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Synthesis of amphibian indolizidine alkaloids and related compounds from enaminone precursors

Darren Lyall Riley

Supervised by Professor J.P. Michael
and Professor C.B. de Koning

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

October 2007

DECLARATION

I declare that the work presented in this thesis is my own, unaided work. It is being submitted for the Degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

_____

Darren Lyall Riley
October 2007

ABSTRACT

The work discussed in this thesis is centered on the synthetic protocol developed for the synthesis of alkaloids in the organic chemistry laboratories at the University of the Witwatersrand. The alkaloids of interest in this thesis are the 5,8-disubstituted indolizidines (–)-**209I [185]** and (–)-**223V [174]**, the piperidine alkaloid (±)-thalictroidine **[257]** as well as several 5-monosubstituted indolizidines including (±)-tashiromine **[330a]** and (±)-5-epi-tashiromine **[330b]**. The work is put into perspective in two parts. The first part is a review of all the classes of alkaloids that have currently been isolated and identified from the skin extracts of amphibians, in particular the Dendrobatidae family of neotropical frogs. The second part gives a chronological review of all previous racemic and enantioselective syntheses of the 5,8-disubstituted indolizidines. This is followed by an overview of the general synthetic approach used in the syntheses of alkaloids in the "Wits" laboratories. Particular emphasis is placed on the enantioselective synthetic strategies, developed by Gravestock, for the synthesis of 5,8-disubstituted indolizidine alkaloids. The aims and strategies to be used in the present project are then introduced.

The racemic synthesis of (±)-thalictroidine **[257]**, used in model studies in order to practice fundamental functional group transformations for the preparation of piperidine systems is reported. The key reactions introduced in this section were the preparation of bromoacetamides, thiolactams and enaminones, the latter by the application of Eschenmoser's sulfide contraction, as well as the reduction of exocyclic carbon-carbon double bonds in six membered vinylogous urethanes. The synthesis of (±)-thalictroidine **[257]**, is the first reported synthesis of the natural product, and spectroscopic and crystallographic data are in agreement with the structure proposed by Kennelly *et al.*[125]

The synthesis of several 5-monosubstituted indolizidines, used in model studies in order to establish fundamental skeletal and functional group transformations for 5,8-disubstituted indolizidines are then shown. Key reactions include the preparation of several enaminones including a vinylogous urethane **[312]** and a Weinreb amide **[314]** from thiolactam **[304]**. These enaminones were cyclised under alkylative conditions to afford 5-substituted indolizidines **[320]** and **[322]** respectively. The synthetic utility of the Weinreb amide for the introduction of unbranched alkyl substituents at the 5-position is introduced, and the utility of

the vinylogous urethane **[320]** is shown by a three step conversion into (±)-tashiromine **[330a]** and (±)-5-epi-tashiromine **[330b]**.

The formal enantioselective synthesis of indolizidine **(–)-209I [185]** is reported. In order to begin the enantioselective synthesis of **(–)-209I [185]**, methodology developed by Gravestock was adapted to the preparation and utilization of vinylogous ureas containing the Weinreb amide functionality. Conjugate addition of the secondary amine *N*-benzyl-*N*-(1*R*)-1-phenylethylamine **[243]** to *tert*-butyl (2*E*)-2-hexenoate **[267]** gave optically pure tertiary amine **[268]**. Debenzylation of this amine gave primary amine **[336]**. Subsequent lactam formation, thionation and sulfide contraction with *N*-methoxy-*N*-methyl-2-bromoacetamide **[271]** yielded vinylogous urea **[272]**. The reduction of *tert*-butyl ester **[272]** to liberate alcohol **[273]** was low yielding and an alternative method was used, which involved the reduction of the *tert*-butyl ester at an early stage of the synthesis, protecting it as a silyl ether, and then liberating the free alcohol at an appropriate stage in the synthesis. The silyl ether was not compatible with the thionation step and was swapped at the lactam stage for an acetate protecting group. Subsequent reactions included an acylative cyclisation to form the indolizidine skeleton and a stereoselective reduction of the carbon-carbon double bond to yield (5*R*,8*S*,8a*S*)-*N*-methoxy-*N*-methyl-5-propyloctahydro-8-indolizinecarboxamide **[275]**. Mono-alkylation of the Weinreb amide functionality and epimerization to 1-[(5*R*,8*R*,8a*S*)-5-propyloctahydro-8-indolizinyl]-1-propanone **[191]** represented a formal synthesis of indolizidine (–)-**209I [185]**.

Approaches towards the synthesis of a late stage common intermediate **[259]** which could have the substituents at both the 5- and 8-positions modified independent of each other at or near the end of the synthesis are discussed. Finally an alternative synthetic approach negating the need for several of the protection and deprotection steps is shown with regards to the synthesis of the structurally related 1,4-disubstituted quinolizidines.

This thesis is dedicated to

My Parents, Ian and Shirley

and

The Love of My Life, Jenny-Lee

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“Only in the leap from the lions head

Will he prove his worth”

~Indiana Jones~

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LIST OF ABBREVIATIONS

AIBN	azobisisobutylonitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Boc_2O	di-*tert*-butyl-dicarbonate
CbzCl	benzyloxycarbonyl chloride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DECP	diethyl cyanophosphonate
DHP	3,4-dihydro-2*H*-pyran-2-methanol
$(DHQD)_2Pyr$	hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether
DIBAL	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNPH	2,4-dinitrophenylhydrazine
FTIR	fourier transform infra red
GC	gas chromatography
GC-MS	gas chromatography-mass spectroscopy
HMPA	hexamethyl phosphoric triamide
HRMS	high-resolution mass spectrometry
KHMDS	potassium hexamethyldisilazide
LD_{50}	lethal dosage 50%
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LTEPA	lithium tris[(3-ethyl-3-phenyl)oxy]aluminum hydride
*m*CPBA	*meta*-chloroperbenzoic acid
MOMCl	methoxymethyl chloride
MsCl	methane sulfonyl chloride
NCS	*N*-chlorosuccinimide
N,*N*'-TCDI	*N*,*N*'-thiocarbonyldiimidazole
NaHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance

PCC	pyridinium chlorochromate
PPTS	pyridinium toluene-*p*-sulfonate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium (0)
p-TsOH	*para*-toluene sulfonic acid
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDMSCl	*tert*-butyldimethylsilyl chloride
TBDPSCl	*tert*-butyldiphenylsilyl chloride
TBSCl	*tert*-butylsilyl chloride
TFA	trifluroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	tetramethylsilane
TsCl	toluene sulfonyl chloride
Wits	University of the Witwatersrand
XRD	x-ray diffraction

CHAPTER 1

A REVIEW OF ALKALOIDS FROM AMPHIBIAN SOURCES, AND REPORTED SYNTHESES OF 5,8-DISUBSTITUTED INDOLIZIDINE ALKALOIDS



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A REVIEW OF ALKALOIDS FROM AMPHIBIAN SOURCES, AND REPORTED SYNTHESES OF 5,8 DISUBSTITUTED INDOLIZIDINE ALKALOIDS

1.1 Introduction

A general definition of alkaloids, is that they comprise a group of naturally occurring compounds having a basic often cyclic, nitrogen-containing functional group, in many respects resembling the alkalis.[1] They are primarily found in the plant kingdom which is a source of more than 10 000 alkaloids. Many of these alkaloids have common household names, and are well known to most people. Common examples include nicotine, the tobacco alkaloid, quinine, used in the treatment of malaria and morphine, an analgesic and narcotic from the opium poppy. Other alkaloids include poisons such as strychnine and coniine, the latter derived from hemlock and famous for being used to poison Socrates; as well as numerous illegal recreational drugs like lysergic acid diethylamide (LSD), cocaine and heroin.

The biological importance of most alkaloids to plants undoubtedly revolves around the fact that they serve as an alleochemical deterrent to herbivores by eliciting a bitter taste.[2] Pharmacologically, alkaloids are of particular interest as they exhibit striking biological activity in insects, mammals and humans. In fact alkaloids have been isolated from plants as both pure substances and mixtures for use as medicinal agents in homeopathy and medicine, leading to the development of modern pharmacology. Today, natural product chemistry and synthetic organic chemistry have both been profoundly affected by the structural elucidation and synthesis of alkaloids with the hopes of finding new and better alkaloids for use in pharmacology and medicine.

Traditionally, a general definition of alkaloids has almost always made mention of the fact that alkaloids have a limited distribution in animals in fact for many years it was believed that alkaloids were only found in plants. However it is now well known that alkaloids occur readily in both invertebrates and vertebrates in the animal kingdom.[3]

The first example of an alkaloid from an animal source was established in 1866 when samandarine was isolated from a European fire salamander[4], Since then amphibians have proved to be a rich source of biologically active lipid-soluble alkaloids. To date, over eight

hundred compounds having been identified, representing twenty four structural classes.[5] Interestingly, the large majority of these alkaloids have been identified from the skin extracts of frogs of the family Dendrobatidae, and as a result are sometimes refered to as 'dendrobatid' alkaloids.[6]

The Dendrobatid family includes 170 species spread across 7 genera.[5] These frogs are small, ranging from 12 mm (*Dendrobates minutus*) to 60 mm (*Dendrobates auratus*), and they generally display aposematic colouring. These frogs are endemic to Central and South America, however there is a population of *D. auratus* in Hawaii introduced over sixty years ago.[7] Alkaloids are, however, not unique to dendrobatid frogs. Frogs and toads from the families Mantellidae, Bufonidae and Myobatrachidae are also known sources of alkaloids.

The toxicity of these frogs is in general a direct result of the alkaloids located in the granular glands in their skins.[8] The toxins seem to fulfill two primary requirements: they prevent predators from eating the frogs by producing a burning sensation, numb feeling or horrible taste; and they prevent bacteria and fungi from colonizing the frog's permanently moist skin.[9] The degree of toxicity varies across species, with some causing only a mild discomfort while others are deadly.

Amphibian alkaloids, with the exception of samandarines and the pseudophrynamines, are all believed to be derived from arthropod dietary sources, although to date only a few of the over eight hundred amphibian alkaloids have been detected in anthropods.[5] Putative sources have been shown to be myrmicine and formicine ants, coccinellid beetles, siphonotid millipedes and orbatid mites.[5] The evidence for a dietary source of these alkaloids stems from the fact that dendrobatid frogs raised in captivity have been shown to contain no skin alkaloids, while wild-caught frogs still maintain alkaloids in captivity for years. To test this theory Daly and co-workers tested a dietary link on *D. auratus*, by capturing *D. auratus* tadpoles, which were reared to adulthood, at which time they were split into two groups. The one group was fed fruit flies devoid of any toxic alkaloids, while the other group was fed on leaf-litter arthropods collected from the frog's natural environment. The trial continued for seven months, after which time, as predicted, the frogs raised on the fruit flies showed no sign of alkaloids, whereas the frogs raised on the leaf-litter arthropods had significant levels of alkaloids.[10-11]

To date the structures of many of these alkaloids have been rigorously established by either NMR spectroscopic analysis or synthesis. However due to the small amounts of material available to study, many still remain tentative with proposed structures based only on mass spectral and FTIR spectral data, with analogies to the structures of well-defined alkaloids.[3]

Due to the large number of different amphibian alkaloids Daly and co-workers introduced a code system for naming each alkaloid. They used the nominal molecular weight of the alkaloid, with a letter added to distinguish between different alkaloids with the same nominal molecular weight. To characterize isomers prefixes (eg. *cis*, *trans*, *epi*, *iso*) and primes (eg. A', A'') are used. In certain cases trivial names are given.[4,12-13]

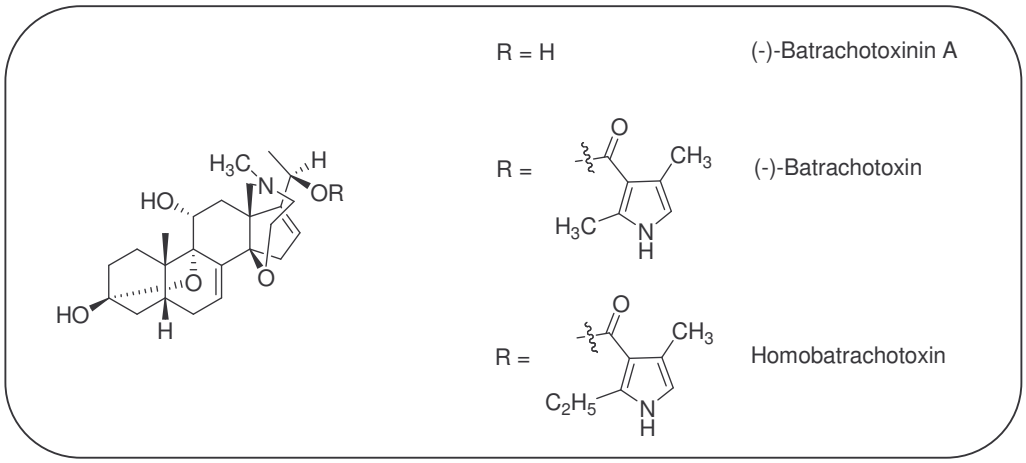
1.2 Review of the major classes of amphibian alkaloids

In the following sections, the major classes of amphibian alkaloids will be introduced. Representative structures will be shown for each class along with some commentary on the source, structure and pharmacological properties. The 5,8-disubstituted indolizidine alkaloids being the alkaloids of interest for this thesis are dealt with in more detail, and previous synthetic approaches will be outlined.

1.2.1 Batrachotoxins

Batrachotoxins are one of two classes of steroidal alkaloids, originally isolated from the poison-dart frogs found in the rain forests west of the Andes in Columbia.[14] It was the knowledge of the native Indians that the skin secretions of certain brightly coloured frogs were sufficiently toxic to be used for poison blow darts.[3,10] This led to studies being initiated at the National Institute of Health, Bethesda, Maryland in 1962 to isolate and identify the toxic principles. Seven years later in 1969 the toxic principles of the poison-dart frogs were shown to be unique steroidal alkaloids, which were named the batrachotoxins.[15] The three major alkaloids were batrachotoxin, homobatrachotoxin, and batrachotoxinin-A. They have been identified in only five species of *Phyllobates*, the true poison-dart frogs.[3,6,15] Only the three Colombian species of the five neotropical species of *Phyllobates* have high levels of batrachotoxins, and all three have been used to poison blow-darts. The two Central American species have low levels, and for certain species of *P. lugubris* there are no detectable levels of batrachotoxins. The highest levels occur in *P. terribilis*, which have 1000 μg of batrachotox-

ins per frog skin, while the other two true poison-dart frogs *P. bicolor* and *P. aurotaenia* have 100 to 200 μg per frog skin.[16]

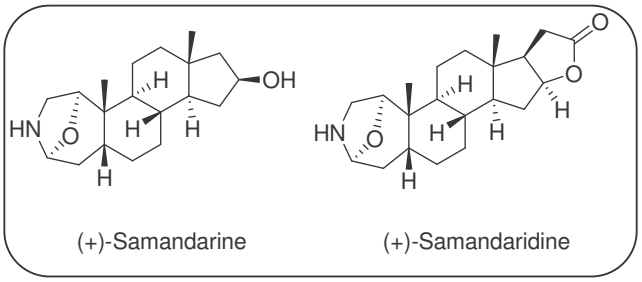


In recent years, batrachotoxins and several congeners have been isolated from non-amphibian sources. One of the remarkable sources is in the skins and feathers of Papua New Guinea birds of the genera *Pitohui* and *Ifrita*.[17-18] The highest levels occur in the hooded pitohui (*P. dichrous*), where it is estimated that 20 μg of homobatrachotoxin are found in the feathers and skin of one bird. The commonly seen congeners include an acetate, crotonates, and a 4'-hydroxypentanoate. Most recently, batrachotoxin, homobatrachotoxin, batrachotoxinin-A, and congeners, including crotonates were discovered in beetles (Melyridae, *Choresine*).[19] These beetles represent a possible dietary source of poison-dart frogs and the toxic passerine birds.

The batrachotoxins represent a unique class of steroidal alkaloids, which contain several unprecedented structural features, namely the homomorpholine ring sharing the steroidal *C*,*D*-ring juncture, 2,4-dialkylpyrrole-3-carboxylate moieties, and a 3,9α-hemiketal oxygen bridge. There are no related natural products, making the biosynthetic origin very interesting. The nature of the ester function at the 20α position is of critical importance to the toxicity[20], with the unesterified congener batrachotoxinin-A being 500 times less toxic than batrachotoxin. Batrachotoxin is extremely toxic (LD_{50} mouse 0.1 μg) with an estimated lethal dose in humans being less than 200 μg. The toxicity is due to the depolarization of nerve and muscle membranes by selective stabilization of sodium channels into an open formation, leading to a massive influx of sodium ions. This influx of sodium ions causes ultrastructural damage, most probably due to changes in osmotic potential. Batrachotoxins have been used extensively in

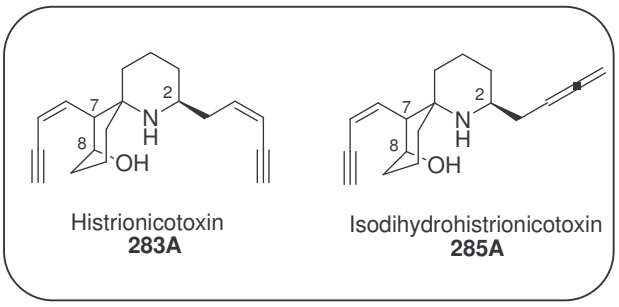
research on voltage-dependant sodium channels.[6] The poison dart frogs have been shown to have batrachotoxin resistant sodium channels,[21-22] allowing them to eat batrachotoxin-containing beetles without ill effect. No studies have to date been done on the sodium channels of the toxic passerine birds, nor have these birds been raised in captivity on alkaloid-free diets.

1.2.2 Samandarines



Samandarines are the second of the two classes of steroidal amphibian alkaloids. They were isolated from the parotid skin glands of the fire and alpine salamanders.[23] The majority of samandarines are characterized by the presence of an oxazolidine ring in the steroidal backbone. Recent evidence suggests that these steroidal alkaloids are synthesized by the salamanders from cholesterol.[24] Samandarine is a highly toxic (LD_{50} mouse 70 μg) centrally active neurotoxin which causes potent local anaesthetic activity.[20] The salamanders are sensitive to their own toxins, and unlike dendrobatid frogs, they continue to produce samandarine alkaloids when reared in captivity.[20]

1.2.3 Histrionicotoxins

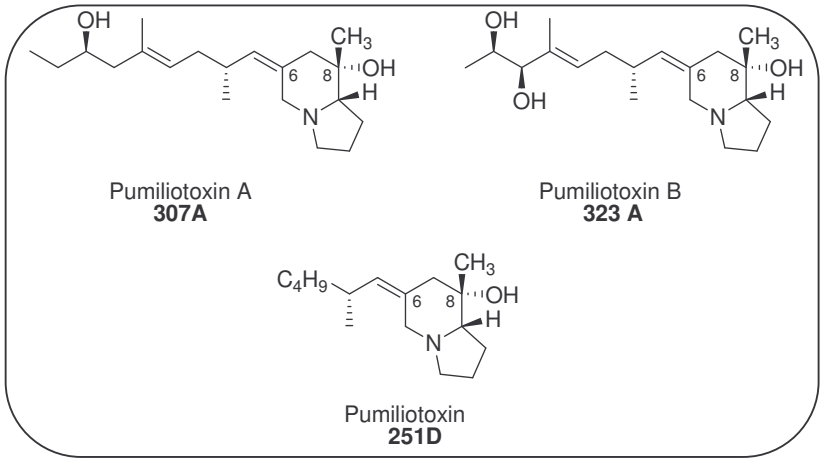


Histrionicotoxins are the major alkaloids found in a brightly coloured species of South American dendrobatid frogs (*Dendrobates histrionicus*) found in western Columbia and north-western Ecuador.[22] These alkaloids are unique to the dendrobatid frogs, with only one exception being a mantellid frog.[16] A New World myrmicine ant is suspected to be the dietary source of histrionicotoxins.[25] To date sixteen histrionicotoxins have been detected. All of these alkaloids have an azaspiro[5.5]undecanol ring system, with alkylidene substituents at the 2- and 7-positions and an axial hydroxyl group at the 8-position. In 1971 histrionicotoxin **283A** and isodihydrohistrionicotoxin **285A** were the first alkaloids of this class to have both their structure and absolute configuration determined.[26]

Histrionicotoxins have been found in the skins of dendrobatid frogs at levels of up to 200 μg/frog. These alkaloids have a relatively low toxicity with 1000 μg in mice only causing locomotor difficulties and prostration.[13,22] However, they would be noxious to a predator, due to bitterness and blockage of nicotinic pathways. Histrionicotoxins act in two ways, firstly by blocking both the outward movement of potassium ions through potassium-ion channels of the surface membrane of muscle and nerve cells.[10] Secondly they block the two-way exchange of sodium and potassium ions through complexes of ion channels and acetylcholine receptors in the "end plate" between a nerve fibre and a muscle cell. Blockage of potassium ions promotes muscle contraction in muscle cells, and prolongs the release of neurotransmitters by nerve cells. The blockage of the ion-channel/acetylcholine-receptor complexes prevents acetylcholine released from nerves from triggering muscle contraction.[6a] Histrionicotoxins have been widely used in the study of noncompetitive blockers of nicotinic receptors and channels.[16]

1.2.4 Pumiliotoxins

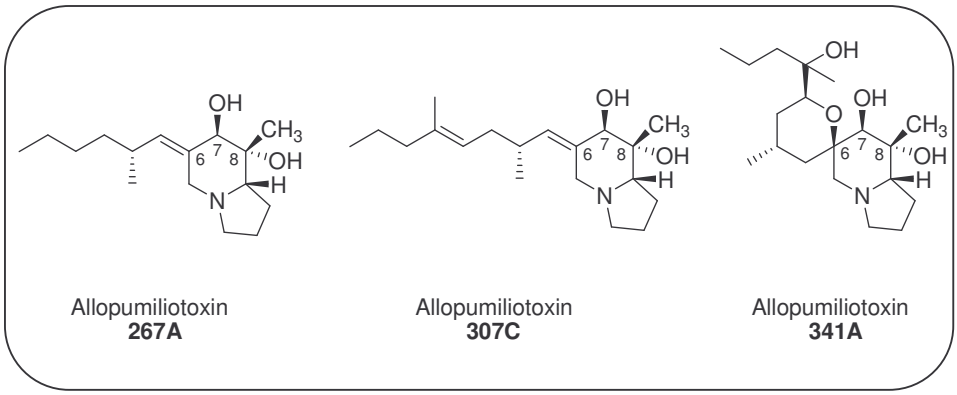
Pumiliotoxins are widely distributed in alkaloid containing anurans from the neotropics (Dendrobatidae, *Dendrobates, Epipedobates, Minyobaes, Phyllobates*), semi-temperate South America (Bufonidae, *Melanophryniscus*), Madagascar (Mantellidae, *Mantella*) and Australia (Myobatrachidae, *Pseudophryne*).[16] Recent studies report the presence of certain pumiliotoxins in formicine ants (*Brachymyrmex* and *Paratrechina*),[27] and in certain oribatid mites,[28] which themselves are prey items for the formicine ants. The first two pumiliotoxins **307A** and **323A** were reported in 1967.[29] However it was only in 1980 that X-ray crystallography of pumiliotoxin **251D**, revealed the basic structure of pumiliotoxins and their 7-hydroxy congeners, the allopumiliotoxins.[30] At present over thirty alkaloids are considered to be pumiliotoxins.[5] This class of alkaloids is characterized by having an indolizidine ring system with equatorial methyl and an axial hydroxyl substituents at the 8-position and an alkylidene substituent at the 6-position.



Pumiliotoxins are relativelty toxic; pumiliotoxin A (LD_{50} mouse 50 μg) and pumiliotoxin B (LD_{50} mouse 20 μg) are found at levels of up to 200 μg/frog.[5] Pumiliotoxins act by causing an influx of sodium ions through voltage dependant sodium channels. This in turn elicits repetitive firing of neurons, because of the effects on sodium channel function.[31] The nature of the side chain at the 6-position is vital in determining toxic activity, illustrated by the fact that the 15,16-*erythro* isomer of pumiliotoxin B has much lower toxicity.[30] Interestingly frogs from the dendrobatid genus *Dendrobates* have a pumiliotoxin 7-hydroxylase that can enantioselectively convert dietary pumiliotoxin into a more toxic allopumiliotoxin (**Section 1.2.5**). This is the only known example where a dietary alkaloid is altered metabolically by a frog.[32] Several subclasses of pumiliotoxins including the 8-deoxypumiliotoxins, 8-dehydrodes-methylpumiliotoxins and 8-desmethylpumiliotoxins have been identified as well.[5]

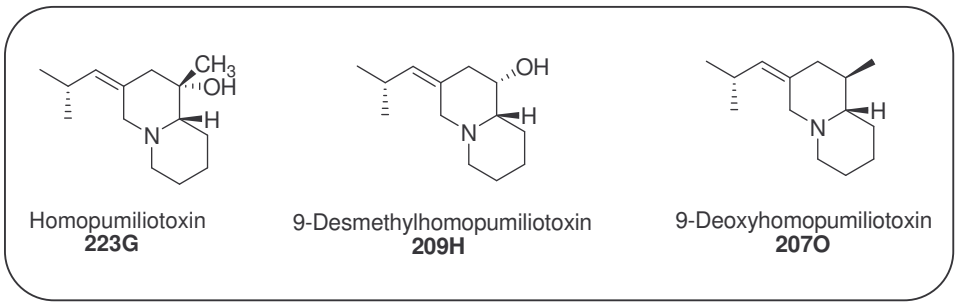
1.2.5 Allopumiliotoxins

Allopumiliotoxins occur widely in alkaloid containing anurans, with about twenty alkaloids being considered to be allopumiliotoxins.[5] They have the same structural features as the pumiliotoxins with an additional equatorial hydroxyl substituent at the 7-position. Major allopumiliotoxins can be present at levels of up to 100 μg/frog, and are about 5 times more toxic than the pumiliotoxins.[25]

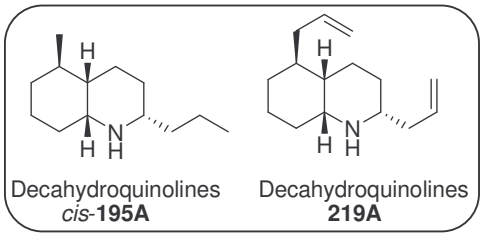


1.2.6 Homopumiliotoxins

Homopumiliotoxins occur in dendrobatid, mantellid and bufonid anurans in levels up to 50 μg/frog.[5] No toxicity or bioactivity data have been reported to date, and no dietary source has been identified. Homopumiliotoxins have the same structural arrangement as pumiliotoxins, however they contain a quinolizidine skeleton as opposed to an indolizidine skeleton. There are seventeen alkaloids identified as being part of this group, however most structures are only tentative at this stage. Two subclasses have been identified, 9-desmethylhomopumiliotoxins and 9-deoxyhomopumiliotoxins.[5]



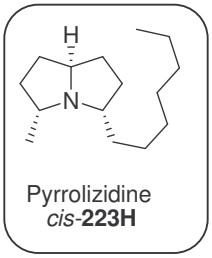
1.2.7 Decahydroquinolines



Decahydroquinolines are commonly found in neotropical dendrobatid frogs, and a putative myrmicine ant dietary source has been identified.[25,33-35] The parent alkaloid *cis*-**195A** was isolated in 1969 from a

small dendrobatid frog (*Dendrobates pumilio*) and its structure was elucidated using X-ray crystallography.[36] Decahydroquinolines contain a quinoline ring system with alkyl/alkylidene substituents at the 2- and 5-positions. There are about fifty alkaloids considered to be members of the 2,5-disubstituted decahydroquinoline class. Some can occur at levels of up to 50 μg/frog however they have relatively low toxicities. A minimal lethal dose in mice for *cis*-**195A** and **219A** is over 250 μg[5]. Decahydroquinolines act as noncompetitive blockers of nicotinic receptors.[16]

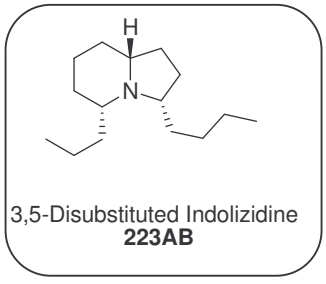
1.2.8 Pyrrolizidines



Pyrrolizidine
cis-**223H**

3,5-Disubstituted pyrrolizidines were first isolated from anuran skin in 1993 from a bufonid (*Melanophrynscus*) toad,[37] and have since been isolated from species of dendrobatid and mantellid frogs.[5] Pyrrolizidines were however first discovered in nature in myrmicine ants in 1980,[38] and one of the anuran pyrrolizidines *cis*-**223H** was shown to be identical to a pyrrolizidine isolated from a thief ant.[5] Pyrrolizidines contain a 5,5 fused skeleton with unbranched alkyl substituents at the 3- and 5-positions. A number of the alkyl substituents are hydroxylated (**237R**, **239K**, **239R**, **239Y** and **267H**), and there are also examples of an ether linkage (**237G**) and a carbonyl functionality (**265J**) At present there are twenty-six alkaloids assigned to the 3,5-disubstituted pyrrolizidine group.[5] Both *cis*- and *trans*-isomers of several of these alkaloids have been shown to occur, leading to four possible diastereomers, namely, *endo-endo*, *exo-exo*, *exo-endo* and *endo-exo*, of which only *endo-endo* has not been detected in nature. Toxicity and biological activity has to date not been studied.

1.2.9 3,5-Disubstituted Indolizidines



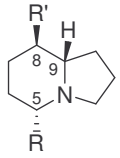
3,5-Disubstituted Indolizidine
223AB

3,5-Disubstituted indolizidines occur randomly in dendrobatid (primarily *Dendrobates*), mantellid (*Mantella*) and bufonid (*Melanophrynisus*) anurans.[5] These indolizidines have also been isolated from myrmicine ants, which are most probably a dietary source for the frogs.[34] The parent structure for this class **223AB**, was isolated in 1978 and its structure was postulated.[13] The structure was later proved in 1981, by comparison of GC and GC-MS data with that of four

synthetic diastereomers.[39] These alkaloids have the characteristic bicyclic indolizidine skeleton with alkyl/alkenyl substituents at the 3- and 5-positions. The alkyl/alkylidene substituents are often hydroxylated. There are nearly thirty alkaloids including stereoisomers assigned to this class, however there is almost no data on toxicity. Indolizidine **239CD** has a minimum lethal dose for mice of 200μg, acting as a noncompetitive blocker of nicotinic receptors.[16]

1.2.10 5,8-Disubstituted Indolizidines

The structures of the first 5,8-disubstituted indolizidines **205A** and **235B''** were described in 1987 based on data from NMR spectroscopic analysis.[40] These indolizidines occur in a wide range of dendrobatid and mantellid (*Mantella*) frogs. They are rare in bufonid (*Melanophryniscus*) toads. At present these alkaloids represent the largest group of amphibian alkaloids with about eighty compounds, including stereoisomers.[5] Structures range from those that are rigorously defined to those which can only be considered tentative. The absolute configuration has been determined for six of these alkaloids (**203A**, **205A**, **207A**, **223J**, **235B'**, **237D**),[41-43] but the presence of both enantiomers in nature is possible.



5,8-disubstituted indolizidine

R = $(CH_2)_3C{\equiv}CH$	R' = CH_3	**205A**
R = $(CH_2)_3C{=}CCH_2CH_3$	R' = CH_3	**235B''**
R = $(CH_2)_2CH_3$	R' = $-CH_2OH$	**197C**
R = $(CH_2)_2CH_3$	R' = $(CH_2)_2CH_3$	**209I**
R = $(CH_2)_2CH_3$	R' = $(CH_2)_3CH_3$	**223V**
R = $(CH_2)_2CH_3$	R' = C_4H_5	**219J**

Many of the 5,8-disubstituted indolizidines have a methyl group at the 8-position, but there are also numerous examples of straight chain alkyl substituents up to four carbons in length. A few of these indolizidines have a hydroxylated alkyl chain at the 8-position (**197C**, **239C**, **263K**, **267E**), and there is one example of a dihydroxylated alkyl chain **281O.**[5] The substituents at the 5-position are far more varied with numerous straight chain alkyl substituents ranging from two to seven carbons and unsaturated chains containing both alkene and alkyne functionalities ranging from three to eight carbons. Many of the alkyl substituents are hydroxylated, there are two examples where a carbonyl functionality is present (**251U**, **267E**) and there is even a hydroxylated alkylidene chain **251B.**[5] The mass spectra of 5,8-

disubstituted indolizidines are dominated by a base peak due to the loss of the α-substituent at the 5-position.[5] For all the 5,8-disubstituted indolizidines with a methyl substituent at the 8-position the base peak occurs at *m*/*z* 138. A subsequent retro Diels-Alder elimination of the *m*/*z* 138 fragment yields a diagnostic ion at *m*/*z* 96 for all 5,8-disubstituted indolizidines. The relative configuration of hydrogens at C-5 and C-9 are assigned by vapour-phase FTIR spectroscopic data.[5] A strong, sharp Bohlmann band at about 2789 cm^{-1} indicates a 5,9*Z* configuration of the attached hydrogens, which is the observed relative configuration for most of the 5,8-disubstituted indolizidines. A weak Bohlmann band at 2810 cm^{-1} indicates a 5,9*E* geometry which has in fact only been confirmed for alkaloid **259B** isolated from a bufonid toad**.** The orientation of the substituent at the 8-position has been shown to be equatorial for certain 5,9*Z*-indolizidines based on data from NMR spectroscopy and synthesis of these alkaloids. The methyl substituent at the 8-position for 5,9*E*-**259B** could be equatorial or axial.[37]

Indolizidines **205A**, **207A**, **209B**, **235B**, **235B'**, **209I**, **223J** and **223V** have been prepared synthetically. A review of all the syntheses of these 5,8-disubstituted indolizidines is presented in **Section 1.3**, outlining the various synthetic approaches and how these syntheses have helped in structural elucidation.

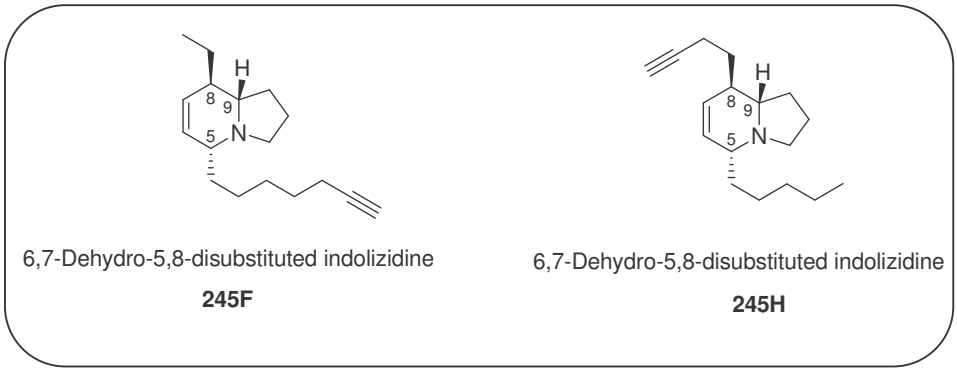
Although most indolizidines occur as minor or trace alkaloids, **235B''**, can be found at levels up to 100 μg per frog. A dietary source has to date not been identified, however alkaloids **205A** and **235B''** were present in leaf litter arthropods, most of which contained ants. Ants and mites therefore are at this point the most probable dietary sources of these 5,8-disubstituted indolizidines.[45] Interestingly a 5-(3-furyl)-8-methylindolizidine has been reported as a trace alkaloid in extracts from the scent gland of beavers.[46]

Toxicity data for 5,8-disubstituted indolizidines has not been reported. Biological activity studies show that these alkaloids are atypical but potent noncompetitive blockers of sodium ion influx through nicotinic receptor channels both in muscle and in ganglia. These alkaloids are atypical noncompetitive blockers as their potencies are reduced rather than enhanced in the presence of the agonist carbamoylcholine.[47] Synthetic **235B'** has been reported to be a very potent and selective blocker of the $\alpha_4\beta_2$ neuronal nicotinic receptor. Alkaloid **205A** greatly enhances the binding of tritiated perhydrohistrionicotoxin (a blocking agent), to a

noncompetitive blocker site on the nicotinic receptor channel of electric ray electroplax.[48] A minor change in the degree of unsaturation in the side-chain greatly affects reactivity. Potency is greatly reduced when a methyl group at the 8-position is replaced by a hydroxymethyl group.[47]

1.2.11 6,7-Dehydro-5,8-Disubstituted Indolizidines

The 6,7-dehydro-5,8-disubstituted indolizidines are a relatively new class of indolizidine alkaloids. These alkaloids occur commonly as minor alkaloids in dendrobatid, mantellid, and bufonid anurans. No dietary source has been identified, although it is thought that ants are a likely possibility. 6,7-Dehydro-5,8-disubstituted indolizidines differ from 5,8-disubstituted indolizidines as it is proposed that there is a double bond at the 6-position. This was shown to be the case for alkaloids **245F** and **245H** where catalytic hydrogenation yielded a perhydro derivative that had the same mass spectra as the expected 5,8-disubstituted indolizidines.[5] The substituents are unbranched alkyl and alkylidene in nature, and are commonly hydroxylated or contain a carbonyl functionality. Most of the indolizidines in this class exhibit a moderate, sharp Bohlmann band at 2787 cm^{-1} indicating a 5,9Z geometry of the attached hydrogen atoms.[5]

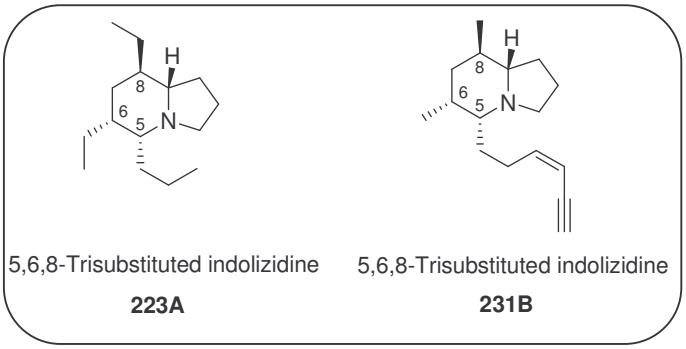


6,7-Dehydro-5,8-disubstituted indolizidine
245F

6,7-Dehydro-5,8-disubstituted indolizidine
245H

There are about thirty alkaloids assigned to the 6,7-dehydro-5,8-disubstituted indolizidine class, however no toxicity or biological activity data have been reported. The large number of alkaloids in this class indicates that there may also be similar 6,7-dehydro-5,6,8-trisubstituted indolizidines and 2,3-dehydro-1,4-disubstituted quinolizidines.[5]

1.2.12 5,6,8-Trisubstituted Indolizidines



5,6,8-Trisubstituted indolizidine **223A** | 5,6,8-Trisubstituted indolizidine **231B**

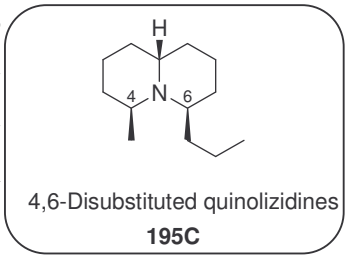
5,6,8-Trisubstituted indolizidines are another relatively new class of amphibian alkaloids, with the structure of the parent member of this class **223A** only being identified in 1997.[48] 5,6,8-Trisubstituted indolizidines are common in dendrobatid frogs, where levels can reach 50 μg/frog in the case of **223A** and **231B**. However, most occur only in trace amounts. These indolizidines are also found in mantellid (*Mantella*) frogs, but rarely in bufonid (*Melanophryniscus*) toads.[5] Non-amphibian sources have been identified and include a myrmicine ant and an oribatid mite.[28]

Although the 5,6,8-trisubstituted indolizidines are a relatively new class they have rapidly grown to become the second largest class of amphibian alkaloids with over seventy alkaloids. Substituents as with the previous classes of indolizidines are unbranched alkyl and alkenyl in nature with the exception of **249H** which is anomalous among izidines in having a branched chain. Analysis of Bohlmann bands indicates both 5,9*Z* and 5,9*E* configurations. Several of the indolizidines assigned to the 5,9*Z* class have a weak Bohlmann signal at 2811 cm^{-1} indicating a 5,9*E* configuration. The conformation was shown to be the less common *cis*-ring fusion, which has the nitrogen lone pair and the H-9 on the same face. Configuration at C-6 and C-8 is not certain in almost all cases. Although this is the second largest class of amphibian alkaloids most structures are at this stage still tentative. No toxicity or biological activity data have been reported for these alkaloids.[5]

1.2.13 4,6-Disubstituted Quinolizidines

4,6-Disubstituted quinolizidines in particular **195C** are found in dendrobatid frogs and mantellid frogs. Quinolizidine **195C** is a major alkaloid from the myrmicine ant (*Diplorhoptrum*), therefore an ant dietary source is possible.[34]

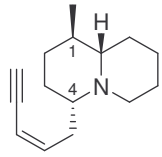
The structure of the first 4,6-disubstituted quinolizidine, **195C,** was reported in 1999,[34] and at present only six alkaloids are assigned to this class. Structurally these alkaloids are characterized by the bicyclic quinolizidine skeleton, with unbranched alkyl/alkenyl substituents at the 4- and 6-positions. The relative configuration of **195C** is 6*Z*, 10*E,*[34] configurations of the other 4,6-disubstituted quinolizidines are unknown. To date no toxicity or biological activity has been reported.



4,6-Disubstituted quinolizidines
195C

1.2.14 1,4-Disubstituted Quinolizidines

The structure of the parent 1,4-disubstituted quinolizidine alkaloid **217A** was reported in 1996, from material isolated from a mantellid frog (*Mantella baroni*).[49] 1,4-Disubstituted quinolizidines **217A**, **231A** and **233A** occur commonly in mantellid frogs at levels up to 50 µg/frog. Most others occur as trace alkaloids in both mantellid frogs and dendrobatid frogs but none have been reported from bufonid toads. Recently a 1,4-disubstituted quinolizidine was tentatively identified from an oribatid mite, pointing towards a possible dietary source[28].



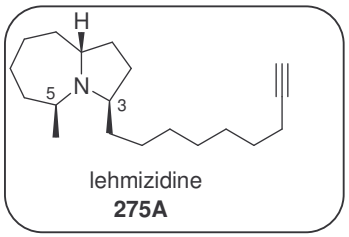
1,4-disubstituted quinolizidine
217A

Structures are mostly tentative, based only on mass spectra and in some cases FTIR data. The absolute configurations of **207I**, **217A** and **233A** are known.[50-52] The substituents at the 1- and 4- positions are alkyl or alkenyl in nature with a few examples being hydroxylated. The predominant relative configuration is 1,4-*trans* based on FTIR spectral data,[50] with alkaloid **207I** being the only example shown to have 1,4-*cis* configuration.[34,50] A Bohlmann band at 2790 cm^{-1} indicates a 4,10*Z* geometry. There are just over twenty alkaloids assigned to this class. No toxicity data has been reported, although a synthetic C-1 epimer of **207I** and a synthetic (+)-**207I** are noncompetitive blockers of nicotinic receptors.[5]

1.2.15 Lehmizidines

The parent structure of izidine **275A** was established in 2001 including relative configuration.[53] They were originally detected only in one population of a Columbian dendrobatid frog (*Dendrobates lehmanni*) after which the class was named.[53] Since then trace

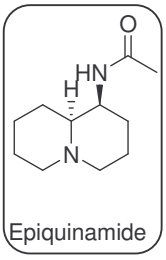
amounts have been identified in other dendrobatid frogs. No dietary source has been identified.



lehmizidine
275A

The lehmizidines have a pyrrolo[1,2-*a*]azepine skeleton with alkyl/alkenyl substituents at the 3-position and a methyl at the 5-position. Several of these alkaloids are shown to contain a carbonyl moiety in the alkyl/alkenyl chain. Lehmizidines can also be ring hydroxylated on the seven membered ring, but positions of the hydroxyl groups are unknown. The absolute configuration is unknown for all lehmizidines, but the relative configuration of the hydrogens at C-5 and C-10 of **275A** is 5*Z*,10*E* relative to the hydrogen at C-3.[53] Other Lehmizidines are postulated to have the same relative configuration. There are nine alkaloids in this izidine class, and all structures except for **275A** are tentative. No toxicity or biological activity data has been reported.[5]

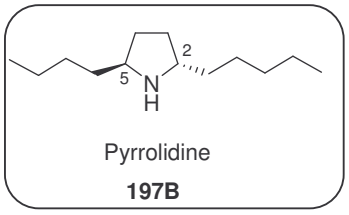
1.2.16 Epiquinamide



Epiquinamide

Epiquinamide is an unprecedented quinolizidine reported in 2003 as a trace alkaloid in extracts from an Ecuadorian dendrobatid frog (*Epipedobates tricolor*).[54] The structure was determined by analysis of mass spectra, FTIR spectra and NMR spectroscopic analysis. Epiquinamide is the only member of its class and has only been detected in *Epipedobates tricolor*. No dietary source has been identified.[54]

1.2.17 Pyrrolidines



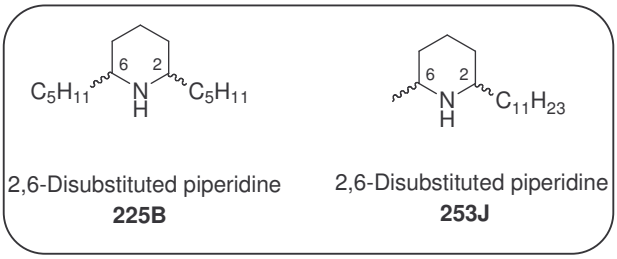
Pyrrolidine
197B

Pyrrolidine **197B** was first identified in 1986 is a major alkaloid found in skin extracts of one population of a Columbian dendrobatid frog (*Dendrobates histrionicus*).[55] 2,5-Disubstituted pyrrolidines have been known since 1976, when they were identified as constituents of myrmicine ant venoms.[56].

Pyrrolidines have unbranched alkyl substituents at the 2- and 5-positions. The *trans*-isomer is more commonly observed. To date nine 2,5-disubstituted pyrrolidines have been identified

from amphibian sources, occurring rarely in dendrobatid and mantellid frogs as trace alkaloids with the exception of **197B**[5]. The occurrence of **197B** as a major alkaloid is surprising, since pyrrolidines were accumulated poorly when fed to a dendrobatid frog.[11] Toxicity of 2,5-disubstituted pyrrolidines has not been reported, but they are noncompetitive blockers of nicotinic receptors[11].

1.2.18 Piperidines



2,6-Disubstituted piperidine **225B**

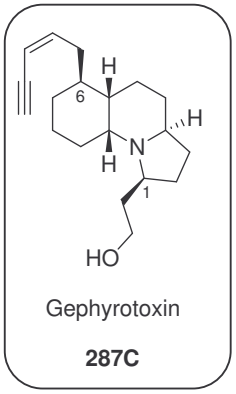
2,6-Disubstituted piperidine **253J**

2,6-Disubstituted piperidines occur rarely in dendrobatid and mantellid frogs as trace alkaloids. Myrmicine ants are a probable dietary source as 2,6-disubstituted piperdine alkaloids were first identified in 1971 in the venom of certain of these ants.[34] The first example of an amphibian 2,6-disubstituted piperidine **225B** was reported in 1986.[55] At that time however the structure of **241D**, a major alkaloid from the skin extracts of a montane Panamanian dendrobatid frog (*Dendrobates speciosus*), had been determined. The structure was only reported in 1988.[57]

Piperidines have alkyl substituents at the 1- and 6-positions. There is commonly an α-methyl substituent at the 1-position. The alkyl chain in the 6-position is often hydroxylated or contains a carbonyl moiety. Alkaloid **211J** is *N*-methylated. The relative configuration of the substituents can be *cis* or *trans*.[58] 2,6-Disubstituted piperidine **253J** is quite toxic to mice and has an antifungal activity. Piperidines are noncompetitive blockers of nicotinic receptors.[16]

A subclass of these piperidines is the 4-hydroxy-2,6-disubstituted piperidines.[57] There is also mass spectral evidence of certain piperidines that are disubstituted with only the smaller substituent in a readily lost α-position.[5]

1.2.19 Gephyrotoxins



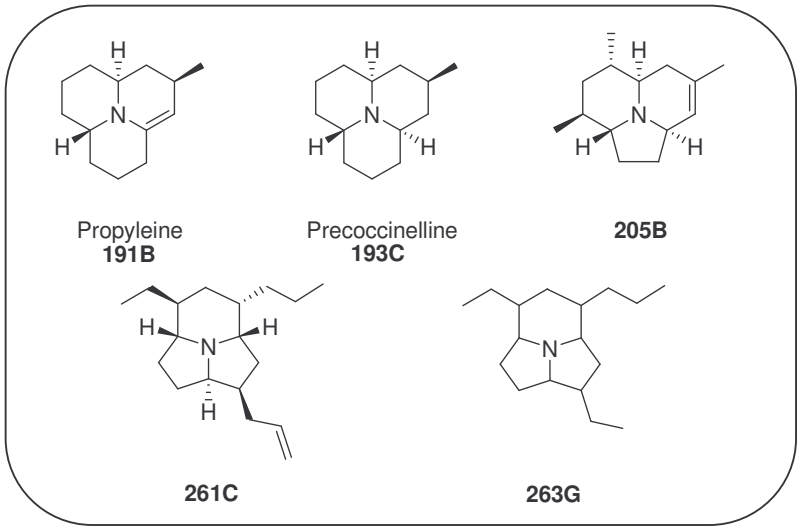
Gephyrotoxin
287C

The gephyrotoxins occur relatively rarely as minor alkaloids in dendrobatid frogs, and only in skin extracts containing 19-carbon histrionicotoxins as major alkaloids. It is likely that the dietary source is ants.[16] The structure of the tricyclic gephyrotoxin **287C** isolated from a Columbian dendrobatid frog (*Dendrobates histrionicus*) was determined in 1977 based on X-ray crystallography.[59] The absolute configuration is known, however there is some doubt as to whether it is the major enantiomer found in the frogs skin.

Gephyrotoxins have a tricyclic pyrrolo[1,2-*a*]quinoline skeleton. There is a CH_2CH_2OH substituent α to nitrogen at the 1-position and there is an alkylidene substituent at the 6-position. Gephyrotoxin **287C** has a low toxicity in mice (LD_{50} >>500 μg). It is also a noncompetitive blocker of nicotinic receptors.[16]

1.2.20 Coccinelline-like Tricyclics

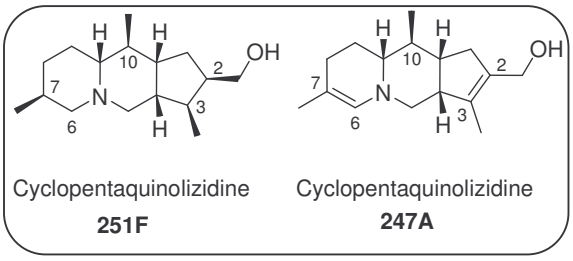
Coccinelline alkaloids were originally found in coccinellid beetles, and have been known since 1971.[60] In 1992 precoccinelline **193C** was reported as a minor alkaloid in a Panamanian dendrobatid frog (*Dendrobates auratus*).[61] Since then a second beetle alkaloid propyleine **191B** was identified from a Peruvian dendrobatid frog (*Epipedobates silverstonei*) and species of *Dendrobates pumilio*.[5]



Coccinelline-like tricyclic alkaloid **205B** containing a decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizidine skeleton, and **261C** and **263G** containing a decahydropyrrolo[2,1,5-*cd*]indolizine skeleton have also been identified.[62] To date five alkaloids have been unambiguously assigned to this class, however approximately sixty alkaloids have been tentatively assigned as being tricyclic and no doubt many will in future be shown to be members of the coccinelline-like tricyclic class.

The coccinelline-like tricyclics occur in dendrobatid, mantellid and bufonid anurans, but always as trace alkaloids.[5] In addition to one of the dietary sources probably being coccinellid beetles, precoccinelline **193C** was recently identified from an oribatid mite.[28] Toxicity of this class of alkaloids has not been identified. The synthetic enantiomer of **205B** is a potent and selective blocker of α-7 nicotinic receptors.[48]

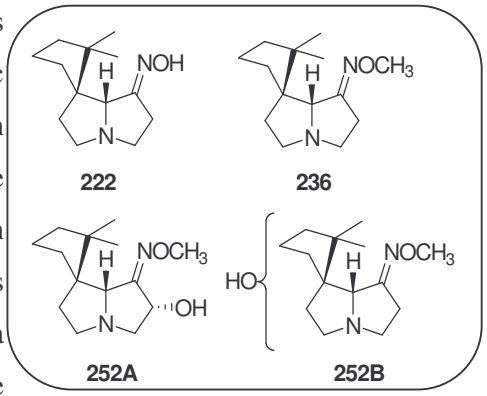
1.2.21 Cyclopentaquinolizidines



The cyclopentaquinolizidine parent alkaloid **251F** was detected in the 1970s in skin extracts from a small Columbian dendrobatid frog (*Minyobates bombetes*),[63] however the structure was undetermined until 1992 when detailed NMR spectroscopy led to the elucidation of its structure.[64] The structure has since been confirmed by synthesis.[65-66] A number of congeners have been isolated and to date there are ten alkaloids assigned to this class[5]. As the name implies these alkaloids have a cyclopenta[*b*]quinolizidine skeleton. They characteristically have three methyl substituents at the 3-, 7- and 10-positions. These alkaloids are disubstituted with a CH_2OH group at the 2-position, and mono-substituted at the 4-position. Substituents are either short chained alkyl fragments (1-2 carbons), or hydrogen. The alkyl substituents are commonly hydroxylated and there is one example of an aldehyde functionality in **249B**. Two examples **245A** and **247A** are dehydro analogues with double bonds at the 2- and 6-positions.[5]

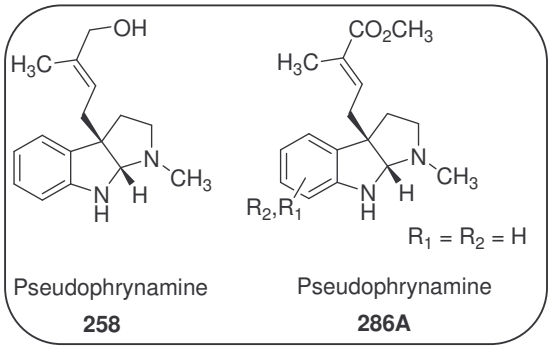
Cyclopentaquinolizidines have only rarely been detected in dendrobatid frogs, with the tiny montane frog *Minyobates bombetes* being the only species where it occurs as a major alkaloid. Toxicity and biological activity has not been investigated.[5]

1.2.22 Spiropyrrolizidines



Spiropyrrolizidines occur rarely in dendrobatid frogs and only as minor or trace alkaloids. Three tricyclic alkaloids isolated from skin extracts of a Panamanian dendrobatid frog (*Dendrobates pumilio*), were incorrectly assigned as being tricyclic amides in 1987.[40] In 1992 NMR spectroscopic analysis established that these three alkaloids have a spiropyrrolizidine oxime structure and they were designated **222**, **236** and **252A**.[67] Certain members in particular **236** have been isolated from skin extracts from mantellid and bufonid anurans.[5] Alkaloid **252B** has been identified as a trace alkaloid in a myobatrachid frog.[68] A siphonotid millipede (*Rhinotus*) source of **236** was reported as recently as 2003.[69] No toxicity data have been reported. (±)-*O*-Methyloxime **236** and (±)-nitropolyzonamine **238** are potent noncompetitive blockers of nicotinic receptors.[16]

1.2.23 Pseudophrynamines

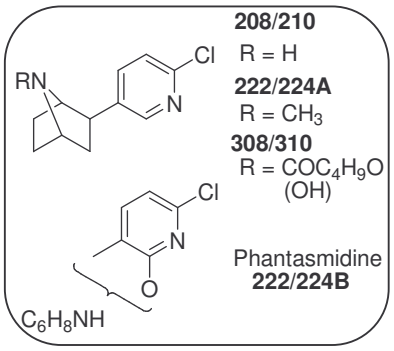


Pseudophrynamines were first detected in myobatrachid (*Pseudophryne*) frogs in 1976.[70] Ten years later the major pseudophrynamines were isolated from the skin extracts of an Australian myobatrachid frog (*Pseudophryne coriacea*), and the structures of **258** and **286A** were determined by NMR spectroscopic experiments.[71] Pseudophrynamines are unique to myobatrachid frogs of the genus *Pseudophryne*, and are found together with the pumiliotoxins.[72] To date more than a dozen pseudophrynamines have been identified from myobatrachid frogs, but some of the structures are still tentative, particularly the alkaloids with molecular weights over 500.[5] Structurally these alkaloids have a pyrrolo[2,3-*b*]indole skeleton, and are often classed as indolic alkaloids. An alkenyl substituent is found at the 3a-position, with a terminal hydroxyl, aldehyde or carboxylic ester moiety. The pyrrolo nitrogen is always methylated, however there is only one example **272A** where the indole nitrogen is methylated.[5] The aromatic ring is

often substituted with methoxy or hydroxyl groups and there are two examples, **300** and **330,** which contain a pyrrolo[2,3-*b*]indol-5(1*H*)-one skeleton.[5] Pseudophrynamines are unique among amphibian skin alkaloids as they do not come from a dietary source, but instead are biosynthesized by the frogs.[72] Although toxicity has not been reported, synthetic (±)-pseudophrynaminol (**258**) is a potent noncompetitive blocker of nicotinic receptors.[16]

1.2.24 Pyridines

A potent analgesic alkaloid isolated from skin extracts of an Ecuadoran dendrobatid frog (*Epipedobates tricolor*) in the late 1970s elicited responses in mice that were similar to the effect of morphine alkaloids but approximately 200 times more potent.[13] The structure of the alkaloid responsible for this analgesic effect was finally reported in 1992 on the basis of NMR spectroscopic data and was shown to be **208/210**.[73] NMR spectroscopic analysis was preformed on the *N*-acetyl derivative.[73] Three derivatives have been identified to date and are known as the epibatidines. The pyridinic alkaloids have a 6-chloro-3-pyridinyl skeleton, and an azabicyclo[2.2.1]-heptane group is found at the 3-position and can be *N*-substituted. A structurally related alkaloid phantasmidine **222/224B** has been isolated from an Ecuadoran dendrobatid frog (*Epipedobates tricolor*).[54]

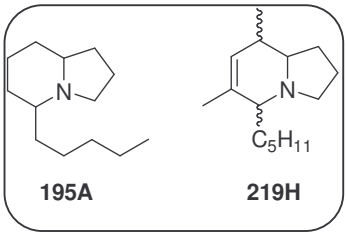


Epibatidine alkaloids have been detected only in South American frogs of the genus *Epipedobates*. A dietary source is presumably a food chain of plant to arthropod to frog. Epibatidines are highly toxic with an LD_{50} of about 0.4 μg per mouse and are potent analgesics about 200 fold greater than morphine. The toxicity and analgesic activity of these alkaloids are due to their ability to activate nicotinic receptors.[74]

1.2.25 Tentative and unclassified alkaloids

There are about 150 alkaloids that have not been classified into any of the 24 structural classes of amphibian skin alkaloids, of interest are the other izidines.

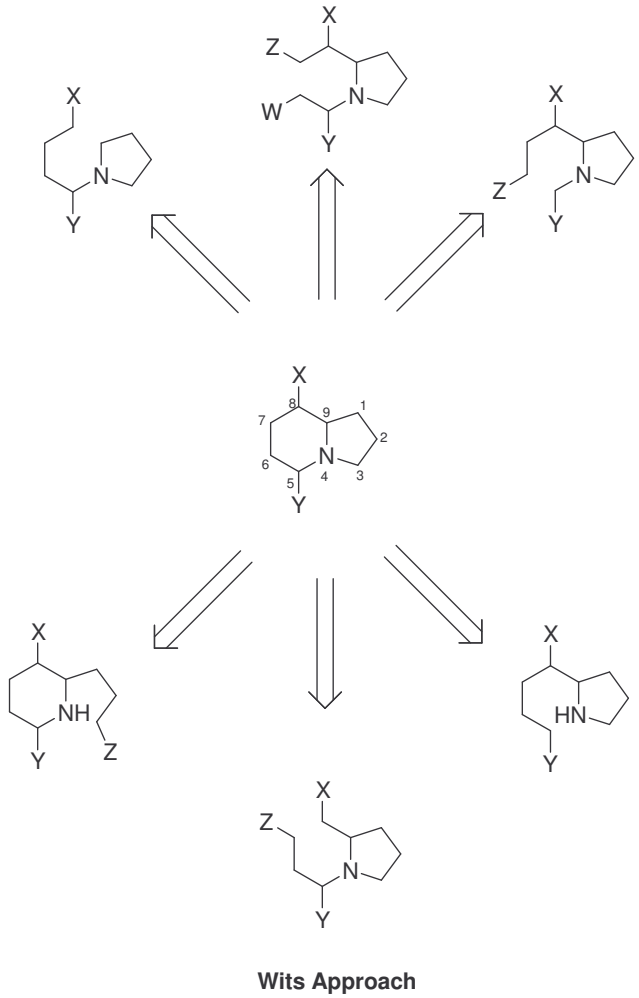
Other Izidines



A number of alkaloids detected in the extracts of anuran skins have mass spectra and empirical formulas which suggest that they are further bicyclic izidines. Classes include 5-monosubstituted indolizidines, although two of the three alkaloids originally thought to belong to this class were shown to be 3,5-disubstituted pyrrolizidines when prepared synthetically.[16,75] 5-Monosubstituted indolizidine **195A** is the only alkaloid identified from amphibian sources that is now part of this class.[5] Several appear to be dehydroizidines, with both the indolizidine and quinolizidine skeletons being observed. There are di-, tri-, and tetrasubstituted izidines as well as ring hydroxylated izidines. Unfortunately, all these alkaloids are only found in trace amounts in dendrobatid frogs, and as a result most of the proposed structures are hypothetical based on analogies, mass spectra and occasionally vapor-phase FTIR spectral data. No toxicity or biological activity studies have been reported. Interestingly *Dendrobates auratus* when fed on leaf-litter arthropods was shown to contain dehydroizidine **219H** as a minor alkaloid.[25]

1.3 Reported syntheses of 5,8-disubstituted indolizidines

To date there have been several reported syntheses of 5,8-disubstituted indolizidines. The majority of groups focus on a primary disconnection between either C-3 and N or C-5 and N as illustrated in **Scheme 1.1** below, thereby affording access to the bicyclic skeleton via a piperidine or pyrrolidine intermediate. Reports of alternative approaches are few, and the approach adopted by our own research group (the "Wits approach") revolves around the utilization of enaminone chemistry allowing us a unique approach to the synthesis of these alkaloids, with a primary disconnection being between C-7 and C-8 (**Chapter 2, Sections 2.2-2.5**) as illustrated below in **Scheme 1.1**.



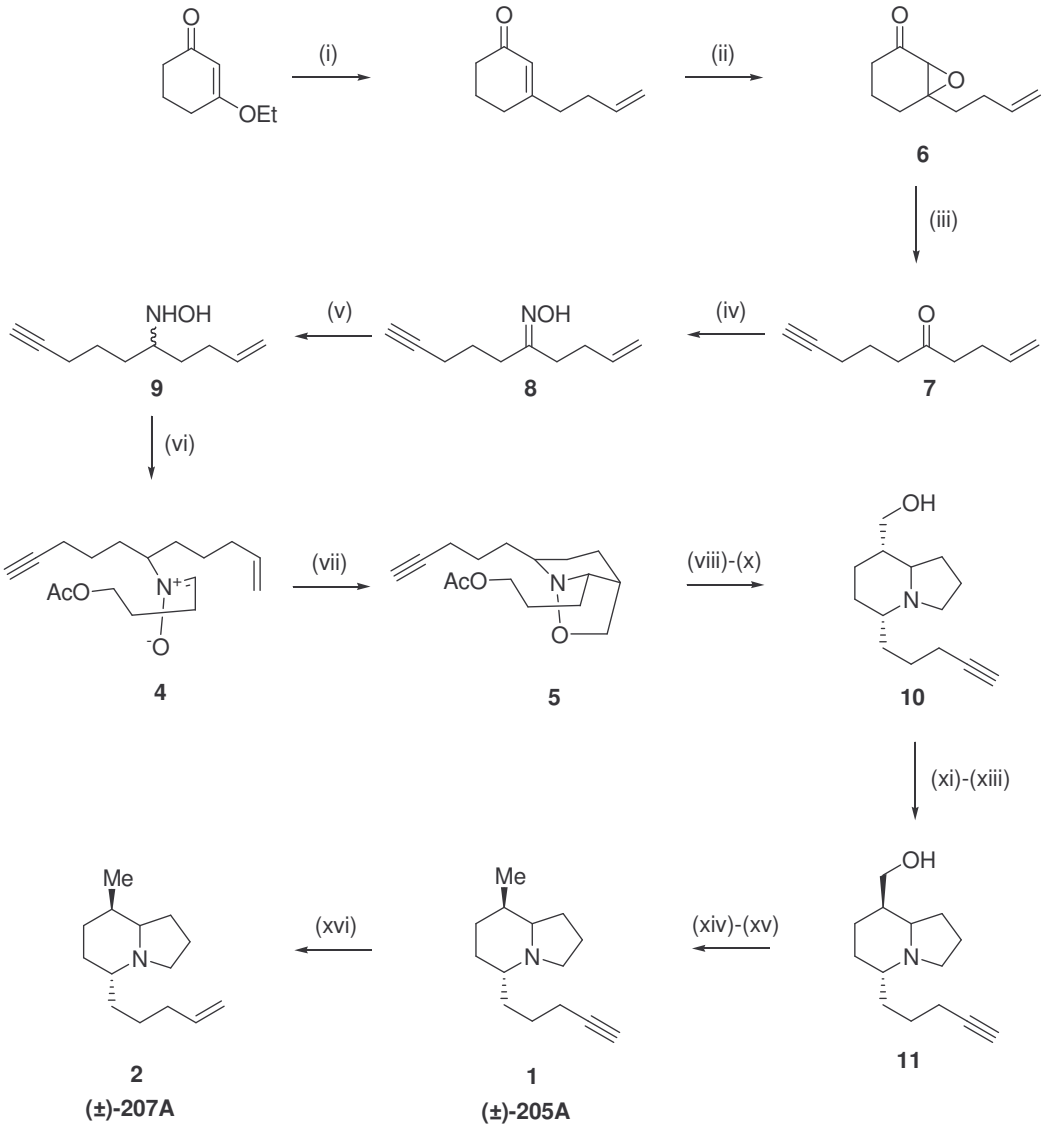
Scheme 1.1: Disconnection approaches utilized in the synthesis of 5,8-disubstituted indolizidines

Presented below is an overview of the previously reported syntheses of 5,8-disubstituted indolizidines, presented in chronological order as far as possible, to highlight the progression of the syntheses over the years.

1.3.1 Holmes and co-workers[76,77]

Holmes *et al.* reported the first formal synthesis of 5,8-disubstituted indolizidine alkaloids in 1988 in a communication published in the *Journal of the American Chemical Society*.[76] This was followed by a full paper in the *Journal of Organic Chemistry* in 1991,[77] detailing the stereoselective synthesis of (±)-indolizidines, **205A [1]** and **207A [2]**, as well as the enantioselective synthesis of (–)-indolizidine **209B [3]**. Their synthetic approach involved building the piperidine ring first, followed by the construction of the pyrrolidine ring, with the key step involving an intramolecular dipolar cycloaddition of the (*Z*)-*N*-alkenylnitrone **[4]** which gave the isoxazolidine **[5]** as the only isolated product (**Scheme 1.2**). The stereocontrol observed in the cycloaddition arises from the preference for a chair-like folding in which the substituent α to nitrogen adopts a *pseudo*-equatorial orientation. The stereoselective synthesis of **(±)-205A [1]** and **(±)-207A [2]** proceeded in 15 and 16 steps respectfully, with an overall yield of 18% for both alkaloids.

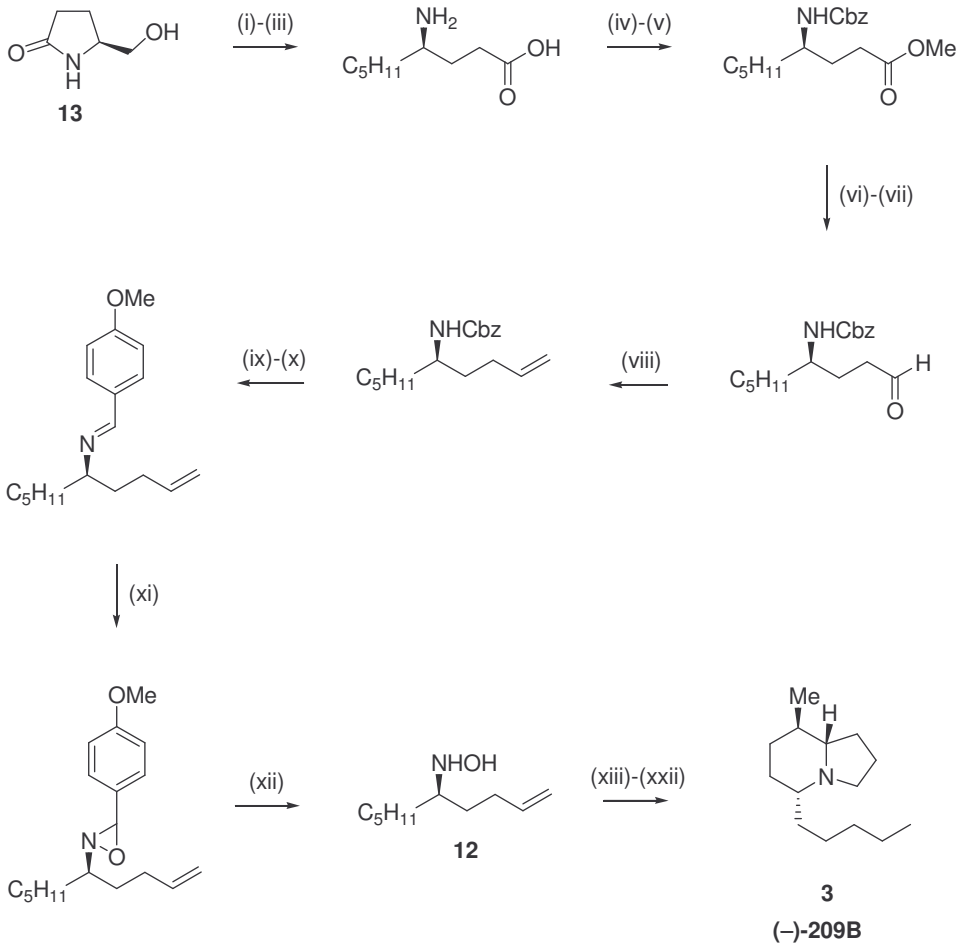
The synthesis of **(±)-205A [1]** and **(±)-207A [2]** began with an Eschenmoser fragmentation of an *α,β*-epoxy ketone **[6]** allowing access to the acetylenic side chain. Acetylenic ketone **[7]** was treated with hydroxylamine to give oxime **[8]**. A sodium cyanoborohydride reduction afforded the unstable (±)-*N*-alkenylhydroxylamine **[9]** which was condensed with 4-acetoxybutanal to give (*Z*)-nitrone **[4]**. The intramolecular dipolar cycloaddition gave the isoxazolidine **[5]**. Hydrolysis of the acetate under alkaline conditions, mesylation accompanied by spontaneous cyclisation and reductive N-O bond cleavage yielded the 5,8-disubstituted indolizidine **[10]**. Conversion into **(±)-205A [1]** and **(±)-207A [2]** required epimerization at the C-8 position and deoxygenation, this was achieved by oxidation to the aldehyde, base-catalyzed epimerization to the equatorial aldehyde, and reduction to the epimeric alcohol **[11]**. Mesylation and displacement with Super-Hydride gave **(±)-205A [1]**, subsequent reduction of **[1]** under hydrogen atmosphere with Lindlar catalyst afforded **(±)-207A [2]**.



Scheme 1.2: *(i) CH_2=$CHCH_2CH_2MgBr$, 96%; (ii) H_2O_2, NaOH (cat), 98%; (iii) H_2NNHTs, 69%; (iv) $NH_2OH.HCl$, 92%; (v) $NaCNBH_3$; (vi) 4-acetoxybutanal; (vii) $PhCH_3$, Δ, 63%, (3 steps); (viii) K_2CO_3 (cat), MeOH, 95%; (ix) MsCl; (x) Zn, HOAc, 99%, (2 steps); (xi) $(COCl)_2$, DMSO; (xii) K_2CO_3 (cat), MeOH; (xiii) $NaBH_4$, 57%, (3 steps); (xiv) MsCl; (xv) $LiEt_3BH$, 90%, (2 steps); (xvi) H_2, Lindlar catalyst, EtOAc, 100%*

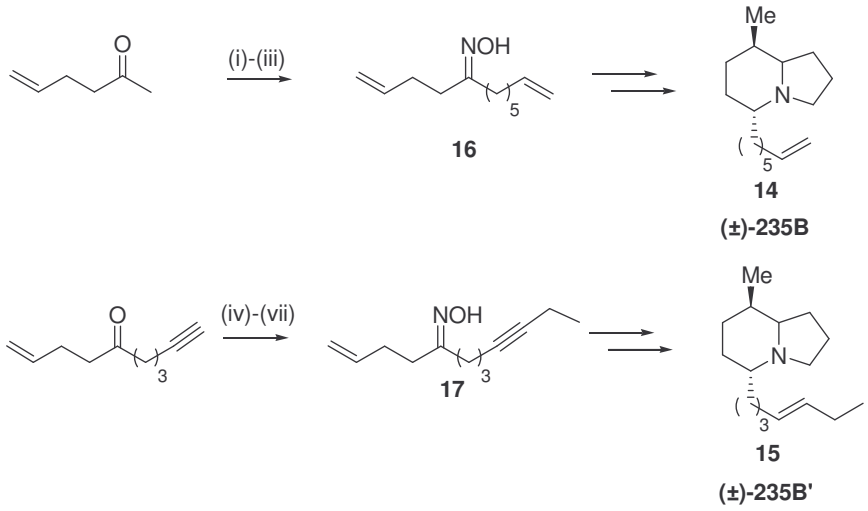
An asymmetric synthesis of **(–)-209B [3]** was achieved by using an enantiomerically pure *N*-alkylhydroxylamine precursor **[12]** synthesized in 53% overall yield from (*S*)-5-(hydroxyl-methyl)-2-pyrrolidone **[13]** by a chain extension sequence (**Scheme 1.3**)[77]. Application of the

previously described intramolecular nitrone methodology afforded enantiomerically pure **(–)-209B [3]** in a 5-9% yield in 22 steps.



Scheme 1.3: (*i) TsCl, 92%; (ii) n-Bu*$_2$*CuLi, 88%; (iii) 2M HCl, Δ, 100%; (iv) CbzCl, 89%; (v) HCl, MeOH, 100%; (vi) DIBAL, 99%; (vii) (COCl)*$_2$*, DMSO, 86%; (viii) Ph*$_3$*P=CH*$_2$*, 91%; (ix) 4,4'-di-tert-butylbiphenyl, Li, 95%; (x) p-MeO-C*$_6$*H*$_4$*-CHO, 100%; (xi) mCPBA, 88%; (xii) NH*$_2$*OH.TsOH, NaOH, (xiii)-(xxiii)* ***Scheme 1.2*** *(steps vi-xvi), 9-17%, (12 steps)*

In 1991 Collins and co-workers reported a synthesis of indolizidines (±)-**235B [14]** and (±)-**235B' [15]**[78] expanding on the Holmes methodology,[76,77] once again using the intramolecular thermal cycloaddition of the (*Z*)-*N*-alkenylnitrones. The synthesis involved the preparation of oximes **[16]** and **[17]** (**Scheme 1.4**) after which the Holmes approach allowed access to **[14]** and **[15]**.



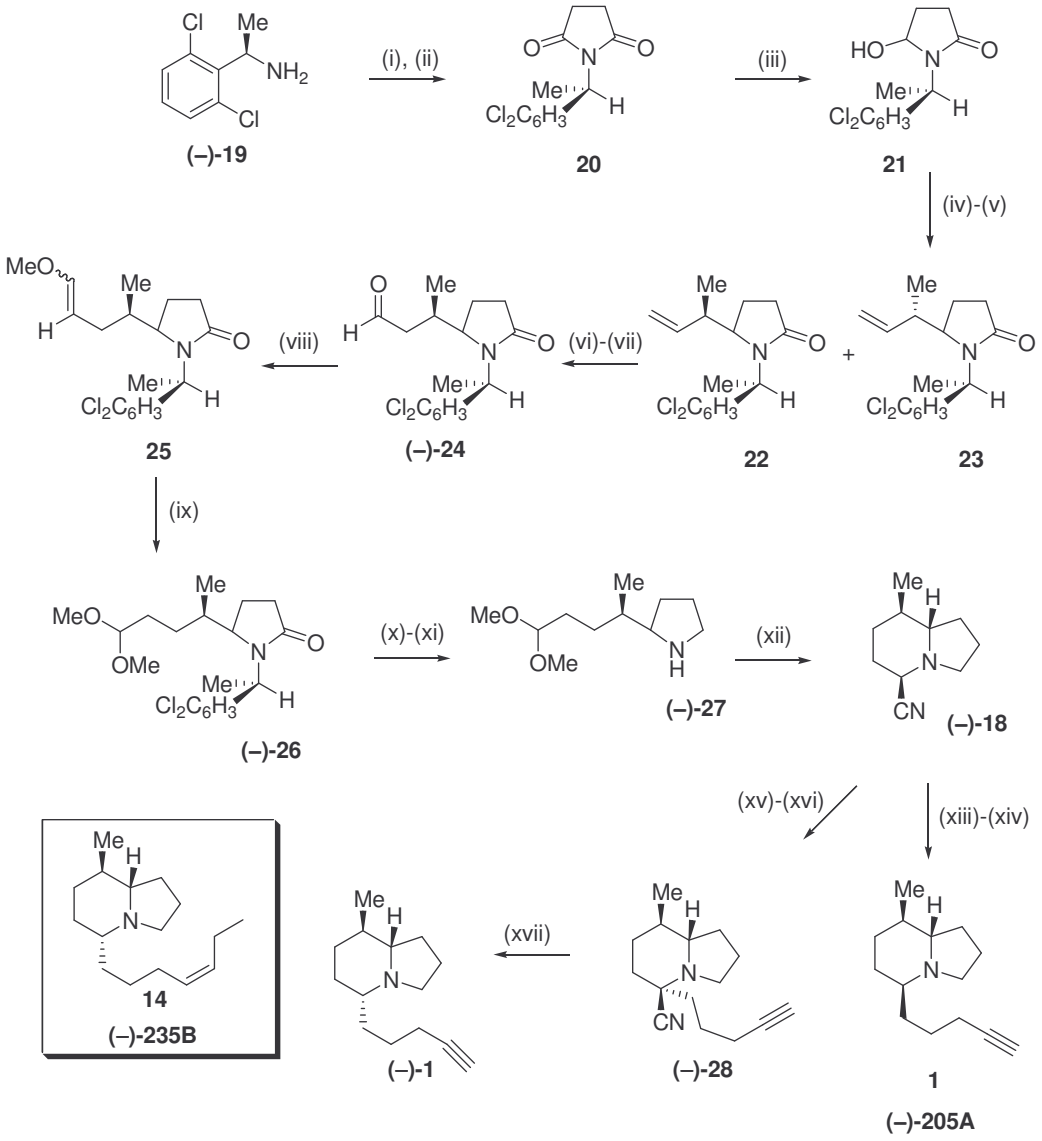
Scheme 1.4: *(i)H_2NNMe_2, 67%; (ii) n-BuLi, $Br(CH_2)_4CH{=}CH_2$; (iii) $NH_2OH.HCl$, NaOAc, 69% (2 steps); (iv) $HOCH_2CH_2OH$, pyridinium toluene-p-sulfonate, 75%; (v) n-BuLi, TMEDA; (vi) EtI, 67% (2 steps);(vii) $NH_2OH.HCl$, 95%*

1.3.2 Polniaszek and Belmont[79,80]

Polniaszek and Belmont were the second group to report a synthesis of 5,8-disubstituted indolizidine alkaloids, publishing a full paper in the *Journal of Organic Chemistry* in 1991[80] detailing the synthesis of indolizidines (–)-**205A [1]** and (–)-**235B [14]**. Their synthesis involved the preparation of a common late-stage intermediate, α-aminonitrile **[18]** which could be readily converted into (–)-**205A [1]** and (–)-**235B [14]** (**Scheme 1.5**).

The synthesis of (–)-**[1]** and (–)-**[14]** began with the thermal condensation of (*S*)-(–)-α-phenethylamine (–)-**[19]** and succinic anhydride. Reduction of the resulting succinimide **[20]** with lithium triethylborohydride produced hydroxy lactam **[21]** as a 95:5 mixture of diastereomers. Tosylation and treatment with crotylmagnesium chloride produced a mixture of two crotyl lactams **[22]** and **[23]** in a 70:30 ratio. The mixture was hydroborated, separated and then oxidized under Swern conditions to give aldehyde (–)-**[24]**. Wittig olefination afforded enol ether **[25]** as an inseparable mixture of *Z* and *E* isomers. Stirring in anhydrous methanol in the presence of camphorsulfonic acid yielded the dimethyl acetal **[26]**. The

lactam (–)-**[26]** was reduced to the corresponding pyrrolidine and the chiral directing group was removed under hydrogenolysis to give amino acetal (–)-**[27]**.

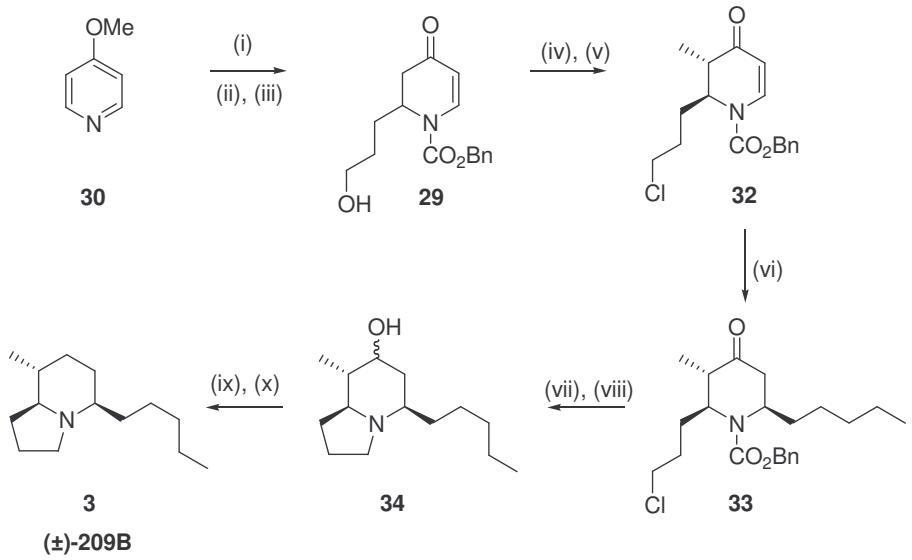


Scheme 1.5: *(i) Succinic anhydride; (ii) THF-n-Bu_2O, CDI, 87% (2 steps); (iii) $LiEt_3BH$, 95%; (iv) p-$MePhSO_2H$, 99%; (v) crotylmagnesium chloride, 99%; (vi) a) $(Sia)_2BH$ b) chromatography, 52%; (vii) $(COCl)_2$, DMSO, 93%; (viii) (methoxymethylidene)triphenyl-phosphorane, 90%; (ix) CSA, MeOH, 99%; (x) $LiAlH_4$, 89%; (xi) H_2, 10% Pd/C, 90%; (xii) KCN, 99%; (xiii) $HC{\equiv}C(CH_2)_3MgBr$, 74%; (xiv) KF, 83%; (xv) a) LDA, b) $HC{\equiv}C(CH_2)_3Cl$, 64%; (xvi) KF, 89%; (xvii) $NaBH_4$, 95%*

Hydrolysis of (–)-**[27]** in the presence of potassium cyanide afforded the key intermediate, the α-aminonitrile (–)-**[18]**. Bruylants' reaction of [1-(trimethylsilyl)pent-1-yn-5-yl]magnesium chloride with α-aminonitrile (–)-**[18]** followed by the removal of the trimethylsilyl group with aqueous potassium fluoride afforded the 5*S*,8*R*,8*aS* configurational isomer of (–)-**205A [1]**. Alternatively alkylation of α-aminonitrile (–)-**[18]**, with 5-(trimethylsilyl)pent-4-yn-1-yl chloride and subsequent desilylation yielded α-aminonitrile (–)-**[28]**. Reduction of the iminium ion derived from (–)-**[28]** afforded the 5*R*,8*R*,8*aS* configurational isomer of **205A** (–)-**[1]**. In a similar manner starting from α-aminonitrile (–)-**[18]** both conformational isomers of **235B** (–)-**[14]** could be obtained by using the appropriate Grignard reagent or haloalkyl compound.

1.3.3 Comins and Zeller[81]

Comins and Zeller reported the synthesis of (±)-indolizidine **209B [3]**, utilizing an *N*-acyldihydropyridone **[29]** (**Scheme 1.6**).

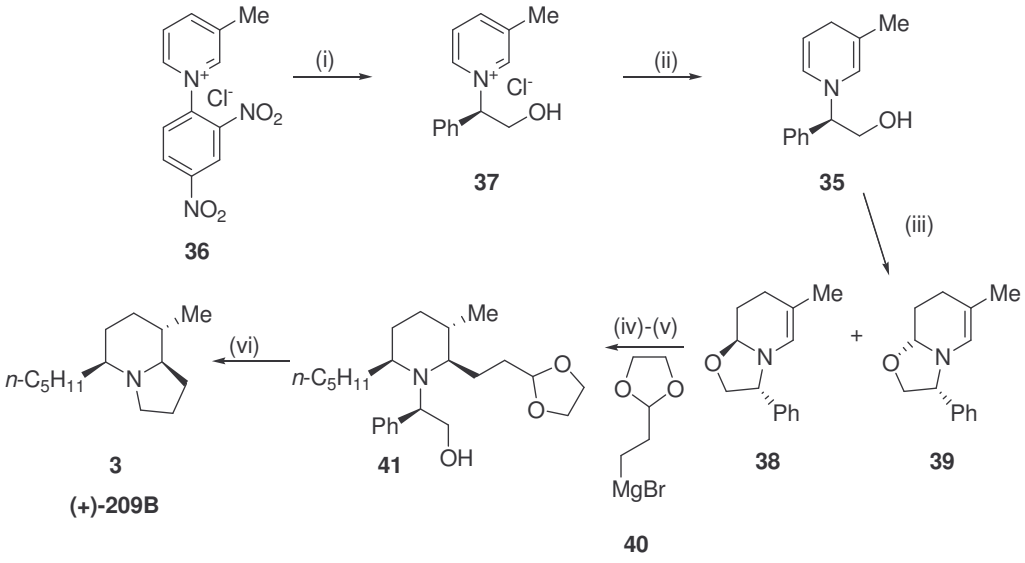


Scheme 1.6: *(i) $ClMgO(CH_2)_3MgCl$ **[31]**; (ii) BzOCOCl; (iii) H_3O^+ 70% (3 steps); (iv) NCS, PPh_3, 85%; (v) NaHMDS, MeI, 90%; (vi) $BF_3.OEt_2$, CuBr, $CH_3(CH_2)_4MgBr$, 82%; (vii) H_2, Pd/C, Li_2CO_3, 87%; (viii) H_2, Pt/C, 85%; (ix) N,N'-TCDI, DMAP, 77%; (x) Bu_3SnH, AIBN, 42%*

The synthesis began with the preparation of dihydropyridone **[29]** from 4-methoxypyridine **[30]**, Grignard reagent **[31]** and benzyl chloroformate. Conversion of **[29]** into the desired diastereomer **[32]** was achieved in two steps. Subsequent copper-mediated 1,4-addition of *n*-pentyl magnesium bromide gave the *cis*-piperidone **[33]**. Hydrogenative removal of the benzyl carbamate and cyclisation was achieved by treating initially with palladium on carbon for the protecting group removal, and later with platinum on carbon for the cyclisation affording alcohol **[34]**. The alcohol was converted into the thiocarbonyl derivative and deoxygenated with tributylstannane and azobisisobutylonitrile to give **(±)-209B [3]** in seven steps in a 10.5% yield from 4-methoxypyridine **[30]**.

1.3.4 Gnecco and co-workers[82]

Gnecco *et al.* reported a short six-step synthesis of indolizidine **(+)-209B [3]** in 1991. The synthesis involved the preparation of the indolizidine from 3-picoline via a 1,4-dihydropyridine intermediate **[35]** (**Scheme 1.7**). Gnecco and co-workers, like Holmes,[76-77] Collins[78] and Comins,[81] decided to prepare the piperidine ring first, however they were the first group to report a synthesis with an initial disconnection between the C-3 and C-4 carbons of the indolizidine skeleton.



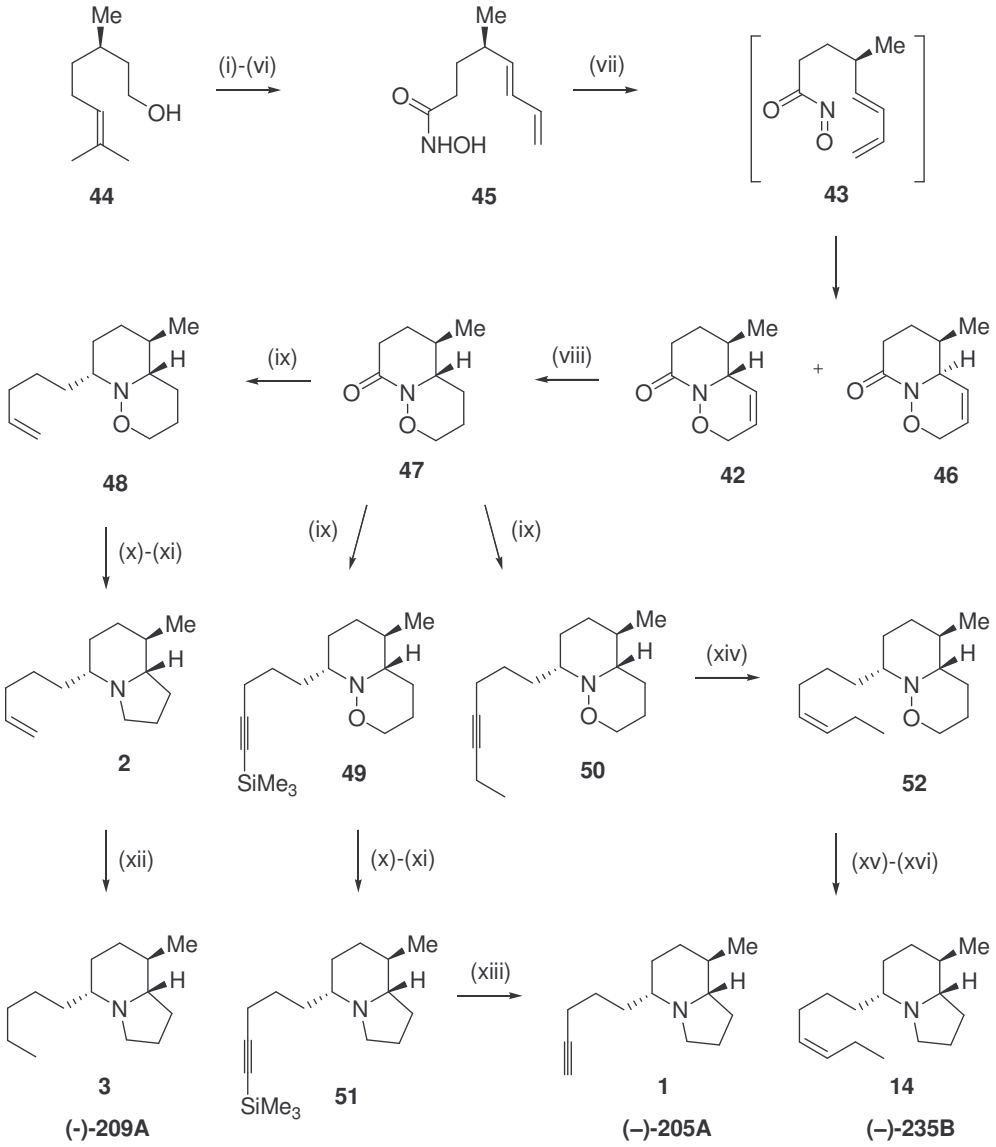
Scheme 1.7: *(i) (R)-(−)-phenylglycinol, 80-85%; (ii) $Na_2S_2O_4$, K_2CO_3; (iii) filtration over alumina, 65% (2 steps); (iv) $CH_3(CH_2)_4MgBr$, 75%; (v)* ***[40]****, 35%; (vi) H_2, H^+, 80%*

Treatment of 3-picoline with 1-chloro-2,4-dinitrobenzene afforded Zincke's salt **[36]**. Subsequent refluxing with (*R*)-(−)-phenylglycinol gave salt **[37]**. Refluxing a two phase mixture of diethyl ether and aqueous **[37]** with sodium sulfate and potassium carbonate yielded the 1,4-dihydropyridine intermediate **[35]**, which isomerized to oxazolidines **[38]** and **[39]** in a 9:1 ratio. Subsequent treatment with *n*-pentylmagnesium bromide followed by treatment with Grignard reagent **[40]** afforded a mixture of three new oxazolidines. The major isomer **[41]** was isolated by flash column chromatography, and hydrogenation in acidic media furnished **(+)-209B [3]** in an overall yield of 8-10%.

1.3.5 Kibayashi and Shishido[83,84]

Kibayashi and Shishido reported a synthesis of indolizidines **205A [1]**, **207A [2]**, **209B [3]** and **235B [14]** in 1992. The synthesis was similar in key aspects to those of Holmes[76-77] and Collins,[78] focusing on the preparation of a bicyclic oxazinolactam **[42]** which could be utilized as a common chiral intermediate. Their approach to the oxazinolactam **[42]** was however unique, involving an asymmetric intramolecular Diels-Alder reaction of the chiral *N*-acylnitroso compound **[43]** (**Scheme 1.8**).

(*R*)-Citronellol **[44]** was used to prepare (*R*)-4-methyl-5-hexanoic acid by known methods,[85] which was then converted into hydroxamic acid **[45]** in six steps. Oxidation of **[45]** by treatment with tetrapropylammonium periodate generated the *N*-acylnitroso compound **[43]** which underwent a spontaneous intramolecular [4+2] cycloaddition, yielding a 1.8:1.0 mixture of *trans* and *cis* bicyclic oxazinolactams **[42]** and **[46]** respectively. The desired product **[42]** was reduced by catalytic hydrogenation, yielding the desired dihydro product **[47]**. The alkylidene chain at position 8 in the target molecules was introduced at this stage by addition of an appropriate Grignard reagent, giving compounds **[48]**, **[49]** and **[50]**. The indolizidine skeleton was then accessed by reductive cleavage of the N-O bond, followed by an intramolecular cyclodehydration upon treatment with triphenylphosphine, carbon tetra bromide and triethylamine to give indolizidines **207A [2]** and **[51]**. Reduction of **207A [2]** under hydrogenation conditions gave indolizidine **209B [3]**, and removal of the trimethylsilyl group from **[51]** afforded indolizidine **205A [1]**, which was shown to be identical to the natural sample.



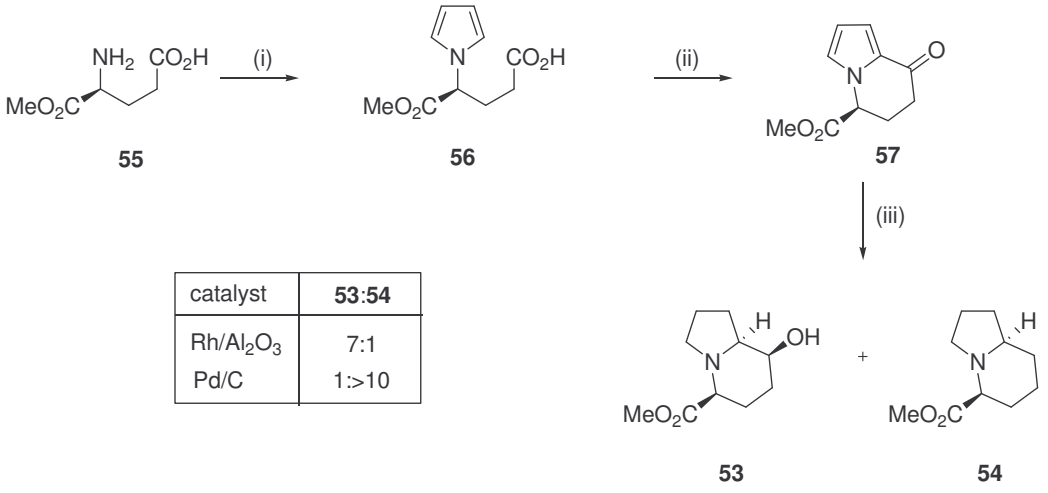
Scheme 1.8: *(i) ref. 85; (ii) CH_2N_2, 88%; (iii) O_3, Me_2S, 76%; (iv) (a) $Ph_3P{=}CH\text{-}CH{=}CH_2$ (b) hv, I_2, THF, 41%; (v) KOH, EtOH/H_2O, 92%; (vi) (a) $(COCl)_2$, (b) NH_2OH, 85%; (vii) n-Pr_4NIO_4, $CHCl_3$, 0°C, 88% (50% **[42]**); (viii) H_2, Pd/C, 96%; (ix) (a) RMgBr, THF, (b) $NaBH_4$, AcOH, 71% **[48]**, 70% **[49]**, 65% **[50]**; (x) Zn, AcOH, THF/H_2O; (xi) PPh_3, CBr_4, NEt_3, 73% **[2]** (2 steps), 73% **[51]** (2 steps); (xii) H_2, Pd/C, 93%; (xiii) KOH, MeOH, 77%; (xiv) (a) $CH_2CH(CH_2)_3MgBr$, THF, (b) $NaBH_4$, AcOH, 71%; (xiv) H_2, Pd/$BaSO_4$, quinoline; (xv) Zn, AcOH, THF/H_2O 87% (2 steps); (xvi) PPh_3, CBr_4, NEt_3, 70%*

Accessing indolizidine **235B [14]** required the reduction of compound **[50]** under a hydrogen atmosphere in the presence of palladium and barium sulfate and quinoline, affording **[52]**. Following this reductive cleavage and intramolecular cyclodehydration gave **235B [14]**.

