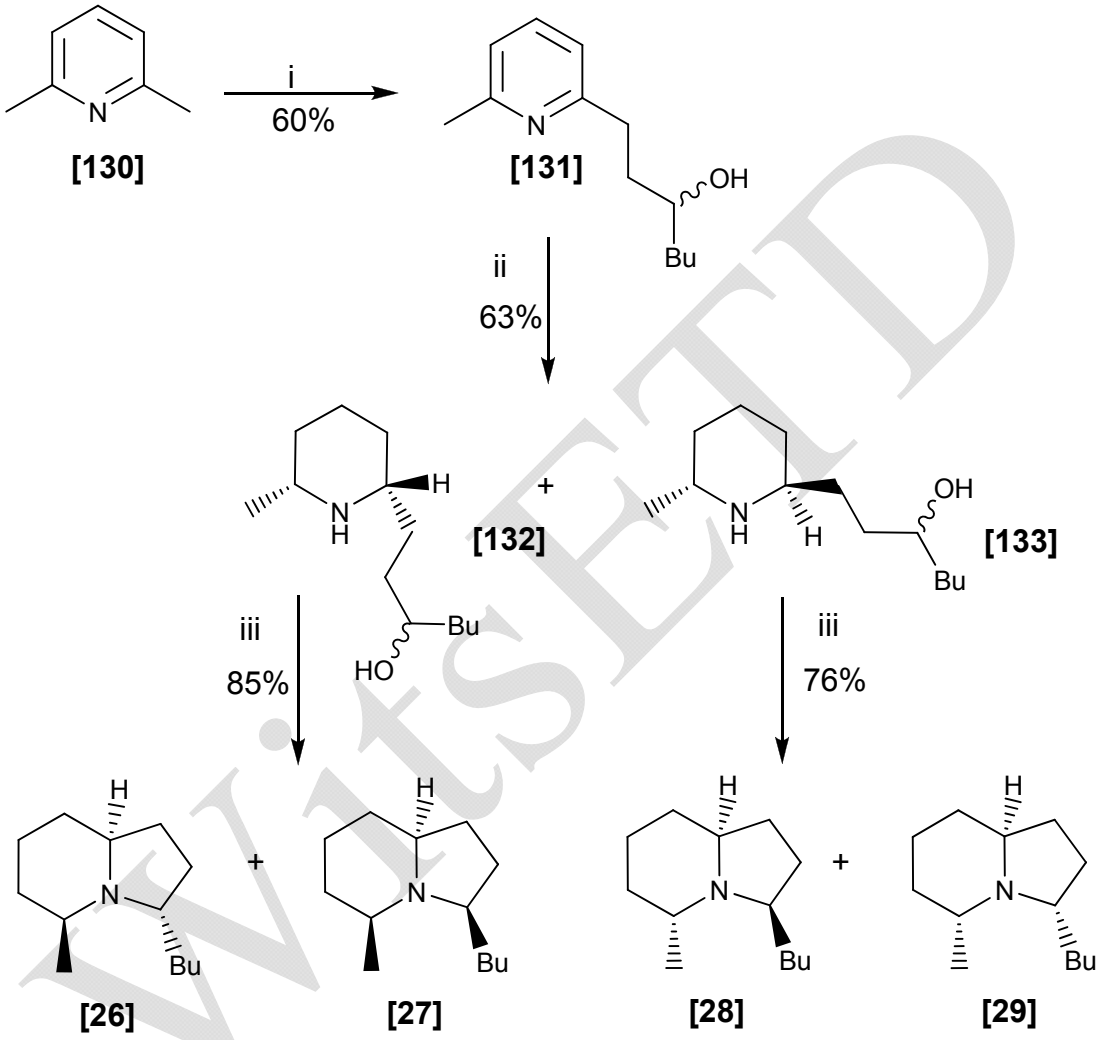


Scheme 1.10: Total synthesis of monomorine I by Somfai and co-workers.[97] *Reagents and conditions: i) t-BuPh$_2$SiCl, Et$_3$N, DMAP, CH$_2$Cl$_2$; ii) m-CPBA, CH$_2$Cl$_2$; iii) NaN$_3$, NH$_4$Cl, MeOCH$_2$CH$_2$OH, H$_2$O, reflux; iv) Ph$_3$P, PhMe, reflux; v)* t*-butyl bromoacetate, K$_2$CO$_3$, 18-crown-6, CH$_3$CN; vi) Bu$_4$NF, THF, 0°C → RT; vii) DMSO, (COCl)$_2$, Et$_3$N, CH$_2$Cl$_2$, -78°C; viii) Ph$_3$PCH$_3$Br, KHMDS, THF, -20°C; ix) LDA, THF, -78°C; x) 5% Rh-C, H$_2$, MeOH; xi) LiAlH$_4$, THF; xii) DMSO, (COCl)$_2$, Et$_3$N, CH$_2$Cl$_2$, -78°C; xiii) (MeO)$_2$POCH$_2$COBu, LiCl, i-Pr$_2$NEt, CH$_3$CN; xiv) 5% Pd-C, H$_2$, MeOH.*

Oliver and Sonnet[64, 100] were one of the first research groups to synthesize monomorine I (see Scheme 1.11). Ritter *et al.*[30] did perform an earlier synthesis, however, at the time they did not know which stereoisomer corresponded to the natural product. Oliver and Sonnet started with 2,6-lutidine (**130**), which was treated with *n*-butyllithium, followed by the addition of 1,2-epoxyhexane to give alcohol (**131**) in 60% yield. Hydrogenation afforded both the *cis* and the *trans* piperidines (**132**) and (**133**) in a 1:1 ratio and a combined yield of 63%. These were separated using spinning band distillation.

WitsETD

Cyclisation of (**132**) using triphenylphosphine bromide followed by triethylamine gave 3-butyl-5-methyloctahydroindolizidines (**26 – 27**) in 85% yield and cyclisation of (**133**) gave (**28 – 29**) in 76% yield. Full interpretation of NMR, IR and MS data allowed assignment of the relative stereochemistry and comparison to the natural products.



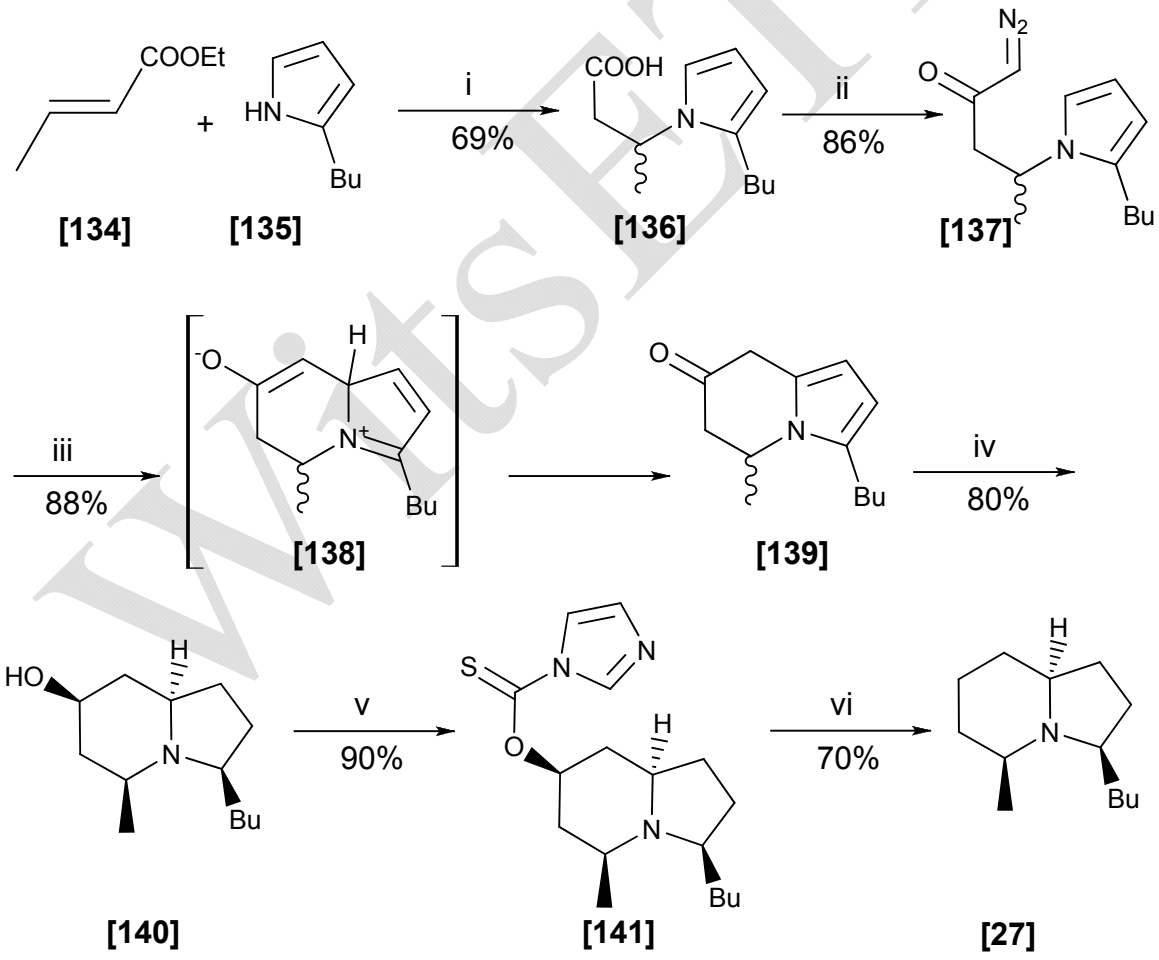
Scheme 1.11: Total synthesis of monomorine I by Oliver and Sonnet.[64, 100] *Reagents and conditions: i) a) BuLi; b) 1,2-epoxyhexane; ii) H_2, PtO_2; iii) a) $Ph_3P.Br_2$; b) Et_3N.*

Disconnection 3: The $C_8 – C_{8a}$ disconnection approach

Jefford *et al.*[105] employed a route that started with a straightforward Michael reaction between ethyl (*E*)-but-2-enoate (**134**) and 2-butylpyrrole (**135**) (see Scheme 1.12). The reaction yielded compound (**136**) in 69% yield, but did not run to completion as 20% of the pyrrole (**135**) was recovered. An Arndt-Eistert chain extension allowed preparation of the key intermediate diazoketone (**137**)

WitsETD

in 86% yield. Rhodium catalysed decomposition of (**137**) resulted in a regioselective cyclisation of the piperidine ring via (**138**) to give (**139**) in 88% yield. Compound (**139**) underwent catalytic reduction in the presence of Adams catalyst and hydrogen gas to give indolizidine (**140**) in 80% yield with all-*cis* geometry due to the stereoselective transfer of hydrogen from the platinum surface. Deoxygenation of (**140**) proved difficult, presumably as the hydroxyl group was in an equatorial position. Jefford *et al.*[105] finally succeeded in removing the hydroxy group by following a procedure developed by Barton and McCombie: The alcohol was converted to an imidazolecarbothionate (**141**) in 90% yield and then reduced by tributylstannane in toluene heated at reflux to give racemic monomorine I (**27**) in 70% yield. The total synthesis was accomplished in six steps with an overall yield of 26%.



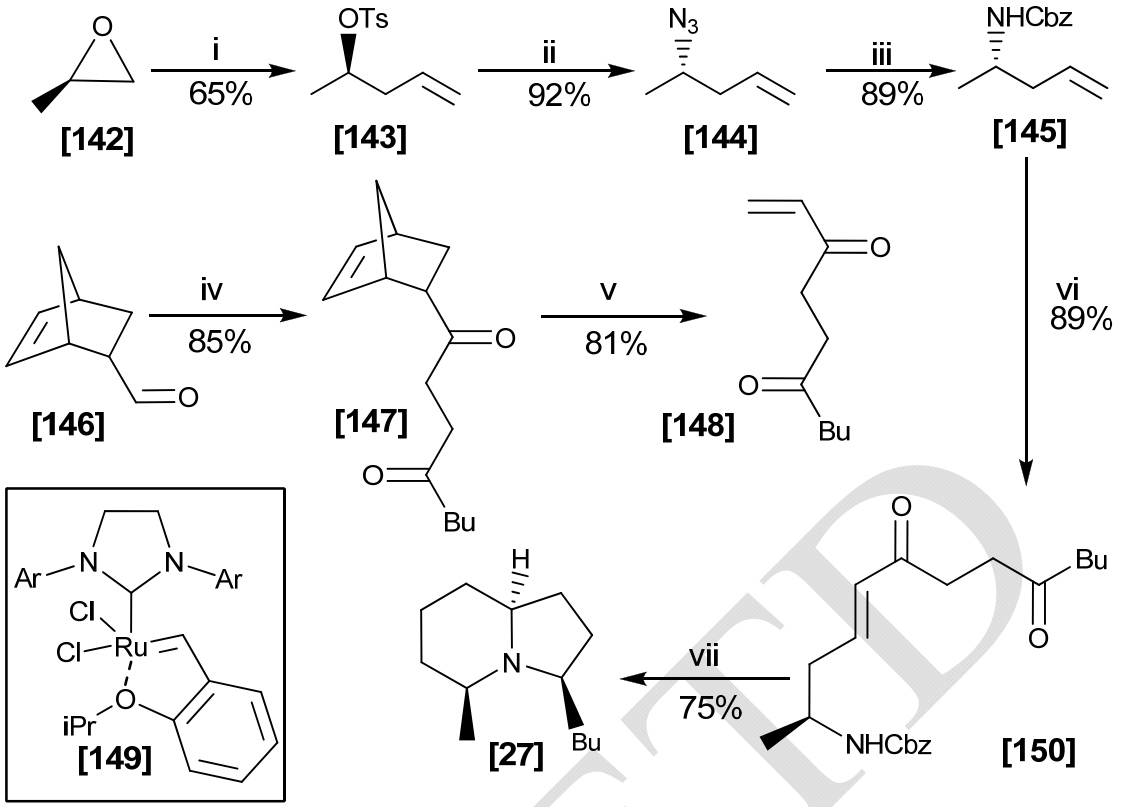
Scheme 1.12: Total synthesis of monomorine I by Jefford and co-workers.[105] *Reagents and conditions: i) KOH, CH_3CN; ii) a)* i-*BuOCOCl,* N-*methylmorpholine; b) CH_2N_2, Et_2O; iii) $Rh_2(OAc)_4$, CH_2Cl_2; iv) PtO_2, EtOH, AcOH, H_2 (20 bar); v)* N,N-*thiocarbonylimidazole, $ClCH_2CH_2Cl$; vi) Bu_3SnH, toluene.*

WitsETD

Disconnection 4: The $C_3 - N, C_5$ - N disconnection approach

Randl and Blechert[110] employed cross metathesis (CM) as the key step in the synthesis of (+)-monomorine I (see Scheme 1.13). The first coupling partner was prepared from the commercially available enantiopure starting material (*R*)-methyloxirane (**142**). This was converted to the corresponding alcohol by a Grignard reaction with vinylmagnesium bromide under regioselective copper-catalysed conditions. The alcohol proved unstable and was immediately tosylated to give (**143**) in 65% yield. Reaction with sodium azide gave azide (**144**) with inversion of stereochemistry. This proved a poor candidate for CM so the azide was reduced to the amine and protected with a benzoyloxycarbonyl (Cbz) group to afford the first coupling partner, compound (**145**). The other coupling partner was prepared via norbornene (**145**) which was prepared from a Stetter reaction of norbornene-2-carbaldehyde (**146**) with hept-1-en-3-one in 85% yield. Flash pyrrolysis of (**147**) afforded the retro Diels-Alder product (**148**) in 81% yield. Alkenes (**145**) and (**148**) were coupled using the Grubbs-Hoveyda catalyst (**149**) to give the cyclisation precursor (**150**) in 89% yield. Hydrogenation of (**150**) with palladium on carbon reduced the alkene, deprotected the amine and caused double reductive amination to give (+)-monomorine I (**27**) in 75% yield. (−)-Indolizidine 195B (**26**) was isolated as a side product in 15% yield. Therefore the amination to create the pyrrole ring must have proceeded with a diastereoselectivity of 5:1. The synthesis was completed in a total of seven steps with an overall yield of 35%.

WitsETD



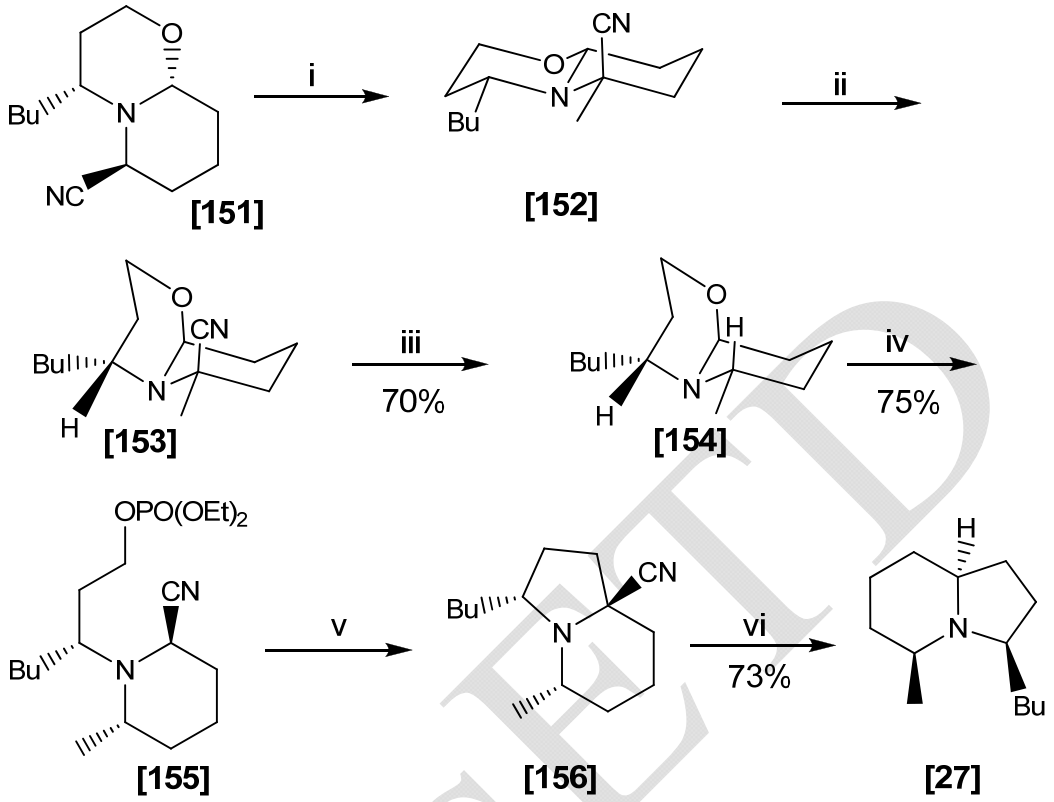
Scheme 1.13: Total synthesis of monomorine I by Randl and co-workers.[105, 110] *Reagents and conditions: i) a) C_2H_3MgBr, Cu(COD)Cl (0.1 eq.), THF, -78°C → RT, 12 hr.; b) TsCl, DMAP (0.1 eq.), CH_2Cl_2, 36 hr.; ii) NaN_3, DMF, 40°C, 12 hr.; iii) a) $LiAlH_4$, Et_2O, 0°C → RT, 2 hr.; b) Cbz-Cl, K_2CO_3, THF, 12 hr.; iv) hept-1-en-3-one, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (0.05 eq.), Et_3N (0.5 eq.), 65°C, 18 hr.; v) flash pyrrolysis, 500°C, 10 mbar; vi) Grubbs-Hoveyda (0.05 eq.), CH_2Cl_2, reflux, 4 hr.; vii) H_2, Pd-C, MeOH, RT, 48 hr.*

Disconnection 5: The C_1 - C_{8a} disconnection approach

By employing dissolving metal conditions, Grierson and Zeller[111] went from 2-butyl-10-cyano-5-oxa-1-azabicyclo[4.4.0]decane (**151**) to racemic monomorine I (**27**) in six steps (see Scheme 1.14). Firstly, the methyl group was introduced using methyl iodide and low temperatures to give the kinetic product (**152**) exclusively. The kinetic product was completely converted to the thermodynamic product (**153**) by heating it at reflux with catalytic zinc bromide. Dissolving metal conditions were employed to remove the cyano group and the product (**154**) was isolated in a 70% yield from the starting material (**151**). Ring opening of compound (**154**) was achieved using diethylcyanophosphate and zinc bromide and gave phosphonate (**155**) in 75% yield. Deprotonation using lithium diisopropylamine allowed stereoselective ring closure to give indolizidine (**156**) as a single diastereomer. To complete the synthesis the second cyano

WITS ETD

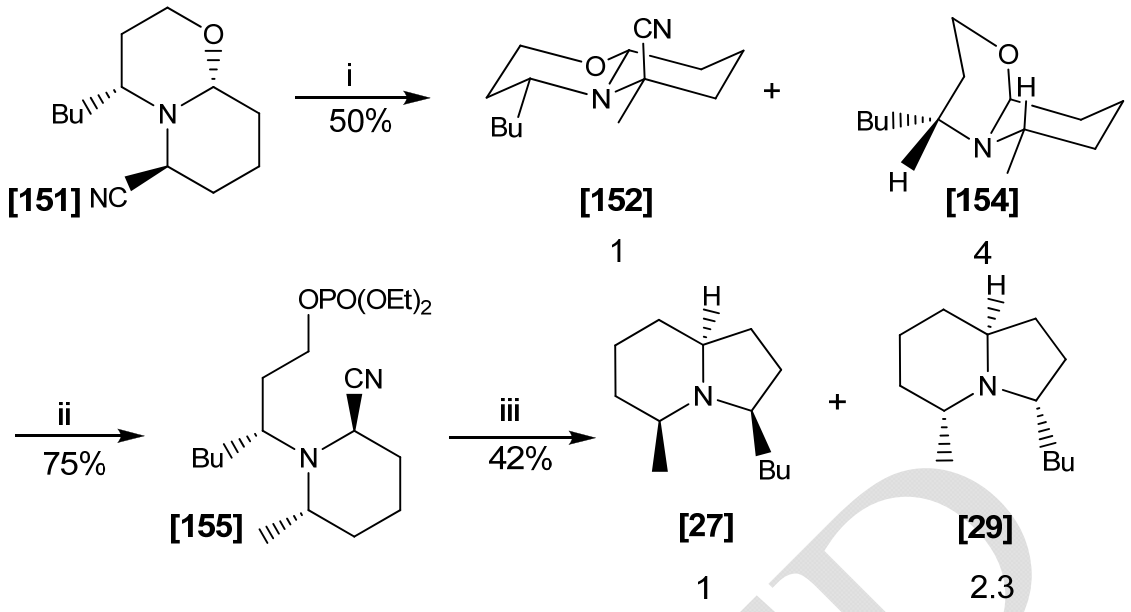
group was removed using dissolving metal conditions and racemic monomorine I (**27**) was isolated in 73% yield. The overall yield for the six steps was 38%.



Scheme 1.14: Total synthesis of monomorine I by Grierson and co-workers.[111] *Reagents and conditions: i)* s*-BuLi, THF-HMPT, -78°C, CH_3I; ii) $ZnBr_2$, reflux; iii) Na/NH_3 (liq.); iv) $(EtO)_2POCN$, $ZnBr_2$; v) LDA, THF, -20°C; vi) Na/NH_3 (liq.).*

Using the same synthetic methodology, monomorine I was also obtained in a mere three steps with an overall yield of 4% (see Scheme 1.15). The first step employed methyl iodide and sodium in ammonia which gave a 1:4 mixture of the kinetic product (**152**) in 10% yield and the thermodynamic (**154**) product with the cyano group already removed in 40% yield. Ring opening of (**154**) using diethylcyanophosphate and zinc dibromide gave compound (**155**) in 75% yield. Lastly, the ring closure of (**155**) to monomorine I (**27**) was achieved directly by using potassium and 18-crown-6. However, there was a loss of stereoselectivity and the *8a*-epimer (**29**) of monomorine I was isolated as the major product with a ratio of 1 : 2.3 and a combined yield of 42%.

WISETD



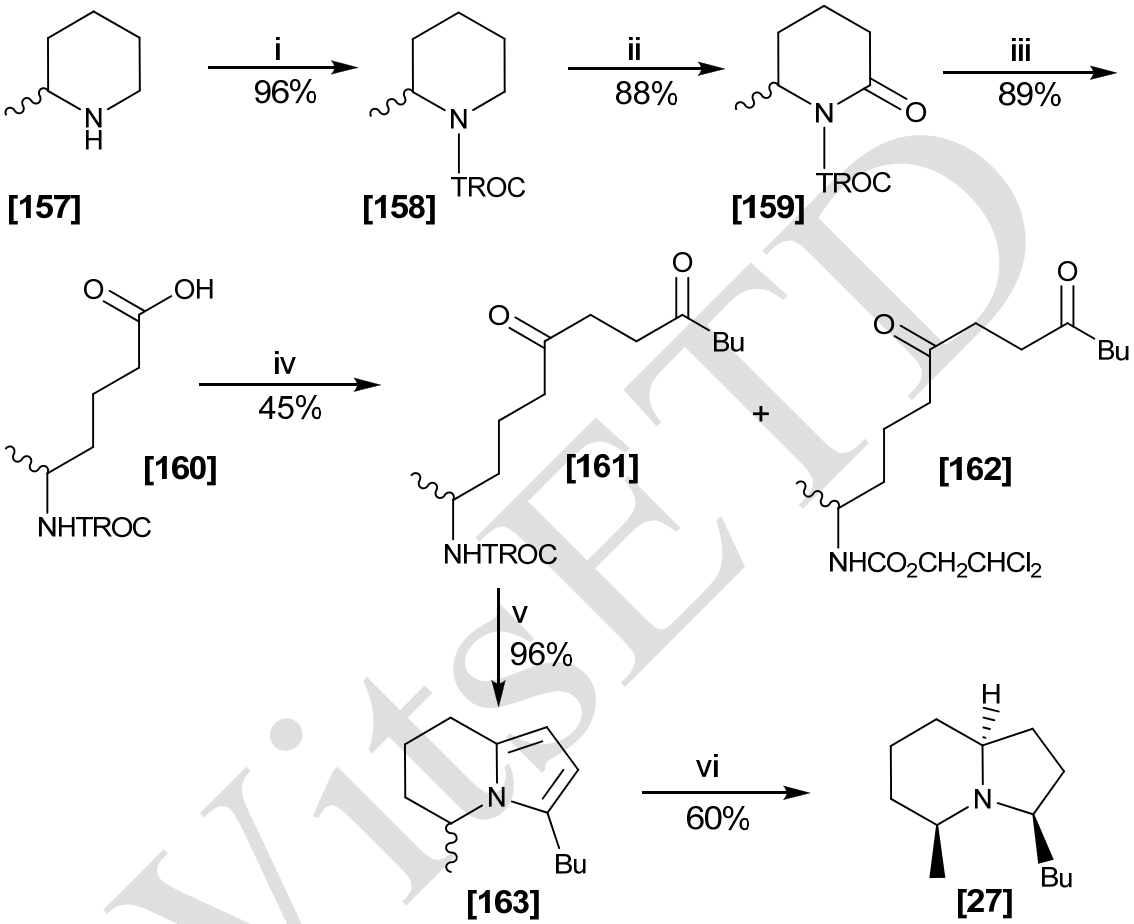
Scheme 1.15: Total synthesis of monomorine I by Grierson and co-workers.[111] *Reagents and conditions: i) ICH_3, Na/NH_3 (liq.); ii) $(EtO)_2POCN$, $ZnBr_2$; iii) K, 18-crown-6, THF.*

Disconnection 6: The C_{8a} – N, C_3 - N disconnection approach

Castano and Echavarren[112] formed both the piperidine and pyrrolidine ring in one step (see Scheme 1.16). 2-Methylpiperidine (**157**) was TROC protected in 96% yield using Schotten-Baumann conditions and TROCCl. The protected piperidine (**158**) was oxidized to give imide (**159**) in 88% yield using sodium periodate and ruthenium trichloride according to the procedure developed by Sharpless and co-workers[121] The imide (**159**) was hydrolysed by heating it at reflux in water and hence the carboxylic acid (**160**) was obtained in 89% yield. The carboxylic acid (**160**) was converted into the corresponding acid chloride and then coupled with a β-stannyl enone in the presence of palladium. The coupled product underwent a spontaneous reduction of the enone. This key step in the synthesis gave the desired diketone (**161**) in 45% yield in addition to the undesired product (**162**), produced by a reduction reaction by tributylstannyl chloride. The low yield of 45% was also attributed to the competitive re-formation of the imide (**159**). Removal of the TROC protecting group from the diketone (**161**) allowed spontaneous cyclisation to form indolizidine (**163**). The optimum conditions for this reaction proved to be sonication in the presence of cadmium with acetic acid and dimethylformamide as the solvent, which gave (**163**) in a 96% yield. The final step was the reduction of the pyrrole ring of (**163**)

WitsETD

with rhodium on carbon in the presence of hydrogen. This gave racemic monomorine I (**27**) and two of its diastereomers (**28** + **29**) in a 2:2:1 ratio, and a combined yield of 60%. Several other hydrogenation conditions proved unsuccessful. Thus racemic monomorine I was synthesized in seven steps with an overall yield of 8%.



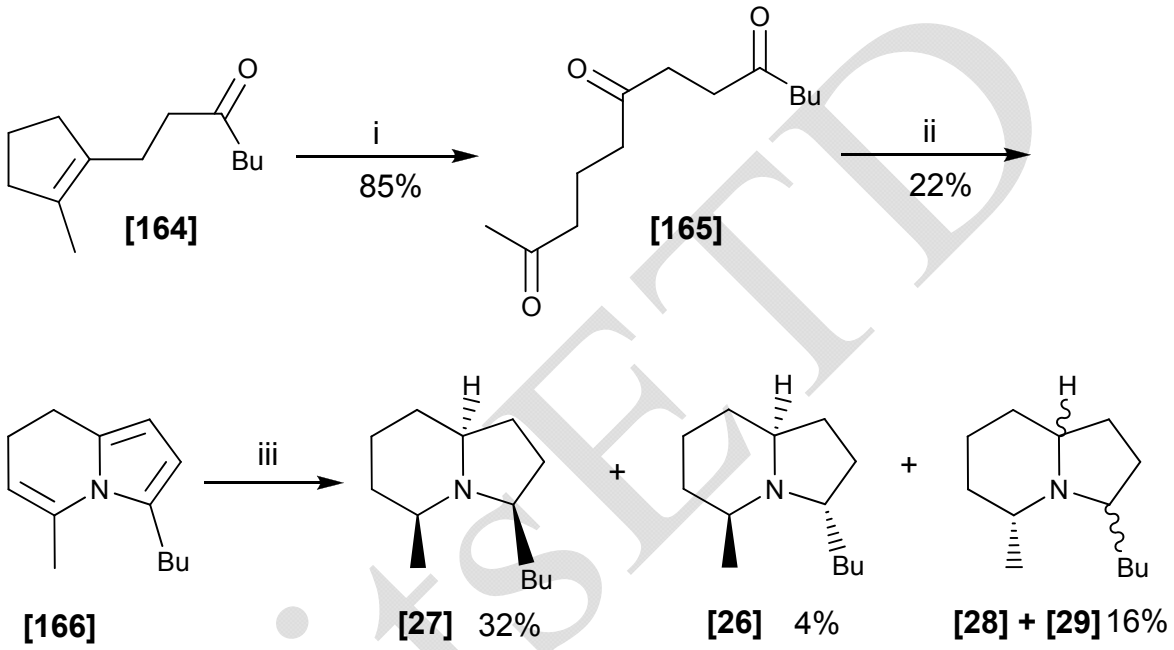
Scheme 1.16: Total synthesis of monomorine I by Castano and co-workers.[112] *Reagents and conditions: i) TROCCl, NaOH; ii) $RuCl_3$ (cat.), $NaIO_4$; iii) H_2O, Δ; iv) a) $SOCl_2$; b) E-$Bu_3SnCHCHCOBu$, $Pd(PPh_3)_4$, dioxane, 100°C; v) Cd, HOAc-DMF, 23°C; vi) H_2, Rh-C, 25°C, EtOH.*

Disconnection 7: The C_3, C_5, C_{8a} - N disconnection approach

Mori, Hori and Sato[113] developed a unusual route to monomorine I involving nitrogen fixation (see Scheme 1.17). The ketone (**164**) was prepared by the method of Shawe and Shiels.[81] Ozonolysis of the ketone (**164**) followed by treatment with dimethyl sulfide gave the triketone (**165**) in 85% yield. The key step in the synthesis was coupling the triketone (**165**) with a titanium nitrogen

WitsETD

complex, formed by the reaction of titanium tetrachloride, lithium and trimethylsilyl chloride under dry air. This gave indolizidine (**166**) in 22% yield. The yield could be increased to 30% by using molecular nitrogen instead of dry air. Finally, the reduction of the pyrrole ring in the presence of rhodium on alumina and hydrogen atmosphere gave racemic monomorine I (**27**) in 32% yield, racemic indolizidine 195B (**26**) in 4% yield and the C-3, C-8a epimers (**28** + **29**) in 16% yield.



Scheme 1.17: Total synthesis of monomorine I by Mori and co-workers.[113] *Reagents and conditions: i) a) O_3; b) Me_2S; ii) Dry air, $TiCl_4$, Li, TMSCl, THF; iii) Rh/Al_2O_3, EtOH, H_2 (20 atm), 34 hr.*

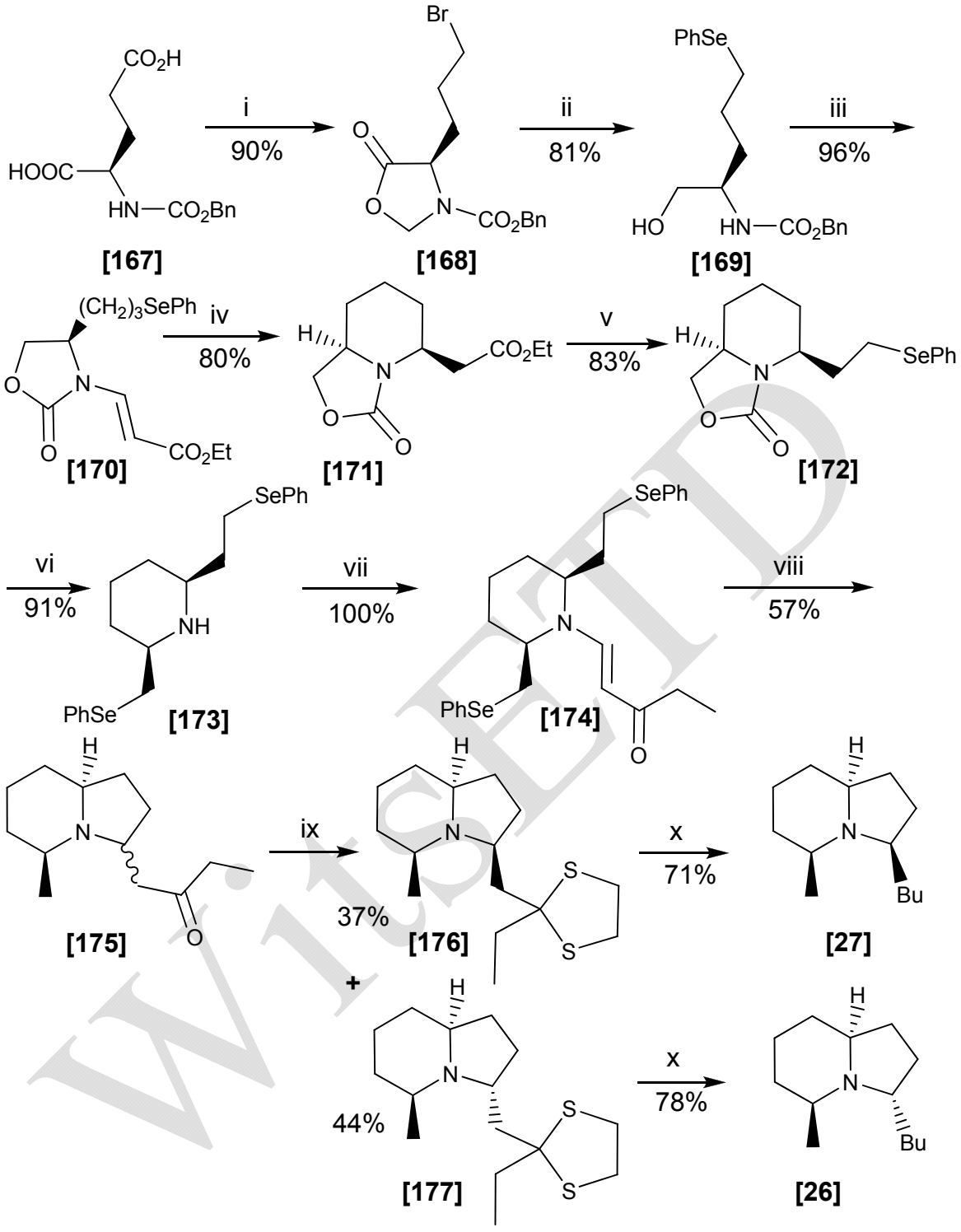
Disconnection 8: The C_2 - C_3 disconnection approach

Starting from benzoyl-protected D-glutamic acid (**167**), Lee and Chung[114] converted it into the corresponding oxazolidinone, which was reduced to the alcohol and brominated to give oxazolidinone (**168**) in 90% yield over three steps (see Scheme 1.18). Oxazolidinone (**168**) was reduced, the *N*-hydroxymethyl group was removed and the bromine was substituted for a phenyl selenide group to give selenide (**169**) in 81% yield over three steps. Prolonged treatment with base gave the cyclic carbamate, and subsequent reaction with ethyl propiolate gave β-amino acrylate (**170**) in 96% yield. Radical cyclisation formed the substituted piperidine ring in 80% yield as a 66:34

WitsETD

mixture of diastereomers. The major *cis* isomer (**171**) was converted into the selenide (**172**) via the alcohol and bromide in 83% yield. The carbamate ring was cleaved to give the diselenide product (**173**) in 91% yield. The nitrogen was realkylated with 1-pentyn-3-one to give (**174**) in 100% yield. The second radical cyclisation formed the indolizidine skeleton in 57% yield as a mixture of diastereomers (**175**). Formation of the corresponding dithioketals allowed separation of the two diastereomers (**176** + **177**) in 37% and 44% yield respectively. Removal of the dithioketal groups with Raney nickel in absolute ethanol gave (+)-monomorine I (**27**) and (+)-indolizidine 195B (**26**) in 71% and 78% yield respectively. Although this was one of the longer syntheses (thirteen steps) it incorporated novel ring closures and effectively used radical cyclisations to give (+)-monomorine I in 6.3% overall yield and indolizidine 195B in 8.3% yield.

WitsETD



Scheme 1.18: Total synthesis of monomorine I by Lee and co-workers.[114] *Reagents and conditions: i) a) $(CH_2O)_n$,* p-*TsOH, PhMe; b) BH_3.THF, 0°C; c) CBr_4, PPh_3, THF, 0°C; ii) a) $LiBH_4$, -78°C; b) KOMe, MeOH; c) $(PhSe)_2$, $NaBH_4$, EtOH, 0°C; iii) a) KOMe, MeOH-THF; b) $HCCCO_2Et$, NMM, CH_2Cl_2; iv) Bu_3SnH, AIBN, PhH; v) a) $LiAlH_4$, -40°C; b) CBr_4, PPh_3, CH_2Cl_2; c) $(PhSe)_2$, $NaBH_4$, EtOH, 0°C; vi) $PhSeSiMe_3$, ZnI_2, PhMe; vii) HCCCOEt, CH_2Cl_2; viii) Bu_3SnH, AIBN, PhH; ix) $HSCH_2CH_2SH$, $BF_3.OEt_2$, CH_2Cl_2, N_2; x) Ra-Ni, EtOH.*

WiSER

This completes the general overview of the total syntheses of monomorine I. Chapter 2 details how our synthesis exploits novel methodology to achieve the total synthesis of both monomorine I and 5-*epi*-monomorine I.

1.4.3.1 Introduction to tricyclic alkaloids

Tricyclic alkaloids have been known to occur in coccinellid beetles since the early 1970s and more recently they have been detected in certain frog species. Due to their structural complexity there are far fewer reported total syntheses of the tricyclic alkaloids compared to the bicyclic alkaloids. The tricyclic alkaloids are rarely detected in Nature and occur in minor and trace amounts when they do. However, there was evidence of their potent biological activity which warrants further investigation.

Certain of the tricyclic alkaloids show a structural relationship to the 3,5-disubstituted indolizidines, as their tricyclic system formally incorporates a 3,5-disubstituted indolizidine within the skeleton. This also means that they could potentially be accessed by closing the two side chains of the indolizidine to form the third ring. One possible method would be ring closing metathesis as shown in Figure 1.7.

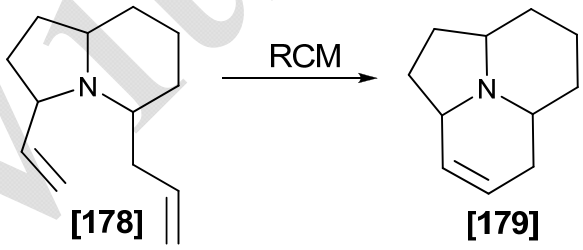


Figure 1.7: Proposed synthetic connection between 3,5-disubstituted indolizidines (**178**) and tricyclic alkaloids (**179**).

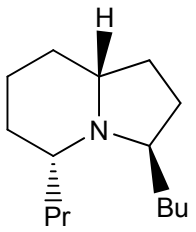
The structural relationship between these two classes of alkaloids drew our interest as it offered an additional area for extending this project. The proposed RCM was an obvious choice for forming the third ring as our research group has some experience with RCM and there was literature precedent for this type of chemistry.

WitsETD

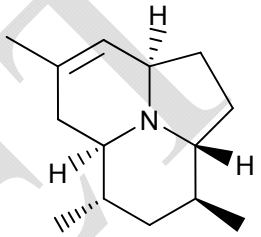
1.4.3.2 Previous synthesis of a tricyclic alkaloid

The work of Smith III and Kim[122] is a good example of exploiting the structural relationship between indolizidines and tricyclic alkaloids, and they have demonstrated the effectiveness of RCM in forming the tricyclic skeleton. Extending methodology developed for the synthesis of the 3,5-disubstituted indolizidine (−)-223AB (**180**), Smith III and Kim were able to synthesize (−)-coccinelline 205B (**47**).

Coccinelline 205B (**47**) is one of the alkaloids isolated from the skin of a neotropical frog *Dendrobates pumilio* which possesses an unusual tricyclic azaacenapthylene ring.



[180]



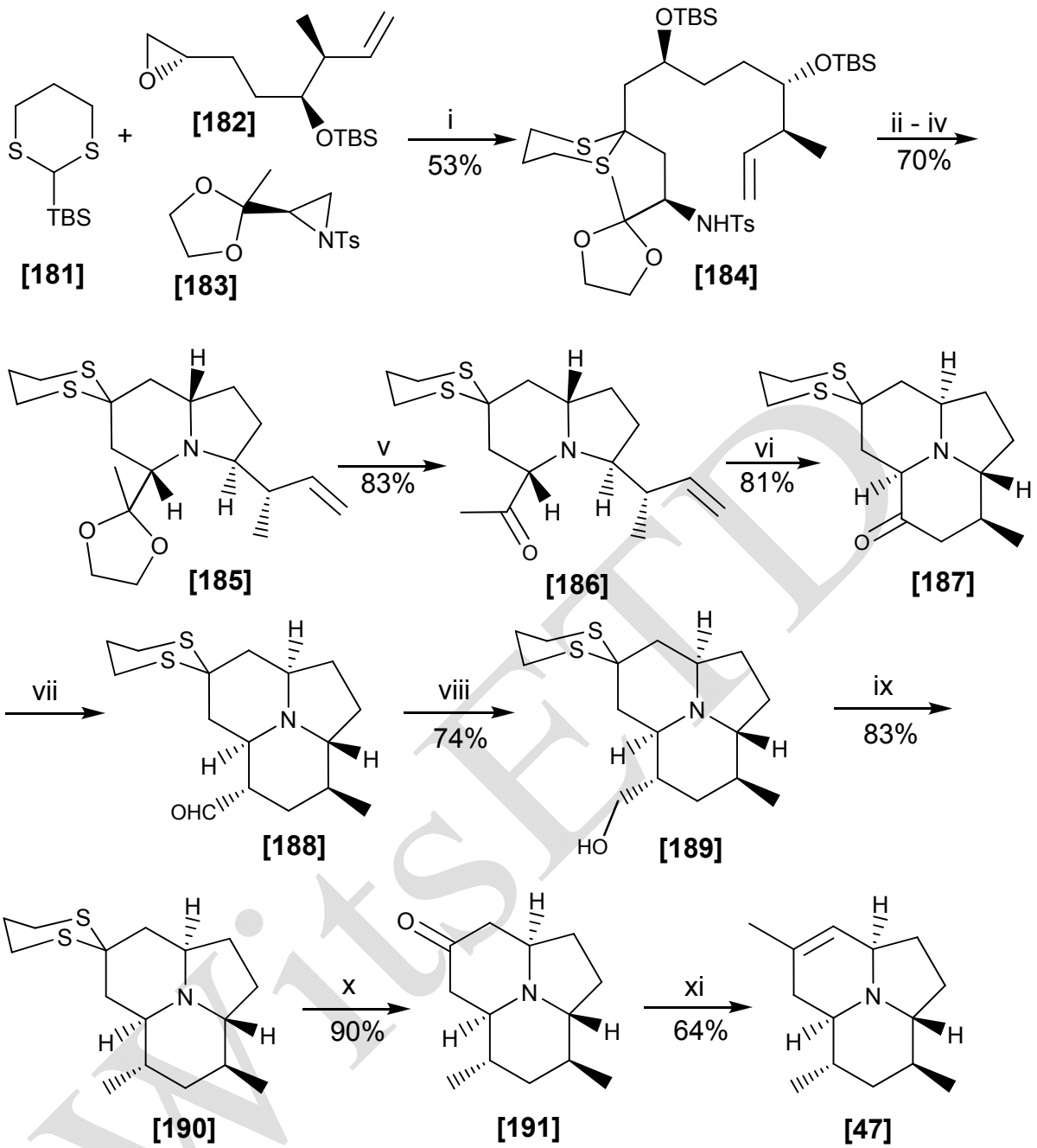
[47]

Smith III and Kim's synthesis proceeds via a lynchpin coupling reaction between TBS dithiane, an epoxide and an aziridine (see Scheme 1.19). The *umpolung* electronics of the dithiane allow successive deprotonations and sequential alkylation with the epoxide and the aziridine electrophiles. The coupling between (**181**), (**182**) and (**183**) proceeded to give the dialkylated dithiane (**184**) in 53% yield, with 31% yield of the monoalkylated dithiane recovered. A one-pot removal of the two TBS groups and mesylation of the alcohols followed by removal of the tosyl group using a sodium amalgam allowed spontaneous cyclisation to form indolizidine (**185**) in 70% yield over the three steps. Indolizidine (**185**) was refluxed in an acidic acetone solution to remove the acetonide group and this gave the ketone (**186**) in 83% yield. The ketone (**186**) was transformed into the corresponding enol silyl ether to provide the second alkene for the intramolecular RCM reaction, which proceeded efficiently to give the tricyclic compound (**187**) in 81% yield over the two steps.

WitsETD

Some difficulty was experienced in obtaining the correct stereochemistry for the C-6 methyl group and Smith III *et al.*[122] overcame this difficulty by proceeding via the methyl enol ether of ketone (**187**). Conversion of (**187**) to the methyl enol ether and hydrolysis to the aldehyde (**188**) produced the desired stereoselectively which can be accounted for by the proposed electrostatic repulsion of the hydronium ion and the ammonium ion – steric hindrance would have favoured the opposite stereoselectivity. The aldehyde (**188**) was reduced to the corresponding alcohol (**189**) in a yield of 74% from the ketone (**187**) over three steps. The alcohol was removed to give compound (**190**) in 83% yield. The dithiane was then removed to give (**191**) in 90% yield. The final steps in the synthesis follow a method developed by Toyooka *et al.*[123] to give (−)-coccinelline 205B (**47**) in 64% yield. The overall yield for the (−)-coccinelline 205B (**47**) using the longest linear sequence of nineteen steps was 5.6%.

WitsETD



Scheme 1.19: Total synthesis of coccinelline 205B by Smith III and co-workers.[122] *Reagents and conditions: i) a) t-BuLi, Et_2O, -78°C → -45°C, 1 hr.; b) (**182**), Et_2O, -78°C → -20°C, 2 hr.; c) (**183**), THF, -78°C to 0°C 2 hr.; ii) TBAF; iii) MsCl, Et_3N, THF; iv) a) K_2CO_3, MeOH, 1 hr; b) 5% Na-Hg, Na_2HPO_4, 15 hr.; v) 2M HCl, acetone, reflux; vi) a) LHMDS, TMSCl, THF, -78°C; b) Grubbs II (0.1 eq.), benzene, 65°C, 15 hr.; vii) a) Ph_3PCH_2OMeCl,* t-*BuOK, THF, RT; b) 6M HCl/THF (1:1), 14 hr.; viii) $NaBH_4$, MeOH, 0°C; ix) a) MsCl, Et_3N, THF; b) $LiHBEt_3$, THF, reflux; x)$PhI(O_2CCF_3)_2$, TFA, CH_3CN-H_2O (1:1), RT; xi) a) Ph_3PCH_3Br,* n-*BuLi, THF; b)* p-*TsOH, benzene.*

Chapter 2 details how our project could be extended to provide a novel synthesis of the tricyclic skeleton. Due to time constraints our investigations into tricyclic alkaloids only extended as far as a model study.

WitsETD

CHAPTER 2
BACKGROUND, AIMS AND SCOPE OF THIS PROJECT

2.1 The "Wits Approach" to indolizidine alkaloids

2.1.1 Introduction to the "Wits Approach"

Alkaloid chemistry in the Backeberg Laboratories in the School of Chemistry at the University of the Witwatersrand has been very active over the past three decades with nine MSc students[124 - 132] and seventeen PhD students[31, 133 - 148] having graduated during this time. Our approach to alkaloid synthesis relies largely on the use of enaminones e.g. (**192**) (see Figure 2.1), especially vinylogous urethanes and vinylogous amides. Alternatively they can be thought of as β-acylated enamines. We exploit these functionally rich moieties to develop generalized methodology, and our particular approach has come to be known as the "Wits approach".[149]

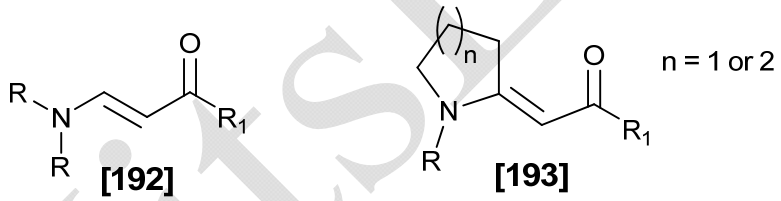


Figure 2.1: Generalised enaminone and corresponding cyclic enaminone.

Invariably we use a secondary or tertiary amine that is part of a pyrrolidine (**193**) or piperidine ring with an exocyclic carbon-carbon double bond conjugated to an electron-withdrawing group. Their reactivity can be modulated by changing the electron-withdrawing group. In our group these serve as scaffolds for alkaloid synthesis, as they are easily incorporated into larger structures and offer opportunity for chemoselective, regioselective, diastereoselective and enantioselective control. This versatility is associated with the ambident nucleophilicity and electrophilicity of enaminones (see Figure 2.2).[149]

WisETD

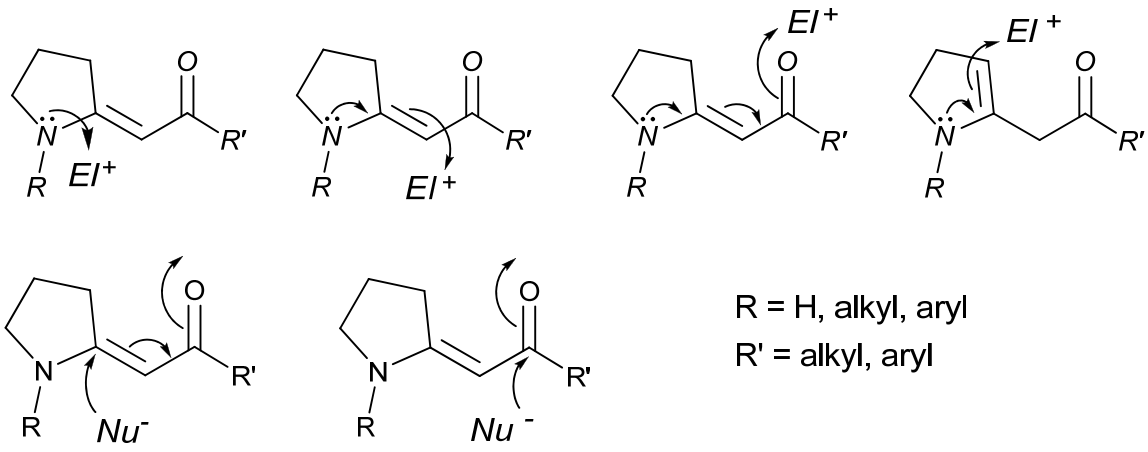
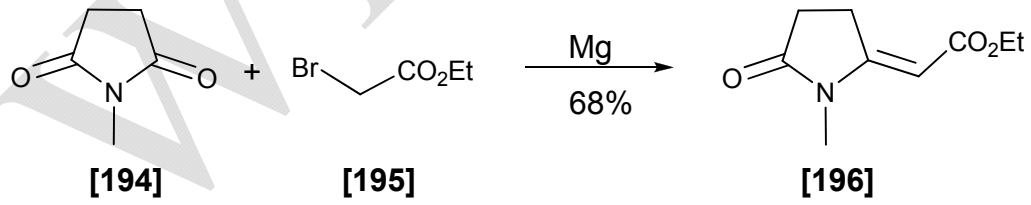


Figure 2.2: Reactive sites of the enaminone system.

The enaminone group is resistant to mild hydrolysis and oxidation owing to the delocalization of charge through the vinyl substituent. In a vinylogous urethane, for example (R' = OR), chemoselective reduction of esters present elsewhere in the molecule is possible, while leaving the vinylogous urethane untouched.

2.1.2 Preparation of enaminones

The earliest preparation of an exocyclic vinylogous urethane was by Lukeš[150] and dates from 1932. They used a Reformatsky reaction to react lactam (**194**) with ethyl bromoacetate (**195**) in the presence of magnesium to form the vinylogous urethane (**196**) in 68% yield (see Scheme 2.1).



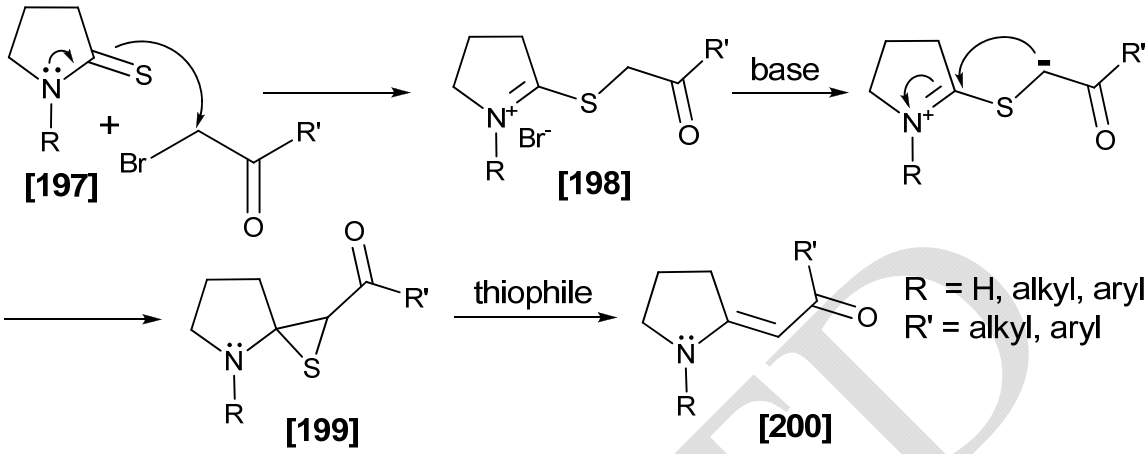
[194] **[195]** **[196]**

Scheme 2.1: Synthesis of an exocyclic vinylogous urethane by Lukeš and co-workers.[150]

One of the favourite methods of accessing enaminones in our laboratories involves reacting a thiolactam (**197**) with an α-halo carbonyl compound to form an α-thioiminium salt (**198**). The salt (**198**) is then treated with a mild base, and an episulfide (**199**) forms. In the presence of a sulfur scavenger the episulfide spontaneously collapses to form the exocyclic double bond and hence the

WISER

enaminone (**200**). This is known as the Eschenmoser sulfide contraction (see Scheme 2.2) after the researcher who developed it,[151] and is one of the easier methods of accessing enaminones.

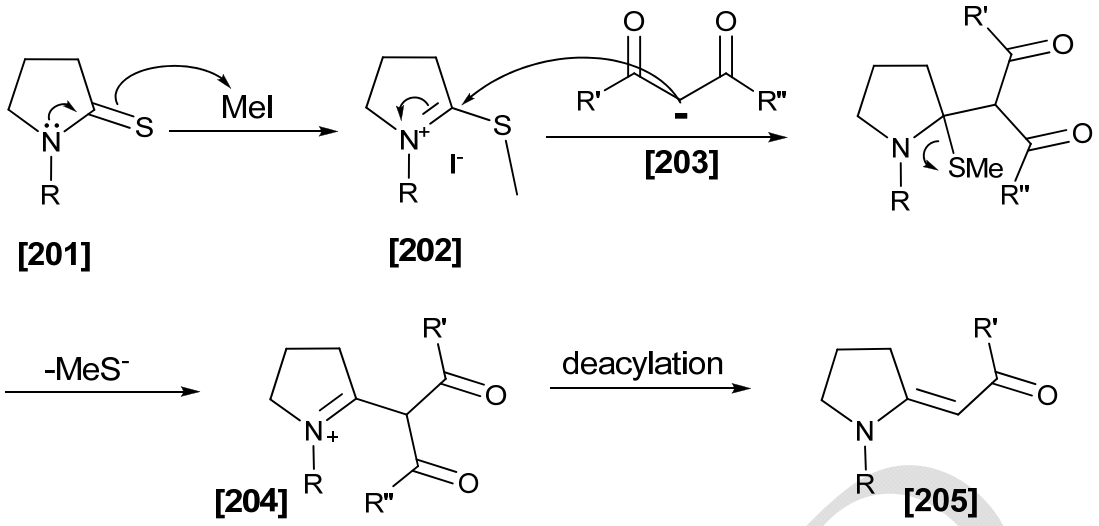


Scheme 2.2: An example of the Eschenmoser sulfide contraction.

A recent study on sulfide contraction reactions indicated that improved yields can be obtained through the addition of sodium iodide and the use of polar aprotic solvents such as acetonitrile or chloroform.[152]

Another method frequently employed at Wits to access exocyclic vinylogous amides or urethanes also starts from a thiolactam (**201**).[153] The thiolactam (**201**) is reacted with methyl iodide to form an α-thioiminium salt (**202**) which is then condensed with an anionic nucleophile (**203**) (e.g. a malonate) to give an intermediate acylated product (**204**). The acylated product (**204**) often spontaneously deacylates to form the enaminone (**205**) (see Scheme 2.3). If necessary, the deacylation reaction can be facilitated by heating the acylated product (**204**) at reflux in an acidic solution.[154]

WitsETD



Scheme 2.3: Formation of exocyclic vinylogous amides via a malonate condensation.

Several other very specific routes to enaminones have also been used at Wits, but they will not be discussed since they were not used in the present project. For example, one such method, entailing a novel Reformatsky reaction with a thiolactam, is illustrated in Scheme 2.7.

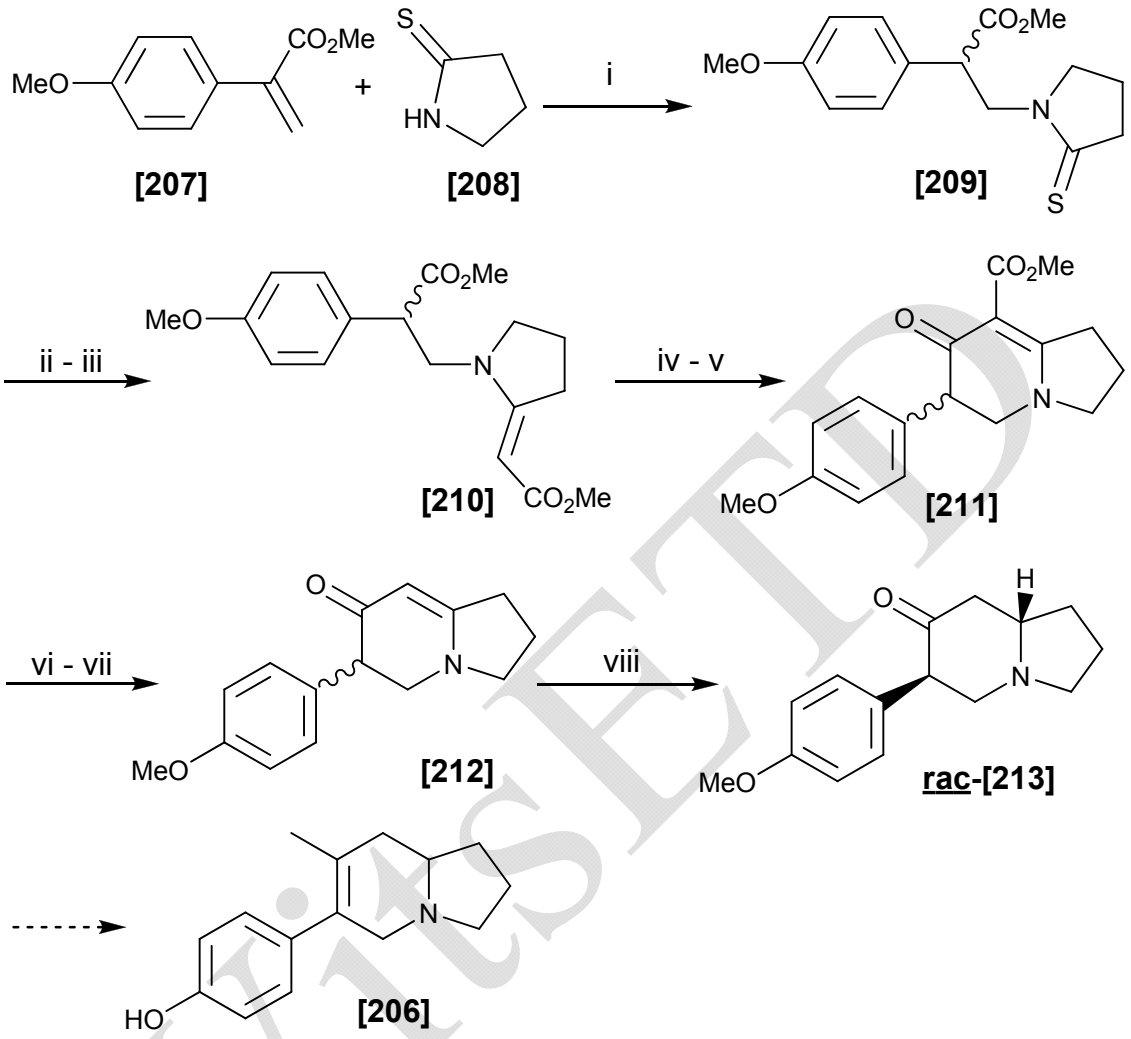
2.1.3 Enaminones in action at Wits

At Wits we have used enaminone methodology to access pyrrolidines, indolizidines, quinolizidines, lehmizidines and perhydroindole alkaloids, pyrrolo[1,2-*a*]indoles and pyrrolo[1,2-*a*]quinolines. Most of these scaffolds exploit the nucleophilicity of the β-position of the enaminone (see Figure 2.2).

Enaminones have been used at Wits as partners in acylative ring closure. One synthesis that utilized this methodology was the formal synthesis of ipalbidine (**206**). The aza-Michael addition of thiolactam (**207**) to the acceptor (**208**) gave the alkylated thiolactam (**209**). This compound underwent an Eschenmoser sulfide contraction with ethyl bromoacetate to form the exocyclic vinylogous urethane (**210**). Selective hydrolysis of the saturated ester followed by formation of a mixed anhydride facilitated the acylative ring closure of (**210**) by increasing the electrophilicity of the carbonyl group, hence allowing the weakly nucleophilic β-position of the enaminone to cyclise onto the anhydride to give the indolizidinone (**211**). Hydrolysis and decarboxylation of (**211**) followed by chemoselective reduction of the enaminone (**212**) gave (**213**), a known

WITSETD

precursor to ipalbidine (**206**) and hence completed the formal synthesis (see Scheme 2.4).[155]

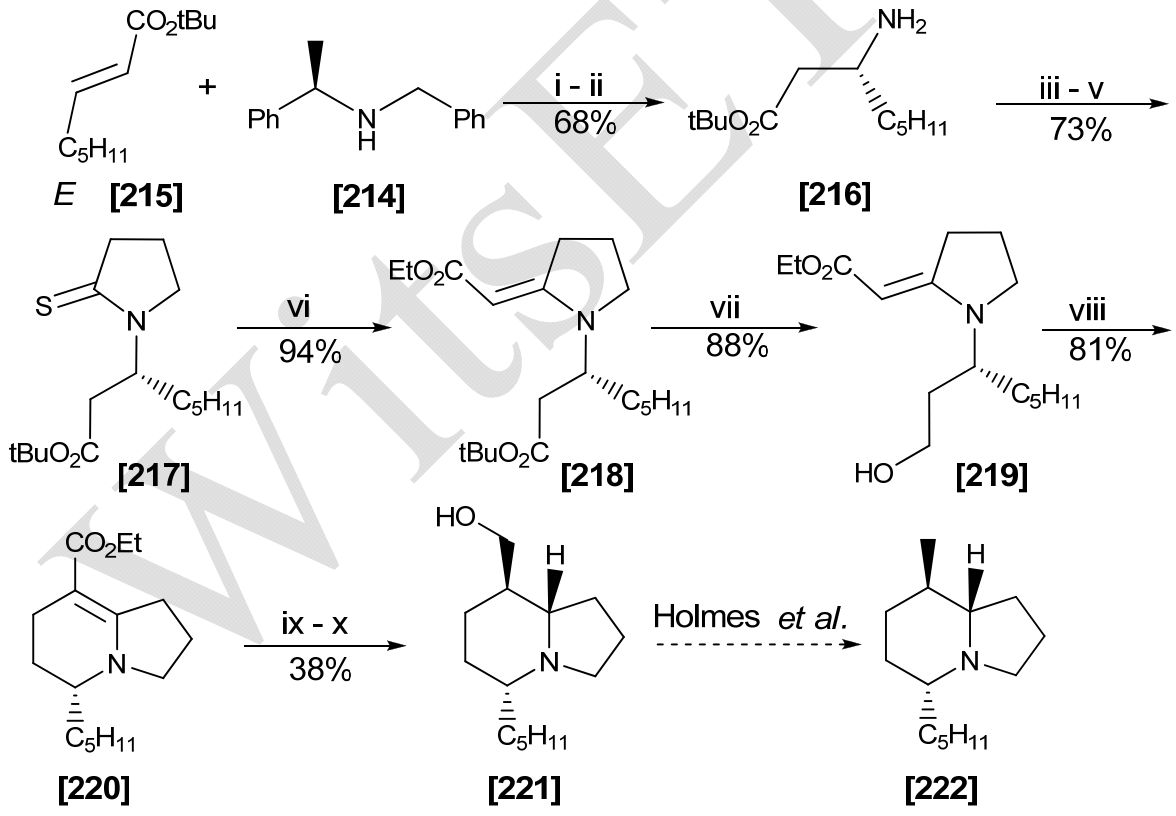


Scheme 2.4: The formal synthesis of ipalbidine by Howard *et al*.[155] *Reagents and conditions: i) NaOH (cat.), THF; ii) $BrCH_2CO_2Me$, THF; iii) Ph_3P, Et_3N, MeCN; iv) NaOH, H_2O, reflux; v) $ClCO_2Me$, Bu_4NI (cat.), THF; vi) KOH, H_2O, reflux; vii) HCl, H_2O, reflux; viii) $LiAlH_4$, THF.*

The other popular cyclisation methodology used at Wits entails alkylative ring closure. A strategically placed alcohol, or a 3-hydroxypropyl substituted onto the pyrrolidine nitrogen, was converted into a better leaving group, such as an iodide, which allowed the weakly nucleophilic β-position of the enaminone to facilitate cyclisation. This approach was nicely demonstrated in the formal synthesis of (–)-indolizidine 209B (see Scheme 2.5).[139, 156] Chiral amine (**214**) was added to the Michael acceptor (**215**) with subsequent debenzylation of the

WitsETD

amine in the presence of palladium-on-carbon to give the primary amine (**216**) in 68% yield over the two steps. Amine (**216**) was condensed with chlorobutyryl chloride and converted into the corresponding thiolactam (**217**) in 73% yield over the three steps. The thiolactam (**217**) then underwent an Eschenmoser sulfide contraction with ethyl bromoacetate to give the vinylogous urethane (**218**) in 94% yield. Chemoselective reduction of the saturated ester gave the alcohol (**219**) in 88% yield. Finally, alkylative ring closure proceeded in the presence of iodine, triphenylphosphine and imidazole to give the bicyclic product (**220**). Chemoselective and diastereoselective reduction of the enaminone and ester gave the alcohol (**221**) in 38% yield over two steps and completed the formal synthesis of (–)-indolizidine 209B (**222**). Following the synthesis of Holmes *et al.*[157] the alcohol (**221**) was defunctionalized via the corresponding methanesulfonate and the total synthesis was completed.



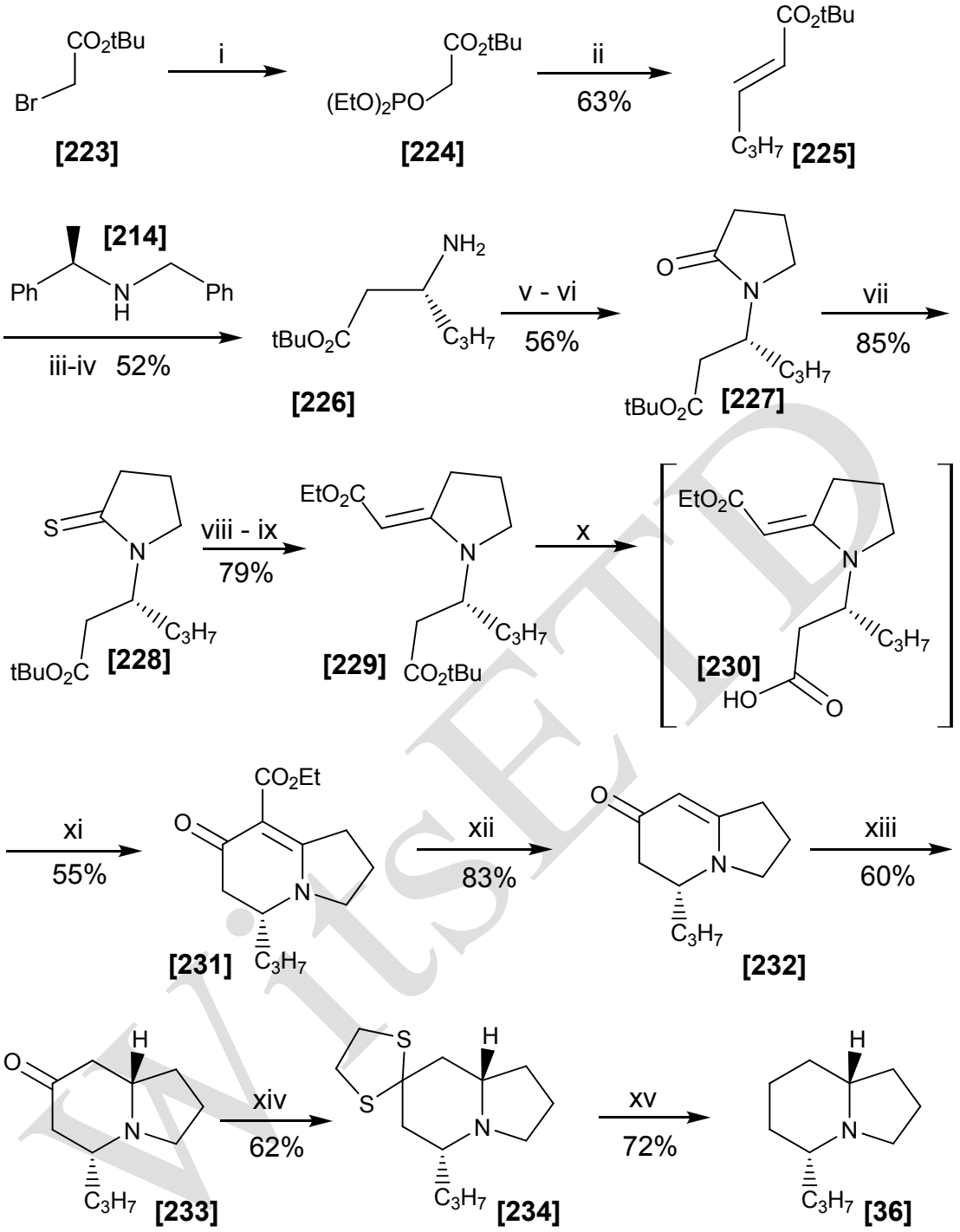
Scheme 2.5: The formal synthesis of (–)-indolizidine 209B (**222**) by Michael and Gravestock.[139, 156] *Reagents and conditions: i) BuLi, THF, -78°C; ii) H_2, (7 atm.), 10% Pd-C, AcOH; iii) $Cl(CH_2)_3COCl$ $NaHCO_3$, $CHCl_3$, reflux; iv) $KOBu^t$, Bu^tOH; v) Lawesson's reagent, PhMe, reflux; vi) a) $BrCH_2CO_2Et$, MeCN, RT; b) Ph_3P, Et_3N. MeCN, RT; vii) $LiAlH_4$, THF, RT; viii) I_2, imidazole, Ph_3P, PhMe, 110°C; ix) H_2, (1 atm.), PtO_2, AcOH, RT; x) $LiAlH_4$, THF, RT.*

WiSETD

As shown in the preceding synthesis (Scheme 2.5), in order to use enaminone reactivity to assist with the enantioselective alkaloid synthesis, it was necessary to introduce at least one stereogenic centre prior to enaminone formation. Chiral auxiliaries should prove a useful tool in the introduction of stereogenic centres, but as yet appropriate chiral auxiliaries remain elusive. The successful stereoselective syntheses of indolizidines following the enaminone route have used β-amino acids, esters and lactones as homochiral building blocks. One of the successful routes uses methodology developed by Davies *et al*.[158] to incorporate the correct stereochemistry. This methodology was successfully used to introduce chirality both in the synthesis of (−)-indolizidine 209B (Scheme 2.5) and (−)-indolizidine I67B (see Scheme 2.6).

Starting from *t*-butyl bromoacetate (**223**) and triethyl phosphite, phosphonate (**224**) was prepared. The phosphonate (**224**) was then reacted in a Horner-Wadsworth-Emmons reaction to give the Michael acceptor (**225**) in 63% yield over the two steps. The alkenoate (**225**) underwent a stereoselective aza-Michael reaction with the dibenzylated chiral amine (**214**). After debenzylation with 10% palladium-on-carbon and hydrogen gas in acetic acid, the enantiomerically pure amine (**226**) was isolated in 52% yield over the two steps. This amine (**226**) was reacted with chlorobutyryl chloride and cyclised to form the lactam (**227**) in 56% yield. The lactam (**227**) was thionated in the presence of Lawesson's reagent to give thiolactam (**228**) in 85% yield. The thiolactam underwent an Eschenmoser sulfide contraction reaction to give the enaminone (**229**) in 79% yield. The enaminone (**229**) was converted to the corresponding mixed anhydride via the carboxylic acid (**230**), and this facilitated acylative ring closure of the enaminone to give hexahydroindolizidinone (**231**) in 55% yield. Using standard transformations, defunctionalisation of the ester, enaminone and the resulting ketone proceeded via (**232**), (**233**) and (**234**) to give (−)-indolizidine 167B (**36**) in a total of fifteen steps and an overall yield of 1.5% (see Scheme 2.6).[159]

WITSETD

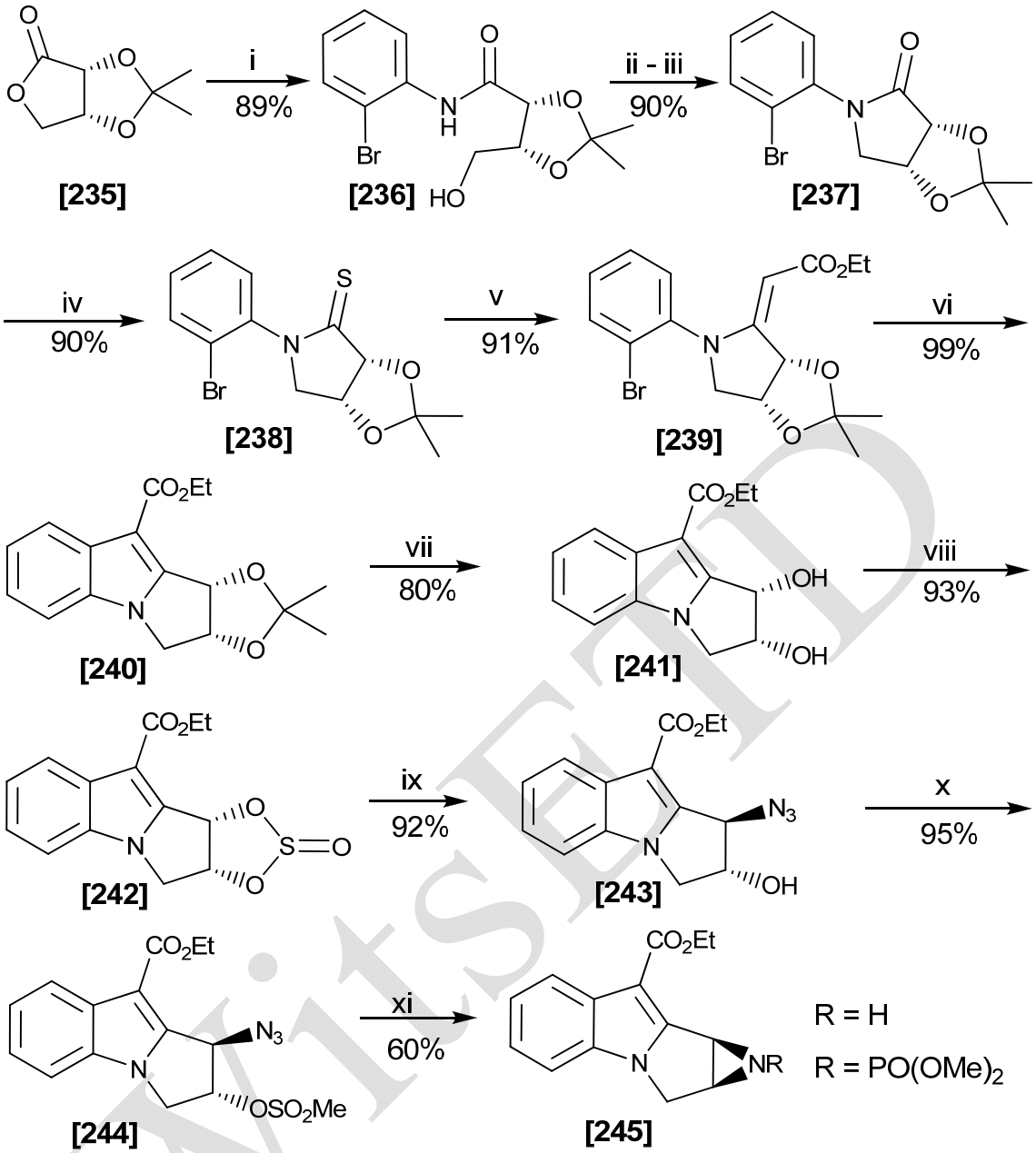


Scheme 2.6: The total synthesis of (–)-indolizidine 167B (**36**) by Michael and Gravestock.[159] *Reagents and conditions: i) $P(OEt)_3$, 110°C; ii) butanal, DBU, LiCl, MeCN, RT; iii) BuLi, THF, -78°C; iv) H_2, (7 atm.), 10% Pd-C, AcOH; v) $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, RT; vi) $KOBu^t$, Bu^tOH; vii) Lawesson's reagent, toluene, reflux; viii) $BrCH_2CO_2Et$, MeCN, RT; ix) Ph_3P, Et_3N, MeCN, RT; x) Me_3SiI, CCl_4, RT; xi) Ac_2O, MeCN, 50°C; xii) KOH, H_2O, reflux, then HCl, reflux; xiii) $LiAlH_4$, THF, RT; xiv) $HS(CH_2)_3SH$, $BF_3.Et_2O$, CF_3CO_2H, RT; xv) Raney-Ni, EtOH, reflux.*

WisETD

Enaminone cyclisations have also been used for the synthesis of aziridinomitosenes (see Scheme 2.7).[160] In a model study, 2-bromoaniline was condensed with the protected *D*-erythronolactone (**235**), which was the source of chirality, to give the alcohol (**236**) in 89% yield. Mesylation of the alcohol (**236**) and subsequent ring closure gave the lactam (**237**) in 90% yield over two steps. Thionation of lactam (**237**) formed the thiolactam (**238**) in 90% yield. Initial attempts at the Eschenmoser sulfide contraction involving the *N*-aryl thiolactam (**238**) proceeded in very low yields, probably due to the decreased nucleophilicity of the sulfur atom owing to conjugation with the aromatic ring. This problem was overcome by using a novel zinc-mediated Reformatsky reaction with ethyl bromoacetate in the presence of catalytic iodine. This produced the vinylogous urethane (**239**) in 91% yield. The next step, the Heck cyclisation, was efficiently catalysed by palladium acetate and cyclisation onto the aromatic ring proceeded to give (**240**) in 99% yield. Deprotection of the alcohols gave the diol (**241**) which was reacted with thionyl chloride to give the cyclic sulfite ester (**242**) in 74% yield over the two steps. Reaction of the cyclic sulfite ester (**242**) with sodium azide regioselectively gave the azide (**243**) in 92% yield and mesylation of the remaining hydroxy group gave (**244**) in 95% yield. Finally, the formation of the aziridine (**245**) completed the total synthesis in 60% yield. In total the synthesis took eleven steps and the overall yield was 25%. This methodology was subsequently applied to the synthesis of a fully functionalised aziridinomitosene, in which the ring was part of a quinone system.[161]

WITSETD

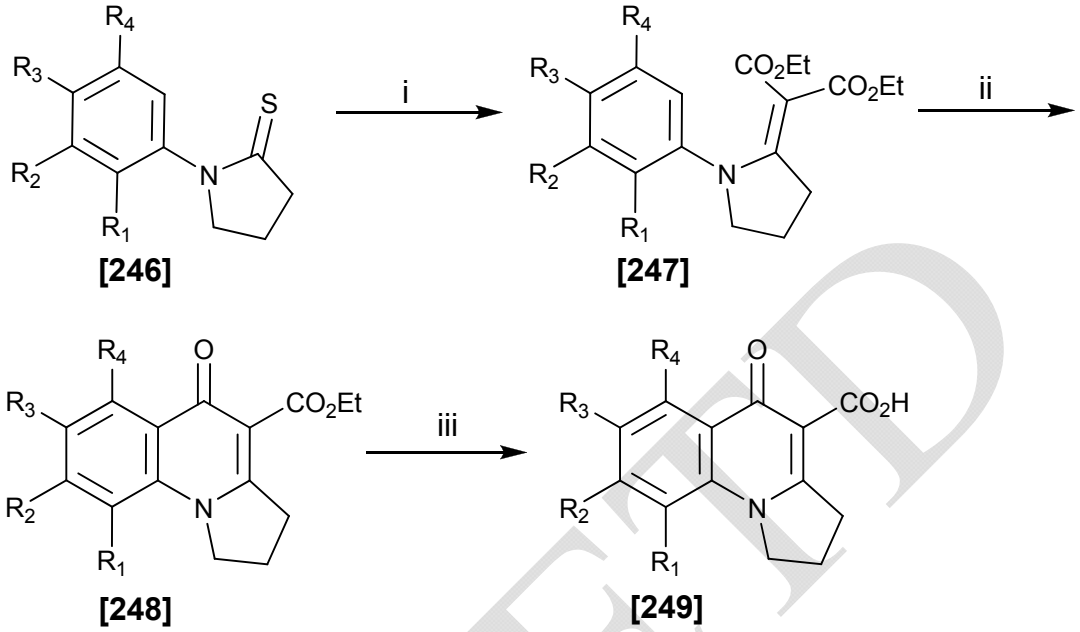


Scheme 2.7: The total synthesis of aziridinomitosene analogues (**245**) by Michael *et al.*[160, 162] *Reagents and conditions: i) 2-bromoaniline, EtMgBr, THF, -78°C; ii) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C, to RT; iii) NaH, THF, RT; iv) Lawesson's reagent, PhMe, reflux; v) Zn (5 eq.), $BrCH_2CO_2Et$ (3 eq.), I_2 (0.2 eq.), THF, ultrasound, then add **[238]**, THF, reflux; vi) $Pd(OAc)_2$ (0.1 eq.), PPh_3 (0.4 eq.), KOAc (7.5 eq.), Bu_4NBr (2.5 eq.), DMF-MeCN-H_2O (1:1:0.2), 100°C, 5 hr.; vii) TFA, THF-H_2O (1:1), RT; viii) $SOCl_2$, Et_3N, CH_2Cl_2, -15°C; ix) NaN_3, DMF, 55°C, then aq. H_2SO_4; x) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C, to RT; xi) $P(OMe)_3$, THF, reflux, then NaH, RT.*

One final example from the Wits laboratories is the synthesis of tricyclic analogues of quinolone antibiotics (see Scheme 2.8).[160] Starting from various *N*-aryl thiolactams (**246**) a modified Reformatsky reaction with diethyl bromomalonate gave the difunctionalised enaminones (**247**). Ring closure onto

WitsETD

the aromatic ring was catalyzed by polyphosphoric acid at elevated temperatures and gave the esters (**248**). The final step was the hydrolysis of the ester group to give the quinolone antibiotic analogues (**249**).



[246] **[247]** **[248]** **[249]**

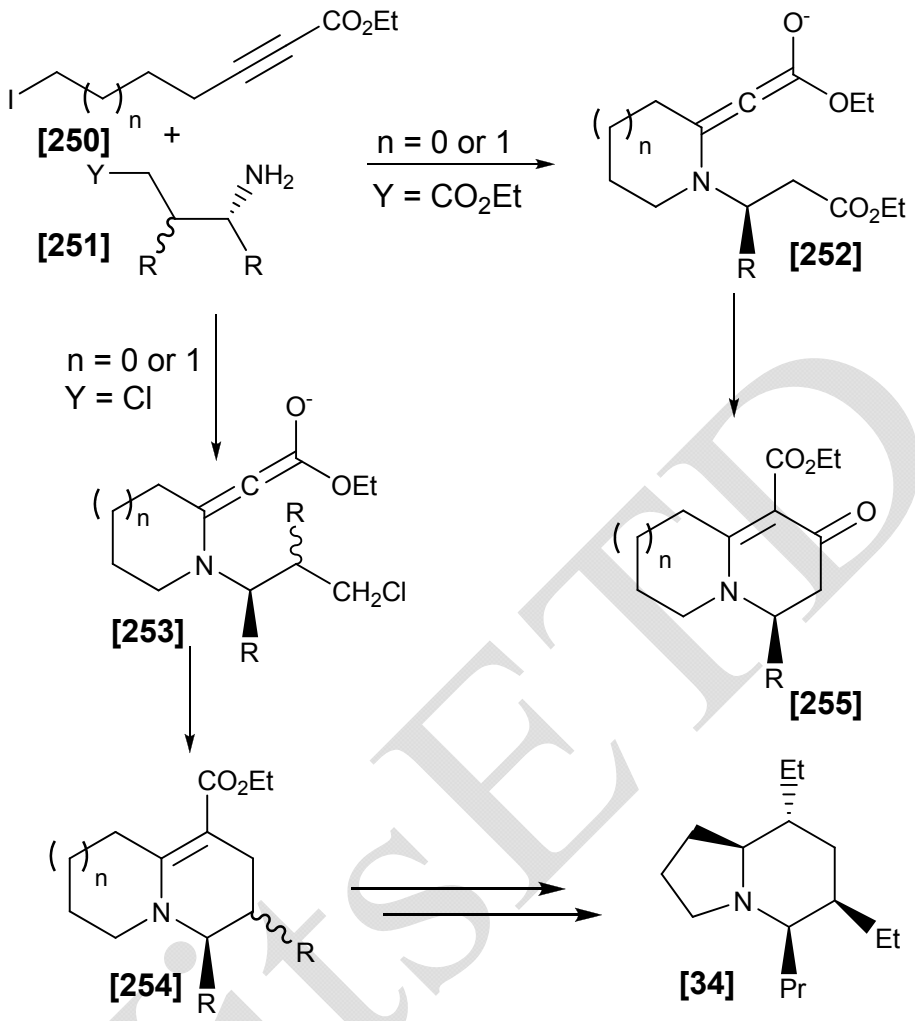
a) $R_1 = R_4 = OMe$, $R_2 = R_3 = H$
b) $R_1 = R_2 = R_3 = R_4 = H$
c) $R_1 = Me$, $R_2 = R_3 = R_4 = H$
d) $R_1 = R_3 = R_4 = H$, $R_2 = Me$
e) $R_1 = R_2 = R_4 = H$, $R_3 = Me$
f) $R_1 = R_2 = R_4 = H$, $R_3 = OMe$
g) $R_1 = R_4 = H$, R_2-$R_3 = OCH_2O$
h) $R_1 = Br$, $R_2 = R_3 = R_4 = H$
i) $R_1 = R_4 = H$, $R_2 = R_3 = F$

Scheme 2.8: The synthesis of tricyclic analogues of quinolones (**249**) by Michael *et al*.[160, 162] *Reagents and conditions: i) $BrCH(CO_2Et)_2$ (4 eq.), Zn (4 eq.), I_2 (0.2 eq.), THF, reflux; ii) PPA, 85-100°C; iii) NaOH, H_2O, reflux, then HCl.*

Other research groups are also currently investigating new methodology pertaining to enaminones. One group in particular is that of Ma and co-workers[163, 164] who employ enaminones in the cyclisation step in the synthesis of indolizidine and quinolizidine alkaloids (see Scheme 2.9). They used a one-pot process, mixing the alkene (**250**) and the amine (**251**) in the presence of potassium carbonate, to produce the allenyl enolate (**252**) or (**253)** *in situ*. The anion (**252**) or (**253**) spontaneously cyclised, alkylatively or acylatively, to give the corresponding bicyclic compound (**254**) or (**255**) respectively. One example of an amphibian indolizidine synthesized via this route was indolizidine 223A

WISER

(**34**), which was synthesized in twelve steps with an overall yield of 14.5%.[163, 165]



Scheme 2.9: The use of vinylogous urethanes in the synthesis of indolizidine and quinolizidine alkaloids by Ma and coworkers.[163]

2.2 Vinylogous sulfonamides

2.2.1 Preparation of vinylogous sulfonamides

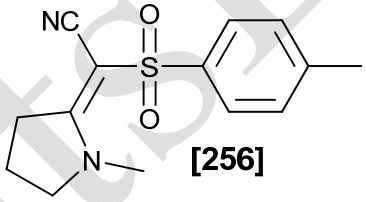
A particular type of "enaminone" analogue, namely the vinylogous sulfonamide, has recently emerged at Wits as an interesting enaminone variant. Its synthetic utility is due to the electron-withdrawing sulfone group, its ability to form α-sulfonyl anions, and its ready removal by hydrogenolytic, alkylative or oxidative cleavage once it has served its purpose. This allows for easy, high-yielding ring closure and the formation of indolizidine products that do not bear substituents at C-8 (Figure 1.1).[30] Vinylogous sulfonamides differ from the

WiSETD

classic enaminones in that the sulfone group does not participate in conjugation whereas the carbonyl group does.[166]

The literature available on sulfone chemistry is abundant and vinylogous sulfonamides are currently receiving a lot of attention by various research groups. Kozerski *et al.*[166] have performed extensive NMR studies on the three tautomeric forms of β-sulfonyl enamines *viz.* the *E*, *Z* and imine tautomers. As the energy difference between the imine and the enamine is very small these tautomers interchange rapidly at most temperatures by a proposed 1,3-sigmatropic proton transfer.

Arias *et al.*[167] have developed a novel preparation of vinylogous sulfonamides by reacting α-lithiated alkyl sulfones with lactams of pyrrolidines and piperidines. Meanwhile, Brillon *et al.*[168] have developed a novel preparation of difunctionalized enamines (**256**) by condensing 2-(phenylsulfonyl)acetonitrile ($PhSO_2CH_2CN$) with thiolactams in the presence of silver carbonate.



[256]

2.2.2 Uses of vinylogous sulfonamides

One of the principal research groups investigating the reactivity of vinylogous sulfonamides is that of Thomas Back.[56] He has demonstrated the utility of his methodology in the synthesis of quinolones[169, 170] piperidines, pyrrolidines, indolizidines and quinolizidines[56] (see Figure 2.3). His research group primarily exploits acetylenic sulfones by deprotonating the α-position in order to facilitate ring closure in an alkylative manner, e.g. in the synthesis of indolizidines and quinolizidines (see Scheme 2.10) or an acylative manner. For example, in the synthesis of (−)-lasubine II (**257**)[171] and pumiliotoxin C (**24**)[172] (see Scheme 2.11 and 2.12). He has reacted acetylenic sulfones with anilines in cycloaddition reactions, e.g. in the synthesis of quinolones I and II (**258**) (see Scheme 2.13). He also uses acetylenic sulfones as efficient dienophiles in

WitsETD

cycloaddition reactions, due to the electron-withdrawing effect of the sulfone. This research group's expertise extends to include the reactivity of allenic sulfones in addition to acetylenic sulfones.

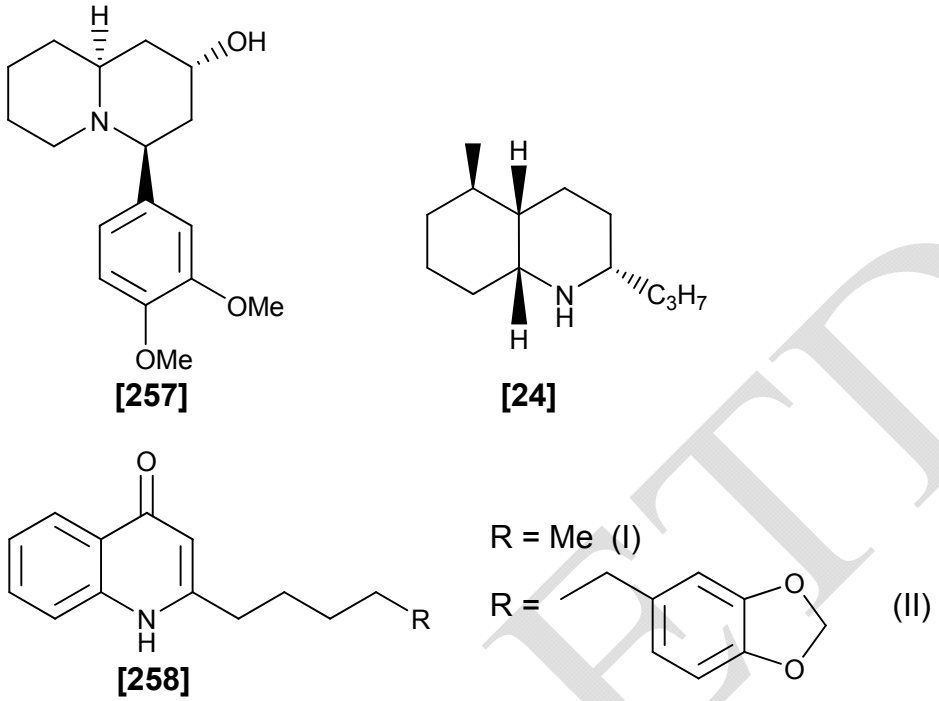
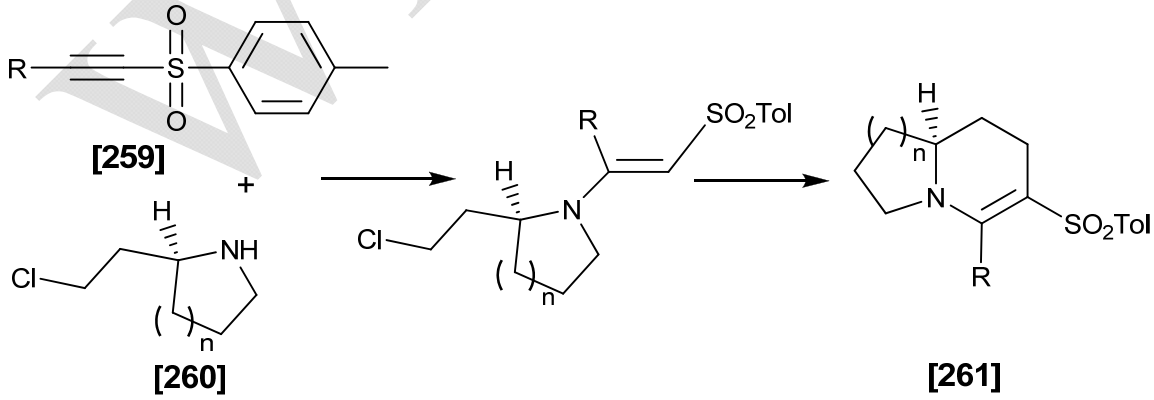
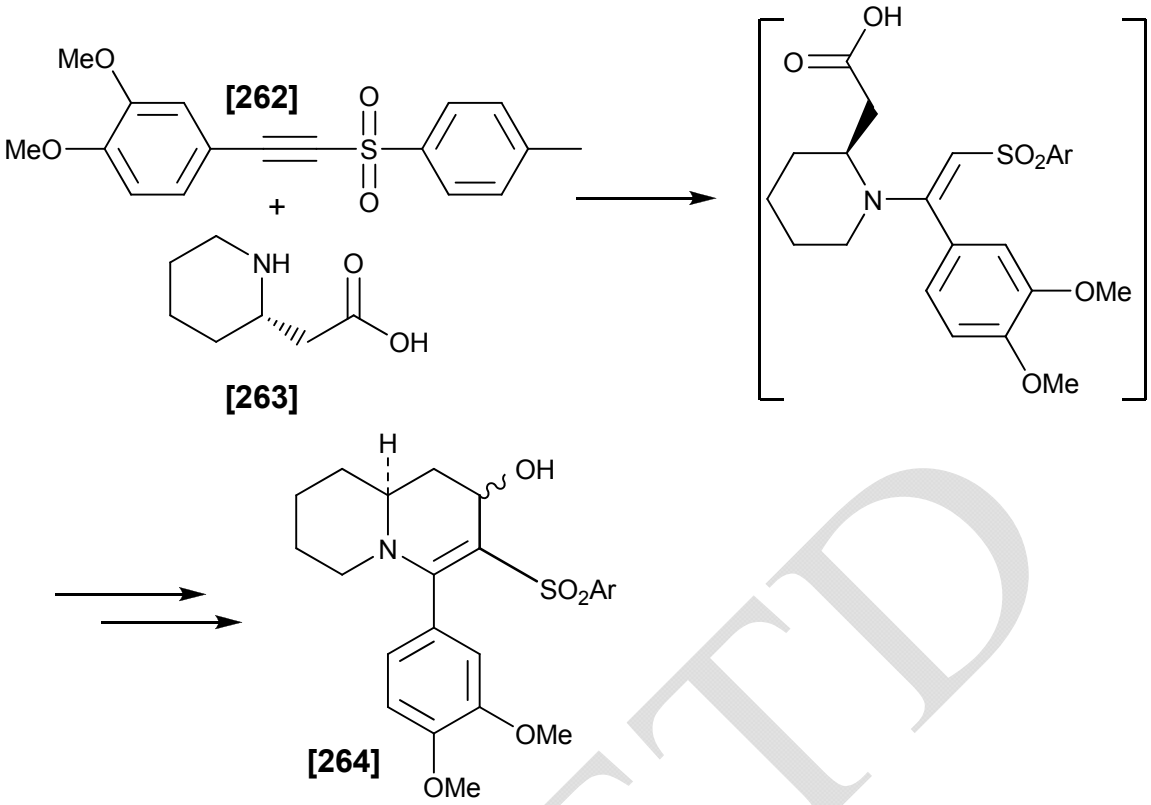


Figure 2.3: Natural products, (−)-Lasubine II (**257**), pumiliotoxin C (**24**) and quinolones I and II (**258**), synthesized using acetylenic sulfones.[56, 169, 170]

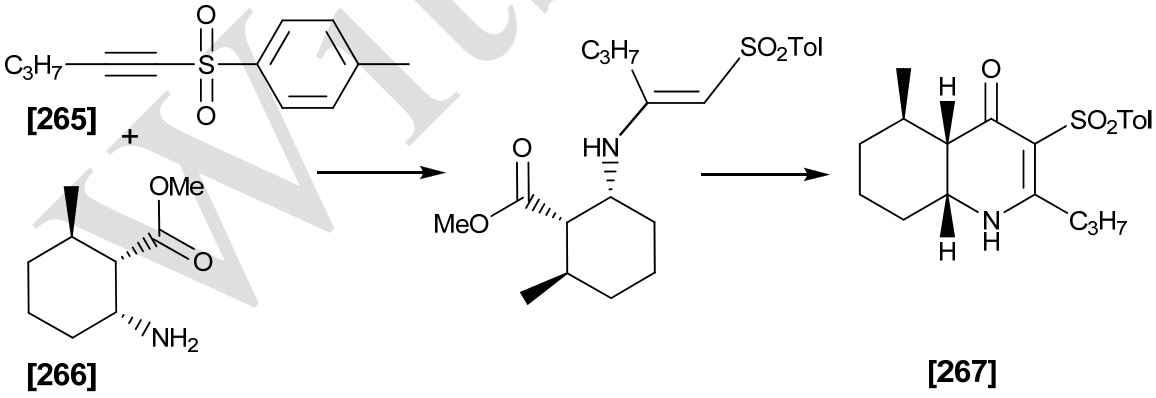


Scheme 2.10: Pyrrolidine (**260**) adds to the acetylenic sulfone (**259**) which facilitates alkylative ring closure to form (**261**), the precursor to indolizidines or quinolizidines.[56]

WitsETD

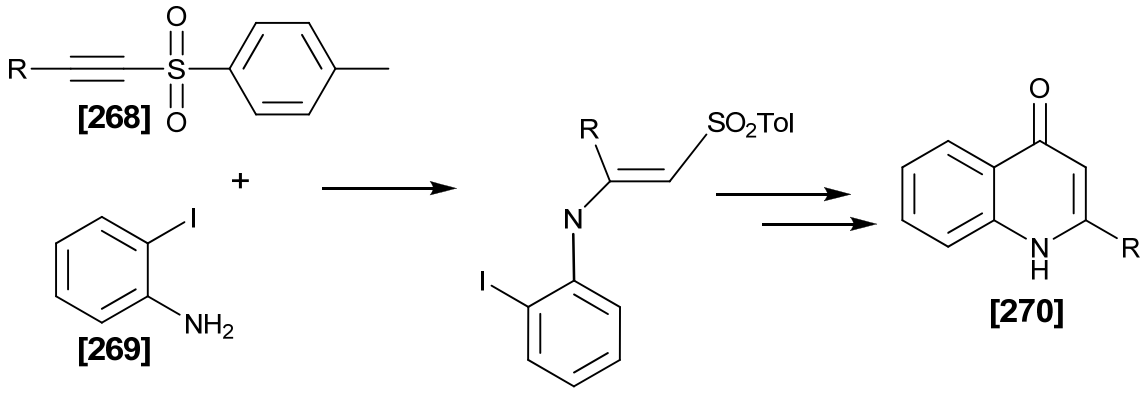


Scheme 2.11: Piperidine (**263**) adds to the acetylenic sulfone (**262**) which facilitates acylative ring closure to form (**264**), the precursor to (−)-lasubine II.[171]



Scheme 2.12: Amine (**266**) adds to the acetylenic sulfone (**265**) which facilitates acylative ring closure to form (**267**), the precursor to pumiliotoxin C.[172]

WitsETD



Scheme 2.13: Aniline (**269**) adds to the acetylenic sulfone (**268**) to form (**270**), the precursor to quinolones I and II.[169, 170]

2.3 Aims and proposed strategies of this project

2.3.1 (−)-Indolizidine 209D

Ibrahim Yillah, a former PhD student in the Wits laboratories, endeavoured to use vinylogous sulfonamides in the "Wits approach" for the total synthesis of (−)-indolizidine 209D (**37**).[31, 173] This indolizidine has since proved to be the incorrectly assigned structure of pyrrolizidine 209K (**39**) and as yet no 5-monosubstituted alkaloids have been confirmed from amphibian origin. Although Yillah completed his PhD in 2002, some of the intermediate molecules in his synthesis were not reliably characterized, in particular, the optical rotation values obtained did not correspond to literature values for analogous compounds. The methodology employed in his synthesis aligns with the methodology chosen for the total synthesis of monomorine I and its diastereomers in this PhD project. In an attempt to familiarise ourselves with this chemistry, to obtain the full characterization information, verify his experimental data, and optimize some of his reactions, we undertook to repeat his total synthesis of (−)-indolizidine 209D (**37**). The work he reported in his PhD thesis is shown in Scheme 2.14.

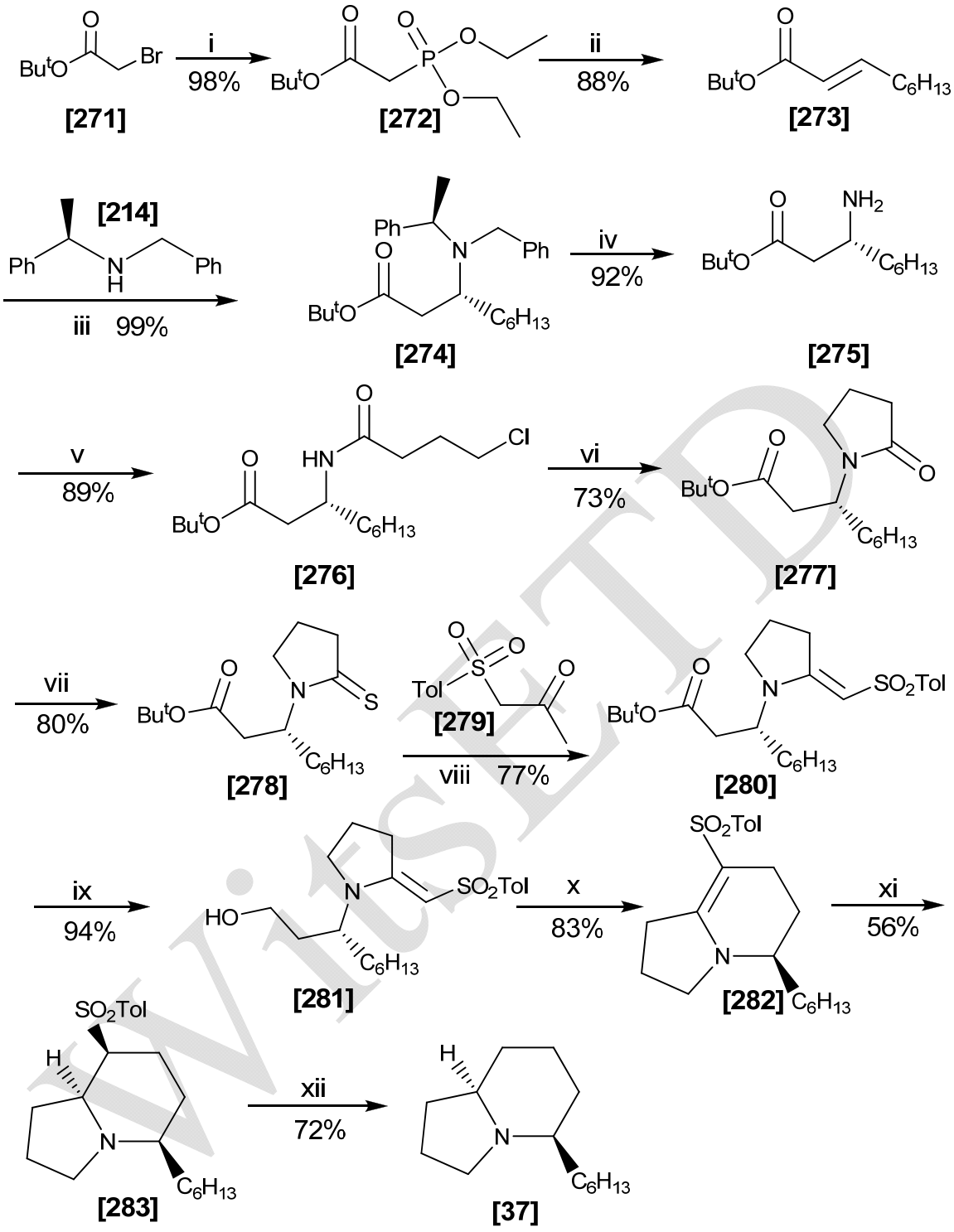
Starting from *t*-butyl bromoacetate (**271**), Horner-Wadsworth-Emmons methodology was utilized to transform phosphonate (**272**) into Michael acceptor (**273**) in 86% yield over two steps. Following the protocol developed by Davies *et al.*[158] aza-Michael addition with a chiral dibenzylated amine (**214**) allowed for

WitsETD

the stereoselective formation of (**274**) in 99% yield. Debenzylation in the presence of palladium-on-carbon afforded amine (**275**) in 92% yield. The condensation of amine (**275**) with 4-chlorobutyryl chloride afforded amide (**276**) in 89% yield. In the presence of a strong base the amide (**276**) cyclised to form the lactam (**277**) in 73% yield. Thionation of the lactam (**277**) afforded the corresponding thiolactam (**278**) in 80% yield. The thiolactam (**278**) was condensed with 1-[(4-methylphenyl)sulfonyl]acetone (**279**) which spontaneously deacylated to give the vinylogous sulfonamide (**280**) in 77% yield. Reduction of the *t*-butyl ester proceeded to give the corresponding alcohol (**281**) in 94% yield. Alkylative cyclisation afforded the bicyclic molecule (**282**) in 83% yield. Finally, reduction of the double bond gave (**283**) in 56% yield, followed by reductive cleavage of the sulfone to give (−)-indolizidine 209D (**37**) in 72% yield. Overall the synthesis took twelve steps and gave (−)-indolizidine 209D (**37**) in 9.9% yield.

Unfortunately, the optical rotation for the final product did not conform to the reported data, thus casting doubt on either the purity of the product or on the stereochemical integrity of the sequence. We chose to reattempt the total synthesis of (−)-indolizidine 209D in order to clarify the stereochemical integrity of this pathway, to optimize the route and to fully characterize the intermediates. This would provide us with ample opportunity to familiarise ourselves with the methodology and the laboratory techniques required to complete the synthesis of monomorine I and its diastereomers at a later stage. Repeating this synthesis in a systematic way would also ultimately allow for the publication of the total synthesis of (−)-indolizidine 209D.

WitsETD



Scheme 2.14: The total synthesis of (−)-indolizidine 209D (**37**) by Michael and Yillah.[31] *Reagents and conditions: i) $P(OEt)_3$, 100°C; ii) heptanal, NaH, Et_2O, RT, 1 hr.; iii) BuLi, THF, -78°C; iv) H_2 (7 atm.), 5% Pd-C, AcOH, 20 hr.; v) $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, RT; vi) $KOBu^t$, Bu^tOH; vii) P_2S_5,$CHCl_3$, RT, 8 hr.; viii) MeI, THF, then (**279**), Et_3N, CH_2Cl_2, 72 hr.; ix) $LiAlH_4$, THF, 15 hr.; x) PPh_3, imidazole, I_2, CH_3CN/toluene (2:1), reflux, 6 hr.; xi) H_2 (7 atm.), PtO_2, MeOH; xii) Na(Hg), Na_2HPO_4.*

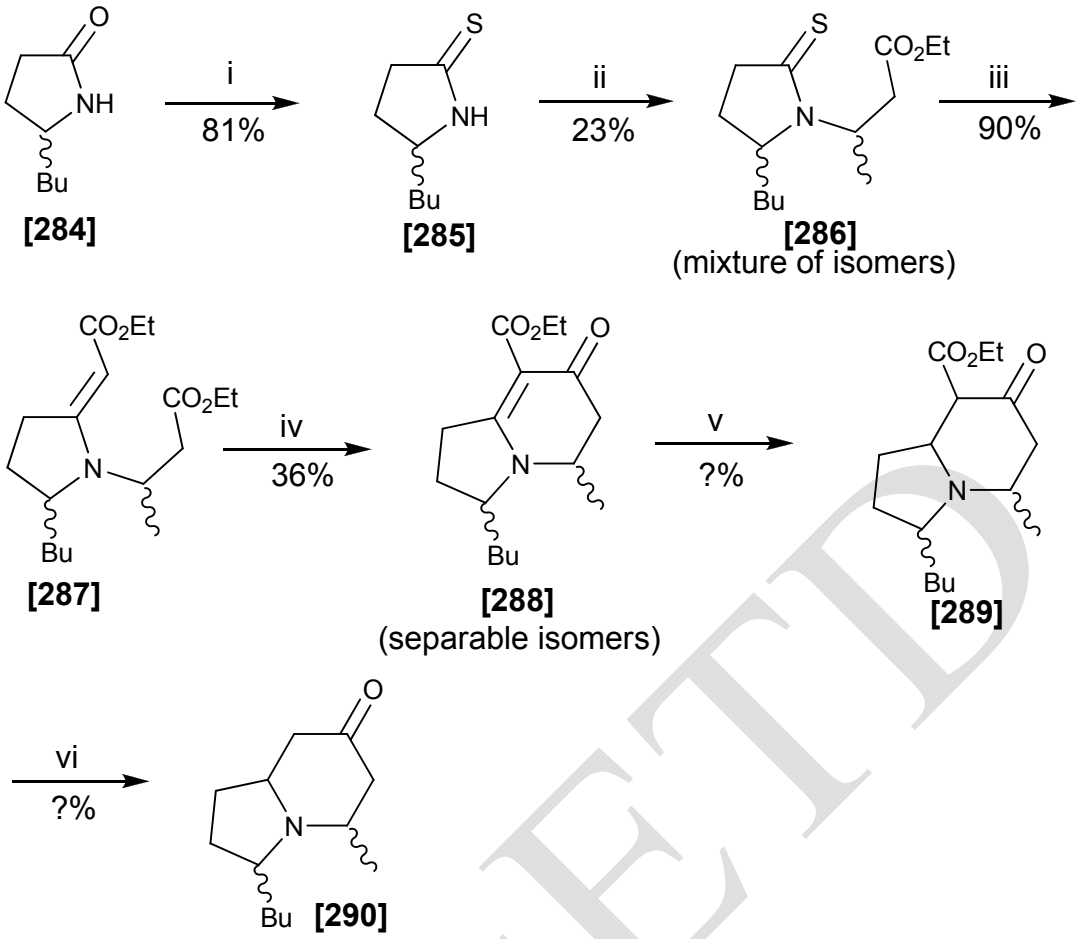
WitsETD

2.3.2 Monomorine I and diastereomers

Interest in the next target, monomorine I, at Wits started in the mid-90s when Penelope Cheesman undertook her Masters degree.[128] She started to investigate the total synthesis of monomorine I, but unfortunately she failed to complete it. However, she did perform numerous investigations leading to several key precursors of monomorine I and thereby verified that the "enaminone route" was potentially viable. Shown below are the key steps she achieved, although she was unable to purify or fully characterize the final two products (see Scheme 2.15).[128]

Starting from the racemic lactam (**284**), the carbonyl was thionated to give thiolactam (**285**) in 81% yield. Alkylation of the thiolactam (**285**) with ethyl crotonate proceeded to give (**286**) in a disappointing yield of 23% and as a mixture of diastereomers. Following the sulfide contraction and formation of the key intermediate, vinylogous urethane (**287**), the cyclisation reaction took place and separable diastereomers (**288**) were isolated in a 1:1 ratio. Unfortunately the following two steps, reduction of the enaminone and decarboxylation, were carried out on minimal material and not enough of the desired products were recovered to give conclusive characterization. There was however, spectroscopic evidence that compound (**289**) and indolizidinone (**290**) had been obtained. The final step in the synthesis, defunctionalisation of the keto group, was never attempted.

WITSETD



Scheme 2.15: Progress towards the total synthesis of monomorine I by Cheesman and Michael.[128] *Reagents and conditions: i) P_4S_{10}, THF, Na_2CO_3; ii) NaH, THF, ethyl crotonate, 12 hr., then reflux for 5 hr.; iii) a) Ethyl bromoacetate, CH_3CN, 0°C, 12 hr.; b) PPh_3, Et_3N, 2hr.; iv) a) NaOH, H_2O, reflux; b) Ac_2O, MeCN, 60°C; v) $LiAlH_4$, THF, 5 hr.; vi) a) KOH, reflux 2 hr;. b) HCl, reflux 1 hr.*

Although Cheesman was close to achieving the target, the mixture of diastereomers was a disadvantage, as was the need for a final defunctionalisation. We chose not to optimise this approach, but rather to investigate a new approach via vinylogous sulfonamides.

In general, indolizidines are particularly appropriate target molecules for total synthesis when exploiting enaminone reactivity. By nucleophilic attack of the enaminone at an appropriately placed electrophilic centre on the R group, one can create the C-7/C-8 bond (see Figure 2.4). When comparing this ring closure to all previous syntheses of monomorine I it was clear that this approach was novel. Furthermore, different levels of stereoselectivity can be attained by controlling the stereochemistry at C-3 and C-5 prior to cyclisation.

WISETD

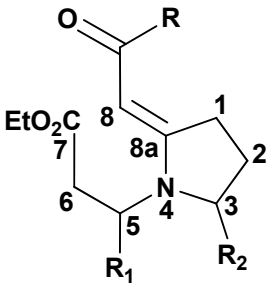


Figure 2.4: An enaminone for a potential C-7/C-8 ring closure to form an indolizidine.

Once the double bond has been incorporated into the second ring, there is the opportunity for stereoselective reduction, potentially guided by the steric effects of the other ring substituents. This reduction would be diastereofacially selective, with the hydrogen atoms delivered to the less hindered face, and is therefore only useful if that is the desired isomer (Figure 2.5).

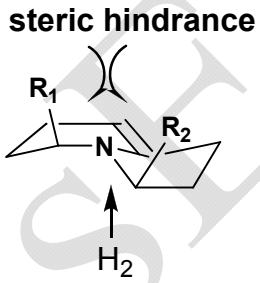


Figure 2.5: Potentially diastereofacially selective reduction of the double bond.

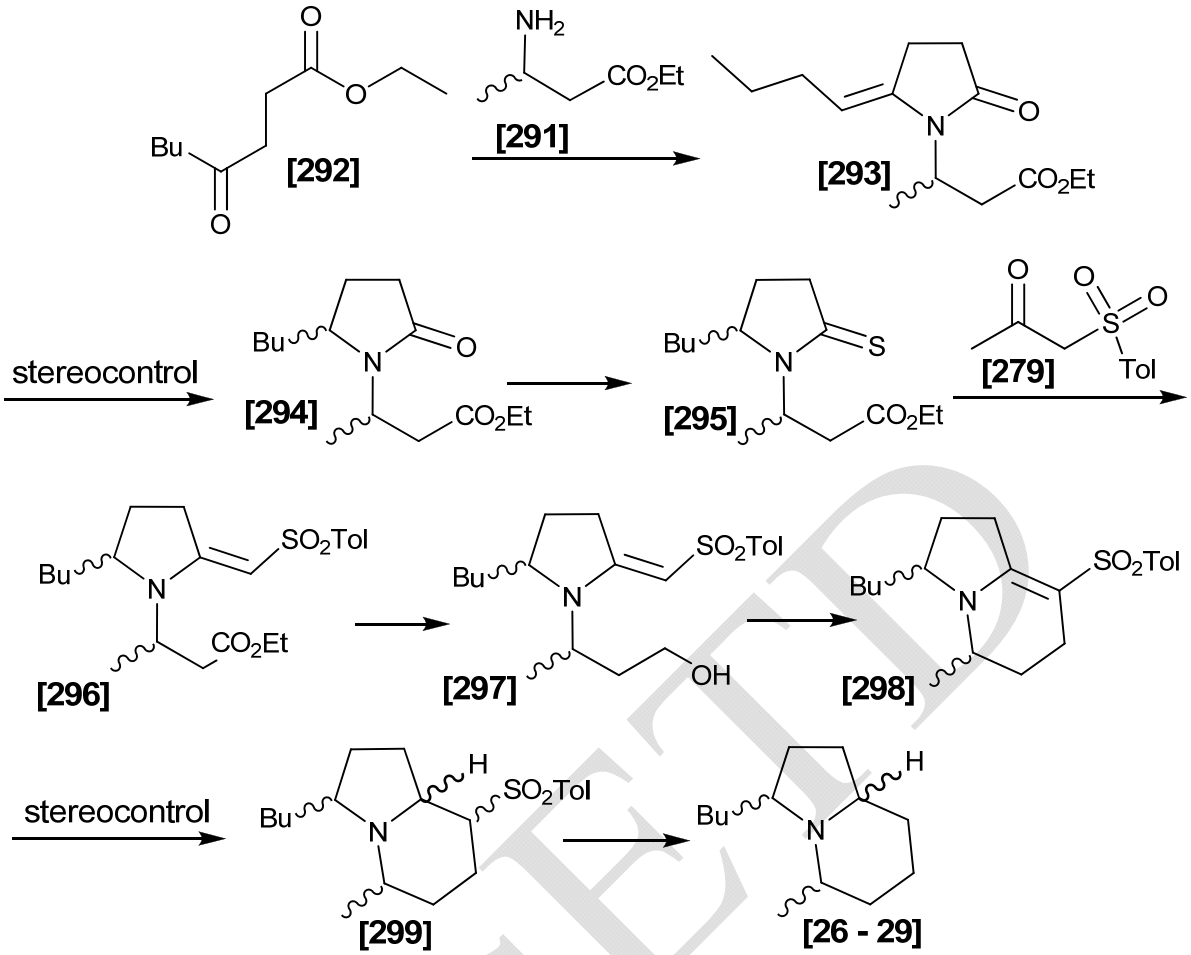
The aim of this second total synthesis was to exploit novel methodology in the synthesis of 3,5-disubstituted indolizidines and to incorporate the key intermediate vinylogous sulfonamide to expand the scope of the "Wits approach".

Our proposed synthetic route (see Scheme 2.16) begins with the preparation of the primary amine (**291**) and the bifunctional electrophile (**292**). The amine (**291**) and the keto-ester (**292**) should condense to give the lactam (**293**). Reduction of the exocyclic double bond to give (**294**) should offer an opportunity for diastereoselective control. Thionation of lactam (**294**) could proceed in the presence of phosphorus pentasulfide or Lawesson's reagent to give thiolactam (**295**). The sulfone reagent ($BrCH_2SO_2Ar$) was not a suitable

WitsETD

substrate for Eschenmoser sulfide contraction, due to the limited reactivity of α-halosulfones towards nucleophilic substitution.[174] Bordwell and Brannen[174] attribute this effect to the inductive and field effects of the sulfonyl oxygen atoms. Instead, an "activated" sulfone (**279**) has been selected which would allow deprotonation and condensation with the iminium salt of thiolactam (**295**) in a manner analogous to the synthesis of (−)-indolizidine 209D. The deacylation should proceed spontaneously. Reduction of ester (**296**) under standard conditions should give the corresponding alcohol (**297**), ready for alkylative ring closure to form the bicyclic skeleton (**298**). Finally, reduction of the double bond using hydrogen and palladium-on-carbon should allow diastereoselective control and provide only one diastereomer of (**299**). Desulfonylation under standard conditions should afford monomorine I (**27**), our target molecule. Should the diastereoselectivity favour one of the other isomers, the synthesis will still be that of a natural product (**26, 28** or **29**) and will still be complementary to the numerous reported syntheses in the literature (refer to Figure 1.6).

WitsETD



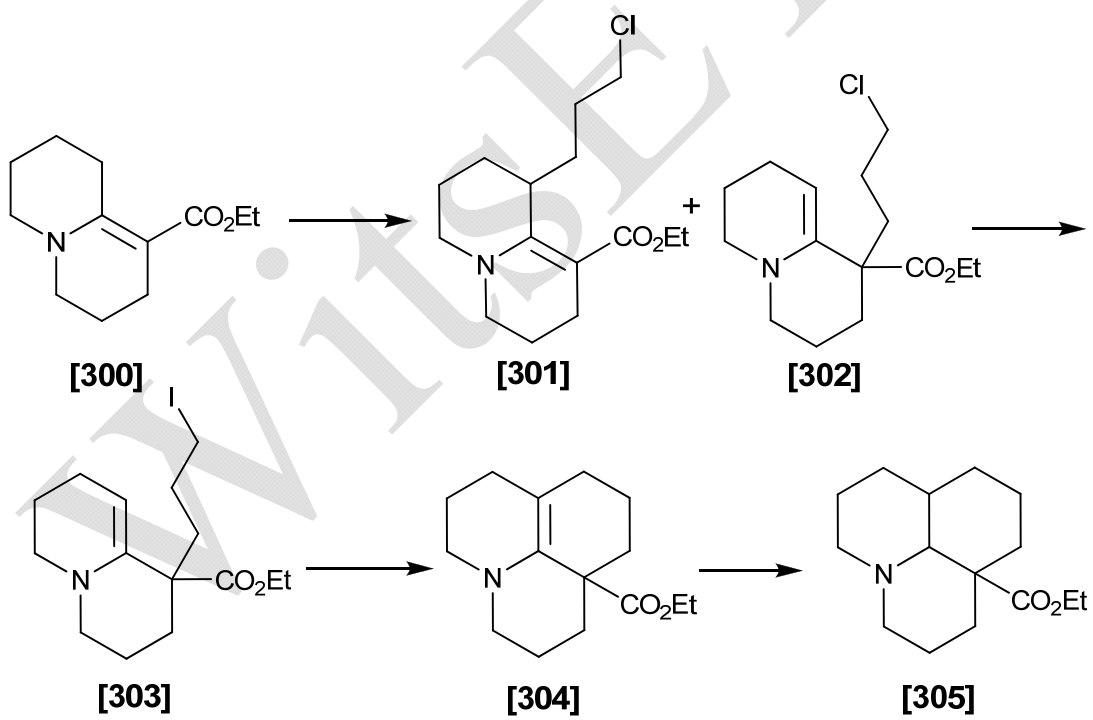
Scheme 2.16: Proposed synthetic route for the total synthesis of monomorine I and/or its isomers.

To perform the enantioselective synthesis of monomorine I and/or its diastereomers, the methodology developed by Davies *et al.*[158] will be incorporated into the preparation of amine (**291**) to provide the amine as a single enantiomer and hence continue the chiral synthesis with a single enantiomer rather than a racemate (see Chapter 3, section 3.2.2 for a more detailed discussion of Davies' methodology and how it has been used in stereoselective aza-Michael addition reactions).

WitsETD

2.3.3 Accessing tricyclic alkaloids

The tricyclic alkaloids are rarely detected in Nature and occur in minor and trace amounts when they do. However, there was evidence of their potent biological activity that warrants further investigation. Due to their structural complexity of tricyclic alkaloids, there are far fewer reported total syntheses of them compared to the bicyclic alkaloids. Very little work on accessing tricyclic alkaloids formally incorporating the indolizidine and quinolizidine systems has been done in the Wits laboratories. A fortuitous result from Howard, Orlek and co-workers[134, 175] led to a hydrojulolidine derivative (**305**) during studies into the total synthesis of lupinine (see Scheme 2.21). Vinylogous urethane (**300**) was alkylated to form a mixture of chlorides (**301**) and (**302**). Following a Finkelstein reaction, compound (**302**) formed the iodide (**303**), which underwent alkylative cyclisation to form the tricyclic product (**304**). Reduction of the enamine gave the hydrojulolidine derivative (**305**).

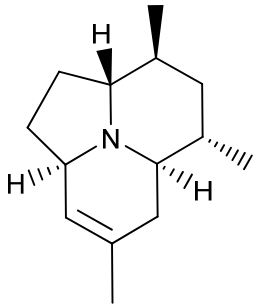


Scheme 2.21: The fortuitous synthesis of a hydrojulolidine derivative (**308**) by Orlek and co-workers.[134, 175]

As was mentioned at the end of Chapter 1, 3,5-disubstituted indolizidine alkaloids show a structural relationship to certain tricyclic alkaloids, as their

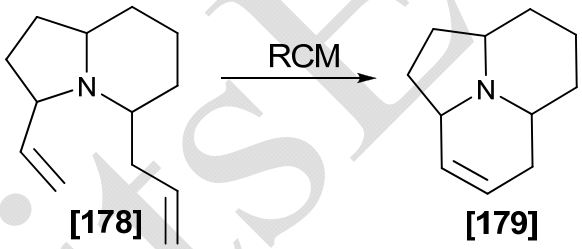
WitsETD

tricyclic system formally incorporates a 3,5-disubstituted indolizidine within the skeleton. One such tricyclic alkaloid was alkaloid 205B (**47**).



[47]

The basic tricyclic skeleton of these alkaloids could potentially be accessed by closing the two side chains of the 3,5 disubstituted indolizidine (**178**) to form the tricyclic system (**179**). One possible method would be ring closing metathesis (RCM) as shown in Figure 2.6.



[178] **[179]**

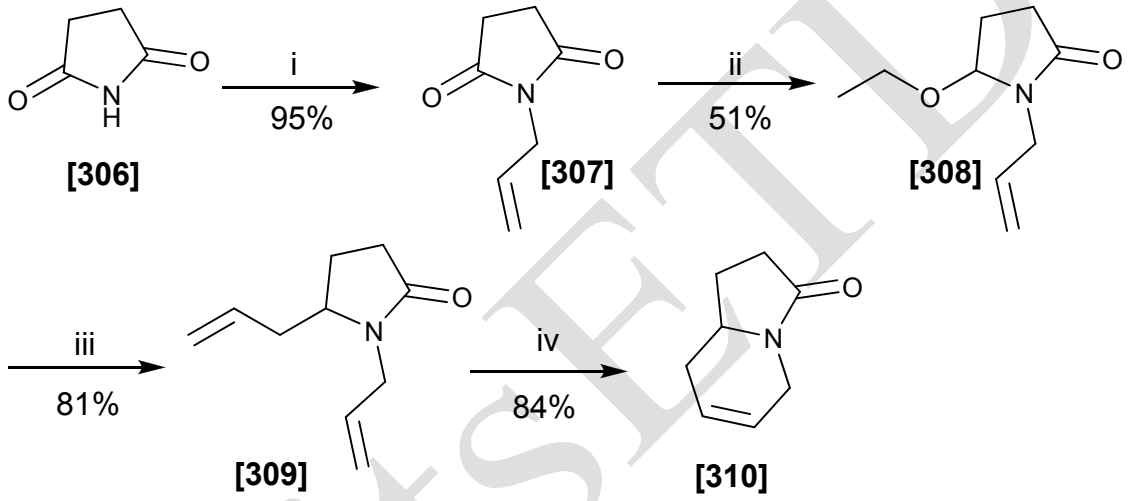
Figure 2.6: Proposed synthetic connection between 3,5-disubstituted indolizidines (**178**) and tricyclic alkaloids (**179**).

Our idea for forming tricyclic alkaloids via RCM was closely related to the method employed by Smith III and Kim (see Scheme 1.19).[122] We hope to prepare the 3,5-disubstituted indolizidine (**178**) using the same methodology applied for synthesis of monomorine I and then use ring closing metathesis to form the final ring. Initially, our aim was to present a model study that would support this synthesis and thus prove its viability. If the model study proved successful then we could build the tricyclic scaffold of an alkaloid such as 205B.

Holmes and co-workers[176] have performed an extensive investigation of RCM using β-, γ- and δ-lactams (for example, see Scheme 2.22). They reacted

WitsETD

pyrrolidine (**306**) with allyl alcohol using Mitsunobu conditions and isolated the *N*-allyl derivative (**307**) in 95% yield. Using mild reducing conditions one of the carbonyls was reduced to give (**308**) in 51% yield. The second allyl group was introduced using trimethylallylsilane in the presence of boron triflouride etherate to give (**309**) in 81% yield. The metathesis reaction was catalysed by the Grubbs I catalyst and gave the bicyclic lactam (**310**) in 84% yield. They have successfully performed the final step in our proposed synthesis using the ruthenium alkylidene known as the Grubbs I catalyst, which is stable and exhibits tolerance to a diverse range of molecules.

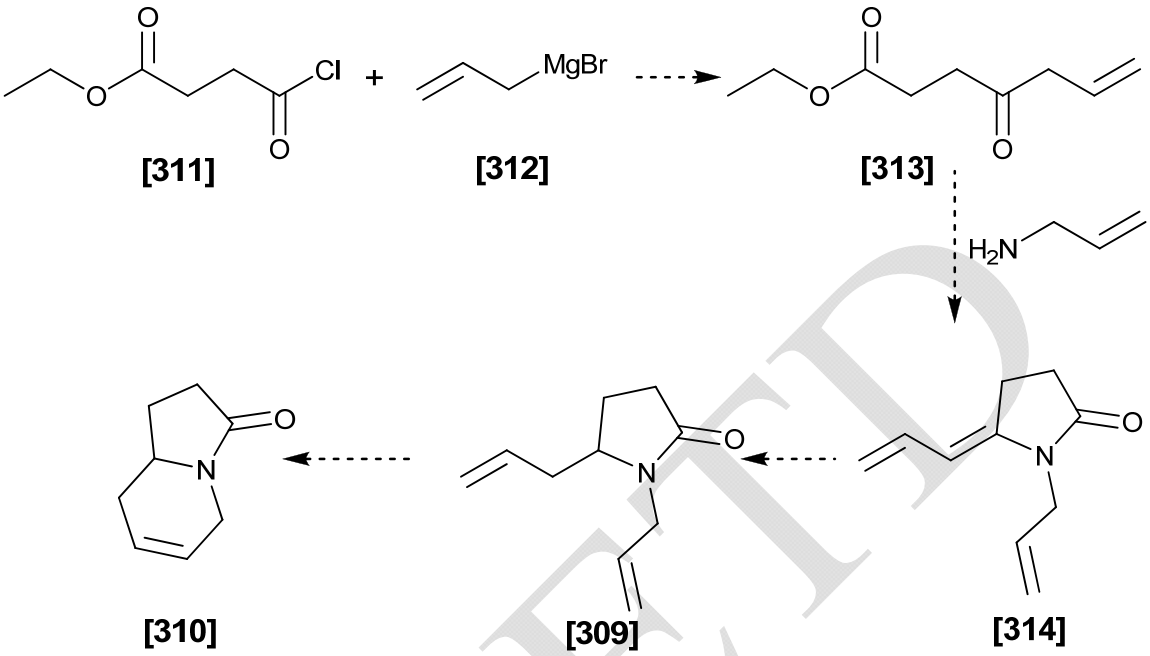


Scheme 2.22: Synthesis of bicyclic molecules from lactams using RCM by Holmes and co-workers.[176] *Reagents and conditions: i) CH_2CHCH_2OH, PPh_3, DEAD, THF; ii) $NaBH_4$, HCl, EtOH, -10°C; iii) $CH_2CHCH_2SiMe_3$, $BF_3.OEt_2$, CH_2Cl_2; iv) 5 mol% Grubbs I, CH_2Cl_2.*

Our proposed model study was designed to determine if the initial reaction conditions in the synthesis of monomorine I would be mild enough to allow for the incorporation of alkene side-chains. We also wanted to explore the ease with which these alkene side-chains undergo RCM (see Scheme 2.23). Starting from the acyl chloride (**311**), a reaction with allylmagnesium bromide (**312**) should provide us with the allylketo-ester (**313**). Condensation of the keto-ester (**313**) with allylamine should proceed in an analogous manner to our proposed monomorine condensation reaction and allow access to lactam (**314**). By selecting a chemoselective reducing agent, for example a silane in trifluoroacetic acid, it should be possible to selectively reduce out the exocyclic

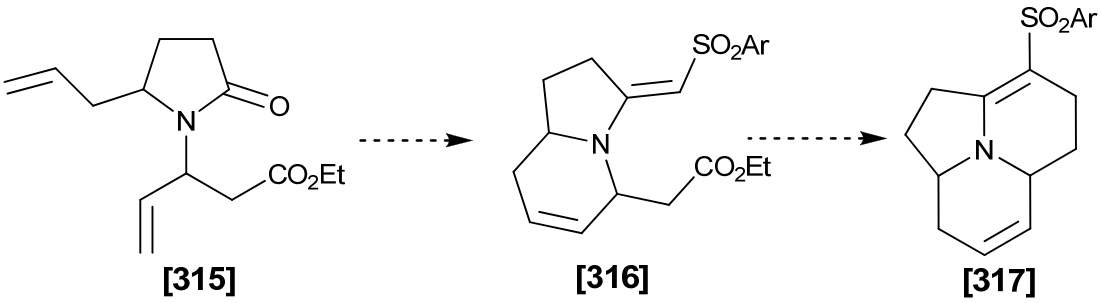
WiSETD

double bond and produce (**309**). Lactam (**309**) would be a promising candidate for RCM as the alkenes are terminal and the ring strain would be minimal. Cyclisation would produce the bicyclic product (**310**).



Scheme 2.23: Proposed model synthesis for the RCM approach.

In order to extend the model study to form the third ring of the desired targets, the allylamine would have to contain an ester side chain, which would ultimately be used to form the third ring (see Scheme 2.24). Lactam (**315**) should undergo RCM in an analogous manner to the model lactam (**313**) and following formation of the vinylogous sulfonamide should form the bicyclic structure (**316**). The bicyclic vinylogous sulfonamide (**316**) could be reacted in an analogous manner to the monomorine I synthesis, effecting ring closure to access the tricyclic compound (**317**).



Scheme 2.24: Proposed synthesis for the formation of the tricyclic skeleton.

WitsETD

2.3.4 Summary of aims

- To repeat Yillah's synthesis of (−)-indolizidine 209D (**37**) while verifying the experimental procedures and fully characterizing all intermediates and (−)-indolizidine 209D (**37**), paying particular attention to the optical rotation values and hence prove the stereochemical integrity of this pathway.
- To synthesize racemic monomorine I (**27**) and/or its diastereomers (**26**, **28** + **29**) using vinylogous sulfonamides for the key cyclisations.
- To utilize Davies' methodology for the enantioselective synthesis of monomorine I (**27**) and/or its diastereomers (**26**, **28** + **29**).
- To explore potential ways of accessing indolizidine-based tricyclic systems, such as 205B (**47**), using model systems.

WitsETD

CHAPTER 3
THE ATTEMPTED TOTAL SYNTHESIS OF (−)-INDOLIZIDINE 209D

3.1 Introduction

The chemistry employed by Ibrahim Yillah during his PhD in the enantioselective synthesis of (−)-indolizidine 209D (**37**)[31] was analogous to our proposed novel synthesis of monomorine I (**27**). Unfortunately, the optical rotation Yillah obtained for (−)-indolizidine 209D (**37**) did not conform to the reported data, thus casting doubt on either the purity of the product or on the stereochemical integrity of the sequence. Owing to the incomplete characterization of some of his intermediates and (−)-indolizidine 209D (**37**), and in particular, the poor correspondence of his reported optical rotation values with the literature, Yillah's work remains unpublished.

We chose to reattempt the total synthesis of (−)-indolizidine 209D (**37**) in order to clarify the stereochemical integrity of this pathway, to optimize the route, and to fully characterize the intermediates. This would also provide us with ample opportunity to familiarize ourselves with the methodology and with the laboratory techniques required in order to complete the synthesis of monomorine I (**27**) and/or its diastereomers at a later stage. Repeating this synthesis in a systematic way would also ultimately allow for the publication of the total synthesis of (−)-indolizidine 209D (**37**).

The basic principle behind Yillah's synthetic route was the use of the vinylogous sulfonamide to assist cyclisation in the formation of the indolizidine skeleton. Using standard transformations the appropriate vinylogous sulfonamide can be prepared which would in turn provide access to the bicyclic system via alkylative ring closure. Stereoselective reduction of the vinylogous sulfonamide and finally desulfonylation should afford (−)-indolizidine 209D (**37**).

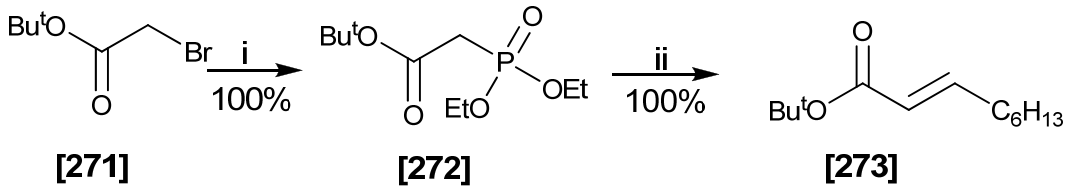
WitsETD

In order to use vinylogous sulfonamides in a stereoselective synthesis, the first stereogenic centre must be introduced prior to the cyclisation reaction. Yillah chose to follow the methodology of Davies *et al*.[158] to introduce the stereochemistry by using a chiral amine to direct the formation of the stereocentre. Their methodology incorporates the optically pure *N*-benzyl-*N*-(1*R*)-1-phenylethylamine (**214**) as a chiral amine nucleophile. Not only was this type of reaction well documented, but it had already been successfully used in the total synthesis of indolizidines (−)-167B (see Scheme 2.6) and (−)-209B (see Scheme 2.5) by Gravestock in our laboratories at Wits.[139]

The conjugate addition of the chiral amine to an alkenoate, or Michael acceptor, proceeded with a high degree of stereoselectivity, especially if the alkenoate contained a *t*-butyl ester group, provided that the alkenoate was a single geometric isomer. The standard literature procedure for producing exclusively the *trans* alkenoate was by means of a Horner-Wadsworth-Emmons variation of the Wittig reaction. This was where our synthesis started.

3.2 Horner-Wadsworth-Emmons reaction; the Michael acceptor

t-Butyl 2-(diethoxyphosphoryl)acetate (**272**), was prepared in quantitative yield starting from *t*-butyl bromoacetate (**271**) and heating at reflux with triethyl phosphite for twelve hours (see Scheme 3.1). The phosphonate structure was confirmed by ^{1}H-NMR spectroscopy, which clearly showed a doublet at 2.88 ppm which can be assigned to the methylene group adjacent to the carbonyl, coupling to the spin-active phosphorus atom with a $^{3}J_{P\text{-}H}$ of 21.5 Hz. The *t*-butyl signal at 1.48 ppm as well as the ethoxy signals at 4.17 and 1.35 ppm allowed conclusive assignment of the *t*-butyl 2-(diethoxyphosphoryl)acetate (**272**). The ^{1}H-NMR, ^{13}C-NMR and IR spectra were all in agreement with the literature values.[154]



[271] **[272]** **[273]**

Scheme 3.1: Formation of the Michael acceptor. *Reagents and conditions: i) $P(OEt)_3$, 110°C, 24 hr.; ii) NaH, heptanal, Et_2O, RT, 1 hr.*

The next reaction, the Horner-Wadsworth-Emmons reaction, proceeded by reacting *t*-butyl 2-(diethoxyphosphoryl)acetate (**272**) with sodium hydride in diethyl ether at 0°C to produce the corresponding stabilized anion. Careful addition of freshly distilled heptanal in diethyl ether from a dropping funnel, followed by warming the mixture to ambient temperature and stirring for two hours, afforded *t*-butyl (*E*)-non-2-enoate (**273**) exclusively as the *trans* isomer in quantitative yield (see Scheme 3.1). The geometry of the double bond was confirmed by the *trans* vicinal coupling constant observed between the alkene hydrogens. The hydrogen in the α-position was observed at 5.73 ppm as a doublet of triplets (*J* 15.6 and 1.5 Hz) and the hydrogen in the β-position was observed at 6.86 ppm as a doublet of triplets (*J* 15.6 and 6.9 Hz). Large vicinal coupling constants between 12 and 18 Hz are characteristic of *trans*-alkenes (**318**). The corresponding *cis*-alkenes (**319**) give vicinal coupling constants between 8 and 12 Hz (see Figure 3.1). None of the *cis* isomer was observed in the ^{1}H-NMR or ^{13}C NMR spectra.



Trans coupling
12 - 18 Hz
[318]

Cis coupling
8 - 12 Hz
[319]

Figure 3.1: Characteristic coupling constants for *trans* and *cis* vicinal coupling in alkenes.

The singlet observed at 1.48 ppm integrating for nine hydrogens, combined with the aliphatic signals between 2.16 and 0.88 ppm which integrated for thirteen hydrogens, confirm the presence of the *t*-butyl ester and the hexyl side chain

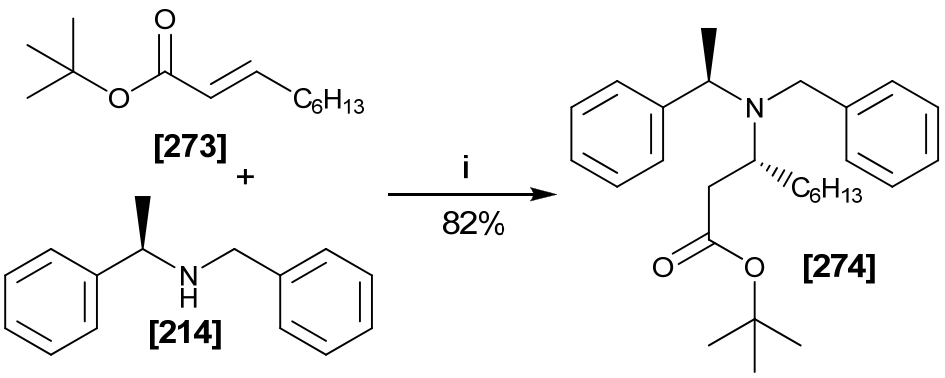
WiSERTD

respectively. The ^{13}C-NMR spectrum clearly indicates the ester carbonyl group at 166.1 ppm and the ester C-O group at 79.9 ppm. The characteristic alkene signals at 148.1 and 122.9 ppm confirm the presence of the alkene functional group. In addition, the FTIR spectrum confirmed the presence of an ester carbonyl group with the stretching absorption band at 1715 cm^{-1}. Finally, mass spectroscopy failed to reveal a parent ion, however, there was a clear peak corresponding to the loss of the *t*-butoxy group at 139.

3.3 Davies methodology: Conjugate addition reaction

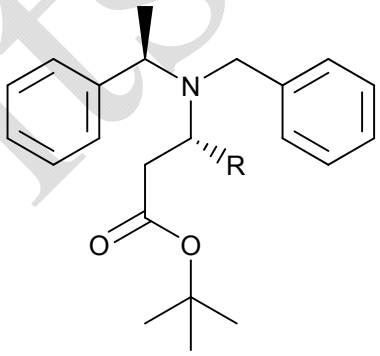
The next step was the conjugate addition reaction of the chiral amine (**214**) to our *trans* alkenoate (**273**) (see Scheme 3.2). This proceeded by the reaction of *N*-benzyl-*N*-(1*R*)-1-phenylethylamine (**214**) with *n*-butyllithium in tetrahydrofuran, cooled to −90°C in a liquid nitrogen/acetone bath, and stirred for thirty minutes to ensure complete deprotonation of the amine. The *t*-butyl (*E*)-non-2-enoate (**273**) was then added by means of a dropping funnel over forty-five minutes and the mixture was stirred for an additional four hours at −90°C before the reaction was quenched with saturated ammonium chloride solution. The product, *t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino} nonanoate (**274**), was isolated in yields as high as 82%. However, the reaction appeared to be extremely sensitive to the quality of the *n*-butyllithium and the ratio of *n*-butyllithium to the amine. The isolated yields decreased rapidly with older stock solutions of *n*-butyllithium, or when the ratio of *n*-butyllithium to amine was greater than 1:1. The product was stable at ambient temperature for at least a week and thereafter it slowly decomposed.

WitsETD



Scheme 3.2: Conjugate addition reaction. *Reagents and conditions: i) a)* n-*BuLi, THF, -90°C, 30 min.; b) (**273**), -90°C, 4 hr.*

Full characterization of the product confirmed its structure. Careful examination of the ^{13}C-NMR spectrum revealed only one set of signals, indicating the presence of only one diastereomer. Another encouraging observation was the optical rotation value recorded for *t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (**274**), as this agreed favourably in sign and magnitude with similar compounds (see Table 3.1). The optical rotation obtained by Yillah was at least twice the magnitude of the analogous compounds and was significantly bigger than the value we obtained.

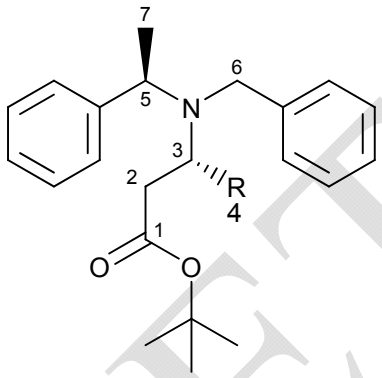


R-side chain	Optical Rotation	Concentration	Solvent
C_3H_7	$[\alpha]_D^{30}$ +7.3	1.24	EtOH[139]
C_5H_{11}	$[\alpha]_D^{25}$ +5.1	1.07	EtOH[139]
C_6H_{13} (274)	**$[\alpha]_D^{20}$ +4.5**	**1.00**	**CH_2Cl_2**
C_6H_{13} (274)	$[\alpha]_D^{20}$ +13.8	1.38	CH_2Cl_2[31]
C_7H_{15}	$[\alpha]_D^{25}$ +5.3	1.03	$CHCl_3$[177]

Table 3.1: Comparison of optical rotation data for analogous aminoesters. (Concentration measured in g/100 mL).

WitsETD

The ^{1}H-NMR and ^{13}C-NMR spectra were in close agreement with similar compounds reported in the literature. Table 3.2 shows selected ^{1}H NMR and ^{13}C NMR spectral data for our conjugate adduct (**274**) with a hexyl side chain in comparison to the published pentyl and heptyl analogues. The spectra obtained by Yillah were virtually identical to the spectra we obtained and therefore are not shown in Table 3.2. Diastereotopic pairs of signals were observed for H-2 and H-6 as they were the methylene groups nearest to the stereogenic centres. No other signals exhibited diastereotopic splitting.

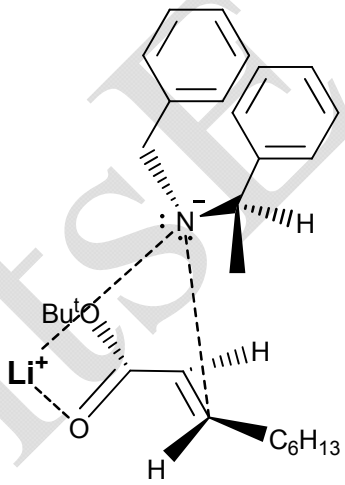


Signal	R = C_5H_{11} [139] / ppm	R = C_6H_{13} (274) / ppm	R = C_7H_{15} [177] / ppm
H-2*A*	1.85 (dd, *J* 14.6, 7.8)	1.86 (dd, *J* 14.5, 9.2)	1.87 (dd, *J* 14.5, 9.2)
H-2*B*	1.96 (dd, *J* 14.6, 3.6)	1.96 (dd, *J* 14.5, 3.7)	1.95 (dd, *J* 14.5, 3.8)
H-3	3.40 – 3.28 (m)	3.35 – 3.24 (m)	3.30 (m)
H-5	3.84 (q, *J* 7.0)	3.86 – 3.74 (m)	3.89 – 3.77 (m)
H-6*A*	3.50 (d, *J* 15.0)	3.48 (d, *J* 15.0)	3.48 (d, *J* 15.0)
H-6*B*	3.82 (d, *J* 15.2)	3.86 – 3.74 (m)	3.89 – 3.77 (m)
H-7	1.35 (d, *J* 7.0)	1.32 (d, *J* 6.9)	1.33 (d, *J* 7.0)
C-1	172.4	172.2	172.3
C-2	37.7	37.9	38.0
C-3	53.6	54.0	54.2
C-4	35.8	33.5	33.6
C-5	58.3	58.4	58.5
C-6	50.1	50.1	50.2
C-7	20.4	20.5	20.5

Table 3.2: Comparison of selected NMR spectral data (in $CDCl_3$) for analogous conjugate adducts. (*J*-values were measured in Hz).

WISETD

The rationalization of the stereochemical outcome of this reaction has been well documented, and according to Davies and co-workers[178] the basic principle behind it was a combination of steric and stereoelectronic effects. According to the proposed model, the lowest energy transition state (**320**) is when the lithium atom chelates to the carbonyl group of the ester and to the lone pair of electrons on the nitrogen (see Figure 3.2). The methyl group places steric strain on the amine, forcing it to assume a "butterfly" conformation, with the benzyl groups parallel to one another and pointing away from the alkene. The bulky ester group assists in positioning the amine with the methyl group on the opposite side. The chelation of the lithium locks the Michael acceptor in position and hence the nitrogen favours *si*-face addition. The methyl group controls the orientation of the amine relative to the Michael acceptor hence controlling the stereochemical outcome.[179]



[320]

Figure 3.2: Rationalized stereochemical transition state (**320**) showing the nitrogen lone pair and the carbonyl oxygen chelating to the lithium atom.[179]

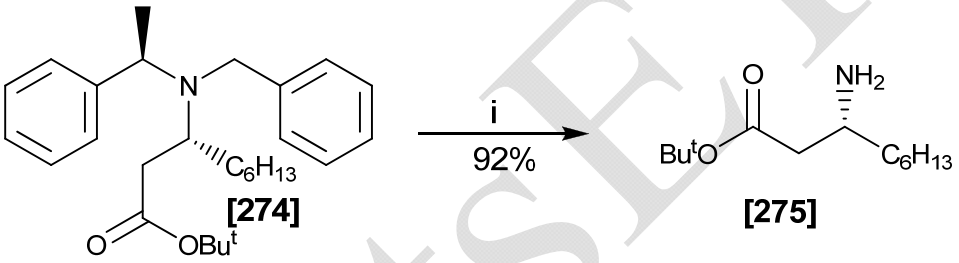
According to Davies *et al.*,[158] the use of a secondary amine is essential for the high diastereomeric excess. The use of the primary amine, α-methylbenzylamine, gave yields in the order of 20 – 30% and *de*'s of 0 – 4%. Low temperature, -78°C to -90°C, is also essential for maintaining *de*'s greater than 95%, while an increase in temperature to 15 °C can lead to a decrease in the de to around 66%.[158] Finally, decreased diastereomeric excess values have been observed with the use of *o*-methoxybenzylamines due to the lithium

WitsETD

chelating to the methoxy group.[158] Davies and co-workers have successfully demonstrated the use of this methodology in the asymmetric synthesis of *Sedum* alkaloids,[180] β-amino acids,[158] 2-aryl-4-aminotetrahydroquinoline-3-carboxylic acid derivatives,[181] and β-pyridyl-β-amino acid derivatives[182] to name but a few.

3.4 Debenzylation reactions

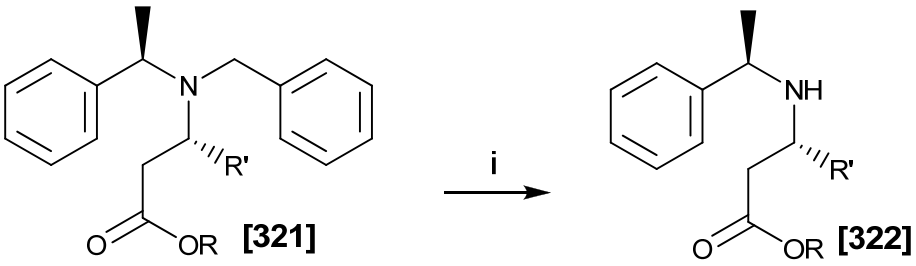
Yillah's thesis indicated that stirring *t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (**274**) in acetic acid with 10% palladium on activated carbon under seven atmospheres of hydrogen pressure would remove both benzyl groups in excellent yields to give the primary amine (**275**) (see Scheme 3.3).



Scheme 3.3: Debenzylation reaction by Yillah.[31] *Reagents and conditions: i) H_2 (7 atm.), 10% Pd-C, AcOH, RT, 20 hr.*

We, however, discovered that the reaction conditions were much more delicate than expected and we frequently isolated either the mono-debenzylated species exclusively, or a mixture of mono- and fully debenzylated species. If mono-debenzylation took place the α-methylbenzyl group was always the benzyl group to remain. The same chemoselectivity has been noted by Davies and co-workers[183, 184] when reducing (**321**) to (**322**) with the use of reagents such as ceric ammonium nitrate and by Yillah[31] with the use of palladium black (see Scheme 3.4).

WitsETD



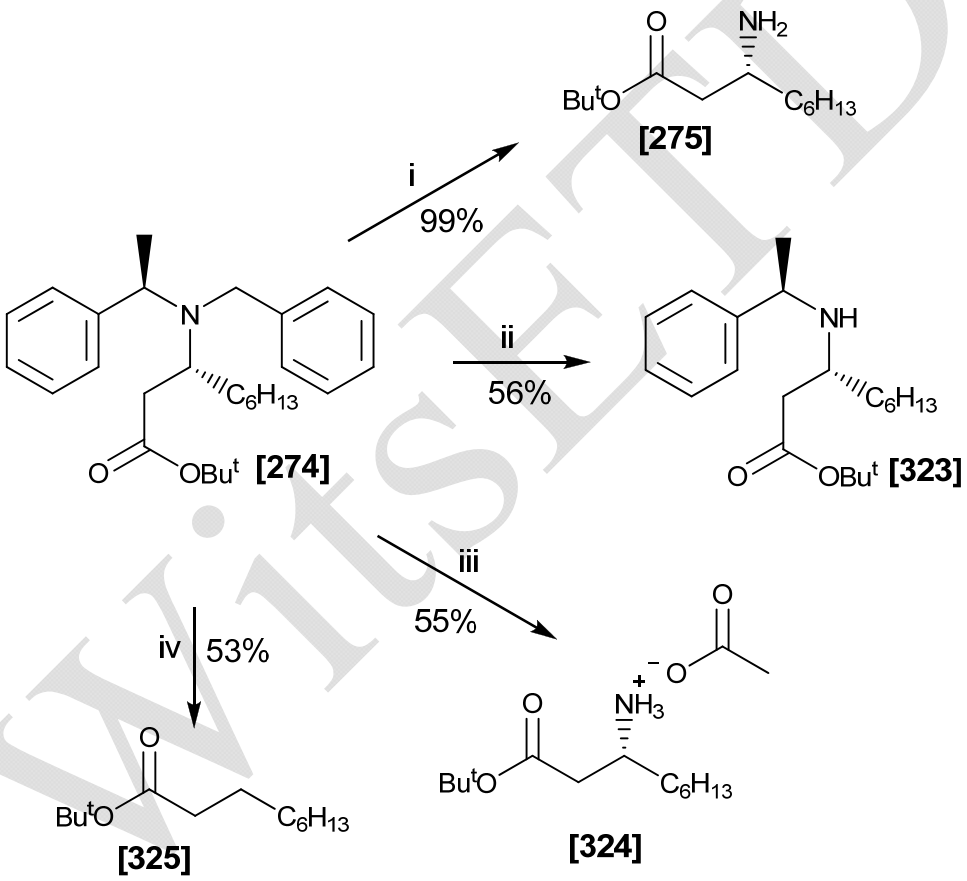
Scheme 3.4: Chemoselective reduction. *Reagents and conditions: R* = i-*Pr, R'* = CH_3 *i) CAN (2.1 eq.), MeCN-*H_2O *(5:1), RT, 85% yield,*[184] *or R* = t-*Bu, R'* = C_6H_{13} *i) Pd-black, HCOOH-MeOH (1:20), RT, 12 hrs.*[31]

We obtained inconsistent results with regards to chemoselectivity (see Scheme 3.5), and when the reactions were repeated under "the same" conditions different product mixtures were obtained. Upon closer examination, the chemoselectivity appeared to be dependent on which batch of catalyst was used for the reaction. Initially, in our case, using palladium catalysts already present in the laboratory, the fully debenzylated species (**275**) was prepared with a high degree of success. However, all the palladium catalysts purchased throughout the course of this project favoured the formation of the mono-debenzylated species (**323**) and often little to none of the desired product (**275**) was obtained.

The results for our debenzylation reactions varied from 99% yield to 0% yield (see Table 3.3). The 5% palladium on carbon was obtained on two different occasions from the local company, Palaborwa Mining Company (PMC). The first batch (2006) worked well, provided that the catalyst loading was quantitative, making it an expensive option. When the solvent system was altered to methanol and acetic acid (3:1) the product was isolated as the acetate salt. In this instance the salt was probably isolated due to incomplete removal of the acetic acid *in vacuo* prior to column chromatography. The second batch from PMC (2009), using quantitative catalyst loading, afforded 53% of the mono-debenzylated species (**323**) and none of the desired product. The 10% palladium-on-carbon supplied by Fluka gave mixtures of the partially and fully debenzylated products, unless the catalyst loading was above 25%, in which case only the fully debenzylated species was obtained. The equivalent catalyst from Sigma-Aldrich gave low yields or none of the desired product, and

WitsETD

the equivalent catalyst from Alfa only ever produced the partially debenzylated product. Even Pearlman's catalyst, activated palladium hydroxide on carbon, required a loading of 25% in order to fully debenzylate the product, and the yields were only moderate. When Pearlman's catalyst was used in conjunction with ethanol, the only product isolated was *t*-butyl nonanoate, presumably formed from the reduction of the retro-Michael addition product, *t*-butyl (*E*)-non-2-enoate (**273**). Unfortunately, platinum dioxide removed the benzyl groups, but went on to catalyse additional transformations and none of the desired product was isolated.



Scheme 3.5: Our observed chemoselectivity for the debenzylation of (**274**). *Reagents and conditions: i) 5% Pd-C (PMC, 1.0 eq.), AcOH, H_2 (7 atm.), RT; ii) 10% Pd-C (Sigma, 0.25 eq.), AcOH, H_2 (7 atm.), RT; iii) 5% Pd-C (PMC, 0.25 eq.), AcOH/MeOH (1:3), H_2 (7 atm.), RT; iv) 10 – 20% $Pd(OH)_2$-C (Sigma, 0.2 eq.), EtOH, H_2 (7 atm.), RT.*

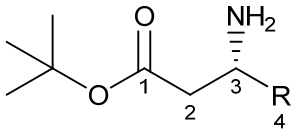
WitsETD

Supplier	Catalyst	Eq.	Solvent	(323)	(275)	(324)	(325)
PMC ('06)	Pd-C 5%	1.0	AcOH	0%	**99%**	0%	0%
PMC ('06)	Pd-C 5%	0.25	AcOH/ MeOH (1:3)	0%	0%	**55%**	0%
PMC ('06)	Pd-C 5%	0.25	AcOH	0%	**56%**	0%	0%
Fluka	Pd-C 10%	0.10	AcOH	**63%**	**36%**	0%	0%
Fluka	Pd-C 10%	0.10	AcOH	**46%**	**54%**	0%	0%
Fluka	Pd-C 10%	0.25	AcOH	0%	**100%**	0%	0%
Sigma	Pd-C 10%	0.25	AcOH	0%	**32%**	0%	0%
Sigma	Pd-C 10%	0.25	AcOH	**56%**	0%	0%	0%
Alfa	Pd-C 10%	0.1	AcOH	**42%**	0%	0%	0%
Alfa	Pd-C 10%	0.2	EtOH	**21%**	0%	0%	0%
Sigma	$Pd(OH)_2$-C	0.1	AcOH	**30%**	0%	0%	0%
Sigma	$Pd(OH)_2$-C	0.25	AcOH	0%	**61%**	0%	0%
PMC ('09)	Pd-C 5%	1.0	AcOH	**53%**	0%	0%	0%
Sigma	$Pd(OH)_2$-C	0.20	EtOH	0%	0%	0%	**53%**

Table 3.3: Effect of catalyst supplier, type, equivalents and solvent on debenzylation.

When the free amine, *t*-butyl (3*R*)-3-amininononanoate (**275**), was isolated its optical rotation was $[\alpha]_D^{20}$ -13.4 (*c* 0.98, CH_2Cl_2), which corresponds well in magnitude and sign to the value reported by Gravestock for *t*-butyl (3*R*)-3-aminooctanoate $[\alpha]_D^{26}$ -17.7 (*c* 1.19, EtOH). Yillah's reported value for (**275**) was $[\alpha]_D^{20}$ -23.4 (*c* 0.98, CH_2Cl_2) nearly twice our value. The ^{1}H-NMR and ^{13}C-NMR spectra correspond reasonably well with those reported by Yillah, with the analogous compound synthesized by Gravestock and the one synthesized by Davies (see Table 3.4). The biggest discrepancy between them was in the position of the NH_2 signal: For the hexyl analogue the NH_2 signal occured at 5.20 ppm, for the pentyl analogue the NH_2 signal occured at 1.84 ppm and the heptyl analogue had no reported signal for the NH_2 substituent. The most obvious evidence of the success of the reaction was the loss of the aromatic signals in the ^{1}H-NMR and ^{13}C-NMR spectra and the appearance of a weak but broad NH_2 signal at 3420 cm^{-1} in the FTIR spectrum.

WitsETD



Signal	R = C_5H_{11} [139] / ppm	R = C_6H_{13} (275) / ppm	R = C_7H_{15} [177] / ppm
NH_2	1.84 (br, s)	5.20 (br, s)	-
H-2*A*	2.39 (dd, *J* 15.6, 4.2)	2.40 (dd, *J* 16.0, 4.2)	2.35 (dd, *J* 15.5, 4.0)
H-2*B*	2.18 (dd, *J* 15.6, 8.7)	2.34 (dd, *J* 16.0, 7.8)	2.15 (dd, *J* 15.5, 8.0)
H-3	3.21 – 3.09 (m)	3.29 – 3.18 (m)	3.10 (br, s)
C-1	172.0	171.5	172.0
C-2	43.6	41.7	43.9
C-3	48.4	48.3	48.3
C-4	37.3	35.9	37.5

Table 3.4: Comparison of selected NMR spectral data (in $CDCl_3$) for analogous primary amines. (*J*-values were measured in Hz).

The acetate salt, (*R*)-1-*tert*-butoxy-1-oxononan-3-aminium acetate (**324**), was isolated as a creamy-white solid and was fully characterized. Its melting point was 69 - 73 °C and its optical rotation was $[\alpha]_D^{20}$ -10.0 (*c* 1.00, CH_2Cl_2), with the same sign as the parent amine. The most significant difference between the free amine (**275**) and the salt (**324**) was the presence of a broad signal at 7.17 ppm in the ^{1}H-NMR corresponding to the NH_3^+ group. The acetate group was observed at 1.96 ppm. The ^{13}C-NMR spectrum showed an additional carbonyl peak at 177.3 ppm corresponding to the acetate ion.

The partially debenzylated species, *t*-butyl (3*R*)-3-[*N*-(1-phenylethyl)amino] nonanoate (**323**), was fully characterized and its optical rotation was $[\alpha]_D^{20}$ +20.4 (*c* 0.91, CH_2Cl_2). Yillah's optical rotation for the same molecule was significantly different in sign and magnitude, with a value of $[\alpha]_D^{20}$ -38.3 (*c* 1.27, CH_2Cl_2). It was clear from the ^{1}H-NMR spectrum that the α-methylbenzyl group was still present, as aromatic signals at 7.38 – 7.17 ppm integrating for five hydrogens were observed. The α-methyl group showed up as a doublet (*J* 6.5 Hz) at 1.33 ppm integrating for three hydrogens, and finally the benzylic CH was observed at 3.89 ppm as a quartet (*J* 6.5 Hz) integrating for one

WisERD

hydrogen. The mono-debenzylated product (**323**) was recovered unchanged after reacting it with 10% palladium hydroxide on carbon in absolute ethanol under seven atmospheres of hydrogen pressure for three days.

A second attempt at removing the remaining α-methylbenzyl group was with ceric ammonium nitrate. There are examples in the literature[182 - 184] of removing one benzyl group, usually, but not exclusively, when the benzyl group has at least one methoxy substituent. *t*-Butyl (3*R*)-3-[*N*-(1-phenylethyl)amino]nonanoate (**323**) and ceric ammonium nitrate were dissolved in acetonitrile/distilled water (1:5) and stirred at ambient temperature overnight. The crude material was extracted and purified by column chromatography to give back unreacted starting material.

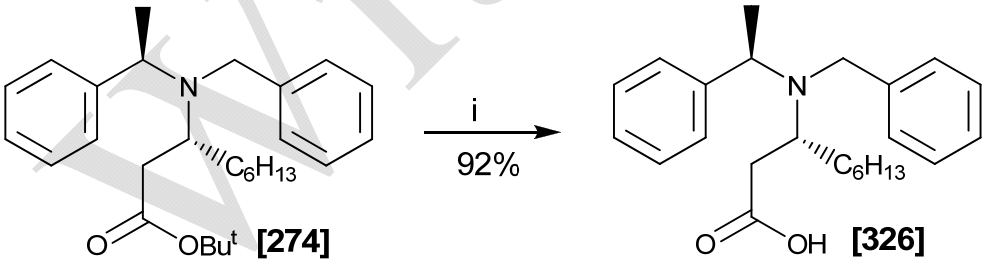
The final method we utilized for the attempted removal of both of the benzyl groups was to react *t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (**274**) in methanol with eight equivalents of ammonium formate and 0.37 equivalents of 10% palladium on carbon (purchased from Alfa) under nitrogen for three hours. The methanolic vapours proved extremely flammable in this particular reaction and the utmost care was required to prevent ignition. Using this method the fully debenzylated *t*-butyl (3*R*)-3-aminononanoate (**275**) was isolated in 74% yield as a clear oil. Unfortunately, this result was not reproducible and a further four attempts produced the mono-debenzylated species (**323**) or the fully reduced *t*-butyl nonanoate (**325**) as the major product (see Table 3.5). The first attempt was the only reaction where the methanolic vapours ignited.

WitsETD

Reaction	% Yield of isolated products		
	(323)	(275)	(325)
1	0%	74%	0%
2	40%	30%	0%
3	0%	12%	67%
4	0%	12%	88%
5	0%	10%	85%

Table 3.5: Debenzylation reactions using ammonium formate and activated palladium.

Another literature procedure,[185] reported the use of formic acid to selectively remove the α-methylbenzyl group from a similar amine without hydrolysing the *t*-butyl ester. We attempted this reaction in the hope that if we could remove the α-methylbenzyl group using formic acid, then we should be able to remove the second benzyl group using palladium-on-carbon. After heating (**274**) at reflux in formic acid for three hours, the reaction was stopped, the formic acid was removed *in vacuo*, and the crude material was purified by column chromatography. The product isolated from the column was (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino} nonanoic acid (**326**) which was obtained in 92% yield (see Scheme 3.6).



Scheme 3.6: Attempted debenzylation of (**274**). *Reagents and Conditions: i) HCOOH, reflux, 3 hr.*

The carboxylic acid (**326**) was optically active, with an optical rotation of $[\alpha]_D^{20}$ -26.9 (*c* 1.08, CH_2Cl_2). ^{1}H-NMR and ^{13}C-NMR spectra were largely similar to the spectra obtained for (**274**), with the exception of the loss of the *t*-butyl signals and the appearance of broad OH signal between 10 - 12 ppm. The

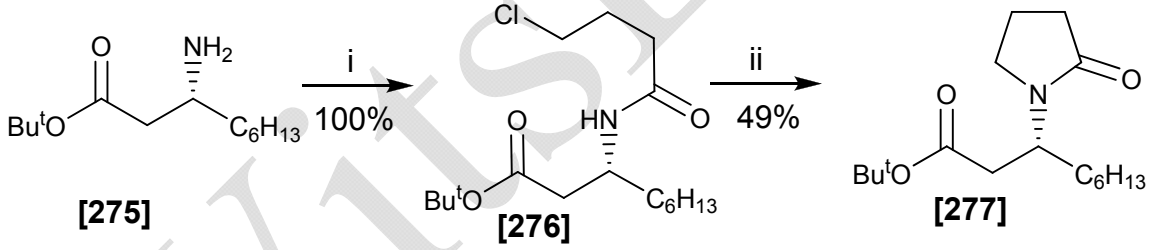
WitsETD

carbonyl signal shifted from 172.2 ppm to 164.2 ppm, within the characteristic region for a carboxylic acid.

The unpredictability of these debenzylation reactions resulted in an excessive delay in the completion of the synthesis and thwarted several attempts to "push material through" to attempt later steps.

3.5 Formation of the lactam and cyclopropane by-products

With the primary amine in hand, the next step was the formation of the lactam ring by reacting the free amine with chlorobutyryl chloride over two steps (see Scheme 3.7). The reaction conditions, optimized by Yillah and Gravestock, involved reacting the amine with chlorobutyryl chloride in chloroform in the presence of sodium bicarbonate. Then, with or without purifying the intermediate amide, cyclisation was effected by the reaction of the amide with potassium *t*-butoxide in *t*-butanol.



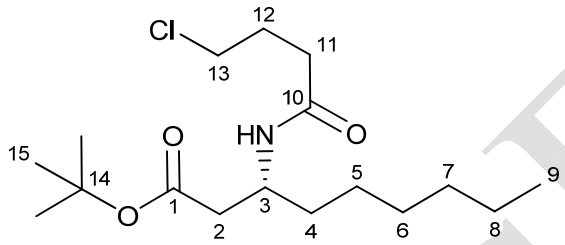
Scheme 3.7: Formation of the lactam ring. *Reagents and conditions: i) $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, RT; ii) $KOBu^t$, Bu^tOH.*

We proceeded by reacting *t*-butyl (3*R*)-3-aminononanoate (**275**) with 1.2 equivalents of chlorobutyryl chloride and with 1.5 equivalents of sodium bicarbonate in chloroform at ambient temperature for twelve hours. For characterization purposes the intermediate amide, *t*-butyl (3*R*)-3-[*N*-(4-chlorobutanoyl)amino]nonanoate (**276**), was purified and isolated as a odoriferous brown oil of low UV activity on TLC plates. The initial isolated yield was quantitative and thereafter the intermediate was not purified prior to the next step. Its optical rotation was $[\alpha]_D^{20}$ +10.5 (*c* 1.00, CH_2Cl_2), slightly higher than the value reported by Gravestock for *t*-butyl (3*R*)-3-[*N*-(4-

WiSER

chlorobutanoyl)amino]octanoate, $[\alpha]_D^{25}$ +6.6 (*c* 1.14, EtOH). Yillah's reported optical rotation was $[\alpha]_D^{20}$ -11.3 (*c* 1.25, CH_2Cl_2), differing in sign from the value we obtained.

The ^{1}H-NMR spectrum for (**276**) showed a broad NH peak at 6.22 ppm, characteristically deshielded by the carbonyl group to a downfield position. The NH peak appeared as a doublet (*J* 8.7 Hz) coupling to the adjacent hydrogen on C-3 (see Figure 3.3). H-3 appeared as a multiplet at 4.28 - 4.16 ppm integrating for one hydrogen atom. The other diagnostic signal was the methylene group adjacent to the chlorine atom, H-13, which appeared as a triplet at 3.61 ppm. The aliphatic signals and the *t*-butyl ester signals did not show significant changes from those observed in amine (**275**).



[276]

Figure 3.3: Numbering of amide (**276**) for assignment of spectroscopic data.

FTIR spectroscopy diagnostically showed both a broad NH peak centred at 3289 cm^{-1}, and two carbonyl groups; the one for the ester appeared at 1725 cm^{-1}, and the one for the amide appeared at 1645 cm^{-1}. ^{13}C-NMR spectroscopy also showed the two carbonyl groups C-10 at 171.4 ppm and C-1 at 171.2 ppm and the methylene group deshielded by the chlorine atom, C-13, at 44.4 ppm. Yillah's reported spectra for (**276**) were in close agreement with the spectra we obtained.

In the presence of freshly sublimed potassium *t*-butoxide and *t*-butanol the amide, *t*-butyl (3*R*)-3-[*N*-(4-chlorobutanoyl)amino]nonanoate (**276**), was deprotonated and cyclised to form the corresponding lactam, *t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)nonanoate (**277**). The *t*-butanol was used to prevent

WitsETD

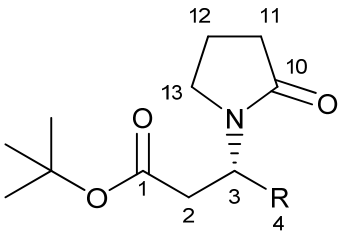
exchange of the ester functionality, and the *t*-butoxide was used as it was previously found to be sufficiently basic to promote the cyclisation. Gravestock reported yields of 82% and 57% for *t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)octanoate, and *t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexanoate respectively. Yillah reported a yield of 73%, whereas our highest yield for the formation of *t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)nonanoate (**277**) was 49%.

The lactam was optically active, $[\alpha]_D^{20}$ +9.5 (*c* 1.00, CH_2Cl_2), with comparable magnitude and sign to Gravestock's intermediate lactam *t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)octanoate which had an optical rotation of $[\alpha]_D^{24}$ +12.4 (*c* 1.29, EtOH). Yillah obtained an optical rotation of $[\alpha]_D^{20}$ +18.6 (*c* 1.99, CH_2Cl_2), twice the magnitude that we obtained.

The most significant changes in the ^{1}H-NMR spectrum of (**277**), compared to (**276**), were the disappearance of the N-H peak, and the slight upfield shift of the H-13 signal. FTIR spectroscopy showed two carbonyl groups; the ester stretching vibration at 1724 cm^{-1} and the amide stretching vibration at 1686 cm^{-1} as is characteristic for a lactam. The N-H band was no longer visible. Low resolution mass spectroscopy showed the parent ion at 297 as well as fragmentation corresponding to the loss of the *t*-butyl group at 241 and loss of the lactam group at 212.

The ^{1}H-NMR and ^{13}C-NMR spectra correspond well with the analogous compounds synthesized by Gravestock (see Table 3.6). The observed geminal coupling constants for H-13*AB* were slightly larger in our lactam compared to those observed by Gravestock. Yillah reported the signals for H-13*AB* as doublets of triplets both with coupling constants of 9.6 and 7.1 Hz. All the other signals were virtually identical, except for the C-4 signals which deviated from each other as the effect of the alkyl chain length comes into play.

WitsETD

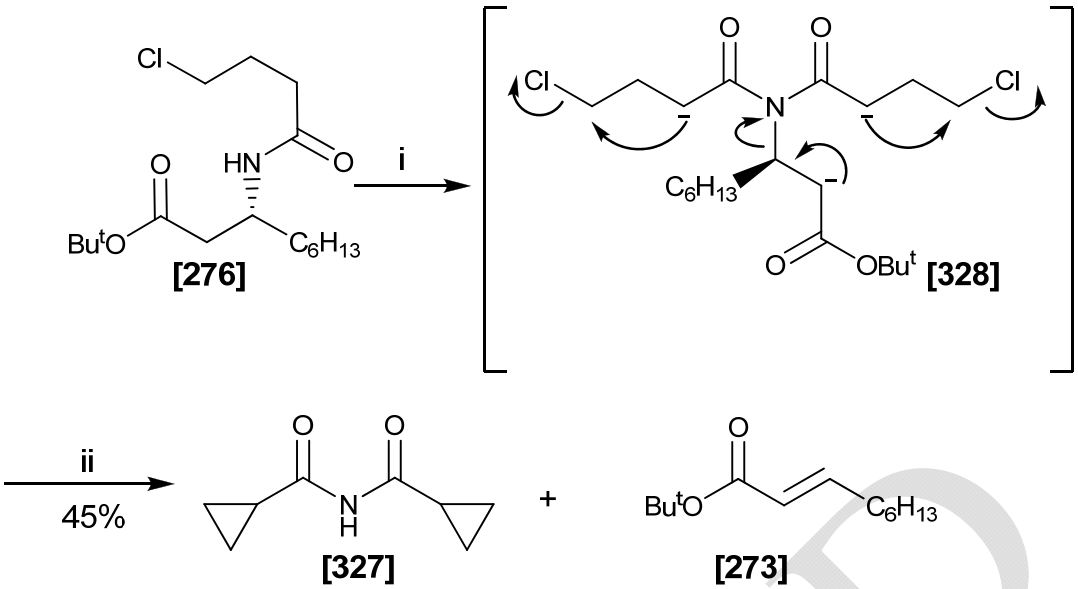


Signal	R = C_3H_7 / ppm	R = C_5H_{11} [139] / ppm	R = C_6H_{13} (277) / ppm
H-2	2.55 – 2.18 (m)	2.51 – 2.31 (m)	2.42 – 2.34 (m)
H-3	4.51 – 4.39 (m)	4.52 – 4.33 (m)	4.53 – 4.36 (m)
H-11	2.55 – 2.18 (m)	2.51 – 2.31 (m)	2.42 – 2.34 (m)
H-12	1.99 (quin., *J* 7.5)	2.06 – 1.91(m)	1.99 (quin., *J* 7.6)
H-13*A*	3.38 (dd, *J* 9.4, 6.9)	3.36 (dd, *J* 9.3, 6.9)	3.38 (dd, *J* 15.7, 7.1)
H-13*B*	3.26 (dd, *J* 9.4, 6.9)	3.28 (dd, *J* 9.3, 6.9)	3.26 (dd, *J* 15.7, 7.9)
C-1	170.3	170.1	170.2
C-2	39.4	39.2	39.3
C-3	48.5	48.6	48.8
C-4	34.3	31.9	32.2
C-10	174.9	174.6	174.8
C-11	31.4	31.9	31.1
C-12	18.3	18.1	18.3
C-13	42.5	42.3	42.4

Table 3.6: Comparison of selected NMR spectral data (in $CDCl_3$) for homologous lactams. (*J*-values were measured in Hz).

The reason for our poor yields seems to be the occurrence of a retro-Michael addition, as we managed to isolate *t*-butyl (*E*)-non-2-enoate (**273**) in several instances. Interestingly, in one instance, we also isolated *N*-(cyclopropanecarbonyl)cyclopropanecarboxamide (**327**). This result can be accounted for by the addition of two equivalents of chlorobutyryl chloride to the free amine (**275**), and subsequent cyclisation of the butyryl chloride groups by deprotonation of all three α-positions of the carbonyl groups (**328**) by the strong base, potassium *t*-butoxide (see Scheme 3.8).

WitsETD



Scheme 3.8: Proposed mechanism for the formation of carboximide (**327**) –all three steps are shown in (**328**), as the sequence was unknown. *Reagents and conditions: i) $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, RT, 12 hr.; ii) $KOBu^t$, Bu^tOH, RT, 72 hr.*

N-(Cyclopropanecarbonyl)cyclopropanecarboxamide **(327**) was isolated in 45% yield as white, crystalline needles of low solubility. The X-ray diffraction crystal structure (see Figure 3.4) revealed the identity of the molecule and showed ordered packing dominated by hydrogen bonding. The symmetric imide packed in chains, typical of the *trans-trans* isomer, rather than the dimers characteristically displayed by the *cis-trans* isomer. These chains stack in a ladder-like arrangement (see Figure 3.5), with parallel layers at approximately 90° to each other. The parallel chains were linked by hydrogen bonds between the carbonyl oxygens and the imide nitrogen. Van der Waals interactions between the cyclic residues also contributed towards stabilizing the crystal structure.

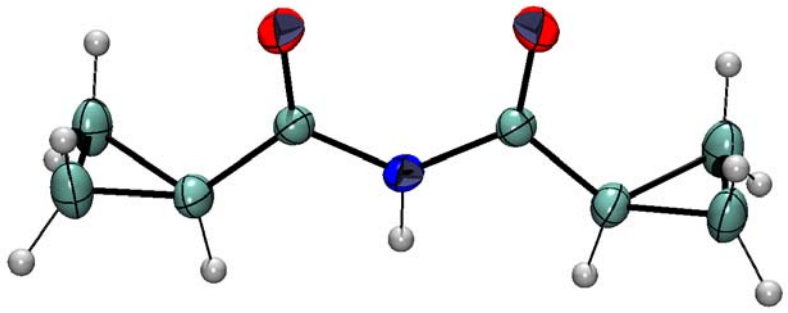


Figure 3.4: The molecular structure of carboximide (**327**). Displacement ellipsoids are drawn at the 50% probability level.

WitsETD

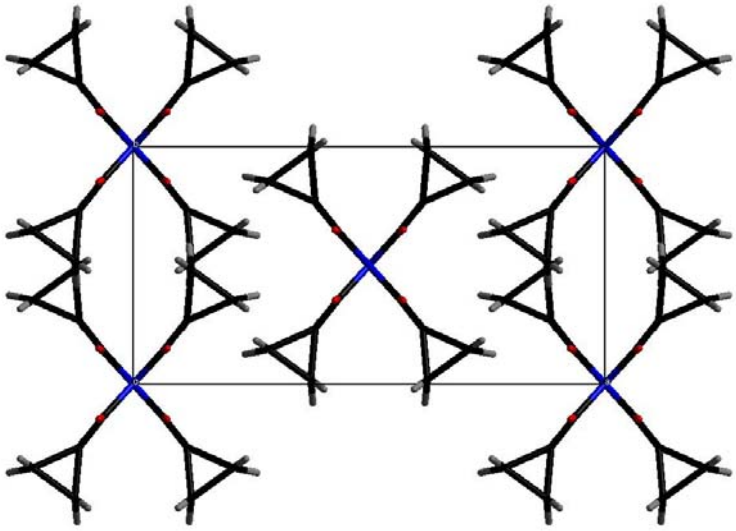
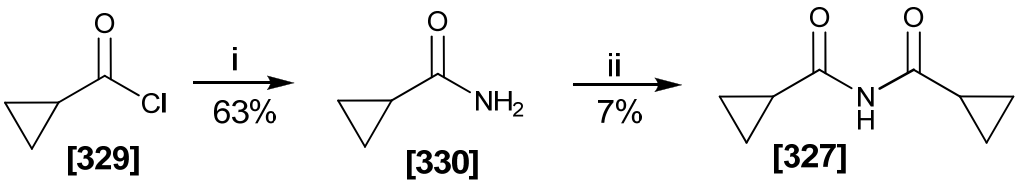


Figure 3.5: Crystal packing of carboximide (**327**), viewed along the *c*-axis.

Owing to the symmetry of the molecule the ^{1}H-NMR spectra shows four signals only. The imide signal occurs as a sharp singlet at 8.65 ppm, shifted heavily downfield due to the presence of two carbonyl groups. The CH signal was observed as a multiplet integrating for two hydrogens at 2.28 – 2.25 ppm, while the other two methylene signals were equivalent but diastereotopic and occur at 1.14 – 1.11 ppm and 0.99 – 0.93 ppm, respectively, with each signal integrating for four hydrogens. There was one corresponding ^{13}C-NMR spectral signal for the methylene groups which occured at 10.3 ppm. The signal at 175.3 ppm corresponds to the carbonyl and the signal at 15.0 ppm corresponds to the CH carbon. The FTIR spectrum showed the carboximide carbonyl at 1710 cm^{-1} and the NH stretching vibration as a broad signal at 3257 – 3161 cm^{-1}.

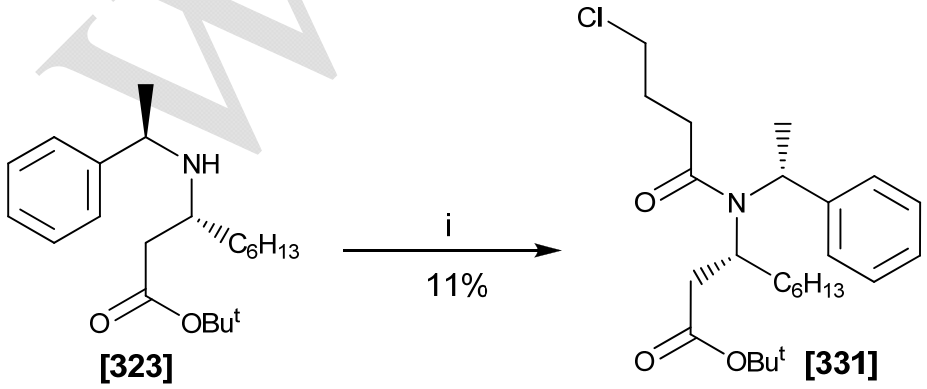
The discovery of this unusual side reaction led to an honours project by Caitlin Zipp, who undertook an alternative synthesis of *N*-(cyclopropanecarbonyl)cyclo propanecarboxamide (**327**) (see Scheme 3.9) and analogous symmetric and asymmetric carboximides.[186, 187] Starting from the commercially available acid chloride (**329**), amide (**330**) was prepared in 63% yield. Amide (**330**) was then deprotenated with sodium hydride and reacted with one equivalent of the acid chloride (**329**) to produce the desired imide (**327**) in 7% yield. Interestingly, of

all the carboximides she synthesized, *N*-(cyclopropanecarbonyl)cyclopropane carboxamide (**327**) was the most difficult to prepare with an overall yield of 4%.[187]



Scheme 3.9: The alternative synthesis of carboximide (**327**). *Reagents and conditions: i) NH_4OH (25% w/w), 12 hr.; ii) a) NaH, THF, b) (**329**), reflux, 12 hr.*

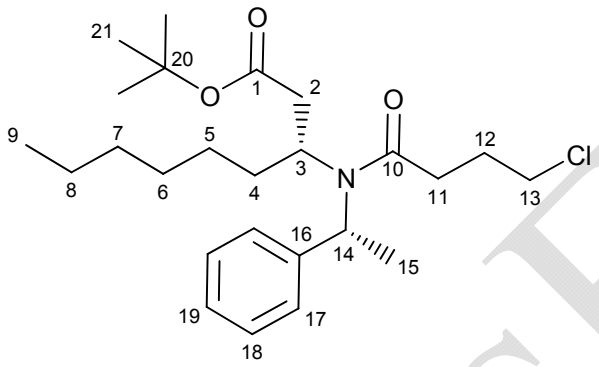
In view of the considerable quantities of the monobenzylated amine (**323**) which had accumulated during the numerous debenzylation attempts, we decided to investigate whether converting it into a tertiary amide would make it more susceptible to debenzylation. *t*-Butyl (3*R*)-3-[*N*-(1-phenylethyl)amino]nonanoate (**323**) was therefore heated at reflux in chloroform with chlorobutyryl chloride in the presence of sodium bicarbonate (see Scheme 3.10). After purification by column chromatography (*R*)-*t*-butyl 3-(4-chloro-*N*-(*R*)-1-phenylethyl) butanamido)nonanoate (**331**) was isolated in 11% yield, and starting material was recovered. The low yields can be accounted for by the decreased nucleophilicity of the secondary amine compared to the corresponding primary amine.



Scheme 3.10*:* Formation of the tertiary amide (**331**). *Reagents and conditions: i) $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, RT.*

WitsETD

Full characterization of compound (**331**) revealed that the α-methylbenzyl group was still present, as was the *t*-butyl ester and the hexyl side chain. In addition to these signals, the ^{1}H-NMR spectrum showed signals at 4.34 ppm, 2.49 ppm and 2.39 – 2.20 ppm corresponding to the chlorobutyryl side chain; H-13, H-12 and H-11, respectively (see Figure 3.6). The NH peak from the starting material was no longer present. The ^{13}C-NMR spectrum showed four new carbon signals at 177.6 ppm (C-10), 68.4 ppm (C-13), 27.7 ppm (C-11) and 22.1 ppm (C-12), corresponding to the chlorobutyryl side chain. The other signals in the carbon spectrum were very similar to the corresponding signals in the starting material.



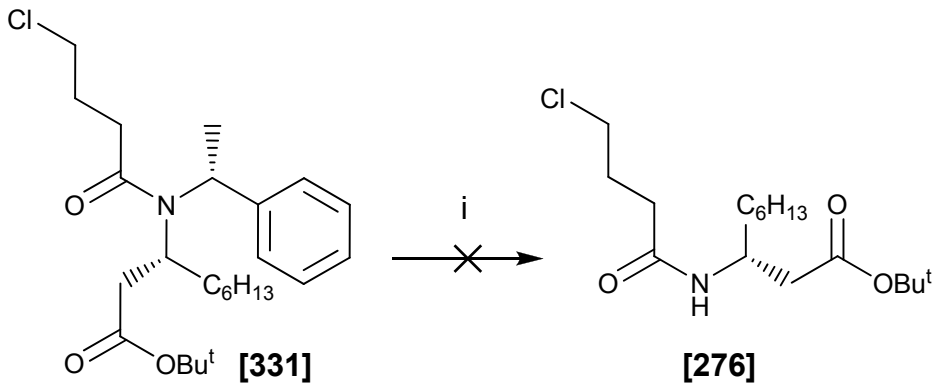
[331]

Figure 3.6: Numbering of amide (**331**) for assignment of spectroscopic data.

The FTIR spectrum showed both the ester and the amide carbonyl groups were present at 1728 cm^{-1} and 1605 cm^{-1}, respectively. No NH stretching vibration was observed. The product was optically active as expected, with an optical rotation of $[\alpha]_D^{20}$ +20.0 (*c* 1.00, CH_2Cl_2).

We attempted to debenzylate the tertiary amide (**331**) by reacting it with 10% palladium on carbon in the presence of acetic acid and seven atmospheres of hydrogen, as the debenzylated product (**276**) could be recycled back into the synthesis. Unfortunately, only starting material was recovered and hence the reaction was abandoned (see Scheme 3.11).

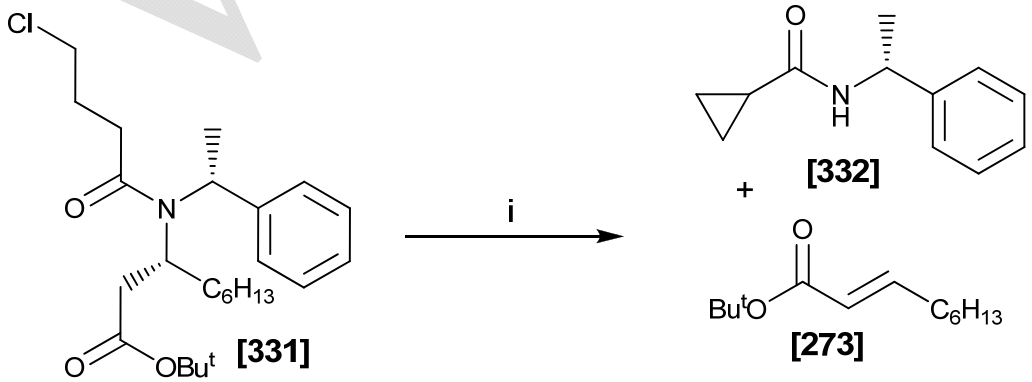
WitsETD



Scheme 3.11: Attempted debenzylation of (**331**). *Reagents and conditions: i) H_2 (7 atm.), 10% Pd-C, AcOH, RT, 20 hr.*

We also attempted to debenzylate the tertiary amide (**331**) by reacting it with ceric ammonium nitrate in acetonitrile/water (1:5) at ambient temperature for twelve hours. After purification, *t*-butyl (3*R*)-3-[*N*-(1-phenylethyl)amino] nonanoate (**323**) was isolated in 100% yield. Clearly the chlorobutyryl side chain was more labile than the α-methylbenzyl group.