1.3.6 Bond and co-workers[86]

Bond and co-workers reported a novel synthesis of indolizidine alkaloid precursors **[53]** and **[54]** in 1993. The synthesis involved an intramolecular Fridel-Crafts acylation of a pyrrole derived from L-glutamic acid **[55]** (**Scheme 1.9**). This was the first synthetic example where the primary disconnection of the indolizidine skeleton was not made between nitrogen and either C-4 or C-5.

The three step synthesis involved the preparation of pyrrole derivatives **[56]** from L-glutamic acid **[55]** by treatment with 2,5-dimethoxytetrahydrofuran under acidic conditions. Intramolecular Friedel-Crafts acylation of **[56]** proceeded smoothly, giving **[57]**. Reduction of **[57]** with rhodium on alumina gave the (*S*)-alcohol precursor **[53]** predominantly, whereas palladium on carbon gave the fully reduced precursor **[54]**. In a subsequent paper by Bond published in 1994 the origins of this chemoselectivity were discussed.[87]



55 56 57 53 54

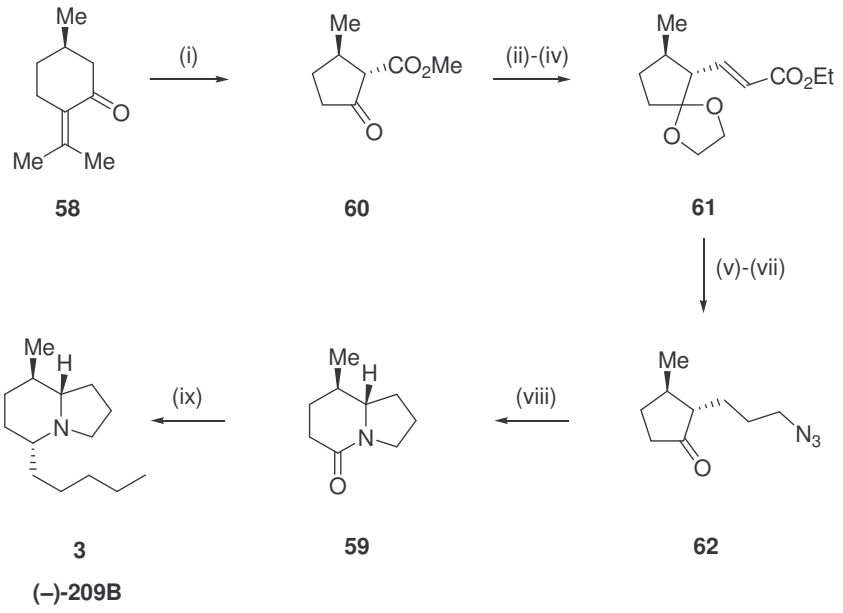
catalyst	53:54
Rh/Al_2O_3	7:1
Pd/C	1:>10

Scheme 1.9: *(i) 2,5-dimethoxytetrahydrofuran, sodium acetate, acetic acid, reflux (10 min), 50%; (ii) dry HCl, MeOH, 20℃ (3h), 50%; (iii) H_2, catalyst, 55 psi (16-24 h), 100%*

1.3.7 Aubé and co-workers[88]

Aubé and co-workers have described a synthesis of **(–)-209B [3]** from pulegone **[58]**. The key step was the formation of a bicyclic lactam **[59]** by the intramolecular Schmidt reaction (**Scheme 1.10**). The synthesis as outlined in detail below was eleven steps long and was accomplished in an overall yield of 22%.

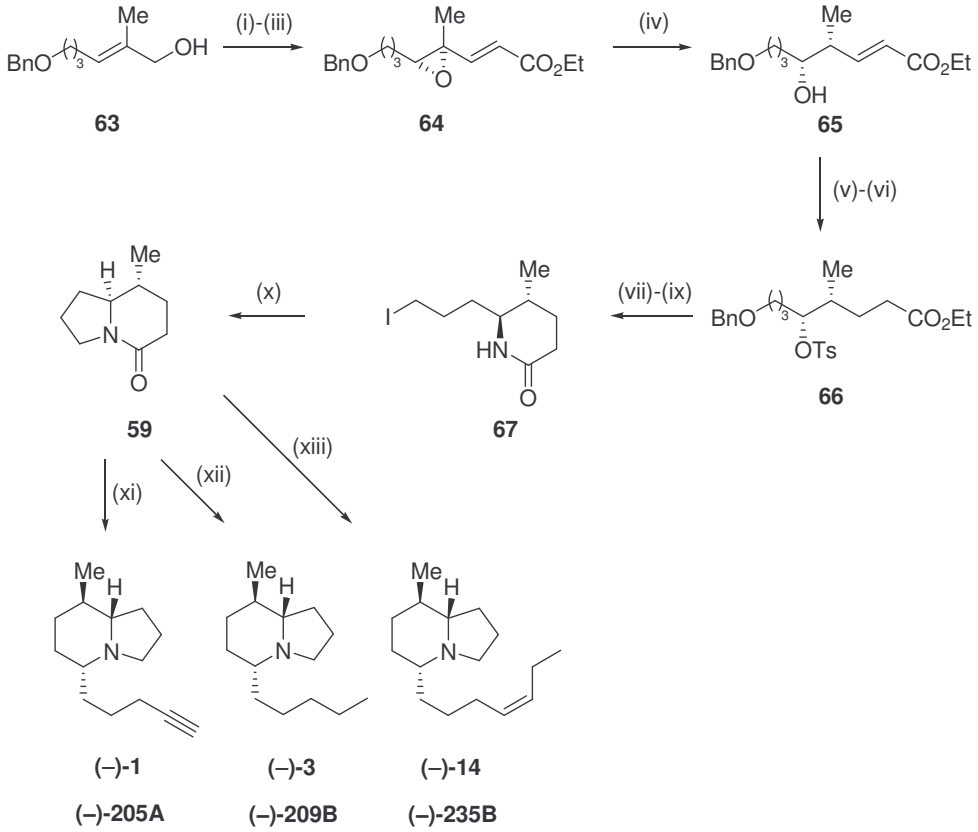
A Favorskii rearrangement of pulegone **[58]** followed by esterification and ozonolysis afforded cyclopentanone **[60]**, which was easily converted into α,β-unsaturated ester **[61]** in three steps. The double bond and ester group were both reduced under dissolving metal conditions, and the resulting alcohol was converted into the azide under Mitsunobu conditions. Mild Lewis acid conditions allowed the selective removal of the ketal in the presence of the azide affording keto azide **[62]**. An intramolecular Schmidt reaction led to formation of bicyclic lactam **[59]**. Treatment of **[59]** with the appropriate Grignard reagent followed by sodium borohydride reduction of the resulting imine gave indolizidine **(–)-209B [3]**.



Scheme 1.10: *(i) (a) Br_2, (b) NaOMe, (c) O_3, Me_2S, 72% (3 steps); (ii) ethylene glycol, H^+, 89%; (iii) $LiAlH_4$, 99%; (iv) (a) PCC, (b) $(EtO)_2P(O)CH_2CO_2Et$, DBU, LiBr, 82% (2 steps); (v) Li, NH_3, 94%; (vi) HN_3, PPh_3, DEAD, 89%; (vii) $LiBF_4$, H_2O/CH_3CN, 93%; (viii) TFA, 89-93%; (ix) (a) $C_5H_{11}MgBr$, (b) $NaBH_4$, 58% (2 steps)*

1.3.8 Satake and Shimizu[89]

Satake and Shimizu reported the chiral synthesis of indolizidines **(–)-209B [3]**, **(–)-205A [1]** and **(–)-235B [14]** in 1993. The approach, like that of Aubé,[88] concentrated on the synthesis of a bicyclic lactam **[59]** which was used as a common precursor (**Scheme 1.11**).

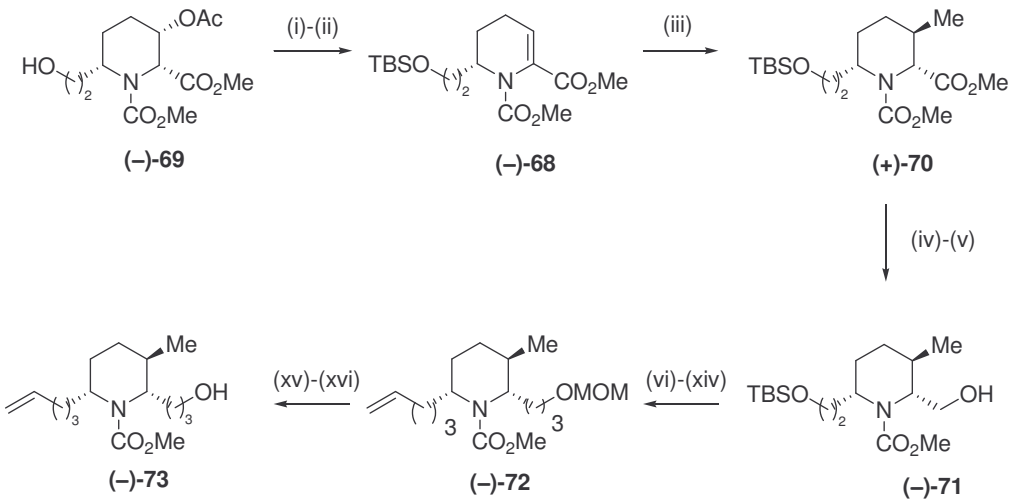


Scheme 1.11: *(i) $Ti(OiPr)_4$, (–)DET, t-BuOOH, CH_2Cl_2, 81%; (ii) $(ClCO)_2$, DMSO, CH_2Cl_2, 89%; (iii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 ℃, 97%; (iv) $Pd_2(dba)_3$, $CHCl_3$, n-Bu_3P, HCO_2H, NEt_3, dioxane, rt, 94%; (v) TsCl. pyridine, 4-DMAP (cat), CH_2Cl_2, 68%; (vi) H_2 (1 atm), Pd/C, AcOEt, NEt_3, 91%; (vii) NaN_3, DMF, 91%; (viii) H_2 (1 atm), Pd/C, AcOEt, 91%; (ix) (a) MsCl, NEt_3, CH_2Cl_2, (b) NaI, acetone; (x) NaH, THF, 68% (3 steps); (xi) (a) $HC{\equiv}CH(CH_2)_3MgBr$, (b) $NaBH_3CN$, MeOH, pH 3, 12%; (xii) n-Bu_4NF, 12%; (xiii) $CH_3(CH_2)_4MgBr$, (b) $NaBH_3CN$, MeOH, pH 3, 64%, (xiii) cis-$CH_3CH_2CH{=}CH(CH_2)_3MgBr$, (b) $NaBH_3CN$, MeOH, pH 3, 27%*

Starting from alcohol **[63]** the alkenyloxirane **[64]** was prepared via Sharpless epoxidation, Swern oxidation and Emmons-Horner olefination reactions. Hydrogenolysis of **[64]** to the homoallylic alcohol **[65]** was achieved with high regio- and stereoselectivity using formic acid with a palladium catalyst. Tosylation of **[65]** followed by hydrogenation of the olefin gave sulfonyl ester **[66]**. Azidation of **[66]**, followed by debenzylation, mesylation and iodation gave compound **[67]**, which was cyclised to bicyclic lactam **[59]** by treatment with sodium hydride. In the same manner as used by Aubé,[88] **[59]** was then converted into **(–)-209B [3]**, **(–)-205A [1]** and **(–)-235B [14]**.

1.3.9 Momose and Toyooka[90]

Momose and Toyooka described the asymmetric synthesis of indolizidines **207A [2]**, **209B [3]** and **235B' [15]** by a highly stereocontrolled Michael reaction of a 6-substituted-2,3-didehydropiperidine-2-carboxylate **[68]** (**Scheme 1.12**).

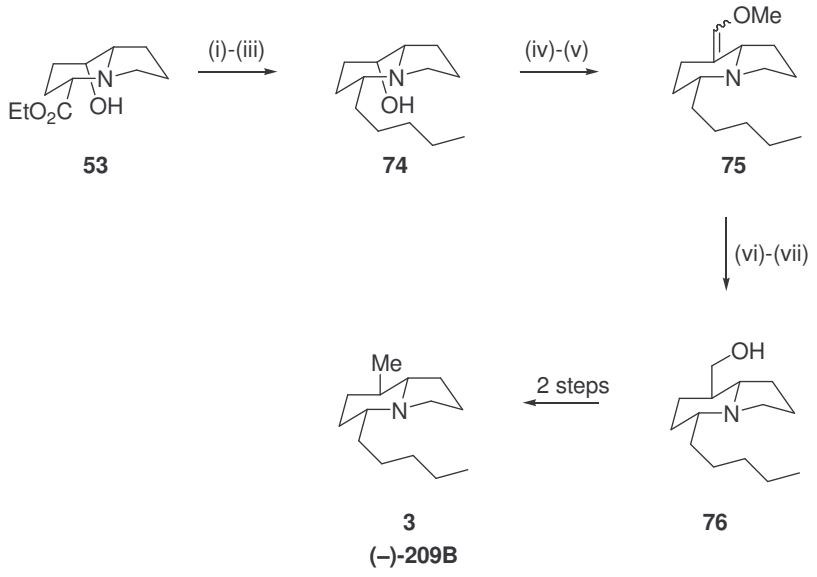


Scheme 1.12: *(i) TBSCl, NEt_3, DMAP, 95%; (ii) NaH, DMF:C_6H_6 (2:1), 50°C, 92%; (iii) Me_2CuLi, –60°C-rt, 92%; (iv) Super-Hydride, 94%; (v) NaH, DMF:C_6H_6 (2:1), 93%; (vi) Swern oxidation; (vii) NaH, $(Et_2O)_2P(O)CH_2CO_2Me$, 90% (2 steps); (viii) H_2, 5% Pd/C, MeOH; (ix) Super-Hydride, rt, 91% (2 steps); (x) MOMCl, Hünig's base, 93%; (xi) TBAF, 95%; (xii) MsCl, NEt_3, 0°C; (xiii) NaI, acetone, 85% (2 steps); (xiv) CH_2=$CHCH_2MgCl$, CuI, –30°C, 74%; (xv) n-PrSLi, HMPA; (xvi) HCl (conc), MeOH, Δ, 65% (2 steps)*

Starting from (−)-**[69]** the 6-substituted-2,3-didehydropiperidine-2-carboxylate (−)-**[68]** was accessed in two steps. The Michael reaction of (−)-**[68]** with lithium dimethyl cuprate in tetrahydrofuran was highly stereoselective giving compound (+)-**[70]** as the sole product. Subsequent reduction of (+)-**[70]** with Super-Hydride and treatment of the resulting alcohol with base afforded oxazolidinone (−)-**[71]**. The C-2 and C-6 side chains were modified to give olefin (−)-**[72]** in nine steps, and subsequent deprotection gave amino alcohol (−)-**[73]**. Transformation of (−)-**[73]** into (−)-**207A [2]** and (−)-**209B [3]** was previously reported by Kibayashi.[83-84]. Similarly **235B' [15]** was synthesized for the first time using the Kibayashi protocol.[83-84]

1.3.10 Jefford and co-workers[91-92]

In 1994 Jefford and co-workers reported the preparation of an indolizidine alkaloid precursor **[53]**[91], using the same methodology already described by Bond.[86-87] This publication was followed up with a full paper in 1995 describing how this precursor **[53]** was converted into indolizidine **209B [3]**[92] (**Scheme 1.13**).



53 **74** **75** **76** **3** **(–)-209B**

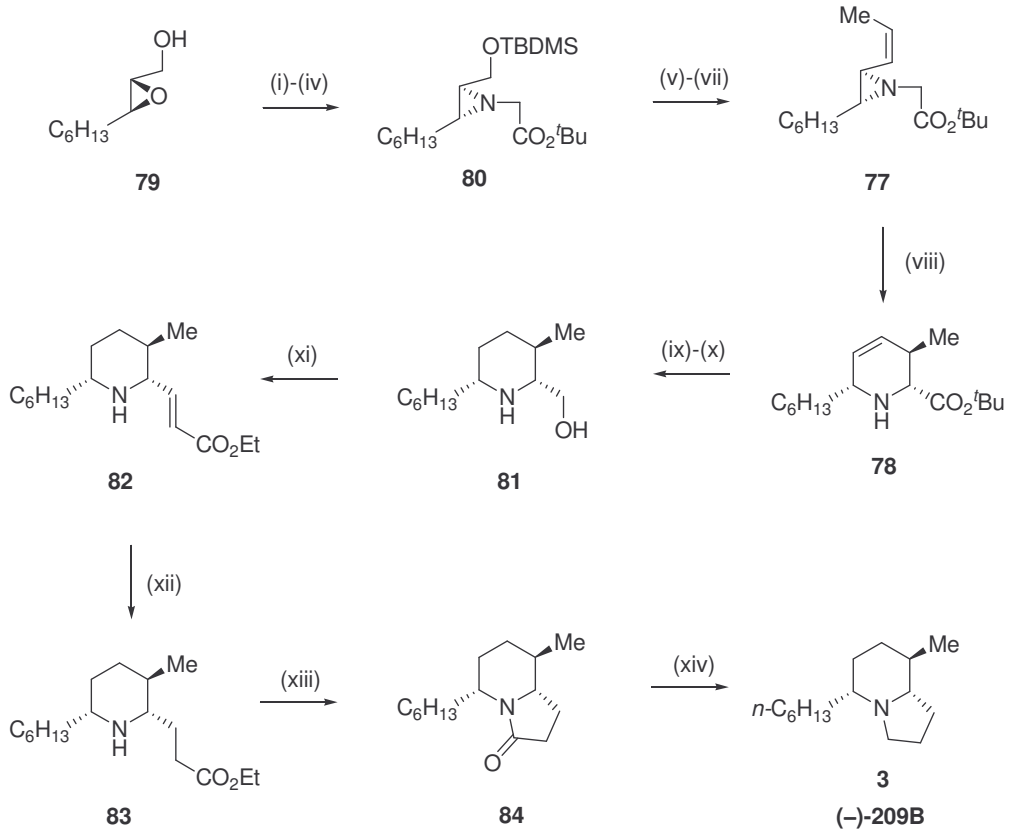
Scheme 1.13: *(i) DIBAL, hexane, –78 °C, 87%; (ii) $C_4H_9PPh_3^+Br^-$, KHMDS, THF, 59%; (iii) H_2, Pt, AcOEt, 92%; (iv) Jones oxidation, 86%; (v) $MeOCH_2PPh_3^+Cl^-$, KHMDS, THF, 54%; (vi) HCl (aq), Et_2O, 94%; (vii) $NaBH_4$, EtOH, 75%*

Starting from precursor **[53]** whose preparation was previously reported by Bond,[86-87] the ester was reduced to the equatorial aldehyde followed by Wittig olefination and hydrogenation to afford **[74]**. Oxidation of the alcohol with Jones' reagent followed by treatment with (methoxymethyl)triphenylphosphonium bromide and potassium hexamethyl-disilazide gave a mixture of (*E*)- and (*Z*)-methyl enol ethers **[75]**. Acid hydrolysis and subsequent reduction yielded alcohol **[76]** which was converted into **209B [3]** in two steps as originally described by Holmes[76-77]. Similarly Jefford *et al.* showed the synthesis of indolizidine (−)-**209B** was possible using the same approach.

1.3.11 Somfai and Åhman[93]

Somfai and Åhman described a novel enantioselective synthesis of (−)-indolizidine **209B [3]**. The synthesis revolved around a highly efficient aza-[2,3]-Wittig rearrangement of vinylaziridines **[77]** into tetrahydropyridine **[78]** (**Scheme 1.14**).

The synthesis starts from the known epoxy alcohol **[79]**. Treatment with sodium azide caused a nucleophillic ring opening of the epoxide, affording a mixture of azido diols. The alcohols were protected by silylation, and when treated with triphenylphosphine in refluxing toluene the aziridine was obtained with opposite stereochemistry to that of the epoxide. The nitrogen substituent was introduced by reaction with *tert*-bromoacetate and potassium carbonate and 18-crown-6 ether in tetrahydrofuran, giving aziridine **[80]**. Subsequent deprotection of the alcohol followed by Swern oxidation and Wittig olefination gave **[77]**. Treatment of **[77]** with LDA afforded the *cis*-2,6-disubstituted tetrahydropyridine derivative **[78]** as a single diastereomer. Hydrogenation of **[78]** followed by reduction with lithium aluminium hydride afforded alcohol **[81]**, after which Swern oxidation and Wittig olefination gave the α,β-unsaturated ester **[82]**. Hydrogenation afforded **[83]** and reduction with trimethylaluminium in benzene gave lactam **[84]**. Finally, reduction of **[84]** with lithium aluminium hydride yielded indolizidine (−)-**209B [3]**.

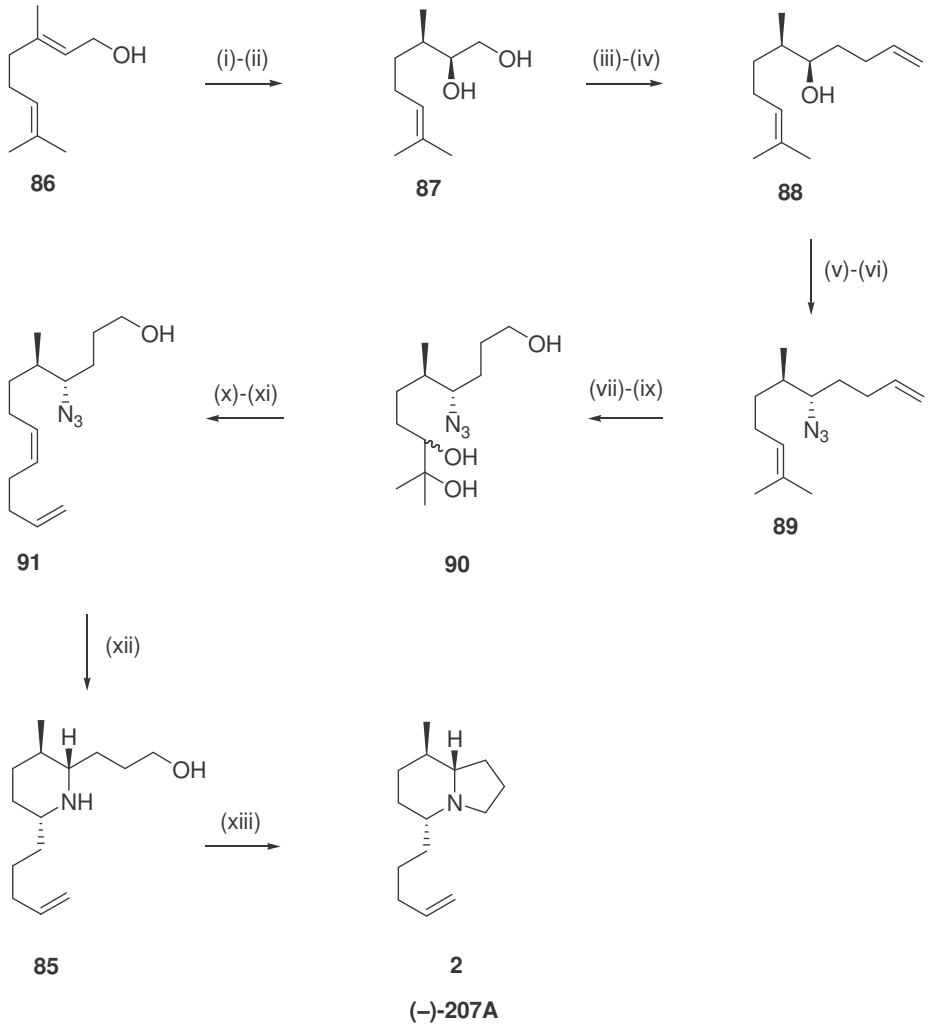


Scheme 1.14: *(i) NaN_3, NH_4Cl, $MeOCH_2CH_2OH/H_2O$, 89%; (ii) t-$BuMe_2SiCl$, CH_2Cl_2, NEt_3, DMAP, 90%; (iii) PPh_3, $PhCH_3$, Δ, 90%; (iv) $BrCH_2CO_2{}^tBu$, K_2CO_3, 18-crown-6, THF, 60%; (v) Bu_4NF, THF, 81%; (vi) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C; (vii) Ph_3PCH_2Me, THF, 80% (2 steps), (viii) LDA, THF, –78 °C, 97%; (ix) H_2, 5% Pd/C, EtOH, 55%; (x) $LiAlH_4$, THF, 0 °C-rt, 90%; (xi) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, then Ph_3PCHCO_2Et, 75%; (xii) H_2, 5% Pd/C, 4 kg/cm^2, EtOH, 84%; (xiii); Me_3Al, C_6H_6, 88%; (xiv) $LiAlH_4$, THF, Δ, 70%*

1.3.12 Taber and co-workers[94]

In 1995 Taber *et al.* reported a synthesis of (–)-indolizidine **207A [2]**. The synthesis was the first which allowed the direct establishment of both the relative and absolute configuration of the alkaloid. The key steps involved an azide cycloaddition followed by a retro-Mitsunobu cyclisation to **[85]** (**Scheme 1.15**).

The synthesis started from geraniol **[86]**. Sharpless epoxidation and subsequent reduction gave 2-hydroxycitronellol **[87]**. Tosylation and treatment with allylmagnesium chloride afforded product **[88]**. The alcohol was converted into azide **[89]** with inversion of configuration by mesylation followed by reaction with sodium azide. Subsequent epoxidation, ozonolysis and treatment with hydrogen perchlorate yielded the triol **[90]**.



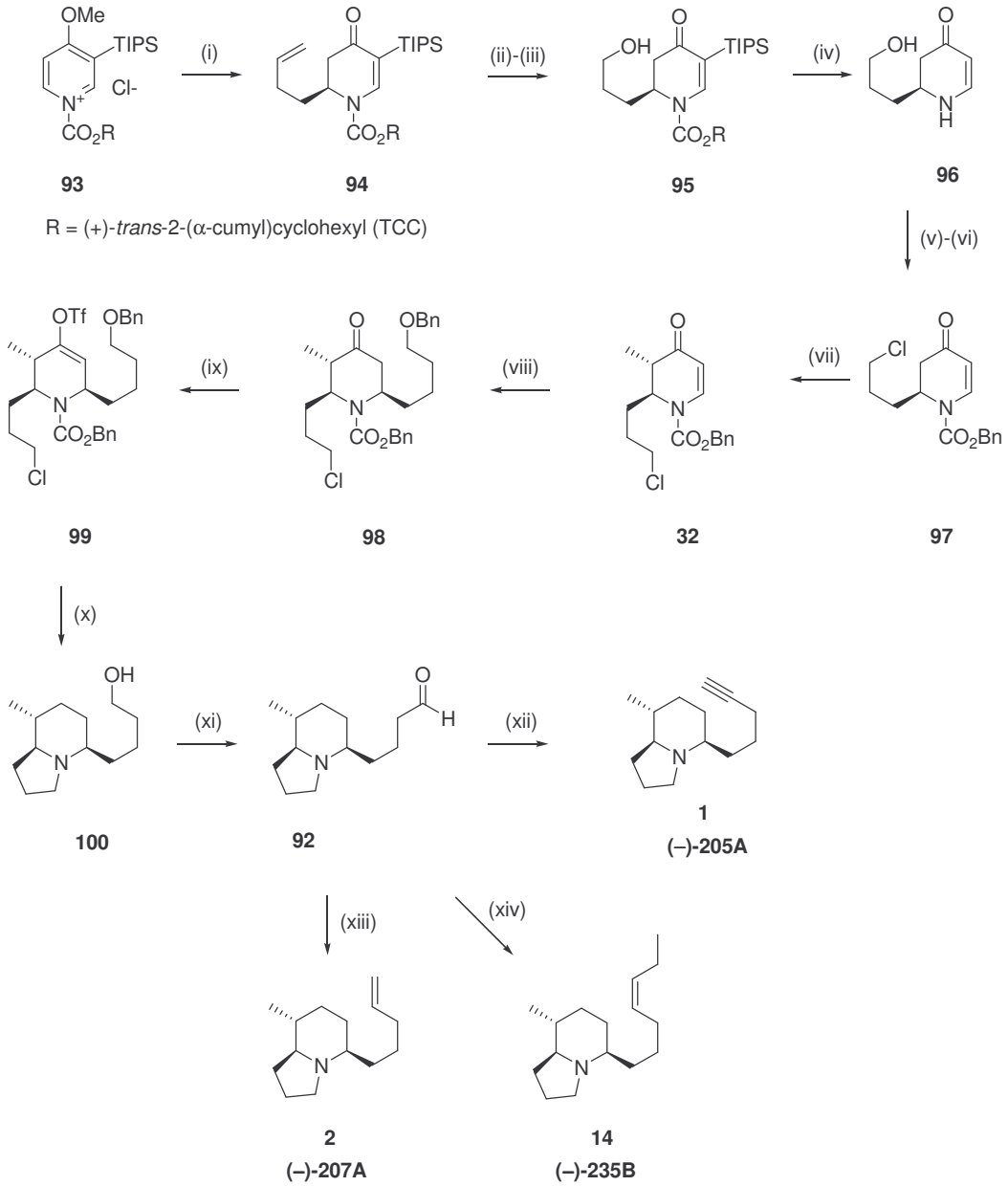
Scheme 1.15: *(i) L-(+)-diethyl tartrate, $(CH_3)_3COOH$, $Ti(OiPr)_4$, CH_2Cl_2, –20ºC (ii) $NaBH_3CN$, $BF_3.OEt_2$, 72% (2 steps); (iii) TsCl, (iv) $CH_2=CHCH_2MgCl$, 87% (2 steps), (v) MsCl, (vi) NaN_3, HMPA, 57% (2 steps); (vii) mCPBA; (viii) O_3, $NaBH_4$; (ix) $HClO_4/H_2O$, 90% (3 steps); (x) $NaIO_4$; (xi) $Ph_3P^+(CH_2)_3CH=CH_2\ Br^-$, BuLi, 57% (2 steps); (xii) DIBAL, 160℃, 63%; (xiii) PPh_3, CCl_4/CH_3CN, 71%*

Treatment with sodium periodate in dichloromethane gave an unstable solution of the aldehyde, which immediately underwent Wittig olefination, giving azide **[91]**. Thermolysis of azide **[91]** proceeded by a dipolar azide cycloaddition and subsequent fragmentation to give the cyclic imine. A selective reduction with DIBAL gave trisubstituted piperidine **[85]**. Cyclisation with triphenylphosphine/carbon tetrachloride afforded indolizidine (–)-**207A [2]**.

1.3.13 Comins and co-workers[95]

In 1997 Comins *et al.* reported that chiral *N*-acyl-2,3-dihydro-4-pyridones are excellent synthetic building blocks for the preparation of indolizidines, and they showed the synthesis of (–)-**205A [1]**, (–)-**207A [2] and** (–)-**235B [14]** from common intermediate **[92]** (**Scheme 1.16**).

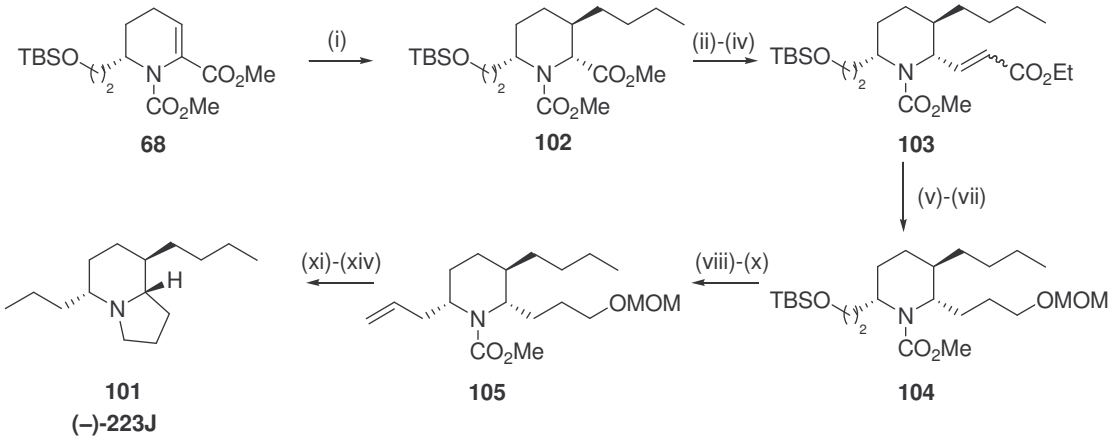
The synthesis was both regio- and stereoselective starting from chiral 1-acylpyridinium salt **[93]**. Treatment with the appropriate Grignard reagent gave the diastereomerically pure dihydropyridone **[94]**, which when exposed to osmium tetroxide afforded the corresponding aldehyde that was then reduced to the alcohol **[95]** with L-selectride. Removal of the chiral auxiliary and protodesilylation gave amino alcohol **[96]**. Selective *N*-acylation with benzyl chloroformate, followed by conversion of the alcohol into the chloride by treatment with triphenylphosphine and *N*-chlorosuccinimide gave **[97]**. Enolate formation using lithium hexamethyldisilazide and reaction with methyl iodide gave the *trans*-2,3-dihydro-4-pyridine **[32]** exclusively. Michael reaction of **[32]** gave (2*S*,3*S*,6*R*)-piperidone **[98]**. Regiospecific enolate formation by deprotonation with lithium hexamethyldisilazide and the addition of *N*-(2-pyridyl)triflimide afforded vinyl triflate **[99]**. Catalytic hydrogenation of the vinyl triflate using 5% platinum on carbon and 20% palladium hydroxide on carbon, followed by heating with sodium carbonate yielded alcohol **[100]**. Dess-Martin oxidation gave precursor **[92]** and a subsequent Seyferth-Gilbert reaction gave (–)-**205A [1]**. Wittig olefination of **[92]** allowed access to (–)-**207A [2]** and (–)-**235B [14]**.



Scheme 1.16: *(i) $CH{=}CH(CH_2)_2MgBr$; then H_3O^+, 91%; (ii) OsO_4 cat., $NaIO_4$; (iii) L-Selectride, 81% (2 steps); (iv) NaOMe, MeOH, 10% HCl, 89%; (v) n-BuLi, BnOCOCl, 79%; (vi) PPh_3, NCS, CH_2Cl_2, 94%; (vii) LHMDS, MeI, 96%; (viii) $BnO(CH_2)_4MgBr$, $CuBr.SMe_2$, $BF_3.OEt_2$, THF, –78°C, 89%; (ix) LHMDS, 2-[N,N-bis(trifluoromethylsulfonyl)amino]pyridine, 87%; (x) (a) H_2, Pt/C, EtOH; (b) H_2, $Pd(OH)_2$/C; (c) Na_2CO_3, 82%; (xi) Dess-Martin oxidation, 97%; (xii) $(MeO)_2P(O)CHN_2$, 41%; (xiii) $PPh_3P{=}CH_2$, 70%; (xiv) $Ph_3P{=}CHCH_2CH_3$, 86%.*

1.3.14 Toyooka *et al.*[96]

In 1997 Toyooka *et al*. reported the synthesis of indolizidine **223J [101]**, building on the protocol they had reported three years earlier.[90] Once again the synthesis involved the preparation of a didehydropiperidinecarboxylate **[68]** (**Scheme 1.17**).

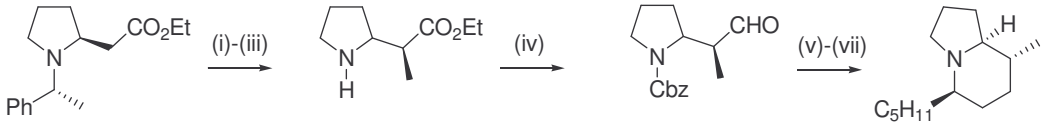


Scheme 1.17: *(i) (n-Butyl)$_2$CuLi, Et$_2$O, 94%; (ii) Super-Hydride, THF, 0°C, 95%; (iii) Swern oxidation; (iv) NaH, (EtO)$_2$P(O)CH$_2$CO$_2$Me, 81% (2 steps); (v) H$_2$, 5% Rh-C, EtOAc, 4 atm; (vi) Super-Hydride, THF, 0°C, 86% (2 steps); (vii) MOMCl, Hünig base, 86%; (viii) TBAF, 89%; (ix) Swern oxidation; (x) CH$_3$P$^+$Ph$_3$ Br$^–$, n-BuLi, THF, 64% (2 steps); (xi) H$_2$, 5% Pd(OH)$_2$; (xii) n-PrSLi, HMPA; (xiii) conc. HCl, MeOH, Δ; (xiv) PPh$_3$, CBr$_4$, NEt$_3$, 43% (4 steps)*

Starting from the 6-substituted-2,3-didehydropiperidine-2-carboxylate **[68]**, the stereoselective Michael reaction with (*n*-butyl)$_2$CuLi in diethyl ether afforded piperidine **[102]**. Selective reduction using Super-Hydride, followed by Swern oxidation and Wittig reaction gave olefin **[103]**. Reduction of the double bond and the ester followed by methoxy methyl protection of the resulting alcohol gave piperidine **[104]**. Desilylation of **[104]** using tetrabutylammonium fluoride, followed by Swern oxidation and Wittig olefination yielded **[105]**. As in their previous paper **[105]** was converted into indolizidine (–)-**223J [101]** using the Kibayashi protocol.[83-84]

1.3.15 Lhommet *et al.*[97]

A highly diastereoselective synthesis of indolizidine (–)-**209B [3]** was described by Lhommet *et al*. in 1998. The key step was the diastereoselective alkylation of a chiral cyclic β-amino ester **[106]** (**Scheme 1.18**). The (*S*,*S*) cyclic β-amino ester **[106]** was prepared in five steps from (*R*)-α-methylbenzylamine.[98] Replacement of the chiral auxiliary with an alternative protecting group gave **[107]** which was necessary to afford the transformation of the ester group into the aldehyde **[108]** using diisobutylaluminium hydride. Wittig olefination allowed the introduction of the pentyl substituent. Hydrogenation of the alkene, nitrogen deprotection, cyclization and diastereoselective reduction of the imine intermediate was achieved in one step by treatment with hydrogen in the presence of platinum oxide, yielding (–)-**209B [3]**.



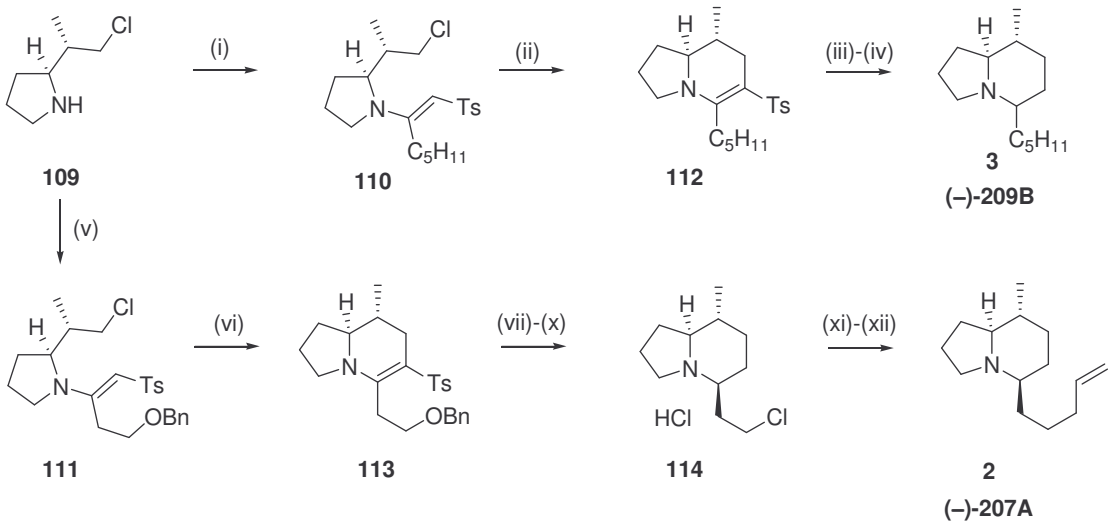
106 **107** **108** **3**
(–)-209B

Scheme 1.18: *(i) LDA, THF –70 °C; (ii) CH_3I, –70 °C; (iii) H_2, 10%Pd/C, EtOH, 93% (3 steps); (iv) $ClCO_2CH_2Ph$, K_2CO_3, $CHCl_3$, 74%; (iv) DIBAL, $PhCH_3$, –78 °C, 71%; (v) (a) $PPh_3{=}CHCOC_5H_{11}$, C_4H_9I, –78 °C-0 °C, (b) $PhCH_3$, 80 °C, 90%; (vii) H_2, PtO_2, MeOH, 50 °C, 56%*

1.3.16 Back and Nakajima[99]

Back and Nakajima reported a synthesis of indolizidines (–)-**209B [3]** and (–)-**207A [2]** in 2000. The synthesis was the first approach to disconnect the indolizidine skeleton between C-6 and C-7, and made use of acetylenic sulfones to access the bicyclic skeleton (**Scheme 1.19**).

Starting from chloroamine **[109]**, treatment with an appropriate acetylenic sulfone gave **[110]**, or **[111]**, and subsequent reaction with lithium diisopropylamide in tetrahydrofuran allowed cyclisation to the bicyclic skeletons **[112]** and **[113]** respectively. Reduction of **[112]** with sodium cyanoborohydride, followed by desulfonylation with sodium in liquid ammonia gave (–)-**209B [3]**. Debenzylation of **[113]** and treatment with thionyl chloride gave hydrochloride salt **[114]**, with the subsequent addition of cuprate **[115]** yielding the desired indolizidine (–)-**207A [2]**.



Scheme 1.19: *(i) $C_5H_{11}C{\equiv}CTs$, CH_2Cl_2, rt; (ii) LDA, THF, 74% (2 steps); (iii) $NaCNBH_3$; (iv) Na-NH_3, 66% (2 steps) (v) $BnO(CH_2)_2C{\equiv}CTs$, CH_2Cl_2, rt; (vi) LDA, THF, 82% (2 steps); (vii) $NaCHBH_3$, TFA-CH_2Cl_2; (viii) Na-NH_3, (ix) H_2, Pd/C, 66% (3 steps); (x) $SOCl_2$, HCl, 74%; (xi) KOH; (xii) $[CH{=}CHCH_2]_2Cu(CN)Li_2$* ***[115]****, 60% (2 steps)*

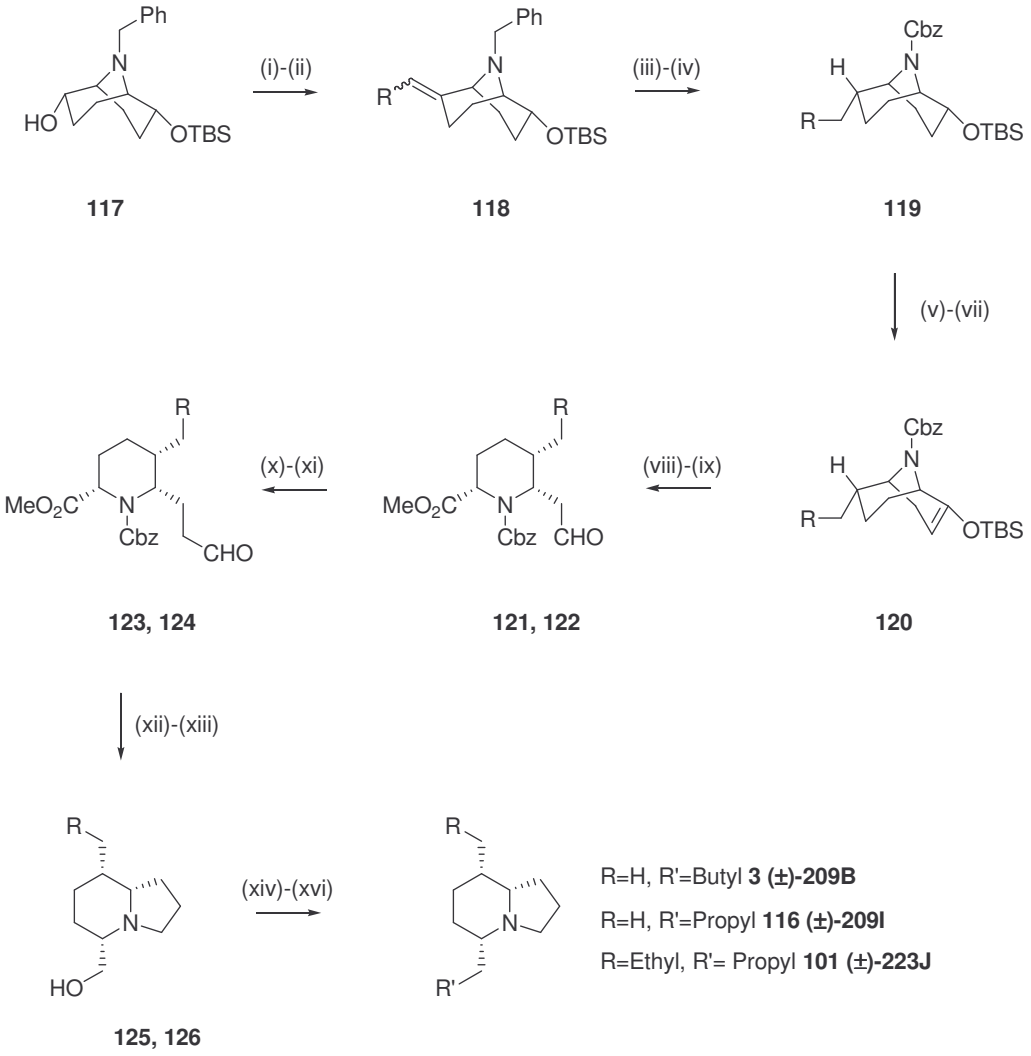
1.3.17 Michael and Gravestock[100]

In 2000 Michael and Gravestock published the synthesis of racemic indolizidine **209B [3]** and its (5*R**,8*S**,8a*S**)-(±) diastereomer, as well as the enantioselective synthesis of (–) **209B [3]** utilizing the Wits approach towards alkaloid synthesis. The synthesis is dealt with in detail in **Chapter 2**.

1.3.18 Rassat and Michel[50]

Rassat and Michel reported one of the first syntheses not to be restricted to the 8-methyl analogues, when they synthesized **209B [3]**, **209I [116]** and **223J [101]** (**Scheme 1.20**), the latter two having an 8-*n*-propyl substituent.

Starting from the 9-azabicyclo[3.3.1]nonane derivative **[117]**, Swern oxidation and Wittig olefination afforded **[118]**. Reduction of the double bond under hydrogenation conditions caused a simultaneous debenzylation. The amine was then protected by carbobenzyloxylation to give **[119]** which was converted into the silyl enol ethers **[120]** in three steps.



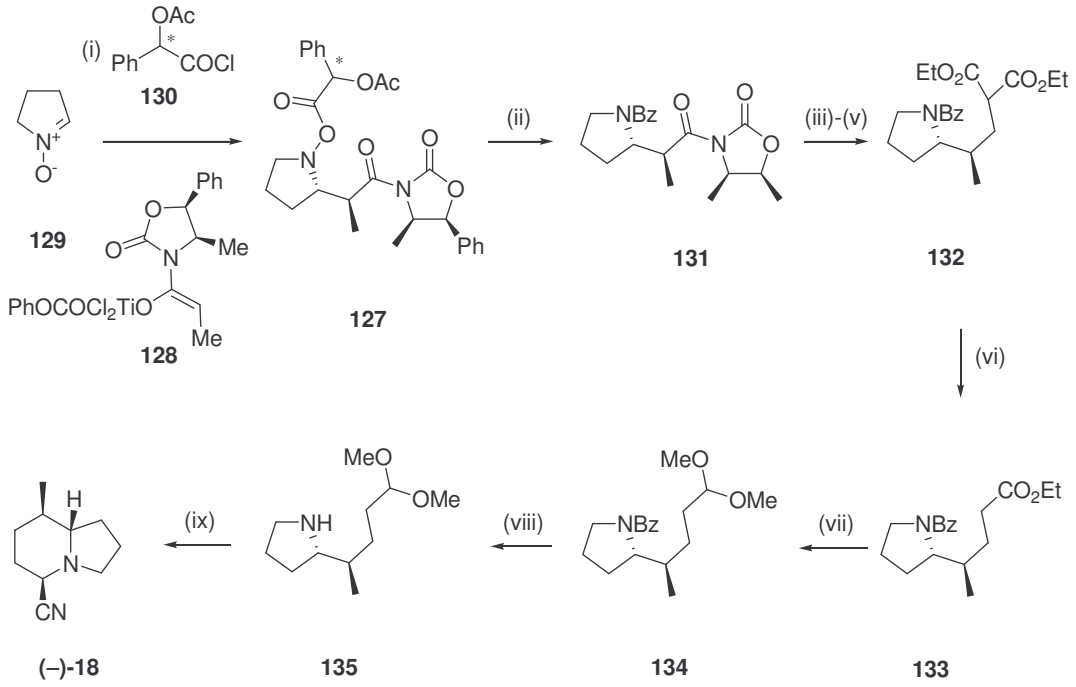
117 **118** **119** **120** **121, 122** **123, 124** **125, 126**

Scheme 1.20: *(i) Swern oxidation, 93%; (ii) (Ph_3PCH_2R)Br, t-BuOK, THF, 92% (R=H), 98% (R=CH_3); (iii) H_2, 10% Pd/C (wet), MeOH; (iv) CbzCl, K_2CO_3, acetone, 95% (R=H) (2 steps); (v) 40% HF, CH_3CN, 97% (R=H), 82% (R=CH_3) (3 steps); (vi) Swern oxidation, 86% (R=H), 81% (R=CH_3); (vii) KH, THF, TBDMSCl, 93% (R=H), 88% (R=CH_3); (viii) (a) O_3, MeOH, CH_2Cl_2, (b) $NaBH_4$, (c) CH_2N_2, 71% (R=H), 71% (R=CH_3); (ix) Swern oxidation, 80% (R=H), 81% (R=CH_3); (x) ($Ph_3PCH_2OCH_3$)Cl, t-BuOK, THF, 51% (R=H); (xi) p-TsOH, acetone, 58% (R=H); (xii) H_2, 10% Pd/C, MeOH/H_2O 47% (R=H), 13% (R=CH_3) (3 steps); (xiii) Super-Hydride, THF 0℃, 76% (R=H), 45% (R=CH_3); (xiv) Swern oxidation; (xv) ($PPh_3(CH_2)_3CH_3$)Br, t-BuOK, THF, 41% (2 steps) or ($PPh_3(CH_2)_2R$)Br, t-BuOK, THF, 64% (R=H) (2 steps), 45% (R=CH_3) (2 steps); (xvi) H_2, 10% Pd/C, MeOH, 66% (±)-**209B [3]**, 64% (±)-**209I [116]**, 78% (±)-**223J [101]***

Swern oxidation followed by ozonlysis of **[120]** opened the bicycle[3.3.1]nonane skeleton, and gave the piperidines **[121]** and **[122]** in three steps. Wittig olefination allowed a chain extension, followed by treatment with *p*-toluene sulfonic acid gave the piperidine-substituted priopionaldehydes **[123]** and **[124]**. Deprotection of the amine by hydrogenation and subsequent treatment with Super-Hydride yielded the bicyclic alcohols **[125]** and **[126]**. Swern oxidation, followed by Wittig olefination and catalytic hydrogenation over palladium on carbon afforded indolizidines **209B [3]**, **209I [116]** and **223J [101]**.

1.3.19 Murahashi *et al.*[101]

Murahashi reported the synthesis of indolizidines **205A [1]** and **235B [14]** in an article detailing the preparation of chiral β-amino acids (**Scheme 1.21**). The key steps involved the reaction of *N*-acyl iminium ions with both boron and titanium(IV) enolates.

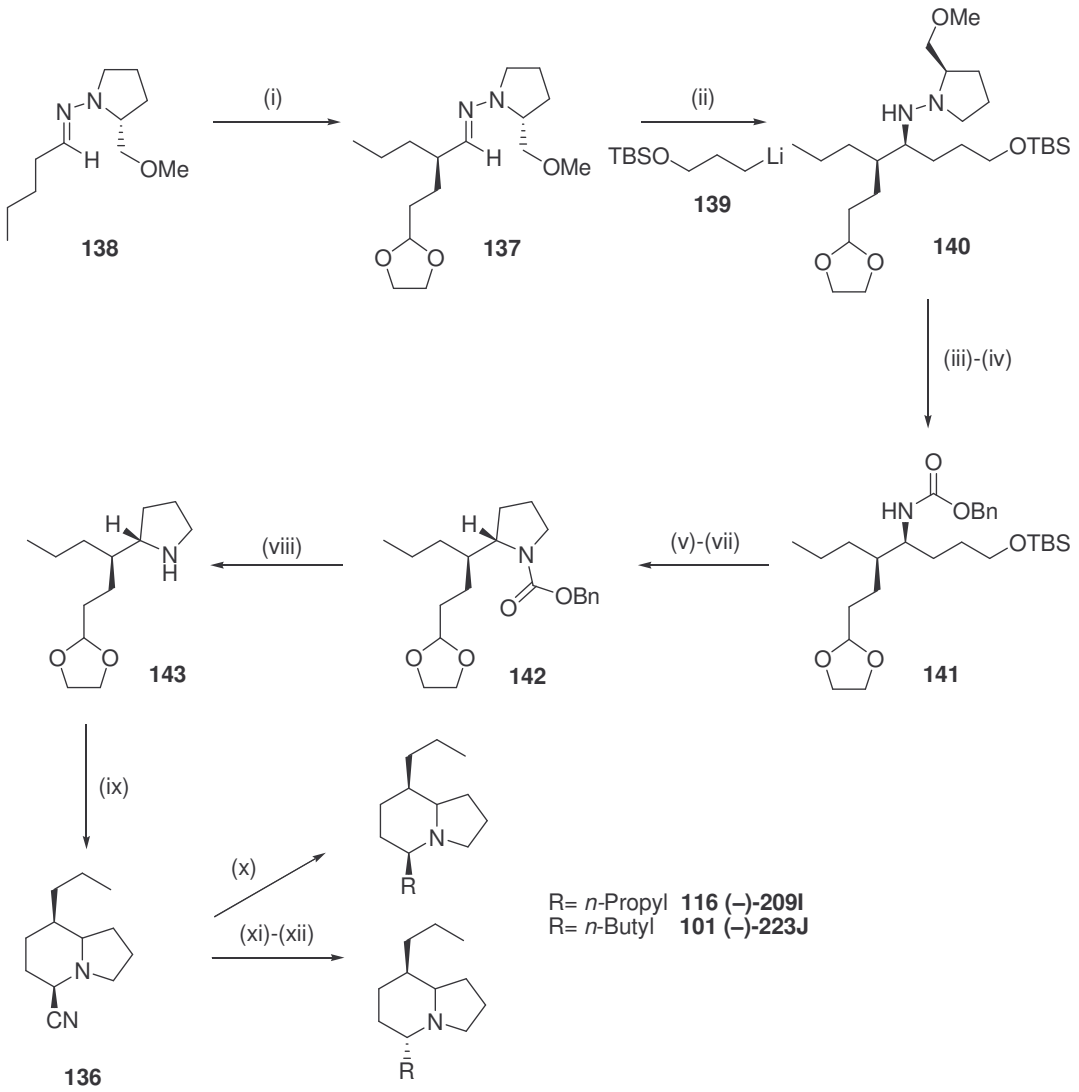


Scheme 1.21: *(i) 56%; (ii) (a) Zn, HCl, (b) BzCl, K_2CO_3, 88%; (iii) $NaBH_4$, 88%; (iv) CBr_4, PPh_3, 96%; (v) $NaCH(CO_2Et)_2$, 86%; (vi) NaCl, H_2O, 79%; (vii) (a) DIBAL, (b), MeOH, H^+, 64%; (viii) H_2, Pd/C, 86%; (ix) KCN, HCl, 98%*

The □-amino acid **[127]** (96% de) was prepared by the reaction of the chiral titanium(IV) enolate **[128]** with an *N*-acyloxyiminium ion which was derived from nitrone **[129]** and chiral acyl chloride **[130]**. Reduction of **[127]** with zinc/hydrochloric acid, followed by protection of the amino group with benzyloxycarbonyl gave **[131]** as a single diastereomer. Reductive cleavage of the chiral auxiliary with sodium borohydride, followed by bromination of the resulting alcohol and treatment with diethyl malonate gave diester **[132]**. Decarboxylation of **[132]** afforded □-amino acid ester (−)-**[133]**, which was reduced to the corresponding aldehyde upon treatment with diisobutylaluminium hydride (DIBAL). Acetal formation with methanol then gave **[134]**. Deprotection of **[134]** under catalytic hydrogenation conditions gave **[135]**. Subsequent treatment with potassium cyanide/hydrochloric acid as reported by Polniaszek[79-80] gave (−)-**[18]** in a 93:7 ratio along with its epimer at the C-5 position. The α-amino nitrile can be converted into **205A [1]** and **235B [14]** as previously reported by Polniaszek.[79-80]

1.3.20 Enders and Thiebes[102]

In 2000 Enders and Thiebes reported the first enantioselective synthesis of indolizidines (−)-**209I [116]** and (−)-**223J [101]** via a common late-stage intermediate amino nitrile **[136]** (**Scheme 1.22**). The synthesis revolved around a diastereoselective 1,2-addition of an organocerium reagent to α-substituted aldehyde RAMP hydrazone (*R*,*R*)-**[137]**. The synthesis started from RAMP-hydrazone (*R*)-**[138]**. Treatment with lithium diisopropylamide and 2-(2-iodoethyl)-1,3-dioxolane allowed alkylation, giving hydrazone (*R*,*R*)-**[137]** (90% d.e.). Both epimers were then subjected to 1,2-addition by an organocerium reagent prepared from **[139]**, yielding **[140]** as a 95:5 mixture of (*R*,*R*,*S*) and (*R*,*S*,*S*) isomers respectively. Reductive *N,N*-bond cleavage followed by protection of the resulting amine with benzyl chloroformate gave **[141]**. Desilylation of **[141]** and subsequent treatment with mesyl chloride and potassium *tert*-butoxide afforded the ring closed product (*R*,*S*)-**[142]**. Deprotection under catalytic hydrogenation conditions gave pyrrolidino acetal (*R*,*S*)-**[143]** which was hydrolysed under acidic conditions in the presence of potassium cyanide to give amino nitrile **[136]**. Treatment of **[136]** with lithium diisopropylamide and alkylation with *n*-propyl or *n*-butyl bromide gave the (5*S*,8*R*,8a*S*) isomers of indolizidines **209I [116]** and **223J [101]**. The corresponding epimers were obtained via Bruylants reaction using *n*-propylmagnesium bromide and *n*-butylmagnesium bromide.

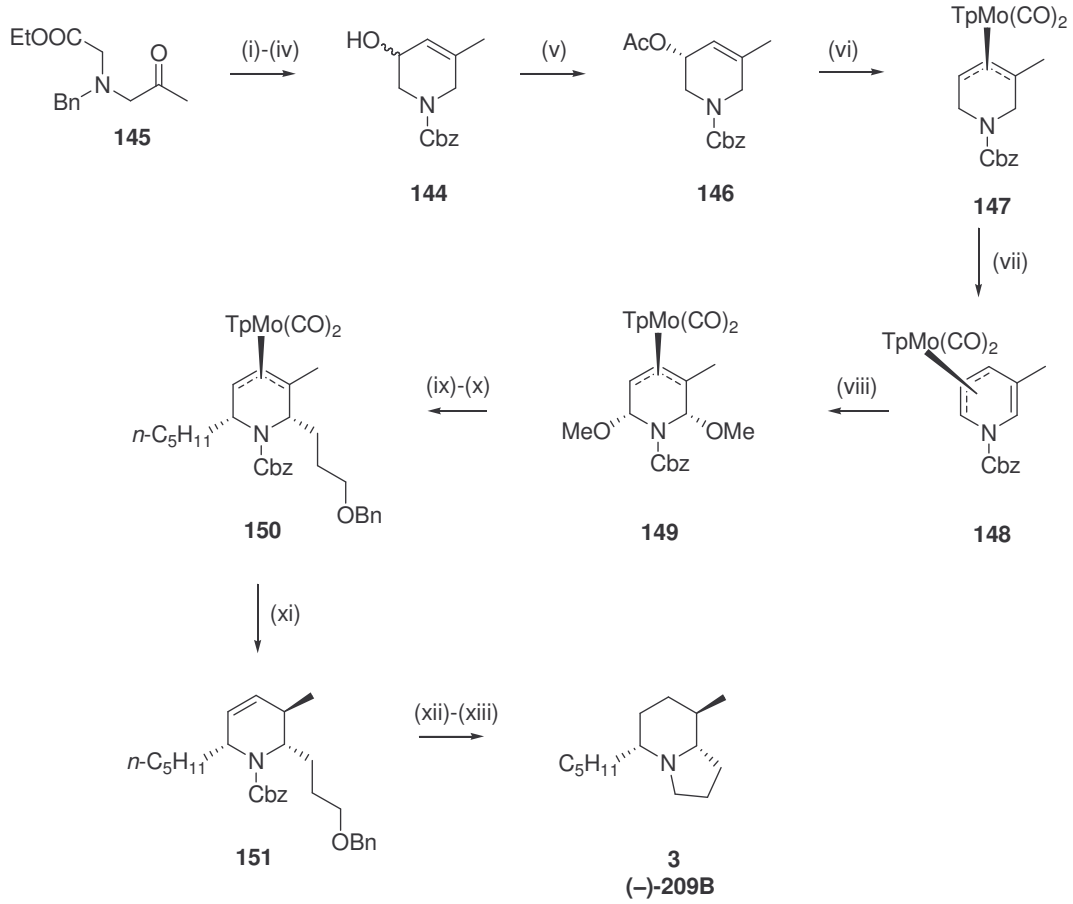


138 **137** **140** **141** **142** **143** **136**

Scheme 1.22: *(i) LDA, 0 ℃, 16 h, then, 2-(2-iodoethyl)-1,3-dioxolane, –100 ℃, 81%; (ii)* ***[139]****, $CeCl_3$, THF, –100℃, 82%; (iii) BH_3.THF, THF, Δ; (iv) $ClCO_2Bn$, K_2CO_3, CH_2Cl_2, 0℃, 86% (2 steps); (v) TBAF, THF, rt, 100%; (vi) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0℃; (vii) t-BuOK, THF, 0℃-rt, 83% (2 steps); (viii) H_2, 1 bar, $Pd(OH)_2$/C, MeOH, rt, 99%; (ix); 10% HCl(aq), CH_2Cl_2, rt, then KCN, pH=3, 92%; (x) RMgBr, THF, 0℃-rt, 91% (R=n-Pr), 87% (R=n-Bu); (xi) LDA, THF, 0℃, then RBr 0℃-rt; (xii) excess $NaBH_4$, EtOH, rt, 88% (R=n-Pr), 89% (R=n-Bu) (2 steps)*

1.3.21 Liebeskind *et al.*[103]

Liebeskind *et al.* reported a total synthesis of (−)-indolizidine **209B [3]** in 2001. The synthesis is particularly interesting as it makes use of enantiopure (η^3-dihydropyridinyl)molybdenum complexes as chiral scaffolds, and allows the preparation of both all *cis*-2,3,6- and 2,6-*cis*-3-*trans*-trisubstituted piperidines, which are used as precursors in the synthesis of **209B [3]** (**Scheme 1.23**).



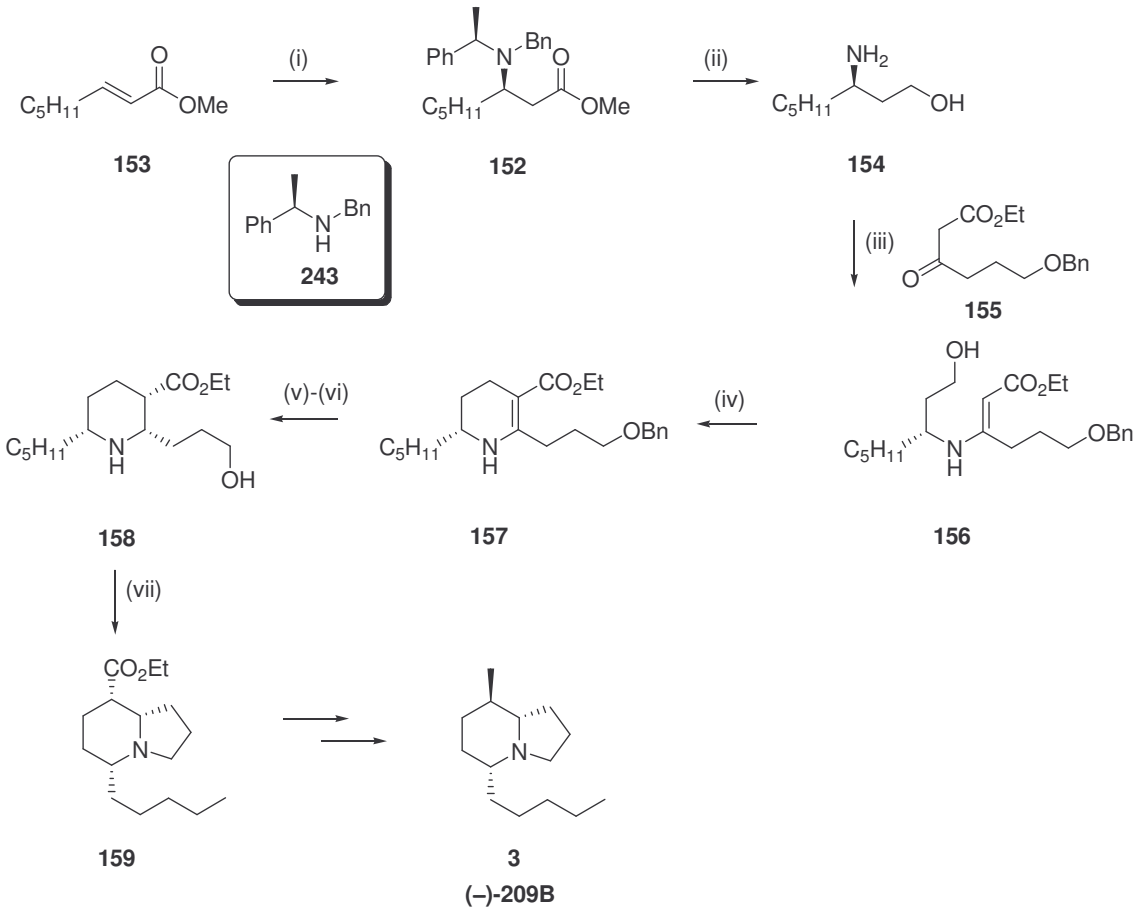
Scheme 1.23: *(i) (a) t-BuOK, (b) Ac_2O, 84%; (ii) (a) MeMgBr, (b) NaOH(aq), 79%; (iii) CbzCl, 86%; (iv) $NaBH_4$, $CeCl_3$, 100%; (v) (a) Lipase AK, CH_2=CHOAc, $PhCH_3$, rt, (b) Ac_2O, NEt_3, DMAP, 82%; (vi) (a) $Mo(DMF)_3(CO)_3$, (b) KTp, 88%; (vii) (a) Ph_3CPF_6, (b) NEt_3, 88%; (viii) (a) Br_2, (b) NaOMe, 95%; (ix) (a) Ph_3CPF_6, (b) $BnO(CH_2)_3MgBr$; (x) (a) HBF_4, (b) n-$CH_3(CH_2)_4MgBr$, 67% (2 steps); (xi) (a) $NOPF_6$, (b) $NaCNBH_3$, 59%; (xii) H_2, Pd/C, 87%; (xiii) (a) PPh_3, CBr_4, (b) NEt_3, 63%*

Allylic alcohol **[144]** was prepared in six steps from **[145]**. Enzymatic kinetic resolution of the racemic allylic alcohol **[144]** gave enantiopure allylic acetate **[146]**. Oxidative addition of $Mo(DMF)_3(CO)_3$ to **[146]** gave the corresponding η^3-dihydropyridinyl complex (+)-**[147]**. Abstraction of the hydride from (+)-**[147]** with Ph_3CPF_6 followed by deprotonation with triethylamine afforded the (η^3-pyridinyl)molybdenum complex **[148]**. Subsequent treatment with bromine and sodium methoxide gave the (dimethoxydihydropyridinyl)molybdenum complex **[149]**. A stepwise substituition of the methoxy groups yielded the 2,3,6-trisubstituted pyridinyl molybdenum complex **[150]**. Reductive demetalation with $NOPF_6$ and sodium cyanoborohydride afforded **[151]**. Finally debenzylation and ring closure by treatment with triphenylphosphine and carbon tetrabromide yielded (−)-indolizidine **209B [3]**.

1.3.22 Ma, Pu and Wang[104]

Ma *et al.* reported a synthesis of (−)-indolizidine **209B [3]** in 2002 from an enantiopure β-amino ester **[152]** using an approach sharing a number of similarities to our previously published Wits approach.[100] Interestingly, they chose to disconnect the bicyclic skeleton at the C3-C4 position (**Scheme 1.24**).

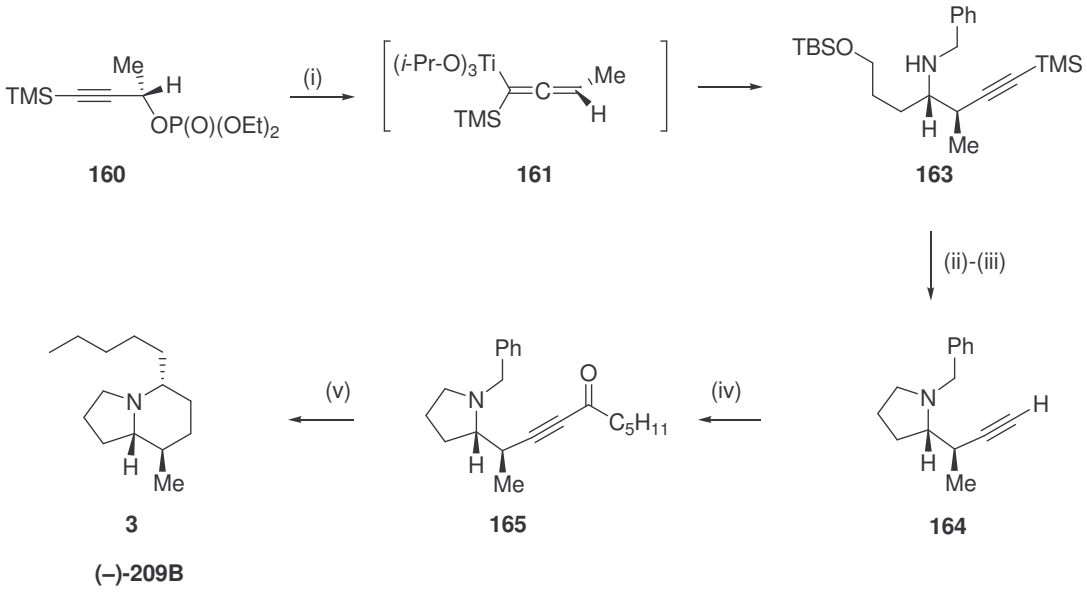
Starting from (*E*)-methyl octenoate **[153]**, the β-amino ester **[152]** was generated. Subsequent debenzylation and reduction of the ester using lithium aluminium hydride afforded amino-alcohol **[154]**. Condensation of **[154]** with β-keto ester **[155]** gave vinylogous urethane **[156]**. Ring closure was achieved by treatment of **[156]** with carbon tetrabromide and triphenylphosphine yielding **[157]**. Hydrogenation in the presence of Raney nickel and debenzylation gave 2,3,6-trisubstituted piperidine **[158]**. Finally treatment of **[158]** with triphenylphosphine and carbon tetrabromide yielded 5,8-indolizidine **[159]**, which is easily converted into indolizidine **209B [3]** as shown by Michael and Gravestock.[100]



Scheme 1.24: *(i) **[243]**, n-BuLi, THF, –78 °C, 90%; (ii) (a) H_2, Pd/C, (b) $LiAlH_4$, THF, 91%; (iii) **[155]**, 70%; (iv) (a) PPh_3, CBr_4, CH_3CN, 0 °C-rt, (b) NEt_3, Δ, 71%; (v) H_2, Raney Ni, 80%; (vi) H_2, PtO_2, 85%; (vii) PPh_3, CBr_4, CH_3CN, 67%*

1.3.23 Sato *et al.*[105]

Sato *et al.* described the preparation of (–)-**209B [3]** utilizing the asymmetric addition of an optically active allenyltitanium to benzyl[4-(*tert*-butyldimethylsilyloxy)butylidene]amine **[160]** as the key reaction (**Scheme 1.25**). The synthesis started from an optically active secondary propargyl phosphate **[160]**, which was used to prepare the allenyltitanium **[161]** with 97.8% e.e. by treatment with Ti(O-*i*-Pr)$_4$ and 2 *iso*-propyl magnesium chloride. The resulting allenyltitanium **[161]** was reacted with **[162]** to give the desired *anti*-product **[163]** and its diastereomers *syn*-**[163]** in a 9:1 ratio.



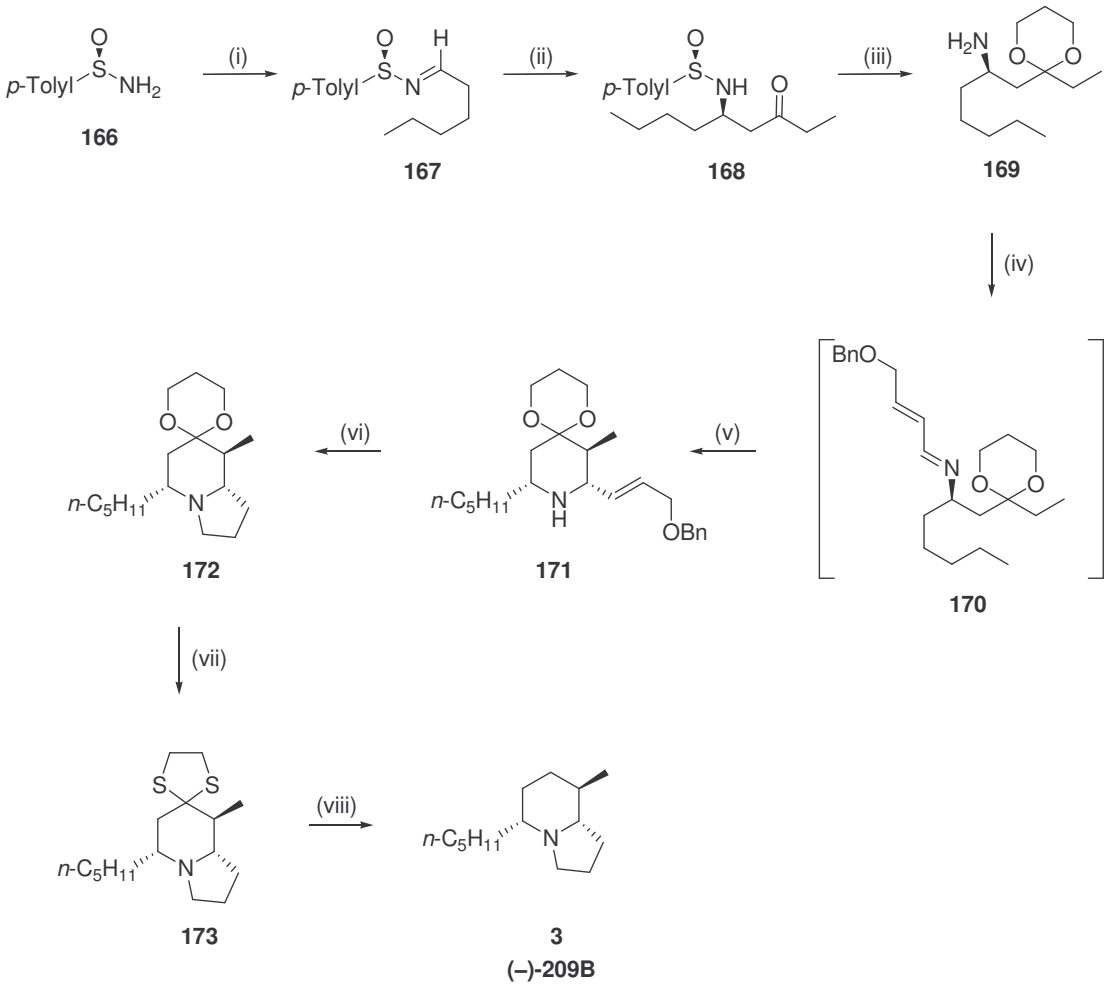
160 **161** **163** **164** **165** **3** **(–)-209B**

Scheme 1.25: *(i) (a) Ti(O-i-Pr)$_4$, 2 i-PrMgCl, (b) PhCH$_2$N=CH(CH$_2$)$_3$OTBS **[162]**, 87%; (ii) TBAF, THF, 89%; (iii) PPh$_3$, imidazole, CCl$_4$, Δ, 91%; (iv) (a) n-BuLi, -78°C, (b) N-methoxy-N-methylhexanamide, -78°C-0°C; (v) H$_2$, 10% Pd/C, MeOH, 56% (2 steps)*

Desilylation of **[163]** with tetrabutylammonium fluoride, followed by cyclisation with triphenylphosphine, imidazole and carbon tetrachloride yielded pyrrolidine **[164]**. Subsequent treatment of **[164]** with *n*-butyllithium and *N*-methoxy-*N*-methylhexanamide afforded the unstable ynone **[165]**, which was subjected to hydrogenation over Pd/C in methanol to give (−)-**209B [3]** in 40% overall yield

1.3.24 Davis and Yang[106]

In 2003 Davis and Yang described a route for the preparation of chiral building blocks which could be used for the preparation of piperidines. They illustrated the utility of the methodology by the preparation of (−)-**209B [3]** (**Scheme 1.26**).

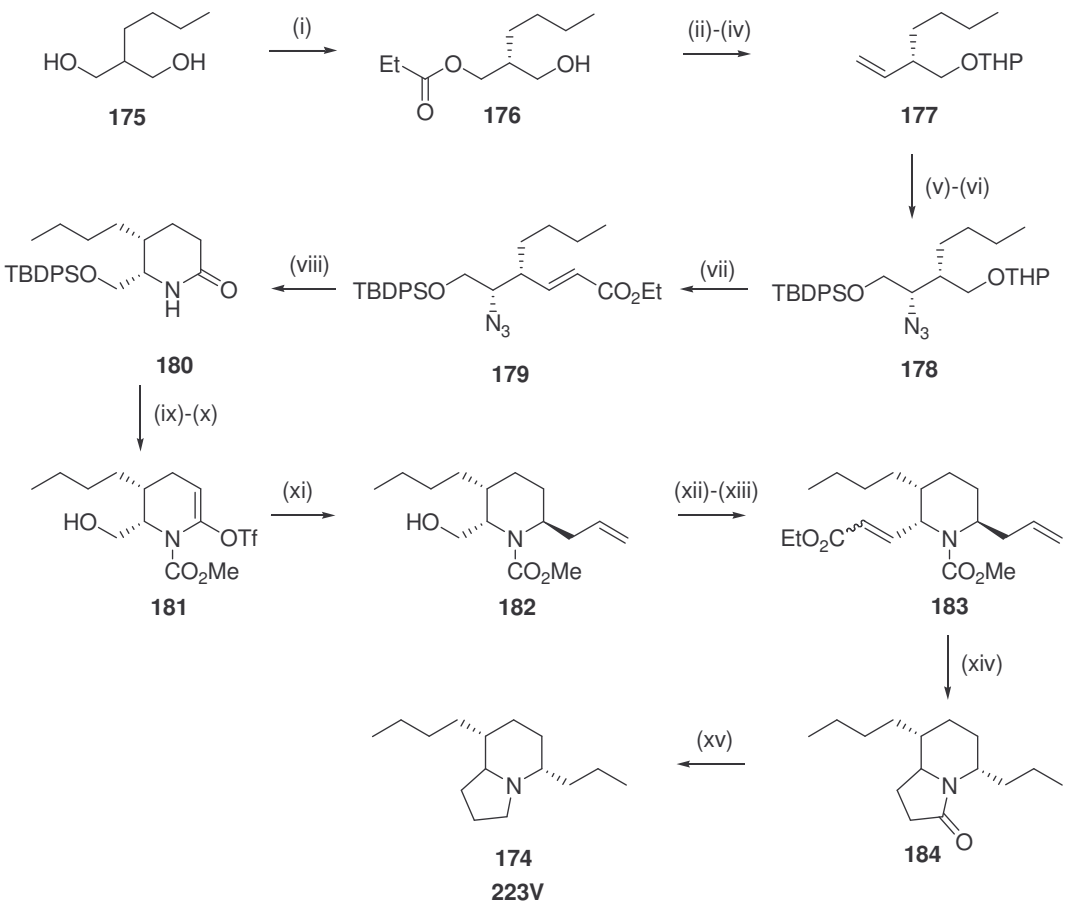


Scheme 1.26: *(i) n-hexanal, $Ti(OEt)_4$, 79%;(ii) $C_2H_5C(O)CH_2K$, –78 °C, 85%; (iii) (a) TsOH, $HO(CH_2)_3OH$, 78 °C, (b) 2.6 N KOH, 87%; (iv) $BnOCH_2CH{=}CHCH{=}O$, $MgSO_4$; (v) TsOH, 75 °C, 61% (2 steps); (vi) (a) H_2, Pd/C, (b) H_2, $Pd(OH)_2$/C, (c) PPh_3, CBr_4, NEt_3, 74%; (vii) $HS(CH_2)_2SH$, $BF_3.OEt_2$, 92%; (viii) Raney nickel, EtOH, 75%*

Starting from commercially available (*R*)-(−)-*p*-toluenesulfinamide **[166]** treatment with *n*-hexanal and $Ti(OEt)_4$ gave sulfinimine **[167],** which was subsequently converted into *β*-amino ketone (*R*,*R*)-(−)-**[168]** by treatment with the potassium enolate of 2-butanone. A two step deprotection-protection sequence gave (*R*)-**[169]**, and subsequent stirring with anhydrous magnesium sulfate and (*E*)-4-benzyloxy-but-2-enal gave crude imine **[170]**. Heating of **[170]** with toluene sulfonic acid gave the Mannich product (−)-**[171]**, alkene reduction, debenzylation and cyclisation was achieved in three steps to give (−)-**[172]**. Conversion of (−)-**[172]** to the corresponding thioketal (−)-**[173]** was achieved by treatment with ethanedithiol and boron trifluoride, subsequent Raney nickel desulfurization gave desired indolizidine (−)-**209B [3]**.

1.3.25 Toyooka and Nemoto[43]

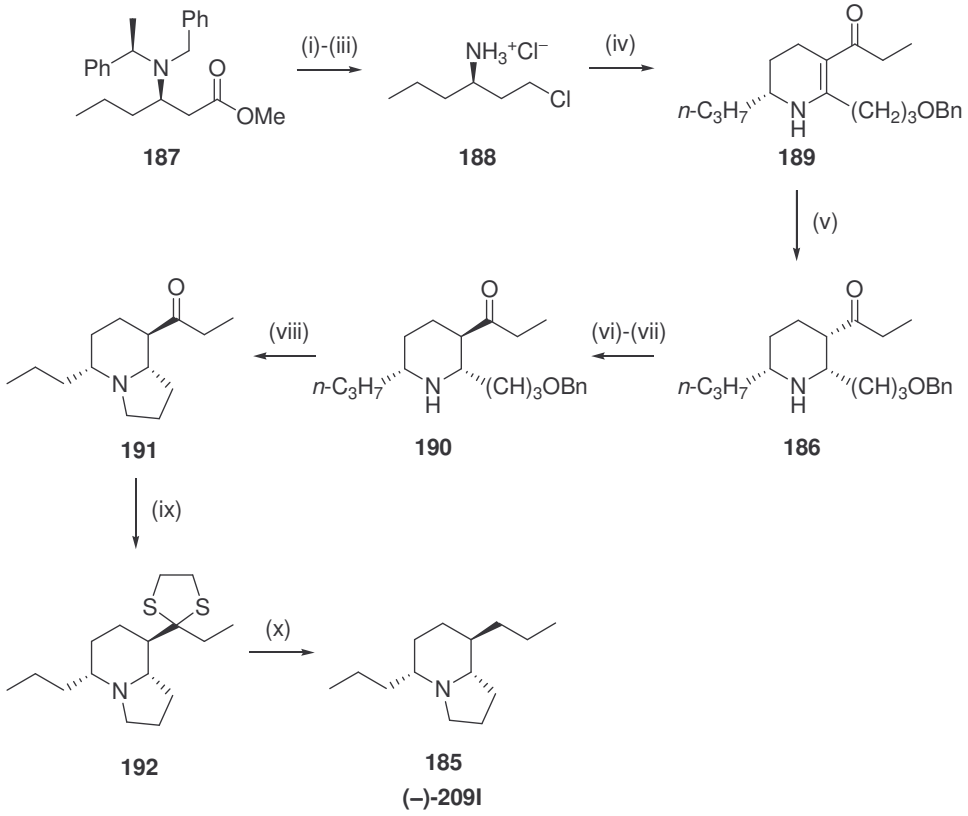
In their third paper published in 2005 Toyooka and Nemoto published an enantioselective synthesis of two 8-epimers of **223V [174]** (**Scheme 1.27**). Starting from the *meso*-diol **[175]** a lipase mediated transesterification afforded the mono-propanoate **[176]**, which was then converted into the olefin **[177]** by treatment with 3,4-dihydro-2*H*-pyran-2-methanol and pyridinium toluene-*p*-sulfonate followed by reaction with potassium carbonate in methanol. Olefin **[177]** underwent Sharpless asymmetric dihydroxylation, thereafter protection of the primary alcohol and substitution of the secondary alcohol afforded azide **[178]**. Selective deprotection of the THP protected alcohol, Swern oxidation and Wittig olefination gave unsaturated ester **[179]**. Hydrogenation of **[179]** yielded the 5,6-*cis*- and *trans*-piperidones. The desired 5,6-*cis* piperidone **[180]**, after conversion into the methyl urethane and treatment with Comins' triflating reagent afforded the enoltriflate **[181]**. Stille coupling of **[181]** using allyltributyltin, and stereoselective reduction gave **[182]**. Subsequent conversion of the methyl-urethane to the Boc-urethane, Swern oxidation and Wittig olefination allowed the elongation of the chain at the 2-position to give **[183]**. Hydrogenation of **[183]**, hydrolysis of the resulting ester, Boc removal and lactam formation using Shioiri's reagent afforded **[184]**. Reduction of the lactam **[184]** with lithium aluminium hydride gave the desired product **[174]**.



Scheme 1.27: *(i) Lipase from* Pseudomonas cepacia *(*Amano PS*), vinyl propanoate, MeCN, 90%; (ii) (a) MsCl, pyridine, CH_2Cl_2, 99% (b) NaI, acetone, 94%; (iii) $LiAlH_4$, THF, 69%; (iv) (a) DHP, PPTS, $CH_2Cl_,$, (b) K_2CO_3, MeOH, (c) Swern oxidation; (d) $CH_3P^+Ph_3I^-$, n-BuLi, THF, 80% (4 steps); (v) $(DHQD)_2Pyr$, K_2OsO_4, $K_3Fe(CN)_6$, K_2CO_3, H_2O/t-BuOH, 0°C, 84%; (vi) (a) TBDPSCl, NEt_3, DMAP, CH_2Cl_2, 99%, (b) MsCl, NEt_3, CH_2Cl_2, 0°C, (c) NaN_3, DMF, 80°C, 73% (2 steps); (vii) (a) PPTS, EtOH, 60°C, (b) Swern oxidation, (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 88% (3 steps); (viii) H_2, 4 atm, 10% Pd/C, EtOAc, 56%; (ix) n-BuLi, $ClCO_2Me$, THF, –78°C-0°C, 98%; (x) LiHMDS, 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, THF, –78°C-40°C,96%; (xi) LiCl, allyltributyltin, $Pd(PPh_3)_4$, THF, rt, 92%; (xii) TFA, $NaBH_3CN$, CH_2Cl_2, –45°C, 65%; (xii) (a) 2M KOH/i-PrOH, 120°C sealed tube; (b) Boc_2O, NaOH, dioxane-H_2O, 70% (2 steps); (xiii) (a) Swern oxidation, (b) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 95% (2 steps); (xiv) (a) H_2, 1 atm, 10% Pd/C, EtOAc, (b) LiOH, H_2O-EtOH, 60°C, (c) TFA, CH_2Cl_2, rt, (d) DEPC, NEt_3, DMF, rt, 91% (4 steps); (xv) $LiAlH_4$, THF, Δ, 81%*

1.3.26 Ma, Zhu and Yu[107]

Ma, Zhu and Yu have subsequently reported a synthesis of indolizidine (−)-**209I [185]** in which they describe a facile one pot formal [4+2] cycloaddition synthesis of the piperidine ring **[186]**. Using this approach they are able to access substituted piperidines, indolizidines and quinolizidines and they report the preparation of indolizidine (−)-**209I [185]** as a representative example (**Scheme 1.28**). Once again their synthesis shares a number of similarities with the "Wits approach",[100] however as in their previous work they continue to disconnect at the C3-C4 bond in the target molecule **[185]**.



Scheme 1.28: *(i) $LiAlH_4$, THF; (ii) $SOCl_2$, $CHCl_3$; (iii) $Pd(OH)_2/C$, H_2 (50 atm), 85% (3 steps); (iv) $C_2H_5COCH{\equiv}CH(CH_2)_3OBn$, Na_2CO_3, NaI, i-PrOH, Δ, 64%; (v) PtO_2, H_2, AcOH, 82%; (vi) NaOMe, MeOH, Δ, 75%; (vii) $Pd(OH)_2$, H_2; (viii) PPh_3, I_2, imidazole, 83% (2 steps); (ix) $HS(CH_2)_2SH$, BF_3.OEt, 65%, (x) Raney-Ni, i-PrOH, 70°C, 81%*

Starting from the *β*-amino ester **[187]** treatment with lithium aluminium hydride, followed by thionyl chloride and debenzylation gave □-chloropropylamine **[188]**. The [4+2] cycloaddition followed and involved the refluxing of a mixture of the □-chloropropylamine **[188]**, 8-benzyloxy-4-octyn-3-one, sodium carbonate and a catalytic amount of sodium iodide in *iso*-propanol. The desired substituted piperidine **[189]** was obtained. Stereoselective hydrogenation of the double bond in **[189]** using Adams' catalyst in glacial acetic acid gave reduced piperidine **[186]**. Epimerization at the 3-position by treatment with sodium methoxide gave the 3-epimer **[190]**, debenzylation with palladium hydroxide under hydrogenation conditions and cyclisation with triphenylphosphine, iodine and imidazole yielded **[191]**. Finally the ketone functionality was removed in two steps by conversion to its 1,2-dithiolane **[192]**, followed by treatment with Raney nickel to afford (–) **209I [185]** in 11 steps in an overall yield of 12.4%.

CHAPTER 2

BACKGROUND, AIMS AND SCOPE OF THIS PROJECT



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BACKGROUND, AIMS AND SCOPE OF THIS PROJECT

2.1 Introduction

This chapter will initially give an outline of the generalized approach used in the synthesis of alkaloids in the laboratories at this University, highlighting the utility and versatility of our "Wits approach". A detailed description of Michael and Gravestock's synthesis of indolizidines **167B [193]** and **209B [3]** will then be given,[100] highlighting how the generalized approach is adapted to the synthesis of indolizidine alkaloids. Thereafter the aims of this project will be introduced, showing the synthetic targets that we are interested in, why we are interested in them and our proposed synthetic approach for these alkaloids. Mention will be made to the ways in which we propose to extend the methodology from the work previously done in these laboratories, as well as the viability of the approach with reference to previous syntheses.

2.2 Enaminones: The "Wits approach" to alkaloid synthesis

The "Wits approach" towards alkaloid synthesis dates back to the early seventies, and is based primarily on the utilization of the enaminone structural unit. Alkaloid synthesis using the "Wits approach" has been an ongoing topic of interest in our labs and to date fourteen Ph.D. theses[108], seven M.Sc. dissertations[109] and numerous publications[100,110] have resulted from our investigations. This structural unit most commonly comprises a nitrogen atom conjugated through a vinyl fragment to an ester (vinylogous urethane **[194]**), although in our laboratories we have investigated and made extensive used of structural relatives of the traditional enaminone, including the vinylogous amides **[195]**, ureas **[196]**, cyanamides **[197]**, nitramines **[198]** and sulphonamides **[199]** shown in **Figure 2.1**. An enaminone can therefore be visualized as a β-acylated enamine. Our interest in the enaminone manifold, revolves around the fact that it displays both ambident nucleophilicity and electrophilicity, in addition it has been shown to participate in radical as well as pericyclic reactions.

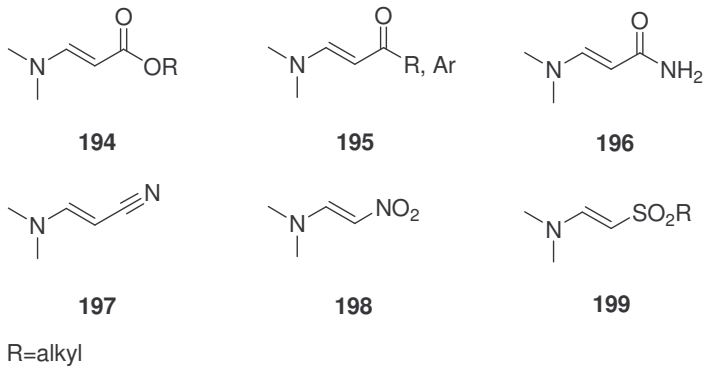


Figure 2.1: *Enaminones and their structural relatives used in our laboratories*

Alkaloids normally have a five- or six-membered nitrogen containing ring, as a result most of the enaminones used in our laboratories comprise either a pyrrolidine or piperidine ring with an exocyclic alkylidene fragment at the C-2 position **[200]**. In almost all cases the nitrogen atom is tertiary in nature (**Figure 2.2**).

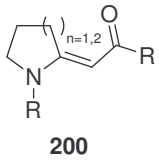
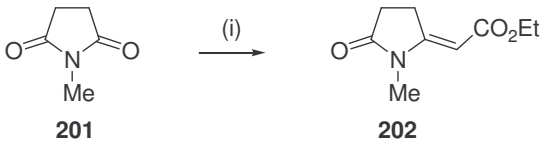


Figure 2.2: *Generalised enaminone structure used in our laboratories*

2.3 Access to enaminones

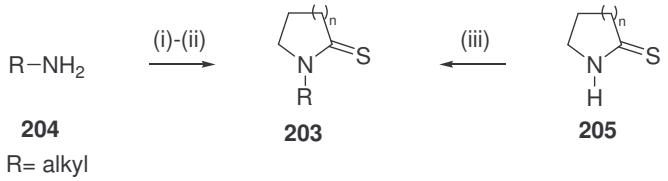
Historically the earliest preparation of an enaminone manifold dates back to 1932, when Lukeš performed a Reformatsky reaction between *N*-methylsuccinimide **[201]** and ethyl bromoacetate (**Scheme 2.1**) to give vinylogous urethane **[202]** in a 68% yield[111].



Scheme 2.1: *(i) $BrCH_2CO_2Et$, Mg, 68%*

Since then several methods have been adopted to prepared enaminones,[112-120] one of the most versatile of which is the Eschenmoser sulphide contraction of thiolactams, originally described by Eschenmoser and co-workers in 1970.[121-123]

In our research group, we initially prepare the desired thiolactams **[203]** by either thionating lactams made from primary amines **[204]** and bifunctional reagents, or by a useful conjugate addition of secondary thiolactams **[205]** to acrylate esters, acrylonitrile and similar acceptors (**Scheme 2.2**).[108-110]

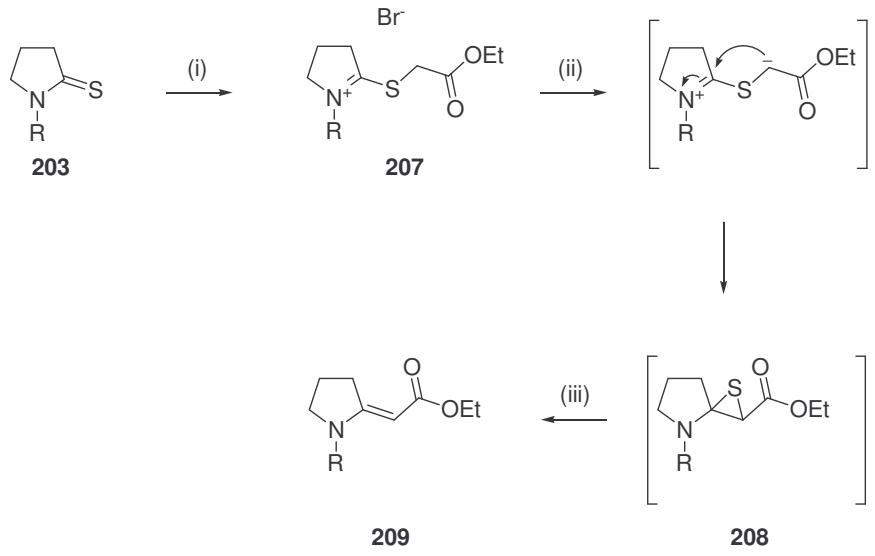


Scheme 2.2: *(i) $Cl(CH_2)_nCOCl$; (ii) Base, P_2S_5 or Lawesson's reagent; (iii) $H_2C=CHX$ (X=COR', CO_2R', CN, SO_2R', etc)*

The next step, the Eschenmoser sulfide contraction has become an important part of our approach towards alkaloid synthesis, and most enaminones synthesized in our laboratories are accessed in this manner.