To investigate if this benzylated species (**331**) would also undergo a retro-Michael addition in the presence of a strong base, we reacted (*R*)-*t*-butyl 3-(4-chloro-*N*-(*R*)-1-phenylethyl)butanamido)nonanoate (**331**) with potassium *t*-butoxide in the presence of *t*-butanol at ambient temperature for twelve hours (see Scheme 3.12). After purification, (*R*)-*N*-(1-phenylethyl)cyclopropane carboxamide (**332**) was isolated as a white crystalline solid in 56% yield with fine needles unsuitable for XRD.



Scheme 3.12: Retro-Michael addition of (**331**). *Reagents and conditions: i) KOBu^t, Bu^{t}OH, RT, 12 hr.*

WitsETD

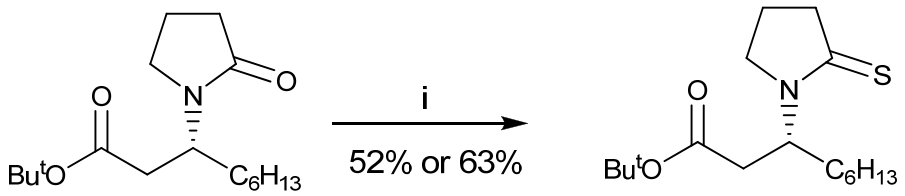
The product (**332**) was characterized by ^{1}H-NMR spectroscopy which showed the α-methylbenzyl group intact and the cyclopropane as three signals at 1.38 – 1.24 ppm for the CH group, and the diastereotopic signals at 0.97 – 0.86 ppm, and 0.74 – 0.61 ppm for the equivalent methylene groups. The NH signal appeared as a doublet (*J* 7.2 Hz) at 6.37 ppm, coupling to the adjacent CH group. ^{13}C-NMR spectroscopy revealed the α-methylbenzyl group as before and the new amide peak at 172.7 ppm and the cyclopropane signals at 21.8 ppm and 7.1 ppm. FTIR spectroscopy showed the amide carbonyl stretching vibration at 1636 cm^{-1} and the NH band at 3330 cm^{-1}. Optical rotation gave an exceptionally high value, with $[\alpha]_D^{20}$ +130.4 (*c* 0.79, CH_2Cl_2).

3.6 Thionation reactions

Now that we had succesfully prepared the lactam, the next step in our synthesis was the functional group interconversion of the lactam (**277**) into the thiolactam (**278**).

Thionation reactions can be chemoselective for lactams and amides even in the presence of esters or ketones.[188] The conditions selected for the transformation from the lactam (**277**) to the corresponding thiolactam (**278**) employed these chemoselective conditions. Two different methods were used. The first method was a modified version of the Brillon procedure,[189] as it was one of the most facile methods available for effecting thionation of lactams (see Scheme 3.13). The Brillon method uses sodium bicarbonate together with phosphorus pentasulfide in dry tetrahydrofuran stirred at ambient temperature for seventy-two hours. In the modified version the sodium bicarbonate was omitted completely and chloroform was used as the solvent. Purification by column chromatography gave the thiolactam, *t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)nonanoate (**278**), in 52% yield.

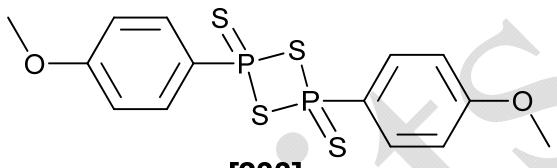
WISETD



[277] **[278]**

Scheme 3.13: Thionation reaction. *Reagents and conditions: i) P_2S_5, $CHCl_3$, RT, 8 hr.; OR i) Lawesson's Reagent, CH_2Cl_2, RT, 72 hr.*

The moderate yield led us to investigate a second method, one that employed Lawesson's reagent (**332**) as the thionating agent (see Figure 3.7). The lactam *t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)nonanoate (**277**) was dissolved in dichloromethane together with Lawesson's reagent (**333**) and stirred at ambient temperature for seventy-two hours. Following extraction and purification, the desired thiolactam (**278**) was obtained in 63% yield. Owing to the increased efficiency of the second method, Lawesson's reagent was employed for all subsequent thionations.



[333]

Figure 3.7: Lawesson's reagent, used to thionate carbonyl groups.

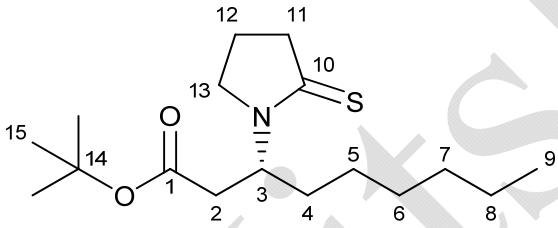
Another variation on the thionation reaction was the Curphey procedure, which used hexamethyldisiloxane as an additive in the presence of phosphorus pentasulfide.[188] It has been shown that this improves the yields to values comparable to those obtained with Lawesson's reagent.[188] This version of the reaction was attempted, but unfortunately the isolated yield of the thiolactam (**278**) was 30%, far lower than the yields obtained using Lawesson's reagent.

There was a slight change in the optical rotation of the thiolactam (**278**) $[\alpha]_D^{20}$ +7.4 (*c* 0.88, CH_2Cl_2) compared to the corresponding lactam (**277**) $[\alpha]_D^{20}$ +9.5 (*c* 1.00, CH_2Cl_2). When our values were compared to those obtained by Gravestock for his thiolactams the value differed significantly in magnitude

WiSER

but shared the same sign. For *t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)octanoate Gravestock obtained a value of $[\alpha]_D^{30}$ +17.2 (*c* 0.90, EtOH), and for *t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)hexanoate he obtained a value of $[\alpha]_D^{30}$ +18.7 (*c* 1.39, EtOH). Yillah obtained an optical rotation of $[\alpha]_D^{20}$ -9.8 (*c* 0.82, CH_2Cl_2) for (**278**), similar magnitude but opposite rotation to our value.

On thionation, the key changes in the ^{1}H-NMR spectrum were the shift of H-3 from 4.4 to 5.4 ppm, of H-13*AB* from 3.4 and 3.3 ppm in the lactam (**277**) to 3.7 and 3.6 ppm in the thiolactam (**278**) (see Figure 3.8). H-11 shifted from 2.4 to 3.0 ppm and H-2*A* shifted from 2.4 to 2.6 ppm in the thiolactam. All other signals were approximately equivalent to the corresponding lactam signals. In the ^{13}C-NMR spectrum, the most significant shift was that of C-10 which shifted from the amide region of 174.8 ppm to 201.7 ppm, an appropriate region for a thiocarbonyl group. C-3 also shifted downfield, from 48.8 to 53.3 ppm as did C-13, from 42.4 to 49.0 ppm.



[278]

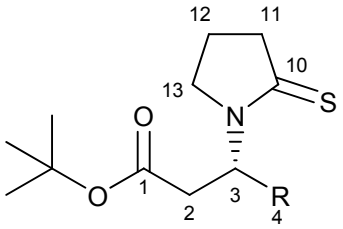
Figure 3.8: Numbering of thiolactam (**278**) for assignment of spectroscopic data.

The FTIR spectrum showed the absence of the strong lactam carbonyl stretching vibration at 1686 cm^{-1} and instead the thiocarbonyl stretching vibration could be seen as a strong signal at 1310 cm^{-1}.

At this point Gravestock's syntheses diverged along a synthetic path involving vinylogous urethanes, so our thiolactam was the final molecule for which we could compare the NMR data in a meaningful way. Table 3.7 highlights the key signals in the ^{1}H-NMR and ^{13}C-NMR spectra comparing *t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)nonanoate (**278**), with *t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)

WitsETD

octanoate and *t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)hexanoate. The thiolactam we prepared shows almost identical ^{1}H-NMR and ^{13}C-NMR spectral data to those thiolactams prepared by Gravestock (see Table 3.7). The spectroscopic data reported by Yillah for (**278**) were virtually the same as the data that we obtained.



Signal	R = C_3H_7 [139] / ppm	R = C_5H_{11} [139] / ppm	R = C_6H_{13} (278) / ppm
H-2	2.55 (dd, *J* 14.3, 6.1)	2.60 – 2.38 (m)	2.55 (dd, *J* 14.4, 6.0)
	2.44 (dd, *J* 14.2, 8.8)		2.43 (dd, *J* 14.4, 9.0)
H-3	5.46 – 5.31 (m)	5.36 (quintet, *J* 7.5)	5.36 (quintet, *J* 7.5)
H-11	3.00 (dt, *J* 7.8, 1.5)	3.04 – 2.96 (m)	3.00 (t, *J* 7.5)
H-12	2.03 (quintet, *J* 7.5)	2.11 – 1.93 (m)	2.03 (quintet, *J* 7.5)
H-13*A*	3.71 (dt, *J* 10.8, 7.2)	3.71 (dt, *J* 10.7, 7.2)	3.71 (dt, *J* 10.7, 7.5)
H-13*B*	3.55 (dt, *J* 10.7, 7.2)	3.56 (dt, *J* 10.7, 7.1)	3.56 (dt, *J* 10.7, 7.5)
C-1	169.6	169.5	169.5
C-2	38.9	38.8	38.8
C-3	53.1	53.3	53.3
C-4	34.4	32.1	32.2
C-10	201.9	201.7	201.7
C-11	45.1	45.0	45.1
C-12	20.0	20.0	20.0
C-13	49.1	49.1	49.0

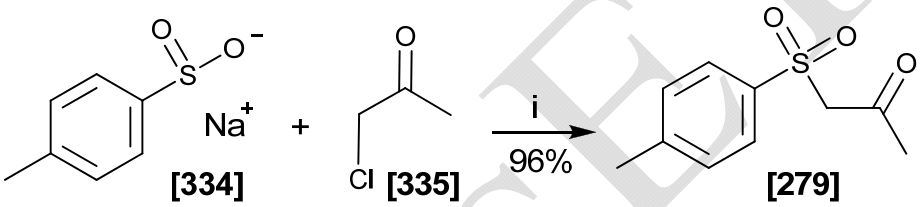
Table 3.7: Comparison of selected NMR spectral data (in $CDCl_3$) for analogous thiolactams. (*J*-values were measured in Hz).

WitsETD

3.7 Formation of the vinylogous sulfonamide

In order to form the vinylogous sulfonamide we needed to perform a modified Knoevenagel reaction between the thiolactam (**278**) and 1-[(4-methylphenyl)sulfonyl]acetone (**279**). First we therefore had to prepare 1-[(4-methylphenyl)sulfonyl]acetone (**279**).

Following the method of Makosza and Golinski,[190] sodium-*p*-toluenesulfinate (**334**) was dissolved in DMSO together with chloroacetone (**335**) and heated to 90°C for four hours (see Scheme 3.14). Following extraction and purification by column chromatography, 1-[(4-methylphenyl)sulfonyl]acetone (**279**) was isolated in 96% yield, as an odoriferous, pink solid with a low melting point (49 – 51ºC).



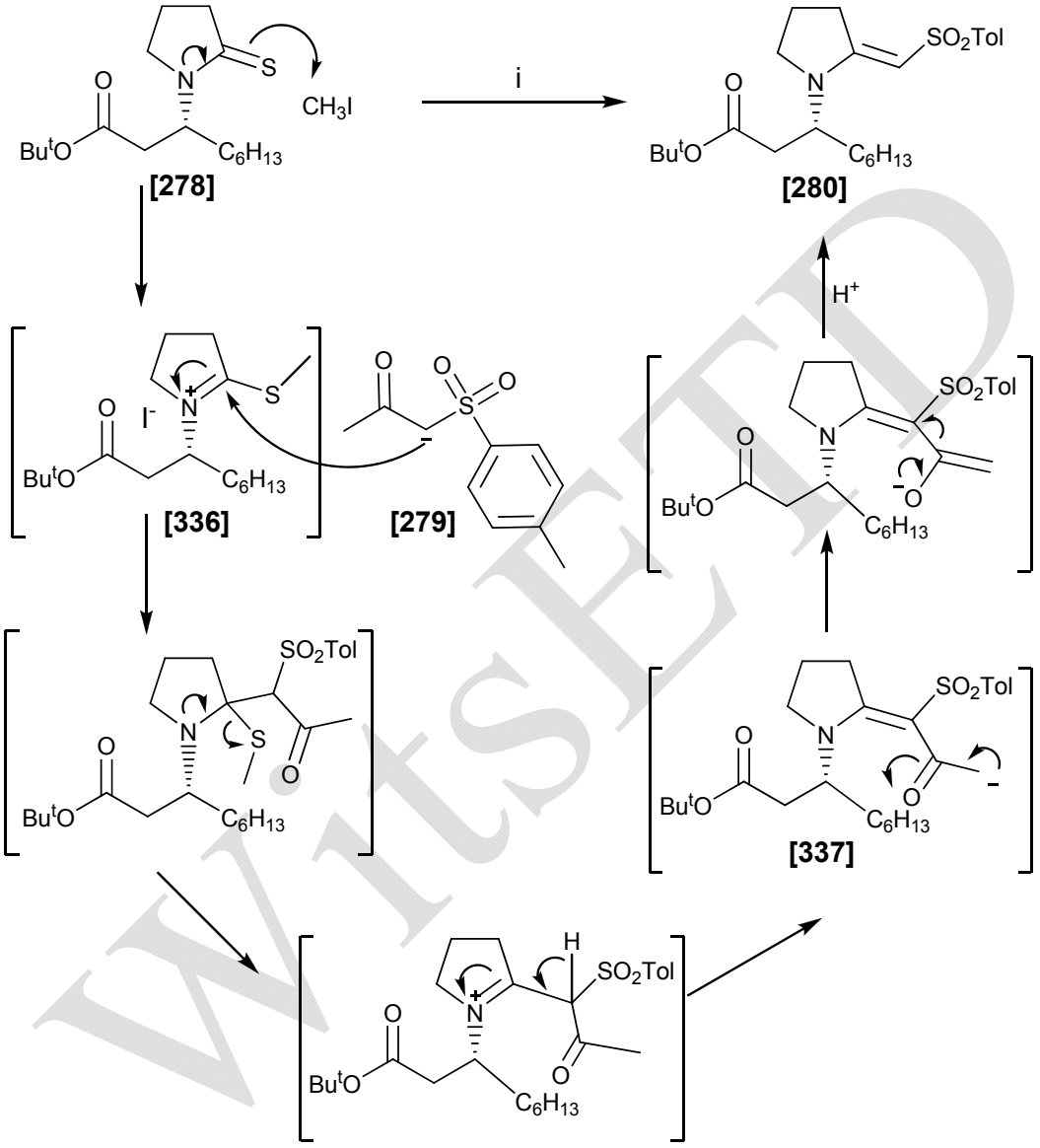
Scheme 3.14: Preparation of 1-[(4-methylphenyl)sulfonyl]acetone (**279**). *Reagents and conditions: i) DMSO, 90°C, 4 hr.*

Full characterization of product (**279**) was in agreement with the literature values.[190] The ^{1}H-NMR spectrum revealed a 1,4-disubstituted aromatic ring showing two doublets each integrating for two hydrogens at 7.76 and 7.37 ppm, respectively. The aromatic methyl group occurred at 2.45 ppm, the methylene signal was at 4.15 ppm and the aliphatic methyl group was at 2.39 ppm, which is the typical region for a methyl adjacent to a carbonyl group. The ^{13}C-NMR spectrum indicated the presence of a ketone at 196.6 ppm, as well as the characteristic aromatic signals at 145.9, 136.2, 130.4, and 128.6 ppm. The FTIR spectrum showed strong stretching bands at 1712 cm^{-1} and 1359 cm^{-1} for the ketone group and the sulfonyl group respectively.

We employed two sets of conditions for the preparation of the vinylogous sulfonamide where we varied the base used to promote the reaction. The first

WitsETD

step in both methods was the formation of the methyl iodide salt (**336**) by reacting *t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)nonanoate (**278**) with methyl iodide in tetrahydrofuran under inert atmosphere and ambient temperature for forty-eight hours (see Scheme 3.15).



Scheme 3.15: Proposed mechanism for vinylogous sulfonamide formation and the base-catalysed deacylation. *Reagents and conditions: i) a) MeI, THF, 72 hr.; b) (**279**), Et_3N, CH_2Cl_2, RT, 96 hr.*

This reaction was performed under strictly anhydrous conditions and the flask was covered in tinfoil to protect the methyl iodide from exposure to light. Once the α-thioiminium salt formation was complete, as judged by TLC, the excess methyl iodide and the tetrahydrofuran were removed *in vacuo* and a premixed

WitsETD

solution of 1-[(4-methylphenyl)sulfonyl]acetone, triethylamine and dichloromethane was carefully added and the reaction was left stirring for a further 96 hours under inert conditions. Following purification by column chromatography two products were obtained: the acylated product *t*-butyl (3*R*)-3-{2-[1-(*p*-toluenesulfonyl)-2-oxopropylidene]-1-pyrrolidinyl}nonanoate (**337**) in 27% yield and the deacylated product, *t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl} nonanoate (**280**), in 28% yield. Unreacted starting material was recovered as the lactam, *t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)nonanoate (**277**), in 25% yield, due to the hydrolysis of the α-thioiminium salt. The spontaneous *in situ* deacetylation in the presence of base can be accounted for by the mechanism shown in Scheme 3.15.

In the second method, triethylamine was replaced by DBU (1,8-diazabicyclo[5.4.0]undecene-7) and the desired product, *t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonanoate (**280**), was obtained in 13% yield, while the acylated product, *t*-butyl (3*R*)-3-{2-[1-(*p*-toluenesulfonyl)-2-oxopropylidene]-1-pyrrolidinyl}nonanoate (**337**), was obtained in 38% yield. Owing to the lower yields obtained in this variation, triethylamine was used for all subsequent reactions. In both methods the vinylogous sulfonamide (**280**) was obtained almost exclusively as the (*E*)-isomer – negligible amounts of the (*Z*)-isomer were observed in the ^{13}C-NMR spectra.

A recent study has shown that using sodium iodide as an additive during the formation of the thioiminium salt should decrease reaction times.[152] In addition, the use of polar, aprotic solvents such as acetonitrile or chloroform increases the efficiency of the salt formation.[152] However, when we attempted these conditions we experienced a reduction in yield.

The optical rotations for *t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonanoate (**280**) and *t*-butyl (3*R*)-3-{2-[1-(*p*-toluenesulfonyl)-2-oxopropylidene]-1-pyrrolidinyl}nonanoate (**337**) were $[\alpha]_D^{20}$ +11.6 (*c* 0.69, CH_2Cl_2) and $[\alpha]_D^{20}$ +44.0 (*c* 1.00, CH_2Cl_2), respectively. Yillah obtained optical rotations of $[\alpha]_D^{20}$ -41.5 (*c* 0.27, CH_2Cl_2) and $[\alpha]_D^{20}$ -59.5 (*c* 0.56, CH_2Cl_2) for

WitsETD

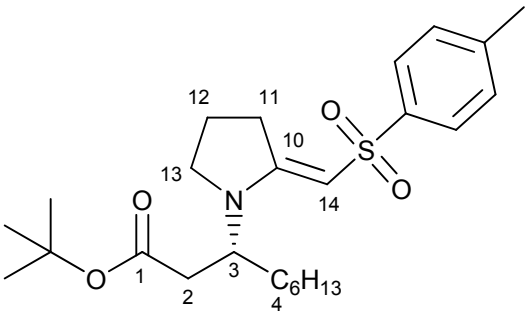
(**280**) and (**337**), respectively. These values were completely different in sign and magnitude to the values we obtained.

Both products were fully characterized and conclusively revealed the incorporation of the tosyl group into the molecule, as well as the loss of the thiocarbonyl signals. Notably, a signal characteristic of an alkene was visible at 5.00 ppm in the ^{1}H-NMR spectrum for *t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonanoate (**280**). This signal was a singlet integrating for one hydrogen and corresponds to (H-14). The acylated product (**337**) did not have this signal, but it did contain an additional methyl group at 2.34 ppm and an additional carbonyl signal at 190.7 ppm in the ^{13}C-NMR spectrum.

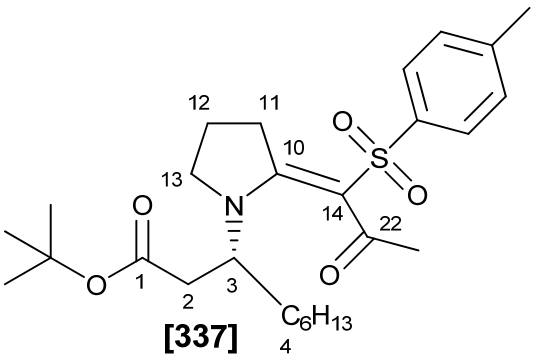
FTIR spectroscopy showed both an ester at 1724 cm^{-1}, an alkene at 1569 cm^{-1}, and a sulfonyl group at 1288 cm^{-1} for *t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonanoate (**280**). The acylated product (**337**) contained two carbonyl groups, 1727 cm^{-1} for the ester and 1687 cm^{-1} for the α-β unsaturated ketone, as well as the sulfonyl group at 1297 cm^{-1}, and the alkene at 1616 cm^{-1}.

When comparing the key differences in the ^{1}H-NMR and ^{13}C-NMR spectra between the acylated and deacylated products (see Table 3.8) H-3 was identical, occurring at 3.93 ppm for both compounds, whereas H-2, H-11, H-12 and H-13 were significantly shifted downfield in the acylated molecule owing to the electron withdrawing effect of the α,β-unsaturated ketone. The ^{13}C-NMR spectrum showed significant differences for the alkene carbons, C-10 and C-14, which occur at 161.5 and 87.7 ppm for the deacylated product (**280**) and at 174.9 and 103.7 ppm for the acylated product (**337**). Again this illustrates the increased deshielding due to the α,β-unsaturated system. C-2 and C-3 of the acylated product (**337**) were also shifted downfield, experiencing decreased electron density, whereas C-11 and C-12 were shifted upfield in the acylated product (**337**).

WitsETD



[280]



[337]

Signal	(280) / ppm	(280) [31] / ppm	(337) / ppm	(337) [31] / ppm
H-2	1.78 (dd, *J* 14.7)	3.36 – 3.23 (m)	2.95 (dd, *J* 15.2)	3.64 – 6.54 (m)
			2.48 – 2.40 (m)	
H-3	3.93 – 3.58 (m)	3.86 (q, *J* 7.9)	3.94 (tt, *J* 8.7)	3.96 (q, *J* 7.5)
H-11	2.90 (t, *J* 7.7)	3.00 (t, *J* 7.1)	3.40 (dt, *J* 15.3)	2.90 (td, *J* 7.6)
			3.03 (dt, *J* 15.3)	
H-12	1.45 – 1.32 (m)	2.46 – 2.39 (m)	2.12 – 1.83 (m)	1.44 – 1.50 (m)
H-13	3.18 (dt, *J* 16.1)	2.46 – 2.39 (m)	3.66 – 3.49 (m)	3.64 – 3.54 (m)
	3.18 (dt, *J* 16.1)			
H-14	5.00 (s)	5.07 (s)	-	-
C-1	169.8	169.75	169.7	174.80
C-2	32.1	46.27	36.9	37.95
C-3	52.2	48.84	58.5	49.16
C-4	31.6	31.59	32.3	36.98
C-10	161.5	161.55	174.9	169.78
C-11	39.0	38.99	37.8	32.34
C-12	26.1	32.08	20.1	31.52
C-13	47.0	52.25	49.1	58.53
C-14	87.9	87.83	103.7	103.88
C-22	-	-	190.7	190.89

Table 3.8: Comparison of selected NMR spectral data (in $CDCl_3$) for vinylogous sulfonamides. (*J*-values measured in Hz, only the first coupling constant is shown).

WiSER

3.8 Attempted deacetylation reactions

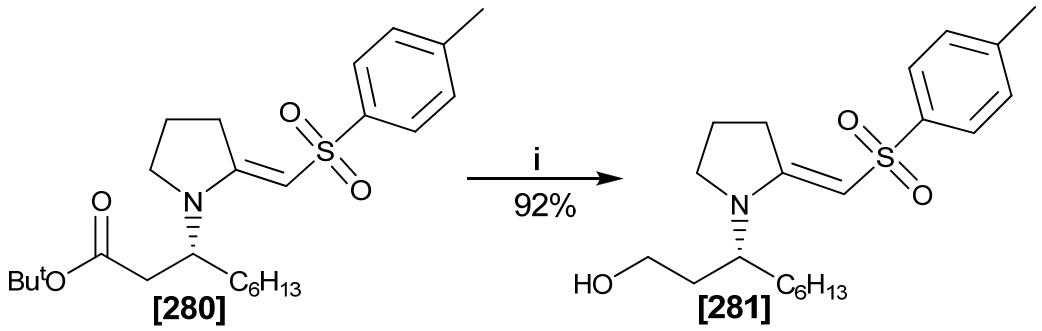
We attempted two acid-catalyzed deacetylation reactions on *t*-butyl (3*R*)-3-{2-[1-(*p*-toluenesulfonyl)-2-oxopropylidene]-1-pyrrolidinyl}nonanoate (**337**), the first heated (**337**) at reflux in neat trifluoroacetic acid for twelve hours, and the other heated at reflux in toluene and trifluoroacetic acid for five hours, while monitoring by TLC. Neither method produced any of the desired product, even the *t*-butyl ester survived the harsh reaction conditions. Analysis of the ^{1}H-NMR spectrum indicated some sort of decomposition, with the loss of the tosyl group. These two procedures were modified from the work of Ban and co-workers;[154] please refer to the literature for the proposed mechanism of the acid-catalysed deacetylation.

Owing to the unsuccessful deacetylation reaction, the product could not be recycled back into the synthetic sequence and this unfortunately meant a serious reduction in overall yield.

3.9 Reduction to the alcohol

In the next step, the *t*-butyl ester group of *t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonanoate (**280**) was reduced to the corresponding alcohol, *t*-butyl (3R)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonan-1-ol (**281**), under standard reduction conditions using lithium aluminium hydride in tetrahydrofuran at ambient temperature for twelve hours (see Scheme 3.16). After purification by column chromatography, the alcohol (**281**) was isolated in 92% yield.

WitsETD



Scheme 3.16: Reduction of the ester (**280**) to the alcohol (**281**). *Reagents and conditions: i) $LiAlH_4$, THF, RT, 15 hr.*

Full characterization revealed the disappearance of the *t*-butyl group and the appearance of the hydroxy group. The ^{1}H-NMR spectrum showed a broad new peak at 2.17 ppm corresponding to the OH and an additional methylene signal was observed at 3.20 ppm as a triplet (*J* 6.7) corresponding to H-1 (see Figure 3.9). The ^{13}C-NMR spectrum showed the absence of the *t*-butyl peaks at 81 ppm and 28 ppm, and the loss of the ester carbonyl at 170 ppm. C-1 was observed as a new signal at 45.9 ppm, deshielded by the adjacent hydroxy group. For the ^{1}H-NMR spectrum, Yillah did not report an O-H signal, he reported H-1 at 3.55 – 3.51 ppm (0.30 ppm higher than our value) and H-3 at 3.55 – 3.51, whereas we observed H-3 at 3.75 – 3.62 ppm. The values Yillah reported for the ^{13}C-NMR spectrum were similar to the values we obtained.

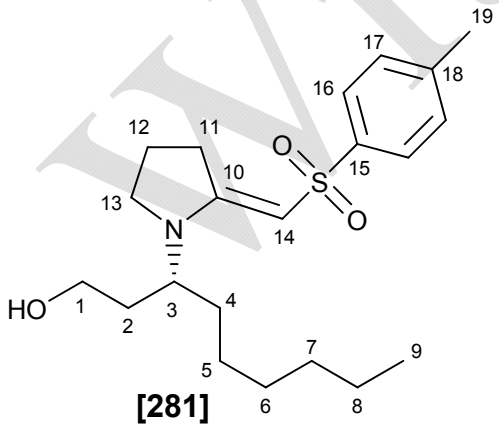


Figure 3.9: Numbering of alcohol (**281**) for assignment of spectroscopic data.

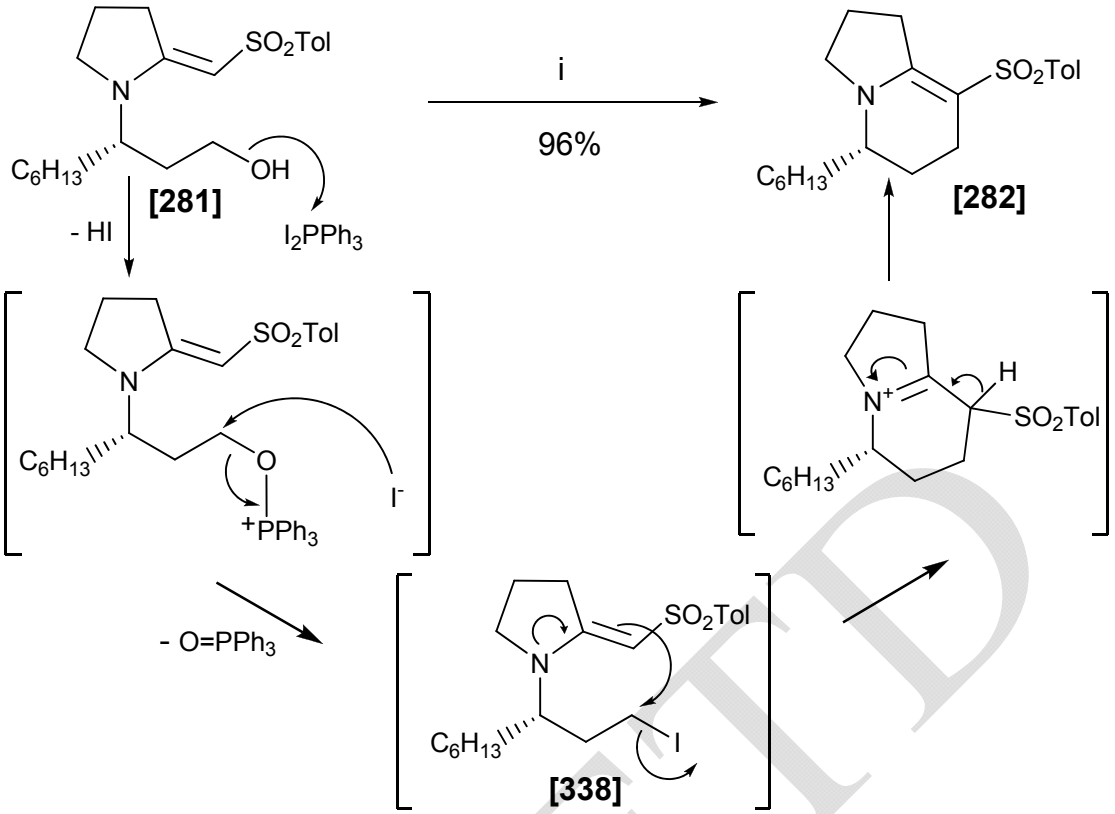
FTIR spectroscopy revealed a broad stretching vibration at 3474 cm^{-1} corresponding to the O-H bond and the ester carbonyl stretching vibration was

no longer observed. The alcohol had significant optical activity, $[\alpha]_D^{20}$ -25.0 (*c* 0.30, CH_2Cl_2), which was opposite in sign compared to the preceding ester. Yillah obtained an optical rotation of $[\alpha]_D^{20}$ -5.3 (*c* 1.25, CH_2Cl_2) for the same molecule. High resolution mass spectrometry showed the parent ion of (**281**) with a mass of 379.2176, in close agreement with the calculated value of 379.2181.

3.10 Cyclisation reaction

The next step in the synthesis was the key step, the novel cyclisation reaction. This reaction makes use of the vinylogous sulfonamide's nucleophilicity to facilitate intramolecular ring closure. The alcohol (**281**) was first converted into an iodide (**338**), which was a better leaving group, using Appel-type reaction conditions;[191] triphenylphosphine, iodine and imidazole, a mild organic base (see Scheme 3.17). The alcohol (**281**) was heated at reflux in toluene together with the triphenylphosphine, iodine and imidazole and once the intermediate iodide (**338**) was formed the vinylogous sulfonamide spontaneously facilitated cyclisation. Following work-up and purification, the bicyclic product, (*5R*)-5-hexyl-1,2,3,5,6,7-hexahydro-8-indolizinyl 4-methylphenyl sulfone (**282**), was isolated in 96% yield as a pale yellow oil that discoloured to blue in the presence of light.

WitsETD

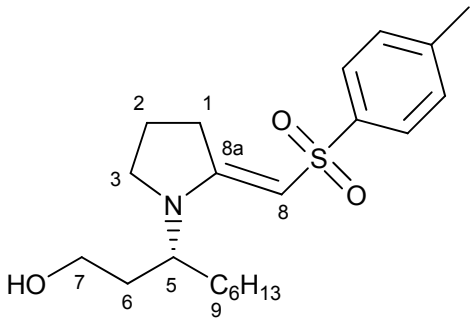


Scheme 3.17: Mechanism for the key cyclisation reaction. *Reagents and conditions: i) PPh_3, imidazole, I_2, toluene, reflux, 6 hr.*

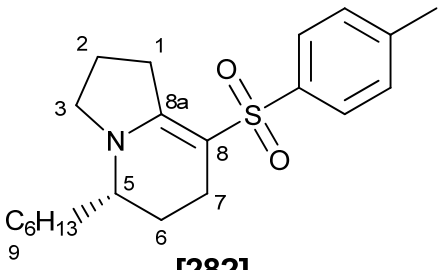
Yillah employed slightly different reaction conditions, using acetonitrile/toluene (2:1) as the solvent. He isolated the desired product in 83% yield. His reported spectra were in close agreement with the spectra we obtained.

The bicyclic product, (*5R*)-5-hexyl-1,2,3,5,6,7-hexahydro-8-indolizinyl 4-methylphenyl sulfone (**282**), retained its optical activity, although again the sign changed from the negative value obtained for the alcohol (**281**) to $[\alpha]_D^{20}$ +9.4 (*c* 0.85, CH_2Cl_2). Yillah reported the optical rotation of (**282**) as $[\alpha]_D^{20}$ +31.0 (*c* 0.36, CH_2Cl_2). The most significant change in the ^{1}H-NMR spectrum was the loss of the alkene proton at 5.09 ppm and the disappearance of the triplet at 3.20 ppm corresponding to C-7 (see Table 3.9).

WitsETD



[281]



[282]

Signal	(281) / ppm	(282) / ppm
H-1	3.08 – 2.96 (m)	3.13 (t, *J* 7.2)
	2.97 – 2.84 (m)	
H-2	1.86 (quintet, *J* 7.4)	1.91(quintet, *J* 7.2)
H-3	3.62 – 3.44 (m)	3.19 (t, *J* 7.1)
H-5	3.75 – 3.62 (m)	3.49 (quintet, *J* 6.9)
H-6	1.71 (q, *J* 6.7)	1.80 – 1.51 (m)
H-7	3.20 (t, *J* 6.7)	1.80 – 1.51 (m)
H-8	5.09 (s)	-
C-1	31.4	32.1
C-2	20.8	29.3
C-3	59.0	51.2
C-5	51.6	53.9
C-6	34.7	31.4
C-7	45.9	31.7
C-8	86.2	92.4
C-8a	162.6	155.1

Table 3.9: Comparison of selected NMR spectral data (in $CDCl_3$) for alcohol and bicyclic products. (*J*-values measured in Hz).

The ^{13}C-NMR spectrum showed several significant changes, most notably C-8 and C-8a shift from 86.2 and 162.6 ppm to 92.4 and 155.1 ppm, respectively. This was because of the change in electronic environment due to the inductive effect of the closed ring system.

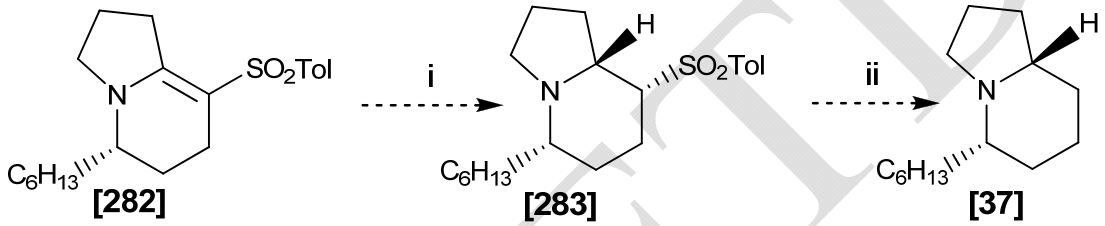
FTIR spectroscopy revealed the loss of the O-H stretching vibration as no band was visible in the region of 3000 – 3500 cm^{-1} characteristic of this bond. The

WITSETD

spectrum showed alkene stretching vibrations at 1593 cm^{-1}, sulfonyl stretching vibrations at 1291 cm^{-1}, and aliphatic stretching vibrations. High resolution mass spectrometry gave a molecular ion at 361.2071, in very close agreement with the calculated value for the compound with the ^{32}S isotope (361.2075).

3.11 Conclusion

Unfortunately, the final two steps in the synthesis were never attempted (see Scheme 3.18). Although the preceding step was successful, not enough of the product (**282**) was available for the next reaction.



Scheme 3.18: Final two steps in the synthesis; reduction and desulfonylation. *Reagents and conditions: i) H_2 (7 atm.), PtO_2, MeOH; ii) Na(Hg), Na_2HPO_4.*

Although the plan was to go back to the beginning of the synthesis and push material through the initial steps so that the final two steps could be optimized and completed, the debenzylation reaction repeatedly failed to remove both benzyl groups. After numerous attempts at removing both benzyl groups the conclusion was reached that the palladium catalysts currently available were not sufficiently active to perform the reaction. It was most frustrating to be thwarted by a reaction which initially worked exceptionally well; we have however, come to accept that with the current difficulties experienced with the debenzylation reaction it has become necessary to explore alternative reactions. There are other chiral amines that could be used in place of *N*-benzyl-*N*-(1*R*)-1-phenylethylamine (**214**), which can be removed under different reaction conditions. For example, the dimethoxy equivalent can be cleaved under oxidative conditions by ceric ammonium nitrate.

WitsETD

Although the total synthesis was not completed, the synthesis was thoroughly explored, we did gain enough experience with this type of chemistry to continue with the racemic synthesis of monomorine I and it isomers, and the optical rotation results that were obtained have values that align well with the analogous compounds synthesized by Gravestock. It was clear that many of the optical rotations recorded by Yillah did not correspond in sign or magnitude to those obtained by Gravestock and Davies for similar compounds. Full characterization of all the intermediate compounds was obtained and the reaction conditions were altered to improve the efficiency of the reactions. Novel side reactions were identified and explored and alternative debenzylation reactions were attempted.

WitsETD

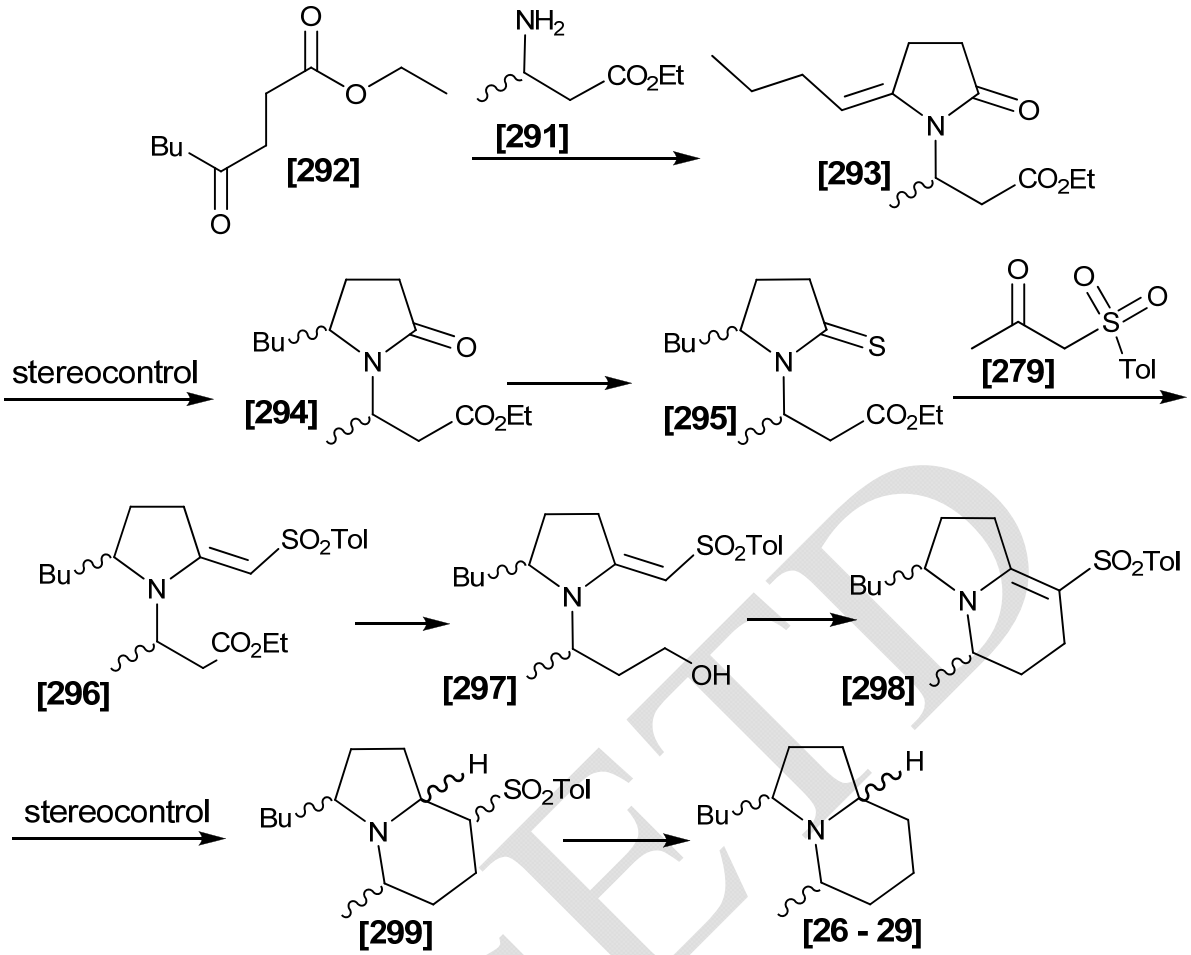
CHAPTER 4
THE TOTAL SYNTHESIS OF MONOMORINE I AND 5-*epi*-MONOMORINE I

4.1 Introduction

Once the synthesis of (−)-indolizidine 209D was well underway (barring unforeseen difficulties), the completion of the synthesis was imminent, we began investigations into the total synthesis of monomorine I and/or its diastereomers. Initially the synthesis of the racemic alkaloid was investigated, as the use of a chiral auxiliary made the enantioselective route more expensive to execute. For conciseness, however, results pertaining to the racemic and enantioselective alternatives are presented in parallel throughout this chapter.

For convenience, a pictorial summary of the strategy to be followed is repeated below (see Scheme 2.16).

WitsETD



Scheme 2.16: Proposed synthetic route for the total synthesis of monomorine I and/or its isomers.

4.2 Preparation of the ketoester and amine precursor

4.2.1 Preparation of the ketoester

Our desired starting material, the ketoester ethyl 4-oxooctanoate (**292**), was a known compound and a review of the literature revealed many different strategies for preparing (**292**) and analogous 1,4-ketoesters. Four of the dominant strategies are outlined in Figure 4.1. Strategy A[192 - 194] executes a three step synthesis from the cheap and readily available starting material ethyl acetoacetate (**339**). Strategy B uses methodology developed by Stetter *et al.*,[195 - 197] and involves an ionic reaction between ethyl acrylate (**340**) and valeraldehyde (**341**), catalysed by a thiazolium-based catalyst. The conditions for this reaction were fairly sensitive and a syringe-pump was required for the addition of the ethyl acrylate in order to prevent unwanted side reactions.

WitsETD

Strategy C[198 - 204] was a Grignard reaction, starting with the fairly expensive ethyl 4-chloro-4-oxobutyrate (**342**). Great care must be taken to ensure that only single addition occurs. There were several additives and catalysts available to help prevent multiple additions, but ultimately it was low temperatures and short reaction times that minimized the unwanted by-products. The advantage of strategy C was that it was a one-step synthesis. Strategy D[205] started from the cheap and readily available succinic anhydride (**343**) and involved two standard transformations to get to the desired ketoester (**292**).

Because ethyl 4-oxooctanoate (**292**) was the starting point for our proposed synthesis of monomorine I, we needed to prepare it in large quantities and high yields. All four strategies were investigated in order to find the most efficient and economical method.

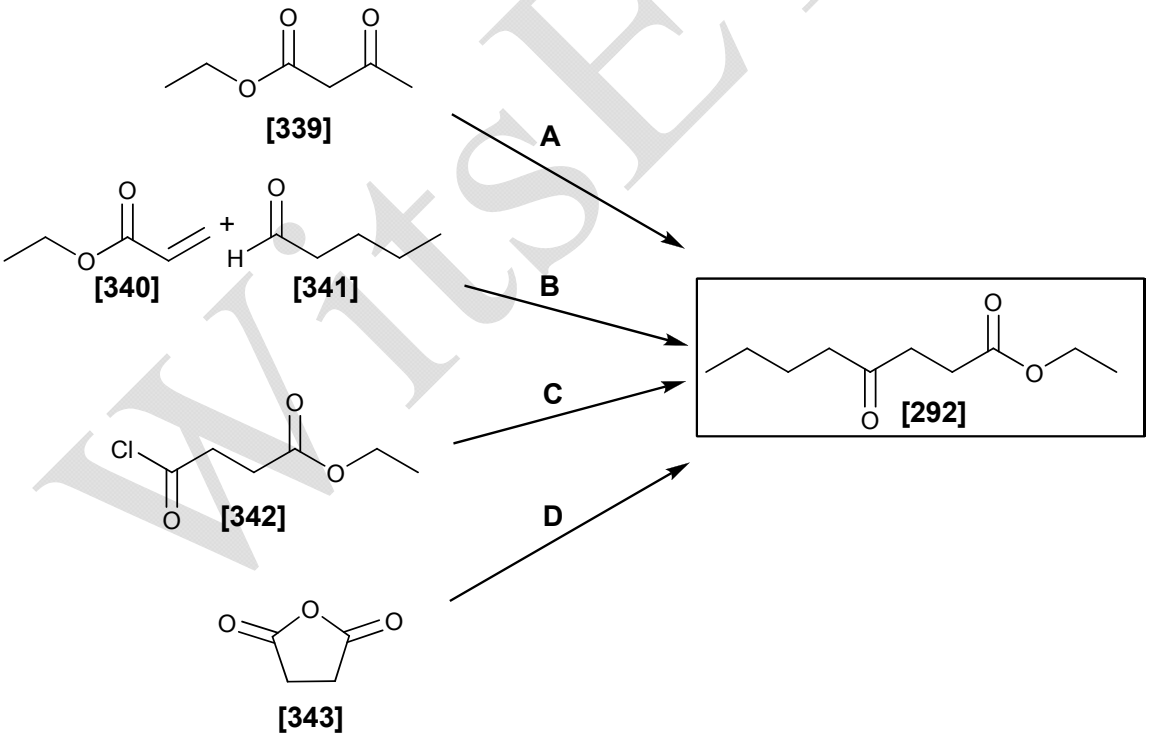


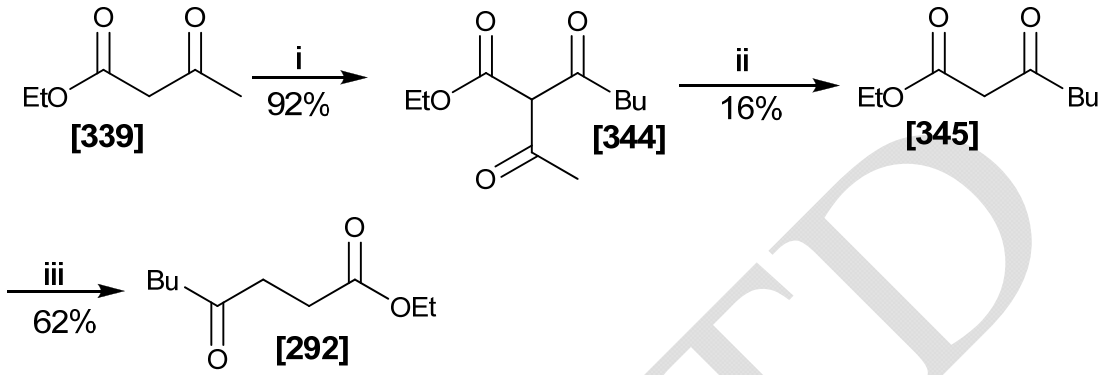
Figure 4.1: Four general routes to ketoester (**292**).

Strategy A[192]

Strategy A was a three-step synthesis starting from the cheap and readily available starting material ethyl acetoacetate (**339**). The first step was the

WitsETD

formation of the stabilized secondary enolate, followed by the addition of valeroyl chloride to form ethyl 2-acetyl-3-oxoheptanoate (**344**). The second step was the deacetylation to form ethyl 3-oxoheptanoate (**345**) (see Scheme 4.1), and the final transformation was a CH_2 insertion reaction to give the desired ketoester (**292**) (see Scheme 4.2).

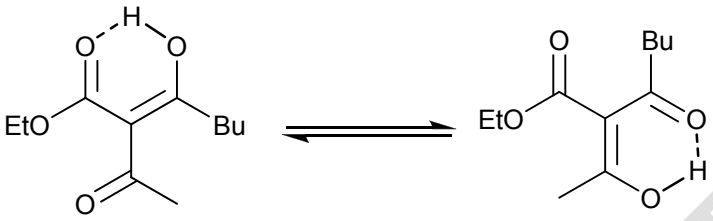


Scheme 4.1: Strategy A, first approach. *Reagents and conditions: i) NaH, THF, valeroyl chloride, RT, 12 hr.; ii) a) NH_3 (gas), Et_2O, 90 min. b) HCl; iii) Et_2Zn, CH_2Cl_2, CH_2I_2, 0 °C − RT, 30 min.*

For the first step, ethyl acetoacetate (**339**) was carefully added to a cooled solution of sodium hydride in tetrahydrofuran. For a 180 mmol scale, a large flask (1 litre), vigorous stirring, and a low molarity of ethyl acetoacetate (0.40 *M*) were required in order to prevent a clumpy emulsion from forming. After the addition was complete, the solution was bright yellow in colour. Valeroyl chloride was added dropwise and the solution gradually turned opaque. The reaction was allowed to warm to ambient temperature and was quenched with distilled water twelve hours later. After extraction and purification by column chromatography, the desired product, ethyl 2-acetyl-3-oxoheptanoate (**344**), was isolated in 92% yield as a clear yellow oil. Presumably (**344**) was found entirely as the enol form, as only one set of spectral signals was observed. Characterization by ^{1}H-NMR spectroscopy revealed that the enol hydrogen had shifted downfield to an astounding 17.80 ppm due to the combined effect of the hydrogen-bonded carbonyl groups. ^{13}C-NMR spectroscopy showed three carbonyl groups at 167.2 ppm, 195.6 ppm and 198.8 ppm. The latter two signals were both in an appropriate region for ketone carbonyls but presumably the two enol tautomers were in equilibrium, giving the enol carbons ketone-like

WitsETD

character (see Figure 4.2). The signal for the central carbon, C-2, appeared at 108.6 ppm. FTIR spectroscopy clearly indicated the presence of three carbonyl stretching vibrations at 1762 cm^{-1}, 1710 cm^{-1} and 1670 cm^{-1} and no signal was observed for the enol OH. This may have been owing to excessive broadening of the O-H signal, because of hydrogen-bonding and the equilibrium, or perhaps the solvent-free conditions of the IR machine prevented the enol from forming.



[344A] **[344B]**

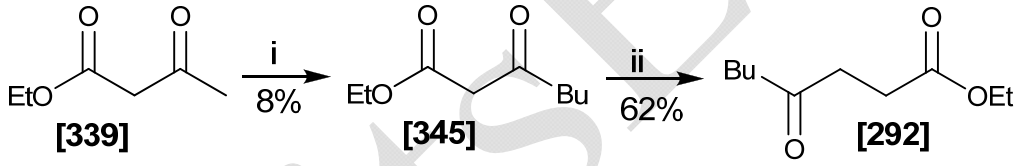
Figure 4.2: Two of the enol tautomers of (**344**).

For the second step, ethyl 2-acetyl-3-oxoheptanoate (**344**) was dissolved in dry diethyl ether and ammonia gas was bubbled through the solution for approximately ninety minutes. This was followed by an acidic work up with dilute hydrochloric acid, followed by extraction of the product into ethyl acetate. According to the literature,[194] the acetyl group should selectively cleave, leaving ethyl 3-oxoheptanoate. After purification by column chromatography, we found that the major product was in fact ethyl acetoacetate (**339**) (84% yield) and the desired compound, ethyl 3-oxoheptanoate (**345**), was the minor product (16% yield). Clearly the reaction was favouring the removal of the wrong acyl group, opposite of what was observed in the literature.[194] The ^{1}H-NMR spectrum showed H-2 as a singlet, moderately shifted to 3.43 ppm, and only two carbonyl signals were observed by ^{13}C-NMR spectroscopy at 202.9 ppm and 167.2 ppm in the characteristic regions for a ketone and an ester carbonyl respectively. FTIR spectroscopy confirmed the presence of only two carbonyl stretching vibrations at 1741 cm^{-1} and 1715 cm^{-1}.

Owing to the low yield of ethyl 3-oxoheptanoate (**345**) (16%) an alternative method was attempted. This method[206] also made use of ethyl acetoacetate

WiSETD

(**339**) as a starting material and then employed a double deprotonation reaction prior to the addition of chloropropane. Firstly, sodium hydride was used to deprotonate the more acidic position, the methylene adjacent to both carbonyls, as the sodium cation could chelate to both the resulting enolate and the carbonyl group. Then, *n*-butyllithium was carefully added and the terminal methylene, adjacent to the ketone, was deprotonated. The lithium could not chelate to the carbonyl as the sodium had already blocked the position. Chloropropane was carefully added and, theoretically, only the terminal carbanion should react with it. The reaction was quenched with distilled water and after extraction and purification by column chromatography, ethyl 3-oxoheptanoate (**345**) was isolated in 8% yield as a clear oil with a pleasant, fruity odour. The low yield was attributed to the inferior quality of the *n*-butyllithium reagent available at the time. The reaction was neither repeated nor optimized, since alternative approaches were already proving more promising (see Strategy C).



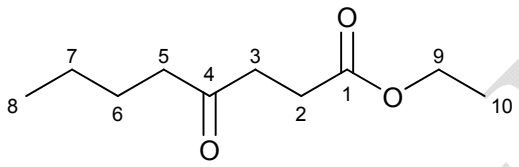
Scheme 4.2: Strategy A, second approach. *Reagents and conditions: i) a) NaH, THF; b)* n-*BuLi; c) chloropropane; ii)* Et_2Zn, CH_2Cl_2, CH_2I_2, *0°C − RT, 30 min.*

Having prepared some of the ethyl 3-oxoheptanoate (**345**), it was possible to attempt the exciting CH_2 insertion reaction. The literature method[193] we chose to follow used neat diethylzinc to perform this transformation. Due to the highly pyrophoric nature of the reagent, great care was taken to ensure dry and oxygen-free conditions for the reaction. Dry dichloromethane and diethylzinc were mixed in a flask under nitrogen and diiodomethane was carefully added. Exothermic bubbling commenced, after which the solution was cooled to 0°C. Ethyl 3-oxoheptanoate (**345**) was rapidly added and the reaction was left for a further thirty minutes. The reaction was quenched with ammonium chloride solution and the organic material was extracted into ethyl acetate. Following purification by column chromatography, the desired product ethyl

WiSER

4-oxooctanoate (**292**), was isolated in 62% yield as a clear oil. Although the reaction was successful and fun to execute, the empty syringe invariably ignited after the addition of diethylzinc was complete and hence the reaction was most definitely not suitable for scale-up.

Ethyl 4-oxooctanoate (**292**) was fully characterized and all spectroscopic data was in agreement with the literature.[195, 207] In the ^{1}H-NMR spectrum, the ethyl group was observed at 4.13 ppm and 1.25 ppm as a quartet and triplet, respectively. The three methylene groups, H-2, H-3 and H-5 (see Figure 4.3), were observed at 2.72 ppm, 2.62 – 2.45 ppm and 2.45 ppm, downfield due to deshielding by the adjacent carbonyls. ^{13}C-NMR spectroscopy showed the ketone, C-4, at 209.5 ppm, and the ester, C-1, at 173.2 ppm, within the expected regions for these functional groups.



[292]

Figure 4.3: Numbering of ester (**292**) for assignment of spectroscopic data.

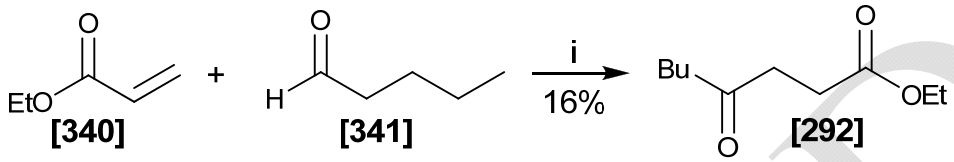
Strategy A gave ethyl 4-oxooctanoate in 9% overall yield (see Scheme 4.1) over three steps, via ethyl 2-acetyl-3-oxoheptanoate (**344**). The two step variation of strategy A gave ethyl 4-oxooctanoate in 5% overall yield (see Scheme 4.2). This was not the most economic and efficient route for preparing our starting material.

Strategy B[195 - 197]

This method used the Stetter reaction, a one step ionic reaction, involving ethyl acrylate (**340**) and valeraldehyde (**341**) (see Scheme 4.3). The thiazolium-based catalyst, 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride, ethyl acrylate, triethylamine and dioxane were mixed together under inert conditions at ambient temperature. A mixture of valeraldehyde and a second portion of ethyl acrylate were added over ten hours using a syringe pump. The

WitsETD

reaction was stopped and the product was extracted into ethyl acetate and rinsed with dilute hydrochloric acid, sodium bicarbonate solution and distilled water. After purification by column chromatography, the desired product, ethyl 4-oxooctanoate (**292**), was isolated in a low yield of 16% and showed contamination by diethyl succinate. The low yield was attributed to the evaporation of the ethyl acrylate during the reaction as well as the sensitive nature of the reaction.



Scheme 4.3: Strategy B, the Stetter reaction. *Reagents and conditions: i) Thiazolium cat., (**340**), Et_3N, dioxane; b) (**340**), (**341**), 10 hr., RT.*

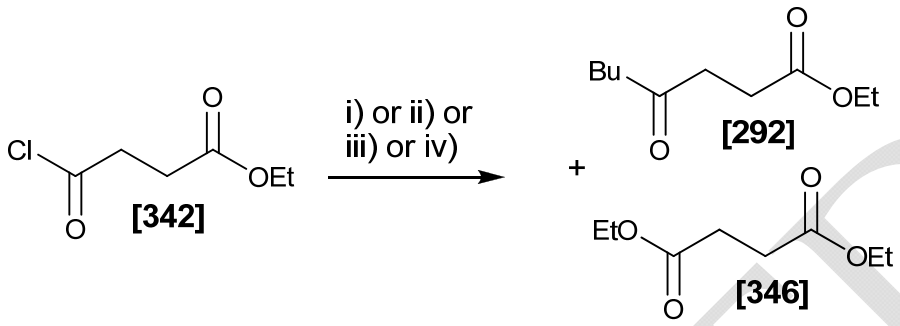
The Stetter reaction was attempted several times further, but the yield did not improve. The physical set up of the system contributed significantly to the evaporation of the ethyl acrylate during the reaction and the decision was made to move on to strategy C rather than spending more time optimizing the conditions.

Strategy C

This method involves a standard organometallic reaction involving addition of either a cuprate[198, 199] or an organolithium reagent to an acyl chloride (see Scheme 4.4).[198, 200 - 204] The challenge of this reaction was controlling the single addition of the organometallic nucleophile by varying the temperature, time, and catalyst. Initially the reaction was attempted using a cuprate. Di-*n*-butylcopper lithium was prepared *in situ* by reacting copper iodide with *n*-butyllithium at -90°C for one hour. Ethyl 4-chloro-4-oxobutyrate (**342**) was added to the cuprate solution and the reaction mixture was warmed to ambient temperature and left stirring for a further twelve hours. Following work-up and purification by column chromatography, the desired product, ethyl 4-oxooctanoate (**292**), was isolated in 80% yield. On closer examination of the ^{1}H-NMR spectrum, it became apparent that the sample was heavily contaminated with diethyl succinate (**346**), (approximately 30% of the sample), which eluted with an

WitsETD

identical R_f value in all the solvent systems tested. Diethyl succinate and ethyl 4-oxooctanoate do however differ in boiling points, with the former being 105°C and the latter 125°C at 15 torr and therefore could be separated by distillation if the scale of the reaction allowed it. For these reasons this reaction was abandoned.



Scheme 4.4: Strategy C, organometallic reaction. *Reagents and conditions: i) a) CuI,* n-*BuLi, THF, -90°C, 1 hr.; b) (**342**), RT, 12 hr. 56%. ii)* n-*BuMgCl, bis-(*N,N-*dimethylaminoethyl)ether, THF, -90°C, 2.5 hr., 21%; iii) a) Bu_3P, THF, -29°C, 25 min.; b)* n-*BuMgCl, 10 min., 93%; iv)* n-*BuMgCl, Fe(acac)$_3$, THF, 0°C, 10 min. 100%.*

The second method[200 - 202] uses the Grignard reagent, *n*-butylmagnesium chloride, premixed with the additive bis-(*N,N*-dimethylaminoethyl)ether, which reportedly coordinates to the magnesium to form a tridentate ligand and reduces the formation of by-products during the reaction. This mixture was added to a solution of ethyl 4-chloro-4-oxobutanoate (**342**) in tetrahydrofuran at –90°C. After twenty minutes TLC indicated no formation of product and the reaction mixture was warmed to ambient temperature and stirred for an additional two hours. After work up and purification by column chromatography, ethyl 4-oxooctanoate (**292**) was isolated in a low yield of 21%.

After reviewing the literature again,[203, 204] tri-*n*-butylphosphine emerged as a potential additive for Grignard reactions to ketoesters. Ethyl 4-chloro-4-oxobutanoate (**342**) was dissolved in tetrahydrofuran and cooled to –29°C in a xylene/liquid nitrogen slurry. Tri-*n*-butylphosphine was carefully added and the solution was stirred for twenty-five minutes. The *n*-butylmagnesium bromide solution was quickly added and the reaction was left stirring for ten minutes before it was quenched with dilute hydrochloric acid. Following extraction and

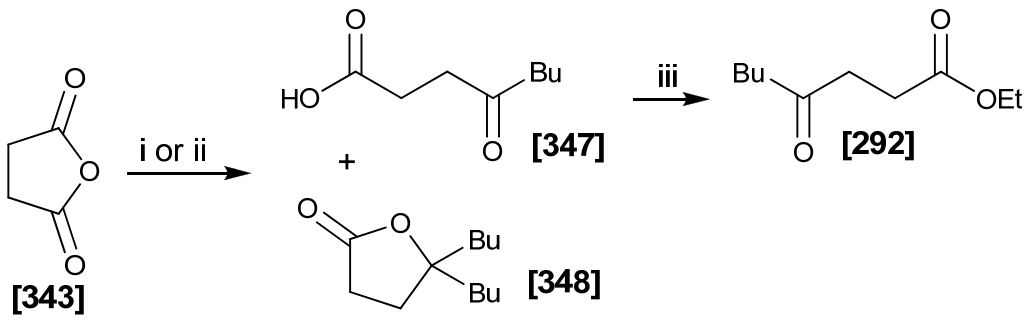
WiSER

purification by column chromatography, ethyl 4-oxooctanoate (**292**) was isolated in 93% yield. This result seemed to indicate that short reaction times were of paramount importance in achieving high yields for this reaction. One of the reactions we had previously attempted using iron(III) acetoacetate as a catalyst had repeatedly given us yields in the region of 40 - 60%. Inspired by the high yield obtained with the tri-*n*-butylphosphine we set about repeating the Grignard reaction catalysed by the iron(III) acetoacetate.[198] Ethyl 4-chloro-4-oxobutanoate (**342**) was dissolved in tetrahydrofuran together with catalytic amounts of iron(III) acetoacetate. The solution was cooled to 0°C and then *n*-butylmagnesium bromide solution was added dropwise from a dropping funnel. After ten minutes the addition was complete and the reaction was immediately quenched with dilute hydrochloric acid. The product was extracted into ethyl acetate and purified by column chromatography to give ethyl 4-oxooctanoate (**292**) in quantitative yield.

Strategy D

Strategy D starts with the readily available succinic anhydride (**343**) and also involves the addition of a cuprate[199] or organolithium reagent,[198] followed by esterification (see Scheme 4.5). First we attempted the Grignard reaction. *n*-Butylmagnesium bromide was prepared *in situ* by reacting bromobutane with magnesium turnings in dry tetrahydrofuran for one hour at 0°C under nitrogen. The Grignard reagent was slowly added to a solution of succinic anhydride (**343**) and a catalytic amount of iron(III) acetoacetate in tetrahydrofuran at ambient temperature. After an hour the reaction was quenched with a dilute hydrochloric acid solution and the product was extracted into diethyl ether. Following purification by column chromatography, 4-oxooctanoic acid (**347**) was isolated in 25% yield as a white crystalline solid. 5,5-Dibutyldihydro-2(3*H*)-furanone (**348**) was isolated as a by-product in 11% yield.

WitsETD



Scheme 4.5: Strategy D, organometallic reaction with succinic anhydride. *Reagents and conditions: i)* n-*BuMgCl, Fe(acac)$_3$, THF, RT, 1 hr. 25%; ii) a) CuI,* n-*BuLi, THF, -90°C, 1 hr.; b) (**343**), RT, 3 hr., 34%; iii) EtOH, H_2SO_4 (cat.), RT, 3 hr. 100%.*

4-Oxooctanoic acid (**347**) was fully characterized and showed the characteristic broad O-H signal at 12 – 10 ppm in the ^{1}H-NMR spectrum. ^{13}C-NMR spectroscopy showed the acid carbonyl signal at 179.1 ppm and the FTIR spectrum showed the broad O-H stretching vibration at 3550 – 3350 cm^{-1}. The by-product, 5,5-dibutyldihyro-2(3*H*)-furanone, gave a simple ^{1}H-NMR spectrum due to the symmetry of the molecule. The lactone signals appeared as triplets at 2.57 ppm and 2.02 ppm, and the butyl chain signals were observed at 1.66 – 1.57 ppm, 1.40 – 1.26 ppm and 0.92 ppm. Only eight signals were observed in the ^{13}C-NMR spectrum. FTIR spectroscopy showed a stretching vibration at 1772 cm^{-1}, characteristic of a lactone carbonyl group.

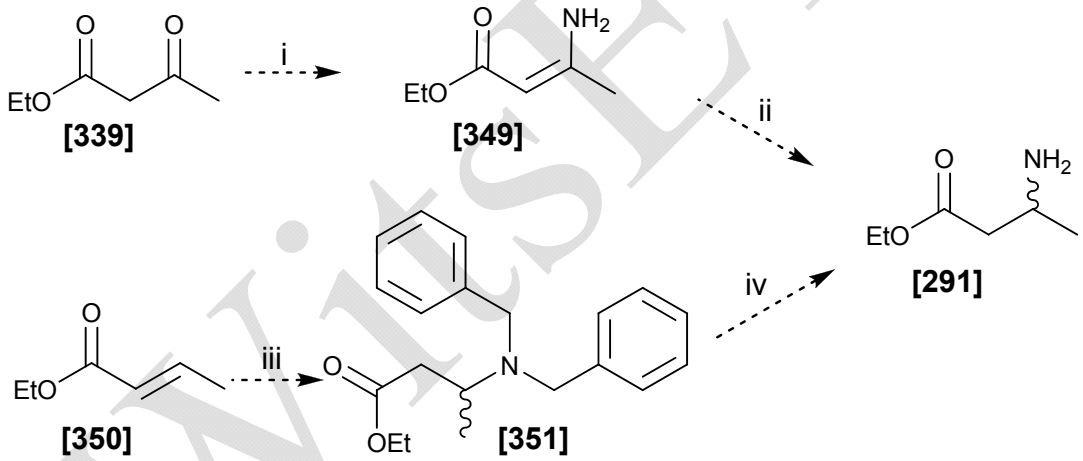
Secondly we attempted the addition of di-*n*-butylcopper lithium to succinic anhydride (**343**) in tetrahydrofuran. The reaction mixture was stirred at ambient temperature for three hours and was then quenched with a saturated ammonium chloride solution. The crude product was extracted into diethyl ether, the solvent removed *in vacuo*, and the crude product was esterified directly by reacting it with acidified absolute ethanol for three hours at ambient temperature.[205] Following work up and purification, ethyl 4-oxooctanoate (**292**) was obtained in 34% yield over the two steps.

The iron (III) acetoacetate catalysed Grignard reaction used in strategy C[198] was clearly the most economic and efficient method for preparing the ketoester (**292**). It required only one step, ten minutes reaction time, relatively little solvent, 3% catalyst loading, and boasted a quantitative yield with no

contamination by by-products, provided that the reaction time was carefully monitored.

4.2.2 Preparation of the racemic amine

During the initial trouble-shooting phase in the development and optimization of the synthetic pathway, we wanted an inexpensive method to prepare the racemic amine, ethyl 3-aminobutyrate (**291**). One of the literature methods[208 - 210] for preparing β-amino esters was by reacting a β-ketoester with an ammonia source and reducing out the resulting imine or its enamine tautomer. We also intended to use methodology developed by Davies and co-workers,[158] incorporating a chiral auxiliary, to access the equivalent enantiopure amine. A comparable racemic pathway can be emulated using dibenzylamine for the aza-Michael reaction. These two potential pathways for accessing the racemic amine (**291**) are shown in Scheme 4.6.



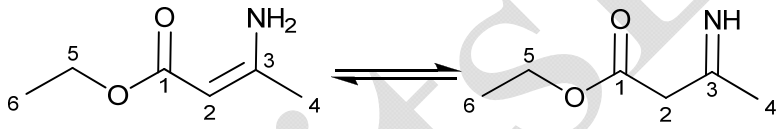
Scheme 4.6: Two potential pathways for accessing racemic amine (**291**). *Reagents and conditions: i) $NH_4CH_3CO_2$, AcOH, reflux, 4 hr.; ii) $NaBH_4$, AcOH; iii) a) dibenzylamine,* n-*BuLi, THF, -90°C, 30 min.; b) (**350**), 2 hr.; iv) Pd/C, H_2 (7 atm.), AcOH, 72 hr.*

When preparing the racemic amine, the nature of the side-chain of the ester group was inconsequential, as it would be reduced to the alcohol later in the synthesis. We therefore chose to attempt the method with the β-ketoester on both ethyl acetoacetate (**339**) (see Scheme 4.6) and on *t*-butyl acetoacetate (**352**) (see Scheme 4.7). First, ethyl acetoacetate was dissolved in benzene in a flask connected to a Dean-Stark apparatus. Acetic acid and ammonium acetate

WitsETD

were then added and the solution was heated at reflux for four hours. After cooling, the solvent was removed *in vacuo* and the residual oil was washed with sodium carbonate and extracted into ethyl acetate. The enamine, (*Z*)-ethyl 3-aminobut-2-enoate (**349A**), was isolated by vacuum distillation in 91% yield as a low melting solid (28 – 30°C). The ^{1}H-NMR spectrum indicated the product (**349A**) was in equilibrium with its imine tautomer (**349B**) in a 3:1 ratio respectively.

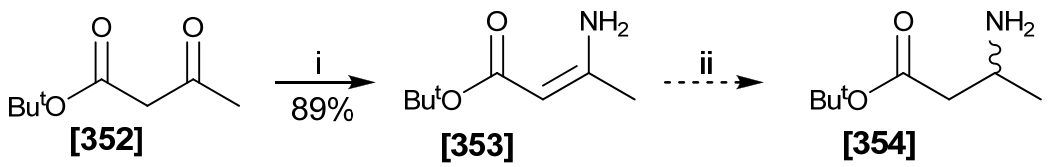
The most significant peaks in the ^{1}H-NMR spectrum included the NH_2 signal, a broad singlet at 8.5 – 7.5 ppm, and the enamine H-2 signal at 4.52 ppm (see Figure 4.4). The only signal which displayed different chemical shifts for the two tautomers was the methyl group, H-4; in (**349A**) the signal was at 1.90 ppm and for (**349B**) the signal shifted to 1.66 ppm. The ^{13}C-NMR spectrum showed doubling up of all the peaks for the tautomers. C-3 appeared at 159.9 ppm for the enamine, and 200.6 ppm for the imine. C-2 appeared at 83.1 ppm for the enamine, and at 49.5 ppm for the imine.



[349A] **[349B]**

Figure 4.4: Numbering of tautomers (**349A**) and (**349B**) of amine for assignment of spectroscopic data.

The identical procedure was carried out with *t*-butyl acetoacetate (**352**). (*Z*)-*t*-Butyl 3-aminobut-2-enoate (**353**) was isolated by vacuum distillation in 89% yield as a low-melting, white, crystalline solid (see Scheme 4.7).

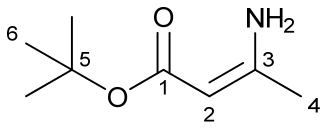


[352] **[353]** **[354]**

Scheme 4.7: Potential pathway for accessing racemic amine (**354**). *Reagents and conditions: i) $NH_4CH_3CO_2$, AcOH, reflux, 4 hr.; ii) $NaBH_4$, AcOH.*

WiSETD

With the increased molecular weight, the melting point of the *t*-butyl 3-aminobut-2-enoate (35 – 37°C) was slightly higher than that of the ethyl equivalent. The ^{1}H-NMR spectrum showed the NH_2 signal at 8.5 – 7.5 ppm as a broad singlet, and the H-2 singlet at 4.46 ppm (see Figure 4.5). None of the imine tautomer was observed for this product (**353**).



[353]

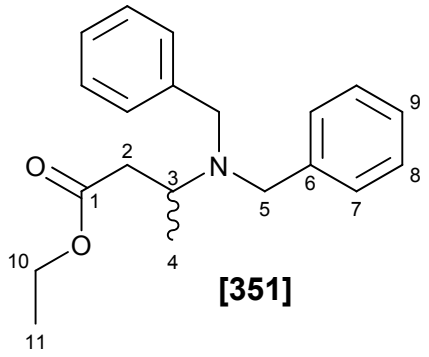
Figure 4.5: Numbering of amine (**353**) for assignment of spectroscopic data.

Both of the enamines were subjected to various reducing conditions[210] with sodium borohydride, sodium triacetoxyborohydride or platinum dioxide in the presence of hydrogen. After purification by column chromatography, none of the desired product was isolated under any of the conditions mentioned. Presumably, the failure to isolate the desired product was due to the high volatility and water solubility of the free amines (**291**) and (**354**) rather than the reaction conditions. No starting material was recovered from these reductions.

Owing to the limited success of these initial attempts at preparing the racemic amine, we decided to move on to model the enantioselective method (see Scheme 4.8).[158] Dibenzylamine was dissolved in tetrahydrofuran under inert conditions and the solution was cooled to −90°C in an acetone/liquid nitrogen slurry. *n*-Butyllithium was carefully added by syringe and the reaction mixture turned from clear to deep red. The mixture was allowed to stir for thirty minutes at −90ºC before a solution of ethyl crotonate in tetrahydrofuran was added from a dropping funnel over forty minutes. After a further two hours, the reaction was quenched and the crude product was extracted. Following purification by column chromatography, ethyl 3-(dibenzylamino)butanoate (**351**) was isolated in 74% yield as a clear and pungent oil (see Figure 4.6). The two benzyl groups were identified in the ^{1}H-NMR spectrum at 7.65 ppm, 7.60 ppm and 7.53 ppm for the aromatic signals and the benzylic protons (H-5*A* and H-5*B*) were

WitsETD

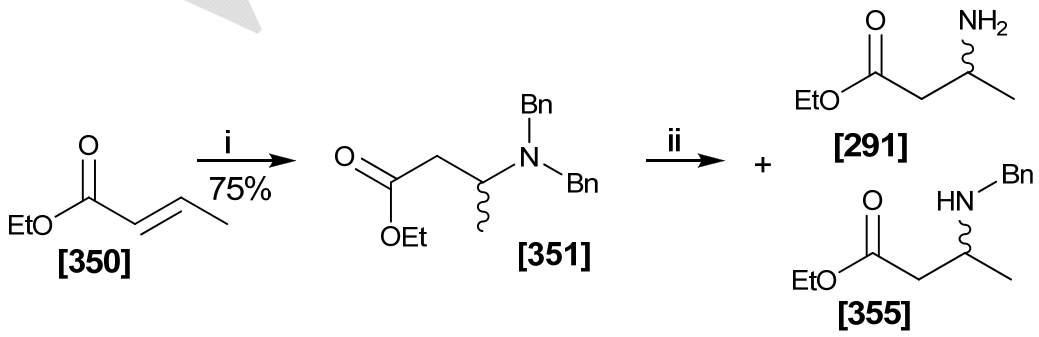
observed as diastereotopic signals at 3.97 ppm and 3.78 ppm, respectively. The alkene signals associated with ethyl crotonate were absent. H-3 occurred as a multiplet at 3.70 – 3.58 ppm, and H-2 was diastereotopic, occurring at 2.96 and 2.59 ppm as two double doublets with a geminal coupling constant of 13.9 Hz. ^{13}C-NMR spectroscopy showed a characteristic ester signal at 172.7 ppm, four signals in the aromatic region, an ethyl ester signal at 60.7 ppm, and signals for the carbons α to the nitrogen at 53.8 ppm (C-5) and 51.3 ppm (C-3).



[351]

Figure 4.6: Numbering of dibenzylamine (**351**) for assignment of spectroscopic data.

Ethyl 3-(dibenzylamino)butanoate (**351**) was subjected to standard debenzylation conditions (see Scheme 4.8).[158] It was dissolved in absolute ethanol together with a catalytic amount of hydrochloric acid and activated 10% palladium on carbon and placed in an hydrogenator under seven atmospheres of hydrogen pressure for seventy-two hours. After filtration through Celite® the partially debenzylated product, ethyl 3-(benzylamino)butanoate (**355**), was isolated in 71% yield.



[350] **[351]** **[291]** **[355]**

Scheme 4.8: Preparation of the racemic amine (**291**). *Reagents and conditions; i) a) dibenzylamine,* n*-BuLi, THF, -90°C, 30 min.; b) (**350**), 3 hr.; ii) Various conditions (see Table 4.1).*

The second debenzylation method we attempted was also in the hydrogenator, but this time acetic acid was used as the solvent.[211] After filtration through Celite®, the crude product was purified by column chromatography. Unfortunately, most of the desired product, ethyl 3-aminobutanoate (**291**), remained fixed to the silica gel and was isolated in a mere 24% yield.

Two other variations of the debenzylation were attempted. One used neat ethanol as a solvent, but neither of the products was isolated. The other used a hydrogen balloon and acidic ethanol for the reaction. The balloon pressure was approximately one atmosphere and in this instance both products were isolated in 15% yield (see Table 4.1).

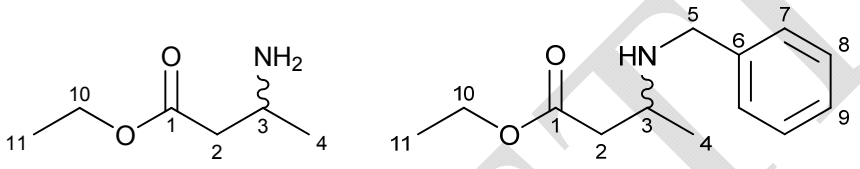
Pressure	Catalyst	Eq. (w/w)	Solvent	(355)	(291)
7.5 atm.	Pd-C 10%	0.48	AcOH	0%	24%
7.5 atm.	Pd-C 10%	0.48	EtOH	0%	0%
≈ 1 atm.	Pd-C 10%	0.48	EtOH/HCl (15:1)	15%	15%
7.5 atm.	Pd-C 10%	0.48	EtOH/HCl (15:1)	71%	0%

Table 4.1: Yields for debenzylations where the product was purified by column chromatography, resulting in reduced yields.

It became clear that using 10% palladium on carbon and acetic acid as the solvent was a viable method for preparing amine (**291**), provided that we did not isolate or purify the amine, but rather used it directly in the next reaction. After the reaction had gone to completion the palladium was removed by filtering the reaction mixture through Celite®, which was rinsed thoroughly with dichloromethane, and the dichloromethane was removed *in vacuo*. The residual acetic acid was not removed *in vacuo*, as the higher temperatures required would result in further loss of the volatile product. The crude mixture was not purified by column chromatography, as that also led to reduced yields. The crude mixture of acetic acid and amine were used immediately in the condensation reaction.

WitsETD

Both the free amine (**291**) and the monobenzylated amine (**355**) were characterized by ^{1}H-NMR spectroscopy (see Figure 4.7). The free amine showed the ethyl group as a quartet at 4.15 ppm and a triplet at 1.27 ppm. The NH_2 signal appeared at 1.71 ppm as a broad singlet. The H-3 signal appeared as a multiplet at 3.42 – 3.34 ppm, and the H-2 group was diastereotopic, showing two double doublets at 2.41 and 2.29 ppm, with a geminal coupling of 15.6 Hz. For the monobenzylated amine in addition to the same signals there were aromatic signals present at 7.40 – 7.21 ppm and a diastereotopic benzylic signal for H-5 at 3.84 and 3.76 ppm, both appearing as doublets with a geminal coupling of 13.0 Hz.



[291] **[355]**

Figure 4.7: Numbering of amine (**291**) and benzylamine (**355**) for assignment of spectroscopic data.

Now that the preparation of the racemic amine via our enantioselective model had proved viable and an inexpensive alternative remained elusive, we ceased to prepare the racemic amine. Instead we purchased it from Sigma-Aldrich as a 90% pure racemic mixture, which was both expensive and unstable, requiring storage at −18°C.

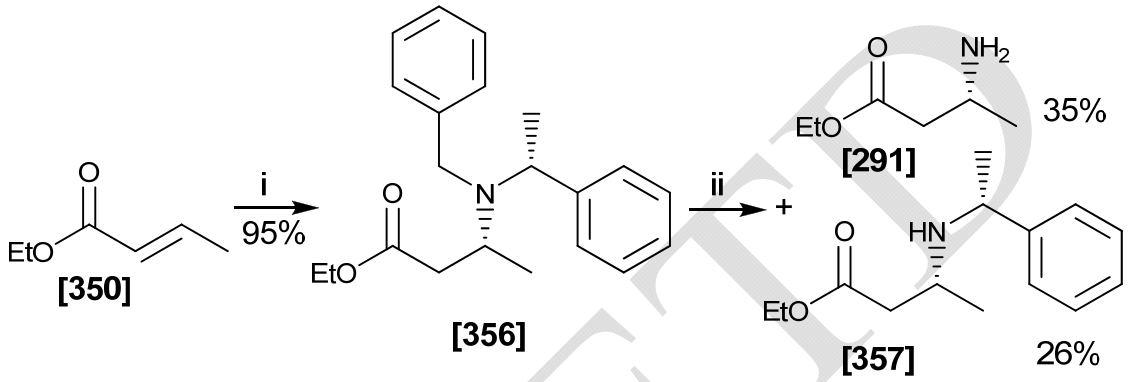
4.2.3 Davies' methodology: enantiopure amine[158]

The only difference between the synthesis of enantiopure ethyl (3*R*)-3-aminobutanoate (**356**) and our model racemic synthesis was a methyl group at the benzylic position of the dibenzylamine. The stereochemistry of this methyl group was principal in directing the formation of the new stereogenic centre (see Chapter 3, Section 3.3 for a full explanation of the stereocontrol).

The chiral amine, benzyl[(1*R*)-1-phenylethyl]amine (**214**), was dissolved in tetrahydrofuran and the solution was cooled to −90ºC (see Scheme 4.9). *n*-Butyllithium was added by syringe and the reaction turned from clear to deep

WITS ETD

red. The mixture was stirred for thirty minutes to allow complete formation of the lithium amide and a solution of ethyl crotonate (**350**) in tetrahydrofuran was then added from a dropping funnel over forty minutes. After an additional two hours the reaction was quenched with an ammonium chloride solution and the product was extracted into dichloromethane. After column chromatography, the product, ethyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}butanoate (**356**), was isolated in 95% yield as a clear oil.



Scheme 4.9: Preparation of the enantiopure amine (**291**). *Reagents and conditions; i) a) benzyl[(1*R*)-1-phenylethyl]amine,* n-*BuLi, THF, -90°C, 30 min.; b) (**350**), 2 hr.; ii) Pd/C, H_2 (7 atm), AcOH, RT, 72 hr.*

The dibenzylated product (**356**) was optically active, with an optical rotation of $[\alpha]_D^{20}$ +7.6 (*c* 1.06, CH_2Cl_2). ^{1}H-NMR spectroscopy showed the presence of two benzyl groups with aromatic signals between 7.42 ppm and 7.17 ppm integrating for ten hydrogen atoms. The benzylic CH_2 appeared as a diastereotopic signal at 3.71 ppm and at 3.69 ppm, both as doublets with geminal coupling of 14.7 Hz. The benzylic CH appeared as a quartet at 3.92 ppm coupling to the methyl group with a coupling constant of 7.0 Hz. H-3 appeared as a multiplet at 3.50 – 3.40 ppm, and H-2 displayed diasterotopic splitting to give signals at 2.36 ppm and 2.10 ppm. Importantly, no doubling up of signals was observed in the ^{13}C-NMR spectrum, indicating the presence of only one diastereomer. FTIR spectroscopy showed aromatic stretching vibrations at 3062 cm^{-1} and 3027 cm^{-1} and the ester carbonyl at 1732 cm^{-1}.

The next step was the removal of the benzyl groups to expose the amine functionality (see Scheme 4.9). This proved to be non-trivial. The first method

WitsETD

we attempted was a debenzylation in the hydrogenator using acetic acid as the solvent and 10% palladium on carbon as the catalyst.[211, 212] After purification by column chromatography the desired free amine (**291**) was isolated in 35% yield and the monobenzylated species, ethyl (3*R*)-3-{[(1*R*)-1-phenylethyl]amino} butanoate (**357**), was isolated in 26% yield.

We also attempted using the reputably better debenzylation catalyst, Pearlman's catalyst (palladium hydroxide on carbon), in absolute ethanol, but isolated a fluffy, white, polymeric compound and none of the desired amine (see Table 4.2).

Pressure	Catalyst	Eq. (w/w)	Solvent	(357)	(291)	polymer
7.5 atm.	Pd/C 10%	0.45	AcOH	26%	35%	0%
7.5 atm.	$Pd\text{-}(OH)_2/C$	0.20	EtOH	0%	0%	100%
7.5 atm.	$Pd\text{-}(OH)_2/C$	0.10	EtOH	0%	0%	100%

Table 4.2: Yields for debenzylations where the product was purified by column chromatography, resulting in reduced yields.

Owing to the difficulties in purifying the amine (**291**) we ceased attempting to isolate it. Using 10% palladium on carbon and acetic acid as the solvent was a reasonably viable method for preparing amine (**291**) and as the next reaction required acetic acid as well (see Section 4.3.1), we filtered the reaction mixture through Celite® to remove the palladium, rinsed thoroughly with dichloromethane, and removed the solvent *in vacuo*. The crude product, together with the residual acetic acid, was immediately used in the next reaction. The yields over the two steps were generally between 30 – 50% and the reaction results were fairly consistent for the first two and a half years of the project. It was only in the last year and a half, when the focus of the project turned to the enantioselective synthesis that the same reaction conditions failed to produce any of the fully debenzylated amine (**291**) and consistently yielded the monobenzylated amine (**357**). The sudden shift in results led us to the conclusion that the batch of palladium catalyst was of paramount importance. Although we continued to attempt the debenzylation with 5% and 10% palladium on carbon from at least four different suppliers (Aldrich, Fluka, Alfa

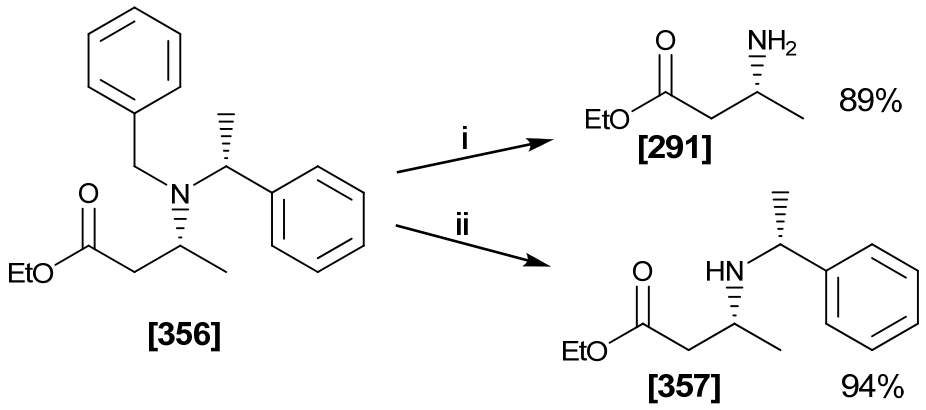
and PMC), varying the ratio (0.10 equivalents – 1.0 equivalents), the solvent (acetic acid, ethanol and methanol), the hydrogen pressure (1 atmosphere – 8 atmospheres), and the reaction length (12 hours – 120 hours) the reaction failed to produce the fully debenzylated amine (**291**), and we finally had to admit defeat. We did not attempt to vary the temperature of the reaction as the hydrogenator was not equiped for high temperatures.

Another debenzylation method we attempted on ethyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}butanoate (**356**) was with ammonium formate and palladium on carbon (0.37 eq.) in methanol. The reaction was left at ambient temperature for three and a half hours until no more starting material was observed by TLC. Following extraction and purification by column chromatography, the monobenzylated product (**357**) was isolated in 69% yield. None of the desired fully debenzylated product was obtained.

We also attempted to remove the second benzyl group from (**357**) by reacting it with Pearlman's catalyst, acetic acid and seven atmospheres of hydrogen pressure. The α-methylbenzyl group could not be removed, only starting material was recovered.

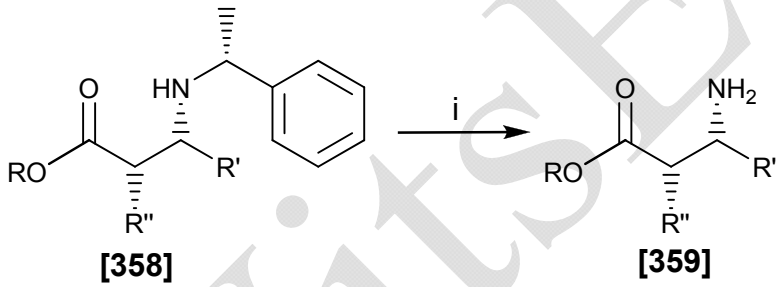
There are examples in the literature of the complete debenzylation of (**356**) to give (**291**) by Fenwick and Davies[211] and by Li *et al.*[212] Li *et al.* observed that in the presence of Pearlman's catalyst, ethanol and four atmospheres of hydrogen pressure for 48 hours, amine (**356**) underwent complete debenzylation to give (**291**) in 89% yield (see Scheme 4.10). They also claimed that in the presence of 10% palladium on carbon (0.125 w/w), ethanol, 5% hydrochloric acid, and one atmosphere of hydrogen pressure for an hour, amine (**356**) underwent monodebenzylation to give (**357**) in 94% yield.[212] This chemoselectivity in the presence of acid was the opposite to the chemoselectivity reported by Fenwick and Davies.[211]

WitsETD



Scheme 4.10: Debenzylation by Li *et al.*[212] *Reagents and conditions: i) H_2 (4 atm.), 20% $Pd(OH)_2$/C, EtOH, RT, 48 hr.; ii) H_2 (1 atm.), 10% Pd/C, EtOH/HCl, RT, 1 hr.*

Cimarelli and Palmieri[213] cleaved an α-methyl benzyl group from a β-amino ester (**358**) (see Scheme 4.11) using acidified methanol and Pearlman's catalyst (67 mg/mmol) to give the primary amine (**359**), displaying none of the chemoselectivity reported by Li *et al*.[212]



Scheme 4.11: Debenzylation by Cimarelli and Palmieri.[209] *Reagents and conditions: i) $Pd(OH)_2$/C (67 mg/mmol), MeOH-H_2O-AcOH (20:2:05), H_2 (3 atm.), RT, 12 hr.*

Fleck *et al*.[214] have also reported the synthesis of (**291**) from (**356**). They required 80% (w/w) Pearlman's catalyst in methanol under thirty psi of hydrogen pressure to remove both benzyl groups from (**356**). Interestingly, they were also the first group, using chiral lithium amides, to detect the by-product (**360**) in the aza-Michael addition (see Figure 4.8). The by-product (**360**) forms when excess of the lithium amide was present in the reaction mixture and it added to the ester as well as the α,β-unsaturated system.[214] We never detected the by-product (**360**) during the synthesis of (**356**).

WitsETD

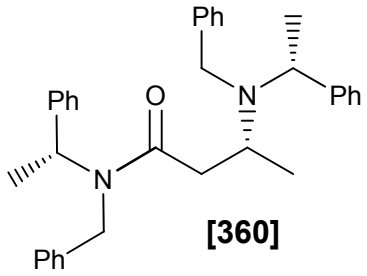
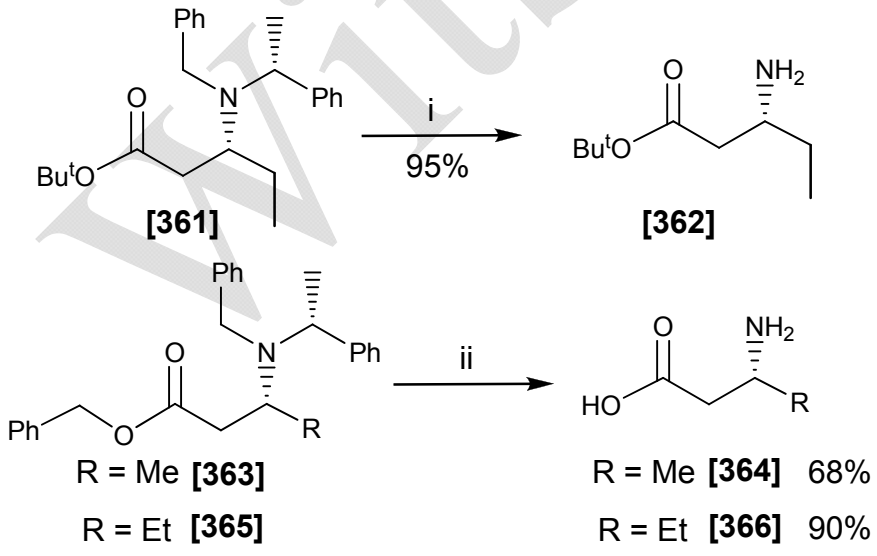


Figure 4.8: Reported by-product (**360)** of the aza-Michael addition reaction.[214]

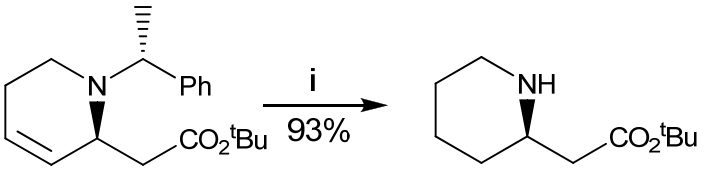
In another publication, Davies *et al.*[158] reported the debenzylation reaction for amines analogous to amine (**291**) (see Scheme 4.12). For an ethyl analogue (**361**) of amine (**356**) Davies *et al.*[158] reported complete debenzylation to give (**362**) in 95% yield in the presence of palladium on carbon, methanol and five atmospheres of hydrogen pressure. For the methyl analogue (**363**) they reported complete debenzylation in the presence of Pearlman's catalyst, ethanol and five atmospheres of hydrogen pressure. Interestingly, their yield for the methyl analogue (**364**) using Pearlman's catalyst was 68%, whereas their yield for the equivalent ethyl analogue (**366**) using palladium on carbon in acetic acid was 90%.[158] Clearly, the methyl group plays a role in reducing the reactivity of (**363**), and possibly does the same to (**356**).



Scheme 4.12: Debenzylations by Davies *et al.*[158] *Reagents and conditions: i) Pd/C, H_2 (5 atm.), MeOH; ii)* ***R=Me*** *a) $Pd(OH)_2$/C, H_2 (5 atm.), EtOH;* ***R=Et*** *b) Pd/C, H_2 (5 atm.), AcOH.*

WitsETD

In a recent publication by Davies *et al.*,[180] the preparation of cyclic β-amino acids required a large amount of Pearlman's catalyst (50% w/w) to remove α-methyl benzyl groups from various cyclic β-amino esters (e.g. **367**) to give the corresponding secondary amine (e.g. **368**) (see Scheme 4.13 for an example). This level of catalyst loading was significantly higher than in their previous publications.



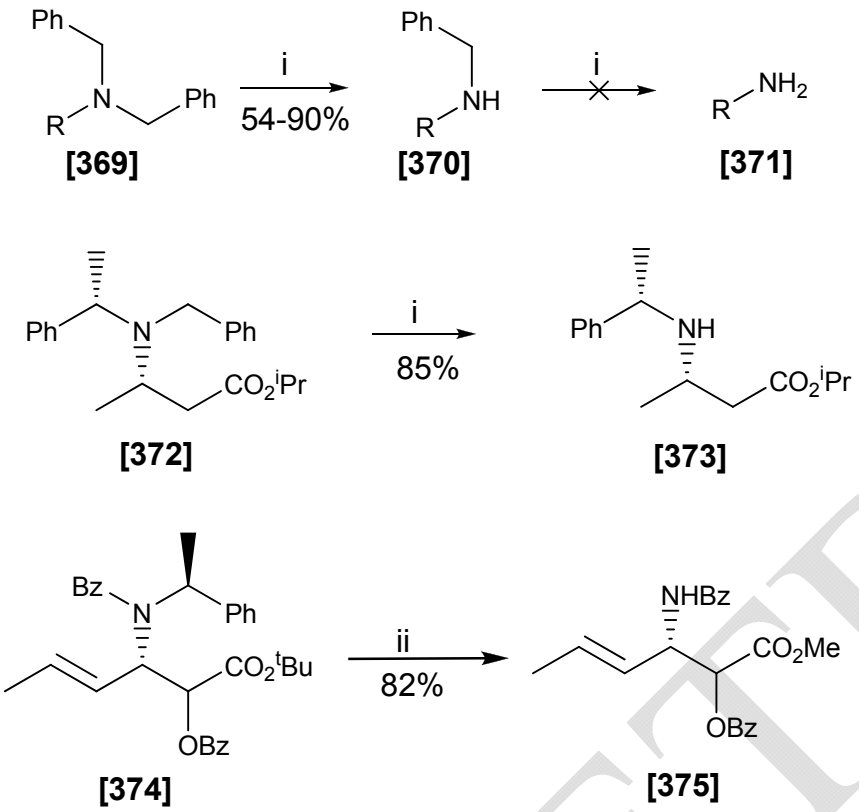
[367] **[368]**

Scheme 4.13: Recent debenzylation by Davies *et al.*[180, 181] *Reagents and conditions: i) H_2 (5 atm.), $Pd(OH)_2/C$ (50% w/w), EtOAc, RT, 12 hr.*

Another method for removing benzyl groups was with the reagent ceric ammonium nitrate (CAN). CAN was usually used for removing *para*-methoxybenzyl groups, but there was literature evidence of CAN cleaving unsubstituted benzyl groups from tertiary amines. Davies and co-workers[184] successfully used CAN in acetonitrile and water to monodebenzylate (**369**) to give (**370**) in 54 – 90% yield depending on the R-group, and to monodebenzylate (**372**) to give (**373**) (see Scheme 4.14).[182] CAN was unable to debenzylate the secondary amines (e.g. **370**) to give primary amines (**371**).

Formic acid displays the opposite chemoselectivity and has been used to selectively cleave α-methylbenzyl groups. For example (**374**) was selectively debenzylated to give (**375**) (see Scheme 4.14).[185] Our limited success with the formic acid debenzylation during the attempted synthesis of (−)-indolizidine 209D dissuaded us from attempting it on (**356**). Other methods in the literature include using dissolving metal conditions such as lithium and ammonia in ethanol to successfully removed α-substituted benzyl groups.[215 - 217]

WitsETD

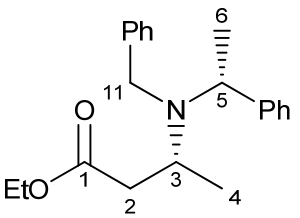


Scheme 4.14: Chemoselective debenzylation by Davies and co-workers.[184, 185] *Reagents and conditions: i) CAN (2.1 eq.), MeCN-H_2O (5:1), RT; ii) a) HCOOH, 50°C; b) $SOCl_2$, MeOH.*

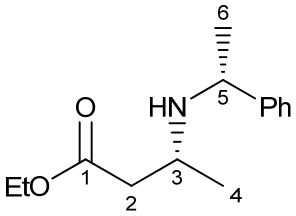
We confirmed what Davies and co-workers[184] reported and selectively cleaved an unsubstituted benzyl group from the tertiary amines (**351**) by reacting it for twelve hours with CAN. After work-up and purification, monobenzylated (**355**) was isolated in 81% yield.

The amine that we did successfully isolate was fully characterized and Table 4.3 compares the key ^{1}H-NMR and ^{13}C-NMR spectroscopic signals and the optical rotation values with those of (**356**) and (**357**).

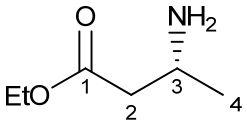
WitsETD



[356]



[357]



[291]

Signal	**(356) / ppm**	**(357) / ppm**	**(291) / ppm**
N-H	-	2.07 (s)	1.71 (s)
H-2	2.36 (dd, *J* 14.1)	2.60 (dd, *J* 15.4)	2.41 (dd, *J* 15.6)
	2.10 (dd, *J* 14.1)	2.43 (dd, *J* 15.4)	2.29 (dd, *J* 15.6)
H-3	3.50 – 3.40 (m)	3.10 (m)	3.38 (m)
H-4	1.14 (d, *J* 6.7)	1.12 (d, *J* 6.5)	1.13 (d, *J* 6.4)
H-5	4.03 – 3.95 (q, *J* 7.0)	4.03 (q, *J* 6.7)	-
H-6	1.35 (d, *J* 7.0)	1.44 (d, *J* 6.7)	-
H-11	3.71 (d, *J* 14.7)	-	-
	3.69 (d, *J* 14.7)		
C-1	172.8	177.0	172.4
C-2	40.2	40.7	44.3
C-3	50.5	48.7	44.1
C-4	14.5	21.3	23.6
C-5	60.5	56.2	-
C-6	18.3	24.3	-
C-11	50.0	-	-
$[\alpha]_D^{20}$	+7.6 (*c* 1.06, CH_2Cl_2)	+23.0 (*c* 1.65, CH_2Cl_2)	+37.0 (*c* 1.20, CH_2Cl_2)

Table 4.3: Comparison of selected NMR spectral data (in $CDCl_3$) for tertiary, secondary and primary amines (**356**), (**357**) and (**291**). (*J*-values were measured in Hz).

Interestingly, the chemical shifts and coupling constants for H-2, H-3, and H-4 were extremely similar in all three compounds; however, C-2, C-3, and C-4 have fairly different chemical shifts. The chemical shifts for C-2 and C-4 increased as the benzyl groups were removed and the chemical shift for C-3 decreased as the nitrogen lost the inductive effect of the benzyl groups. The optical rotation values for (**356**), (**357**) and (**291**) were compared with the

WitsETD

available literature values. For ethyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino} butanoate (**356**) we measured $[\alpha]_D^{20}$ +7.6 (*c* 1.06, CH_2Cl_2), which compared favourably with the literature value of $[\alpha]_D^{25}$ +4.9 (*c* 1.0, $CHCl_3$), and compared well with the values reported for analogous aminoesters, which range from $[\alpha]_D^{30}$ +7.3 to $[\alpha]_D^{20}$ +4.5 (refer to Table 3.1 in Chapter 3).[218] For ethyl (3*R*)-3-{[(1*R*)-1-phenylethyl]amino}butanoate (**357**) we measured $[\alpha]_D^{20}$ +23.0 (*c* 1.65, CH_2Cl_2) which was slightly lower than the reported value, $[\alpha]_D^{25}$ +31.1 (*c* 1.0, $CHCl_3$),[218] but compared favourably with the measured value for the analogous aminoester (**323**), $[\alpha]_D^{20}$ +20.4 (*c* 0.91, CH_2Cl_2). For ethyl (3*R*)-aminobutanoate (**291**) we measured $[\alpha]_D^{20}$ +37.0 (*c* 1.20, CH_2Cl_2), which did not compare well with either of values reported in the literature $[\alpha]_D^{20}$-7.5 (1.00, CH_3OH)[219] and $[\alpha]_D^{20}$-10.6 (1.00 CH_3OH),[220] nor did it compare well to the value we measured for analogous amine, *t*-butyl (3*R*)-3-aminononanoate (**275**), $[\alpha]_D^{20}$ -13.4 (*c* 0.98, CH_2Cl_2). Unfortunately, owing to the volatile nature of the amine, we were unable to repeat the optical rotation measurement.

Although there are some inconsistencies in the literature with regards to chemoselectivity, there are still many publications reporting successful debenzylation reactions using Davies methodology. Unfortunately, our system has ceased to work and a new approach will have to be examined in the future.

4.3 Preparation of *N*,5-disubstituted pyrrolidin-2-ones

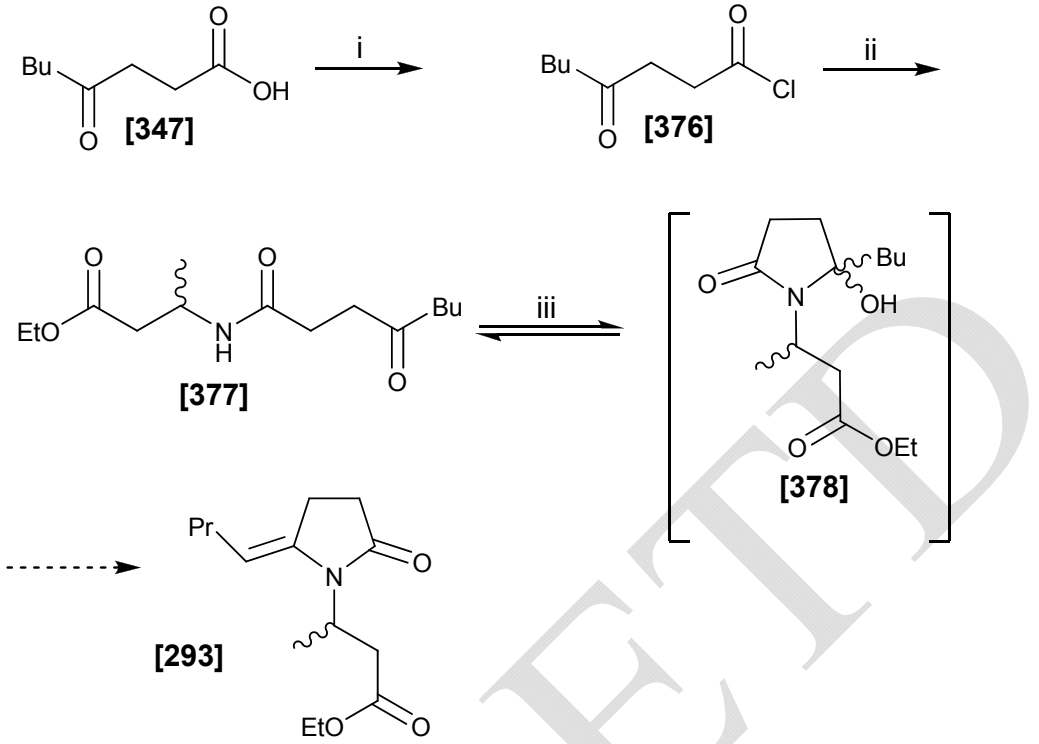
Now that the two precursors, ketoester (**292**) and amine (**291**), had been synthesized, the next objective was to condense them to give the key pyrrolidin-2-one (**293**). Relevant results will be described in this section.

4.3.1 Condensation reactions

The first condensation reaction we tried was the two step method to form (**377**) demonstrated by Penny Cheesman[128, 221] (see Scheme 4.15). Starting with 4-oxooctanoic acid (**347**), we converted it into the corresponding acid chloride by stirring with oxalyl chloride for two hours at ambient temperature. The acid chloride (**376**) was then reacted with racemic ethyl 3-aminobutanoate (**291**) and triethylamine in dichloromethane for fourteen hours. Following purification by

WISER

column chromatography, ethyl 3-[(4-oxooctanoyl)amino]butanoate (**377**) was isolated as a white solid in 51% yield over the two steps.



Scheme 4.15: Proposed synthesis of lactam (**293**) by Cheesman.[128] *Reagents and conditions: i) oxalyl chloride, RT, 2 hr.; ii) (**291**), Et_3N, CH_2Cl_2; iii) TFA.*

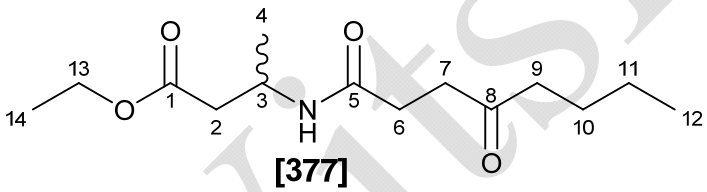
Before trying the ring closure, the ethyl 3-[(4-oxooctanoyl)amino]butanoate (**377**) was placed in an NMR tube with catalytic trifluoroacetic acid, in order to investigate whether the open chain form (**377**) was in equilibrium with the cyclised form (**378**). ^{1}H-NMR spectral data were collected at frequent intervals and after twenty-four hours tiny peaks started appearing in the spectra at 5.00 ppm, 2.05 ppm and 1.45 ppm, indicating the presence of the cyclised structure (**378**). These peaks had an intensity of approximately 5% of the open-chain form. After a week no further increase in the intensity of these ^{1}H-NMR spectral signals was observed.

In order to drive the equilibrium forward the ethyl 3-[(4-oxooctanoyl)amino]butanoate (**377**) was heated at reflux in toluene with five equivalents of acetic acid for seventy-two hours while the reaction was monitored by TLC. After three days the reaction was stopped; 100% conversion

WitsETD

had occurred and the cyclised, dehydrated product, ethyl 3-[(*2E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (**293**), was isolated in quantitative yield, exclusively as the *E*-isomer.

The first product, ethyl 3-[(4-oxooctanoyl)amino]butanoate (**377**) was fully characterized and the N-H signal appeared as a doublet at 6.18 ppm, coupling to adjacent H-3 (see Figure 4.9). H-3 appeared as a multiplet at 4.28 – 4.21 ppm, and H-2, H-6, H-7 and H-9 showed up as multiplets in the region 2.68 – 2.31 ppm. The ethyl and butyl chains were also evident. The ^{13}C-NMR spectrum had one ketone and two ester/amide carbonyls at 209.1 ppm, 170.6 ppm and 170.1 ppm, respectively, and four signals at 41.5 ppm, 41.1 ppm, 39.2 ppm and 36.6 ppm in the appropriate region for methylene carbons adjacent to carbonyl groups. The FTIR spectrum showed a broad band at 3306 cm^{-1} corresponding to the NH stretching vibration, and three carbonyl groups at 1731 cm^{-1}, 1707 cm^{-1} and 1640 cm^{-1} corresponding to the ester, ketone and amide, respectively. The ^{1}H-NMR and ^{13}C-NMR spectra were fully assigned with the aid of COSY and HSQC spectra.



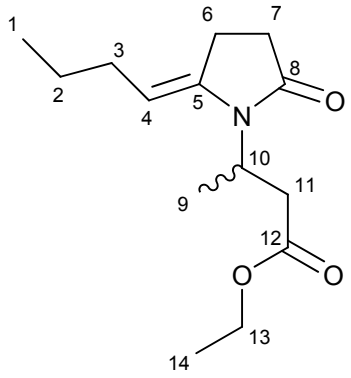
[377]

Figure 4.9: Numbering of amide (**377**) for assignment of spectroscopic data.

Ethyl 3-[(*2E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (**293**) was characterized by ^{1}H-NMR spectroscopy and showed distinct differences from the ring-open form (**377**). The key difference was the appearance of the alkene signal at 4.77 ppm, corresponding to H-4 (see Figure 4.10). The signal corresponding to H-10 was a multiplet at 4.45-4.37 ppm and the adjacent diastereotopic protons H-11 appeared as two double doublets at 3.04 ppm and 2.81 ppm. The ^{13}C-NMR spectrum showed only two carbonyl signals at 175.7 ppm and 171.4 ppm, indicating the absence of the ketone. An enamine was clearly present, with signals at 138.7 ppm and 101.0 ppm and C-6 and C-7 had shifted upfield to 29.2 ppm and 21.6 ppm. FTIR spectroscopy also showed the

WitsETD

presence of only two carbonyl groups; the ester and the amide at 1735 cm^{-1} and 1669 cm^{-1}, respectively. Finally, there was no longer an NH peak at 3000 cm^{-1}.



[293]

Figure 4.10: Numbering of lactam (**293**) for assignment of spectroscopic data.

In order to ascertain whether the alkene was exocyclic or endocyclic, both a COSY and a NOESY experiment were performed. These experiments showed short range and long range coupling between hydrogen atoms. C-H correlation experiments were also performed to assist with assignment (see Figure 4.11). Highlighted with coloured arrows are two examples: In blue, C-4 correlates to H-4, and in red, C-11 was diastereotopic and correlated to two signals, H-11*A* and H-11*B*.

WitsETD

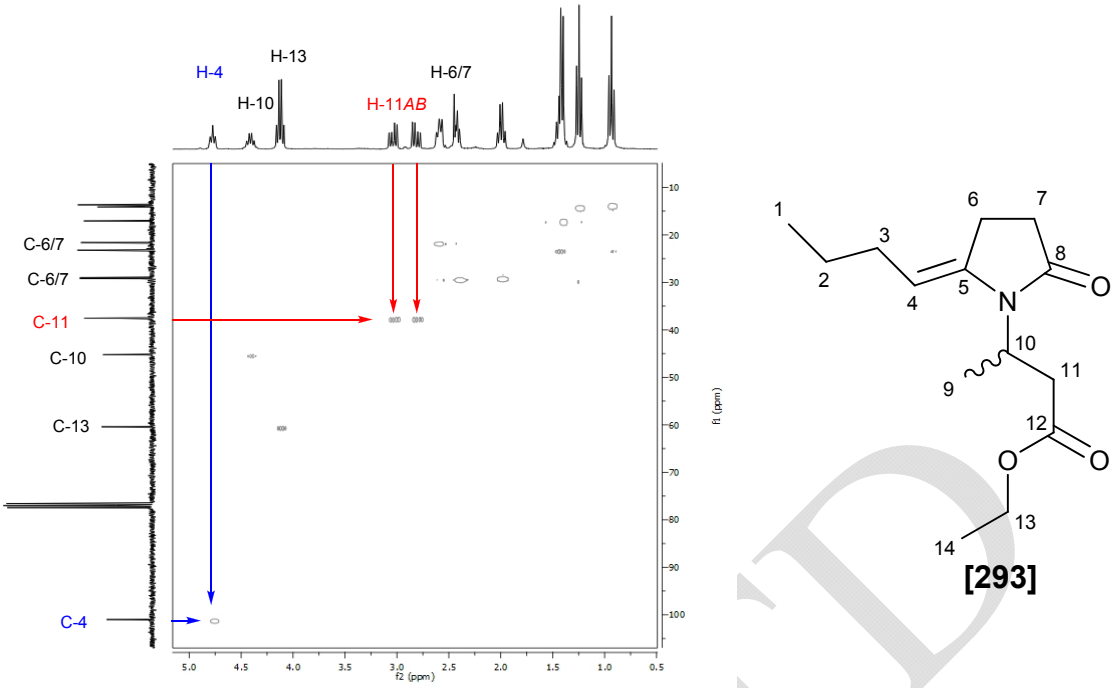


Figure 4.11: C-H correlation experiment (in $CDCl_3$) for lactam (**293**).

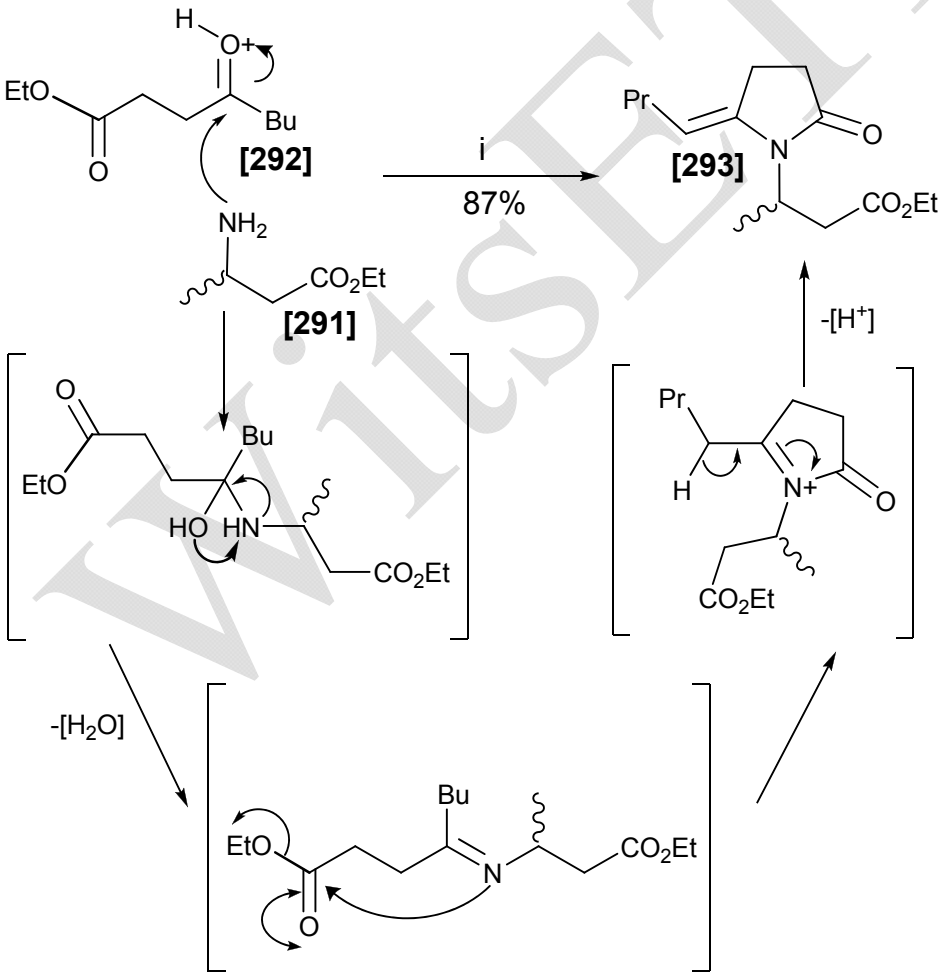
It was clear from the ^{13}C-NMR spectrum that the product was a single geometric isomer, as no doubling up of signals was observed. The next experiment we performed was a selective NOE irradiation, in order to establish whether the geometry of the double bond was *E* or *Z*. When irradiating H-4 at 4.77 ppm, H-9 and H-11 showed a positive response, while H-6 and H-7 showed no response. This indicated that the product was exclusively the *E* isomer, as H-4 was on the same side of the double bond as H-9 and H-11.

Although Penny Cheesman's proposed route to ethyl 3-[(*2E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (**293**) was successful,[128, 221] we wondered whether the product could not be accessed directly by heating ethyl 4-oxooctanoate (**292**) with ethyl 3-aminobutyrate (**291**) to reflux in toluene. Our initial attempt proved successful and after seventy-two hours of heating to reflux in toluene we isolated ethyl 3-[(*2E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (**293**) in 52% yield.[222] For this first attempt, the ethyl 3-aminobutyrate was the crude material from the debenzylation reaction. When the reaction was repeated with the commercially available ethyl 3-aminobutyrate the yield dropped to an

WISER'D

unsatisfactory 21%. This led us to the fortuitous discovery that the acetic acid contaminating the crude amine was catalyzing the reaction.

The reaction was attempted with catalytic *p*-toluenesulfonic acid which gave the product in 50% yield. After several investigations, both in the microwave reactor, and with various proportions of the reagents, it was found that five equivalents of acetic acid, two equivalents of the ester, and one equivalent of the amine heated at reflux for a minimum of seventy-two hours gave the optimum yield of 87%. The reaction was set-up in with a Dean-Stark apparatus, which assisted in removing water from the reaction flask and helped to drive the reaction forward. Our suggested mechanism for the acid-catalysed reaction is shown in Scheme 4.16.



Scheme 4.16: Suggested mechanism for the formation of (**293**). *Reagents and conditions: i) AcOH, toluene, reflux, 72 hr.*

WitsETD

When the reaction was repeated using the enantiopure amine, ethyl (3*R*)-aminobutanoate (**291**), the optically active product, ethyl (3*R*)-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (**293**)**,** was isolated in 46% yield with an optical rotation of $[\alpha]_D^{20}$ -10.0 (*c* 1.20, CH_2Cl_2). All other characterization was identical to the racemate.

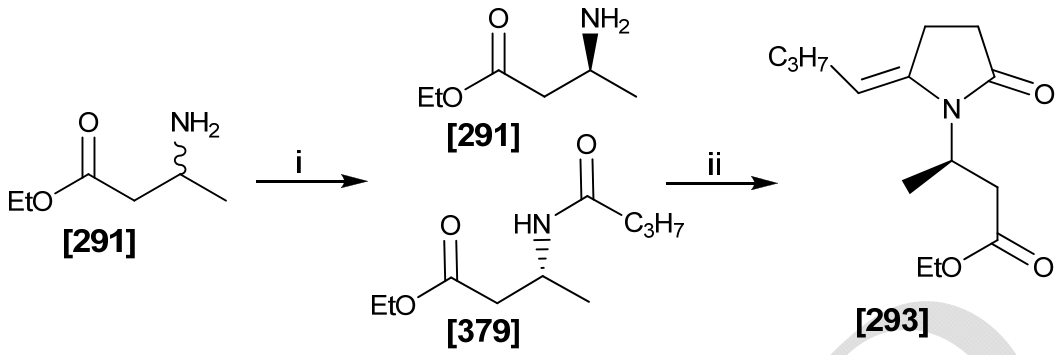
In our system, the presence of exclusively the *E*-isomer opened up possibilities for the stereoselective reduction of the alkene using a chiral reducing agent. In many instances it is the mixture of geometric isomers that prevents the use of chiral reducing agents, as they are only selective if exclusively one geometric isomer is present. We did not pursue this option as chiral reducing agents were prohibitively expensive and we wanted to complete the synthesis of both diastereomers as both intermediates should lead to natural products.

4.3.2 Attempted enzymatic resolution

At this stage, the opportunity to explore enzymatic resolution emerged. The principle behind enzymatic resolution is that the enzyme selectively catalyzes the reaction with one enantiomer only, leaving the other enantiomer untouched. There was literature precedent[223 - 225] that *CAL B* (*Candida antarctica lipase B*) selectively catalyses the acylation of ethyl (3*R*)-aminobutyrate and not the reaction with ethyl (3*S*)-aminobutyrate. This would allow us to access the (+)-isomer of monomorine I and its diastereomers, the opposite of our current route. This also offers a cost effective way to resolve a racemate into its individual isomers. Working with enzymes requires special attention to the reaction conditions, as high temperatures can denature the enzyme and the effective pH range was limited.[223] Only certain solvents are compatible with the enzymatic reaction and often the reaction mixture was heterogeneous.[223]

The biochemistry department of the CSIR (Council for Scientific and Industrial Research) offered us their expertise and the use of their laboratories and enzymes in order to attempt this reaction. The reaction itself was straight forward (see Scheme 4.17), *CAL B* and ethyl 3-aminobutyrate (**291**) were mixed in ethyl butanoate for twenty-five hours at ambient temperature. The enzyme was removed by filtration through a sintered glass funnel and the

residue was rinsed with ethyl acetate. Here we deviated from the literature procedure.[224]



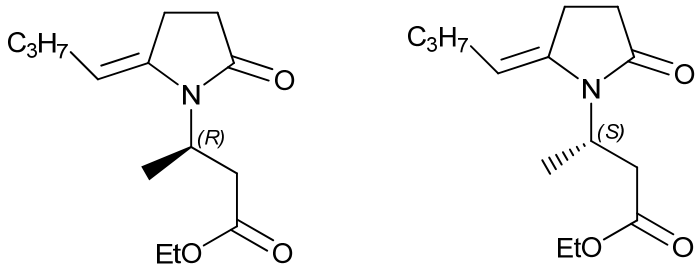
Scheme 4.17: Enzymatic resolution of racemic (**291**). *Reagents and conditions: i)* CAL B*, ethyl butanoate, RT, 25 hr. ii) (**292**), AcOH, toluene, reflux, 72 hr.*

In order to avoid difficulties with the volatility of the amine and the complications associated with column chromatography, Gedey *et al.*[224] reacted the crude mixture with acetic anhydride, thus converting any remaining amine (**291**) into the corresponding amide which was easier to purify. The reaction *ee*'s were calculated using the amide (**379**). Our synthesis was not compatible with this method of isolation, as the free amine was necessary for subsequent reactions (see Scheme 4.17).

Instead, we chose to react the crude mixture of ethyl butanoate, ethyl (3*S*)-aminobutyrate (**291**) and ethyl (3*R*)-butyramidobutanoate (**379**) together with ethyl 4-oxooctanoate (**292**) in the condensation reaction (see Scheme 4.17) and hence isolate the stable product (**293**). The various products were separated by column chromatography and (**293**) was isolated in 33% yield over the two steps. The optical rotation of (**293**) was measured as $[\alpha]_D^{20}$ +1.0 (*c* 1.00, CH_2Cl_2). This was a rather disappointing value, because although the positive sign indicates an excess of the *S*-enantiomer, the magnitude was a mere 10% of the magnitude of the *R*-enantiomer which gives the reaction an enantiomeric excess of only 10% (see Figure 4.12).[b] HPLC on a chiral column was ideally required to calculate *ee*'s accurately, but optimizing the HPLC conditions did not seem warranted in view of the low optical activity. This poor result was attributed to the incomplete resolution of the racemate, owing to short reaction

[b] *Enantiomeric excess was calculated based on the formula:* ee = $([\alpha]_{obs}/[\alpha]_{max})$ x 100

times or inactive enzymes. Owing to lack of experience with this type of reaction, and as the *S*-enantiomer of the chiral amine, benzyl[(1*S*)-1-phenylethyl]amine, was also commercially available we chose not to optimize the enzymatic resolution.



***R*-[293]** ***S*-[293]**

Figure 4.12: The configuration for both enantiomers of lactam (**293**).

4.3.3 Diastereoselective reduction and optimization

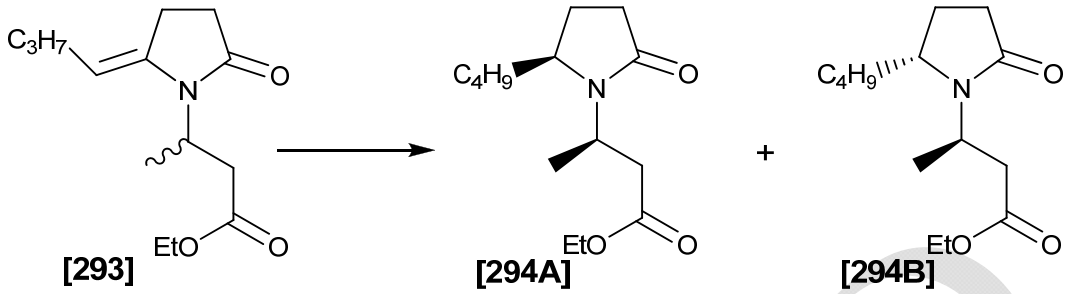
The next step in the synthesis was the first real opportunity for diastereoselectivity. The reduction of the exocyclic double bond introduces the second stereogenic centre into the molecule; and theoretically, the first stereogenic centre should offer a platform for stereoselectivity, even with achiral reagents.

For the first reduction we attempted, ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (**293**) was reacted with catalytic palladium on carbon in absolute ethanol under seven atmospheres of hydrogen pressure.[226] After purification, ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (**294**) was isolated as an inseparable mixture of diastereomers in a ratio of 2:3 in quantitative yield (see Scheme 4.18). The minor isomer, (the '*cis*' isomer), has been designated isomer A (**294A**) and the major isomer, (the '*trans*' isomer), has been designated isomer B (**294B**).[c] The isomer ratio was determined by the relative

[c] *The terms 'cis' and 'trans' refer to the relative stereochemistry of the methyl and the butyl chains in the bicyclic products (**298**), (**299**) and the target compounds (**26 – 29**). Although, technically they are meaningless in the monocyclic products (**294**), (**295**), (**296**) and (**297**), they have been used in this thesis to distinguish the two diastereomeric pathways.*

WitsETD

integration in the ^{1}H-NMR spectrum of the hydrogen atoms at the two stereogenic centres, H-5 and H-10 (see Figure 4.13). The identification of the two isomers will be described later.



Scheme 4.18: Diastereoselective reduction of (**293**). *Reagents and conditions: i) Various conditions (see Table 4.4).*

The limited stereoselectivity with the palladium catalyzed reduction was owing to the free rotation around the N-C bond, which prevents the methyl group from blocking either face of the lactam ring.

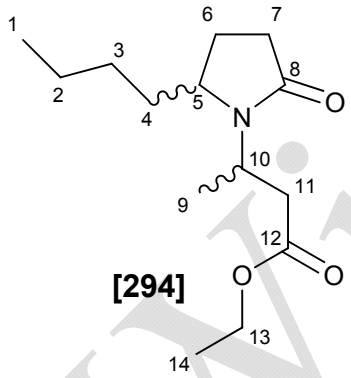


Figure 4.13: Numbering of lactam (**294**) for assignment of spectroscopic data.

Initially, prompted by the expense of the palladium, we decided to try a reduction with triethylsilane and titanium tetrachloride in dichloromethane.[215] The general protocol for the reaction was as follows: Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (**293**) was dissolved in freshly distilled dichloromethane and cooled to −90ºC. Titanium tetrachloride was added and the reaction mixture was stirred for five minutes. Triethylsilane was then added by syringe and the reaction was allowed to warm to ambient temperature and react for forty-eight hours. The reaction was quenched with a saturated

WitsETD

ammonium chloride solution and the product was extracted into dichloromethane. Purification by column chromatography gave ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (**294**) as an inseparable mixture of diastereomers in 84% yield. Surprisingly, the ratio of isomers was 1:4, again favouring isomer B (**294B**). This increase in stereocontrol indicated that the reagents used were having an effect on the stereoelectronics or the steric hindrance experienced by the hydrogen source.

Our first hypothesis for the observed stereocontrol was that the oxophilic titanium tetrachloride must be coordinating to the lactam carbonyl and the ester carbonyl and limiting the free rotation of the N-C bond. By coordinating to the ester and the lactam, the free rotation of the side chain was blocked and the stereocontrol increased. In order to examine this hypothesis a series of different protic and Lewis acids was employed to catalyze the reaction under identical conditions. Trifluoroacetic acid, aluminium trichloride, boron trifluoride etherate, tin tetrachloride and zirconium tetrachloride were all tested. All of them showed lower selectivity than the titanium tetrachloride (see Table 4.4), but all of them favoured isomer B (**294B**).

Catalyst	**H-Source**	**Ratio (A:B)**	**Yield**
Pd-C 10% [a]	H_2	2:3	100%
TFA [b]	Et_3SiH	2:3	94%
$AlCl_3$ [b]	Et_3SiH	3:4	100%
$BF_3.Et_2O$ [b]	Et_3SiH	4:5	90%
$SnCl_4$ [b]	Et_3SiH	2:3	80%
$TiCl_4$ [b]	Et_3SiH	1:4	84%
$ZrCl_4$ [b]	Et_3SiH	3:4	79%
$TiCl_4$ [c]	Ph_3SiH	1:5	85%
$Ti(OPr^i)_4$ [b]	Et_3SiH	-	0%
$La(F_3CSO_3)_3$ [b]	Et_3SiH	-	0%

Table 4.4: Attempted diastereoselective reductions of (**293**). *a) 50% (w/w) Pd-C 10%, H_2 (7 atm.), EtOH, RT, 72 hr.; b) Lewis acid, Et_3SiH, CH_2Cl_2, -90°C, 2 hr., increased to RT, 72 hr.; c) Lewis acid, Ph_3SiH, CH_2Cl_2, -90°C, 2 hr. increased to RT, 72 hr.*

WitsETD

Our second hypothesis was that the titanium tetrachloride was more effective than the other Lewis acids as it has a higher affinity for oxygen. Lanthanum has a higher affinity for oxygen than titanium, so we attempted the reaction using lanthanum trifluoromethanesulfonate. Interestingly, none of the desired product was isolated, but 85% yield of the open chain amide, ethyl 3-[(4-oxooctanoyl)amino]butanoate (**377**) was isolated.

Still presuming stereocontrol based on steric hindrance, we attempted two further reactions, one using titanium isopropoxide as a bulky Lewis acid, and the other using triphenylsilane as a bulky hydrogen source in place of triethylsilane. The titanium isopropoxide failed to catalyze the reaction and starting material was recovered. The triphenylsilane, however, improved the stereoselectivity to a ratio of 1:5.

Pleased with the level of stereocontrol we had achieved in the absence of expensive chiral reagents, we ceased exploring physical reactions and turned our attention to explaining the observed results. The increased stereoselectivity observed with the bulky hydrogen source indicates steric hindrance as a major contributor. However, later in the synthesis (see Section 4.4.5) we were able to separate and characterize more advanced intermediates, convert them back into the lactams (**294A**) and (**294B**), and thus retrospectively assign the relative configuration of these lactams. The favoured diastereomer (**294B**) was confirmed as the *trans* isomer (*R,R* or *S,S*). This means that the hydrogen was added from the same face that the methyl group was “blocking”.

A search of the Cambridge Structural Database (CSD Version 5.30, May 2009)[227] for all compounds containing titanium coordinated to two carbonyl oxygen atoms, and at least two chlorine atoms resulted in forty hits, with the coordination geometry around the titanium atom being octahedral in all cases. It seemed reasonable to assume a similar coordination with our molecule. Several attempts were made to model a potential transition state using Hyperchem[228] that could explain the observed stereocontrol. Upon closer examination of a local energy minimum conformation it became apparent that with the titanium coordinating to both the ester and the amide it forms an eight-

WitsETD

membered ring. This eight-membered ring puckers, pushing the methyl group out of the plane. The molecular dynamic / simulated annealing experiments were only performed on the *R*-enantiomer, as the *S*-enantiomer would mirror the result and hence favour the same selectivity.

After repeating the molecular dynamic / simulated annealing ten times, two energy conformers were identified for the *R*-enantiomer (**293**). The first conformer was slightly lower in energy than the second conformer (2.4 kcal/mol) and of the ten simulated annealing experiments, eight of them produced the first conformer and two of them produced the second conformer. In the first conformer, the methyl group was forced down, opening up the top face for attack by the hydrogen (see Figure 4.14). When the hydrogen added the butyl group was pushed down and the new stereogenic centre formed with an *R* configuration.

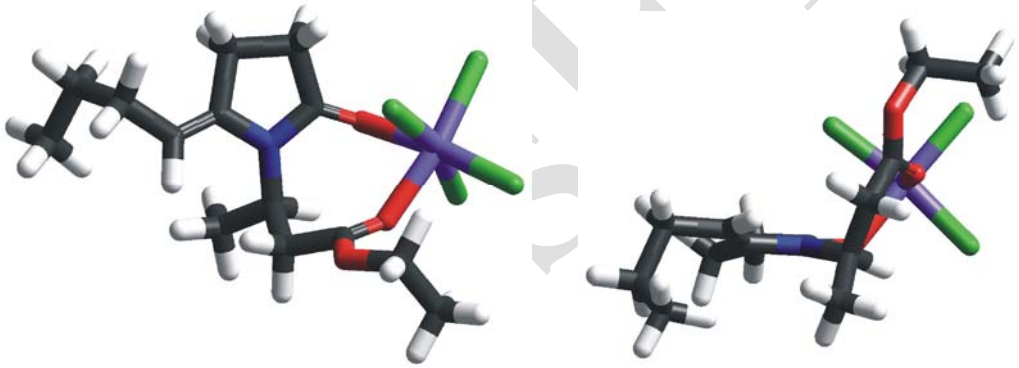


Figure 4.14: Two views of *R*-enantiomer (**293**) first low energy conformer coordinated to titanium tetrachloride, methyl group pointing down: addition from top face.

In the second case, the low energy conformer produced by Hyperchem[228] failed to provide us with a satisfactory steric-hindrance model. In the second low energy conformer for the *R*-enantiomer (**293**), the methyl group was forced up, pointing away from the alkene entirely (see Figure 4.15). In the conformer shown below neither face is particularly hindered and therefore the hydrogen could add from the top or the bottom to form either diastereomer. As yet the stereoelectronic effect of the coordinated Lewis acid has not been examined.

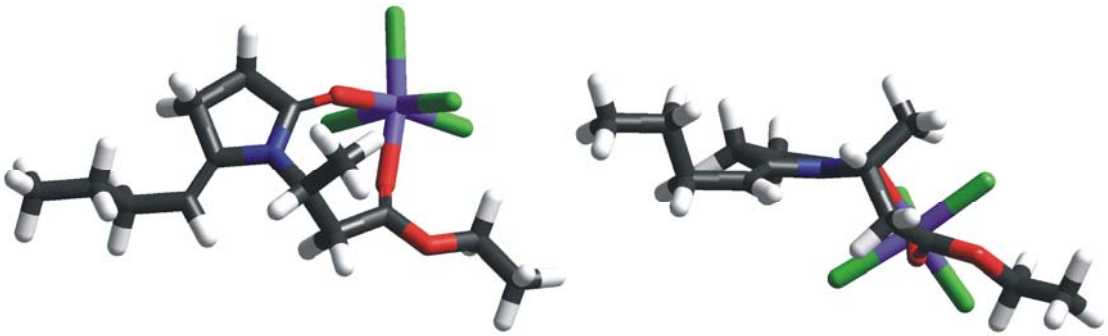


Figure 4.15: Two views of *R*-enantiomer (**293**) second low energy conformer coordinated to titanium tetrachloride, methyl group pointing up: addition from either face.

Initially, the diasteromers were fully characterized as a mixture, however, later in the synthesis (see Section 4.4.5) we were able to separate and characterize more advanced intermediates, convert them back into the lactams (**294A**) and (**294B**), and thus a pure sample of each isomer was obtained and fully characterized. The reduction of the alkene was indicated by the absence of the ^{1}H-NMR spectroscopic signal at 5.00 ppm. H-10 and H-5 were shifted downfield due to the nitrogen, and appeared as multiplets (refer to Figure 4.13). For the *cis* isomer they appeared at 3.97 – 3.94 ppm and 3.68 – 3.63 ppm, respectively, and for the *trans* isomer they appeared at 4.20 – 4.10 ppm and 3.61 – 3.55 ppm, respectively. H-11, H-6 and H-7 all displayed diastereotopic splitting for the *cis* isomer, however, for the *trans* isomer H-11 appeared as a doublet, while H-6 and H-7 exhibited diastereotopic splitting. The ^{13}C-NMR spectrum had no alkene signals, but did have an additional signal present at 60.0 ppm for the *cis* isomer and 58.1 ppm for the *trans* isomer, corresponding to C-5. C-10 appeared at 46.8 ppm and 46.1 ppm for the *cis* and *trans* isomers respectively. FTIR spectroscopy showed two carbonyl signals, one at 1731 cm^{-1} and one at 1679 cm^{-1}, corresponding to the ester and amide, respectively.

COSY (see Figure 4.16) and HSQC experiments were conducted to allow definitive assignment of all the signals. Figure 4.14 shows two short range interactions for (**294A**): The first interaction is shown in blue, H-13 couples to H-14, the second interaction is shown in red, H-10 couples to H-9, and the diastereotopic H-11*B* and H-11*A*.

WISER

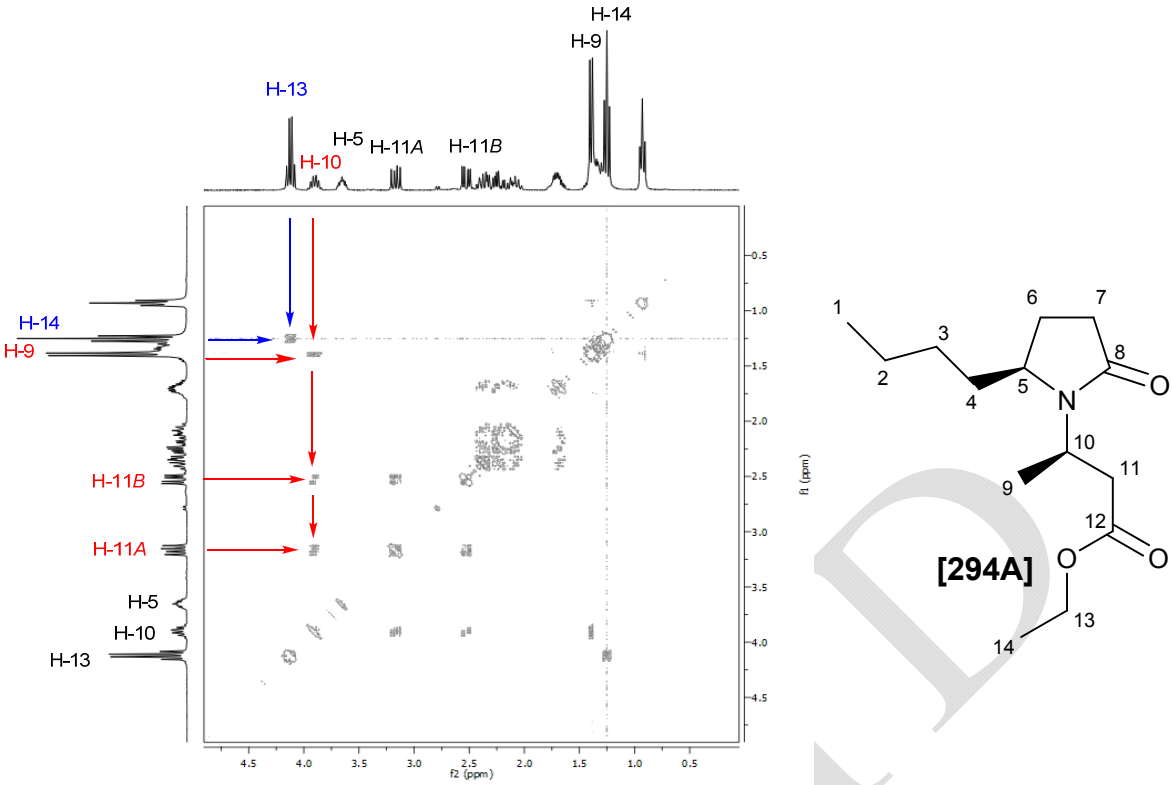


Figure 4.16: COSY experiment (in $CDCl_3$) for lactam (**294A**).

We were able to repeat the reduction with the enantiopure ethyl (3*R*)-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (**293**) and chose to use the palladium catalysed reduction, as it provided quantitative yield and both of the diastereomers, and hence could be used for the total synthesis of both monomorine I and its diastereomer. No optical rotation was recorded for the product as it was an inseparable mixture of diastereomers. All other characterization was identical to the racemate.

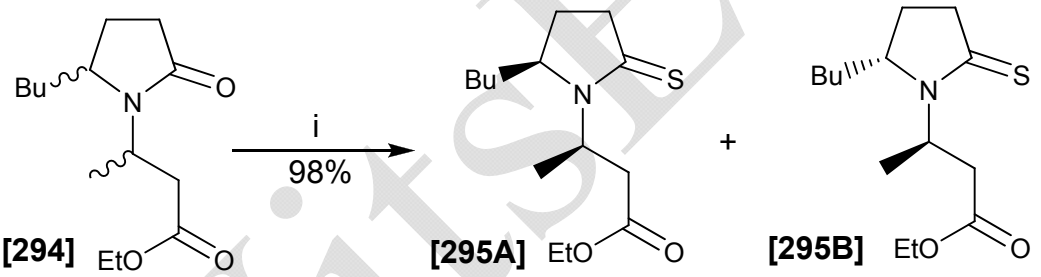
4.4 Preparation and cyclisation of the vinylogous sulfonamide

Now that we had successfully prepared the lactam (**294**), our synthetic strategy converged with the pathway used in the attempted synthesis of (−)-indolizidine 209D. The next task was to prepare the vinylogous sulfonamide and form the bicyclic structure of the indolizidine.

WisE

4.4.1 Thionation reaction and separation of diastereomers

The thionation reaction followed standard literature conditions[229] using Lawesson's reagent. Although commercial Lawesson's reagent was more expensive than the phosphorus pentasulfide, it could conveniently be prepared from phosphorus pentasulfide and anisole. This reaction, while odoriferous, was relatively easy to execute and an ample supply of Lawesson's reagent was available. A diastereomeric mixture of ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (**294**) and Lawesson's reagent were stirred in dry dichloromethane at ambient temperature under a nitrogen atmosphere for ninety-six hours (see Scheme 4.19). The solvent was removed *in vacuo* and the organic residue was purified by column chromatography to give ethyl 3-(2-butyl-5-thioxo-1-pyrrolidinyl)butanoate (**295**) in 98% yield as a mixture of diastereomers with an identical ratio to the starting material (i.e. 2:3 favouring (**295B**) using the diastereomeric mixture obtained from the palladium reduction).

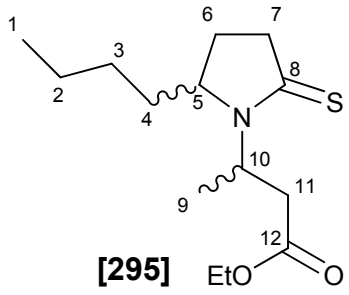


Scheme 4.19: Thionation of lactam (**294**) to form separable thiolactam diastereomers. *Reagent and conditions: i) Lawesson's reagent, CH_2Cl_2, RT, 72 hr.*

The R_f values on silica gel TLC plates for isomer A and isomer B showed a maximum difference in a 10% ethyl acetate-hexane solution: Isomer A ran with an R_f of 0.25 and isomer B ran with an R_f of 0.22. While at least 80% of the collected fractions contained both isomers, repeated and exhaustive column chromatography allowed partial separation of the diastereomers. Sufficient racemic material was available to separate enough material to continue the synthesis separately with each racemic diastereomer. Without more precious enantiomerically pure intermediate (**295**), there was, unfortunately, insufficient material to allow for exhaustive chromatography, and the enantiopure diastereomers were used as a mixture for all subsequent steps.

WitsETD

The racemic isomers were characterized separately. The most significant spectroscopic changes from the lactam (**294**) to the thiolactam (**295**) were the chemical shifts of H-5 and H-10, and the C-8 shift from the carbonyl region at 174 ppm to the thiocarbonyl region of 200 ppm (see Figure 4.17). The individual isomers differed significantly in the chemical shift of H-5 and H-10. For the *cis* isomer H-5 appeared as a multiplet at 4.11-4.02 ppm and H-10 at 4.80 – 4.72 ppm, while the *trans* isomer H-5 possessed a broader multiplet 4.11 – 3.95 ppm and H-10 was further downfield at 5.30 – 5.10 ppm.

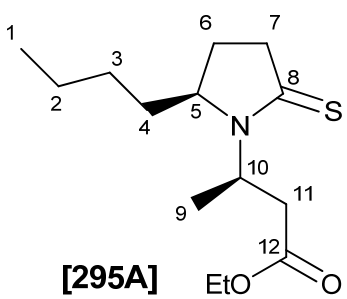


[295]

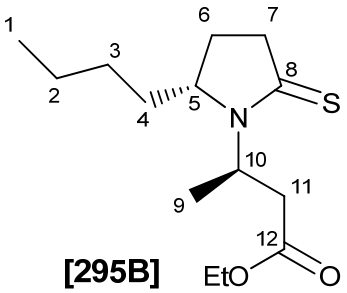
Figure 4.17: Numbering of thiolactam (**295**) for assignment of spectroscopic data.

Table 4.5 shows a list of the significant ^{1}H-NMR and ^{13}C-NMR spectroscopic signals in each isomer and the corresponding signals in (**278**), the thiolactam isolated during the attempted synthesis of (−)-indolizidine 209D. With the exception of H-5, the observed signals for (**278**) were almost identical to those observed for (**295A**) and (**295B**).

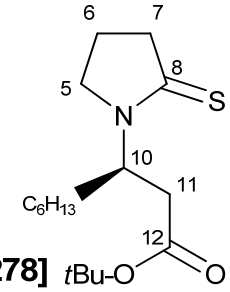
WitsETD



[295A]



[295B]



[278]

Signal	(295A) / ppm	(295B) / ppm	(278) / ppm
H-4	1.90 – 1.60 (m)	1.85 – 1.68 (m)	-
H-5	4.11 – 4.02 (m)	4.11 – 3.95 (m)	3.71 (dt, *J* 10.7, 7.5)
			3.56 (dt, *J* 10.7, 7.5)
H-6	2.25 – 2.04 (m)	2.20 – 2.04 (m)	2.03 (quintet, *J* 7.5)
	1.90 – 1.60 (m)	1.58 – 1.46 (m)	
H-7	3.10 – 2.85 (m)	*3*.10 – 2.85 (m)	3.00 (t, *J* 7.5)
H-9	1.52 (d, *J* 7.1)	1.41 (d, *J* 7.0)	1.64 – 1.55 (m)
H-10	4.80 – 4.72 (m)	5.30 – 5.10 (m)	5.36 (quintet, *J* 7.5)
H-11	3.53 (dd, *J* 6.3, 16.2)	2.79 (dq, *J* 7.5, 15.5)	2.55 (dd, *J* 14.4, 6.0)
	2.48 (dd, *J* 8.0, 16.2)		2.43 (dd, *J* 14.4, 9.0)
C-4	33.7	34.2	-
C-5	67.7	65.5	49.0
C-6	26.1	26.4	20.0
C-7	45.1	44.4	45.1
C-8	200.9	201.9	201.7
C-9	17.5	18.9	32.2
C-10	51.3	51.0	53.3
C-11	38.3	38.8	38.8
C-12	171.6	170.9	169.5

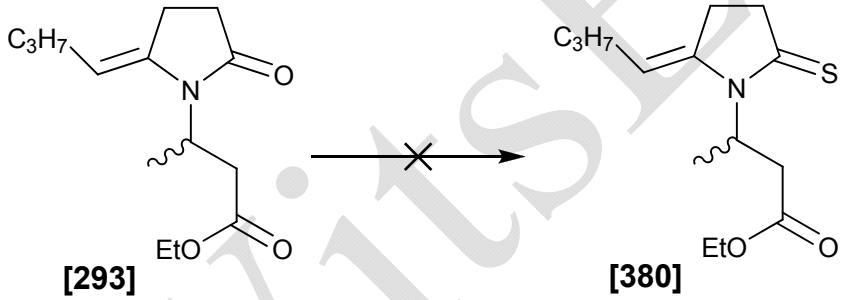
Table 4.5: Comparison of selected NMR spectral data (in $CDCl_3$) for thiolactam (**295A**), (**295B**), (**278**). (*J*-values were measured in Hz).

For the three ^{13}C-NMR spectra, the signals for C-7, C-8, C-10, C-11, and C-12 were virtually identical, while those for C-5, C-6, and C-9 differed significantly. The chemical shifts for C-5 were 67.7 ppm, 65.5 ppm and 49.0 ppm, for (**295A**), (**295B**) and (**278**), respectively. This highlights the deshielding effect of the butyl chain on C-5, and although these compounds were very similar, it clearly

WitsETD

indicated a difference in electronic structure between these three compounds which could have resulted in different degrees of reactivity in subsequent reactions. The same effect was seen for C-6, which has chemical shifts of 26.1 ppm, 26.4 ppm and 20.0 ppm for (**295A**), (**295B**) and (**278**), respectively. Interestingly, the effects of the methyl group versus the hexyl chain on the chemical shift of C-10 were almost identical. C-10 occurs at 51.3 ppm, 51.0 ppm and 53.3 ppm for (**295A**), (**295B**) and (**278**), respectively, with only a slight increase in the deshielding effect for the hexyl chain.

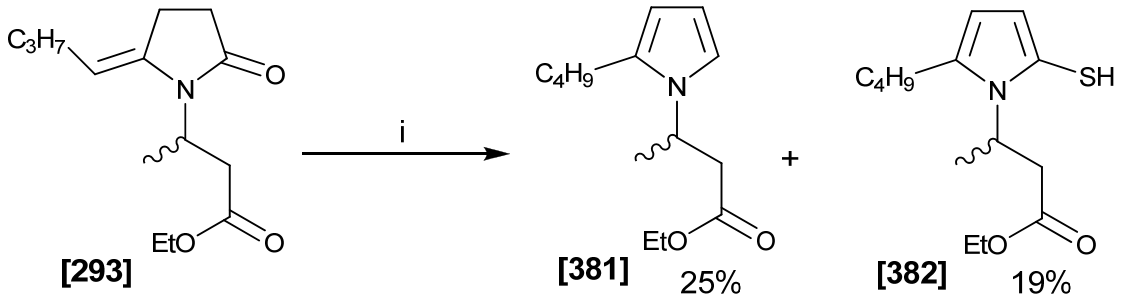
In the literature the examples of lactam thionations were in the absence of an exocyclic alkene. Although our lactam (**293**) contained an exocyclic alkene, we wondered whether our reaction sequence was flexible and decided to attempt the thionation reaction on (**293**) directly, as (**380**) would offer different levels of stereocontrol for the reduction of the double bond to form (**294**) (see Scheme 4.20).



Scheme 4.20: Proposed thionation of (**293**). *Reagent and conditions: i) Lawesson's reagent, CH_2Cl_2, RT, 72 hr.*

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (**293**) was dissolved in distilled dichloromethane at ambient temperature under a nitrogen atmosphere. Lawesson's reagent was added, and the reaction was left stirring at ambient temperature for ninety-six hours. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography. None of the desired thiolactam (**380**) was isolated. However, two other interesting products were isolated, ethyl 3-(2-butyl-1*H*-pyrrol-1-yl)butanoate (**381**) in 25% yield, and ethyl 3-(2-butyl-5-sulfanyl-1*H*-pyrrol-1-yl)butanoate (**382**) in 19% yield.

WitsETD



[293] [381] 25% [382] 19%

Scheme 4.21: Thionation of (**293**) produced two unexpected pyrroles (**381**) and (**382**). *Reagent and conditions: i) Lawesson's reagent, CH_2Cl_2, RT, 72 hr.*

The thiolactam (**380**) must have formed and the exocyclic alkene spontaneously rearranged, favouring the stabilization of the aromatic pyrrole system in (**382**). The desulfurisation of (**382**) to form (**381**) was less easy to explain. Although this particular reaction had no further application in our synthesis, it does offer a novel way of preparing substituted pyrroles and would be an interesting reaction to investigate further in the future.

Both products were characterized and showed the pyrrole signals in the ^{1}H-NMR spectrum at 6.62 ppm, 6.10 ppm, and 5.84 ppm for (**381**) and at 6.28 ppm and 5.73 ppm for (**382**). The ^{13}C-NMR spectral signals for the pyrrole ring were at 133.0 ppm, 115.2 ppm, 107.5 ppm, and 105.0 ppm for (**381**) and at 134.4 ppm, 131.9 ppm, 111.4 ppm, and 104.1 ppm for (**382**).

4.4.2 Condensation of thiolactam with β-ketosulfone

In order to form the vinylogous sulfonamide, we needed to perform a modified Knoevenagel reaction between the thiolactam (**295**) and 1-[(4-methylphenyl)sulfonyl]acetone (**279**). The preparation of 1-[(4-methylphenyl)sulfonyl]acetone (**279**) is described in section 3.7 in Chapter 3.[190]

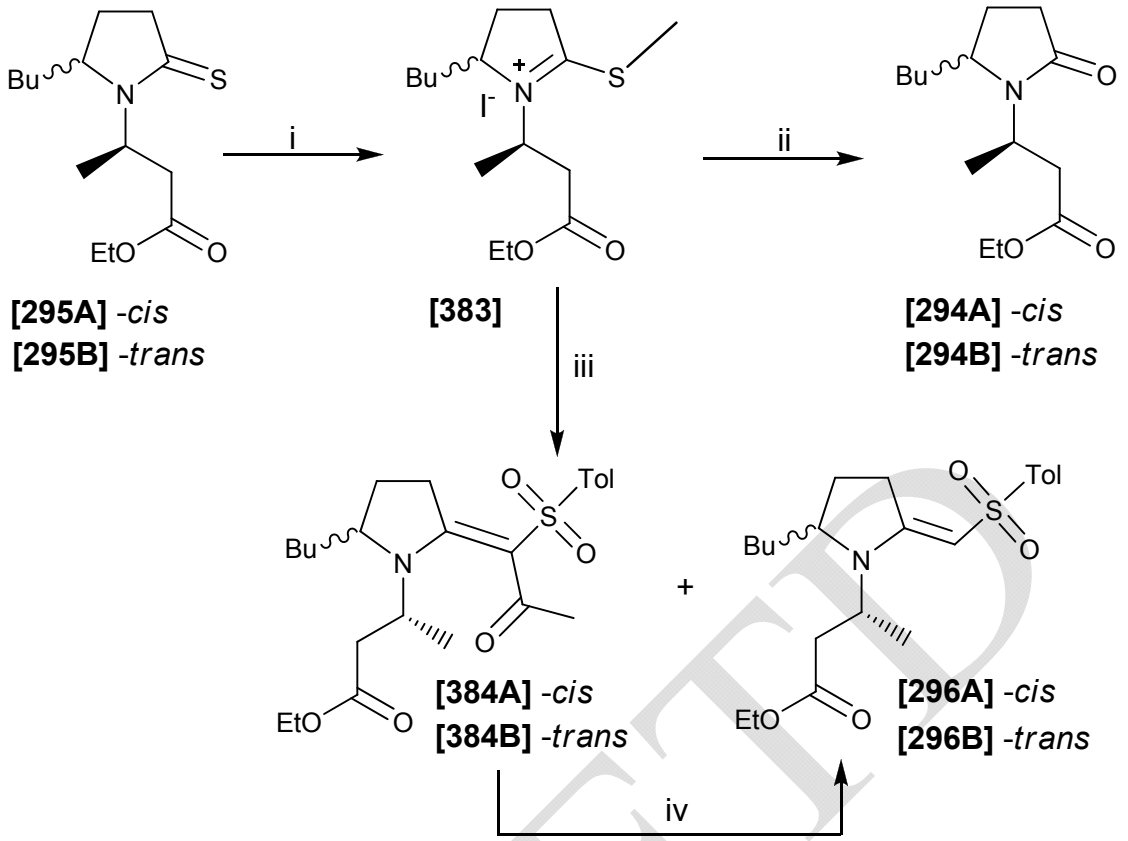
We prepared the vinylogous sulfonamide (**296**) by reacting the thiolactam (**295**) with excess methyl iodide in tetrahydrofuran under an inert atmosphere.[173] After twenty-four hours the starting material was no longer visible by TLC and the α-thioiminium salt (**383**) could be seen on the baseline. In this instance, the α-thioiminium salt did not precipitate from solution, but remained as a thick yellow oil. After the solvent and excess methyl iodide was removed *in vacuo*, a premixed solution of triethylamine and 1-[(4-methylphenyl)sulfonyl]acetone

WitsETD

(**279**) in dichloromethane were added to the α-thioiminium salt (**383**). The new reaction mixture was stirred for ninety-six hours at ambient temperature and was monitored by TLC. When the reaction had gone to completion, it was quenched with distilled water. The organic products were extracted into dichloromethane and purified by column chromatography. In our first attempt, none of the desired product was obtained, only the hydrolysis product of the α-thioiminium salt, ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (**294**) was isolated in 81% yield (see Scheme 4.23). This indicated that the conditions used were not completely water-free.

The reaction was repeated under strictly anhydrous conditions and two products were isolated, ethyl 3-((*E*)-2-butyl-5-(2-oxo-1-tosylpropylidene)pyrrolidin-1-yl)butanoate (**384**) in 45% yield, and the desired product, ethyl 3-((5*E*)-2-butyl-5-{[4-methylphenyl)sulfonyl]methylene} pyrrolidinyl)butanoate (**296**), in 25% yield (see Scheme 4.23). This mixture of acylated (**296**) and deacylated (**295**) vinylogous sulfonamides was expected, as a similar result was obtained during the attempted total synthesis of (−)-indolizidine 209D (see Section 3.7). Two further variations of this synthesis were attempted; they followed the same general protocol, but employed a different solvent and/or base for the second part of the reaction (see Table 4.6). The method with the highest combined yield used triethylamine and dichloromethane and hence this was the method used for the individual diastereomers (see Table 4.6).

WITSETD



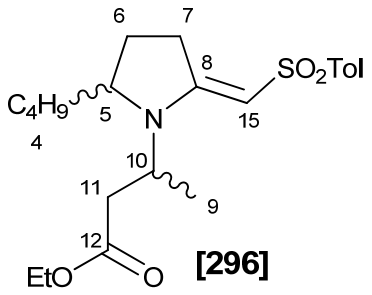
Scheme 4.23: The formation of the α-thioiminium salt (**383**) and the two possible pathways, hydrolysis back to (**294**) or reaction with (**279**) to form (**384**). *Reagents and conditions: i) MeI, THF, 48 hr.; ii) H_2O; iii) (**279**), Et_3N, CH_2Cl_2, RT, 96 hr.; iv) TFA, reflux, 30 min.*

Base/Solvent	Isomer	(296)	(384)
Et_3N/ CH_2Cl_2	A and B	25%	45%
Et_3N/ CH_2Cl_2	A	37%	37%
Et_3N/ CH_2Cl_2	B	23%	30%
K_2CO_3/ DMF	A and B	39%	0%
DBU/ CH_2Cl_2	A and B	49%	0%

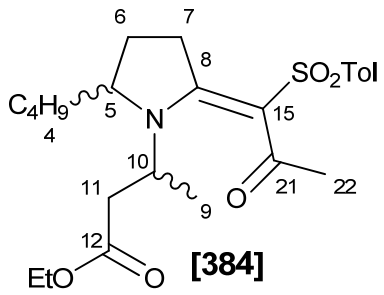
Table 4.6: Comparison of yields for vinylogous sulfonamides (**296**) and (**384**) under reaction conditions at ambient temperature.

Both the acylated diastereomers (**384A**) and (**384B**), and the deacylated diastereomers (**296A**) and (**296B**) were fully characterised. The key ^{1}H-NMR and ^{13}C-NMR spectroscopic signals for both isomers and both products are summarized in Table 4.7.

WITS ETD



[296]



[384]

Signal	(296A) *cis*	(296B) *trans*	(384A) *cis*	(384B) *trans*
H-4	1.95 – 1.82 (m)	2.00 – 1.79 (m)	1.80 – 1.63 (m)	1.79 – 1.63 (m)
			1.40 – 1.23 (m)	1.50 – 1.20 (m)
H-5	3.73 – 3.68 (m)	3.68 – 3.62 (m)	4.25 – 4.10 (m)	4.22 – 4.15 (m)
H-6	1.70 – 1.62 (m)	1.72 – 1.65 (m)	3.41 (dd)	2.78 (d)
	1.62 – 1.51 (m)	1.59 – 1.51 (m)	2.55 – 2.42 (m)	2.28 – 2.10 (m)
H-7	2.92 – 2.80 (m)	2.68 – 2.52 (m)	3.76 (m)	3.96 – 3.86 (m)
	2.45 – 2.31 (m)		2.74 (dt)	2.73 – 2.55 (m)
H-9	1.32 (d, *J* 6.9)	1.32 (d, *J* 6.9)	1.39 (d, *J* 7.2)	1.54 (d, *J* 6.7)
H-10	3.98 – 3.91 (m)	4.05 – 3.90 (m)	4.03 (m)	4.38 – 4.31 (m)
H-11	3.11 – 3.01 (m)	3.12 – 3.02 (m)	2.10 – 1.95 (m)	2.10 – 1.95 (m)
	2.92 – 2.80 (m)	2.88 – 2.75 (m)	1.80 – 1.63 (m)	1.79 – 1.63 (m)
H-15	4.99 (s)	4.98 (s)	-	-
H-22	-	-	2.34 (s)	2.30 (s)
C-5	62.5	61.4	55.7	60.3
C-6	25.7	26.2	38.0	40.7
C-7	38.2	38.6	35.0	38.6
C-8	159.7	160.4	170.4	169.5
C-9	17.5	18.0	27.5	18.5
C-10	48.3	48.3	62.8	56.6
C-11	33.8	34.1	25.4	24.7
C-12	170.7	170.3	174.4	174.5
C-15	87.4	87.4	104.4	104.9
C-21	-	-	189.9	189.3
C-22	-	-	22.3	21.2

Table 4.7: Comparison of selected NMR spectral data (in $CDCl_3$) for vinylogous sulfonamides. (Chemical shifts are reported in ppm. *J*-values were measured in Hz).

WitsETD

When comparing the two products (**296**) and (**384**), the most notable difference in the ^{1}H-NMR spectra was the presence of the enamine signal (H-15) at 4.99 ppm in (**296**), and the presence of the methyl signal (H-22) at 2.34 ppm in (**384**). The ^{13}C-NMR spectra also differ significantly; C-21 and C-22 occurred at 189.9 ppm and 22.3 ppm in the acylated product (**384**) and were absent in the deacylated product (**296**). The alkene signals C-8 and C-15 occurred at 159.7 ppm and 87.4 ppm in the deacylated product (**296**), and at 170.4 and 107.4 ppm in the acylated product (**384**), illustrating the electron withdrawing effect of the conjugation to the acyl group. H-5, H-6 and H-7 were also affected by the delocalization of charge in the acylated product (**384**) and were significantly deshielded compared to the deacylated molecule (**296**). H-11 was more deshielded in the deacylated product (**296**) than the acylated product (**384**). A similar trend was observed in the ^{13}C-NMR spectra, C-6 and C-10 were more deshielded in the acylated product (**384**), while C-11 was more deshielded in the deacylated product (**296**).

When comparing the diastereomers, the spectroscopic signals of greatest interest were the signals near the stereogenic centres, *viz.* C-5, C-6, C-9, and C-10. In the deacylated product (**296**), the spectra for each isomer were virtually indistinguishable. In the acylated product (**384**), the isomers were significantly different. For (**384A**), C-5, C-6, and C-7 occur at 55.7 ppm, 38.0 ppm, and 35.0 ppm, whereas for (**384B**), the corresponding signals occur at 60.3 ppm, 40.7 ppm and 38.6 ppm, consistently 3 - 4 ppm further downfield. C-9 and C-10 show the reverse trend; in (**384A**) they occur at 27.5 ppm and 62.8 ppm, respectively, whereas in (**384B**) they occur at 18.5 ppm and 56.6 ppm, 6 - 9 ppm further upfield.

The FTIR spectrum for the deacylated product (**296**) showed a single carbonyl group at 1731 cm^{-1} corresponding to the ester, whereas the acylated product (**384**) showed two carbonyl groups at 1731 cm^{-1} and 1680 cm^{-1}, confirming the presence of the ketone group in addition to the ester functionality.

WISETD

4.4.3 Deacetylation reactions[154]

In order to maximize the overall yield, the acylated product (**384**) had to be deacetylated and cycled back into the synthesis as (**296**). We attempted two methods for deacetylating (**384**). The first method involved heating (**384**) to reflux in acetic acid and toluene, and the second method employed heating (**384**) to reflux in neat trifluoroacetic acid. Both methods were successful (see Table 4.8). Interestingly, in both methods, the ester did not hydrolyse but remained unaffected by the acidic conditions. This was an unexpected but extremely useful result, as it meant the product (**296**) could be cycled straight back into the main synthesis without any additional transformations (e.g. reducing the carboxylic acid to the corresponding alcohol or esterifying the carboxylic acid).

Of the two sets of conditions employed, heating (**384**) to reflux in neat trifluoroacetic acid for thirty minutes proved to be more effective than heating to reflux in acetic acid and toluene for fourteen hours. The ^{1}H-NMR spectrum of the additional material isolated by column chromatography from these reactions indicated that the prolonged heating to reflux led to decomposition of the vinylogous sulfonamide, as there were no longer aromatic peaks present in the spectra. The by-products were never fully identified. These two procedures were modified from the work of Ban and co-workers,[154] please refer to the literature for the proposed mechanism of the acid-catalysed deacetylation.

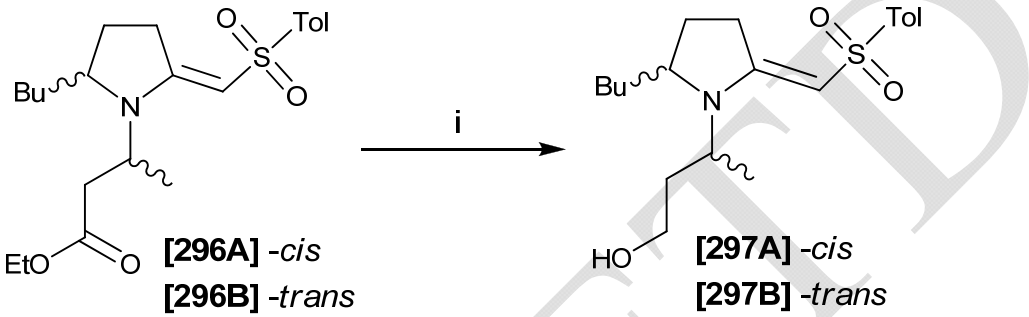
Conditions	Isomer	Yield of (296)
AcOH, toluene, reflux 14 hr.	A and B	45%
TFA, reflux, 30 min.	A	67%
TFA, reflux, 30 min.	B	54%

Table 4.8: Deacetylation of (**384**), conditions and yields.

4.4.4 Reduction of the ester

Textbook conditions[1, 173] were used to convert the ethyl ester into the corresponding alcohol. Ethyl 3-((5*E*)-2-butyl-5-{[(4-methylphenyl)sulfonyl] methylene}pyrrolidinyl) butanoate (**296**) was dissolved in tetrahydrofuran under

a nitrogen atmosphere. Lithium aluminium hydride was then added and the reaction mixture was left to stir at ambient temperature for twelve hours (see Scheme 4.25). Distilled water was added to quench the reaction and the solution was filtered through Celite® to remove residual lithium salts. Purification by column chromatography produced the desired product, 3-((5*E*)-2-butyl-5-{[(4-methylphenyl)sulfonyl] methylene}pyrrolidinyl)-1-butanol (**297**), in 92% yield as a clear oil. When the reaction was repeated with single diastereomers, the yields decreased slightly to 87% and 78% for (**297A**) and (**297B**), respectively.

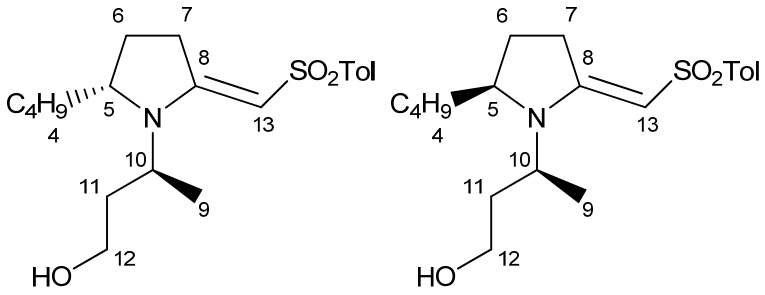


Scheme 4.25: Reduction of the ethyl ester (**296**) to the corresponding alcohol (**297**). *Reagents and conditions: i) $LiAlH_4$, THF, RT, 15 hr.*

Both diastereomers of the alcohol (**297**) were fully characterized. Significantly, the ^{1}H-NMR spectral signals at 4.09 ppm and 1.15 ppm, and the ^{13}C-NMR spectral signals at 60.7 ppm and 14.0 ppm corresponding to the ethyl ester were absent from the spectra. The ester carbonyl group was absent from the FTIR spectrum, and a characteristic OH stretching vibration was observed in the region of 3481 cm^{-1}.

Table 4.9 shows the key signals for isomer (**297A**) (*R,S* and *S,R*) and isomer (**297B**) (*R,R* and *S,S*). The ^{1}H-NMR spectra were virtually the same, with slight shifts observed in some of the signals. Notably, the signal for H-13 was observed at 5.07 ppm for the *cis* isomer (**297A**) and at 4.95 ppm for the *trans* isomer (**297B**). The ^{13}C-NMR spectra showed slight variation in the chemical shifts of C-5, C-8, C-9, C-10, and C-11. This was expected as these were the carbon atoms at the stereogenic centres or adjacent to them.

WISETD



Signal	(297A) / ppm	(297B) / ppm
H-4	2.02 – 1.53 (m)	1.96 – 1.53 (m)
H-5	3.74 – 3.60 (m)	3.72 – 3.58 (m)
H-6	2.02 – 1.53 (m)	1.96 – 1.53 (m)
H-7	3.04 (ddd)	3.15 – 3.03 (m)
	2.82 (dt)	2.81 – 2.69 (m)
H-9	1.31 – 1.16 (m)	1.35 – 1.08 (m)
H-10	3.74 – 3.60 (m)	3.72 – 3.58 (m)
H-11	2.02 – 1.53 (m)	1.96 – 1.53 (m)
H-12	3.74 – 3.60 (m)	3.72 – 3.58 (m)
H-13	5.07(s)	4.95 (s)
C-4	27.7	27.7
C-5	60.3	61.3
C-6	29.9	29.7
C-7	33.9	34.0
C-8	160.4	160.9
C-9	17.2	18.1
C-10	48.5	48.1
C-11	36.6	36.1
C-12	59.2	59.4
C-13	86.1	86.2

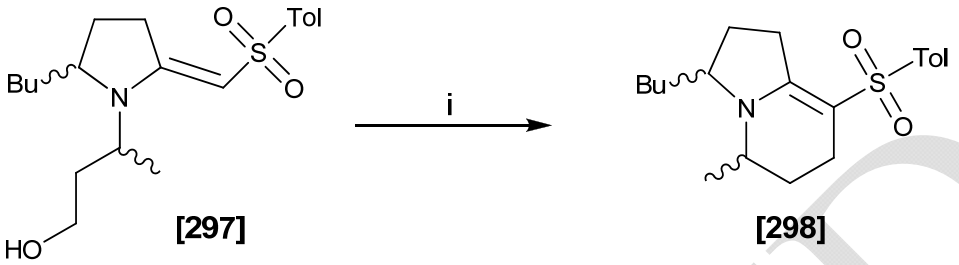
Table 4.9: Comparison of selected NMR spectral data (in $CDCl_3$) for diastereomers of alcohol (**297**).

4.4.5 Cyclisation reaction[139, 230]

The next step was the key step, the ring closure to form the bicyclic skeleton. As illustrated in the attempted total synthesis of (−)-indolizidine 209D, this reaction makes use of the vinylogous sulfonamide's nucleophilicity to facilitate

WitsETD

intramolecular ring closure. The initial investigations into this reaction were performed on the diastereomeric mixture of the alcohol (**297**). The alcohol (**297**) was heated at reflux in toluene together with triphenylphosphine, iodine, and imidazole. Once the intermediate iodide had formed, the vinylogous sulfonamide spontaneously facilitated cyclisation (see Scheme 4.26).

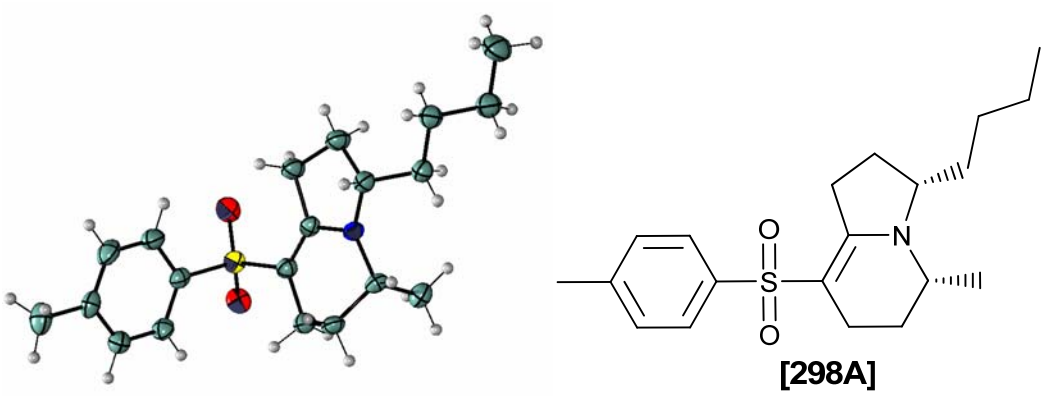


Scheme 4.26: Formation of the bicyclic skeleton facilitated by the vinylogous sulfonamide. *Reagent and conditions: i) PPh_3, imidazole, I_2, toluene, reflux, 3 hr.*

The first attempt at this reaction yielded starting material, but the subsequent attempt, using completely dry and inert conditions, yielded the diastereomeric mixture of the bicyclic product, 3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]-1,2,3,5,6,7-hexahydroindolizine (**298**), in 85% yield as a sticky, pale-pink oil. These conditions were repeated using single diastereomers and for the *cis* isomer (*R,S* and *S,R*) a yield of 78% was obtained whereas the *trans* isomer (*R,R* and *S,S*) yielded a less satisfactory 67%. The ring closure for the *trans* isomer (*R,R* and *S,S*) was repeated and the yield did not improve. The reason for the lower yield may be owing to steric interference of the butyl group.

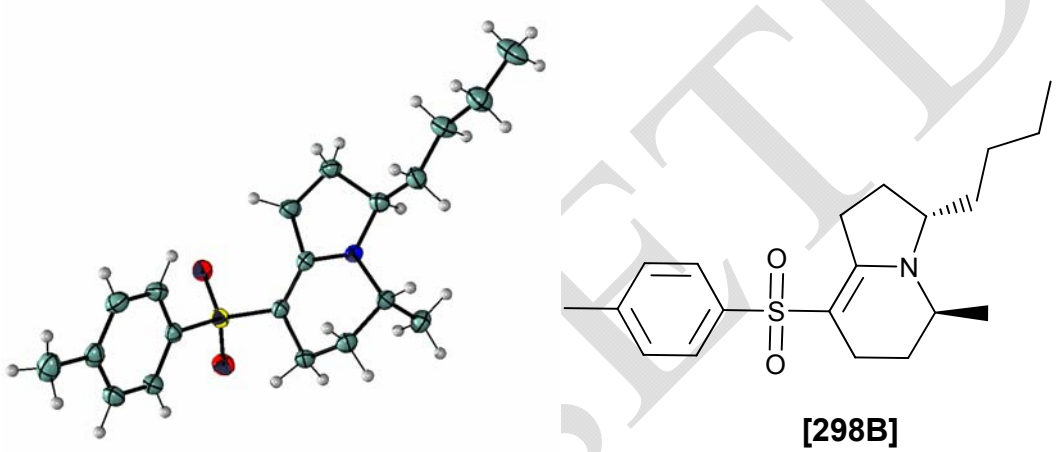
Following slow evaporation from ethyl acetate and hexane, several tiny pink crystals of each of the diastereomers were isolated. These crystals were successfully characterized by X-ray diffraction and the crystal structure of each diastereomer was obtained. This was an extremely exciting result, as it finally allowed for conclusive assignment of the relative stereochemistry of the two diastereomers. Diastereomer A, the minor diastereomer, showed a *cis* arrangement (*R,S* and *S,R*) of the butyl and methyl groups (see Figure 4.18), whereas isomer B, the major diastereomer, showed a *trans* arrangement (*R,R* and *S,S*) (see Figure 4.19).

WisETD



[298A]

Figure 4.18: The molecular structure of the *cis* isomer (*R,S* and *S,R*) of vinylogous sulfonamide (**298A**). Displacement ellipsoids are drawn at the 50% probability level.



[298B]

Figure 4.19: The molecular structure of the *trans* isomer (*R,R* and *S,S*) of vinylogous sulfonamide (**298B**). Displacement ellipsoids are drawn at the 50% probability level.

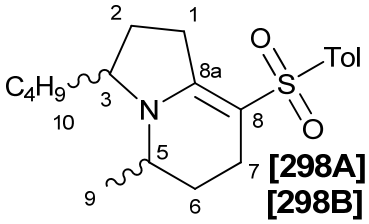
In addition to X-ray diffraction, both isomers were fully characterized. Loss of the hydroxy-group was evident from the FTIR spectrum, which lacked the O-H stretching vibration, as well as from HRMS, which produced parent ions of 347.1917 and 347.1921 for the *cis* isomer (**298A**) and *trans* isomer (**298B**), respectively. Both of these values agree well with the calculated value of 347.1919. ^{1}H-NMR spectroscopy showed the disappearance of the H-8 signal at 5 ppm, and both the ^{1}H-NMR and ^{13}C-NMR spectra showed significant changes in their chemical shifts for the signals corresponding to H-7, H-6, H-5, and C-8, C-7, C-6, and C-5, respectively.

Table 4.10 lists the key ^{1}H-NMR and ^{13}C-NMR spectroscopy signals for both isomers (**298A**) and (**298B**), and compares them with the bicyclic vinylogous

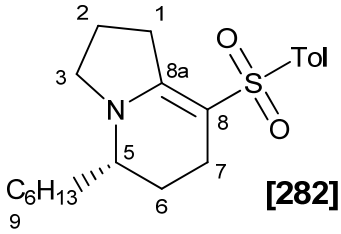
sulfonamide (**282**) formed during the attempted total synthesis of (−)-indolizidine 209D. As expected, the signals which displayed the greatest variation were the ones corresponding to C-3 and C-5, the substitution points. For the *cis* isomer (**298A**) they occur at 48.0 ppm and 64.6 ppm, respectively. For the *trans* isomer (**298B**) they occur at 45.5 ppm and 60.1 ppm, respectively, and for the monosubstituted (**282**) they occur at 51.2 ppm and 53.9 ppm, respectively. The *n*-butyl chain donated electron density, shifting the C-3 signal for (**298A**) and (**298B**) upfield relative to (**282**), whereas the effect of the hexyl group of (**282**) shifts C-5 further upfield relative to C-5 for (**298A**) and (**298B**), which have a methyl group attached to C-5. C-8 and C-8a were virtually identical for all three compounds. Notably, the signal corresponding to C-1 occurred at 32.1 ppm in (**282**), but at 18.5 ppm and 17.1 ppm in (**298A**) and (**298B**). For the ^{1}H-NMR spectra, most of the signals were overlapping multiplets in the region of 3.50 – 1.00 ppm. Diastereotopic splitting was clearly observed in (**298A**) for H-1, H-2, H-6 and H-7, whereas in (**298B**) only H-2 and H-10 showed clear diastereotopic splitting. Compound (**282**) did not show clear diastereotopic splitting, however, it may have been obscured by the overlapping of signals.

The bicyclic vinylogous sulfonamide isomers (**298A**) and (**298B**), had significantly different melting points; the *cis* isomer (**298A**) had a melting point of 122 – 123°C while the *trans* isomer (**298B**) had a melting point of 99 – 101°C

WitsETD



[298A] -*cis*
[298B] -*trans*



[282]

Signal	(298A) / ppm	(298B) / ppm	(282) / ppm
H-1	2.47 – 2.40 (m)	2.36 – 2.29 (m)	3.13 (t, *J* 7.2)
	2.30 – 2.19 (m)		
H-2	2.11 – 2.00 (m)	2.04 – 1.96 (m)	1.91(quin., *J* 7.2)
	1.68 – 1.50 (m)	1.72 – 1.53 (m)	
H-3	3.50 – 3.42 (m)	3.50 – 3.45 (m)	3.19 (t, *J* 7.1)
H-5	3.43 – 3.34 (m)	3.50 – 3.45 (m)	3.49 (quin., *J* 6.9)
H-6	1.85 – 1.75 (m)	1.72 – 1.53 (m)	1.80 – 1.51 (m)
	1.47 – 1.18 (m)		
H-7	3.27 – 3.17 (m)	3.11 – 3.01 (m)	1.80 – 1.51 (m)
	2.93 (dt, 17.4, 8.1)		
H-9	1.06 (d, *J* 6.6)	1.05 (d, *J* 6.6)	1.38 – 1.25 (m)
H-10	1.15 – 1.08 (m)	1.72 – 1.53 (m)	-
		1.37 – 1.21 (m)	
C-1	18.5	17.1	32.1
C-2	27.5	27.3	29.3
C-3	48.0	45.5	51.2
C-5	64.6	60.1	53.9
C-6	34.7	31.7	31.4
C-7	29.7	30.1	31.7
C-8	91.8	91.9	92.4
C-8a	154.8	155.2	155.1
C-9	21.2	21.4	25.6
C10	27.0	26.9	-

Table 4.10: Comparison of selected NMR spectral data (in $CDCl_3$) for bicyclic vinylogous sulfonamides. (*J*-values were measured in Hz).

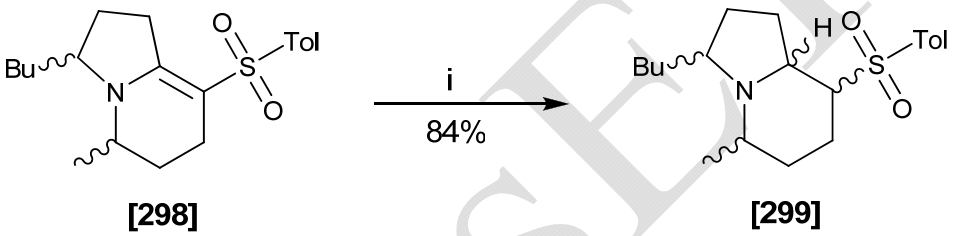
WitsETD

4.5 Completion of the synthesis

Now that the bicyclic skeleton was formed, all that remained to do was the defunctionalization of the vinylogous sulfonamide. During the attempted total synthesis of (−)-indolizidine 209D, this was as far as we were able to proceed owing to lack of material. This meant the next two steps were optimized and investigated specifically for monomorine I and its isomers.

4.5.1 Reduction of the vinylogous sulfonamide

The next step, the reduction of the vinylogous sulfonamide (see Scheme 4.27), offered us a second opportunity for stereocontrol, as the bicyclic structure constrains free rotation. Using a platinum-catalysed reduction, we assumed that the hydrogen would stereoselectiviely favour *cis*-addition.



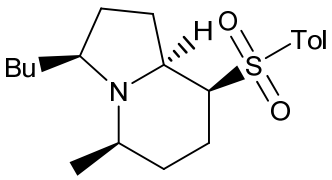
[298] **[299]**

Scheme 4.27: Reduction of the vinylogous sulfonamide (**298**) to give indolizidine (**299**). *Reagents and conditions: i) H_2 (7 atm.), PtO_2, MeOH, 12 hr.*

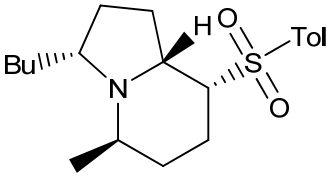
The reduction was performed using platinum dioxide (Adams' catalyst) together with 3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]-1,2,3,5,6,7-hexahydro indolizine (**298**) in acetic acid under seven atmospheres of hydrogen pressure.[31] When the reaction was performed using the diastereomeric mixture, a yield of 84% for 3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl] octahydroindolizine (**299**) was obtained. When the reaction was repeated with pure *cis* isomer (**298A**), a yield of 88% for (**299A**) was obtained, and when it was repeated with pure *trans* isomer (**298B**), a 72% yield of (**299B**) was obtained (see Figure 4.20). The orientation of H-8a was not explicitly proved, but was inferred from the subsequent desulfonylation (Section 4.5.2) and the assumed *cis*-hydrogenation.

WitsETD

The second method we attempted for the reduction of the double bond was using sodium borohydride in methanol at ambient temperature for four hours.[171] Following extraction and purification by column chromatography, the desired product (**299**) was obtained in 13% yield, and starting material was recovered in 50% yield.



[299A]



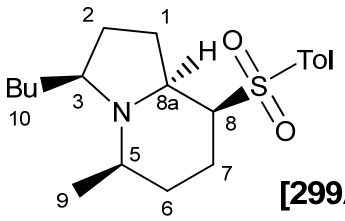
[299B]

Figure 4.20: Dominant relative stereochemistry of all four stereogenic centres for both isomers.

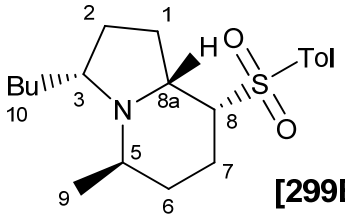
Both isomers were fully characterized. The key spectroscopic changes compared to the preceding compounds were the appearance of H-8 and H-8a in the ^{1}H-NMR spectra, and the significant shift of C-8a and C-8 from 154.8 ppm and 91.8 ppm to 67.1 ppm and 59.5 ppm in the *cis* isomer (**299A**) and from 155.2 ppm and 91.9 ppm to 62.9 ppm and 47.0 ppm in the *trans* isomer (**299B**). The two isomers had virtually identical ^{1}H-NMR spectra, both with overlapping multiplets in the region of 0.80 – 3.50 ppm (see Table 4.11).

For the *cis* isomer, (**299A**), H-8 was visible as a triplet, coupling to H-7 only, whereas in the *trans* isomer, (**299B**), H-8 appeared as a multiplet, coupling to H-7 and H-8a. H-8a appeared at 2.58 – 2.48 ppm for the *cis* isomer (**299A**) and at 3.49 – 3.02 ppm for the *trans* isomer (**299B**). The ^{13}C-NMR spectra for both isomers were largely the same, with the major differences occurring at the four stereogenic centres, C-3, C-5, C-8a, and C-8. For the *cis* isomer (**299A**), these signals were at 63.4 ppm, 61.6 ppm, 59.5 ppm, and 67.1 ppm, whereas for the *trans* isomer (**299B**), these signals were at 60.2 ppm, 56.5 ppm, 47.0 ppm, and 62.9 ppm, respectively, with all four of the signals significantly upfield of the *cis* counterpart, indicative of the different stereoelectronics in each system.

WiSETD



[299A]



[299B]

Signal	(299A) / ppm	(299B) / ppm
H-1	1.82 – 1.15 (m)	1.52 – 1.02 (m)
H-2	1.82 – 1.15 (m)	1.52 – 1.02 (m)
H-3	2.62 (m)	2.67 – 2.54 (m)
H-5	3.33 (m)	3.49 – 3.02 (m)
H-6	2.25 – 2.13 (m)	1.80 – 1.65 (m)
H-7	2.25 – 2.13 (m)	2.07 – 1.98 (m)
H-8	3.03 (t, *J* 7.5)	3.49 – 3.02 (m)
H-8a	2.58 – 2.48 (m)	3.49 – 3.02 (m)
H-9	0.91 (d, *J* 7.5)	0.99 – 0.81 (m)
H-10	1.82 – 1.15 (m)	1.52 – 1.02 (m)
C-1	29.0	28.5
C-2	28.7	28.0
C-3	63.4	60.2
C-5	61.6	56.5
C-6	39.2	33.0
C-7	30.5	29.7
C-8	59.5	47.0
C-8a	67.1	62.9
C-9	21.6	20.7
C-10	27.7	27.8

Table 4.11: Comparison of selected NMR spectral data (in $CDCl_3$) for indolizidine isomers. (*J*-values were measured in Hz).

During this stereoselective hydrogenation, the two unconstrained groups were the butyl chain, and the tolyl group. In an attempt to understand the stereoselective reduction of (**298A**) and (**298B**), the crystal structures of both were imported into Hyperchem,[228] and various torsion angles involving the butyl chain were manually altered, such that the butyl chain was positioned above

WitsETD

the plane of the ring (see Figure 4.21 and 4.22). These conformations illustrate how the butyl group may have hindered the reduction of the double bond from the top face of the ring in both diastereomers.

For (**298A**), the *cis* isomer, the modelled conformer (see Figure 4.21) clearly showed the top face of the molecule was sterically hindered by both the methyl and the butyl group. In the conformation shown, the tolyl group also contributes to blocking the top face. However, free rotation of the tolyl group around the S-C bond meant that any steric hindrance contribution was the same for both faces.

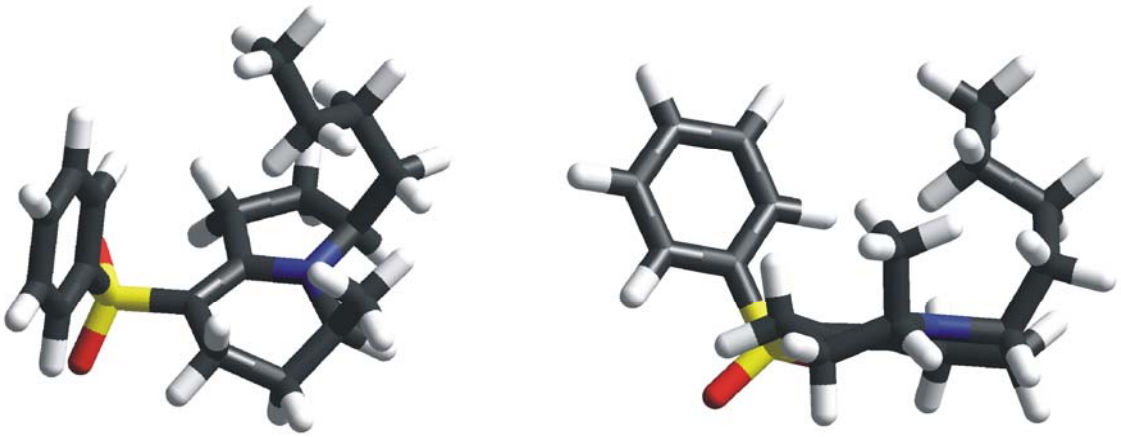


Figure 4.21: Possible conformation for (**298A**), indicating the sterically hindered top face from two different views.

Using Hyperchem,[228] the following model was obtained for (**298B**), the *trans* isomer (see Figure 4.22), and in this case, the stereocontrol was not quite as complete. In the conformation shown, the methyl group and the butyl group blocked opposite faces, and the tolyl group, with free rotation, could block either face. The butyl chain, with more degrees of freedom than the methyl, appears to play a greater role in steric hindrance and blocked the top face, while the methyl group hardly blocked the bottom face at all. The overall stereochemical control for the *trans* isomer was significantly less than for the *cis* isomer.