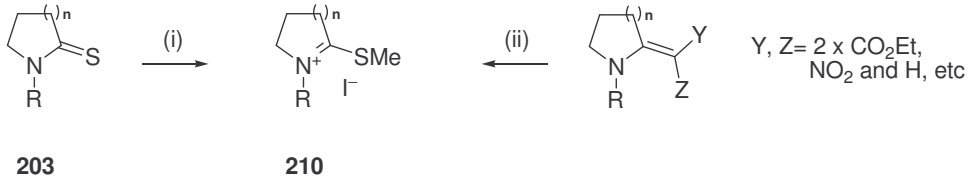
The sulphide contraction involves the reaction of a tertiary thioamide **[203]** with an α-halocarbonyl **[206]** (or related structure) to give *N*,*N*-dialkylthioiminoester salt **[207]** (**Scheme 2.3**). The resulting salt **[207]** in the presence of a suitable base is deprotonated on the methylene group, which in turn reacts intramolecularly at the iminium carbon atom to form a thiirane intermediate **[208]**. In the presence of a suitable thiophile the sulfur is extruded affording the desired enaminone **[209]**.

The tertiary nature of the nitrogen atom is important as it enhances the electrophillic nature of the iminium ion, thus only a weak base like triethylamine is necessary to afford the formation of the thiirane intermediate at room temperature. However in cases where a secondary nitrogen or an electron withdrawing substituent is used harsher conditions are required, and sometimes a whole alternative approach is neccessary to access the desired enaminone.



Scheme 2.3: *(i) $BrCH_2CO_2Et$* ***[206]****, CH_3CN; (ii) NEt_3, CH_3CN; (iii) PPh_3, CH_3CN*

An alternative route that we use to access enaminones is the condensation of methylthioiminium salts **[210]** with relatively acidic components like nitromethane or β-dicarbonyl compounds[109a, 110f] (**Scheme 2.4**).

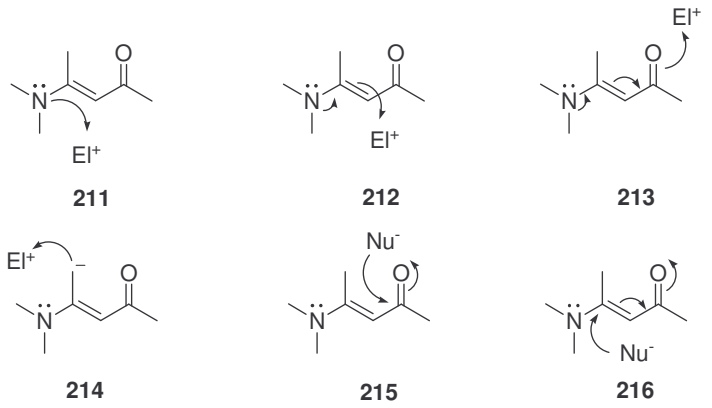


Scheme 2.4: *(i) MeI, THF; (ii) K_2CO_3, DMF, $CH_2(CO_2Et)_2$, $MeNO_2$ etc*

2.4 Reactivity of enaminones and their structural analogues

The ambient nucleophilicity and electrophilicity of enaminones is illustrated in **Scheme 2.5** below, giving an overview of the utility of this structural unit. The enaminone can act as a nucleophile through the nitrogen atom **[211]**, however this nucleophilicity can be extended to the enamine carbon **[212]** and the carbonyl group **[213]** by conjugation. An additional nucleophilic site can be generated at the site β to the nitrogen atom **[214]** by either

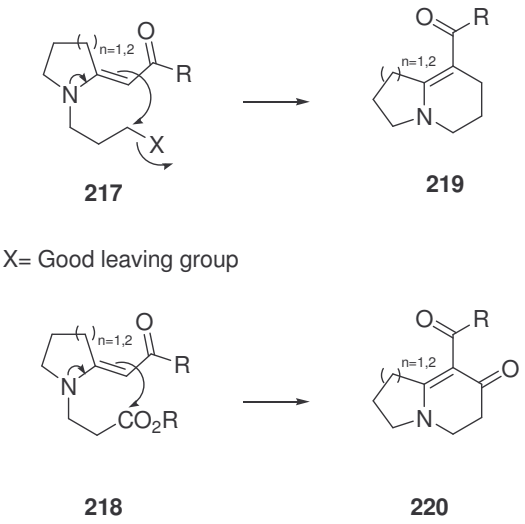
deprotonation with a strong base, or acid-induced tautomerisation. The enaminone unit can also act as an electrophile, undergoing both 1,2- and 1,4-addition reactions **[215, 216]**.



Scheme 2.5: *Nucleophilic and electrophilic reaction sites of enaminones*

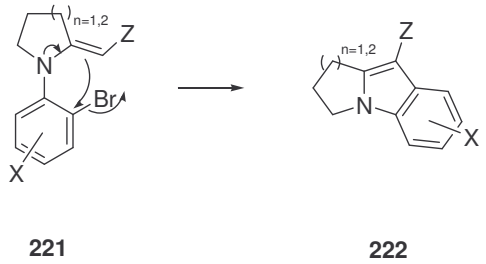
2.4.1 Nucleophilic reactivity of enaminones

The exocyclic enaminone skeletons that we build can make use of nucleophilic properties to access more complex bicyclic and tricyclic ring systems. If we take our generalized enaminone **[200]** shown above in **Figure 2.2**, and incorporate a leaving group X **[217]** or a carbonyl functionality **[218]**, we can create numerous indolizidine and quinolizidine ring systems **[219, 220]** utilizing the nucleophilic nature of the enaminone scaffold (**Scheme 2.6**). Disappointingly we have been unable to produce the corresponding pyrrolizidine ring systems using the same approach.



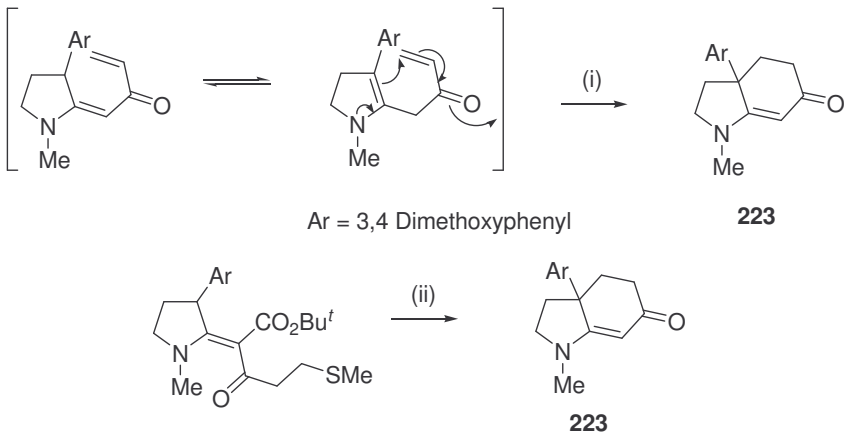
Scheme 2.6: *Cycloalkylation and cycloacylation illustrating the nucleophilic nature of enaminones*

An alternative cyclisation approach that we have employed utilizing the same nucleophilic sites is a Heck cycloarylation of *N*-(2-bromoaryl) exocyclic enaminones **[221]**, to access a tricyclic skeleton incorporating the pyrrolizidine ring system **[222]** (**Scheme 2.7**).[108f,109d ,110l]



Scheme 2.7: *Cycloarylation illustrating the nucleophilic nature of enaminones*

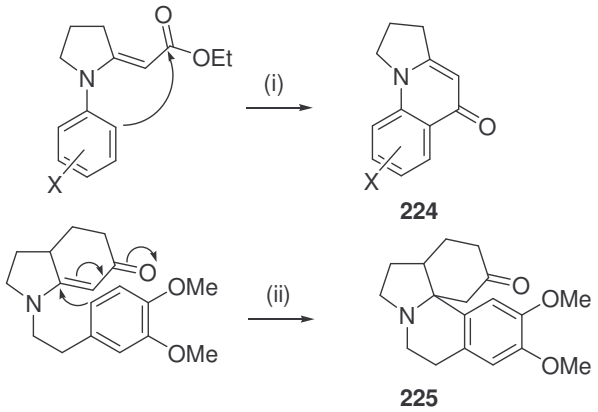
We can also utilize the reactivity of the site β to nitrogen (**Scheme 2.8**) to access indole type structures **[223]**. As illustrated by Katz's synthesis of (±)-Δ^7-mesembrine,[108d,110d,110h] which was later extended by Zwane.[108e,110i]



Scheme 2.8: *Cyclisation illustrating the nucleophilic nature of the site β to nitrogen in enaminones; (i) (i-Pr)$_2$NEt, 72%; (ii) CF$_3$CO$_2$H, ultrasound, 71%*

2.4.2 Electrophilic reactivity of enaminones

The electrophilic nature of enaminones can also be utilized to afford more complex tricyclic skeletons. In **Scheme 2.9** a 1,2-addition reaction to a carbonyl allows access to tricyclic 4-quinolines **[224]**[109a]. Similarly the *Erythrina* alkaloid skeleton **[225]** is accessed via a 1,4-addition reaction[109f].

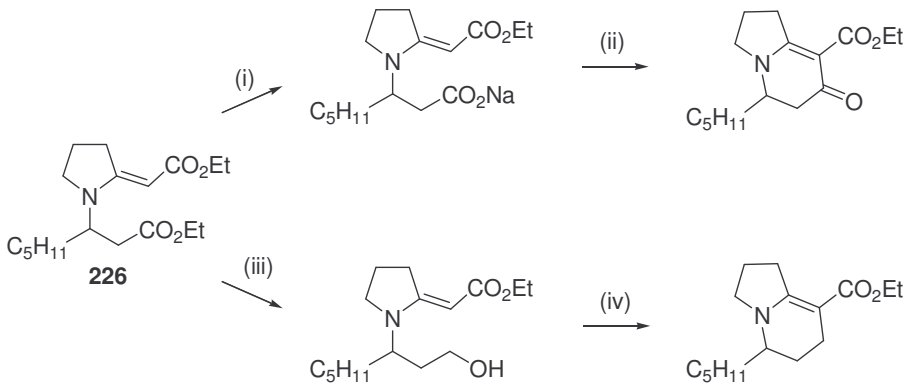


Scheme 2.9: *1,2- and 1,4-cycloaddition reaction illustrating the electrophillic nature of enaminones; (i) PPA, Δ; (ii) P$_2$O$_5$, MeSO$_3$H*

2.5 Selectivity of enaminones

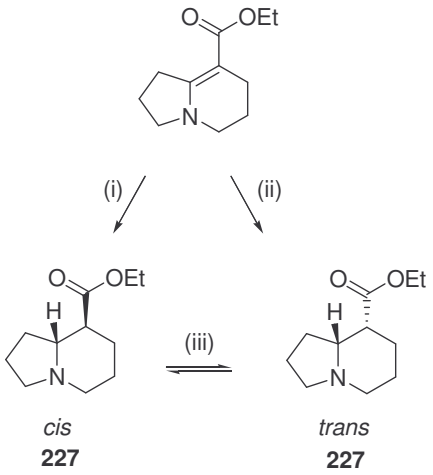
An important aspect of any generalized synthetic approach is the degree of selectivity that the approach allows the researcher. Our "Wits approach" utilizing enaminones lends itself well to chemoselectivity in the presence of other functional groups, as well as diastereoselectivity and enantioselectivity.

The addition of other functional groups to compounds containing enaminone functionalities opens the door to perform chemoselective reactions, even in cases when there are two of the same functional group present. An example of this chemoslectivity is illustrated in **Scheme 2.10**, where a saturated ester **[226]** is either hydrolysed or reduced in the presence of the vinylogous urethane which remains unscathed[100].



Scheme 2.10: *(i) NaOH, H_2O, Δ; (ii) Ac_2O, MeCN, rt, 86% (2 steps); (iii) $LiAlH_4$, THF, 91%; (iv) CBr_4, PPh_3, MeCN, Δ, 85%*

Diastereoselective transformations can also be employed to obtain desired diastereoisomeric products, and in the case of bicyclic systems like the indolizidines and quinolizidines (**Scheme 2.11**) the *cis*-**[227]** and or *trans*-**[227]** products can be obtained by utilizing the appropriate reduction conditions. Furthermore, interconversion between the two diastereomers can then afford only the *cis*-**[227]** or the *trans*-**[227]** products. **Sections 2.6.1** and **2.6.2** highlight some of these transformations, with reference to Gravestocks synthesis of indolizidines (±)-**209B [3]** and (−)-**209B [3]** [100,108h].



Scheme 2.11: *(i) $NaCNBH_3$, MeOH, pH 3, (ii) $H_2(g)$, $PtO_2.xH_2O$, Glacial Acetic Acid,(iii) NaOMe, MeOH, Δ*

Enantioselective control is described in detail in **Section 2.6.2** where our various approaches are discussed in relation to Gravestock's enantioselective synthesis of indolizidine alkaloid (–)-**209B [3]**[100,108h].

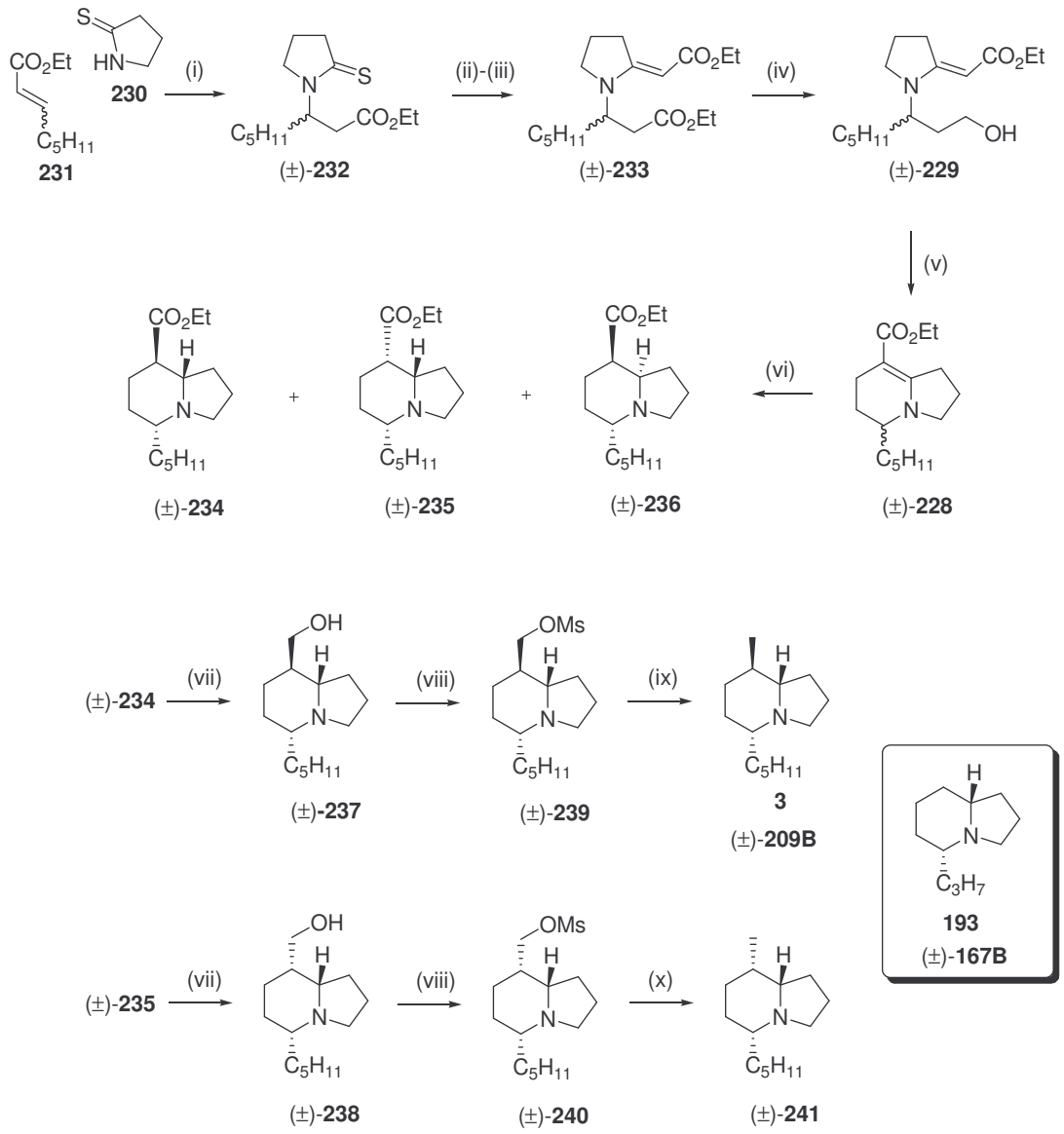
2.6 Synthesis of Indolizidines 167B [193] and 209B [3]

2.6.1 Synthesis of Racemic Indolizidine 209B [3]

The "Wits approach" to the synthesis of indolizidine alkaloids involves a unique disconnection between the C7-C8 bond, to allow the bicyclic skeleton **[228]** to be accessed via the enaminone moiety **[229]** as shown in **Scheme 2.12**. This unconventional approach is unique to our laboratories as far as the synthesis of 5,8-disubstituted indolizidines are concerned. Gravestock was able to use this approach to synthesise indolizidines (±)-**167B [193]** and (±)-**209B [3]**, after which he was able to complete a formal synthesis of (–)-**209B (3)**[100,108h]. The following two sections give a detailed description of these syntheses, as they form the basis of this thesis.

The racemic approach started with the conjugate addition of pyrrolidine-2-thione **[230]** to ethyl oct-2-enoate **[231]**, this was achieved by treatment with a catalytic amount of sodium hydroxide in tetrahydrofuran at room temperature, yielding the thiolactam (±)-**[232]** (74%)

(**Scheme 2.12**). The resulting thiolactam (±)-**[232]** was alkylated with ethyl bromoacetate, followed by a Eschenmoser sulfide contraction by treatment with triethylamine and triphenylphosphine in acetonitrile to give the desired vinylogous urethane (±)-**[233]** (85%). A chemoselective reduction of the saturated ester group of (±)-**[233]**, by treatment with lithium aluminium hydride in tetrahydrofuran at room temperature reduced the desired ester affording alcohol (±)-**[229]** (91%). In order to achieve cyclization it was necessary to convert the hydroxy group into a better leaving group. This was achieved by treating with carbon tetrabromide and triphenylphosphine in the presence of triethylamine, giving the desired indolizidine (±)-**[228]** (85%). The next step was the diastereoselective reduction of the carbon-carbon double bond, by treatment with sodium cyanoborohydride at pH 4, the major product was the desired diastereomers (±)-**[234]** (33%), however there was a significant proportion of the isomer (±)-**[235]** (14%) and a third diastereomer tentatively assigned as (±)-**[236]** (13%). A much better diastereoselectivity was achieved when the indolizidine (±)-**[228]** was hydrogenated over platinum dioxide in acetic acid, hydrogen was delivered in a *cis* fashion from the least hindered face to give mainly (±)-**[234]** (71%) with a small quantity of (±)-**[235]** (6%). The two diastereomers (±)-**[234]** and (±)-**[235]** were separately reduced to the corresponding alcohols by treatment with lithium aluminium hydride in tetrahydrofuran at 0°C, resulting in (±)-**[237]** (92%) and (±)-**[238]** (100%). The stereochemistry of (±)-**[237]** was confirmed by comparison of spectroscopic data with that of Holmes *et al.*[77-78] and Jefford *et al.*[91-92] who had previously synthesized indolizidine **209B [3]**. Treatment of (±)-**[237]** and (±)-**[238]** with methanesulfonyl chloride and triethylamine in dichloromethane afforded the mesylates (±)-**[239]** and (±)-**[240]** (88%). Crude (±)-**[239]** was demesylated by treatment with lithium triethylborohydride to give (±)-**209B [3]** (40%, 2 steps). Reductive demesylation of (±)-**[240]** with lithium triethylborohydride proved to be erratic, however treatment with Raney nickel in boiling ethanol afforded the new diastereomer (±)-**[241]** (65%). Gravestock was also able to synthesis indolizidine (±)-**167B [193]** using similar methodology.

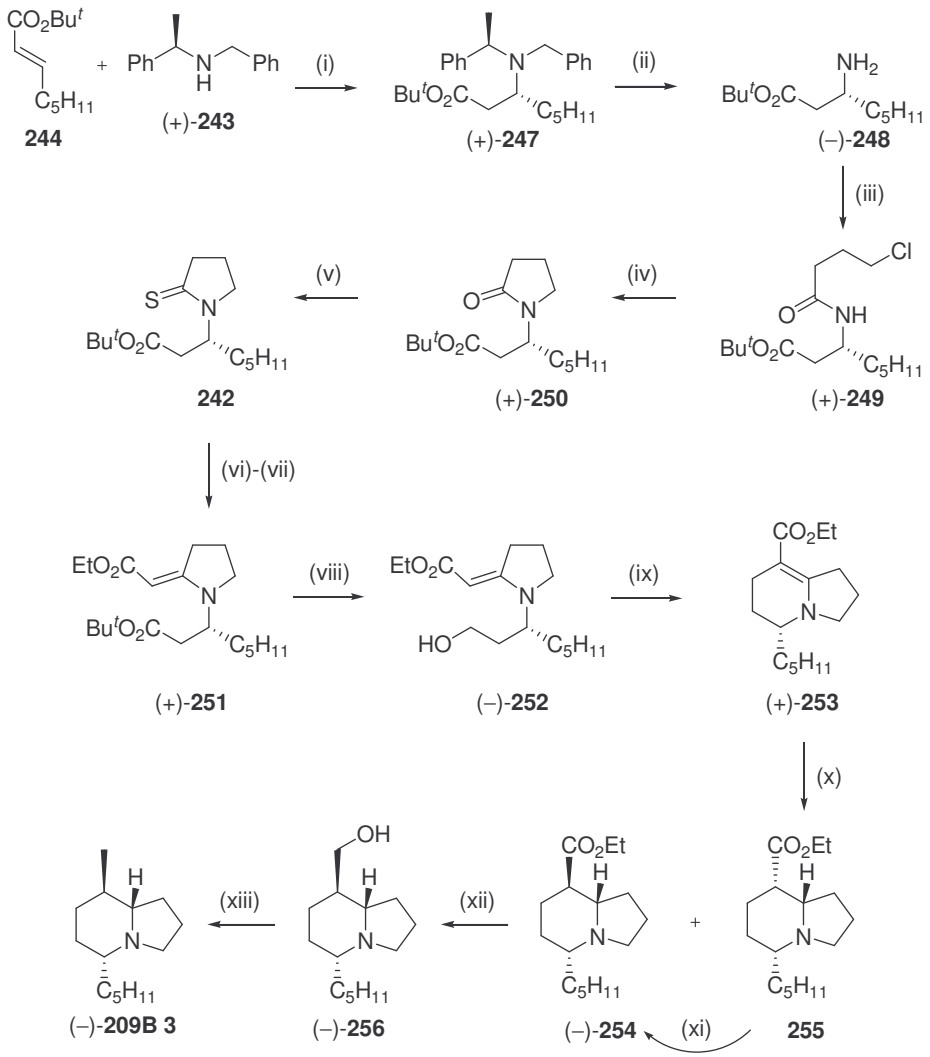


Scheme 2.12: *(i) NaOH (cat.), THF, rt, 74%; (ii) $BrCH_2CO_2Et$, MeCN, rt; (iii) PPh_3, NEt_3, MeCN, rt, 85% (2 steps); (iv) $LiAlH_4$, THF, 0 °C to rt, 91%; (v) (a) CBr_4, PPh_3, NEt_3, MeCN, 0 °C to rt, (b) rt to Δ, 85%; (vi) $NaBH_3CN$, HCl (pH 4), EtOH, rt, (±)-**[234]** (33%), (±)-**[235]** (14%), (±)-**[236]** (13%) or H_2 (1atm), PtO_2, AcOH, rt, (±)-**[234]** (71%), (±)-**[235]** (6%), (±)-**[236]** (0%); (vii) $LiAlH_4$, THF, 0 °C to rt, (±)-**[237]** (92%), (±)-**[238]** (100%); (viii) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0 °C, (±)-**[239]** (88%); (ix) $LiEt_3BH$ (1M in THF), THF, 0 °C, 40% (2 steps); (x) Raney Ni, EtOH, Δ, 65%*

2.6.2 Enantioselective synthesis of indolizidine (–)-209B [3]

Gravestock's enantioselective synthesis of indolizidine (–)-**209B [3]**, was significant within our laboratories since all of our preceding syntheses of alkaloids were racemic. In order to modify the racemic synthesis of (±)-**209B [3]** to produce a single enantiomer, it was decided to introduce the required stereochemistry early on in the synthesis, thereby allowing access to the thiolactam **[242]**, which contains the first of the targets three stereogenic centres (**Scheme 2.13**). Initially attempts involved the conjugate addition of pyrrolidin-2-thione **[230]** to an octyl-2-enoyl system bearing a chiral auxillary, however under the required kinetic reaction conditions diastereomeric ratios were always close to 1:1. The solution came from methodology developed by Davies *et al.*[124] where they described the synthesis of enantomerically pure β-amino esters. In what has proved to be a fairly general route (*R)*-(+)-*N*-benzyl-*N*-α-methylbenzylamine **[243]** undergoes a conjugate addition with various *tert*-butyl-(2*E*)-alk-2-enoates, to give the desired adducts in excellent yields and high diastereoselectivities (>95% de), and with a predictable stereochemical outcome. Debenzylation under hydrogenolytic conditions yields the enantiomerically pure β-amino esters.

The required starting materials for the synthesis of (–)-**209B [3]** are (*R)*-(+)-*N*-benzyl-*N*-α-methylbenzylamine **[243]** and the enoate substrate *tert*-butyl-(2*E*)-oct-2-enoate **[244]**. The success of the Davies method requires that the enoate **[244]** is free of its geometric isomer, as such it is prepared from hexanal **[245]** and *tert*-butyldiethoxyphosphorylacetate **[246]** by a Horner-Wadsworth-Emmons Wittig olefination (96%). The anion of chiral amine **[243]**, prepared by treatment with *n*-butyllithium in tetrahydrofuran at −78°C, was added slowly to **[244]** affording the diastereomerically pure amino ester (+)-**[247]** (76%). Debenzylation of (+)-**[247]**, under 7 atm hydrogen with 10% palladium on carbon in acetic acid yielded the pure β-amino ester (–)-**[248]**, which was subsequently converted to chloroamide (+)-**[249]** by treatment with 4-chlorobutryl chloride and sodium carbonate in refluxing chloroform. The crude (+)-**[249]** was cyclised by treatment with potassium *tert*-butoxide in dry *tert*-butanol to give lactam (+)-**[250]** (82%, 2 steps). Thionation of (+)-**[250]** proceeded smoothly using Lawesson's reagent in refluxing toluene (89%), the sulphide contraction with ethyl bromoacetate in acetonitrile yielded the desired (*R)*-(+)-vinylogous urethane (+)-**[251]** (94%).



Scheme 2.13: *(i)(a) (+)-**[243]** , n-BuLi, THF, –78 °C, (b) **[244]**, 76%; (ii) H_2 (7 atm), 10% Pd/C, HOAc, rt, 76%; (iii) $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, Δ; (iv) $KOBu^t$, Bu^tOH, rt, 82% (2 steps); (v) Lawesson's reagent, PhMe, Δ, 89%; (vi) $BrCH_2CO_2Et$, MeCN, rt; (vii) PPh_3, NEt_3, MeCN, rt, 94% (2 steps); (viii) $LiAlH_4$, THF, rt, 88%; (ix) I_2, Imidazole, PPh_3, PhMe, 110 °C, 81%; (x) H_2 (1 atm), PtO_2, AcOH, rt, 85% (12:88); (xi) NaOEt (cat.), EtOH, Δ, 40%; (xii) $LiAlH_4$, THF, 94%; (xiii) see ref. 76-77.*

Chemoselective reduction of (+)-**[251]** with lithium aluminium hydride in tetrahydrofuran afforded alcohol (–)-**[252]**, which underwent cycloalkylation by treatment with triphenylphosphine, iodine and imidazole in refluxing toluene to give the bicyclic urethane (+)-**[253]** (81%). Reduction of the carbon-carbon double bond of (+)-**[253]** was achieved by

catalytic hydrogenation with platinum oxide in acetic acid resulting in an 88:12 mixture of (−)-**[254]** and **[255]** (85%). The axial ester group of **[255]** was successfully epimerized when heated with a catalytic amount of sodium ethoxide in ethanol to (−)-**[254]** (40%). Finally reduction of (−)-**[254]** with lithium aluminium hydride afforded alcohol (−)-**[256]** (94%), thereby completing the formal synthesis of indolizidine (−)-**209B [3]**. Conversion of (−)-**[256]** into (−)-**209B (2)** has already been demonstrated by Holmes.[76-77]

2.7 Aims and Strategies of the Present Project

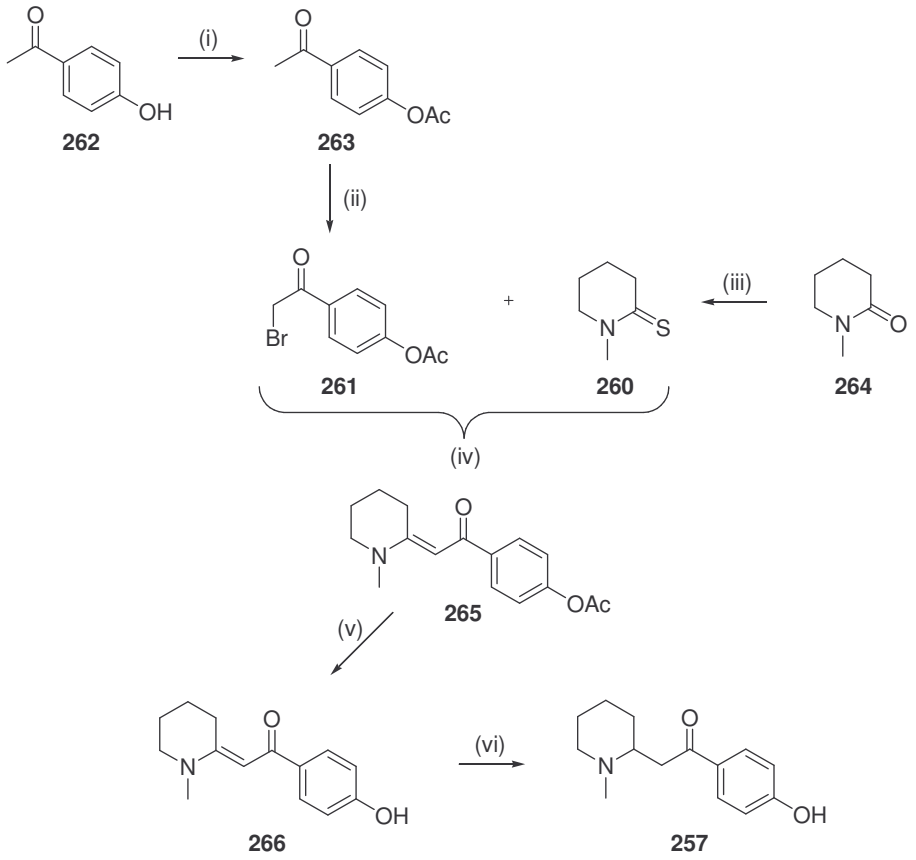
Having discussed the important features of the "Wits approach" to alkaloid synthesis, and having looked at Gravestock's syntheses in detail, we will now illustrate our plan to extend this methodology firstly for the synthesis of a simple piperidine alkaloid thalictroidine **[257]**, secondly for the synthesis of three previously identified 5,8-disubstituted indolizidines **197C [258], 209I [185]** and **223V [174]**, thirdly for the preparation of a late stage common intermediate **[259]** for the general preparation of almost any 5,8-disubstituted indolizidines. Finally we will illustrate how this methodology may be applied to the synthesis of 1,4-disubstituted quinolizidines.

2.7.1 Thalictroidine [257]

Thalictroidine **[257]** is a piperidine alkaloid which was isolated from a North American flowering plant Blue Cohosh (*Caulophyllum thalictroides*) in 1999[125]. The plant is traditionally used in certain dietary preparations, however interest was sparked when some of the alkaloids isolated from the plant were shown to be toxic and/or teratogenic. As it is a relatively newly discovered alkaloid, it was chosen as a simple target for structural elucidation, and the synthesis can be readily be adapted from our "Wits approach" to alkaloids.

Scheme 2.14 details the proposed synthetic route we envisaged using, employing the "Wits approach" to alkaloid synthesis. The synthesis of thalictroidine **[257]** requires the preparation of thiolactam **[260]** and phenacyl bromide **[261]** from commercially available staring materials. This can be achieved by protecting *p*-hydroxyacetophenone **[262]** as an acetate (*step i*) **[263]**, and then subjecting it to bromination to yield **[261]** (*step ii*). 1-Methyl-2-

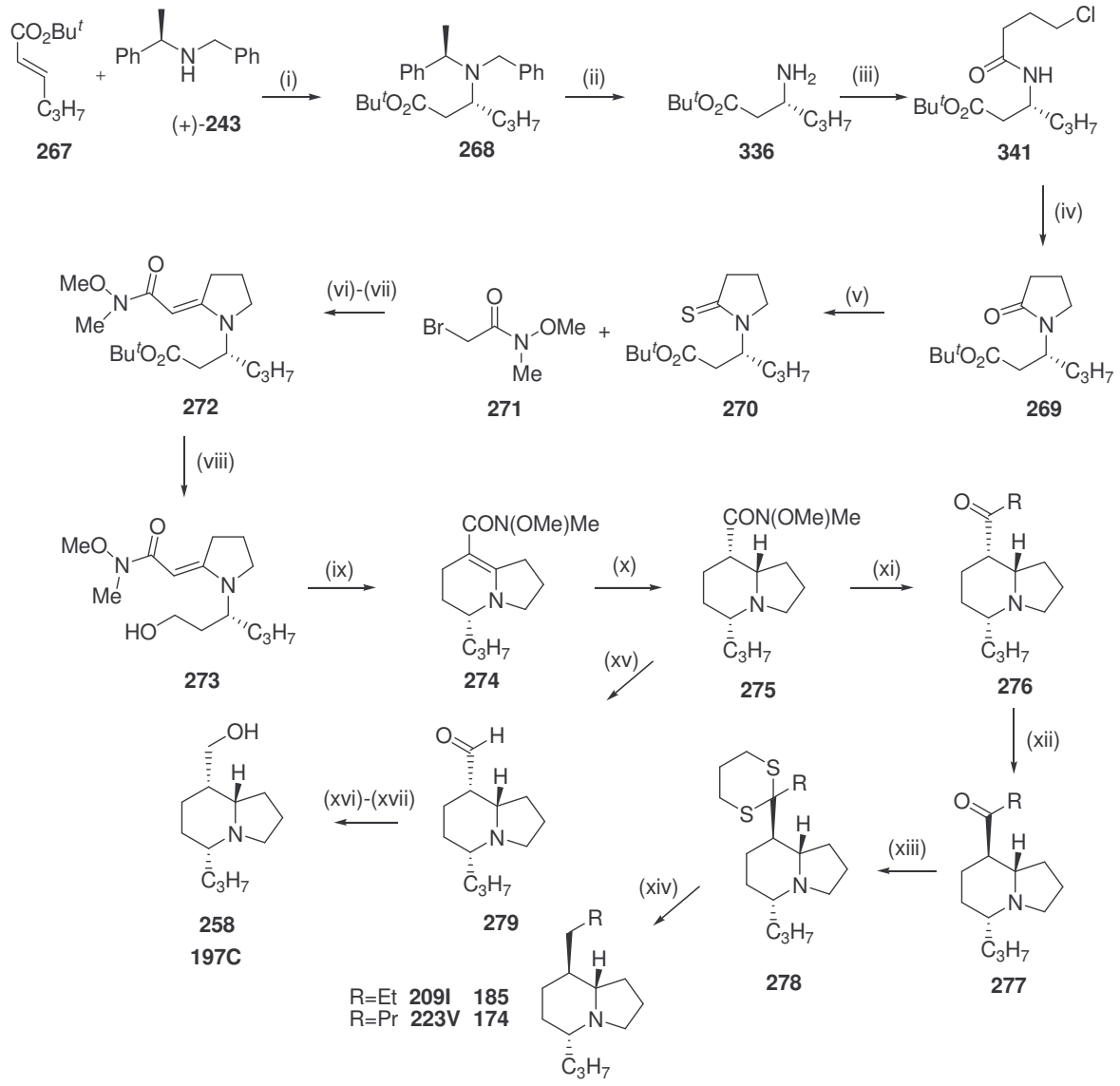
piperidone **[264]** can be thionated to give **[260]** (*step iii*). Transformation of the thiolactam **[260]** into the desired enaminone **[265]** (*step iv*) can be accomplished by sulphide contraction with **[261]**. Deprotection of **[265]** to **[266]** (*step v*), and reduction (*step vi*) should afford thalictroidine **[257]**. Protection of **[262]** with a chiral protecting group like (1*S*)-(+)-camphorsulfonyl chloride, could allow bias towards one enantiomer when reducing the carbon-carbon double bond, and this will also be investigated.



Scheme 2.14: *Proposed synthetic route for thalictroidine [257]*

2.7.2 Alkaloids 197C [258], 209I [185], 223V [174]

It was proposed that by using and expanding on the methodology established by Gravestock, as outlined in **Section 2.3**, indolizidines **197C [258], 209I [185]** and **223V [174]** could be accessed as shown in **Scheme 2.15**.



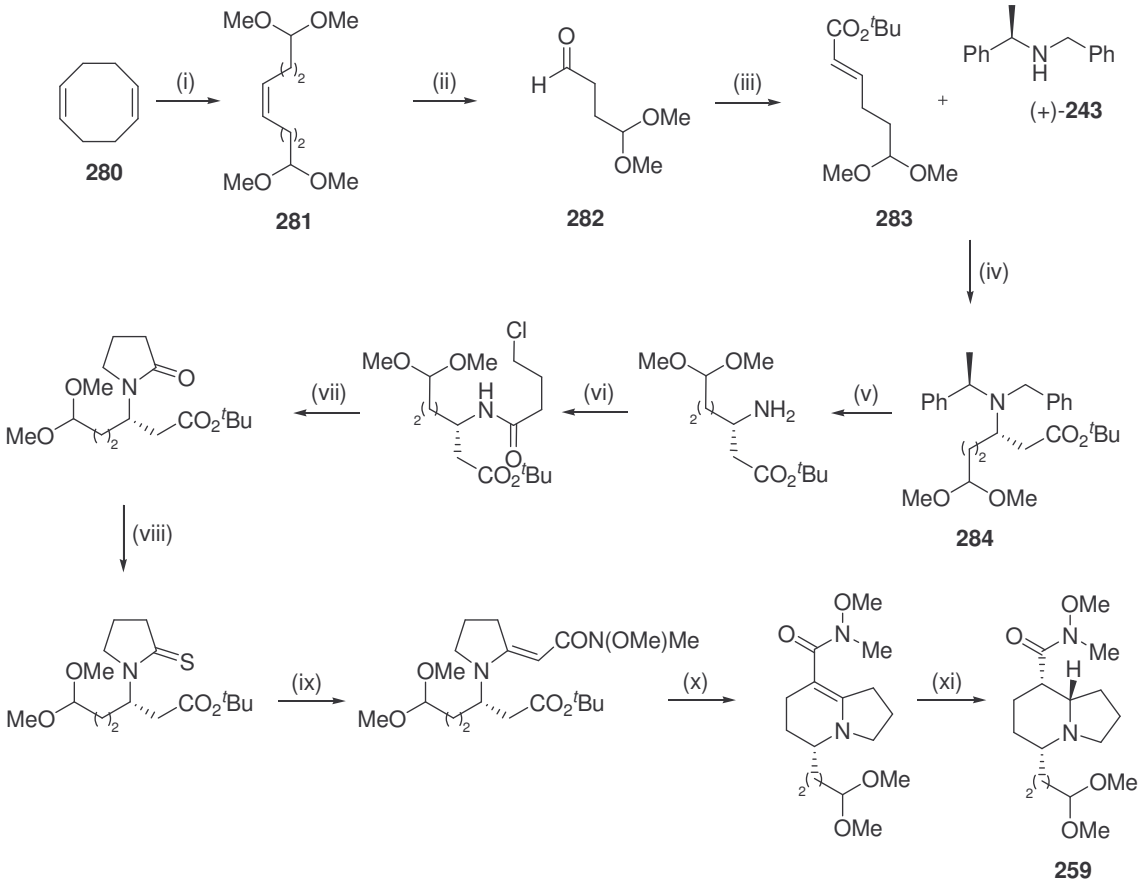
Scheme 2.15: *Proposed synthetic route for 5,8-disubstituted indolizidines **197C [258], 209I [185]** and **223V [174]***

Starting from enoate **[267]** the first step (*step i*) involves the conjugate addition of (*R)*-(+)-*N*-benzyl-*N*-α-methylbenzylamine **[243]**. Debenzylation of the amino ester **[268]** (*step ii*), and subsequent lactam formation (*steps iii and iv*) will afford the desired lactam **[269]**, which can be thionated to yield the important thiolactam **[270]** (*step v*). Sulphide contraction with 2-bromo-*N*-methoxy-*N*-methylacetamide **[271]** should lead to the desired enaminone **[272]** (*steps vi and vii*), characterized now by an incorporated Weinreb amide functionality. The Weinreb amide adds more versatility to the enaminone, and will hopefully allow us access to

a wider range of indolizidines than was previously possible using the existing methodology. Chemoselective reduction of the enaminone **[272]**, to the required alcohol **[273]** (*step viii*) and subsequent cycloalkylation (*step ix*) should lead to **[274]**. A stereoselective reduction of the carbon-carbon double bond at this stage will lead to the indolizidine **[275]** with the incorrect stereochemistry at C-8 (*step x*). Alkylation of the Weinreb amide **[275]**, will hopefully result in the monoalkylated product **[276]** being formed (*step xi*), the stereochemistry at C-8 can then be inverted to give the desired stereochemical arrangement as shown for **[277]** (*step xii*). Subsequent protection as the corresponding thioacetal **[278]** (*step xiii*) and desulfurisation (*step xiv*) should lead to indolizidines **209I [185]** and **223V [174]** with the correct stereochemistry. Furthermore reduction of **[275]** to the aldehyde **[279]** (*step xv*) may be possible, with subsequent epimerization and reduction (*step xvi and xvii)* then allowing access to **197C [258]**.

2.7.3 Preparation of a late stage common intermediate [259] for the synthesis of 5,8-disubstituted indolizidines

A drawback to the "Wits approach" to date is that it only allows for the modification of the substituent at the 8-position near the end of the synthesis, with the substituent at the 5-position having to be introduced early on. The establishment of the substituent at the 5-position early on has two main drawbacks; a) It means a long synthesis has to be repeated each time a new substituent is needed, and b) It limits the choice of substituents to simple saturated alkyl chains, as one of the later steps involves the stereoselective reduction of a carbon-carbon double bond by hydrogenation, and as a result any alkene or alkyne functionality would be lost at this stage. In response to this problem we envisaged the development of a late stage common intermediate which would allow the functionalisation of both chains after the reductive hydrogenation step. This intermediate would then allow us access to approximately 80% of the naturally occurring 5,8-disubstituted indolizidines that have been identified to date (**Scheme 2.16**).

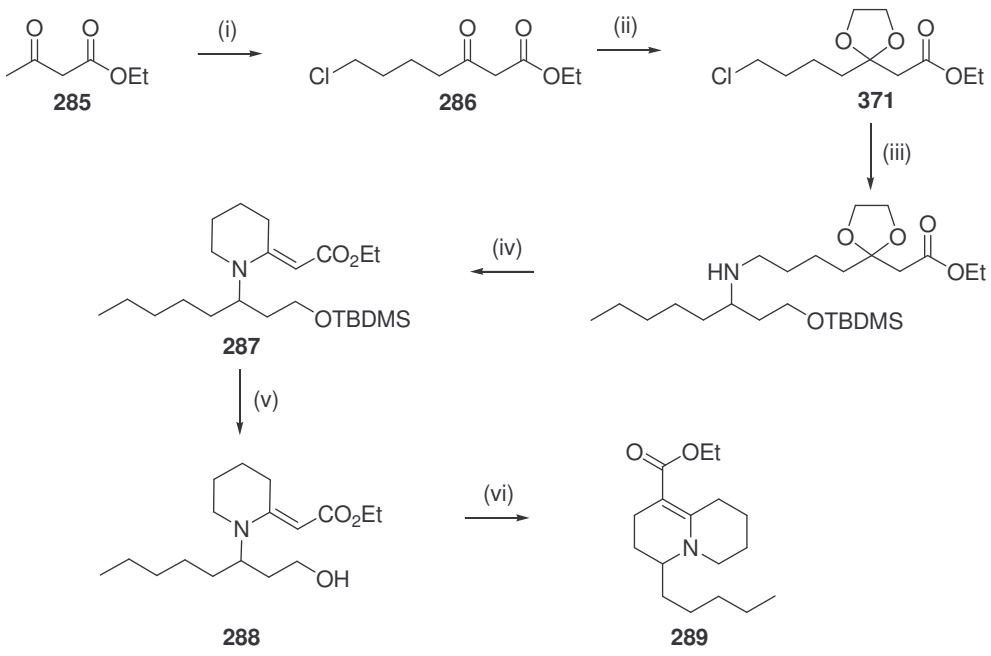


Scheme 2.16: *Proposed synthetic route toward a late stage common intermediate **[259]** for the synthesis of 5,8-disubstituted indolizidines*

Starting from cyclooctadiene **[280]** we invisage a stepwise ozonolysis *via* **[281]** to aldehyde **[282]** (*steps i and ii*). Horner-Wadsworth-Emmons Wittig olefination would give us the desired enolate **[283]** (*step iii*), which could then undergo a conjugate addition with (*R)*-(+)-*N*-benzyl-*N*-α-methylbenzylamine **[243]** (*step iv*) affording amino ester **[284]**. As with the route proposed in **Section 2.7.2**, debenzylation (*step v*), lactam formation (*steps vi and vii*), thionation (*step viii*), sulphide contraction (*step ix*), cycloalkylation (*step x*) and finally stereoselective reduction of the carbon-carbon double bond (*step* xi) will hopefully yield the desired intermediate **[259]**. If successful, **[259]** could potentially be converted into a library of indolizidines in several steps.

2.7.4 Extension of the methodology to 1,4-disubstituted quinolizidines

A further application to the methodology that we are interested in investigating is its applicability to the synthesis of the analogous 1,4-disubstituted quinolizidines. Previously San-Fat described the enantioselective synthesis of such alkaloids using the "Wits approach"[108k], however the synthesis was marred by the fact that the *tert*-butyl ester moiety used to ensure good stereoselectivity during the chiral alkylation step could not be removed later on in the synthesis. As a result several additional deprotections and re-protections had to be performed in order to access the desired quinolizidines. We felt that these additional steps detracted from the elegance of the synthesis, and made it too long winded. An alternative synthesis to access the desired bicyclic system, but still in keeping with the "Wits approach" is thus proposed (**Scheme 2.17**).



Scheme 2.17: *Alternative cyclisation proposed for the synthesis of 1,4-disubstituted quinolizidines*

Starting from ethyl-3-oxobutanoate **[285]**, we envisaged an alkylation at the primary carbon when treated with 1-bromo-4-chlorobutane (*step i*), followed by an acetyl protection of the ketone **[286]** (*step ii*). The key steps would involve the monoalkylation of a suitable primary

amine, followed by an acetyl deprotection which should facilitate ring closure to give **[287]** (*steps iii & iv*). Following the standard "Wits approach", deprotection of the silyl group will afford alcohol **[288]** (*step v*) and finally the standard cycloalkylation should afford **[289]** (*step vi*). If successful **[289]** could be converted into a small library of 1,4-disubstituted quinolizidines.

2.8 Summary of Aims

The main aims for this project can be summarized as follows:

- To extend the synthetic utility of enaminones in alkaloid synthesis, in particular by looking at the advantages offered by the incorporation of a Weinreb amide into the enaminone functionality.

- To use and expand on the methodology established by D. Gravestock for the enantioselective synthesis of 5,8-disubstituted indolizidines, for the synthesis of indolizidines **197C [258], 209I [185]** and **223V [174]** (**Figure 2.3**).

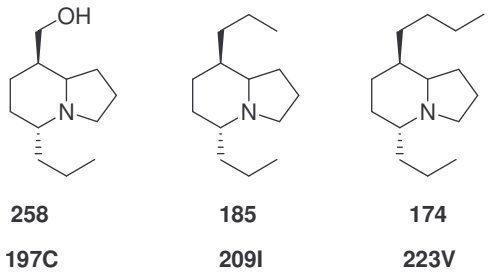
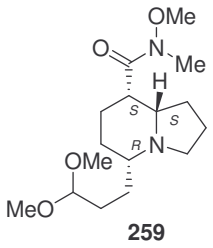


Figure 2.3: *Indolizidines **197C [258], 209I [185]** and **223V [174]***

- To synthesize a late stage common intermediate **[259]** (**Figure 2.4**), that would allow us access to most naturally occurring 5,8-disubstituted indolizidines.



259

Figure2.4: *The late stage common intermediate **[259]***

- To investigate an alternative approach for the synthesis of 1,4-disubstituted quinolizidines.

CHAPTER 3

SYNTHESIS OF (±)-THALICTROIDINE [257]

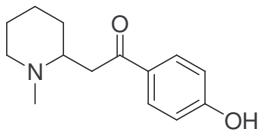


CHAPTER 3

SYNTHESIS OF (±)-THALICTROIDINE [257]

3.1 Introduction

This chapter concerns the preparation of the piperidine alkaloid thalictroidine **[257]** in racemic form (**Figure 3.1**). Attempts at an enantioselective synthesis will also be discussed.



257

Figure 3.1: *Thalictroidine [257]*

Thalictroidine **[257]** was originally isolated in 1999 by Kennelly *et al.*[125] from a North American flowering plant "Blue Cohosh" (*Caulophyllum thalictroides*), which is used in certain dietary preparations. Investigations of the plant metabolites were sparked when it was discovered that some of the alkaloids found in the plant were toxic or teratogenic.[125] We chose to synthesize this alkaloid **[257]** following the steps outlined in **Scheme 2.14** to gain experience in the methodology utilized in the "Wits" approach towards alkaloid synthesis.

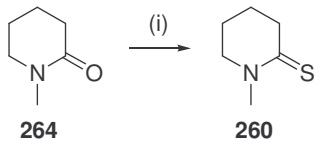
The next section of this chapter describes the synthesis of racemic thalictroidine **[257]**, highlighting the steps which will be important in the synthesis of indolizidines. These include the thionation of 1-methylpiperidine-2-one **[264]** and the preparation of the phenacyl bromide **[261]** (**Section 3.2.1**). Subsequent reactions include the sulfide contraction between **[260]** and **[261]**, and the reduction of the exocyclic carbon-carbon double bond of the resulting enaminone **[265]** (**Sections 3.2.2** & **3.2.3**).

The final section describes an alternative route for the enantioselective preparation of thalictroidine **[257]**. The chiral approach focuses on tethering chiral camphorsulfonyl chloride **[290]** to *p*-hydroxyacetophenone **[262]** in an attempt to create a stereochemical bias during the reduction of the double bond.

3.2 Synthesis of (±)-thalictroidine [257]

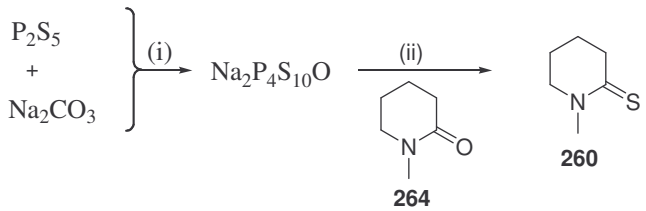
3.2.1 Preparation of starting materials

1-Methylpiperidine-2-thione **[260]** was prepared by stirring 1-methylpiperidine-2-one **[264]** with phosphorus pentasulfide in refluxing benzene overnight (**Scheme 3.1**). Our best result gave a 90% yield on a 27.8 mmol scale. The expected thiolactam **[260]** was obtained as clear crystals and the melting point and spectroscopic data corresponded closely with literature values[126].



Scheme 3.1: *(i) P_2S_5, C_6H_6, Δ, 24 h, 90%*

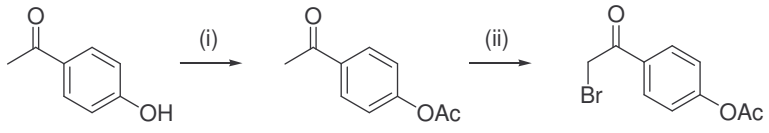
The thionation was also performed under milder conditions by stirring with phosphorus pentasulfide in chloroform[127] at room temperature as well as by Brillon's procedure.[128] The yields obtained were 37% and 66% respectively. The Brillon procedure involves the preparation of an *in situ* reagent by stirring phosphorus pentasulfide and sodium carbonate in a 2:1 ratio in tetrahydrofuran. The two components are stirred until a homogeneous solution has formed, which is accompanied by the vigorous evolution of carbon dioxide. The exact structure of the intermediate is still not known; however, the proposed molecular formula of the reagent is $Na_2P_4S_{10}O$ (**Scheme 3.2**).



Scheme 3.2: *(i) THF, rt, 20-30 min; (ii) rt, 5 h 66%*

1-Methylpiperidine-2-thione **[260]** was characterized by the appearance of a thiocarbonyl signal at 199.3 ppm in the ^{13}C NMR spectrum. Furthermore, the mass spectrum showed an ion at *m/z* 129.06098 (100%), with M^+ requiring 129.06122. The obtained melting point of 34-35 °C was comparable with the literature value of 36-39 °C.[126]

p-Acetoxyacetophenone **[263]** was prepared by the acetylation of *p*-hydroxyacetophenone **[262]** according the conditions outlined by Corson *et al.*[129] in which they obtained a yield of 93% for the acetylated product (**Scheme 3.3**).



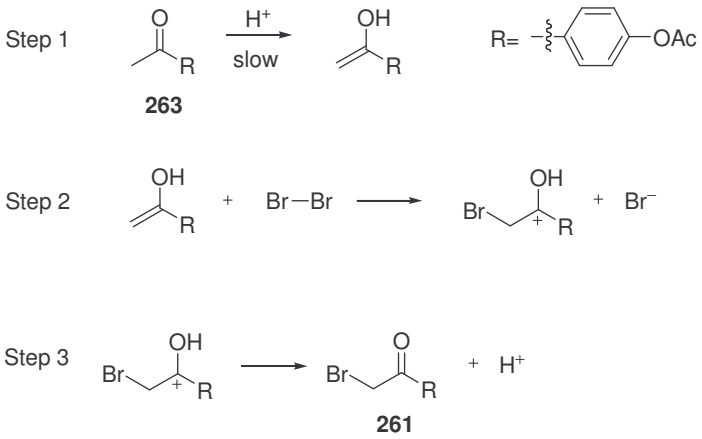
262 **263** **261**

Scheme 3.3: *(i) Ac_2O, 7.5% NaOH(aq), 0 °C-rt, 24 h, 94%; (ii) Br_2, HBr(cat.), $CHCl_3$, 30 min, 83%*

The acetylation involved the slow addition of acetic anhydride to a solution of *p*-hydroxyacetophenone **[262]** in an aqueous sodium hydroxide solution. In our hands, the acetylation was successfully carried out on a 37.0 mmol scale in a comparable yield of 94% (**Scheme 3.3**). The melting point of 55-56 °C was comparable with the literature value of 54 °C reported by Corson *et al.*[129] The compound was characterized by the appearance of a signal at 2.32 ppm in the ^1H NMR spectrum integrating for three protons and corresponding to the acetate CH_3. The acetate carbon signals were also seen at 166.8 (C=O) and 21.1 ppm (CH_3) in the ^{13}C NMR spectrum. The FTIR spectrum also clearly showed two carbonyl signals at 1759 cm^{-1} and 1682 cm^{-1} due to the ester and ketone carbonyl groups respectively. The mass spectrum showed the molecular ion at *m/z* 178.06394 with the required mass being 178.06299.

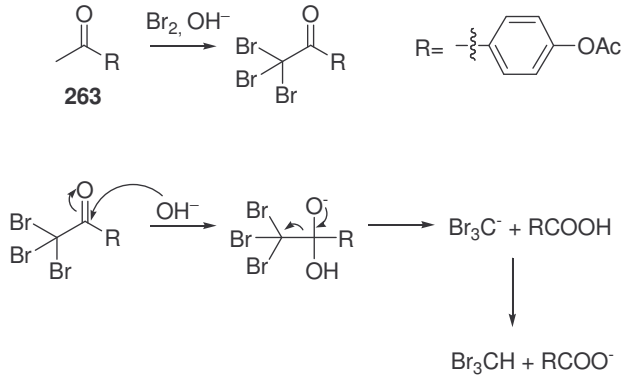
The bromination to access α-bromo-4-acetoxyacetophenone **[261]** was achieved using the reaction conditions outlined by Rosenmund and Pfroeffer[130], who obtained a 77% yield of the desired bromoketone **[261]** (**Scheme 3.2**). They treated a solution of *p*-acetoxyacetophenone **[263]** in chloroform with bromine. The reaction was initiated by heating a small amount of the

sample until hydrogen bromide gas was evolved. This sample was immediately added to the bulk of the solution. The hydrogen bromide gas is required in catalytic amounts, allowing the bromination to proceed through the enol form of the ketone, which is promoted by the protonation of the carbonyl group oxygen atom (**Scheme 3.4**).



Scheme 3.4: *Proposed mechanism for the acid-catalysed bromination of a ketone*

The rate of formation of the enol decreases as the α-hydrogens are replaced by bromine atoms, as the bromine atoms reduce the basicity of the carbonyl group. As a result the use of catalytic base to generate the enol is not suitable as it increases the basicity of the carbonyl group, and the reaction can not be stopped once the ketone has been brominated once.[131] Furthermore in the case of our substrate there is a methyl group α to the carbonyl group, and under basic conditions it would undergo a bromoform reaction instead (**Scheme 3.5**).[132]



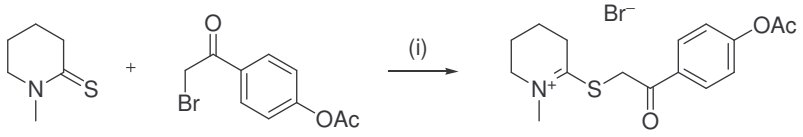
Scheme 3.5: *The bromoform reaction*

At room temperature we found that there was sufficient hydrogen bromide present in the bromine that we used to catalyse the reaction without any heating. The reaction proceeded quickly and was completed within minutes in an 83% yield. The ^{1}H NMR spectrum were characterized by the loss of the ketone CH_3 signal at 2.59 ppm and the appearance of a CH_2Br signal as a singlet integrating for two protons at 4.43 ppm. The mass spectrum showed an ion at *m/z* 255.97435 (6%) with $C_{10}H_9O_3Br$ requiring 255.97351, and the melting point of 68 °C was comparable with the literature value of 67 °C reported by Rosenmund and Pfroeffer.[130]

The bromination was also attempted by refluxing *p*-acetoxyacetophenone **[263]** and *N*-bromosuccinimide in dry carbon tetrachloride overnight. Upon workup and purification, however, only unreacted *p*-acetoxyacetophenone **[263]** was recovered.

3.2.2 Eschenmoser sulfide contraction[121-123] between 1-methylpiperidine-2-thione [260] and α-bromo-4-acetoxyacetophenone [261]

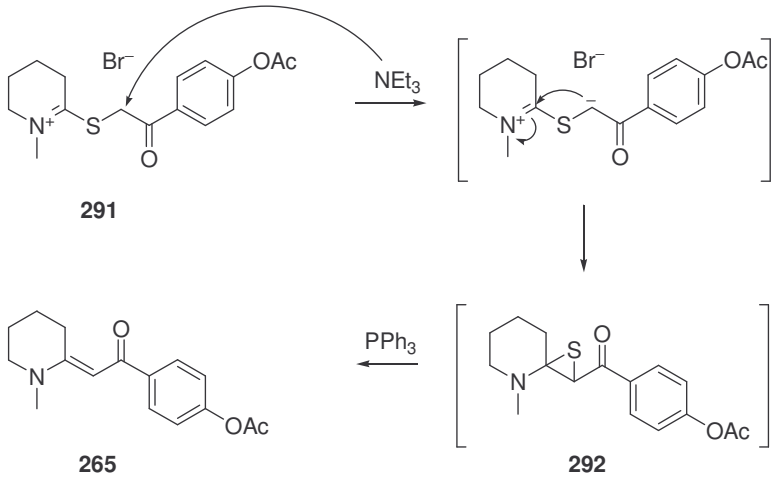
The overnight reaction of 1-methylpiperidine-2-thione **[260]** and α-bromo-4-acetoxyacetophenone **[261]** in acetonitrile gave the corresponding *S*-alkylated bromide salt **[291]** (**Scheme 3.6**).



260 **261** **291**

Scheme 3.6: *(i) CH_2Cl_2, rt, 24 h*

Deprotonation of the acidic proton between the sulfur and the ketone with triethylamine and subsequent cyclisation affords the thiirane intermediate **[292]** (**Scheme 3.7**). Finally the sulfur atom is removed by treatment with the thiophile triphenylphosphine, yielding the desired enaminone **[265]** in a 69% yield (**Scheme 3.7**). The contraction affords only the corresponding *E*-isomer, as the methyl substituent at the 1-position of the piperidine ring hinders the formation of the *Z*-isomer. Assignment of the stereochemistry is based on the chemical shift of the methylene protons at C-3 of the heterocyclic ring (approximately 3.3 indicating a *trans*-s-*cis* structure, whereas approximately 2.7 would have indicated a *cis*-s-*cis* structure).



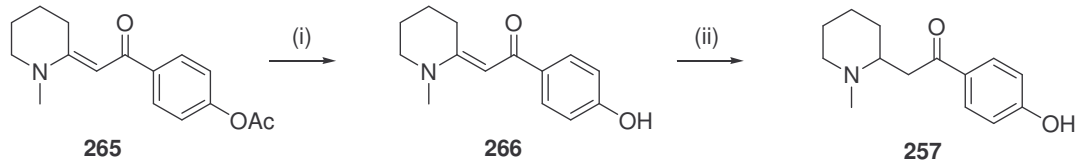
Scheme 3.7: *PPh_3, NEt_3, CH_3CN, 3-24 h, 69% (2 steps)*

Purification of the crude enaminone **[265]** in the presence of unreacted triphenylphosphine and triphenylphosphine sulfide residues can be challenging, as separation by column chromatography using ethyl acetate/hexane mixtures is often ineffective. Fortunately the enaminones that we work with generally have a much lower affinity for dichloromethane as the mobile phase than the triphenylphosphine and triphenylphosphine sulfide. The unreacted triphenylphosphine residues can therefore be removed by initial elution with dichloromethane; thereafter the desired products can be obtained by elution with suitable ethyl acetate/hexane mixtures. The more polar triphenylphosphine oxide residues which are formed occasionally remain on the baseline in ethyl acetate/hexane mixtures, and as such they are not as problematic. In the case of very polar enaminones an alternative approach that we have used extensively is to perform a simple acid-base workup. An initial acid extraction using 2 M hydrochloric acid separates the enaminones from the phosphine impurities which can not be protonated, and therefore remain in the organic phase. Subsequent addition of ammonia solution to basify the aqueous layer and extraction into dichloromethane yields the desired products as almost chromatographically pure samples. Utilising the acid-base extraction work-up and purification through a short plug of silica afforded us the desired enaminone **[265]**. The ^{1}H NMR spectrum showed the presence of an expected vinyl singlet at 5.61 ppm. The ^{13}C NMR spectrum had a signal at 90.5 ppm characteristic of an enaminone vinyl carbon. Furthermore the thiocarbonyl carbon signal around 200 ppm in 1-methyl piperidine-2-thione

[260] was absent. The FTIR spectrum show a characteristic α,β unsaturated ketone stretch at 1691 cm^{-1} and finally the mass spectrum possessed an ion at *m/z* 273.13601 (54%) and the parent ion of $C_{16}H_{19}NO_3$ requires 273.13649.

3.2.3 Completion of the synthesis of (±)-thalictroidine [257]

We initially envisaged the preparation of the desired target by deprotecting the phenol group and subsequently reducing the exocyclic carbon-carbon double bond. The deprotection of **[265]** proceeded smoothly under mild conditions using potassium carbonate in methanol to afford a slow release of sodium methoxide, which removes the acetate group. The desired phenol **[266]** was obtained as a green solid in an 85% yield (**Scheme 3.8**).



265 **266** **257**

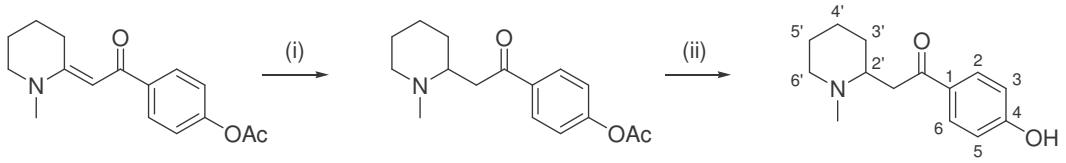
Scheme 3.8: *(i)K_2CO_3, MeOH, rt, 1-3 h, 85%; (ii) $NaCNBH_3$, pH 4, rt, 1 h, 43%*

The loss of the acetate singlet at 2.98 ppm, and the appearance of a broad OH peak between 2.60 and 4.00 integrating for one proton in the ^1H NMR spectrum showed that the deprotection was successful. The acetate carbon signals at 169.2 ($O\underline{C}OCH_3$) and 19.4 ($OCO\underline{C}H_3$) were also absent from the ^{13}C NMR spectrum. FTIR spectrum had a characteristic hydroxyl peak at 3422 cm^{-1} with no acetate carbonyl signal around 1720 cm^{-1} and the mass spectrum possessed an ion at *m/z* 231.12526 (47%), while the parent ion of $C_{14}H_{17}NO_2$ requires 231.12593.

The reduction of **[266]** proved to be more challenging than initially expected. Several attempts were made to reduce the carbon-carbon double bond under hydrogenation conditions using 10% palladium on carbon and Adams' catalyst under various reaction conditions, to no avail. In all cases the palladium catalyst gave no reduced product, whereas the platinum catalyst seemed to reduce both the carbon-carbon double bond and the carbonyl group. Lithium aluminium hydride also showed no evidence of any reduction occurring. Finally,

reduction with sodium cyanoborohydride under acidic conditions afforded (±)-thalictroidine **[257]** in a 43% yield as a dark green solid (**Scheme 3.8**). The spectroscopic data obtained were comparable to those published by Kennelly *et al*.,[125] thus confirming the proposed structure of the natural product. We felt at this point that deprotection of the hydroxyl group may have led to the formation of a zwitterion species formed by proton transfer between the acidic phenol and the basic enaminone, and as such we were losing product in the aqueous workup. When repeated without an aqueous workup, however, we found no improvement in the yield and we were unable to optimize the reaction further.

We were not pleased with the poor yield for the final step, and as such decided to first reduce the enaminone and then perform the deprotection. Reduction of **[265]** using the establish sodium cyanoborohydride method afforded the desired product **[293]** in a 46% yield as a dark green solid (**Scheme 3.9**).



265 **293** **257**

Scheme 3.9: *(i) $NaCNBH_3$, pH 4, rt, 1 h, 46%; (ii) K_2CO_3, MeOH, rt, 1-3 h, 80%*

The loss of the vinyl proton at 5.61 ppm in the ^{1}H NMR spectrum indicated that the reduction was successful. Furthermore there were no carbon signals around 170 and 90 ppm in the ^{13}C NMR spectrum further indicating the reduction of the double bond. The mass spectrum contained an ion at *m/z* 275.15385 (6%) and the parent ion of $C_{16}H_{21}NO_3$ requires 275.15214.

The reduction of the exocyclic double bond was once again low yielding. However as the phenol was protected as an acetate the formation of a zwitterion species could be eliminated as the reason for the low yield. Once again, despite several attempts we were unable to optimize the reaction.

Deprotection of **[293]** using sodium carbonate in methanol proceeded smoothly, affording (±)-thalictroidine **[257]** in an 80% yield (**Scheme 3.9**). Once again the spectroscopic data were comparable to those published by Kennelly *et al.*[125] as summarized below in **Tables 3.1 and 3.2.**

Table 3.1: Comparison of ^{1}H NMR spectroscopic data for (±)-thalictroidine **[257]**

Proton	**^{1}H NMR ($CDCl_3$) Riley (300 MHz)**	**^{1}H NMR ($CDCl_3$) Kennelly *et al.*[125] (300 MHz)**
H-2 & H-6	7.79 (d, *J* 8.5 Hz)	7.81 (d, *J* 8.8 Hz)
H-3 & H-5	6.83 (d, *J* 8.6 Hz)	6.81 (d, *J* 8.8 Hz)
CH_2COa	3.42 (dd, *J* 5.1 & 16.7 Hz)	3.38 (dd, *J* 5.4 & 16.6 Hz)
H-2' & H-6'a	3.21-2.92 (m)	3.07 (m) & 3.03 (dt, *J* 3.4 & 11.5 Hz)
CH_2COb	2.87 (dd, *J* 5.9 & 16.7 Hz)	2.85 (dd, *J* 6.3 & 16.6 Hz)
H-6'b	2.48-2.41 (m)	2.39 (dt, *J* 5.0 & 11.0 Hz)
NCH_3	2.41 (s)	2.38 (s)
H-3', H-4' and H-5'	1.85-1.38 (m)	1.75-1.40 (m)

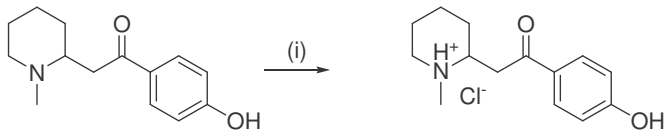
Table 3.2: Comparison of ^{13}C NMR spectroscopic data for (±)-thalictroidine **[257]**

Carbon	**^{13}C NMR ($CDCl_3$) Riley (300MHz)**	**^{13}C NMR ($CDCl_3$) Kennelly *et al.*[125] (300 MHz)**
C=O	197.2	196.4
C-4	163.8	164.0
C-2 & C-6	131.0	131.0
C-1	128.2	127.8
C-3 & C-5	116.4	116.4
C-2'	59.8	59.9
C-6'	56.4	56.4
NCH_3	43.2	42.7
$\underline{C}H_2CO$	41.6	41.2
C-3'	31.6	31.2

C-5'	25.0	24.5
C-4'	23.6	23.4

3.2.4 Preparation of the hydrochloride salt [294] of thalictroidine [257]

We attempted to obtain a crystal structure of thalictroidine **[257]** to provide further evidence for the structure of the natural product. As thalictroidine **[257]** is an oil we decided to convert it into the corresponding hydrochloride salt **[294]** by treatment with dry hydrogen chloride gas (**Scheme 3.10**).



257 **294**

Scheme 3.10: *(i) Dry HCl (g), MeOH*

The hydrochloride salt **[294]** obtained was recrystallised from methanol, and a single crystal XRD structure was obtained. The crystal data, data collection and refinement parameters are shown below in **Table 3.3**.

Table 3.3: Crystal Data, data collection and refinement parameters

Empirical Formula	$C_{14}H_{22}ClNO_3$	
Formula weight	287.78	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal System	Orthorhombic	
Space Group	Pca2(1)	
Unit Cell Dimensions	a = 27.727(3) Å	α = 90°
	b = 7.0807(11) Å	β = 90°
	c = 7.4199(9) Å	γ = 90°

Volume	1456.7(3) $Å^3$
Z	4
Density (calculated)	1.312 $Mg.m^{-3}$

Table 3.3 continued: Crystal Data, data collection and refinement parameters

Absorption coefficient	0.266 mm^{-1}
F(000)	616
Crystal Size	0.40 × 0.11 × 0.05 mm^3
Theta range for data collection	1.47 to 26.99°
Index ranges	–35<=h<=29, –6<=k<=9, –9<=l<=9
Reflections collected	5962
Independent reflections	2867 [R(int) = 0.0779]
Completeness to theta = 26.99°	99.7%
Absorption correction	Integration
Max. and min. transmission	0.9868 and 0.9010
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2867 / 2 / 181
Goodness of fit on F^2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.1022
R indices (all data)	R1 = 0.0756, wR2 = 0.1251
Absolute structure parameter	–0.09(10)
Largest diff. peak and hole	0.233 and –0.231 $e.Å^{-3}$

The structure is shown schematically by the ORTEP diagram illustrated below in **Figure 3.2**. The crystal structure confirmed the structure of thalictroidine **[257]** proposed by Kennelly *et al.*[123] The structure is that of the hydrochloride salt of thalictroidine **[294]**, and as such consists of a piperidine ring joined to an aromatic carbonyl through a CH_2 group. The phenolic alcohol is seen in the position para to the ketone. The nitrogen atom is protonated and sp^3 hybridised, and is hydrogen bonded to a chloride anion. The crystal also contains one molecule of water that is hydrogen bonded to the phenolic alcohol. The geometry observed

for the six-membered piperidine ring indicates that it is in a chair conformation, and the aromatic ring is nearly perpendicular to the piperidine ring.

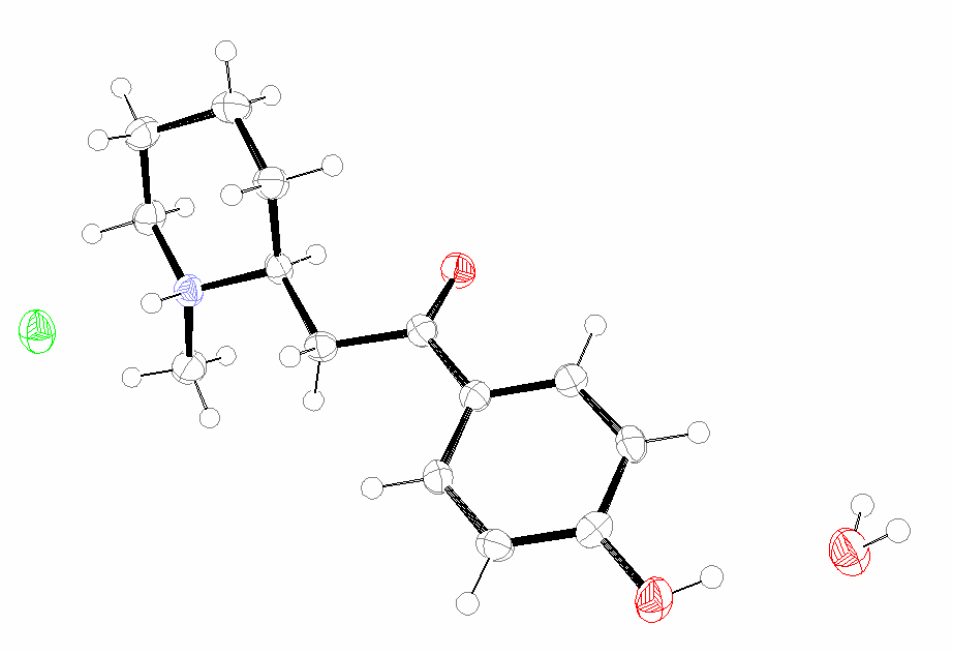


Figure 3.2: *ORTEP diagram of the hydrochloride salt of thalictroidine* ***[294]*** *(Showing the 50% probability thermal ellipsoids for all non-hydrogen atoms)*

The unit cell is orthorhomobic, with z = 4 and has a *Pca2*(1) space group (**Figures 3.3 and 3.4**). When viewed along the *a*-axis there appears to be π-stacking between the aromatic rings, and the chloride anions are sandwiched between the two layers of molecules.

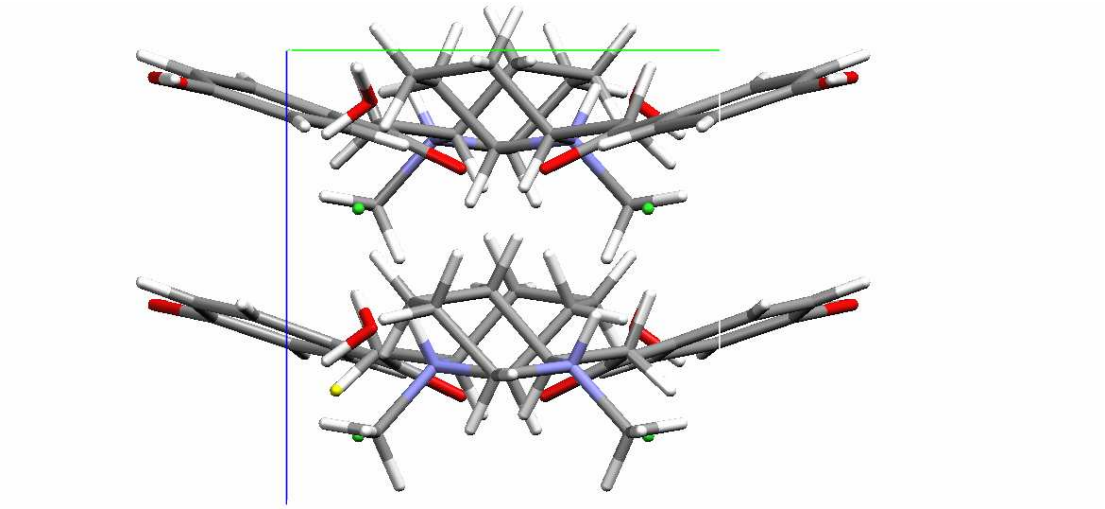


Figure 3.3: *Packing pattern viewed along the a-axis*

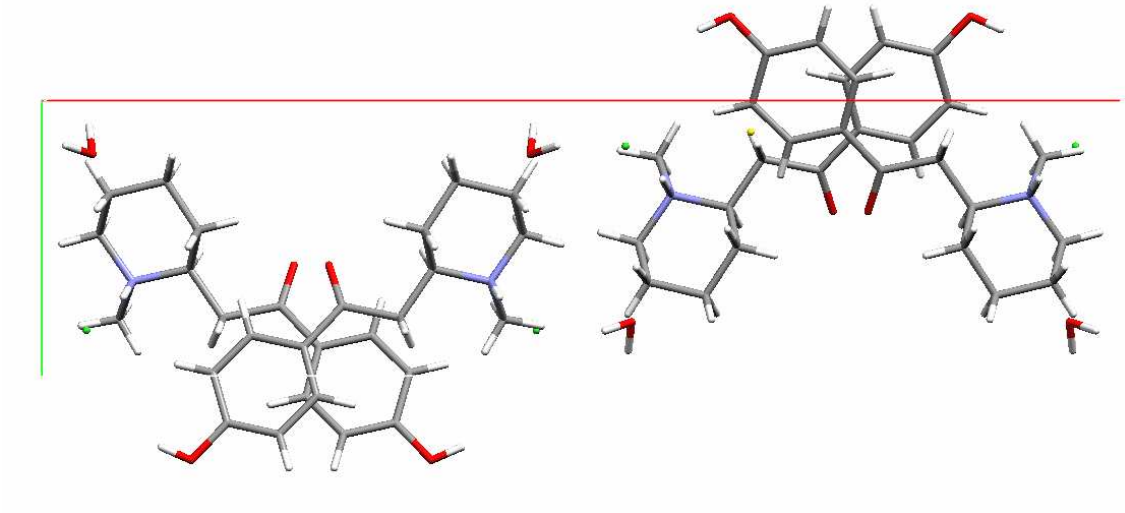


Figure 3.4: *Packing pattern viewed along the c-axis*

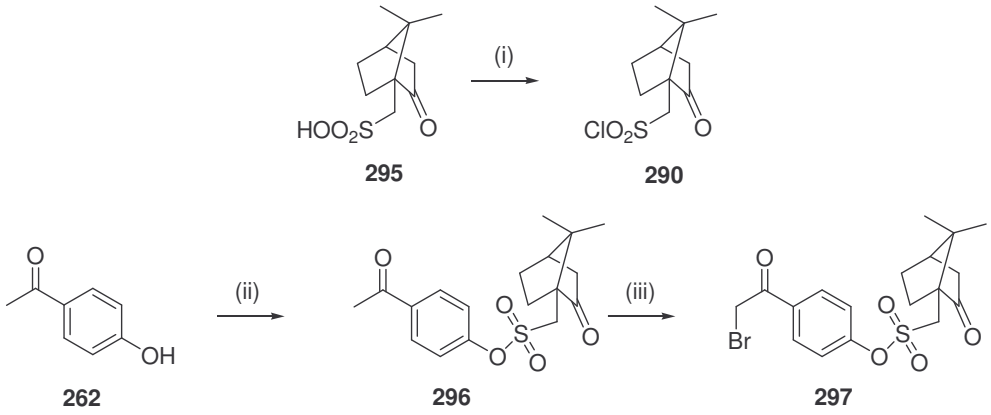
3.3 Attempted enantioselective synthesis of thalictroidine [257]

During the synthesis of thalictroidine **[257]**, we wondered if we could achieve any degree of stereocontrol by attaching a chiral auxiliary to the phenol hydroxyl group of **[262]**. As the hydroxyl group is quite far from the stereogenic centre in thalictroidine **[257]** we envisaged the need for a fairly large chiral auxiliary if we hoped to see any selectivity in the sodium cyanoborohydride reduction. In addition, in order to determine the stereochemistry in the

proposed enantioselective synthesis we would ideally require a crystal structure of thalictroidine **[257]** while tethered to a chiral auxiliary. As a result we chose to use a camphorsulfonyl group owing to its size and crystalline nature, which we hoped would provide enough steric hindrance for a stereoselective reduction and provide a crystalline product.

3.3.1 Preparation of the chiral auxiliary [290] and tethering it to *p*-hydroxyacetophenone [262]

The chiral camphorsulfonyl auxiliary was prepared from commercially available (1*S*)-(+)-10-camphorsulfonic acid **[295]**, which was refluxed with thionyl chloride for approximately one hour, yielding (1*S*)-(+)-camphorsulfonyl chloride **[290]** as a fine white solid in a 98% yield on a 22 mmol scale (**Scheme 3.11**).



Scheme 3.11: *(i) $SOCl_2$, Δ, 1 h, 98% or PCl_5, 0 °C, 4 h, 30%; (ii)* ***[290]****, NEt_3, CH_2Cl_2, 1 h, 88%; (iii) Br_2, $CHCl_3$, 30 min, 84%*

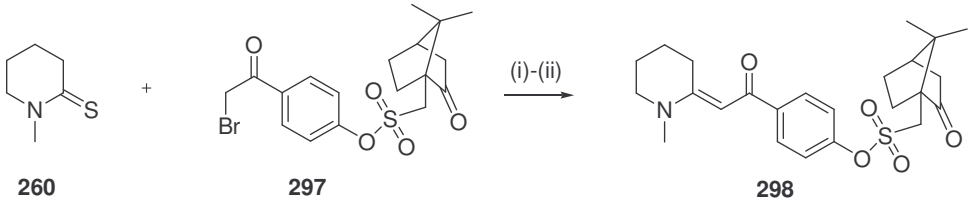
(1*S*)-(+)-Camphorsulfonyl chloride **[290]** was also prepared by treating (1*S*)-(+)-10-camphorsulfonic acid **[295]** with phosphorus pentachloride; however, yields were erratic with a best result of only 30%. Spectroscopic data were comparable with those published previously in the literature.[133] The mass spectrum requires 250.04304 for $C_{10}H_{15}ClO_3S$ and the required peak was present at *m/z* 250.04490 (0.25%).

The (1*S*)-(+)-camphorsulfonyl chloride **[290]** was tethered to *p*-hydroxyacetophenone **[262]** by treatment with triethylamine in dichloromethane. The reaction was accompanied by the evolution of hydrochloric acid gas along with the precipitation of the product **[296]**. The desired product 1-[(4-acetylphenylsulfonyl)methyl]-7,7-dimethybicyclo-[2.2.1]-heptan-2-one **[296]** was obtained as a yellow-orange solid in an 88% yield on a 14.6 mmol scale. The use of a 7.5% aqueous solution of sodium hydroxide as the base resulted in a 2.2:1 ratio of the desired product to starting material. Sodium hydride was also used, yielding a 1.5:1 ratio of desired product to starting material. The FTIR spectra showed no sign of any broad signals above 3000 cm^{-1}, indicating the loss of an alcohol group. The mass spectrum possessed an ion at *m/z* 351.12525 [$(M+N)^+$ 4%, $C_{18}H_{23}O_5S$ requires 351.12662].

Bromination of **[296]** using the protocol of Rosenmund and Pfroeffer[130] gave the desired phenacyl bromide **[297]** as a colourless solid in an 84% yield on a 0.56 mmol scale. The ^1H NMR spectrum showed a characteristic loss of a CH_3 signal at 2.61 ppm accompanied by the appearance of a CH_2Br singlet at 4.42 ppm. The ^{13}C NMR spectrum also showed the loss of a CH_3 signal at 26.6 and the appearance of a CH_2Br signal at 30.4 ppm. The mass spectrum showed an ion at *m/z* 335.09641 (7%), corresponding to $M^+–CH_2Br$, $C_{17}H_{19}O_5S$ requires 335.09532.

3.3.2 Sulfide contraction of 1-methylpiperidine-2-thione [260] and phenacyl bromide [297]

A standard sulfide contraction between 1-methylpiperidine-2-thione **[260]** and phenacyl bromide **[297]** afforded the desired vinylogous amide **[298]** as an orange solid in a 64% yield on a 4.7 mmol scale (**Scheme 3.12**).



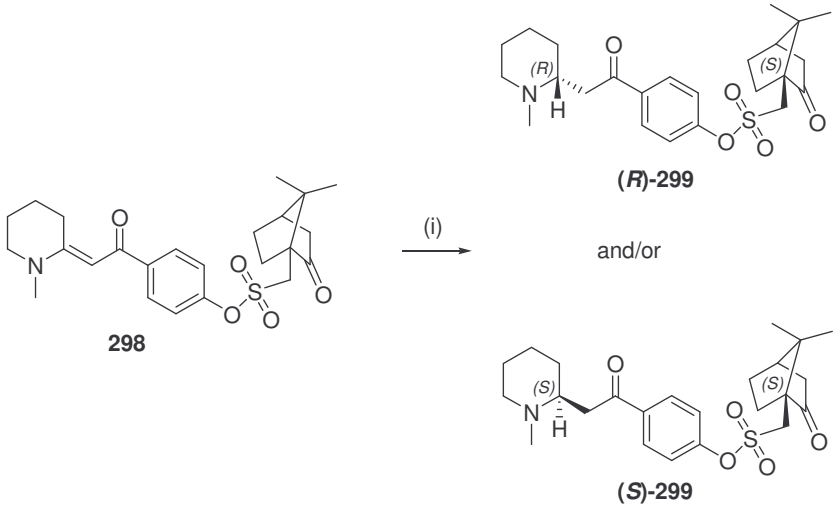
260 **297** **298**

Scheme 3.12: *(i) CH_2Cl_2, rt, 24 h; (ii) PPh_3, NEt_3, CH_3CN, 3-24 h, 64% (2 steps)*

A vinyl proton appeared as a singlet in the ^{1}H NMR spectrum at 5.59 ppm and the corresponding carbon signal was found at 90.4 ppm in the ^{13}C NMR spectrum. The loss of the thiocarbonyl signal at 199.3 ppm and the appearance of an additional carbonyl signal at 185.8 ppm and a vinyl carbon signal at 165.4 ppm pointed towards the fact that the vinylogous amide **[298]** had been formed. The FTIR spectrum also had two clear carbonyl signals at 1744 cm^{-1} and 1690 cm^{-1}. The mass spectrum showed an ion at *m/z* 445.19287 (13%), and M^{+} requires 445.19229.

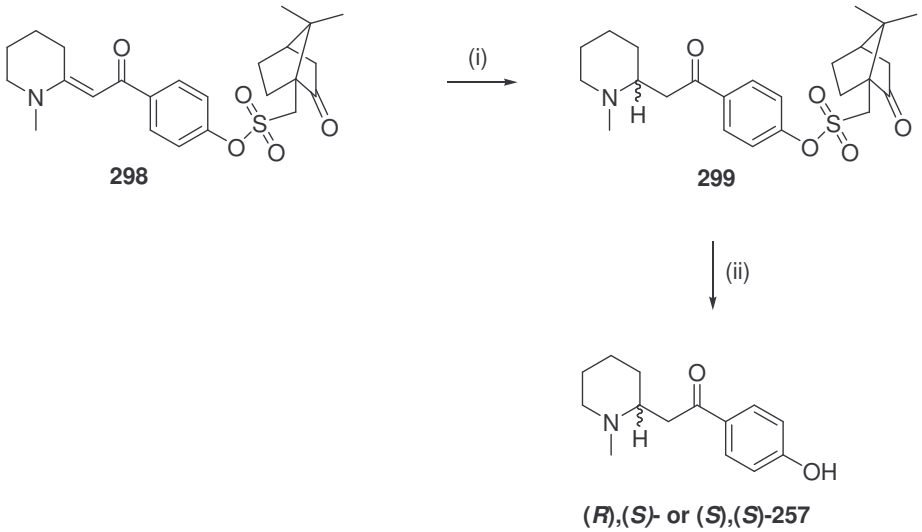
3.3.3 Reduction of vinylogous amide [298] and removal of the chiral auxiliary to give thalictroidine [257]

At this stage we wanted to reduce the vinylogous amide **[298]**, and in doing so introduce a second stereogenic centre (**Scheme 3.13**). The chiral auxiliary provides a fixed absolute reference point, but there is the possibility of producing both the *R* and *S* configurations at the newly created stereogenic centre after reduction. We hoped that one would be formed in excess, but we still expected to see both diastereomers, which we hoped to separate and characterize individually.



Scheme 3.13: *(i) $NaCNBH_3$, pH 4, rt, 1 h*

The reduction of vinylogous amide **[298]** with sodium cyanoborohydride in methanol under acidic conditions afforded the desired product **[299]** in a 46% yield. However, to our disappointment the product was not crystalline and despite numerous attempts we were unable to crystallize **[299]** (**Scheme 3.14**).



Scheme 3.14: *(i) $NaCNBH_3$, pH 4, rt, 1 h, 46%; (ii) 0.3M, KOH (aq), rt, 1 h, 100%*

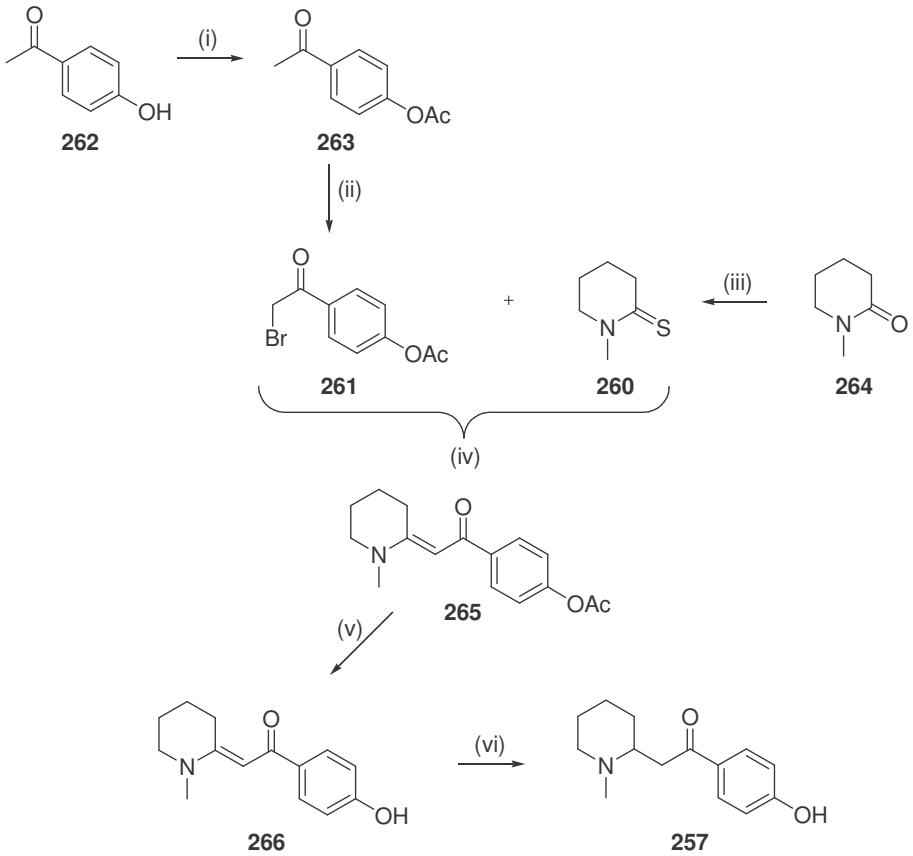
In the ^{1}H NMR spectrum the vinyl proton singlet at 5.59 ppm disappeared along with the alkene carbon signals at 165.4 and 90.4 ppm in the ^{13}C spectra. The proton signals at 2.76-2.62 ppm integrating for one proton and 1.67-1.62 integrating for two protons were due to the NCH and the CH_2CO protons respectively. The mass spectrum showed an ion at *m/z* 447.20745 (6%), and the parent ion requires 447.20794. To our surprise the ^{13}C spectra showed no sign of any doubling up of peaks, which is characteristic of diastereomers. However, as the two stereogenic centers are eleven bonds apart an explanation would be that they are simply too far apart to result in a noticeable difference in the diastereomers.

We initially tried to remove the chiral auxiliary by refluxing **[299]** in an aqueous sodium hydroxide solution (1M), however we only recovered an unidentifiable product. Under milder conditions of stirring in a 0.3M potassium hydroxide solution for one hour we recovered thalictroidine **[257]** in a quantitative yield as a clear oil (**Scheme 3.12**). Once again the spectroscopic data were comparable to those published by Kennelly *et al*.[125]

3.4 Conclusion

We were able to prepare (±)-thalictroidine **[257]** in an overall yield of 23% along the shortest synthetic path and 20% along the longest synthetic path highlighted below in **Scheme 3.15**, and our synthesis along with the obtained crystal structure proved the structure of the natural product originally proposed by Kennelly *et al*.[125]

Attempts to achieve an enantioselective synthesis by using a chiral camphorsulfonyl auxiliary were not successful. At this stage, having gained expertise in several key steps in the "Wits approach" to alkaloid synthesis, we decided to press on with the primary aim of the project, namely, the synthesis of 5,8-disubstituted indolizidines (**Chapters 4 & 5**). An enantioselective synthesis of thalictroidine **[257]** was therefore put on hold for the time being, as further investigations would not show us anything new pertaining to the "Wits approach" for the preparation of 5,8-disubstituted indolizidines and related 1,4-disubstituted quinolizidines.



Scheme 3.15: *(i) Ac_2O, 7.5% NaOH(aq), 0 ℃-rt, 24 h, 94%; (ii) Br_2, HBr(cat.), $CHCl_3$, 30 min, 83%, (iii) P_2S_5, C_6H_6, Δ, 24 h, 90%, (iv) (a) CH_2Cl_2, rt, 24 h, (b) PPh_3, NEt_3, CH_3CN, 3-24 h, 69% (2 steps), (iii) Na_2CO_3, MeOH, rt, 1-3 h, 85%; (ii) $NaCNBH_3$, pH 4, rt, 1 h, 43%*

CHAPTER 4

SYNTHESIS OF MONO-SUBSTITUTED INDOLIZIDINES

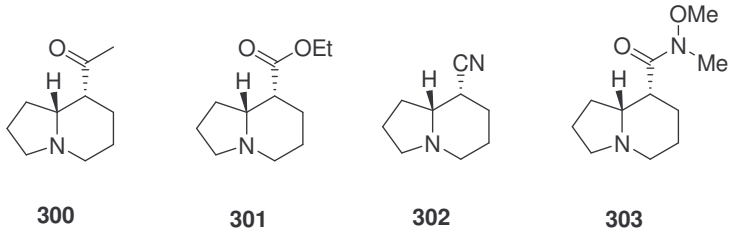


CHAPTER 4

SYNTHESIS OF MONO-SUBSTITUTED INDOLIZIDINES

4.1 Introduction

This chapter concerns the preparation of a variety of racemic mono-substituted indolizidines. We wanted to prepare these indolizidines following the key steps outlined in the "Wits approach" to alkaloid synthesis (**Chapter 2**) to gain experience in the preparation of indolizidines, in particular steps vi, vii, ix and x outlined in **Scheme 2.15**, **Section 2.7.2.** A more important aspect to this line of research was to examine the impact of the substituent at what would be the 5-position in 5,8-disubstituted indolizidines. We show the progress towards the preparation of indolizidines with a ketone **[300]**, carboxylic ester **[301]**, nitrile **[302]** and Weinreb amide **[303]** substituent at the 5-position (**Figure 4.1**). The synthesis of these four systems **[300-303]** would allow us insight into how the different substituents affect the preparation of the bicyclic indolizidine skeleton. Further investigations were performed to determine whether or not these groups could be converted into substituents commonly seen at the 5-position of naturally occurring 5,8-disubstituted indolizidines.

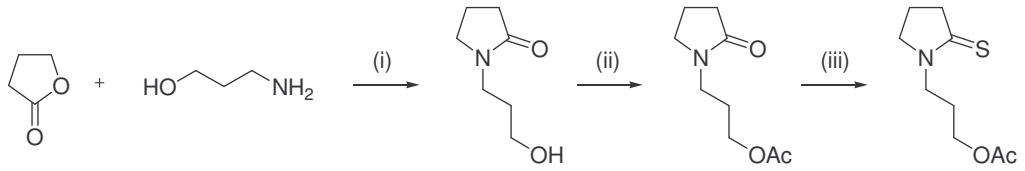


300 **301** **302** **303**

Figure 4.1: *5-substituted indolizidines*

4.2 Preparation of starting materials

The preparation of all four 5-substituted indolizidines was envisaged going through 3-(2-thioxo-1-pyrrolidinyl)-propyl acetate **[304]**, which was prepared in three steps from commercially available 3-amino-1-propanol **[305]** and γ-butyrolactone **[306]**[110m] (**Scheme 4.1**).