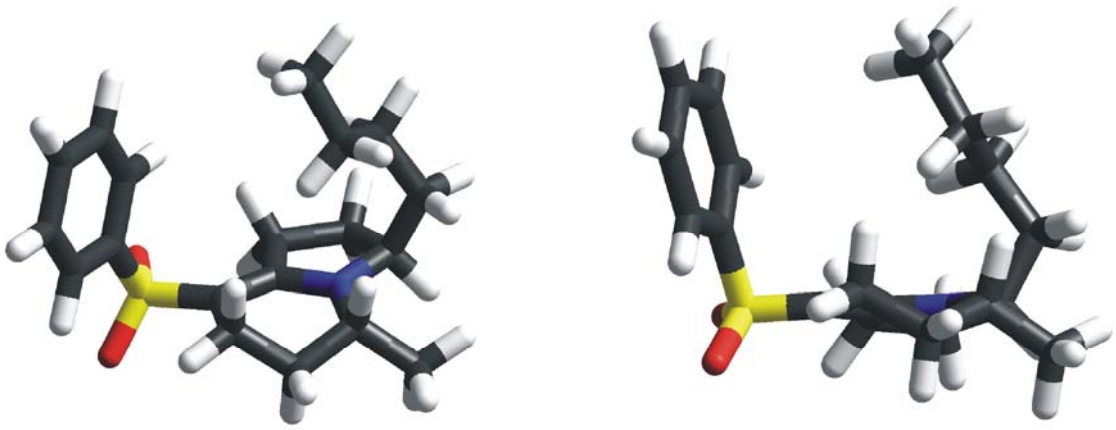
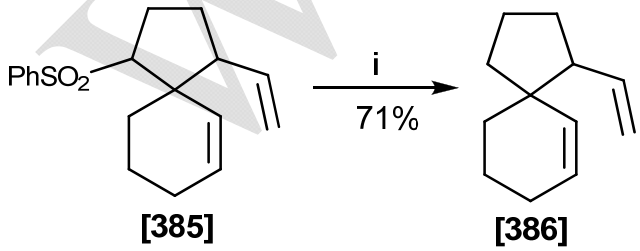


Figure 4.22: Possible conformation for (**298B**), indicating the sterically hindered top face from two different views.

4.5.2 Desulfonylation reaction

4.5.2.1 Methods of desulfonylation

Sulfones have been extensively used in natural product synthesis and the sulfone group is usually cleaved off after it has performed its function. Standard literature desulfonylation include reduction desulfonylation, alkylative desulfonylation and oxidative desulfonylation.[231] The method we were most interested in was reductive desulfonylation. One of the methods in the literature used magnesium dissolved in ethanol or methanol. This method was devised by Carpino and co-workers[232] and used by Chakraborty and Simpkins who desulfonylated (**385**) to form the spirocyclic product (**386**) (see Scheme 4.28).[233]

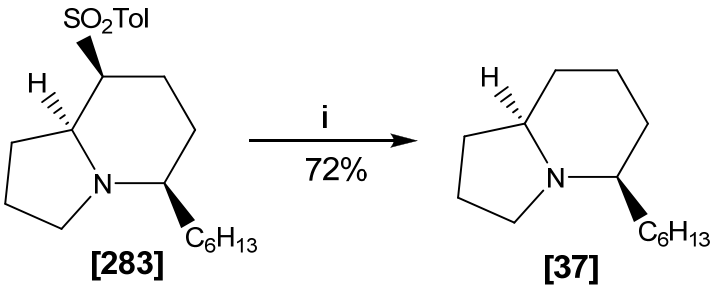


Scheme 4.28: Reductive desulfonylation by Chakraborty and Simpkins.[233] *Reagents and conditions: i) Mg, EtOH, 2-5 hr.*

For the final step in the total synthesis of (−)-indolizidine 209D, Yillah[31] used the desulfonylation conditions of Trost,[234] or Carretero and Dominguez;[235] which made use of a sodium amalgam reduction. This reaction was carried out

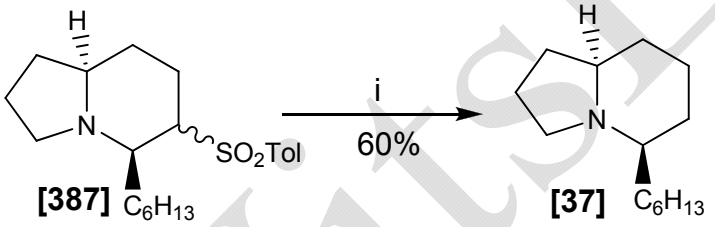
WISER

in methanol at ambient temperature for three to fifteen hours (see Scheme 4.29).



Scheme 4.29: Reductive desulfonylation by Yillah and Michael.[31] *Reagents and conditions: i) Na/Hg (6%), Na_2HPO_4,, 3 – 15 hr.*

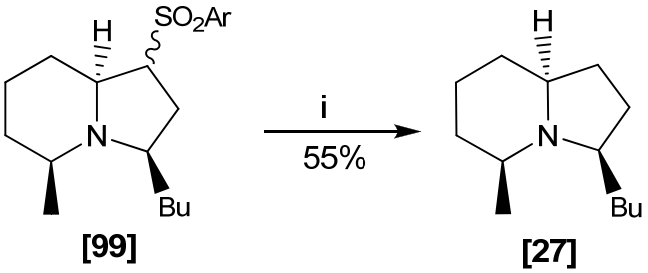
The preferred desulfonylation method of Thomas Back's research group[56, 236] was under Birch reduction condition, using sodium in liquid ammonia. As illustrated in his total synthesis of monomorine I, this reaction was effective despite its moderate yield (see Scheme 4.30).[56]



Scheme 4.30: Reductive desulfonylation by Back and Nakajima.[56] *Reagents and conditions: i) Na, NH_3 liq.*

Craig and Berry[67] made use of a sodium naphthalenide solution to reductively cleave the sulfone group.[67] These harsh conditions cleave the sulfone group within minutes at ambient temperature to give the indolizidine in moderate yield (see Scheme 4.31).

WISER

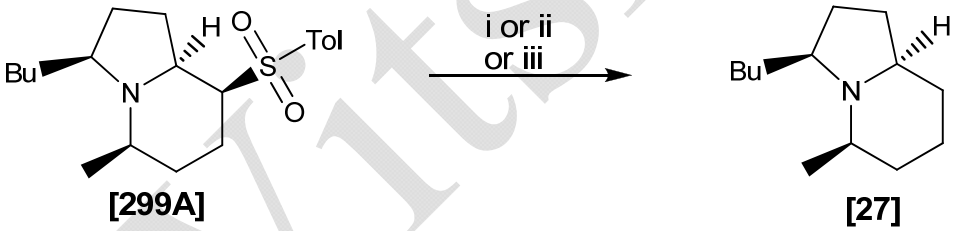


[99] [27]

Scheme 4.31: Reductive desulfonylation by Craig and Berry.[67] *Reagents and conditions: i) $Na^+C_{10}H_8^-$ (3.5 eq.), THF, RT, 5 min.*

4.5.2.2 Desulfonylation

The final step in the synthesis, reductive desulfonylation (see Scheme 4.32), took several attempts and different methods before it was successfully achieved. Initially, the method reported by Yillah[31, 234] was attempted. A sodium amalgam was freshly prepared and added to a mixture of 3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydroindolizine (**299**) and sodium hydrogen phosphate in methanol. This method was attempted several times and repeatedly starting material was recovered, even when the temperature and reaction time were modified.



[299A] [27]

Scheme 4.32: Desulfonylation of (**299A**) to give monomorine I (**27**). *Reagents and conditions: i) Na/Hg (6%), Na_2HPO_4,, 3 – 15 hr.; ii) Mg, EtOH, 2 – 5 hr.; iii) $Na^+C_{10}H_8^-$ (15 eq.), THF, RT, 15 min.*

The second method we attempted was that of Chakraborty and Simpkins,[233] reacting (**299**) with magnesium turnings in methanol at 50°C for three hours. When the reaction had gone to completion, as monitored by TLC, the crude product was purified by column chromatography and a diastereomeric mixture of monomorine I, 5-*epi*-monomorine I, and indolizidine 195B was isolated in a combined yield of 60%. Owing to the limited amount of material isolated, the diastereomers could not be separated, and isomers were characterized as a

UnivEd

mixture by ^{13}C-NMR spectroscopy only (the ^{1}H-NMR spectrum had completely overlapping signals between 0.80 ppm and 3.50 ppm and the individual isomers could not be distinguished). Fortunately, ^{13}C-NMR spectrum has been reported in the literature for all the isomers of monomorine I, thus making the indentification of the various alternative isomers possible.

The third method we attempted was that of Craig and Berry,[67] using sodium naphthalenide in tetrahydrofuran for reductive desulfonylation. Following the exact conditions of Craig and Berry, a pure sample of the *cis* isomer of 3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydroindolizine (**299A**) was mixed with three and a half equivalents of sodium naphthalenide for five minutes before the reaction was quenched and the product was purified by column chromatography. Racemic monomorine I was isolated as a pale oil in 23% yield based on consumed starting material. The reaction was repeated with the ratio of sodium naphthalenide to (**299A**) increased to 15:1, and the reaction time increased to fifteen minutes. After purification by column chromatography on silica gel through a Pasteur pipette, monomorine I was isolated in 73% yield.

The same method was used with the *trans* isomer (**299B**), using a 1:8 ratio of 3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydroindolizine (**299B**) to sodium naphthalenide, and reacting at ambient temperature for fifteen minutes. Following purification by column chromatography through a Pasteur pipette, the 5-*epi*-monomorine I was isolated in 71% yield as a pale oil that discoloured to turquoise over time. The final mixed fraction collected from the column showed some starting material, 5-*epi*-monomorine I and evidence of indolizidine 195B in the ^{13}C-NMR spectrum, however, the quantities were insufficient for full characterization. The presence of indolizidine 195B together with 5-*epi*-monomorine I was in agreement with the model proposed in Figure 4.19, which suggested the stereocontrol in the reduction of the double bond was not as complete as with the *cis* isomer, as the methyl and butyl groups blocked opposite faces of the molecule.

The spectroscopic characterization of both monomorine I (see Figure 4.23) corresponded well to the literature values.[93, 100, 103] Table 4.12 tabulates the

WISER

spectroscopic data we obtained for racemic monomorine I in comparison to those reported by Artis,[103] Royer[93] and Sonnet.[100] Our spectral data were virtually indistinguishable to those obtained by Artis *et al.*[103] and differred by at most 0.1 ppm from those obtained by Royer *et al*.[93] The spectral data obtained by Sonnet *et al*.[100] differred from ours by up to 1.1 ppm, *viz.* the signal corresponding to C-3, reported at 61.8 ppm by Sonnet in contrast to the 62.90 ppm we observed. However, Sonnet's data were the oldest in the literature (1975) and were obtained on a less sensitive instrument.

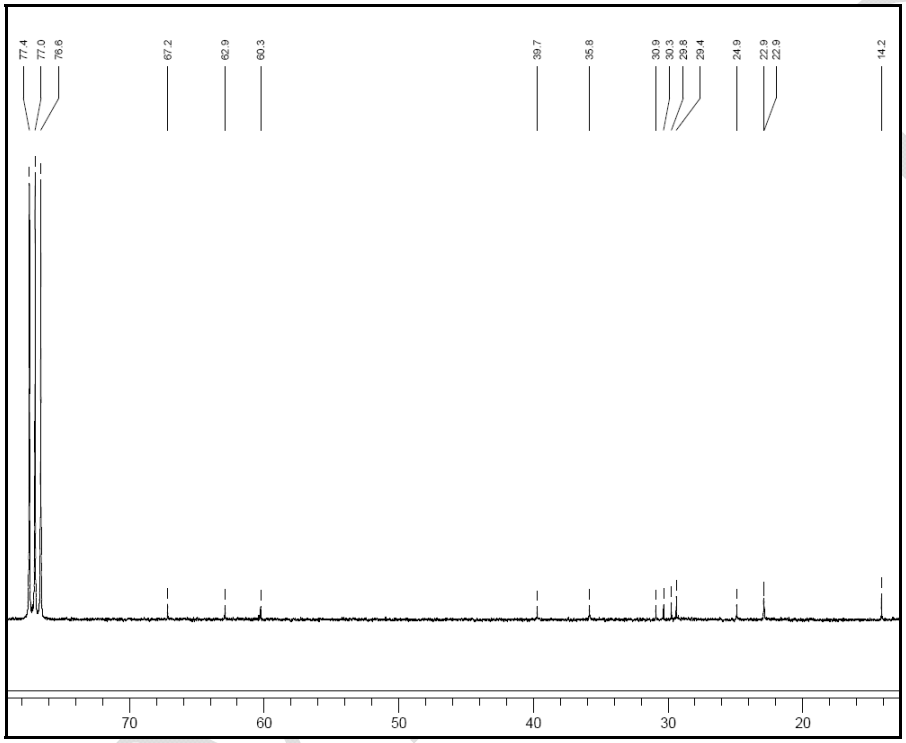
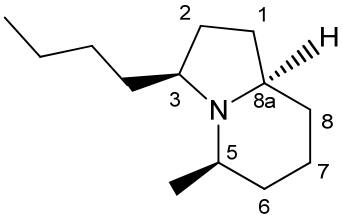


Figure 4.23: The ^{13}C-NMR spectrum (in $CDCl_3$) that we obtained for monomorine I.

Owing to the volatility of the molecule, high resolution mass spectrometry, under standard EI conditions, produced no parent ion; however, the milder method of chemical ionisation (APCI) gave a low resolution parent ion at 195.37, which compares reasonably with the calculated value of 195.1987. FTIR spectroscopy showed the presence of a Bohlmann band[237] at 2860 cm^{-1}, indicating at least one hydrogen antiperiplanar to the nitrogen lone pair.

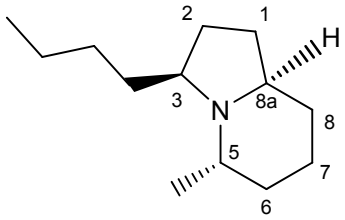


Signal	(27)	Artis *et al.*[103]	Royer *et al.*[93]	Sonnet *et al.*[100]
C-1	30.91	30.90	31.1	31.8
C-2	29.76	29.76	29.8	29.7
C-3	62.90	62.91	63.0	61.8
C-5	60.26	60.27	60.3	59.7
C-6	35.84	35.83	36.1	36.4
C-7	24.91	24.90	25.1	25.3
C-8	30.34	30.33	30.5	30.9
C-8a	67.17	67.16	67.3	67.6
CH_3	22.86	22.90	22.9	22.9
CH_2	39.73	39.73	39.8	39.8
CH_2	29.40	29.42	29.4	28.7
CH_2	22.90	22.90	23.0	23.2
CH_3	14.16	14.17	14.2	14.3

Table 4.12: Comparison of spectroscopic data (in $CDCl_3$) for monomorine I (**27**) with literature data. (All chemical shifts were measured in ppm).

Table 4.13 displays the spectroscopic data we obtained for 5-*epi*-monomorine I (see Figure 4.24) compared to those obtained by Artis *et al.*,[103] and by Sonnet *et al*.[100] Our spectral data were in close agreement with those obtained by Artis,[103] differing by up to 0.16 ppm. The spectral data obtained by Sonnet *et al*.[100] again had one signal that differred by 0.90 ppm, the signal for C-6, reported at 30.1 ppm by Sonnet *et al*.[100] in contrast to the 29.12 ppm we observed.

WISETD



Signal	(28)	Artis *et al.*[103]	Sonnet *et al.*[100]
C-1	32.34	32.44	33.2
C-2	31.46	31.58	32.0
C-3	55.49	55.39	55.4
C-5	47.38	47.33	47.2
C-6	32.21	32.37	33.1
C-7	19.26	19.31	19.8
C-8	29.12	29.25	30.1
C-8a	59.21	59.13	58.7
CH_3	7.60	7.53	7.4
CH_2	28.82	28.80	28.44
CH_2	28.12	28.19	28.36
CH_2	23.08	23.10	23.5
CH_3	14.09	14.09	14.3

Table 4.13: Comparison of spectroscopic data (in $CDCl_3$) for 5-*epi*-monomorine I (**28**) with literature data. (All chemical shifts were measured in ppm).

Despite the volatility of the molecule, high resolution mass spectrometry produced a parent ion at 195.1976 which compares well with the calculated value of 195.1987. FTIR spectroscopy for 5-*epi*-monomorine I also had a Bohlmann band[237] at 2859 cm^{-1}, as expected, indicating at least one hydrogen antiperiplanar to the nitrogen lone pair.

WISETD

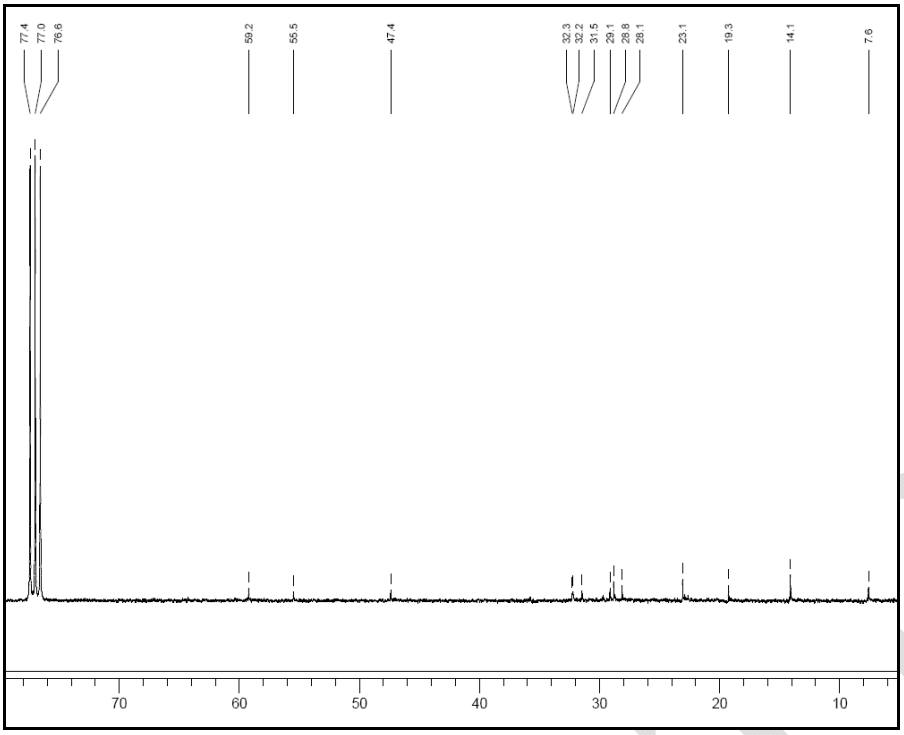
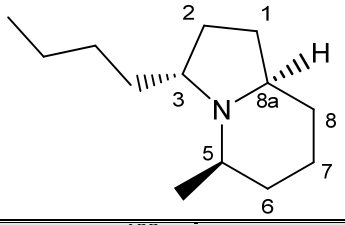


Figure 4.24: The ^{13}C-NMR spectrum ($CDCl_3$) that we obtained for 5-*epi*-monomorine I.

Table 4.14 displays the spectroscopic data we obtained for indolizidine 195B compared to those obtained by Artis *et al.*,[103] Takahata *et al.*[84] and by Sonnet *et al*.[100] The only spectral evidence of indolizidine 195B (**26**) was obtained in a mixed sample of monomorine I, 5-*epi*-monomorine I and indolizidine 195B. The ^{13}C-NMR spectrum was carefully examined, and by comparison to the literature we were able to discern the presence of all three diastereomers. We never succeeded in characterizing a pure sample of indolizidine 195B. Our spectral data were in close agreement with those obtained by Artis,[103] differing by up to 0.25 ppm. The spectral data obtained by Sonnet *et al*.[100] had one signal that differred significantly from those obtained by Artis *et al.*,[103] Takahata *et al.*[84] and by us; the value Sonnet *et al*.[100] obtained for C-3 was 56.6 ppm, which differred from ours by 2.3 ppm. The other signals obtained by Sonnet *et al*.[100] agreed well with the values we obtained.

WitsETD



Signal	(26)	Artis *et al.*[103]	Takahata *et al.*[84]	Sonnet *et al.*[100]
C-1	32.39	32.39	32.28	33.0
C-2	26.33	26.32	26.32	26.8
C-3	58.92	58.80	58.92	56.6
C-5	51.91	52.00	52.09	51.8
C-6	34.58	34.52	34.44	35.3
C-7	24.73	24.72	24.71	24.9
C-8	30.05	30.02	29.98	30.6
C-8a	58.71	58.96	59.00	58.9
CH_3	20.46	20.45	20.39	20.9
CH_2	24.84	24.89	24.97	25.2
CH_2	29.27	29.18	29.14	29.6
CH_2	23.11	23.03	23.01	23.3
CH_3	14.19	14.24	14.20	14.3

Table 4.14: Comparison of spectroscopic data (in $CDCl_3$) for indolizidine 195B (**26**) with literature data. (All chemical shifts were measured in ppm).

Thus the total synthesis of racemic monomorine I and 5-*epi*-monomorine I was successfully completed using new methodology involving a vinylogous sulfonamide-assisted cyclisation. Key to this synthesis were the two steps which contain a high degree of stereocontrol, the reduction of the exocyclic alkene, and the reduction of the vinylogous sulfonamide.

4.6 Alternative approach via monobenzylated intermediates

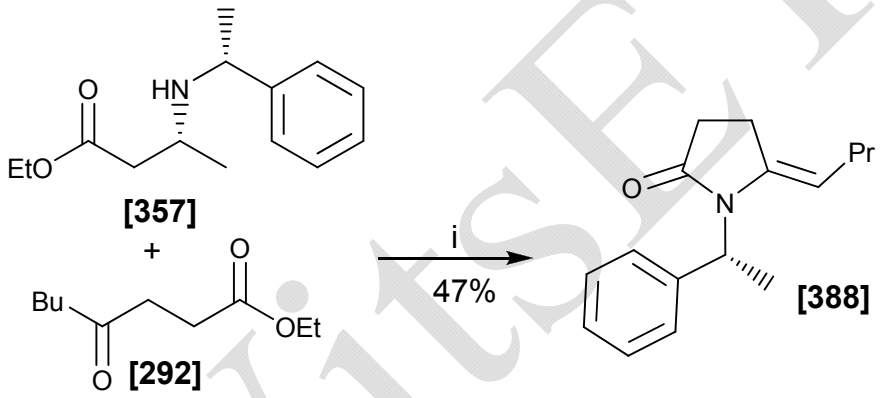
When the debenzylation reaction of the chiral amine (see Section 4.2.3) ceased to remove both benzyl groups, we accumulated a fair amount of the monodebenzylated amine (**357**). Owing partly to the need to circumvent the failing debenzylation reaction and partly to the fortuitous reaction described in

WiSER

Section 4.6.1, we investigated a side-route to enantiopure monomorine I and its isomers, making using of monobenzylated intermediates.

4.6.1 Condensation reaction

Owing to the volatility of the free amine (**291**) subsequent to debenzylation, the amine was usually used directly in the condensation reaction without further purification. During the condensation reaction, a partially debenzylated amine (**357**) was accidentally reacted with the ketoester (**292**) and a novel product was isolated in 47% yield over the two steps (**388**) (see Scheme 4.33). Upon closer examination it became apparent that a retro-Michael addition had occurred, with the loss of ethyl crotonate (see Scheme 4.34) and the condensation reaction had taken place between (*R*)-α-methylbenzylamine and the ketoester (**292**).



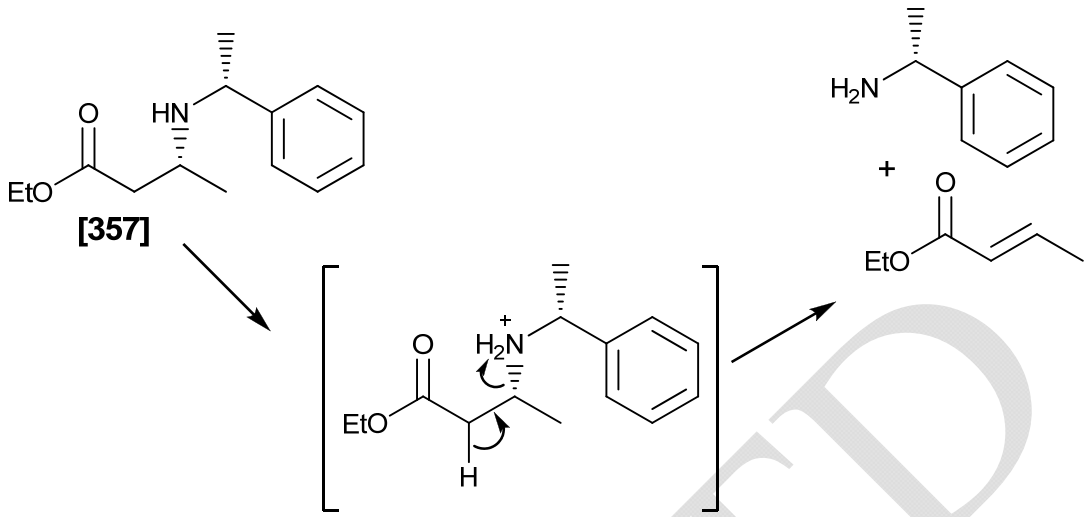
Scheme 4.33: Condensation reaction between (**357**) and (**292**). *Reagents and conditions: i) AcOH, toluene, reflux, 72 hr.*

Although this benzylated lactam (**388**) was not our intended product, it contains striking similarities to the desired lactam (**293**), and provided that the benzyl group could be removed at a later stage this could be an alternative route for the synthesis of indolizidine alkaloids.

In order to prove the hypothesized retro-Michael addition, we condensed the ketoester (**292**) directly with (*R*)-α-methylbenzylamine by heating to reflux in toluene and acetic acid for seventy-two hours. Following purification, (*R,E*)-5-

WitsETD

butylidene-1-(1-phenylethyl)pyrrolidin-2-one (**388**) was isolated in quantitative yield, thus confirming the occurrence of the retro-Michael addition.



Scheme 4.34: Proposed mechanism for the acid catalyzed retro-Michael addition. *Reagents and conditions: AcOH, toluene, reflux, 72 hr.*

The product (**388**) was optically active, with an optical rotation of $[\alpha]_D^{20}$ +43.1 (*c* 1.30, CH_2Cl_2). It was characterized by ^{1}H-NMR and ^{13}C-NMR spectroscopy and, analogous to the lactam (**293**), it was isolated exclusively as the *E*-isomer. The ^{1}H-NMR and ^{13}C-NMR spectra clearly showed the presence of the α-methyl benzyl group with signals at 7.28 - 7.24 ppm integrating for five hydrogens, and a benzylic signal at 5.65 ppm integrating for one hydrogen (see Figure 4.25). The signal at 5.65 ppm was split into a quartet with a *J* value of 7.2 Hz, coupling to a doublet at 1.71 ppm which integrated for three hydrogens. Another key signal was the triplet at 4.39 ppm, corresponding to the alkene hydrogen.

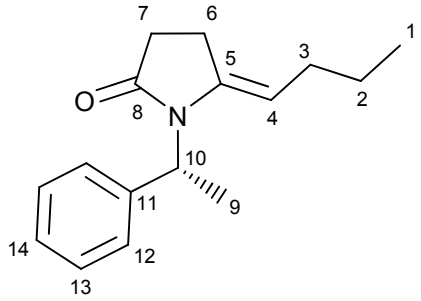


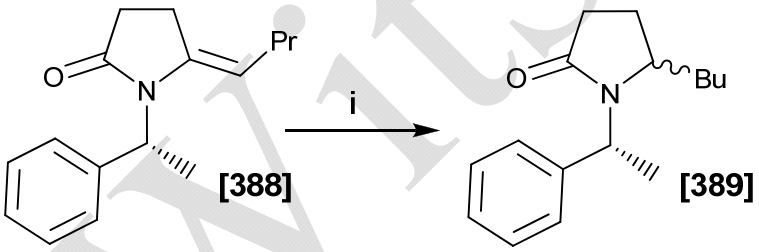
Figure 4.25: Numbering of lactam (**388**) for assignment of spectroscopic data.

WISER

The ^{13}C-NMR spectrum showed the enamine carbons at 136.6 ppm and 104.0 ppm (C-5 and C-4) as well as the lactam carbonyl (C-8) at 175.7 ppm. Signals corresponding to the propyl chain and the benzyl group were also present, as were C-6 and C-7. FTIR spectroscopy confirmed the presence of the lactam with a stretching vibration at 1666 cm^{-1}, and low resolution mass spectroscopy showed a fragmentation pattern consistent with the assigned structure. High resolution mass spectrometry was not performed as the parent ion at 243 coincided with the reference peak used during the experimentation.

4.6.2 Stereoselective reduction

The next step was the stereoselective reduction of the exocyclic alkene (see Scheme 4.35). This reduction was analogous to the stereoselective reduction of lactam (**293**), but instead of the ethyl ester group, there was now a bulkier benzyl group. According to the proposed stereocontrol, the carbonyl of the ester could coordinate to the titanium tetrachloride (see Figure 4.14 and Figure 4.15), hence restricting free rotation and creating a face bias. However, the benzyl group of (**388**) does not coordinate to titanium and hence the selectivity should be markedly different.



Scheme 4.35: Diastereoselective reduction of (**388**) to form lactam (**389**). *Reagents and conditions: i) Various conditions (see Table 4.15).*

Three different reducing conditions were employed. The first was a palladium-catalysed reduction in the presence of acetic acid and hydrogen under pressure, the second was with titanium tetrachloride and triethylsilane, and the third made use of titanium tetrachloride and the bulky hydrogen source, triphenylsilane (see Table 4.15). Interestingly, the greatest stereoselectivity was observed for the palladium-catalysed reduction, with a ratio of 7:1 for the diastereomers. The triethylsilane reduction was moderately stereoselective,

WitsETD

with a ratio of 3:1, and the triphenylsilane reduction was not selective at all, giving a 1:1 ratio of the isomers. This trend was exactly the opposite of what was observed with the reduction of lactam (**293**) (refer to Table 4.3), which supported the theory that the titanium must have coordinated to the ester carbonyl in order to facilitate the steric hindrance.

Catalyst	H-Source	Ratio (A:B)	Yield
Pd-C 10%	H_2	7:1	89%
$TiCl_4$	Et_3SiH	3:1	68%
$TiCl_4$	Ph_3SiH	1:1	100%

Table 4.15: Diastereoselective reductions of (**388**). *a) 10% (w/w) Pd-C 10%, H_2 (7 atm.), AcOH, RT, 72 hr.; b) Lewis acid, Et_3SiH, CH_2Cl_2, -90°C, 2 hr., increased to RT, 72 hr.; c) Lewis acid, Ph_3SiH, CH_2Cl_2, -90°C, 2 hr. increased to RT, 72 hr.*

The outcome of the palladium-catalysed hydrogenation was slightly harder to explain. With lactam (**293**) the selectivity was 2:3, favouring the *trans* isomer (*R,R* or *S,S*). With lactam (**388**) the selectivity was 7:1, but as the benzyl group could freely rotate, there should not have been more steric hindrance on one face than the other. Unfortunately, owing to the nature of the lactam we were unable to form salts or grow crystals, and as a result the absolute stereochemistry of the major isomer remains unknown. Not knowing which diastereomer was favoured made it difficult to rationalize or model a scenario that could explain the observed outcome. The one big difference between the palladium-catalysed reduction of (**293**) and of (**388**) was the solvent; compound (**388**) was reduced in the presence of acetic acid rather than absolute ethanol. The acid may have encouraged imine formation and altered the puckering of the lactam ring. Alternatively, the acid may have stabilized different conformations of (**388**) which had greater steric hindrance than the conformation found in absolute ethanol.

At this stage in the synthesis the diastereomers (**389A**) and (**389B**) were not separable, however we did successfully separate them at a later stage, and by hydrolysis back to the lactam, we were able to characterize each isomer individually. Both of them showed optical activity, isomer A (**389A**), the major

isomer, had an optical rotation of $[\alpha]_D^{20}$ +15.7 (*c* 1.15, CH_2Cl_2), while isomer B (**389B**), the minor isomer, had a high optical rotation value of $[\alpha]_D^{20}$ +131.6 (*c* 0.98, CH_2Cl_2).

In contrast to the preceding compound (**388**), the alkene signal at 4.39 ppm was no longer present and a new multiplet corresponding to H-5 was seen at 3.73-3.67 ppm for isomer A (**389A**) and at 3.26-3.18 ppm for isomer B (**389B**) (see Figure 4.26). The signal corresponding to H-4 shifted upfield to the aliphatic region while the signals for H-6 and H-7 showed diastereotopic splitting. The ^{13}C-NMR spectra for both isomers showed the absence of the enamine carbons and C-5 and C-4 were observed at 56.9 ppm and 33.9 ppm for isomer A (**389A**) and at 57.2 ppm and 34.7 ppm for isomer B (**389B**). FTIR spectroscopy indicated the presence of a lactam carbonyl at 1681 cm^{-1} and 1674 cm^{-1} for (**389A**) and (**389B**) respectively, and HRMS produced a molecular ion of 245.1765, in close agreement with the calculated value of 245.1780.

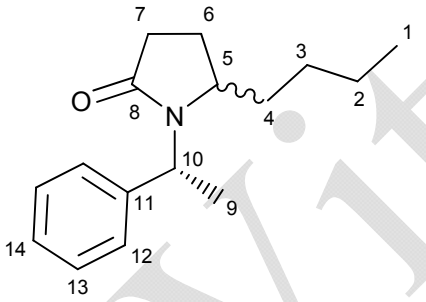


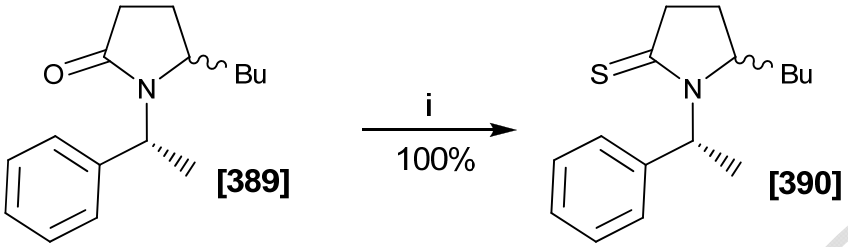
Figure 4.26: Numbering of lactam (**389**) for assignment of spectroscopic data.

4.6.3 Thionation reaction and separation of diastereomers

Following an analogous pattern to the monomorine I synthesis, thionation of lactam (**389**) should allow separation of the diastereomers. Two different sets of thionation conditions were attempted. The first thionation used phosphorus pentasulfide in dichloromethane stirring at ambient temperature for seventy-two hours. Following extraction and purification by column chromatography, the desired thiolactam (**390**) was isolated in 66% yield. During the second thionation, the lactam (**389**) was reacted with hexamethyldisiloxane,

WitsETD

phosphorus pentasulfide and dichloromethane at ambient temperature for seventy-two hours.[188] Following purification, the desired product was isolated in quantitative yield. As expected, the isomers could be separated by careful chromatography (see Scheme 4.36).

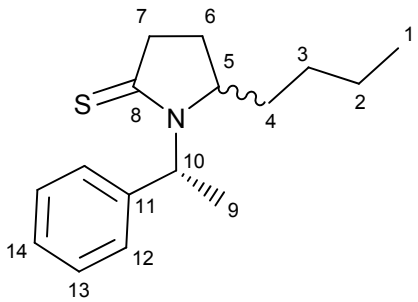


Scheme 4.36: Thionation of lactam (**389**) to form (**390**). *Reagents and conditions: i) P_2S_5, HMDO, $CHCl_3$, RT, 8 hr.*

Both isomers had unusually high optical rotation values, with isomer A (**390A**), the minor isomer, having an optical rotation of $[\alpha]_D^{20}$ + 226.7 (*c* 0.75, CH_2Cl_2) and isomer B (**390B**), the major isomer, having an optical rotation of $[\alpha]_D^{20}$ +383.6 (*c* 1.22, CH_2Cl_2).

The key change in the ^{13}C-NMR spectra for the thiolactam isomers in comparison to their precursor lactams was the shift of the carbonyl carbon (C-8) from 175.2 ppm and 175.0 ppm for (**390A**) and (**390B**), respectively, to the thiocarbonyl region of 201.8 ppm for both isomers. FTIR spectroscopy also showed the C-S stretching vibration at 1447 cm^{-1} and 1450 cm^{-1} for (**390A**) and (**390B**), respectively. When comparing the two isomers, their ^{1}H-NMR spectra were fairly different (see Table 4.16). Notably, the quartet corresponding for H-10 occurs at 6.30 ppm for (**390A**) and at 6.55 ppm for (**390B**). H-5 followed the same trend, occurring at 3.51 – 3.47 ppm for (**390A**) and at 4.05 – 3.99 ppm for (**390B**). Both isomers displayed greater diastereotopic splitting for H-6 than for H-7, due to the closer proximity to the stereogenic centre at C-5. Looking at the differences in their ^{13}C-NMR spectra, (**390A**) had C-5 at 64.4 ppm and C-10 at 55.6 ppm, whereas (**390B**) had C-5 at 63.8 ppm and C-10 at 53.7 ppm.

WitsETD



Signal	(390A) / ppm	(390B) / ppm
H-4	1.67 – 0.96 (m)	1.05 – 0.77 (m)
H-5	3.51 – 3.47 (m)	4.05 – 3.99 (m)
H-6	2.02 – 1.88 (m)	2.18 – 2.05 (m)
	1.67 – 0.96 (m)	1.78 – 1.69 (m)
H-7	3.12 – 3.00 (m)	3.16 – 2.95 (m)
H-9	1.70 (d, *J* 7.2)	1.66 (d, *J* 7.2)
H-10	6.30 (q, *J* 7.2)	6.55 (q, *J* 7.2)
C-4	33.5	33.2
C-5	64.4	63.8
C-6	29.7	27.3
C-7	43.7	43.6
C-8	201.8	201.8
C-9	16.4	15.1
C-10	55.6	53.7

Table 4.16: Comparison of selected NMR spectral data (in $CDCl_3$) for thiolactam isomers (**390A**) and (**390B**). (*J*-values were measured in Hz).

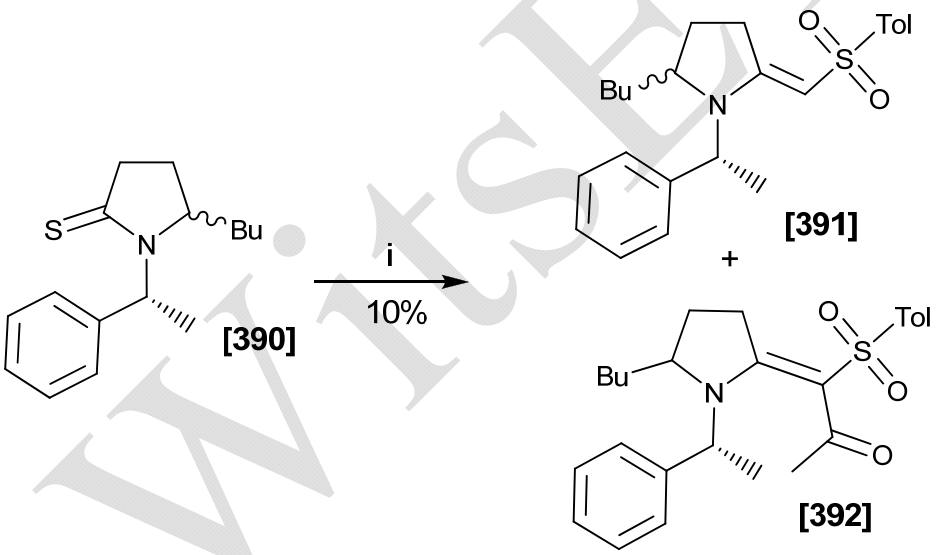
4.6.4 Preparation of the vinylogous sulfonamide

At this stage none of the monobenzylated intermediates (**388**), (**389**), and (**390**) had shown any sign of solidifying to allow us to obtain crystal structures and conclusive evidence as to which diastereomer was favoured. We had hoped that the formation of the vinylogous sulfonamide would finally allow for strong enough intermolecular forces such as additional π-π stacking to aid crystallization of at least one of the isomers.

In two separate reactions, each isomer of (*R*)-5-butyl-1-(1-phenylethyl)pyrrolidine-2-thione (**390**) was dissolved in dichloromethane

WiSE ID

together with sodium iodide and methyl iodide and stirred at ambient temperature for forty-eight hours to allow for complete salt formation.[188] The solvent was removed and a premixed solution of triethylamine, 1-[(4-methylphenyl)sulfonyl]acetone (**279**) and dichloromethane were added to the α-thioiminium salt and left to react for a further ninety-six hours. Following work up and purification, the major product from both reactions was (*R*)-5-butyl-1-(1-phenylethyl)pyrrolidin-2-one (**389**), the hydrolysis product of the salt. In the case of isomer A, a small amount of (*R,E*)-2-butyl-1-(1-phenylethyl)-5-(tosylmethylene)pyrrolidine (**391**) and (*E*)-1-(5-butyl-1-((*R*)-1-phenylethyl) pyrrolidin-2-ylidene)-1-tosylpropan-2-one (**392**) was obtained as a mixture in 10% yield (see Scheme 4.37). The low yield of the desired product may be due to the presence of moisture during the reaction or due to low reactivity of the substrate due to the bulkiness of the benzyl group. The product that was obtained showed no signs of solidifying.



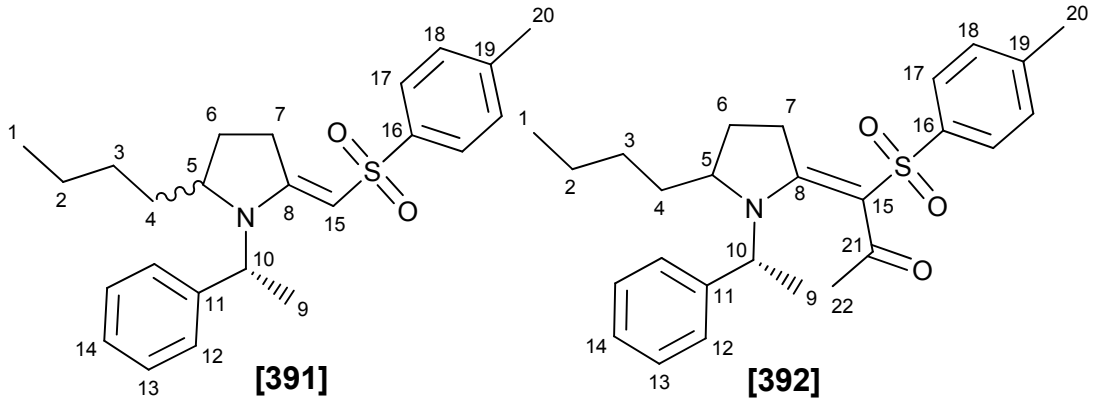
Scheme 4.37: Formation of vinylogous sulfonamides (**391**) and (**392**). *Reagents and conditions: i) a) MeI, THF, 48 hr.; b) (**279**), Et_3N, CH_2Cl_2, RT, 96 hr.*

Although the isolated product was a mixture of the acylated (**392**) and deacylated (**391**) vinylogous sulfonamides, use of a COSY spectrum made it possible to distinguish key signals from the two compounds and to assign them. Of particular importance was the presence of the vinyl signal at 4.89 ppm for (**391**) and the presence of additional methyl singlet at 2.40 ppm for (**392**).

WitsETD

When the NMR spectral data for (**391**) and (**392**) were compared with the spectral data for the analogous vinylogous sulfonamides (**296A**) and (**384A**) there were some strong correlations (see Table 4.17). The signals corresponding to H-4, H-5 and H-6 were further upfield in (**391**) and (**392**) compared with the corresponding signals in (**296A**) and (**384A**), while H-9 and H-10 for (**391**) and (**392**) were downfield shifted compared to (**296A**) and (**384A**) owing to the electron-withdrawing effect of the phenyl substituent. The signal corresponding to H-7 in both (**391**) and (**392**) matched well in chemical shift, but did not show the pronounced diastereotopic splitting of (**296A**) and (**384A**), respectively. The key signals were almost identical, with H-15 of (**391**) corresponding well with H-15 of (**296A**) and H-22 of (**392**) corresponding well with H-22 of (**384A**).

WitsETD



[391] [392]

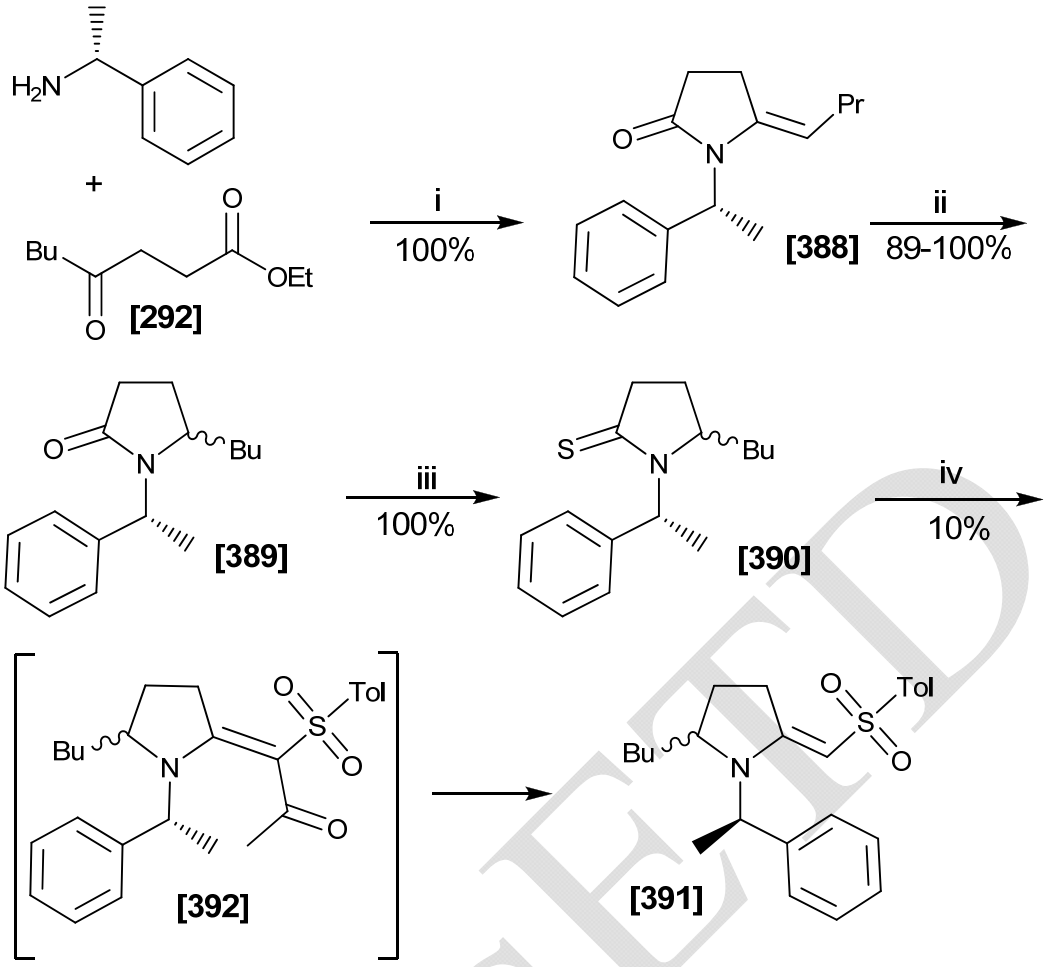
Signal	(296A) / ppm	(391) / ppm	(384A) / ppm	(392) / ppm
H-4	1.95 – 1.82 (m)	1.75 – 1.04 (m)	1.80 – 1.63 (m)	1.75 – 1.04 (m)
			1.40 – 1.23 (m)	
H-5	3.73 – 3.68 (m)	3.40 – 3.32 (m)	4.25 – 4.10 (m)	3.51 (tt, *J* 8.9, 2.8)
H-6	1.70 – 1.62 (m)	2.07 – 1.81 (m)	3.41 (dd)	2.07 – 1.81 (m)
	1.62 – 1.51 (m)		2.55 – 2.42 (m)	
H-7	2.92 – 2.80 (m)	2.89 – 2.78 (m)	3.76 (m)	3.16 – 3.01 (m)
	2.45 – 2.31 (m)		2.74 (dt)	
H-9	1.32 (d, *J* 6.9)	1.61 (d, *J* 7.1)	1.39 (d, *J* 7.2)	1.70 (d, *J* 7.2)
H-10	3.98 – 3.91 (m)	4.72 (q, *J* 7.1)	4.03 (m)	6.31 (q, *J* 7.2)
H-11	3.11 – 3.01 (m)	-	2.10 – 1.95 (m)	-
	2.92 – 2.80 (m)		1.80 – 1.63 (m)	
H-15	4.99 (s)	4.89 (s)	-	-
H-22	-	-	2.34 (s)	2.40 (s)

Table 4.17: Comparison of selected NMR spectral data (in $CDCl_3$) for vinylogous sulfonamides. (*J*-values were measured in Hz).

4.6.5 Attempted debenzylations

The synthetic pathway of the monobenzylated species (see Scheme 4.38 for the overall summary of the route) would only be useful in the synthesis of indolizidine alkaloids if the *N*-benzyl group could be removed at some stage in the synthesis. We attempted to debenzylate at three different stages: from the enamide (**388**), from the lactam (**389**), and from the thiolactam (**390**) (see Scheme 4.39)

WitsETD

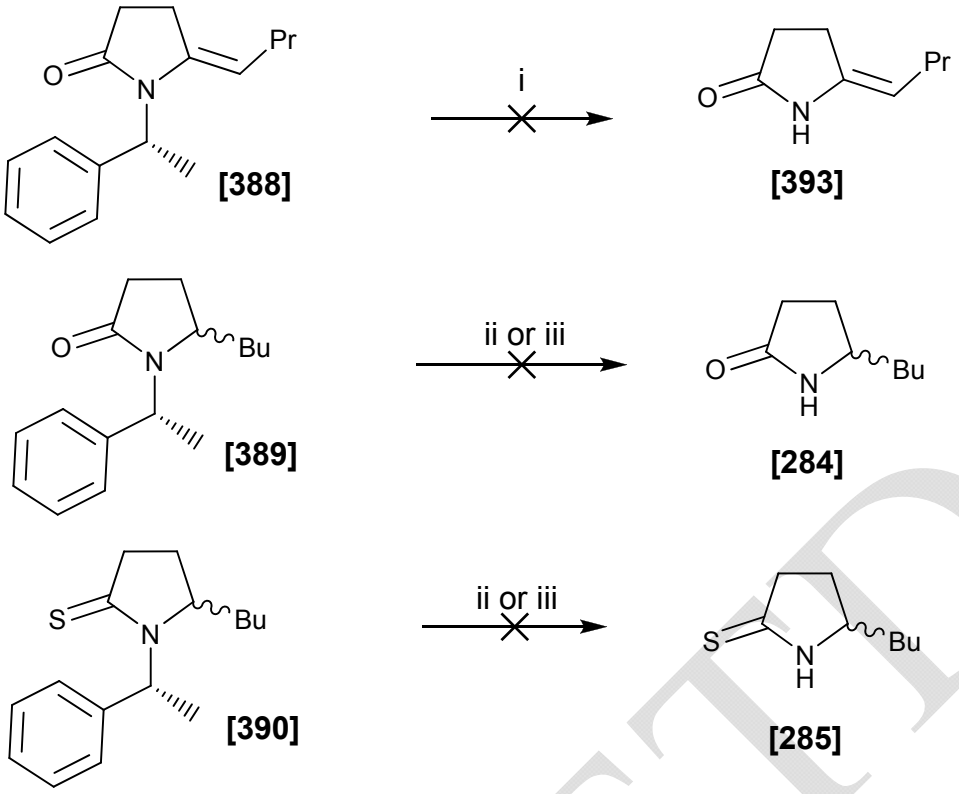


Scheme 4.38: Synthetic pathway via monobenzylated intermediates. *Reagents and conditions: i) AcOH, toluene, reflux, 72 hr.; ii*) *50% (w/w) Pd-C 10%, H_2 (7 atm.), EtOH, RT, 72 hr.; OR $TiCl_4$, Ph_3SiH, CH_2Cl_2, -90°C, 2 hr. increased to RT, 72 hr.; iii) P_2S_5, HMDO, $CHCl_3$, RT, 8 hr.; iv) a) MeI, THF, 48 hr.; b) (**279**), Et_3N, CH_2Cl_2, RT, 96 hr.*

The first attempted debenzylation reacted the lactam (**389**) with 50% Pearlman's catalyst in acetic acid under five atmospheres of hydrogen pressure for ninety-six hours. Following work-up and purification, only starting material was recovered in 85% yield.

The second attempted debenzylation was performed on the thiolactam (**390**), together with Pearlman's catalyst and acetic acid, under seven atmospheres of hydrogen pressure for seventy-two hours. Following work-up and purification, only starting material was recovered in 100% yield.

WISETD



Scheme 4.39: Attempted debenzylation reactions. *Reagents and conditions: i) Pd/C (10%), NH_4HCO_2, MeOH, RT, 3 hr.; ii) $Pd(OH)_2/C$, H_2 (5 atm.), AcOH, 96 hr.; iii) CAN (4 eq.), MeCN-H_2O (5:1), RT, 12 hr.*

The third attempt was an ammonium formate reduction of the enamide (**388**), using methanol, ammonium formate and 10% palladium on carbon. The solution was stirred for three hours and then filtered through Celite® and the residue was purified by column chromatography. Again only starting material was recovered in 65% yield.

The final two attempted debenzylations used ceric ammonium nitrate, as there was literature evidence that debenzylations of lactams was possible.[216, 217] The standard procedure involved dissolving four equivalents of ceric ammonium nitrate in acetonitrile and water (1:5 ratio) and stirring at ambient temperature for twelve hours. This procedure was followed using lactam (**389**) and only starting material was recovered in 100% yield. When this procedure was used on the thiolactam (**390**), starting material was recovered in 61% yield, and the remaining material hydrolysed to reform lactam (**389**) in 39% yield.

WITSETD

From these five failed attempts, it became apparent that removing the benzyl group was not a trivial matter. Unfortunately, this meant that it was impossible to cycle the material back into the synthesis of enantiopure monomorine I and 5-*epi*-monomorine I. Although we strongly suspect that this route favours the *cis* isomer (*R,S*) rather than the *trans* isomer (*R,R*), we were unable to obtain crystals of any of the intermediates and it remains speculation. If this route were optimised and debenzylation achieved, it could offer greater overall yields of monomorine I (the *R,S* isomer), as the diastereoselectivity was a pleasing 7:1.

4.7 Conclusion

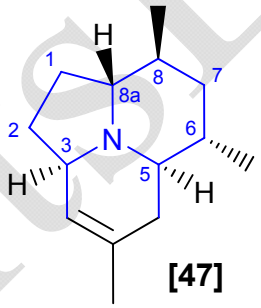
The syntheses of (±)-monomorine I and (±)-5-*epi*-monomorine I were both successful. From where the synthetic path diverged, the key intermediates (**295A**) and (**295B**), respectively, the overall yield for monomorine I was 24% and for 5-*epi*-monomorine I the yield was 12%. The yield for the key intermediates (**295A**) and (**295B**), from ethyl 4-chloro-4-oxobutyrate, were dependent on which diastereoselective reduction was performed. Using the palladium-catalysed reduction, (**295A**) and (**295B**) were synthesized with an overall yield of 34% and 51%, respectively, and using the titanium tetrachloride and triphenylsilane reduction (**295A**) and (**295B**) were synthesized with an overall yield of 12% and 60%, respectively. Hence the utility of vinylogous sulfonamides in accessing 3,5-disubstituted indolizidine alkaloids was successfully demonstrated. Unfortunately, the synthesis of enantiopure monomorine I and 5-*epi*-monomorine I never reached completion as the debenzylation reactions repeatedly failed to give the desired result. Clearly our method of introducing the first chiral centre needs to be carefully re-examined and a new route determined. Frustratingly, the initial attempts at debenzylating the chiral amine were successful and only the latter attempts failed to work. After thorough investigation of this problem we can only conclude that the commercially available palladium catalysts were not of the same quality as the catalysts originally available in the laboratory, possibly because of a trace contaminant.

WitsETD

CHAPTER 5
A MODEL STUDY FOR APPLYING RING-CLOSING METATHESIS IN THE SYNTHESIS OF INDOLIZIDINE-BASED ALKALOIDS

5.1 Introduction

Certain tricyclic alkaloids, for example coccinelline 205B (**47**), show a structural relationship to the 3,5-disubstituted indolizidines, as their tricyclic system formally incorporates a 3,5-disubstituted indolizidine within the skeleton (see Figure 5.1). The structural relationship between these two classes of alkaloids drew our interest as it offered an additional area for extending this PhD project. Ring-closing metathesis (RCM) was an obvious choice for forming the third ring as our research group has some experience with RCM reactions[238, 239] and there was literature precedent for this type of chemistry.[122]

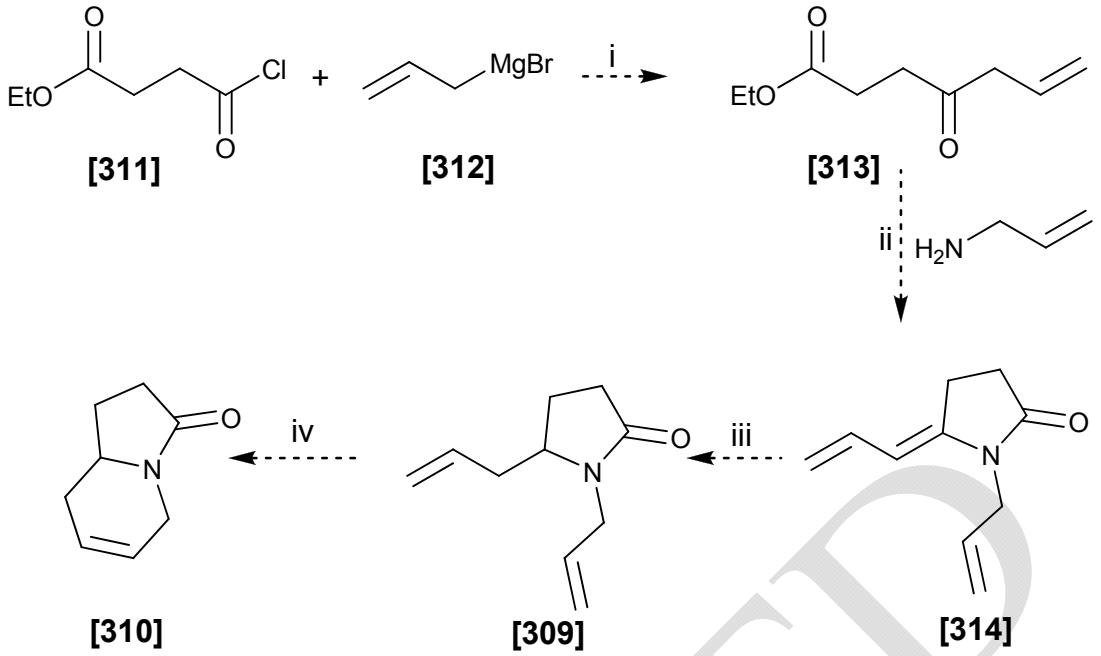


[47]

Figure 5.1: Structural relationship between 3,5-disubstituted indolizidine alkaloids (shown in blue) and the tricyclic alkaloid (**47**).

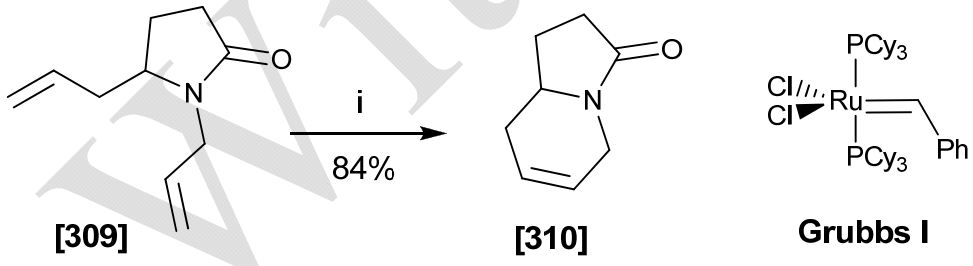
We proposed a model study to explore the use of RCM in an analogous condensation reaction to the one we used during the total synthesis of monomorine I (see Scheme 4.16). Our proposed model study (see Scheme 5.1) was designed to determine if the initial reaction conditions in the synthesis of monomorine I would be mild enough to allow for the incorporation of alkene side-chains.

WitsETD



Scheme 5.1: Proposed model synthesis for the RCM approach. *Reagents and conditions: i) $Fe(acac)_3$, THF, 0°C, 10 min.; ii) AcOH, toluene, reflux, 72 hr.; iii) $TiCl_4$, Ph_3SiH, CH_2Cl_2, -90°C, 2 hr., increased to RT, 72 hr. iv) 5 mol% Grubbs II, toluene.*

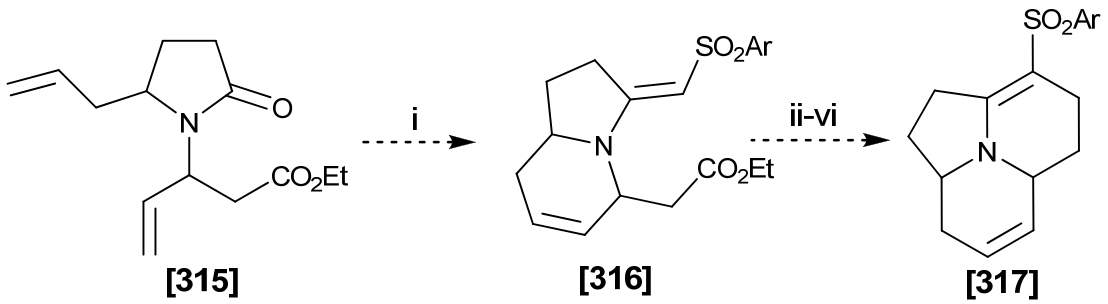
Holmes and co-workers[176] have performed an extensive investigation of RCM using β-, γ- and δ-lactams. They have successfully performed the final step in our proposed synthesis using the ruthenium alkylidene known as Grubbs I to catalyse the RCM (see Scheme 5.2).



Scheme 5.2: Synthesis of bicyclic molecules from lactams using RCM by Holmes and co-workers.[176] *Reagents and conditions: i) 5 mol% Grubbs I, CH_2Cl_2.*

In order to extend the proposed model study to form the tricyclic system, the allylamine would have to contain an ester side chain, which would ultimately be used to form the third ring (see Scheme 5.3). See Chapter 2 for a more detailed discussion.

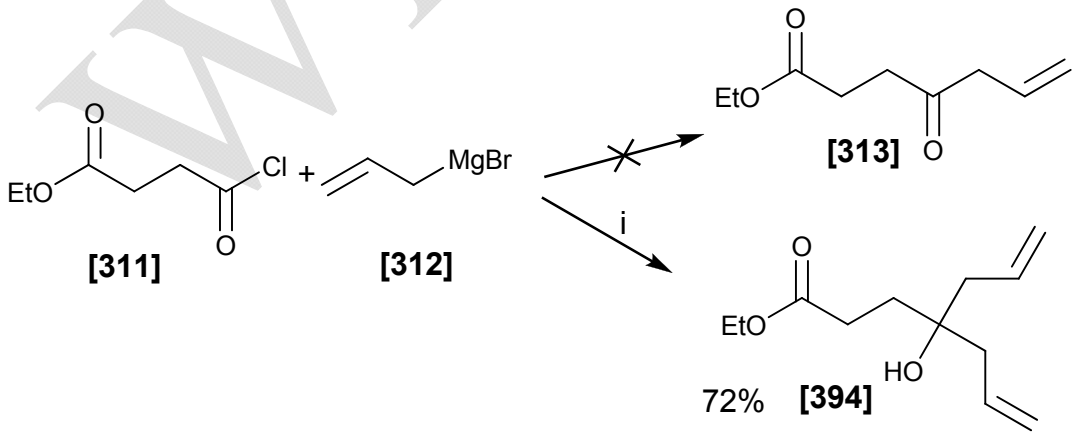
WitsETD



Scheme 5.3: Proposed synthesis for the formation of the tricyclic skeleton. *Reagents and conditions: i) 5 mol% Grubbs II, toluene; ii) Lawesson's reagent,CH_2Cl_2, RT, 72 hr.; iii) a) MeI, THF, 48 hr.; b) (**279**), Et_3N, CH_2Cl_2, RT, 96 hr.; iv) TFA, reflux, 30 min.; v) $LiAlH_4$, THF, RT, 15 hr.; vi) PPh_3, imidazole, I_2, toluene, reflux, 3 hr.*

5.2 Preparation of allylic ketoesters

Our first challenge was to synthesize ketoester (**313**) which proved to be non-trivial. The first method we attempted was the proposed Grignard reaction between ethyl 4-chloro-4-oxobutyrate (**311**) and allylmagnesium bromide (**312**), using iron(III) acetoacetate as a catalyst (see Scheme 5.4), which was analogous to our first step in the synthesis of monomorine I (see Section 4.2.1). Despite maintaining the reaction at –10°C and quenching it with dilute hydrochloric acid after a mere seven minutes, double addition of the allylmagnesium bromide occurred and ethyl 4-allyl-4-hydroxyhept-6-enoate (**394**) was isolated in 72% yield.



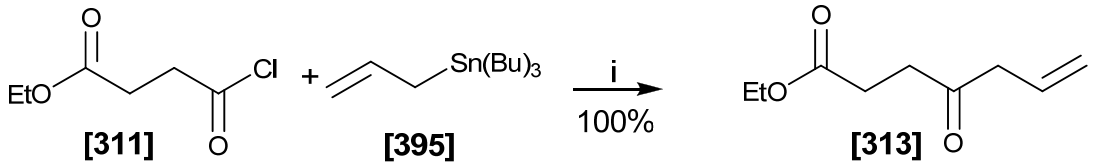
Scheme 5.4: Grignard reaction between (**311**) and (**312**) resulted in the di-addition product (**394**). *Reagents and conditions: i) $Fe(acac)_3$, THF, -10°C, 7 min.*

WISER

The alcohol (**394**) was characterized by ^{1}H-NMR spectroscopy and showed the alkene signals at 5.84 ppm integrating for two hydrogens and at 5.18 – 5.07 ppm integrating for four hydrogens. The ethyl ester signals were at 4.16 ppm and 1.26 ppm and the OH showed as a singlet at 1.56 ppm. The ^{13}C-NMR spectrum confirmed the presence of the ester with a signal at 172.1 ppm and the alkene with signals at 133.5 ppm and 118.6 ppm, respectively. The carbon adjacent to the hydroxyl group was observed at 73.7 ppm. FTIR spectroscopy confirmed the presence of the ester and the alcohol functionalities with signals at 1716 cm^{-1} and at 3090 cm^{-1}.

This result confirmed that the increased reactivity of the allylmagnesium bromide compared to the butylmagnesium bromide used in the synthesis of monomorine I, meant an alternative method had to be employed. A variety of methods were attempted, all with limited success: Firstly, we tried substituting iron(III) acetoacetate by tributylphosphine, or we used allylzinc bromide instead of allylmagnesium bromide,[240] or allyl(chloro)dimethylsilane. We also attempted going via the less reactive aldehyde instead of the acid chloride. All methods resulted either in multiple additions of the allyl group or more complex products that were not identified. Finally, we tried using a stannane nucleophile.

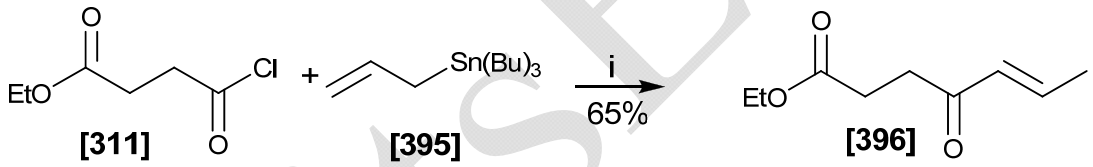
Ethyl 4-chloro-4-oxobutyrate (**311**) was reacted with allyl tri-*n*-butyl tin (**395**) together with Wilkinson's catalyst in dichloromethane in a sealed tube at 65°C for five hours (see Scheme 5.5). The solvent was removed *in vacuo* and the crude material was purified by column chromatography to give ethyl 4-oxohept-6-enoate (**313**) in quantitative yield, slightly contaminated by tri-*n*-butyltin chloride.



Scheme 5.5: Organometallic reaction for the formation of allylketoester (**313**). *Reagents and conditions: i) Wilkinson's cat., CH_2Cl_2, 65°C, 5 hr.*

Ethyl 4-oxohept-6-enoate (**313**) was characterized by ^{1}H-NMR spectroscopy which revealed a terminal alkene at 5.98 – 5.88 ppm integrating for one hydrogen and at 5.16 ppm, integrating for two hydrogens. The ^{13}C-NMR spectrum showed the ketone carbonyl at 206.4 ppm, the ester carbonyl at 172.4 ppm and the alkene at 130.2 ppm and 118.7 ppm.

Despite the high toxicity of the allyl tri-*n*-butyl tin, this was a pleasing result and we set about repeating it. The reaction was set up as before, and after five hours at 65°C, the reaction was left stirring at ambient temperature for twelve hours (see Scheme 5.6). The solvent was removed *in vacuo* and the crude oil was rinsed with acetonitrile and hexane to remove the residual tin. The acetonitrile fraction was rinsed a further two times, and the solvent was then removed *in vacuo.* The crude material was purified by column chromatography to give ethyl (5*E*)-4-oxohept-5-enoate (**396**) in 65% yield as a mixture of geometric isomers (*cis*:*trans* ratio 1:2).



Scheme 5.6: Organometallic reaction for the formation of allylketoester (**396**). *Reagents and conditions: i) Wilkinson's cat., CH_2Cl_2, 65°C, 5 hr., then cooled to RT, 12 hr.*

It was clear from the NMR spectra that the alkene was no longer terminal and had shifted to the internal position in conjugation with the carbonyl; in the ^{1}H-NMR spectrum the alkene signals occurred at 6.90 ppm and 6.16 ppm as a doublet of quartets and a doublet, both integrating for only one hydrogen. The adjacent methyl group had two signals, a doublet at 1.91 ppm for the *trans* isomer and a doublet at 1.54 ppm for the *cis* isomer. The ^{13}C-NMR spectrum confirmed the presence of both *cis* and *trans* isomers, as most of the signals were duplicated.

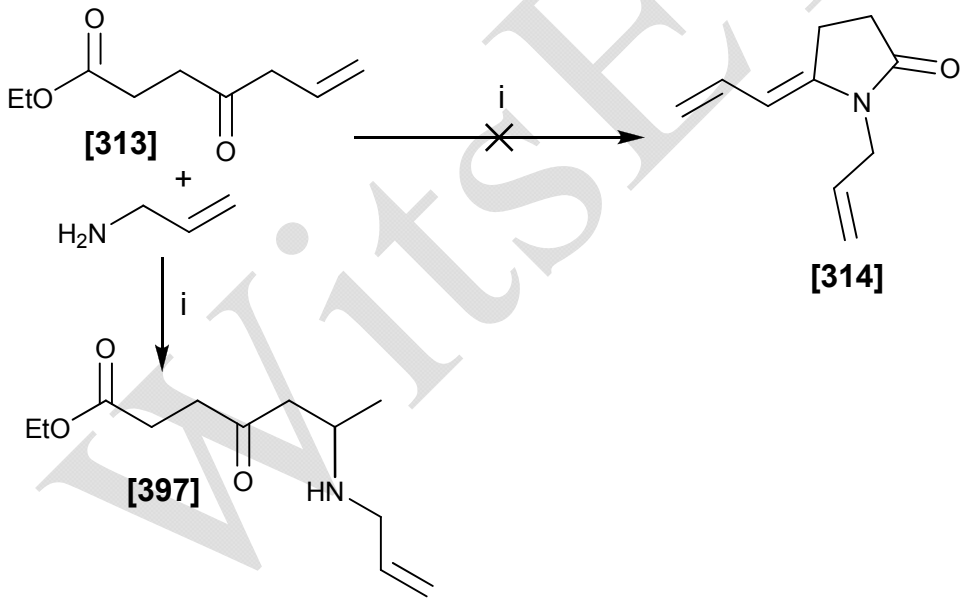
This result was disappointing, as the double bond had clearly shifted to a more stable position after over-exposure to Wilkinson's catalyst, despite the relatively

WiSER

mild conditions. At a later stage we discovered that (**313**) spontaneously isomerizes to (**396**) after standing at ambient temperature for several days.

5.3 Attempted condensation reactions

More of ethyl 4-oxohept-6-enoate (**313**) was prepared, being careful not to let it react for too long or stand in the presence of Wilkinson's catalyst. Immediately after purification (**313**) was set up to react with allylamine in toluene and acetic acid heated at reflux (see Scheme 5.7). Unfortunately, the conditions were too harsh and (**313**) isomerised to (**396**) prior to reacting with the amine. The amine appeared to react with the Michael acceptor rather than the ketone, and although the product of the reaction was not fully characterized, it was clear from the spectroscopic results that the ester and the ketone were still present, as was a terminal alkene.

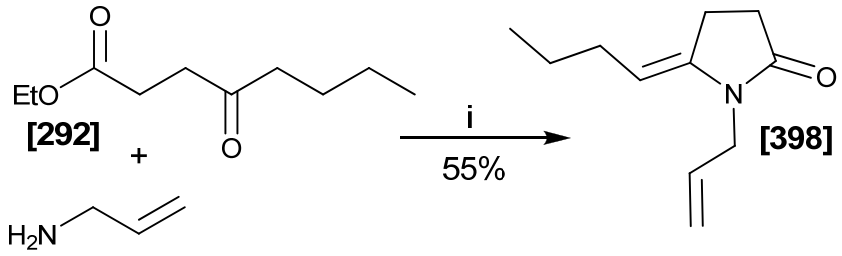


Scheme 5.7: Attempted condensation reaction with (**313**) and allylamine. *Reagents and conditions: i) AcOH, toluene, reflux, 72 hr.*

In order to confirm that the problem with the condensation reaction was due to the allylketoester (**313**), and not the allylamine, we attempted a condensation reaction between allylamine and ethyl 4-oxooctanoate (**292**) under our standard conditions: toluene and acetic acid heated at reflux for seventy-two hours. The

WitsETD

condensation reaction worked perfectly and (5*E*)-1-allyl-5-butylidenepyrrolidin-2-one (**398**) was isolated in 55% yield (see Scheme 5.8).



Scheme 5.8: Condensation reaction between ketoester (**292**) and allylamine. *Reagents and conditions: i) AcOH, toluene, reflux, 72 hr.*

(5*E*)-1-Allyl-5-butylidenepyrrolidin-2-one (**398**) was fully characterized and, analogous to earlier condensation reactions, (**398**) was isolated as a single geometric isomer (see Figure 5.2). The key ^{1}H-NMR spectral signals include the terminal alkene signals, H-10 and H-11 at 5.78 – 5.65 ppm and 5.17 – 5.12 ppm, respectively, the internal alkene signal, H-4, at 4.66 ppm, and H-9 which occurred at 4.09 ppm as a doublet. The ^{13}C-NMR spectrum had one carbonyl signal at 175.1 ppm and four alkene signals at 138.7 ppm, 131.8 ppm, 116.7 ppm and 101.3 ppm. The HRMS produced a parent ion at 179.1325, in excellent correspondence to the required 179.1310.

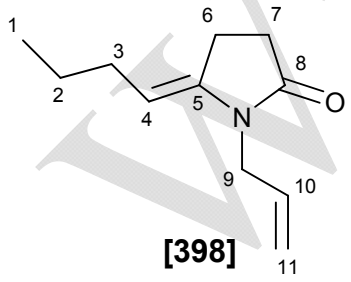
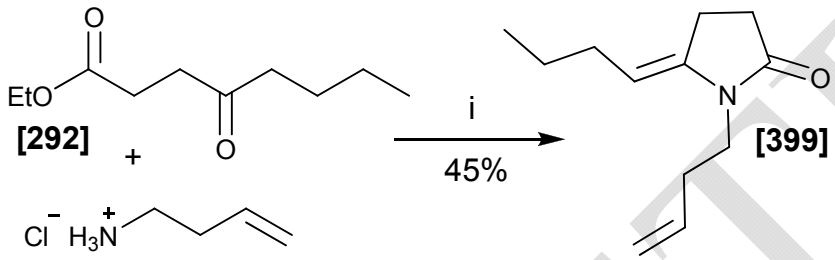


Figure 5.2: Numbering of lactam (**398**) for assignment of spectroscopic data.

Inspired by the successful condensation with allylamine, we decided to see if bicyclic structures could be formed by RCM using the exocyclic alkene that forms during the condensation. (5*E*)-1-Allyl-5-butylidenepyrrolidin-2-one (**398**) presented us with a poor candidate for RCM, as the ring strain involved in forming a four-membered ring would probably interfere with the metathesis. We

WITSETD

purchased butenylamine hydrochloride in order to prepare the analogous RCM precursor (**399**), which would be more suitable for RCM as it could form a five-membered ring.[d] Butenylamine hydrochloride was thus condensed with ketoester (**292**) under our standard conditions; toluene and acetic acid heated at reflux for seventy-two hours (see Scheme 5.9). After purification by column chromatography, (5*E*)-1-but-3-enyl-5-butylidenepyrrolidin-2-one (**399**) was isolated as a yellow oil in 45% yield. The use of the readily available hydrochloride salt instead of the free amine did not seem to affect the reaction.



Scheme 5.9: Condensation reaction between ketoester (**292**) and butenylamine. *Reagents and conditions: i) AcOH, toluene, reflux, 72 hr.*

(5*E*)-1-But-3-enyl-5-butylidenepyrrolidin-2-one (**399**) was characterized by NMR spectroscopy (see Figure 5.3). Again, the key signals in the ^{1}H-NMR spectrum were for the internal and the terminal alkenes; H-11 at 5.85 – 5.71 ppm, H-12 at 5.10 – 5.02 ppm and H-4 at 4.65 ppm. In contrast to (**398**), there was an additional methylene signal at 2.33 – 2.26 ppm corresponding to H-10.

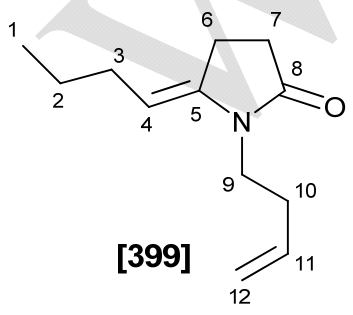
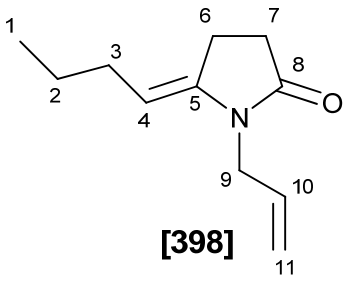


Figure 5.3: Numbering of lactam (**399**) for assignment of spectroscopic data.

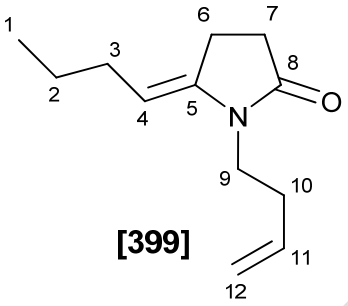
[d] *Pentenylamine hydrochloride would be a better precursor, as the condensation product could undergo RCM to form an indolizidine skeleton. However, it was prohibitively expensive for a purely speculative investigation.*

WISER

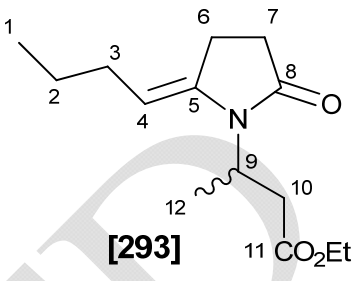
Table 5.1 compares the three condensation products (**389**), (**399**) and (**293**) which had virtually indistinguishable signals for the lactam and butyl side-chain (H-3, H-4, H-6, H-7, C-4, C-5, C-6, C-7 and C-8). The nitrogen side chains showed obvious differences for C-9, C-10 and C-11 as the functionality changed.



[398]



[399]



[293]

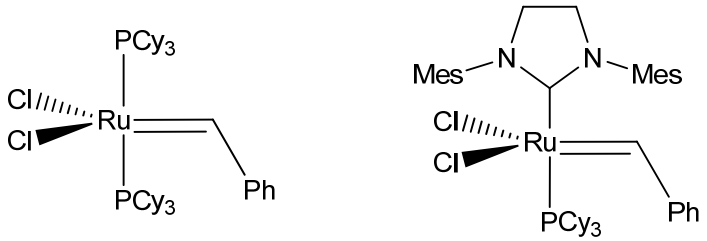
Signal	**(398) / ppm**	**(399) / ppm**	**(293) / ppm**
H-3	1.98 (q, *J* 7.2)	2.00 (q, *J* 7.2)	2.00 (q, *J* 7.3)
H-4	4.66 (t, *J* 7.2)	4.65 (t, *J* 7.2)	4.77 (t, *J* 7.4)
H-6	2.74-2.44 (m)	2.60 (t, *J* 7.2)	2.58 (t, *J* 8.0)
H-7	2.74-2.44 (m)	2.50 – 2.44 (m)	2.42 (t, *J* 8.0)
H-9	4.09 (d, *J* 5.1)	3.53 (t, *J* 7.2)	4.45 – 4.37 (m)
H-10	5.78 – 5.65 (m)	2.33 – 2.26 (m)	3.04 (dd, *J* 7.4, 15.7)
			2.81 (dd, *J* 7.3, 15.7)
H-11	5.17 – 5.12 (m)	5.85 – 5.71 (m)	-
C-4	101.3	100.6	101.0
C-5	138.7	139.0	138.7
C-6	21.2	21.3	21.6
C-7	28.7	28.9	29.2
C-8	175.1	175.4	175.7
C-9	42.1	39.0	45.2
C-10	131.8	30.8	37.6
C-11	116.7	134.9	171.4

Table 5.1: Comparison of NMR spectral data (in $CDCl_3$) for enamides (**398**), (**399**) and (**293**). (*J*-values given in Hz).

WitsETD

5.4 Ring-closing metathesis reactions

RCM reactions are traditionally catalysed by Grubbs I, 1st generation catalyst or by Grubbs II, 2nd generation catalyst (see Figure 5.4). We chose to use Grubbs II for our attempted RCM reactions, as it exhibits tolerance to a diverse range of functionality.[241, 242]

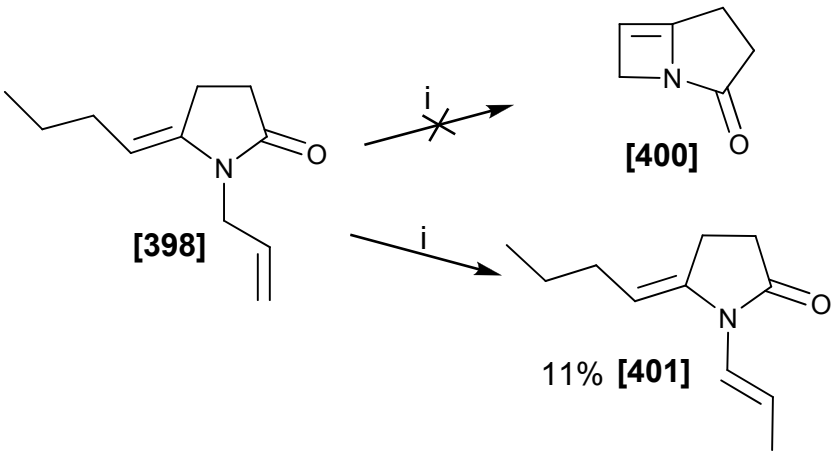


Grubbs I **Grubbs II**

Figure 5.4: Grubbs I and Grubbs II.

The two compounds we had prepared (**398**) and (**399**) were not the ideal candidates for RCM due to the internal alkene and potential ring strain. In spite of this, we decided to attempt RCM, as (**398**) and (**399**) were easy to prepare. We initially attempted the RCM in toluene at ambient temperature in the presence of Grubbs II. TLC indicated that no reaction was occurring and so we heated the solution to reflux for twelve hours (see Scheme 5.10). After purification by column chromatography none of the desired product (**400**) was obtained. However, a small amount of the starting material had isomerised to give us (*E*)-5-butylidene1-(prop-1-enyl)pyrrolidin-2-one (**401**) in 11% yield. No other products were isolated.

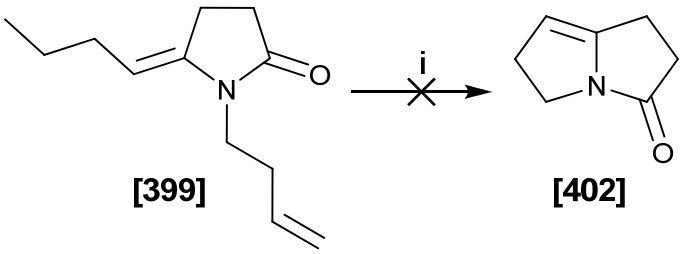
WiSETD



Scheme 5.10: Attempted RCM reaction on (**398**). *Reagents and conditions: i) 5 mol% Grubbs II, toluene, reflux, 12 hr.*

(*E*)-5-Butylidene1-(prop-1-enyl)pyrrolidin-2-one (**401**) was fully characterized, and the spectroscopic data obtained were largely similar to the precursor (**398**). The key difference was the terminal alkene signal at 5.78 – 5.65 ppm and 5.17 – 5.12 ppm was absent and instead an alkene signal integrating for two hydrogens was present at 6.09 – 5.96 ppm. The adjacent methyl group was observed as a doublet at 1.81 ppm integrating for three hydrogens. Interestingly, only one geometric isomer was observed. The ^{13}C-NMR spectrum had four alkene signals at 139.2 ppm, 122.4 ppm, 121.3 ppm and 102.7 ppm.

The butenyl alkene (**399**) was a marginally better candidate for RCM, as it would form a pyrrolizinone (**402**), with less ring strain than (**401**). However, internal alkenes, which are not as susceptible to RCM as terminal alkenes, could still cause problems (see Scheme 5.11).



Scheme 5.11: Attempted RCM reaction of (**399**). *Reagents and conditions: i) 5 mol% Grubbs II, toluene, reflux, 12 hr.*

WitsETD

The reaction was attempted twice; once in toluene at ambient temperature for five days, from which only starting material was recovered, and once in a toluene solution heated at reflux for twelve hours, which decomposed all the starting material.

5.5 Conclusion

These results were extremely disappointing, as clearly the proposed model study (see Scheme 5.1) proved to be an invalid synthetic pathway. The work of Holmes and co-workers,[176] Kim and co-workers[242] and Smith III *et al*.[122] has already shown the potential of RCM in the synthesis of bicyclic and tricyclic nitrogenous compounds, but in order to incorporate this methodology into our current synthetic strategy we would need to modify the allylketoester (**313**) into a more stable precursor that can withstand the condensation reaction (see Figure 5.5). The simplest modification would be to change the allyl chain into a terminal butenyl chain which would be less susceptible to isomerisation. The second major consideration would be to revise the synthetic route for accessing lactam (**315**) and hence extend the vinylogous sulfonamide methodology to include tricyclic alkaloids. Time did not allow for further investigations into this synthetic strategy but it certainly holds potential.

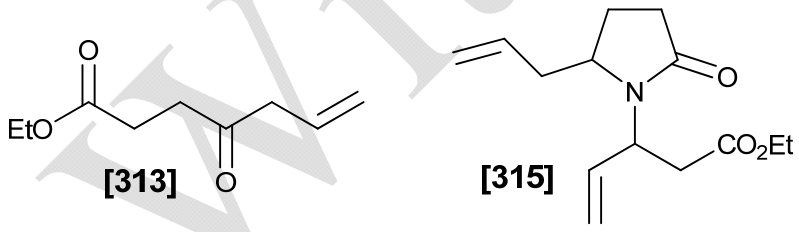


Figure 5.5: Allylketoester (**313**) and lactam (**315**).

WitsETD

CHAPTER 6
SUMMARY, FUTURE PROSPECTS, AND CONCLUSION

6.1 Summary

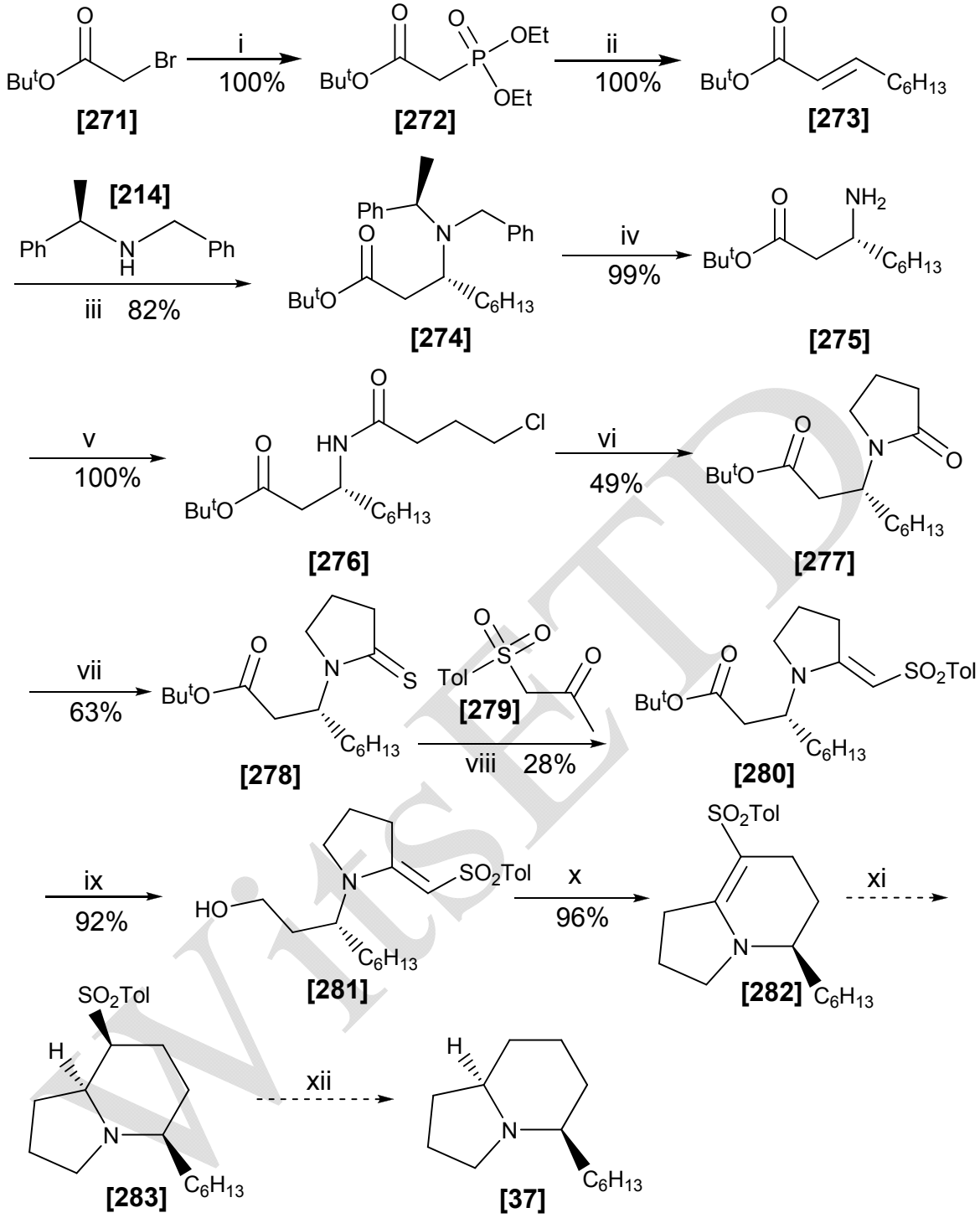
6.1.1 Attempted total synthesis of (−)-indolizidine 209D

Our first aim at the start of this project was to repeat Yillah's synthesis of (−)-indolizidine 209D,[31] while verifying the experimental procedures and fully characterizing all intermediates as well as (−)-indolizidine 209D, particularly the optical rotation values. We succeeded in completing the first ten steps of the total synthesis (see Scheme 6.1), and obtained optical rotation values that correspond reasonably in sign and magnitude to the data obtained for the homologous synthesis by Gravestock[139, 230] (see Table 6.1). Our data do, however, differ significantly from those obtained by Yillah (see Table 6.1).

Compound	**Yillah[31]** **(R= C_6H_{13})** ($c \approx 1.0$, CH_2Cl_2)	**Our data** **(R= C_6H_{13})** ($c \approx 1.0$, CH_2Cl_2)	**Gravestock[230]** **(R= C_5H_{11})** ($c \approx 1.0$, EtOH)
(274)	$[\alpha]_D^{20}$ +13.8	$[\alpha]_D^{20}$ +4.5	$[\alpha]_D^{25}$ +5.1
(275)	$[\alpha]_D^{20}$ -23.4	$[\alpha]_D^{20}$ -13.4	$[\alpha]_D^{26}$ -17.7
(276)	$[\alpha]_D^{20}$ -11.3	$[\alpha]_D^{20}$ +10.5	$[\alpha]_D^{25}$ +6.6
(277)	$[\alpha]_D^{20}$ +18.6	$[\alpha]_D^{20}$ +9.5	$[\alpha]_D^{24}$ +12.4
(278)	$[\alpha]_D^{20}$ -9.8	$[\alpha]_D^{20}$ +7.4	$[\alpha]_D^{30}$ +17.2
(280)	$[\alpha]_D^{20}$ -41.5	$[\alpha]_D^{20}$ +11.6	-
(281)	$[\alpha]_D^{20}$ -5.3	$[\alpha]_D^{20}$ -25.0	-
(282)	$[\alpha]_D^{20}$ +31.0	$[\alpha]_D^{20}$ +9.4	-

Table 6.1: Comparison of optical rotation data. 'R' refers to the alkyl side chain for compounds (**274 - 282**) and for the analogous compounds synthesized by Gravestock.

witsETD



Scheme 6.1: The attempted total synthesis of (−)-indolizidine 209D. *Reagents and conditions: i) $P(OEt)_3$, 110°C, 24 hr.; ii) NaH, heptanal, Et_2O, RT, 1 hr.; iii) a) (**214**),* n-*BuLi, THF, -90°C, 30 min.; b) (**273**), -90°C, 4 hr.; iv) H_2 (7 atm.), 5% Pd-C (1.0 eq.), AcOH, 48 hr.; v) $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, RT, 12 hr.; vi) $KOBu^t$, Bu^tOH, RT, 72 hr.; vii) Lawesson's reagent,CH_2Cl_2, RT, 72 hr.; viii) a) MeI, THF, 72 hr.; b) (**279**), Et_3N, CH_2Cl_2, RT, 96 hr.; ix) $LiAlH_4$, THF, RT, 15 hr.; x) PPh_3, imidazole, I_2, toluene, reflux, 6 hr. xi) H_2 (7 atm.), PtO_2, MeOH; xii) Na(Hg), Na_2HPO_4.*

WitsETD

Our yields for the first ten steps in the synthesis compared favourably with those obtained by Yillah, with the exception of steps (iv), (vi) and (viii) (see Scheme 6.1). For steps (vi), and (viii), the low yield we observed in both cases was due to the formation of by-products that could not be cycled back into the synthesis. Step (iv), the debenzylation step, initially worked excellently (99% yield), but then it ceased to fully debenzylate (**274**), with the monodebenzylated product frequently isolated. This continuous failure of this reaction prevented us from making enough of the amine (**275**) to complete the synthesis. The problem was investigated and several alternative methods were attempted, but to no avail.

In conclusion, we successfully completed ten out of the twelve steps in the synthesis of (−)-indolizidine 209D (**37**). We obtained optical rotation data that align well with similar molecules, we isolated several novel side-products, and most importantly, we gained sufficient experience with the methodology to continue with the synthesis of monomorine I and its isomers.

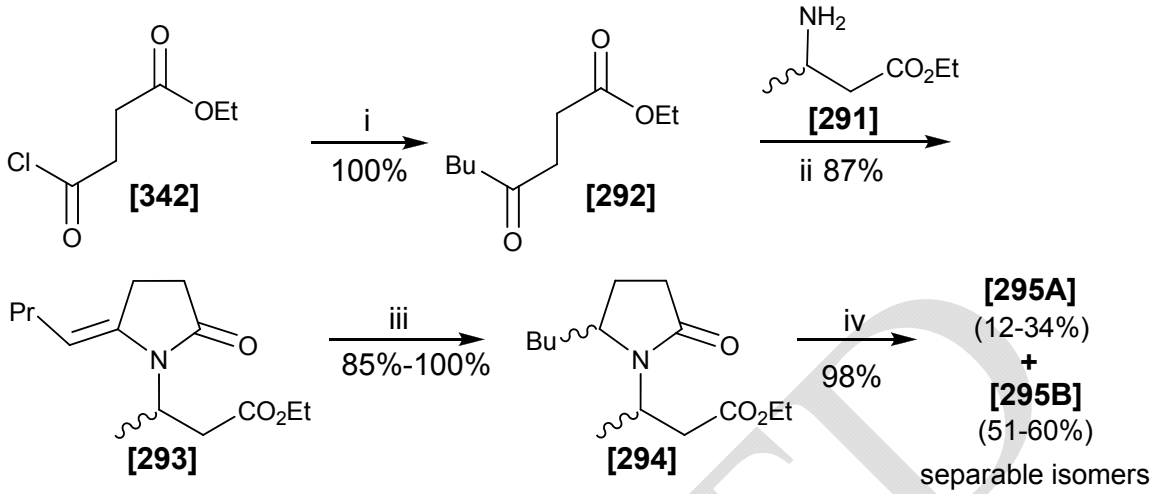
6.1.2 Total synthesis of (±)-monomorine I

Our second aim was to synthesize racemic monomorine I and/or its diastereomers using vinylogous sulfonamides for the key cyclisations. Basically, we wanted to extend the methodology used in the attempted synthesis of the 5-monosubstituted indolizidine 209D (**37**) to include 3,5-disubstituted indolizidines such as monomorine I (**27**). The alkyl side-chain at the 3-position had to be introduced prior to the formation of the lactam ring, hence this synthesis only corresponds with the synthesis of indolizidine 209D after the formation of the lactam (**294**). Starting from achiral material, the first four steps in the synthesis were the basis for the synthesis of both monomorine I and its' isomer 5-*epi*-monomorine I (see Scheme 6.2).

Step (iii) was our first opportunity for stereocontrol, and by exploiting the functionality present we were able to adjust the stereoselectivity from (2:3) to (1:5), in both instances favouring the *trans*-isomer that was the precursor of 5-*epi*-monomorine I. After the thionation reaction (step iv), the key intermediate diastereomers (**295A**) and (**295B**) were separated by column chromatography.

WitsETD

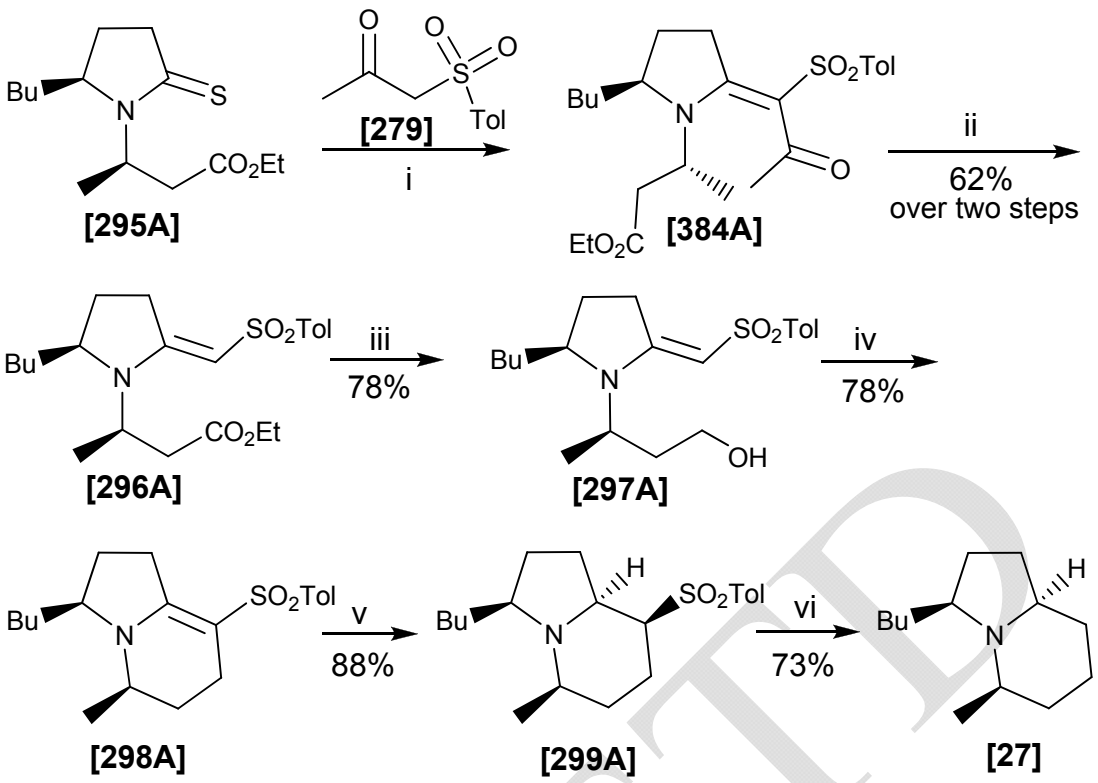
The overall yield for the monomorine I precursor, the *cis*-isomer (**295A**), was between 12 - 34%, depending on the conditions employed for step (iii).



Scheme 6.2: The synthesis of monomorine I precursor (**295A**). *Reagents and conditions: i)* n-*BuMgCl, Fe(acac)$_3$, THF, 0°C, 10 min.; ii) AcOH, toluene, reflux, 64 hr.; iii*) *50% (w/w) Pd-C 10%, H_2 (7 atm.), EtOH, RT, 72 hr.; OR $TiCl_4$, Ph_3SiH, CH_2Cl_2, -90°C, 2 hr. increased to RT, 72 hr.; iv) Lawesson's reagent,CH_2Cl_2, RT, 72 hr.*

Once the diastereomers (**295A**) and (**295B**) were separated, the synthesis of monomorine I was carried out independently of the 5-*epi*-monomorine I synthesis. Scheme 6.3 shows the total synthesis of racemic monomorine I from (**295A**). In general, all the yields for the *cis*-isomer were higher than for the *trans*-isomer, and the stereoselective reduction (step v) had greater stereocontrol than the equivalent step for the *trans*-isomer. (±)-Monomorine I was isolated as a single isomer, in 24% yield (from **295A**). The spectroscopic data obtained compared well to the literature. Hence, monomorine I was synthesized via a novel ring closure in a reasonable number of steps and with an overall yield comparable to those observed in the literature (see Chapter 1).

WitsETD



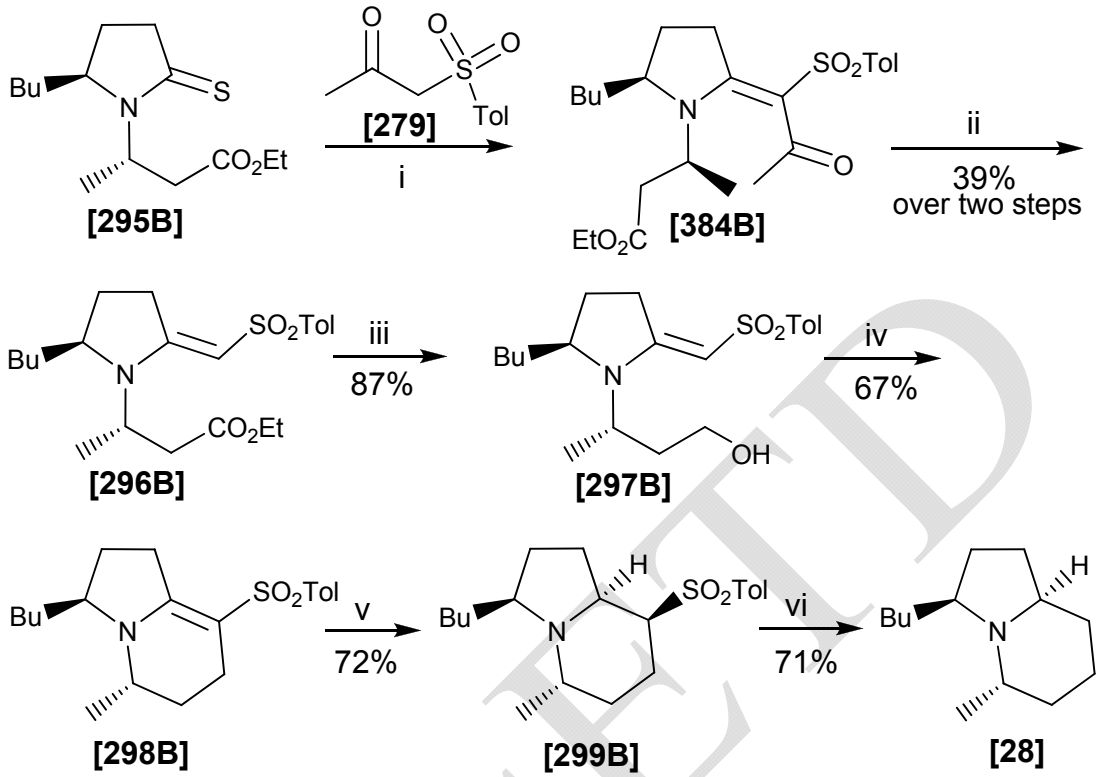
Scheme 6.3: The synthesis of (±)-monomorine I. *Reagents and conditions: i) a) MeI, THF, 48 hr.; b) (**279**), Et_3N, CH_2Cl_2, RT, 96 hr.; ii) TFA, reflux, 30 min.; iii) $LiAlH_4$, THF, RT, 15 hr.; iv) PPh_3, imidazole, I_2, toluene, reflux, 3 hr. v) H_2 (7 atm.), PtO_2, MeOH; vi) $Na^+C_{10}H_8^-$ (15 eq.), THF, RT, 15 min.*

6.1.3 Total synthesis of (±)-5-*epi*-monomorine I

The route we pioneered to lactam (**294**) provided us with a synthetic pathway to both monomorine I and 5-*epi*-monomorine I (see Scheme 6.2), and to our delight, not only could we manipulate the diastereoselectivity, but we could also separate the thiolactam isomers by column chromatography. The overall yield, from ethyl 4-chloro-4-oxooctanoate, for the *trans*-isomer (**295B**) was between 51-60%, depending on the conditions employed for the diastereoselective step (iii) (see Scheme 6.2). Once the diastereomers (**295A**) and (**295B**) were separated, the synthesis of 5-*epi*-monomorine I was carried out independently (see Scheme 6.4). In general, all the yields for the *trans*-isomer were lower than for the *cis*-isomer. In some of the steps the reason for the lower yield may be due to steric interference of the butyl group. The reduction (step v) had lower stereoselectivity than for the *cis*-isomer, and trace amounts of a third diastereomer, indolizidine 195B, were also detected after the final

WitsETD

desulfonylation (step vi). (±)-5-*epi*-Monomorine I was isolated in 12% yield (from **295B**) and the spectroscopic data obtained compared well to the literature.



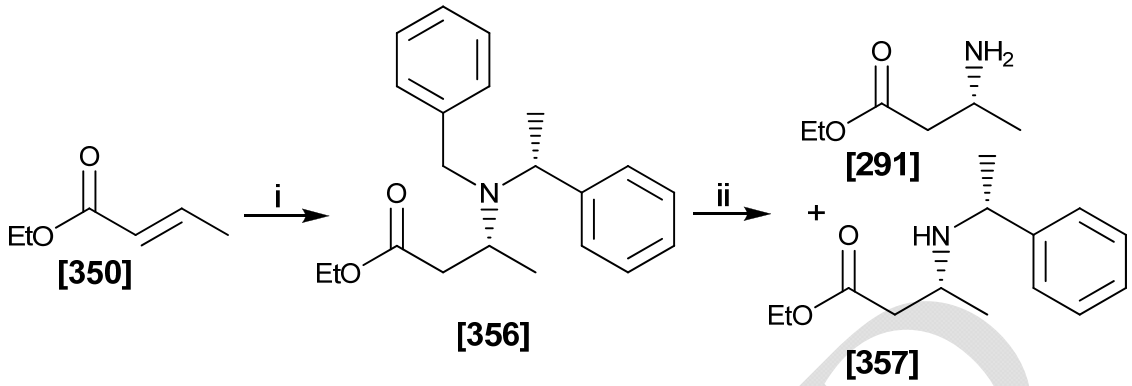
Scheme 6.4: The synthesis of (±)-5-*epi*-monomorine I. *Reagents and conditions: i) a) MeI, THF, 48 hr.; b) (**279**), Et_3N, CH_2Cl_2, RT, 96 hr.; ii) TFA, reflux, 30 min.; iii) $LiAlH_4$, THF, RT, 15 hr.; iv) PPh_3, imidazole, I_2, toluene, reflux, 3 hr. v) H_2 (7 atm.), PtO_2, MeOH; vi) $Na^+C_{10}H_8^-$ (8 eq.), THF, RT,15 min.*

6.1.4 Attempted enantioselective synthesis

Our third aim for this project was to incorporate Davies' methodology[158] into our strategy, and hence complete the enantioselective synthesis of monomorine I and/or its diastereomers. Although the literature precedent was great,[158, 180 - 182, 184] and Davies' methodology has been used in similar syntheses in the Wits laboratories,[156] we were unable to achieve this aim. Analogous to the problems we experiences with the synthesis of indolizidine 209D, the benzylated amine (**356**) initially underwent complete debenzylation but later attempts at the reaction ceased to produce any of the desired amine (**291**). Instead we isolated the monobenzylated species (**357**) (see Scheme 6.5). After investigating several variations of the palladium-catalysed debenzylation, we concluded that

WISETD

the quality of the catalyst was the reason that the reaction ceased to go to completion.



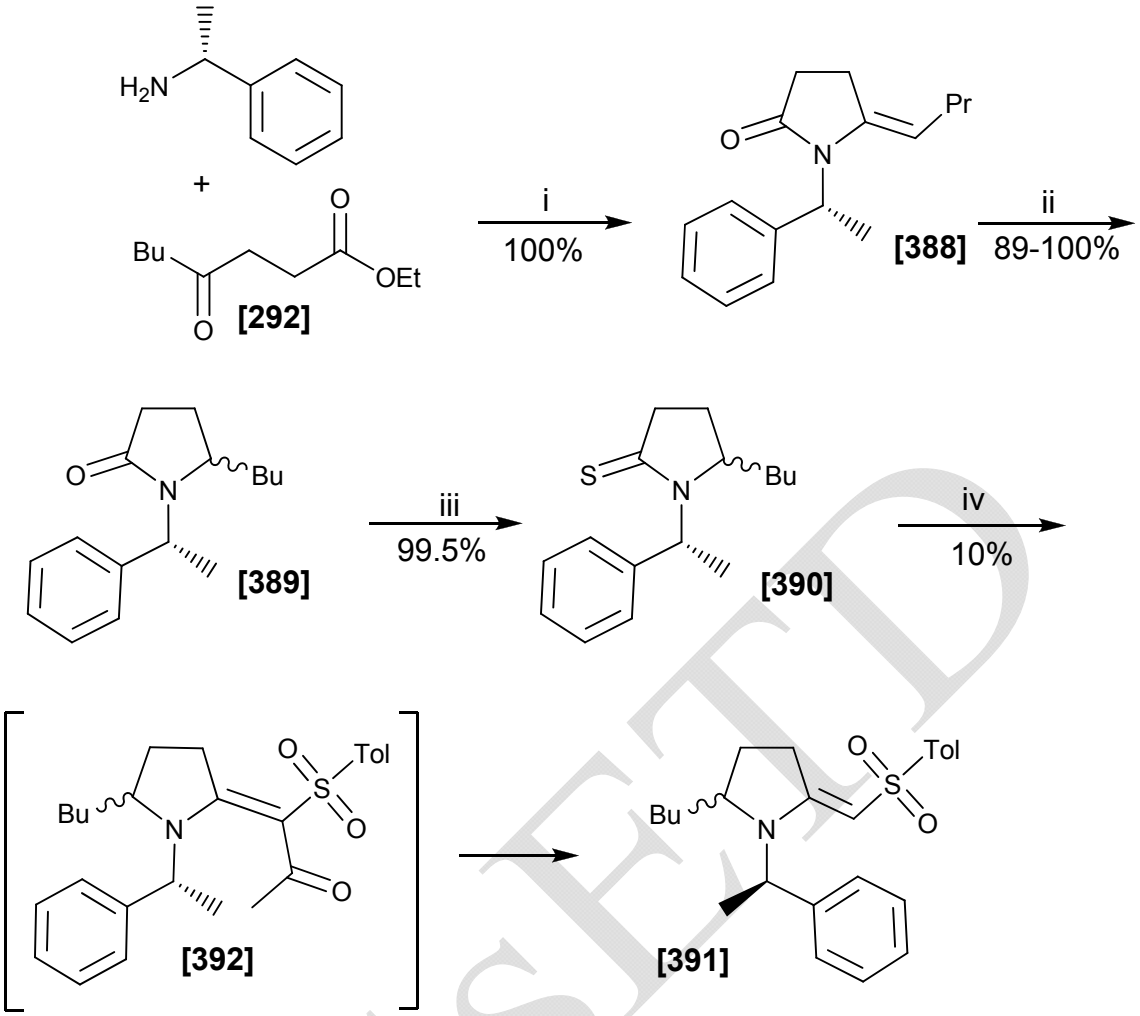
Scheme 6.5: Preparation of the enantiopure amine (**291**). *Reagents and conditions; i) a) benzyl[(1*R*)-1-phenylethyl]amine,* n-*BuLi, THF, -90°C, 30 min.; b) (**350**), 2 hr., 95%; ii) Pd/C, H_2 (7 atm), AcOH, 72 hr.*

We were able to prepare enough of the amine (**291**) to attempt the synthesis of enantiopure (−)-monomorine I and (−)-5-*epi*-monomorine I. However, there was insufficient material to allow for the separation of the diastereomers (**295A**) and (**295B**), and as a result no optical rotation values were measured.

6.1.5 Benzylated analogues

While we were still investigating the debenzylation reaction, we accidentally condensed the monobenzylated amine (**357**) with the keto-ester (**292**). This led us to the fortuitous discovery of the enamide (**388**) which was remarkably similar to the compound we were trying to synthesize (**293**). We decided to explore the same synthetic methodology on the “benzylated analogues” (see Scheme 6.6) in the hope that the benzyl group could be removed at a later stage, and the material cycled back into the synthesis of the enantiopure indolizidines. The condensation reaction using (*R*)-α-methylbenzylamine rather than (**357**) gave superior yields and provided us with a shorter and more convenient method for introducing the chiral centre.

WitsETD



Scheme 6.6: The synthesis of monobenzylated analogues. *Reagents and conditions: i) AcOH, toluene, reflux, 72 hr.; ii) 50% (w/w) Pd-C 10%, H_2 (7 atm.), EtOH, RT, 72 hr.; OR $TiCl_4$, Ph_3SiH, CH_2Cl_2, -90°C, 2 hr. increased to RT, 72 hr.; iii) P_2S_5, HMDO, $CHCl_3$, RT, 8 hr.; iv) a) MeI, THF, 48 hr.; b) (**279**), Et_3N, CH_2Cl_2, RT, 96 hr.*

Analogous to the monomorine I synthesis, the reduction at step (ii) was diastereoselective, with the highest selectivity being a 1:7 ratio of isomers. The thionation step (iii) also allowed separation of the isomers by column chromatography. We were only able to attempt step (iv) once, and unfortunately most of the material hydrolysed to the lactam (**389**), due to moisture present in the reaction. The product that was recovered was a mixture of (**392**) and (**391**) in 10% combined yield.

For compounds (**388**), (**389**) and (**390**) we did attempt to remove the benzyl group using Pearlman's catalyst with hydrogen, ammonium formate with

WITSETD

palladium on carbon, or ceric ammonium nitrate. No debenzylation was observed under any of the conditions we employed.

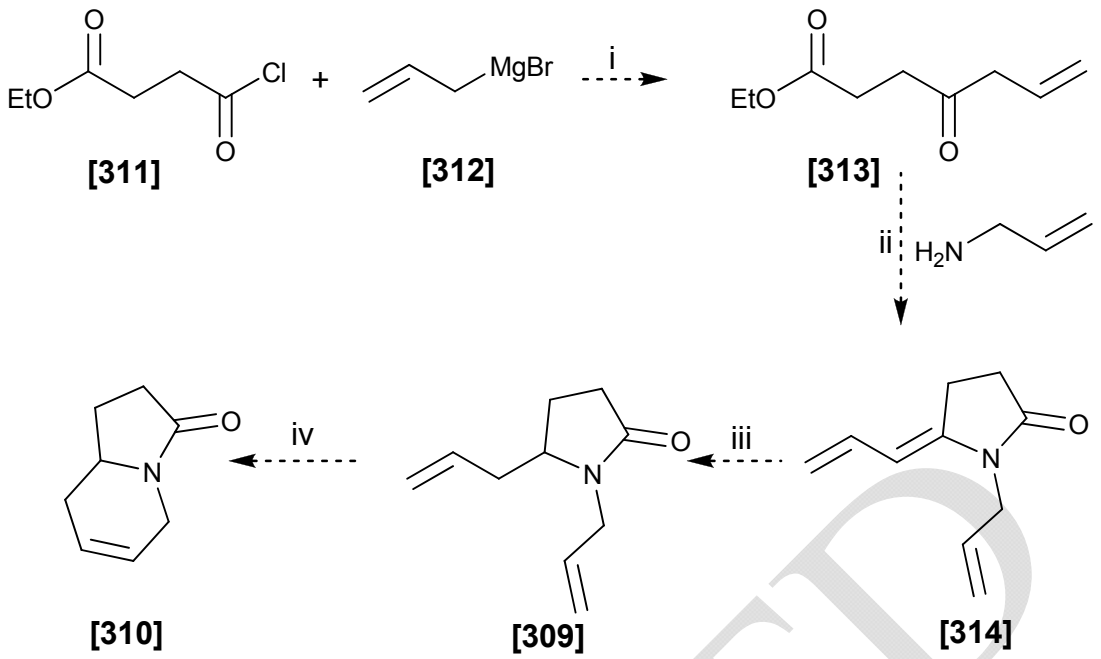
The synthetic pathway for the monobenzylated analogues warrants further investigation as it had a higher degree of diastereoselectivity, higher yields, and fewer steps than the original pathway for the synthesis of (−)-monomorine I.

6.1.6 Model study for ring-closing metathesis

Our final aim for this project was to explore potential ways of accessing indolizidine-based tricyclic systems using model systems and ring-closing metathesis. We were hoping to extend our methodology to include more complex alkaloid systems such as the tricyclic alkaloid 205B, which incorporates the 3,5-disubstituted indolizidine skeleton into its structure.

The results we obtained were extremely disappointing. We finally succeeded in preparing the allylketoester (**313**) when the alkene isomerised to the conjugated internal position, giving an intermediate that acts as a Michael-acceptor when heated with the allylamine. Clearly, the proposed model study (see Scheme 6.7) proved to be an invalid synthetic pathway. The work of Holmes and co-workers,[176] Kim and co-workers,[242] and Smith III *et al*.[122] has already shown the potential of RCM in the synthesis of bicyclic and tricyclic nitrogenous compounds, but in order to incorporate this methodology into our current synthetic strategy, we would need to modify the allylketoester (**313**) into a more stable precursor that can withstand the condensation reaction. The simplest modification would be to change the allyl chain into a terminal butenyl chain which would not be as susceptible to isomerisation. Time did not allow for further investigations into this synthetic strategy but there is certainly potential.

WitsETD



Scheme 6.7: Proposed model synthesis for the RCM approach. *Reagents and conditions: i) $Fe(acac)_3$, THF, 0°C, 10 min.; ii) AcOH, toluene, reflux, 72 hr.; iii*) $TiCl_4$, Ph_3SiH, CH_2Cl_2, -90°C, 2 hr., increased to RT, 72 hr. iv) 5 mol% Grubbs II, toluene.*

6.2 Future prospects

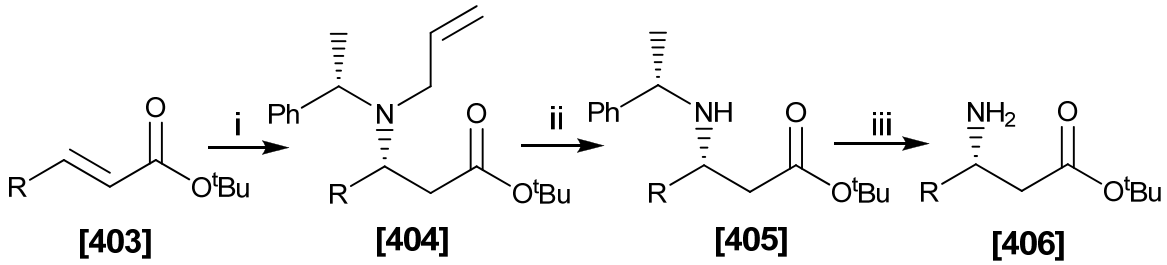
6.2.1 A new chiral auxiliary

The biggest difficulty faced during this project was the introduction of the chiral centre using Davies' methodology, and in order to complete the total synthesis of (−)-indolizidine 209D, (−)-monomorine I and (−)-5-*epi*-monomorine I, it is mandatory that this hurdle is overcome. The next few pages offer alternative methods for introducing the amine enantioselectively to the generic alkenoate (**403**), and then removing the chiral auxiliary to give the aminoester (**406**).

Davies *et al.*[211] have recently developed a novel chiral amine, (α-methylbenzyl)allylamine, which extended the scope of their strategy to include functional groups such as alkenes. The most important feature of this chiral amine is that it can be completely deprotected without using hydrogenation conditions (see Scheme 6.8). The allyl group can be selectively cleaved from compound (**404**), using Wilkinson's catalyst, and the α-methylbenzyl group can be selectively cleaved from compound (**405**) using dissolving metal conditions. The reported yields for a range of alkyl and alkenyl

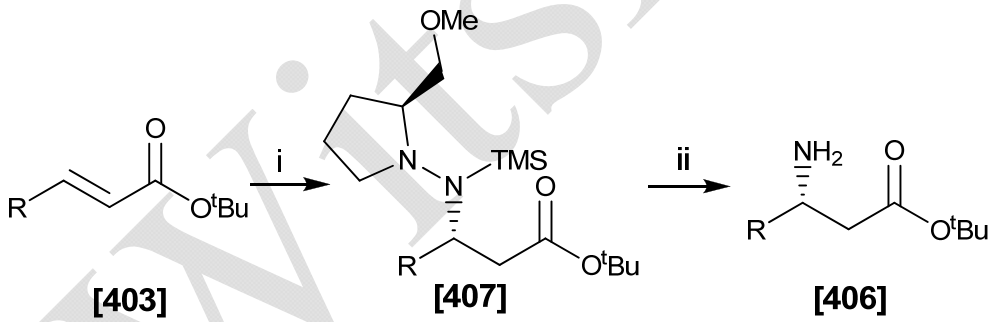
WiseTD

R-groups were between 92 – 99% for the three steps, and the *de*'s were above 98%.[211]



Scheme 6.8: Aza-Michael addition by Davies *et al*.[211] *Reagents and conditions: i) (S)-(α-methylbenzyl)allylamine,* n-*BuLi, THF, -78°C; ii) $(PPh_3)_3RhCl$; iii) Na/NH_3.*

Enders *et al.*[243] developed a method for introducing the amino-group via TMS-SAMP, (*S*)-(−)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (see Scheme 6.9). This method avoids the use of palladium-catalysed hydrogenation. Compound (**407**) was deprotected in two steps; treatment with silica followed by a Raney-nickel reduction. The Scheme below has been demonstrated for a range of alkyl R-groups, with *ee*'s between 90 – 98%.[179]

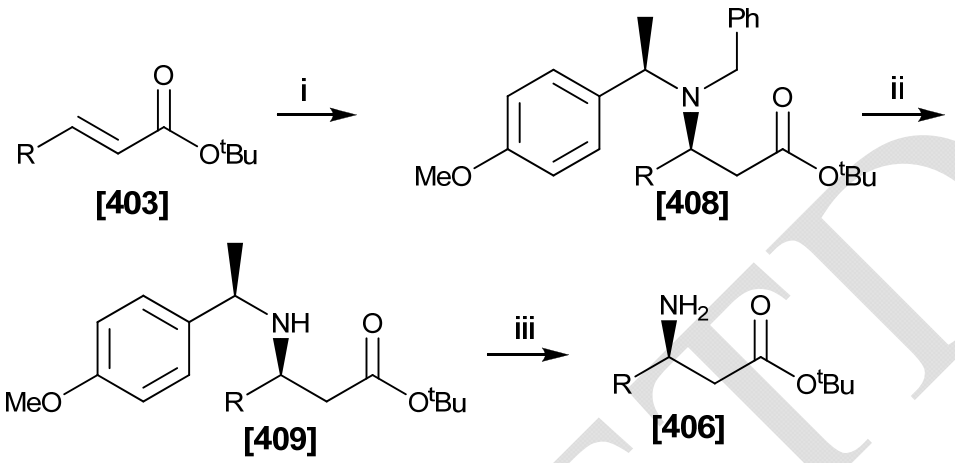


Scheme 6.9: Aza-Michael addition by Enders *et al.*[243] *Reagents and conditions: i) TMS-SAMP,* n-*BuLi, THF, -78°C; ii) a) SiO_2, EtOAc; b) Raney-Ni/H_2.*

Davies and co-workers[182, 183, 184] have also worked with another chiral amine, (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamine, which has slightly different chemical properties than *N*-benzyl-*N*-(1*R*)-1-phenylethylamine (**214**), the chiral amine we used during this project. The presence of the methoxy group makes the amine more susceptible to oxidative cleavage when reagents such as ceric ammonium nitrate (CAN) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) are used.[183, 184] Scheme 6.10 illustrates the chemoselective debenzylation of

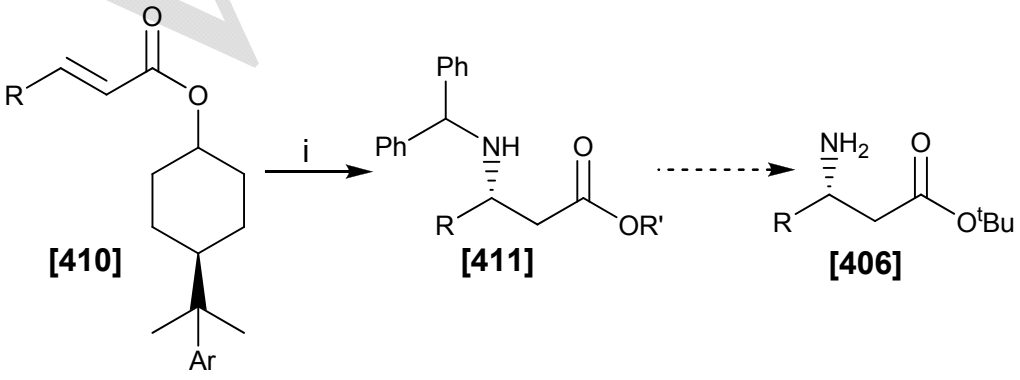
WitsETD

compound (**408**), followed by removal of the 4-methoxybenzyl group from (**409**). Davies and co-workers[182] obtained *ee*'s of 97%, whereas Zhang and co-workers,[244] who used formic acid to remove the 4-methoxybenzyl group, reported *ee*'s of 95%. In both of the reported cases, the R-group was a β-pyridyl.[182]



Scheme 6.10: Aza-Michael addition by Davies and co-workers[182, 184] *Reagents and conditions: i) (*R)-N-*benzyl*-N-*α-methyl-4-methoxybenzylamine,* n-*BuLi, THF, -78°C; ii) CAN (2.1 eq.) MeCN: H_2O (1:5), RT; iii) CAN (4.0 eq.), MeCN : H_2O (1:5), RT; OR iii) HCO_2H, Et_3SiH.*

Another method of introducing the stereogenic centre is to use a chiral ester to direct the aza-Michael addition. d'Angelo and co-workers[245] have successfully demonstrated this method (see Scheme 6.11) with *de*'s for compound (**411**) greater than 99% when R was a methyl group. The one disadvantage of this method is the high pressure required to introduce the amine.[179, 245]



Scheme 6.11: Aza-Michael addition by d'Angelo and co-workers[245] *Reagents and conditions: i) Ph_2CHNH_2, 14 - 15 bar.*

WISETD

6.2.2 Extending the reach of the Wits methodology

Having successfully completed the synthesis of two 3,5-dialkylated indolizidine alkaloids, we wish to apply our methodology to a broader range of alkaloids within this family. Additional 3,5-disubstituted ant and amphibian alkaloids are shown in Figure 6.2. Some of them differ from monomorine I only in the length of the alkyl substituents [compounds (**90**), (**91**) and (**92**)], while others contain alkenes or hydroxy-groups [compounds (**88**), (**412**), (**413**), (**414**), (**415**) and (**30**)]. We have already glimpsed the difficulties that can be encountered when incorporating an alkene into the side-chain, and incorporating an alcohol would also introduce interesting problems and nuances into the synthesis.

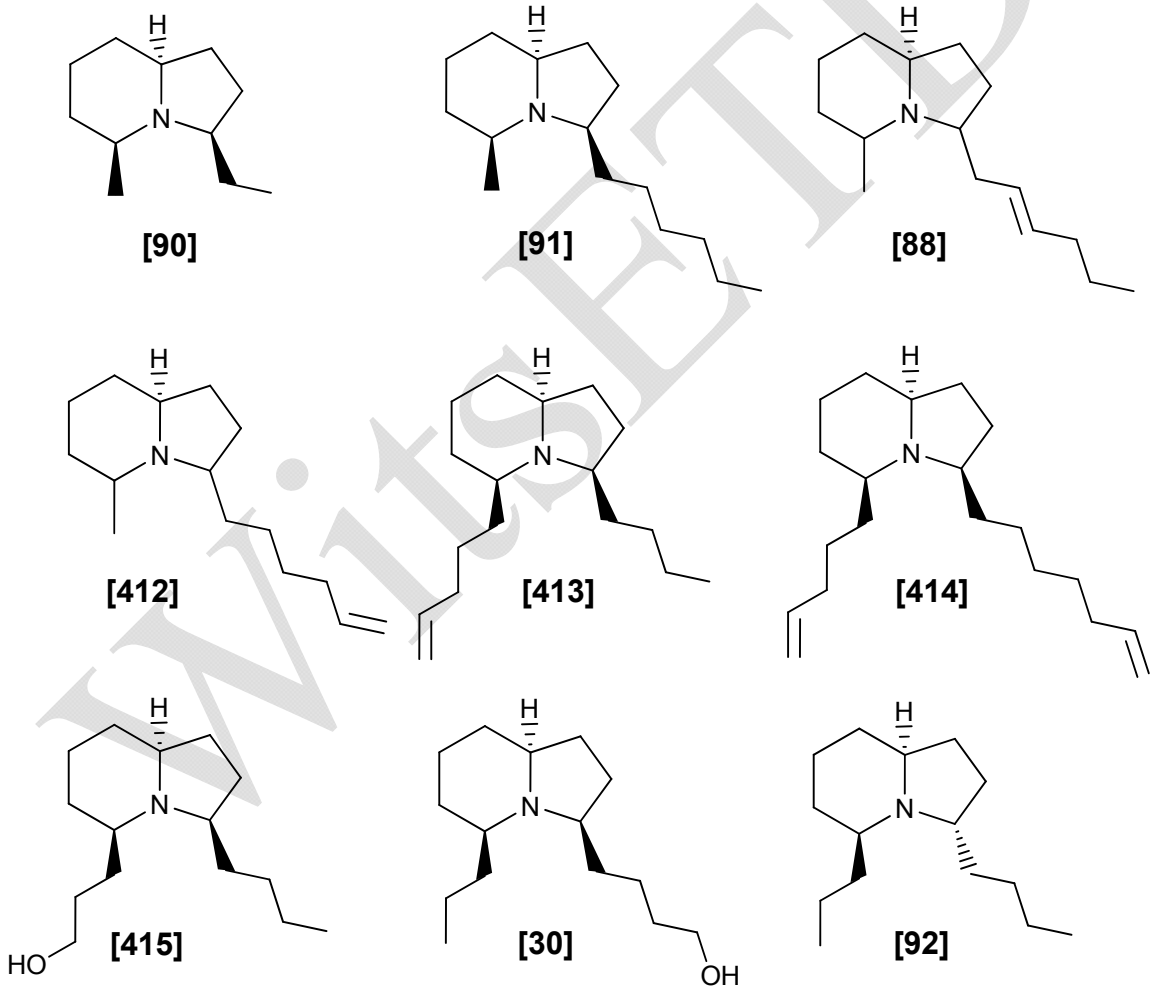


Figure 6.2: A range of ant and amphibian 3,5-disubstituted indolizidines.

The basic synthetic strategy would be the same, (see Figure 6.3). Lactam (**416**) would be accessed from a condensation reaction between ketoester (**417**) and

WitsETD

amine (**418**). The ketoester could be prepared from acid chloride (**311**) using a Grignard reaction, and the amine could be accessed via an aza-Michael addition reaction with the alkenoate (**419**). Various parameters would need to be changed and optimized, especially for the targets with functionalized side-chains. The hydroxy-groups would need to be protected to prevent interference with the cyclisation reaction, and the reduction reactions would have to be chemoselective, or the alkenes would also need protection.

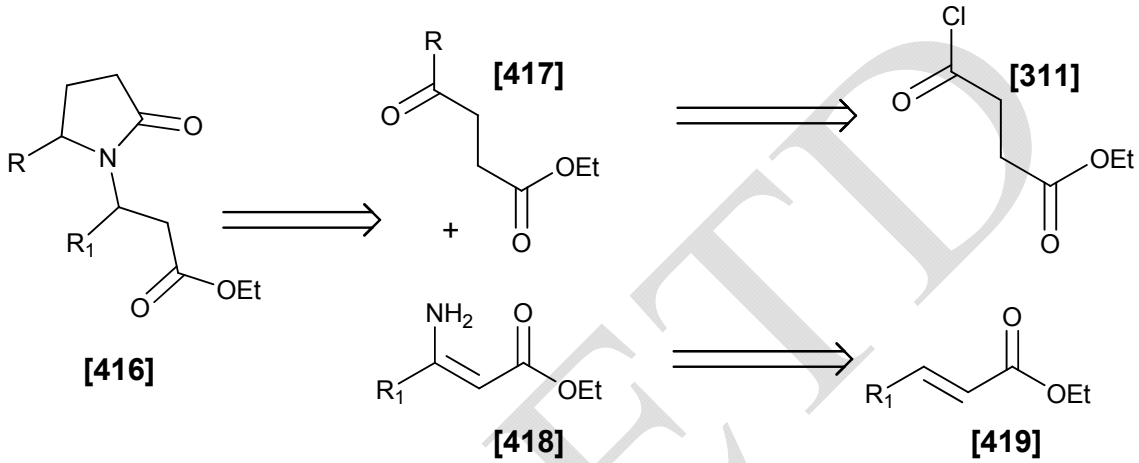


Figure 6.3: Retrosynthetic scheme of the pyrrolidinone intermediate.

6.2.3 Partnering up with ring-closing metathesis

On closer examination of our brief explorations into RCM, it is clear that the positioning of the alkene groups is critical for the success of the synthetic strategy. The work of Holmes and co-workers,[176] Kim and co-workers,[242] and Smith III *et al*.[122] has already demonstrated the potential of RCM in the synthesis of bicyclic and tricyclic nitrogenous compounds. However, in all three cases, both alkene groups are terminal, and neither alkene is positioned where it can isomerise into conjugation.

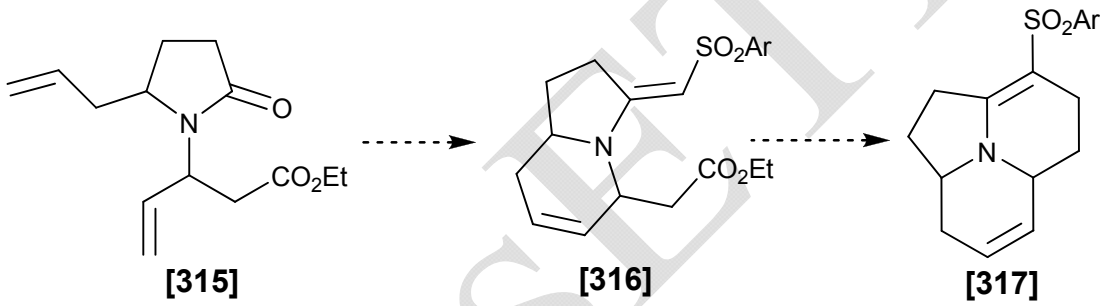
Therefore, in order to incorporate this methodology into our current synthetic strategy, we would need to modify the allylketoester (**313**) into a more stable precursor that can withstand the condensation reaction (see Figure 6.4). The simplest modification would be to change the allyl chain into a butenyl chain which would not be as susceptible to isomerisation (**405**).

WitsETD



Figure 6.4: Allylketoester (**313**) and the modified analogue (**405**).

Our original idea was to develop a route to access lactam (**315**) and hence apply RCM to form the bicyclic system (**316**) (see Scheme 6.12). Then the vinylogous sulfonamide methodology could be used to extend it to a tricyclic system (**317**). Future workers will need to revise the synthetic route for accessing lactam (**315**), avoiding condition such as toluene and acetic acid heated at reflux, as this potentially offers a novel route to the tricyclic skeleton.



Scheme 6.12: Proposed synthesis for the formation of the tricyclic skeleton (**317**).

6.3 Conclusion

In conclusion, the use of vinylogous sulfonamides as the key intermediate for forming the bicyclic skeleton of indolizidine alkaloids, (−)-indolizidine 209D, (±)-monomorine I and (±)-5-*epi*-monomorine I was proven a successful strategy. Unfortunately, the method of introducing the chiral centre presented us with problems we were unable to overcome. We did, however, explore additional side routes to try and circumvent the problem, and in the process uncovered interesting by-products, not to mention red herrings! Our attempt to extend the methodology to tricyclic systems was not successful, although it did pave the way for future workers to investigate the use of RCM in conjunction with vinylogous sulfonamides in the synthesis of targets with even greater structural complexity.

WitsETD

CHAPTER 7
EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 3

7.1 General experimental procedures

7.1.1 Purification of solvents and reagents

Solvents used for chromatographic purposes were distilled before use by means of conventional distillation procedures. Unless otherwise stated, solvents used for reaction purposes were dried over an appropriate drying agent and then distilled under nitrogen gas. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium wire using benzophenone as an indicator. Toluene was distilled from sodium lumps. Dichloromethane (CH_2Cl_2), dimethylformamide (DMF) and acetonitrile (MeCN) were distilled from calcium hydride. Potassium *t*-butoxide was resublimed under vacuum immediately prior to use. *n*-Butyllithium was titrated immediately prior to use, using the titration method outlined by Krasovskiy and Knochel.[246]

7.1.2 Chromatography

Separation of compounds by column chromatography was performed using Merck or Fluka silica-gel (particle size 0.063-0.200 mm). R_f values quoted are for thin layer chromatography (TLC) which was performed using Merck silica-gel 60 F_{254} or on Fluka silica-gel 60 F_{254} coated on aluminium sheets. Compounds on the TLC plates were viewed under UV light, or by staining the plates with basic potassium permanganate, bromocresol green, iodine or Dragendorff's reagent as appropriate.

7.1.3 Spectroscopic and physical data

^{1}H NMR spectra were recorded either on a Bruker AVANCE 300 spectrometer or on a Bruker DRX-400 spectrometer at the indicated frequency. Chemical shifts are reported on the δ scale relative to tetramethylsilane as an internal standard. The chemical shifts are reported as follows: Value (number of hydrogens, description of signal, coupling constant(s) in Hz where applicable, and assignment). Abbreviations used include: s (singlet), d (doublet), t (triplet),

WiSETD

q (quartet) and m (multiplet). Diastereotopic hydrogens are differentiated with the suffix *A* and *B*. COSY spectra were routinely run to enable more complete assignment of the signals.

^{13}C NMR spectra were recorded either on a Bruker AVANCE 300 spectrometer or on a Bruker DRX-400 spectrometer at frequencies of 75 MHz or 100 MHz respectively. Chemical shifts are reported on the δ scale relative to the central signal of deuterated chloroform, taken as 77.00 ppm. DEPT and C-H spectra were routinely run to enable more complete assignments of the signals.

Infra-red spectra were recorded on a Bruker Tensor 27 Fourier Transform spectrometer with diamond ATR attachment. Abbreviations used in describing the signals are: s (strong), m (medium), w (weak), br (broad). Assignments are only indicated for key signals.

Optical rotations were obtained on a Jasco DIP-370 Digital Polarimeter. The reported values each represent an average of consistent measurements. The concentration of the sample is given in g / 100 mL of solvent.

Melting points were recorded using a JM 626 melting-point apparatus with microscope and a digital thermometer.

High-resolution mass spectra (ESI/EI) were recorded either on a VG70 MS (Mass spectrum CC Pyramid data system), a VG70 SEQ (VG 11-205J or Mar II data system), or on a DFS High Resolution Magnetic Sector mass spectrometer.

Crystallographic information was obtained using intensity data collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 kV, 30 mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the programme SAINT+.[247] The crystal structure was solved by direct methods using SHELXTL[248] and WINGX.[249] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares

WitsETD

calculations based on F^2 using SHELXTL.[248] Hydrogen atoms were first located in the difference map, then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams were generated using SHELXTL[248] and PLATON.[250] Crystal structures were grown using Mercury 1.4.[251]

All molecular dynamic/simulated annealing calculations (MD/SA) were performed using Hyperchem,[228] together with the Generalised Amber Force Field (GAFF)[252, 253] parameters. Where parameters were not available (i.e. parameters involving titanium), new, crude ones were developed. A typical MD/SA simulation designed to discover stable conformations, began by an initial heating phase of 5 ps from 0 K to 1200 K. The run phase was then varied between 0 ps and 18 ps at 1200 K. This was subsequently followed by a cooling phase from 1200 K to 0 K over 50 ps. At this point the molecule was subjected to a full energy minimisation.

7.1.4 Additional general procedures and terminology

Evaporation *in vacuo* refers to the removal of solvent under reduced pressure at 40 - 50°C on a rotary evaporator.

Hydrogenations were set up in a Büchi*glas*uster picoclave "Parr Hydrogenator" with a built in stirrer and a maximum pressure of 10 bar.

Dean-Stark apparatus refers to a U-shaped glass apparatus which allows solvent heated at reflux to collect and separate by density in the side arm before flowing back into the flask, hence aiding the removal of a dense solvent such as H_2O from the reaction. We prepared a modified Dean-Stark apparatus whereby the solution heats to reflux and passes through a catchment area of molecular sieves before returning to the round bottom flask.

7.1.5 Nomenclature and compound numbering

The compounds prepared during this project are named in the following experimental sections according to systematic nomenclature. However, the numbering system used in the diagrams of the compounds is one adopted for

WitsETD

convenience and to allow easier comparison between NMR assignments and does not reflect the systematic numbering of these compounds.

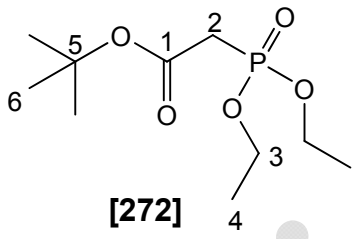
WitsETD

7.2 Towards the total synthesis of enantiopure (−)-indolizidine 209D

7.2.1 Horner-Wadsworth-Emmons reaction

7.2.1.1 Preparation of *t*-butyl 2-(diethoxyphosphoryl)acetate (272)

Triethyl phosphite (4.7 mL, 28 mmol) was added to *t*-butyl bromoacetate (3.7 mL, 25 mmol) in a RBF fitted with a condenser, under a nitrogen atmosphere. The mixture was heated at reflux at 110°C for 24 hours until starting material could not be detected by TLC analysis. The reaction was cooled and the crude product was rinsed with distilled H_2O (25 mL) and extracted into EtOAc (2 × 25 mL). The combined organic extracts were dried with sodium sulfate and filtered. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (30% EtOAc/hexane) to give ***t*-butyl 2-(diethoxyphosphoryl)acetate (272)** (6.31 g) as a clear oil in quantitative yield. The obtained spectra correspond with literature values.[154]



[272]

R_f 0.10 (30% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.17 (4H, dq, $J_{P\text{-}H}$ 14.3, J 7.1, H-3), 2.88 (2H, d, $J_{P\text{-}H}$ 21.5, H-2), 1.48 (9H, s, H-6), 1.35 (6H, t, J 7.1, H-4).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 164.6 (d, $J_{P\text{-}C}$ 6.3, C-1), 81.7 (C-5), 62.2 (d, $J_{P\text{-}C}$ 6.2, C-3), 35.4 (d, $J_{P\text{-}C}$ 133.2, C-2), 27.2 (C-6), 16.1 (d, $J_{P\text{-}C}$ 6.3, C-4).

^{31}P (121 MHz, $CDCl_3$) δ_P /**ppm** 321.4 (P).

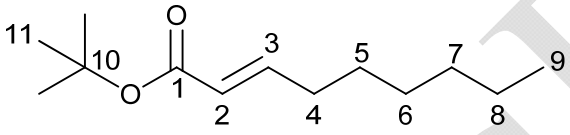
$\nu_{max.}$ / **cm^{-1}**: 2981 (m, C-H), 2934 (m, C-H), 1725 (s, C=O), 1394 (m), 1368 (m), 1286 (s, P=O), 1255 (s, P=O), 1164 (m), 1113 (m), 1029 (s), 959 (s), 829 (w).

***m/z**:* 197 (36%), 179 (100), 151 (53), 123 (41), 81 (9), 57 (40).

WitsETD

7.2.1.2 *t*-Butyl (*E*)-2-nonenoate (273)

An oven-dried, 100 mL RBF was charged with sodium hydride (60% in oil, 1.50 g, 37.5 mmol) and pre-distilled Et_2O (60 mL), under an atmosphere of nitrogen gas. The resulting suspension was cooled to 0°C in an ice bath and ***t*-butyl 2-(diethoxyphosphoryl)acetate (272)** (6.31 g, 25.0 mmol) was added dropwise over 10 minutes. Heptanal (3.8 mL, 28 mmol) in Et_2O (15 mL) was added by dropping funnel over 15 minutes. The ice bath was removed and the mixture was stirred at ambient temperature for an additional hour. The reaction was quenched by the addition of saturated ammonium chloride solution (20 mL) and then extracted into Et_2O (3 × 50 mL). The combined organic extracts were dried with sodium sulfate and filtered. The solvent was evaporated *in vacuo* and the crude product was purified using column chromatography (2% - 5% EtOAc/hexane) to give ***t*-butyl (*E*)-2-nonenoate (273)** (5.31 g, 100% yield) as a clear oil in quantitative yield.



[273]

R_f 0.72 (5% EtOAc/hexane)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 6.86 (1H, dt, *J* 15.6, 6.9, H-3), 5.73 (1H, dt, *J* 15.6, 1.5, H-2), 2.20-2.12 (2H, m, H-4), 1.48 (9H, s, H-11), 1.36-1.23 (8H, m, H-5, H-6, H-7, H-8), 0.88 (3H, t, *J* 6.7, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 166.1 (C-1), 148.1 (C-3), 122.9 (C-2), 79.9 (C-10), 32.0 (C-4), 31.7 (C-5), 28.8 (C-6), 28.1 (C-11), 28.0 (C-7), 22.5 (C-8), 14.0 (C-9).

$\nu_{max.}$ / **cm^{-1}**: 2957 (m, C-H), 2927 (m, C-H), 2857 (m, C-H), 1715 (s, C=O), 1653 (m, C=C), 1457 (m), 1367 (m), 1152 (s), 1124 (s), 978 (m), 851 (w).

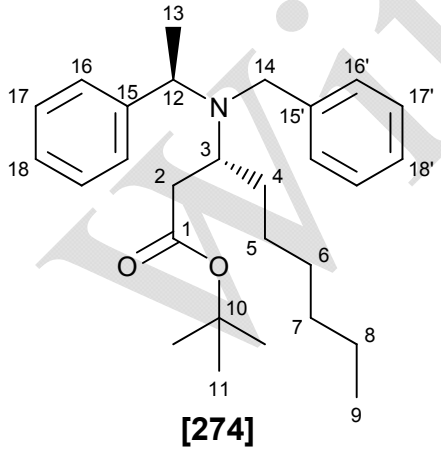
m/z: 157 (36%), 139 (16), 115 (100), 97 (88), 70 (57), 55 (82).

WitsETD

7.2.2 Conjugate addition reaction

7.2.2.1 *t*-Butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (274)

N-Benzyl-*N*-(1*R*)-1-phenylethylamine (5.97 g, 28.3 mmol) was mixed with pre-distilled THF (100 mL) in an oven dried RBF under a nitrogen atmosphere and the mixture was cooled to -90°C in a liquid nitrogen/acetone bath. Freshly titrated *n*-butyllithium in hexane (1.2 *M*, 26 mmol) was carefully added and the mixture was stirred for 30 minutes. A pronounced colour change from clear to deep red was observed as the *n*-butyllithium was added and the red colour remained throughout stirring. ***t*-Butyl (*E*)-2-nonenoate (273)** (5.00 g, 23.5 mmol) was mixed with THF (20 mL) and added over a period of 30 minutes by means of a dropping funnel. The reaction was kept at -90°C for a further 4 hours, and during this time the colour of the mixture lightened. The reaction was quenched by the addition of saturated ammonium chloride solution (20 mL). The THF was removed *in vacuo* and the product was extracted into EtOAc (3 × 50 mL), dried with sodium sulfate and filtered. The solvent was removed *in vacuo* and the resulting crude yellow oil was purified by column chromatography (5% EtOAc/hexane) to give ***t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (274)** (8.12 g, 82% yield) as a pale yellow oil.



[274]

R_f 0.63 (10% EtOAc/hexane), $[\alpha]_D^{20}$ +4.5 (*c* 1.00, CH_2Cl_2)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.47-7.17 (10H, m, Ar-H), 3.86-3.74 (2H, m, H-12, H-14*A*), 3.48 (1H, d, *J* 15.0, H-14*B*), 3.35-3.24 (1H, m, H-3), 1.96 (1H, dd, *J* 14.5, 3.7, H-2*A*), 1.86 (1H, dd, *J* 14.5, 9.2, H-2*B*), 1.61-1.15 (10H, m, H-4,

WitsETD

H-5, H-6, H-7, H-8), 1.39 (9H, s, H-11), 1.32 (3H, d, *J* 6.9, H-13), 0.88 (3H, t, *J* 6.7, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 172.2 (C-1), 143.2 (C-15/15`), 142.1 (C-15/15`), 128.2 (C-16/16`), 128.1 (C-16/16`), 128.0 (C-17/17`), 127.9 (C-17/17`), 126.8 (C-18/18`), 126.5 (C-18/18`), 79.8 (C-10), 58.4 (C-12), 54.0 (C-3), 50.1 (C-14), 37.9 (C-2), 33.5 (C-4), 31.9 (C-5), 29.3 (C-6), 28.1 (C-11), 26.9 (C-7), 22.7 (C-8), 20.5 (C-13), 14.1 (C-9).

$v_{max.}$ / **cm^{-1}**: 2929 (m, C-H), 2857 (m, C-H), 1726 (s, C=O), 1455 (m), 1368 (m), 1146 (s), 956 (w), 848 (w), 702 (s).

m/z: 423 (1%, M), 408 (2), 352 (4), 338 (32), 308 (30), 282 (22), 250 (10), 204 (28), 178 (64), 146 (26), 105 (100), 91 (89). Found 423.3131, $C_{28}H_{41}O_2N$ requires 423.3137.

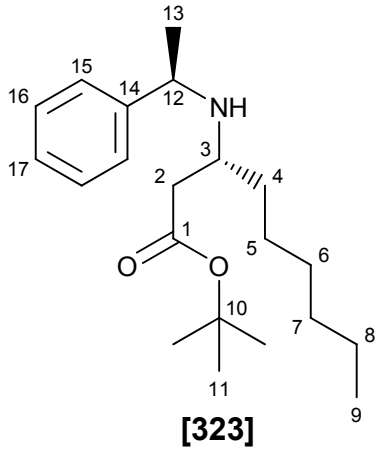
7.2.3 Debenzylation reactions

7.2.3.1 *t*-Butyl (3*R*)-3-[N-(1-phenylethyl)amino]nonanoate (323) and *t*-butyl (3*R*)-3-aminononanoate (275)

Method A

10% Palladium on carbon (80 mg, 0.10 eq.) was added to a mixture of ***t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (274)** (0.80 g, 1.9 mmol) dissolved in AcOH (5 mL). The resulting suspension was set up under 7 atmospheres of hydrogen pressure in a hydrogenator and stirred at ambient temperature for 48 hours. The solution was then filtered through Celite® and rinsed with CH_2Cl_2 (150 mL) in order to remove the residual catalyst. The CH_2Cl_2 was removed *in vacuo* and the AcOH was removed using toluene as an azeotrope. The crude yellow oil was purified by column chromatography (10% EtOAc/hexane - 10% MeOH/EtOAc) to give ***t*-butyl (3*R*)-3-aminononanoate (275)** (204 mg, 46% yield) and ***t*-butyl (3*R*)-3-[*N*-(1-phenylethyl)amino]nonanoate (323)** (340 mg, 54% yield) both as clear oils.

WiSER



[323]

R_f 0.56 (20% EtOAc/hexane), $[\alpha]_D^{20}$ +20.4 (*c* 0.91, CH_2Cl_2)

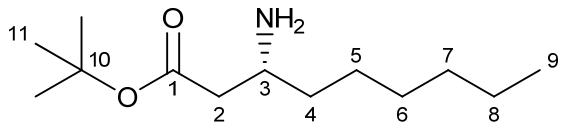
^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.38-7.17 (5H, m, H-15, H-16, H-17), 3.89 (1H, q, *J* 6.5, H-12), 2.76-2.68 (1H, m, H-3), 2.66-2.50 (1H, s, N-H), 2.37 (1H, dd, *J* 14.4, 5.9, H-2*A*), 2.26 (1H, dd, *J* 14.4, 4.4, H-2*B*), 1.45 (9H, s, H-11), 1.33 (3H, d, *J* 6.5, H-13), 1.30-1.09 (10H, m, H-4, H-5, H-6, H-7, H-8), 0.85 (3H, t, *J* 6.8, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 171.8 (C-1), 145.9 (C-14), 128.3 (C-15/16), 126.8 (C-17), 126.7 (C-15/16), 80.2 (C-10), 55.1 (C-12), 52.2 (C-3), 39.6 (C-2), 35.1 (C-4), 31.7 (C-5), 29.2 (C-6) , 28.1 (C-11), 25.7 (C-7), 24.7 (C-8), 22.5 (C-13), 14.0 (C-9).

$\nu_{max.}$ / **cm^{-1}**: 3194 (w, br, N-H), 2957 (m, C-H), 2926 (m, C-H), 2856 (m, C-H), 1724 (s, C=O), 1666 (w), 1454 (m), 1366 (m), 1150 (s), 953 (w), 843 (w), 700 (s).

m/z: 333 (1%, M), 318 (3), 262 (16), 248 (11), 218 (18), 192 (46), 172 (7), 120 (17), 105 (100), 88 (20), 79 (8). Found 333.2662, $C_{21}H_{35}O_2N$ requires 333.2668.

WitsETD



[275]

R_f 0.33 (100% EtOAc), $[\alpha]_D^{20}$ -13.4 (*c* 0.98, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 5.20 (2H, s, N-H), 3.29-3.18 (1H, m, H-3), 2.40 (1H, dd, *J* 16.0, 4.2, H-2*A*), 2.34 (1H, dd, *J* 16.0, 7.8, H-2*B*), 1.46 (9H, s, H-11), 1.46-1.21 (10H, m, H-4, H-5, H-6, H-7, H-8), 0.88 (3H, t, *J* 6.4, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 171.5 (C-1), 80.9 (C-10), 48.3 (C-3), 41.7 (C-2), 35.9 (C-4), 31.6 (C-5), 29.1 (C-6), 28.1 (C-11), 25.7 (C-7), 22.5 (C-8), 14.0 (C-9).

$\nu_{max.}$ / **cm^{-1}**: 3420 (br, N-H), 2957 (m, C-H), 2928 (m, C-H), 2858 (m, C-H), 1727 (s, C=O), 1558 (s), 1393 (m), 1368 (m), 1150 (s), 948 (w), 842 (w).

m/z: 229 (1%, M), 172 (14), 144 (7), 114 (43), 88 (100), 56 (53). Found 229.2036, $C_{13}H_{27}O_2N$ requires 229.2042.

Method B

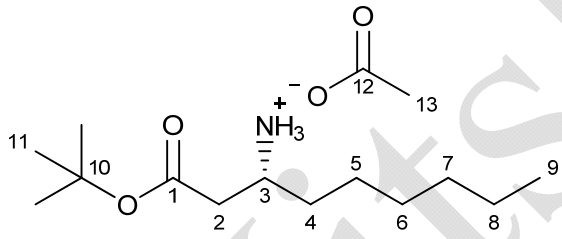
5% Palladium on carbon (400 mg, 1.0 eq.) was added to a mixture of ***t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (274)** (0.40 g, 0.95 mmol) dissolved in AcOH (3 mL). The resulting suspension was set up under 7 atmosphere of hydrogen pressure in a hydrogenator and stirred at ambient temperature for 48 hours. The solution was then filtered through Celite® and rinsed with CH_2Cl_2 (150 mL) in order to remove the residual catalyst. The CH_2Cl_2 was removed *in vacuo* and the AcOH was removed using toluene as an azeotrope. The crude yellow oil was purified by column

WitsETD

chromatography (10% EtOAc/hexane -10% MeOH/EtOAc) to give ***t*-butyl (3*R*)-3-aminononanoate (275)** (215 mg, 99% yield) as a pale yellow, gummy oil.[e]

Method C

5% Palladium on carbon (2.17 g, 0.25 eq.) was added to a mixture of ***t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (274)** (8.66 g, 20.5 mmol) dissolved in AcOH (5 mL) and MeOH (15 mL). The resulting suspension was set up under 5 atmospheres of hydrogen pressure in a hydrogenator and stirred at ambient temperature for 96 hours. The solution was then filtered through Celite® and rinsed with CH_2Cl_2 (150 mL) in order to remove the residual catalyst. The CH_2Cl_2 was removed *in vacuo* and the AcOH was removed using toluene as an azeotrope. The crude oil was purified by column chromatography (10% EtOAc/hexane - 10% MeOH/EtOAc) to give **(*R*)-1-*t*-butoxy-1-oxononan-3-aminium acetate (324)** (3.26 g, 55% yield) as a creamy-white solid.



[324]

M.p. 69 -73 °C

R_f 0.06 (50% EtOAc/hexane), $[\alpha]_D^{20}$ -10.0 (*c* 1.00, CH_2Cl_2)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.17 (3H, s, N-H), 3.34-3.14 (1H, m, H-3), 2.48-2.44 (2H, m, H-*2*), 1.96 (3H, s, H-13), 1.66-1.50 (2H, m, H-4), 1.45 (9H, s, H-11), 1.38-1.23 (8H, m, H-5, H-6, H-7, H-8), 0.88 (3H, t, *J* 6.5, H-9).

[e] *The yields for partially and fully debenzylated products were extremely variable and a range of catalysts from different suppliers was used. See Chapter 3 for the detailed explanation.*

WitsETD

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 177.3 (C-12), 171.2 (C-1), 81.3 (C-10), 48.2 (C-3), 39.8 (C-2), 34.6 (C-4), 31.6 (C-5), 29.1 (C-6), 28.0 (C-11), 25.6 (C-7), 23.3 (C-13), 22.5 (C-8), 14.0 (C-9).

$\nu_{max.}$ / **cm^{-1}**: 3500-2800 (br, N-H), 2957 (m, C-H), 2930 (m, C-H), 2860 (m, C-H), 1731 (s, C=O), 1560 (s), 1395 (s), 1369 (m), 1231 (m), 1157 (s), 949 (w), 843 (w), 650 (w).

Method D

A 100 mL RBF was charged with MeOH (15 mL) and ***t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (274)** (500 mg, 1.18 mmol). Ammonium formate (596 mg, 9.45 mmols) was added and the solution was stirred under a nitrogen atmosphere until the solution was homogenous. 10% Palladium on carbon (185 mg, 0.37 eq.) was carefully stirred into the mixture (the methanolic vapours readily ignited if the system was not properly flushed with nitrogen). The reaction was left at ambient temperature for 3 hours until TLC indicated that all the starting material was consumed. The mixture was filtered through Celite® and rinsed with MeOH (2 × 20 mL) to remove the catalyst. The solvent was removed *in vacuo* and the residue was rinsed with sodium hydroxide solution (1.0 *M*, 8 mL) and extracted into CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried with sodium sulfate and the solvent was removed *in vacuo*. Purification of the crude oil by column chromatography (5% - 100% EtOAc/hexane) gave ***t*-butyl (3*R*)-3-aminononanoate (275)** (200 mg, 74% yield) as a clear oil.[f]

Method E

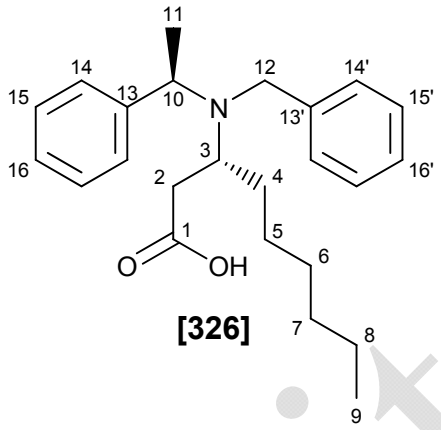
10 - 20% Palladium hydroxide on carbon (2.00 g, 0.25 eq.) was added to a mixture of ***t*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (274)** (8.00 g, 18.9 mmol) dissolved in absolute EtOH (30 mL). The resulting suspension was set up under 7 atmosphere of hydrogen pressure in a hydrogenator and stirred at ambient temperature for 48 hours. The solution was then filtered through Celite® and rinsed with CH_2Cl_2 (150 mL) in order to remove

[f] *Unfortunately this reaction was not reproducible; see Chapter 3 for a detailed discussion.*

the residual catalyst. The solvent was removed *in vacuo* and the crude yellow oil was purified by column chromatography (5% - 100% EtOAc/hexane) to give ***t*-butyl nonanoate (325)** (2.12 g, 53% yield) as a clear oil.

Method F

***t*-Butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoate (274)** (500 mg, 1.18 mmol) was dissolved in formic acid (5 mL) and was heated at reflux for 3 hours. The reaction mixture was cooled, the formic acid removed *in vacuo*, and the crude residue purified by column chromatography (20% - 100% EtOAc/hexane) to give **(3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}nonanoic acid (326)** (400mg, 92% yield).



[326]

R_f 0.49 (50% EtOAc/hexane), $[\alpha]_D^{20}$ -26.9 (*c* 1.08, CH_2Cl_2)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 11.2-10.8 (1H, s, O-H), 7.33-7.24 (10H, m, Ar-H), 4.16 (1H, q, *J* 7.2, H-10), 3.92 (1H, d, *J* 14.0, H-12*A*), 3.84 (1H, d, *J* 14.0, H-12*B*), 3.41-3.34 (1H, m, H-3), 2.37 (1H, dd, *J* 16.8, 4.8, H-2*A*), 2.07 (1H, dd, *J* 16.8, 10.8, H-2*B*), 1.70-1.62 (1H, m, H-4*A*), 1.57 (3H, d, *J* 6.9, H-11), 1.41-1.12 (9H, m, H-4*B*, H-5, H-6, H-7, H-8), 0.88 (3H, t, *J* 7.2, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 174.2 (C-1), 139.3 (C-13/C-13'), 135.8 (C-13/C-13'), 129.2, 128.8, 128.7, 128.4, 128.2, 128.0 (C-14, C-14', C-15, C-15', C-16, C-16'), 60.3 (C-10), 56.8 (C-3), 49.5 (C-12), 35.0 (C-2), 31.5 (C-4), 30.4 (C-5), 29.2 (C-6), 26.7 (C-7), 22.5 (C-8), 17.8 (C-11), 13.9 (C-9)

WitsETD

$v_{max.}$ / **cm^{-1}**: 2955 (m, C-H), 2928 (m, C-H), 2856 (m, C-H), 1716 (s, C=O), 1492 (s), 1396 (m), 1375 (m), 1273 (m), 1207 (m), 749 (m), 700 (s).

m/z: no parent ion, 352 (5%), 308 (16), 282 (27), 250 (17), 204 (18), 178 (42), 146 (40), 105 (100). $C_{24}H_{33}O_2N$ requires 367.2511.

Method G

***t*-Butyl (3*R*)-3-[*N*-(1-phenylethyl)amino]nonanoate (323)** (0.30 g, 0.90 mmols) was dissolved in absolute ethanol (3 mL) with palladium hydroxide (10 - 20%, 30 mg, 0.10 eq.). The reaction was set up under 7 atmospheres of hydrogen pressure in the hydrogenator at ambient temperature for 72 hours. The reaction mixture was filtered through Celite® to remove the catalyst, and was rinsed with CH_2Cl_2 (150 mL). The solvent was removed *in vacuo* and then the crude product was dried under high vacuum for 20 minutes. ^{1}H-NMR spectra of the crude material indicated 100% recovery of starting material and that no debenzylation had occurred.

Method H

***t*-Butyl (3*R*)-3-[*N*-(1-phenylethyl)amino]nonanoate (323)** (0.50 g, 1.5 mmol) and ceric ammonium nitrate (3.29 g, 6.00 mmol) were dissolved in MeCN/H_2O (1:5, 12 mL) and stirred at ambient temperature for 12 hours. The reaction was quenched with saturated sodium bicarbonate solution (10 mL) and filtered through cotton wool. The product was extracted into CH_2Cl_2 (4 × 20 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (5% - 50% EtOAc/hexane) to give back starting material ***t*-butyl (3*R*)-3-[*N*-(1-phenylethyl)amino]nonanoate (323)** (250 mg, 50% recovery).

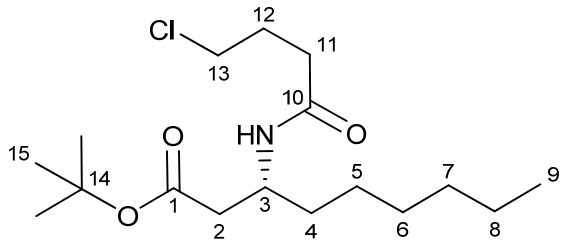
7.2.4 Formation of the lactam and cyclopropane by-products

7.2.4.1 *t*-Butyl (3*R*)-3-[*N*-(4-chlorobutanoyl)amino]nonanoate (276)

In an oven dried flask, ***t*-butyl (3*R*)-3-aminononanoate (275)** (0.22 mg, 0.94 mmol) was dissolved in $CHCl_3$ (2 mL) followed by the addition of sodium bicarbonate (0.12 g, 1.4 mmol) and 10 minutes of stirring. Chlorobutyryl chloride (126 µl, 1.1 mmol) was then added and the reaction was left stirring at

WISER

ambient temperature for 12 hours. The mixture was filtered to remove residual solids and was rinsed thoroughly with CH_2Cl_2 (2 × 20 mL). The solvent was removed *in vacuo* and the crude material was purified by column chromatography (10% - 50% EtOAc/hexane). The product, ***t*-butyl (3*R*)-3-[*N*-(4-chlorobutanoyl)amino]nonanoate (276)**, was only UV-active at high concentrations and was recovered as a odoriferous, pale brown oil in quantitative yield (314 mg, 100% yield).



[276]

R_f 0.63 (20% EtOAc/hexane), $[\alpha]_D^{20}$ +10.5 (*c* 1.00, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 6.22 (1H, d, *J* 8.7, N-H), 4.28-4.16 (1H, m, H-3), 3.61 (2H, t, *J* 6.6, H-13), 2.54 (1H, t, *J* 7.2, H-11*A*), 2.46-2.30 (1H, m, H-11*B*), 2.39-2.32 (2H, m, H-2), 2.16-2.01 (2H, m, H-12), 1.45 (9H, s, H-15), 1.47-1.10 (10H, m, H-4, H-5, H-6, H-7, H-8), 0.87 (3H, t, *J* 6.5, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 171.4 (C-10), 171.2 (C-1), 81.2 (C-14), 46.2 (C-3), 44.4 (C-13), 39.6 (C-2), 34.1 (C-4), 33.4 (C-11), 30.8 (C-5), 29.0 (C-6), 28.2 (C-12), 28.0 (C-15), 26.0 (C-7), 22.5 (C-8), 14.0 (C-9).

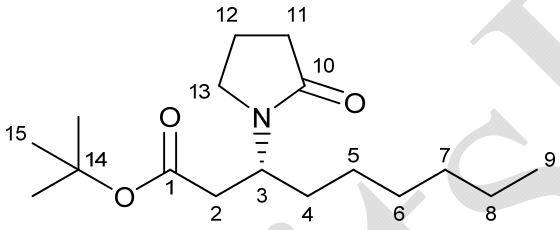
$\nu_{max.}$ / **cm^{-1}**: 3289 (br, N-H), 2928 (m, C-H), 2857 (m, C-H), 1725 (s, OC=O), 1645 (s, NC=O), 1545 (m), 1367 (m), 1256 (m), 1153 (s), 947 (w).

m/z: 333 (2%, M), 277 (25), 260 (21), 224 (26), 192 (56), 172 (77), 156 (96), 112 (100), 88 (74), 57 (85). Found 333.2064, $C_{17}H_{32}O_3N^{35}Cl$ requires 333.2071.

WiSETD

7.2.4.2 *t*-Butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)nonanoate (277)

Potassium *t*-butoxide was carefully sublimed and *t*-butanol was pre-distilled. ***t*-Butyl (3*R*)-3-[*N*-(4-chlorobutanoyl)amino]nonanoate (276)** (1.96 g, 5.90 mmol) was dissolved in *t*-butanol (10 mL) and the potassium *t*-butoxide (1.32 g, 11.7 mmol) was carefully added to the solution under a nitrogen atmosphere. The mixture was left to stir at ambient temperature for 72 hours and was quenched by the careful addition of AcOH (5 mL). The solution was rinsed with distilled H_2O (20 mL) and extracted into CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried with sodium sulfate, filtered, and the solvent removed *in vacuo*. The crude oil was purified by column chromatography (30% EtOAc/hexane) to give ***N*-(cyclopropanecarbonyl) cyclopropane carboxamide (327)** (400 mg, 45% yield), ***t*-butyl (*E*)-2-nonenoate (273)** (290 mg, 23%) and the desired product ***t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)nonanoate (277)** (850 mg, 49% yield) as a clear oil.



[277]

R_f 0.23 (30% EtOAc/hexane), $[\alpha]_D^{20}$ +9.5 (*c* 1.00, CH_2Cl_2)

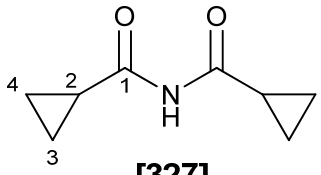
^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.53-4.36 (1H, m, H-3), 3.38 (1H, dd, *J* 15.7, 7.1, H-13*A*), 3.26 (1H, dd, *J* 15.7, 7.9, H-13*B*), 2.42-2.34 (4H, m, H-11, H-2), 1.99 (2H, quintet, *J* 7.6, H-12), 1.48-1.39 (2H, m, H-4), 1.42 (9H, s, H-15), 1.35-1.15 (10H, m, H-4, H-5, H-6, H-7, H-8), 0.87 (3H, t, *J* 6.5, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 174.8 (C-10), 170.2 (C-1), 80.7 (C-14), 48.8 (C-3), 42.4 (C-13), 39.3 (C-2), 32.2 (C-4), 31.4 (C-5), 31.1 (C-11), 28.9 (C-6), 27.8 (C-15), 26.0 (C-7), 22.5 (C-8), 18.3 (C-12), 14.0 (C-9).

WiSETD

$v_{max.}$ / **cm^{-1}**: 2926 (m, C-H), 2857 (m, C-H), 1724 (s, OC=O), 1686 (s, NC=O), 1422 (m), 1367 (m), 1267 (m), 1220 (m), 1150 (s), 953 (w), 843 (w).

m/z: 297 (2%, M), 241 (43), 224 (27), 212 (7), 182 (100), 156 (56), 138 (22), 112 (42), 57 (71). Found 297.2298, $C_{17}H_{31}O_3N$ requires 297.2304.



[327]

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 8.65 (1H, s, N-H), 2.28-2.25 (2H, m, H-2), 1.14-1.11 (4H, m, H-3/H-4), 0.99-0.93 (4H, m, H-3/H-4).

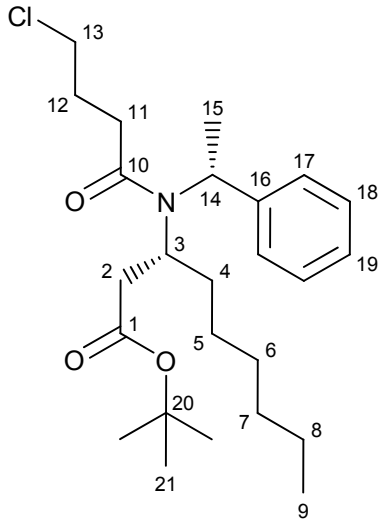
^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 175.3 (C-1), 15.0 (C-2), 10.3 (C-3, C-4).

$v_{max.}$ / **cm^{-1}**: 3257-3161 (br, N-H), 2923 (m, C-H), 2853 (m, C-H), 1710 (m, C=O), 1519 (m), 1461 (m), 1379 (s), 1212 (s), 1168 (s), 1111 (s), 1061 (s), 1035 (m), 943 (s).

7.2.4.3 (*R*)-*t*-Butyl 3-(4-chloro-*N*-(*R*)-1-phenylethyl)butanamido)nonanoate (331)

A 10 mL RBF was charged with ***t*-butyl (3*R*)-3-[*N*-(1-phenylethyl)amino] nonanoate (323)** (500 mg, 1.5 mmols) and sodium bicarbonate (0.22 g, 2.6 mmols) in dry $CHCl_3$ (8 mL). Chlorobutyryl chloride (0.32 g, 2.2 mmols) was added by syringe and the mixture was heated at reflux for 12 hours. The solid sodium bicarbonate was filtered off and the residue was rinsed with CH_2Cl_2 (20 mL). The solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (5% - 50% EtOAc/hexane). The product, **(*R*)-*t*-butyl 3-(4-chloro-*N*-(*R*)-1-phenylethyl)butanamido)nonanoate (331)** (70 mg, 11% yield) was isolated as a yellow oil.

WitsETD



[331]

R_f 0.47 10% (EtOAc/hexane) $[\alpha]_D^{20}$ +20.0 (*c* 1.00, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.36-7.18 (5H, m, H-19, H-20, H-21), 4.34 (2H, t, *J* 7.1, H-13), 3.89 (1H, q, *J* 6.6, H-16), 2.71 (1H, quintet, *J* 5.7, H-3), 2.49 (2H, t, *J* 8.0, H-11), 2.39-2.20 (4H, m, H-2, H-12), 1.39 (9H, s, H-15), 1.24 (3H, d, *J* 6.6, H-17), 1.35-1.18 (10H, m, H-4, H-5, H-6, H-7, H-8), 0.90 (3H, t, *J* 7.5, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 177.6 (C-10), 171.8 (C-1), 145.9 (C-18), 128.2 (C-19), 126.7 (C-21), 126.6 (C-20), 80.1 (C-14), 68.4 (C-13), 54.9 (C-16), 52.1 (C-3), 39.5 (C-2), 35.1 (C-4), 31.7 (C-5), 29.1 (C-6), 28.0 (C-15), 27.7 (C-11), 25.7 (C-7), 24.7 (C-17), 22.5 (C-8), 22.1 (C-12), 14.0 (C-9).

$\nu_{max.}$ / **cm^{-1}**: 2960 (m, C-H), 2929 (m, C-H), 2859 (m, C-H), 1728 (s, OC=O), 1605 (w, NC=O), 1456 (m), 1369 (m), 1259 (m), 1156 (s), 764 (w), 703 (m).

7.2.4.4 Attempted debenzylation reaction

Method A

(*R*)-*t*-Butyl 3-(4-chloro-*N*-(*R*)-1-phenylethyl)butanamido)nonanoate (331) (50 mg, 0.11 mmol) was dissolved in AcOH (10 mL). Palladium hydroxide (10 - 20%, 40 mg, 0.80 eq.) was added and the reaction was set up under 7.5 atmospheres of hydrogen pressure in the hydrogenator. The reaction was stirred at ambient temperature for 48 hours. The catalyst was removed by

WitsETD

filtration through Celite® and the product was thoroughly rinsed with acetone (50 mL). The solvent was removed *in vacuo* and the crude material was purified by column chromatography (10% - 50% EtOAc/hexane). None of the desired product was isolated.

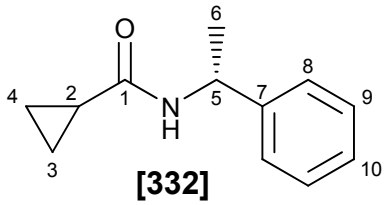
Method B

(*R*)-*t*-Butyl 3-(4-chloro-*N*-(*R*)-1-phenylethyl)butanamido)nonanoate (331), (100 mg, 0.22 mmol) and ceric ammonium nitrate (482 mg, 0.880 mmol) were dissolved in MeCN/H_2O (1:5, 6 mL) and stirred at ambient temperature for 12 hours. The reaction was quenched with saturated sodium bicarbonate solution (10 mL) and filtered through cotton wool. The product was extracted into CH_2Cl_2 (3 × 15 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (20% - 50% EtOAc/hexane) to give ***t*-butyl (3*R*)-3-[*N*-(1-phenylethyl)amino]nonanoate (323)** (73 mg, 100% yield).

7.2.4.5 (*R*)-*N*-(1-Phenylethyl)cyclopropanecarboxamide (332)

(*R*)-*t*-Butyl 3-(4-chloro-*N*-(*R*)-1-phenylethyl)butanamido)nonanoate (331), (500 mg, 1.5 mmol) was dissolved in *t*-butanol (10 mL). Freshly sublimed potassium *t*-butoxide (337 mg, 3.00 mmol) was carefully added and the reaction was stirred for 72 hours at ambient temperature. The reaction was quenched by the careful addition of AcOH (5 mL). The solution was rinsed with distilled H_2O (20 mL) and extracted into CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried with sodium sulfate, filtered, and the solvent removed *in vacuo*. The crude oil was purified by column chromatography (30% EtOAc/hexane) to give **(*R*)-*N*-(1-phenylethyl)cyclopropanecarboxamide (332)** (171 mg, 56% yield) as a white, crystalline solid.

WITHDRAWN



[332]

M.p. 82 -84 °C

R_f 0.63 (50% EtOAc/hexane), $[\alpha]_D^{20}$ +130.4 (*c* 0.79, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.35-7.22 (5H, m, H-8, H-9, H-10), 6.37 (1H, d, *J* 7.2, N-*H*), 5.11 (1H, quintet, *J* 7.0, H-5), 1.44 (3H, d, *J* 7.0, H-6), 1.38-1.24 (1H, m, H-2), 0.97-0.86 (2H, m, H-3/H-4), 0.74-0.61 (2H, m, H-3/H-4).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 172.7 (C-1), 143.5 (C-7), 128.5 (C-8), 127.1 (C-10), 126.1 (C-9), 48.7 (C-5), 21.8 (C-2), 14.6 (C-6), 7.1 (C-3, C-4).

$\nu_{max.}$ / **cm^{-1}**: 3330 (s, N-H), 3033 (w, C-H), 2972 (m, C-H), 2932 (m, C-H), 1636 (s, NC=O), 1525 (s), 1495 (s), 1395 (m), 1236 (s), 1133 (w), 958 (s), 764 (s).

m/z: 189 (17%, M), 174 (20), 160 (14), 145 (35), 130 (8), 120 (84), 106 (100). Found 189.11452, $C_{12}H_{15}ON$ requires 189.11536.

7.2.5 Thionation reactions

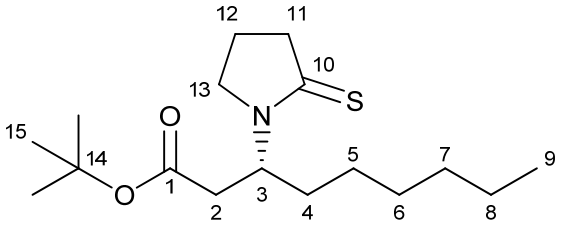
7.2.5.1 *t*-Butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)nonanoate (278)

Method A

First, ***t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)nonanoate (277)** (480 mg, 1.61 mmol) was dissolved, and then Lawesson's reagent (366 mg, 0.90 mmol) suspended in freshly distilled CH_2Cl_2 (10 mL) in an oven-dried RBF under a nitrogen atmosphere. The solution was left stirring at ambient temperature for 72 hours. The reaction was quenched by the addition of saturated sodium bicarbonate solution (10 mL) and then extracted into CH_2Cl_2 (3 × 20 mL). The combined organic fractions were dried with sodium sulfate, the solvent removed *in vacuo*, and the crude material purified by column chromatography (20%

WitsETD

EtOAc/hexane). The desired product, ***t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)nonanoate** (**278**) was obtained as a pale yellow, odoriferous oil (320 mg, 63% yield).



[278]

R_f 0.51 (20% EtOAc/hexane), $[\alpha]_D^{20}$ +7.4 (*c* 0.88, CH_2Cl_2)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 5.36 (1H, quintet, *J* 7.5, H-3), 3.71 (1H, dt, *J* 10.7, 7.5, H-13*A*), 3.56 (1H, dt, *J* 10.7, 7.5, H-13*B*), 3.00 (2H, t, *J* 7.5, H-11), 2.55 (1H, dd, *J* 14.4, 6.0, H-2*A*), 2.43 (1H, dd, *J* 14.4, 9.0, H-2*B*), 2.03 (2H, quintet, *J* 7.5, H-12), 1.64-1.55 (2H, m, H-4), 1.43 (9H, s, H-15), 1.38-1.20 (8H, m, H-5, H-6, H-7, H-8), 0.87 (3H, t, *J* 6.6, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 201.7 (C-10), 169.5 (C-1), 81.0 (C-14), 53.3 (C-3), 49.0 (C-13), 45.1 (C-11), 38.8 (C-2), 32.2 (C-4), 31.5 (C-5), 28.9 (C-6), 27.8 (C-15), 25.7 (C-7), 22.4 (C-8), 20.0 (C-12), 13.9 (C-9).

$\nu_{max.}$ / **cm^{-1}**: 2926 (m, C-H), 2856 (m, C-H), 1722 (s, C=O), 1491 (m), 1446 (s), 1310 (s, C=S), 1220 (s), 953 (w), 842 (w).

m/z: 313 (18%, M), 280 (34), 256 (94), 224 (100), 212 (8), 173 (27), 154 (5), 128 (17), 102 (55). Found 313.2070, $C_{17}H_{31}O_2N^{32}S$ requires 313.2076.

Method B

First, ***t*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)nonanoate (277)** (0.20 g, 0.67 mmol) was dissolved, and then phosphorus pentasulfide (90 mg, 0.20 mmol) suspended in dry $CHCl_3$ (3 mL) in an oven-dried RBF under a nitrogen atmosphere. The heterogeneous mixture was stirred at ambient

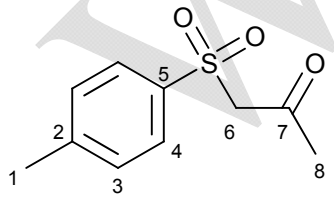
WitsETD

temperature for 72 hours. The reaction was quenched by the addition of saturated sodium bicarbonate solution (10 mL) and then extracted into CH_2Cl_2 (3 × 10 mL). The organic fractions were combined and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (20% EtOAc/hexane) to give ***t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)nonanoate (278)** (109 mg, 52% yield) was obtained as a pale yellow, odoriferous oil.

7.2.6 Formation of the vinylogous sulfonamide

7.2.6.1 Preparation of 1-[(4-methylphenyl)sulfonyl]acetone (279)[190]

Sodium-*p*-toluenesulfinate (10.00 g, 56.0 mmol) was dissolved in DMSO (25 mL), together with chloroacetone (4.47 mL, 57.6 mmol) and the resulting mixture was heated to 90ºC under nitrogen and stirred for 4 hours. During this period, the clear solution turned dark brown. The solution was cooled and washed with distilled H_2O (50 mL) before extracting into CH_2Cl_2 (6 × 50 mL). The organic fractions were combined and then rinsed with distilled H_2O to remove residual DMSO. The organic fractions were dried with magnesium sulfate and the solvent was removed *in vacuo* to give a crude brown oil which was further purified by silica column chromatography (40% EtOAc/hexane). The resulting product, **1-[(4-methylphenyl)sulfonyl]acetone (279)**, was a odoriferous, brown, low melting solid (11.41 g, 96% yield). Full characterization was in agreement with the reported literature values.[190]



[279]

Mp. 49-51ºC (lit. ref. 50-51ºC)[190]

R_f 0.53 (40 % EtOAc/hexane)

WitsETD

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.76 (2H, d, *J* 8.2, H-4), 7.37 (2H, d, *J* 8.2, H-3), 4.15 (2H, s, H-6), 2.45 (3H, s, H-1), 2.39 (3H, s, H-8).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 196.6 (C-7), 145.9 (C-5), 136.2 (C-2), 130.4 (C-4), 128.6 (C-3), 68.2 (C-6), 31.8 (C-8), 22.0 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2924 (m, C-H), 2360 (m, C-H), 1712 (s, C=O), 1597 (m), 1462 (m), 1359 (s, SO_2), 1317 (s), 1147 (s, SO_2), 1083 (m), 812 (m), 746 (m).

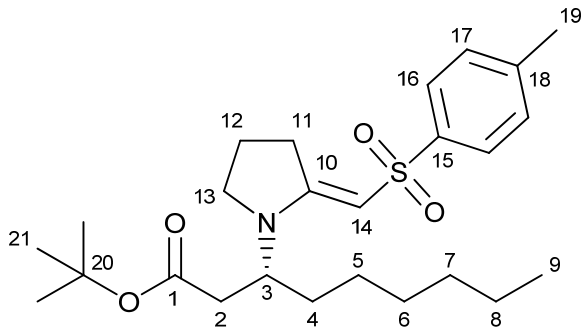
m/z: 212 (15%, M), 170 (26), 155 (45), 148 (29), 105 (18), 91 (100), 77 (5), 65 (24), 43 (30). Found 212.0521, $C_{10}H_{12}O_3{}^{32}S$ requires 212.0507.

7.2.6.2 *t*-Butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl} nonanoate (280)

Method A

In an oven-dried RBF, under a nitrogen atmosphere, the α-thioiminium salt was prepared by reacting ***t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)nonanoate (278)** (500 mg, 1.59 mmol) with freshly distilled methyl iodide (0.15 mL, 2.4 mmol) in THF (5 mL). After 72 hours at ambient temperature the starting material was no longer visible by TLC. The solvent was removed *in vacuo* and a premixed solution of **1-[(4-methylphenyl)sulfonyl]acetone (279)** (675 mg, 3.18 mmol) and triethylamine (0.66 mL, 4.8 mmol) in CH_2Cl_2 (5 mL) was carefully added to the α-thioiminium salt. The reaction was left stirring at ambient temperature for an additional 96 hours and was quenched with distilled H_2O (3 mL), extracted into CH_2Cl_2 (3 × 10 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (20% EtOAc/hexane). ***t*-Butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)nonanoate (277)** (120 mg, 25% recovery) ***t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonanoate (280)** (200 mg, 28% yield), and the acylated product***, t*-butyl (3*R*)-3-{2-[1-(*p*-toluenesulfonyl)-2-oxopropylidene]-1-pyrrolidinyl} nonanoate (337)**, (210 mg, 27% yield) were isolated from the column. The desired product **(280)** was first isolated as a yellow oil, but it quickly discoloured to brown.

WISER



[280]

R_f 0.47 (30% EtOAc/hexane), $[\alpha]_D^{20}$ +11.6 (*c* 0.69, CH_2Cl_2)

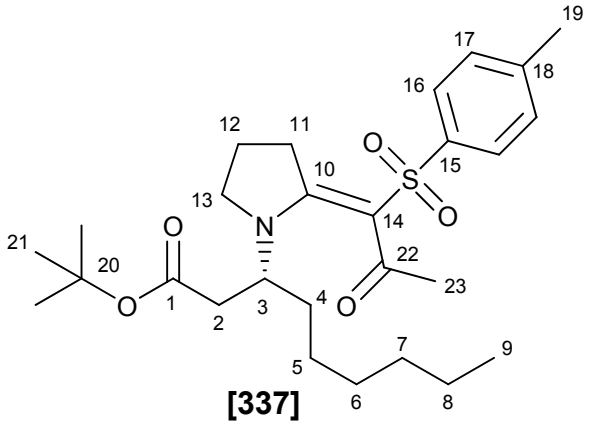
^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.68 (2H, d, *J* 8.1, H-16), 7.16 (2H, d, *J* 8.1, H-17), 5.00 (1H, s, H-14), 3.93-3.58 (1H, m, H-3), 3.18 (1H, dt, *J* 16.1, 7.1, H-13*A*), 3.18 (1H, dt, *J* 16.1, 8.9, H-13*B*), 2.90 (2H, t, *J* 7.7, H-11), 2.32 (3H, s, H-19), 1.78 (2H, dt, *J* 14.7, 5.7, H-2*AB*), 1.45-1.32 (2H, m, H-12), 1.27 (9H, s, H-21), 1.23-1.10 (10H, m, H-4, H-5, H-6, H-7, H-8), 0.80 (3H, t, *J* 6.6, H-9).

^{13}C (100 MHz, $CDCl_3$) δ_C /**ppm** 169.8 (C-1), 161.5 (C-10), 143.0 (C-15), 141.7 (C-17), 129.2 (C-16), 126.1 (C-18), 87.9 (C-14), 81.2 (C-20), 52.2 (C-3), 47.0 (C-13), 39.0 (C-11), 32.1 (C-2), 31.6 (C-4), 29.7 (C-5), 29.0 (C-6), 27.9 (C-21), 26.1 (C-12), 22.5 (C-7), 21.4 (C-8), 20.9 (C-19), 14.0 (C-9).

$\nu_{max.}$ / **cm^{-1}**: 2926 (m, C-H), 2856 (m, C-H), 2360 (w), 2115 (w), 1724 (s, C=O), 1569 (s, C=C), 1288 (m, SO_2), 1132 (s), 1083 (s), 847 (m).

m/z: 449 (2%, M), 429 (9), 376 (6), 355 (12), 294 (23), 238 (79), 196 (94), 179 (18), 105 (48), 91 (100), 56 (44). Found 449.2594, $C_{25}H_{39}O_4N^{32}S$ requires 449.2600.

WitsETD



[337]

R_f 0.30 (30% EtOAc/hexane), $[\alpha]_D^{20}$ +44.0 (*c* 1.00, CH_2Cl_2)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.74 (2H, d, *J* 8.1, H-16), 7.25 (2H, d, *J* 8.1, H-17), 3.94 (1H, tt, *J* 8.7, 4.3, H-3), 3.66-3.49 (2H, m, H-13*AB*), 3.40 (1H, dt, *J* 15.3, 9.1, H-11*A*), 3.03 (1H, dt, *J* 15.3, 6.6, H-11*B*), 2.95 (1H, dd, *J* 15.2, 4.3, H-2*A*), 2.48-2.40 (1H, m, H-2*B*), 2.39 (3H, s, H-19), 2.34 (3H, s, H-23), 2.12-1.83 (2H, m, H-12*AB*), 1.72-1.51 (2H, m, H-4*AB*), 1.46 (9H, s, H-21), 1.42-1.27 (8H, m, H-5, H-6, H-7, H-8), 0.88 (3H, t, *J* 6.7, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 190.7 (C-22), 174.9 (C-10), 169.7 (C-1), 142.9 (C-18), 142.1 (C-15), 129.3 (C-17), 125.8 (C-16), 103.7 (C-14), 81.1 (C-20), 58.5 (C-3), 49.1 (C-13), 37.8 (C-11), 36.9 (C-2), 32.3 (C-4), 31.4 (C-5), 30.4 (C-23), 28.8 (C-6), 27.9 (C-21), 25.9 (C-7), 22.5 (C-8), 21.3 (C-19), 20.1 (C-12), 13.9 (C-9).

$\nu_{max.}$ / **cm^{-1}**: 2930 (m, C-H), 2860 (m, C-H), 2363 (w), 1727 (s, OC=O), 1687 (m, C=O), 1616 (m, C=C), 1520 (m), 1297 (s, S=O), 1141 (s), 815 (m).

m/z: 492 (1%, M+1), 418 (6), 376 (12), 336 (24), 320 (9), 280 (100), 238 (91), 196 (15), 172 (6), 139 (15), 126 (54), 108 (21). Found 491.2700, $C_{27}H_{41}O_5N^{32}S$ requires 491.2705.

WISER

Method B

In an oven-dried RBF, under a nitrogen atmosphere, the α-thioiminium salt was prepared by reacting ***t*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)nonanoate (278)** (320 mg, 1.02 mmol) with freshly distilled methyl iodide (0.10 mL, 1.5 mmol) in THF (5 mL). After 48 hours at ambient temperature the solvent was removed *in vacuo* and a premixed solution of **1-[(4-methylphenyl)sulfonyl]acetone (279)** (435 mg, 2.05 mmol) and DBU (0.46 mL, 3.0 mmol) in CH_2Cl_2 (5 mL) was carefully added to the α-thioiminium salt. The reaction was left stirring at ambient temperature for an additional 72 hours and was quenched with distilled H_2O (3 mL), extracted into CH_2Cl_2 (3 × 10 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (20% EtOAc/hexane). The desired product ***t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonanoate (280)** (60 mg, 13% yield) and the acylated product, ***t*-butyl (3*R*)-3-{2-[1-(*p*-toluenesulfonyl)-2-oxopropylidene]-1-pyrrolidinyl}nonanoate (337)** (190 mg, 38% yield) were both isolated as yellow oils.

7.2.6.3 Attempted deacetylation reactions

Method A[154]

***t*-Butyl (3*R*)-3-{2-[1-(*p*-toluenesulfonyl)-2-oxopropylidene]-1-pyrrolidinyl} nonanoate (337)** (200 mg, 0.41 mmols) was dissolved in TFA (3 mL) and heated at reflux for 12 hours. The reaction mixture was cooled and then rinsed with an ammonia solution (10%, 15 mL). The organic compounds were extracted into CH_2Cl_2 (3 × 20 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (100% EtOAc). None of the desired product, ***t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonanoate (280)**, was isolated.