306 305 307 308 304

Scheme 4.1: *(i) 250 °C, sealed tube, 18 h, 81%; (ii) Ac_2O, pyridine, 0 °C, 10 min, then, rt, 18 h, 87%; (iii) Na_2CO_3, P_2S_5, THF, 5 h, 90%*

3-Amino-1-propanol **[305]** was condensed with γ-butyrolactone **[306]** in a sealed Carius tube at 250 °C, to give 1-(3-hydroxypropyl)-pyrrolidin-2-one **[307]** in an 81% yield on a 312 mmol scale. 1-(3-Hydroxypropyl)-pyrrolidin-2-one **[307]** was obtained as a clear oil and its boiling point and spectroscopic data corresponded with those reported in the literature[110m]. The ^{1}H NMR spectrum showed the presence of a hydroxyl group at 3.69 ppm. The ^{13}C NMR spectrum had a characteristic carbonyl peak at 176.1 ppm, and a peak at 58.2 ppm corresponding to the CH_2OH carbon. The mass spectrum possessed an ion at *m/z* 143.09591 (18%) and the parent ion of $C_7H_{13}NO_2$ requires 143.09463. The FTIR spectrum showed a broad OH signal at 3380 cm^{-1} as well as a lactam carbonyl signal at 1655 cm^{-1}.

The unprotected hydroxyl group on 1-(3-hydroxypropyl)-pyrrolidin-2-one **[307]** was then protected as an acetate by treatment with acetic anhydride and pyridine. 3-(2-Oxo-1-pyrrolidinyl)-propyl acetate **[308]** was obtained as a clear oil in an 87% yield on a 144 mmol scale. The acetate **[308]** had a boiling point of 146-148 °C at 2 mmHg. The ^{1}H NMR spectrum showed the loss of the hydroxyl peak at 3.69 ppm, and the corresponding appearance of a singlet integrating for three protons at 2.06 ppm representing the acetate CH_3. The ^{13}C NMR spectrum showed an additional carbonyl peak at 170.7 ppm due to the acetate carbonyl. The FTIR spectrum showed a characteristic ester carbonyl stretch at 1735 cm^{-1} in addition to the lactam carbonyl peak at 1674 cm^{-1}. The mass spectrum possessed an ion at *m/z* 185.10543 (19%) and the parent ion of $C_{19}H_{15}NO_3$ requires 185.10519. The spectroscopic data compared well with those previously reported.[110m]

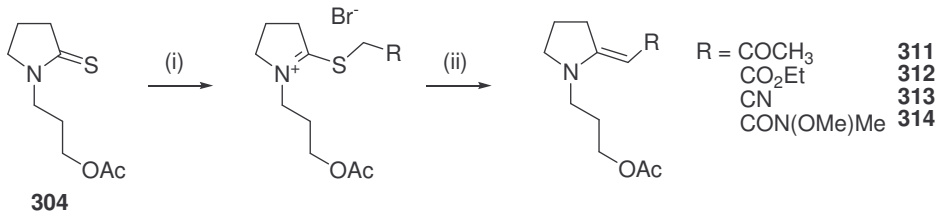
The protected lactam **[308]** was thionated in accordance with the Brillion procedure[128], by treatment with phosphorus pentasulfide and sodium carbonate in tetrahydrofuran, affording 3-(2-thioxo-1-pyrrolidinyl)-propyl acetate **[304]** in a 90% yield on a 28 mmol scale. The ^{1}H

NMR spectrum showed the loss of the $CH_2C=O$ protons at 2.38 ppm and the corresponding appearance of the $CH_2C=S$ protons at 3.04 ppm. The ^{13}C NMR spectrum showed the loss of the lactam carbonyl at 174.8 ppm and the appearance of the thiolactam carbonyl at 201.6 ppm. The mass spectrum possessed an ion at *m/z* 201.08194 (100%) and the parent ion of $C_{19}H_{15}NO_2S$ requires 201.08235, once again the spectroscopic data were comparable with those reported previously.[110m]

4.3 The Eschenmoser sulfide contraction[121-123]

4.3.1 Proposed reagents for the sulfide contraction

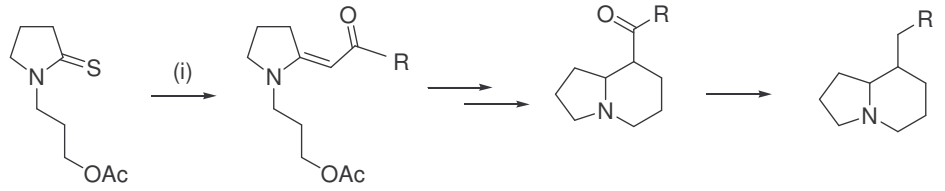
Having prepared the thiolactam **[304]**, the next step was its homologation using the sulfide contraction reaction (**Scheme 4.2**). An important aspect that we were interested in at this stage was how readily the substituents intended to end up at the 5-position of the indolizidine system could be introduced at this stage. This group, labeled R, needs to be easily modified into the typical types of substituents found at this position in natural products. The most commonly seen substituents are unbranched saturated or sometimes unsaturated alkyl chains, and as such this R-group must facilitate the introduction of these groups.



Scheme 4.2: *i) $BrCH_2R$, CH_3CN, rt, 24 h; ii) PPh_3, NEt_3, CH_3CN, 5 h*

The most straightforward, although ultimately least attractive route, would be to have some sort of a vinylogous amide (R=COR', R'= alkyl chain), as all that would be required to modify the chain would simply be to defunctionalise the carbonyl group (**Scheme 4.3**). Unfortunately this method would require the thiolactam **[304]** to be homologated with the correct length chain early on in the synthesis at the sulfide contraction stage (*step i)*. The disadvantages should be immediately apparent. One would have to repeat most of the

synthetic steps for each different target compound, and one is limited to saturated chains as one of the later steps involves the catalytic hydrogenation of an exocyclic double bond.



304

R = saturated alkyl chain

Scheme 4.3: *Proposed modification of the vinylogous amide system*

A better approach would rather be to add the desired chain late in the synthesis, allowing modification into a wide range of different compounds from a single late stage common intermediate. A possible reagent of choice for the sulfide contraction would be ethyl bromoacetate, allowing access to a vinylogous urethane **[301]**. The vinylogous urethanes are useful as they can either be reduced to the corresponding alcohol (*step i*), mesylated (*step ii*) and then alkylated using a suitable organometallic reagent (*step iii*) (**Scheme 4.4**).

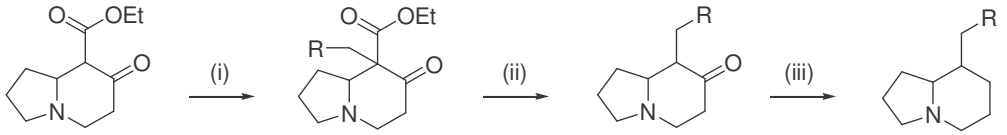


301

R = saturated or unsaturated alkyl chain

Scheme 4.4: *Proposed modification of vinylogous urethanes by direct substitution*

Alternatively the enaminone double bond can be reduced, and the alkyl substituent could be introduced by base-assisted substitution (*step i)*, followed by decarboxylation (*step ii)* (**Scheme 4.5**). In this case the carboxylic ester needs to be part of a β-ketoester system **[309]**, requiring an acylative cyclization, and this unfortunately leaves the complication of removing the ketone functionality in the ring late in the synthesis (*step iii).*

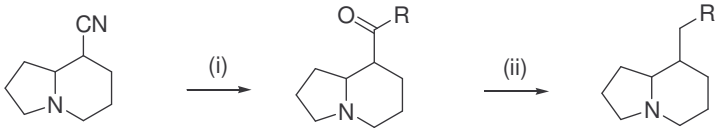


309

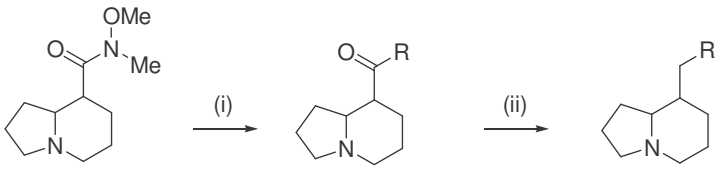
R= saturated or unsaturated alkyl chain

Scheme 4.5: *Proposed modification of vinylogous urethanes by base-assisted substitution*

A more straightforward approach would be the use of bromoacetonitrile or *N*-methoxy-*N*-methyl-2-bromoacetamide **[271]** to introduce a nitrile or a Weinreb amide at the 5-position, as both can potentially be mono-alkylated directly by treatment with a suitable organometallic reagent to afford the corresponding ketone (*step i*) (**Scheme 4.6**).



302



303

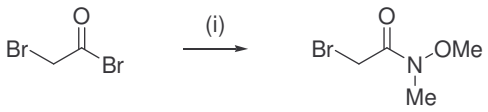
R= saturated or unsaturated alkyl chain

Scheme 4.6: *Proposed modification of the vinylogous nitrile and urea systems*

Subsequent carbonyl removal would then yield the desired substituent (*step ii*). The *N*-methoxy-*N*-methyl-2-bromoacetamide **[271]**, in particular was outlined initially as the most promising reagent, as Weinreb amides have been utilized extensively for the straightforward preparation of ketones by simply treatment with a suitable Grignard or organolithium species. Interestingly the synthesis and use of enaminones containing Weinreb amides appears not to have been reported other than in our own work.[108j] A more comprehensive overview of the

synthesis and synthetic utility of Weinreb amides is given in **Section 4.7.4**. In the case of the nitrile, although mono-alkylation is often reported, one can sometimes experience complications with side reactions in systems with protons α to the nitrile carbon as they are acidic. As a result, treatment with a Grignard or organolithium reagent can cause deprotonation at the α position.

We decided to investigate all four of these classes using bromoacetone, ethyl bromoacetate, bromoacetonitrile and *N*-methoxy-*N*-methyl-2-bromoacetamide **[271]** as the alkylating reagents. The latter was prepared by the treatment of bromoacetyl bromide **[310]** with *N*,*O*-dimethylhydroxylamine hydrochloride and pyridine (**Scheme 4.7**) affording the desired bromoacetamide **[271]** as a crystalline colourless solid in a 64% yield on a 55 mmol scale. The spectroscopic data corresponded well with those previously reported[134].



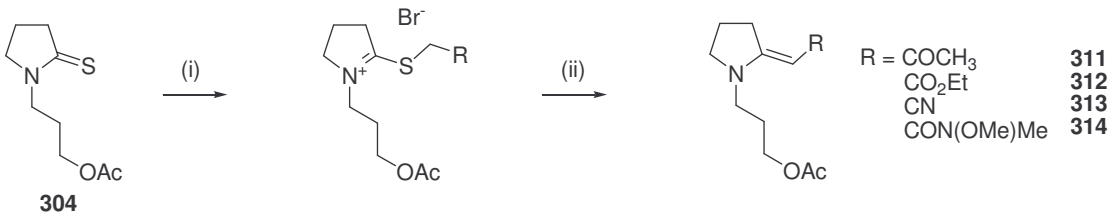
310 **271**

Scheme 4.7: *(i) Me(NH)(O)Me.HCl, Py, CH_2Cl_2, 0-20 °C, 18 h, 64%*

The CH_2Br protons appear as two singlets at 4.27 and 4.02 ppm in the ^1H NMR spectrum integrating for two protons. The OCH_3 protons also appear as two individual singlets at 3.81 and 3.76 ppm integrating for three protons together. Finally, the NCH_3 group shows a singlet at 3.25 ppm integrating for three protons. The ^{13}C NMR spectrum had characteristic carbonyl peaks at 167.3 and 167.1 ppm, and OCH_3 and NCH_3 peaks at 61.4 and 40.6 ppm respectively. The CH_2Br peak is observed at 25.1 ppm.

4.3.2 Preparation of the enaminones

The Eschenmoser sulfide contraction[121-123] was used to access the enaminones **[311-314]** in accordance with the procedure outlined in **Section 3.2.2.** by simply using an appropriate alkylating reagent to form the desired S-alkylated halide salt. Subsequent treatment with triethylamine and triphenylphosphine yielded the desired products **[311-314]** (**Scheme 4.8**).



Scheme 4.8: *(i) $BrCH_2R$, CH_3CN, rt, 24 h; (ii) PPh_3, NEt_3, CH_3CN, 5 h*

Treatment of 3-(2-thioxo-1-pyrrolidinyl)propyl acetate **[300]** with the appropriate □-halogenated carbonyl derivative using the general procedure and work-up gave the four desired enaminones, the yields for which are shown below in **Table 4.1**.

Table 4.1: Yields for the Eschenmoser sulfide contraction

Compound	R	α-Halocarbonyl	Yield (%)	Scale (mmol)
[311]	$COCH_3$	$BrCH_2COCH_3$	95	5.1
[312]	$CO_2CH_2CH_3$	$BrCH_2CO_2CH_2CH_3$	90	19.3
[313]	CN	$BrCH_2CN$	44	5.0
[314]	$CON(OCH_3)CH_3$	$BrCH_2CO(OCH_3)CH_3$ **[271]**	85	33.5

An alternative approach used to prepare 3-[(2*E*)-2-(2-oxopropylidene)-pyrrolidinyl]-propyl acetate **[311]** involved the treatment of chloroacetone, which is resistant to the standard sulfide contraction procedure, with sodium iodide to form iodoacetone *in situ* in accordance with the Finkelstein procedure[135]. The iodoacetone then readily undergoes the contraction affording the desired enamine **[311]** in a 76% yield on a 0.97 mmol scale.

In the case of ethyl (2*E*)-{1-[3-(acetyloxy)propyl]-2-pyrrolidinylidene}ethanoate **[312]** the ^1H NMR spectrum showed the appearance of the characteristic vinyl proton at 4.53 ppm as a singlet integrating for one proton. The ester $OC\underline{H}_2CH_3$ group appeared as a quartet integrating for two protons at 4.09 ppm and the $OCH_2C\underline{H}_3$ as a triplet integrating for three protons at 1.25 ppm. The ^{13}C NMR spectrum showed the loss of the characteristic thiocarbonyl peak at 201.6 ppm, as well as the appearance of the corresponding vinyl carbons at 169.3 and 77.9 ppm. The ester $O\underline{C}H_2CH_3$ and $OCH_2\underline{C}H_3$ signals appeared at 58.1 and 14.6 ppm respectively. The

mass spectrum possessed an ion at *m/z* 255.14773 (27%) and the parent ion of $C_{13}H_{21}NO_4$ requires 255.14706. The FTIR spectrum showed two carbonyl signals at 1736 and 1586 cm^{-1}.

The remaining three enaminones were all characterized in a similar fashion. The characteristic signals used to determine that these compounds had formed are outlined below in **Table 4.2**.

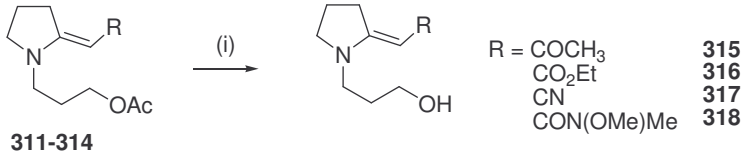
Table 4.2: Selected spectroscopic data for the Eschenmoser sulfide contraction

	^{1}H NMR (ppm)	**^{13}C NMR (ppm)**	**HRMS m/z (EI)**	**FTIR (cm^{-1})**
[311]	5.05 (C=CH) 2.09 (C=CHCOCH_3)	170.8 (C=CH-) 165.1 (COCH_3) 89.5 (C=CH) 20.8 (COCH_3)	$C_{12}H_{19}NO_3$ Calculated: 225.13649 Found: 225.13555	1736 (OC=O) 1538 (C=O)
[312]	4.53 (C=CH) 4.09 (OC$H_2$$CH_3$) 1.29 ($OCH_2CH_3$)	169.3 (C=CH) 77.9 (C=CH) 58.1 (O$CH_2$$CH_3$) 14.6 ($OCH_2CH_3$)	$C_{13}H_{21}NO_4$ Calculated: 255.14706 Found: 255.14773	1736 (C=O) 1586 (C=O)
[313]	3.67 (C=CH)	170.7 (C=CH) 122.5 (C≡N) 53.6 (C=CH)	$C_{11}H_{16}N_2O_2$ Calculated: 208.12118 Found: 208.12880	2187 (C□N) 1734 (OC=O)
[314]	5.01 (C=CH) 3.67 ($NOCH_3$) 3.15 (NCH_3)	170.8 (C=CH) 164.3 (C=O) 76.7 (C=CH) 60.8 ($NOCH_3$) 33.0 (NCH_3)	$C_{13}H_{22}N_2O_4$ Calculated: 270.15796 Found: 270.15621	1734 (OC=O) 1646(NC=O)

In all four cases the *trans*-s-*cis* structure was shown by virtue of the chemical shifts of the C-3 of the heterocyclic ring all approximately 3.2 ppm.

4.4 Deprotection of the vinylogous enaminones

The prepared enaminones **[311-314]** were deprotected to afford the corresponding alcohols **[315-318]** by treatment with potassium methoxide, generated *in situ* from potassium carbonate and methanol as outline in **Section 3.2.3.** (**Scheme 4.9**). The yields for which are outlined in **Table 4.3** below



311-314

Scheme 4.9: *(i) K_2CO_3, MeOH, rt, 3 h*

Table 4.3: Yields for the hydrolysis of the acetates

Compound	R	Yield (%)	Scale (mmol)
[315]	$COCH_3$	82	2.87
[316]	$CO_2CH_2CH_3$	85	15.0
[317]	CN	89	5.85
[318]	$CON(OCH_3)CH_3$	83	23.9

The ^{1}H NMR spectrum of ethyl (2*E*)-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]ethanoate **[316]** showed the loss of the acetate singlet at 2.08 ppm and the appearance of a broad hydroxyl singlet at 1.92 ppm. The C$\underline{H}_2$OAc triplet signal at 4.07 ppm has shifted up-field to 3.67 ppm, indicating the conversion to a C$\underline{H}_2$OH group. The ^{13}C NMR spectrum also showed the loss of the acetate signals at 170.9 and 20.8 ppm and the appearance of a CH_2OH signal at 52.6 ppm. The mass spectrum possessed an ion at *m/z* 213.13665 (39%) and the parent ion of $C_{11}H_{19}NO_3$ requires 213.13649. The FTIR spectrum showed the presence of a hydroxyl group by virtue of a broad OH signal at 3415 cm^{-1}. The remaining three deprotected enaminones were characterized in a similar fashion, as highlighted in **Table 4.4** below.

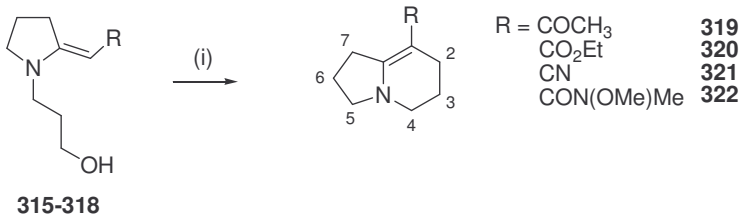
Table 4.4: Selected spectroscopic data for the acetate removal

	^{1}H NMR (ppm)	^{13}C NMR (ppm)	HRMS m/z (EI)	FTIR (cm^{-1})
[315]	3.68 (C<u>H</u>$_2$OH) 2.30 (OH)	52.6 (CH_2OH)	$C_{10}H_{17}NO_2$ Calculated: 183.12593 Found: 183.12533	3366 (O-H)
[316]	3.67 (C<u>H</u>$_2$OH) 1.92 (-OH)	52.7 (CH_2OH)	$C_{11}H_{19}NO_3$ Calculated: 213.13649 Found: 213.13665	3415 (O-H)
[317]	3.64 (C<u>H</u>$_2$OH) 2.47 (OH)	52.7 (CH_2OH)	$C_9H_{14}N_2O$ Calculated: 166.11061 Found: 166.10937	3404 (O-H)
[318]	3.68 (C<u>H</u>$_2$OH) 2.04 (OH)	52.3 (CH_2OH)	$C_{11}H_{20}N_2O_3$ Calculated: 228.14739 Found: 228.14788	3353 (O-H)

4.5 Alkylative cyclisation of the deprotected vinylogous enaminones

The cyclisation of the deprotected enaminones **[315-318]** was of great interest to us, as it gave us insight into how general the procedure is. In addition it allowed us to determine whether or not the Weinreb amide functionality would be suitable to use in the chiral synthesis of indolizidines as proposed in **Sections 2.7.2** and **2.7.3.**

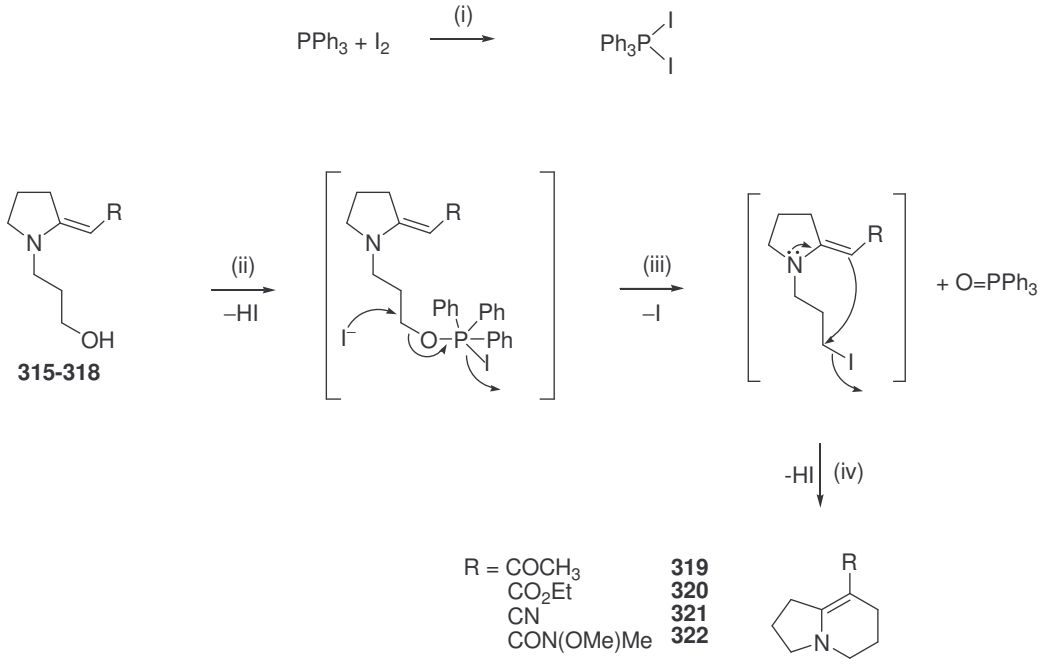
The cyclisation was achieved by initially treating the deprotected enaminones **[315-318]** with imidazole and triphenylphosphine in acetonitrile at ambient temperature, followed by iodine[136]. Finally the reaction mixture was heated up to reflux temperature for 45-60 minutes affording the cyclised products **[319-322]** (**Scheme 4.10**).



315-318

Scheme 4.10: *(i) Imidazole, PPh_3, I_2, CH_3CN:$PhCH_3$, Δ, 45 min*

The mechanism for the alkylative cyclisation is shown below in **Scheme 4.11**. The triphenylphosphine and iodine initially react to form diiodo(triphenyl)phosphorane (*step i*). The imidazole then facilitates the deprotonation and subsequent substitution of the hydroxy hydrogen with phosphorane (*step ii*), thereafter the iodine substitutes the phosphorane group giving the corresponding iodinated product and triphenylphosphine oxide (*step iii*). As described in **Section 2.4.1.** under refluxing conditions the nucleophilicity of the nitrogen is extended to the enamine carbon allowing cyclisation to occur at the exocyclic carbon-carbon double bond (*step iv*), affording the bicyclic indolizidine skeleton.



Scheme 4.11: *Alkylative cyclization*

Purification by column chromatography after the standard work-up afforded the desired cyclised vinylogous urethane **[320]** and cyanamide **[321]**. The yields for them are outlined in **Table 4.5** below. In the case of the cyclised vinylogous urea **[322]** flash column chromatography had to be employed to achieve effective separation from the triphenylphosphine oxide residues. Finally in the case of the cyclised vinylogous amide **[319]** the triphenylphosphine oxide residues were partially removed by recrystallisation from hexane.

Table 4.5: Yields for cyclisations of the deprotected enaminones

Compound	R	Yield (%)	Scale (mmol)
[319]	$COCH_3$	27*	38.5
[320]	$CO_2CH_2CH_3$	59	4.05
[321]	CN	72	3.51
[322]	$CON(OCH_3)CH_3$	64	2.79

* Traces of triphenylphosphine oxide present

In the ^{1}H NMR spectrum the formation of the vinylogous urethane **[320]** was shown by the loss of the characteristic vinyl proton at 4.56 ppm. In addition the spectrum showed four triplets each integrating for two protons, a pair at 3.19 and 3.06 ppm corresponding to H-4 and H-5, and a pair at 2.96 and 2.25 ppm corresponding to H-2 and H-7. Two quintets at 1.82 ppm also integrating for two protons showed the presence of H-3 and H-6. Finally a quartet integrating for two protons, and a triplet integrating for three protons at 4.00 and 1.16 ppm provides evidence for the carboxylic ester substituent at the 1-position. The ^{13}C NMR spectrum showed the presence of the $\underline{C}OCH_2CH_3$ carbonyl at 168.1 ppm as well as the alkene carbons C-8 and C-1 at 158.6 and 86.9 ppm respectively. The HRMS showed the parent ion at 195.12471 and $C_{11}H_{17}NO_2$ requires 195.12593.

The same procedure was used to determine whether the other cyclised enaminones **[320-322]** had formed. The characteristic signals used to determine that these compounds had formed are outlined in **Table 4.6** below.

Table 4.6: Selected spectroscopic data for the cyclization of the *N*-hydroxypropyl enaminones

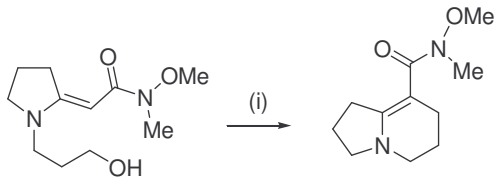
	^{1}H NMR (ppm)	^{13}C NMR (ppm)	HRMS m/z (EI)
[319]	3.27 & 3.11 (H-4 & H-5) 3.05 & 2.33 (H-2 & H-7) 2.03 ($COCH_3$) 1.84-1.70 (H-3 & H-6)	N/A*	N/A*
[320]	3.19 & 3.06 (H-4 & H-5) 2.96 & 2.25 (H-2 & H-7) 4.00 ($OC\underline{H}_2CH_3$) 1.82 (H-3 & H-6) 1.16 ($OC\underline{H}_2CH_3$)	168.1 (C=O) 158.6 (C-8) 86.9 (C-1)	$C_{11}H_{17}NO_2$ Calculated: 195.12593 Found: 195.12471
[321]	3.33 & 3.15 (H-4 & H-5) 2.74 & 2.23 (H-2 & H-7) 1.97 & 1.84 (H-3 & H-6)	159.2 (C-8) 123.8 (CN) 64.2 (C-1)	$C_9H_{12}N_2$ Calculated: 148.10005 Found: 148.09995
[322]	3.62 (OMe) 3.26 & 3.18 (H-4 & H-5) 3.06 (NMe) 3.01 & 2.38 (H-2 & H-7) 1.90 & 1.83 (H-3 & H-6)	174.4 (C-8) 157.7 (C=O) 90.0 (C-1) 59.7 (OCH_3) 34.3 (NCH_3)	$C_{11}H_{18}N_2O_2$ Calculated: 210.13683 Found: 210.13519

*Further characterization was not done as the sample still had triphenylphosphine oxide residues present, despite recrystallisation from hexane. At this stage we decided to use the crude mixture in the next step, hoping that purification would then be easier.

Although we were able to purify the bicyclic vinylogous urethane **[320]** and cyanamide **[321]** by standard chromatographic techniques, purification of the bicyclic vinylogous urea **[322]** required more careful flash column chromatography. The bicyclic ketone **[319]** proved to be most problematic as it has the same R_f as triphenylphosphine oxide, the byproduct of the triphenylphosphine, and as such could not be purified by chromatographic techniques. Several attempts were made to remove the triphenylphosphine oxide residues by recrystallisation from hexane with a best recovery of 27% of the ketone **[319]** which still showed traces of the

impurities. As a result of the problems associated with the purification of these compounds we felt it pertinent to investigate alternative methods for synthesizing the cyclized products.

As we were most interested in the Weinreb amide and its applicability to the synthesis of indolizidines we investigated the use of alternatives to triphenylphosphine (**Scheme 4.12**) for the preparation of the vinylogous urea **[322]**.

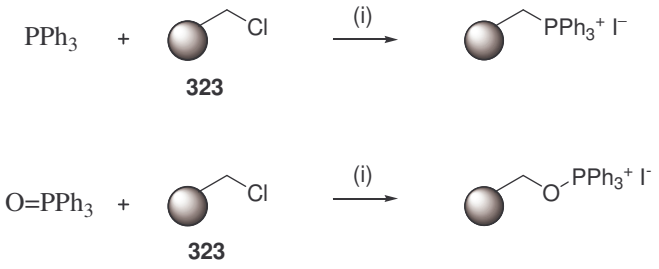


318 **322**

Scheme 4.12: *(i) Imidazole,* ***PBu$_3$*** *or* ***POEt$_3$****, I_2, CH_3CN:$PhCH_3$, Δ, 45 min*

We had hoped that the polarity of the oxidized by-products would be sufficiently different from that of the bicyclic urea **[322]**, to allow purification by standard column chromatography. We initially chose tributylphosphine, unfortunately, although the desired product was formed, purification in this case proved impossible even under flash chromatographic conditions. We then decided to try triethyl phosphite, as it had proved effective in circumventing the same problem when performing Eschenmoser sulfide contractions. It was used as it is sparingly soluble in water and can therefore be removed by washing with water if chromatographic separation was not feasible. The reaction did not proceed as well as hoped, with the crude ^{1}H NMR spectrum only showing trace amounts of the desired product being formed. Separation was again not possible by chromatography and despite extensive efforts to remove the oxidized by-product by washing with water the ^{1}H NMR spectrum still showed vast amounts of contamination.

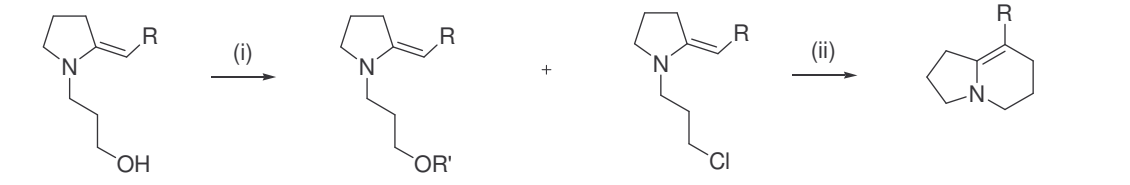
A second alternative was to use high-loading chloromethylated polystyrene (Merrifield resin) **[323]** to mop up the triphenylphosphine and triphenylphosphine oxide residues after the reaction was finished according to the protocol outlined by Lipshutz and Blomgren[137]. Upon addition of sodium iodide and stirring overnight at room temperature the Merrifield resin **[323]** acts as a scavenger resin, removing all triphenylphosphine present (**Scheme 4.13**).



Scheme 4.13: *(i) NaI, acetone, rt*

The authors also showed that triphenylphosphine oxide could be removed completely, and that the resin was chemoselective for triphenylphosphine and triphenylphosphine oxide in the presence of most nucleophiles including basic amines. The approach initially seemed very attractive, as the amount of resin **[323]** required was reasonable, with 1 g of resin being required to remove 2 mmol of phosphine at 25 °C. In all attempts, however, we were still left with contaminated samples despite stirring with an excess of the resin **[323]**. The protocol certainly looked promising, however, due to the costs of the resin we decided to investigate an alternative approach.

The third alternative that we looked into was to convert the alcohol into a different leaving group such as a mesylate or a tosylate (**Scheme 4.14**), which in turn could then be replaced by iodine to enhance the rate of cyclisation[109g]. Nucleophilic substitution of the iodo group would then give us the cyclised products as described previously, however with no triphenylphosphine or triphenylphosphine oxide residues present, purification should then be trivial.



R = CN	**317**	R = CN R' = Ts	**324**	R = CN	**325**	R = CN	**321**
R = CON(OMe)Me	**318**	R = CON(OMe)Me R' =Ts	**326**	R = CON(OMe)Me	**327**	R = CON(OMe)Me	**322**
		R = CN R' = Ms	**328**				
		R = CON(OMe)Me R' = Ms	**329**				

Scheme 4.14: *(i) TsCl or MsCl, NEt_3, DMAP, CH_2Cl_2, rt, 18 h; (ii) NaI, CH_3CN, Δ, 45 min*

The tosylation/mesylation was achieved by treating the *N*-hydroxypropyl enaminones with a solution of either toluenesulfonyl chloride or methanesulfonyl chloride in the presence of triethylamine and a catalytic amount of DMAP. The procedure was attempted on both the vinylogous cyanamide **[317]** and the vinylogous urea **[318]**, and in both cases the tosylation worked giving the desired products **[324** and **325]** and **[326** and **327]** in a 19 and 71% yield on a 4.2 and 0.9 mmol scale respectively. In addition to the expected product, the corresponding chlorinated product was also obtained in small amounts, and in the case of the vinylogous cyanamide careful column chromatography afforded a small amount of the pure chlorinated product **[325]** for spectroscopic analysis. The mesylated products **[328** and **329]** decomposed when they were subjected to column chromatography and as such were used directly in the subsequent cyclisation step.

In the case of the vinylogous cyanamide the ^{1}H NMR spectrum showed the loss of the hydroxyl protons at 2.47 ppm. The corresponding appearance of doublets at 7.79 ppm and 7.38 ppm each integrating for two hydrogens, showed the presence of the aromatic hydrogens from the tosyl group. In addition a singlet integrating for three hydrogens at 2.47 ppm showed the presence of the tosyl CH_3. In the ^{13}C NMR spectrum the corresponding aromatic signals from the tosyl group were seen at 145.2, 132.5, 129.9 and 127.8 ppm and the tosyl methyl was seen at 20.7 ppm. The FTIR spectrum also showed no broad peak above 3000 cm^{-1}, indicating the hydroxyl group was protected.

In the ^{1}H NMR spectrum the chlorinated by-product was also characterized by the loss of the hydroxyl protons at 2.47 ppm. The $C\underline{H}_2OH$ triplet at 3.64 ppm was replaced by a CH_2Cl triplet at 3.56 ppm.

In a similar fashion the tosylated vinylogous urea was shown to have formed by the presence of the aromatic doublets at 7.79 and 7.36 ppm, and the tosyl CH_3 at 2.45 ppm in the ^{1}H NMR spectrum. Once again, as expected, the peak corresponding to the hydroxyl proton at 2.04 ppm was missing. The ^{13}C NMR spectrum again showed the presence of the tosyl aromatic protons at 144.9, 132.7, 129.9 and 127.8 ppm, and the tosyl CH_3 at 21.2 ppm.

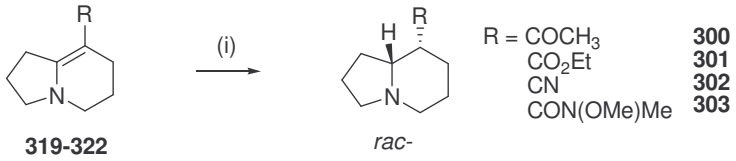
Having the tosylated/mesylated products in hand we attempted to cyclise the vinylogous cyanamide and urea by refluxing with sodium iodide in acetonitrile. All attempts to cyclise

the tosylated product resulted only in the recovery of the unreacted tosylate and chloride starting materials. The mesylated product fared worse with only decomposed material being recovered. In a final attempt to afford the desired products we attempted the cyclisation in a microwave reactor; however the results were the same as described above in both cases.

Finally we reverted to the original procedure, and resorted to separating the product and triphenylphosphine oxide residues from the baseline impurities by column chromatography. Once the baseline impurities were removed it was possible to remove most of the triphenylphosphine oxide by recystallisation from hexane. The relatively impure product was then subjected to the catalytic reduction of the enaminone system, after which purification was possible as described below in **Section 4.6**.

4.6 Catalytic reduction of the enaminone system

The catalytic reduction of the cyclised enaminones **[301-303]** was achieved by subjecting them to hydrogenation conditions at one atmosphere in the presence of Adams' catalyst ($PtO_2.xH_2O$) in an acidic solvent such as glacial acetic acid (**Scheme 4.15**).



319-322 *rac-*

Scheme 4.15: *(i) H_2(g), 1 atm, Adams' catalyst, glacial acetic acid, 24 h, rt*

There are two possible routes that the hydrogenation might take for the reduction[138]. Both involve the absorption of hydrogen onto the catalyst's surface, thereby weakening the H-H bond and allowing its delivery across a double bond. One possibility is a direct catalytic hydrogenation of the conjugated enaminones with hydrogen being delivered across the C-1/C-8 bond (**Figure 4.2**).

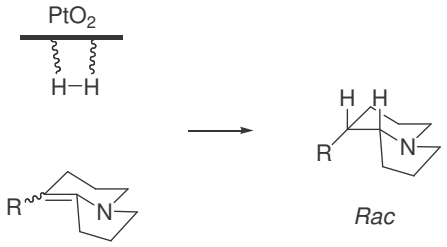


Figure 4.2: *Hydrogenation across the C-1/C-8 bond*

The other is a catalytic hydrogenation of an iminium system (**Figure 4.3**), wherein the molecule is protonated thereby generating the iminium system. Hydrogen is then delivered across the C-8a/N bond, and under a basic workup the nitrogen is deprotonated.

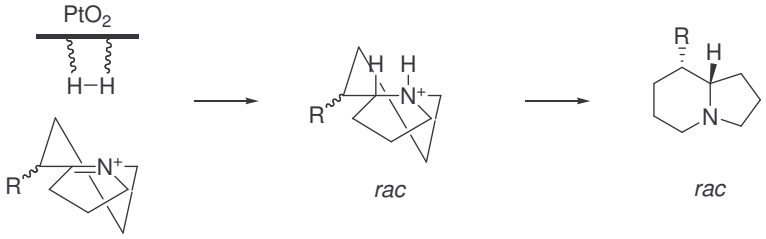


Figure 4.3: *Hydrogenation across the C-8 – N bond*

Whether or not this is the case is still debatable as the conjugated tertiary amine is a weak base, and the acid source in the reaction, glacial acetic acid is a weak acid itself, therefore it may not be strong enough to protonate the molecule. Regardless of which mechanism is in play the outcome is the same. Further reference to the stereochemical consequences of this reduction are delt with in detail in **Section 5.17**.

After the usual workup and purification by column chromatography the desired 5-substituted indolizidines were obtained, the yields for which are outlined below in **Table 4.7**.

Table 4.7: Yields for reduction of the cyclised enaminones

Compound	R	Yield (%)	Scale (mmol)	Diastereomeric Ratio (cis/trans)
[300]	$COCH_3$	0	8.51	N/A
[301]	$CO_2CH_2CH_3$	72	2.63	85:15
[302]	CN	85	1.95	92:8
[303]	$CON(OCH_3)CH_3$	25*	0.82	95:5

* Based on the *N*-hydroxypropyl enaminone

As the nitrogen in the reduced indolizidines is now basic an acid-base extraction could also be performed in addition to the usual workup to remove any residual triphenylphosphine oxide residues still present after the previous step. The products were obtained as a racemic mixture of diastereomers, as expected the major diastereomer showed the characteristic *cis* addition of hydrogen across the double bond. However, in the case of ethyl octahydro-8-indolizinecarboxylate **[301]** careful flash column chromatography afforded us small portions of pure samples of both the diastereomers (±)-**[301a]** and (±)-**[301b]** illustrated below in **Figure 4.4**.

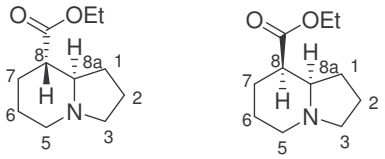


Figure 4.4: *Diastereomers of ethyl octahydro-8-indolizinecarboxylate **[301]***

The *cis* and *trans* compounds were identified by comparing the NMR spectroscopic data with analogous compounds containing a pentyl chain at the 4-position prepared previously in the Wits laboratories[100]. In the ^{1}H NMR spectrum, proton H-8a in diastereomer (±)-**[301a]** was identified at 2.13 ppm as a quartet, integrating for one proton with a coupling constant of 9.0 Hz. The corresponding proton in the other diastereomer (±)-**[301b]** could not be identified. Other characteristic signals that could be identified were H-3_{eq} at 3.06 and 2.96 ppm in (±)-**[301a]** and (±)-**[301b]** respectively, H-3_{ax} could only be identified in (±)-**[301b]** as a multiplet at 2.14-2.07 ppm. The carboxylic ester CH_2 was clearly seen as a quartet integrating for two

protons at 4.13 ppm in (±)-**[301a]** and as a multiplet integrating for two protons at 4.16-3.99 in (±)-**[301b]**. The terminal CH_3- was identified in both (±)-**[301a]** and (±)-**[301b]** as a triplet, integrating for three protons, at 1.26 and 1.18 ppm respectively.

The ^{13}C NMR spectra were more useful as they showed the loss of the alkene carbons at 158.6 and 86.9 ppm. The carbonyl group was present in both (±)-**[301a]** and (±)-**[301b]** at 174.3 and 173.0 ppm respectively. The HRMS possessed an ion at *m/z* 197.13962 (8%) for (±)-**[301a]**, and 197.14182 (43%) for (±)-**[301b]**, and the parent ion of $C_{11}H_{19}NO_2$ requires 197.14158. The remaining cyclised systems were identified in a similar manner. The data is summarized below in **Table 4.8.**

Table 4.8: Spectroscopic data for the catalytic reduction of the enaminone system

	^{1}H NMR (ppm)	**^{13}C NMR (ppm)**	**HRMS m/z (EI)**
[301a]	2.13 (H-8)	174.3 (C=O)	$C_{11}H_{19}NO_2$
	3.06 (H-3_{eq})		Calculated: 197.14158
	4.13 (OC$\underline{H}_2$CH$_3$)		Found: 197.13962
	1.26 (OCH$_2$C$\underline{H}_3$)		
[301b]	2.96 (H-3_{eq})	173.0 (C=O)	$C_{11}H_{19}NO_2$
	2.14-2.07 (H-3_{ax})		Calculated: 197.14158
	4.16-3.99 (OC$\underline{H}_2$CH$_3$)		Found: 197.14182
	1.18 (OCH$_2$C$\underline{H}_3$)		
[302]	3.16-3.02 (H-3_{eq})	120.0 (C≡N)	N/A
		63.3 (C-8a)	
		31.9 (C-8)	
[303]	3.67 (NOCH$_3$)	174.7 (C=O)	$C_{11}H_{20}N_2O_2$
	3.18 (NCH$_3$)	63.5 (C-8a)	Calculated: 212.15248
	3.08-2.94 (H-8 & H-8a)	61.2 (NOCH$_3$)	Found: 212.15176
		37.0 (C-8)	
		29.6 (NCH$_3$)	

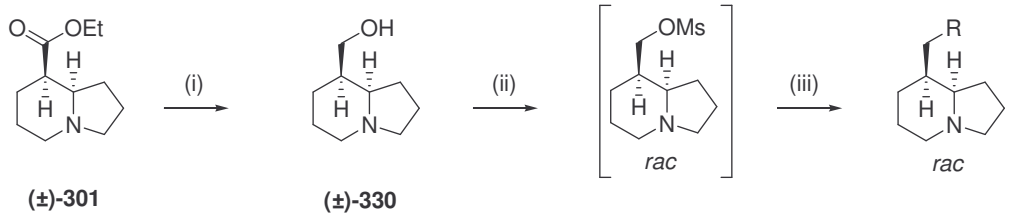
Unfortunately, to our disappointment the reduction of the alkene fragment in the bicyclic cyanamide **[321]** was not reproducible. We were only able isolated the desired compound once, despite repeating the reaction several times, altering reaction times and pressure to try optimize the reaction conditions. In most cases, the nitrile group appeared to have been fully or partially reduced. In the case of the reduction of **[319]** which still had triphenylphosphine residues present we were unable to isolate any product. Interestingly we were also never able to isolate any of the reduced vinylogous urea **[303]** when the starting material **[322]** had anything more than trace amounts of the triphenylphosphine residues present.

4.7 Functionalising the substituent

Having synthesized the desired mono-substituted indolizidines **[301-303]**, we decided to investigate the applicability of the various groups for the addition of substituents found in the 5-position of the naturally occurring 5,8-disubstituted indolizidines. These attempted modifications are dealt with below class by class.

4.7.1 Reduction and alkylation of the carboxylic ester [301]

We envisaged being able to reduce the carboxylic ester moiety in ethyl octahydro-8-indolizinecarboxylate **[301]** to an alcohol **[330]**, which could then be mesylated, allowing alkylation with a suitable Grignard reagent as outlined in **Scheme 4.16** below.

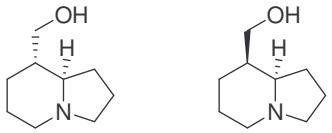


(±)-301 **(±)-330**

Scheme 4.16: *(i) $LiAlH_4$, Et_2O, 3 h, 85%; (ii) MsCl, NEt_3, CH_2Cl_2, 324 h; (iii) RMgBr, THF*

4.7.1.1 Preparation of (±)-tashiromine [330a] and (±)-5-epitashiromine [330b]

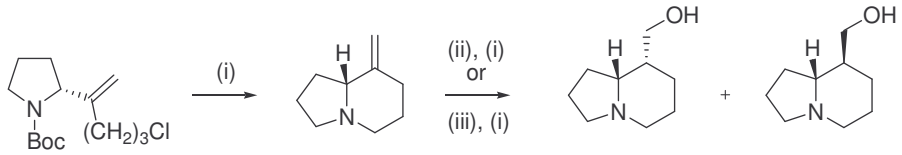
Reduction of the diastereomeric mixture of **[301]** to the corresponding alcohol and subsequent separation of the resulting diastereomers represents a complete synthesis of the (±)-tashiromine **[330a]** and its epimer (±)-5-epitashiromine **[330b]** (**Figure 4.5**).



(±)-330a **(±)-330b**

Figure 4.5: *(±)-Tashiromine* ***[330a]*** *and (±)-5-epitashiromine* ***[330b]***

(±)-Tashiromine **[330a]** and (±)-5-epitashiromine **[330b]** have both been prepared previously and prior to 2005 all syntheses of these indolizidines involved the use of either chiral auxiliaries or molecules derived from the chiral pool[139-142]. In 2005 Dieter *et al.*[143] described an asymmetric preparation of 2-alkenyl-*N*-Boc-pyrrolidines **[331]** which, when *N*-Boc deprotected, cyclised via intramolecular *N*-alkylation yielding an indolizidine **[332]** skeleton. Hydroboration-oxidation of **[332]** and finally amine–BH_3 cleavage using trimethyl silyl chloride in methanol afforded a racemic mixture of the two diastereomers **[330a]** and **[330b]** (**Scheme 4.17**). The two diastereomers were then separated by flash column chromatography affording (+)-tashiromine **[330a]** (98:2 er) and (+)-5-epitashiromine **[330b]** (95:5 er) in a diastereomeric ratio of 70:30 (82%) to 80:20 (85%) depending on the reaction conditions.

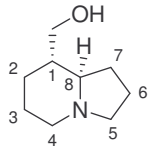


331 **332** **330a** **330b**

Scheme 4.17: *(i) (a) Me_3SiCl, MeOH, 12 h, 25 °C, $NaHCO_3$; (b) H_2, Pd/C (10%), CH_2Cl_2, 12 h; (ii) (a) BH_3.THF (2.2 eq.), THF, 0-25 °C, 1 h, then 60 °C, 1h; (b) 10 M NaOH (3 eq.), H_2O_2 (30%, 5 eq.), 0-25 °C, 12 h, 96%; (iii) (a) BH_3.THF, THF, 0-25 °C, 1 h; (b) 9-BBN (1 eq.), THF, 60 °C, 1 h; (c) 10 M NaOH (3 eq.), H_2O_2 (30%, 5 eq.), 0-25 °C, 12 h, 96%*

Interestingly Dieter *et al.*[143] noted that (+)-epitashiromine **[330b]** displayed a dextrorotatory rotation after initial isolation, which changed to a levorotatory rotation after additional passage through silica gel, a phenomenon that had been previously reported in 1998[139c].

We introduced the racemic mixture of **[301]** to a slurry of lithium aluminium hydride in diethyl ether. Upon workup and purification by flash column chromatography using a 95:4.75:0.25 ratio of methanol:dichloromethane:ammonium hydroxide as eluent we obtained (±)-tashiromine **[330a]** (**Figure 4.6**) and its epimer (±)-5-epitashiromine **[330b]** (**Figure 4.7**) as pure compounds in an 87:13 ratio in 87% yield respectively on an 4.3 mmol scale. The spectroscopic data compared well with previously published results.[143-144] The data are summarized below in **Tables 4.9** - **4.12**. Separation of the diastereomers using flash column chromatography had previously been described by Dieter *et al.* although they claimed to have used a 95:4.75:0.25 ratio of dichloromethane:methanol:ammonium hydroxide as eluent. We found that under these conditions the product remained on the baseline, and when we changed to the more polar solvent system separation became straightforward. The HRMS showed 155.12940 (93%) and 155.12955 (81%) for (±)-tashiromine **[330a]** and (±)-5-epitashiromine **[330b]** respectively, and $C_9H_{17}NO$ requires 155.13101.



(±)-330a

Figure 4.6: *(±)-Tashiromine **[330a]***

Table 4.9: Comparison of ^{1}H NMR spectroscopic data for (±)-Tashiromine **[330a]**

Proton	^{1}H NMR ($CDCl_3$) Riley (300 MHz)	^{1}H NMR ($CDCl_3$) Dieter[143]
C$\underline{H}_{2a}$OH	3.60 (dd, *J* 10.7, 4.6 Hz, 1H)	3.62 (dd, *J* 10.7, 4.6 Hz, 1H)
C$\underline{H}_{2b}$OH	3.43 (dd, *J* 10.7, 6.5 Hz, 1H)	3.48 (dd, *J* 10.8, 6.1 Hz, 1H)
OH	3.25 (s, broad, 1H)	

Table 4.9 continued: Comparison of ^{1}H NMR spectroscopic data for (±)-Tashiromine **[330a]**

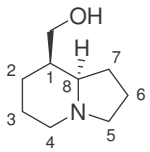
Proton	^{1}H NMR ($CDCl_3$) Riley (300 MHz)	^{1}H NMR ($CDCl_3$) Dieter[143]
H-4$_{eq}$ & H-5$_{eq}$	3.12-3.04 (m, 2H)	3.15-3.02 (m, 2H)
H*	2.08 (q, *J* 9.1, 1H)	2.09-2.01 (m, 1H),
H*	1.98-1.85 (m, 1H)	2.05-1.80 (m, 3H)
H*	1.94 (ddd, *J* 16.7, 12.4, 2.8, 2H)	
H*	1.85-1.59 (m, 4H)	1.74-1.37 (m, 7H)
H*	1.55-1.42 (m, 2H)	
H*	1.04 (ddd, *J* 24.7, 12.4, 5.0, 2H)	1.23-1.15 (m, 1H)

* Remianing hydrogens

Table 4.10: Comparison of ^{13}C NMR spectroscopic data for (±)-Tashiromine **[330a]**

Carbon	^{13}C NMR ($CDCl_3$) Riley (300MHz)	^{13}C NMR ($CDCl_3$) Dieter[143]	^{13}C NMR ($CDCl_3$) Kim[144]
C-8	66..5	65.6	65.8
CH_2OH	65.0	65.6	65.0
C-5	54.0	53.5	53.6
C-4	52.6	52.6	52.1
C-1	44.3	44.3	44.1
C-2*	28.8	28.9	28.5
C-7*	27.5	27.4	27.1
C-3*	24.9	24.9	24.6
C-6	20.6	20.8	20.2

*Interchangeable



(±)-330b

Figure 4.7: *(±)-5-epitashiromine **[330b]***

Table 4.11: Comparison of ^{1}H NMR spectroscopic data for (±)-5-epitashiromine **[330b]**

Proton	^{1}H NMR ($CDCl_3$) Riley (300 MHz)	^{1}H NMR ($CDCl_3$) Dieter[143]
OH	4.53 (s, broad, 1H)	
C$\underline{H}_{2a}$OH	4.12 (dd, *J* 10.7, 4.5, 1H)	4.15 (dd, *J* 10.9, 4.1 Hz, 1H)
C$\underline{H}_{2b}$OH	3.74 (dd, *J* 10.7, 1.8, 1H)	3.71 (br d, *J* 9.7Hz, 1H)
H-4$_{eq}$	3.11-3.07 (m, 1H)	3.11-3.05 (m, 1H)
H-5$_{eq}$	3.01 (ddd, *J J* 9.1, 2.9, 1.8, 1H)	3.03-2.91 (m, 1H),
H-8	2.29-2.23 (m, 1H)	2.36-2.24 (m, 1H)
H*	2.07-1.95 (m, 3H)	2.12-1.93 (m, 3H)
H*	1.93-1.87 (m, 2H)	1.90-1.61 (m, 6H)
H*	1.84-1.65 (m, 4H)	
H*	1.64-1.47 (m, 2H)	1.60-1.42 (m, 2H)

* Remianing hydrogens

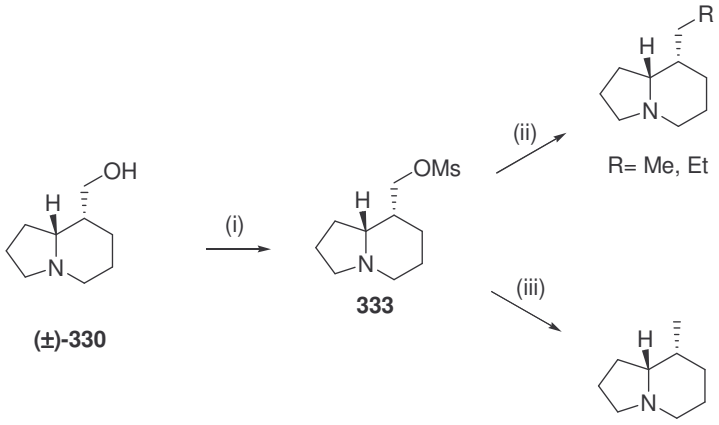
Table 4.12: Comparison of ^{13}C NMR spectroscopic data for (±)-5-epitashiromine **[330b]**

Carbon	^{13}C NMR ($CDCl_3$) Riley (300MHz)	^{13}C NMR ($CDCl_3$) Dieter[143]	^{13}C NMR ($CDCl_3$) Kim[145]
C-8	66.5	66.8	66.8
CH_2OH	64.9	66.5	65.7
C-5	54.3	54.4	54.5
C-4	53.3	54.0	53.5
C-1	35.4	35.3	35.3
C-2*	29.9	30.5	30.6
C-7*	25.6	25.7	25.8
C-3*	22.9	23.2	23.3
C-6	20.6	20.8	20.8

*Interchangeable

4.7.1.2 Mesylation and alkylation of alcohol [330]

Mesylation of the diastereomeric mixture of alcohol **[330]** under standard conditions appeared to proceed smoothly by tlc, however on work-up the product obtained rapidly discoloured and spectroscopic analysis indicated an unidentifiable product (**Scheme 4.18**).

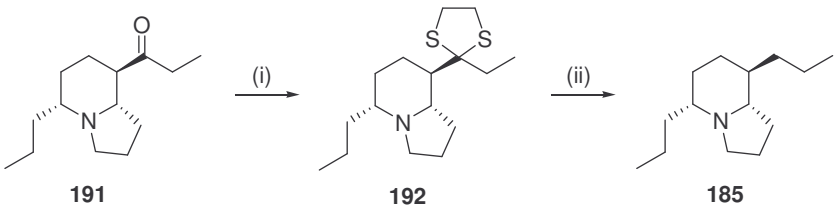


Scheme 4.18: *(i) MsCl, CH_2Cl_2, 0 °C-rt; (ii) RMgBr, THF, 0 °C-rt, 24 h 0%; (iii) Raney nickel, i-PrOH, Δ, 3 h, 0%*

As a result we decided to use the mesylated alcohol **[333]** immediately in the alkylation step on a 0.2-0.3 mmol scale. Ethylmagnesium bromide and methylmagnesium iodide were used as alkylating reagents, and despite promising tlc analysis no product could be recovered after work-up. Treatment with Raney nickel to defuntionalise the mesylate **[333]**, leaving behind a methyl substituent also proved fruitless. A possible reason for the failure of this approach is that the nucleophilic nitrogen may be reacting preferentially in either an intra- or intermolecular manner with the mesylate, a good leaving group. If this is the case it would make this approach useless, however, we have in the past successfully mesylated alcohols on analogous indolizidines and quinolizidines and then defunctionalised them by treatment with Raney nickel.[100, 108k, 108h] We also felt that we may have been losing the compounds due to volatility problems, but because we were more interested in the Weinreb amide and nitrile functionalisations we decided to abandon any further investigation into this route.

4.7.2 Defunctionalisation of the carbonyl group in the bicyclic ketone

We had originally planned to test the removal of the carbonyl group by converting the bicyclic ketone **[300]** to the thioacetal derivative. Subsequent treatment with Raney nickel should then have afforded the desired ethyl chain. However, due to the inability to purify the precursors in the previous two steps we were not able to test this approach. Fortunately there is precedent for the removal of the carbonyl group using this method. Ma and Zhu[107] in their synthesis of indolizidine (–)-**209I [185]** converted ketone **[191]** into thioacetal **[192]** by treatment with 1,2-ethanedithiol and boron trifluoride diethyl etherate. The thioacetal **[192]** was then defunctionalised by exposure to Raney nickel in isopropanol to afford **209I [185]** (**Scheme 4.19**). This approach is useful, as we could prepare comparable ketones from our nitrile and Weinreb amide precursors.

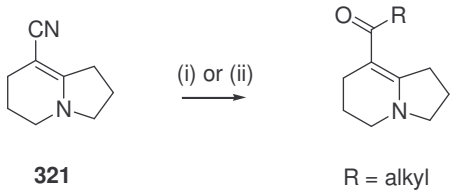


Scheme 4.19: *(i) $HSCH_2CH_2SH$, $BF_3OEt_2.Et_2O$, 65%; (ii) Raney-nickel, i-PrOH, 70°C, 81%*

4.7.3 Attempted alkylation of the bicyclic nitrile [321]

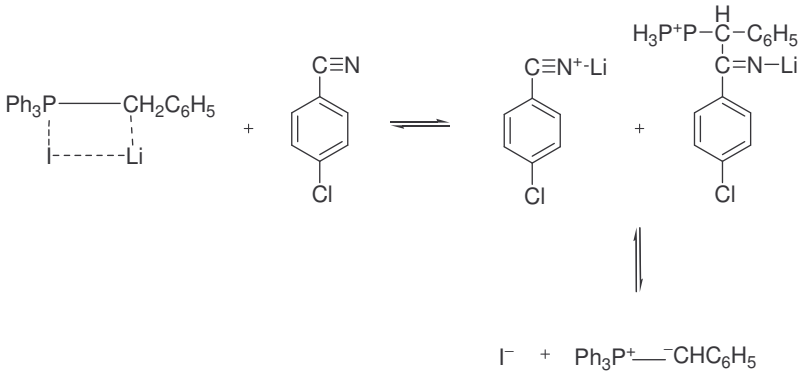
Owing to the reproducibility problems associated with the catalytic reduction of the enaminone backbone in the 1,2,3,5,6,7-hexahydro-8-indolizinecarbonitrile **[321]** we envisaged having to alkylate the nitrile prior to the reduction step. Alkylation prior to the catalytic reduction was not really desirable as it limited us to the preparation of saturated chains at the 5-position. However, having prepared the material we felt it would still be interesting to see if we could alkylate the nitrile **[321]** with the enaminone backbone in place.

We attempted two alkylating routes, the first involved the direct reaction of the nitrile **[321]** with an appropriate Grignard reagent, and the second involved the use of alkylidenephosphoranes to afforded the desired transformation as reported by Barnhardt, Jr. and McEwen[145] (**Scheme 4.20**).



Scheme 4.20: *(i) RMgBr, THF, –78 °C - rt; (ii) a) $Ph_3P^+CH_3Br^-$, n-BuLi, 1h, b) LiI,* ***[321]****, Δ 48 h*

We attempted several alkylations of the nitrile **[321]** using methyllithium or ethylmagnesium chloride at temperatures ranging from −78 °C to room temperature. In all cases unidentifiable products were obtained. It was during these investigations that we came across a report by Barnhardt, Jr. and McEwen[145] detailing the use of alkylidenephosphoranes to convert nitriles into ketones. They reported that the reaction of both aliphatic and aromatic nitriles with ylides derived from a range of phosphonium iodides, followed by acid-catalyzed hydrolysis afforded very good yields of the corresponding ketones. The use of phosphonium bromides and chlorides however afforded very limited if any conversion to ketones. They suggest that the reactivity of the phosphonium iodides is because they form homogeneous solutions when reacting with organolithium compounds, whereas the corresponding chlorides and bromides form heterogeneous mixtures. They also showed that the addition of powdered lithium iodide to an unreactive chloride or bromide caused the reaction to occur in high yield. A mechanism is proposed wherein the lithium ion complexes with the nitrile, increasing its electrophillic nature (**Scheme 4.21**).



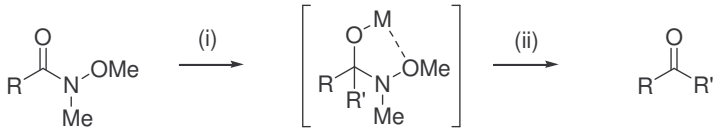
Scheme 4.21: *Proposed mechanism of the condensation step*

Using a similar protocol with a milder workup outlined by Taber and Cai[146] we treated **[321]** with *n*-butyllithium in diethyl ether. Powdered anhydrous lithium iodide was added after one hour of refluxing and the solution was refluxed for a further hour. The nitrile **[321]** was then added and the mixture was refluxed for 48 hours, after which time the residue was hydrolysed with methanol:water. The standard purification only afforded recovered starting material. Although the method was unsuccessful it could potentially be more useful when applied to the reduced bicyclic nitrile **[302]**. Unfortunately due to the problems associated with the over reduction of **[321]**, we were unable to produce material on which to test this approach.

4.7.4 Attempted alkylation of the Weinreb amide

4.7.4.1 Overview of the synthetic utility of Weinreb's amide

The synthesis and utility of the Weinreb amide was originally reported by Weinreb and Nahm.[147] Since then Weinreb amides have been used regularly to produce ketones and aldehydes by their reaction with Grignard or organolithium reagents. The synthetic utility of the Weinreb amide revolves primarily around the fact that they can be used to produce both ketones and aldehydes when treated with large excesses of organometallics.[148] The problem of multiple additions is overcome owing to the chelation of the metal ion between the carbonyl oxygen and the *N*-methoxy oxygen, preventing the collapse of the tetrahedral intermediate **[334]** until an aqueous acidic or basic work-up is used (**Scheme 4.22**).



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Scheme 4.22: *Mechanism of Grignard/organolithium addition to a Weinreb amide; (i) R'MgBr (excess) or R'Li (excess); (ii) Acidic or basic hydrolysis*

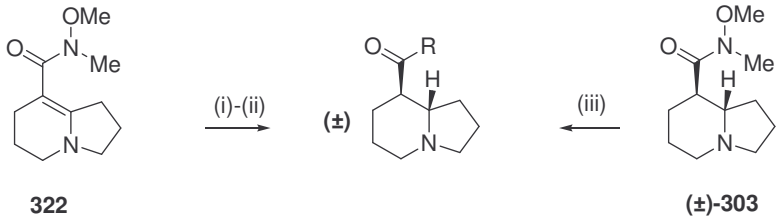
Weinreb amides have traditionally been prepared from carboxylic acid halides, by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride.[149] Esters and lactones have also been used by treating them *N*,*O*-dimethylhydroxylamine hydrochloride and trimethyl aluminium[150-158] or

chloro(dimethyl)aluminium[159], and hindered esters have been converted into the amide by the treatment of *N*,*O*-dimethylhydroxylamine hydrochloride with the magnesium amide [Me(MeO)N-MgCl][160]. $Sn[N(TMS)_2]_2$ and *N*,*O*-dimethylhydroxylamine hydrochloride also convert esters into amides[161]. The direct conversion of carboxylic acids into Weinreb amides has been reported using numerous acid activating agents.[148a, 162] Aldehydes are not converted into the amides directly, however under oxidative conditions in the presence of *N*,*O*-dimethylhydroxylamine hydrochloride and triethylamine they give the corresponding Weinreb amides[148a].

The most useful application of Weinreb amides is in the synthesis of ketones from various alkyl, alkenyl, alkynyl, aryl and heteroaryl Grignards and organolithiums[148a]. The Weinreb amide has also been successfully used to synthesize aldehydes by treatment with lithium aluminium hydride,[163] Vitride,[164] [LiAl(O-*t*-Bu)$_3$H], [165] LTEPA[165] and modified-AD-mix-β.[166] In addition Murphy *et al.* showed the conversion of Weinreb amides to ketones via a nonclassical Wittig reaction.[167]

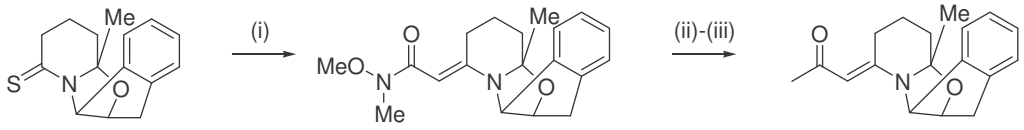
4.7.4.2 Attempted alkylation of the Weinreb amide

Investigations were undertaken on the potential alkylation of both the saturated **[303]** and unsaturated cyclised mono-substitued indolizidines **[322]** (**Scheme 4.23**). In the case of the unsaturated system **[322]**, alkylation was attempted using methyllithium, *n*-butyllithium, ethylmagnesium bromide and allylmagnesium bromide on a 0.2-0.47 mmol scale. In all four cases we were only able to recover unreacted starting material.



Scheme 4.23: *(i) a) RMgBr, THF, 0-25 °C b) NH_4Cl; (ii) H_2(g), $PtO_2.xH_2O$, glacial acetic acid, rt; (iii)RMgBr, THF, 0-25 °C b) NH_4Cl*

This result was not unexpected. In fact Mechelke and Meyers[168] reported that Weinreb amides incorporated into an enaminone backbone were resistant to alkylation with organometallics. When the alkene fragment was reduced, the amide then underwent the expected mono-alkylation when treated with a Grignard or alkyl organolithium reagent (**Scheme 4.24**).



Scheme 4.24: *(i) N-methoxy-N-methyl-2-bromoacetamide; then $P(OMe)_3$, NEt_3, Δ, 69%; (ii) Pd/C, H_2 (60 psi), Na_2CO_3, EtOAc, 96%; (iii) MeLi, THF, –78 °C, 85%*

As with the unsaturated system **[322]** we attempted to alkylated the saturated system **[303],** using methyllithium, *n*-butyllithium, ethylmagnesium bromide and allylmagnesium bromide on a 0.3-0.6 mmol scale. To our disappointment we were unable to recover any of the alkylated products, despite repeating the reactions several times using different amounts of the organometallic reagent. Despite the outcome of the Weinreb amide alkylations, we decided that in light of the overwhelming amount of literature precedent, this was still the best bet for the enantioselective preparation of 5,8-disubstituted indolizidines. This topic will be pursued in **Section 5.17**.

4.8 Summary of the results for the attempted synthesis of 5-substituted indolizidines

At the onset of this model study we already agreed that the preparation of vinylogous amides was the least attractive route. It required that the alkyl substituent be introduced early on at the sulfide contraction stage, and it limited us to the preparation of saturated substituents due to the late stage catalytic hydrogenation of the exocyclic double bond.

The use of vinylogous urethanes, although feasible, is not really attractive as it involves the cumbersome preparation of mesylates and the subsequent substitution using organometallics. The model study clearly showed that the mesylates, if formed, are particularly unstable and we were not able to isolated and purify any of them.

The lack of reproducibility in the catalytic hydrogenation of the exocyclic double bond of the vinylogous cyanamide required that any alkylation would have to be done prior to the reduction step. This once again would limit us to saturated substituents. In the model study however, the nitrile remained untouched when treated with organometallic while the enaminone backbone was still in place.

Despite the outcome of the Weinreb amide alkylations we decided the preparation of vinylogous ureas was still the best bet for the enantioselective synthesis of our target 5,8-disubstituted indolizidines. The vinylogous urea was stable with regards to the sulfide contraction, alkylative cyclisation and catalytic hydrogenation steps. The apparent ease of conversion of the Weinreb amide into corresponding ketones is well documented in the literature, and appears to suffer fewer reactivity problems than the equivalent nitrile. As a result we decide to proceed with the attempted enantioselective synthesis of indolizidines **[174, 185 and 258]** utilizing the Weinreb amide functionality to introduce the appropriate substituent at the 5-position.

CHAPTER 5

ENANTIOSELECTIVE SYNTHESIS OF 5,8-DISUBSTITUTED INDOLIZIDINES



CHAPTER 5

ENANTIOSELECTIVE SYNTHESIS OF 5,8-DISUBSTITUTED INDOLIZIDINES

5.1 Introduction

This chapter is concerned with the progress towards the enantioselective preparation of three 5,8-disubstituted indolizidines **209I [185]**, **223V [174]** and **197C [258]** (**Figure 5.1**).

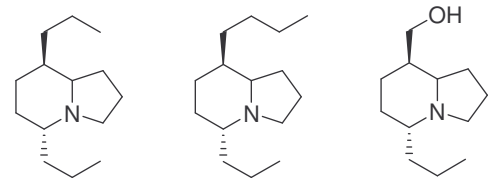
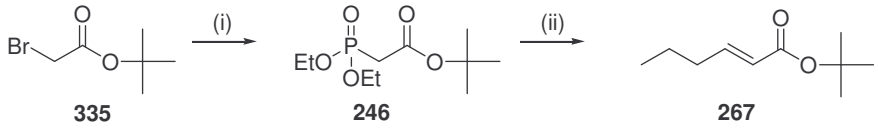


Figure 5.1: *Indolizidines **209I [185], 223V [174]** and **197C [258]***

The synthesis of these three alkaloids formed the primary focus of my doctoral studies. We aimed to achieve an enantioselective synthesis based on the "Wits approach" methodology developed in our labs, in particular the work done by Gravestock[100, 108h] as outlined in **Chapter 2**. In addition the insights gained into the use of a Weinreb amide at the 5-position of an indolizidine, introduced previously in **Chapter 4**, were used to extend the known methodology.

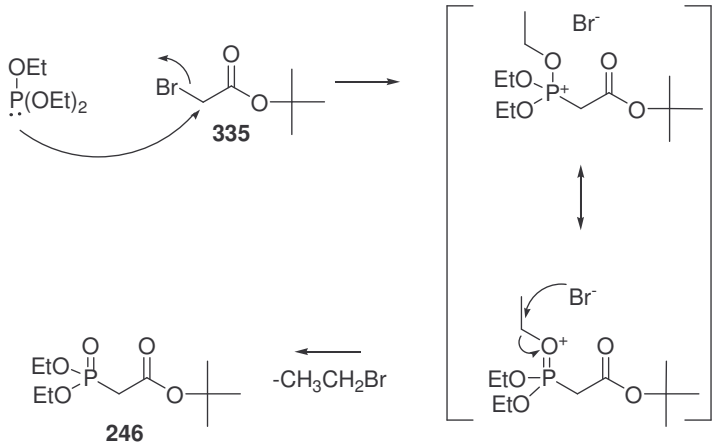
5.2 Preparation of *tert*-butyl (2*E*)-2-hexenoate [267]

The required starting materials for the enantioselective synthesis are (*R)*-(+)-*N*-benzyl-*N*-α-methylbenzylamine **[243]** which was purchased commercially, and the enoate substrate *tert*-butyl (2*E*)-oct-2-enoate **[267]**. *tert*-Butyl (2*E*)-oct-2-enoate **[267]** is synthesized from *tert*-butyl bromoacetate **[335]** in two steps (**Scheme 5.1**).



Scheme 5.1: *(i) $P(OEt)_3$, Δ, 4 h, 90%; (ii) LiCl, DBU, $CH_3(CH_2)_2CHO$, 24 h, 80%*

The initial step involved an Arbuzov reaction[169] between *tert*-butyl bromoacetate **[335]** and triethyl phosphite, affording the phosphonate **[246]** in a 90% yield on a 91 mmol scale after distillation (**Scheme 5.2**).

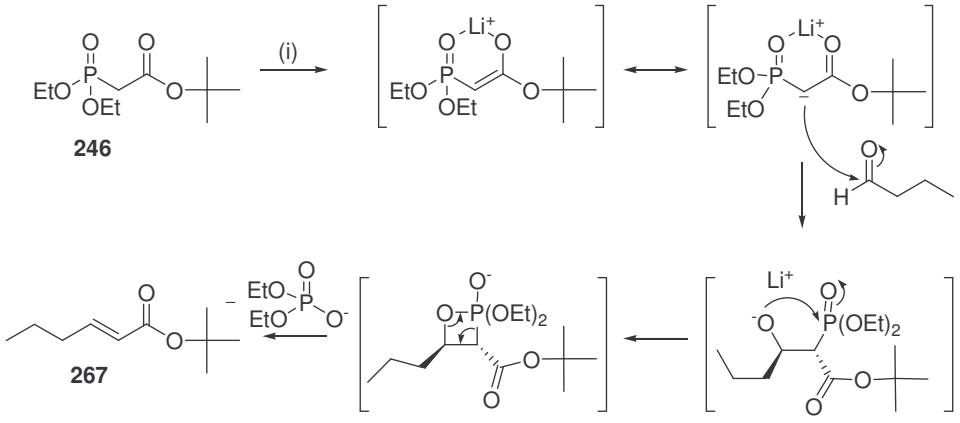


Scheme 5.2: *Arbuzov reaction*

The obtained boiling point of 115 °C at 1 mmHg was comparable to the values quoted in the literature.[100, 108h, 108k] Spectroscopic data corresponded with those published previously. The ^{1}H NMR spectrum was characterized by the presence of a singlet integrating for nine protons corresponding to the *tert*-butyl hydrogens at 1.48 ppm, and a doublet at 2.88 ppm (J = 21.5 Hz) intergrating for two protons corresponding to the $CH_2P{=}O$ group. The $CH_2P{=}O$ carbon was split into a doublet (J = 133.5 Hz) seen at 35.5 ppm in the ^{13}C NMR spectrum; the coupling constant shows the coupling to the phosphorus atom. The FTIR spectrum showed a carbonyl stretch at 1731 cm^{-1}.

The phosphonate **[246]** was then subjected to a Horner-Wadsworth-Emmons Wittig olefination[170] by treatment with lithium chloride, 1,8-diazabicyclo[5.4.0]undec-7-ene and

freshly distilled butanal. The reaction is a modification of the standard Wittig reaction, and is used as it affords the geometrically pure *E*-□,□-unsaturated ester. The selectivity arises from the chelation of the lithium ions with the deprotonated phosphonoacetate (**Scheme 5.3**). Treatment with butanal then affords only the desired *E*-isomer.

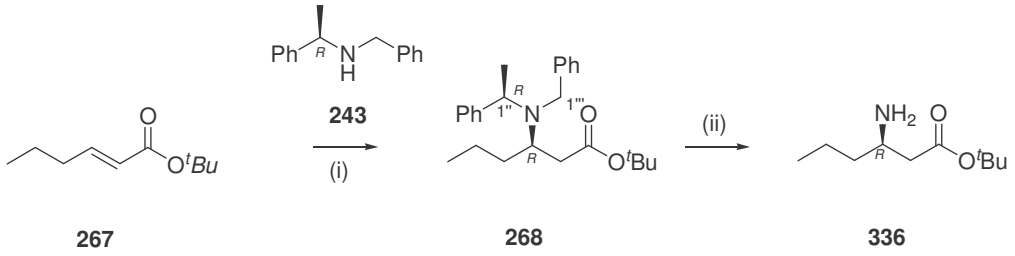


Scheme 5.3: *(i) DBU, LiCl, CH_3CN, 80%*

After purification by distillation, *tert*-butyl (2*E*)-2-hexenoate **[267]** was obtained as a clear liquid in an 80% yield on a 63 mmol scale, with none of the *Z*-isomer present. Spectroscopic data were comparable to those reported by Gravestock[100, 108h]. In the ^{1}H NMR spectrum the alkene protons were clearly seen as a doublet of triplets integrating for one proton at 6.86 ppm (*J* 6.9 and 15.2 Hz) and a doublet integrating for one proton at 5.74 ppm (*J* 15.6 Hz). The coupling constants of 15.5 and 15.5 Hz confirmed the desired *E*-geometry. The ^{13}C NMR spectrum showed the characteristic alkene carbons at 147.9 and 123.1 ppm.

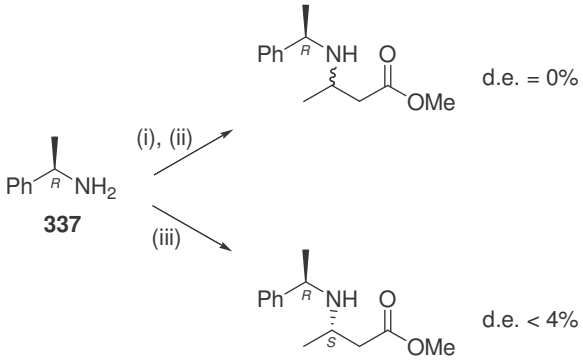
5.3 Preparation of *tert*-butyl (3*R*)-3-amino-hexanoate [336]

Having prepared the desired enoate **[267]** in the correct *E*-configuration we then needed to introduce the chirality at what would become the 5-position. This was done by employing the methodology developed by Davies and co-workers[124] (**Scheme 5.4**).



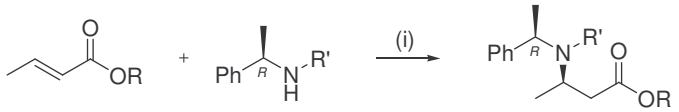
Scheme 5.4: *(i) n-BuLi, -78 °C, THF, 3 h, 77%; (ii) 7 atm H_2(g), 10% Pd/C, AcOH, 3 d, 65%*

The Davies group has been interested in the preparation of □-amino esters as important intermediates in the synthesis of pharmaceutical drugs, and to date have developed a generalized approach to access enantiomerically pure □-amino esters.[124] Their protocol involves the addition of various chirally pure lithium amides to □,□-unsaturated esters. They initially reported the addition of lithium *N*-(3,4-dimethoxybenzyl)-□-methylbenzylamide to an iron crotyl complex *E*-[(C_5H_5)Fe(CO)(PPh_3)(COCH=CHMe)] in good diastereoselectivity.[171] In a subsequent report the Michael addition between lithium (*R*)-□-methylbenzylamide amine **[337]** and simple *E*-crotonates was described[124] (**Scheme 5.5**).



Scheme 5.5: *(i) n-BuLi, THF, -78 °C; (ii) CH_3CH=$CHCO_2Me$; (iii) CH_3CH=$CHCO_2Me$, EtOH, Δ*

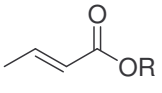
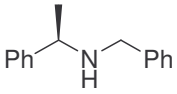
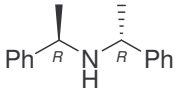
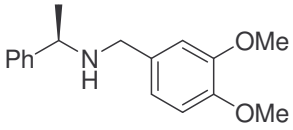
To their disappointment the reactions showed little or no selectivity at all. The use of more bulky secondary amines however afforded the desired alkylated adducts in good yield and high diastereoselectivity[124] (**Scheme 5.6**).



Scheme 5.6: *(i) n-BuLi, THF, -78 °C*

The nature of the ester also seemed to play an important role with α,β-unsaturated *tert*-butyl esters giving the best selectivity[124] (**Table 5.1**).

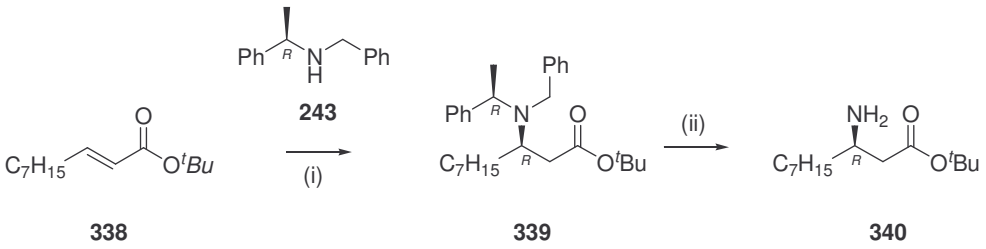
Table 5.1: Selectivity and yields for the addition of chiral amines to various α,β-unsaturated esters

 **R**	 **243**		
Me	95 (85%)	>99* (57%)	95 (68%)
CH_2Ph	95 (88%)	98** (23%)	96 (74%)
t-Bu	>99 (82%)	>99* (27%)	>99 (83%)

* None of the minor diastereomer was detected

** 0 °C

Since their initial observations Davies and co-workers have applied and reported this methodology on numerous substrates including crotonates, cinnamates, cyclopentanoates[172], cyclohexanoates[173], α,β-unsaturated acrylates possessing ethyl, *iso*-propyl, benzyl, *E*-CH_3CH=CH and 2-furyl groups[174-176]. They have also reported the addition of (*R)*-(+)-*N*-benzyl-*N*-α-methylbenzylamine **[243]** to *E-tert*-butyl dec-2-enoate **[338]**[124]. The conjugated product **[339]** was formed in a 91% yield with diastereoselectivity >95%. The debenzylated amino ester **[340]** was then obtained after a high pressure hydrogenation in a 92% yield (**Scheme 5.7**).



338 **339** **340**

Scheme 5.7: *(i) n-BuLi, -78 °C, 91%; (ii) 7 atm H_2(g), Pd/C, AcOH, 92%*

This result prompted Gravestock to investigate the addition of lithiated (*R)*-(+)-*N*-benzyl-*N*-α-methylbenzylamine **[243]** to various *tert*-butyl *E*-alk-2-enoates in our laboratories.[108h] Gravestock demonstrated the preparation of a number of debenzylated amino esters in both high yield and diastereoselectivity. A comparison with the model proposed by Davies[124], allowed the assignment of the absolute configuration.

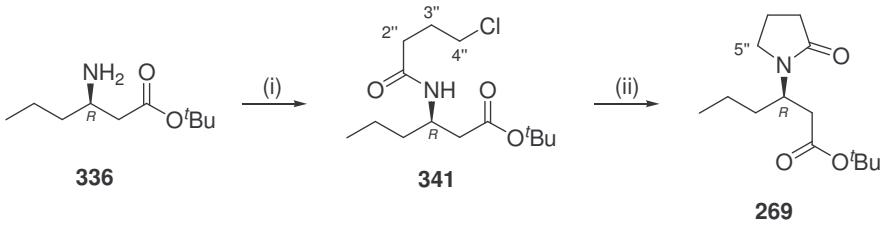
In the present project to afford the Davies alkylation product a solution of (*R)*-(+)-*N*-benzyl-*N*-α-methylbenzylamine **[243]** in tetrahydrofuran was cooled to −78 °C and lithiated with *n*-butyllithium. The enoate **[267]** was then added to the lithiated amine dropwise, and after three hours at −78 °C the reaction was worked up. The crude product was purified by column chromatography to give *tert*-butyl (3*R*)-3-{benzyl[(1*S*)-1-phenylethyl]amino}hexanoate **[268]** in a 77% yield on a 15.5 mmol scale. The spectroscopic data compared well with those reported previously by Gravestock.[100] The ^{1}H NMR spectrum showed the loss of the alkene protons at 6.86 and 5.74 ppm. The aromatic protons were shown by a multiplet at 7.43-7.20 ppm intergrating for ten protons, and the benzylic protons were seen as a quartet at 3.81 ppm in the case of H-1'' and as two doublets at 3.81 and 3.48 ppm in the case of H-1'''. Finally a methyl group was shown by the presence of a doublet intergrating for three protons at 1.32 ppm. The ^{13}C NMR spectrum also showed the loss of the characteristic alkene protons at 147.9 and 123.1 ppm, once again the benzyl groups were shown by the presence of aromatic protons in the 143.1-126.5 ppm region, benzylic protons at 79.8 and 50.1 ppm and the methyl substituent at 20.5 ppm. The product was optically active, and gave an optical rotation of $[\alpha]_D^{19}$ +8.00 (*c* 2.00 $CHCl_3$).

The next step involved a high pressure debenzylation of the free amino ester **[268]** by treatment with hydrogen at 7 atmospheres in glacial acetic acid in the presence of 10%

palladium on carbon for 3 days. The desired primary amine **[336]** was obtained in 65% yield on a 9.2 mmol scale as a light yellow oil. The spectroscopic data correlated well with those obtained by Gravestock.[100] The ^{1}H NMR spectrum showed the loss of the benzyl groups by the disappearance of the aromatic protons (7.43-7.20 ppm), benzylic protons (3.81 and 3.48 ppm) and the methyl substituent (1.32 ppm). The spectrum showed the NH_2 protons as a singlet intergrating for two protons at 1.50 ppm. The ^{13}C spectrum also showed the loss of the aromatic carbons (143.1-126.5 ppm), benzylic carbons (79.8 and 50.1 ppm) and the methyl substituent (20.5 ppm). The product was optically active, and gave an optical rotation of $[\alpha]_D^{21}$ + 1.43 (*c* 0.70 $CHCl_3$).

5.4 Acylation and cyclisation of the primary amine [336]

The construction of the five-membered ring involved the acylation of the primary amine **[336]** with 4-chlorobutyryl chloride, followed by treatment with potassium *tert*-butoxide to afford the lactam **[269]** (**Scheme 5.8**)



336 **341** **269**

Scheme 5.8: *(i) $Cl(CH_2)_3COCl$, NEt_3, CH_2Cl_2, 0 °C, 30 min, 96%; (ii) KO^tBu, t-BuOH, 5 h, 73%*

Freshly distilled 4-chlorobutyryl chloride was added dropwise to a solution of *tert*-butyl (3*R*)-3-aminohexanoate **[336]** and triethylamine in dichloromethane at 0 °C. The resulting condensation between the amine and the acid chloride was extremely vigorous, with a rapid evolution of hydrogen chloride gas being observed. The reaction went to completion in a few minutes, and once worked up and purified by column chromatography gave *tert*-butyl (3*R*)-3-[(4-chlorobutanoyl)amino]hexanoate **[341]** as an orange oil in a 96% yield on a 5.1 mmol scale. The ^{1}H NMR spectrum showed the NH as a broad doublet integrating for one proton at 6.18 ppm. H-2'' and H-4'' were seen as triplets at 2.35 and 3.60 ppm, and the H-3'' protons

were obsevred as a quintet at 2.11 ppm. The ^{13}C NMR spectrum showed the presence of a new carbonyl group at 170.9 ppm. An optical rotation of $[\alpha]_D^{23}$ 1.75 (*c* 2.28, absolute EtOH) was observed for **[341]**.

The cyclization of the amide **[341]** was initially attempted using the protocol described by Manhas and Jeng,[177] which had been used extensively by Stanbury[108i] and Gravestock[108h] in our labs (**Scheme 5.8**). The amide **[341]** was treated with potassium *tert*-butoxide in dry *tert*-butanol, and after 24 hours the reaction mixture was neutralized with glacial acetic acid. After the usual workup and purification by column chromatography, *tert*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexanoate **[269]** was obtained as a yellow oil with the best yield being 40% on a 1.9 mmol scale. In comparison, Gravestock[108h] reported a 56% yield across two steps for the same substrate. Despite several attempts we were unable to improve our yield and it appeared that the longer the reaction stirred for, and the more potassium *tert*-butoxide we used or the larger the reaction scale was, the lower the yields were. The decrease in the yields was thought to be due to the formation of a series of unidentifiable by-products, most probably arising from the elimination of hydrogen chloride gas and the subsequent re-arrangement of the alkene fragment. Having failed to optimize the cyclization we investigated the use of sodium methoxide in methanol and sodium ethoxide in ethanol to afford the ring closed product; however in both cases the reaction failed with a quantitative recovery of starting material being obtained.

The formation of the unwanted by-products when treating the amide **[341]** with potassium *tert*-butoxide was eventually overcome by simply adding the potassium-*tert*-butoxide portionwise over 5 h. We found that the addition of 0.1 equivalents of the base every 30 min prevented the formation of any side products, even when we had added 1.5 equivalents in total of the base. After tlc analysis indicated the complete consumption of starting material, the reaction was neutralized with glacial acetic acid as usual, worked-up and purified by column chromatography to afford the desired *tert*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexanoate **[269]** as a yellow oil in a 73% yield on a 6.9 mmol scale. The spectroscopic data correlated well with those reported by Gravestock[100, 108h]. The product was optically active, giving an optical rotation of $[\alpha]_D^{18}$ –5.03 (*c* 1.59, $CHCl_3$). The ^1H NMR spectrum showed the loss of the characteristic broad doublet of the amide hydrogen at 6.18 ppm. The CH_2Cl protons at 3.60 ppm in the starting material had disappeared and were

replaced by the protons on the C-5'' position at 3.38 and 3.26 ppm. The ^{13}C NMR spectrum showed the loss of the characteristic CH_2Cl signal at 44.4 ppm, and the appearance of the C-5'' signal at 42.4 ppm. The FTIR spectrum showed two carbonyl stretches at 1723 and 1686 cm^{-1}.

5.5 Thionation of the lactam [269]

We initially investigated the use of Lawesson's reagent[178-180] for the thionation of lactam **[269]**, as this was the procedure of choice for Gravestock. In addition it has been used on numerous occasions in our laboratories for the thionation of *N*-aryl lactams (**Scheme 5.9**).

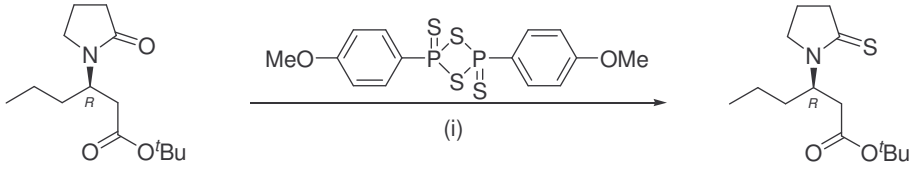
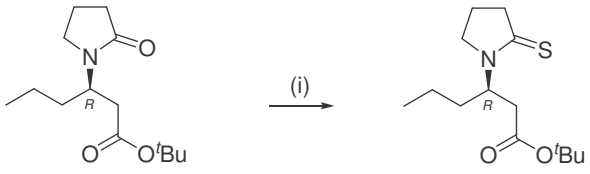


Figure 5.9: *(i) $PhCH_3$, Δ, 5 h, 68%*

Removal of the solvent and purification by column chromatography yielded *tert*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)hexanoate **[270]** as a yellow oil in a 68% yield on a 0.9 mmol scale. The use of the mild Brillon method[128] discussed in **Section 3.2.1** was also investigated (**Scheme 5.10**).



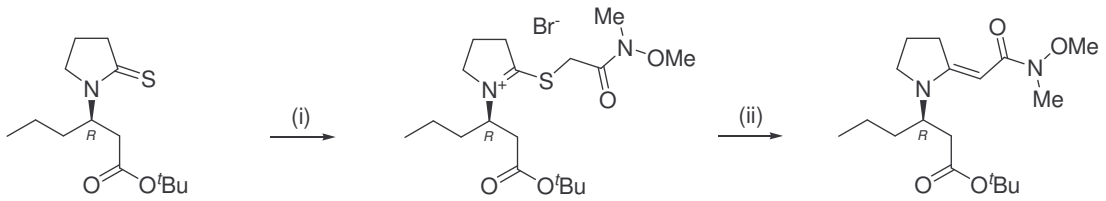
Scheme 5.10: *(i) P_2S_5, Na_2CO_3, THF, 5 h, 80%*

The active reagent was generated *in situ* by stirring phosphorus pentasulfide and sodium carbonate in a 2:1 ratio in tetrahydrofuran. Once a homogeneous solution had formed, the

lactam **[269]** was introduced, and the solution was stirred for 5 h, after which time the standard Brillon work-up and purification by column chromatography afforded *tert*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)hexanoate **[270]** as a yellow oil in an 80% yield on a 0.5 mmol scale. To our surprise the Brillon[128] procedure actually gave better results, and as such was used as our method of choice, not only because of the better yield, but also because of the lower cost of the reagents. The spectroscopic data corresponded well with those reported by Gravestock[100, 108h]. The ^{1}H NMR spectrum showed a shift in the $CH_2C{=}O$ protons at 2.42-2.34 ppm, to 3.00 ppm indicating the conversion to $CH_2C{=}S$. The ^{13}C NMR spectrum showed the loss of the carbonyl peak at 170.2 ppm and the corresponding appearance of a thiocarbonyl peak at 201.8 ppm. The observed optical rotation for **[270]** is $[\alpha]_D^{22}$ **+**17.9 (*c* 0.96, EtOH abs.)

5.6 The sulfide contraction

The sulfide contraction was performed using the method outlined in **Sections 3.2.2** and **4.3.2.**[121-123] Reaction of the thiolactam **[270]** with *N*-methoxy-*N*-methyl-2-bromoacetamide **[271]** gave the vinylogous urea **[272]** in a 77% yield on a 1.5 mmol scale (**Scheme 5.11**).



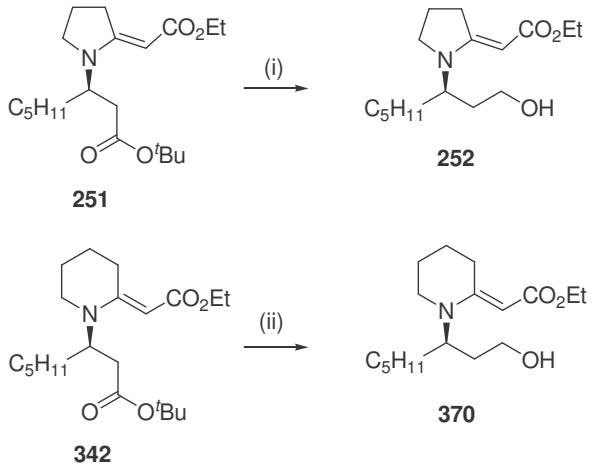
Scheme 5.11: *(i) N-methoxy-N-methyl-2-bromoacetamide **[271]**, CH_3CN, rt, 24 h; (ii) PPh_3, NEt_3, CH_3CN, 3 h, 77% (two steps)*

The ^{1}H NMR spectrum showed the characteristic vinyl proton as a singlet integrating for one proton at 5.26 ppm. In addition the OMe and Me peaks were shown by two singlets, both integrating for three protons, at 3.68 and 3.14 ppm. The $CH_2C{=}S$ signal shifted from 3.00 ppm to a multiplet at 3.32-3.19 ppm, indicating the conversion into a $C\underline{H}_2C{=}CH$- group. The ^{13}C NMR spectrum showed the loss of the characteristic thiocarbonyl peak at 201.8 ppm. The

alkene carbons and the amide carbonyl were shown by signals at 170.1, 77.7 and 164.7 ppm respectively. Finally the OMe and Me groups were found at 60.8 and 33.0 ppm respectively.

5.7 Attempted reduction of the *tert*-butyl ester [272]

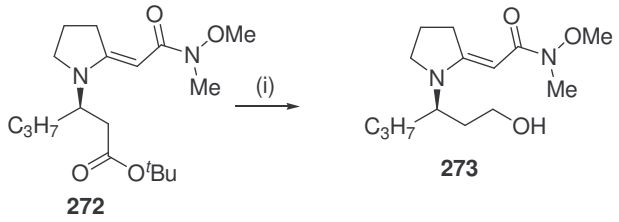
The next step in the synthesis required the reduction of the *tert*-butyl ester of the vinylogous urea **[272]** to afford the corresponding alcohol **[273]**. The reduction was initially seen as being potentially problematic for several reasons. The *tert*-butyl ester is sterically hindered and as such is only really susceptible to reduction using lithium aluminium hydride, although there are reports of the reduction being performed with sodium borohydride albeit in low yield in almost all cases[181]. The Weinreb amide itself is susceptible reduction when treated with lithium aluminium hydride, but with the enaminone backbone still in place its reactivity should be somewhat masked (**Section 4.6.4.1**). Gravestock showed that the *tert*-butyl group could be reduced to the alcohol **[252]** readily with lithium aluminium hydride in the presence of a vinylogous urethane,[100, 108h] however San-Fat found the same reduction on the analogous six membered ring system **[342]** to be low yielding and irreproducible[108k] (**Scheme 5.12**).