Method B[154]

***t*-Butyl (3*R*)-3-{2-[1-(*p*-toluenesulfonyl)-2-oxopropylidene]-1-pyrrolidinyl} nonanoate (337)** (190 mg, 0.39 mmols) was dissolved in toluene (3 mL). TFA (0.15 mL, 1.9 mmols) was added and the mixture was heated at reflux for 5 hours, while being monitored by TLC. The mixture was cooled and the reaction

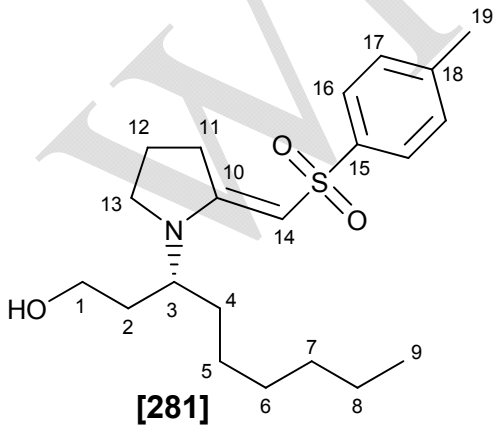
WitsETD

was quenched by the addition of an ammonia solution (10%, 15 mL). The organic material was extracted in CH_2Cl_2 (3 × 15 mL) and the combined organic fractions were dried with sodium sulfate. The solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (100% EtOAc). None of the desired product, ***t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl} nonanoate (280)**, was isolated.

7.2.7 Reduction of the ester

7.2.7.1 *t*-Butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl} nonan-1-ol (281)

In an oven-dried RBF charged with THF (5 mL), ***t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonanoate (280)** (0.11 g, 0.24 mmol) was dissolved and lithium aluminium hydride (25 mg, 0.67 mmol) was carefully added. The reaction was stirred at ambient temperature for 15 hours and quenched by the addition of CH_2Cl_2 (10 mL), distilled H_2O (1 mL) and sodium hydroxide solution (2.0 *M*, 1 mL) sequentially. The mixture was filtered through Celite® and the solvent was removed *in vacuo*. The product, ***t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl}nonan-1-ol (281)** (83 mg, 92% yield), was isolated with sufficient purity that no chromatography was required.



[281]

R_f 0.14 (50% EtOAc/hexane), $[\alpha]_D^{20}$ -25.0 (*c* 0.30, CH_2Cl_2)

WitsETD

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.74 (2H, d, *J* 8.1, H-16), 7.23 (2H, d, *J* 8.1, H-17), 5.09 (1H, s, H-14), 3.75-3.62 (1H, m, H-3), 3.62-3.44 (2H, m, H-13*AB*), 3.20 (2H, t, *J* 6.7, H-1), 3.08-2.96 (1H, m, H-11*A*), 2.97-2.84 (1H, m, H-11*B*), 2.39 (3H, s, H-19), 2.17 (1H, br, O-*H*), 1.86 (2H, quintet, *J* 7.4, H-12), 1.71 (2H, q, *J* 6.7, H-2), 1.56-1.39 (2H, m, H-4), 1.29-1.12 (8H, m, H-5, H-6, H-7, H-8), 0.86 (3H, t, *J* 6.8, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 162.6 (C-10), 143.4 (C-15), 141.7 (C-18), 129.2 (C-17), 125.8 (C-16), 86.2 (C-14), 59.0 (C-13), 51.6 (C-3), 45.9 (C-1), 34.7 (C-2), 32.3 (C-4), 31.7 (C-7), 31.4 (C-11), 29.0 (C-6), 26.2 (C-8), 22.5 (C-5), 21.4 (C-19), 20.8 (C-12), 14.0 (C-9).

$\nu_{max.}$ / **cm^{-1}**: 3474 (br, O-H), 2927 (m, C-H), 2857 (m, C-H), 1563 (s, C=C), 1272 (m, S=O), 1126 (s), 1079 (s), 847 (m), 653 (m).

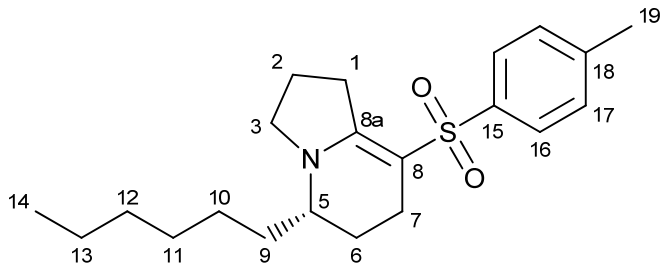
m/z: 355 (9%), 281 (14), 259 (6), 224 (11), 218 (29), 207 (42), 198 (27), 182 (57), 155 (64), 139 (55), 124 (48), 111 (81), 105 (100). Found 379.2176, $C_{21}H_{33}O_3N^{32}S$ requires 379.2181.

7.2.8 Cyclisation reaction

7.2.8.1 (*5R*)-5-Hexyl-1,2,3,5,6,7-hexahydro-8-indolizinyl-4-methylphenyl sulfone (282)

Triphenylphosphine (0.17 g, 0.65 mmol), imidazole (18 mg, 0.26 mmol) and iodine (66 mg, 0.26 mmol) were sequentially dissolved in toluene (7 mL). The alcohol, ***t*-butyl (3*R*)-3-{2-[(*E*)-(*p*-toluenesulfonyl)methylene-1-pyrrolidinyl} nonan-1-ol (281)** (50 mg, 0.13 mmol) was added and the mixture was heated at reflux for 6 hours. The solvent was removed *in vacuo* and the residue was partitioned between distilled H_2O (10 mL) and CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried with sodium sulfate, the solvent removed *in vacuo*, and the crude material purified by column chromatography (30% EtOAc/hexane). **(*5R*)-5-Hexyl-1,2,3,5,6,7-hexahydro-8-indolizinyl-4-methyl phenylsulfone (282)** (45 mg, 96% yield) was isolated as a yellow oil which discoloured to blue in the presence of light.

WitsETD



[282]

R_f 0.80 (50% EtOAc/hexane), $[\alpha]_D^{20}$ +9.4 (*c* 0.85, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.69 (2H, d, *J* 8.1, H-16), 7.26 (2H, d, *J* 8.1, H-17), 3.49 (1H, quintet, *J* 6.9, H-5), 3.19 (2H, t, *J* 7.1, H-3), 3.13 (2H, t, *J* 7.2, H-1), 2.39 (3H, s, H-19), 1.91 (2H, quintet, *J* 7.2, H-2), 1.80-1.51 (4H, m, H-6, H-7), 1.38-1.25 (10H, m, H-9, H-10, H-11, H-12, H-13), 0.85 (3H, t, *J* 6.9, H-14).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 155.1 (C-8a), 141.9 (C-15), 141.7 (C-18), 129.9 (C-16), 126.1 (C-17), 92.4 (C-8), 53.9 (C-5), 51.2 (C-3), 32.1 (C-1), 31.7 (C-7), 31.4 (C-6), 29.3 (C-2), 25.6 (C-9), 24.6 (C-10), 22.6 (C-19), 21.4 (C-11), 21.1 (C-12), 19.4 (C-13), 14.0 (C-14).

$\nu_{max.}$ / **cm^{-1}**: 2928 (m, C-H), 2856 (m, C-H), 1593 (s, C=C), 1291 (s, S=O), 1142 (s), 1128 (s), 1079 (s), 1077 (m), 813 (m), 665 (m).

m/z: 361 (32%, M), 304 (7), 276 (89), 206 (100), 204 (14), 164 (8), 149 (10), 134 (16), 122 (98). Found 361.2071, $C_{21}H_{31}O_2N^{32}S$ requires 361.2075.

WitsETD

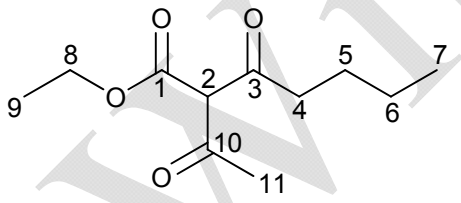
CHAPTER 8
EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 4

8.1 The total synthesis of monomorine I and 5-*epi*-monomorine I

8.1.1 Preparation of ethyl 4-oxooctanoate

8.1.1.1 Preparation of ethyl 2-acetyl-3-oxoheptanoate (344)[192]

Sodium hydride (60% in oil, 7.20 g, 180 mmol) was dissolved in freshly distilled THF (400 mL) in an oven-dried 1 litre RBF. The solution was cooled to 0°C and ethyl acetoacetate (25.0 mL, 195 mmol) was added dropwise over 45 minutes while the solution was vigorously stirred to prevent an emulsion from forming. The solution proceeded to turn yellow. Valeroyl chloride (18.1 g, 150 mmol) was added dropwise and the solution turned opaque and milky. The reaction mixture was allowed to warm to ambient temperature and was left reacting for a further 12 hours. The reaction was quenched by the careful addition of distilled H_2O (200 mL). The product was extracted into EtOAc (3 × 200 mL) and dried with magnesium sulfate. The solvent was removed *in vacuo* and the crude oil was purified by column chromatography (5% EtOAc/hexane) to give **ethyl 2-acetyl-3-oxoheptanoate (344)** (29.50 g, 92% yield) as a pale yellow oil.



[344]

R_f 0.84 (10% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 17.80 (1H, s, H-2), 4.28 (2H, q, *J* 7.2, H-8), 2.66 (2H, t, *J* 7.5, H-4), 2.34 (3H, s, H-11), 1.75-1.55 (2H, m, H-5), 1.50-1.22 (5H, m, H-9, H-6), 0.92 (3H, t, *J* 7.2, H-7).

WitsETD

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 198.8 (C-10), 195.6 (C-3), 167.2 (C-1), 108.6 (C-2), 60.6 (C-8), 37.4 (C-4), 27.8 (C-5), 25.5 (C-11), 22.4 (C-6), 14.1 (C-9), 13.7 (C-7).

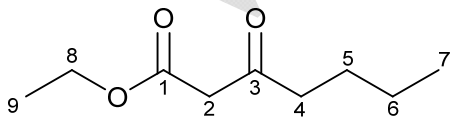
$\nu_{max.}$ / **cm^{-1}**: 2960 (m, C-H), 2934 (m, C-H), 2874 (m, C-H), 1762 (m, C=O), 1710 (s, C=O), 1670 (m, C=O), 1556 (m), 1415 (m), 1368 (m), 1218 (s), 1075 (s).

m/z: 214 (6%, M), 199 (38), 192 (3), 185 (10), 172 (38), 157 (100), 153 (35), 139 (76), 130 (55), 126 (35), 115 (21), 111 (26). Found 214.11920, $C_{11}H_{18}O_4$ requires 214.12051.

8.1.1.2 Ethyl 3-oxoheptanoate (345)[194]

Method A

Ethyl 2-acetyl-3-oxoheptanoate (344) (13.2 g 62.0 mmol) was dissolved in dry Et_2O (40 mL) and ammonia gas was bubbled through the solution for 90 minutes at ambient temperature (approximately 3 equivalents of ammonia were added). The solution was rinsed with distilled H_2O (2 × 100 mL) and stirred in an HCl solution (10% (v/v), 60 mL) for 2 hours. The organic layer was rinsed with saturated sodium bicarbonate solution (100 mL), dried with sodium sulfate and then the solvent was removed *in vacuo*. The crude material was purified by column chromatography (5% EtOAc/hexane) to give **ethyl acetoacetate (339)** (6.80 g, 84% yield) as the major product and the desired product, **ethyl 3-oxoheptanoate (345**), (1.69 g, 16% yield) as the minor product.



[345]

R_f 0.71 (10% EtOAc/hexane)

WitsETD

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.20 (2H, q, *J* 7.2, H-8), 3.43 (2H, s, H-2), 2.55 (2H, t, *J* 7.3, H-4), 1.63-1.53 (2H, m, H-5), 1.37-1.26 (5H, m, H-6, H-7) 0.91 (3H, t, *J* 7.2, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 202.9 (C-3), 167.2 (C-1), 61.2 (C-8), 49.2 (C-2), 42.6 (C-4), 25.4 (C-5), 22.0 (C-6), 14.0 (C-9), 13.7 (C-7).

$v_{max.}$ / **cm^{-1}**: 2960 (m, C-H), 2935 (m, C-H), 2874 (m, C-H), 1741 (s, C=O), 1715 (s, C=O), 1312 (s), 1234 (s), 1152 (s), 1030 (s).

m/z: 172 (8%, M), 157, (4), 143 (9), 130 (44), 115 (17), 102 (10), 88 (31), 85 (100), 84 (45), 69 (24), 57 (95).

Method B[206]

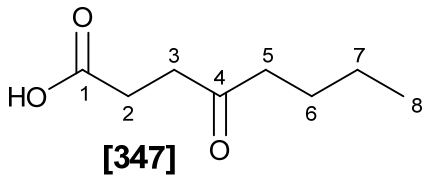
Sodium hydride (943 mg, 23.6 mmol) was dissolved in dry THF (50 mL) and the solution cooled to 0ºC in an ice-bath. Ethyl acetoacetate (2.00 mL, 15.7 mmol) was added dropwise and the solution was allowed to stir for 15 minutes. *n*-Butyllithium (1.6 *M*, 15.0 mL, 23.6 mmol) was slowly added by syringe and the solution was stirred for an additional 15 minutes. Finally, chloropropane (2.3 mL, 25.9 mmol) was added dropwise to the reaction mixture. The reaction was monitored by TLC until the ethyl acetoacetate appeared to have reacted completely and the reaction was then quenched by the addition of distilled H_2O (30 mL). The product was extracted into EtOAc (3 × 50 mL), rinsed with distilled H_2O (2 × 100 mL) and brine (2 × 50 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (5% EtOAc/hexane) to give **ethyl 3-oxoheptanoate (345)** (200 mg, 8% yield) as a clear oil with a pleasant, fruity odour. The low yield was likely due to inferior quality of the *n*-butyllithium.

8.1.1.3 Preparation of 4-oxooctanoic acid (347)[198]

n-Butylmagnesium bromide was prepared *in situ* by reacting bromobutane (8.1 mL, 75 mmol) with magnesium turnings (1.95 g, 80.0 mmol) in dry THF (100 mL) for 1 hour at 0°C under nitrogen. In a separate RBF succinic

WitsETD

anhydride (5.00 g, 50.0 mmol) was dissolved in THF (70 mL) together with a catalytic amount of iron (III) acetoacetate, (530 mg, 1.50 mmol). The Grignard reagent (0.75 *M*, 67 mL, 50 mmol) was added dropwise to the succinic anhydride solution over 40 minutes. The colour of the solution gradually changed from deep red to yellow. The reaction was stirred for an additional hour before it was quenched with an HCl solution (10% (v/v), 30 mL). The product was extracted into Et_2O (3 × 50 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (50 mL) and distilled H_2O (2 × 50 mL) and dried with sodium sulfate. The Et_2O was removed *in vacuo* and the crude product was purified by column chromatography (5% EtOAc/hexane) to give the desired product, **4-oxooctanoic acid (347)** (2.00 g, 25% yield), and **5,5-dibutyldihydro-2(*3H*)-furanone (348)** (550 mg, 11% yield) as a by-product.



[347]

M.p. 49-51ºC

R_f 0.15 (10% EtOAc/hexane)

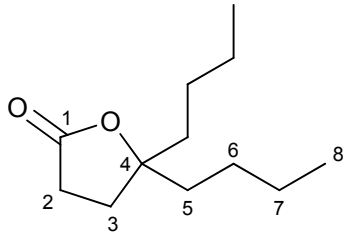
^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 12.00-10.00 (1H, br, O-H), 2.72 (2H, t, *J* 6.4, H-2), 2.63 (2H, t, *J* 6.4, H-3), 2.45 (2H, t, *J* 6.7, H-5), 1.63-1.53 (2H, m, H-6), 1.37-1.24 (2H, m, H-7), 0.91 (3H, t, *J* 7.3, H-8).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 209.4 (C-4), 179.1 (C-1), 42.8 (C-5), 37.1 (C-3), 28.2 (C-2), 26.3 (C-6), 22.7 (C-7), 14.2 (C-8).

$v_{max.}$ / **cm^{-1}**: 3550-3350 (br, OH), 2958 (m, C-H), 2930 (m, C-H), 2868 (m, C-H), 1703 (br, s, 2 × C=O), 1410 (m), 1347 (m), 1249 (m), 1208 (s), 1178 (m), 950 (s).

WitsETD

m/z: 158 (1%, M), 141 (8), 116 (62), 111 (9), 101 (75), 98 (79), 85 (92), 73 (24), 70 (6), 57 (100), 41 (41). Found 158.0950, $C_8H_{14}O_3$ requires 158.0943.



[348]

R_f 0.32 (10% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 2.57 (2H, t, *J* 8.4, H-3), 2.02 (2H, t, *J* 8.5, H-2), 1.66-1.57 (4H, m, H-5), 1.40-1.26 (8H, m, H-6, H-7), 0.92 (6H, t, *J* 6.2, H-8).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 177.4 (C-1), 89.5 (C-4), 38.9 (C-5), 31.2 (C-2), 29.6 (C-3), 26.0 (C-6), 23.4 (C-7), 14.3 (C-8).

$\nu_{max.}$ / **cm^{-1}**: 2959 (m, C-H), 2938 (m, C-H), 2875 (m, C-H), 1772 (s, C=O), 1469 (m), 1231 (m), 1194 (m), 1160 (m), 935 (m).

m/z: 199 (1%, M), 141 (100), 95 (5), 85 (7), 57 (10), 41 (9). Found 199.1679, $C_{12}H_{23}O_2$ (M+1) requires 199.1698.

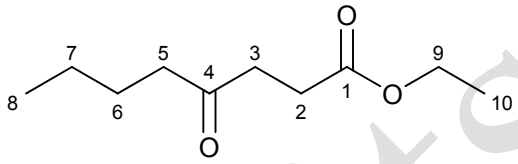
8.1.1.4 Preparation of ethyl 4-oxooctanoate (292)

Method A[198, 199]

THF (4 mL) and Et_2O (12 mL) were distilled and degassed with nitrogen for 30 minutes. Di-*n*-butylcopper lithium was prepared *in situ* by reacting copper iodide (762 mg, 4.00 mmol) with *n*-butyllithium (1.6 *M*, 5.0 mL, 8.0 mmol) at −90ºC under a nitrogen atmosphere for 1 hour (the solution turned black upon addition of *n*-butyllithium). Ethyl 4-chloro-4-oxobutyrate (1.04 mL, 7.30 mmol) was added to the cuprate by syringe at −90ºC, and the reaction mixture was allowed to warm to ambient temperature and stir for a further 12 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride (20

WiSETD

mL) and the biphasic solution was stirred for 40 minutes. Once the pH of the solution was neutral the product was extracted into Et_2O (4 × 30 mL). The combined organic extracts were dried with magnesium sulfate and the solvent was removed *in vacuo.* The crude product was purified by column chromatography (5% EtOAc/hexane) to give **ethyl 4-oxooctanoate (292)** as a pale yellow oil (530 mg, 56% yield), with contamination by **diethyl succinate (346)** (305 mg, 24% yield), a by-product from the reaction. When the reaction was scaled up (48 mmol) the production of **diethyl succinate (346)** increased to 42% yield and the yield of the **ethyl 4-oxooctanoate (292)** went down to 2%. For all the solvent systems investigated, **diethyl succinate (346)** and **ethyl 4-oxooctanoate (292)** have identical R_f values on silica TLC plates, making separation by column chromatography extremely difficult. They do however differ in boiling points (at 15 torr. diethyl succinate boils at 105°C and ethyl 4-oxooctanoate boils at 125°C) and could be separated by distillation if the scale of the reaction allowed it.



[292]

R_f 0.63 (20% EtOAc/hexane)

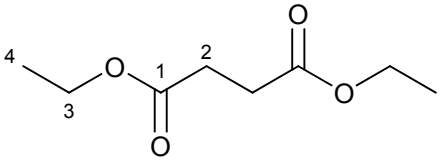
^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.13 (2H, q, *J* 7.1, H-9), 2.72 (2H, t, *J* 7.0, H-3), 2.62-2.45 (2H, m, H-2), 2.45 (2H, t, *J* 7.0, H-5), 1.63-1.55 (2H, m, H-6), 1.34-1.27 (2H, m, H-7), 1.25 (3H, t, *J* 7.1, H-10), 0.91 (3H, t, *J* 7.3, H-8).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 209.5 (C-4), 173.2 (C-1), 61.0 (C-9), 42.9 (C-5), 37.4 (C-3) 28.4 (C-2), 26.3 (C-6), 22.7 (C-7), 14.5 (C-10), 14.3 (C-8).

$\nu_{max.}$ / **cm^{-1}**: 2959 (m, C-H), 2935 (m, C-H), 2874 (m, C-H), 1737 (s, C=O), 1720 (s, C=O), 1413 (w), 1374 (m), 1350 (w), 1197 (s), 1163 (s), 1021 (m).

WitsETD

m/z: 187 (1%, M+1), 144 (55), 141 (65), 129 (47), 111 (8), 101 (100), 85 (57), 73 (12), 57 (61), 41 (25). Found 187.1353, $C_{10}H_{18}O_3$ (M+1) requires 187.1334.



[346]

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.15 (4H, q, *J* 7.2, H-3), 2.62 (4H, s, H-2), 1.26 (6H, t, *J* 7.2, H-4).

Method B[200 - 202]

Bis-(*N,N*-dimethylaminoethyl)ether (4.4 mL, 35 mmol) was reacted with *n*-butylmagnesium chloride (2.0 *M*, 18 mL, 35 mmol) in THF (80 mL), at 0ºC under nitrogen, to allow formation of a tridentate ligand. After 20 minutes, this solution was added dropwise to a solution of ethyl 4-chloro-4-oxobutanoate (5.0 mL, 35 mmol) in THF (20 mL) at -90ºC. After 20 minutes, TLC still indicated that starting material was present and the reaction mixture was allowed to warm to ambient temperature and stir for 2 hours. The reaction was quenched by the addition of saturated ammonium chloride solution (75 mL). The THF was removed *in vacuo* and the product was extracted into EtOAc (5 × 70 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the product was purified by column chromatography (5% EtOAc/hexane) to give **ethyl 4-oxooctanoate (292)** (1.35 g, 21%) as a clear oil.

Method C[195, 196]

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (0.75 g, 3.0 mmol) was dissolved in dioxane (30 mL) with Et_3N (2.5 mL, 18 mmol) and ethyl acrylate (3.2 mL, 30 mmol) in a 3-necked RBF. The flask was fitted with a condenser which was sealed with a KOH drying tube. It was also fitted with a nitrogen leak (1 bubble/second) and a septum. A mixture of valeraldehyde (3.2 mL, 30 mmol), a second portion of ethyl acrylate (3.2 mL, 30 mmol) and dioxane (5 mL) was added by syringe pump over 10 hours. The reaction was left for a further 6 hours at ambient temperature. The dioxane was removed *in vacuo* and the organic residue was redissolved in EtOAc. The organic layer

WITSED

was rinsed with an HCl solution (5% (v/v), 50 mL), saturated sodium bicarbonate solution (2 × 50 mL) and distilled H_2O (2 × 50 mL). The organic layer was dried with magnesium sulfate and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (20% EtOAc/hexane) to give **ethyl 4-oxooctanoate (292)** (901 mg, 16% yield) with slight contaminated by **diethyl succinate (346)**.

Method D[193]

A flame-dried, nitrogen-flushed 50 mL RBF was charged with dry CH_2Cl_2 (17 mL) and neat diethyl zinc (0.60 mL, 5.8 mmol). This was done very carefully by means of a nitrogen flushed syringe as the diethyl zinc ignites readily on contact with air. Diiodomethane (0.50 mL, 5.8 mmol) was carefully added and as soon as exothermic bubbling was initiated the solution was cooled to 0ºC. After 10 minutes of stirring, **ethyl 3-oxoheptanoate (345)** (0.19 g, 1.1 mmol) was rapidly added by syringe. The reaction was left at ambient temperature for an additional 30 minutes and then quenched by the addition of saturated ammonium chloride solution (10 mL). The product was extracted into Et_2O (3 × 25 mL), and the combined organic extracts were rinsed with brine (25 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (5% EtOAc/hexane) to give **ethyl 4-oxooctanoate (292)** (125 mg, 62% yield) as a clear oil.

Method E[199]

Di-*n*-butylcopper lithium was prepared *in situ* by reacting copper iodide (720 mg, 4.00 mmol) with *n*-butyllithium (1.6 *M*, 5.00 mL, 8.00 mmol) in THF (4 mL) at -90 °C under a nitrogen atmosphere for 1 hour. Succinic anhydride (727 mg, 7.27 mmol) was carefully added to this solution and the reaction was stirred for a further 3 hours at ambient temperature. The reaction was quenched by the addition of saturated ammonium chloride solution (10 mL) and the biphasic solution was stirred for 30 minutes before being acidified with an HCl solution 5% (v/v) and extracted into Et_2O (12 mL). The Et_2O was removed *in vacuo* and the residue was redissolved in EtOH (10 mL). Approximately 5 drops of concentrated H_2SO_4 were added and the reaction was allowed to stir for 3 hours. The solvent was then removed *in vacuo* and the crude material was

WITSETD

partitioned between EtOAc (20 mL) and distilled H_2O (20 mL). The organic fraction was dried with sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (5% EtOAc/hexane) gave **ethyl 4-oxooctanoate (292)** (250 mg, 34% yield over the two steps).

Method F[203, 204]

Ethyl 4-chloro-4-oxobutanoate (1.0 mL, 7.0 mmol), was dissolved in THF (10 mL) in a flame-dried RBF. The solution was cooled to -29°C in a xylene/liquid nitrogen bath under a nitrogen atmosphere. Tri-*n*-butylphosphine (1.9 mL, 7.7 mmol) was carefully added and the solution was stirred for 25 minutes. This was followed by the rapid addition of *n*-butylmagnesium bromide (2.0 *M*, 4.0 mL, 8.0 mmol) by syringe. The reaction was left stirring for an additional 10 minutes and was then quenched with aqueous HCl (1.0 *M*, 5 mL). The reaction mixture was poured into a flask containing additional HCl (1.0 *M*, 80 mL) and the product was extracted into EtOAc (3 × 50 mL). The organic fractions were combined and rinsed with sodium bicarbonate solution (1% (w/w), 50 mL), followed by brine (50 mL) and finally dried with sodium sulfate. The EtOAc was evaporated *in vacuo* and the crude product was purified by column chromatography (5% EtOAc/hexane) to give **ethyl 4-oxooctanoate (292)** (1.21 g, 93% yield) as a clear oil.

Method G[198]

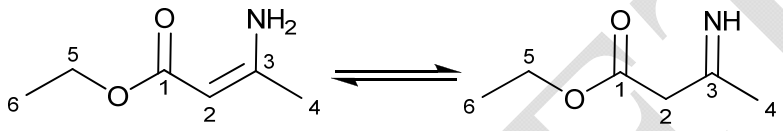
Ethyl 4-chloro-4-oxobutanoate (5.0 mL, 35 mmol), was dissolved in THF (100 mL) together with iron (III) acetoacetate (0.371 g, 1.05 mmol) in an oven-dried RBF, under a nitrogen atmosphere. The solution was cooled to 0°C and *n*-butylmagnesium bromide (1.75 *M*, 20 mL, 35 mmol) was added dropwise from a dropping funnel. The addition was complete after 10 minutes and the reaction was quenched by adding aqueous HCl (10% (v/v), 60 mL). The product was extracted into EtOAc (3 × 50 mL), washed with saturated sodium bicarbonate solution (60 mL), rinsed with distilled H_2O (50 mL) and dried with sodium sulfate. The EtOAc was evaporated *in vacuo* and the crude product was purified by column chromatography (5% EtOAc/hexane) to give **ethyl 4-oxooctanoate (292)** (6.51 g, 100% yield).

WiSER

8.1.2 Preparation of ethyl 3-aminobutyrate

8.1.2.1 (*Z*)-Ethyl 3-aminobut-2-enoate (349)[208 - 210]

Ethyl acetoacetate (15.2 mL, 120 mmol) was dissolved in benzene (150 mL) in a 250 mL RBF connected to a Dean-Stark apparatus. AcOH (6 mL) and ammonium acetate (18.5 g, 240 mmol) were added and the solution was heated at reflux for 4 hours. The solution was then cooled and the benzene and AcOH were removed *in vacuo.* The residual oil was redissolved in EtOAc (100 mL) and washed with saturated sodium carbonate solution (100 mL), dried with sodium sulfate and evaporated down *in vacuo*. The product was isolated by vacuum distillation to give **(*Z*)-ethyl 3-aminobut-2-enoate (349)** (14.0 g 91% yield) as a clear oil. The ^{1}H-NMR spectrum indicated that the product was in equilibrium with its tautomer in a (3:1) ratio respectively.



[349A] **[349B]**

M.p. 28 -31 °C

R_f 0.71 (50% EtOAc/hexane)

Major Tautomer (**349A**)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 8.5-7.5 (2H, br, s, N-H_2), 4.52 (1H, s, H-2), 4.10 (2H, q, *J* 7.1, H-5), 1.90 (3H, s, H-4), 1.25 (3H, t, *J* 7.1, H-6).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 169.9 (C-1), 159.9 (C-3), 83.1 (C-2), 58.0 (C-5), 21.6 (C-4), 14.1 (C-6).

Minor Tautomer (**349B**)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 8.5-7.5 (1H, br, s, N-H), 4.52 (2H, s, H-2), 4.10 (2H, q, *J* 7.1, H-5), 1.66 (3H, s, H-4), 1.25 (3H, t, *J* 7.1, H-6).

WitsETD

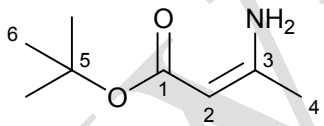
^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 200.6 (C-3), 166.8 (C-1), 60.9 (C-5), 49.5 (C-2), 29.6 (C-4), 13.6 (C-6).

$\nu_{max.}$ / **cm^{-1}**: 3413 (m, N-H), 3320 (m, N-H), 2981 (w, C-H), 2929 (w, C-H), 2896 (w, C-H), 1655 (m), 1614 (s), 1553 (s), 1476 (w), 1452 (w), 1377 (w), 1291 (s), 1165 (s), 1113 (m), 1046 (m), 980 (m), 781 (s).

m/z: 129 (53%, M), 119 (29), 105 (100).

8.1.2.2 (*Z*)-*t*-Butyl 3-aminobut-2-enoate (353)[208 - 210]

t-Butyl acetoacetate (3.32 mL, 20.0 mmol) was dissolved in benzene (75 mL) in a 250 mL RBF connected to a Dean-Stark apparatus. AcOH (2 mL) and ammonium acetate (3.08 g, 40.0 mmol) were added and the solution was heated at reflux for 3 hours. The benzene and the AcOH were removed *in vacuo* and the residual oil was redissolved in EtOAc (100 mL). The organic layer was washed with saturated sodium carbonate solution (100 mL) and distilled H_2O (2 × 100 mL), and then dried with sodium sulfate. The EtOAc was removed *in vacuo* and the product was purified by vacuum distillation to give **(*Z*)-*t*-butyl 3-aminobut-2-enoate (353)** (2.79 g, 89% yield) as a low-melting, crystalline, white solid.



[353]

M.p. 35 -37 °C

R_f 0.74 (50% EtOAc/hexane)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 8.5-7.5 (2H, br, s, N-H_2), 4.46 (1H, s, H-2), 1.87 (3H, s, H-4), 1.47 (9H, s, H-6).

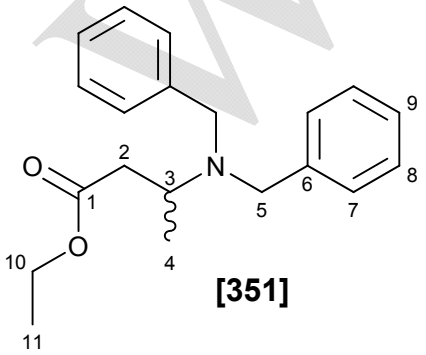
WitsETD

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 170.2 (C-1), 158.7 (C-3), 85.9 (C-2), 78.1 (C-5), 28.6 (C-6), 22.3 (C-4).

$\nu_{max.}$ / **cm^{-1}**: 3411 (s, N-H), 3320 (s, N-H), 2982 (w, C-H), 2929 (w, C-H), 2896 (w, C-H), 1655 (m), 1614 (s), 1552 (s), 1476 (w), 1453 (w), 1376 (w), 1290 (s), 1165 (s), 1113 (m), 1047 (m), 980 (m), 781 (s).

8.1.2.3 Preparation of ethyl 3-(dibenzylamino)butanoate (351)[158]

Freshly distilled dibenzylamine (4.95 mL, 25.8 mmol) was dissolved in THF (100 mL) in oven-dried glassware and cooled to −90ºC under nitrogen. *n*-Butyllithium (1.6 *M*, 15 mL, 24 mmol) was added by syringe and the reaction mixture turned from clear to deep red. The mixture was allowed to stir for 30 minutes at −90ºC at which point a solution of ethyl crotonate (2.66 mL, 21.5 mmol) in THF (45 mL) was added from a dropping funnel over 40 minutes. The reaction was maintained at −90ºC for a further 2 hours before it was quenched with saturated ammonium chloride solution (50 mL) and warmed to ambient temperature. The THF was removed *in vacuo*, distilled H_2O (60 mL) was added to the aqueous solution and the product was extracted into CH_2Cl_2 (6 × 30 mL). The organic fractions were combined and dried with sodium sulfate. The CH_2Cl_2 was evaporated *in vacuo* and the crude product was purified by column chromatography (5% EtOAc/hexane) to give racemic **ethyl 3-(dibenzylamino)butanoate (351)** (4.93 g, 74%) as a clear and pungent oil.



[351]

R_f 0.43 (10% EtOAc/hexane)

WITSETD

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.65 (2H, t, *J* 7.0, H-9), 7.60 (4H, t, *J* 7.0, H-8), 7.53 (4H, d, *J* 7.0, H-7), 4.46 (1H, q, *J* 7.1, H-10*A*), 4.33 (1H, q, *J* 7.1, H-10*B*), 3.97 (2H, d, *J* 13.7, H-5*A*), 3.78 (2H, d, *J* 13.7, H-5*B*), 3.70-3.58 (1H, m, H-3), 2.96 (1H, dd, *J* 7.7, 13.9, H-2*A*), 2.59 (1H, dd, *J* 7.0, 13.9, H-2*B*), 1.50 (3H, t, *J* 7.1, H-11), 1.42 (3H, d, *J* 6.7, H-4).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 172.7 (C-1), 140.4 (C-6), 129.2 (C-7), 128.5 (C-8), 127.2 (C-9), 60.7 (C-10), 53.8 (C-5), 51.3 (C-3), 39.6 (C-2), 14.5 (C-4, C-11).

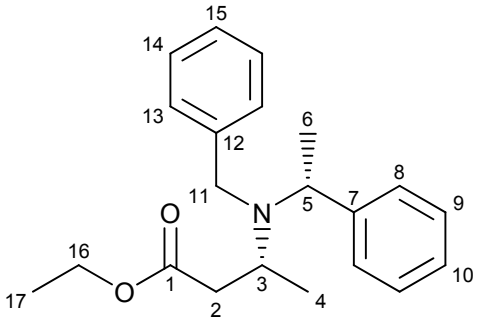
$\nu_{max.}$ / **cm^{-1}**: 3062 (w, Ar), 3027 (w, Ar), 2975 (m, C-H), 2934 (m, C-H), 2803 (m), 1734 (s, C=O), 1495 (m), 1454 (m), 1368 (m), 1297 (m), 1190 (s, C-N), 1095 (m, C-N), 1031 (m), 747 (s), 698 (s).

m/z: 311 (5%, M), 296 (9), 224 (93), 220 (11), 181 (7), 132 (9), 105 (18), 91 (100), 77 (10). Found 311.1894, $C_{20}H_{25}O_2N$ requires 311.1885.

8.1.2.4 Ethyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}butanoate (356)[158]

Benzyl[(1*R*)-1-phenylethyl]amine (2.02 mL, 9.67 mmol) was dissolved in THF (30 mL) in oven-dried glassware and cooled to −90ºC under nitrogen. *n*-Butyllithium (0.7 *M*, 12.9 mL, 9.03 mmol) was added by syringe and the reaction turned from clear to deep red. The mixture was allowed to stir for 30 minutes at −90ºC before a solution of ethyl crotonate (1.00 mL, 8.06 mmol) in THF (16 mL) was added from a dropping funnel over 35 minutes. The reaction was maintained at −90ºC for a further 2 hours before it was quenched with saturated aqueous ammonium chloride (50 mL) and warmed to ambient temperature. The THF was evaporated *in vacuo*, distilled H_2O (20 mL) was added to the aqueous solution and the product was extracted into CH_2Cl_2 (5 × 40 mL). The organic fractions were combined and dried with sodium sulfate. The CH_2Cl_2 was evaporated *in vacuo* and the crude product was purified by column chromatography (5% EtOAc/hexane) to give **ethyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}butanoate (356)** (2.49 g, 95% yield) as a clear and pungent oil.

WISETD



[356]

R_f 0.43 (10 % EtOAc/hexane), $[\alpha]_D^{20}$ +7.6 (*c* 1.06, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.42-7.17 (10H, m, Ar-H), 3.99 (1H, q, *J* 7.2, H-16), 3.92 (2H, q, *J* 7.0, H-5), 3.71 (1H, d, *J* 14.7, H-11*A*), 3.69 (1H, d, *J* 14.7, H-11*B*), 3.50-3.40 (1H, m, H-3), 2.36 (1H, dd, *J* 5.9, 14.1, H-2*A*), 2.10 (1H, dd, *J* 8.0, 14.1, H-2*B*), 1.35 (3H, d, *J* 7.0, H-6), 1.16 (3H, t, *J* 7.2, H-17), 1.14 (3H, d, *J* 6.7, H-4).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 172.8 (C-1), 144.7 (C-7), 142.2 (C-12), 128.7, 128.5, 128.4, 128.1, 127.1, 127.0 (C-8, C-9, C-10, C-13, C-14, C-15), 60.5 (C-16), 58.2 (C-5), 50.5 (C-3), 50.0 (C-11), 40.2 (C-2), 19.0 (C-17), 18.3 (C-6), 14.5 (C-4).

$\nu_{max.}$ / **cm^{-1}**: 3062 (w, Ar), 3027 (w, Ar), 2975 (m, C-H), 2934 (m, C-H), 1732 (s, C=O), 1494 (m), 1453 (s), 1371 (s), 1296 (s), 1193 (s), 749 (s), 700 (s).

m/z: 325 (8%, M), 310 (30), 248 (4), 238 (71), 220 (20), 134 (54), 120 (5), 105 (100), 77 (19), 51 (5). Found 325.2067, $C_{12}H_{27}O_2N$ requires 325.2042.

8.1.2.5 Ethyl 3-aminobutanoate (291)

Method A[158, 212]

Ethyl 3-(dibenzylamino)butanoate (351) (1.0 g, 3.2 mmol) was dissolved in absolute EtOH (15 mL). Activated palladium on carbon (10%, 483 mg, 0.150 g/mmol) and a catalytic amount of concentrated HCl (1 mL) were added and the mixture was stirred in a hydrogenator under 7 atmospheres of

WisERD

hydrogen pressure for 72 hours. The solution was then filtered through Celite® to remove the palladium catalyst. The Celite® was thoroughly rinsed with CH_2Cl_2 (300 mL) and the solvent removed *in vacuo* using toluene as an azeotrope to remove the residual AcOH. The organic residue was redissolved in CH_2Cl_2 (30 mL) and stirred with solid sodium bicarbonate (3 spatulas full) for 5 hours. The sodium bicarbonate was filtered off, thoroughly rinsed and then the CH_2Cl_2 was removed *in vacuo* to give the partially debenzylated product, **ethyl 3-(benzylamino)butanoate (355)** (540 mg, 71% yield).[g]

Method B

Ethyl 3-(dibenzylamino)butanoate (351) (4.00 g, 12.9 mmol) was dissolved in glacial AcOH (55 mL). Activated palladium on carbon (10%, 1.93 g, 0.150 g/mmol) was added and the mixture stirred in a hydrogenator under 7.5 atmospheres of hydrogen pressure for 72 hours. The solution was then filtered through Celite® to remove the palladium catalyst. The Celite® was rinsed thoroughly with distilled H_2O (100 mL) and CH_2Cl_2 (100 mL) and the organic solvent was removed *in vacuo*. The aqueous solution was basified with solid sodium bicarbonate and the product was back-extracted into CH_2Cl_2 (6 × 50 mL). The organic fractions were combined and dried with potassium carbonate and the CH_2Cl_2 was removed *in vacuo* to give crude **ethyl 3-aminobutanoate (291)**. A pure sample of **ethyl 3-aminobutanoate (291)** (400 mg, 24% yield) was obtained by careful chromatography (100% EtOAc - 10% MeOH/EtOAc) for characterization purposes.[h]

Method C

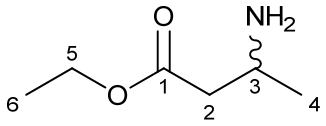
Ethyl 3-(dibenzylamino)butanoate (351) (0.20 g, 0.60 mmol) and ceric ammonium nitrate (667 mg, 1.20 mmol) were dissolved in a 1:5 mixture of

[g] *The yields for partially and fully debenzylated products were extremely variable. See Chapter 4 for the detailed explanation.*

[h] *When the reaction was repeated no water was used in the work up, and low temperatures were employed when removing solvent in vacuo. Column chromatography was avoided as it resulted in reduced yields, and instead the crude amine was used directly in the next reaction. Residual AcOH peaks persisted in the crude NMR spectra of these products, but the use of higher temperatures, H_2O, or column chromatography drastically reduces the yield as the amine is volatile and partially soluble in water.*

WITSETD

MeCN and distilled H_2O (10 mL) and the reaction mixture stirred at ambient temperature for 12 hours. The reaction was quenched with saturated sodium bicarbonate solution (10 mL) and filtered through cotton wool to remove any precipitate. The product was extracted into CH_2Cl_2 (4 × 20 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (5% - 50% EtOAc/hexane) to give **ethyl 3-(benzylamino)butanoate (355)** (108 mg, 81% yield) as a pale yellow oil.[i]



[291]

R_f 0.11 (10% MeOH/EtOAc)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.15 (2H, q, *J* 7.1, H-5), 3.42-3.34 (1H, m, H-3), 2.41 (1H, dd, *J* 4.6, 15.6, H-2*A*), 2.29 (1H, dd, *J* 8.4, 15.6, H-2*B*), 1.71 (2H, s, N*H*$_2$), 1.27 (3H, t, *J* 7.1, H-6), 1.13 (3H, d, *J* 6.4, H-4).

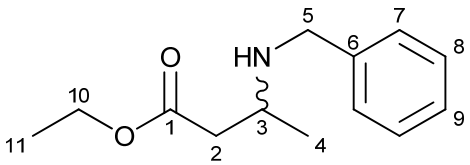
^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 172.4 (C-1), 60.3 (C-5), 44.3 (C-2), 44.1 (C-3), 23.6 (C-4), 14.3 (C-6).

$\nu_{max.}$ / **cm^{-1}** 3370 -3200 (br, NH_2), 2976 (m, C-H), 2932 (m, C-H), 1733 (s, C=O), 1644 (s), 1552 (s), 1377 (m), 1189 (m).

m/z: 132 (24%, M), 128 (13), 116 (7), 84 (7), 70 (14), 57 (18), 44 (100), 42 (13). Found 132.1026, $C_6H_{13}NO_2$ requires 132.1025.

[i] *Racemic ethyl 3-aminobutyrate is commercially available from Sigma-Aldrich as a 90% pure, racemic mixture. For all subsequent reactions requiring the racemic amine the commercially available product was used.*

WitsETD



[355]

R_f 0.14 (10% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.34-7.17 (5H, m, H-7, H-8, H-9), 4.16-3.98 (2H, m, H-10*AB*), 3.64 (1H, d, *J* 13.8, H-5*A*), 3.44 (1H, d, *J* 13.8, H-5*B*), 3.31 (1H, quintet, *J* 6.9, H-3), 2.62 (1H, dd, *J* 13.8, 7.8, H-2*A*), 2.26 (1H, dd, *J* 13.8, 6.9, H-2*B*), 1.24 (1H, s, N*H*), 1.19 (3H, t, *J* 7.2, H-11), 1.09 (3H, d, *J* 6.6, H-4).

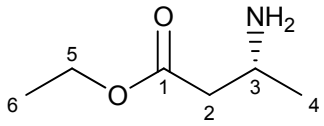
^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 172.3 (C-1), 140.0 (C-6), 128.7 (C-7), 128.0 (C-8), 126.8 (C-9), 60.2 (C-10), 53.3 (C-5), 50.9 (C-3), 37.6 (C-2), 14.1 (C-4), 14.0 (C-11).

8.1.2.6 Ethyl (3*R*)-3-aminobutanoate (291)

Method A[158]

Ethyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}butanoate (356) (0.570 g, 1.75 mmol) was dissolved in glacial AcOH (5 mL). Activated palladium on carbon (10%, 262 mg, 0.150 g/mmol) was added and the reaction was left in a hydrogenator under 7.5 atmospheres of hydrogen pressure for 72 hours. The solution was filtered through Celite® to remove the palladium catalyst. The Celite® was thoroughly rinsed with CH_2Cl_2 (300 mL) and the solvent was removed *in vacuo*, using toluene as an azeotrope to remove the residual AcOH. The organic residue was redissolved in CH_2Cl_2 (30 mL) and stirred with solid sodium bicarbonate (3 spatulas full) for 5 hours. The sodium bicarbonate was filtered off, rinsed thoroughly and the CH_2Cl_2 was removed *in vacuo.* The crude material was purified by column chromatography (100% EtOAc - 10% MeOH/EtOAc) and two products were identified; **ethyl (3*R*)-aminobutanoate (291)** (80 mg, 35% yield) and **ethyl (3*R*)-3-{[(1*R*)-1-phenylethyl]amino}butanoate (357)** (110 mg, 26% yield).

WISETD



[291]

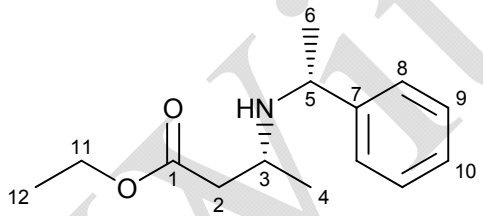
R_f 0.11 (10% MeOH/EtOAc), $[\alpha]_D^{20}$ +37.0 (*c* 1.20, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.15 (2H, q, *J* 7.1, H-5), 3.41-3.35 (1H, m, H-3), 2.41 (1H, dd, *J* 4.6, 15.6, H-2*A*), 2.29 (1H, dd, *J* 8.4, 15.6, H-2*B*), 1.71 (2H, s, NH_2), 1.27 (3H, t, *J* 7.1, H-6), 1.13 (3H, d, *J* 6.4, H-4).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 172.4 (C-1), 60.3 (C-5), 44.3 (C-2), 44.1 (C-3), 23.6 (C-4), 14.3 (C-6).

$\nu_{max.}$ / **cm^{-1}**: 3370 (br, NH), 2976 (m, C-H), 2932 (m, C-H), 1733 (s, C=O), 1644 (s), 1552 (s).

m/z: 132 (24%, M), 128 (13), 116 (7), 84 (7), 70 (14), 57 (18), 44 (100), 42 (13). Found 132.1026, $C_6H_{13}NO_2$ requires 132.1025.



[357]

R_f 0.12 (10% EtOAc/hexane), $[\alpha]_D^{20}$ +23.0 (*c* 1.65, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.39-7.25 (5H, m, H-8, H-9, H-10), 4.12 (2H, q, *J* 7.1, H-11), 4.03 (1H, q, *J* 6.7, H-5), 3.17-3.06 (1H, m, H-3), 2.60 (1H, dd, *J* 5.2, 15.4, H-2*A*), 2.43 (1H, dd, *J* 7.1, 15.4, H-2*B*), 2.07 (1H, s, NH), 1.44 (3H, d, *J* 6.7, H-6), 1.25 (3H, t, *J* 7.1, H-12), 1.12 (3H, d, *J* 6.5, H-4).

WitsETD

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 177.0 (C-1), 144.7 (C-7), 129.1 (C-8), 128.1 (C-10), 127.5 (C-9), 61.1 (C-11), 56.2 (C-5), 48.7 (C-3), 40.7 (C-2), 24.3 (C-6), 21.3 (C-4), 14.95 (C-12).

$\nu_{max.}$ / **cm^{-1}**: 2970 (m, C-H), 1761 (s, C=O), 1455 (m), 1371 (m), 1185 (s), 1080 (m), 753 (m), 702 (s).

m/z: 235 (2%, M), 220 (100), 185 (8), 174 (6), 158 (9), 148 (77), 132 (88), 120 (68), 116 (22), 105 (100). **APCI** Found 235.72, $C_{14}H_{21}NO_2$ requires 235.16.

Method B

A 100 mL RBF was charged with MeOH (20 mL) and **ethyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}butanoate (356)** (500 mg, 1.54 mmol). Ammonium formate (776 mg, 12.3 mmol) was added and the solution was stirred under a nitrogen atmosphere until the solution was homogenous. Palladium on carbon (10%, 185 mg, 0.37 eq.) was carefully stirred into the mixture (the methanolic vapours readily ignited if the system was not properly flushed with nitrogen). The reaction was left at ambient temperature for 3.5 hours, until TLC indicated that all the starting material was consumed. The reaction mixture was filtered through Celite® and rinsed with MeOH (2 × 20 mL) to remove the catalyst. The solvent was removed *in vacuo* and the residue was rinsed with NaOH solution (1.0 *M*, 8 mL) and extracted into CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried with sodium sulfate and the solvent removed *in vacuo*. Purification of the crude oil by column chromatography (5% - 100% EtOAc/hexane) gave **ethyl (3*R*)-3-{[(1*R*)-1-phenylethyl]amino}butanoate (357)** (250 mg, 69% yield) as a clear oil.

Method C

Ethyl (3*R*)-3-{[(1*R*)-1-phenylethyl]amino}butanoate (357) (0.69 g, 2.9 mmol) was dissolved in AcOH (5 mL) with palladium hydroxide (10 - 20%, 70 mg, 0.10 eq.). The reaction was set up under 7 atmospheres of hydrogen pressure in the hydrogenator at ambient temperature for 72 hours. The reaction mixture was filtered through Celite® and rinsed with CH_2Cl_2 (150 mL) to remove the

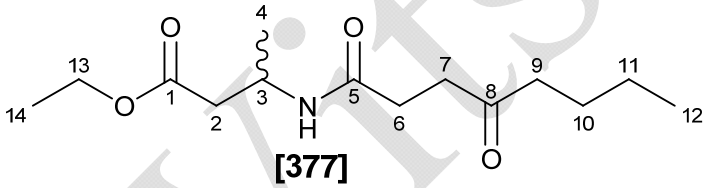
WitsETD

residual catalyst. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (50% - 100% EtOAc/hexane). No products were isolated, but starting material was recovered (420 mg, 61% recovery).

8.1.3 Condensation reaction

8.1.3.1 Ethyl 3-[(4-oxooctanoyl)amino]butanoate (377)[128, 221]

4-Oxooctanoic acid (347) (200 mg, 1.26 mmol) was dissolved in dry CH_2Cl_2 (7 mL) and cooled to 0ºC. Oxalyl chloride (0.22 mL, 2.5 mmol) was added and the reaction was left stirring for 2 hours at ambient temperature. The excess oxalyl chloride and CH_2Cl_2 were removed *in vacuo* and the crude product was placed under high vacuum for 1 hour to remove any residual oxalyl chloride. Fresh CH_2Cl_2 (10 mL) was added to the organic residue, followed by ethyl 3-aminobutanoate (90%, 0.19 mL, 1.26 mmol) and Et_3N (0.17 mL, 1.3 mmol). The reaction mixture was stirred at ambient temperature for 14 hours before the solvent was removed *in vacuo* and the crude product was purified by column chromatography (40% EtOAc/hexane) to give **ethyl 3-[(4-oxooctanoyl) amino]butanoate (377)** (170 mg, 51% yield over the two steps) as a white solid.



[377]

M p. 52-53.5 °C

R_f 0.31 (10 % EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 6.18 (1H, d, *J* 7.6, NH), 4.28-4.21 (1H, m, H-3), 4.08 (2H, q, *J* 7.1, H-13), 2.68 (2H, t, *J* 6.6, H-6), 2.42-2.31 (6H, m, H-2, H-7, H-9), 1.55-1.45 (2H, m, H-10), 1.27-1.24 (2H, m, H-11), 1.20 (3H, t, *J* 7.1, H-14), 1.14 (3H, d, *J* 6.8, H-4), 0.83 (3H, t, *J* 7.3, H-12).

WitsETD

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 209.1 (C-8), 170.6 (C-1), 170.1 (C-5), 59.5 (C-13), 41.5 (C-9), 41.1 (C-3), 39.2 (C-7), 36.6 (C-6), 29.0 (C-2), 24.9 (C-10), 21.3 (C-11), 19.0 (C-14), 13.2 (C-4), 12.8 (C-12).

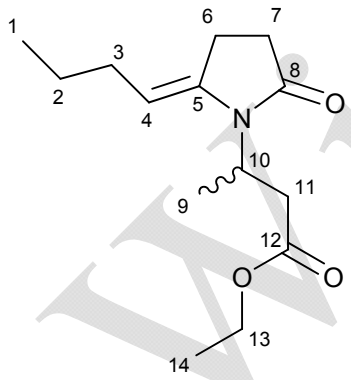
$\nu_{max.}$ / **cm^{-1}**: 3306 (br, NH), 2960 (m, C-H), 2934 (m, C-H), 2871 (m, C-H), 1731 (s, OC=O), 1707 (s, C=O), 1640 (s, NC=O), 1546 (m), 1374 (m), 1228 (m).

m/z: Found 271.1767, $C_{14}H_{25}O_4N$ requires 271.1784.

8.1.3.2 Ethyl 3-[(*2E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293)

Method A

Ethyl 3-[(4-oxooctanoyl)amino]butanoate (377) (60 mg, 0.22 mmol) was set up to reflux with AcOH (20 mg, 1.11 mmol) in toluene (7 mL) for 72 hours. The solution was cooled, the solvent removed *in vacuo*, and the product purified by column chromatography (10% EtOAc/hexane) to give **ethyl 3-[(*2E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293)** in quantitative yield, exclusively as the *trans* isomer (as verified by NOE experiments).



[293]

R_f 0.27 (20% EtOAc/hexane)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.77 (1H, t, *J* 7.4, H-4), 4.45-4.37 (1H, m, H-10), 4.12 (2H, q, *J* 7.1, H-13), 3.04 (1H, dd, *J* 7.4, 15.7, H-11*A*), 2.81 (1H, dd, *J* 7.3, 15.7, H-11*B*), 2.58 (2H, t, *J* 8.0, H-6/H-7), 2.42 (2H, t, *J* 8.0, H-6/H-7), 2.00 (2H,

WitsETD

q, *J* 7.3, H-3), 1.47-1.42 (2H, m, H-2), 1.41 (3H, d, *J* 6.9, H-9), 1.25 (3H, t, *J* 7.1, H-14), 0.93 (3H, t, *J* 7.3, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 175.7 (C-8), 171.4 (C-12), 138.7 (C-5), 101.0 (C-4), 60.4 (C-13), 45.2 (C-10), 37.6 (C-11), 29.2 (C-6/C-7), 29.0 (C-3), 23.2 (C-2), 21.6 (C-6/C-7), 17.1 (C-9), 14.1 (C-14), 13.7 (C-1).

$v_{max.}$ / **cm^{-1}**: 2959 (m, C-H), 2934 (m, C-H), 2872 (m, C-H), 1735 (s, OC=O), 1669 (s, NC=O), 1408 (m), 1373 (m), 1241 (s), 1186 (s), 1096 (m), 1031 (m).

m/z: 253 (22%, M), 229 (45), 224 (66), 214 (78), 208 (14), 168 (68), 141 (100), 130 (74). Found 253.1376, $C_{14}H_{23}O_3N$ requires 253.1678.

Method B[222]

Ethyl 4-oxooctanoate (292) (700 mg, 3.8 mmol) and ethyl 3-aminobutanoate (90%, 0.56 mL, 3.8 mmol) were dissolved in toluene (25 mL) and heated at reflux for 30 hours using a Dean-Stark apparatus. The toluene was removed *in vacuo* and the residue was purified by column chromatography (20% EtOAC/hexane) to give **ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293)** (200 mg, 21% yield) and residual **ethyl 4-oxooctanoate (292)** (320 mg, 45% recovery).

Method C

Ethyl 4-oxooctanoate (292) (2.00 g, 10.7 mmol), ethyl 3-aminobutanoate (90%, 1.58 mL, 10.8 mmol) and a catalytic amount of *p*-toluenesulfonic acid (103 mg, 0.54 mmol) were dissolved in toluene (60 mL) and heated at reflux for 30 hours using a Dean-Stark apparatus with molecular sieves (4Å) in the side-arm. The toluene was removed *in vacuo* and the residue was purified by silica column chromatography (10% EtOAC/hexane) to give **ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl] butanoate (293)** (1.37 g, 50% yield) and **ethyl 4-oxooctanoate** (**292**) (840 mg, 42% recovery).

WitsETD

Method D

Ethyl 4-oxooctanoate (292) (2.00 g, 10.7 mmol), ethyl 3-aminobutanoate (90%, 1.05 mL, 6.44 mmol) and glacial AcOH (2.15 g, 35.8 mmol) were dissolved in toluene (18 mL) and heated at reflux for 64 hours using a modified Dean-Stark apparatus. The solution was cooled and rinsed with saturated sodium bicarbonate solution (20 mL). The product was then extracted into EtOAc (3 × 30 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the residue purified by column chromatography (10% EtOAC/hexane) to give **ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl] butanoate (293)** (1.43 g, 87% yield) as a clear oil.

8.1.3.3 Ethyl (3*R*)-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate

Ethyl 4-oxooctanoate (292) (2.04 g, 11.0 mmol), **ethyl (3*R*)-aminobutanoate (291)** (844 mg, 6.44 mmol) and glacial AcOH (2.15 g, 35.8 mmol) were dissolved in toluene (10 mL) and heated at reflux for 72 hours using a modified Dean-Stark apparatus. The solution was cooled and then rinsed with saturated sodium bicarbonate solution (20 mL). The product was extracted into EtOAc (3 × 30 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by column chromatography (10% EtOAC/hexane) to give **ethyl (3*R*)-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293)** as a clear oil (753 mg, 46% yield) and **ethyl 4-oxooctanoate** (**292**) (1.02 g, 50% recovery).

All characterization was identical to the racemate with the exception of the optical rotation.

$[\alpha]_D^{20}$ -10.0 (*c* 1.20, CH_2Cl_2)

8.1.3.4 Ethyl (3*S*)-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate[223 - 225]

Ethyl 3-aminobutyrate (90%, 0.45 mL, 3.0 mmol) was mixed together with ethyl butyrate (4 mL) and *CAL*-B (*Candida antarctica lipase* B)[j] (50 mg, 17 mg/mmol) and the solution was stirred at ambient temperature for 25 hours. The enzyme

[j] *The* CAL-*B was kindly donated by Dean Brady from the Council for Scientific and Industrial Research (CSIR)*

WITSETD

was filtered off through a sintered glass funnel and the residue was rinsed with EtOAc (20 mL). The EtOAc was removed *in vacuo* and the crude mixture of ethyl butyrate, free amine and acylated amine were heated at reflux together with **ethyl 4-oxooctanoate (292**) (700 mg, 3.75 mmol), AcOH (0.45 mL, 7.5 mmol) and toluene (10 mL). The reaction mixture was allowed to reflux for 72 hours and the solution was then cooled and the solvent removed *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to give **ethyl (3*S*)-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293)** (250 mg, 33% yield based on the racemate).[k]

All characterization was identical to the racemate with the exception of optical rotation.

$[\alpha]_D^{20}$ +1.0 (*c* 1.00, CH_2Cl_2).

8.1.4 Stereoselective reduction of the exocyclic alkene

8.1.4.1 Ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (294)

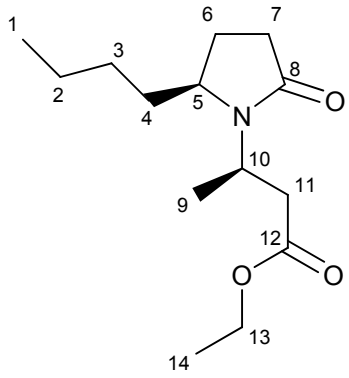
Method A[215, 226]

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293) (0.20 g, 0.79 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 mL) and cooled to −90ºC under nitrogen. Titanium tetrachloride (0.19 mL, 1.7 mmol) was added and the reaction mixture was stirred for 5 minutes. Triethylsilane (0.38 mL, 2.4 mmol) was then added by syringe and the reaction was allowed to warm to ambient temperature and react for 48 hours. The reaction was quenched by the addition of saturated ammonium chloride solution (10 mL) and the product was extracted in CH_2Cl_2 (4 × 30 mL). The combined organic fractions were dried with sodium sulfate and the solvent was evaporated *in vacuo*. Purification of the crude material by column chromatography (50% EtOAc/hexane) gave **ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (294)** (170 mg, 84% yield) as an

[k] *Liljeblad et al. successfully used enzymatic resolution to separate (*R*)- and (*S*)-ethyl 3-aminobutyrate, however, for practical reasons they isolated both the products as acetamides by reacting the resolved mixture of the free amine of the (*S*)-enantiomer and the acylated (*R*)-enantiomer with acetic anhydride. This protocol would not be useful in our synthetic route as we require the primary amine for our condensation reaction.*

inseparable (1:4) mixture of diastereomers. The minor isomer, (the *S,R* and *R,S* isomer), has been designated isomer A and the major isomer, (the *R,R* and *S,S* isomer), has been designated isomer B.[I]

Diastereomer A (*S,R* and *R,S*)



[294A]

R_f 0.15 (20% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.12 (2H, q, *J* 7.2, H-13), 3.94-3.87 (1H, m, H-10), 3.68-3.63 (1H, m, H-5), 3.17 (1H, dd, *J* 16.1, 8.4, H-11*A*), 2.53 (1H, dd, *J* 16.1, 6.0, H-11*B*), 2.42-2.05 (4H, m, H-6*AB*, H-7*AB*), 1.75-1.65 (2H, m, H-4), 1.39 (3H, d, *J* 6.9, H-9), 1.40-1.26 (4H, m, H-2, H-3), 1.25 (3H, t, *J* 7.2, H-14), 0.93 (3H, t, *J* 6.9, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 174.7 (C-8), 170.3 (C-12), 60.0 (C-5), 59.9 (C-13), 46.8 (C-10), 38.3 (C-11), 33.8 (C-4), 30.6 (C-7), 26.8 (C-6), 23.9 (C-3), 22.4 (C-9), 18.0 (C-2), 13.8 (C-1), 13.7 (C-14).

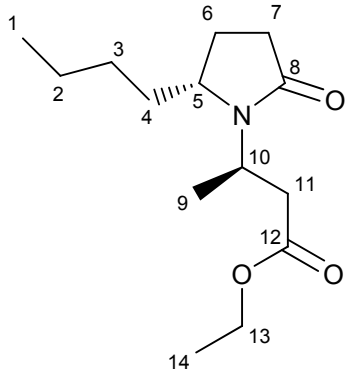
$\nu_{max.}$ / **cm^{-1}**: 2958 (m, C-H), 2933 (m, C-H), 2873 (m, C-H), 1731 (s, OC=O), 1679 (s, NC=O), 1444 (m), 1424 (m), 1372 (s), 1291 (s), 1247 (m), 1193 (s), 1094 (m), 1029 (s), 670 (m).

[I] *The diastereomer ratio was determined by the relative integration of the H-5 and H-10 signals in the ^{1}H-NMR spectra for isomer A and isomer B.*

WiSETD

m/z: 255 (22%, M), 212 (6), 210 (35), 198 (100), 168 (76), 152 (88), 140 (89), 110 (82). Found 255.1823, $C_{14}H_{23}O_3N$ requires 255.1834.

Diastereomer B (*R,R* and *S,S*)



[294B]

R_f 0.15 (20% EtOAc/hexane)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.20-4.10 (1H, m, H-10), 4.14 (2H, q, *J* 7.2, H-13), 3.62-3.55 (1H, m, H-5), 2.78 (2H, d, *J* 7.5, H-11), 2.46-2.03 (4H, m, H-6*AB*, H-7*AB*), 1.77-1.64 (2H, m, H-4), 1.45-1.22 (4H, m, H-2, H-3), 1.31 (3H, d, *J* 6.9, H-9), 1.25 (3H, t, *J* 7.2, H-14), 0.92 (3H, t, *J* 7.1, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 174.3 (C-8), 169.6 (C-12), 60.4 (C-13), 58.1 (C-5), 46.1 (C-10), 38.7 (C-11), 34.3 (C-4), 30.5 (C-7), 27.1 (C-6), 24.3 (C-3), 22.6 (C-2), 18.6 (C-9), 14.0 (C-1), 13.9 (C-14).

$v_{max.}$ / **cm^{-1}**: 2957 (m, C-H), 2933 (m, C-H), 2872 (m, C-H), 1732 (s, OC=O), 1681 (s, NC=O), 1445 (m), 1420 (m), 1372 (s), 1292 (s), 1248 (s), 1191 (s), 1091 (m), 1030 (s), 666 (m).

m/z: 255 (7%, M), 207 (18), 198 (84), 168 (38), 152 (100), 140 (35), 110 (84). Found 255.1823, $C_{14}H_{23}O_3N$ requires 255.1834.

WiSETD

Method B

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293) (0.20 g, 0.79 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 mL) and cooled to −90ºC under nitrogen. TFA (0.14 mL, 1.8 mmol) was added and the reaction mixture was stirred for 5 minutes. Triethylsilane (0.38 mL, 2.4 mmol) was then added by syringe and the reaction was allowed to warm to ambient temperature and react for 60 hours. The reaction was quenched by the addition of saturated ammonium chloride solution (10 mL) and the product was extracted in CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried with sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (50% EtOAc/hexane) gave **ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (294)** (190 mg, 94% yield) as a (2:3) mixture of diastereomers, again favouring diastereomer B.

Method C

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293) (0.10 g, 0.39 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 mL) and cooled to −90ºC under nitrogen. Freshly distilled boron trifluoride etherate (0.11 mL, 0.87 mmol) was added and the reaction mixture was stirred for 5 minutes. Triethylsilane (0.19 mL, 1.2 mmol) was then added by syringe and the reaction was allowed to warm to ambient temperature and react for 48 hours. The reaction was quenched by the addition of saturated ammonium chloride solution (10 mL) and the product was extracted into CH_2Cl_2 (4 × 30 mL). The combined organic extracts were dried with sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (50% EtOAc/hexane) gave **ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (294)** (90 mg, 90% yield) as a (4:5) mixture of diastereomers, favouring diastereomer B.

Method D

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293) (0.10 g, 0.39 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 mL) and cooled to −90ºC under nitrogen. Tin (IV) tetrachloride (0.10 mL, 0.87 mmol) was added and the reaction mixture was stirred for 5 minutes. Triethylsilane (0.19 mL,

WitsETD

1.2 mmol) was added then by syringe and the reaction was allowed to warm to ambient temperature and react for a further 30 hours. The reaction was quenched by the addition of saturated ammonium chloride solution (10 mL) and the product was extracted into CH_2Cl_2 (4 × 30 mL). The combined organic extracts were dried with sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (50% EtOAc/hexane) gave starting material, **ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293)**, (20 mg, 20% recovery) and **ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (294)** (80 mg, 80% yield) as a (2:3) mixture of diastereomers, favouring diastereomer B.

Method E

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293) (0.20 g, 0.79 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 mL) and cooled to −90ºC under nitrogen. Zirconium tetrachloride (405 mg, 1.74 mmol) was added and the reaction mixture was stirred for 5 minutes. Triethylsilane (0.19 mL, 1.2 mmol) was then added by syringe and the reaction was allowed to warm to ambient temperature and react for 48 hours. The reaction was quenched by the addition of saturated ammonium chloride solution (20 mL) and the product was extracted in CH_2Cl_2 (4 × 30 mL). The combined organic fractions were dried with sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (50% EtOAc/hexane) gave **ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (294)** (160 mg, 79% yield) as a (3:4) mixture of diastereomers, favouring diastereomer B.

Method F

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293) (0.10 g, 0.39 mmol) was dissolved in freshly distilled CH_2Cl_2 (7 mL) and cooled to −90ºC under nitrogen. Aluminium trichloride (115 mg, 0.860 mmol) was added and the reaction mixture was stirred for 5 minutes. Triethylsilane (0.19 mL, 1.2 mmol) was then added by syringe and the reaction was allowed to warm to ambient temperature and react for 72 hours. The reaction was quenched by the addition of saturated ammonium chloride solution (20 mL) and the product was extracted in CH_2Cl_2 (4 × 30 mL). The combined organic extracts were dried with

sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (50% EtOAc/hexane) gave **ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (294)** (100 mg, 100% yield) as a (3:4) mixture of diastereomers, favouring diastereomer B.

Method G

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293) (0.10 g, 0.39 mmol) was dissolved in freshly distilled CH_2Cl_2 (7 mL) and cooled to −90ºC under nitrogen. Titanium isopropoxide (0.23 mL, 0.86 mmol) was added and the reaction mixture was stirred for 5 minutes. Triethylsilane (0.19 mL, 1.2 mmol) was then added by syringe and the reaction was allowed to warm to ambient temperature and react for 48 hours. The reaction was quenched by the addition of saturated ammonium chloride solution (20 mL) and the product was extracted in CH_2Cl_2 (4 × 30 mL) – the two layers formed an emulsion and had to be filtered through a sintered glass funnel before separation was possible. The combined organic extracts were dried with sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (50% EtOAc/hexane) gave back the starting material, **ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293),** (70 mg, 70% recovery).

Method H

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293) (0.10 g, 0.39 mmol) was dissolved in freshly distilled CH_2Cl_2 (7 mL) and cooled to −90ºC under nitrogen. Lanthanum triflouromethanesulfonate (504 mg, 0.86 mmol) was added and the reaction mixture was stirred for 25 minutes. Triethylsilane (0.19 mL, 1.2 mmol) was then added by syringe and the reaction was maintained at −90ºC for 2 hours before allowing the reaction to warm to ambient temperature and react for a further 96 hours. The reaction was quenched by the addition of saturated ammonium chloride solution (5 mL) and the product was extracted in CH_2Cl_2 (4 × 30 mL). The combined organic fractions were dried with sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (50% EtOAc/hexane) gave the ring-opened product **ethyl 3-[(4-oxooctanoyl)amino]butanoate (377)** (90 mg, 85% yield).

WitsETD

Method I

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293) (0.10 g, 0.39 mmol) was dissolved in freshly distilled CH_2Cl_2 (7 mL) and cooled to −90ºC under nitrogen. Titanium tetrachloride (0.10 mL, 0.86 mmol) was added and the reaction mixture was stirred for 7 minutes. Triphenylsilane (307 mg, 1.18 mmol) was then added and the reaction was maintained at −90ºC for 2 hours before it was allowed to warm to ambient temperature and react for 96 hours. The reaction was quenched by the addition of saturated ammonium chloride solution (5 mL) and the product was extracted in CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried with sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (50% EtOAc/hexane) gave **ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (294)** (85 mg, 85% yield) as a (1:5) mixture of diastereomers, favouring diastereomer B.

Method J[226]

Ethyl 3-[(2*E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (293) (90 mg, 0.35 mmol) was dissolved in absolute EtOH (3 mL). Activated palladium on carbon (10%, 40 mg, 0.115 g/mmol) was added, and the reaction mixture was set-up in a test-tube in the hydrogenator under 7.5 atmospheres of hydrogen pressure for 60 hours. The solution was filtered through Celite® and thoroughly rinsed with CH_2Cl_2 (200 mL) to remove the catalyst. The solvent was evaporated *in vacuo* and the resulting crude product was thoroughly dried under high vacuum to give **ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (294)** (90 mg, 100% yield) as a mixture of diastereomers (in a 2:3 ratio), favouring diastereomer B.

8.1.5 Thionation reactions

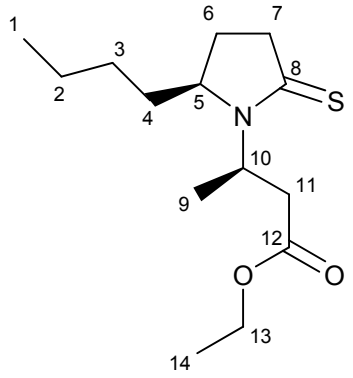
8.1.5.1 Ethyl 3-(2-butyl-5-thioxo-1-pyrrolidinyl)butanoate (295)

The diastereomeric mixture of **ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl) butanoate (294)** (1.53 g, 5.97 mmol) and Lawesson's reagent (1.33 g, 3.28 mmol) were mixed in dry CH_2Cl_2 (40 mL) and stirred at ambient temperature under a nitrogen atmosphere for 96 hours. The CH_2Cl_2 was removed *in vacuo* and the organic residue was purified by column

WitsETD

chromatography (15% EtOAc/hexane) to give **ethyl 3-(2-butyl-5-thioxo-1-pyrrolidinyl)butanoate (295)** (1.580 g, 98%) as a mixture of diastereomers, in the same ratio as the starting material. The diastereomers were partially separable by column chromatography (10% EtOAc/hexane).

Diastereomer A (*S,R* and *R,S*)



[295A]

R_f 0.25 (10% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 4.80-4.72 (1H, m, H-10), 4.15 (2H, q, *J* 7.2, H-13), 4.11-4.02 (1H, m, H-5), 3.53 (1H, dd, *J* 6.3, 16.2, H-11*A*), 3.10-2.85 (2H, m, H-7), 2.48 (1H, dd, *J* 8.0, 16.2, H-11*B*), 2.25-2.04 (1H, m, H-6*A*), 1.90-1.60 (3H, m, H-4, H-6*B*), 1.52 (3H, d, *J* 7.1, H-9), 1.40-1.26 (4H, m, H-2, H-3) 1.27 (3H, t, *J* 7.1, H-14), 0.93 (3H, t, *J* 7.0, H-1).

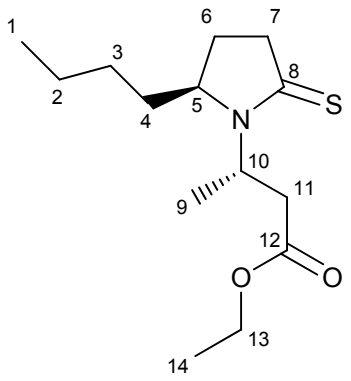
^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 200.9 (C-8), 171.6 (C-12), 67.7 (C-5), 61.0 (C-13), 51.3 (C-10), 45.1 (C-7), 38.3 (C-11), 33.7 (C-4), 28.0 (C-2), 26.1 (C-6), 23.0 (C-3), 17.5 (C-9), 14..5 (C-14), 14.4 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2957 (m, C-H), 2933 (m, C-H), 2872 (m, C-H), 1736 (s, C=O), 1498 (m), 1456 (s), 1425 (m), 1375 (m), 1312 (s, C=S), 1274 (s), 1180 (s), 1031 (m).

m/z: 271 (100%, M), 242 (57), 238 (50), 226 (29), 198 (72), 184 (13), 158 (26), 130 (43), 114 (36), 84 (8), 71 (12), 41 (35). Found 271.1606, $C_{14}H_{25}O_2N^{32}S$ requires 271.1606.

WitsETD

Diastereomer B (*R,R* and *S,S*)



[295B]

R_f 0.22 (10% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 5.30-5.10 (1H, m, H-10), 4.13 (2H, q, *J* 7.1, H-13), 4.11-3.95 (1H, m, H-5), *3*.10-2.85 (2H, m, H-7), 2.79 (2H, dq, *J* 7.5, 15.5, H-11*AB*), 2.20-2.04 (1H, m, H-6*A*), 1.85-1.68 (2H, m, H-4), 1.58-1.46 (1H, m, H-6*B*), 1.41 (3H, d, *J* 7.0, H-9), 1.40-1.26 (4H, m, H-2, H-3) 1.25 (3H, t, *J* 7.1, H-14), 0.92 (3H, t, *J* 6.9, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 201.9 (C-8), 170.9 (C-12), 65.5 (C-5), 61.2 (C-13), 51.0 (C-10), 44.4 (C-7), 38.8 (C-11), 34.2 (C-4), 28.0 (C-2), 26.4 (C-6), 23.0 (C-3), 18.9 (C-9), 14.5 (C-14), 14.4 (C-1).

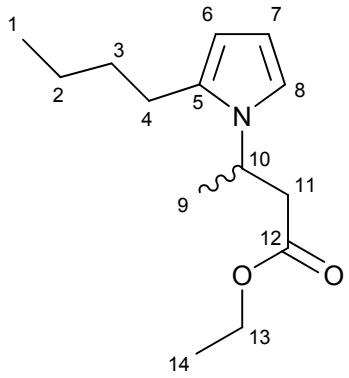
$v_{max.}$ / **cm^{-1}**: 2960 (m, C-H), 2935 (m, C-H), 2874 (m, C-H), 1736 (s, C=O), 1497 (m), 1462 (s), 1427 (m), 1375 (m), 1303 (s, C=S), 1199 (s), 1086 (m), 1033 (m).

m/z: 271 (100%, M) 242 (59), 238 (52), 214 (19), 198 (85), 175 (12), 157 (23), 130 (45), 115 (18), 84 (15), 71 (13), 41 (38). Found 271.1613, $C_{14}H_{25}O_2N^{32}S$ requires 271.1606.

WitsETD

8.1.5.3 Ethyl 3-(2-butyl-1*H*-pyrrol-1-yl)butanoate (381) and ethyl 3-(2-butyl-5-sulfanyl-1*H*-pyrrol-1-yl)butanoate (382)

Ethyl 3-[(*2E*)-2-butylidene-5-oxopyrrolidinyl]butanoate (294) (0.16 g, 0.79 mmol) was dissolved in distilled CH_2Cl_2 (5 mL) at ambient temperature under a nitrogen atmosphere. Lawesson's reagent (0.18 g, 0.44 mmol) was added and the reaction was stirred at ambient temperature for 96 hours. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography (10% EtOAc/hexane) to give **ethyl 3-(2-butyl-1*H*-pyrrol-1-yl)butanoate (381)** (40 mg, 25% yield) and **ethyl 3-(2-butyl-5-sulfanyl-1*H*-pyrrol-1-yl)butanoate (382)** (30 mg, 19% yield).



[381]

R_f 0.66 (50% EtOAc/hexane)

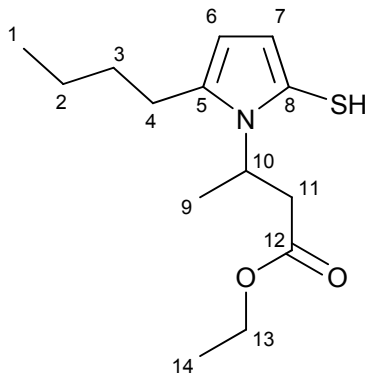
^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 6.62 (1H, d, *J* 1.8, H-8), 6.10 (1H, dd, *J* 3.1, 1.8, H-7), 5.84 (1H, d, *J* 3.1, H-6), 4.64-4.57 (1H, m, H-10), 4.10 (2H, q, *J* 7.1, H-13), 2.75-2.65 (2H, m, H-11*AB*), 2.58 (2H, t, *J* 7.8, H-4), 1.65-1.56 (4H, m, H-2, H-3), 1.44 (3H, d, *J* 6.8, H-9), 1.21 (3H, t, *J* 7.1, H-14), 0.95 (3H, t, *J* 7.3, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 170.1 (C-12), 133.0 (C-5), 115.2 (C-8), 107.5 (C-7), 105.0 (C-6), 60.7 (C-13), 47.5 (C-10), 42.8 (C-4), 31.2 (C-11), 26.0 (C-3), 22.6 (C-2), 22.0 (C-9), 14.1 (C-14), 13.9 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2959 (m, C-H), 2934 (m, C-H), 2873 (m, C-H), 1732 (s, C=O), 1532 (w), 1455 (w), 1378 (m), 1301 (w), 1192 (s), 1095 (m), 1030 (m).

m/z: 238 (50%, M+1), 219 (49), 204 (100), 192 (52), 178 (95), 164 (65).

WitsETD



[382]

R_f 0.10 (50% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 6.28 (1H, s, H-7), 5.73 (1H, s, H-6), 4.54-4.47 (1H, m, H-10), 4.10 (2H, q, *J* 7.1, H-13), 2.71-2.65 (2H, m, H-11*AB*), 2.52 (2H, t, *J* 7.7, H-4), 1.62-1.57 (3H, m, H-3, S-H), 1.48-1.37 (2H, m, H-2), 1.40 (3H, d, *J* 6.8, H-9), 1.21 (3H, t, *J* 7.1, H-14), 0.94 (3H, t, *J* 7.3, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 171.0 (C-12), 134.4 (C-5), 131.9 (C-8), 111.4 (C-7), 104.1 (C-6), 60.5 (C-13), 47.3 (C-10), 42.9 (C-4), 30.9 (C-11), 26.1 (C-3), 22.6 (C-2), 21.7 (C-9), 14.1 (C-14), 14.0 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 3366 (br, S-H), 2960 (m, C-H), 2935 (m, C-H), 2873 (m, C-H), 1732 (s, C=O), 1455 (m), 1373 (s), 1301 (m), 1195 (s), 1096 (m), 1030 (s), 855 (w).

m/z: no parent ion 266 (8), 257 (28), 255 (100), 236 (22), 224 (18), 202 (14), 193 (29), 185 (17), 164 (44), 159 (73).

WitsETD

8.1.6 Formation of the vinylogous sulfonamide

8.1.6.1 Ethyl 3-((5*E*)-2-butyl-5-{[4-methylphenyl)sulfonyl]methylene} pyrrolidinyl)butanoate (296)[173]

Method A

Ethyl 3-(2-butyl-5-thioxo-1-pyrrolidinyl)butanoate (295) (80 mg, 0.29 mmol) was dissolved in THF (5 mL) in oven-dried glassware under a nitrogen atmosphere. Methyl iodide (0.10 mL, 1.6 mmol) was added by syringe and the reaction mixture was stirred at ambient temperature under nitrogen for 24 hours. At this stage, the starting material had been consumed and the moisture-sensitive iodine salt could be seen on the baseline of the silica TLC plate (40% EtOAc/hexane). The THF and excess methyl iodide were removed under high vacuum at 0ºC to give a crude, brown oil. Et_3N (0.07 mL, 0.5 mmol) and **1-[(4-methylphenyl)sulfonyl]acetone (279)**[m] (64 mg, 0.30 mmol) were premixed in CH_2Cl_2 (5 mL) 10 minutes prior to addition to the crude salt. The reaction was stirred in an oil bath at 25ºC under a nitrogen atmosphere for 96 hours before a second portion of Et_3N (0.07 mL, 0.5 mmol) was added. After 24 hours the reaction was quenched with distilled H_2O (2 mL), and the organic material was extracted into CH_2Cl_2 (6 × 15 mL). The combined organic fractions were dried with sodium sulfate, the solvent was removed *in vacuo* and the crude material was purified by column chromatography (40% EtOAc/hexane). **Ethyl 3-(2-butyl-5-oxo-1-pyrrolidinyl)butanoate (294)** (80 mg, 81% recovery) was isolated, indicating that hydrolysis had occurred. None of the desired product was obtained.

Method B

Ethyl 3-(2-butyl-5-thioxo-1-pyrrolidinyl)butanoate (295) (630 mg, 2.33 mmol) was dissolved in THF (5 mL) in oven-dried glassware under a nitrogen atmosphere. Methyl iodide (0.72 mL, 12 mmol) was added by syringe at 0ºC and the flask was protected from light by a covering of tin foil. The reaction warmed to ambient temperature and stirred under nitrogen for 48 hours. At this stage the starting material had been consumed and the moisture-sensitive iodine salt could be seen on the baseline of the TLC plate (40%

[m] *See Chapter 7, section 7.2.6.1 for the synthesis and characterization of 1-[(4-methylphenyl) sulfonyl]acetone (**279**).*

WITSETD

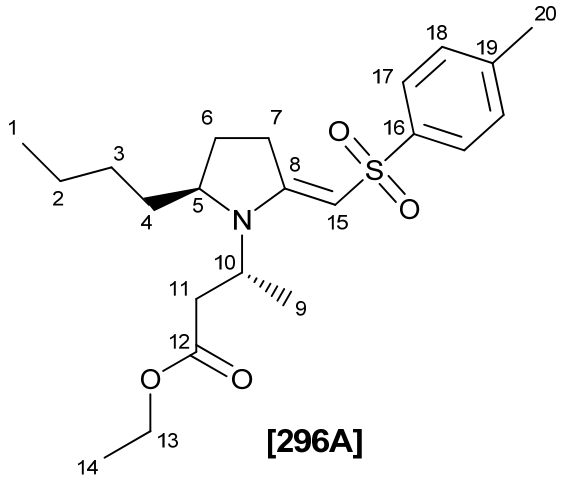
EtOAc/hexane). The THF and excess methyl iodide were removed *in vacuo* to give a brown oil. Et_3N (0.65 mL, 4.66 mmol) and **1-[(4-methylphenyl)sulfonyl]acetone (279)** (544 mg, 2.56 mmol) were premixed in CH_2Cl_2 (5 mL) 10 minutes prior to addition to the brown oil. This mixture was left stirring at ambient temperature under a nitrogen atmosphere for 96 hours before the solvent was removed *in vacuo* and the organic residue was partitioned in distilled H_2O (10 mL) and CH_2Cl_2 (10 mL). The crude product was extracted into CH_2Cl_2 (6 × 15 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (30% EtOAc/hexane) to give **ethyl 3-(*E*)-2-butyl-5-(2-oxo-1-tosylpropylidene)pyrrolidin-1-yl)butanoate (384)** (450 mg, 45% yield), and the desired product, **ethyl 3-((5*E*)-2-butyl-5-{[4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)butanoate (296)**, (240 mg, 25% yield).

This method was repeated with pure diastereomer A (*S,R* and *R,S*) (3.03 mmol) to give **ethyl 3-(*E*)-2-butyl-5-(2-oxo-1-tosylpropylidene)pyrrolidin-1-yl)butanoate (384A)** (500 mg, 37% yield), and **ethyl 3-((5*E*)-2-butyl-5-{[4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)butanoate (296A)** (450 mg, 37% yield).

This method was repeated with pure diastereomer B (*R,R* and *S,S*) (2.75 mmol) to give **ethyl 3-(*E*)-2-butyl-5-(2-oxo-1-tosylpropylidene) pyrrolidin-1-yl) butanoate (384B)** (370 mg, 30% yield) and **ethyl 3-((5*E*)-2-butyl-5-{[4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)butanoate (296B)** (260 mg, 23% yield).

WitsETD

Diastereomer A (*S,R* and *R,S*)



[296A]

R_f 0.61 (40% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.76 (2H, d, *J* 8.1, H-17), 7.24 (2H, d, *J* 8.1 H-18), 4.99 (1H, s, H-15), 4.12 (2H, q, *J* 6.9, H-13), 3.98-3.91 (1H, m, H-10), 3.73-3.68 (1H, m, H-5), 3.11-3.01 (1H, m, H-11*A*), 2.92-2.80 (2H, m, H-11*B*, H-7*A*), 2.45-2.31 (1H, m, H-7*B*), 2.39 (3H, s, H-20), 1.95-1.82 (2H, m, H-4), 1.70-1.62 (1H, m, 6*A*), 1.62-1.51 (1H, m, 6*B*), 1.32 (3H, d, *J* 6.9, H-9) 1.27-1.15 (7H, m, H-2, H-3, H-14), 0.89 (3H, t, *J* 7.1, H-1).

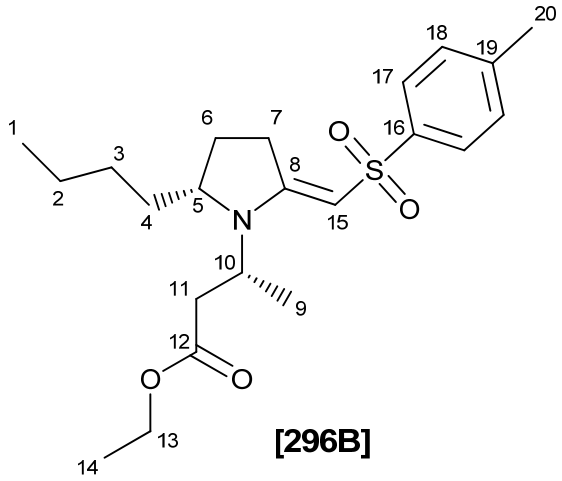
^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 170.7 (C-12), 159.7 (C-8), 143.1 (C-19), 141.6 (C-16), 129.1 (C-18), 125.9 (C-17), 87.4 (C-15), 62.5 (C-5), 60.7 (C-13), 48.3 (C-10), 38.2 (C-7), 33.8 (C-11), 29.8 (C-4), 27.6 (C-2), 25.7 (C-6), 22.5 (C-20), 21.3 (C-3), 17.5 (C-9), 14.0 (C-14), 13.9 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2932 (m, C-H), 2870 (m, C-H), 2513 (w, C=C), 1713 (s, C=O), 1564 (s), 1459 (m), 1415 (m), 1372 (m, S=O), 1281 (s), 1132 (s), 1083 (s), 841 (m).

m/z: 407 (5%, M), 378 (2), 343 (3), 322 (19), 255 (10), 252 (57), 236 (10), 210 (18), 198 (79), 196 (25), 172 (19), 168 (42), 152 (100). Found 407.2126, $C_{22}H_{33}O_4N^{32}S$ requires 407.2130.

WISETD

Diastereomer B (*R,R* and *S,S*)



[296B]

R_f 0.61 (40% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.76 (2H, d, *J* 8.1, H-17), 7.24 (2H, d, *J* 8.1 H-18), 4.98 (1H, s, H-15), 4.09 (2H, q, *J* 7.1, H-13), 4.05-3.90 (1H, m, H-10), 3.68-3.62 (1H, m, H-5), 3.12-3.02 (1H, m, H-11*A*), 2.88-2.75 (1H, m, H-11*B*), 2.68-2.52 (2H, m, H-7*AB*), 2.39 (3H, s, H-20), 2.00-1.79 (2H, m, H-4), 1.72-1.65 (1H, m, 6*A*), 1.59-1.51 (1H, m, 6*B*), 1.32 (3H, d, *J* 6.9, H-9) 1.27-1.15 (7H, m, H-2, H-3, H-14), 0.89 (3H, t, *J* 7.1, H-1).

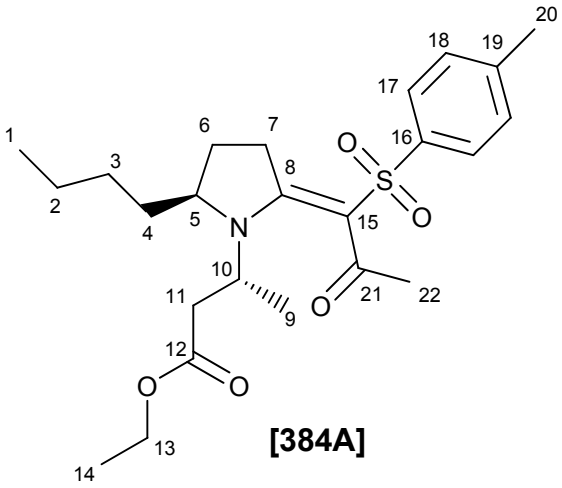
^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 170.3 (C-12), 160.4 (C-8), 143.2 (C-19), 141.6 (C-16), 129.1 (C-18), 125.9 (C-17), 87.4 (C-15), 61.4 (C-5), 60.7 (C-13), 48.3 (C-10), 38.6 (C-7), 34.1 (C-11), 29.6 (C-4), 27.7 (C-2), 26.2 (C-6), 22.5 (C-20), 21.3 (C-3), 18.0 (C-9), 14.0 (C-14), 13.8 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2955 (m, C-H), 2933 (m, C-H), 2872 (m, C-H), 2604 (m, C=C), 2498 (w, C=C), 1731 (s, C=O), 1563 (s), 1457 (m), 1416 (m), 1398 (m, S=O), 1279 (s), 1131 (s), 1081 (s), 1034 (m), 814 (m), 813 (m).

m/z: 407 (2%, M), 378 (3), 362 (2), 343 (3), 320 (5), 296 (5), 253 (20), 252 (100), 236 (25), 224 (7), 206 (10), 196 (50), 194 (24), 173 (8), 172 (45). Found 407.2143, $C_{22}H_{33}O_4N^{32}S$ requires 407.2130.

WISETD

Diastereomer A (*S,R* and *R,S*)



[384A]

R_f 0.43 (30% EtOAc/hexane)

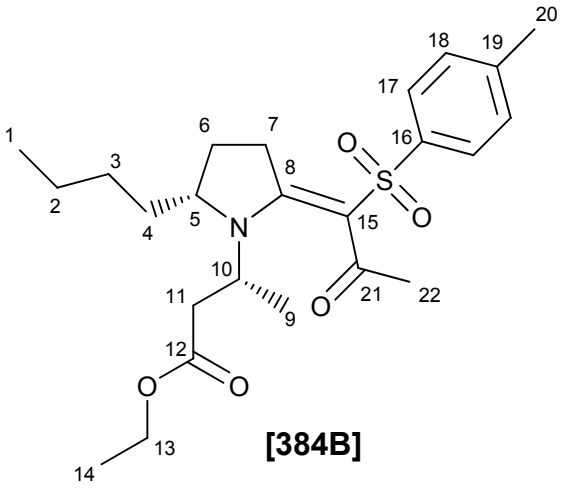
^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.72 (2H, d, *J* 8.5, H-17), 7.27 (2H, d, *J* 8.5, H-18), 4.25-4.10 (3H, m, H-5, H-13), 4.03 (1H, m, H-10), 3.76 (1H, m, H-7*A*), 3.41 (1H, dd, *J* 15.6, 1.6, H-6*A*), 2.74 (1H, dt, *J* 16.4, 7.9, H-7*B*), 2.55-2.42 (1H, m, H-6*B*), 2.40 (3H, s, H-20), 2.34 (3H, s, H-22), 2.10-1.95 (1H, m, H-11*A*), 1.80-1.63 (2H, m, H-11*B*, H-4*A*), 1.40-1.23 (8H, m, H-4*B*, H-2, H-3, H-14), 1.39 (3H, d, *J* 7.2, H-9), 0.92 (3H, t, *J* 6.9, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 189.9 (C-21), 174.4 (C-12), 170.4 (C-8), 142.6 (C-19), 142.0 (C-16), 129.3 (C-18), 125.6 (C-17), 104.4 (C-15), 62.8 (C-10), 60.6 (C-13), 55.7 (C-5), 38.0 (C-6), 35.0 (C-7), 33.5 (C-4), 30.0 (C-20), 27.5 (C-9), 25.4 (C-11), 24.0 (C-3), 22.3 (C-22), 19.5 (C-2), 13.9 (C-14), 13.7 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2958 (m, C-H), 2933 (m, C-H), 2872 (m, C-H), 1731 (s, OC=O), 1680 (m, C=O), 1615 (m), 1494 (s), 1396 (s), 1373 (s, S=O), 1297 (s), 1089 (s), 1056 (m), 1029 (m).

WitsETD

Diastereomer B (*R,R* and *S,S*)



[384B]

R_f 0.36 (30% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.75 (2H, d, *J* 7.8, H-17), 7.26 (2H, d, *J* 7.8, H-18), 4.38-4.31 (1H, m, H-10), 4.22-4.15 (1H, m, H-5), 4.12 (2H, q, *J* 7.2, H-13) 3.96-3.86 (1H, m, H-7*A*), 2.78 (1H, d, *J* 7.2, H-6*A*), 2.73-2.55 (1H, m, H-7*B*), 2.40 (3H, s, H-20), 2.30 (3H, s, H-22), 2.28-2.10 (1H, m, H-6*B*), 2.10-1.95 (1H, m, H-11*A*). 1.79-1.63 (2H, m, H-11*B*, H-4*A*), 1.54 (3H, d, *J* 6.7, H-9), 1.50-1.20 (8H, m, H-4*B*, H-2, H-3, H-14), 0.92 (3H, t, *J* 6.9, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 189.3 (C-21), 174.5 (C-12), 169.5 (C-8), 142.7 (C-19), 142.0 (C-16), 129.3 (C-18), 125.7 (C-17), 104.9 (C-15), 61.2 (C-13), 60.3 (C-5), 56.6 (C-10), 40.7 (C-6), 38.6 (C-7), 35.1 (C-4), 30.3 (C-20), 27.0 (C-3), 24.7 (C-11), 22.5 (C-2), 21.2 (C-22), 18.5 (C-9), 13.8 (C-14), 13.7 (C-1).

$v_{max.}$ / **cm^{-1}**: 2958 (m, C-H), 2933 (m, C-H), 2872 (m, C-H), 1731 (s, OC=O), 1681 (s, C=O), 1616 (w), 1495 (m), 1397 (m, S=O), 1296 (s), 1141 (s), 1053 (m), 1029 (m).

Method C

Ethyl 3-(2-butyl-5-thioxo-1-pyrrolidinyl)butanoate (295) (0.17 g, 0.63 mmol) was dissolved in THF (10 mL) in oven-dried glassware, under a nitrogen

WitsETD

atmosphere. Methyl iodide (0.19 mL, 3.1 mmol) was added by syringe and the reaction was stirred at ambient temperature for 24 hours. At this stage the starting material had been consumed and the moisture-sensitive iodine salt could be seen on the baseline of the TLC plate (40% EtOAc/hexane). The THF and excess methyl iodide were removed *in vacuo* to give a brown oil. K_2CO_3 (174 mg, 1.26 mmol) and **1-[(4-methylphenyl)sulfonyl]acetone (279)** (267 mg, 1.26 mmol) were premixed in DMF (7 mL) 10 minutes prior to addition to the crude salt. This mixture was left stirring in an oil bath at 25ºC under a nitrogen atmosphere for 96 hours before it was quenched with distilled H_2O (2 mL), and the organic material was extracted into CH_2Cl_2 (6 × 15 mL). The combined organic extracts were dried with sodium sulfate, the solvent was removed *in vacuo* and the crude material was purified by column chromatography (30% EtOAc/hexane) to give **ethyl 3-((5*E*)-2-butyl-5-{[4-ethylphenyl)sulfonyl]methylene}pyrrolidinyl) butanoate (296)** (100 mg, 39% yield) as a mixture of diastereomers.