Scheme 5.12: *(i) (a) $LiAlH_4$ (2.0 eq.), THF, 24 h, 88%; (ii) $LiAlH_4$ (2.3 eq.), THF, 16 h, 29%*

As we were interested in the five-membered systems we felt confident that with careful optimization the reduction of the *tert*-butyl ester was a distinct possibility. We added the vinylogous urea **[272]** to a slurry of lithium aluminium hydride in dry THF at 0 °C. The reaction slurry was warmed to room temperature and stirred overnight. The usual work-up

involved washing with water and 15% sodium hydroxide several times, and after column chromatography we recovered (2*E*)-2-{1-[(1*R*)-1-(2-hydroxyethyl)butyl]-2-pyrrolidinylidene}-*N*-methoxy-*N*-methylethanamide **[273]** as a yellow oil in only a 10% yield on a 0.49 mmol scale (**Scheme 5.13**)



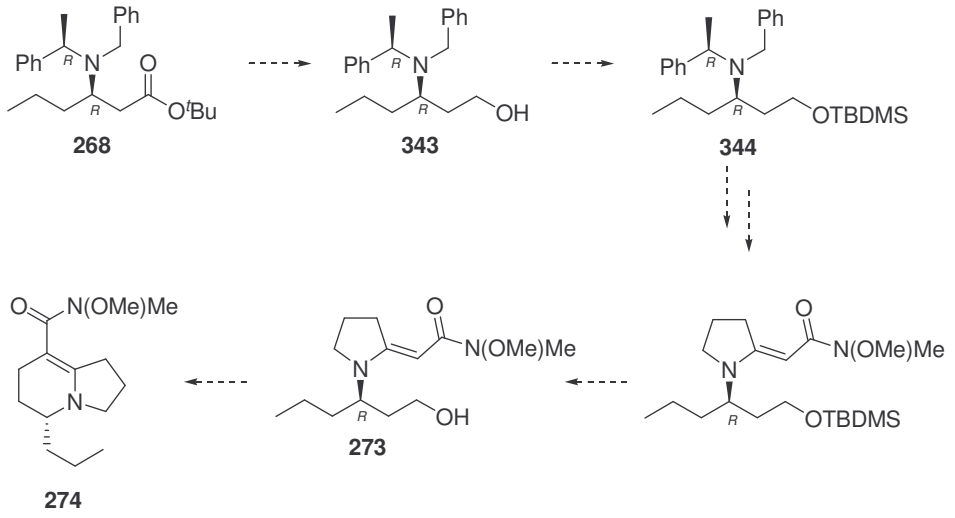
272 **273**

Scheme 5.13: *(i) $LiAlH_4$, THF, 0 °C – rt, 24 h, 11%*

The reaction was repeated several times using different quantities of lithium aluminium hydride, different solvents such as toluene, diethyl ether, as well as solvent mixtures of diethyl ether and toluene. The reaction proved to be both low yielding and to have results that were not reproducible.

5.8 An alternative approach to the enantioselective synthesis

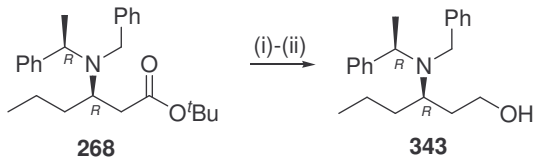
Owing to the problems associated with the reduction of the *tert*-butyl ester, we investigated an alternative approach. This still involved using the *tert*-butyl ester to ensure good enantioselectivity during the Wittig olefination[170] and Davies alkylation[124], however, we would then remove the ester early in the synthesis and replace it with a suitable protecting group. The approach mirrors the strategy San-Fat used to overcome the same problem[108k], and involves the reduction of the *tert*-butyl group immediately after the addition of the chiral amine. The resulting alcohol **[343]** is then protected as a silyl ether [**344]** and the synthesis then follows the same steps proposed in **Section 2.7.2**. An outline of the alternative synthesis highlighting the relevant changes is shown below in **Scheme 5.14**.



Scheme 5.14: *Alternative approach for the enantioselective synthesis of 5,8-disubstituted indolizidines*

5.9 Reduction of the *tert*-butyl ester of [268] and subsequent silylatio

The reduction of the chiral amine **[268]** to the alcohol **[343]** was achieved using the methodology described by Davies[182], wherein a cooled slurry of lithium aluminium hydride in diethyl ether was prepared. The chiral amine **[268]** was then added to this slurry dropwise, the solution was warmed to room temperature and stirred for 16 h. The usual work-up and purification by column chromatography then yielded the alcohol **[343]** in a 97% yield on a 32 mmol scale (**Scheme 5.15**).



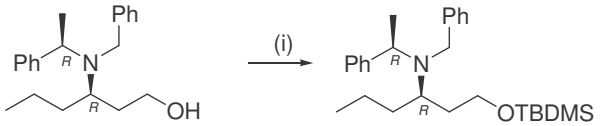
Scheme 5.15: *(i) $LiAlH_4$, Et_2O, 0 °C; (ii)* ***[268]****, Et_2O, 0 °C, 16 h, 97%*

The ^{1}H NMR spectrum showed the loss of the *tert*-butyl protons by the disappearance of the singlet at 1.39 ppm. The spectrum of the alcohol also showed the C$\underline{H}_2$OH protons as two multiplets at 3.24-3.17 ppm and 2.83-2.76 ppm each integrating for one proton. The hydroxyl

proton was also visible as a singlet integrating for one at 2.64 ppm. The ^{13}C NMR spectrum also showed the loss of the characteristic *tert*-butyl carbons at 79.8 and 28.0 ppm, and the carbonyl at 172.2 ppm, the CH_2OH carbon was visible at 56.7 ppm. The HRMS showed 311.22532 (100%) and the parent ion $C_{21}H_{29}NO$ requires 311.22491. The FTIR showed no carbonyl stretch, but the hydroxyl group was clearly shown by the broad signal at 3367 cm^{-1}. The product showed optical activity with $[\alpha]_D^{19}$ −32.1 (*c* 1.09, $CHCl_3$).

The subsequent protection of the alcohol **[343]** as the *tert*-butyl(dimethyl)silyl ether **[344]** was chosen as the silyl group is acid labile but resistant to basic conditions. As several succeeding steps required the use of strong bases such as potassium *tert*-butoxide, but no strong acids, the silyl group appeared to be the protecting group of choice. San-Fat in her synthesis of quinolizidine alkaloids found that the silyl group was not compatible with the thionation step.[108k] Pelly, however, did research on the five-membered ring systems and found that the silyl group was compatible with both the thionation and the sulfide contraction conditions.[109g, 110q] As we were working on the five-membered systems we envisaged none of the associated problems that San-Fat had encountered[108k].

Following the protocol described by Öhrlein and co-workers,[183] imidazole was added to a solution of the alcohol in dry dimethylformamide. To this was added the *tert*-butyl(dimethyl)silyl chloride in dry dimethylformamide dropwise. The mixture was stirred at room temperature for 16 h, after the work-up and purification by column chromatography the silyl ether **[344]** was obtained as a clear oil in an 88% yield on a 30.0 mmol scale (**Scheme 5.16**)



343 **344**

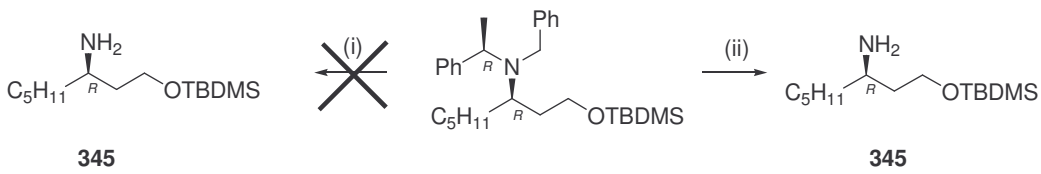
Scheme 5.16: *(i) (a) Imidazole, DMF, (b) TBDMSCl, DMF, 16 h, 88%*

The ^1H NMR spectrum showed the presence of the *tert*-butyl protons at 0.85 ppm and the $SiMe_2$ protons at −0.02 ppm and no hydroxyl peak could be found. The ^{13}C NMR spectrum

showed the *tert*-butyl carbons at 18.3 and 26.0 ppm, as well as the characteristic $SiMe_2$ carbons at –5.3 ppm. The HRMS showed 425.30974 (100%) with $C_{27}H_{43}NOSi$ requiring 425.31139. There was no evidence of an alcohol peak in the FTIR spectrum. The product **[344]** was optical active, and gave a rotation of $[\alpha]_D^{20}$ +18.9 (*c* 1.27, $CHCl_3$).

5.10 Debenzylation of the protected alcohol [344]

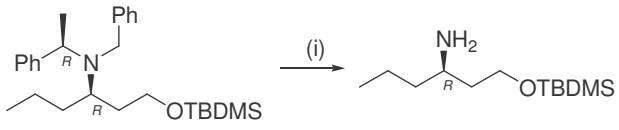
San-Fat found that the debenzylation in hydrogen at 7 atmospheres using 10% palladium on activated carbon when performed in glacial acetic acid afforded none of the debenzylated silyl ether **[345]**. Instead when she used a protocol described by Davies involving the use of Pearlmann's catalyst[124] (20% palladium hydroxide on activated carbon) at 5 atmospheres the desired compound **[345]** was formed in a quantitative yield (**Scheme 5.17**).



345 **345**

Scheme 5.17: *(i) 10% Pd/C, H_2(g) 7 atm, AcOH, 3 d; (ii) 20% $Pd(OH)_2$/C, H_2(g) 5 atm, abs. EtOH, 16 h, 100%*

We found that the use of Pearlmann's catalyst was not necessary. We treated the protected alcohol **[344]** with 10% palladium on activated carbon in hydrogen at 7 atmospheres in absolute ethanol instead of glacial acetic acid for 3 days. The standard workup and purification by column chromatography yielded the debenzylated amine **[346]** in an 85% yield on a 26 mmol scale (**Scheme 5.18**).



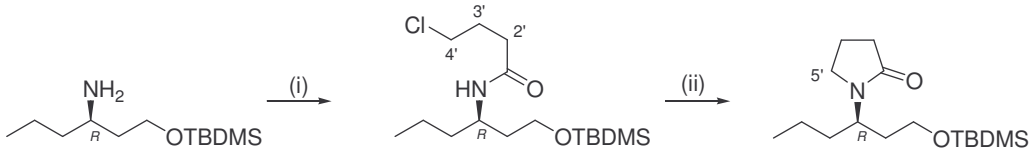
344 **346**

Scheme 5.18: *(i) 10% Pd/C, H_2(g) 7 atm, EtOH, 3 d, 85%*

The ^{1}H NMR spectrum confirmed the debenzylation by the loss of the aromatic protons at 7.40-7.16 ppm, the benzylic protons at 3.87, 3.78 and 3.64 ppm and the methyl group at 1.29 ppm. The NH_2 group was seen as a broad singlet integrating for two protons at 1.50 ppm. The ^{13}C NMR spectrum also showed the loss of the corresponding aromatic (144.9-126.3 ppm), benzylic (61.9 & 50.2 ppm) and methyl protons (20.5 ppm). The product was optically active, with an optical rotation of $[\alpha]_D^{21}$ +1.43 (*c* 0.70, $CHCl_3$). Although the free amine **[346]** appeared to be stable at room temperature, it was used immediately as it was found to be volatile at room temperature.

5.11 Lactam formation

The five-membered lactam ring **[347]** now needed to be formed (**Scheme 5.19**).



346 **348** **347**

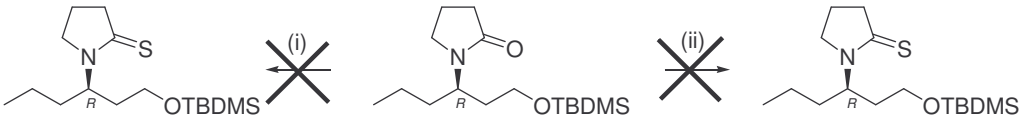
Scheme 5.19: *(i) $Cl(CH_2)_3COCl$, NEt_3, CH_2Cl_2, 0 °C, 30 min, 100%; (ii) $KOBu^t$, t-BuOH, 5 h, 94%*

The free amine **[346]** in the presence of triethylamine in dichloromethane was treated with 4-chlorobutryl chloride as previously described. Vigorous evolution of hydrogen chloride gas was observed, and after thirty minutes the reaction was quenched and worked up. Purification by column chromatography afforded the acylated product **[348]** in a quantitative yield on an 11.5 mmol scale. The ^{1}H NMR spectrum showed the NH signal as a broad doublet at 6.10 ppm. There were two triplets both integrating for two protons at 3.57 and 2.28 ppm due to H-4' and H-2' respectively. The H-3' signal was seen as a quintet integrating for two protons at 2.08 ppm. The FTIR spectrum showed the NH group by a broad stretch at 3281 cm^{-1}. The product was optically active, giving a rotation of $[\alpha]_D^{23}$ −1.75 (*c* 2.28, EtOH abs). The obtained amide **[348]** also decomposed rapidly and as such was used immediately.

The ring closure was performed by the portionwise addition of potassium *tert*-butoxide to the acylated amine **[348]** in dry *tert*-butanol, as described in **Section 5.4**. The lactam **[347]** was obtained in a 94% yield on a 10.7 mol scale. The ^{1}H NMR spectrum showed the shifting of the CH_2Cl signal at 3.57 ppm to a multiplet at 3.32-3.18 ppm and the loss of the broad doublet at 6.10 ppm representing the NH group. The FTIR spectrum showed a carbonyl stretch at 1668 cm^{-1} and the HRMS showed 299.22292 (74%) with $C_{16}H_{33}NO_2Si$ requiring 299.22806. The optical rotation of **[347]** was $[\alpha]_D^{19}$ –9.86 (*c* 0.71, $CHCl_3$).

5.12 Attempted thionation of the lactam [347]

We were now in the position to thionate the lactam **[347]** (**Scheme 5.20**). Initially we refluxed the lactam with Lawesson's reagent[178-180] in toluene for 5 h, and to our disappointment we only recovered an unidentifiable product.



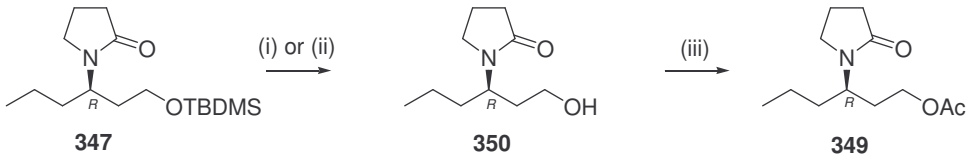
347

Scheme 5.20: *(i) Lawesson's reagent, $PhCH_3$, Δ, 5 h, 0%; (ii) P_2S_5, Na_2CO_3, THF, 5 h, 0%*

We then tried using the Brillon procedure[128] that Pelly had used to successfully thionate five-membered ring lactams containing a silyl ether group.[109g, 110q] Once again we were not able to isolate any of the thionated lactam, despite the complete consumption of starting material. The inability to thionate the lactam **[347]** was a great disappointment, and we had to now be content with replacing the silyl ether with a second protecting group.

5.13 Deprotection of the lactam [347] and reprotection as an acetate [349]

Fortunately the synthesis did not need to be re-designed completely. In an analogous manner to San-Fat[108k], we opted to desilylate the lactam **[347]** and replace it with an acetate to afford **[349]** (**Scheme 5.21**).



Scheme 5.21: *(i) TBAF, THF, 100 min, 74% or (ii) HF, MeOH, 100 min, 74%; (iii) Ac_2O, Py, 16 h , 84%*

The acetate was the protecting group used in the model study described in **Chapter 4**, and on the model system was shown to be tolerant not only of the thionation but also the sulfide contraction procedure. The acetate was also easily removed from the enaminones under standard conditions. As a result we were now confident that the acetate protecting group would allow us to access the deprotected vinylogous urea **[273]**. Unfortunately, it is not feasible to introduce the acetate at the same stage where the silyl ether was introduced as the subsequent lactam formation made use of potassium *tert*-butoxide which would simply cleave off the acetate group.

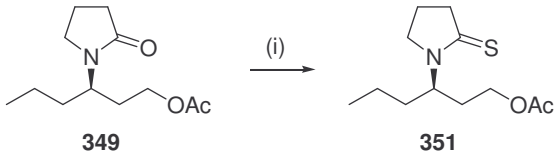
The lactam **[347]** was initially treated with tetrabutylammonium fluoride, a mild source of F^-, in dry tetrahydrofuran. After the required workup and purification by column chromatography the desilylated lactam **[350]** was obtained as a clear oil in a 74% yield on a 0.3 mmol scale. Attempts to scale up the desilylation resulted in a decrease in the yield of product recovered. We instead found that treating the lactam **[347]** with 40% hydrofluoric acid under dilute conditions in methanol afforded the desired lactam in a 74% yield but this time on a 6.3 mmol scale. The ^{1}H NMR spectrum showed the loss of the *tert*-butyl protons at 0.86 ppm and the $SiMe_2$ protons at 0.02 and 0.01 ppm. The hydroxyl proton was seen as a singlet integrating for one proton at 3.11 ppm. The ^{13}C NMR spectrum also showed the loss of the *tert*-butyl carbons at 25.9 and 18.2 ppm, as well as the $SiMe_2$ carbons at −5.39 and −5.44 ppm. The HRMS showed 185.14044 (100%) and $C_{10}H_{19}NO_2$ requires 185.14158. The product showed an optical rotation of $[\alpha]_D^{23}$ −0.61 (*c* 11.5, EtOH, abs).

The acetylation was performed by treating the alcohol **[350]** with acetic anhydride in pyridine as described in **Section 4.2**. The acetylated product **[349]** was obtained as a clear oil in an 84% yield on a 9.0 mmol scale. The ^{1}H NMR spectrum showed the acetate $-CH_3$ group as a

singlet intergrating for three protons at 2.04 ppm. The corresponding carbon signal was seen at 20.9 ppm in the ^{13}C NMR spectrum, in addition to a new carbonyl signal at 171.0 ppm. The HRMS of $C_{12}H_{21}NO_3$ requires 227.15214 and showed 227.14413 (32%). The product was optically active, giving a rotation of $[\alpha]_D^{23}$ +1.89 (*c* 11.1, $CHCl_3$).

5.14 Thionation of the acetate-protected lactam [349]

We now had a system analogous to that of the model study (**Chapter 4**). Using the Brillon protocol[128] that was successful in the model study we attempted to thionate the acetate-protected lactam **[349]** (**Scheme 5.22**).



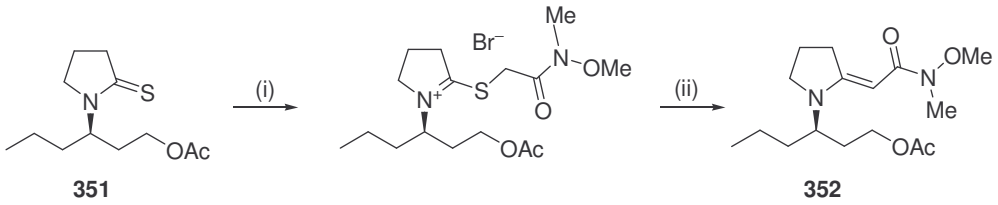
349 **351**

Scheme 5.22: *(i) (a) P_2S_5, Na_2CO_3, THF (b)* ***[349]****, THF, 3 h, 91%*

Phosphorus pentasulfide and sodium carbonate were stirred in dry tetrahydrofuran. Once a homogeneous solution had formed the lactam **[349]** was added in one portion. The mixture was stirred at room temperature for 3 h, after which time the usual workup and purification by column chromatography afforded the thiolactam **[351]** as a yellow oil in a 91% yield on a 7.3 mmol scale. The ^1H NMR spectrum showed a shift in the triplet for $CH_2C{=}O$ at 2.40 ppm to a triplet at 3.03 ppm due to the $CH_2C{=}S$ group. The ^{13}C NMR spectrum showed the loss of the characteristic carbonyl signal at 171.0 ppm and the corresponding appearance of the thiocarbonyl signal at 202.3 ppm. The HRMS showed 243.12852 (100%) and $C_{12}H_{21}NO_2S$ requires 243.12930. The thiolactam **[351]** had an optical rotation of $[\alpha]_D^{17}$ +23.7 (*c* 1.69, $CHCl_3$).

5.15 Sulfide contraction and acetate removal

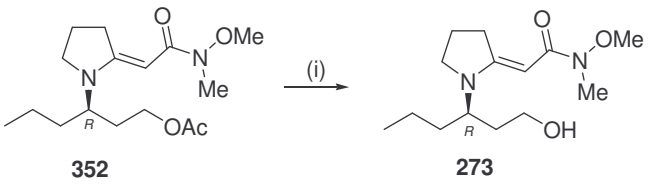
The sulfide contraction[121-123] was performed in the usual manner by treating thiolactam **[351]** with *N*-methoxy-*N*-methyl-2-bromoacetamide **[271]** (**Scheme 5.23**).



Scheme 5.23: *(i)* ***[271]****, CH_3CN, rt, 24 h; (ii) PPh_3, NEt_3, CH_3CN, 3 h*

In an effort to achieve a high yield, we followed the protocol of van der Westhuyizen,[108j] using 1.8 equivalents of the *N*-methoxy-*N*-methyl-2-bromoacetamide **[271]** and 1.5 equivalents of triphenylphosphine and triethylamine. We were however disappointed as the crude vinylogous urea **[352]** was still contaminated with triphenylphosphine residues after the acid-base extraction and further purification by flash column chromatography was ineffective. The contaminated product **[352]** was used directly in the next step where purification was possible. The ^{1}H NMR spectrum showed the characteristic vinyl proton as a singlet integrating for one proton at 5.19 ppm, the OMe and Me groups were seen as singlets both integrating for three protons at 3.66 and 3.14 ppm. The ^{13}C NMR spectrum clearly showed an additional carbonyl group at 165.4 ppm, as well as the OMe and Me carbons at 67.0 and 33.0 ppm. The characteristic alkene protons were visible at 170.8 and 76.9 ppm.

Although the vinylogous urea **[352]** was still contaminated with triphenylphosphine residues, we felt that once the acetate was removed the alcohol **[273]** would be significantly more polar than the phosphine residues, therefore making purification by standard column chromatography trivial. The acetate was removed using the standard procedure of treatment with potassium carbonate in methanol (**Scheme 5.24**), and the desired alcohol was obtained in 59% overall yield (3 steps), based on thiolactam **[351]** on a 6.5 mmol scale.

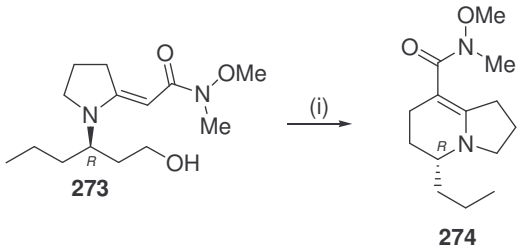


Scheme 5.24: *(i) K_2CO_3, MeOH, 64% (3 steps from* ***[351]****)*

The ^{1}H NMR spectrum showed the loss of the acetate CH_3 at 2.04 ppm. The ^{13}C NMR spectrum showed the loss of the characteristic acetate carbonyl at 172.1 ppm and the acetate CH_3 at 20.8 ppm. The FTIR spectrum showed a broad stretch at 3358 cm^{-1} indicating the presence of the hydroxyl group.

5.16 Alkylative cyclisation

The standard alkylative cyclisation was achieved by dissolving the alcohol **[273]** in a 2:1 ratio mixture of toluene:acetonitrile.[108k, 136] The dissolved alcohol **[273]** was then treated with imidazole and tripenylphosphine, and once a homogeneous solution had formed iodine was introduced in one portion. The reaction mixture was refluxed for about 45 minutes. The bicyclic amide **[274]** was obtained as an orange oil in 47% yield on a 0.38 mmol scale (**Scheme 5.25**).

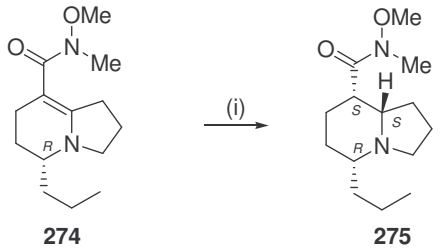


Scheme 5.25: *(i) (a) Imidazole, PPh_3, CH_3CN:$PhCH_3$ (1:2), (b) I_2, Δ, 47%*

The ^{1}H NMR spectrum showed no sign of the hydroxyl group. However, more characteristically the signals due to the $C\underline{H}_2OH$ protons at 3.96-3.86 ppm and the vinyl proton at 5.25 ppm were absent. The ^{13}C NMR spectrum showed the characteristic alkene protons at 174.4 and 90.1 ppm. The HRMS showed 252.18281 and $C_{14}H_{24}N_2O_2$ requires 252.18378.

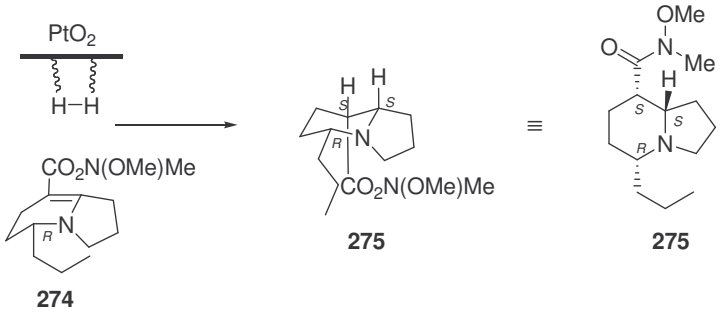
5.17 Catalyic hydrogenation

We were now at the point where we could investigate the stereoselective reduction of the double bond. The bicyclic enaminone **[274]** was treated with Adams' catalyst ($PtO_2.xH_2O$) in glacial acetic acid under a hydrogen atmosphere (1 atm) for 24 h (**Scheme 5.26**).



Scheme 5.26: *(i) Adams' catalyst, $H_2(g)$ 1 atm, glacial acetic acid, 24 h, 80%*

After purification the desired indolizidine **[275]** was isolated as a single diastereomer as a yellow oil in an 80% yield on a 0.7 mmol scale. The stereochemical outcome can be explained by the fact that the hydrogen is adsorbed onto the surface of the catalyst, which is bulky in comparison to the molecule. The hydrogen will therefore be delivered from the less hindered face of the double bond (**Scheme 5.27**).



Scheme 5.27: *Stereochemical basis for the catalytic reduction of the double bond*

In our case the bulky propyl chain at the 5-position ensures that the hydrogen is delivered from the opposite face, and since the propyl chain is in the *R*-configuration exclusively the reduction is diastereoselective.[138] The reduction will therefore occur from one face only regardless of whether it is going through the neutral molecule or the iminium species, and in this case the selectivity is completely governed by steric hindrance with little or no opportunity for stereoelectronic effects to play a role.[138]

The singlets at 3.65 and 3.17 ppm in the ^{1}H NMR spectrum indicated that the Weinreb amide was still in place. This was further shown by the signals at 174.9, 61.0 and 35.8 ppm in the

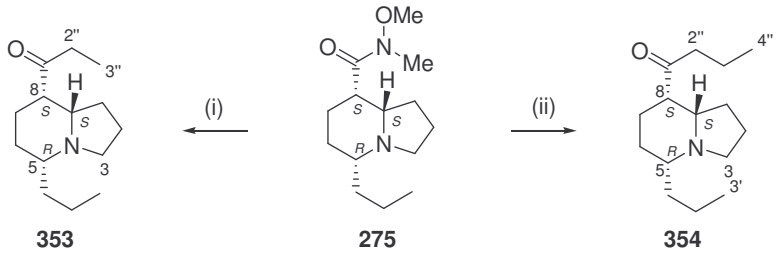
^{13}C NMR spectrum. The ^{1}H NMR spectrum is very complicated and the only other characterisable signals are a doublet of triplets at 3.33 ppm integrating for 1 proton due to the equatorial hydrogen at C-3, and the triplet at 0.90 ppm due to the terminal CH_3. The ^{13}C NMR spectrum showed the loss of the characteristic alkene signals at 174.4 and 90.1 ppm, and the characteristic signals for C-8 and C-8a were observed at 43.9 and 65.7 ppm. The product was optically active, giving a rotation of $[\alpha]_D^{21}$ −57.3 (3.07, EtOH, abs).

5.18 Modification of the Weinreb amide

Having synthesized the key bicyclic indolizidine we were now at the point where the synthesis could diverge, allowing us access to several 5,8-disubstituted indolizidines. The progress towards the synthesis of indolizidines **209I [185]** and **223V [174]** will be dealt with below in **Section 5.18.1**.

5.18.1 Alkylation of the Weinreb amide

In order to access **209I [185]** and **223V [174]** we needed to introduce the appropriate length alkyl chain at the 8-position. This was done by treating the bicyclic Weireb amide **[275]** with ethylmagnesium bromide for **209I [185]** and *n*-propylmagnesium chloride for **223V [174]**. The Weinreb amide was dissolved in dry tetrahydrofuran and cooled to −78 °C, the Grignard reagent was added and the solution was slowly warmed to room temperature (**Scheme 5.28**).



353 **275** **354**

Scheme 5.28: *(i) (a) EtMgBr, THF, –78 °C-rt, 24 h (b) 0.2N $HCl_{(aq)}$, 83%; (ii) (a) n-PrMgCl, THF, –78 °C-rt, 24 h (b) 0.2 N $HCl_{(aq)}$, 26%*

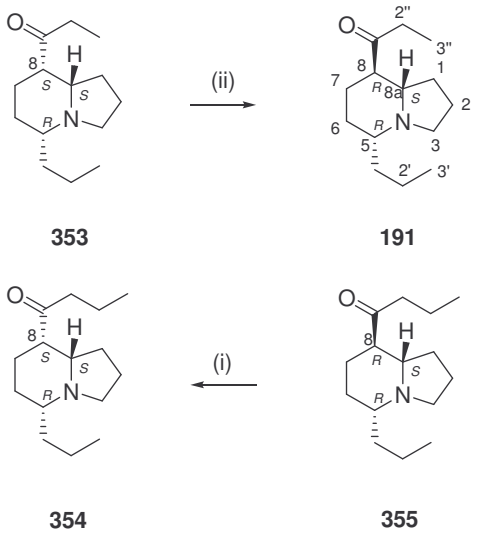
The reaction mixture was stirred for 24 hours after which the chelation complex (**Section 4.7.4.1**) was quenched by treatment with 0.2 N HCl solution. Purification by column chromatography afforded the desired alkylated products **[353]** and **[354]** albeit in widely different yields of 83 and 26% yield respectively. The low yield appeared to be due to the loss of product during the purification stage, as analysis of the crude product indicated a good recovery of material and NMR analysis showed the crude mixture to be mainly the desired products. Interestingly, when we tried to collapse the chelation complex using saturated aqueous ammonium chloride we were unable to recover any product.

The preparation of the ethyl ketone **[353]** was shown by the loss of the singlets at 3.65 and 3.17 ppm in the ^{1}H NMR spectrum and the appearance of a second triplet at 1.01 ppm integrating for three protons due to the ethyl chains terminal CH_3. Additional characteristic peaks in the ^{1}H NMR spectrum include a doublet of triplets at 3.28 ppm due to the equatorial proton at the 3 position, and a multiplet at 2.81 due to the protons at the 8 position. A doublet of quartets at 2.63 ppm and a multiplet at 2.52-2.39 ppm due to the protons at the 2'' position, and a multiplet at 2.15-2.02 ppm integrating for two protons due to the proton at the 5 position and the axial proton at the 3 position. The triplet due to the terminal CH_3 on the chain at the 5 position is still clearly visible at 0.91 ppm. Characteristic signals in the ^{13}C NMR spectrum include a ketone carbonyl signal at 213.6 ppm, and a signal at 7.7 ppm due to the terminal carbon at the 3'' position. The HRMS showed 223.19358 (94%) with $C_{14}H_{25}NO$ requiring 223.19361. The product showed an optical rotation of $[\alpha]_D^{19}$ +48.3 (*c* 0.95, $CHCl_3$).

The propyl ketone **[354]** also showed the loss of the singlets at 3.65 and 3.17 ppm in the ^{1}H NMR spectrum. In this case a second triplet due to the terminal CH_3 at the 4'' position was seen at 0.90 ppm overlying the triplet at 0.91 ppm due to the terminal CH_3 at the 3' position. As in the previous case the equatorial proton at the 3 position was visible as a doublet of triplets at 3.29 ppm. The protons □ to the ketone at the 2'' position were visible as two doublets of triplets at 2.58 and 2.41 ppm. The proton at position 8 appeared as a multiplet between 2.83 and 2.77 ppm. Finally the axial proton at the 3 position and the proton at the 5 position appeared together as a multiplet between 2.25 and 2.08 ppm. The ^{13}C NMR spectrum showed a ketone carbonyl signal at 212.9 ppm. The product was optically active, giving a rotation of $[\alpha]_D^{18}$ +7.60 (*c* 0.92 $CHCl_3$)

5.18.2 Epimerisation of the alkylated indolizidines [353, 354]

We were now at the stage where we could epimerize the ketone substituent at the 5-position to afford us products with the correct stereochemistry observed in the natural compounds. Simple base-catalysed epimerization of **[353]** and **[354]** by refluxing with sodium methoxide in methanol for three hours afforded the epimerized indolizidines **[191]** and **[355]** in 80 and 48% yields respectively on a 0.04 and 0.03 mmol scale (**Scheme 5.29**).



Scheme 5.29: *(i) Na, MeOH, Δ, 80%; (ii) Na, MeOH, Δ, 48%*

In both cases the success of the epimerization was shown by the disappearance of the signal for the proton at the 8 position as it shifts upfield, where it is obscured by the signals in the 2.15-1.00 ppm region. Epimerized ethyl ketone **[191]** has been prepared previously by Ma[107], and a comparison of our spectral data and those published by Ma is shown below in **Tables 5.2 – 5.3**.

Table 5.2: Comparison of ^{1}H NMR spectroscopic data for **[191]** with results published by Ma *et al.*[107]

Proton	^{1}H NMR ($CDCl_3$) Riley (300 MHz)	^{1}H NMR ($CDCl_3$) Ma *et al.*[107] (300 MHz)
H-3_{eq}	3.27 (dt, *J* 1.9 & 8.3 Hz)	3.24 (dt, *J* 2.7 & 9.0 Hz)
H-2''	2.59-2.35 (m)	2.55-2.38 (m)
Remaining H's	2.15-1.16 (m)	2.12-1.82 (m)
Remaining H's		1.79-1.62 (m)
Remaining H's		1.46-1.13 (m)
H-3''	1.04 (t, *J* 7.3 Hz)	1.04 (t, *J* 7.5 Hz)
H-3'	0.91 (t, *J* 7.1 Hz)	0.92 (t, *J* 6.3 Hz)

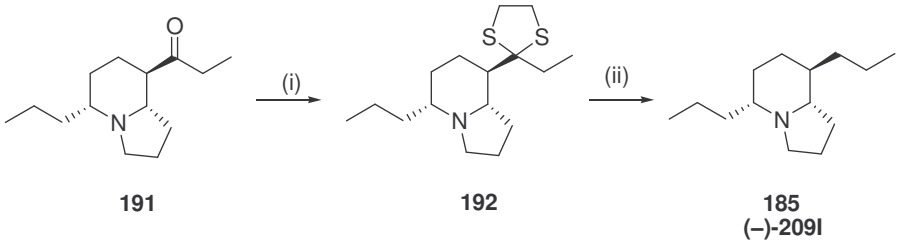
Table 5.3: Comparison of ^{13}C NMR spectroscopic data for **[191]** with results published by Ma *et al.*[107]

Carbon	^{13}C NMR ($CDCl_3$) Riley (300 MHz)	^{13}C NMR ($CDCl_3$) Ma *et al.*[107] (300 MHz)
C=O	213.4	213.5
C-8a	65.5	65.4
C-5	62.8	62.8
C-8	54.4	54.7
C-3	50.9	51.0
C-2''	36.6	36.8
C-1'	36.0	36.0
C-1	30.3	30.4
C-6	28.9	29.0
C-7	28.4	28.4
C-2	20.4	20.4
C-2'	18.9	18.9
C-3'	14.4	14.5
C-3''	7.6	7.6

The HRMS showed 223.19248 (84%) and the parent ion of $C_{14}H_{25}NO$ requires 223.19361. Finally the observed optical rotation $[\alpha]_D^{17}$ −74.3 (*c* 0.35 $CHCl_3$) was comparable with the results published by Ma[107] $[\alpha]_D^{20}$ −84.4 (*c* 1.0 $CHCl_3$).

5.18.3 Completion of the synthesis of indolizidine 209I [185]

The preparation of epimerized ketone **[191]** represents a formal synthesis of **209I [185]**. Ma already reported that **[191]** could be converted into indolizidine **209I [185]** in two steps (**Scheme 5.30**).



Scheme 5.30: *(i) 1,2-ethanedithiol, $BF_3.OEt_2$, 65%, (ii) Raney-Ni, i-PrOH, 70°C, 81%*

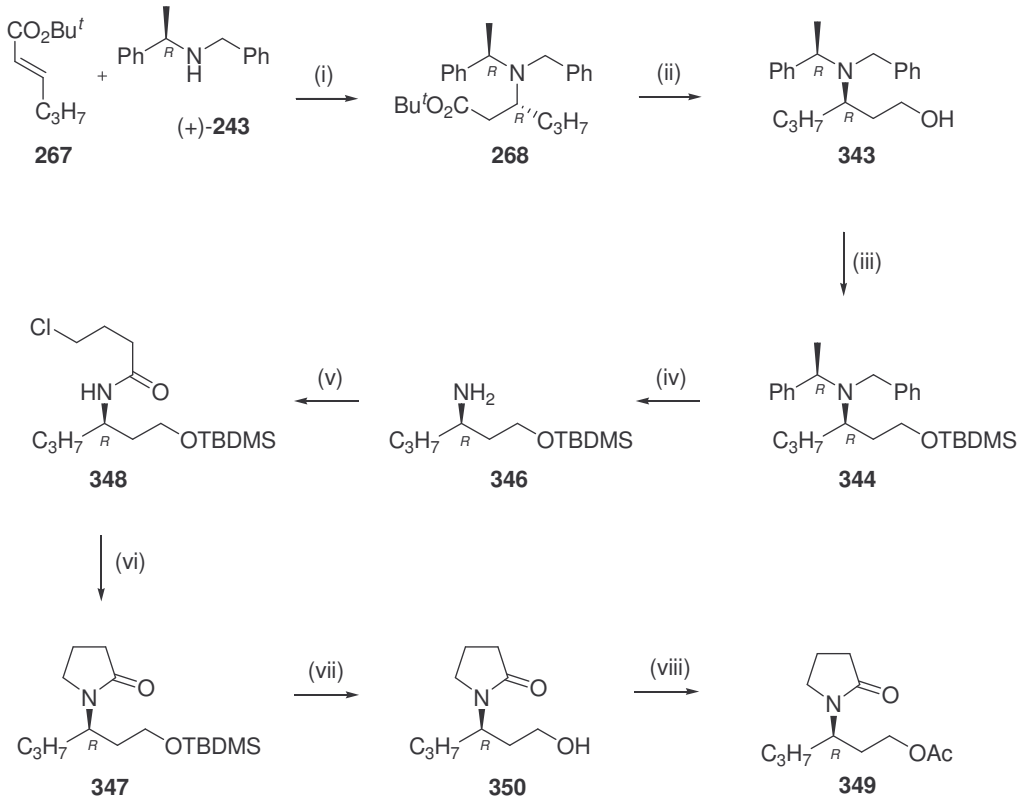
Ma showed that treatment of the ketone **[191]** with boron trifluoride etherate and ethanedithiol afforded the thioacetal **[192]** in a 65% yield, and subsequent defunctionalisation with Raney nickel in *iso*-propanol at 70 °C afforded indolizidine **209I [185]** in an 81% yield.[107]

Unfortunately, we were unable to recover enough of the epimerized ketones **[191]** and **[355]** to repeat to work done by Ma[107] for the preparation of **209I [185]**, or to prepare **223V [174]** using the same protocol.

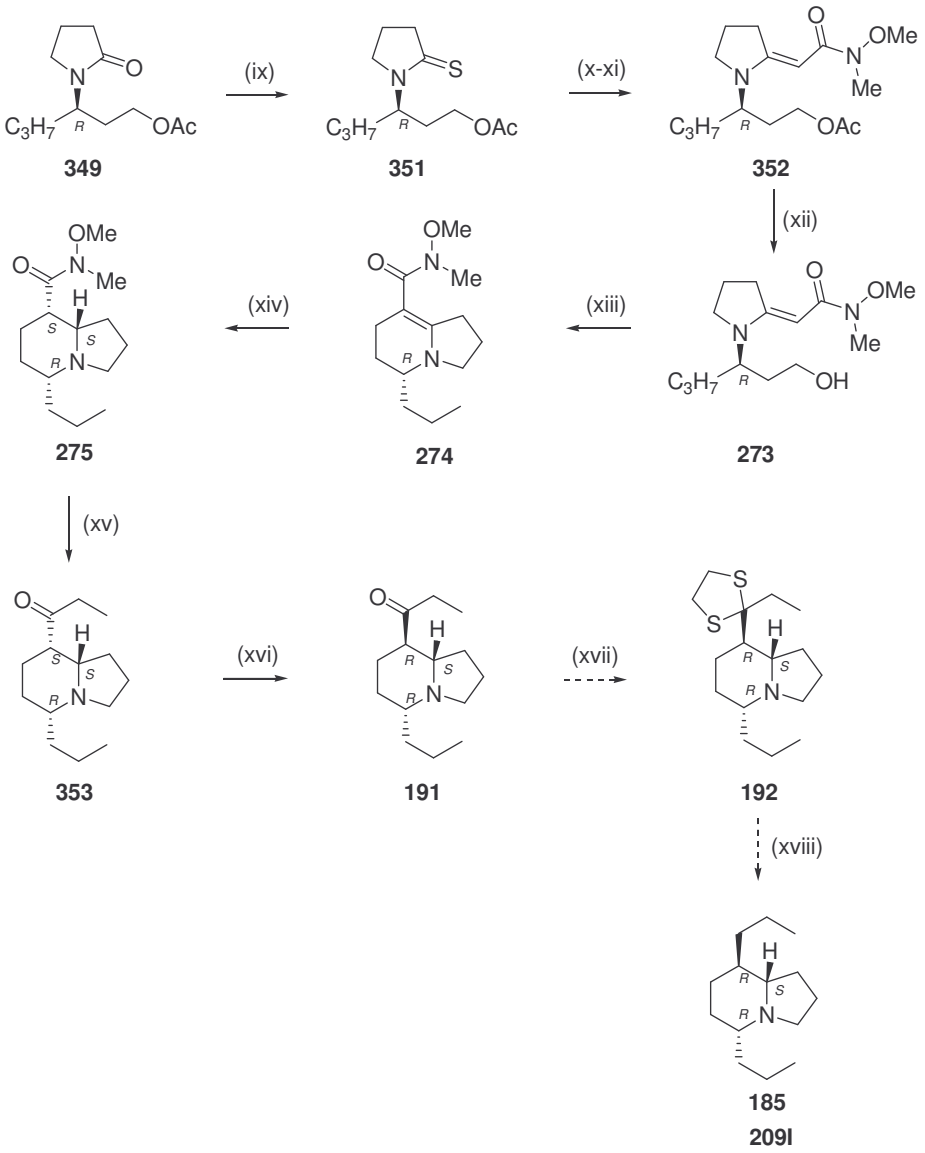
5.19 Conclusion

The formal preparation of **209I [185]** using the "Wits approach", in particular Gravestock's methodology[100], showed that there were distinct differences in reactivity depending on the substituent at the 5-position. Differences are highlighted all through **Chapter 5**, the key difference being the inability to reduce the *tert*-butyl ester **[272]** at an advanced stage of the synthesis. An alternative approach to access alcohol **[273]** was employed and involved the

reduction of the *tert*-butyl ester at an earlier point in the synthesis, followed by a series of protections and deprotections before being able to access the desired alcohol **[273]**. Owing to the time constraints and lack of material we were not able to prepare indolizidines **197C [258]** and **223V [174]**. The formal enantioselective preparation of **209I [185]** was achieved in 18 steps in an overall yield of 3.1% and is shown below in **Schemes 5.31** and **5.32**.



Scheme 5.31: *(i) (a) –78 °C, THF, 30 min, (b)* ***[267]****, –78 °C, 3 h, 77%; (ii) $LiAlH_4$, Et_2O, 16 h, 97%; (iii) TBDMSCl, imidazole, DMF, rt, 24 h, 88%; (iv) 10% Pd/C, absolute EtOH, H_2(g), 7 atm, 3 d, 88%; (v) $Cl(CH_2)_3COCl$, NEt_3, CH_2Cl_2, 30 min, 100%; (vi) KBu^tO, t-BuOH, 5 h, 94%; (vii) HF, MeOH, 3 h, 90%; (viii) Ac_2O, Py, rt, 16 h, 84%*



Scheme 5.32: *(ix) P_2S_5, Na_2CO_3, THF, rt, 3 h, 91%; (x)* ***[271]****, CH_3CN, rt, 16 h; (xi) PPh_3, NEt_3, CH_3CN, rt, 3 h; (xii) K_2CO_3, MeOH, rt, 3 h, 64% (3 steps); (xiii) imidazole, PPh_3, NEt_3, CH_3CN:$PhCH_3$, Δ, 1 h, 47%; (xiv) $PtO_2.xH_2O$, glacial acetic acid, H_2(g), 1 atm, rt, 24 h, 80%; (xv) (a) EtMgBr, THF, rt, 24 h, 83%; (xvi) Na, MeOH, Δ, 3 h, 80% (xvii) $HS(CH_2)_2SH$, $BF_3.OEt_2$, 65%, (xviii) Raney-Ni, i-PrOH, 70°C, 81%*

CHAPTER 6

PROGESS TOWARDS THE SYNTHESIS OF A LATE STAGE COMMON INTERMEDIATE [259] FOR THE PREPARATION OF 5,8-DISUBSTITUTED INDOLIZIDINES

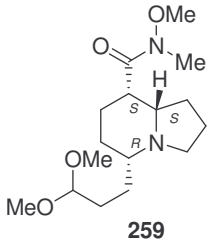


CHAPTER 6

PROGESS TOWARDS THE SYNTHESIS OF A LATE STAGE COMMON INTERMEDIATE [259] FOR THE PREPARATION OF 5,8-DISUBSTITUTED INDOLIZIDINES

6.1 Introduction

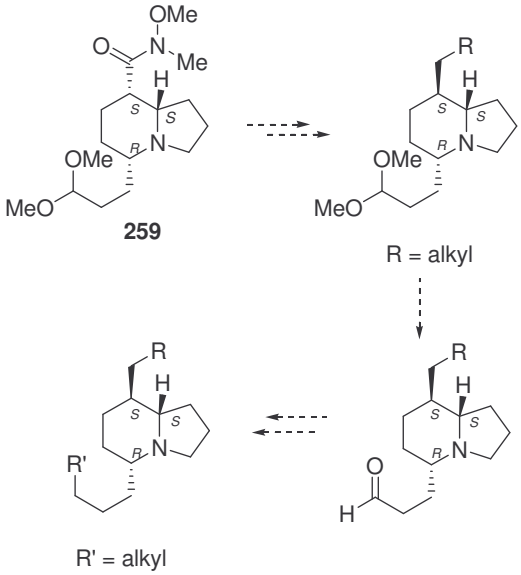
This chapter concerns our attempts to synthesise a late stage common intermediate **[259]** (**Figure 6.1**) which could be converted into almost any 5,8-disubstituted indolizidine.



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Figure 6.1: *The late stage common intermediate **[259]***

We envisaged that the introduction of an acetal protected aldehyde at the 5-position would allow us a handle to selectively modify the substituents at the 5- and the 8-positions (**Scheme 6.1**).

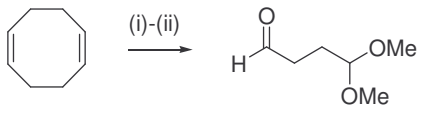


Scheme 6.1: *Stepwise modification of the substituents at the 5- and 8-positions*

The acetal protecting group is resistant to organometallic alkylating reagents and as such we would be able to selectively alkylate and epimerize the Weinreb amide to afford a range of both saturated and unsaturated substituents. Subsequent acetal removal under acidic conditions would afford the corresponding aldehyde from which there are several routes that can be followed, depending on the substituent required. The drawback to using the acetal protecting group is its lability in acidic media; it will require the modification of several steps to limit exposure to acid sources. The preparation of such a common late stage intermediate will pave the way for the first synthesis where the substituents at both the 5- and the 8-position could be introduced at or near the end of the synthesis. This route would fit in with our "Wits approach" towards alkaloid synthesis, and would allow the preparation of more than 90% of the naturally occurring 5,8-disubstituted indolizidines from **[259]** in just a few steps.

6.2 Preparation of 4,4-dimethoxybutanal [282]

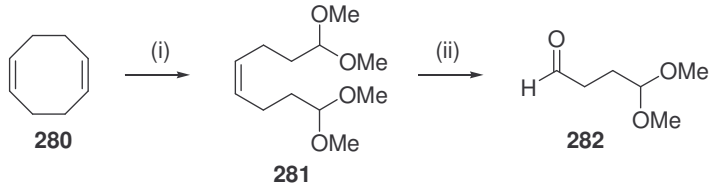
The preparation of the desired key intermediate **[259]** required the preparation of 4,4-dimethoxybutanal **[282]**, the preparation of which is not straightforward. The direct monoacetalization of the corresponding dialdehyde has not been reported. There are several methods reported for the preparation of **[282]**; however, most methods are cumbersome, requiring numerous steps or suffer from low overall yields[184-193]. We decided to use the two-step protocol described by Li, Wang and Zhao[194] which they claimed overcame many of the drawbacks traditionally experienced during the preparation of this monoacetalized dialdehyde **[282]**. They reported a stepwise ozonolysis of 1,5-cyclooctadiene **[280]** to access **[282]** in two steps in an overall yield of 82% (**Scheme 6.2**).



280 **282**

Scheme 6.2: *(i) (a) O_3, CH_2Cl_2:MeOH, –78°C, (b) p-TsOH, rt, 1 h, (c) Me_2S, H^+, rt, 24 h; (ii) (a) O_3, CH_2Cl_2, –78°C, (b) Me_2S, 82% (2 steps)*

In order to determine the time required to afford the partial ozonolysis of 1,5-cyclooctadiene **[280]**, we initially determined the relative rate of ozonolysis by testing how long it took for the double ozonolysis of 1,5-cyclooctadiene **[280]**. This was done by monitoring the time it took for a solution of 1,5-cyclooctadiene **[280]** in dichloromethane:methanol at −60°C to start turning blue when exposed to ozone. When the solution started turning blue it would indicate that it was saturated with excess ozone. 1,5-Cyclooctadiene **[280]** was then treated with ozone in a dichloromethane:methanol solvent mixture at −60°C for the appropriate time required for the delivery of one molar equivalent of ozone. Treatment with *para*-toluenesulfonic acid followed by reduction with dimethyl sulfide afforded *cis*-4-octene-1,8-dialdehyde which was protected *in situ* by the methanol in the presence of the acid catalyst to give **[281]** (**Scheme 6.3**).



Scheme 6.3: *(i) (a) O_3, CH_2Cl_2: MeOH, –60°C, (b) p-TsOH, rt, 1 h, (c) Me_2S, H^+, rt, 24 h, 65%; (ii) (a) O_3, CH_2Cl_2, –60°C, (b) Me_2S 0% or PPh_3 47%*

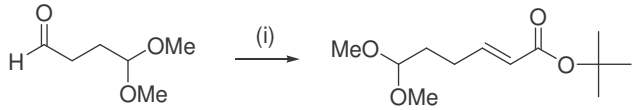
Our best result for **[281]** was a 65% yield on a 192 mmol scale, and despite repeating the reaction numerous times on various scales we could not optimize the yield any further. The ^{1}H NMR spectrum showed the characteristic alkene signal at 5.38 ppm as a broad triplet integrating for two protons and the methoxy signals appeared as a singlet at 3.32 ppm integrating for twelve protons. The C<u>H</u>$(OMe)_2$ proton also gave a characteristic triplet at 4.36 ppm integrating for two protons. The alkene carbons and the methoxy carbons were seen at 129.3 and 52.6 ppm in the ^{13}C NMR spectrum, the <u>C</u>H$(OMe)_2$ carbon was found at 104.0 ppm.

The protected *cis*-4-octene-1,8-dialdehyde **[281]** was then dissolved in dichloromethane and treated with ozone at −60 °C until the solution turned blue, indicating the complete ozonolysis of **[281]** (**Scheme 6.3**). Treatment with dimethyl sulfide to reduce the ozonide in accordance with Li, Wang and Zhao's protocol[194] did not afford the desired 4,4-dimethoxyaldehyde

[282]. Li, Wang and Zhao did however make mention of the fact that owing to the unpleasant smell of dimethyl sulfide, on large scales they used slightly less than one equivalent of dimethyl sulfide and finished the reduction with triphenylphosphine. We found that regardless of the scale, treatment with only dimethyl sulfide yielded none of the desired aldehyde **[282]**. However, when using only triphenylphosphine as the reductant we obtained the aldehyde **[282]** as a clear oil in a 47% yield on a 91 mmol scale. The aldehyde was characterized by the appearance of a triplet at 9.74 ppm integrating for one proton in the ^{1}H NMR spectrum and the disappearance of the alkene signal at 5.38 ppm. The aldehyde carbon was seen in the ^{13}C NMR spectrum at 202.0 ppm and the alkene signal at 129.3 ppm was missing. The FTIR spectrum showed a strong characteristic carbonyl stretch at 1729 cm^{-1}, and the HRMS showed 132.07753 (100%) and the parent ion of $C_6H_{12}O_3$ requires 132.07864.

6.3 Preparation of *tert*-butyl (2*E*)-6,6-dimethoxy-2-hexenoate [283]

The monoacetylated aldehyde **[282]** was subjected to the standard Horner-Wadsworth-Emmons Wittig olefination[170] by treatment with phosphonate **[246]**, DBU and lithium chloride. The desired *E*-isomer **[283]** was isolated in 59% yield on a 5 mmol scale (**Scheme 6.4**).



282 **283**

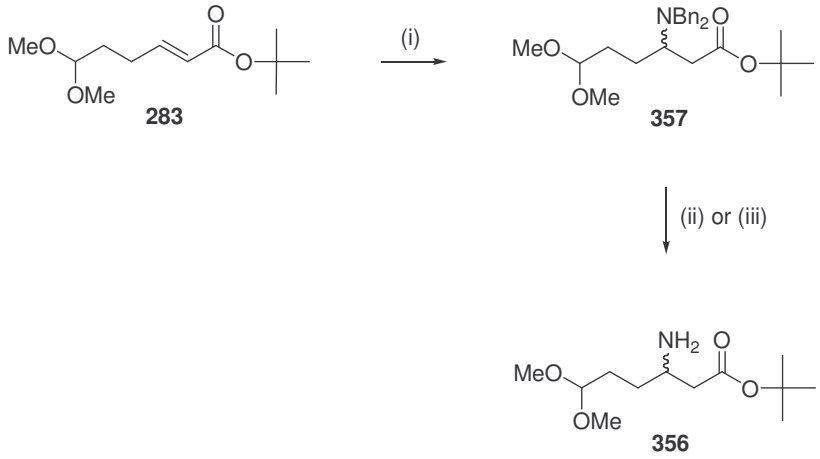
Scheme 6.4: *(i) $(EtO)_2POCH_2CO_2C(CH_3)_3$* ***[246],*** *DBU, LiCl, CH_3CN, 24 h, 59%*

The yield obtained is significantly lower than the 80% for the preparation of *tert*-butyl (2*E*)-2-hexenoate **[267]** (**Section 5.2**). A possible explanation is that there is increased steric hindrance due to the acetal protecting group which is inhibiting the addition of the phosphonate **[246]** to the aldehyde. Increasing the reaction temperature may improve the yield; however we felt that it may also lead to the formation of the unwanted *Z*-isomer and as such did not try refluxing the reaction mixture. Leaving the reaction to stir for longer than 24 hours did not show any improvement in the yield. The ^{1}H NMR spectrum showed the alkene protons as two doublets of triplets at 6.86 (*J* 6.9 & 15.6Hz) and 5.76 ppm (*J* 1.6 & 15.6 Hz);

the *J* coupling constant of 15.6 Hz confirms the *E*-geometry. The ^{13}C NMR spectrum showed the characteristic alkene peaks at 146.8 and 123.4 ppm. The *tert*-butyl ester carbonyl group was characterized by a very strong signal at 1717 cm^{-1} in the FTIR spectrum.

6.4 Preparation of *tert*-butyl 3-amino-6,6-dimethoxyhexanoate [356]

The Michael addition of dibenzylamine to *tert*-butyl (2*E*)-6,6-dimethoxy-2-hexenoate **[283]** was perfomed according to the Davies alkylation protocol[124] (**Section 5.3**), yielding *tert*-butyl 3-(dibenzylamino)-6,6-dimethoxyhexanoate **[357]** in 69% yield on a 42.3 mmol scale (**Scheme 6.5**). As this synthetic route was a model study, and at this stage we were not concerned with an enantioselective synthesis of **[259]**, we decided to use the relatively cheap dibenzylamine as a substitute for the more expensive (*R*)-(+)-*N*-benzyl-*N*-α-methylbenzylamine **[243]** which was used during the enantioselective synthesis (**See Section 5.3**).



Scheme 6.5: *(i) HNBn$_2$, n-BuLi, –78 °C, 69%; (ii) 7 atm H$_2$(g), Pd/C (10%), EtOH, 3d, 92% or (iii) 7 atm H$_2$(g), Pd/C (20%), EtOH, 3d, 100%*

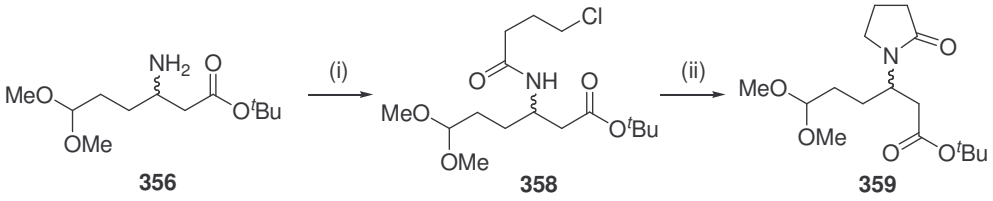
The success of the alkylation was shown by the disappearance of the alkene protons at 6.86 and 5.76 ppm, and the corresponding appearance of the aromatic protons in the 7.36-7.18 ppm region of the ^{1}H NMR spectrum. The benzylic protons are also clearly seen as doublets at 3.71 and 3.67 ppm. The ^{13}C NMR spectrum also showed the presence of the aromatic protons between 139.7 and 126.9 ppm, and the benzylic protons at 55.0 ppm. The FTIR spectrum

showed the characteristic aromatic stretches as weak signals at 3063 and 3028 cm^{-1}. Finally the HRMS showed 427.27214 and the parent ion of $C_{26}H_{37}NO_4$ requires 427.27226.

The high pressure debenzylation was previously performed in glacial acetic acid[124] (**Section 5.3**). However, in order to preserve the acetal protecting group we chose to use ethanol instead. At seven atmospheres of hydrogen, in ethanol using 10% palladium on carbon we obtained *tert*-butyl 3-amino-6,6-dimethoxyhexanoate **[356]** in a 92% yield after 3 days. The yield was improved to 100% when using 20% palladium on carbon. The ^{1}H NMR spectrum showed the loss of the characteristic aromatic (7.36-7.18 ppm) and benzylic protons (3.71 and 3.67 ppm) respectively, this loss was also shown in the ^{13}C NMR spectrum (139.7-126.9 & 55.0 ppm). Finally the FTIR spectrum showed an NH_2 signal at 3377 cm^{-1}.

6.5 Acylation and cyclisation of the primary amine [356]

As with the enantioselective synthesis (**Section 5.4**) the lactam ring was accessed by acylating the amine with 4-chlorobutanoyl chloride followed by cyclisation by treatment with potassium *tert* butoxide (**Scheme 6.6**).



356 **358** **359**

Scheme 6.6: *(i) $Cl(CH_2)_3COCl$, NEt_3, CH_2Cl_2, 0 °C, 30 min, 99%; (ii) K^tBuO, t-BuOH, 5 h, 53%*

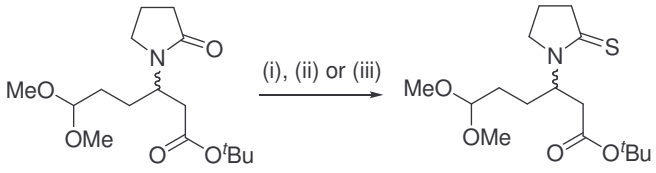
The dropwise addition of freshly distilled 4-chlorobutanyoyl chloride to *tert*-butyl 3-amino-6,6-dimethoxyhexanoate **[356]** in dichloromethane under basic conditions facilitated the acylation of the primary amine. A primary concern was the vigorous evolution of hydrogen chloride gas. We found that the use of a solid base such as sodium hydrogen carbonate as described by Gravestock was ineffective in neutralizing the acid, and the ^{1}H NMR spectrum clearly showed the loss of the acetal methoxy groups, regardless of how many molar equivalents of the base were used. We solved the deacetalation problem by switching to a

homogeneous base, and found that when 4-chlorobutanoyl chloride was added dropwise to **[356]** in dichloromethane in the presence of 2.2 molar equivalents of triethylamine, we were able to recover *tert*-butyl 3-[(4-chlorobutanoyl)amino]-6,6-dimethoxyhexanoate **[358]** in 99% yield. The ^{1}H NMR spectrum showed the NH proton as a broad doublet at 6.26 ppm integrating for one proton. The $COCH_2$ and CH_2Cl protons were seen as triplets, both intergrating for two protons at 2.35 and 3.60 ppm, and the $COCH_2C\underline{H_2}CH_2Cl$ protons appeared as a quintet at 2.11 ppm. The acetal methoxy protons were still clearly seen as two singlets integrating for three protons each at 3.32 and 3.31 ppm. The ^{13}C NMR spectrum showed an additional carbonyl group at 171.1 ppm, and once again the two methoxy signals at 53.0 and 52.9 ppm were still visible. The FTIR spectrm showed the NH stretch as a strong broad signal at 3330 ppm, and the two carbonyl stretches were also clearly visible as a strong signals at 1729 and 1654 cm^{-1}.

Treatment of *tert*-butyl 3-[(4-chlorobutanoyl)amino]-6,6-dimethoxyhexanoate **[358]** with potassium *tert*-butoxide in *tert*-butanol in accordance with the protocol outline in **Section 5.4** afforded the required lactam **[359]** in 53% yield (**Scheme 6.6**). The success of the reaction was shown by the disappearance of the broad doublet at 6.26 ppm due to the NH proton in the starting material and the shift in the signal at 3.60 ppm due to the CH_2Cl protons to 2.11 ppm in the ^{1}H NMR spectrum. The FTIR spectrum showed no NH signals above 3000 cm^{-1}, and once again the carbonyl stretches were visible as two strong signals at 1724 and 1688 cm^{-1}.

6.6 Thionation of the lactam [359]

The thionation of lactam **[359]** (**Scheme 6.7**) was attempted on several occasions using both the Brillon procedure[128] (**Section 3.2.1**), and the Lawesson's[178-180] approach (**Section 5.5**) and despite working well on our other systems we were unable to recover any thionated product.



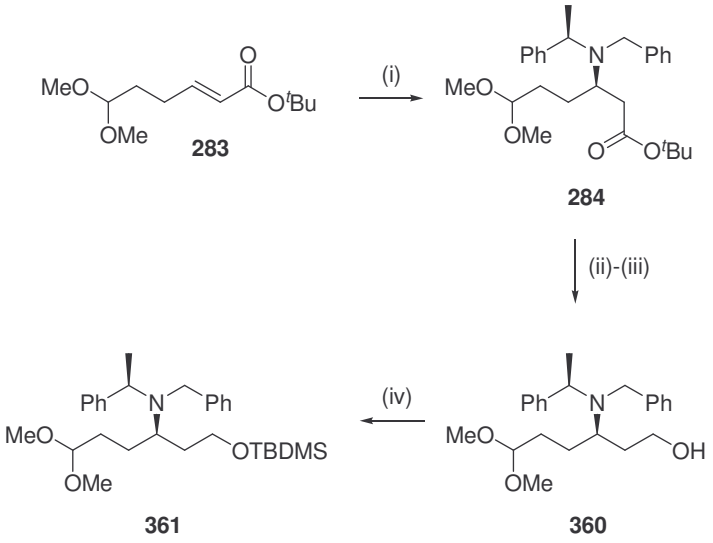
359 **439**

Scheme 6.7: *(i) P_2S_5, Na_2CO_3, THF, 3-5 h, 0%; (ii) Lawesson's reagent, $PhCH_3$, Δ, 5 h, 0%; (iii) Lawesson's reagent, microwave, 100 W, 120°C, 90 sec*

With no success using our two standard approaches, we attempted to thionate the lactam **[359]** by treating it with Lawesson's reagent under solventless conditions in a microwave reactor. At 100 watts we raised the temperature to 120 °C, however after only 90 seconds we recovered an unidentifiable black product. As the thionation reaction requires the use of bulky reagents, we felt that the acetal and *tert*-butyl ester groups were too bulky to allow access to the lactam carbonyl inhibiting the formation of the 4-membered cyclic intermediate.

6.7 An alternative approach

At this stage we decided that further investigations into the thionation of lactam **[359]** were probably not going to be feasible, and instead decided to try the alternative approach described in **Section 5.8**. The success of this alternative procedure for the preparation of the bicyclic vinylogous urea **[274]** prompted us to attempt the Davies alkylation[124] on **[283]** using (*R*)-(+)-*N*-benzyl-*N*-α-methylbenzylamine **[243]** instead of the achiral dibenzylamine. As previously described this approach required the reduction of the *tert*-butyl ester after the Davies alkylation[124], and subsequent silylation with *tert*-butyl dimethyl silyl chloride (**Scheme 6.8**).



Scheme 6.8: *(i) (R)-(+)-N-benzyl-N-α-methylbenzylamine **[243]**, n-BuLi, -78 °C, 47%; (ii) $LiAlH_4$, Et_2O, 0 °C; (iii) **[284]**, Et_2O, 0 °C, 16 h, 98%; (iv) (a) Imidazole, DMF, (b) TBDMSCl, DMF, 16 h, 76%*

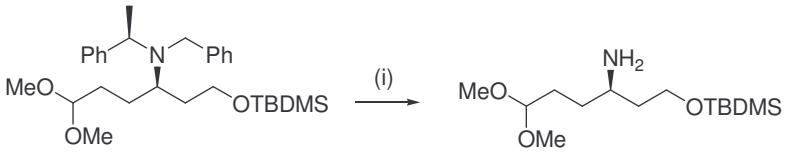
The alkylation of **[283]** proceeded smoothly, yielding **[284]** in 47% yield when following the standard protocol[124], albeit in a lower yield than when performed using dibenzylamine. As previously the success of the reaction was shown by the presence of aromatic proton signals in the ^{1}H NMR spectrum in the 7.44-7.21 ppm region. The benzylic protons appeared as an AB doublet at 3.79 and 3.48 ppm integrating for one proton each and a quartet at 3.82 ppm also integrating for one proton. The methyl substituent was also apparent as a doublet, integrating for three protons at 1.34 ppm. The FTIR spectrum showed the characteristic aromatic stretches at 3083, 3062 and 3026 cm^{-1}.

The reduction of the *tert*-butyl ester[182] **[284]** using lithium aluminium hydride in diethyl ether afforded alcohol **[360]** in 98% yield on a 2.5 mmol scale. The loss of the *tert*-butyl ester was shown by the disappearance of the singlet at 1.43 ppm in the ^{1}H NMR spectrum, as well as the loss of the carbonyl signal at 172.2 ppm in the ^{13}C NMR spectrum. The FTIR spectrum showed an OH stretch as a strong broad signal at 3380 cm^{-1}. The HRMS showed 371.24536 (100%) and $C_{23}H_{33}NO_3$ requires 371.24604.

The silylation proceeded smoothly by treating alcohol **[360]** in dimethylformamide with imidazole and *tert*-butyldimethylsilyl chloride[183], affording the silylated product **[361]** in a 76% yield on a 3.4 mmol scale. The ^{1}H NMR spectrum showed the silylation was successful by the appearance of the $SiMe_2$ protons as a singlet at −0.07 ppm integrating for six protons, and the *tert*-butyl protons as a singlet at 0.80 ppm integrating for nine protons. The ^{13}C NMR spectrum also showed the $SiMe_2$ carbons at −5.3 ppm and the *tert*-butyl carbons at 18.3 and 26.0 ppm. The FTIR spectrum had no broad alcohol stretch in the region above 3000 cm^{-1}. The HRMS showed 485.32116 and the parent ion of $C_{29}H_{47}NO_3Si$ requires 485.33252.

6.8 Debenzylation of the silylated alcohol [361]

Treatment of the silylated alcohol **[361]** with 10% palladium on carbon and hydrogen at 7 atmospheres in absolute ethanol afforded the debenzylated amine **[362]** in 98% yield on a 2.4 mmol scale (**Scheme 6.9**).



361 **362**

Scheme 6.9: *(i) 10% Pd/C, H_2(g) 7 atm, EtOH, 3 d, 98%*

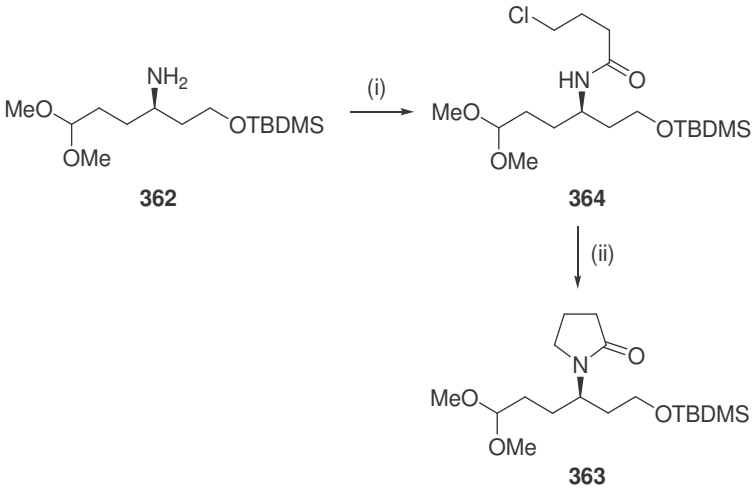
After the standard workup and purification by column chromatography, the ^{1}H NMR spectrum showed the loss of the aromatic protons (7.26-7.08 ppm), the benzylic protons (3.82, 3.75 and 3.58 ppm) and the benzylic methyl substituent (1.25 ppm). The ^{13}C NMR spectrum also did not show any aromatic protons (144.6-126.4 ppm) or benzylic protons (61.7 and 50.1 ppm). The FTIR spectrum showed the NH_2 stretch at 3356 cm^{-1} as a broad medium strength signal.

6.9 Lactam formation

To our surprise acylation and cyclisation of the amine **[362]** to access lactam **[363]** using 4-chlorobutyryl chloride (**Scheme 6.10**) did not afford the expected lactam **[363]**. The acylation

proceeded smoothly, giving *N*-[(1*R*)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4,4-dimethoxybutyl]-4-chlorobutanamide **[364]** in 99% yield. The ^{1}H NMR spectrum showed the characteristic triplets at 3.58 and 2.29 ppm due to the $ClCH_2$ and $COCH_2$ protons respectively. The quintet at 2.09 ppm due to the $COCH_2C\underline{H}_2CH_2Cl$, was also clearly visible. The ^{13}C NMR spectrum showed a carbonyl signal at 170.9 ppm, and the FTIR spectrum also showed the NH stretch at 3399 cm^{-1}.

The cyclisation with potassium *tert*-butoxide, however, yielded an unidentifiable black residue, which after column chromatography did not show any traces of the expected lactam **[363]**.



362 **364** **363**

Scheme 6.10: *(i) $Cl(CH_2)_3COCl$, NEt_3, CH_2Cl_2, 0 °C, 30 min, 99%; (ii) Bu^tOK, t-BuOH, 5 h, 0%*

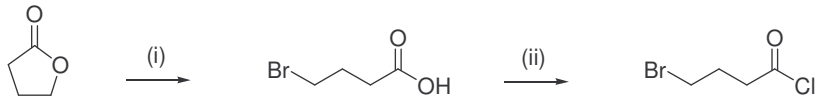
We attempted the cyclisation step using sodium ethoxide in ethanol as a base (**Scheme 6.11**). However we were once again unable to isolate any of the lactam **[363]**.



364 **363**

Scheme 6.11: *(i) Na, EtOH , rt, 24 h, 0%*

We thought that we may have better luck if we had a better leaving group than chlorine present, and as such, decided to use 4-bromobutyryl chloride **[365]**. The 4-bromobutyryl chloride **[365]** was prepared in two steps from γ-butyrolactone **[366]** (**Scheme 6.12**).



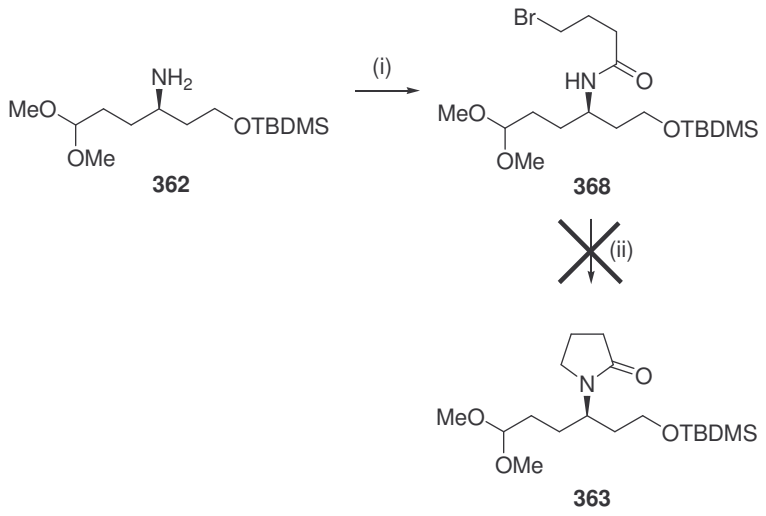
366 **367** **365**

Scheme 6.12: *(i) (a) HBr, H_2SO_4, Δ, 2 h (b) rt, 24 h, 68%; (ii) (a) oxalyl chloride, cat. NEt_3, CH_2Cl_2, 0 °C, 3 h, (b) rt, 16 h, 88%*

γ-Butyrolactone **[366]** was refluxed with hydrobromic acid and a small amount of concentrated sulfuric acid for 2 hours, thereafter the solution was stirred at room temperature for 24 hours[195]. After workup and purification by recrystallisation from dichloromethane, 5-bromobutanoic acid **[367]** was obtained as a beige solid in a 68% yield on a 68 mmol scale.

The 5-bromobutanoic acid **[367]** was then converted into the corresponding acid chloride by treatment with oxalyl chloride in dichloromethane at 0 °C, in the presence of a catalytic amount of triethylamine[196]. The desired acid chloride **[365]** was obtained in 88% yield on a 79 mmol scale after purification by distillation.

Acylation of **[362]** using 4-bromobutyryl chloride proceeded smoothly. As usual, the reaction was complete within a few minutes and was characterized by the evolution of hydrogen chloride gas. The acylated amine decomposed rapidly at room temperature and the crude product **[368]** was used immediately in the cyclisation step. To our disappointment despite several attempts, treatment with potassium *tert*-butoxide in *tert*-butanol afforded only an unidentifiable product (**Scheme 6.13**).



Scheme 6.13: *(i) $Br(CH_2)_3COCl$, NEt_3, CH_2Cl_2; (ii) K^tOBu t-BuOH, rt, 5 h, 0%*

6.10 Conclusion

Owing to the time constraints of the project we were unable to look at alternative methods of accessing lactam **[363]**. If we had been successful in preparing **[363]** we would still have needed to remove the silyl protecting group and re-protect the lactam as an acetate **[369]** due to the problems associated with thionating the lactam in the presence of a silyl ether as described in **Section 5.12**. An overview of our planned synthetic route to access lactam **[363]** and its conversion into the late stage common intermediated **[259]** is discussed in detail in **Section 8.2.3.**

CHAPTER 7

APPLICABILITY OF THE METHODOLOGY TO THE SYNTHESIS OF 1,4-DI-SUBSTITUTED QUINOLIZIDINES

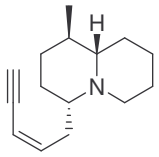


CHAPTER 7

APPLICABILITY OF THE METHODOLOGY TO THE SYNTHESIS OF 1,4-DI-SUBSTITUTED QUINOLIZIDINES

7.1 Introduction

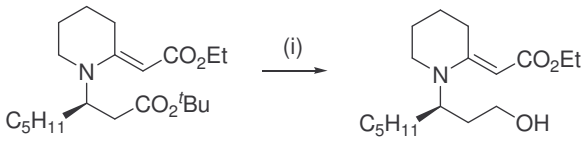
This chapter is concerned with the application of the methodology described in **Chapters 2-6** towards the synthesis of the structurally related class of amphibian alkaloids, the 1,4-disubstituted quinolizidines. Shown below in **Figure 7.1** is a representative example: **217A**, the first quinolizidine reported[49] (**Chapter 1, Section 1.2.14**).



217A

Figure 7.1: *Structure of 1,4-disubstituted quinolizidine **217A***

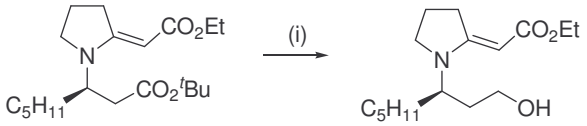
Quinolizidines have been synthesized before in our laboratories using the "Wits approach", but they have proved to be somewhat more challenging targets. During the course of her doctoral studies San-Fat described the preparation of quinolizidines.[108k] However, once she had formed the six-membered vinylogous urethane **[342]** (**Scheme 7.1**) she was able to reduce the *tert*-butyl ester to the alcohol **[370]** only in low yield. The problem was that the conjugated ester was rather labile, and the C=C bond was easily reduced as well.



342 **370**

Scheme 7.1: *(i) $LiAlH_4$, THF, 19 h, 29%*

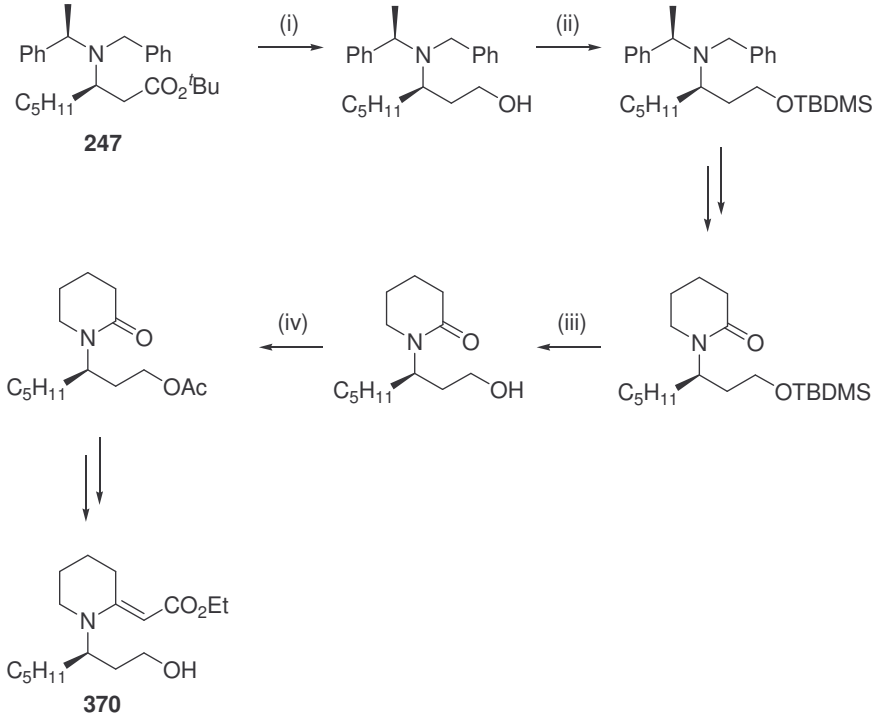
In comparison Gravestock reported a 91% yield for the reduction of the analogous five-membered system **[251]** (**Scheme 7.2**), and as such the enaminone unit in this system was far more resistant to competing reduction.[100, 108h]



251 **252**

Scheme 7.2: *$LiAlH_4$, THF, 0 °C to rt, 91%, 24 h*

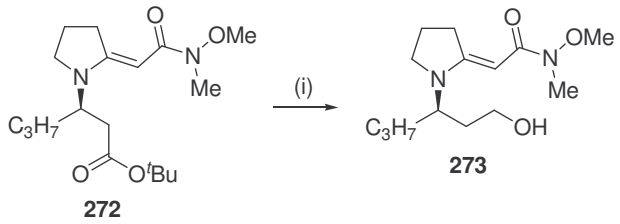
San-Fat had to be content with a more long-winded approach, which involved a series of deprotections and reprotections before being able to access the desired alcohol **[370]** in a reasonable and reproducible yield[108k] (**Scheme 7.3**).



247 **370**

Scheme 7.3: *(i) $LiAlH_4$, Et_2O, 0 °C, **[247]**, rt, 97%; (ii) TBDMSCl, imidazole, DMF, rt, 99%; (iii) 40% HF, MeOH, rt, 89%; (iv) Ac_2O, Py, rt, 100%*

As related in **Section 5.7**, when we attempted to reduce the *tert*-butyl ester of the vinylogous urea **[272]** we were only able to isolated the alcohol **[273]** product in a low 10% yield (**Scheme 7.4**).



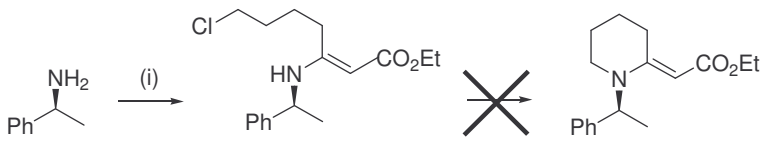
272 **273**

Scheme 7.4: *(i) $LiAlH_4$, THF, 0 °C – rt, 24 h, 10%*

The reduction of the *tert*-butyl ester is therefore not as general as we had hoped for the five-membered systems. The work reported in this chapter therefore relates an alternative approach that can be used for the preparation of 5,8-disubstituted indolizidines and 1,4-disubstituted quinolizidines, negating the need for the reduction of a *tert*-butyl ester group late in the synthesis.

7.2 Approach A

San-Fat originally tried to solve the reactivity problem by looking at the condensation of 7-chloro-3-oxoheptanoate **[371]** with primary amines, followed by an alkylative cyclisation[108k] (**Scheme 7.5**). Michael[108b] and Hosken[109a] had successfully adapted this approach from Carrié[197], when they prepared a series of *N*-aryl vinylogous urethanes by treating various substituted anilines with ethyl 6-chloro-3-oxohexanoate.

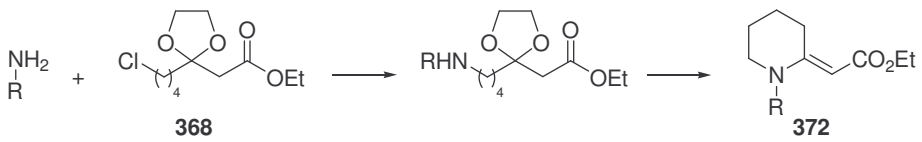


Scheme 7.5: *(i) $Cl(CH_2)_4COCH_2CO_2Et$ **[371]**, CH_2Cl_2, room temperature, 16 h, 100% or $Cl(CH_2)_4COCH_2CO_2Et$, THF, Δ, 16 h, 81%*

San-Fat was unsuccessful in forming any six membered ring systems. The initial condensation proceeded well in high yield, however the cyclisations inevitably yielded unreacted starting material. Reaction conditions used to attempt the cyclisation included the conversion of the chloro group into an iodo group by a Finkelstein reaction, followed by treatment with various bases such as potassium carbonate, sodium bicarbonate or sodium hydroxide[108k].

7.3 Approach B

The route we investigated was similar to the Carrié approach[197], however it involved a change in the timing of the reactions. We envisaged the alkylation of a primary amine with ethyl [2-(4-chlorobutyl)-1,3-dioxolan-2-yl]acetate **[368]**. Subsequent acetal removal and condensation should afford the piperidine system **[372]** (**Scheme 7.6**).

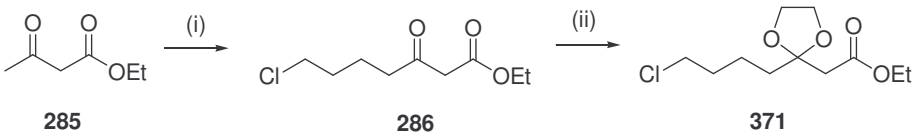


Scheme 7.6: *Alternative approach to access vinylogous urethanes*

The approach is particularly appealing since, as it stands, it would allow us to access the cyclised enaminone **[372]** from the primary amine in only two steps.

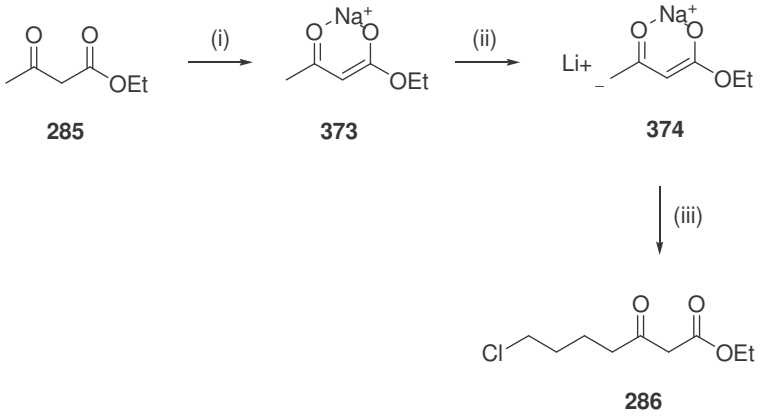
7.4 Preparation of ethyl [2-(4-chlorobutyl)-1,3-dioxolan-2-yl]acetate [371]

Ethyl [2-(4-chlorobutyl)-1,3-dioxolan-2-yl]acetate **[371]** is easily prepared in two steps from ethyl acetoacetate **[285]** (**Scheme 7.7**).[197] In the first step ethyl acetoacetate **[285]** was converted into a dianion by treatment with sodium hydride, followed by *n*-butyllithium. Subsequent treatment with 1-bromo-3-chloropropane afforded **[286]** in an 80% yield on a 32 mmol scale.



Scheme 7.7: *(i) (a) NaH, THF, 0 °C,* ***[285]****, 10 min (b) n-BuLi, THF, 0 °C, 10 min, (c) Cl(CH₂)₃Br, THF, –50 °C, (d) –15°C, 24 h, 80%; (ii) HO(CH₂)₂OH, p-TsOH, C₆H₆, Dean-Stark, 24 h, 83%*

Treatment of ethyl acetoacetate **[285]** with one equivalent of sodium hydride deprotonates the more acidic proton on the carbon α to both the carbonyl groups (**Scheme 7.8**, *Step i*). Subsequent treatment of the resulting anion **[373]** with *n*-butyllithium affords the desired dianion **[374]** (*Step ii*). Under kinetic conditions electrophilic substitution of 1-bromo-3-chloropropane occurs preferentially at the terminal carbon of the dianion as the coordinated sodium cation hinders attack at the more reactive site (*Step iii*).[197]



Scheme 7.8: *(i) NaH, THF, 0 °C,* ***[285]****, 10 min; (ii) n-BuLi, THF, 0 °C, 10 min; (iii) (a) Cl(CH₂)₃Br, THF, –50 °C (b) –15 °C, 24 h, 80%*

The ^{1}H NMR spectrum showed the presence of the chlorinated butyl chain by the presence of two triplets both integrating for two protons at 3.54 and 2.61 ppm as well as a multiplet at 1.85-1.70 ppm integrating for four protons. Interestingly, signals due to the stabilized enol form were clearly visible.

The acetal protection of **[286]** was achieved by refluxing in benzene in the presence of ethanediol and a catalytic amount of *para*-toluenesulfonic acid. The reaction vessel was fitted with a Dean-Stark apparatus for the azeotropic removal of water, thereby ensuring the reaction ran to completion and there was no competitive acetal removal occurring. The acetal-protected product **[371]** was obtained in an 83% yield on a 5.6 mmol scale.

The success of the reaction was shown by the appearance of a multiplet at 3.97-3.86 ppm in the ^{1}H NMR spectrum integrating for four protons due to the acetal CH_2 groups. The ^{13}C NMR spectrum also showed the loss of the characteristic ketone carbonyl signal at 206.5 ppm. The HRMS showed 206.07067 and $C_9H_{15}O_3Cl$ requires 206.07097.

7.5 Monoalkylation of primary amines

In order for our proposed reaction scheme to be successful we first had to contend with the problem of mono-alkylating a primary amine. Mono-alkylation of a primary amine is not trivial as alkylation increases the nucleophilic nature of the nitrogen, and as a result one tends to get a mixture of products, even if only one equivalent of the alkylating agent is used. We felt that the larger the primary amine, the more likely it would result in the preferential formation of the mono-alkylated product. We chose to use cyclohexanamine as our model amine. Before we attempted any alkylations we first needed to perform a Finkelstein reaction[135] on **[368]** to afford the iodo-analogue **[375]** as we felt direct substitution of the chlorine was unlikely to occur in good yield (**Scheme 7.9**).



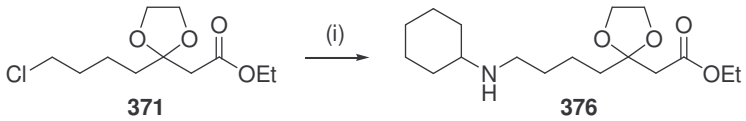
368 **375**

Scheme 7.9: *(i) NaI, CH_3CN, Δ, 3 h*

Refluxing **[371]** with sodium iodide in acetonitrile yielded the iodinated product as a brown oil. Analysis of the ^{1}H NMR spectrum of the crude product showed the substitution was successful as the triplet due to the CH_2Cl protons at 3.46 ppm in the starting material had

shifted to 3.19 ppm indicating conversion to a CH_2I group. The product decomposed rapidly, and was used crude in the next step.

Owing to the instability of the iodo adducts we decided to prepare the iodinated species *in situ* for use in the alkylation of various primary amines (**Scheme 7.10**).



371 **376**

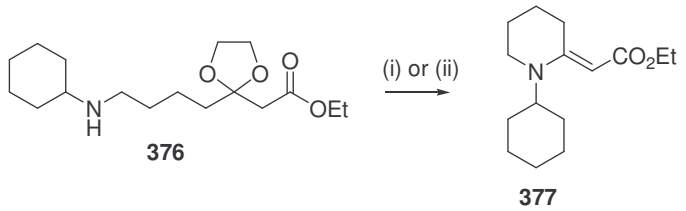
Scheme 7.10: *(i) (a) NaI, CH_3CN, Δ, 3h, (b) K_2CO_3, 4 Å molecular sieves, cyclohexanamine, Δ, 18 h, 75%*

Treatment of **[371]** with sodium iodide in refluxing acetonitrile for 3 hours, afforded the *in situ* iodo-species. Potassium carbonate and crushed 4 Å molecular sieves were added to the reaction mixture followed by one equivalent of cyclohexanamine. After refluxing for a further eighteen hours the reaction was worked up and after purification we isolated the mono-alkylated product **[376]** in 75% yield on a 2 mmol scale. The ^{1}H NMR spectrum showed the presence of the cyclohexylamine CH_2 protons as a doublet of triplets integrating for four protons at 2.24 ppm and two multiplets at 1.88-1.51 ppm and 1.32-1.23 ppm. The CH_2Cl triplet had shifted from 3.46 ppm in the chlorinated starting material to 3.53 ppm in the alkylated product indicating the formation of a NHC$\underline{H}_2$ group. The NH proton was observed as a multiplet at 3.36-3.28 ppm. Owing to rapid decomposition further characterization was not possible.

7.6 Alkylative cyclisation

Having successfully mono-alkylated cyclohexanamine, the next step involved the removal of the acetal protecting group and alkylative cyclisation to afford the piperidine enaminone **[377]**. We predicted that after the acetal removal the now secondary amine would immediately condense with the deprotected ketone, affording the desired enaminone **[377]**. We found that simply treating the alkylated products with acid was ineffective in removing the acetal group. The most promising results came from refluxing **[376]** with sodium iodide

and cerium trichloride heptahydrate for three hours[198], or by treating **[376]** with freshly distilled boron trifluoride etherate in dichloromethane at 0 °C overnight[199]. The desired cyclised product **[377]** was obtained in 10 and 49% yield respectively (**Scheme 7.11**).



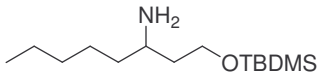
376 **377**

Scheme 7.11: *(i) NaI, $CeCl_3.7H_2O$, Δ, 3 h, 10%, (ii) $BF_3.OEt_2$, CH_2Cl_2, 0 °C, 24 h, 49%*

The ^{1}H NMR spectrum showed the presence of the characteristic vinyl proton as a singlet at 4.86 ppm integrating for one proton. Furthermore the multiplet at 3.97-3.86 ppm due to the acetal protons was gone. The ^{13}C NMR spectrum showed the vinyl carbons at 169.3 and 109.0 ppm. The HRMS shows 251.18870, with $C_{15}H_{25}NO_2$ requiring 251.18853.

7.7 Application of approach B to the preparation of quinolizidines

To test the approach for the preparation of quinolizidines we chose to prepare and use 1-{[*tert*-butyl(dimethyl)silyl]oxy}-3-octanamine **[378]** (**Figure 7.2**) which coincides with the work performed by San-Fat[108k].



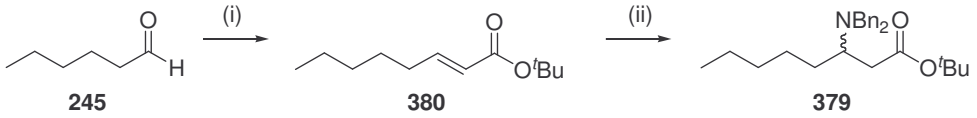
378

Figure 7.2: *1-{[tert-Butyl(dimethyl)silyl]oxy}-3-octanamine [378]*

We envisaged the preparation of 1-{[*tert*-butyl(dimethyl)silyl]oxy}-3-octanamine **[378]** from hexanal **[245]** and *tert*-butyl diethoxyphosphorylacetate **[246]** using the "Wits approach".

7.7.1 Wittig olefination and alkylative addition of dibenzylamine

The preparation of *tert*-butyl 3-(dibenzylamino)octanoate **[379]** was achieved in two steps from hexanal **[245]** and *tert*-butyl diethoxyphosphorylacetate **[246]** (**Scheme 7.12**)



245 **380** **379**

Scheme 7.12: *(i) $(EtO)_2POCH_2COC(CH_3)_3$ **[246]**, LiCl, DBU, CH_3CN, rt, 24 h, 89%; (ii) $NH(Bn)_2$, THF, –78 °C, 30 min, **[380]**, 3 h, 78%*

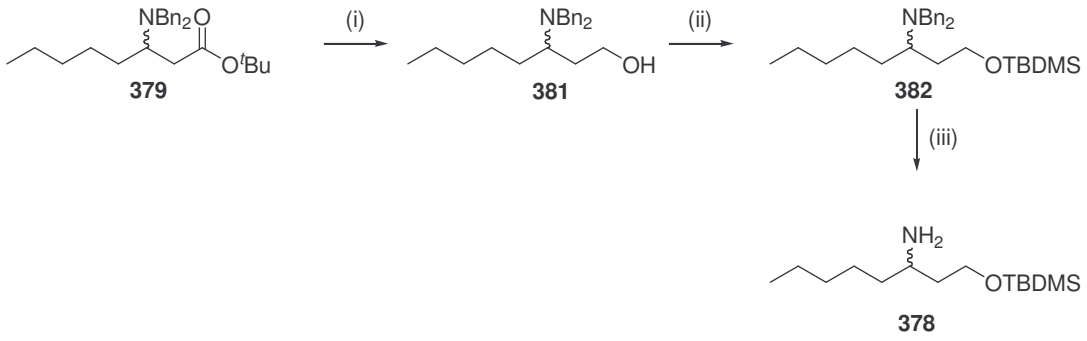
The Wittig olefination of hexanal **[245],** using the Horner-Wadsworth-Emmons protocol[170] afforded *tert*-butyl (2*E*)-2-octenoate **[380]** as a single isomer in 89% yield on a 29 mmol scale. The ^{1}H NMR spectrum showed the alkene protons as doublets of triplets intergrating for one proton each at 6.86 (*J* 7.0 & 15.5 Hz) and 5.73 ppm (*J* 1.4 & 14.9 Hz). The coupling constant of 15.2 Hz indicates an *E*-geometry. The ^{13}C NMR spectrum also showed the characteristic alkene carbon signals at 148.1 and 122.9 ppm.

Alkylation with freshly distilled dibenzylamine, according to the Davies protocol[124], yielded **[379]** in a 78% yield on a 23 mmol scale. As expected, the ^{1}H NMR spectrum showed the aromatic protons as a multiplet integrating for ten protons at 7.35-7.20 ppm, as well as the benzylic protons as doublets of doublets integrating for two protons each at 2.62 and 2.11 ppm respectively. The ^{13}C NMR spectrum also showed the presence of aromatic carbons in the 140.0-126.8 ppm region as well as the benzylic carbons at 55.3 ppm. The HRMS showed 395.28300 and $C_{26}H_{37}NO_2$ requires 395.28243.

7.7.2 Reduction of the *tert*-butyl ester, silylation and debenzylation.

The work outlined in **Section 5.7**, as well as that done by San-Fat[108k] suggests that reduction of the *tert*-butyl ester after the enaminone has been formed is not feasible. We decided at this stage to reduce the ester to the alcohol **[381]** and then protect it as the *tert*-butyldimethylsilyl ether **[382]** (**Scheme 7.13**). As this route dispenses with the need for the thionation step,

which is incompatible with the silyl ether (**Section 5.12**) we envisaged no problems with using the silyl protecting group.