Method D

Ethyl 3-(2-butyl-5-thioxo-1-pyrrolidinyl)butanoate (295) (626 mg, 2.31 mmol) was dissolved in THF (7 mL) in oven-dried glassware under a nitrogen atmosphere. Methyl iodide (0.72 mL, 12 mmol) was added by syringe and the reaction was stirred at ambient temperature for 48 hours. The THF and excess methyl iodide were removed *in vacuo* to give a brown oil. DBU (0.70 mL, 4.6 mmol) and **1-[(4-methylphenyl)sulfonyl]acetone (279)** (980 mg, 4.62 mmol) were premixed in CH_2Cl_2 (10 mL) 10 minutes prior to addition to the oily residue. This mixture was left stirring in an oil bath at 25ºC under a nitrogen atmosphere for 72 hours before the reaction was quenched with distilled H_2O (2 mL), and the organic material was extracted into CH_2Cl_2 (6 × 15 mL). The combined organic extracts were dried with sodium sulfate, the solvent was removed *in vacuo* and the crude material was purified by column chromatography (30% EtOAc/hexane) to give **ethyl 3-((5*E*)-2-butyl-5-{[4-methylphenyl)sulfonyl] methylene}pyrrolidinyl)butanoate (296)** (458 mg, 49% yield) as a mixture of diastereomers.

WitsETD

8.1.6.2 Deacylation reactions

Method A

Racemic **ethyl 3-(*E*)-2-butyl-5-(2-oxo-1-tosylpropylidene)pyrrolidin-1-yl)butanoate (384)** (0.32 g, 0.71 mmol) was heated at reflux in AcOH (0.23 mL, 3.8 mmol) and toluene (5 mL) for 14 hours. The reaction mixture was cooled and partitioned with saturated sodium bicarbonate solution (5 mL) and extracted into EtOAc (5 × 20 mL). The combined organic fractions were then dried with sodium sulfate, the solvent removed *in vacuo* and the crude material purified by column chromatography (30% EtOAc/hexane) to give **ethyl 3-((5*E*)-2-butyl-5-{[4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)butanoate (296)** (130 mg, 45% yield).

Method B[154]

Diastereomer A (*R,S* and *S,R*), **ethyl 3-(*E*)-2-butyl-5-(2-oxo-1-tosylpropylidene)pyrrolidin-1-yl)butanoate (384A)**, (500 mg, 1.11 mmol) was heated at reflux in TFA (5 mL) for 30 minutes. The mixture was cooled, rinsed with saturated sodium bicarbonate solution until it was basic and the organic material extracted into EtOAc (50 mL). The organic layer was then dried with sodium sulfate and the solvent removed *in vacuo*. The crude product was purified by column chromatography (30% EtOAc/hexane) to give **ethyl 3-((5*E*)-2-butyl-5-{[4-methylphenyl)sulfonyl]methylene}pyrrolidinyl) butanoate (296A)** (300 mg, 67% yield).

Diastereomer B (*R,R* and *S,S*), **ethyl 3-(*E*)-2-butyl-5-(2-oxo-1-tosylpropylidene)pyrrolidin-1-yl)butanoate (384B)**, (0.37 g, 0.82 mmol) was heated at reflux in TFA (5 mL) for 30 minutes. The mixture was cooled, rinsed with saturated sodium bicarbonate solution until it was basic, and the organic material extracted into EtOAc (50 mL). The organic layer was then dried with sodium sulfate and the solvent removed *in vacuo*. The crude product was purified by column chromatography (30% EtOAc/hexane) to give **ethyl 3-((5*E*)-2-butyl-5-{[4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)butanoate (296B)** (180 mg, 54% yield).

WITSETD

8.1.7 Reduction of the ester

8.1.7.1 3-((5*E*)-2-Butyl-5-{[(4-methylphenyl)sulfonyl]methylene} pyrrolidinyl)-1-butanol (297)[173]

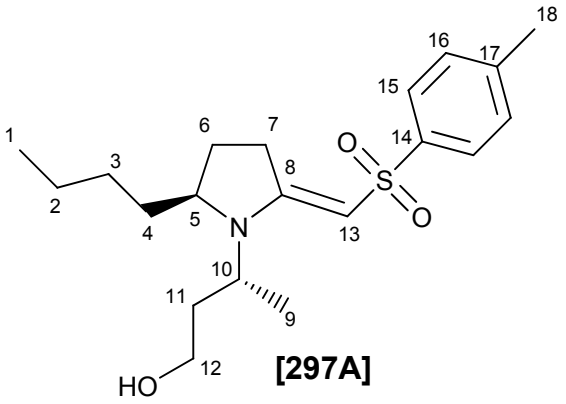
Ethyl 3-((5*E*)-2-butyl-5-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidinyl) butanoate (296) (560 mg, 1.37 mmol) was dissolved in THF (20 mL) and cooled to 0°C in an ice-bath under a nitrogen atmosphere. Lithium aluminium hydride (78 mg, 2.1 mmol) was added and after 20 minutes the ice-bath was removed and the reaction mixture was left to stir at ambient temperature for 12 hours. Monitoring the reaction progress by TLC revealed that the starting material had been consumed. The reaction was thus quenched by the addition of distilled H_2O (5 mL), saturated NaOH solution (5 mL) and more distilled H_2O (5 mL). The solution was then filtered through Celite® and rinsed thoroughly with CH_2Cl_2 (200 mL) to remove residual lithium aluminium hydride. The solvent was removed *in vacuo* to give a crude, brown oil which was purified by column chromatography (50% EtOAc/hexane) to give **3-((5*E*)-2-butyl-5-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)-1-butanol (297)** (460 mg, 92% yield) as a clear oil.

This method was repeated with pure diastereomer A (*S,R* and *R,S*), **ethyl 3-((5*E*)-2-butyl-5-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidinyl) butanoate (296A)** (450 mg, 1.10 mmol), to give **3-((5*E*)-2-butyl-5-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)-1-butanol (297A)** (350 mg, 87% yield).

This method was repeated with pure diastereomer B (*R,R* and *S,S*), **ethyl 3-((5*E*)-2-butyl-5-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidinyl) butanoate (296B)** (660 mg, 1.62 mmol), to give **3-((5*E*)-2-butyl-5-{[(4-methylphenyl) sulfonyl]methylene}pyrrolidinyl)-1-butanol (297B)** (460 mg, 78% yield).

WiSER

Diastereomer A (*S,R* and *R,S*)



[297A]

R_f 0.27 (50% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.75 (2H, d, *J* 7.3, H-15), 7.24 (2H, d, *J* 7.9, H-16), 5.07 (1H, s, H-13), 3.74-3.60 (4H, m, H-5, H-10, H-12), 3.04 (1H, ddd, *J* 17.4, 9.5, 2.9, H-7*A*), 2.82 (1H, dt, *J* 17.4, 8.4, H-7*B*), 2.39 (3H, s, H-18), 2.02-1.53 (6H, m, H-4, H-6, H-11), 1.31-1.16 (7H, m, H-2, H-3, H-9), 0.88 (3H, t, *J* 7.0, H-1).

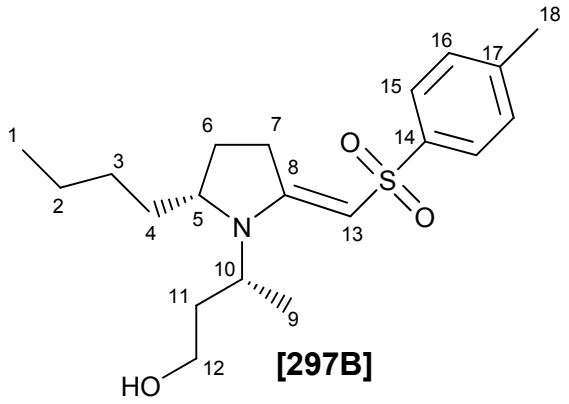
^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 160.4 (C-8), 143.3 (C-17), 141.5 (C-14), 129.1 (C-16), 125.8 (C-15), 86.1 (C-13), 60.3 (C-5), 59.2 (C-12), 48.5 (C-10), 36.6 (C-11), 33.9 (C-6/7), 29.9 (C-6/7), 27.7 (C-4), 25.8 (C-3), 22.5 (C-18), 21.3 (C-2), 17.2 (C-9), 14.0 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 3481 (br, O-H), 2933 (m, C-H), 2873 (m, C-H), 1562 (s), 1460 (m), 1419 (m), 1381 (m, S=O), 1276 (s), 1130 (s), 1083 (s), 846 (m).

m/z: 365 (3%, M), 341 (4), 330 (12), 320 (4), 308 (27), 294 (17), 277 (18), 264 (38), 238 (28), 210 (42), 196 (21), 166 (100). Found 365.2036, $C_{20}H_{31}O_3N^{32}S$ requires 365.2025.

WitsETD

Diastereomer B (*R,R* and *S,S*)



[297B]

R_f 0.30 (50% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.75 (2H, d, *J* 7.3, H-15), 7.24 (2H, d, *J* 7.9, H-16), 4.95 (1H, s, H-13), 3.72-3.58 (4H, m, H-5, H-10, H-12), 3.15-3.03 (1H, m, H-7*A*), 2.81-2.69 (1H, m, H-7*B*), 2.39 (3H, s, H-18), 1.96-1.53 (6H, m, H-4, H-6, H-11), 1.35-1.08 (7H, m, H-2, H-3, H-9), 0.87 (3H, t, *J* 7.0, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 160.9 (C-8), 143.2 (C-17), 141.6 (C-14), 129.2 (C-16), 125.8 (C-15), 86.2 (C-13), 61.3 (C-5), 59.4 (C-12), 48.1 (C-10), 36.1 (C-11), 34.0 (C-6/7), 29.7 (C-6/7), 27.7 (C-4), 26.0 (C-3), 22.5 (C-18), 21.3 (C-2), 18.1 (C-9), 13.9 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 3459 (br, O-H), 2928 (m, C-H), 2859 (m, C-H), 1562 (s), 1460 (m), 1419 (m), 1381 (m, S=O), 1276 (s), 1130 (s), 1083 (s), 846 (m).

m/z: 365 (1%, M), 347 (3), 330 (24), 322 (8), 308 (39), 294 (22), 264 (58), 238 (49), 210 (44), 196 (46), 166 (100). Found 365.2019, $C_{20}H_{31}O_3N^{32}S$ requires 365.2025.

WitsETD

8.1.8 Cyclisation reaction

8.1.8.1 3-Butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]-1,2,3,5,6,7-hexa hydroindolizine (298)[139, 230]

Method A

3-((5*E*)-2-butyl-5-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)-1-butanol (297) (40 mg, 0.11 mmol) was dissolved in MeCN (8 mL), under nitrogen at ambient temperature. Triphenylphosphine (87 mg, 0.33 mmol), imidazole (37 mg, 0.55 mmol) and iodine (56 mg, 0.22 mmol) were sequentially added to the reaction mixture at 3 minute intervals. The reaction was heated at reflux for 5 hours, left for 12 hours at ambient temperature and heated at reflux for an additional 2 hours as starting material was still evident by TLC. The reaction mixture was then rinsed with saturated sodium bicarbonate solution (25 mL) and back-extracted into EtOAc (3 × 30 mL). The combined organic fractions were dried with sodium sulfate and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (50% EtOAc/hexane) to give back starting material contaminated by triphenylphosphine oxide (85 mg).

Method B

Triphenylphosphine (493 mg, 1.88 mmol), imidazole (128 mg, 1.88 mmol) and iodine (319 mg, 1.26 mmol) were mixed in dry toluene (20 mL) in an oven-dried flask. **3-((5*E*)-2-Butyl-5-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)-1-butanol (297)** (0.23 g, 0.63 mmol) was carefully added to this mixture and the reaction was heated at reflux for 3 hours under nitrogen. No more starting material was detected by TLC, so the reaction was allowed to cooled and then rinsed with saturated sodium bicarbonate solution (25 mL). The organic material was extracted into CH_2Cl_2 (5 × 30 mL) and the combined organic fractions were dried with sodium sulfate and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (80% Et_2O/hexane) to give **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]-1,2,3,5,6,7-hexahydro indolizine (298)** (185 mg, 85% yield) as a sticky pink oil from which several crystals were obtained by slow evaporation in an EtOAc/hexane mixture.

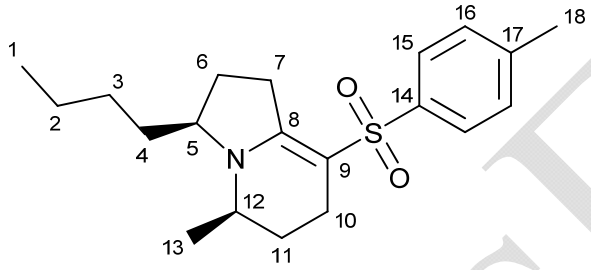
This method was repeated with pure diastereomer A (*S,R* and *R,S*), **3-((5*E*)-2-**

WitsETD

butyl-5-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)-1-butanol (297A) (0.35 g, 0.96 mmol), to give **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]-1,2,3,5,6,7-hexahydroindolizine (298A)** (260 mg, 78% yield).

This method was repeated with pure diastereomer B (*R,R* and *S,S*), **3-((5*E*)-2-butyl-5-{[(4-methylphenyl)sulfonyl]methylene}pyrrolidinyl)-1-butanol (297B)** (0.17 g, 0.47 mmol), to give **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]-1,2,3,5,6,7-hexahydroindolizine (298B)** (110 mg, 67% yield).

Diastereomer A (*S,R* and *R,S*)



[298A]

M.p.122 -123°C

R_f 0.74 (50% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.69 (2H, d, *J* 7.9, H-15), 7.23 (2H, d, *J* 8.0, H-16), 3.50-3.42 (1H, m, H-5), 3.43-3.34 (1H, m, H-12), 3.27-3.17 (1H, m, H-10*A*), 2.93 (1H, dt, *J* 17.4, 8.1, 10*B*), 2.47-2.40 (1H, m, H-7*A*), 2.39 (3H, s, H-18), 2.30-2.19 (1H, m, H-7*B*), 2.11-2.00 (1H, m, H-6*A*), 1.85-1.75 (1H, m, H-11*A*), 1.68-1.50 (1H, m, H-6*B*), 1.47-1.18 (1H, m, H-11*B*), 1.15-1.08 (6H, m, H-2, H-3, H-4), 1.06 (3H, d, *J* 6.6, H-13), 0.92 (3H, t, *J* 6.9, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 154.8 (C-8), 141.8 (C-14), 141.4 (C-17), 129.1 (C-15), 125.8 (C-16), 91.8 (C-9), 64.6 (C-12), 48.0 (C-5), 34.7 (C-11), 29.7

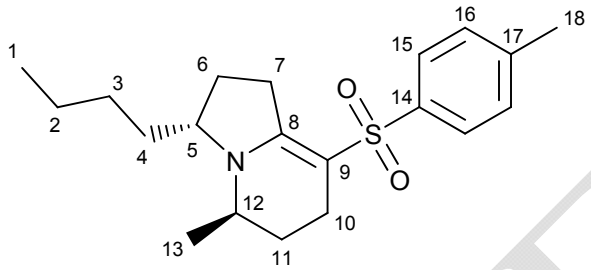
WitsETD

(C-10), 27.7 (C-2), 27.5 (C-6), 27.0 (C-4), 22.6 (C-3), 21.2 (C-13), 21.0 (C-18), 18.5 (C-7), 13.9 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2930 (m, C-H), 2858 (m, C-H), 1591 (s), 1449 (w), 1375 (w, S=O), 1279 (s), 1147 (m), 1128 (s), 1089 (s), 670 (s).

m/z: 347 (20%, M), 332 (2), 290 (100), 279 (2), 226 (2), 205 (6), 192 (7), 167 (8), 162 (11). Found 347.1917, $C_{20}H_{29}O_2N^{32}S$ requires 347.1919.

Diastereomer B (*R,R* and *S,S*)



[298B]

M.p. 99 -101°C

R_f 0.74 (50% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.69 (2H, d, *J* 7.9, H-15), 7.23 (2H, d, *J* 8.0, H-16), 3.50-3.45 (2H, m, H-5, H-12), 3.11-3.01 (2H, m, H-10*AB*), 2.39 (3H, s, H-18), 2.36-2.29 (2H, m, H-7*AB*), 2.04-1.96 (1H, m, H-6*A*), 1.72-1.53 (4H, m, H-6*B*, H-11*AB*, H-4*A*), 1.37-1.21 (5H, m, H-2, H-3, H-4*B*), 1.05 (3H, d, *J* 6.6, H-13), 0.90 (3H, t, *J* 6.9, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 155.2 (C-8), 141.8 (C-14), 141.7 (C-17), 129.2 (C-15), 126.0 (C-16), 91.9 (C-9), 60.1 (C-12), 45.5 (C-5), 31.7 (C-11), 30.1 (C-10), 27.9 (C-2), 27.3 (C-6), 26.9 (C-4), 22.8 (C-3), 21.4 (C-13), 19.2 (C-18), 17.1 (C-7), 14.0 (C-1).

WitsETD

$v_{max.}$ / **cm^{-1}**: 2929 (m, C-H), 2857 (m, C-H), 1590 (s), 1459 (w), 1375 (w, S=O), 1279 (s), 1128 (s), 1086 (s), 661 (s).

m/z: 347 (18%, M), 319 (2), 298 (3), 290 (100), 277 (9), 261 (1), 226 (1), 207 (8), 192 (8), 176 (6). Found 347.1921, $C_{20}H_{29}O_2N^{32}S$ requires 347.1919.

8.1.9 Reduction of the vinylogous sulfonamide

8.1.9.1 3-Butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydroindolizine (299)

Method A[31]

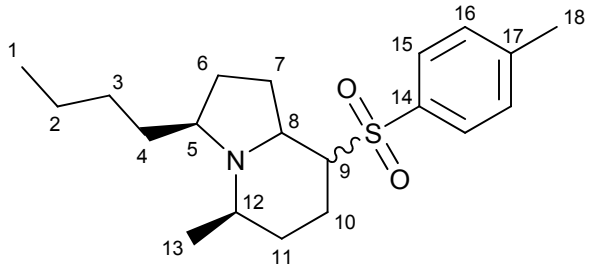
3-Butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]-1,2,3,5,6,7-hexahydro indolizine (298) (80 mg, 0.23 mmol) was dissolved in AcOH (4 mL) and reacted with platinum dioxide (3 mg, 0.05 eq.) under 7.5 atmospheres of hydrogen pressure for 12 hours at ambient temperature. The reaction mixture was filtered through Celite® to remove the catalyst and rinsed thoroughly with CH_2Cl_2 (200 mL). The solvent was removed *in vacuo* and the residue was partitioned in distilled H_2O (20 mL) and CH_2Cl_2 (3 × 20 mL). The organic fractions were rinsed with saturated sodium hydrogen carbonate solution (20 mL), dried with sodium sulfate and the solvent was removed *in vacuo* to give the crude product. This was purified by column chromatography (30% EtOAc/hexane) to give the product, **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydroindolizine (299)**, (67 mg, 84% yield) as a clear oil that discolours to pink on standing.

This method was repeated with pure diastereomer A (*S,R* and *R,S*), **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydroindolizine (298A)** (0.15 g, 0.42 mmol), to give **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydro indolizine (299A)** (130 mg, 88% yield).

This method was repeated with pure diastereomer B (*R,R* and *S,S*), **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydroindolizine (298B)** (0.11 g, 0.32 mmol), to give **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydro indolizine (299B)** (80 mg, 72% yield).

WitsETD

Diastereomer A (*S,R* and *R,S*)



[299A]

R_f 0.58 (30% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.84 (2H, d, *J* 8.1, H-15), 7.29 (2H, d, *J* 8.1, H-16), 3.33 (1H, m, H-12), 3.03 (1H, t, *J* 7.5, H-9), 2.62 (1H, m, H-5), 2.58-2.48 (1H, m, H-8), 2.43 (3H, s, H-18), 2.25-2.13 (4H, m, H-10, H-11*AB*), 1.82-1.15 (10H, m, H-2, H-3, H-4, H-6, H-7), 0.91 (3H, d, *J* 7.5, H-13), 0.88 (3H, t, *J* 6.3, H-1).

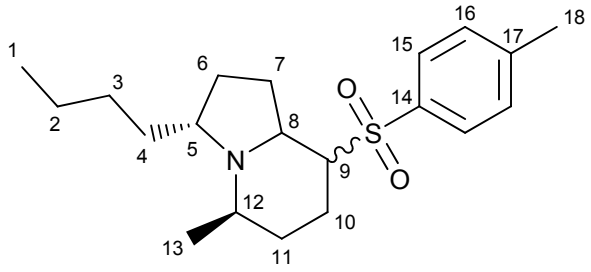
^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 143.9 (C-14), 138.4 (C-17), 129.5 (C-16), 129.2 (C-15), 67.1 (C-8), 63.4 (C-5), 61.6 (C-12), 59.5 (C-9), 39.2 (C-11), 30.5 (C-10), 29.0 (C-7), 28.7 (C-6), 27.7 (C-4), 26.1 (C-3), 22.9 (C-2), 22.1 (C-18), 21.6 (C-13), 14.2 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2958 (m, C-H), 2928 (m, C-H), 2859 (Bohlmann), 1598 (m), 1454 (m), 1377 (m, S=O), 1306 (s), 1275 (s), 1140 (s), 1084 (s), 818 (m).

m/z: Found 349.1839, $C_{20}H_{31}O_2N^{32}S$ requires 349.2075.

WiSER

Diastereomer B (*R,R* and *S,S*)



[299B]

R_f 0.71 (50% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.79 (2H, d, *J* 7.2, H-15), 7.30 (2H, d, *J* 7.2, H-16), 3.49-3.02 (3H, m, H-12, H-9, H-8), 2.67-2.54 (1H, m, H-5), 2.43 (3H, s, H-18), 2.07-1.98 (2H, m, H-10), 1.80-1.65 (2H, m, H-11), 1.52-1.02 (10H, m, H-2, H-3, H-4, H-6, H-7), 0.99-0.81 (6H, m, H-13, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 144.0 (C-14), 137.9 (C-17), 129.4 (C-16), 128.7 (C-15), 62.9 (C-8), 60.2 (C-5), 56.5 (C-12), 47.0 (C-9), 33.0 (C-11), 29.7 (C-10), 28.5 (C-7), 28.0 (C-6), 27.8 (C-4), 25.7 (C-3), 23.0 (C-2), 21.5 (C-18), 20.7 (C-13), 14.1 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2958 (s, C-H), 2927 (s, C-H), 2857 (Bohlmann), 1597 (m), 1454 (m), 1378 (m, S=O), 1313 (s), 1301 (s), 1142 (s), 1085 (m), 815 (m).

m/z: 349 (36%, M), 347 (88), 334 (100), 294 (100), 194 (100), 178 (90), 149 (85), 136 (100), 105 (100). Found 349.1601, $C_{20}H_{31}O_2N^{32}S$ requires 349.2075.

Method B[171]

3-Butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]-1,2,3,5,6,7-hexahydro indolizine (298) (0.16 g, 0.46 mmol) and sodium borohydride (26 mg, 0.69 mmol) were dissolved in MeOH (7 mL) and stirred at ambient temperature for 4 hours. TLC showed no significant conversion of starting material. The reaction was heated to 60°C and was allowed to react for a further 20 hours. The solvent was removed *in vacuo* and the residue was partitioned in distilled

WITFD

H_2O (20 mL) and CH_2Cl_2 (3 × 20 mL). The organic fractions were combined and dried with sodium sulfate and the solvent was removed *in vacuo.* The crude material was purified by column chromatography (40% EtOAc/hexane) to give **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]-1,2,3,5,6,7-hexahydroindolizine (298)** (80 mg, 50% recovery) and the desired product, **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydroindolizine (299)** (15 mg, 13% yield).

8.1.10 Desulfonylation

8.1.10.1 3-Butyl-5-methyloctahydroindolizine, monomorine I (27), 5-*epi*-monomorine I (28)

Method A[234, 236, 254]

A 6% (w/w) sodium amalgam was prepared by placing sodium (1.5 g, 65 mmol) freshly rinsed in hexane (to remove traces of paraffin oil) in a dry flask. The hexane was removed under high vacuum. A few drops of mercury (25.0 g, 126 mmol) were slowly added by dropping funnel. The flask was then heated with a Bunsen burner until the amalgam ignited, at which point the flame was removed and the remaining mercury was slowly added. The flask was heated again to melt the amalgam so that it could be poured into a crucible where it was cooled under the flow of nitrogen gas. The amalgam was crushed with a mortar and pestle and stored in a dessicator. Anhydrous sodium hydrogen phosphate (193 mg, 1.36 mmol) was pre-dried for 12 hours in a 130°C oven and then dissolved in distilled MeOH (7 mL). **3-Butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydroindolizine (299)** (120 mg, 0.34 mmol) and the sodium amalgam (515 mg, 1.50 g/mmol) were added to the MeOH solution and the reaction stirred at ambient temperature for 14 hours. TLC analysis was inconclusive so the reaction was stopped, filtered through Celite® to remove the mercury, and rinsed thoroughly with CH_2Cl_2 (20 mL). The organic layer was partitioned with distilled H_2O, dried with sodium sulfate and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (30% EtOAc/hexane) to give back the starting material, **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydroindolizine (299)** (80 mg, 67% recovery).

WISER

Method B[233]

Magnesium turnings were pre-activated by washing in an HCl solution (0.5% (v/v), 30 mL) rinsing with distilled H_2O, EtOH, and Et_2O respectively, and then drying for several days at 150°C. The activated magnesium turnings (64 mg, 2.7 mmol) were mixed with MeOH (5 mL) and heated to 50°C until hydrogen evolution was constant. **3-Butyl-5-methyl-8-[(4-methylphenyl)sulfonyl] octahydroindolizine (299)** (58 mg, 0.17 mmol) was added to the methanolic mixture. The reaction was maintained at 50°C for 3 hours and during this time two further portions of magnesium turnings (64 mg, 2.7 mmol) were added. The solution was cooled, filtered through Celite®, and rinsed thoroughly with CH_2Cl_2 (100 mL). The solvent was removed *in vacuo* and the resulting residue was redissolved in Et_2O (80 mL) and refiltered to remove the solid magnesium methoxide. After evaporation *in vacuo* the oily residue that remained was purified by column chromatography (30% EtOAc/hexane) to give **3-butyl-5-methyloctahydroindolizine** (20 mg, 60% yield) as a mixture of **monomorine I (27)**, **5-*epi*-monomorine I (28)** and **indolizidine 195B (26)** (as confirmed by ^{13}C-NMR spectroscopy only).

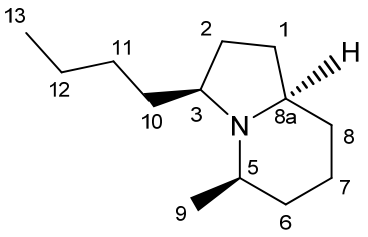
RACEMIC MONOMORINE I (27)

Method C

Sodium metal (40 mg, 1.8 mmol) was reacted with naphthalene (224 mg, 1.75 mmol) in THF (10 mL) for 1 hour in an oven-dried flask under inert atmosphere, until a dark green solution of sodium naphthalenide had formed. Isomer A of **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl] octahydroindolizine (299A)** (44 mg, 0.12 mmol) was added to the sodium naphthalenide and the mixture was stirred for 15 minutes at ambient temperature whilst constantly monitoring by TLC. The reaction was quenched by addition of saturated ammonium chloride solution (20 mL) and the organic products were extracted into CH_2Cl_2 (3 × 30 mL). The combined organic fractions were dried with sodium sulfate and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (20% - 50% EtOAc/hexane) to give **(±)-monomorine I (27)** (18 mg, 73% yield) as a pale yellow oil.

WitsETD

Diastereomer A (relative stereochemistry)



[27]

R_f 0.25 (30% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 2.51-2.43 (1H, m, H-3), 2.31-2.15 (1H, m, H-5), 2.14-2.03 (1H, m, H-8a), 1.88-1.05 (16H, m, H-1, H-2, H-6, H-7, H-8, H-10, H-11, H-12), 1.15 (3H, d, *J* 6.3, H-9), 0.98 (3H, t, *J* 6.8, H-13).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 67.17 (C-8a), 62.90 (C-3), 60.26 (C-5), 39.73 (C-9), 35.84 (C-6), 30.91 (C-1), 30.34 (C-8), 29.76 (C-2), 29.40 (C-10), 24.91 (C-7), 22.90 (C-11), 22.86 (C-13), 14.16 (C-12).

$\nu_{max.}$ / **cm^{-1}**: 2958 (m, C-H), 2930 (m, C-H), 2860 (Bolhmann), 1457 (m), 1380 (m), 1319 (m), 1304 (m), 1208 (w), 1133 (m), 1089 (w), 816 (w).

m/z: no molecular ion 193 (6%), 170 (36), 155, 45), 138 (100), 107 (41). **APCI** Found 195.37, $C_{13}H_{25}N$ requires 195.1987.

RACEMIC 5-*epi*-MONOMORINE I (28)

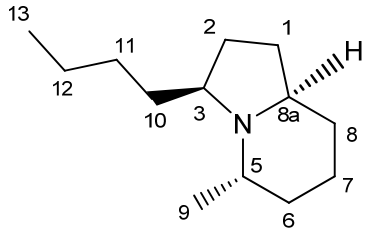
Method D

Sodium metal (40 mg, 1.8 mmol) was reacted with naphthalene (224 mg, 1.75 mmol) in THF (10 mL) for 30 minutes in an oven-dried flask under inert atmosphere until a dark green solution of sodium naphthalenide had formed. Isomer B of **3-butyl-5-methyl-8-[(4-methylphenyl)sulfonyl]octahydro indolizine (299B)** (75 mg, 0.21 mmol) was added to the sodium naphthalenide and the mixture was stirred for 15 minutes at ambient temperature whilst constantly monitoring by TLC. The reaction was quenched by addition of saturated ammonium chloride solution (10 mL) and the organic products were

WISER

extracted into CH_2Cl_2 (3 × 30 mL). The combined organic fractions were dried with sodium sulfate and the solvent was removed *in vacuo*. The crude material was purified by column chromatography through a Pasteur pipette (0% - 100% EtOAc/hexane) to give racemic **5-*epi*-monomorine I (28)** (31 mg, 71% yield) as a pale yellow oil that discoloured to turquoise over time.

Diastereomer B (relative stereochemistry)



[28]

R_f 0.17 (50% EtOAc/hexane)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 3.45-3.30 (1H, m, H-5), 2.51-2.38 (2H, m, H-3, H-8a), 1.87-1.07 (16H, m, H-1, H-2, H-6, H-7, H-8, H-10, H-11, H-12), 0.92-0.83 (6H, m, H-9, H-13).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 59.21 (C-8a), 55.49 (C-3), 47.38 (C-5), 32.34 (C-1), 32.21 (C-6), 31.46 (C-2), 29.12 (C-8), 28.82 (C-9), 28.12 (C-10), 23.08 (C-11), 19.26 (C-7), 14.09 (C-12), 7.60 (C-13).

$\nu_{max.}$ / **cm^{-1}**: 2957 (s, C-H), 2927 (s, C-H), 2859 (Bolhmann), 1455 (m), 1375 (m), 1261 (w), 1201 (w), 1146 (w), 1078 (w), 784 (m), 745 (m).

m/z: 195 (6%, M), 194 (12), 180 (70), 148 (8), 138 (100), 128 (26), 124 (13). Found 195.1976, $C_{13}H_{25}N$ requires 195.1987.

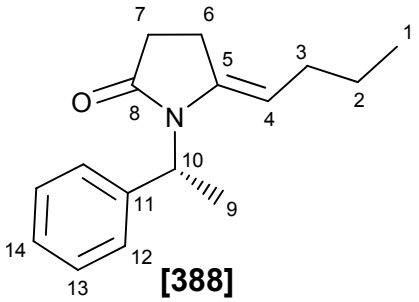
WitsETD

8.2 Investigation of monobenzylated analogues

8.2.1 (*R,E*)-5-Butylidene-1-(1-phenylethyl)pyrrolidin-2-one (388)

Method A

Ethyl 4-oxooctanoate (292) (6.60 g, 35.4 mmols) was dissolved in toluene (30 mL). Crude **ethyl (3*R*)-3-{[(1*R*)-1-phenylethyl]amino}butanoate (357)** (29.5 mmols) in AcOH (<5 mL) was added to the toluene and the mixture was heated at reflux for 72 hours in a modified Dean Stark apparatus filled with molecular sieves. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (10% EtOAc/hexane) to give **(*R,E*)-5-butylidene-1-(1-phenylethyl)pyrrolidin-2-one (388)** (3.40 g, 47% yield over two steps).



[388]

R_f 0.11 (10% EtOAc/Hexane), $[\alpha]_D^{20}$ +43.1 (*c* 1.30, CH_2Cl_2)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.28-7.24 (5H, m, H-12, H-13, H-14), 5.65 (1H, q, *J* 7.2, H-10), 4.39 (1H, t, *J* 7.4, H-4), 2.63-2.51 (4H, m, H-6, H-7), 1.85-1.78 (2H, m, H-3), 1.71 (3H, d, *J* 7.2, H-9), 1.19 (2H, s, *J* 7.4, H-2), 0.72 (3H, t, *J* 7.4, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 175.7 (C-8), 139.7 (C-11), 136.6 (C-5), 128.4 (C-12), 126.7 (C-14), 126.3 (C-13), 104.0 (C-4), 48.8 (C-10), 29.0 (C-7), 28.8 (C-3), 22..9 (C-2), 21.2 (C-6), 15.4 (C-9), 13.3 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2957 (w, C-H), 2931 (w, C-H), 2871 (w, C-H), 1714 (m), 1666 (s, C=O), 1449 (w), 1398 (m), 1372 (m), 1336 (w), 1239 (m), 1201 (w), 689 (m).

WitsETD

m/z: 243 (10%, M), 214 (6), 203 (82), 198 (11), 189 (22), 174 (5), 160 (100), 152 (7), 146 (31), 141 (27), 132 (24), 120 (29), 110 (47), 104 (89).[n]

Method B

Ethyl 4-oxooctanoate (292) (0.15 g, 0.90 mmols) was dissolved in toluene (10 mL). *R*-Methylbenzylamine (54 mg, 0.45 mmols) and AcOH (135 mg, 2.25 mmols) were added to the toluene and the mixture was heated at reflux for 72 hours in a modified Dean Stark apparatus filled with molecular sieves. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (10% EtOAc/hexane) to give **(*R,E*)-5-butylidene-1-(1-phenylethyl)pyrrolidin-2-one (388)** (110 mg, quantitative yield).

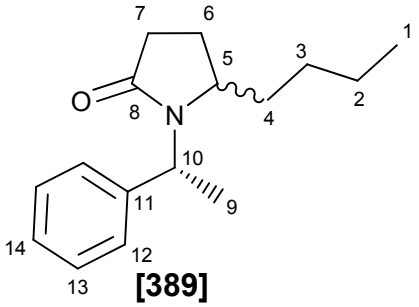
8.2.2 (*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidin-2-one (389)

Method A

(*R,E*)-5-Butylidene-1-(1-phenylethyl)pyrrolidin-2-one (388) (0.30 g, 1.2 mmols) was dissolved in CH_2Cl_2 (10 mL) and cooled to -90°C. Titanium tetrachloride (0.30 mL, 2.7 mmols) was carefully added and the reaction mixture was left to stir for 10 minutes before triphenylsilane (0.96 g, 3.7 mmols) was added and the solution slowly warmed to ambient temperature. The reaction was left stirring at ambient temperature for 72 hours and was then quenched by adding saturated ammonium chloride solution (10 mL). The product was extracted into CH_2Cl_2 (3 x 50 mL) and the combined organic fractions were dried with sodium sulfate. Purification by column chromatography (10% - 40% EtOAc/hexane) gave **(*R*)-5-butyl-1-(1-phenylethyl)pyrrolidin-2-one (389)** as a clear oil in quantitative yield as an inseparable mixture of diastereomers in a 1:1 ratio.

[n] *No HRMS was performed as the molecular ion coincides with the reference peak.*

WitsETD



[389]

R_f 0.26 (40% EtOAc/hexane)

ISOMER A $[\alpha]_D^{20}$ +15.7 (*c* 1.15, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.37 (2H, d, *J* 7.2, H-12), 7.32-7.20 (3H, m, H-13, H-14), 5.38 (1H, q, *J* 7.2, H-10), 3.73-3.67 (1H, m, H-5), 2.54-2.43 (1H, m, H-7*A*), 2.38-2.28 (1H, m, H-7*B*), 2.19-2.12 (1H, m, H-6*A*), 1.71-1.67 (1H, m, H-6*B*), 1.63 (3H, d, *J* 7.2, H-9), 1.26-1.14 (1H, m, H-4*A*), 1.08-0.80 (5H, m, H-4*B*, H-3, H-2), 0.72 (3H, t, *J* 6.8, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 175.2 (C-8), 142.0 (C-11), 129.9 (C-14), 128.5 (C-13), 127.0 (C-12), 56.9 (C-5), 49.2 (C-10), 33.9 (C-4), 30.5 (C-7), 26.7 (C-3), 24.3 (C-6), 22.3 (C-2), 16.1 (C-9), 13.7 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2931 (m, C-H), 2861 (m, C-H), 1681 (s, C=O), 1457 (m), 1417 (m), 1375 (m), 1289 (m), 1212 (m), 1185 (m), 700 (s).

ISOMER B $[\alpha]_D^{20}$ +131.6 (*c* 0.98, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.37 (2H, d, *J* 7.2, H-12), 7.32-7.20 (3H, m, H-13, H-14), 5.38 (1H, q, *J* 7.2, H-10), 3.26-3.18 (1H, m, H-5), 2.54-2.43 (1H, m, H-7*A*), 2.38-2.28 (1H, m, H-7*B*), 2.19-2.12 (1H, m, H-6*A*), 1.71-1.67 (1H, m, H-6*B*), 1.63 (3H, d, *J* 7.2, H-9), 1.26-1.14 (1H, m, H-4*A*), 1.08-0.80 (5H, m, H-4*B*, H-3, H-2), 0.72 (3H, t, *J* 6.8, H-1).

WISETD

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 175.0 (C-8), 139.7 (C-11), 128.3 (C-13), 127.4 (C-14), 127.3 (C-12), 57.2 (C-5), 50.5 (C-10), 34.7 (C-4), 30.4 (C-7), 26.9 (C-3), 24.2 (C-6), 22.5 (C-2), 18.2 (C-9), 13.8 (C-1).

$\nu_{max.}$ / **cm^{-1}**: 2956 (m, C-H), 2930 (m, C-H), 2871 (w), 1674 (s, C=O), 1456 (m), 1418 (m), 1375 (w), 1320 (m), 1291 (m), 1216 (m), 1151 (m), 700 (s).

m/z: 245 (14%, M), 198 (7), 188 (19), 174 (6), 160 (18), 146 (10), 120 (8), 110 (11), 105 (100). Found 245.1765, $C_{16}H_{23}ON$ requires 245.1780.

Method B

(*R,E*)-5-Butylidene-1-(1-phenylethyl)pyrrolidin-2-one (388) (0.50 g, 2.1 mmols) was dissolved in AcOH (7 mL) and 10% palladium on carbon (100 mg, 0.20 eq.) was carefully added. The reaction was set up in a hydrogenator under 2 atmospheres of hydrogen pressure. The reaction was left at ambient temperature for 48 hours before the catalyst was removed by filtering the reaction mixture through Celite®. The product was rinsed through the Celite® with CH_2Cl_2 (75 mL) and the crude material was purified by column chromatography (10% - 40% EtOAc/Hexane) to give **(*R*)-5-butyl-1-(1-phenylethyl)pyrrolidin-2-one (389)** (450 mg, 89% yield) as a clear oil. The diastereomer ratio was 7:1 favouring isomer A.

Method C

(*R,E*)-5-Butylidene-1-(1-phenylethyl)pyrrolidin-2-one (388) (1.7 g, 7.0 mmols) was dissolved in CH_2Cl_2 (20 mL) and cooled to -90°C. Titanium tetrachloride (1.7 mL, 15 mmols) was carefully added and the reaction mixture was left to stir for 10 minutes before triethylsilane (3.3 mL, 21 mmols) was added; the solution was then slowly warmed to ambient temperature. The reaction was left stirring at ambient temperature for 72 hours and was then quenched by adding saturated ammonium chloride solution (10 mL). The product was extracted into CH_2Cl_2 (3 x 50 mL) and the combined organic fractions were dried with sodium sulfate. Purification by column chromatography (10% - 40% EtOAc/hexane) gave **(*R*)-5-butyl-1-(1-**

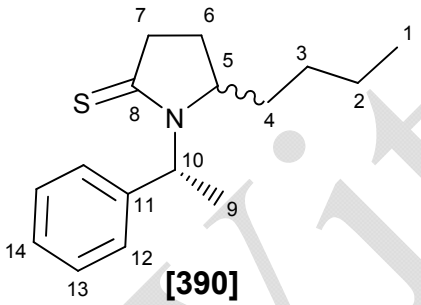
WitsETD

phenylethyl)pyrrolidin-2-one (389) (1.15 g, 68% yield) as a clear oil with a diastereomer ratio of 3:1, favouring isomer A.

8.2.3 (*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidine-2-thione (390)

Method A

(*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidin-2-one (389) (0.20 g, 0.81 mmol) was dissolved in CH_2Cl_2 (7 mL) in an oven-dried flask. Phosphorus pentasulfide (0.20 g, 0.45 mmols) was added and the heterogeneous mixture was stirred for 72 hours at ambient temperature, under a nitrogen atmosphere. The reaction was quenched by the addition of saturated sodium bicarbonate solution (10 mL) and the product was extracted into CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried with sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (10% - 20% EtOAc/hexane) gave **(*R*)-5-butyl-1-(1-phenylethyl)pyrrolidine-2-thione (390)** (140 mg, 66% yield) as a mixture of diastereomers which were partially separable by column chromatography.



[390]

ISOMER A (minor isomer)

R_f 0.34 (10% EtOAc/hexane), $[\alpha]_D^{20}$ + 226.7 (*c* 0.75, CH_2Cl_2)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.38-7.26 (5H, m, H-12, H-13, H-14), 6.30 (1H, q, *J* 7.2, H-10), 3.51-3.47 (1H, m, H-5), 3.12-3.00 (2H, m, H-7*AB*), 2.02-1.88 (1H, m, H-6*A*), 1.70 (3H, d, *J* 7.2, H-9), 1.67-0.96 (7H, m, H-2, H-3, H-4, H-6*B*), 0.89 (3H, t, *J* 7.2, H-1).

WitsETD

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 201.8 (C-8), 138.3 (C-11), 128.7 (C-12), 128.0 (C-14), 127.6 (C-13), 64.4 (C-5), 55.6 (C-10), 43.7 (C-7), 33.5 (C-4), 29.7 (C-6), 25.8 (C-2), 22.4 (C-3), 16.4 (C-9), 13.9 (C-1).

$v_{max.}$ / **cm^{-1}**: 2956 (m, C-H), 2925 (m, C-H), 2856 (m, C-H), 1683 (w), 1447 (s, C=S), 1422 (m), 1267 (m), 1095 (m), 1026 (m), 699 (s).

m/z: 261 (12%, M), 245 (14), 228 (8), 205 (6), 188 (19), 176 (7), 160 (9), 146 (6), 120 (8), 105 (100). Found 261.1547, $C_{16}H_{23}N^{32}S$ requires 261.1551.

ISOMER B (major isomer)

R_f 0.27 (10% EtOAc/hexane), $[\alpha]_D^{20}$ +383.6 (*c* 1.22, CH_2Cl_2)

^1H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.45 (2H, dd, *J* 7.5, 1.2, H-12), 7.34-7.27 (3H, m, H-13, H-14), 6.55 (1H, q, *J* 7.2, H-10), 4.05-3.99 (1H, m, H-5), 3.16-2.95 (2H, m, H-7*AB*), 2.18-2.05 (1H, m, H-6*A*), 1.78-1.69 (1H, m, H-6*B*), 1.66 (3H, d, *J* 7.2, H-9), 1.05-0.77 (6H, m, H-2, H-3, H-4), 0.65 (3H, t, *J* 7.0, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 201.8 (C-8), 140.1 (C-11), 128.3 (C-12), 127.7 (C-14), 127.1 (C-13), 63.8 (C-5), 53.7 (C-10), 43.6 (C-7), 33.2 (C-4), 27.3 (C-6), 26.4 (C-3), 22.2 (C-2), 15.1 (C-9), 13.7 (C-1).

$v_{max.}$ / **cm^{-1}**: 2955 (m, C-H), 2929 (m, C-H), 2870 (m, C-H), 1681 (w), 1450 (s, C=S), 1422 (s) 1314 (s), 1271 (s), 699 (s).

m/z: 261 (100%, M), 245 (42), 228 (67), 205 (33), 188 (59), 176 (50), 162 (51), 144 (32), 128 (20), 120 (50). Found 261.1539, $C_{16}H_{23}N^{32}S$ requires 261.1551.

Method B

(*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidin-2-one (389) (1.05 g, 4.28 mmol) was dissolved in CH_2Cl_2 (50 mL) in an oven-dried flask. Phosphorus pentasulfide (476 mg, 1.07 mmols) and hexamethyldisiloxane (1.36 mL, 6.42 mmol) were

WitsETD

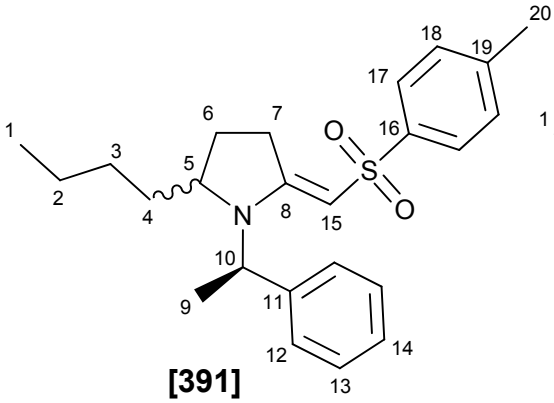
added and the heterogeneous mixture was stirred for 72 hours at ambient temperature under a nitrogen atmosphere. The reaction was quenched by the addition of saturated sodium bicarbonate solution (10 mL) and the product was extracted into CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried with sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography (10% - 20% EtOAc/hexane) gave **(*R*)-5-butyl-1-(1-phenylethyl)pyrrolidine-2-thione (390)** (1.12 g, 100% yield) as a mixture of diastereomers.

8.2.4 (*R,E*)-2-Butyl-1-(1-phenylethyl)-5-(tosylmethylene)pyrrolidine (391)

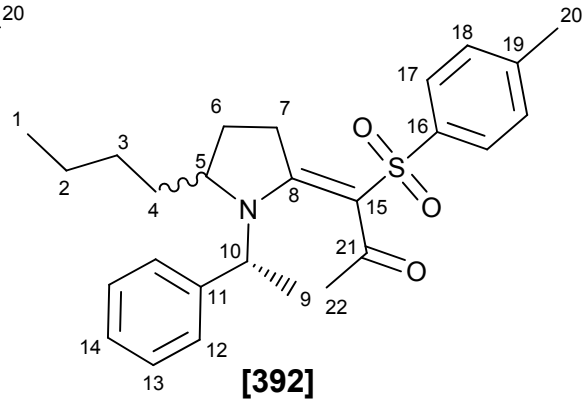
Method A

(*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidine-2-thione (390) (0.25 g, 0.96 mmol) was dissolved in freshly dried and distilled THF (5 mL) in oven-dried glassware under a nitrogen atmosphere. Methyl iodide (0.30 mL, 4.8 mmol) was added and the reaction was left stirring under nitrogen for 48 hours. The THF and excess methyl iodide were removed *in vacuo* to give a brown oil. Et_3N (0.26 mL, 1.9 mmol) and **1-[(4-methylphenyl)sulfonyl]acetone (279)** (224 mg, 1.06 mmol) were mixed together in CH_2Cl_2 (5 mL) 10 minutes prior to addition to the brown oil. This mixture was left stirring at ambient temperature under a nitrogen atmosphere for 96 hours before the solvent was removed *in vacuo* and the organic residue was partitioned in distilled H_2O (10 mL) and CH_2Cl_2 (10 mL). The crude product was extracted into CH_2Cl_2 (6 × 15 mL), dried with sodium sulfate, and the solvent removed *in vacuo*. The crude material was purified by column chromatography (30% EtOAc/hexane) to give the hydrolysis product, **(*R*)-5-butyl-1-(1-phenylethyl)pyrrolidin-2-one (389)** in 38% yield (90 mg, 0.36 mmol), and a mixture of **(*R,E*)-2-butyl-1-(1-phenylethyl)-5-(tosylmethylene) pyrrolidine (391)** and **(*E*)-1-(5-butyl-1-((*R*)-1-phenylethyl)pyrrolidin-2-ylidene)-1-tosylpropan-2-one (392)** in 10% combined yield (40 mg, 0.10 mmol)

WITSETD



[391]



[392]

ISOMER A **(391)**

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.64 (2H, d, *J* 8.1, H-17), 7.38-7.20 (5H, m, H-12, H-13, H-14), 7.22 (2H, d, *J* 8.1, H-18), 4.89 (1H, s, H-15), 4.72 (1H, q, *J* 7.1, H-10), 3.40-3.32 (1H, m, H-5), 2.89-2.78 (2H, m, H-7*AB*), 2.07-1.81 (2H, m, H-6*AB*), 1.61 (3H, d, *J* 7.1, H-9), 1.75-1.04 (6H, m, H-2, H-3, H-4), 0.82 (3H, t, *J* 7.1, H-1).

ISOMER B **(392)**

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 7.38-7.20 (7H, m, H-12, H-13, H-14, H-17), 7.22 (2H, d, *J* 8.1, H-18), 6.31 (1H, q, *J* 7.2, H-10), 3.51 (1H, tt, *J* 8.9, 2.8, H-5), 3.16-3.01 (2H, m, H-7*AB*), 2.40 (3H, s, H-22), 2.07-1.81 (2H, m, H-6*AB*), 1.70 (3H, d, *J* 7.2, H-9), 1.25 (3H, s, H-20), 1.75-1.04 (6H, m, H-2, H-3, H-4), 0.83 (3H, t, *J* 7.0, H-1).

ISOMER A and B **(391) = A; (392) = B**

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 201.4 (C-21B), 160.5 (C-8AB), 143.5, 141.6, 139.2, 138.4 (C-19AB, C-16AB), 129.9, 129.2 (C-17AB, C-18AB), 128.7, 128.5 (C-11AB), 128.0 (C-15B), 127.7, 127.6, 127.5, 127.0, 126.0 (C-12AB, C-13AB, C-14AB), 88.2 (C-15A), 64.4, 62.2, 55.6, 54.1 (C-5AB, C-10AB), 43.7, 34.0 (C-7AB), 33.6, 29.8, 29.7, 27.9, 27.4, 26.4, 25.8 (C-2AB, C-3AB, C-4AB, C-6AB), 22.5, 22.4 (C-20AB), 21.4, 16.4 (C-9AB), 13.9, 13.8 (C-1AB).

$\nu_{max.}$ / **cm^{-1}**: 2956 (m, C-H), 2929 (m, C-H), 2860 (m, C-H), 1683 (w), 1566 (s), 1454 (s), 1279 (s), 1132 (s), 1084 (s), 847 (w), 701 (m), 577 (m).

WISEID

8.2.5 Attempted debenzylation reactions

Method A

(*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidin-2-one (389) (0.20 g, 0.81 mmol) was dissolved in AcOH (10 mL) and set up in a hydrogenator with palladium hydroxide (40 mg, 0.2 eq.) under 5 atmospheres of hydrogen pressure. The reaction was left at ambient temperature for 4 days. The residual catalyst was removed by filtering the solution through Celite® and rinsing with acetone (50 mL). The solvent was removed *in vacuo* and the crude product was purified by column chromatography (40% EtOAc/hexane). Only starting material was isolated (170 mg, 85% recovery).

Method B

(*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidine-2-thione (390) (80 mg, 0.31 mmol) was dissolved in AcOH (5 mL) and set up in a hydrogenator with palladium hydroxide (8 mg, 0.1 eq.) under 7 atmospheres of hydrogen pressure. The reaction was left at ambient temperature for 3 days. The residual catalyst was removed by filtering the solution through Celite® and rinsing with CH_2Cl_2 (20 mL). The solvent was removed *in vacuo* and the crude product was purified by column chromatography (10% EtOAc/hexane). Only starting material was isolated (80 mg, 100% recovery).

Method C

(*R,E*)-5-Butylidene-1-(1-phenylethyl)pyrrolidin-2-one (388) (0.20 g, 0.82 mmol) was dissolved in methanol (11 mL). Ammonium formate (414 mg, 6.58 mmol) was added and the solution was stirred under a nitrogen atmosphere until the solution was homogenous. 10% Palladium on carbon (74 mg, 0.37 eq.) was carefully stirred into the mixture (the methanolic vapours readily ignited if the system was not properly flushed with nitrogen). The reaction was left at ambient temperature for 3 hours. The mixture was filtered through Celite® and rinsed with CH_2Cl_2 (2 × 20 mL) to remove the catalyst. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (10% EtOAc/hexane) to give starting material (130 mg, 65% recovery).

WitsETD

Method D

(*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidin-2-one (389) (0.10 g, 0.41 mmol) and ceric ammonium nitrate (894 mg, 1.60 mmol) were dissolved in MeCN/H_2O (1:5, 6 mL) and stirred at ambient temperature for 12 hours. The reaction mixture was filtered through cotton wool and the product extracted into CH_2Cl_2 (4 × 20 mL). The organic extracts were combined and rinsed with saturated sodium bicarbonate solution (20 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (20% EtOAc/hexane) to give back starting material (100 mg, 100% recovery).

Method E

(*R*)-5-Butyl-1-(1-phenylethyl)pyrrolidin-2-thione (390) (0.22 g, 0.84 mmol) and ceric ammonium nitrate (1.85 g, 3.37 mmol) were dissolved in MeCN/H_2O (1:5, 60 mL) and stirred at ambient temperature for 12 hours. The reaction was quenched with saturated sodium bicarbonate solution (20 mL) and filtered through cotton wool. The product was extracted into CH_2Cl_2 (4 × 20 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (20% EtOAc/hexane) to give **(*R*)-5-butyl-1-(1-phenylethyl)pyrrolidin-2-one (389)** (80 mg, 39% yield), and starting material (134 mg, 61% recovery).

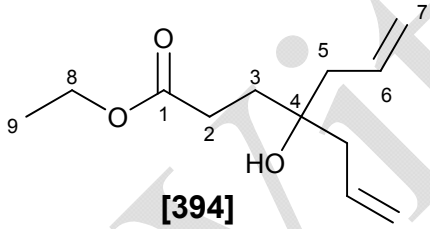
WISER

CHAPTER 9
EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 5

9.1 Preparation of allylic ketoesters

9.1.1 Ethyl 4-allyl-4-hydroxyhept-6-enoate (394)

Iron(III) acetoacetate (0.13 g, 0.36 mmol) was dissolved in dry THF (10 mL) in an oven-dried RBF. Ethyl 4-chloro-4-oxobutyrate (0.92 mL, 6.1 mmol) was added and the mixture was cooled to -10°C. After 10 minutes, allylmagnesium bromide (1.0 *M*, 6.7 mL) was quickly added and the reaction mixture was stirred for an additional 7 minutes. The reaction was quenched with HCl (1.0 *M*, 10 mL) and extracted into EtOAc (3 × 40 mL). The combined organic fractions were rinsed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL) and dried with sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (30% - 40% EtOAc/hexane) to give **ethyl 4-allyl-4-hydroxyhept-6-enoate (394)** (510 mg, 72% yield).



[394]

R_f 0.51 (40% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 5.84 (2H, m, H-6), 5.18-5.07 (4H, m, H-7), 4.16 (2H, q, *J* 7.2, H-8), 2.64 (4H, m, H-3, H-4), 2.24 (4H, d, *J* 7.4, H-5), 1.56 (1H, s, O*H*),1.26 (3H, t, *J* 7.2, H-9).

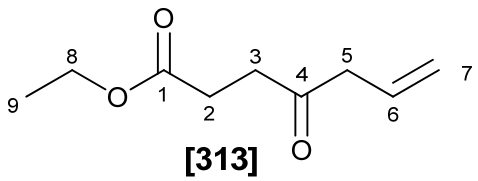
^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 172.1 (C-1), 133.5 (C-6), 118.6 (C-7), 73.7 (C-4), 60.7 (C-8), 43.5 (C-5), 32.1 (C-3), 28.8 (C-2), 14.0 (C-9).

WitsETD

$v_{max.}$ / **cm^{-1}**: 3090 (w, O-H), 2980 (w, C-H), 2934 (w, C-H), 1716 (s, C=O), 1638 (w), 1417 (m), 1375 (m), 1163 (s), 1021 (m), 997 (m), 915 (s).
m/z: 211 (48%, M-1), 191 (31), 183 (25), 173 (8), 155 (16), 147 (7), 129 (100), 121 (10), 107 (72).

9.1.2 Ethyl 4-oxohept-6-enoate (313)

Ethyl 4-chloro-4-oxobutyrate (0.50 mL, 2.8 mmol), allyl tri-*n*-butyl tin (0.95 mL, 3.1 mmol) and Wilkinson's catalyst (26 mg, 0.03 mmol) were dissolved in CH_2Cl_2 (3 mL) in a sealed tube and heated to 65°C for 5 hours. The CH_2Cl_2 was removed *in vacuo* and the crude material was purified by column chromatography (5% EtOAc/hexane) to give **ethyl 4-oxohept-6-enoate (313)** in quantitative yield, slightly contaminated by tri-*n*-butyl tin chloride.



[313]

R_f 0.10 (5% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 5.98-5.88 (1H, m, H-6), 5.20-5.12 (2H, m, H-7), 4.12 (2H, q, *J* 7.2, H-8), 3.22 (2H, d, *J* 6.9, H-5), 2.76 (2H, t, *J* 6.3, H-3), 2.58 (2H, t, *J* 6.3, H-2), 0.92 (3H, t, *J* 7.2, H-9).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 206.4 (C-4), 172.4 (C-1), 130.2 (C-6), 118.7 (C-7), 60.4 (C-8), 47.4 (C-5), 36.7 (C-3), 27.8 (C-2), 13.8 (C-9).

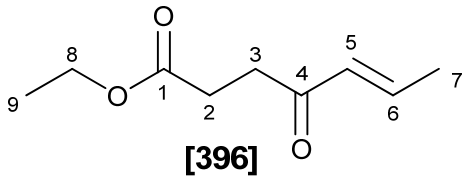
m/z: 171 (4%, M+1), 161 (7), 142 (5), 129 (15), 125 (100), 124 (100), 119 (3), 105 (4).

9.1.3 Ethyl (5*E*)-4-oxohept-5-enoate (396)

Ethyl 4-chloro-oxobutyrate (0.50 mL, 2.8 mmol), allyl tri-*n*-butyl tin (0.95 mL, 3.1 mmol) and Wilkinson's catalyst (26 mg, 0.03 mmol) were dissolved in CH_2Cl_2 (3 mL) in a sealed tube and heated to 65°C for 5 hours. The reaction

WitsETD

mixture was left stirring at ambient temperature for 12 hours. The CH_2Cl_2 was removed *in vacuo* and rinsed with MeCN/hexane to remove the residual tin. The MeCN fraction was rinsed with hexane (2 × 15 mL) and the solvent was removed *in vacuo.* The crude material was purified by column chromatography (5% EtOAc/hexane) to give **ethyl (5*E*)-4-oxohept-5-enoate (396)** (310 mg, 65% yield) as a mixture of geometric isomers (*cis*:*trans* ratio 1:2).



[396]

R_f 0.10 (5% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 6.90 (1H, dq, *J* 15.9, 6.6, H-6), 6.16 (1H, d, *J* 15.9, H-5), 4.13 (2H, q, *J* 7.2, H-8), 2.87 (2H, t, *J* 6.6, H-3), 2.62 (2H, t, *J* 6.6, H-2), 1.91 (2H, d, *J* 6.6, H-7*trans*), 1.54 (1H, d, *J* 6.6, H-7*cis*), 1.25 (3H, t, *J* 7.2, H-9).

trans

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 197.9 (C-4), 172.7 (C-1), 142.8 (C-5), 131.5 (C-6), 60.4 (C-8), 34.2 (C-3), 27.9 (C-2), 18.1 (C-7), 14.0 (C-9).

cis

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 205.2 (C-4), 172.3 (C-1), 142.8 (C-5), 131.5 (C-6), 60.5 (C-8), 37.7 (C-3), 27.7 (C-2), 17.4 (C-7), 14.0 (C-9).

$\nu_{max.}$ / **cm^{-1}**: 2982 (w, C-H), 2932 (w, C-H), 1732 (s, C=O), 1699 (m, C=O), 1674 (m), 1635 (m), 1417 (m), 1208 (s), 1163 (s), 1096 (m), 1023 (m), 972 (m).

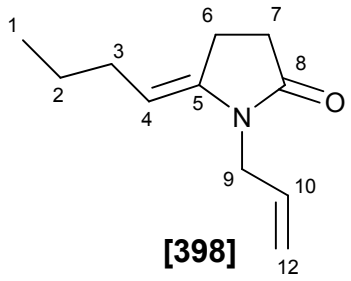
m/z: 171 (10%, M+1), 161 (19), 129 (43), 125 (76), 124 (59), 119 (18), 107 (5), 105 (15), 101 (100). Found 171.10207, $C_9H_{16}O_3$ (M+1) requires 171.10157.

WitsETD

9.2 Attempted condensation reactions

9.2.1 (5*E*)-1-Allyl-5-butylidenepyrrolidin-2-one (398)

Ethyl 4-oxooctanoate (292) (1.04 g, 5.60 mmol), allylamine (0.21 mL, 2.8 mmol) and glacial AcOH (0.84 mL, 14.0 mmol) were dissolved in toluene (10 mL) and heated at reflux for 72 hours using a modified Dean-Stark apparatus. The solution was cooled, the solvent removed *in vacuo* and the residue purified by column chromatography (10% EtOAC/hexane) to give **(5*E*)-1-allyl-5-butylidenepyrrolidin-2-one (398)** (277 mg, 55% yield) as a yellow oil. The *trans* geometry was verified by selective NOE experiments.



[398]

R_f 0.17 (10% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 5.78-5.65 (1H, m, H-10), 5.17-5.12 (2H, m, H-11), 4.66 (1H, t, *J* 7.2, H-4), 4.09 (2H, d, *J* 5.1, H-9), 2.74-2.44 (4H, m, H-6, H-7), 1.98 (2H, q, *J* 7.2, H-3), 1.39 (2H, sestet, *J* 7.2, H-2), 0.90 (3H, t, *J* 7.2, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 175.1 (C-8), 138.7 (C-5), 131.8 (C-10), 116.7 (C-11), 101.3 (C-4),42.1 (C-9), 28.7 (C-7), 28.6 (C-3), 23.1 (C-2), 21.2 (C-6), 13.5 (C-1).

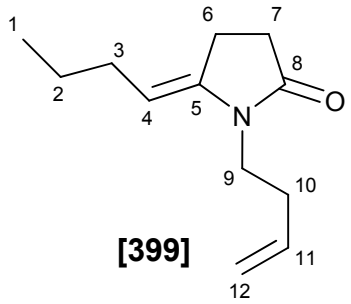
$\nu_{max.}$ / **cm^{-1}**: 2958 (m, C-H), 2930 (m, C-H), 2872 (m, C-H), 1664 (s, C=O), 1412 (s), 1339 (s), 1229 (m), 1177 (m), 1124 (m), 1077 (m), 991 (w), 955 (w), 921 (m), 654 (m).

WitsETD

m/z: 179 (7%, M), 164 (3), 151 (10), 150 (100), 148 (8), 137 (55), 136 (11), 122 (29), 108 (10). Found 179.1325, $C_{11}H_{17}ON$ requires 179.1310.

9.2.2 (5*E*)-1-But-3-enyl-5-butylidenepyrrolidin-2-one (399)

Ethyl 4-oxooctanoate (292) (342 mg, 1.80 mmol), butenylamine hydrochloride (0.10 g, 0.92 mmol) and glacial AcOH (0.28 mL, 4.6 mmol) were dissolved in toluene (5 mL) and heated at reflux for 72 hours using a modified Dean-Stark apparatus. The solution was cooled, the solvent removed *in vacuo* and the residue purified by column chromatography (10% EtOAC/hexane) to give **(5*E*)-1-but-3-enyl-5-butylidenepyrrolidin-2-one (399)** (80 mg, 45% yield) as a yellow oil. The *trans* geometry was verified by selective NOE experiments.



[399]

R_f 0.14 (10% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 5.85-5.71 (1H, m, H-11), 5.10-5.02 (2H, m, H-12), 4.65 (1H, t, *J* 7.2, H-4), 3.53 (2H, t, *J* 7.2, H-9), 2.60 (2H, t, *J* 7.2, H-6) 2.50-2.44 (2H, m, H-7), 2.33-2.26 (2H, m, H-10), 2.00 (2H, q, *J* 7.2, H-3), 1.42 (2H, sestet, *J* 7.2, H-2), 0.92 (3H, t, *J* 7.2, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 175.4 (C-8), 139.0 (C-5), 134.9 (C-11), 116.8 (C-12), 100.6 (C-4), 39.0 (C-9), 30.8 (C-10), 28.9 (C-7), 28.7 (C-3), 23.3 (C-2), 21.3 (C-6), 13.7 (C-1).

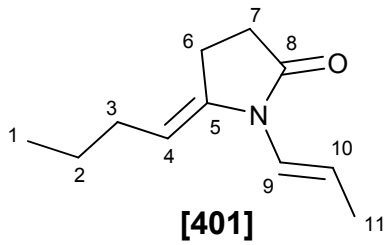
$\nu_{max.}$ / **cm^{-1}**: 2958 (m, C-H), 2872 (m, C-H), 1662 (s, C=O), 1414 (m), 1363 (m), 1262 (w), 1178 (m), 1126 (m), 1077 (m), 961 (w), 916 (m).

WitsETD

9.3 Ring-closing metathesis reactions

9.3.1 (*E*)-5-Butylidene1-(prop-1-enyl)pyrrolidin-2-one (401)[242, 176]

(5*E*)-1-Allyl-5-butylidenepyrrolidin-2-one (389) (200 mg, 1.12 mmol) and Grubbs second generation catalyst (47 mg, 0.06 mmol) were dissolved in toluene (7 mL) and heated at reflux for 12 hours. The solution was cooled and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to give **(*E*)-5-butylidene1-(prop-1-enyl)pyrrolidin-2-one (401)** (40 mg, 11% yield) as a by-product.



[401]

R_f 0.14 (10% EtOAc/hexane)

^{1}H (300 MHz, $CDCl_3$) δ_H /**ppm** 6.09-5.96 (2H, m, H-9, H-10), 4.91-4.85 (1H, td, *J* 7.2, 2.1, H-4), 2.66-2.60 (2H, m, H-7), 2.55-2.50 (2H, m, H-6), 1.98 (2H, q, *J* 7.2, H-3), 1.81 (3H, d, *J* 5.4, H-11), 1.35-1.29 (2H, m, H-2), 0.90 (3H, t, *J* 7.2, H-1).

^{13}C (75 MHz, $CDCl_3$) δ_C /**ppm** 174.8 (C-8), 139.2 (C-5), 122.4 (C-9), 121.3 (C-4), 102.7 (C-10), 29.4 (C-7), 28.8 (C-3), 23.1 (C-2), 21.3 (C-6), 15.9 (C-1), 13.7 (C-11).

$\nu_{max.}$ / **cm^{-1}**: 2960 (m, C-H), 2874 (m, C-H), 1699 (s, C=O), 1541 (m), 1457 (m), 1375 (m), 1188 (m), 1079 (s), 668 (w).

m/z: 179 (28%, M), 166 (18), 150 (85), 148 (20), 139 (24), 124 (32), 122 (19), 110 (100), 108 (28). $C_{11}H_{17}ON$ requires 179.1310.

WISETD

9.3.2 Attempted RCM: (5*E*)-1-But-3-enyl-5-butylidenepyrrolidin-2-one (399)[242]

Method A

(5*E*)-1-But-3-enyl-5-butylidenepyrrolidin-2-one (399) (20 mg, 0.10 mmol) and Grubbs second generation catalyst (6 mg, 0.005 mmol) were dissolved in toluene (3 mL) and stirred at ambient temperature for 5 days. The solvent was removed *in vacuo* and the crude material was purified by column chromatography to give back unreacted starting material (15 mg, 75% recovery).

Method B

(5*E*)-1-But-3-enyl-5-butylidenepyrrolidin-2-one (399) (210 mg, 1.08 mmol) and Grubbs second generation catalyst (46 mg, 0.05 mmol) were dissolved in toluene (10 mL) and heated at reflux for 12 hours. The solvent was removed *in vacuo* and the crude material was purified by column chromatography. ^{1}H-NMR spectra indicated decomposition of the starting material and none of the desired product.

WitsETD

REFERENCES

(1) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, 2004.

(2) Solomons, G.; Fryhle, C. *Organic Chemistry, 7th ed.*; John Wiley & Sons, Inc., 2000.

(3) Pelletier, S. W. In *Alkaloids: Chemistry and Biological Perspectives* 1983; Vol. 1, p 1.

(4) Moss, G.; Smith, P.; Tavernier, D. *Pure Appl. Chem.* **1995**, *67*, 1307 - 1375.

(5) Meyers, A. I.; Singh, S. *Tetrahedron Lett.* **1967**, *8*, 5319.

(6) Howard, A. S.; Michael, J. P. *The Alkaloids* **1986**, *28*, 183 - 308.

(7) Michael, J. P. *The Alkaloids* **2001**, *55*, 91 - 258.

(8) Daly, J. W.; Garraffo, H. M.; Spande, T. F. *The Alkaloids* **1993**, *43*, 185 - 287.

(9) Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 579 - 602.

(10) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520 - 542.

(11) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 719 - 741.

(12) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458 - 475.

(13) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625 - 649.

(14) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603 - 626.

(15) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191 - 222.

(16) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139 - 165.

(17) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556 - 1575.

(18) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, p 193; and references therein.

(19) Takahata, H.; Momose, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic press, Inc.: San Diego, 1993; Vol. 44, p 189; and references therein.

(20) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162 - 172.

(21) Garraffo, H. M.; Spande, T. F.; Daly, J. W.; Baldessari, A.; Gros, E. G. *J. Nat. Prod.* **1993**, *56*, 357 - 373.

WITSETD

(22) Daly, J. W.; Garraffo, H. M.; Jain, P.; Spande, T. F.; Snelling, R. R.; Jaramillo, C.; Rand, A. S. *J. Chem. Ecol.* **2000**, *26*, 73 - 85.

(23) Jones, T. H.; Torres, J. A.; Spande, T. F.; Garraffo, H. M.; Blum, M. S.; Snelling, R. R. *J. Chem. Ecol.* **1996**, *22*, 1221 - 1236.

(24) Saporito, R. A.; Garraffo, H. M.; Donnelly, M. A.; Edwards, A. L.; Longino, J. T.; Daly, J. W. *Proc. Natl. Acad. Sci., U S A* **2004**, *101*, 8045 - 8050.

(25) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F. *J. Nat. Prod.* **1993**, *56*, 1016 - 1038.

(26) Daly, J. W.; Spande, T. F.; Whittaker, N.; Highet, R. J.; Feigl, D.; Nishimori, N.; Tokuyama, T.; Myers, C. W. *J. Nat. Prod.* **1986**, *49*, 265 - 280.

(27) Gorman, J. S. T.; Jones, T. H.; Spande, T. F.; Snelling, R. R.; Torres, J. A.; Garraffo, H. M. *J. Chem. Ecol.* **1998**, *24*, 933 - 943.

(28) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227 - 1240.

(29) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949 - 1958.

(30) Ritter, F. J.; Rotgans, I. E. M.; Talman, E.; Verwiel, P. E. J.; Stein, F. *Experientia* **1973**, *29*, 530 - 531.

(31) Yillah, I. Ph.D. Thesis, University of the Witwatersrand, 2002.

(32) Takahata, H.; Kubota, M.; Ihara, K.; Okamoto, N.; Momose, T.; Azer, N.; Eldefrawi, A. T.; Eldefrawi, M. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3289 - 3301.

(33) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688 - 4693.

(34) Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 465 - 467.

(35) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, *46*, 2101 - 2103.

(36) Wu, H.; Yu, M.; Zhang, Y.; Zhao, G. *Chin. J. Chem.* **2009**, *27*, 183 - 188.

(37) Cuny, G. D.; Buchwald, S. L. *Synlett* **1995**, 519 - 522.

(38) Bubnov, Y. N.; Klimkina, E. V.; Ignatenko, A. V. *Russ. Chem. Bull. (Engl. Transl.)* **1998**, *47*, 941.

WISEED

(39) Chênevert, R.; Ziarani, G. M.; Morin, M. P.; Dosser, M. *Tetrahedron: Asymmetry* **1999**, *10*, 3117 - 3122.
(40) Takahata, H.; Ichinose, M. *Heterocycles* **2006**, *67*, 407 - 411.
(41) Carbonnel, S.; Troin, Y. *Heterocycles* **2002**, *57*, 1807 - 1830.
(42) Åhman, J.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747 - 9756.
(43) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119 - 3122.
(44) Reddy, P. G.; Baskaran, S. *J. Org. Chem.* **2004**, *69*, 3093 - 3101.
(45) Kim, G.; Lee, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2073 - 2076.
(46) Comins, D. L.; Zhang, Y. *J. Am. Chem. Soc.* **1996**, *118*, 12248 - 12249.
(47) Comins, D. L.; Joseph, S. P.; Hong, H.; Al-awar, R. S.; Foti, C. J.; Zhang, Y.; Chen, X.; LaMunyon, D. H.; Guerra-Weltzien, M. *Pure Appl. Chem.* **1997**, *69*, 477 - 481.
(48) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398 - 404.
(49) Pohmakotr, M.; Prateeptongkum, S.; Chooprayoon, S.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2008**, *64*, 2339 - 2347.
(50) Kim, G.; Jung, S.; Kim, W. *Org. Lett.* **2001**, *3*, 2985 - 2987.
(51) Kim, G.; Shim, J. H.; Kim, J. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 1832 - 1834.
(52) Gebauer, J.; Dewi, P.; Blechert, S. *Tetrahedron Lett.* **2005**, *46*, 43 - 46.
(53) Yu, R. T.; Lee, E. E.; Malik, G.; Rovis, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 2379 - 2382.
(54) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Wen-Keu, F.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183 - 10194.
(55) Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett.* **1996**, *37*, 1445 - 1446.
(56) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543 - 4552.
(57) Reddy, P. G.; Varghese, B.; Baskaran, S. *Org. Lett.* **2003**, *5*, 583 - 585.
(58) Ritter, F. J.; Brüggemann-Rotgans, I. E. M.; Verkuil, E.; Persoons, C. J. In *Proc. Symp.*; Noirot, C., Howse, P. E., Masne, G. L., Eds.; French Section of the I. U. S. S. I: Univ. Dijon, 1975, p 66 - 103.

WISETD

(59) Ritter, F. J.; Persoons, C. J. *Netherlands J. Zoo.* **1975**, *25*, 261 - 275.

(60) *"The Ants"*; Hölldobler, B.; Wilson, E. O., Eds.; The Belknap Press of Harvard University Press Cambridge: Massachusetts, 1990.

(61) Jones, T. H.; Highet, R. J.; Blum, M. S.; Fales, H. M. *J. Chem. Ecol.* **1984**, *10*, 1233 - 1247.

(62) Ritter, F. J.; Brüggemann-Rotgans, I. E. M.; Verwiel, P. E. J.; Persoons, C. J.; Talman, E. *Tetrahedron Lett.* **1977**, *30*, 2617 - 2618.

(63) Koyama, T.; Matsubara, M.; Ogura, K.; Brüggemann, M.; Vrielink, A. *Nat. Wis.* **1983**, *70*, 469 - 470.

(64) Oliver, J. E.; Sonnet, P. E. *J. Org. Chem.* **1974**, *39*, 2662 - 2663.

(65) Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1988**, *29*, 5767 - 5768.

(66) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396 - 1408.

(67) Berry, M. B.; Craig, D.; Jones, P. S.; Rowlands, G. J. *Chem. Commun.* **1997**, 2141 - 2142.

(68) Momose, T.; Toshima, M.; Seki, S.; Koike, Y.; Toyooka, N.; Hirai, Y. *J. Chem. Soc., Perkin Trans. I* **1997**, 1315 - 1321.

(69) Momose, T.; Toshima, M.; Toyooka, N.; Hirai, Y.; Eugster, C. H. *J. Chem. Soc., Perkin Trans. I* **1997**, 1307 - 1313.

(70) Riesinger, S. W.; Löfstedt, J.; Pettersson-Fasth, H.; Bäckvall, J. *Eur. J. Org. Chem.* **1999**, 3277 - 3280.

(71) Lesma, G.; Colombo, A.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 590 - 596.

(72) Momose, T.; Toyooka, N.; Seki, S.; Hirai, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2072 - 2074.

(73) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399 - 5400.

(74) Paderes, M. C.; Chemler, S. R. *Org. Lett.* **2009**, *11*, 1915 - 1918.

(75) Conchon, E.; Gelas-Mialhe, Y.; Remuson, R. *Tetrahedron: Asymmetry* **2006**, *17*, 1253 - 1257.

WISETD

(76) Fleurant, A.; Saliou, C.; Celerier, J. P.; Platzer, N.; Moc, T. V.; Lhommet, G. *J. Heterocycl. Chem.* **1995**, *32*, 255 - 258.

(77) Zhang, S.; Xu, L.; Miao, L.; Shu, H.; Trudell, M. L. *J. Org. Chem.* **2007**, *72*, 3133 - 3136.

(78) Vavrecka, M.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 438 - 444.

(79) McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323 - 1324.

(80) MacDonald, T. L. *J. Org. Chem.* **1980**, *45*, 193 - 194.

(81) Shawe, T. T.; Shiels, C. J.; Gray, S. M.; Conard, J. L. *J. Org. Chem.* **1994**, *57*, 1323 - 1324.

(82) Yuguchi, M.; Tokuda, M.; Orito, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1031 - 1032.

(83) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 102 - 103.

(84) Takahata, H.; Bandoh, H.; Momose, T. *Tetrahedron* **1993**, *49*, 11205 - 11212.

(85) Ito, M.; Kibayashi, C. *Tetrahedron Lett.* **1990**, *31*, 5065 - 5068.

(86) Ito, M.; Kibayashi, C. *Tetrahedron* **1991**, *47*, 9329 - 9350.

(87) Solladié, G.; Chu, G.-H. *Tetrahedron Lett.* **1996**, *37*, 111 - 114.

(88) Angle, S. R.; Breitenbucher, J. G. *Tetrahedron Lett.* **1993**, *34*, 3985 - 3988.

(89) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1313 - 1328.

(90) Muraoka, O.; Zheng, B.-Z.; Okumura, K.; Tabata, E.; Tanabe, G.; Kubo, M. *J. Chem. Soc., Perkin Trans. I* **1997**, 113 - 119.

(91) Pattenden, L. C.; Adams, H.; Smith, S. A.; Harrity, J. P. A. *Tetrahedron* **2008**, *64*, 2951 - 2961.

(92) Bates, R. W.; Song, P. *Synthesis* **2009**, *4*, 655 - 659.

(93) Royer, J.; Husson, H.-P. *J. Org. Chem.* **1985**, *50*, 670 - 673.

(94) Yamaguchi, R.; Hata, E.; Matsuki, T.; Kawanisi, M. *J. Org. Chem.* **1987**, *52*, 2094 - 2096.

(95) Nagasaka, T.; Kato, H.; Hayashi, H.; Shioda, M.; Hikasa, H.; Hamaguchi, F. *Heterocycles* **1990**, *30*, 561 - 566.

WISETD

(96) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088 - 4097.

(97) Somfai, P.; Jarevang, T.; Lindström, U. M.; Svensson, A. *Acta Chem. Scand.* **1997**, *51*, 1024 - 1029.

(98) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074 - 2075.

(99) Kuhakarn, C.; Seehasombat, P.; Jaipetch, T.; Pohmakotr, M.; Reutrakul, V. *Tetrahedron* **2008**, *64*, 1663 - 1670.

(100) Sonnet, P. E.; Oliver, J. E. *J. Heterocycl. Chem.* **1975**, *12*, 289 - 294.

(101) Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *42*, 5513 - 5514.

(102) Jefford, C. W.; Sienkiewicz, K.; Thornton, S. R. *Tetrahedron Lett.* **1994**, *35*, 4759 - 4762.

(103) Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456 - 2466.

(104) Jefford, C. W. *Pure Appl. Chem.* **1996**, *68*, 799 - 804.

(105) Jefford, C. W.; Tang, Q.; Zaslona, A. *Helv. Chim. Acta* **1989**, *72*, 1749 - 1752.

(106) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513 - 3518.

(107) Amos, R. I. J.; Gourlay, B. S.; Molesworth, P. P.; Smith, J. A.; Sprod, O. R. *Tetrahedron* **2005**, *61*, 8226 - 8230.

(108) Higashiyama, K.; Nakahata, K.; Takahashi, H. *J. Chem. Soc., Perkin Trans I.* **1994**, 351 - 353.

(109) Kim, G.; Jung, S.; Lee, E.; Kim, N. *J. Org. Chem.* **2003**, *68*, 5395 - 5398.

(110) Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879 - 8882.

(111) Zeller, E.; Grierson, D. S. *Synlett* **1991**, 878 - 880.

(112) Castano, A. M.; Cuerva, J. M.; Echavarren, A. M. *Tetrahedron Lett.* **1994**, *35*, 7435 - 7438.

(113) Mori, M.; Hori, M.; Sato, Y. *J. Org. Chem.* **1998**, *63*, 4832 - 4833.

(114) Lee, E.; Kang, T. S.; Chung, C. K. *Bull. Korean Chem. Soc.* **1996**, *17*, 212 - 214.

WitsETD

(115) Bloch, R.; Brillet-Fernandez, C.; Kühn, P.; Mandville, G. *Heterocycles* **1994**, *38*, 1589 - 1594.

(116) Takahata, H.; Bandoh, H.; Momose, T. *Heterocycles* **1993**, *36*, 2777 - 2782.

(117) Céliméne, C.; Dhimane, H.; LeBail, M.; Lhommet, G. *Tetrahedron Lett.* **1994**, *35*, 6105 - 6106.

(118) Céliméne, C.; Dhimane, H.; Lhommet, G. *Tetrahedron* **1998**, *54*, 10457 - 10468.

(119) Céliméne, C.; Dhimane, H.; Saboureau, A.; Lhommet, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1585 - 1588.

(120) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178 - 5189.

(121) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. J. *J. Org. Chem.* **1981**, *46*, 3936 - 3938.

(122) Smith III, A. B.; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547 - 2557.

(123) Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 3808 - 3810.

(124) Hosken, G. D. M.Sc. Dissertation, University of the Witwatersrand, 1988.

(125) Jungmann, C. M. M.Sc. Dissertation, University of the Witwatersrand, 1992.

(126) Wilson, C. M. M.Sc. Dissertation, University of the Witwatersrand, 1993.

(127) Brankin, G. T. M.Sc. Dissertation, University of the Witwatersrand, 1993.

(128) Cheesman, P. S. M.Sc. Dissertation, University of the Witwatersrand, 1996.

(129) Malefetse, T. J. M.Sc. Dissertation, University of the Witwatersrand, 1996.

(130) Pelly, S. C. M.Sc. Dissertation, University of the Witwatersrand, 1997.

(131) Nattrass, G. L. M.Sc. Dissertation, University of the Witwatersrand, 1997.

WISETD

(132) Mthembu, S. T. M.Sc. Dissertation, University of the Witwatersrand, 2008.
(133) Michael, J. P. Ph.D. Thesis, University of the Witwatersrand, 1975.
(134) Orlek, B. S. Ph.D. Thesis, University of the Witwatersrand, 1976.
(135) Meerholz, C. A. Ph.D. Thesis, University of the Witwatersrand, 1977.
(136) Katz, R. B. Ph.D. Thesis, University of the Witwatersrand, 1983.
(137) Zwane, M. I. Ph.D. Thesis, University of the Witwatersrand, 1991.
(138) Chang, S. S.-F. Ph.D. Thesis, University of the Witwatersrand, 1991.
(139) Gravestock, D. Ph.D. Thesis, University of the Witwatersrand, 1996.
(140) Stanbury, T. V. Ph.D. Thesis, University of the Witwatersrand, 1999.
(141) van der Westhuyzen, C. W. Ph.D. Thesis, University of the Witwatersrand, 2001.
(142) Fat, C. S. Ph.D. Thesis, University of the Witwatersrand, 2002.
(143) Petersen, R. L. Ph.D. Thesis, University of the Witwatersrand, 2004.
(144) Krause, R. W. M. Ph.D. Thesis, University of the Witwatersrand, 2005.
(145) Pienaar, D. P. Ph.D. Thesis, University of the Witwatersrand, 2005.
(146) Parsons, A. S. Ph.D. Thesis, University of the Witwatersrand, 1992.
(147) Morgans, G. L. Ph.D. Thesis, University of the Witwatersrand, 2008.
(148) Riley, D. R. Ph.D. Thesis, University of the Witwatersrand, 2008.
(149) Michael, J. P.; de Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979 - 988.
(150) Lukeš, R. *Coll. Czech. Chem. Comm.* **1932**, *4*, 81.

WitsETD

(151) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710 - 734.

(152) Neto, B. A. D.; Lapis, A. A. M.; Bernd, A. B.; Russowsky, D. *Tetrahedron* **2009**, 2484 - 2496.

(153) Hart, D. J.; Hong, W.-P.; Hsu, L.-Y. *J. Org. Chem.* **1987**, *52*, 4665 - 4673.

(154) Oishi, T.; Nagai, M.; Onuma, T.; Moriyama, H.; Tsutae, K.; Ochiai, M.; Ban, Y. *Chem. Pharm. Bull.* **1969**, *17*, 2306 - 2313.

(155) Howard, A. S.; Gerrans, G. C.; Michael, J. P. *J. Org. Chem.* **1980**, *45*, 1713 - 1715.

(156) Michael, J. P.; Gravestock, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1919 - 1928.

(157) Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393 - 1405.

(158) Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; Mortimer, A. J. P.; Russel, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1793 - 1811.

(159) Michael, J. P.; Gravestock, D. *Synlett* **1996**, 981 - 982.

(160) Michael, J. P.; de Koning, C. B.; Petersen, R. L.; Stanbury, T. V. *Tetrahedron Lett.* **2001**, *42*, 7513 - 7516.

(161) Michael, J. P.; de Koning, C. B.; Mudzunga, T. T.; Petersen, R. L. *Synlett* **2006**, *19*, 3284 - 3288.

(162) Michael, J. P.; de Koning, C. B.; Stanbury, T. V. *Tetrahedron Lett.* **1996**, *37*, 9403 - 9406.

(163) Zhu, W.; Dong, D.; Pu, X.; Ma, D. *Org. Lett.* **2005**, *7*, 705 - 708.

(164) Cai, G.; Zhu, W.; Ma, D. *Tetrahedron* **2006**, *62*, 5697 - 5708.

(165) Ma, S.; Xu, B.; Zhao, S. *Synthesis* **2000**, 139 - 143.

(166) Kozerski, L.; Kwiecien, B.; Krajewski, P.; Kawecki, R.; Bednarek, E.; Sitkowski, J.; Bocian, W.; Kozminski, W.; Hansen, P. E. *New J. Chem.* **2002**, *26*, 1060 - 1069.

(167) Arias, L. A.; Arbelo, D.; Alzerreca, A.; Prieto, J. A. *J. Heterocycl. Chem.* **2001**, *38*, 29 - 33.

(168) Brillon, D.; Sauve, G. *J. Org. Chem.* **1990**, *55*, 2246 - 2249.

WISEED

(169) Back, T. G.; Parvez, M.; Wulff, J. E. *J. Org. Chem.* **2003**, *68*, 2223 - 2233.

(170) Back, T. G.; Wulff, J. E. *Chem. Commun.* **2002**, *16*, 1710 - 1711.

(171) Back, T. G.; Hamilton, M. D. *Org. Lett.* **2002**, *4*, 1779 - 1781.

(172) Back, T. G.; Nakajima, K. *Tetrahedron Lett.* **1997**, *38*, 989 - 992.

(173) Michael, J. P.; de Koning, C. B.; Malefetse, T. J.; Yillah, I. *Org. Biomol. Chem.* **2004**, *2*, 3510 - 3517.

(174) Bordwell, F. G.; Brannen, W. T. *J. Am. Chem. Soc.* **1964**, *86*, 4645 - 4650.

(175) Gerrans, G. C.; Howard, A. S.; Orlek, B. S. *Tetrahedron Lett.* **1975**, *16*, 4171 - 4172.

(176) Tarling, C. A.; Holmes, A. B.; Markwell, R. E.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. I* **1999**, 1695 - 1701.

(177) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165 - 176.

(178) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999 - 2008.

(179) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657 - 9672.

(180) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192 - 10213.

(181) Davies, S. G.; Mujtaba, N.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1959 - 1962.

(182) Bull, S. D.; Davies, S. G.; Fox, D. J.; Gianotti, M.; Kelly, P. M.; Pierres, C.; Savory, E. D.; Smith, A. D. *J. Chem. Soc., Perkin Trans. I* **2002**, 1858 - 1868.

(183) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *Chem. Commun.* **2000**, 337 - 338.

(184) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *J. Chem. Soc., Perkin Trans. I* **2000**, 3765 - 3774.

(185) Brackenridge, I.; Davies, S. G.; Fenwick, D. R.; Ichihara, O.; Polywka, M. E. C. *Tetrahedron* **1999**, *55*, 533 - 540.

(186) Zipp, C. F.; Fernandes, M. A.; Michael, J. P.; Winks, S. *Acta Cryst.* **2009**, *C65*, 553 - 554.

WITS ETD

(187) Zipp, C. F. Honours Project, University of the Witwatersrand, 2008.
(188) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461 - 6473.
(189) Brillon, D. *Synth. Commun.* **1990**, *20*, 3085 - 3095.
(190) Makosza, M.; Golinski, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488 - 1490.
(191) Appel, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801 - 811.
(192) Stacy, G. W.; Khan, M. S.; Moe, H.; Bresson, C. R.; Razniak, S. L. *Cortical Steroid Analogs. V* **1966**, *31*, 1757 - 1761.
(193) Brogan, J. B.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 6444 - 6446.
(194) Anderson, G. W.; Halverstadt, I. F.; Miller, W. H.; Roblin, R. O. *Studies in Chemotherapy X.* **1945**, *67*, 2197 - 2200.
(195) Stetter, H.; Basse, W.; Nienhaus, J. *Chem. Ber.* **1980**, *113*, 690 - 698.
(196) Stetter, H.; Kuhlmann, H.; Haese, W. *Organic Syntheses* **1993**, *Coll. 8*, 620 - 625.
(197) Stetter, H.; Marten, K. *Liebigs Ann. Chem.* **1982**, 240 - 249.
(198) Cardellicchio, C.; Fiandanese, V.; Machese, G.; Ronzini, L. *Tetrahedron Lett.* **1987**, *28*, 2035 - 2056.
(199) Benincori, T.; Rizzo, S.; Pilati, T.; Ponti, A.; Sada, M.; Pagliarini, E.; Ratti, S.; Guiseppe, C.; Ferra, L.; Sannicolo, F. *Tetrahedron: Asymmetry* **2004**, *15*, 2289 - 2298.
(200) Wang, X.; Sun, X.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 305 - 307.
(201) Wang, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3141 - 3144.
(202) Wang, X.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 5593 - 5595.
(203) Maeda, H.; Hino, N.; Yamauchi, Y.; Ohmori, H. *Chem. Pharm. Bull.* **2000**, *48*, 1196 - 1199.
(204) Maeda, H.; Okamoto, J.; Ohmori, H. *Tetrahedron Lett.* **1996**, *37*, 5381 - 5384.

WITSETD

(205) Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*; 5th ed.; Longman Scientific and Technical: New York, 1989.

(206) Keränen, M. D.; Kot, K.; Hollmann, C.; Eilbracht, P. *Org. Biomol. Chem.* **2004**, *2*, 3379 - 3384.

(207) Koehler, B. *Bulletin de la Societe Chimique de France* **1910**, *4*, 219.

(208) Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 902 - 903.

(209) Palmieri, G.; Cimarelli, C. *ARKIVOC* **2006**, *vi*, 104 - 126.

(210) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328 - 5335.

(211) Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1109 - 1110.

(212) Li, Q.; Chu, D.; Raye, K.; Claiborne, A.; Seif, L.; Macri, B.; Plattner, J. *Tetrahedron Lett.* **1995**, *36*, 8391 - 8394.

(213) Cimarelli, C.; Palmieri, G. *J. Org. Chem.* **1996**, *61*, 5557 - 5563.

(214) Fleck, T. J.; McWhorter, W. W.; DeKam, R. N.; Pearlman, B. A. *J. Org. Chem.* **2003**, *68*, 9612 - 9617.

(215) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656 - 1662.

(216) Qui, J.; Silverman, R. B. *J. Med. Chem.* **2000**, *43*, 706 - 720.

(217) Trauner, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 6513 - 6516.

(218) Miniejew, C.; Outurquin, F.; Pannecoucke, X. *Tetrahedron* **2006**, *62*, 2657 - 2670.

(219) Park, S. H.; Lee, S. H.; Lee, S. Y. *J. Chem. Research (S),* **2001**, 498 - 499.

(220) Koszelewski, D.; Lavandera, I.; Clay, D.; Rozzell, D.; Kroutil, W. *Adv. Synth. Catal.* **2008**, *350*, 2761 - 2766.

(221) Collado, I.; Lete, E.; Sotomayor, N.; Villa, M. *Tetrahedron* **1995**, *51*, 4701 - 4710.

(222) Albrecht, A.; Kedzia, J.; Koszuk, J.; Warzycha, E.; Janecki, T. *Tetrahedron Lett.* **2004**, *47*, 2353 - 2355.

(223) Liljeblad, A.; Kanerva, L. T. *Tetrahedron* **2006**, *62*, 5831 - 5854.

WISETD

(224) Gedey, S.; Liljeblad, A.; Fülöp, F.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1999**, *10*, 2573 - 2581.
(225) Sánchez, V. M.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1997**, *8*, 37 - 40.
(226) Rinehart, K. L.; Harbour, G. C.; Graves, M. D.; Cheng, M. T. *Tetrahedron Lett.* **1983**, *24*, 1593 - 1596.
(227) Allen, F. H. *Acta Crystallogr. Sec. B* **2002**, *58*, 380 - 388.
(228) Hyperchem *Hypercube, Inc., Gainesville, FL* **2002**.
(229) Scheibye, S.; Kristensen, J.; Lawesson, S.-O. *Tetrahedron* **1979**, *35*, 1339 - 1343.
(230) Michael, J. P.; Gravestock, D. *J. Chem. Soc., Perkin Trans. I* **2000**, 1919 - 1928.
(231) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547 - 10658.
(232) Brown, A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749 - 1750.
(233) Chakraborty, R.; Simpkins, N. S. *Tetrahedron* **1991**, *47*, 7689 - 7698.
(234) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *39*, 3477 - 3478.
(235) Carretero, J. C.; Dominguez, E. *J. Org. Chem.* **1993**, *58*, 1596 - 1600.
(236) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566 - 6571.
(237) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157 - 2167.
(238) Pathak, R.; Panayides, J.-L.; Jeftic, T. D.; de Koning, C. B.; van Otterlo, W. A. L. *S. Afr. J. of Chem.* **2007**, *60*, 1 - 7.
(239) van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B. *Synlett* **2003**, 1859 - 1861.
(240) Ranu, C.; Majee, A.; Das, A. R. *Tetrahedron Lett.* **1995**, *27*, 4885 - 4888.
(241) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117 - 7140.
(242) Kang, S. W.; Kim, Y. H.; Kim, S. H. *Bull. Korean Chem. Soc.* **2008**, *29*, 755 - 757.
(243) Enders, D.; Walh, H.; Bettray, W. *Angew. Chem. Int. Ed.* **1995**, *34*, 455 - 457.

WitsETD

(244) Zhong, H. M.; Cohen, J. H.; Abdel-Magid, A. F.; Kenney, B. D.; Maryanoff, C. A.; Shah, R. D.; J., V. J. F.; Zhang, F.; Zhang, X. *Tetrahedron Lett.* **1999**, *36*, 7721.

(245) Dumas, F.; Mezrah, B.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293 - 2304.

(246) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890 - 891.

(247) *SAINT+*; Version 6.02, (includes XPREP and SADABS), Bruker AXS Inc., Madison, Wisconsin, USA ed. 1999.

(248) Sheldrick, G. M. *Shelxs97 and Shelxsl97* **1997**, *University of Gottingen, Germany*.

(249) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837 - 838.

(250) Spek, A. L. *Acta Crystallogr. Sec. A* **1990**, *46*, C34 - C34.

(251) Bruno, I. J.; Cole, J. C.; Edgington, P. R.; Kessler, M. K.; Macrae, C. F.; McCabe, P.; Pearson, J.; Taylor, R. *Acta Crystallogr. Sec. B* **2002**, *58*, 389 - 397.

(252) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta Jr., S.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765 - 784.

(253) Wang, J.; Wolf, R.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. *J. Comput. Chem.* **2004**, *25*, 1157 - 1174.

(254) Zhai, H.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2007**, *72*, 3853 - 3858.

WiSETD