Scheme 7.13: *(i) $LiAlH_4$, Et_2O, 0 °C, **[379]**, 3 h, 70%; (ii) Imidazole, TBDMSCl, DMF, rt, 24 h, 71%; (iii) H_2(g), 10% Pd/C, EtOH, 94%*

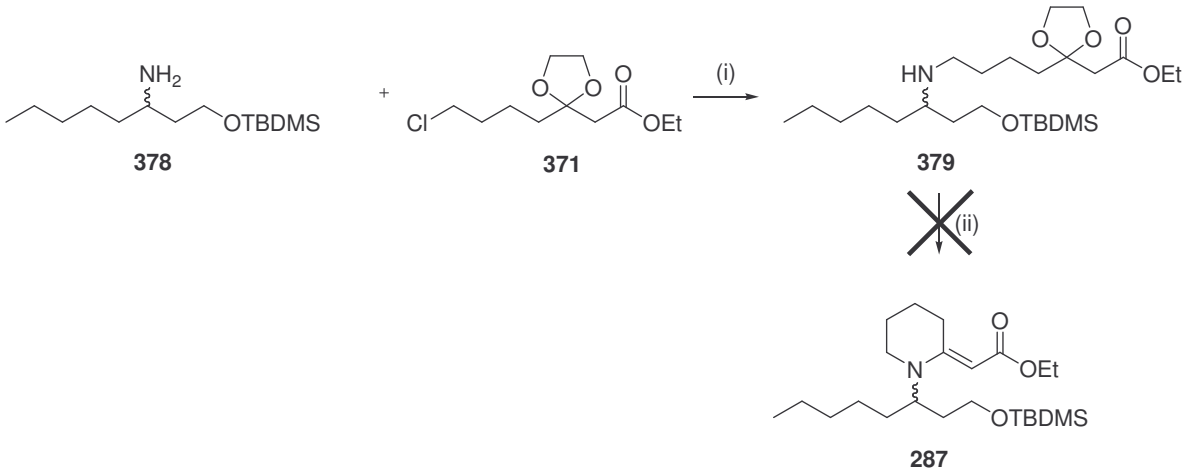
Reduction of the *tert*-butyl ester with lithium aluminium hydride in diethyl ether proceeded smoothly, affording alcohol **[381]** in a 70% yield after workup and purification on a 3.8 mmol scale. The ^{1}H NMR spectrum showed the loss of the *tert*-butyl protons at 1.42 ppm and the appearance of alcohol signal as a broad singlet at 4.60 ppm. The ^{13}C NMR spectrum also showed the loss of the characteristic *tert*-butyl carbon signals at 80.0 and 28.0 ppm. The HRMS spectrum found 325.24060 with $C_{26}H_{37}NO_2$ requiring 325.24056.

Subsequent silylation by treatment with imidazole and *tert*-butyldimethylsilyl chloride in dimethylformamide[183] afforded the silyl ether **[382]** in 71% yield on an 8.5 mmol scale. The silylation was shown to be successful by the appearance of the characteristic $Si(CH_3)_2$ and $C(CH_3)_3$ signals as singlets integrating for six and nine protons respectively at 0.85 and 0.08 ppm in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum also showed the characteristic signals for the $Si(CH_3)_2$ carbons at −5.27 ppm and the $C(CH_3)_3$ carbons at 26.0 and 18.3 ppm. The HRMS showed 439.32680 and M^+ for $C_{28}H_{45}NOSi$ requires 439.32704.

Finally the high pressure debenzylation, performed under hydrogenation conditions in absolute ethanol in the presence of 10% palladium on carbon,, afforded the desired amine **[378]** in 94% yield on a 6.0 mmol scale. The ^{1}H NMR spectrum showed the loss of the characteristic aromatic and benzylic protons.

7.7.3 Alkylative addition and cyclisation

Having prepared 1-{[*tert*-butyl(dimethyl)silyl]oxy}-3-octanamine **[378]**, we were now able to test the critical mono-alkylation, followed by the deprotection of the acetal and subsequent cyclisation to afford the desired cyclised enaminone **[287]** (**Scheme 7.14**).



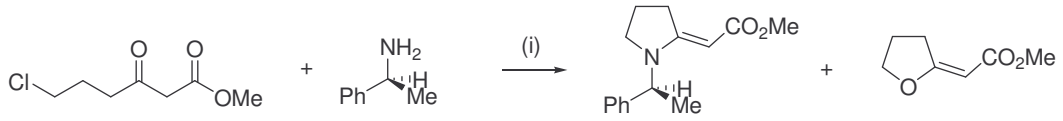
Scheme 7.14: *(i) NaI, K_2CO_3, Δ, 24 h, 73%; (ii) $BF_3.Et_2O$, CH_2Cl_2, 0 °C, 24 h, 0% or $CeCl_3.7H_2O$, NaI, Δ, 3 h, 0% or PPTs, H_2O, acetone, rt, 24 h, Δ, 24 h, 0% or AcOH, THF, H_2O, 40-45 °C, 24 h, 0% or $PdCl_2$, acetone, rt, 24 h, 0%*

Subjecting 1-{[*tert*-butyl(dimethyl)silyl]oxy}-3-octanamine **[378]** to the alkylative addition of **[371]** by treatment with potassium carbonate and sodium iodide as described above in **Section 7.5** proceeded smoothly, yielding the desired mono-alkylated amine **[379]** in a 73% yield on a 0.37 mmol scale. The mono-alkylated amine was extremely unstable and decomposed in less than an hour at room temperature.

The deprotection of the acetal and cyclisation was first attempted using the methods shown to be successful in **Section 7.6**. Treatment with boron trifluoride etherate[199] was unsuccessful with an unidentifiable product being isolated, which showed that the silyl protecting group had been removed. Treatment with acetic acid or cerium trichloride heptahydrate:sodium iodide[198] only afforded unreacted starting material in a 75% or 91% recovery. Cyclisation using *para*-toluenesulfonic acid gave an unidentifiable product and finally a palladium

mediated cyclisation using palladium chloride in acetone[200] afforded starting material in a 68% recovery.

During the course of the above mentioned investigations we came across a report by Lhommet and co-workers.[201] in which they described the preparation of chiral pyrrolidine and piperidine β-enamino esters starting from ω-halo β-keto esters. Preparation of pyrrolidine enamino ester **[380]** was trivial through the reaction of 6-chloro-3-oxohexanoate **[381]** with (*S*)-1-phenylethylamine **[382]** in the presence of iodine, sodium sulfate and disodium hydrogen phosphate in accordance with a previously reported procedure[108b, 109a, 197] (**Scheme 7.15**).

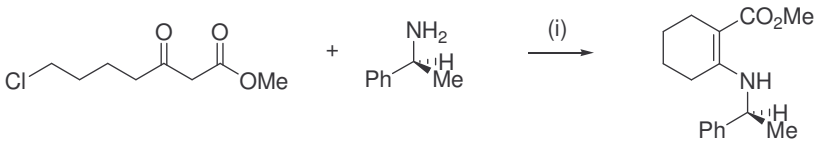


381 **382** **380** **383**

Scheme 7.15: *(i) Na_2HPO_4, Na_2SO_4, I_2, 60% **[380]**, ~10% [383]*

The desired compound **[380]** was obtained in 60% yield, along with about 10% of the tetrahydrofuranyl derivative **[383]** resulting from the *O*-cycloalkylation of **[381]**.

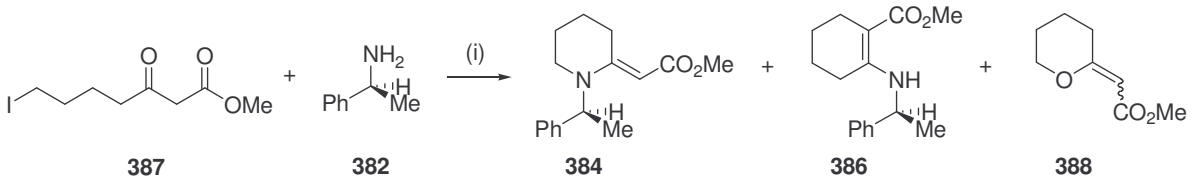
Lhommet found, by contrast that the application of this methodology for the preparation of piperidine enamino ester **[384]** was not straightforward. The use of 7-chloro-3-oxoheptanoate **[385]** to access **[384]** under the same conditions afforded a quantitative recovery of product **[386]** (**Scheme 7.16**).



385 **382** **386**

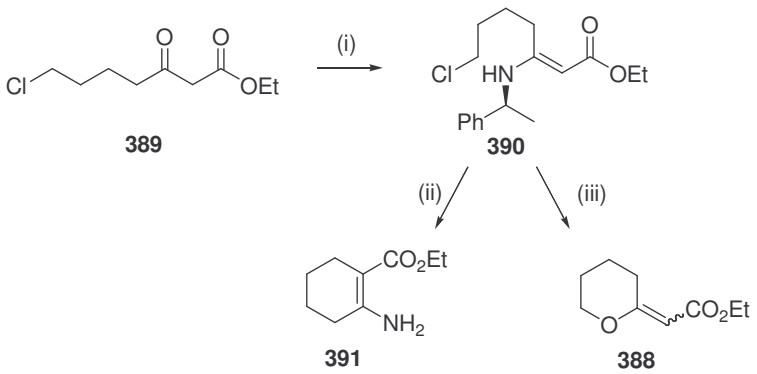
Scheme 7.16: *(i) Na_2HPO_4, Na_2SO_4, I_2, 100%*

It seems that when forming the five-membered ring the initial substitution of the halogen by the amine is favoured, whereas when forming the six-membered ring the amine preferentially reacts with the keto moiety. Lhommet and co-workers found that by converting the chloro group in **[385]** to an iodo **[387]** they obtained a mixture of the desired piperidine enamino ester **[384]** together with the cyclohexene derivative **[386]** and the tetrahydropyranyl derivative **[388]** in a 25:55:20 ratio (**Scheme 7.17**)[201].



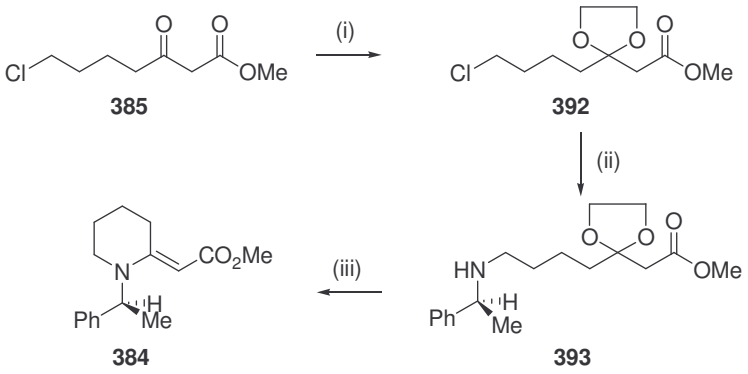
Scheme 7.17: *(i) Na_2HPO_4, Na_2SO_4, I_2, 25% **[384]**, 55% **[386]**, 20% **[388]***

The above results were observed in our own laboratories when San-Fat attempted to use this approach to access an analogous piperidine enamino ester.[108k] San-Fat found that treatment of (1*S*)-1-phenylethylamine and 7-chloro-3-oxoheptanoate **[389]** in dichloromethane afforded C-alkylated product **[390]** which was isolated in quantitative yield. Treatment of **[390]** with potassium hexamethyldisilazide in dry tetrahydrofuran yielded the debenzylated cyclohexene by-product **[391]**, whereas refluxing with sodium iodide in super dry acetone afforded the tetrahydropyranyl derivative **[383]** (**Scheme 7.18**).[108k]



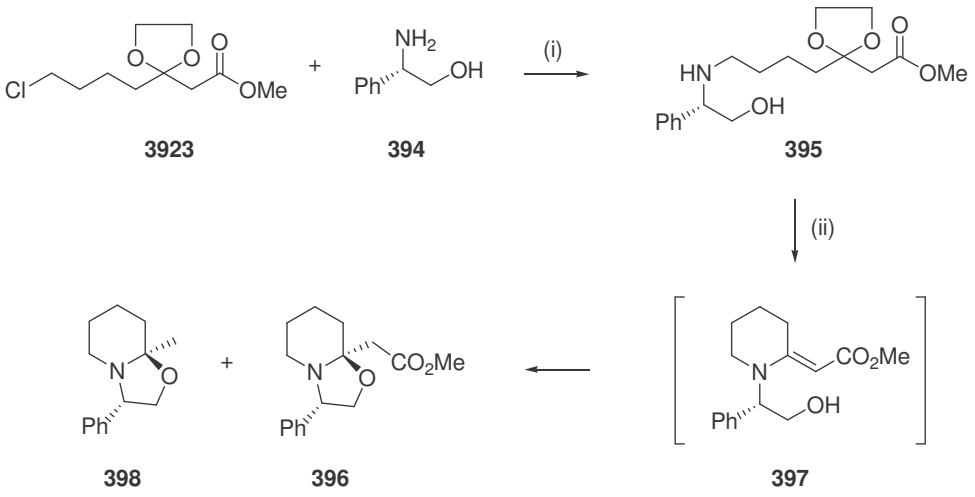
Scheme 7.18: *(i) CH_2Cl_2, (1S)-1-phenylethyl amine, rt, 16 h, 100%, (ii) KHMDS, THF, –78 °C, 100 min, 27%, (iii) NaI, acetone, Δ, 16 h, 89%*

In light of the above results Lhommet and co-workers.[201] decided to protect the keto functionality of **[385]** in the same manner as we have described above in **Sections 7.3** and **7.4**. They found that substitution occurred readily at the halogen by refluxing dioxolane **[392]** with sodium carbonate, *tetra*-butylammonium iodide and sodium iodide, affording mono-alkylated amine **[393]** in a 97% crude yield. Deprotection and spontaneous cyclisation was achieved by treatment with boron trifluoride etherate in dichloromethane yielding **[384]** in 74% yield (**Scheme 7.19**).



Scheme 7.19: *(i) $HO(CH_2)_2OH$, $HC(OMe)_3$, cat. p-TsOH, 82% (ii) Na_2CO_3, TBAI, NaI, **[382]** (97% crude), (iii) $BF_3.Et_2O$, CH_2Cl_2, 74%*

The results reported by Lhommet *et al.*[201] confirm that the protocol can be used for the preparation of both pyrrolidine and piperidine β-enamino esters. The use of boron trifluoride etherate to deprotect acetal groups[199] has however been the downfall in our particular case as it is incompatible with the silyl ether protecting group which was used to circumvent the problems associated with reducting the *tert*-butyl ester late in the synthesis (**Section 5.7**). In fact Lhommet *et al.*[201] found that when their protocol was applied to (*S*)-phenylglycinol **[394]**, compound **[395]** formed in 95% crude yield, but the deprotection-cyclisation step afforded bicyclic derivative **[396]** as a mixture of diastereomers in 67% yield instead of the desired **[397]** (**Scheme7.20**). In addition the formation of the decarboxylation product **[398]** was also observed.



Scheme 7.20: *(i) Na_2CO_3, TBAI, NaI, 95% crude (ii) $BF_3.Et_2O$, CH_2Cl_2, 67%*

7.8 Conclusion

In our case the boron trifluoride etherate in addition to deprotecting the acetal is a source of F^-, and as a result readily removes the silyl ether, exposing the hydroxyl group. We propose that the reaction then follows the same path as shown above in **Scheme 7.20** affording a mixture of bicyclic compounds. In order to use this route we would therefore have to remove the silyl ether and reprotect the resulting hydroxy group. As a result this route does not negate any of the deprotections and reprotections that San-Fat had to be content with during her synthesis of 1,4-disubstituted quinolizidines, and unfortunately does not offer a shorter alternative to the route described by San-Fat[108k]. The approach described for the preparation of pyrrolidine β-enamino esters, may however still afford a significantly shorter route to 5,8-disubstituted indolizidines incorporating the "Wits approach" described in detail in **Chapters 2-6**. This approach is outlined in detail as part of the future work in **Section 8.2** of this thesis.

CHAPTER 8

SUMMARY, CONCLUSION AND FUTURE WORK



CHAPTER 8

SUMMARY, CONCLUSIONS AND FUTURE WORK

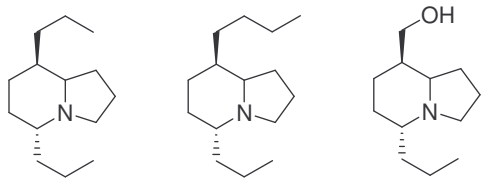
8.1 Summary and conclusions

The aims of this project were discussed in **Section 2.8**. The main aims will be discussed in turn, thereby giving an idea of the success of the project.

- *To extend the synthetic utility of enaminones in alkaloid synthesis, in particular by looking at the advantages offered by the incorporation of a Weinreb amide into the enaminone functionality.*

As highlighted in **Chapters 3, 4** and **5**, the ambident nucleophilicity and electrophilicity of enaminones was useful in the construction of piperidine, 5-monosubstituted and 5,8-disubstituted indolizidines. The incorporation of the Weinreb amide functionality into the enaminone backbone gave us a handle to introduce various substituents at the 8-position of the 5,8-disubstituted indolizidines, through its unique ability to undergo mono-alkylations in the presence of excess Grignard reagents. In addition, the Weinreb amide was compatible with all of the key functional group conversions necessary for the synthesis of both 5-monosubstituted and 5,8-disubstituted indolizidines, such as sulfide contractions, alkylative cyclisations and catalytic hydrogenations.

- *To use and expand on the methodology established by Gravestock for the enantioselective synthesis of 5,8-disubstituted indolizidines, for the synthesis of indolizidines **197C [258], 209I [185]** and **223V [174]**.*

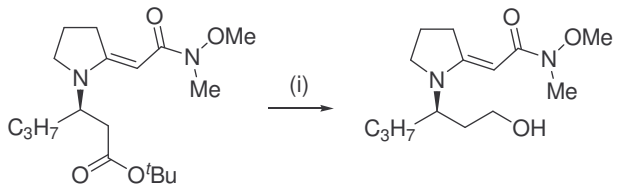


185 **174** **258**

209I **223V** **197C**

Figure 8.1: *Indolizidines **209I [185], 223V [174]** and **197C [258]***

Initial attempts to use Gravestock's methodology[100] to prepare vinylogous urethanes incorporating the Weinreb amide functionality were successful. Unfortunately, the reduction of the *tert*-butyl ester to form alcohol **[273]** was problematic and low yielding (**Scheme 8.1** and **Section 5.7**), and an alternative approach following the work done by San-Fat had to be employed (**Section 5.8**).

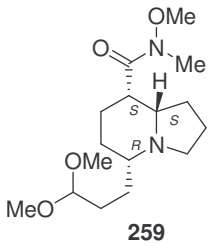


272 **273**

Scheme 8.1: *(i) $LiAlH_4$, THF, 0 °C – rt, 24 h, 11%*

The successful formal enantioselective synthesis of indolizidines (–)-**209I [185]** and progress made towards the preparation of indolizidine **223V [174],** further demonstrated how the use of the Weinreb amide functionality could extend the known methodology to include the preparation of indolizidines with a variety of substituents at the 8-position. In addition, several of the protocols described by Gravestock were improved, including the two-step lactam formation which is now high yielding and does not suffer from competing elimination reactions. Thionation of the resulting lactam **[349]**, using the more cost effective Brillon protocol[128], was also shown to be higher yielding and easier to purify than when performed with the more expensive, yet traditionally used, Lawesson's reagent[178-180]. Time constraints of the project prevented us from completing the synthesis of indolizidine **197C [258]** and **223V [174]**, however, based on the evidence from the formal preparation of (–)-**209I [185]** we do not envisage any complications in preparing these alkaloids in the future.

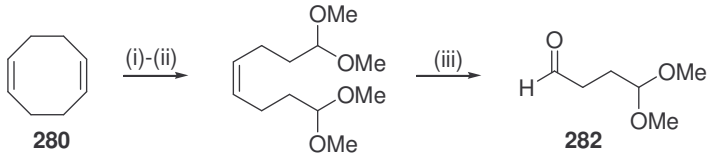
- *To synthesize a late stage common intermediate **[259]**, that would allow us access to most naturally occurring 5,8-disubstituted indolizidines.*



259

Figure 8.2: *The late stage common intermediate **[259]***

Although the preparation of a late stage intermediate **[259]** was not completed, a great deal of the methodological groundwork has been done, paving the way for the future preparation of **[259]**. Key aspects include the preparation of a monoacetylated aldehyde **[282]** from cyclooctadiene **[276]** (**Scheme 8.2**), and the modification of the debenzylation and the lactam formation steps to prevent the loss of the acetyl protecting group under acidic conditions.

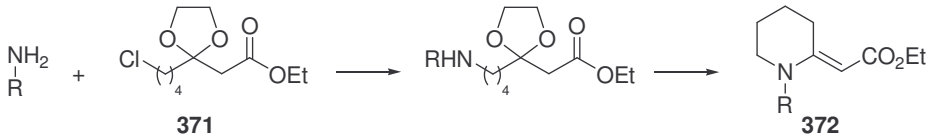


280 **281** **282**

Scheme 8.2: *(i) (a) O_3, CH_2Cl_2: MeOH, –60°C, (b) p-TsOH, rt, 1 h, (c) Me_2S, H^+, rt, 24 h, 65 %; (iii) (a) O_3, CH_2Cl_2, –60°C, (b) Me_2S 0% or PPh_3, 47%.*

- *To investigate an alternative approach for the synthesis of 1,4-disubstituted quinolizidines.*

Investigations into an alternative approach towards the preparation of the structurally related 1,4-disubstituted quinolizidines, negating the need for the reduction of a *tert*-butyl ester group late in the synthesis were undertaken. The proposed route involved the mono-alkylation of a primary amine with ethyl [2-(4-chlorobutyl)-1,3-dioxolan-2-yl]acetate **[371]**, followed by acetal removal and condensation to afford a piperidine system (**Scheme 8.3**).



Scheme 8.3: *Proposed route to access vinylogous urethanes*

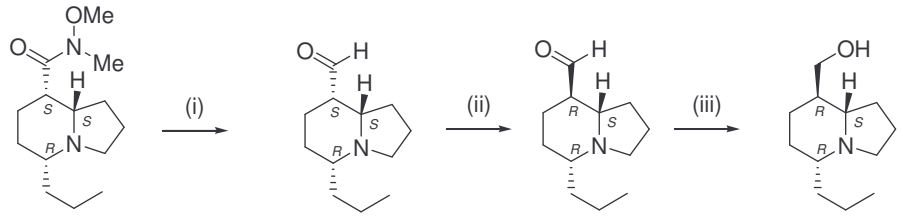
We were able to demonstrate the successful mono-alkylation of primary amines with **[371]**, but we only had limited success removing the acetal group and cyclising to access the desired piperidine skeletons. A literature review suggests that while the preparation of pyrrolidines using this method is feasible, the corresponding preparation of piperidines is marred by low yields and side reactions.

As can be seen from the summary above, many of the key aims of the project were met the most notably of which was the enantioselective preparation of indolizidine (−)-**209I [185]**. The important contributions made by this project include the successful establishment of methodology for the preparation of vinylogous urethanes incorporating the Weinreb amide functionality, and the utilization of this methodology for the enantioselective synthesis of 5,8-disubstituted indolizidines, and the use of the Weinreb amide's unique reactivity to introduce a variety of substituents at the 8-position.

8.2 Future work

8.2.1 Proposed synthetic route for the synthesis of 197C [258]

Indolizidine **197C [258]** was originally identified as one of the synthetic targets during the course of this project. Unfortunately owing to time constraints and lack of material we were never able to synthesise it. Given below is the proposed synthetic route that we had outlined to access **197C [258]** starting from Weinreb amide **[275]** (**Scheme 8.1**)



275 **399** **400** **258** **197C**

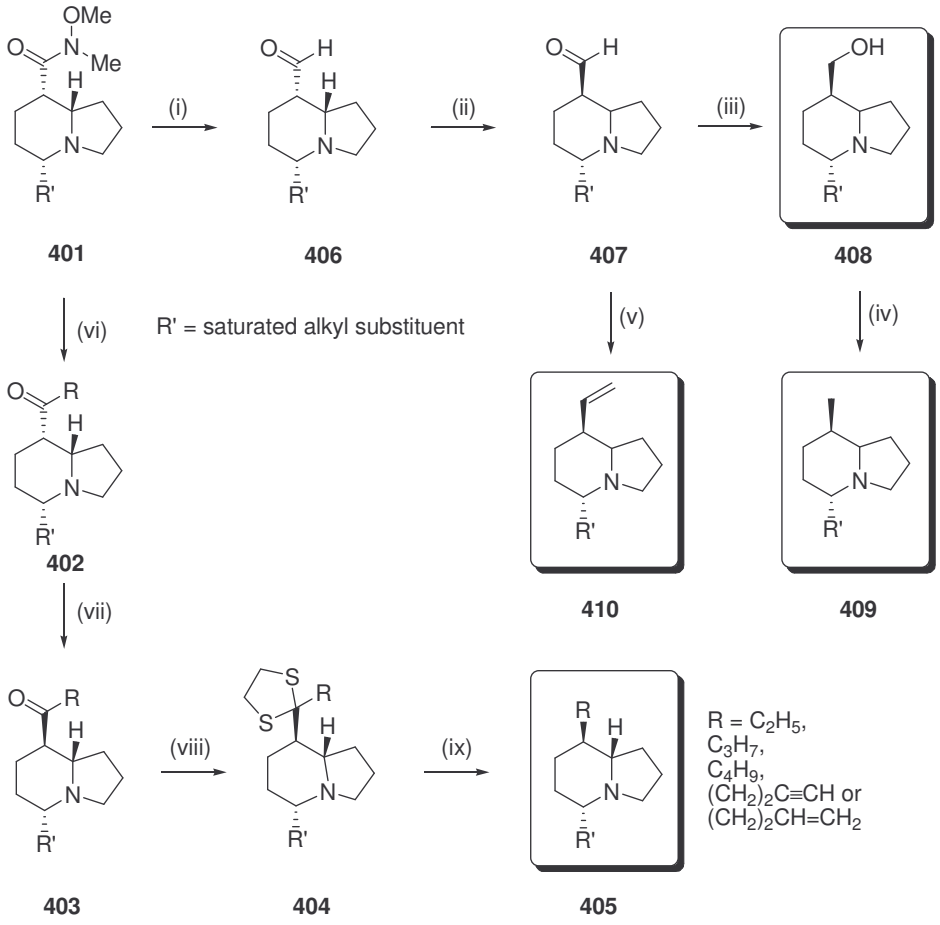
Scheme 8.1: *(i) $LiAlH_4$, THF, 0°C; (ii) Na, MeOH, Δ; (iii) $LiAlH_4$, THF, 0 °C*

Indolizidine **197C [258]** is unique in our target molecules as it has a $–CH_2OH$ substituent as opposed to a simple alkyl substituent at the 8-position. Weinreb amides can be readily reduced to their corresponding aldehydes when treated with lithium aluminium hydride. Accessing the aldehyde **[399]** would afford us the opportunity of epimerizing at the 8-position to the stereochemistry found in the natural product **[400]**. Finally, reduction of the epimerized aldehyde would afford indolizidine **197C [258]**.

8.2.2. Introduction of different groups at the 5-position

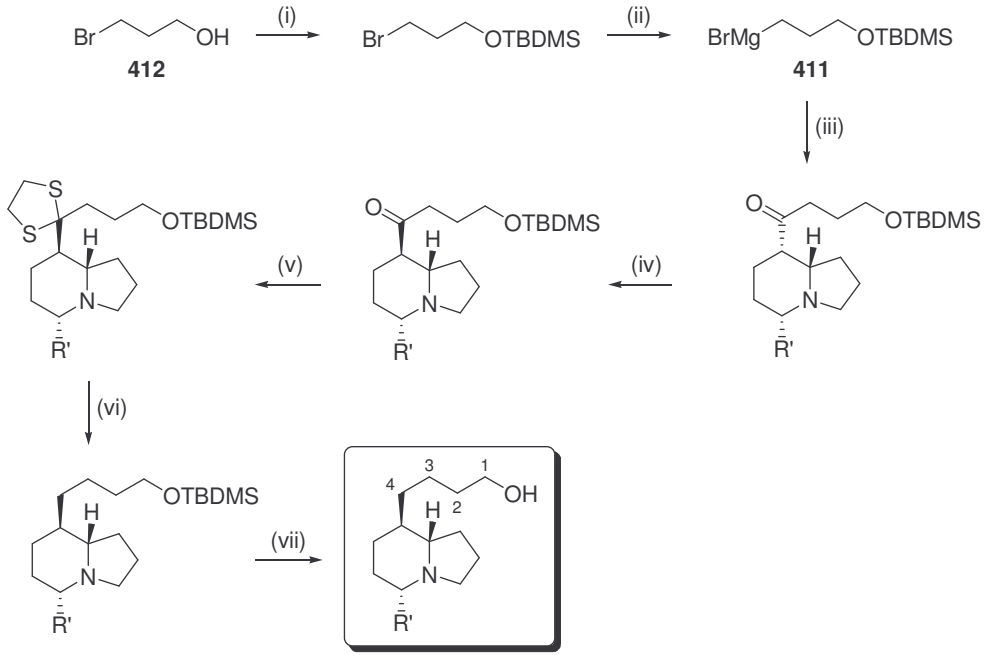
The successful enantioselective synthesis of indolizidine (−)-**209I [185]** has established the methodology required for the future enantioselective synthesis of known 5,8-disubstituted indolizidines. The results obtained during the course of this project suggest that we should be able to adapt this methodology for the preparation of indolizidines with any unbranched saturated or unsaturated substituents, with or without oxygen functionalities at the 8-position that have currently been identified in natural products. Unfortunately, we are limited to the preparation of indolizidines with a saturated alkyl substituent at the 5-position. Nevertheless this methodology should allow us to access 25 of the 78 5,8-disubstituted indolizidines described in Daly's review of amphibian alkaloids published in 2005.[5] Highlighted below in **Scheme 8.2** is our proposed synthetic route to access these various substituents. The substituents that have been identified in natural products are shown in blocks.

In accordance with the protocol outlined in **Sections 5.17.1-5.17.3**, Weinreb amide **[401]** can be alkylated with a suitable Grignard or organo-lithium reagent affording **[402]**. Epimerisation to **[403]**, and two-step carbonyl defunctionalisation via **[404]** should afford the desired indolizidines **[405]** with either saturated or unsaturated substituents at the 8-position. Reduction of the Weinreb amide **[401]** to the corresponding aldehyde **[406]**, followed by epimerization to **[407]** and reduction should allow access to **[408]** with a CH_2OH group at the 8-position, which in turn can be defunctionalised, affording the commonly seen methyl substituent **[409]**. Another substituent that is seen in natural products is a vinyl fragment at the 8-position **[410]**; accessing this should be possibly by simple Wittig olefination of epimerized aldehyde **[407]**.



Scheme 8.2: *(i) $LiAlH_4$, Et_2O, (ii) Na, MeOH, Δ, (iii) $LiAlH_4$, Et_2O, (iv) (a) MsCl, NEt_3, CH_2Cl_2 (b) Raney Nickel, i-PrOH, (v) $Ph_3P^+CH_3\ Br^-$, n-BuLi, (vi) RMgBr or RLi, THF, (vii) Na, MeOH, Δ, (viii) $HS(CH_2)_2SH$, BF_3OEt, (ix) Raney Nickel, i-PrOH*

A further four indolizidines contain saturated alkyl substituents at the 5-position with an alcohol functionality. Unfortunately in all four cases the position of the alcohol group has not been established. Assuming that a terminal alcohol group is the most likely arrangement we can also access these systems by preparing Grignard reagent **[411]** from 3-bromopropanol **[412]** (**Scheme 8.3**).



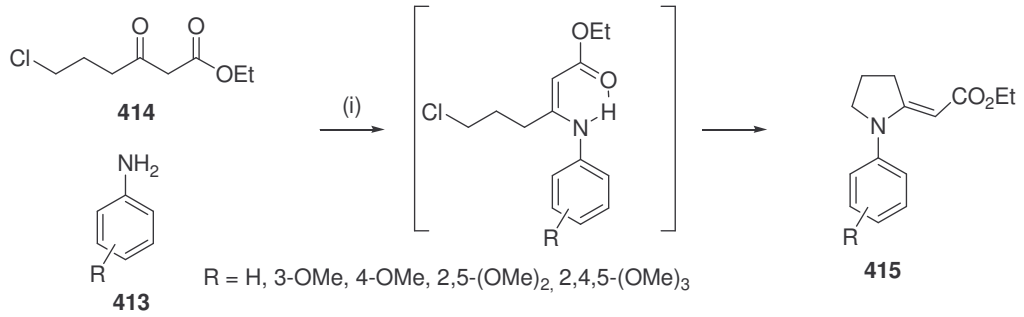
Scheme 8.3: *(i) TBDMSCl, imidazole, DMF, (ii) Mg, THF, (iii)* ***[401]****, THF, (iv) Na, MeOH, Δ, (v) $HS(CH_2)_2SH$, BF_3OEt, (vi) Raney Nickel, i-PrOH, (vii) HF, MeOH*

If successful, comparison of data with those recorded on the natural products may help to establish if these alcohol groups are terminal in nature, if not it is still possible repeat the synthesis giving the alcohol functionality at the 2 or 3 positions as indicated in **Scheme 8.2** by treatment with a suitably substituted Grignard reagent. Finally, to access the indolizidine with the alcohol at the 4-position would simple require the condensation of the Weinreb amide with propylmagnesium bromide, followed by reduction of the resulting ketone with lithium aluminium hydride to access the required alcohol.

The only substituent not accounted for in the above proposed synthetic routes is a $C_4H_9O_2$ chain with two alcohol groups. However, one could imagine preparing this sort of system in an analogous manner to the ones prepared in **Scheme 8.3**. It simply requires the preparation of an appropriate Grignard reagent with two protected alcohols, and repeating the synthesis until the correct substitution pattern is obtained.

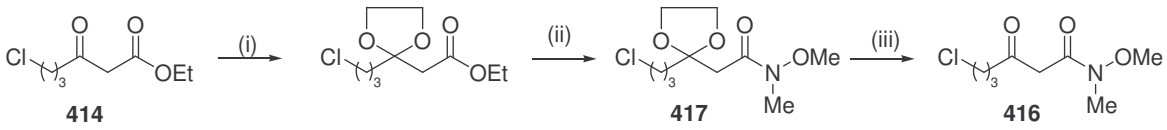
8.2.3 A more streamlined approach towards 5,8-disubstituted indolizidines

A possible shorter synthetic route that can be investigated is analogous to that used by Michael[108b] and Hosken[109a] adapted from the work of Carrié[197]. In their investigations they reacted various anilines **[413]** with ethyl 6-chloro-3-oxohexanoate **[414]** to produce a number of *N*-aryl vinylogous urethanes **[415]** as shown in **Scheme 8.4**.



Scheme 8.4: *(i) Na_2SO_4, Na_2HPO_4, I_2 (cat.)*

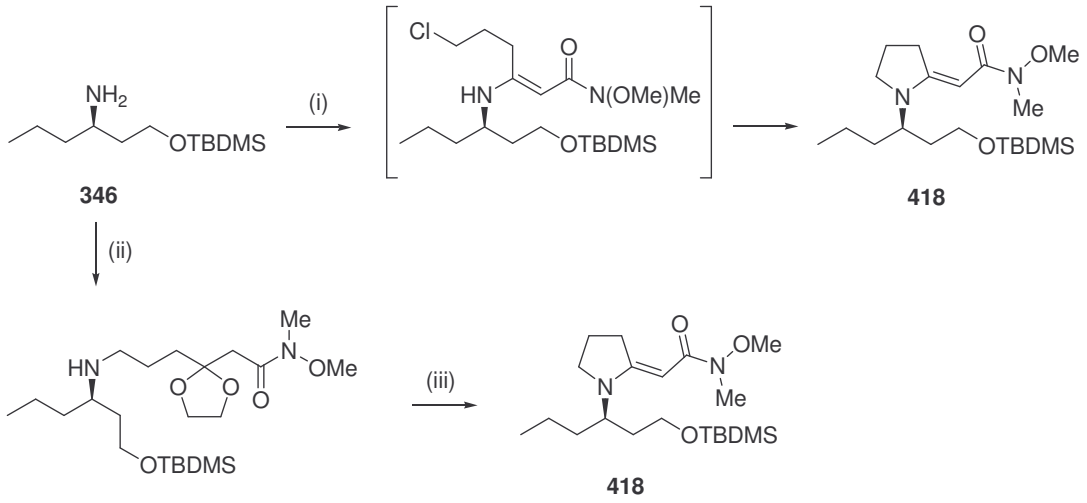
We feel that it may be possible to convert ethyl 6-chloro-oxohexanoate **[414]**, whose preparation is well established, into the analogous Weinreb amide **[416]** in three steps as shown below in **Scheme 8.5**.



Scheme 8.5: *(i) $HO(CH_2)_2OH$, p-TsOH, C_6H_6, (ii) Me(NH)(O)Me.HCl, $AlMe_3$ or Me(NH)(O)Me.HCl, $AlMe_2Cl$ or Me(NH)(O)Me.HCl, [Me(MeO)N-MgCl], (iii) H^+, MeOH*

Acetal protection of ethyl 6-chloro-oxohexanoate **[414]** followed by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of either trimethylaluminium or chloro(dimethyl)aluminium should afford the Weinreb amide **[417]**. Finally deprotection of **[417]** should afford the required 6-chloro-*N*-methoxy-*N*-methyl-3-oxohexanamide **[416]**.

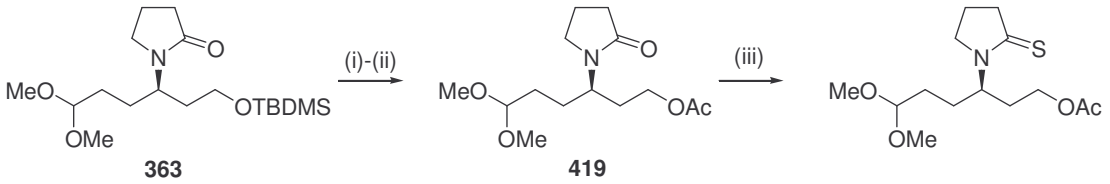
6-Chloro-*N*-methoxy-*N*-methyl-3-oxohexanamide **[416]** when treated with amine **[346]** should undergo a spontaneous condensation and cyclisation to give vinylogous urea **[418]** (**Scheme 8.6**). Alternatively, amine **[346]** could be mono-alkylated with **[417]**, and once the acetal group is removed, the system should cyclise to give **[418]**. Although we showed that this second route was not feasible for the preparation of piperidine systems, literature precedent suggests the pyrrolidine systems are likely to be formed in good yields.



Scheme 8.6: *(i)* ***[416]****, Na_2SO_4, Na_2HPO_4, I_2 (cat.), CH_2Cl_2, (ii)* ***[417]****, NaI, K_2CO_3, TBAI, Δ, (iii) NaI, $CeCl_3.7H_2O$ or $BF_3.OEt$*

The successful application of this route would cut the number of synthetic steps from twenty to eleven, and the use of boron trifluride etherate in *step iii* may also facilitate the cyclisation and the removal of the silyl protecting group all in on step, cutting the number of synthetic steps down to ten.

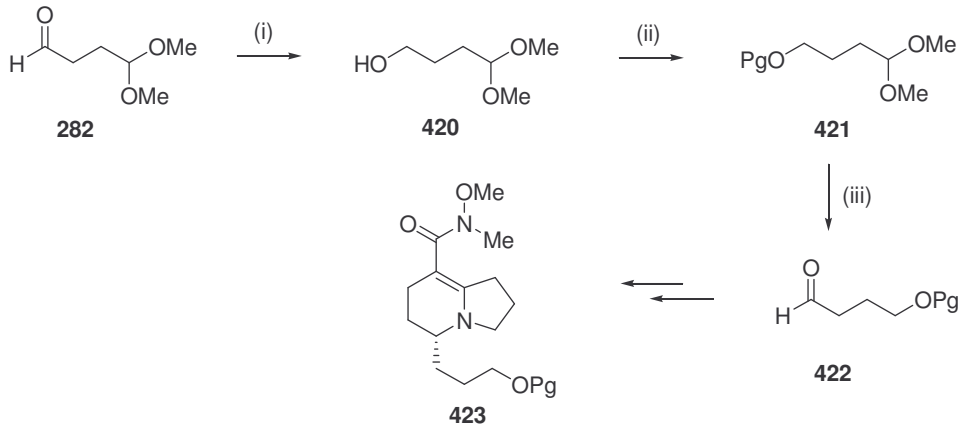
As highlighted in **Chapter 6** the preparation of a late stage common intermediate **[259]** with an acetal protected aldehyde in the 5-position the synthesis was marred by low yields and was incompatible with the thionation step. As discussed in **Section 6.9** conversion of the *tert*-butyldimethylsilyl ether **[363]** to an acetate **[419]** may free up the steric hindrance in the system enough to allow the thionation to occur (**Scheme 8.7**).



363 419

Scheme 8.7: *(i) TBAF, THF; (ii) Ac_2O, Py; (iii) P_2S_5, Na_2CO_3, or Lawesson's reagent, $PhCH_3$, Δ*

The difficulties experienced with this route are probably a combination of both steric hindrance and acetal lability, and as a result may require the use of a more robust protecting group. A possible alternative is to have a protected alcohol instead of a protected aldehyde, which can be deprotected and oxidized to the required aldehyde when one needs to functionalise the chain in the 8-position. Starting with monoacetalized dialdehyde **[282]**, the preparation of which was shown in **Section 6.2**, treatment with lithium aluminium hydride should give alcohol **[420]**, which can be protected, yielding **[421]** (**Scheme 8.8**). Acetal removal will afford aldehyde **[422]**, and following the general protocol outlines in **Section 6.2** intermediate **[423]** can be accessed in several steps. When required the alcohol can be deprotected and oxidized to the aldehyde.

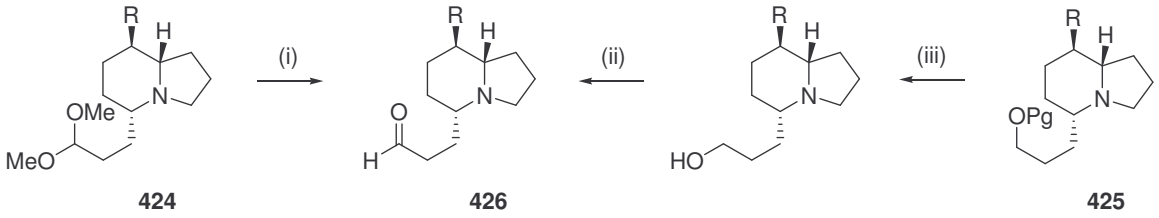


282 420 421 422 423

Scheme 8.8: *(i) $LiAlH_4$, THF, (ii) protecting group addition, (iii) H^+*

The most feasible way of accessing different substituents at both the 5- and 8-positions would be to first functionalize the 5-position as described above and shown in **Scheme 8.2.3** affording intermediate **[424]** or **[425]**. In the case of **[424]** simple acetal removal will afford

the required aldehyde **[426]**. If using the protected alcohol **[425]**, deprotection followed by oxidation should give **[426]** (**Scheme 8.9**).

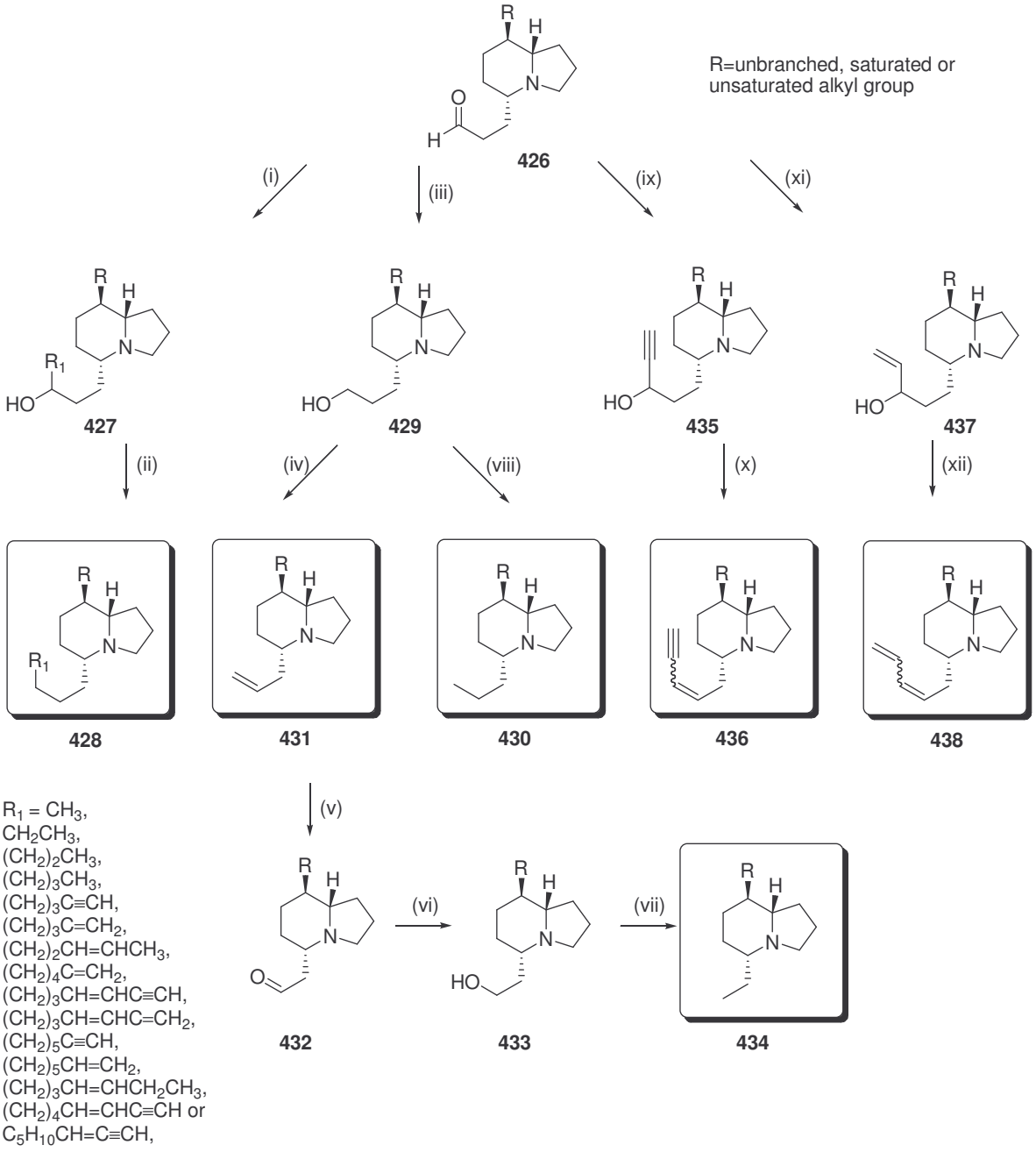


Scheme 8.9: *(i) H^+, H_2O, (ii) protecting group removal, (iii) PCC*

8.2.4 Introduction of different groups at the 8-position

Having accessed **[426]** a large variety of the substituents currently identified in natural products can be accessed in a few steps. Highlighted below in **Scheme 8.10** is our proposed synthetic route to access these various substituents. Once again the substituents that have been identified in natural products are shown in blocks.

Saturated and unsaturated alkyl substituents possessing four or more carbon atoms can be accessed by treatment of **[426]** with a suitable Grignard or organo-lithium reagent, giving alcohol **[427]**. Removal of the alcohol functionality by converting it into the corresponding mesylate and exposing it to Raney nickel will afford indolizidine **[428]**. To access a three-carbon saturated alkyl chain all that is required is to reduce aldehyde **[426]** to the corresponding alcohol **[429]** which can be defunctionalised to give indolizidine **[430]**. Access to a two carbon saturated alkyl substituent is also possible through alcohol **[429]**, which when dehydrated gives alkene **[431]**. Subsequent ozonolysis gives aldehyde **[432]** and reduction of the aldehyde gives alcohol **[433]**. The resulting alcohol group can be removed as described above, affording indolizidine **[434]**. Treatment of aldehyde **[426]** with acetylene in the presence of sodamide in liquid ammonia will afford alcohol **[435]**, which can be dehydrated to give indolizidine **[436]**. Finally, treatment of **[426]** with vinylmagnesium bromide will give alcohol **[437],** as described previously, dehydration will yield indolizidine **[438]** with a conjugated substituent at the 5-position.



Scheme 8.10: *(i) R-MgBr, THF or R-Li, THF; (ii) (a) MsCl, CH_2Cl_2, (b) Raney Nickel, i-PrOH; (iii) $LiAlH_4$, THF; (iv) $SOCl_2$, Py; (v) (a) O_3, CH_2Cl_2, (b) Me_2S, CH_2Cl_2; (vi) $LiAlH_4$, THF; (vii) (a) MsCl, CH_2Cl_2; (b) Raney Nickel, i-PrOH; (viii) (a) MsCl, CH_2Cl_2 (b) Raney Nickel, i-PrOH; (ix) HC≡CH, $NaNH_2$, NH_3(l); (x) $SOCl_2$, Py; (xi) H_2C=CHMgBr, THF; (xii) $SOCl_2$, Py*

In conclusion, it has been shown that using the methodology developed in this project it is possible to access a variety of 5,8-disubstituted indolizidines. In conjunction with the proposed future work we have laid the ground work for the development of a true general approach which can be used to access almost any 5,8-disubstituted indolizidines that have already been identified in nature. The synthesis of these compounds will allow us to confirm the structures and absolute stereochemistries of these alkaloids, many of which have only been given tentative structural assignments.

CHAPTER 9

EXPERIMENTAL

GENERAL DETAILS



CHAPTER 9

EXPERIMENTAL
GENERAL DETAILS

9.1 Purification of solvents and reagents

All reagents used for reactions and preparative chromatography were distilled. Solvents used in reactions were pre-dried in their reagent bottles and then distilled over the appropriate drying mediums under a nitrogen atmosphere.

- Tetrahydrofuran and diethyl ether were pre-dried over sodium wire, and distilled from sodium metal wire and benzophenone.
- Toluene and benzene was pre-dried over sodium wire, and distilled from sodium metal.
- Acetonitrile, dichloromethane, methanol and *tert*-butanol were distilled from calcium hydride.
- Triethylamine was distilled from, and stored over potassium hydroxide.
- *N*,*N*-dimethylformamide was distilled from, and stored over 4 Å molecular sieves.
- Pyridine was distilled from a 1:1 mixture of potassium hydroxide and 4 Å molecular sieves, and stored over potassium hydroxide.
- Acetic anhydride was distilled, and stored over 4 Å molecular sieves.
- Triethyl phosphate was dried over sodium metal overnight and distilled from sodium immediately prior to use.
- Absolute ethanol was used without further purification.

Chloroform was dried by passing it through a column of alumina (Merck aluminium oxide; basic; grade activity I). Potassium *tert*-butoxide was resublimed under vacuum immediately prior to use. Anhydrous lithium chloride was obtained after drying under reduced pressure (1 mmHg) at 140 °C for 24 hours. Tosyl chloride was purified according to Perrin[202] before use and stored in a dessicator until required. It was purified by dissolving (~10 g) in the minimum volume of dichloromethane (~25 cm^3), filtered, and diluted with hexane (5 × 25 cm^3) to precipitate the impurities. The solution was then filtered and concentrated *in vacuo* to 40 cm^3.

White crystals precipitated on standing (*m.p.* was in agreement with the literature value of 67-69 °C). Toluene sulfonic acid was recrystallised from concentrated hydrochloric acid.

9.2 Experimental techniques

All reactions were performed under an inert atmosphere (either nitrogen or argon) using a standard manifold line connected to a vacuum pump. The nitrogen and argon were dehydrated by bubbling the gas through sulfuric acid, and then neutralizing by passing through sodium hydroxide pellets. The vessels were oven dried, then flame dried while under vacuum and were allowed to cool to room temperature under the inert atmosphere.

The microwave reactor used is the CEM Discovery, and operating conditions employed are outlined in the experimental procedures.

9.3 Chromatographic separations

The R_f values quoted are for thin layer chromatography (TLC) on aluminium-backed Macherey-Nagel ALUGRAMSil G/UV_{254} plates pre-coated with 0.25 mm silica gel 60 or Aldrich TLC plates, silica gel on aluminium. Spray reagents were used on thin layer chromatography plates for the detection of compounds that were not highly UV active. General reagents used include acidic vanillin, basic $KMNO_4$, acidic ceric ammonium sulfate, acidic anisaldehyde and iodine adsorbed onto silica. Acidic DNPH was used for the detection of ketones and aldehydes, and Dragendorff's reagent was used for the detection of lactams.

Macherey-Nagel Silica gel 60 (particle size 0.063 – 0.200 mm) was used as the adsorbent for conventional preparative column chromatography, with a silica to product ratio of 30:1. The silica was packed into a suitable column, and the indicated solvent was passed through several times under pressure, until no air bubbles were visible in the column. The crude product was adsorbed onto silica, loaded onto the silica surface and covered with a plug of cotton wool. The elution process was performed using the indicated solvent mixtures either under gravitation or air pump pressure conditions.

Whatman Partisil Prep 40 (particle size 0.040 – 0.063 mm) was used for preparative flash chromatography. The elution solvent system was adjusted to afford an R_f of 0.30-0.35. The column was prepared as described above, and the elution process was performed using the indicated solvent system at a flow rate of 5 cm/min.

9.4 Spectroscopic and physical data

All melting points were obtained on a Reichert hot-stage microscope, and are uncorrected.

Optical rotations were obtained on a Jasco DIP-370 Digital Polarimeter. The values reported each represent an average of several consistent measurements.

Infrared spectra were obtained on a Bruker Vector 22 spectrometer, or a Varian 800FTIR spectrometer (Scimitar Series). The absorptions are reported on the wavenumber (cm^{-1}) scale, in the range 400-4000 cm^{-1}. The signals are reported: value (relative intensity, assignment if possible). Abbreviations used in quoting spectra are: v = very, s = strong, m = medium, w = weak.

Hydrogen (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance-300 at 300.13 MHz respectively using standard pulse sequences. The probe temperature for all experiments was 300±1 K. All spectra were recorded in deuterated chloroform ($CDCl_3$) in 5 mm NMR tubes unless otherwise stated. Chemical shirts are reported in parts per million (ppm) relative to tetramethylsilane as internal standard, in the case of ^1H NMR and relative to the central signal of deuterated chloroform taken at δ 77.00 for the ^{13}C NMR. The ^1H NMR chemical shifts are reported: value (number of hydrogens, splitting pattern, coupling constant(s) in hertz (Hz) where applicable, assignment). ^{13}C NMR chemical shifts are reported: value (assignment). DEPT, CH-correlated and COSY spectra were sometimes used for the complete assignment of NMR signals. Abbriviations used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

High-resolution mass spectra were recorded on a VG7-SEQ Double Focussing Mass Spectrometer at 70 eV and 200 μA. The polarity was positive, ionization employed was EI,

with a resolution of 3000, a mass range of 3000 amu (8kV) and a scan rate of 5 secs/decade. Data are quoted: *m/z* value (relative abundance).

Crystal structure intensity data were collected on a Bruker SMART 1K CCD area diffractometer with graphite monochromated Mo K_α radiation (50kV, 30 mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the program *SAINT+*.[203] and face indexed absorption corrections were made using the program XPREP.[203] The crystal structure was solved by direct methods using *SHELXTL*.[204] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matric least-squares calculations based on F^2 using *SHELXTL*.[204] Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using *SHELXTL*,[204] *PLATON* [205] and *Mercury*.[206]

9.5 Other general procedures

Bulb-to-bulb distillations were performed under reduced pressure (1mm Hg) in a Kugelrohr apparatus.

Concentration of evaporation *in vacuo* refers to the removal of solvent under reduced pressure (~ 20 mm Hg, 45 °C) on a rotary evaporator and final drying on an oil pump (~ 1-2 mmHg) at room temperature. Solvents dried under "high vacuum (oil pump)" were also dried using an oil pump.

Yields are calculated from the mass of the immediate synthetic precursor used, unless otherwise specified.

9.6 Nomenclature and numbering of compounds

The compounds prepared during the course of this project are named in the following sections according to systematic nomenclature. However, the numbering system used to illustrate the diagrams of these compounds is one adopted for convenience and is not meant to reflect systematic numbering of these compounds.

CHAPTER 10

EXPERIMENTAL RELATING TO CHAPTER 3

THE SYNTHESIS OF (±)-THALICTRODINE

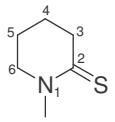
[257]



CHAPTER 10

EXPERIMENTAL RELATING TO CHAPTER 3
THE SYNTHESIS OF (±)-THALICTRODINE [257]

10.1 1-Methyl-2-piperidinethione [260]



260

Method 1[127]

A solution of 1-methyl-2-piperidone **[264]** (5.00 g, 44.0 mmol) and phosphorus pentasulfide (2.20 g, 17.0 mmol, 0.40 equiv.) in dry chloroform (30 cm^3) was stirred at room temperature for 24 h. The solution was then quenched with a saturated aqueous sodium bicarbonate solution (50 cm^3) and extracted with chloroform (3 × 50 cm^3). Then the combined organic extracts were washed with water (50 cm^3), dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield a yellow oil. This was purified by column chromatography on silica gel using 30-50% ethyl acetate:hexane as eluent to give 1-methyl-2-piperidinethione **[260]**, as clear crystals (1.97 g, 16.3 mmol, 37%); **mp** 36 °C (literature[127] mp 36-39 °C); $\mathbf{R_f}$ 0.44 (50% ethyl acetate: hexane); $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 2952 (C-H str, m), 2870 (C-H str, m), 1534 (s), 1450 (CH_3 bend, m), 1407 (m), 1349 (CH_3 bend, s), 1222 (C-N str, s), 1097 (C-N, m); **^{1}H** 3.48 (2 H, t, *J* 6.1 Hz, H-6), 3.47 (3 H, s, NCH_3), 3.00 (2 H, t, *J* 6.4 Hz, H-3), 1.92 (2 H, tt, *J* 3.1 and 6.1 Hz, H-5), 1.75 (2 H, tt, *J* 3.1 and 6.1 Hz, H-4); **^{13}C** 199.3 (C-2), 52.9 (C-6), 43.2 (C-3), 41.3 (NCH_3), 22.8 (C-4), 20.5 (C-5); **HRMS m/z (EI)** 129.06098 (M^+ 100%, $C_6H_{11}NS$ requires 129.06122), 128 (56), 114 (26), 96 (13), 68 (20), 55 (17).

Method 2[128]

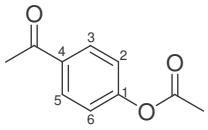
A solution of phosphorus pentasulfide (4.70 g, 21.1 mmol, 2.0 equiv.) and sodium carbonate (1.12 g, 10.6 mmol, 1.0 equiv.) in dry tetrahydrofuran (75 cm^3) was stirred for 15 min, to this was added 1-methyl-2-piperidone **[264]** (1.20 g, 10.6 mmol) in one portion and the solution was stirred for 24 h. The solution was then quenched with a 10% aqueous sodium carbonate

solution (50 cm^3), ethyl acetate (40 cm^3) and hexane (10 cm^3). The aqueous phase was extracted with dichloromethane (3 × 40 cm^3), and the organic phases were combined, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield a yellow oil. This was then purified by column chromatography on silica gel using 30-50% ethyl acetate:hexane as eluent to give 1-methyl-2-piperidinethione **[260]** as clear crystals (0.660 g, 7.00 mmol, 66%); product characterized as shown above.

Method 3

To solution of 1-methyl-2-piperidone **[264]** (2.00 g, 17.6 mmol) in dry benzene (90 cm^3), was added phosphorus pentasulfide (3.99 g, 17.9 mmol, 1.0 equiv.) in one portion. This suspension was refluxed for 24 h. The supernatant benzene was decanted off and filtered through celite. Dichloromethane (100 cm^3) was added to the residue and gently heated with a hairdryer for approximately 2 min. The supernatant was again decanted off and filtered through celite. To the remaining residue was added ammonia solution (100 cm^3), and it was stirred until a homogeneous solution formed. The aqueous solution was extracted with dichloromethane (3 × 100 cm^3), dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield a yellow oil which was purified by column chromatography on silica gel using 30-50% ethyl acetate: hexane as eluent. The 1-methyl-2-piperidinethione **[260]** was obtained as clear crystals (1.81 g, 13.9 mmol, 79%); product characterized as shown above.

10.2 *p*-Acetoxyacetophenone [263][129]

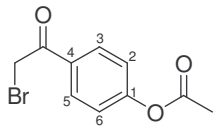


263

Acetic anhydride (5.20 cm^3, 55.5 mmol, 1.5 equiv.) was added dropwise over 5 min to a solution of *p*-hydroxyacetophenone **[262]** (5.04 g, 37.0 mmol, 1.0 equiv.) in an aqueous sodium hydroxide solution (7.5%, 40 cm^3) at 5-10 °C. The mixture was stirred at 5-10 °C for 1 h, during which time the product precipitated out as a white solid. The solution was filtered under suction and rinsed with chilled water to remove any excess sodium hydroxide. The

white solid obtained was recrystallised from ethanol-water to yield *p*-acetoxyacetophenone **[263]** (6.13 g, 94%) as a colourless solid; **mp** 55-56 °C (literature[129] 54 °C); $\mathbf{R}_f$ 0.71 (50% ethyl acetate: hexane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3022 (Ar-H str, m), 2402 (m), 1759 (C=O ester, s), 1682 (C=O ketone, s), 1598 (C=C Ar, m), 1513 (C=C Ar, m), 1424 (CH_3 bend, m), 1366 (CH_3 bend, m), 1216 (C-O, s), 767 (s); **^{1}H** 7.99 (2 H, dd, *J* 4.7 and 8.8 Hz, H-3 and H-5), 7.19 (2 H, dd, *J* 4.7 and 8.8 Hz, H-2 and H-6), 2.59 (3 H, s, CH_3CO), 2.32 (3 H, s, CH_3CO_2); **^{13}C** 196.8 ($CH_3\underline{C}O$), 168.8 ($CH_3\underline{C}O_2$), 154.3 (C-1), 134.7 (C-4), 129.9 (C-3 and C-5), 121.7 (C-2 and C-6), 26.5 ($\underline{C}H_3CO$), 21.1 ($\underline{C}H_3CO_2$); **HRMS m/z (EI)** 178.06394 (M^+ 6%, $C_{10}H_{10}O_3$ requires 178.06299), 136 (38), 121 (100), 107 (2), 93 (28), 77(9), 65(26).

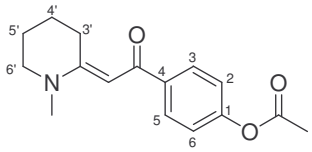
10.3 4-(2-Bromoacetyl)phenyl acetate [261][130]



261

To a solution of *p*-acetoxyacetophenone **[263]** (1.00 g, 5.80 mmol) in dry chloroform (20.0 cm^3) was added bromine (0.120 cm^3, 0.400 g, 2.3 mmol, 0.4 equiv.) in one portion. The solution was stirred at room temperature until it turned clear. Bromine (0.180 cm^3, 0.600 g, 3.50 mmol, 0.7 equiv.) in dry chloroform (10.0 cm^3) was then added dropwise and stirring was continued until the solution remained clear. The solution was washed with water (20.0 cm^3), the organic fraction was dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a yellow oil, which was recrystallised from methanol-water to give 4-(2-bromoacetyl)phenyl acetate **[261]** as a colourless solid (1.15 g, 4.47 mmol, 77%); **mp** 68 °C (literature[130] 67 °C); $\mathbf{R}_f$ 0.68 (50% ethyl acetate:hexane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3023 (Ar-H str, m), 2362 (m), 1762 (C=O ester, m), 1687 (C=O ketone, m), 1601 (C=C Ar, m), 1514 (C=C Ar, m), 1426 (w), 1371 (w), 1278 (m), 1214 (C-O, s), 773 (Ar-H out of plane bend, s); **^{1}H** 8.02 (2 H, dd, *J* 4.7 and 8.5, H-3 and H-5), 7.23 (2 H, dd, *J* 4.7 and 8.5, H-2 and H-6), 4.43 (2 H, s, CH_2Br), 2.33 (3 H, s, CH_3CO_2); **^{13}C** 190.0 ($BrCH_2\underline{C}O$), 168.6 ($CH_3\underline{C}O_2$), 154.9 (C-1), 131.4 (C-4), 129.9 (C-3 and C-5), 121.7 (C-2 and C-6), 30.6 (CH_2Br), 21.1 ($\underline{C}H_3CO_2$); **HRMS m/z (EI)** 255.97435 (M^+ 6%, $C_{10}H_9O_3Br$ requires 255.97351), 214 (31), 163 (39), 121 (100), 107 (21), 93(14), 65(12).

10.4 4-[(2*E*)-2-(1-Methyl-2-piperidinylidene)ethanoyl]phenyl acetate [265]

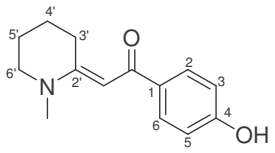


265

Method 1

1-Methyl-2-piperidinethione **[260]** (0.580 g, 4.46 mmol, 1.0 equiv.) was dissolved in dichloromethane (5.00 cm^3). In a separate vessel 4-(2-bromoacetyl)phenyl acetate **[261]** (1.26 g, 3.49 mmol, 1.1 equiv.) was dissolved in dichloromethane (5 cm^3). Once the contents of both vessels had dissolved, they were mixed together and stirred for 30 min. The solvent was removed *in vacuo* to yield a white salt, which was stirred for 24 h at rt and the salt was then dissolved in acetonitrile (20.0 cm^3). In a separate vessel triethyl phosphite (0.84 cm^3, 4.90 mmol, 1.1 equiv.) and triethylamine (0.68 cm^3, 0.496 g, 4.90 mmol, 1.1 equiv.) were dissolved in acetonitrile (10 cm^3). Once the salt had dissolved the contents of the two vessels were mixed together. The solution rapidly turned yellow, and was stirred for 1 h at rt. The reaction mixture was evaporated *in vacuo* to give a brown solid, which was purified by column chromatography (40% ethyl acetate:hexane - ethyl acetate) to yield 4-[(2*E*)-2-(1-methyl-2-piperidinylidene)ethanoyl]phenyl acetate **[265]** as a yellow solid (0.923 g, 3.08 mmol, 69%); **mp** 119°C-122.5 °C; $\mathbf{R}_f$ 0.41 (ethyl acetate); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3022 (Ar-H str, m), 2404 (w), 1746 (C=O ester, m), 1691 (C=O α,β unsaturated ketone, w), 1647 (C=C, w), 1610 (C=C Ar, w), 1531 (C=C Ar, s), 1216 (C-O, s), 1043 (C-N, m); **^{1}H** 7.86 (2 H, dd, *J* 4.7 and 8.7 Hz, H-3 and H-5), 7.09 (2 H, dd, *J* 4.7 and 8.7 Hz, H-2 and H-6), 5.61 (1 H, s, CH=C), 3.34 (2 H, t, *J* 6.2 Hz, H-6'), 3.31 (2 H, t, *J* 6.4 Hz, H-3'), 2.98 (3 H, s, CH_3CO_2), 2.30 (3 H, s, NCH_3), 1.82 (2 H, tt, *J* 3.1 and 6.2 Hz, H-5'),1.66 (2 H, tt, *J* 3.1 and 6.1 Hz, H-4'); **^{13}C** 186.4 (C=CH<u>C</u>O), 169.2 (O<u>C</u>OCH_3), 165.1 (C-2'), 152.0 (C-1), 140.8 (C-4), 128.5 (C-3 and C-5), 120.9 (C-2 and C-6), 90.5 (C=<u>C</u>H), 52.1 (C-6'), 40.3 (NCH_3), 28.4 (C-3'), 23.1 (C-4'), 21.1 (C-5'), 19.4 (O<u>C</u>OCH_3); **HRMS m/z (EI)** 273.13601 (M^+ 54%, $C_{16}H_{19}NO_3$ requires 273.13649), 272 (34), 256 (100), 230 (24), 214 (57), 202 (9), 138 (30), 121 (28), 110 (44), 93 (5), 82 (14), 44 (8).

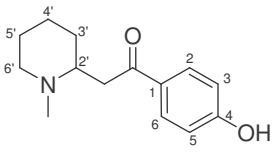
10.5 (2*E*)-1-(4-Hydroxyphenyl)-2-(1-methyl-2-piperidinylidene)ethanone [266]



266

Sodium carbonate (0.0960 g, 0.917 mmol, 1.2 equiv.) was added to a solution of 4-[(2*E*)-2-(1-methyl-2-piperidinylidene)ethanoyl]phenyl acetate **[265]** (0.151 g, 0.554 mmol) in methanol (20.0 cm^3), and stirred at room temperature for 4 h. The solution was filtered through celite, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a green solid which was purified by column chromatography on silica gel using 5% methanol:ethyl acetate The (2*E*)-1-(4-hydroxyphenyl)-2-(1-methyl-2-piperidinylidene)ethanone **[266]** was obtained as a clear oil (0.102 g, 0.734 mmol, 80%); $\mathbf{R}_f$ 0.71 (10% ethanol:dichloromethane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3422 (O-H str, s), 1647 (C=O α,β unsaturated ketone, m), 1550 (m), 1073 (C-N, m); **^{1}H** 7.72 (2H, d, *J* 8.6 Hz, H-2 and H-6), 6.80 (2H, d, *J* 8.7 Hz, H-3 and H-5), 5.64 (1H, s, C=CH), 4.00-2.60 (1H, broad s, OH), 3.36 (2H, t, *J* 6.1 Hz, H-6'), 3.26 (2H, t, *J* 6.4 Hz, H-3'), 3.00 (3H, s, NCH_3), 1.87-1.79 (2H, m, H-5'), 1.73-1.65 (2H, m, H-4'); **^{13}C** 185.7 (C=O), 163.3 (C-2'), 158.8 (C-4), 133.4 (C-1), 128.2 (C-2 and C-6), 114.0 (C-3 and C-5), 89.4 (=CH), 51.1 (C-6'), 39.5 (NCH_3), 27.4 (C-3'), 22.4 (C-4'), 18.7 (C-5'); **HRMS m/z (EI)** 231.12526 (M^+ 47%, $C_{14}H_{17}NO_2$ requires 231.12593), 230 (28), 215 (19), 214 (100), 202 (13), 138 (22), 121 (22), 110 (30), 82 (11), 69 (17), 65 (11), 57 (14), 55 (17), 43 (13), 41 (17).

10.6 (±)-Thalictroidine [257] from [266]

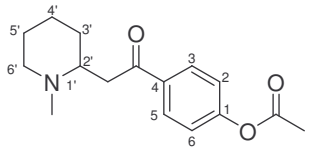


257

Sodium cyanoborohydride (0.040 g, 0.55 mmol, 1.1 equiv.) was added to a solution of (2*E*)-1-(4-hydroxyphenyl)-2-(1-methyl-2-piperidinylidene)ethanone **[266]** (0.050 g, 0.021 mmol) and bromocresol green (0.5% in ethanol, 1 drop) in methanol (3 cm^3). Hydrochloric acid (conc.)

was added dropwise until the solution remained orange (pH 4) and the solution was stirred at rt for 1 h. The solution was quenched with aqueous sodium hydroxide (2 M, 10 cm^3), the aqueous phase was extracted with dichloromethane (3 × 10 cm^3) and the organic fractions were combined, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a glassy solid. This was purified by column chromatography on silica gel using 50% ethyl acetate:hexane as eluent to give (±)-thalictroidine **[257]** as a dark green gum (0.021 g, 0.0090 mmol, 43%); $\mathbf{R}_f$ 0.42 (20% ethanol:dichloromethane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3421 (O-H str, s), 2100 (w), 1655 (C=O, s), 1220 (C-O, m), 1107 (m), 773 (w); **^{1}H** 7.79 (2H, d, *J* 8.5 Hz, H-2 and H-6), 6.83 (2H, d, *J* 8.6 Hz, H-3 and H-5), 3.42 (1H, dd, *J* 5.1 and 16.7 Hz, CH_2COa), 3.21-2.92 (2H, m, H-2' and H-6'a), 2.87 (1H, dd, *J* 5.9 and 16.7 Hz, CH_2COb), 2.48-2.41 (1H, m, H-6'b), 2.41 (3H, s, NCH_3), 1.85-1.38 (6H, m, H-3', H-4' and H-5'); **^{13}C** 197.2 (C=O), 163.8 (C-4), 131.0 (C-2 and C-6), 128.2 (C-1), 116.4 (C-3 and C-5), 59.8 (C-2'), 56.4 (C-6'), 43.2 (NCH_3), 41.6 (CH_2CO), 31.6 (C-3'), 25.0 (C-5'), 23.6 (C-4'); **HRMS m/z (EI)** 233.14350 (M^+ 5%, $C_{14}H_{19}NO_2$ requires 233.14158), 136 (47), 121 (100), 110 (5), 99 (6), 98 (75), 97 (12), 96 (10), 93 (27), 70 (5), 65 (21), 43 (8), 42 (8), 39 (13).

10.7 4-[2-(1-Methyl-2-piperidinyl)acetyl]phenyl acetate [293]

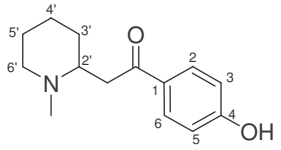


293

Sodium cyanoborohydride (0.040 g, 0.55 mmol, 1.1 equiv.) was added to a solution of 4-[(2*E*)-2-(1-methyl-2-piperidinylidene)ethanoyl]phenyl acetate **[265]** (0.14 g, 0.50 mmol) and bromocresol green (1 drop) in methanol (5 cm^3). Hydrochloric acid (conc.) was added dropwise until the solution remained orange (pH 4) and the solution was stirred at rt for 1.5 h. The solution was quenched with water (10 cm^3), ethyl acetate (20 cm^3) and brine (10 cm^3). The aqueous phase was extracted with ethyl acetate (3 × 50 cm^3) and the organic fractions were combined, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a green solid which was purified by column chromatography on silica gel using 5% triethylamine:ethyl acetate as eluent to give 4-[2-(1-methyl-2-piperidinyl)acetyl]phenyl acetate **[293]** as a dark green solid (0.064 g, 0.23 mmol, 46%)**;** $\mathbf{R}_f$ 0.54 (5%

methanol:dichloromethane); ν_{max} **(film)/cm^{-1}** 3022 (Ar-H str, s), 2402 (w), 1754 (C=O ester, m), 1676 (C=O ketone, m), 1602 (C=C Ar, m), 1516 (C=C Ar, m), 1427 (C=C Ar, w), 1369 (w), 1216 (C-O, s), 1169 (m), 1044 (C-N, m); **^{1}H** 8.07 (2H, d, *J* 8.7 Hz, H-3 and H-5), 7.23 (2H, d, *J* 8.7 Hz, H-2 and H-6), 4.01 (1H, dd, *J* 5.4 and 18.6 Hz, CH_2COa), 3.75-3.71 (1H, m, H-2'), 3.50-3.46 (1H, m, H-6'a), 3.27 (1H, dd, *J* 5.2 and 18.6 Hz, CH_2COb), 2.91-2.83 (1H, m, H-6'b), 2.67 (3H, s, NCH_3), 2.33 (3H, s, CH_3CO_2), 2.28-1.54 (6H, m, H-3', H-4' and H-5'); **^{13}C** 194.9 ($CH_2\underline{C}O$), 168.7 ($CH_3\underline{C}O_2$), 155.2 (C-1), 133.0 (C-4), 130.2 (C-3 and C-5), 122.2 (C-2 and C-6), 60.5 (C-2'), 56.5 (C-6'), 40.8 (NCH_3), 40.7 ($\underline{C}H_2CO$), 30.0 (C-3'), 29.7 (C-5'), 22.5 (C-4'), 21.1 ($\underline{C}H_3CO_2$); **HRMS m/z (EI)** 275.15385 (M^+ 6%, $C_{16}H_{21}NO_3$ requires 275.15214), 256 (6), 220 (8), 219 (13), 149 (6), 138 (11), 121 (21), 99 (8), 98 (100), 97 (9), 83 (6), 73 (8), 71 (6), 70 (8), 69 (12), 60 (8), 57 (11), 55 (11), 45 (8), 43 (13), 41 (11).

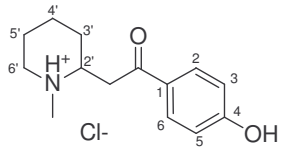
10.8 (±)-Thalictroidine [257] from [293]



257

Potassium carbonate (0.037 g, 0.254 mmol, 1.1 equiv.) was added to a solution of 4-[2-(1-methyl-2-piperidinyl)acetyl]phenyl acetate **[293]** (0.064 g, 0.231 mmol) in methanol (10 cm^3), and stirred at room temperature for 1 h.The solution was filtered through celite, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a green solid which was purified by column chromatography on silica gel using 5% methanol:ethyl acetate to yield (±)-thalictroidine **[257]** as a brown gum (0.042 g, 0.18 mmol, 80%); characterisation as described in **Section 10.6**.

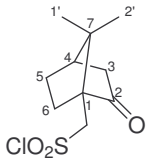
10.9 2-[2-(4-Hydroxyphenyl)-2-oxoethyl]-1-methylpiperidinium chloride [294]



294

Dry hydrogen chloride gas was generated by adding concentrated sulfuric acid dropwise to concentrated hydrochloric acid. The hydrogen chloride gas generated was then passed through activated carbon and self-indicating silica before being bubbled through a stirred solution of (±)-thalictroidine **[257]** (0.200 g, 0.45 mmol) in dry methanol (5 cm^3). The product separated out as a white oil which solidified upon standing. The crude crystalline product was recrystallised from ethanol to give 2-[2-(4-hydroxyphenyl)-2-oxoethyl]-1-methylpiperidinium chloride **[294]** as light pink crystals; **mp** 119-123 °C; $\mathbf{R_f}$ 0.42 (10% ethanol:dichloromethane); $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3021 (Ar-H, s), 2402 (s), 1695 (C=O, w), 1516 (C=C Ar, m), 1216 (C-O, s), 1075 (C-N, m), 774 (s), 670 (s); **^{1}H** (d-DMSO) 7.92 (2H, d, *J* 8.7 Hz, H-2 and H-6), 6.95 (2H, d, *J* 8.7 Hz, H-3 and H-5), 4.5-2.5 (1H, broad s, OH), 3.64-3.59 (2H, m, H-6'), 3.36-3.27 (2H, m, CH_2), 3.07-3.00 (1H, m, H-2'), 2.67 (3H, s, NCH_3), 1.90-1.45 (6H, m, H-3', H-4' and H-5'); **^{13}C** 195.8 (C=O), 163.7 (C-4), 131.8 (C-2 and C-6), 128.7 (C-1), 116.4 (C-3 and C-5), 60.3 (C-2'), 55.0 (C-6'), 39.3 (NCH_3), 22.1 (CH_2), 28.9 (C-3'), 28.9 (C-4'), 21.9 (C-5'); **HRMS m/z (EI)** 233.14350 (M^+ 5%, $C_{14}H_{19}NO_2$ requires 233.14158), 136 (47), 121 (100), 110 (5), 99 (6), 98 (75), 97 (12), 96 (10), 93 (27), 70 (5), 65 (21), 43 (8), 42 (8), 39 (13).

10.10 (1*S*)-(+)-Camphorsulfonyl chloride [290]



290

Method 1

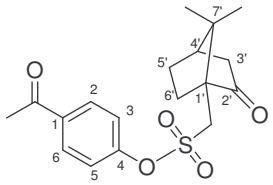
(1*S*)-(+)-10-Camphorsulfonic acid **[295]** (5.00 g, 22.0 mmol) was added to a vessel containing phosphorus pentachloride (4.48 g, 21.5 mmol, 1.0 equiv.) at 0 ^{o}C. The reaction is very vigorous evolving hydrogen chloride gas, and as a result was stirred slowly at first. Stirring was continued at room temperature until all the contents had completely dissolved. The solution was left to stand for 4 h. It was then poured onto crushed ice, and ice was added until all evidence of reaction disappeared. The fine white product was collected by suction filtration and washed several times with cold water. The solid was immediately dried under high vacuum to yield (1*S*)-(+)-camphorsulfonyl chloride **[290]** as a fine white solid (1.59 g, 6.60 mmol, 30%); $\mathbf{[\alpha]_D^{20}}$ +19.5 (*c* 1.80 H_2O); **mp** 66-68^{o}C (literature[133] mp 67-68^{o}C); $\mathbf{R_f}$ 0.82 (50% ethyl acetate: hexane); $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3020 (s), 2968 (C-H str, w), 2400 (w), 1749 (C=O, s), 1417 (CH_3 bend, w), 1377 (SO_2Cl, s), 1216 (SO_2Cl, s), 1173 (m), 1054 (w), 929 (w), 778 (vs), 669 (s); **^{1}H** 4.31 (1H, d, *J* 14.6 Hz, CH_2SO_2Cla), 3.74 (1H, d, *J* 14.6 Hz, CH_2SO_2Clb), 2.51-2.46 (1H, m, H-6a), 2.47-2.40 (1H, m, H-3a), 2.17 (1H, t, *J* 4.5 Hz, H-4), 2.09 (1H, m, H-5a), 2.03-1.96 (1H, d, *J* 18.6 Hz, H-3b), 1.83-1.73 (1H, m, H-6b), 1.53-1.45 (1H, m, H-5b), 1.14 (3H, s, H-2'), 0.93 (3H, s, H-1'); **^{13}C** 212.7 (C-2), 64.3 (CH_2SO_2Cl), 59.7 (C-1), 48.1 (C-7), 42.8 (C-4), 42.3 (C-3), 26.8 (C-5), 25.3 (C-6), 19.7 ($C\underline{C}H_3$)*, 19.6 ($C\underline{C}H_3$)*; **HRMS m/z (EI)** 250.04490 (M^+ 0.25%, $C_{10}H_{15}ClO_3S$ requires 250.04304), 151 (67), 133 (10), 123 (68), 110 (11), 109 (100), 108 (11), 107 (21), 95 (12), 93 (27), 91 (13), 81 (66), 79 (17), 77 (12), 69 (14), 67 (40), 55 (22), 53 (18), 43 (14), 41 (38), 39 (15).

* These assignments may be interchanged

Method 2

(1*S*)-(+)-10-Camphorsulfonic acid **[295]** (20.0 g, 86.2 mmol) was added to a vessel containing thionyl chloride (41.0 g, 345 mmol, 4.0 equiv.). The reaction mixture was refluxed for 1 h. The solution that formed was cooled, evaporated *in vacuo*, and dried under high vacuum to yield pure (1S)-(+)-camphorsulfonyl chloride **[290]** as a fine white solid (21.1 g, 84.5 mmol, 98%); product characterized as described above.

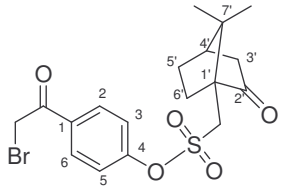
10.11 1-[(4-Acetylphenylsulfonyl)methyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one [296]



296

To a solution of *p*-hydroxyacetophenone **[262]** (1.98 g, 14.6 mmol) and triethylamine (5.10 cm^3 , 3,69 g, 36.5 mmol, 2.5 equiv.) in dichloromethane (30 cm^3) was added (1*S*)-(+)-camphorsulfonyl chloride **[290]** (7.30 g, 29.2 mmol, 2.0 equiv.) in dichloromethane (10 cm^3) dropwise over 5 minutes. Effervescence was observed as hydrogen chloride gas was evolved, and the product precipitated. The solution was left to stir for 1 h, the solvent was removed *in vacuo* in a fume hood to give a yellow-orange solid. The crude solid was recrystallised from ethanol to yield 1-[(4-acetylphenylsulfonyl)methyl]-7,7-dimethybicyclo[2.2.1]heptan-2-one **[296]** as colourless crystals (4.47 g, 12.9 mmol, 88%); **mp** 55-56 ^oC; $\mathbf{R}_f$ 0.71 (50% ethyl acetate:hexane); $\mathbf{[\alpha]_D^{20}}$ +29.7 (*c* 4.18, MeOH); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3022 (Ar-H str, m), 2971 (C-H str, w), 2404 (w), 2361 (s), 1745 (C=O, s), 1687 (C=O Ar, s) 1593 (C=C Ar, m) 1513 (C=C Ar, s) 1422 (CH_3 bend, m), 1370 (SO_2O, s), 1262 (C-O, m), 1216 (SO_2O, s), 1151 (s), 1050 (s); **^{1}H** 8.02 (2H, d, *J* 8.8 Hz, H-2 and H-6), 7.40 (2H, d, *J* 8.8 Hz, H-3 and H-5), 3.86-3.84 (1H, d, *J* 15.0 Hz, CH_2SO_2a), 3.24 (2H, d, *J* 15.0 Hz, CH_2SO_2b), 2.61 (3H, s, CH_3CO), 2.54 (1H, m, H-6'a), 2.44 (1H, m, H-3'a), 2.16 (1H, t, *J* 4.5 Hz, H-4'), 2.12-2.09 (1H, m, H-5'a), 1.99 (1H, d, *J* 18.5 Hz, H-3'b), 1.79-1.70 (1H, m, H-6'b), 1.52-1.45 (1H, m, H-5'b), 1.16 (3H, s, CCH_3), 0.92 (3H, s, CCH_3); **^{13}C** 213.8 (C-2'), 196.5 ($CH_3\underline{C}O$), 152.5 (C-4), 135.7 (C-1), 130.3 (C-2 and C-6), 122.0 (C-3 and C-5), 58.1 (C-1'), 48.2 (CH_2SO_2), 48.0 (C-7'), 42.8 (C-4'), 42.4 (C-3'), 26.8 (C-5'), 26.6 (CH_3O), 25.1 (C-6') , 19.8 ($C\underline{C}H_3$)*, 19.6 ($C\underline{C}H_3$)*; **HRMS m/z (EI)** 351.12525 ((M+N)$^+$ 4%, $C_{18}H_{23}O_5S$ requires 351.12662), 215 (100), 151 (79), 123 (93), 109 (94), 107 (34), 93 (30), 81 (78), 67 (44), 55 (21). * These assignments may be interchanged.

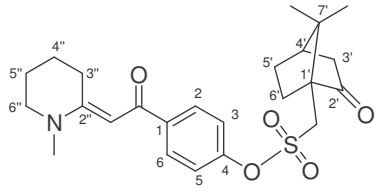
10.12 4-(2-Bromoacetyl)phenyl (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate [297]



297

To a solution of 1-[(4-acetylphenylsulfonyl)methyl]-7,7-dimethybicyclo[2.2.1]heptan-2-one **[296]** (0.198 g, 0.564 mmol, 1.0 equiv.) in dry chloroform (5 cm^3) was added bromine (0.011 cm^3, 0.033 g, 0.209 mmol, 0.37 equiv.) in one portion and the mixture was stirred until it turned clear. Bromine (0.018 cm^3, 0.057 g, 0.356 mmol, 0.63 equiv.) in dry chloroform (5 cm^3) was then added dropwise and stirring was continued until the solution remained clear. The solution was washed with water (10 cm^3), the organic fraction was dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a yellow oil, which was recrystallised from methanol-water to give 4-(2-bromoacetyl)-phenyl-(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate **[297]** as a colourless solid (0.205 g, 0.474 mmol, 84%); **mp** 55-56 ^oC; $\mathbf{R}_f$ 0.71 (50% ethyl acetate:hexane); $\mathbf{[\alpha]_D^{21}}$ +24.5 (*c* 3.31, MeOH); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3022 (Ar-H, m), 2975 (C-H str, w), 2404 (w), 2361 (s), 1745 (C=O, s), 1690 (C=O Ar, s), 1647 (w), 1515 (C=C Ar, s), 1425 (m), 1216 (SO_2O, vs), 1154 (w), 1043 (s); ^{1}**H** 8.07 (2H, d, *J* 8.8 Hz, H-2 and H-6), 7.44 (2H, d, *J* 8.8 Hz, H-3 and H-5), 4.42 (2H, s, CH_2Br), 3.86 (1H, d, *J* 15.0 Hz, CH_2SO_2a), 3.25 (2H, d, *J* 15.0 Hz, CH_2SO_2b), 2.54-2.52 (1H, m, H-6'a), 2.50-2.39 (1H, m, H-3'a), 2.17 (1H, t, *J* 4.5 Hz, H-4'), 2.12-2.08 (1H, m, H-5'a), 1.99 (1H, d, *J* 18.6 Hz, H-3'b), 1.79-1.70 (1H, m, H-6'b), 1.53-1.44 (1H, m, H-5'b), 1.16 (H-2''), 0.92 (H-1''); ^{13}**C** 213.8 (C-2'), 189.9 ($BrCH_2\underline{C}O$), 153.1 (C-4), 132.5 (C-1), 131.1 (C-2 and C-6), 122.3 (C-3 and C-5), 58.1 (C-1'), 48.4 (CH_2SO_2), 48.0 (C-7'), 42.9 (C-4'), 42.4 (C-3'), 30.4 (CH_2Br), 26.9 (C-5'), 25.2 (C-6') , 19.9 ($C\underline{C}H_3$)*, 19.7 ($C\underline{C}H_3$)*; **HRMS m/z (EI)** 335.09641 ($M^+ - CH_2Br$ 7%, $C_{17}H_{19}O_5S$ requires 335.09532), 216 (41), 215 (100), 133 (21), 123 (99), 121 (29), 109 (99), 107 (51), 93 (48), 81 (93), 79 (21), 67 (61), 55 (28). * These assignments may be interchanged

10.13 4-[(2*E*)-2-(1-Methyl-2-piperidinylidene)ethanoyl]phenyl(7,7-dimethyl-2-oxobicyclo-[2.2.1]hept-1-yl)methanesulfonate [298]



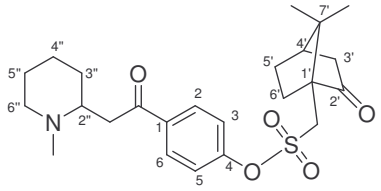
298

1-Methylpiperidine-2-thione **[260]** (0.610 g, 4.70 mmol, 1.0 equiv.) was dissolved in dichloromethane (5 cm^3). In a separate vessel 4-(2-bromoacetyl)phenyl(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate **[297]** (2.21 g, 5.16 mmol, 1.1 equiv.) was dissolved in dichloromethane (5 cm^3). Once the contents of both vessels had dissolved, they were mixed together and stirred for 30 min. The solvent was removed *in vacuo* to yield a white salt, which was stirred at room temperature for 24 h and the salt was dissolved in acetonitrile (25 cm^3). In a separate vessel triphenylphosphine (1.35 g, 5.16 mmol, 1.1 equiv.) and triethylamine (0.72 cm^3, 0.520 g, 5.1 mmol, 1.1 equiv.) were mixed in acetonitrile (20 cm^3). Once the salt had dissolved the contents of the two vessels were mixed together. The solution rapidly turned yellow, and was stirred at room temperature for 1 h, during which time a precipitate formed. The solution was filtered through celite, and the solvent was removed *in* vacuo to yield an orange solid, which was triturated in ethyl acetate for 1.5 h, after which time the solution was again filtered through celite. The solution was extracted with aqueous hydrochloric acid (2 M, 3 × 40 cm^3), the aqueous extracts were combined and basified to pH 11 with aqueous ammonia solution, and the basified solution was extracted with dichloromethane (3 × 50 cm^3). The organic fractions were combined, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield an orange solid. The solid was purified by column chromatography (5% triethylamine:ethyl acetate) to yield 4-[(2*E*)-2-(1-methyl-2-piperidinylidene)ethanoyl]phenyl(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate **[298]** as an orange solid (1.34 g, 3.01 mmol, 64%); **mp** 123-124°C; $\mathbf{R}_f$ 0.49 (ethyl acetate); $\mathbf{[\alpha]_D^{21}}$ +26.6 (*c* 2.56, methanol); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3021 (Ar-H str, m), 2969 (C-H str, w), 2404 (w), 2361 (s), 1744 (C=O, s), 1690 (C=O Ar, m), 1647 (C=C Ar, m), 1532 (C=C Ar, s), 1482 (m), 1423 (m), 1365 (m), 1216 (SO_2O, vs), 1146 (C-N, w), 1046 (C-N, m); **^{1}H** 7.89 (2H, d, *J* 8.5 Hz, H-2 and H-6), 7.31 (2H, d, *J* 8.5 Hz, H-3 and H-5), 5.59 (1H, s,

C=CH), 3.81 (1H, d, *J* 15.0 Hz, CH_2SO_2a), 3.39-3.30 (4H, 2 × t, *J* 5.9 and 6.0 Hz, H-3''and H6''), 3.20 (2H, d, *J* 15.0 Hz, CH_2SO_2b), 3.00 (3H, s, NCH_3), 2.59-2.49 (1H, m, H-6'a), 2.46-2.37 (1H, m, H-3'a), 2.15-2.04 (2H, m, H-4' and H-5'a), 1.97 (1H, d, *J* 18.5 Hz, H-3'b), 1.88-1.69 (5H, m, H-6'b, H-4'' and H-5''), 1.50-1.42 (1H, m, H-5'b), 1.16 (3H, s, CCH_3), 0.90 (3H, s, CCH_3); **^{13}C** 213.9 (C-2'), 185.8 (C=CHCO), 165.4 (C-2''), 150.4 (C-4), 142.1 (C-1), 128.9 (C2 and C-6), 121.3 (C-3 and C-5), 90.4 (C=CHCO), 58.1 (C-1'), 52.1 (C-6''), 47.9 (C-7'), 47.6 (CH_2SO_2), 42.8 (C-4'), 42.4 (C-3'), 40.3 (NCH_3), 28.4 (C-3''), 26.8 (C-5'), 25.1 (C-6'), 23.0 (C-4''), 19.9 (CCH_3)*, 19.6 (CCH_3)*, 19.3 (C-5''); **HRMS m/z (EI)** 445.19287 (M^+ 13%, $C_{24}H_{31}NO_5S$ requires 445.19229), 428 (31), 230 (100), 214 (9), 202 (11), 138 (7), 110 (10).

* These assignments may be interchanged

10.14 4-[2-(1-Methyl-2-piperidinyl)acetyl]phenyl(7,7-dimethyl-2-oxobicyclo[2.2.1]-hept-1-yl)methanesulfonate [299]

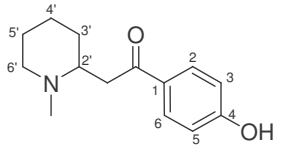


299

Sodium cyanoborohydride (0.145 g, 2.26 mmol, 1.1 equiv.) was added to a solution of 4-[(2*E*)-2-(1-methyl-2-piperidinylidene)ethanoyl]phenyl(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate **[298]** (0.917 g, 2.06 mmol) and bromocresol green (0.5% in ethanol, 1 drop) in methanol (25 cm^3). Hydrochloric acid (conc.) was added dropwise until the solution remained orange (pH 4) and the solution was stirred at rt for 1 h. The solution was quenched with water (30 cm^3), ethyl acetate (50 cm^3) and brine (30 cm^3), the aqueous phase was extracted with ethyl acetate (3 × 50 cm^3) and the organic fractions were combined, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give an orange oil. The oil was purified by column chromatography on silica gel using 5% triethylamine:ethyl acetate as eluent to give 4-[2-(1-methyl-2-piperidinyl)acetyl]phenyl(7,7-dimethyl-2-oxobicyclo-[2.2.1]hept-1-yl)methanesulfonate **[299]**, as an orange oil (0.923 g, 2.06 mmol, 100%); $\mathbf{R}_f$ 0.22 (10% triethylamine:ethyl acetate); $\mathbf{[\alpha]_D^{20}}$ +22.2 (*c* 1.76, methanol); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}**

3021 (Ar-H, s), 2965 (C-H str, s), 2401 (w), 1748 (C=O, s), 1682 (C=O Ar, s), 1597 (C=C Ar, s), 1500 (C=C Ar, s), 1416 (s), 1377 (CH_3 bend, s), 1266 (C-N, s), 1216 (SO_2O, s), 1175 (s), 1150 (s), 1055 (C-N, m), 1015 (m), 869 (s), 771 (s), 668 (s); **^{1}H** 7.96 (2H, d, *J* 8.8 Hz, H-2 and H-6), 7.34 (2H, d, *J* 8.8 Hz, H-3 and H-5), 3.77 (1H, d, *J* 15.0 Hz, CH_2SO_2a), 3.28 (1H, dd, *J* 4.7 and 16.0 Hz, H-3''a), 3.17 (1H, d, *J* 15.0 Hz, CH_2SO_2b), 2.83-2.76 (1H, m, H-3''b), 2.83-2.73 (1H, m, H-6''a), 2.76-2.62 (1H, m, H-2''), 2.50-2.38 (1H, m, H-6'a), 2.40-2.31 (1H, m, H-3'a), 2.19 (3H, s, NCH_3), 2.15-2.11 (1H, m, H-6''b), 2.10 (1H, t, *J* 4.4 Hz, H-4'), 2.05-1.96 (1H, m, H-5'a), 1.94-1.88 (1H, d, *J* 18.1 Hz, H-3'b), 1.71-1.67 (1H, m, H-6'b), 1.71-1.65 (2H, m, H-4''a and H-5''a), 1.67-1.62 (2H, m, $\underline{C}H_2CO$), 1.54-1.36 (1H, m, H-5'b), 1.30-1.10 (2H, m, H-4''b, H-5''b), 1.08 (3H, s, CCH_3)*, 0.84 (3H, s, CCH_3)*; **^{13}C** 213.7 (C-2'), 197.6 ($CH_2\underline{C}O$), 152.5 (C-4), 135.7 (C-1), 130.1 (C-2 and C-6), 121.9 (C-3 and C-5), 59.2 (C-2''), 58.0 (C-1'), 56.1 (C-6''), 48.1 (SO_2CH_2), 47.9 (C-7'), 43.5 (NCH_3), 42.7 (C-4'), 42.3 (C-3'), 42.1 (C-3''), 32.1 (C-4''), 26.7 (C-5'), 25.6 ($\underline{C}H_2CO$), 25.0 (C-6'), 23.5 (C-5''), 19.7 ($C\underline{C}H_3$)*, 19.5 ($C\underline{C}H_3$)*; **HRMS m/z (EI)** 447.20745 (M^+ 6%, $C_{24}H_{33}NO_5S$ requires 447.20794), 277 (13), 232 (29), 215 (23), 151 (14), 123 (25), 121 (11), 109 (29), 99 (14), 98 (100), 97 (25), 96 (21), 81 (27), 70 (13), 67 (19), 55 (15). * These assignments may be interchanged

10.15 (±)-Thalictroidine [257] from [299]



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A solution of 4-[2-(1-methyl-2-piperidinyl)acetyl]phenyl(7,7-dimethyl-2-oxobicyclo-[2.2.1]hept-1-yl)methanesulfonate **[299]** (0.066 g, 0.147 mmol) was added to aqueous potassium hydroxide (0.3 M, 0.089 g) in methanol (5 cm^3) in one portion. The solution was stirred at room temperature for 1 h, after which time it was acidified with aqueous acetic acid, the solvent and water were evaporated *in vacuo* to yield a white solid. This was purified by column chromatography on silica gel using 5% triethylamine:ethyl acetate to yield (±)-thalictroidine **[257]** as a dark orange oil (0.041 g, 100%); characterisation as described previously in **Section 10.6**

CHAPTER 11

EXPERIMENTAL RELATING TO CHAPTER 4

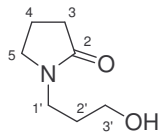
SYNTHESIS OF 5-SUBSTITUTED INDOLIZIDINES



CHAPTER 11

EXPERIMENTAL RELATING TO CHAPTER 4
SYNTHESIS OF 5-SUBSTITUTED INDOLIZIDINES

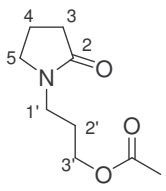
11.1 1-(3-Hydroxypropyl)-2-pyrrolidin-2-one [307][110m]



307

A mixture of 3-amino-1-propanol **[305]** (12.9 g, 24.0 cm^3, 312 mmol, 1.05 eq.) and γ-butyrolactone **[306]** (22.4 g, 22.8 cm^3, 149 mmol) was heated at 250 °C for 18 h in a sealed Carius tube placed in a tube furnace. After cooling, the crude product was taken up in dichloromethane (230 cm^3, 10 $cm^3.mmol^{-1}$) and dried (anhydrous magnesium sulfate), and the resulting orange oil was distilled (134°C at 0.8 mm Hg, lit.[110m], 123-128 °C at 0.5 mm Hg) to give 1-(3-hydroxypropyl)pyrrolidin-2-one **[307]** as a clear liquid (37.24 g, 260 mmol, 81%); $\mathbf{R}_f$ 0.23 (50% hexane-acetone); ν_{max} **(film)/cm^{-1}** 3380 (O-H str, s), 2936 (C-H str, s), 2871 (C-H str, s), 1655 (C=O str, s), 1425 (s), 1289 (s), 1053 (C-O str, s); **^{1}H** 3.69 (1H, br s, OH), 3.54 (2H, t, *J* 5.7 Hz, H-3'), 3.44 (2H, t, *J* 6.0 Hz, H-5), 3.41 (2H, t, *J* 6.2 Hz, H-1'), 2.43 (2H, t, *J* 8.1 Hz, H-3), 2.06 (2H, quintet, *J* 7.6 Hz, H-4), 1.70 (2H, quintet, *J* 6.0 Hz, H-2'); **^{13}C** 176.1 (C-2), 58.2 (C-3'), 47.5 (C-5), 38.8 (C-1'), 30.7 (C-3), 29.5 (C-2'), 17.9 (C-4); **HRMS m/z (EI)** 143.09591 (M^+ 18%, $C_7H_{13}NO_2$ requires 143.09463), 128 (56), 41 (42), 69(48), 70 (57), 98 (100), 99 (41), 112 (22), 125 (51), 126 (25), 131 (25).

11.2 3-(2-Oxo-1-pyrrolidinyl)propyl acetate [308][110m]

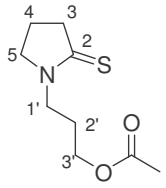


308

A solution of acetic anhydride (14.8 g, 13.6 cm^3, 144 mmol, 1.5 eq.) in pyridine (11.4 g, 11.9 cm^3, 96.0 mmol, 1.5 eq.) was added dropwise over 10 min to a stirred solution of 1-(3-

hydroxypropyl)pyrrolidin-2-one **[307]** (13.8 g, 96.0 mmol) in pyridine (5.06 g, 7.80 cm^3, 64.0 mmol, 1.0 eq.) at 0 °C under argon. The solution was allowed to warm to 25 °C over 5 h. Ethyl acetate (290 cm^3, 3 $cm^3.mmol^{-1}$) was added and the mixture was washed with saturated ammonium chloride solution made slightly basic with 25% ammonia solution (145 cm^3, 1.5 $cm^3.mmol^{-1}$), dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo*. The crude product was purified by distillation at 146-148 °C at 2 mm Hg, to yield 3-(2-oxo-1-pyrrolidinyl)propyl acetate **[308]** (15.5 g, 75.4 mmol, 87%) as a clear oil; $\mathbf{R}_f$ (50% hexane-acetone) 0.47; ν_{max} **(film)/cm^{-1}** 2955 (C-H str, m), 1734 (OC=O str, s), 1666 (C=O ketone str, s), 1230 (C-N str, s), 1042 (C-O str, s); **^{1}H** 4.08 (2H, t, *J* 6.43 Hz, H-3'), 3.41 (2H, t, *J* 7.1 Hz, H-5), 3.37 (2H, t, *J* 7.2 Hz, H-1'), 2.38 (2H, t, *J* 8.1 Hz, H-3), 2.06 (3H, s, $OCOCH_3$), 2.04 (2H, quintet, *J* 7.8 Hz, H-4), 1.88 (2H, quintet, *J* 6.8 Hz, H-2'); **^{13}C** 174.8 (C-2), 170.7 ($O\underline{C}OCH_3$), 61.7 (C-3'), 47.0 (C-5), 39.3 (C-1'), 30.7 (C-3), 26.2 (C-2'), 20.7 ($OCO\underline{C}H_3$), 17.7 (C-4); **HRMS m/z (EI)** 185.10543 (M^+ 19%, $C_9H_{15}NO_3$ requires 185.10519), 41 (26), 43 (35), 70 (71), 98 (100), 112 (21), 125 (51), 126 (22).

11.3 3-(2-Thioxo-1-pyrrolidinyl)propyl acetate [304][110m]

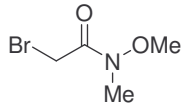


304

To a suspension of phosphorus pentasulfide (18.6 g, 83.5 mmol, 3.0 eq.) in tetrahydrofuran (200 cm^3, 7.2 $cm^3.mmol^{-1}$) was added sodium carbonate (4.42 g, 41.8 mmol, 1.5 eq.). The mixture was stirred at rt until the solution became homogeneous. To this solution was added 3-(2-oxo-1-pyrrolidinyl)propyl acetate **[308]** (5.15 g, 27.8 mmol) in tetrahydrofuran (50 cm^3, 1.8 $cm^3.mmol^{-1}$). Sodium carbonate (10%, 200 cm^3, 7.2 $cm^3.mmol^{-1}$), ethyl acetate (150cm^3, 5.4 $cm^3.mmol^{-1}$) and hexane (50 cm^3, 1.8 $cm^3.mmol^{-1}$) were added after 5 h. The aqueous phase was extracted with dichloromethane (3 × 100 cm^3). The combined organic phases were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a yellow oil. The crude product was purified by column chromatography with (25% acetone:hexane) as eluent to give 3-(2-thioxo-1-pyrrolidinyl)propyl acetate **[304]** as a clear oil (5.03 g, 24.94 mmol, 90%); $\mathbf{R}_f$ (33 % acetone:hexane) 0.42; ν_{max} **(film)/cm^{-1}** 2955 (C-H str, m), 2878 (C-H

str, m), 1733 (C=O str, s), 1510 (s), 1229 (C-N str, s) 1041 (C-O str, s), 969 (s) **^{1}H** 4.12 (2H, t, *J* 6.3 Hz, H-3'), 3.85 (2H, t, *J* 7.3 Hz, H-5), 3.74 (2H, t, *J* 7.3 Hz, H-1'), 3.04 (2H, t, *J* 7.9 Hz, H-3), 2.08 (2H, m, *J* 7.9 Hz, H-2'), 2.07 (3H, s, $OCOCH_3$), 2.03 (2H, m, *J* 6.70, H-4); **^{13}C** 201.4 (C-2), 170.8 ($O\underline{C}OCH_3$), 61.7 (C-5), 54.8 (C-3'), 44.9 (C-1'), 44.8 (C-3), 25.4 (C-2'), 20.8 (C-4), 19.6 ($OCO\underline{C}H_3$); **HRMS m/z (EI)** 201.08194 (M^+ 100%, $C_9H_{15}NO_2S$ requires 201.08235), 41 (27), 43 (46), 85 (45), 98 (22), 102 (23), 115 (81), 126 (25), 128 (48), 142 (61), 168 (29).

11.4 2-Bromo-*N*-methoxy-*N*-methylacetamide [271][134]



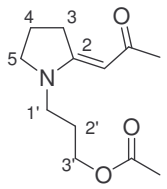
271

To a slurry of *N*,*O*-dimethylhydroxylamine hydrochloride (2.03 g, 24.9 mmol) in dichloromethane (45 cm^3, 1.8 $cm^3.mmol^{-1}$) was added pyridine (3.93 g, 4.00 cm^3, 49.7 mmol, 2.0 eq.). Bromoacetyl bromide **[310]** (4.52 g, 2.0 cm^3, 22.4 mmol, 0.9 eq.) was added dropwise to the slurry over 5 minutes. The reaction mixture was stirred at 0 °C for 15 minutes, warmed to rt and stirred for a further 18 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (35 cm^3, 1.4 $cm^3.mmol^{-1}$) and stirred for 40 minutes. The organic and aqueous layers were separated. The organic extract was washed with 6 M hydrochloric acid (50 cm^3) and brine (50cm^3). The aqueous extract was extracted using dichloromethane (3 × 50 cm^3). The organic fractions were combined, dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford a brown oil. The crude oil was purified by distillation to give 2-bromo-*N*-methoxy-*N*-methylacetamide **[271] a**s a clear oil which solidified on standing (1.54 g, 8.46 mmol, 94%); $\mathbf{R}_f$ 0.26 (30% ethyl acetate:hexane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3445 (N-H, br, m), 2955 (C-H str, s), 2879 (C-H str, s), 1736 (C=O, s), 1670 (C=O, s), 1183 (C-O, s); **^{1}H** 4.27 (1.4H, s, CH_2Br), 4.03 (0.6H, s, CH_2Br), 3.80 (0.9H, s, OCH_3), 3.77 (2.1H, s, OCH_3), 3.24 (3H, s, NCH_3); **^{13}C** 167.3 (C=O), 167.1 (C=O), 61.4 (OCH_3), 40.6 (NCH_3), 25.1 (CH_2Br).

11.5 General procedure for the sulfide contraction of 3-(2-thioxo-1-pyrrolidinyl)propyl acetate [304]

The thiolactam **[304]** and α-bromoketone, ester, amide or nitrile were reacted in dry dichloromethane (2 $cm^3.mmol^{-1}$) for 5 h. The solvent was removed under high vacuum and the resulting salt was stirred at rt for 18 h to complete the reaction. The salt was dissolved in acetonitrile (3 $cm^3.mmol^{-1}$) and in a separate reaction vessel triphenylphosphine (1.05 eq.) and dry triethylamine (1.05 eq.) were dissolved in acetonitrile (3 $cm^3.mmol^{-1}$). Once both solutions were homogeneous the contents of the two vessels were mixed together and stirred at rt for 5 h, during which time a white precipitate was formed. The solution was filtered through a pad of celite and evaporated *in vacuo*. The residue was taken up in ethyl acetate (10 $cm^3.mmol^{-1}$), triturated for 30 minutes and again filtered through a pad of celite. The filtrate was extracted with HCl (2 M, 3 × 10 $cm^3.mmol^{-1}$), the aqueous extracts were basified to pH 11 with ammonia solution (35%) and back extracted with dichloromethane (3 × 10 $cm^3.mmol^{-1}$). The organic extracts were combined, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield the crude products. The products were purified by column chromatography.

11.5.1 3-[(2*E*)-2-(2-Oxopropylidene)pyrrolidinyl]propyl acetate [311]

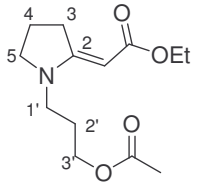


311

3-(2-Thioxo-1-pyrrolidinyl)propyl acetate **[304]** (1.03 g, 5.09 mmol) and 1-bromoacetone (0.733 g, 0.45 cm^3, 5.35 mmol, 1.05 eq.) were reacted in dry dichloromethane (10 cm^3, 2 $cm^3.mmol^{-1}$) for 5 h, thereafter the solvent was removed *in vacuo* and the resulting salt was stirred for 18 h. The salt was dissolved in acetonitrile (15.5 cm^3, 3 $cm^3.mmol^{-1}$) and a homogeneous solution of triphenylphosphine (1.41 g, 5.35 mmol, 1.05 eq.) and triethylamine (0.541 g, 0.750 cm^3, 5.35 mmol, 1.05 eq.) in acetonitrile (15.5 cm^3, 3 $cm^3.mmol^{-1}$) was added to the salt. The mixture was stirred for 5 h, after which time the standard work-up yielded the crude products as a yellow oil. Purification by column chromatography (2% methanol:di-

chloromethane) yielded 3-[(2*E*)-2-(2-oxopropylidene)-pyrrolidinyl]-propyl acetate **[311]** as a light yellow oil (1.09 g, 4.84 mmol, 95%); $\mathbf{R}_f$ 0.28 (5% methanol:dichloromethane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2955 (C-H str, w), 1736 (C=O, s), 1636 (C=C str, m), 1538 (=C-C=O str, vs), 1483 (m), 1366 (m), 1296 (m), 1229 (C-N str, s), 1202 (s), 1169 (s), 1042 (C-O str, m), 969 (m), 933 (m); **^{1}H** 5.05 (1H, s, C=CH), 4.10 (2H, t, *J* 6.2 Hz, H-3'), 3.39 (2H, t, *J* 7.2 Hz, H-5), 3.31 (2H, t, *J* 7.2 Hz, H-1'), 3.23 (2H, t, *J* 7.8 Hz, H-3), 2.09 (3H, s, C=CHCOC$\underline{H}_3$), 2.06 (3H, s, OCOCH_3), 1.95 (4H, m, H-4 & H-2'); **^{13}C** 194.1 (C=C$\underline{C}$OCH_3), 170.8 (C-2), 165.1 (O$\underline{C}$OCH_3), 89.5 (C=CH), 61.7 (C-5), 52.5 (C-3'), 43.1 (C-1'), 33.3 (C-4), 30.6 (C=CCO$\underline{C}H_3$), 25.5 (C-2'), 20.9 (C-3), 20.8 (OCO$\underline{C}H_3$); **HRMS m/z (EI)** 225.13555 (M^+ 100%, $C_{12}H_{19}NO_3$ requires 225.13649).

11.5.2 Ethyl (2*E*)-{1-[3-(acetyloxy)propyl]-2-pyrrolidinylidene}ethanoate [312][110m]

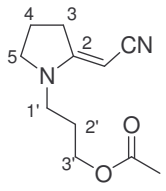


312

A solution of 3-(2-thioxo-1-pyrrolidinyl)propyl acetate **[304]** (3.89 g, 19.3 mmol) and ethyl bromoacetate (3.91 g, 2.25 cm^3, 20.3 mmol, 1.05 eq.) in dry dichloromethane (40 cm^3, 2 cm^3.mmol^{-1}) was allowed to stir for 5 h, after which time the solvent was removed *in vacuo*, and the salt was stirred for 18 h at rt. The salt was redissolved in acetonitrile (61 cm^3, 3 cm^3.mmol^{-1}), and a homogeneous solution of triphenylphosphine (5.33 g, 20.3 mmol, 1.05 eq.) and triethylamine (2.05 g, 2.83 cm^3, 20.3 mmol, 1.05 eq.) was added in one portion, after 5 h the normal work-up afforded the crude product as a yellow oil. Purification by column chromatography (30% ethyl acetate:hexane) afforded ethyl (2*E*)-{1-[3-(acetyloxy)propyl]-2-pyrrolidinylidene}ethanoate **[312]** as a light yellow oil (4.18 g, 17.5 mmol, 90%); $\mathbf{R}_f$ 0.44 (50% ethyl acetate:hexane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2972 (C-H str, m), 1736 (OC=O str, s), 1680 (C=C str,s) 1586 (=CC=O str, s), 1230 (C-N str, s), 1134 (s), 1052 (C-O str, s) **^{1}H** 4.53 (1H, s, =CH), 4.08 (2H, q, *J* 7.2 Hz, $CO_2C\underline{H}_2CH_3$), 4.07 (2H, t, *J* 6.5 Hz, H-3'), 3.38 (2H, t, *J* 7.2 Hz, H-5), 3.27 (2H, t, *J* 7.2 Hz, H-1'), 3.16 (2H, t, *J* 7.8 Hz, H-3), 2.08 (3H, s, OCOC$\underline{H}_3$), 1.95 (2H, quintet, *J* 7.5 Hz, H-2'), 1.92 (2H, quintet, *J* 6.8 Hz, H-4), 1.25 (3H, t, *J* 7.1 Hz,

$CO_2CH_2C\underline{H}_3$); **^{13}C** 170.9 ($O\underline{C}OCH_3$), 169.3 (C-2), 164.7 ($\underline{C}O_2Et$), 77.9 (=CH), 61.7 (C-5), 58.2 ($CO_2\underline{C}H_2CH_3$), 52.6 (C-3'), 43.0 (C-1'), 32.5 (C-4), 25.3 (C-2'), 21.0 (C-3), 20.8 ($OCO\underline{C}H_3$), 14.6 ($CO_2CH_2\underline{C}H_3$); **HRMS m/z (EI)** 255.14773 (M^+ 27%, $C_{13}H_{21}NO_4$ requires 255.14706), 43 (24), 97 (21), 168 (44), 169 (42), 196 (100), 210 (47), 212 (21), 255 (27).

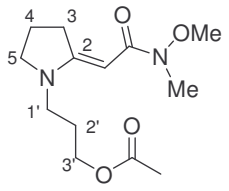
11.5.3 3-[(2*E*)-2-(Cyanomethylene)pyrrolidinyl]propyl acetate [313]



313

3-(2-Thioxo-1-pyrrolidinyl)propyl acetate **[304]** (1.01 g, 5.00 mmol) and bromoacetonitrile (0.630 g, 0.370 cm^3, 5.25 mmol, 1.05 eq.) were stirred in dry dichloromethane (10 cm^3, 2 $cm^3.mmol^{-1}$) for 5 h, and thereafter the solvent was removed *in vacuo* to yield the desired salt. The salt was stirred at rt for 18 h, then it was dissolved in acetonitrile (15 cm^3, 3 $cm^3.mmol^{-1}$). To this was added a homogeneous solution of triphenylphosphine (1.38 g, 5.25 mmol, 1.05 eq.) and triethylamine (0.531 g, 5.25 mmol, 1.05 eq.) in acetonitrile (15 cm^3, 3 $cm^3.mmol^{-1}$). Standard work-up and purification by column chromatography (ethyl acetate) afforded 3-[(2*E*)-2-(cyanomethylene)pyrrolidinyl]propyl acetate **[313]** as a light yellow oil (0.462 g, 2.22 mmol, 44%); $\mathbf{R}_f$ (ethyl acetate) 0.69; $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2963 (C-H str, m), 2187 (C≡N str, s), 1734 (OC=O str, s), 1600 (C=C str, s), 1229 (C-N str, s), 1039 (C-O str, s); **^{1}H** 4.07 (2H, t, *J* 6.2 Hz, H-3'), 3.67 (1H, s, C=CH), 3.45 (2H, t, *J* 6.9 Hz, H-5), 3.20 (2H, t, *J* 7.1 Hz, H-3), 2.88 (2H, t, *J* 7.6 Hz, H-1'), 2.08 (3H, s, $OCOCH_3$), 2.00 (2H, quintet, *J* 7.5 Hz, H-2'), 1.90 (2H, quintet, *J* 6.4 Hz, H-4); **^{13}C** 170.7 (C-2), 165.4 ($O\underline{C}OCH_3$), 122.5 (C=$\underline{C}$HCN), 61.4 (C-5), 53.6 (C=CH), 53.5 (C-3'), 42.9 (C-1'), 32.6 (C-4), 25.3 (C-3), 20.8 (C-2'), 20.7 ($OCO\underline{C}H_3$); **HRMS m/z (EI)** 208.12280 (M^+ 51%, $C_{11}H_{16}N_2O_2$ requires 208.12118), 41 (28), 42 (10), 43 (50), 94 (11), 96 (11), 97 (13), 107 (10), 108 (27), 109 (13), 121 (97), 122 (100), 135 (18), 149 (85), 165 (18), 168 (36).

11.5.4 3-((2*E*)-2-{2-[Methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)propylacetate [314]



314

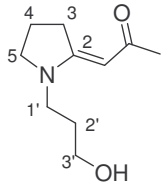
3-(2-Thioxo-1-pyrrolidinyl)propyl acetate **[304]** (6.73 g, 33.5 mmol) and 2-bromo-*N*-methoxy-*N*-methylacetamide **[271]** (6.39 g, 35.1 mmol, 1.05 eq.) were reacted in dry dichloromethane (67 cm^3, 2 $cm^3.mmol^{-1}$) for 5 h. The solvent was removed under high vacuum and the resulting salt was stirred at rt for 18 h. The salt was dissolved in acetonitrile and a homogeneous solution of triphenylphosphine (9.21 g, 35.1 mmol, 1.05 eq.) and triethylamine (3.55 g, 4.90 cm^3, 35.1 mmol, 1.05 eq.) was added in one portion. After 5 h the standard work-up afforded the crude product as a yellow oil. Purification by column chromatography (10% methanol:dichloromethane) afforded 3-((2*E*)-2-{2-[methoxy(methyl)-amino]-2-oxoethylidene}pyrrolidinyl)propyl acetate **[314]** as a light yellow oil (7.73 g, 28.6 mmol, 85%); $\mathbf{R}_f$ (20% methanol:ethyl acetate) 0.81; $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2939 (C-H str, m), 1734 (OC=O str, s), 1646 (C=ON str, s), 1426 (m), 1367 (m) 1233 (C-N str, s), 1042 (C-O str, s) **^{1}H** 5.01 (1H, s, C=CH), 4.11 (2H, t, *J* 6.3 Hz, H-3'), 3.67 (3H, s, OCH_3), 3.36 (2H, t, *J* 7.0 Hz, H-5), 3.31 (2H, t, *J* 6.8 Hz, H-1'), 3.21 (2H, t, *J* 7.4 Hz, H-3), 3.15 (3H, s, NCH_3), 2.07 (3H, s, $OCOCH_3$), 1.94 (4H, m, H-4 & H-2'); **^{13}C** 171.8 ($O\underline{C}OCH_3$), 170.8 (C-2), 164.3 ($\underline{C}ON(OCH_3)CH_3$), 76.7 (=CH), 61.9 (C-5), 60.8 (OCH_3), 52.4 (C-3'), 43.0 (C-1'), 33.0 (NCH_3), 32.5 (C-4), 25.4 (C-3), 21.2 (C-2'), 20.8 ($OCO\underline{C}H_3$); **HRMS m/z (EI)** 270.15621 (M^+ 1%, $C_{13}H_{22}N_2O_4$ requires 270.15796), 43 (12), 74 (22), 148 (12), 168 (13) 210 (100), 211 (13).

11.6 General procedure for acetate hydrolysis

To a stirred solution of the required enaminone in methanol (3.6 $cm^3.mmol^{-1}$) was added potassium carbonate (1.1-2.0 eq.). After 3 h the mixture was filtered through celite. The filtrate was evaporate *in vacuo*, and then taken up in chloroform (10 $cm^3.mmol^{-1}$) and washed with a saturated sodium chloride solution (10 $cm^3.mmol^{-1}$). The aqueous phases were back

extracted with chloroform (3 x 10 $cm^3.mmol^{-1}$), dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to afford the crude product. The crude mixture was purified by column chromatography to yield the desired alcohols.

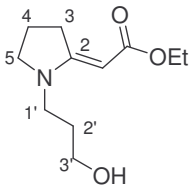
11.6.1 (1*E*)-1-[1-(3-Hydroxypropyl)-2-pyrrolidinylidene]-2-propanone [315]



315

To a stirred solution of 3-[(2*E*)-2-(2-oxopropylidene)pyrrolidinyl]propyl acetate **[311]** (0.792 g, 3.51 mmol) in methanol (13 cm^3, 3.6 $cm^3.mmol^{-1}$) was added potassium carbonate(0.534 g, 3.86 mmol, 1.1 eq.), after 3 h the reaction was worked-up. The crude product was purified by column chromatography (dichloromethane then 5% methanol:dichloromethane) to yield (1*E*)-1-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]-2-propanone **[315]** (0.527 g, 2.87 mmol, 82%) as a yellow oil; $\mathbf{R}_f$ 0.22 (5% methanol: dichloromethane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3366 (O-H str, s), 2927 (C-H str, s), 2872 (C-H str, s), 1732 (s), 1630 (C=C str, s), 1568 (=C-C=O str, s), 1427 (s), 1367 (s), 1236 (C-N str, s), 1047 (C-O str, s); **^{1}H** 5.10 (1H, s, C=CH), 3.68 (2H, t, *J* 6.0 Hz, H-3'), 3.42 (2H, t, *J* 7.3 Hz, H-5), 3.36 (2H, t, *J* 7.1 Hz, H-1'), 3.22 (2H, t, *J* 7.8 Hz, H-3), 2.30 (1H, s broad, OH), 2.06 (3H, s, $COC\underline{H}_3$), 1.95 (2H, quintet, *J* 7.5 Hz , H-2'), 1.84 (2H, quintet, *J* 6.6 Hz, H-4); **^{13}C** 194.3 (=$C\underline{C}OCH_3$), 165.7 (C-2), 89.4 (=CH), 59.7 (C-5), 52.6 (C-3'), 43.2 (C-1'), 33.6 (C-4), 30.5 (=$CCO\underline{C}H_3$), 29.0 (C-2'), 20.9 (C-3); **HRMS m/z (EI)** 183.12533 (M^+ 100% $C_{10}H_{17}NO_2$ requires 183.12593)

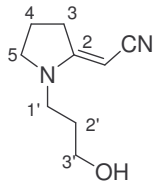
11.6.2 Ethyl (2*E*)-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]ethanoate [316][110m]



316

A solution of ethyl (2*E*)-{1-[3-(acetyloxy)propyl]-2-pyrrolidinylidene}ethanoate **[312]** (4.19 g, 17.6 mmol) and potassium carbonate (2.68 g, 19.3 mmol, 1.1 eq.) in methanol (63 cm^3, 3.6 $cm^3.mmol^{-1}$) was stirred for 3 h. The standard workup and purification by column chromatography (50% ethyl acetate:hexane then ethyl acetate) afforded ethyl (2*E*)-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]ethanoate **[316]** (3.19 g, 15.0 mmol, 85%) as a yellow oil; $\mathbf{R}_f$ (50% ethyl acetate:hexane) 0.18; $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3415 (O-H str, s), 2940 (C-H str, s), 2872 (C-H str, s), 1579 (C=O str, s), 1132 (s), 1052 (C-O str, s); **^{1}H** 4.56 (1H, s, C=CH), 4.08 (2H, q, *J* 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 3.67 (2H, t, *J* 6.0 Hz, H-3'), 3.39 (2H, t, *J* 7.1 Hz, H-5), 3.31 (2H, t, *J* 7.2 Hz, H-1'), 3.15 (2H, t, *J* 7.8 Hz, H-3), 1.99 (1H, s broad, OH), 1.94 (2H, quintet, *J* 7.5 Hz, H-2'), 1.82 (2H, quintet, *J* 6.6 Hz, H-4), 1.25 (3H, t, *J* 7.1 Hz, $CO_2CH_2C\underline{H}_3$); **^{13}C** 169.6 (C-2), 165.0 ($\underline{C}O_2CH_2CH_3$), 77.4 (=CH), 60.0 (C-5), 58.3 ($CO_2\underline{C}H_2CH_3$), 52.7 (C-3'), 43.0 (C-1'), 32.7 (C-4), 28.9 (C-2'), 21.0 (C-3), 14.7 ($CO_2CH_2\underline{C}H_3$); **HRMS m/z (EI)** 213.13665 (M^+ 39%, $C_{11}H_{19}NO_3$ requires 213.13649), 41 (26), 96 (69), 97 (68), 98 (33), 108 (23), 110 (25), 126 (36), 154 (27), 168 (84), 169 (100).

11.6.3 (2*E*)-[1-(3-Hydroxypropyl)-2-pyrrolidinylidene]ethanenitrile [317]

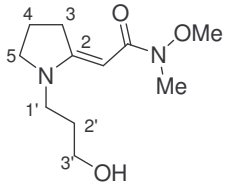


317

To a stirring solution of 3-[(2*E*)-2-(cyanomethylene)pyrrolidinyl]propyl acetate **[313]** (1.37 g, 6.56 mmol) in methanol (24 cm^3, 3.6 $cm^3.mmol^{-1}$) was added potassium carbonate (1.31 g, 13.1 mmol, 2.0 eq.). The mixture was stirred for 3 h, after which time the standard work-up and purification by column chromatography (5% methanol:dichloromethane) yielded (2*E*)-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]ethanenitrile **[317]** (0.972 g, 5.85 mmol, 89%) as a yellow oil; $\mathbf{R}_f$ 0.41 (5% methanol:dichloromethane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3403 (O-H str, s), 2942 (C-H str, s), 2873 (C-H str, s), 2178 (C≡N str, s), 1595 (vs), 1289 (s), 1052 (C-O str, s) **^{1}H** 3.73 (1H, s, =CH), 3.64 (2H, t, *J* 5.6, H-3'), 3.47 (2H, t, *J* 6.9, H-5), 3.25 (2H, t, *J* 7.1, H-1'), 2.86 (2H, t, *J* 7.8, H-3), 2.47 (1H, s broad, OH), 1.99 (2H, quintet, *J* 7.3, H-2'), 1.79 (2H,

quintet, *J* 6.5, H-4); **^{13}C** 165.8 (C-2), 123.2 (CN), 59.4 (C-5), 53.6 (=CH), 52.7 (C-3'), 43.0 (C-1'), 32.7 (C-4), 28.9 (C-2'), 20.7 (C-3); **HRMS m/z (EI)** 166.10937 (M^+ 41%, $C_9H_{14}N_2O$ requires 166.11061), 135 (17), 126 (27), 122 (100), 121 (65), 109 (17), 98 (22), 96 (17), 94 (18), 41 (24).

11.6.4 (2*E*)-2-[1-(3-Hydroxypropyl)-2-pyrrolidinylidene]-*N*-methoxy-*N*-methyl-ethanamide [318]



318

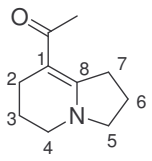
3-((2*E*)-2-{2-[Methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)propyl acetate **[314]** (7.73 g, 28.6 mmol) and potassium carbonate (7.91 g, 57.2 mmol, 2.0 eq.) were stirred in methanol (100 cm^3, 3.6 $cm^3.mmol^{-1}$) for 3 h. Thereafter the normal work-up and purification by column chromatography (10% methanol:dichloromethane) gave (2*E*)-2-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]-*N*-methoxy-*N*-methylethanamide **[318]** (5.45 g, 23.9 mmol, 83%) as a yellow oil; $\mathbf{R}_f$ 0.85 (30 % methanol:dichloromethane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3353 (O-H str, s), 2938 (C-H str, s), 2874 (C-H str, s) 1646 (C=C str, s), 1613 (C=O str, s), 1438 (s), 1423 (s), 1360 (s), 1170 (s), 1019 (s); **^{1}H** 5.14 (1H, s, C=CH), 3.68 (2H, t, *J* 6.0 Hz, H-3'), 3.67 (3H, OCH_3), 3.38 (2H, t, *J* 7.0 Hz, H-5), 3.36 (2H, t, *J* 6.9 Hz, H-1'), 3.22 (2H, t, *J* 7.8 Hz, H-3), 3.14 (3H, s, NCH_3), 2.04 (1H, s, OH), 1.93 (2H, quintet, *J* 6.8 Hz, H-2'), 1.84 (2H, quintet, *J* 6.3 Hz, H-4); **^{13}C** 172.1 (C-2), 164.8 ($\underline{C}ON(OCH_3)CH_3$), 76.3 (C=CH), 60.9 ($OCH_3$), 59.9 (C-5), 52.3 (C-3'), 42.9 (C-1'), 33.1 (C-4), 32.6 (NCH_3), 29.1 (C-2'), 21.2 (C-3); **HRMS m/z (EI)** 228.14788 (M^+ 2%, $C_{11}H_{20}N_2O_3$ requires 228.14739), 108 (5), 110(5), 120 (5), 150 (5), 168 (100), 169 (12).

11.7 General procedure for the alkylative ring closure

A stirring solution of alcohol in acetonitrile:toluene (6.2 $cm^3.mmol^{-1}$:3.1 $cm^3.mmol^{-1}$) was charged with triphenylphosphine (2.0-3.0 eq.) and imidazole (2.0-3.0 eq.). Once the solids had dissolved iodine (2.0 eq.) was added in one portion. The homogeneous solution was stirred

under reflux for 1 h. The reaction was quenched by the addition of a solution of saturated sodium hydrogen carbonate (10 $cm^3.mmol^{-1}$), and the aqueous residues were extracted with ethyl acetate (3 × 10 $cm^3.mmol^{-1}$). The combined organic fractions were washed with saturated aqueous sodium thiosulfate (10 $cm^3.mmol^{-1}$). The organic washings were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield the crude product. Purification by column chromatography yielded the desired bicyclic compounds.

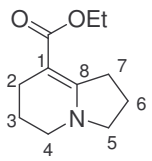
11.7.1 1-(1,2,3,5,6,7-Hexahydro-8-indolizinyl)ethanone [319]



319

Triphenylphosphine (10.1 g, 38.5 mmol, 3.0 eq.) and imidazole (2.63 g, 38.5 mmol, 3.0 eq.) was added to a stirring solution of (1*E*)-1-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]-2-propanone **[315]** (2.35 g, 12.9 mmol) in acetonitrile:toluene (80 cm^3: 40 cm^3, 6.2 $cm^3.mmol^{-1}$:3.1 $cm^3.mmol^{-1}$). Thereafter iodine (6.50 g, 25.7 mmol) was added in one portion, and the homogeneous solution was refluxed for 1h. Standard workup and purification by column chromatography (5% methanol:dichloromethane) gave 1-(1,2,3,5,6,7-hexahydro-8-indolizinyl)-ethanone **[319]** (0.567 g, 3.43 mmol, 27%) as a clear oil; $\mathbf{R}_f$ 0.32 (5% methanol:dichloromethane); ^{1}**H** 7.60-7.34 (triphenylphosphine residues), 3.27 (2H, m, H-4)*, 3.14-3.01 (4H, m, H-5 & H-2)*, 2.33 (2H, m, H-7)*, 2.03 (3H, s, $COCH_3$), 1.84-1.70 (4H, m, H-3 & H-6). * These assignments may be interchanged.

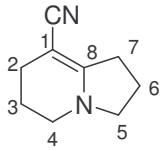
11.7.2 Ethyl 1,2,3,5,6,7-hexahydro-8-indolizinecarboxylate [320]



320

Ethyl (2*E*)-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]ethanoate **[3162]** (0.865 g, 4.05 mmol) in acetonitrile:toluene (26 cm^3:13 cm^3, 6.2 $cm^3.mmol^{-1}$:3.1 $cm^3.mmol^{-1}$) was charged with triphenylphosphine (3.19 g, 12.2 mmol, 3.0 eq.) and imidazole (0.827 g, 12.2 mmol, 3.0 eq.), thereafter iodine (2.06 g, 8.10 mmol, 2.0 eq.) was added in one portion, and the solution was refluxed for 1 h. The regular work-up and purification by column chromatography (30% ethyl acetate:hexane) afforded ethyl 1,2,3,5,6,7-hexahydro-8-indolizinecarboxylate **[320]** (0.438 g, 2.39 mmol, 59%) as a clear oil; $\mathbf{R}_f$ (50% ethyl acetate:hexane) 0.61; $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2943 (C-H str, m), 2845 (C-H str, m), 1674 (C=O str, s), 1584 (vs), 1425 (m), 1368 (m), 1255 (vs), 1215 (s), 1181 (s), 1095 (vs), 1041 (s), 763 (s); **^{1}H** 4.00 (2H, q, *J* 7.0, $CO_2C\underline{H}_2CH_3$), 3.19 (2H, t, *J* 7.0, H-4)$^{\#}$, 3.06 (2H, t, *J* 6.0, H-5)$^{\#}$, 2.96 (2H, t, *J* 8.0, H-7), 2.25 (2H, t, *J* 6.5, H-2), 1.82 (2H, quintet, *J* 7.5, H-3)*, 1.82 (2H, quintet, *J* 6.0, H-6)*, 1.16 (3H, t, *J* 7.0, $CO_2CH_2C\underline{H}_3$); **^{13}C** 168.1 ($\underline{C}O_2CH_2CH_3$), 158.6 (C-8), 86.9 (C-1), 57.8 (C-5), 52.4 ($CO_2\underline{C}H_2CH_3$), 44.5 (C-4), 32.2 (C-6), 21.1 (C-7), 20.9 (C-2), 20.5 (C-3), 14.3 ($CO_2CH_2\underline{C}H_3$).***** These assignments may be interchanged, $^{\#}$ These assignments may be interchanged.

11.7.3 1,2,3,5,6,7-Hexahydro-8-indolizinecarbonitrile [321]

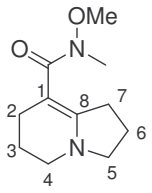


321

A stirring solution of (2*E*)-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]ethanenitrile **[317]** (0.583 g, 0.519 g, 3.51 mmol) in acetonitrile:toluene (21 cm^3:11 cm^3, 6.2 $cm^3.mmol^{-1}$:3.1 $cm^3.mmol^{-1}$) was charged with triphenylphosphine (1.84 g, 7.02 mmol, 2.0 eq.) and imidazole (0.479 g, 7.02 mmol, 2.0 eq.). Iodine (1.76 g, 7.02 mmol, 2.0 eq.) was then added and the solution was refluxed for 1 h. Standard work-up and purification by column chromatography (5% methanol:dichloromethane) gave 1,2,3,5,6,7-hexahydro-8-indolizinecarbonitrile **[321]** as a clear oil (0.375 g, 2.53 mmol, 72%); $\mathbf{R}_f$ 0.75 (methanol:dichloromethane 5:95)**;** $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2930 (C-H str, s), 2849 (C-H str, s), 2173 (C≡N str, s), 1615 (C=C str, vs), 1289 (vs); **^{1}H** 3.33 (2H, t, *J* 6.8 Hz , H-4)$^{\#}$, 3.15 (2H, t, *J* 5.4 Hz, H-5)$^{\#}$, 2.74 (2H, t, *J* 7.7 Hz, H-7), 2.23 (2H, t, *J* 6.1 Hz, H-2), 1.97 (2H, quintet, *J* 7.3 Hz, H-3)*, 1.84 (2H, quintet, *J* 5.9 Hz, H-6)*; **^{13}C** 159.2 (C-8), 123.8 (CN), 64.2 (C-1), 53.2 (C-5), 44.0 (C-4), 30.6 (C-6), 22.1 (C-7),

21.0 (C-2), 20.7 (C-3); **HRMS m/z (EI)** 148.09995 (M^+ 73%, $C_9H_{12}N_2$ requires 148.10005), 41 (10), 92 (9), 108 (20), 120 (13), 145 (11), 147, (100), 148 (73). * These assignments may be interchanged, # These assignments may be interchanged.

11.7.4 *N*-Methoxy-*N*-methyl-1,2,3,5,6,7-hexahydro-8-indolizinecarboxamide [322]



322

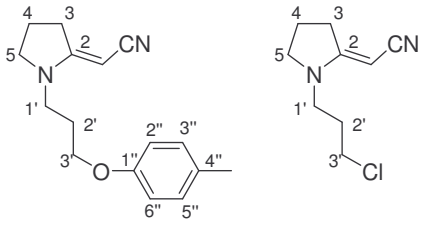
A solution of (2*E*)-2-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]-*N*-methoxy-*N*-methylethanamide **[318]** (0.776 g, 2.79 mmol) was dissolved in acetonitrile:toluene (17 cm^3:8.5 cm^3, 6.2 $cm^3.mmol^{-1}$:3.1 $cm^3.mmol^{-1}$). To this was added triphenylphosphine (1.46 g, 5.58 mmol, 2.0 eq.) and imidazole (0.380 g, 5.58 mmol, 2.0 eq.) followed by iodine (1.42 g, 5.58 mmol, 2.0 eq.). The solution was refluxed for 1 h. Normal work-up and purification by flash column chromatography (5% ethanol:ethyl acetate) yielded *N*-methoxy-*N*-methyl-1,2,3,5,6,7-hexahydro-8-indolizinecarboxamide **[322]** (0.375 g, 1.78 mmol, 64%); $\mathbf{R}_f$ (5% methanol:dichloromethane) 0.19; **^{1}H** 3.62 (3H, s, OCH_3), 3.26 (2H, t, *J* 7.0, H-4)#, 3.18 (2H, t, *J* 5.6, H-5)#, 3.06 (3H, s, NCH_3), 3.01 (2H, t, *J* 7.8, H-7), 2.38 (2H, t, *J* 6.0, H-2), 1.90 (2H, quintet, *J* 5.8, H-3)*, 1.83 (2H, quintet, *J* 5.8, H-6)*; **^{13}C** 174.4 (C-8), 157.7 (CON(OMe)Me), 90.0 (C-1), 59.7 (OCH_3), 52.6 (C-5), 45.0 (C-4), 34.3 (NCH_3), 31.7 (C-6), 23.6 (C-7), 21.9 (C-2), 21.2 (C-3); **HRMS m/z (EI)** 210.13519 (M^+ 38% $C_{11}H_{18}N_2O_2$ requires 210.13683).
* These assignments may be interchanged, # These assignments may be interchanged.

11.8 General procedure for tosylation and mesylation of alcohols

To a solution of toluenesulfonyl chloride (1.4 eq.) or methanesulfonyl chloride (1.4 eq.) in dichloromethane (9 $cm^3.mmol^{-1}$) at rt was added triethylamine (9.8 eq.) and DMAP (0.1 eq.). After 30 minutes the alcohol was added in one portion. The solution turned brown over time and after 18 h the solution was washed with water (10 $cm^3.mmol^{-1}$). The organic layer was separated, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield a

brown solid. The crude solid was purified by column chromatography) to yield the desired products.

11.8.1 3-[(2*E*)-2-(Cyanomethylene)pyrrolidinyl]propyl 4-methylbenzenesulfonate [324] and (2*E*)-[1-(3-chloropropyl)-2-pyrrolidinylidene]ethanenitrile [325]



324 **325**

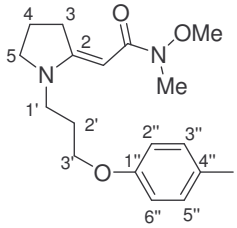
Triethylamine (4.14 g, 5.71 cm^3, 40.9 mmol, 9.8 eq.) and DMAP (0.0550 g, 0.418 mmol, 0.1 eq.) were added to a solution of toluenesulfonyl chloride (1.15 g, 5.85 mmol, 1.4 eq.) in dichloromethane at rt. After 30 min (2*E*)-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]ethanenitrile **[317]** (0.694 g, 4.18 mmol) was added in one portion. The standard work-up and purification by column chromatography (30% then 50% ethyl acetate hexane) afforded 3-[(2*E*)-2-(cyanomethylene)pyrrolidinyl]propyl-4-methylbenzenesulfonate **[320]** (0.261 g, 0.811 mmol, 19%) as a yellow solid and (2*E*)-[1-(3-chloropropyl)-2-pyrrolidinylidene]ethanenitrile **[324]** (trace) as a brown oil; $\mathbf{R}_f$ (50% ethyl acetate:hexane) 0.17; ν_{max} **(film)/cm^{-1}** 2967 (C-H str, m), 2178 (C≡N str, s), 1599 (C=C aromatic str, s), 1493 (C=C aromatic str, s) 1359 (s), 1311 (s), 1293 (s), 1171 (s), 1120 (s), 1054 (C-O str, s), 1019 (s); **^{1}H** 7.79 (2H, d, *J* 8.2 Hz, H-2'' & H-6''), 7.38 (2H, d, *J* 8.1 Hz, H-3'' & H-5''), 4.04 (2H, t, *J* 5.8 Hz, H-3'), 3.55 (1H, s, C=CH), 3.38 (2H, t, *J* 6.9 Hz, H-3), 3.18 (2H, t, *J* 6.9 Hz, H-5), 2.81 (2H, t, *J* 7.7 Hz, H-1'), 2.47 (3H, s, PhC$\underline{H}_3$), 1.92-1.91 (4H, m, H-2' & H-4); **^{13}C** 165.4 (C-2), 145.2 (C-1''), 132.5 (C-4''), 129.9 (C-3'' & C-5''), 127.8 (C-2'' & C-6''), 122.3 (CN), 67.4 (C-3'), 54.0 (C-5), 53.8 (C=CH), 42.4 (C-1'), 32.6 (C-4), 25.6 (C-3), 21.6 (C-2'), 20.7 (Ph$\underline{C}H_3$)**.**

Spectrosopic data for (2*E*)-[1-(3-chloropropyl)-2-pyrrolidinylidene]ethanenitrile **[325]**

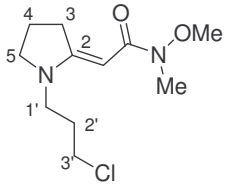
$\mathbf{R}_f$ (ethyl acetate:hexane 1:1) 0.31; ν_{max} **(film)/cm^{-1}** 2963 (C-H str, s), 2868 (C-H str, s), 2187 (C≡N str, s), 1598 (C=C aromatic str, vs), 1428 (s), 1272 (s); **^{1}H** 3.73 (1H, s, C=CH), 3.56

(2H, t, *J* 6.1 Hz, H-3'), 3.47 (2H, t, *J* 6.9 Hz, H-5), 3.30 (2H, t, *J* 6.9 Hz, H-1'), 2.88 (2H, t, *J* 7.8 Hz, H-3), 2.03 (2H, quintet, *J* 6.2 Hz, H-2'), 2.00 (2H, quintet, *J* 7.4 Hz, H-4); **^{13}C** 165.5 (C-2), 122.5 (CN), 53.9 (C-5), 53.9 (C-5), 43.3 (C-1'), 42.0 (C-3'), 32.6 (C-4), 28.9 (C-2'), 20.8 (C-3); **HRMS m/z (EI)** 184.07618 (M^+ 100%, $C_9H_{13}ClN_2$ requires 184.076731).

11.8.2 3-((2*E*)-2-{2-[Methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)propyl 4-methylbenzenesulfonate [326] and (2*E*)-2-[1-(3-chloropropyl)-2-pyrrolidinylidene]-*N*-methoxy-*N*-methylethanamide [327]



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327

To a solution of toluenesulfonyl chloride (0.245 g, 1.25 mmol, 1.4 eq.) in dichloromethane (7.8 cm^3, 8.7 $cm^3.mmol^{-1}$) was added triethylamine (0.889 g, 1.2 cm^3 8.78 mmol, 9.8 eq.) and DMAP (11.0 mg, 9×10^{-2} mmol, 0.1 eq.). The solution was stirred at rt for 30 min after which time (2*E*)-2-[1-(3-hydroxypropyl)-2-pyrrolidinylidene]-*N*-methoxy-*N*-methylethanamide **[318]** (0.202 g, 0.896 mmol) was added in one portion. The normal work-up and purification by column chromatography (30% ethyl acetate:hexane) yielded 3-((2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)propyl-4-methylbenzenesulfonate **[326]** (0.204 g, 0.639 mmol, 71%) as a brown oil containing trace amounts of (2*E*)-2-[1-(3-chloropropyl)-2-pyrrolidinylidene]-*N*-methoxy-*N*-methylethanamide **[327]**; $\mathbf{R}_f$ (50% ethyl acetate:hexane) 0.37; $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3450 (s), 2942 (C-H str, s), 1652 (C=O str, s), 1493 (s), 1172 (vs), 1119 (vs), 1032 (C-O str, vs), 1010 (vs); **^{1}H** 7.79 (2H, d, *J* 8.2, H-3'' & H-5''), 7.36 (2H, d, *J* 8.0, H-2'' & H-6''), 5.04 (1H, s, =CH), 4.05 (2H, t, *J* 5.9, H-3'), 3.65 (3H, s, OCH_3), 3.29 (2H, t, *J* 7.0, H-5), 3.28 (2H, t, *J* 7.0, H-1'), 3.21-3.17 (2H, m, H-3), 3.14 (3H, s, NCH_3), 2.45 (3H, s, Ph$C\underline{H}_3$), 1.95 (2H, quintet, *J* 6.6, H-2'), 1.88, (2H, quintet, *J* 7.5, H-4), **^{13}C** 171.6 (C-2), 164.1 (C=O), 144.9 (C-1''), 132.7 (C-4''), 129.9 (C-3'' & C-5''), 127.8 (C-2'' & C-6''), 77.1 (=CH), 67.7 (C-3'), 60.9 (OCH_3), 52.5 (C-5), 42.4 (C-1'), 32.9 (NCH_3), 32.4 (C-4), 25.6 (C-3), 21.6 (C-2'), 21.2 (Ph$\underline{C}H_3$).

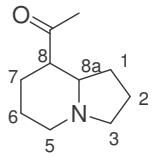
Identifiable peaks for (2*E*)-2-[1-(3-chloropropyl)-2-pyrrolidinylidene]-*N*-methoxy-*N*-methyl-ethanamide **[327]**

^{1}H 5.16 (1H, s, =CH), 3.68 (3H, s, OCH_3), 3.42 (2H, t, *J* 7.1, H-5), 3.41 (2H, t , *J* 6.9, H-1'), 3.38 (2H, t, *J* 6.5, H-3), 3.17 (3H, s, NCH_3), 2.11-2.00 (4H, m, H-4 & H-2').

11.9 Catalytic reduction of the enaminone system

The required bicyclic enaminone was dissolved in glacial acetic acid (5.5 $cm^3.mmol^{-1}$). To this was added Adams' catalyst (5×10^{-2} $g.mmol^{-1}$) and the stirring mixture was placed under a hydrogen atmosphere (1 atmosphere) and left for 24 h. The mixture was filtered through celite and washed copiously with ethanol, wereafter it was evaporated *in vacuo* to yield the crude products. Purification by column chromatography yielded the desired reduced compounds.

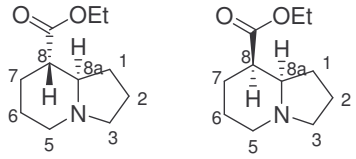
11.9.1 Attempted synthesis of 1-octahydro-8-indolizinylethanone [300]



300

Bicyclic enaminone **[319]** (0.300 g, 1.82 mmol) was dissolved in ethanol (24 cm^3, 13 $cm^3.mmol^{-1}$) and subjected to hydrogenation at 5 atmospheres in the presence of Adams' catalyst (0.091 g, 0.05 $g.mmol^{-1}$), after 24 h the standard workup and purification by column chromatography yielded an unidentifiable product.

11.9.2 Ethyl (8*S*,8a*R*)-octahydro-8-indolizinecarboxylate [301a] and ethyl (8*R*,8a*R*)-octahydro-8-indolizinecarboxylate [301b]



301a **301b**

1,2,3,5,6,7-Hexahydro-8-indolizinecarboxylate **[320]** (0.513 g, 2.63 mmol) was dissolved in glacial acetic acid (14.5 cm^3, 5.5 $cm^3.mmol^{-1}$), Adams' catalyst (0.132 g, 5×10^{-2} $g.mmol^{-1}$) was added, and the stirred solution was hydrogenated at 1 atmosphere for 24 h. The regular workup followed by column chromatography gave Ethyl (8*S*,8a*R*)-octahydro-8-indolizine-carboxylate **[301a]** and ethyl (8*R*,8a*R*)-octahydro-8-indolizinecarboxylate **[301b]** as a mixture of diastereomers in the ratio **[301b]**:**[301a]** 85:15 (0.375 g, 0.722 mmol, 72%) as a clear oil. The mixture was partially separated by flash column chromatography (5% methanol:dichloro-methane) affording pure samples of **[301a]** and **[301b]** for characterization.

Fraction 1 [301a]

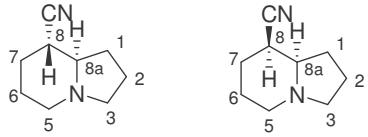
R_f 0.36 (5% methanol:dichloromethane); **ν_{max} (film)/cm^{-1}** 3420 (s), 2932 (C-H str, m), 2851 (C-H str, m), 1726 (s), 1665 (s), 1293 (m), 1192 (s), 1173 (s), 1119 (s), 1026 (C-O str, s); **^{1}H** 4.13 (2H, q, *J* 7.0 Hz, $C\underline{H}_2CH_3$), 3.06 (2H, dt, *J* 2.0 & 8.8 Hz, H-3_{eq}), 2.26-2.22 (1H, m, H^*), 2.13 (1H, q, *J* 9.0 Hz, H-8a), 2.06-1.90 (4H, m, H^*), 1.86-1.56 (4H, m, H^*), 1.55-1.37 (2H, m, H^*), 1.26 (3H, t, *J* 7.0 Hz, $CH_2C\underline{H}_3$); **^{13}C** 174.3 (C=O), 65.1 (C-8a), 60.1 ($O\underline{C}H_2CH_3$), 54.0 (C-3), 52.2 (C-5), 48.1 (C-8), 29.1 (C-6), 28.1 (C-7), 24.7 (C-6), 20.5 (C-2), 14.2 ($OCH_2\underline{C}H_3$); **HRMS m/z (EI)** 197.13962 (M^+ 7%, $C_{11}H_{19}NO_2$ requires 197.14158), 182 (100), 164, (48), 154 (16), 136 (57), 111 (11), 108 (21), 83 (20), 70 (12), 55 (17), 41 (28).* Remaining hydrogens.

Fraction 2 [301b]

R_f 0.29 (5% methanol:dichloromethane); **ν_{max} (film)/cm^{-1}** 3402 (s), 2940 (C-H str, s), 1727 (C=O str, vs), 1660 (s), 1587 (s), 1302 (s), 1182 (s), 1156 (s), 1107 (s), 1022 (s); **^{1}H** 4.16-3.99 (2H, m, $OC\underline{H}_2CH_3$), 3.04-2.96 (2H, m, H-3_{eq}), 2.71-2.70 (1H, m, H^*), 2.14-2.07 (1H, m, H-

3_{ax}), 2.05-1.88 (4H, m, H*), 1.83-1.33 (6H, m, H*), 1.18 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$); **^{13}C**; 173.0 (C=O), 64.3 (C-8a), 59.7 ($O\underline{C}H_2CH_3$), 54.7 (C-3), 52.8 (C-5), 41.5 (C-8), 26.4 (C-7)#, 26.1 (C-1)#, 22.3 (C-6), 20.4 (C-2), 14.1 ($OCH_2\underline{C}H_3$); **HRMS m/z (EI)** 197.14182 (M^+ 43%, $C_{11}H_{19}NO_2$ requires 197.14158), 41 (46), 43 (40), 55 (35), 57 (48), 69 (47), 70 (36), 71 (31), 83 (51), 96 (92), 97 (93), 122 (42), 149 (71), 150 (35), 152 (41), 168 (100), 196 (41).* Remaining hydrogens, # These assignments may be interchanged.

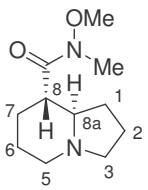
11.9.3 (8*S*,8a*R*)-octahydro-8-indolizinecarbonitrile [302a] and (8*R*,8a*R*)-octahydro-8-indolizinecarbonitrile [302b]



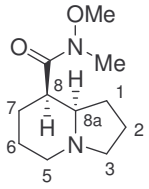
302a **302b**

Vinylogous cyanamide **[321]** (0.472 g, 3.19 mmol) was dissolved in glacial acetic acid (17.5 cm^3, 5.5 $cm^3.mmol^{-1}$) in the presence of Adams' catalyst (0.160 g, 0.05 $g.mmol^{-1}$). Subsequent hydrogenation at 1 atmosphere over 24 h, followed by the normal workup and purification by column chromatography (5% methanol:dichloromethane) gave an inseparable diastereomeric mixture of (8*S*,8a*R*)-octahydro-8-indolizinecarbonitrile **[302a]** and (8*R*,8a*R*)-octahydro-8-indolizinecarbonitrile **[302b]** in a ratio of **[302b]**:**[302a]** 92:8 as an orange oil (0.629 g, 3.19 mmol, 85%); $\mathbf{R}_f$ 0.13 (methanol:dichloromethane 1:19); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2923 (C-H str, s), 2854 (C-H str, s), 2360 (C≡N str, s), 1728, (s), 1658 (s), 1456 (s), 1260 (s), 1092 (s), 1062 (s), 1029 (s); **^{1}H** 3.16-3.02 (2H, m, H-3_{eq}), 2.96-2.95 (1H, m, H*), 2.16-1.58 (12H, m, H*), 1.49 (2H, dt, *J* 4.1 & 13.1, H*); **^{13}C** 120.0 (CN), 63.3 (C-8a), 53.8 (C-3), 52.2 (C-5), 31.9 (C-8), 28.4 (C-1), 27.5 (C-7), 22.0 (C-2), 20.4 (C-6).* Remaining hydrogens.

11.9.4 (8*S*,8a*R*)-*N*-methoxy-*N*-methyloctahydro-8-indolizinecarboxamide [303a] and (8*R*,8a*R*)-*N*-methoxy-*N*-methyloctahydro-8-indolizinecarboxamide [303b]



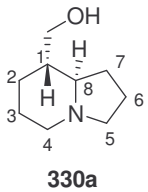
303a



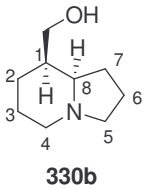
303b

A solution of bicyclic enaminone **[322]** (0.173 g, 0.823 mmol) in glacial acetic acid (4.5 cm^3, 5.5 $cm^3.mmol^{-1}$), in the presence of Adams' catalyst (0.041 g, 5×10^{-2} $g.mmol^{-1}$) was hydrogenated for 24 h at 1 atmosphere. The standard workup and purification by column chromatography (5% methanol:dichloromethane) afforded (8*S*,8a*R*)-*N*-methoxy-*N*-methyloctahydro-8-indolizinecar-boxamide **[303a]** and (8*R*,8a*R*)-*N*-methoxy-*N*-methyloctahydro-8-indolizinecarboxamide **[303b]** as inseparable diastereomers in a ratio **[303b]**:**[303a]** 95:5 as a yellow oil (0.0430 g, 0.203 mmol, 25%); ν_{max} **(film)/cm^{-1}** 2928 (C-H, s), 1663 (C=O, s), 1441 (m), 1378 (m), 1342 (m), 1160 (m), 1100 (m), 1039 (w), 998 (s), 963 (m); **^{1}H** 3.67 (3H, s, $NOCH_3$), 3.18 (3H, s, NCH_3), 3.08-2.94 (2H, m, H-8 & H-8a), 2.38-2.31 (1H, m, H*), 2.26-1.98 (3H, m, H*), 1.95-1.43 (8H, m, H*); **^{13}C** 174.7 (C=O), 63.5 (C-8a), 61.2 ($NOCH_3$), 54.4 (C-3), 51.8 (C-5), 37.0 (C-8), 29.6 (NCH_3), 26.1 (C-1), 25.2 (C-7), 22.8 (C-2), 20.4 (C-6); **HRMS m/z (EI)** 212.15176 (M^+ 62%, $C_{11}H_{20}N_2O_2$ requires 212.15248).* Remaining hydrogens.

11.10 (±)-Tashiromine [330a] and (±)-5-epitashiromine [330b]



330a



330b

A mixture of ethyl (8*S*,8a*R*)-octahydro-8-indolizinecarboxylate **[301a]** and ethyl (8*R*,8a*R*)-octahydro-8-indolizinecarboxylate **[301b]** (0.675 g, 3.42 mmol) in diethyl ether (13.7 cm^3, 4 $cm^3.mmol^{-1}$) was added dropwise to a slurry of lithium aluminium hydride (0.196 g, 5.13 mmol, 1.5 eq.) in diethyl ether (6.8 $cm^3.mmol^{-1}$) at 0 °C. The mixture was warmed to rt and

stirred for 16 h. The reaction was quenched by the sequential addition of water (0.8 cm^3), sodium hydroxide (0.8 cm^3, 15% w/v) and finally water (2.4 cm^3). The solids were removed by passing the mixture through a thin pad of celite. The filtrate was dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield (±)-tashiromine **[330a]** and its epimer (±)-5-epitashiromine **[330b]** as a mixture of diastereomers in the ratio **[330b]**:**[330a]** (13:87, 0.464 g, 2.99 mmol, 87%). The two of diastereomers were separated by flash column chromatography using methanol:dichloromethane:ammonium hydroxide (95:4.75:0.25) as eluent.

(±)-Tashiromine **[330a]**

^{1}H 3.60 (1H, dd, *J* 10.7 & 4.6 Hz, C$\underline{H}_{2a}$OH), 3.43 (1H, dd, *J* 10.7 & 6.5 Hz, C$\underline{H}_{2a}$OH), 3.25 (1H, s broad, OH), 3.12-3.04 (2H, m, H-4_{eq} & H-5_{eq}), 2.08 (1H, q, *J* 9.1 Hz), 1.98-1.85 (1H, m, H*), 1.94 (2H, ddd, *J* 16.7, 12.4 & 2.8 Hz, H*), 1.85-1.59 (4H, m, H*), 1.55-1.42 (2H, m, H*), 1.04 (2H, ddd, *J* 24.7, 12.4 & 5.0 Hz, H*); **^{13}C** 66.5 (C-8), 65.0 (CH_2OH), 54.0 (C-5), 52.6 (C-4), 44.3 (C-1), 28.8 (C-2)$^\#$, 27.5 (C-7)$^\#$, 24.9 (C-3)$^\#$, 20.6 (C-6); **HRMS m/z (EI)** 155.12940 (M^+ 93% $C_9H_{17}NO$ requires 155.13101).* Remaining hydrogens, $^\#$ These assignments may be interchanged.

(±)-5-Epitashiromine **[330b]**

^{1}H 4.53 (1H, s broad, OH), 4.12 (1H, dd, *J* 10.7 & 4.5 Hz, CH_{2a}OH), 3.74 (1H, dd, *J* 10.7 & 1.8 Hz, -CH_{2b}OH), 3.11-3.07 (1H, m, H-4_{eq}), 3.01 (1H, ddd, *J* 9.1, 2.9, 1.8 Hz, H-5_{eq}), 2.29-2.23 (1H, m, H-8), 2.07-1.95 (3H, m, H*), 1.93-1.87 (2H, m, H*), 1.84-1.65 (4H, m, H*), 1.64-1.47 (2H, m, H*); **^{13}C** 66.5 (C-8), 64.9 (CH_2OH), 54.3 (C-5), 53.3 (C-4), 35.4 (C-1), 29.9 (C-2)$^\#$, 25.6 (C-7)$^\#$, 22.9 (C-3)$^\#$, 20.6 (C-6); **HRMS m/z (EI)** 155.12955 (M^+ 81% $C_9H_{17}NO$ requires 155.13101). *Remaining hydrogens, $^\#$ These assignments may be interchanged.

CHAPTER 12

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 5

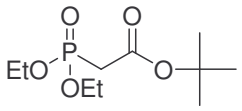
ENANTIOSELECTIVE SYNTHESIS OF 5,8-DISUBSTITUTED INDOLIZIDINES



CHAPTER 12

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 5
ENANTIOSELECTIVE SYNTHESIS OF 5,8-DISUBSTITUTED INDOLIZIDINES

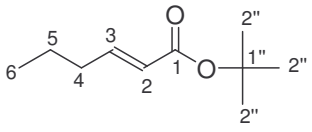
12.1 *tert*-Butyl diethoxyphosphorylacetate [246][169]



246

Triethyl phosphite was treated with sodium metal overnight and then distilled to remove traces of water. The distilled triethyl phosphite (16.6 g, 17.3 cm^3, 100 mmol, 1.1 eq.) and *tert*-butyl bromoacetate **[335]** (17.6 g, 13.3 cm^3, 91.0 mmol) were heated at 110 °C under argon for 4 h. The crude mixture was cooled to rt and purified by distillation (oil pump, *ca* 1 mmHg). *tert*-Butyl diethoxyphosphorylacetate **[246]** (20.6 g, 82.0 mmol, 90%) was obtained as a colourless liquid. **Bp** 115 °C (*ca* 1 mmHg); $\mathbf{R}_f$ 0.10 (5% ethyl acetate:hexane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2982 (C-H str, m), 2935 (C-H str, m), 1731 (C=O str, s), 1648 (w), 1549 (w), 1532 (w), 1514 (w), 1463 (C-H bend, m), 1397 (s), 1372 (C-H bend, s), 1288 (C-O str, s), 1260 (P=O str, s), 1169 (C-O str, m), 1114 (m), 1028 (P-O str, s), 965 (s); **^{1}H** 4.16 (2H, q, *J* 7.2 Hz, $OC\underline{H}_2CH_3$), 2.88 (2H, d, *J* 21.5 Hz, $CH_2P{=}O$), 1.48 (9H, s, $C(CH_3)_3$), 1.35 (6H, t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$); **^{13}C** 164.9 (d, *J* 6.4 Hz, C=O), 81.9 ($\underline{C}(CH_3)_3$), 62.4 (d, *J* 6.2 Hz, 2 × $O\underline{C}H_2CH_3$), 35.5 (d, *J* 133.2 Hz, $CH_2P{=}O$), 27.8 ($C(\underline{C}H_3)_3$), 16.2 (d, *J* 6.3 Hz, 2 × $OCH_2\underline{C}H_3$).

12.2 *tert*-Butyl (2*E*)-2-hexenoate [267][108h]

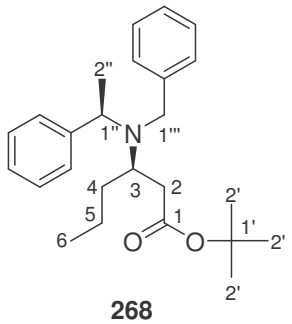


267

To a stirred suspension of vacuum-dried (140 °C, overnight, *ca* 1 mmHg) lithium chloride (4.05 g, 95.4 mmol, 1.2 eq.) in dry acetonitrile (317 cm^3, 2.00 $cm^3.mmol^{-1}$) was added *tert*-butyl diethoxyphosphorylacetate **[246]** (20.0 g, 18.6 cm^3, 79.4 mmol), 1,8-diazobicyclo-

[5.4.0]undec-7-ene (DBU) (13.3 g, 13.1 cm^3, 87.2 mmol, 1.1 eq.) and butanal (6.29 g, 7.86 cm^3, 87.2 mmol, 1.1 eq.). The mixture was stirred at rt for 24 h. The reaction was quenched with water and the solvent was evaporated *in vacuo*. The residue was taken up in water (100 cm^3), extracted with dichloromethane (3 × 100 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield a light yellow oil. The crude oil was purified by distillation (oil pump, *ca* 1 mmHg) to afford *tert*-butyl (2*E*)-2-hexenoate **[267]** (10.80 g, 63.42 mmol, 80%) as a colourless liquid. $\mathbf{R}_f$ 0.37 (5% ethyl acetate:hexane); ν_{max} **(film)/cm^{-1}** 2981 (C-H str, m) , 2934 (C-H str, w), 1726 (C=O str, s), 1650 (C=C str, w), 1479 (w), 1457 (C-H bend, w), 1394 (s), 1368 (C-H bend, s), 1286 (C-O str, s), 1255 (C-H bend, s), 1216 (w), 1164 (C-O str, s), 1114 (s), 1050 (s), 1020 (s), 958 (C-H out-of-plane bend, s); **^{1}H** 6.86 (1H, dt, *J* 6.9 and 15.5 Hz, H-3), 5.74 (1H, d, *J* 15.5 Hz, H-2), 2.15 (2H, q, *J* 7.1 Hz, H-4), 1.54-1.42 (2H, m, H-5), 1.48 (9H, s, H-2''), 0.93 (3H, t, *J* 7.4 Hz, H-6).

12.3 *tert*-Butyl (3*R*)-3-{benzyl[(1*S*)-1-phenylethyl]amino}hexanoate [268][108h]

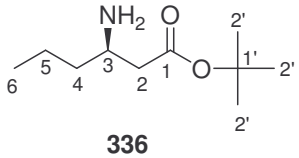


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A solution of *N*-benzyl-*N*-(1*R*)-1-phenylethylamine **[243]** (4.67 g, 4.63 cm^3, 22.1 mmol, 1.1eq.), in dry tetrahydrofuran (90.0 cm^3, 4.50 $cm^3.mmol^{-1}$) was cooled to −78 °C and treated with *n*-butyllithium (1.40 M, 15.8 cm^3, 22.1 mmol, 1.1 eq.). The resulting red solution was stirred at −78 °C for 30-45 min before adding a solution of *tert*-butyl (2*E*)-2-hexenoate **[267]** (3.42 g, 20.1 mmol) in tetrahydrofuran (20.0 cm^3, 1.00 $cm^3.mmol^{-1}$) dropwise. The resulting mixture was stirred at −78 °C for 3 h before quenching with a solution of saturated ammonium chloride (50 cm^3). The mixture was warmed to rt and the solvent was removed *in vacuo*. The residue was diluted with water (50 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered

and evaporated *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography using 5% ethyl acetate:hexane as eluent. The *tert*-butyl (3*R*)-3-{benzyl[(1*S*)-1-phenylethyl]amino}hexanoate **[268]** (5.916 g, 15.50 mmol, 77%) was obtained as a light yellow oil. $\mathbf{R}_f$ 0.54 (50% ethyl acetate:hexane); $[\alpha]_D^{19}$ +8.00 (*c* 2.0, chloroform); ν_{max} **(film)/cm^{-1}** 3084 (Ar C-H str, w), 3062 (Ar C-H str, w), 3027 (Ar C-H str, w), 2961 (C-H str, m), 2931 (C-H str, m), 2872 (C-H str, w), 1723 (C=O str, s), 1601 (Ar C=C str, w), 1493 (m), 1454 (C-H bend, m), 1391 (w), 1367 (C-H bend, m), 1342 (m), 1296 (m), 1256 (C-H bend, w), 1144 (C-N str, vs), 1095 (C-N str, m), 1074 (w), 1027 (C-C str, w), 989 (m); ^{1}**H** 7.43-7.20 (10H, m, Ar-H's), 3.81 (1H, q, *J* 7.2 Hz, H-1''), 3.81 (1H, d, *J* 15.3 Hz, H-1'''a), 3.48 (1H, d, *J* 15.0 Hz, H-1'''b), 3.33 (1H, quintet, *J* 4.2 Hz, H-3), 1.99-1.82 (1H, m, H-2), 1.64-1.19 (4H, m, H-4 and H-5), 1.39 (9H, s, H-2'), 1.32 (3H, d, *J* 7.0 Hz, H-2''), 0.85 (3H, t, *J* 7.2 Hz, H-6); ^{13}**C** 172.2 (C-1), 143.1 (quaternary Ar-C), 142.1 (quaternary Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 128.1 (Ar-C), 127.9 (Ar-C), 126.8 (Ar-C), 126.5 (Ar-C), 79.8 (C-1'), 58.3 (C-1''), 53.7 (C-1'''), 50.1 (C-3), 37.8 (C-2), 35.8 (C-4), 28.0 (C-2'), 20.5 (C-2''), 20.05 (C-5), 14.1 (C-6).

12.4 *tert*-Butyl (3*R*)-3-aminohexanoate [336][108h]

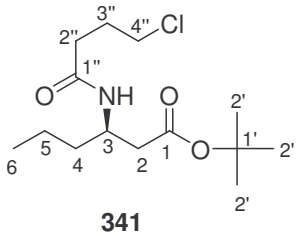


336

A solution of *tert*-butyl (3*R*)-3-{benzyl[(1*S*)-1-phenylethyl]amino}hexanoate **[268]** (5.36 g 14.0 mmol) in glacial acetic acid (60.0 cm^3, 4.30 cm^3.mmol^{-1}) was treated with 10% palladium on activated carbon (2.11 g, 0.150 g.mmol^{-1}). The mixture was stirred for 3 d under 7 atmospheres of hydrogen gas. The mixture was filtered through celite, followed by several washings with water to remove the catalyst. The filtrate was basified with saturated aqueous sodium hydrogen carbonate solution. The resulting mixture was extracted with dichloromethane (4 × 50 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford a milky oil. The crude oil was purified by column chromatography using 10-20% methanol:ethyl acetate as eluent to give *tert*-butyl (3*R*)-3-aminohexanoate **[336]** (1.72 g, 9.20 mmol, 65%) as a light yellow oil. $\mathbf{R}_f$ 0.25 (10% methanol:ethyl acetate); $[\alpha]_D^{21}$ +1.43 (*c* 0.70, $CHCl_3$) ν_{max} **(film)/cm^{-1}** 3291 (N-H str, w br),

2960 (C-H str, s), 2932 (C-H str, s), 2873 (C-H str, s), 1726 (C=O str, s), 1651 (N-H bend, s), 1547 (s), 1457 (C-H bend, s), 1392 (C-H bend, m), 1367 (C-H bend, s), 1308 (s), 1256 (s), 1153 (C-N str, vs), 1039 (w), 953 (N-H rock, m); **^{1}H** 3.19-3.13 (1H, m, H-3), 2.37 (1H, dd, *J* 15.5 Hz and 4.0 Hz , H-2a), 2.16 (1H, dd, *J* 15.4 Hz and 8.9 Hz, H-2b), 1.50 (2H, s, NH_2), 1.46 (9H, s, H-2'), 1.41-1.31 (4H, m, H-4 and H-5), 0.95-0.86 (3H, m, H-6); **^{13}C** 172.0 (C-1), 80.3 (C-1'), 48.1 (C-3), 43.9 (C-2), 39.7 (C-4), 28.1 (C-2'), 19.1 (C-5), 14.0 (C-6).

12.5 *tert*-Butyl (3*R*)-3-[(4-chlorobutanoyl)amino]hexanoate [341][108h]

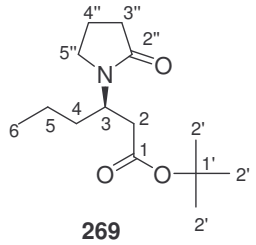


341

Distilled 4-chlorobutanoyl chloride (0.905 g, 0.720 cm^3, 6.42 mmol, 1.2 eq.) was added dropwise to a solution of *tert*-butyl (3*R*)-3-aminohexanoate **[336]** (1.00 g, 5.35 mmol) and triethylamine (1.35 g, 1.86 cm^3, 13.4 mmol, 2.5 eq.) in dichloromethane (23 cm^3, 4.3 $cm^3.mmol^{-1}$) at 0 °C. The solution effervesced and was stirred at rt for 30 min. The mixture was diluted with dichloromethane (30 cm^3), and evaporated *in vacuo*. The residue was dissolved in dichloromethane and then washed with water (30 cm^3) and brine (30 cm^3). The aqueous extracts were back extracted with dichloromethane (3 × 30 cm^3). The organic extracts were combined, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield an orange oil. The crude oil was purified by column chromatography using ethyl acetate as the eluent to yield *tert*-butyl (3*R*)-3-[(4-chlorobutanoyl)amino]hexanoate **[341]** (1.49 g, 5.11 mmol, 96%) as an orange oil. **R_f** 0.88 (5% methanol: dichloromethane); **$[\alpha]_D^{23}$** −1.75 (*c* 2.28, absolute ethanol); **ν_{max} (film)/cm^{-1}** 3283 (N-H str, w br), 2961 (C-H str, s), 2933 (C-H str, s), 2874 (C-H str, s), 1722 (C=O ester str, vs), 1639 (C=O amide str, s), 1544 (N-H bend, s), 1447 (C-H bend, s), 1367 (C-H bend, s), 1298 (m), 1255 (C-H bend, m), 1229 (m), 1217 (m), 1153 (C-O str, vs), 1037 (w), 990 (w); **^{1}H** 6.18 (1H, d, *J* 8.7 Hz, NH), 4.29-4.18 (1H, m, H-3), 3.60 (1H, t, *J* 6.3 Hz, H-4''), 2.43 (2H, dd, *J* 6.8 and 5.4 Hz, H-2), 2.35 (2H, t, *J* 7.1 Hz, H-2''), 2.11 (2H, quintet, *J* 6.8 Hz, H-3''), 1.55-1.24 (4H, m, H-4 and H-5), 1.46 (9H, s, H-2'), 0.92 (3H, t, *J* 7.2 Hz, H-6); **^{13}C** 171.3 (C-1), 170.9 (C-1''), 81.1 (C-

1’), 45.9 (C-3), 44.4 (C-4’’), 39.6 (C-2), 36.3 (C-2’’), 33.4 (C-4), 28.2 (C-2’), 28.0 (C-3’’), 19.4 (C-5), 13.8 (C-6).

12.6 *tert*-Butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexanoate [269]



269

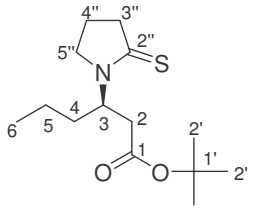
Method 1[108h]

tert-Butyl (3*R*)-3-[(4-chlorobutanoyl)amino]hexanoate **[341]** (1.41 g, 4.82 mmol) was treated with potassium *tert*-butoxide (1.08 g, 9.64 mmol, 2.0 eq.) in dry *tert*-butyl alcohol (28.0 cm^3, 6.50 $cm^3.mmol^{-1}$). The mixture was stirred at rt for 24 h. Glacial acetic acid was added to neutralize the mixture. The solvent was evaporated *in vacuo* to yield a milky yellow residue. The residue was taken up in dichloromethane (50 cm^3) and washed with water (50 cm^3). The aqueous extracts were back extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to afford an orange oil. The crude oil was purified by column chromatography using 30% ethyl acetate:hexane as the eluent to yield *tert*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexanoate **[269]** (0.489 g, 1.92 mmol, 40%) as a yellow oil. $\mathbf{R}_f$ 0.30 (50% ethyl acetate:hexane); $\mathbf{[\alpha]_D^{18}}$ –5.03 (*c* 1.59, chloroform); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3226 (w), 2962 (C-H str, s), 2933 (C-H str, s), 2874 (C-H str, s), 1723 (C=O ester str, vs), 1686 (C=O amide str, vs), 1460 (C-H bend, s), 1423 (s), 1393 (w), 1317 (s), 1285 (m), 1257 (s), 1207 (s), 1150 (C-N str, vs), 1111 (s), 1041 (w), 972 (m); $^{\mathbf{1}}$**H** 4.51-4.41 (1H, m, H-3), 3.38 (1H, dt, *J* 7.0 and 8.9 Hz, H-5’’a), 3.26 (1H, dt, *J* 7.0 and 9.1 Hz, H-5’’b), 2.42-2.34 (4H, m, H-2 and H-3’’), 1.99 (2H, quintet, *J* 7.5 Hz, H-4’’), 1.59-1.36 (2H, m, H-4), 1.42 (9H, s, H-2’), 1.27 (2H, dq, *J* 7.3 and 14.7 Hz, H-5), 0.92 (3H, t, *J* 7.3 Hz, H-6); $^{\mathbf{13}}$**C** 174.7 (C-1), 170.2 (C-2’’), 80.7 (C-1’), 48.4 (C-3), 42.4 (C-5’’), 39.3 (C-2), 34.3 (C-4), 31.4 (C-3’’), 27.8 (C-2’), 19.3 (C-5), 18.2 (C-4’’), 13.7 (C-6).

Method 2

tert-Butyl (3*R*)-3-[(4-chlorobutanoyl)amino]hexanoate **[341]** (2.01 g, 6.88 mmol) was dissolved in dry *tert*-butyl alcohol (21.0 cm^3, 3.00 $cm^3.mmol^{-1}$). To this solution was added potassium *tert*-butoxide (1.16 g, 10.3 mmol, 1.5 eq.) in portions (~0.100 g per addition) over a 5 h period. After the final addition the mixture was stirred for a further 30 min, and thereafter glacial acetic acid was added to neutralize the mixture. The solvent was removed from the neutralized mixture by evaporation *in vacuo*. The resulting residue was dissolved in dichloromethane (50 cm^3) and washed with water (50 cm^3). The aqueous extracts were extracted with dichloromethane (3 x 50 cm^3), and the combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford an orange oil. Purification of the crude oil by column chromatography using 30% ethyl acetate:hexane as eluent yielded *tert*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexanoate **[269]** (1.28 g, 5.00 mmol, 73%) as a yellow oil; characterization as described above.

12.7 *tert*-Butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)hexanoate [270]



270

Method 1[108h]

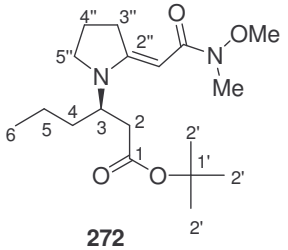
tert-Butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexanoate **[269]** (0.232 g, 0.910 mmol), was added to a stirred solution of Lawessons' reagent (0.188 g, 0.450 mmol, 0.5 eq.) in toluene (4 cm^3, 4 $cm^3.mmol^{-1}$). The solution was stirred at reflux for 5 h, after which time the solvent was removed *in vacuo* to yield a red oil. The crude red oil was purified by column chromatography with dichloromethane followed by 30% ethyl acetate:hexane to yield *tert*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)hexanoate **[270]** (0.168 g, 0.0690 mmol, 68%) as a yellow oil. $\mathbf{R}_f$ 0.35 (20% ethyl acetate:hexane); $\mathbf{[\alpha]_D^{22}}$ **+**17.9 (*c* 0.96, absolute ethanol); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2970 (C-H str, s), 2932 (C-H str, s), 2873 (C-H str, m), 1722 (C=O str, vs), 1598

(w), 1572 (w), 1492 (s), 1447 (C-H bend, s), 1426 (w), 1391 (w), 1367 (C-H bend, s), 1315 (C=S, s), 1284 (s), 1253 (s), 1229 (s), 1150 (C-N str, vs), 1127 (C-O str, s), 1099 (s), 1061 (w), 1031 (w), 956 (m); **^{1}H** 5.43-5.33 (1H, m, H-3), 3.71 (1H, dt, *J* 7.2 and 10.6 Hz, H-5''a), 3.56 (1H, dt, *J* 7.2 and 10.6 Hz, H-5''b), 3.00 (2H, dt, *J* 3.0 and 7.7 Hz, H-3''), 2.54 (2H, dd, *J* 6.0 and 14.4 Hz, H-2a), 2.45 (2H, dd, *J* 9.0 and 14.4 Hz, H-2b), 2.03 (2H, quintet, *J* 7.5 Hz, H-4''), 1.67-1.53 (2H, m, H-4), 1.43 (9H, s, H-2'), 1.40 (2H, m, H-5), 0.94 (3H, t, H-6); **^{13}C** 201.8 (C-2''), 169.5 (C-1), 81.1 (C-1'), 53.1 (C-3), 49.1 (C-5''), 45.1, (C-2''), 38.8 (C-2), 34.3 (C-4), 27.8 (C-2'), 20.0 (C-4''), 19.1 (C-5), 13.8 (C-6).

Method 2

To a suspension of phosphorus pentasulfide (1.32 g, 5.88 mmol, 3.0 eq.) in tetrahydrofuran (140 cm^3, 7.20 cm^3.mmol^{-1}) was added sodium carbonate (0.311 g, 2.94 mmol, 1.5 eq.), and the mixture was stirred at rt until the solution became homogeneous. To this solution was added *tert*-butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexanoate **[269]** (5.00 g, 19.6 mmol) in tetrahydrofuran (35.0 cm^3, 1.80 cm^3.mmol^{-1}). Aqueous sodium carbonate (10%, 140 cm^3), ethyl acetate (105 cm^3) and hexane (35 cm^3) were added after 5 h. The aqueous phase was extracted with dichloromethane (3 × 80 cm^3). The combined organic phases were then dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to give a yellow oil. The crude product was purified by column chromatography using 25% acetone:hexane as eluent, to give *tert*-butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)hexanoate **[270]** (0.369 g, 0.461 mmol, 80%) as a yellow oil. The compound was characterized as described above.

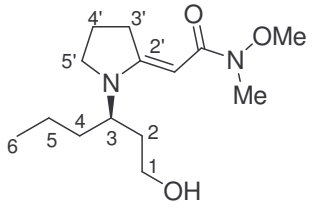
12.8 *tert*-Butyl (3*R*)-3-((2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)-hexanoate [272]



272

tert-Butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)hexanoate **[270]** (0.530 g, 1.95 mmol 1.0 eq.) and 2-bromo-*N*-methoxy-*N*-methylacetamide **[271]** (0.430 g, 2.34 mmol, 1.2 eq.) were dissolved in dry acetonitrile (4.00 cm^3, 2.00 $cm^3.mmol^{-1}$). The mixture was stirred for 16 h at rt, after which time the solvent was removed *in vacuo* affording a white salt. The obtained salt was re-dissolved in dry acetonitrile (4.00 cm^3, 2.00 $cm^3.mmol^{-1}$) and to this was added triphenylphosphine (0.614 g, 2.34 mmol, 1.2 eq.) followed by triethylamine (0.237 g, 0.330 cm^3, 2.34 mmol, 1.2 eq.). The solution was stirred for 3 h, during which time a white precipitate formed. The solution was filtered through a celite pad, the solvent was removed *in vacuo* and the resulting residue was triturated in ethyl acetate for 30 min. The solution was again filtered through celite, and the filtrate was then extracted with aqueous hydrochloric acid (2.0M, 3 × 50 cm^3). The aqueous extracts were basified to ~ pH 10 with an ammonia solution, and then extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield a yellow oil. The crude oil was purified by column chromatography using 5% methanol:dichloromethane, to afford *tert*-butyl (3*R*)-3-((2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)hexanoate **[272]** as a light yellow oil (0.509 g, 1.50 mmol, 77%). ν_{max} **(film)/cm^{-1}** 3084 (w), 3062 (w), 3027 (C=C-H str, w), 2970 (C-H str, s), 2932 (C-H str, s), 2872 (C-H str, w), 1724 (C=O str, vs), 1601 (w), 1493 (m), 1454 (C-H bend, s), 1367 (C-H bend, s), 1297 (m), 1256 (w), 1230 (s), 1217 (s), 1205 (s), 1143 (C-N str, vs), 1094 (C-O str, m), 1074 (w), 1026 (m), 990 (w); **^{1}H** 5.26 (1H, s, C=CH), 4.17-4.07 (1H, m, H-3), 3.68 (3H, s, OCH_3), 3.32-3.19 (4H, m, H-3'' and H-5''), 3.14 (3H, s, NMe), 2.44 (2H, dd, *J* 6.0 and 7.1 Hz, H-2), 1.88 (2H, quintet, *J* 7.3 Hz, H-4''), 1.67-1.45 (2H, m, H-4), 1.41 (9H, s, H-2'), 1.36-1.20 (2H, m, H-5), 0.93 (3H, t, *J* 7.3 Hz, H-6); **^{13}C** 172.1 (C-1), 170.1 (C-2''), 164.7 CON(O CH_3) CH_3), 80.8 (C-1'), 77.7 (C=CH), 60.8 (O CH_3), 51.3 (C-3), 45.6 (C-5''), 39.0 (C-2), 34.3 (C-4), 33.0 (CH_3), 32.6 (C-3), 27.8 (C-2'), 21.1 (C-4), 19.3 (C-5), 13.7 (C-6).

12.9 (2*E*)-2-{1-[(1*R*)-1-(2-Hydroxyethyl)butyl]-2-pyrrolidinylidene}-*N*-methoxy-*N*-methylethanamide [273] from [272]

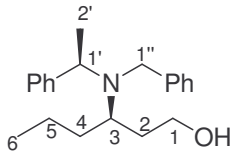


273

tert-Butyl-(3*R*)-3-((2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)hexanoate **[272]** (0.167 g, 0.490 mmol) was added to a slurry of lithium aluminium hydride (0.0220 g, 0.590 mmol, 1.2 eq.) in diethyl ether (1.00 cm^3, 2.00 $cm^3.mmol^{-1}$) at 0 °C. The slurry was warmed to rt and stirred for 16 h. The reaction was quenched by the sequential addition of water (0.1 cm^3), sodium hydroxide (0.1 cm^3, 15% w/v) and finally water (0.2 cm^3). The solids were filtered off by passing the mixture through a thin pad of celite and washing several times with dichloromethane. The filtrate was dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield a brown-orange oil. Purification of the oil by column chromatography using 5% ethanol:dichloromethane as eluent afforded (2*E*)-2-{1-[(1*R*)-1-(2-hydroxyethyl)butyl]-2-pyrrolidinylidene}-*N*-methoxy-*N*-methylethanamide **[273]** as a clear oil (0.0150 g, 0.0600 mmol, 11%). $\mathbf{R}_f$ 0.59 (10% ethanol:dichloromethane); $\mathbf{[\alpha]_D^{20}}$ +3.85 (*c* 1.04 absolute ethanol); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3358 (O-H str, m br), 2955 (C-H str, s), 2931 (C-H str, s), 2870 (C-H str, s), 2360 (s), 2342 (s), 1617 (C=O str, s), 1553 (vs), 1485 (w), 1460 (C-H bend, w), 1411 (s), 1199 (C-N str, s); **^{1}H** 5.25 (1H, s, C=CH), 3.96-3.86 (2H, m, H-1), 3.66 (3H, s, OCH_3), 3.69-3.42 (1H, m, H-3), 3.26 (2H, t, *J* 7.9 Hz, H-5'), 3.19 (2H, dt, *J* 6.6 and 2.7 Hz, H-3'), 3.14 (3H, s, NCH_3), 1.90 (2H, quintet, *J* 7.3 Hz, H-4'), 1.79-1.65 (2H, m, H*), 1.60 (2H, ddd, *J* 15.0, 8.4 and 3.8 Hz, H-2a), 1.49 (2H, ddd, *J* 13.7, 8.2 and 3.9 Hz, H-2b), 1.42-1.23 (2H, m, H*), 0.92 (3H, t, *J* 7.3 Hz, H-6); **^{13}C** 172.4 (C-2'), 165.9 ($\underline{C}ON(OCH_3)CH_3$), 76.4 (C=CH), 60.9 ($OCH_3$), 59.4 (C-1), 50.6 (C-5'), 45.3 (C-3), 35.0 (C-2), 34.8 (C-4), 33.1 (NCH_3), 32.9 (C-4'), 21.2 (C-3'), 19.5 (C-5), 13.9 (C-6).

* Remaining hydrogens

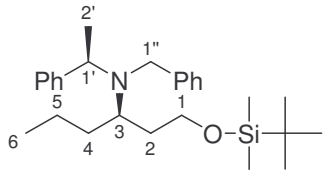
12.10 (3*R*)-3-{Benzyl[(1*S*)-1-phenylethyl]amino}-1-hexanol [343]



343

Lithium aluminium hydride (1.36 g, 35.8 mmol, 1.1 eq.) was added to a stirred solution of *tert*-butyl (3*R*)-3-((2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)hexanoate **[268]** (12.4 g, 32.6 mmol) in diethyl ether (65.0 cm^3, 2.00 $cm^3.mmol^{-1}$) at 0 °C. The mixture was warmed to rt and stirred for 16 h. The reaction was quenched by the sequential addition of water (7.2 cm^3), sodium hydroxide (7.2 cm^3, 15% w/v) and finally water (21.7 cm^3). The solids were removed by passing the mixture through a thin celite pad. The filtrate was dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield a light yellow oil. The solids and celite were recovered and dried in a desiccator, once dry they were ground to a fine powder. The powder was stirred in dichloromethane (100 cm^3), filtered and evaporated *in vacuo* to afford more of the light yellow oil. The crude oils were combined and purified by column chromatography using 20% ethyl acetate:hexane as eluent to give (3*R*)-3-{benzyl[(1*S*)-1-phenylethyl]amino}-1-hexanol **[343]** (9.84 g, 31.6 mmol, 97%) as a clear oil. $\mathbf{R}_f$ 0.82 (50% ethyl acetate:hexane); $\mathbf{[\alpha]_D^{19}}$ –32.1 (*c* 1.09, chloroform); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3367 (O-H, s br), 3084 (ArC-H str, w), 3062 (ArC-H str, w), 3027 (ArC-H str, w), 2956 (C-H str, s), 2931 (C-H str, s), 2870 (C-H str, s), 1602 (ArC=C str, w), 1493 (C-H bend, s), 1452 (s), 1373 (C-H bend, s), 1204 (m), 1140 (C-N str, s), 1052 (C-O str, s), 1027 (s), 905 (s); **^{1}H** 7.40-7.19 (10H, m, Ar-H's), 3.95 (1H, q, *J* 6.9 Hz, H-1'), 3.84 (1H, d, 13.7 Hz, H-1''a), 3.68 (1H, d, 13.8 Hz, H-1''b), 3.52-3.45 (1H, m, H-3), 3.24-3.17 (1H, m, H-1a), 2.83-2.76 (1H, m, H-1b), 2.64 (1H, s, -OH), 1.74-1.49 (2H, m, H-2), 1.45-1.23 (4H, m, H-4 and H-5), 1.39 (3H, d, *J* 6.9 Hz, H-2'), 0.93 (3H, t, *J* 7.1 Hz, H-6); **^{13}C** 143.9 (quaternary Ar-C), 140.8 (quaternary Ar-C), 129.0 (Ar-C), 128.3 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 126.9 (Ar-C), 126.9 (Ar-C), 61.8 (C-1'), 56.7 (C-1), 54.8 (C-3), 49.9 (C-1''), 34.9 (C-2), 33.7 (C-4), 20.8 (C-2'), 15.1 (C-5), 14.4 (C-6); **HRMS m/z (EI)** 311.22532 (M^+ 100%, $C_{21}H_{29}NO$ requires 311.22491)

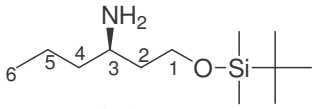
12.11 (3*R*)-*N*-Benzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-[(1*S*)-1-phenylethyl]-3-hexanamine [344]



344

tert-Butyldimethylsilyl chloride (5.04 g, 33.1 mmol, 1.1 eq.) in dimethylformamide (18.0 cm^3, 0.60 cm^3.mmol) was added dropwise to a stirred solution of (3*R*)-3-{benzyl[(1*S*)-1-phenylethyl]amino}-1-hexanol **[343]** (9.37 g, 30.1 mmol) and imidazole (4.11 g, 60.1 mmol, 2.0 eq.) in dimethylformamide (36.0 cm^3, 1.20 cm^3.mmol). The mixture was then stirred for 24 h. The reaction mixture was washed with ice/water (180 cm^3), and the aqueous residues were extracted with dichloromethane (5 × 180 cm^3). The combined organic residues were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo*. The residue was re-dissolved in dichloromethane (180 cm^3) and washed with water (4 × 180 cm^3). The organic extract was dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield a crude yellow oil. Purification by column chromatography using 10% ethyl acetate:hexane as eluent afforded (3*R*)-*N*-benzyl-1-{[*tert*-butyl-(dimethyl)silyl]oxy}-*N*-[(1*S*)-1-phenylethyl]-3-hexanamine **[344]** (11.2 g, 26.3 mmol, 88%), as a clear oil. $\mathbf{R}_f$ 0.72 (10% ethyl acetate:hexane); $\mathbf{[\alpha]_D^{20}}$ **+**18.9 (*c* 1.27, chloroform); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}**; 3085 (ArC-H str, w), 3063 (ArC-H str, w), 3028 (ArC-H str, w), 2955 (C-H str, s), 2929 (C-H str, s), 2857 (C-H str, s), 1743 (w), 1602 (Ar C=C str, w), 1493 (s), 1454 (s), 1373 (s), 1362 (s), 1253 (s), 1205 (m), 1144 (C-N str, m), 1089 (C-O str, vs), 1027 (m), 1005 (m), 980 (m), 938 (vs); **^{1}H** 7.40-7.16 (10H, m, Ar-H's), 3.87 (1H, q, *J* 6.9 Hz, H-2'), 3.78 (1H, d, *J* 14.9 Hz, H-1''a), 3.64 (1H, d, *J* 14.8 Hz, H-1''b), 3.46 (1H, ddd, *J* 13.6, 8.0 and 6.9 Hz, H-1a), 3.27 (1H, ddd, *J* 9.8, 8.5 and 5.5 Hz, H-1b), 2.68 (1H, quintet, *J* 6.1 Hz, H-3), 1.63-1.41 (2H, m, H-2), 1.38-1.20 (4H, m, H-4 and H-5), 1.29 (3H, d, *J* 6.9 Hz, H-2'), 0.89-0.82 (3H, m, H-6), 0.85 (9H, s, $C(CH_3)_3$), –0.02 (6H, s, $Si(CH_3)_2$); **^{13}C** 144.9 (quaternary Ar-C), 142.7 (quaternary Ar-C), 128.3 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 126.6 (Ar-C), 126.3 (Ar-C), 61.9 (C-1'), 58.1 (C-1), 53.8 (C-3), 50.2 (C-1''), 35.3 (C-2), 34.5 (C-4), 26.0 ($C(\underline{C}H_3)_3$), 20.5 (C-2'), 18.9 (C-5), 18.3 ($\underline{C}(CH_3)_3$), 14.3 (C-6), –5.3 ($Si(CH_3)_2$); **HRMS m/z (EI)** 425.30974 (M^+ 100%, $C_{27}H_{43}NOSi$ requires 425.31139), 427 (12), 426 (46), 424 (50), 423 (24), 422 (62), 419 (2).

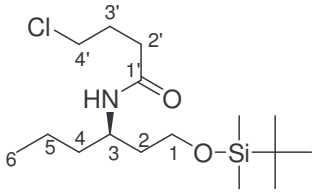
12.12 (3*R*)-1-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-hexanamine [346]



346

10% Palladium on carbon (3.97 g, 0.150 g.mmol^{-1}), was added to a mixture of (3*R*)-*N*-benzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-[(1*S*)-1-phenylethyl]-3-hexanamine **[344]** (11.1 g, 26.1 mmol) in absolute ethanol (104 cm^3, 4.00 cm^3.mmol^{-1}). The stirred mixture was subjected to hydrogenation at 7 atmospheres for 3 d. The mixture was then filtered through celite and washed copiously with absolute ethanol. The ethanol was removed *in vacuo* to yield a grey oil. The oil was purified by column chromatography using ethyl acetate as the eluent to afford (3*R*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-3-hexanamine **[346]** (5.11 g, 22.1 mmol, 85%) as a clear oil. $\mathbf{R}_f$ 0.38 (ethyl acetate); $\mathbf{[\alpha]_D^{21}}$ **+**1.43 (*c* 0.70, chloroform); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3377 (N-H str, s br), 2935 (C-H str, s), 2871 (C-H str, s), 1737 (w), 1615 (m), 1550 (N-H bend, vs), 1460 (C-H bend, m), 1386 (C-H bend, m), 1310 (C-N str, m), 1170 (s), 1099 (s), 1053 (C-O str, s), 994 (s); **^{1}H** 3.77-3.67 (2H, m, H-1), 2.90-2.84 (1H, m, H-3), 1.67-1.23 (6H, m, H-2, H-4 and H-5), 1.50 (2H, s, -NH_2), 0.89 (3H, t, *J* 6.5 Hz, H-6), 0.87 (9H, s, C(C$\underline{H}_3$)$_3$), 0.03 (6H, s, -Si(CH_3)$_2$); **HRMS m/z (EI)** Inconsistent results were obtained.

12.13 *N*-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)butyl]-4-chlorobutanamide [348]

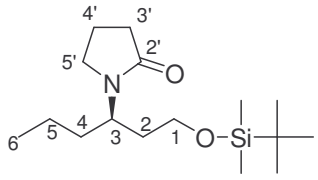


348

4-Chlorobutyryl chloride (1.95 g, 1.10 cm^3, 13.8 mmol, 1.2 eq.) was added dropwise to a solution of (3*R*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-3-hexanamine **[346]** (2.67 g, 11.5 mmol) and triethylamine (2.91 g, 4.00 cm^3, 28.8 mmol, 2.5 eq.) in dry dichloromethane (46.0 cm^3, 4.00 cm^3.mmol^{-1}), causing a vigorous evolution of hydrogen chloride gas. The mixture was stirred for 30 min, after which time the reaction was quenched with dichloromethane (50 cm^3)

and evaporated *in vacuo*. The residue was dissolved in dichloromethane (50 cm^3) and washed with water (50 cm^3) and brine (50 cm^3). The aqueous extracts were back extracted with dichloromethane (3 × 50 cm^3). The organic extracts were combined, dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield an orange oil. The crude oil was purified by column chromatography using 50% ethyl acetate:hexane, to yield *N*-[(1*R*)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)butyl]-4-chlorobutanamide **[348]** (3.89 g, 11.6 mmol, 100%) as a yellow oil. $\mathbf{[\alpha]_D^{23}}$ −1.75 (*c* 2.28, absolute ethanol); $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3281 (N-H str, vs br), 3075 (w), 2957 (C-H str, s), 2932 (C-H str, s), 2873 (C-H str, s), 1727 (s), 1642 (C=O str, vs), 1546 (vs), 1464 (C-H bend, s), 1442 (s), 1369 (C-H bend, s), 1306 (w), 1254 (s), 1217 (w), 1155 (C-N str, s), 1048 (C-O str, s), 955 (w); **^{1}H** 6.10 (1H, d, NH), 4.11-3.97 (1H, m, H-3), 3.81-3.63 (2H, m, H-1), 3.57 (2H, t, *J* 6.2 Hz, H-4'), 2.28 (2H, t, *J* 7.2 Hz, H-2'), 2.08 (2H, quintet, *J* 6.44 Hz, H-3'), 1.84-1.53 (2H, m, H-2), 1.51-1.39 (2H, m, H-4), 1.37-1.19 (2H, m, H-5), 0.92-0.85 (2H, m, H-6), 0.89 (9H, s, $C(C\underline{H}_3)_3$), 0.05 (6H, s, 2 × $Si(CH_3)_2$); **HRMS m/z (EI)** Inconsistent results were obtained.

12.14 1-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)butyl]-2-pyrrolidinone [347]

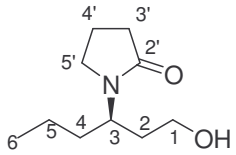


347

Potassium *tert*-butoxide (1.80 g, 16.1 mmol, 1.5 eq.) was added in portions (~0.100 g per addition) to a solution of *N*-[(1*R*)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-butyl]-4-chlorobutanamide **[348]** (3.60 g, 10.7 mmol) in dry *tert*-butanol (32.0 cm^3, 3.00 $cm^3.mmol^{-1}$) over a 5 h period. The mixture was neutralized with glacial acetic acid, and the solvent was removed *in vacuo*. The resulting residue was dissolved in dichloromethane (100 cm^3) and washed with water (100 cm^3). The aqueous extracts were extracted with dichloromethane (3 × 100 cm^3), and the combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford an orange oil. Purification of the crude oil by column chromatography using 30% ethyl acetate:hexane as eluent yielded 1-[(1*R*)-1-(2-{[*tert*-butyl-(dimethyl)silyl]oxy}ethyl)butyl]-2-pyrrolidinone **[347]** (3.00 g, 10.0 mmol, 94%) as a light

yellow oil. $\mathbf{R}_f$ 0.58 (50% ethyl acetate:hexane); $\mathbf{[\alpha]_D^{19}}$ –9.86 (*c* 0.71, chloroform); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3368 (w), 2954 (C-H str, s), 2929 (C-H str, s), 2857 (C-H str, s), 1738 (w), 1668 (C=O str, s), 1542 (w), 1493 (w), 1463 (C-H bend, s), 1423 (s), 1362 (C-H bend, m), 1315 (m), 1285 (C-N str, s), 1095 (C-O str, s), 1007 (m), 942 (m); **^{1}H** 4.21-4.05 (1H, m, H-3), 3.63-3.46 (2H, m, H-1), 3.32-3.18 (2H, m, H-5'), 2.36 (2H, t, *J* 8.1 Hz, H-3'), 1.96 (2H, quintet, *J* 7.44 Hz, H-4'), 1.72-1.65 (2H, m, H-2), 1.50-1.39 (2H, m, H-4), 1.28-1.19 (2H, m, H-5), 0.88 (3H, t, *J* 7.3 Hz, H-6), 0.86 (9H, s, $C(CH_3)_3$), 0.02 (3H, s, $Si(CH_3)_2$), 0.01 (3H, s, $Si(CH_3)_2$); **^{13}C** 174.3 (C-1'), 60.7 (C-1), 48.5 (C-3), 42.3 (C-5'), 35.6 (C-2), 34.6 (C-4), 31.5 (C-3'), 25.9 ($C(\underline{C}H_3)_3$), 19.4 (C-5), 18.26 (C-4') 18.23 ($\underline{C}(CH_3)_3$), 13.8 (C-6), –5.39 ($Si(CH_3)_2$), –5.44 ($Si(CH_3)_2$); **HRMS m/z (EI)** 299.22292 (M^+ 74%, $C_{16}H_{33}NO_2Si$ requires 299.22806), 298 (100), 297 (6), 296, (2), 295 (4), 293 (1).

12.15 1-[(1*R*)-1-(2-Hydroxyethyl)butyl]-2-pyrrolidinone [350]



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Method 1

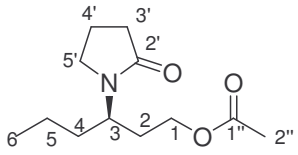
1-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)butyl]-2-pyrrolidinone **[347]** (0.100 g, 0.330 mmol) was dissolved in dry tetrahydrofuran (12.0 cm^3, 4.00 cm^3.mmol^{-1}) and cooled to 0 °C. To this was added tetrabutylammonium fluoride (1.0 M in THF, 0.700 cm^3, 2.0 eq.) in one portion. The reaction mixture was stirred for 100 min at rt. The reaction was quenched with water (20 cm^3), and extracted with ethyl acetate (3 × 20 cm^3), thereafter the combined organic fractions were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield a clear oil. Purification by column chromatography using ethyl acetate as eluent afforded 1-[(1*R*)-1-(2-hydroxyethyl)butyl]-2-pyrrolidinone **[350]** (0.0461 g, 0.248 mmol, 74%) as a clear oil. $\mathbf{R}_f$ 0.30 (ethyl acetate); $\mathbf{[\alpha]_D^{23}}$ –0.61 (*c* 11.5, absolute ethanol); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3395 (O-H str, s br), 2954 (C-H str, s), 2872 (C-H str, s), 1738 (s), 1655 (C=O str, vs), 1542 (w), 1494 (m), 1463 (O-H bend, s), 1424 (C-H str, s), 1367 (O-H bend, s), 1316 (w), 1289 (s), 1264 (s), 1229 (s), 1217 (s), 1112 (w), 1048 (C-O str, s), 1011 (w), 935 (w); **^{1}H**

4.23-4.14 (1H, m, H-3), 3.52 (1H, ddd, *J* 3.2, 5.3 and 11.8 Hz, H-1a), 3.33 (1H, dd, *J* 3.5 and 10.7 Hz, H-1b), 3.28-3.11 (2H, m, H-5'), 3.11 (1H, s, OH), 2.41 (2H, dt, *J* 12.3 and 7.8 Hz, H-3'), 1.99 (2H, quintet, *J* 7.5 Hz, H-4'), 1.76-1.64 (2H, m, H-2), 1.56-1.35 (2H, m, H-4), 1.32-1.17 (2H, m, H-5), 0.87 (3H, t, *J* 7.3 Hz, H-6) **^{13}C** 176.4 (C-2'), 58.4 (C-1), 47.3 (C-3), 41.9 (C-5'), 34.6 (C-4), 34.4 (C-2), 31.1 (C-3'), 19.5 (C-5), 18.1 (C-4'), 13.7 (C-6); **HRMS m/z (EI)** 185.14044 (M^+ 100%, $C_{10}H_{19}NO_2$ requires 185.14158) 186 (16), 185 (100), 184 (2), 183 (10), 181 (1).

Method 2

Aqueous hydrofluoric acid (40%, 10.1 cm^3, 1.6 cm^3.mmol^{-1}) was added slowly to a solution of 1-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)butyl]-2-pyrrolidinone **[347]** (1.89 g, 6.32 mmol) in methanol (240 cm^3, 38 cm^3.mmol). The reaction mixture was stirred at rt for 2 h, before the careful addition of saturated aqueous sodium hydrogen carbonate (380 cm^3), whereupon effervescence was observed. The reaction mixture was then extracted with ethyl acetate (3 × 200 cm^3) and the combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield a light yellow oil. The crude oil was purified by column chromatography using ethyl acetate as eluent to give 1-[(1*R*)-1-(2-hydroxyethyl)butyl]-2-pyrrolidinone **[350]** (1.06 g, 5.69 mmol, 90%) as a clear oil; characterized as described above.

12.16 (3*R*)-3-(2-Oxo-1-pyrrolidinyl)hexyl acetate [349]

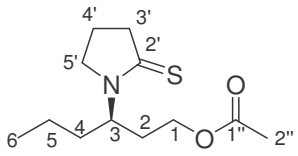


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A solution of acetic anhydride (1.37 g, 1.30 cm^3, 13.5 mmol, 1.5 eq.) in dry pyridine (0.710 g, 0.800 cm^3, 8.97 mmol, 1.0 eq.) was added dropwise to a stirred solution of 1-[(1*R*)-1-(2-hydroxyethyl)butyl]-2-pyrrolidinone **[350]** (1.66 g, 8.97 mmol) in pyridine (1.06 g, 1.10 cm^3, 13.5 mmol, 1.5 eq.). The mixture was stirred at rt for 16 h, after which time the reaction was quenched with ethyl acetate (45 cm^3) and washed with saturated aqueous ammonium chloride

(3 × 55 cm^3), which was then made basic to pH 10 with ammonia solution. The combined aqueous extracts were extracted further with dichloromethane (3 × 55 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield a crude yellow oil. The crude oil was purified by column chromatography 40% ethyl acetate:hexane as eluent, to yield (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexyl acetate **[349]** (1.72 g, 7.57 mmol, 84%) as a clear oil. $\mathbf{R}_f$ 0.33 (50% ethyl acetate:hexane); $\mathbf{[\alpha]_D^{23}}$ **+**1.89 (*c* 11.1, chloroform); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2957 (C-H str, s), 2934 (C-H str, s), 2873 (C-H str, m), 1736 (C=O ester str, vs), 1678 (C=O amide str, vs), 1542 (w), 1493 (m), 1462 (C-H bend, s), 1423 (s), 1367 (C-H bend, s), 1315 (w), 1284 (w), 1232 (C-O str, vs), 1167 (w), 1114 (w), 1093 (w), 1036 (C-O str, s) 979 (w); **^{1}H** 4.26-4.16 (1H, m, H-3), 4.01 (2H, t, *J* 6.7 Hz, H-1), 3.33-3.20 (2H, m, H-5'), 2.40 (2H, t, *J* 8.0 Hz, H-3'), 2.06-1.97 (2H, quintet, *J* 7.46 Hz, H-4'), 2.04 (3H, s, H-2''), 1.88-1.76 (2H, m, H-2), 1.57-1.37 (2H, m, H-4), 1.34-1.20 (2H, m, H-5), 0.91 (3H, t, *J* 7.2 Hz, H-6); **^{13}C** 175.1 (C-2'), 171.0 (C-1''), 61.5 (C-1), 47.9 (C-3), 41.9 (C-5'), 34.5 (C-4), 31.3 (C-3'), 31.2 (C-2), 20.9 (C-2''), 19.3 (C-5), 18.2 (C-4'), 13.8 (C-6); **HRMS m/z (EI)** 227.14413 (M^+ 32%, $C_{12}H_{21}NO_3$ requires 227.15214), 226 (100).

12.17 (3*R*)-3-(2-Thioxo-1-pyrrolidinyl)hexyl acetate [351]

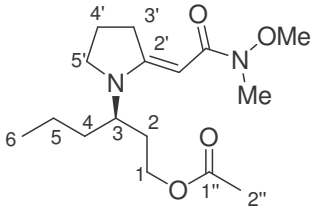


351

Phosphorus pentasulfide (4.87 g, 21.9 mmol, 3.0eq.) and sodium carbonate (1.17 g, 11.0 mmol, 1.5 eq.) were dissolved in dry tetrahydrofuran (55.0 cm^3, 7.20 $cm^3.mmol^{-1}$), the reaction was exothermic and effervescence was observed. Once a homogeneous solution had formed, (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexyl acetate **[349]** (1.66 g, 7.31 mmol) was slowly added. The solution was stirred at rt for 3 h, after which the reaction was quenched by the addition of aqueous sodium carbonate (10%, 55 cm^3), and vigorous effervescence was observed. The solution was stirred for a further 10 min before adding ethyl acetate (40 cm^3) and hexane (13 cm^3). The organic phase was separated and the aqueous phase was further extracted with dichloromethane (3 × 30 cm^3). The combined organic phases were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield a yellow oil. The crude

oil was purified by column chromatography using 30% ethyl acetate:hexane as eluent to give (3*R*)-3-(2-thioxo-1-pyrrolidinyl)hexyl acetate **[351]** (1.61 g, 6.63 mmol, 91%) as a yellow oil. $\mathbf{R}_f$ 0.25 (30% ethyl acetate:hexane); $\mathbf{[\alpha]_D^{17}}$ **+**23.7 (*c* 1.69, chloroform); **^{1}H** 5.19-5.10 (1H, m, H-3), 4.03 (2H, t, *J* 6.6 Hz, H-5'), 3.62-3.47 (2H, m, H-1), 3.03 (2H, t, *J* 7.8 Hz, H-3'), 2.08-1.98 (2H, m, H-4'), 2.02 (3H, s, H-2''), 1.93-1.79 (2H, m, H-2), 1.62-1.50 (2H, m, H-4), 1.39-1.15 (2H, m H-5), 0.91 (3H, t, *J* 7.2 Hz, H-6); **^{13}C** 202.3 (C=S), 171.0 (C=O), 61.2 (C-1), 53.1 (C-3'), 48.6 (C-3), 45.1 (C-5'), 34.7 (C-4), 31.5 (C-2), 21.0 (C-2''), 20.0 (C-4'), 19.2 (C-5), 13.9 (C-6)**; HRMS m/z (EI)** 243.12852 (M^+ 100% $C_{12}H_{21}NO_2S$ requires 243.12930).

12.18 (3*R*)-3-((2*E*)-2-{2-[Methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)hexyl acetate [352]

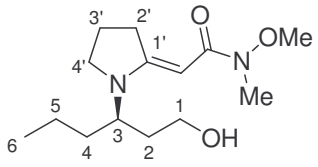


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(3*R*)-3-(2-Thioxo-1-pyrrolidinyl)hexyl acetate **[351]** (1.58 g, 6.51 mmol) and 2-bromo-*N*-methoxy-*N*-methylacetamide **[271]** (2.13 g, 11.7 mmol, 1.8 eq.) were dissolved in dry acetonitrile (26.0 cm^3, 4.00 $cm^3.mmol^{-1}$) and stirred at rt for 16 h. The solvent and excess bromoacetamide were removed *in vacuo*, and the residue was re-dissolved in acetonitrile (26.0 cm^3, 4.00 $cm^3.mmol^{-1}$), to this was added triphenyl phosphine (2.57 g, 9.77 mmol, 1.5 eq.), followed by triethylamine (0.988 g, 1.36 cm^3, 9.77 mmol, 1.5 eq.). The mixture was stirred at rt for 3 h, during which time a white precipitate formed. The reaction mixture was filtered through a thin pad of celite, and washed with ethyl acetate (100 cm^3), thereafter the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (150 cm^3), and triturated for 30 min, and again filtered through a thin pad of celite. The filtrate was extracted with aqueous hydrochloric acid (2 M, 3 × 50 cm^3) and the aqueous extracts were basified to pH 10 using ammonia solution. The basified extracts were then extracted with dichloromethane (3 × 100 cm^3), and the combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford a crude orange oil. Spectroscopic analysis showed a mixture of (3*R*)-3-((2*E*)-2-{2-[methoxy(methyl)amino]-2-

oxoethylidene}pyrrolidinyl)hexyl acetate **[352]** and triphenylphosphine residues which were inseparable by column chromatography, and as such the mixture was carried forward crude (~ 2g); **^{1}H** 7.70-7.43 (PPh_3 contaminant), 5.19 (1H, s, C=CH), 4.11-3.90 (2H, m, H-1), 3.85-3.75 (1H, m, H-3), 3.66 (3H, s, OCH_3), 3.28-3.19 (4H, m, H-3' and H-5'), 3.14 (3H, s, NCH_3), 2.04 (3H, s, H-2''), 1.95-1.83 (4H, m, H-4' and H-2), 1.67-1.39 (2H, m, H-4), 1.34-1.22 (2H, m, H-5), 0.92 (3H, t, *J* 7.3 Hz, H-6); **^{13}C** 172.1 (C-1''), 170.8 (C-2'), 165.4 (*C*ON(OCH_3)CH_3), 133.1-128.3 (PPh_3 contaminant), 76.9 (C=CH), 61.4 (C-5'), 60.7 (OCH_3), 50.8 (C-1), 45.3 (C-3), 34.4 (C-4), 33.0 (NCH_3), 32.8 (C-4'), 31.2 (C-3'), 21.1 (C-2), 20.8 (C-2''), 19.4 (C-5), 13.8 (C-6).

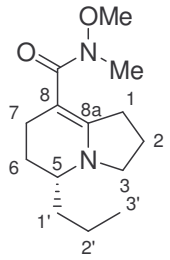
12.19 (2*E*)-2-{1-[(1*R*)-1-(2-Hydroxyethyl)butyl]-2-pyrrolidinylidene}-*N*-methoxy-*N*-methylethanamide [273]



273

Potassium carbonate (1.35 g, 9.77 mmol, 1.5 eq.) was added to a stirred solution of crude (3*R*)-3-((2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)hexyl acetate **[352]** (~ 2g, ~6.5 mmol) in dry methanol (10.4 cm^3, 1.60 $cm^3.mmol^{-1}$). The mixture was stirred at rt for 3 h, after which time the mixture was filtered through a thin pad of celite and the solvent was removed *in vacuo* to afford an orange oil. The crude orange oil was purified by column chromatography using 5% methanol:dichloromethane as eluent to afford (2*E*)-2-{1-[(1*R*)-1-(2-hydroxyethyl)butyl]-2-pyrrolidinylidene}-*N*-methoxy-*N*-methylethanamide **[273]** (1.05 g, 4.16 mmol, 64%, 3 steps from **[351]**) as a clear oil; The product was characterized as previously shown in **Section 12.9**.

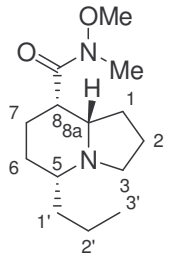
12.20 (5*R*)-*N*-Methoxy-*N*-methyl-5-propyl-1,2,3,5,6,7-hexahydro-8-indolizinecarboxamide [274]



274

Imidazole (0.0790 g, 1.14 mmol, 3.0 eq.) and triphenylphosphine (0.301 g, 1.14 mmol, 3.0 eq.) were added to a stirred solution of (2*E*)-2-{1-[(1*R*)-1-(2-hydroxyethyl)butyl]-2-pyrrolidinylidene}-*N*-methoxy-*N*-methylethanamide **[273]** (0.103 g, 0.379 mmol) in acetonitrile:toluene (2.30 cm^3:1.10 cm^3). The solution was stirred for 30 min, after which time iodine (0.192 g, 0.758 mmol, 2.0 eq.) was added in one portion. The resulting homogenous solution was refluxed for 1 h. The reaction was quenched with saturated sodium hydrogen carbonate solution (4 cm^3), and extracted with ethyl acetate (3 × 20 cm^3). The combined organic fractions where washed with saturated aqueous sodium thiosulfate (20 cm^3), separated, dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to give a yellow solid. The crude solid was purified by column chromatography initially eluting the unreacted triphenylphosphine with dichloromethane, then eluting the product using 5% methanol:dichloromethane. (5*R*)-*N*-Methoxy-*N*-methyl-5-propyl-1,2,3,5,6,7-hexahydro-8-indolizinecarboxamide **[274]** was obtained as a light yellow oil (0.0450 g, 17.8 mmol, 47%); ν_{max} **(film)/cm^{-1}** 2928 (C-H str, s), 2857 (C-H str, s), 1630 (C=C str, s), 1555 (C=O str, vs), 1438 (C-H bend, m), 1401 (m), 1361 (m), 1281 (C-O str, vs), 1194 (C-N str, m), 1154 (m), 1118 (m), 1024 (C-O str, s), 1003 (s), 937 (s); **^{1}H** 3.63 (3H, s, OCH_3), 3.48 (1H, ddd, *J* 9.0, 8.1 and 5.2 Hz, H-5), 3.24-2.91 (2H, m, H-3), 3.07 (3H, s, NCH_3), 2.34 (2H, t broad, *J* 6.1 Hz, H-7)*, 1.98-1.82 (2H, m, H-1)*, 1.80-1.52 (4H, m, H-2 and H-6), 1.45-1.21 (4H, m, H-1' and H-2'), 0.95 (3H, t, *J* 6.9 Hz, H-3'); **^{13}C** 174.4 (C-8), 157.4 (C=O$N(OCH_3)CH_3$), 90.1 (C-8a), 59.7 (OCH_3), 53.8 (C-3), 51.0 (C-5), 35.1 (C-2), 34.4 (C-1'), 32.1 (NCH_3), 25.3 (C-1), 21.5 (C-6), 20.6 (C-7), 19.0 (C-2'), 14.1 (C-3'); **HRMS m/z (EI)** 252.18281 (M^+ 100% $C_{14}H_{24}N_2O_2$ requires 252.18378), 253 (16), 251 (11), 250 (5), 248 (12), 246 (6), 244 (3). *These signals are interchangeable.

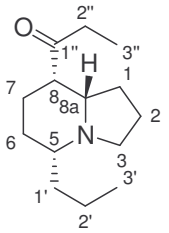
12.21 (5*R*,8*S*,8a*S*)-*N*-Methoxy-*N*-methyl-5-propyloctahydro-8-indolizinecarboxamide [275]



275

Adams catalyst (0.0340 g, 5×10^{-2} g.mmol^{-1}) was added to a solution of (5*R*)-*N*-methoxy-*N*-methyl-5-propyl-1,2,3,5,6,7-hexahydro-8-indolizinecarboxamide **[274]** (0.169 g, 0.670 mmol) in glacial acetic acid (3.70 cm^3, 5.50 cm^3.mmol^{-1}). This was stirred at rt at 1 atmosphere hydrogen for 24 h. The solution was filtered through a pad of celite, washed several times with ethanol, and evaporated *in vacuo* affording a grey oil. The crude oil was taken up in water (50 cm^3) and neutralized with saturated aqueous sodium hydrogen carbonate solution. The neutralized aqueous fraction was extracted into dichloromethane (3 × 50 cm^3), the combined organic extracts where then dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford a grey oil. The crude oil was purified by column chromatography using 5% methanol:dichloromethane as eluent, to yield (5*R*,8*S*,8a*S*)-*N*-methoxy-*N*-methyl-5-propyloctahydro-8-indolizinecarboxamide **[275]** as a clear oil (0.136 g, 0.533 mmol, 80%); **$[\alpha]_D^{21}$** –57.3 (3.07, absolute ethanol); **ν_{max} (film)/cm^{-1}** 2955 (C-H str, s), 1668 (C=O str, vs), 1459 (C-H bend, s), 1372 (C-H bend, s), 1097 (C-O str, s), 996 (s); **^{1}H** 3.65 (3H, s, OCH_3), 3.33 (1H, dt, *J* 8.1 and 1.9 Hz, H-3$_{eq}$), 3.17 (3H, s, NCH_3), 2.14-2.07 (1H, m, H*), 2.04-1.91 (2H, m, H*), 1.86-1.76 (3H, m, H*), 1.74-1.50 (5H, m, H*), 1.48-1.33 (4H, m, H*), 0.90 (3H, t, *J* 7.0 Hz H-3'); **^{13}C** 174.9 (C=O), 65.7 (C-8a), 64.2 (C-5), 61.0 (OCH_3), 51.6 (C-3), 43.9 (C-8), 36.7 (C-1'), 35.8 (NCH_3), 28.1 (C-1)$^\#$, 27.3 (C-6)$^\#$, 27.1 (C-7)$^\$$, 19.9 (C-2)$^\$$, 18.9 (C-2'), 14.5 (C-3'); **HRMS m/z (EI)** Inconsistent results were obtained.* Remaining hydrogens, $^\#$ These signals are interchangeable, $^\$$ These signals are interchangeable.

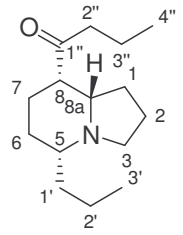
12.22 1-[(5*R*,8*S*,8a*S*)-5-Propyloctahydro-8-indolizinyl]-1-propanone [353]



353

Ethylmagnesium bromide in tetrahydrofuran (1.24 M, 1.20 cm^3, 1.49 mmol, 5.0 eq.) was added slowly to a solution of (5*R*,8*S*,8a*S*)-*N*-methoxy-*N*-methyl-5-propyloctahydro-8-indolizinecarboxamide **[275]** (0.0760 g, 0.300 mmol) in tetrahydrofuran (3.00 cm^3, 10.0 $cm^3.mmol^{-1}$) at 0 °C. The reaction was allowed to warm to rt, and was stirred for a further 24 h. The reaction was then quenched with 6 *N* hydrochloric acid solution and evaporated *in vacuo*. The residue was taken up in water (50 cm^3), basified with ammonia solution, and extracted with diethyl ether (3 × 50 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford a light yellow oil. The crude oil was purified by passing it through a short plug of silica, using 5% methanol:dichloromethane as the eluent. 1-[(5*R*,8*S*,8a*S*)-5-Propyloctahydro-8-indolizinyl]-1-propanone **[353]** was obtained as a clear oil (0.0560 g, 0.250 mmol, 83%). $\mathbf{R}_f$ 0.50 (10% methanol:dichloromethane); $\mathbf{[\alpha]_D^{19}}$ +48.3 (*c* 0.95, $CHCl_3$); **^{1}H** 3.28 (1H, dt, *J* 8.7 and 2.1 Hz, H-3_{eq}), 2.81 (1H, m, H-8), 2.63 (1H, dq, *J* 17.7 and 7.2 Hz, H-2''a), 2.52-2.39 (1H, m, H-2''b), 2.15-2.02 (2H, m, H-3_{ax}, H-5), 1.96-1.14 (13H, m, H*), 1.01 (3H, t, *J* 7.5 Hz, H-3''), 0.91 (3H, t, *J* 7.0 Hz, H-3'); **^{13}C** 213.6 (C-1''), 65.2 (C-8a), 63.9 (C-5), 51.7 (C-3), 48.5 (C-8), 37.6 (C-2''), 36.9 (C-1'), 27.9 (C-1), 27.4 (C-6), 26.9 (C-7), 20.4 (C-2), 18.6 (C-2'), 14.6 (C-3'), 7.7 (C-3''); **HRMS m/z (EI)** 223.19358 (M^+ 94% $C_{14}H_{25}NO$ requires 223.19361), 222 (100), 221 (55), 220 (6), 219 (8). * Remaining hydrogens.

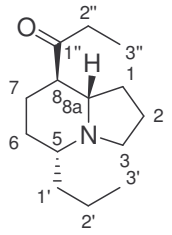
12.23 1-[(5*R*,8*S*,8a*S*)-5-Propyloctahydro-8-indolizinyl]-1-butanone [354]



354

To a stirred solution of (5*R*,8*S*,8a*S*)-*N*-methoxy-*N*-methyl-5-propyloctahydro-8-indolizine-carboxamide **[275]** (0.050 g, 0.197 mmol) in tetrahydrofuran (2.00 cm^3, 10.0 $cm^3.mmol^{-1}$) at 0 °C was added propylmagnesium chloride (1.53 M, 1.00 cm^3, 0.985 mmol, 5.0 eq.) in diethyl ether in one portion. The reaction mixture was warmed to rt, and stirred for 24 h. The reaction was quenched with 6 *N* hydrochloric acid solution and the solvent was removed *in vacuo*. The residue was diluted with water (50 cm^3), basified with ammonia solution, and extracted with diethyl ether (3 × 50 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* affording an orange oil. The crude oil was purified by column chromatography using 5% methanol:dichloromethane as the eluent yielding 1-[(5*R*,8*S*,8a*S*)-5-propyloctahydro-8-indolizinyl]-1-butanone **[354]** was obtained as a clear oil (0.012 g, 0.050 mmol, 26%). $\mathbf{R}_f$ 0.35 (5% methanol:dichloromethane); $\mathbf{[\alpha]_D^{18}}$ +7.60 (*c* 0.92 $CHCl_3$); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}**; **^{1}H** 3.29 (1H, dt, *J* 8.3 and 2.2 Hz, H-3_{eq}), 2.83-2.77 (1H, m, H-8), 2.58 (1H, dt, *J* 17.1 and 7.4 Hz, H-2''), 2.41 (1H, dt, *J* 17.1 and 7.1 Hz, H-2''), 2.25-2.08 (2H, m, H-3_{ax} and H-5), 2.04-1.22 (15H, m, H*), 0.91 (3H, t, *J* 6.9 Hz, H-3'), 0.90 (3H, t, *J* 7.4 Hz, H-4''); **^{13}C** 212.9 (C=O), 65.1 (C-8a), 63.9 (C-5), 51.6 (C-3), 48.3 (C-8), 46.3 (C-2''), 38.8 (C-1'), 36.7 (C-1), 29.7 (C-6), 27.7 (C-7), 20.4 (C-2), 18.6 (C-2'), 17.0 (C-3''), 14.5 (C-3'), 13.8 (C-4''). * Remaining hydrogens

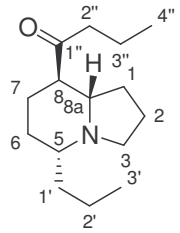
12.24 1-[(5*R*,8*R*,8a*S*)-5-Propyloctahydro-8-indolizinyl]-1-propanone [191]



191

A mixture of sodium (0.010 g, 0.042 mmol, 1.0 eq.) in dry methanol (5.0 cm^3) was stirred until a homogenous solution of sodium methoxide had formed. To this solution was added 1-[(5*R*,8*S*,8a*S*)-5-propyloctahydro-8-indolizinyl]-1-propanone **[353]** (0.0094 g, 0.042 mmol) in one portion. The reaction mixture was refluxed for 3 h and then cooled to rt. The solvent was removed *in vacuo*, and the resulting residue was re-dissolved in water (10 cm^3) and extracted with diethyl ether (3 × 20 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* giving a yellow oil. The crude oil was purified by column chromatography using 5% methanol:dichloromethane and a few drops of propylamine as eluent. 1-[(5*R*,8*R*,8a*S*)-5-Propyloctahydro-8-indolizinyl]-1-propanone **[191]** was obtained as a clear oil (0.0075 g, 0.034 mmol, 80%). $\mathbf{R}_f$ 0.50 (10% methanol:dichloromethane); $\mathbf{[\alpha]_D^{17}}$ –74.3 (*c* 0.35, chloroform); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2958 (C-H str, s), 2930 (C-H str, s), 2873 (C-H str, s), 2783 (C-H str, m), 2360 (w), 1715 (C=O str, s), 1693 (s), 1458 (C-H bend, s), 1373 (C-H bend, m), 1262 (m), 1192 (m), 1120 (s), 1019 (m), 800 (m); **^{1}H** 3.27 (1H, dt, 8.3 and 1.9 Hz, H-3_{eq}), 2.59-2.35 (3H, m, H-2'' and H-5), 2.15-1.16 (15H, m, H*), 1.04 (3H, t, *J* 7.3 Hz, H-3''), 0.91 (3H, t, *J* 7.1 Hz, H-3'); **^{13}C** 213.4 (C=O), 65.5 (C-8a), 62.8 (C-5), 54.4 (C-8), 50.9 (C-3), 36.6 (C-2''), 36.0 (C-1'), 30.3 (C-1), 28.9 (C-6), 28.4 (C-7), 20.4 (C-2), 18.9 (C-2'), 14.4 (C-3'), 7.6 (C-3''); **HRMS m/z (EI)** 223.19248 (M^+ 84% $C_{14}H_{25}NO$ requires 223.19361), 222 (100), 221 (46), 220 (5), 219 (6). * Remaining hydrogens.

12.25 1-[(5*R*,8*R*,8a*S*)-5-Propyloctahydro-8-indolizinyl]-1-butanone [354]



354

A mixture of sodium (0.0080 g, 0.035 mmol, 1.0 eq.) in dry methanol (4.2 cm^3) was stirred until a homogenous solution of sodium methoxide had formed. (5*R*,8*S*,8a*S*)-*N*-methoxy-*N*-methyl-5-propyloctahydro-8-indolizinecarboxamide **[354]** (0.0084 g, 0.035 mmol) was added to the solution of sodium methoxide. The solution was refluxed for 3 h, after which time it was cooled to rt. The solvent was removed *in vacuo*, the residue was redissolved in water (10 cm^3) and extracted with diethyl ether (3 × 20 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* giving a yellow oil. The crude oil was purified by column chromatography using 5% methanol:dichloromethane and a few drops of propylamine as eluent. 1-[(5*R*,8*R*,8a*S*)-5-Propyloctahydro-8-indolizinyl]-1-butanone **[355]** was obtained as a clear oil (4.0 mg, 0.017 mmol, 48%). $\mathbf{R}_f$ 0.30 (1:19 methanol:dichloromethane); $[\alpha]_D^{21}$ –35.7 (0.56, chloroform); ^{1}**H** 3.25 (1H, t broad, *J* 6.9 Hz, H-3_{eq}), 2.48-2.35 (3H, m, H-2'' and H-5), 2.14-1.04 (16H, m, H*), 0.93-0.86 (6H, m, H-3' and H-4''). * Remaining hydrogens

CHAPTER 13

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 6

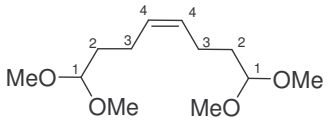
EXPERIMENTAL PROCEDURES RELATING TO PROGESS TOWARDS THE SYNTHESIS OF A LATE STAGE COMMON INTERMEDIATE [259] FOR THE PREPARATION OF 5,8-DISUBSTITUTED INDOLIZIDINES



CHAPTER 13

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 6 EXPERIMENTAL PROCEDURES RELATING PROGESS TOWARDS THE SYNTHESIS OF A LATE STAGE COMMON INTERMEDIATE [259] FOR THE PREPARATION OF 5,8-DISUBSTITUTED INDOLIZIDINES

13.1 (4*Z*)-1,1,8,8-Tetramethoxy-4-octene [281][194]



281

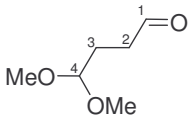
Initially the time required to afford the partial ozonolysis of 1,5-cyclooctadiene **[280]** was determined by observing the amount of time required for the complete ozonolysis of the 1,5-cyclooctadiene **[280]**.

Initially 1,5-cyclooctadiene **[280]** (1.00 g, 1.10 cm^3, 9.25 mmol) was dissolved in methanol (10.0 cm^3, 1.10 $cm^3.mmol^{-1}$) and dichloromethane (10.0 cm^3, 1.10 $cm^3.mmol^{-1}$) and cooled to −60 °C. The mixture was treated with ozone at a flow rate of 160 L O_2/h, and the reaction was stopped when the solution started turning blue, indicating the presence of unreacted ozone. The reaction was repeated a dozen times, and the complete ozonolysis of 1,5-cyclooctadiene took an average of 54 seconds/mmol of 1,5-cyclooctadiene **[280]** at a flow rate of 160 L O_2/h. The time require for the partial ozonolysis of 1,5-cyclooctadiene **[280]** would therefore require a reaction time of 26 seconds/mmol of 1,5-cyclooctadiene **[280]** at a flow rate of 160 L O_2/h.

1,5-Cyclooctadiene **[280]** (32.0 g, 36.3 cm^3, 296 mmol) was dissolved in methanol (320 cm^3, 1.1 $cm^3.mmol^{-1}$) and dichloromethane (320 cm^3, 1.10 $cm^3.mmol^{-1}$). The mixture was cooled to −60 °C and treated with ozone for 128 min at a flow rate of 160 L O_2/h. The reaction mixture was purged with oxygen for 5 min, after which time *p*-toluenesulfonic acid (4.34 g, 22.8 mmol, 0.1 eq.) was added in one portion. The reaction mixture was warmed to rt and stirred for 1 hour, at which time dimethyl sulfide (27.1 g, 32.0 cm^3, 436 mmol, 1.5 eq.) was added. The mixture was stirred at rt for 24 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (320 cm^3, 1.10 $cm^3.mmol^{-1}$), and extracted

with chloroform (3 × 200 cm^3). The organic extracts were combined, dried (anhydrous sodium sulfate) and evaporated *in vacuo* to give chromatographically pure (4*Z*)-1,1,8,8-tetramethoxy-4-octene **[281]** as a clear liquid (44.7 g, 192 mmol, 65%); ν_{max} **(film)/cm^{-1}** 2946 (C-H str, m), 2830 (C-H str, m), 1728 (m), 1446 (C-H bend, m), 1384 (C-H bend, m), 1365 (m), 1191 (m), 1124 (C-O str, vs), 1055 (C-O str, vs), 994 (w); **^{1}H** 5.38 (2H, t, *J* 4.9 Hz, H-4), 4.36 (2H, t, *J* 5.7 Hz, H-1), 3.32 (12H, s, OCH_3), 2.10-2.08 (4H, m, H-3), 1.66-1.64 (4H, m, H-2); **^{13}C** 129.3 (C-4), 104.0 (C-1), 52.6 (OCH_3), 32.3 (C-2), 22.3 (C-3); **HRMS m/z (EI)** Inconsistent results were obtained.

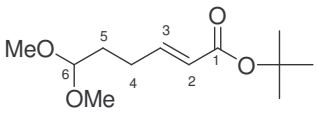
13.2 4,4-Dimethoxybutanal [282][194]



282

(4*Z*)-1,1,8,8-Tetramethoxy-4-octene **[281]** (21.2 g, 91.3 mmol) was dissolved in dichloromethane (183 cm^3, 2.00 $cm^3.mmol^{-1}$) and cooled to −60 °C. The mixture was treated with ozone until the solution turned blue. The system was purged with oxygen for 5 min, and warmed to rt. Triphenylphosphine (23.9 g, 91.3 mmol, 1.0 eq.) was added to the solution, which was stirred at rt for 24 h. The solvents were removed *in vacuo* in a fume hood. The residue was redissolved in diethyl ether (180 cm^3, 2.00 $cm^3.mmol^{-1}$) and washed with water (2 × 90 cm^3, 1 $cm^3.mmol^{-1}$). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford a white crystalline solid. The crude product was purified initially by column chromatography using dichloromethane followed by ethyl acetate. The columned residue was then purified by vacuum distillation (45-49 °C, 2 mmHg) to afford 4,4-dimethoxybutanal **[282]** as a clear liquid (11.5 g, 86.4 mmol, 47%); ν_{max} **(film)/cm^{-1}** 3431 (s), 2946 (C-H str, s), 1729 (C=O str, s), 1550 (m), 1447 (C-H bend, m), 1125 (C-O str, s), 1065 (C-O str, s); **^{1}H** 9.72 (1H, t, *J* 1.6 Hz, H-1), 4.36 (1H, t, *J* 5.6, H-4), 3.31 (6H, s, 2 × OCH_3), 2.46 (2H, dt, *J* 1.6 & 7.2 Hz, H-2), 1.90 (2H, dt, *J* 5.5 & 7.2 Hz, H-3); **^{13}C** 202.3 (C-1), 104.1 (C-4), 53.5 (2 × OCH_3), 39.5 (C-2), 25.8 (C-3); **HRMS m/z (EI)** 132.07753 (M^+ 100% $C_6H_{12}O_3$ requires 132.07864).

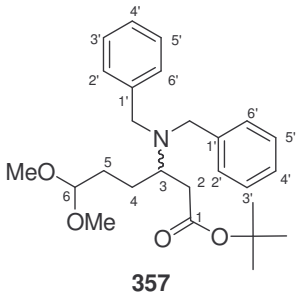
13.3 *tert*-Butyl (2*E*)-6,6-dimethoxy-2-hexenoate [283]



283

To a stirred suspension of vacuum-dried (140 °C, overnight, *ca* 1 mm Hg) lithium chloride (0.238 g, 5.55 mmol, 1.2 eq.) in dry acetonitrile (10.0 cm^3, 2.00 $cm^3.mmol^{-1}$) was added *tert*-butyl diethoxyphosphorylacetate **[282]** (1.17 g, 1.10 cm^3, 4.63 mmol), 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) (0.775 g, 0.760 cm^3, 5.10 mmol, 1.1 eq.) and 4,4-dimethoxybutanal (0.673 g, 5.10 mmol, 1.1 eq.). The mixture was stirred at rt for 24 h. The reaction was quenched with water and the solvent was evaporated *in vacuo*. The residue was extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield a light yellow oil. The crude oil was purified by column chromatography to afford *tert*-butyl (2*E*)-6,6-dimethoxy-2-hexenoate **[283]** (0.691 g, 3.01 mmol, 59%) as a colourless liquid; $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 2979 (C-H str, w), 2938 (C-H str, w), 1717 (C=O str, vs), 1655 (C=C str, w), 1369 (C-H bend, m), 1252 (w), 1229 (w), 1217 (w), 1148 (C-O str, vs), 979 (w); **^{1}H** 6.86 (1H, dt, *J* 6.9 & 15.6 Hz, H-3), 5.76 (1H, dt, *J* 1.6 & 15.6 Hz, H-2), 4.37 (1H, t, *J* 5.7 Hz, H-6), 3.32 (6H, s, 2 × OCH_3), 2.24 (2H, ddd, *J* 1.5, 7.1 & 15.2 Hz, H-4), 1.75 (2H, ddd, *J* 5.8, 7.8 & 8.9 Hz, H-5), 1.48 (9H, s, $C(CH_3)_3$); **^{13}C** 165.9 (C-1), 146.8 (C-3), 123.4 (C-2), 103.7 (C-6), 80.1 ($\underline{C}(CH_3)_3$), 52.8 (2 × O CH_3), 30.9 (C-5), 28.1 ($C(\underline{C}H_3)_3$), 28.0 ($C(\underline{C}H_3)_3$), 27.1 (C-4).

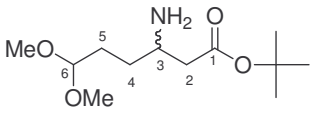
13.4 *tert*-Butyl 3-(dibenzylamino)-6,6-dimethoxyhexanoate [357]



357

A solution of freshly distilled dibenzylamine (10.0 g, 9.75 cm^3, 50.7 mmol, 1.2 eq.) in dry tetrahydrofuran (167 cm^3, 4.00 $cm^3.mmol^{-1}$) at −78 °C was treated with *n*-butyllithium (1.4 M, 33.2 cm^3, 46.5 mmol, 1.1 eq.). The resulting dark red solution was stirred for 30 min, after which time *tert*-butyl (2*E*)-6,6-dimethoxy-2-hexenoate **[283]** (10.3 g, 42.3 mmol) in tetrahydrofuran (48 cm^3, 1 $cm^3.mmol^{-1}$) was added dropwise over 10 min. The mixture was stirred at −78 °C for 3 h. The reaction was quenched with an aqueous solution of saturated ammonium chloride (105 cm^3, 2.50 $cm^3.mmol^{-1}$) and the mixture was warmed to rt. The solvent was removed *in vacuo*, and the residue was diluted with water (105 cm^3, 2.50 $cm^3.mmol^{-1}$). The residue was extracted with dichloromethane (3 × 100 cm^3, 2.50 $cm^3.mmol^{-1}$) and the combined organic extracts were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography using 5% ethyl acetate:hexane as eluent. *tert*-Butyl 3-(dibenzylamino)-6,6-dimethoxyhexanoate **[357]** (0.685 g, 1.60 mmol, 69%) was obtained as a light yellow oil; $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3063 (ArC-H str, w), 3028 (ArC-H str, w), 2976 (C-H str, w), 2934 (C-H str, w), 2829 (C-H str, w), 1722 (C=O str, s), 1495 (w), 1454 (C-H bend, m), 1390 (w), 1366 (C-H bend, s), 1292 (w), 1253 (w), 1150 (s), 1123 (C-O str, s), 1071 (C-O str, s), 1028 (w), 953 (s); **^{1}H** 7.36-7.18 (10H, m, ArH's), 4.13-4.08 (1H, m, H-6), 3.71 (2H, d, *J* 13.5 Hz, C$\underline{H}_2$Ph), 3.36 (2H, d, *J* 13.9 Hz, C$\underline{H}_2$Ph), 3.22 (3H, s, OCH_3), 3.21 (3H, s, OCH_3), 3.10-3.01 (1H, m, H-3), 2.67 (1H, dd, *J* 4.5 & 13.7 Hz, H-2a), 2.10 (1H, dd, *J* 8.9 & 13.7 Hz, H-2b), 1.84-1.33 (4H, m, H-4 & H-5), 1.43 (9H, s, $C(CH_3)_3$); **^{13}C** 172.2 (C-1), 139.7 (C-1'), 129.0 (C-2' & C-6'), 128.1 (C-3' & C-5'), 126.9 (C-4'), 104.1 (C-6), 80.2 [$\underline{C}(CH_3)_3$], 55.0 (2 × $\underline{C}H_2$Ph), 53.4 (C-3), 52.8 (OCH_3), 52.5 (OCH_3), 35.8 (C-2), 29.3 (C-5), 28.0 [$C(\underline{C}H_3)_3$], 26.2 (C-4); **HRMS m/z (EI)** 427.27214 (M^+ 2%, $C_{26}H_{37}NO_4$ requires 427.27226), 91 (66), 132 (10), 132 (11), 268 (54), 269 (10), 280 (18), 280 (13), 312 (97), 312 (100), 313 (21), 313 (23), 324 (79), 324 (81), 325 (19), 336 (11), 340 (10), 396 (15), 396 (15), 412 (17), 412 (19).

13.5 *tert*-Butyl 3-amino-6,6-dimethoxyhexanoate [356]



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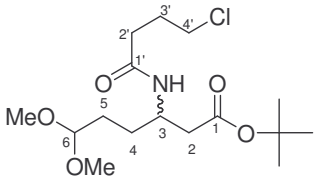
Method 1

A solution of *tert*-butyl 3-(dibenzylamino)-6,6-dimethoxyhexanoate **[357]** (1.03 g, 2.34 mmol) in absolute ethanol (21.0 cm^3, 9.00 $cm^3.mmol^{-1}$) was treated with 10% palladium on carbon (0.351 g, 0.150 $g.mmol^{-1}$). The mixture was placed in an autoclave and stirred for 3 d at 7 atmospheres of hydrogen gas. The reaction mixture was filtered through celite, and washed several times with ethanol. The solvent was removed *in vacuo* to afford a grey oil. The crude oil was purified by column chromatography 5% methanol:ethyl acetate as eluent to yield *tert*-butyl 3-amino-6,6-dimethoxyhexanoate **[356]** (0.543 g, 2.20 mmol, 94%) as a clear oil; characterized as described below.

Method 2

A solution of *tert*-butyl 3-(dibenzylamino)-6,6-dimethoxyhexanoate **[357]** (5.71 g, 13.3 mmol) in absolute ethanol (120 cm^3, 9.00 $cm^3.mmol^{-1}$) was treated with 20% palladium hydroxide on carbon (2.00 g, 0.150 $g.mmol^{-1}$). The mixture was placed in an autoclave and stirred for 3 d under 7 atmospheres of hydrogen gas. The reaction mixture was filtered through celite, and washed several times with ethanol. The solvent was removed *in vacuo* to afford a grey oil. The crude oil was purified by column chromatography with 5% methanol:ethyl acetate as eluent to yield *tert*-butyl 3-amino-6,6-dimethoxyhexanoate **[356]** (3.30 g, 13.3 mmol, 100%) as a clear oil; $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3377 (N-H str, w), 2971 (C-H str, m), 2936 (C-H str, m), 2831 (C-H str, m), 1724 (C=O str, s), 1679 (w), 1454 (C-H bend, m), 1367 (C-H bend, s), 1296 (w), 1252 (w), 1230 (w), 1217 (w), 1149 (s), 1125 (C-O str, s), 1053 (C-O str, s), 952 (m); **^{1}H** 4.37 (1H, t, *J* 5.5 Hz, H-6), 3.32 (6H, s, 2 × OCH_3), 3.19-3.10 (1H, m, H-3), 2.38 (1H, dd, *J* 4.0 & 15.5 Hz, H-2a), 2.10 (1H, dd, *J* 8.8 & 15.5 Hz, H-2b), 1.78-1.57 (2H, m, H-5), 1.56-1.32 (4H, m, H-4 & NH_2), 1.46 (9H, s, $C(CH_3)_3$); **HRMS m/z (EI)** Inconsistent results were obtained.

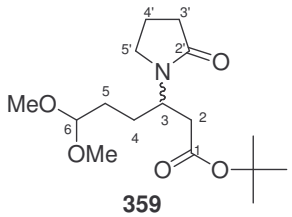
13.6 *tert*-Butyl 3-[(4-chlorobutanoyl)amino]-6,6-dimethoxyhexanoate [358]



358

tert-Butyl 3-amino-6,6-dimethoxyhexanoate [356] (0.501 g, 2.02 mmol) and triethylamine (0.430 g, 0.59 cm^3, 4.25 mmol, 2.1 eq.) in dichloromethane (8.70 cm^3, 4.30 $cm^3.mmol^{-1}$) were cooled to 0 °C. 4-Chlorobuyryl chloride (0.343 g, 0.270 cm^3, 2.42 mmol, 1.2 eq.) was added slowly to the reaction mixture, and was accompanied by vigourous effervescence. The mixture was stirred for 30 min at rt, after which it was diluted with dichloromethane (10 cm^3, 5 $cm^3.mmol^{-1}$). The solvent was removed *in vacuo* and the resulting residue was re-dissolved in dichloromethane (20 cm^3, 10 $cm^3.mmol^{-1}$). The organic fraction was washed with water (20 cm^3, 10 $cm^3.mmol^{-1}$), followed by brine (20 cm^3, 10 $cm^3.mmol^{-1}$). The organic fraction was dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford a crude orange oil. The crude oil was purified by column chromatography 5% methanol:dichloromethane as eluent to yield *tert*-butyl 3-[(4-chlorobutanoyl)amino]-6,6-dimethoxyhexanoate [358] (0.701 g, 1.99 mmol, 99%) as an orange oil; ν_{max} (film)/cm^{-1} 3330 (N-H str, s br), 2918 (C-H str, s), 1729 (C=O ester str, s), 1654, (C=O amide str, s), 1419 (C-H bend, s), 1376 (C-H bend, s), 1297 (w), 1172 (C-N str, s), 1146 (C-O, str, s), 1054 (C-O str, s), 869 (w); ^{1}H 6.26 (1H, d, *J* 8.9 Hz, NH), 4.36 (1H, t, *J* 5.0 Hz, H-6), 4.27-4.19 (1H, m, H-3), 3.60 (2H, t, *J* 6.3 Hz, H-4'), 3.32 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 2.44 (2H, dd, *J* 3.5 & 5.2 Hz, H-2), 2.35 (2H, t, *J* 7.2 Hz, H-2'), 2.11 (2H, quintet, *J* 6.6 Hz, H-3'), 1.68-1.54 (4H, m, H-4 & H-5), 1.45 (9H, s, $C(CH_3)_3$); ^{13}C 171.1 (C-1'), 171.0 (C-1), 104.0 (C-6), 81.2 [$\underline{C}(CH_3)_3$], 53.0 (OCH_3), 52.9 (OCH_3), 46.0 (C-3), 45.9 (C-4), 44.4 (C-4'), 39.7 (C-2), 33.4 (C-2'), 29.2 (C-5), 28.9 (C-3'), 28.0 ($C(\underline{C}H_3)_3$); HRMS m/z (EI) Inconsistent results were obtained.

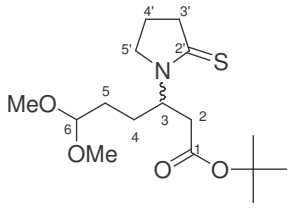
13.7 *tert*-Butyl 6,6-dimethoxy-3-(2-oxo-1-pyrrolidinyl)hexanoate [359]



359

tert-Butyl 3-[(4-chlorobutanoyl)amino]-6,6-dimethoxyhexanoate **[358]** (0.619 g, 1.76 mmol) was treated with potassium *tert*-butoxide (0.392 g, 3.52 mmol, 2.0 eq.) in dry *tert*-butanol (11.0 cm^3, 6.50 $cm^3.mmol^{-1}$). The mixture was stirred at rt for 24 h. The mixture was neutralized with glacial acetic acid and the solvent was evaporated *in vacuo* to yield a milky residue. The residue was taken up in dichloromethane (20 cm^3, 10 $cm^3.mmol^{-1}$) and washed with water (20 cm^3, 10 $cm^3.mmol^{-1}$). The aqueous extracts were back-extracted with dichloromethane (3 × 50 cm^3, 25 $cm^3.mmol^{-1}$). The combined organic extracts were combined, dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford an orange oil. The crude oil was purified by column chromatography using 30% ethyl acetate:hexane as eluent to yield *tert*-butyl *tert*-butyl 6,6-dimethoxy-3-(2-oxo-1-pyrrolidinyl)hexanoate **[359]** (0.292 g, 0.926 mmol, 53%) as a yellow oil**;** ν_{max} **(film)/cm^{-1}** 2976 (C-H str, m), 2935 (C-H str, m), 2831 (C-H str, m), 1724 (C=O str, s), 1688 (C=O str, s), 1457 (C-H bend, m), 1423 (m), 1391 (w), 1367 (C-H bend, s), 1284 (m), 1252 (m), 1148 (C-N str, s), 1125 (C-O str, s), 1056 (C-O str, s), 954 (m)**;** ^{1}**H** 4.49-4.39 (1H, m, H-3), 4.35 (1H, t, *J* 5.0 Hz, H-6), 3.41-3.23 (2H, m, H-5'), 3.32 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 2.40 (2H, dd, *J* 13.6 & 14.2 Hz, H-2), 2.36 (2H, dt, *J* 1.8 & 7.7 Hz, H-3'), 2.11 (2H, quintet, H-4'), 1.63-1.54 (4H, m, H-4 & H-5), 1.42 (9H, s, $C(CH_3)_3$); ^{13}**C** 174.9 (C-1), 170.0 (C-2'), 104.1 (C-6), 80.9 [$\underline{C}(CH_3)_3$], 53.14 (OCH_3), 53.12 (OCH_3), 48.5 (C-3), 42.4 (C-5'), 39.4 (C-2), 31.4 (C-3'), 29.3 (C-5), 27.9 [$C(\underline{C}H_3)_3$], 27.0 (C-4), 18.3 (C-4').

13.8 *tert*-Butyl 6,6-dimethoxy-3-(2-thioxo-1-pyrrolidinyl)hexanoate [439]



439

Attempt 1

To a suspension of phosphorus pentasulfide (0.115 g, 0.508 mmol, 3.0 eq.) in tetrahydrofuran (1.40 cm^3, 8.00 $cm^3.mmol^{-1}$) was added sodium carbonate (0.0271 g, 0.254 mmol, 1.5 eq.), the mixture was stirred at rt until the solution became homogeneous. To this solution was *tert*-butyl 6,6-dimethoxy-3-(2-oxo-1-pyrrolidinyl)hexanoate **[359]** (0.0530 g, 0.169 mmol) in tetrahydrofuran (0.3 cm^3, 2 $cm^3.mmol^{-1}$). Sodium carbonate (10%, 1.4 cm^3, 8 $cm^3.mmol^{-1}$), ethyl acetate (0.4 cm^3, 6 $cm^3.mmol^{-1}$) and hexane (0.13 cm^3, 2 $cm^3.mmol^{-1}$) were added after 5 h. The aqueous phase was extracted with dichloromethane (3 × 10 cm^3). The combined organic phases were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to give a yellow oil. The crude product was purified by column chromatography using 30% ethyl acetate:hexane as elutent to give an unidentifiable mixture of products as a yellow oil.

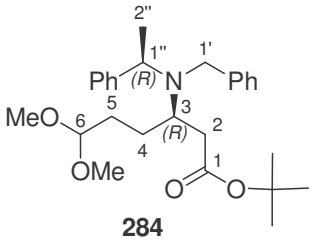
Attempt 2

tert-Butyl 6,6-dimethoxy-3-(2-oxo-1-pyrrolidinyl)hexanoate **[359]** (0.105 g, 0.330 mmol), was added to a stirred solution of Lawesson's reagent (0.0810 g, 0.199 mmol, 0.6 eq.) in toluene (1.3 cm^3, 4$cm^3.mmol^{-1}$). The solution was stirred at reflux for 5 h, after which time the solvent was removed *in vacuo* to yield a red oil. The crude red oil was purified by column chromatography using 30% ethyl acetate:hexane as eluent to yield an unidentifiable product as a yellow oil.

Attempt 3

tert-Butyl 6,6-dimethoxy-3-(2-oxo-1-pyrrolidinyl)hexanoate **[359]** (0.0950 g, 0.300 mmol) and Lawesson's reagent (0.0860 g, 0.210 mmol, 0.7 eq.) were placed in a pressure vessel and treated with microwaves at 100 Watts and 120 °C for 90 seconds. The mixture turned black and column chromatography afforded only an unidentifiable product as a dark red oil.

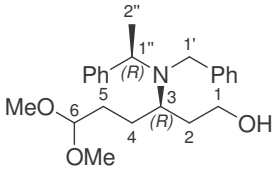
13.9 *tert*-Butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}-6,6-dimethoxyhexanoate [284]



284

A solution of freshly distilled *N*-benzyl-*N*-(1*R*)-1-phenylethylamine **[243]** (2.80 g, 2.78 cm^3, 13.3 mmol, 1.1 eq.) in dry tetrahydrofuran (54.0 cm^3, 4.50 $cm^3.mmol^{-1}$) was cooled to −78 °C and treated with *n*-butyllithium (1.4 M, 9.48 cm^3, 13.3 mmol, 1.1 eq.). The resulting dark red solution was stirred for 45 min, after which time *tert*-butyl (2*E*)-6,6-dimethoxy-2-hexenoate **[283]** (2.05 g, 12.1 mmol) in tetrahydrofuran (12.0 cm^3, 1.00 $cm^3.mmol^{-1}$) was added dropwise over 10 min. The mixture was stirred at **–**78 °C for 3 h. The reaction was quenched with a solution of saturated aqueous ammonium chloride (30 cm^3). The mixture was warmed to rt. The solvent was removed *in vacuo*, and the residue was diluted with water (30 cm^3). The residue was extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography using 10% ethyl acetate:hexane as eluent, and *tert*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}-6,6-dimethoxyhexanoate **[284]** (2.48 g, 5.61 mmol, 47%) was obtained as a yellow oil; $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3083 (ArC-H str, w), 3062 (ArC-H str, w), 3026 (ArC-H str, w), 2969 (C-H str, w), 2925 (C-H str, w), 2830 (C-H str, w), 1736 (C=O str, m), 1603 (w), 1493 (s), 1451 (C-H bend, s), 1368 (C-H bend, m), 1303 (w), 1201 (m), 1124 (C-N str, s), 1071 (m), 1057 (m), 1027 (C-O str, s), 988 (m); **^{1}H** 7.44-7.21 (10H, m, Ar-H's), 4.26 (1H, t, *J* 5.8 Hz, H-6), 3.82 (1H, q, *J* 6.9 Hz, H-1''), 3.79 (1H, d, *J* 8.5 Hz, H-1'a), 3.48 (1H, d, *J* 14.9 Hz, H-1'b), 3.33-3.27 (1H, m, H-3), 3.29 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 2.04-1.82 (4H, m, H-2), 1.60-1.23 (4H, m, H-4 & H-5), 1.39 (9H, s, $C(CH_3)_3$), 1.34 (3H, d, *J* 7.0 Hz, H-2'').

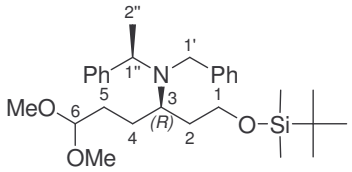
13.10 (3*R*)-3-{Benzyl[(1*R*)-1-phenylethyl]amino}-6,6-dimethoxy-1-hexanol [360]



360

tert-Butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}-6,6-dimethoxyhexanoate **[284]** (1.12 g, 2.54 mmol) was slowly added to a slurry of lithium aluminium hydride (0.106 g, 2.80 mmol, 1.1 eq.) in diethyl ether (5.1 cm^3, 2 $cm^3.mmol^{-1}$) at 0 °C. The solution was warmed to rt and stirred for 24 h. The reaction was quenched by the sequential addition of water (0.5 cm^3, 0.2 $cm^3.mmol^{-1}$), sodium hydroxide (0.5 cm^3, 15% w/v, 0.2 $cm^3.mmol^{-1}$) and finally water (1.5 cm^3, 0.6 $cm^3.mmol^{-1}$). The solids were removed by passing the mixture through a thin pad of celite. The filtrate was dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield a clear oil. The crude oil was purified by column chromatography 50% ethyl acetate:hexane to yield (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}-6,6-dimethoxy-1-hexanol **[360]** as a clear oil (0.925 g, 2.49 mmol, 98%); $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3380 (O-H str, m br), 3084 (ArC-H str, w), 3061 (ArC-H str, w), 3027 (ArC-H str, w), 2956 (C-H str, s), 2931 (C-H str, s), 2870 (C-H str, m), 1739 (w), 1602 (w), 1542 (s), 1493 (s), 1452 (C-H bend, s), 1373 (C-H bend, s), 1277 (w), 1257 (w), 1204 (C-N str, s), 1140 (w), 1109 (w), 1052 (C-O str, s), 1027 (s), 906 (m); **^{1}H** 7.41-7.20 (10H, m, Ar-H's), 4.31 (1H, t, *J* 5.4 Hz, H-6), 3.94 (1H, q, *J* 6.8 Hz, H-1''), 3.82 (1H, d, *J* 13.9 Hz, H-1'a), 3.72 (1H, d, *J* 13.9 Hz, H-1'b), 3.55-3.48 (1H, m, H-1a), 3.31 (6H, s, 2 × OCH_3), 3.27-3.18 (2H, m, H-1b), 2.82-2.73 (1H, m, H-3), 2.31 (1H, s broad, OH), 1.79-1.50 (6H, m, H-2, H-4 and H-5), 1.39 (3H, d, *J* 6.9 Hz, H-2''); **^{13}C** 143.8 (ArC), 140.9 (ArC), 128.9 (ArC), 128.4 (ArC), 128.1 (ArC), 127.0 (ArC), 126.9 (ArC), 104.4 (C-6), 61.6 (C-1''), 56.9 (C-1), 54.5 (C-3), 52.8 (OCH_3), 52.6 (OCH_3), 49.9 (C-1'), 33.6 (C-2), 30.4 (C-5), 27.3 (C-4), 15.7 (C-2''); **HRMS m/z (EI)** 371.24536 (M^+ 100%, $C_{23}H_{33}NO_3$ requires 371.24604), 372 (54), 370 (40).

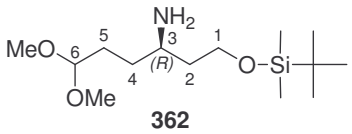
13.11 (3*R*)-*N*-Benzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-6,6-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-3-hexanamine [361]



361

tert-Butyldimethylsilyl chloride (0.557 g, 3.70 mmol, 1.1 eq.) in dimethylformamide (2.20 cm^3, 0.600 cm^3.mmol) was added dropwise to a stirred solution of (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}-6,6-dimethoxy-1-hexanol **[360]** (1.25 g, 3.36 mmol) and imidazole (0.461 g, 6.73 mmol, 2.0 eq.) in dimethylformamide (4.40 cm^3, 1.20 cm^3.mmol). The mixture was stirred for 24 h. The reaction mixture was washed with ice/water (22 cm^3, 6 $cm^3.mmol^{-1}$), and the aqueous residues were extracted with dichloromethane (5 x 22 cm^3, 6 $cm^3.mmol^{-1}$). The combined organic residues were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo*. The residue was re-dissolved in dichloromethane (22 cm^3, 6 $cm^3.mmol^{-1}$) and washed with water (4 x 22 cm^3, 6 $cm^3.mmol^{-1}$). The organic extract was dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to yield a crude yellow oil. Purification by column chromatography using 10% ethyl acetate:hexane as eluent afforded (3*R*)-*N*-benzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-6,6-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-3-hexanamine **[361]** (1.25 g, 2.56 mmol, 76%), as a clear oil; ν_{max} **(film)/cm^{-1}** 3062 (ArC-H str, w), 3028 (ArC-H str, w), 2952 (C-H str, s), 2930 (C-H, str, s), 2885 (C-H str, w), 2856 (C-H str, m), 2829 (C-H str, m), 1738 (w), 1602 (w), 1493 (m), 1471 (s), 1453 (C-H bend, s) 1362 (C-H bend, s), 1253 (C-N str, s), 1194 (m), 1124 (vs), 1082 (C-O str, vs), 1006 (w), 939 (w); **^{1}H** 7.37-7.14 (10H, m, aromatic protons), 4.17 (1H, t, *J* 5.4 Hz, H-6), 3.82 (1H, q, *J* 7.2 Hz, H-1''), 3.75 (1H, d, *J* 15.2 Hz, H-1'a), 3.58 (1H, d, *J* 15.0 Hz, H-1'b), 3.44-3.36 (1H, m, H-1a), 3.30-3.22 (1H, m, H-1b), 3.23 (3H, s, OCH_3), 3.22 (3H, s, OCH_3), 2.68-2.62 (1H, m, H-3), 1.84-1.76 (1H, m, H-2a), 1.58-1.38 (3H, m, H-2b & H-5), 1.34-1.18 (2H, m, H-4), 1.25 (3H, d, *J* 6.9 Hz, H-2''), 0.80 (9H, s, $C(CH_3)_3$), -0.07 (6H, s, $Si(CH_3)_2$); **^{13}C** 144.6 (ArC), 142.4 (ArC), 128.2 (ArC), 128.1 (ArC), 128.0 (ArC), 127.9 (ArC), 126.7 (ArC), 126.4 (ArC), 104.6 (C-6), 61.7 (C-1''), 58.3 (C-1), 53.9 (C-3), 52.8 (OCH_3), 52.4 (OCH_3), 50.1 (C-1'), 34.2 (C-2), 30.3 (C-5), 27.6 (C-4), 26.0 ($C(\underline{C}H_3)_3$), 19.4 (C-2''), 18.3 ($\underline{C}(CH_3)_3$), -5.3 ($Si(CH_3)_2$); **HRMS m/z (EI)** 485.32116 (M^+ 50%, $C_{29}H_{47}NO_3Si$ requires 485.33252), 484 (100), 483 (17), 482 (38).

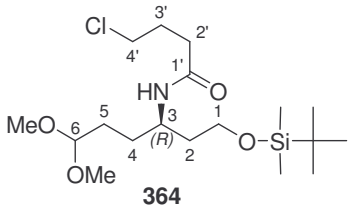
13.12 (3*R*)-1-{[*tert*-Butyl(dimethyl)silyl]oxy}-6,6-dimethoxy-3-hexanamine [362]



362

A solution of (3*R*)-*N*-benzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-6,6-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-3-hexanamine **[361]** (1.19 g, 2.44 mmol) in absolute ethanol (10.0 cm^3, 4.00 $cm^3.mmol^{-1}$) was placed in an autoclave and hydrogenated under a hydrogen atmosphere in the presence of 10% palladium on carbon (0.366 g, 0.150 $g.mmol^{-1}$). The mixture was stirred at 7 atmospheres for 3 d, then filtered through a pad of celite and washed several times with ethanol. The solvent was removed *in vacuo* affording a crude grey oil. The crude oil was purified by column chromatography to yield (3*R*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-6,6-dimethoxy-3-hexanamine **[362]** (0.639 g, 2.19 mmol, 98%) as a clear oil**;** ν_{max} **(film)/**cm^{-1} 3356 (N-H str, m br), 2951 (C-H str, s), 2929 (C-H str, s), 2856 (C-H str, s), 2832 (C-H str, s), 1738 (w), 1592 (w), 1471 (s), 1463 (C-H bend, s), 1385 (C-H bend, s), 1362 (s), 1253 (s), 1217 (w), 1193 (w), 1125 (C-N str, vs), 1054 (C-O str, vs), 1007 (w), 955 (w); **^{1}H** 4.35 (1H, t, *J* 5.5 Hz, H-6), 3.81-3.67 (2H, m, H-1), 3.31 (6H, s, 2 × OCH_3), 2.96-2.88 (1H, m, H-3), 2.12 (2H, s, NH_2), 1.77-1.58 (2H, m, H-2), 1.55-1.31 (4H, m, H-4 & H-5), 0.87 (9H, s, $C(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$); **^{13}C** 104.6 (C-6), 61.1 (C-1), 52.9 (OCH_3), 52.7 (OCH_3), 49.2 (C-3), 39.9 (C-2), 32.7 (C-5), 29.1 (C-4), 25.9 [$C(\underline{C}H_3)_3$], 18.2 [$\underline{C}(CH_3)_3$], -5.4 [$Si(CH_3)_2$]; **HRMS m/z (EI)** Inconsistent results were obtained

13.13 *N*-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4,4-dimethoxybutyl]-4-chlorobutanamide [364]

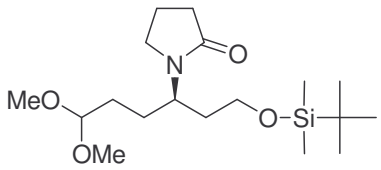


364

A solution of (3*R*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-6,6-dimethoxy-3-hexanamine **[362]** (0.586 g, 2.01 mmol) and triethylamine (2.03 g, 2.80 cm^3, 20.1 mmol, 10.0 eq.) in

dichloromethane (8.00 cm^3, 4.00 $cm^3.mmol^{-1}$) was cooled to 0 °C. 5-Chlorobutyryl chloride (0.340 g, 0.200 cm^3, 2.41 mmol, 1.2 eq.) was added slowly to the reaction mixture upon which vigorous effervescence of hydrogen chloride gas was observed. The reaction mixture was warmed to rt and stirred for 30 min after which it was diluted with dichloromethane (10 cm^3, 5 $cm^3.mmol^{-1}$). The solvent was removed *in vacuo* and the resulting residue was re-dissolved in dichloromethane (20 cm^3, 10 $cm^3.mmol^{-1}$). The organic fraction was washed with water (20 cm^3, 10 $cm^3.mmol^{-1}$), followed by brine (7 cm^3, 10 $cm^3.mmol^{-1}$). The organic fraction was dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford a crude red oil. The crude oil was purified by column chromatography to give *N*-[(1*R*)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4,4-dimethoxybutyl]-4-chlorobutanamide **[364]** as an orange oil (0.790 g, 1.99 mmol, 99%); $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3339 (N-H str, s br), 2918 (C-H str, s), 2850 (C-H str, m), 1726 (C=O str, s), 1648 (C=O str, s), 1542 (w), 1509 (w), 1442 (C-H bend, s), 1380 (C-H bend, s), 1311 (w), 1256 (C-N str, m), 1217 (m), 1199 (m), 1060 (C-O str, vs), 876 (w); **^{1}H** 6.16 (1H, s broad, *J* 8.3 Hz, NH), 4.34 (1H, t, *J* 5.0 Hz, H-6), 4.09-3.98 (1H, m, H-3), 3.78 (1H, ddd, *J* 4.7, 8.7 & 10.9 Hz, H-1a), 3.68 (1H, dt, *J* 5.3 & 10.5 Hz, H-1b), 3.58 (2H, t, *J* 6.2 Hz, H-4'), 3.31 (6H, s, 2 × OCH_3), 2.29 (2H, t, *J* 7.1 Hz, H-2'), 2.09 (2H, quintet, *J* 6.7 Hz, H-3'), 1.85-1.70 (2H, m, H-2), 1.68-1.52 (4H, m, H-4 & H-5), 0.90 (9H, s, $C(CH_3)_3$), 0.062 (3H, s, $SiCH_3$), 0.056 (3H, s, $SiCH_3$); **^{13}C** 170.9 (C-1'), 104.5 (C-6), 60.3 (C-1), 53.1 (OCH_3), 53.0 (OCH_3), 47.6 (C-3), 44.5 (C-4'), 36.0 (C-2), 33.5 (C-2'), 29.2 (C-5), 29.0 (C-4), 28.2 (C-3'), 25.9 ($C(\underline{C}H_3)_3$), 18.2 ($\underline{C}(CH_3)_3$) -5.47 ($SiCH_3$), -5.49 ($SiCH_3$); **HRMS m/z (EI)** Inconsistent results were obtained.

13.14 1-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4,4-dimethoxybutyl]-2-pyrrolidinone [363] from [364]

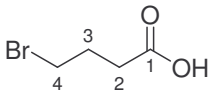


363

N-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4,4-dimethoxybutyl]-4-chlorobutanamide **[364]** (0.316 g, 0.800 mmol) was dissolved in dry *tert*-butanol (2.40 cm^3, 3.00 $cm^3.mmol^{-1}$).

To this was added potassium *tert*-butoxide (0.135 g, 1.20 mmol, 1.5 eq.) in portions (~0.020 g per addition) over a 5 h period. After the final addition the mixture was stirred for a further 30 min, and thereafter glacial acetic acid was added to neutralize the mixture. The solvent was removed from the neutralized mixture by evaporation *in vacuo*, the resulting residue was dissolved in dichloromethane (20 cm^3) and wash with water (20 cm^3). The aqueous extracts were extracted with dichloromethane (3 × 20 cm^3), and the combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afforded a brown oil. Purification of the crude oil by column chromatography afforded only decomposed material.

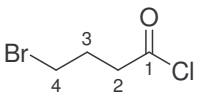
13.15 5-Bromobutanoic acid [367]



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γ-Butyrolactone **[366]** (10.0 g, 9.05 cm^3, 99.9 mmol) was dissolved in hydrobromic acid solution (48%, 60.0 cm^3) containing concentrated sulfuric acid (98%, 3.00 cm^3). The solution was refluxed for 2 h, and then stirred at rt for a further 24 h. The solution was washed with chilled water (20 cm^3, 0.2 $cm^3.mmol^{-1}$) and saturated aqueous sodium hydrogen carbonate solution (10 cm^3, 0.1 $cm^3.mmol^{-1}$) and extracted with diethyl ether (4 × 100 cm^3, 1 $cm^3.mmol^{-1}$). The organic fractions were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford an orange solid. The crude solid was purified by recrystallisation from dichloromethane and hexane to give 5-bromobutanoic acid **[367]** as a beige solid (11.4 g, 68.4 mmol, 68%). **mp** 35-38 °C (literature 36-38.5 °C); ν_{max} **(film)/cm^{-1}** 2970 (C-H str, s br), 2254 (s), 1711 (C=O str, vs), 1437 (C-H bend, s), 1289 (s), 1236 (s), 1134 (w), 912 (vs); ^{1}**H** 11.1 (1H, s broad, OH), 3.49 (2H, dt, *J* 0.9 & 6.6 Hz, H-4), 2.58 (2H, t, *J* 7.0. Hz, H-2), 2.19 (2H, quintet, *J* 6.7 Hz, H-3); ^{13}**C** 179.1 (C-1), 32.3 (C-2), 32.2 (C-4), 27.3 (C-3).

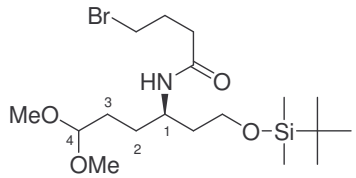
13.16 5-Bromobutanoyl chloride [365]



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A stirred solution of 5-bromobutanoic acid **[367]** (15.0 g, 89.7 mmol) in dichloromethane (63.0 cm^3, 0.700 $cm^3.mmol^{-1}$) was cooled to 0 °C. Oxalyl chloride in dichloromethane (2 M, 49.0 cm^3, 98.7 mmol, 1.1 eq.) was added slowly by syringe. A drop of triethylamine was added to the mixture upon which a slight effervescence was observed. The mixture was stirred at 0 °C for 3 h, before being warmed to rt and left to stir for 16 h. The solvent was removed *in vacuo* to give a crude orange oil. The crude oil was purified by distillation (55 °C, 1,5 mmHg) to afford 5-bromobutanoyl chloride **[365]** as a clear oil (15.7 g, 78.9 mmol, 88%).

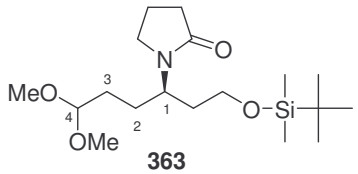
13.17 *N*-[1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4,4-dimethoxybutyl]-4-chlorobutanamide [368]



368

A solution of 1-{[*tert*-butyl(dimethyl)silyl]oxy}-6,6-dimethoxy-3-hexanamine **[362]** (0.203 g, 0.699 mmol) and triethylamine (0.156 g, 0.210 cm^3, 1.54 mmol, 2.2 eq.) in dichloromethane (3.00 cm^3, 4.30 $cm^3.mmol^{-1}$) was cooled to 0 °C. 5-Bromobutanoyl chloride **[365]** (0.169 g, 0.110 cm^3, 0.909 mmol, 1.3 eq.) was added slowly to the reaction mixture upon which vigorous effervescence of hydrogen chloride gas was observed. The reaction mixture was warmed to rt and stirred for 30 min after which it was diluted with dichloromethane (3.5 cm^3). The solvent was removed *in vacuo* and the resulting residue was re-dissolved in dichloromethane (7 cm^3). The organic fraction was washed with water (7 cm^3), followed by brine (7 cm^3). The organic fraction was dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford *N*-[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4,4-dimethoxybutyl]-4-chlorobutanamide **[368]** as a crude red oil. The crude oil rapidly turned black and as such was not purified and was used immediately.

13.18 Attempted preparation of 1-[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4,4-dimethoxybutyl]-2-pyrrolidinone [363] from [368]



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Attempt 1

N-[1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4,4-dimethoxybutyl]-4-chlorobutanamide **[368]** (0.854 g, 5.44 mmol) in dry *tert*-butanol (35.0 cm^3, 6.50 $cm^3.mmol^{-1}$) was treated with potassium *tert*-butoxide (1.21 g, 10.9 mmol, 2.0 eq.). The mixture was stirred at rt for 24 h. Glacial acetic acid was used to neutralize the reaction mixture. The solvent was evaporated *in vacuo* to yield a milky residue. The residue was taken up in dichloromethane (55 cm^3, 10 $cm^3.mmol^{-1}$) and washed with water (55 cm^3, 10 $cm^3.mmol^{-1}$). The aqueous extracts were back extracted with dichloromethane (3 × 140 cm^3, 25 $cm^3.mmol^{-1}$). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and evaporated *in vacuo* to afford an orange oil. Column chromatography yielded an unidentifiable product.

CHAPTER 14

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 7

EXPERIMENTAL PROCEDURES RELATING TO THE APPLICABILITY OF THE METHODOLOGY TO THE SYNTHESIS OF 1,4-DISUBSTITUTED QUINOLIZIDINES

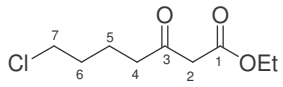


CHAPTER 14

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 7

EXPERIMENTAL PROCEDURES RELATING TO THE APPLICABILITY OF THE METHODOLOGY TO THE SYNTHESIS OF 1,4-DI-SUBSTITUTED QUINOLIZIDINES

14.1 Ethyl 7-chloro-3-oxoheptanoate [286][197]

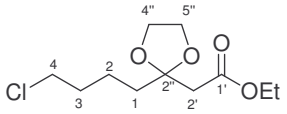


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A slurry of sodium hydride (60% in oil, 1.78 g, 44.0 mmol, 1.1 eq.) in dry tetrahydrofuran (100 cm^3, 2.30 $cm^3.mmol^{-1}$) was cooled to 0 °C. To this was added ethyl acetoacetate **[285]** (5.21 g, 5.10 cm^3, 40.0 mmol) dropwise. The solution was stirred for 10 min at 0 °C, after which *n*-butyllithium in hexane (1.4 M, 2.681 g, 30.0 cm^3, 40 mmol, 1.05 eq.) was added dropwise. The solution turned orange and was stirred at 0 °C for 10 min. The resulting dianion was cooled to −50 °C, and 1-bromo-3-chloropropane (6.30 g, 4.00 cm^3, 40.0 mmol) was added slowly by syringe. The temperature was allowed to rise to −15 °C, and stirred for 24 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (100 cm^3) cooled to 0 °C, and the reaction mixture was allowed to warm to rt. The solvents were remove *in vacuo*, the residue was re-dissolved in water (100 cm^3) and extracted with diethyl ether (3 × 100cm^3). The ether extracts were washed with brine (100 cm^3), dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a crude yellow oil. The crude oil was purified by column chromatography using 20% ethyl acetate:hexane as eluent yielding ethyl 7-chloro-3-oxoheptanoate **[286]** as a yellow oil (6.64 g, 32.1 mmol, 80%); **^{1}H** 12.11 (1H, s, OH)*, 4.99 (1H, s, =CH)*, 4.20 (2H, q, *J* 7.1 Hz, $OC\underline{H}_2CH_3$), 3.71 (2H, q, *J* 7.0 Hz, $OC\underline{H}_2CH_3$)*, 3.54 (2H, t, *J* 6.1 Hz, H-7), 3.44 (2H, s, H-2), 2.76 (2H, t, *J* 6.9 Hz, H-7)*, 2.61 (2H, t, *J* 5.4 Hz, H-4), 2.48 (2H, t, *J* 6.8 Hz, H-4)*, 2.08 (2H, quintet, *J* 6.0 Hz, H-6)*, 1.85-1.70 (4H, m, H-5 and H-6), 1.28 (3H, t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$), 1.24 (3H, t, *J* 7.0 Hz, $OCH_2C\underline{H}_3$)*; **^{13}C** 206.5 (C-3), 200.1 (C-3)*, 167.1 (C-1), 166.9 (C-1)*, 89.4 (C-2)*, 61.4 ($O\underline{C}H_2CH_3$), 61.3 ($OC\underline{H}_2CH_3$)*, 49.2 (C-2), 44.5 (C-7), 44.0 (C-7)*, 41.9 (C-4), 39.5 (C-4)*, 34.1 (C-6)*, 31.7 (C-6), 21.0 (C-5)*, 20.6 (C-5), 14.2 ($OCH_2C\underline{H}_3$)*, 14.0 ($OCH_2C\underline{H}_3$); **HRMS m/z (EI)** 206.07067 (M^+ 100%, $C_9H_{15}O_3Cl$ requires 206.07097).

* Indicates the peaks for the stabilized enol form of the ketone, and all intergrations are given relative to each other and not relative to the ketone.

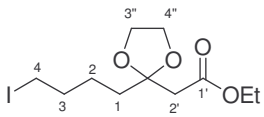
14.2 Ethyl [2-(4-chlorobutyl)-1,3-dioxolan-2-yl]acetate [371]



371

Ethyl 7-chloro-3-oxoheptanoate **[286]** (1.39 g, 6.72 mmol) was dissolved in dry benzene (40.0 cm^3, 6.00 $cm^3.mmol^{-1}$) in a 100 cm^3 round bottom flask fitted with a Dean and Stark apparatus. Ethanediol (1.28 g, 1.12 cm^3, 20.2 mmol, 3.0 eq.) was added in one portion. A catalytic amount of toluenesulfonic acid (0.019 g, 0.1 mmol, 0.01 eq.) was added and the mixture was refluxed for 24 h. The mixture was cooled to rt, washed with saturated aqueous sodium hydrogen carbonate solution (100 cm^3) and brine (100 cm^3). The organic layers were separated, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to afford an orange oil. The crude orange oil was purified by column chromatography using 30% ethyl acetate:hexane as eluent affording ethyl [2-(4-chlorobutyl)-1,3-dioxolan-2-yl]acetate **[371]** as a yellow oil (1.40 g, 5.56 mmol, 83%); ν_{max} **(film)/cm^{-1}** 2984 (C-H str, s), 2965 (C-H str, s), 2893 (C-H str, s), 1733 (C=O str, vs), 1446 (C-H bend, m), 1372 (C-H bend, m), 1308 (m), 1215, (m), 1101 (m), 1037 (C-O str, s), 911 (vs), 734 (C-Cl str, vs); **^{1}H** 4.08 (2H, q, *J* 7.1 Hz, $OC\underline{H}_2CH_3$), 3.97-3.86 (4H, m, H-4'' and H-5''), 3.46 (2H, t, *J* 6.7 Hz, H-4), 2.57 (2H, s, H-2'), 1.95-1.68 (4H, m, H-1 and H-3), 1.54-1.43 (2H, m, H-2), 1.19 (3H, t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$); **^{13}C** 169.3 (C-1'), 109.0 (C-2''), 65.0 (C-4'' and C-5''), 60.4 ($O\underline{C}H_2CH_3$) 44.7 (C-4), 42.5 (C-2'), 36.7 (C-1), 32.4 (C-3), 20.8 (C-2), 14.0 ($OCH_2\underline{C}H_3$).

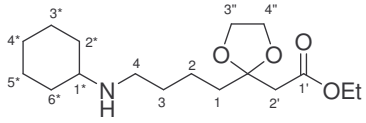
14.3 Ethyl [2-(4-iodobutyl)-1,3-dioxolan-2-yl]acetate [375]



375

Sodium iodide (0.363 g, 2.42 mmol, 1.2 eq.) was dissolved in a minimum volume of acetonitrile (10.0 cm^3, 5.00 $cm^3.mmol^{-1}$). To this was added ethyl [2-(4-chlorobutyl)-1,3-dioxolan-2-yl]acetate **[371]** (0.500 g, 2.00 mmol) in one portion. The reaction mixture was refluxed in the dark for 3 h, during which time sodium chloride precipitated. The mixture was cooled to rt, washed with water (50 cm^3) and extracted with ethyl acetate (3 × 30 cm^3). The organic extracts were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give ethyl [2-(4-iodobutyl)-1,3-dioxolan-2-yl]acetate **[375]** as a brown oil (~0.4 g). The crude product was used without further purification. **^{1}H** 4.16 (2H, q, *J* 7.1 Hz, $OC\underline{H}_2CH_3$), 4.05-3.96 (4H, m, H-4'' and H-5''), 3.19 (2H, t, *J* 6.9 Hz, H-4), 2.64 (2H, s, H-2'), 1.95-1.78 (4H, m, H-1 and H-3), 1.55-1.52 (2H, m, H-2), 1.27 (3H, t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$).

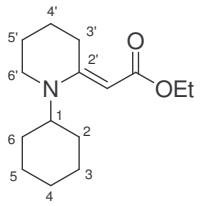
14.4 Ethyl {2-[4-(cyclohexylamino)butyl]-1,3-dioxolan-2-yl}acetate [376]



376

Cyclohexanamine (2.00 mmol, 1.0 eq.) and ethyl [2-(4-chlorobutyl)-1,3-dioxolan-2-yl]acetate **[371] (**0.501 g, 2.00 mmol) were dissolved in acetonitrile (30.0 cm^3, 15.0 $cm^3.mmol^{-1}$). To this solution was added crushed 4 Å molecular sieves (~ 1 g) and potassium carbonate (0.406 g, 3.0 mmol, 1.5 eq.). The reaction mixture was refluxed in the dark for 18 h. The mixture was cooled to rt, and washed with water (50 cm^3) and brine (50 cm^3). The aqueous fractions were extracted with ethyl acetate (3 × 30 cm^3), and the combined organic fractions were dried (anhydrous magnesium sulfate), filtered and evaporate *in vacuo* to afford a crude orange oil. The crude oil was purified by column chromatography to afford ethyl {2-[4-(cyclohexylamino)butyl]-1,3-dioxolan-2-yl}acetate **[376]** as a yellow oil (0.470 g, 1.50 mmol, 75%). **^{1}H** 4.17-4.07 (3H, m, $OC\underline{H}_2CH_3$ and H-1*), 4.00-3.93 (4H, m, H-3'' and H-4''), 3.53 (2H, t, *J* 6.8 Hz, H-4), 3.36-3.28 (1H, m, NH), 2.64 (2H, s, H-2'), 2.24 (4H, dt, *J* 6.2 and 17.4 Hz, H-2* and H-6*), 1.88-1.51 (8H, m, H-3*, H-4*, H-5* and H-1), 1.32-1.23 (7H, m, H-2, H-3 and $OCH_2C\underline{H}_3$).

14.5 Ethyl (2*E*)-(1-cyclohexyl-2-piperidinylidene)ethanoate [377]



377

Method 1

Crude ethyl {2-[4-(cyclohexylamino)butyl]-1,3-dioxolan-2-yl}acetate **[376]** (2.00 mmol) was dissolved in acetonitrile (20.0 cm^3, 10.0 $cm^3.mmol^{-1}$). To the reaction mixture was added sodium iodide (0.046 g, 15 mol%) and cerium trichloride heptahydrate (1.12 g, 3.00 mmol). The reaction mixture was refluxed for 3 h, and then quenched with 0.5 M hydrochloric acid (10 cm^3, 5 $cm^3.mmol^{-1}$). The aqueous fractions were extracted with diethyl ether (3 × 30 cm^3, 15$cm^3.mmol^{-1}$). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (30 cm^3, 15 $cm^3.mmol^{-1}$) and brine (30 cm^3, 15 $cm^3.mmol^{-1}$), dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give an orange oil. The crude orange oil was purified by column chromatography to yield ethyl (2*E*)-(1-cyclohexyl-2-piperidinylidene)ethanoate **[377]** as a yellow oil (0.0500 g, 0.200 mmol, 10%). $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3020 (s), 2937 (C-H str, m), 2859 (C-H str, m), 2400 (m), 2360 (m), 2342 (m), 1720 (w), 1663 (C=O str, s), 1578 (s), 1450 (w), 1424 (w), 1216 (C-O str, vs), 1150 (w), 1134 (w), 1058 (w); **^{1}H** 4.86 (1H, s, C =CH), 4.21 (2H, q, *J* 4.5 and 9.9 Hz, $OC\underline{H}_2CH_3$), 3.99 (1H, dt, *J* 5.2 and 11.3 Hz, H-1), 3.67-3.61 (2H, m, H-6'), 2.58-2.50 (2H, m, H-3'), 1.95-1.30 (14H, m, H*), 1.28 (3H, t, *J* 7.2 Hz, $OCH_2C\underline{H}_3$); **^{13}C** 169.3 (C-2'), 109.0 (C=CH), 65.0 (C-1 and C-6'), 60.4 ($O\underline{C}H_2CH_3$), 44.7 (C-6'), 42.5 (C-2 and C-6), 36.7 (C-3'), 32.4 (C-4), 20.8 (C-3 and C-5), 14.0 ($OCH_2\underline{C}H_3$); **HRMS m/z (EI)** 251.1887 (M^+ 100%, $C_{15}H_{25}NO_2$ requires 251.18853) 252 (68), 206 (52), 169 (62), 164 (54), 156 (68), 97 (56), 55 (43).

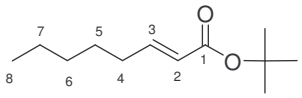
* Remaining hydrogens

Method 2

Ethyl {2-[4-(cyclohexylamino)butyl]-1,3-dioxolan-2-yl}acetate **[376]** (0.424 g, 1.35 mmol) in dichloromethane (20.0 cm^3, 15.0 $cm^3.mmol^{-1}$) was cooled to 0 °C and treated with freshly

distilled boron trifluoride etherate (1.92 g, 1.70 cm^3, 13.5 mmol, 10.0 eq.). The reaction mixture was stirred at 0 °C for 24 h, and then quenched with saturated aqueous sodium hydrogen carbonate (54 cm^3). The mixture was warmed to rt and extracted with dichloromethane (3 × 30 cm^3). The combined organic fractions were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a yellow oil. The crude yellow oil was purified by column chromatography to yield ethyl (2*E*)-(1-cyclohexyl-2-piperidinylidene)ethanoate **[377]** as a yellow oil (0.165 g, 0.659 mmol, 49%); characterized as described above.

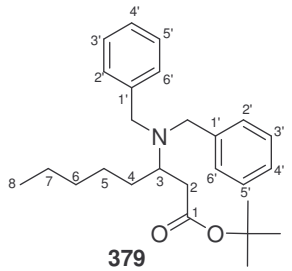
14.6 *tert*-Butyl (2*E*)-2-octenoate [380][108k]



380

To a stirred suspension of vacuum-dried (140 °C, overnight, *ca* 1 mm Hg) lithium chloride (1.63 g, 38.4 mmol, 1.2 eq.) in dry acetonitrile (65.0 cm^3, 2.00 $cm^3.mmol^{-1}$) was added *tert*-butyl (diethoxyphosphoryl)acetate **[246]** (8.07 g, 7.50 cm^3, 31.2 mmol), 1,8-diazobicyclo-[5.4.0]undec-7-ene (DBU) (5.36 g, 5.30 cm^3, 35.2 mmol, 1.1 eq.) and hexanal **[245]** (3.52 g, 35.2 mmol, 1.1 eq.). The mixture was stirred at rt for 24 h. The reaction was quenched with water. The solvent was evaporated *in vacuo*, and the residue was extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield a light yellow oil. The crude oil was purified by column chromatography using 5% ethyl acetate:hexane as eluent to afford *tert*-butyl (2*E*)-2-octenoate **[380]** (5.66 g, 28.5 mmol, 89%) as a colourless liquid. $\mathbf{R}_f$ 0.60 (1:19 ethyl acetate:hexane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 2968 (C-H str, s), 2929 (C-H str, s), 2865 (C-H str, s), 1715 (C=O, vs), 1652 (s), 1463 (C-H bend, s), 1294 (C-H bend, s), 1260 (s), 1160 (s), 1040 (w), 983 (m); **^{1}H** 6.86 (1H, dt, *J* 7.0 and 15.5 Hz, H-3), 5.73 (1H, dt, *J* 1.4 and 14.9 Hz, H-2), 2.16 (2H, ddt, 1.3, 6.8 and 7.5 Hz, H-4), 1.48 (9H, s, $C(CH_3)_3$), 1.31 (6H, m, H-5, H-6 and H-7), 0.89 (3H, t, *J* 6.8 Hz, H-8); **^{13}C** 166.2 (C-1), 148.1 (C-3), 122.9 (C-2), 79.9 ($\underline{C}(CH_3)_3$), 32.0 (C-4), 31.4 (C-6), 28.2 ($C(\underline{C}H_3)_3$), 27.7 (C-5), 22.4 (C-7), 13.9 (C-8).

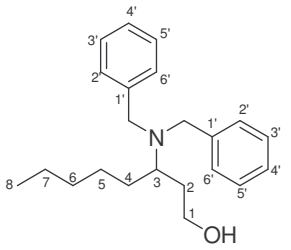
14.7 *tert*-Butyl 3-(dibenzylamino)octanoate [379]



379

A stirring solution of dibenzylamine (5.74 g, 5.60 cm^3, 29.1 mmol, 1.1 eq.) in dry tetrahydrofuran (120 cm^3, 5.30 $cm^3.mmol^{-1}$) was cooled to –78 °C. To this solution was added 1.4 M *n*-butyllithium in hexane (1.86 g, 20.3 cm^3, 29.1 mmol, 1.1 eq.) by syringe. The solution rapidly turned dark red in colour and was stirred at −78 °C for a further 30 min. *tert*-Butyl (2*E*)-2-octenoate **[380]** (4.46 g, 22.5 mmol) in tetrahydrofuran (30.0 cm^3, 1.00 $cm^3.mmol^{-1}$) was then added dropwise over 10 min. The solution turned yellow, and was stirred for a further 3 h at −78 °C. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (75 cm^3). The mixture was warmed to rt. The solvent was removed *in vacuo*, and the residue was diluted with water (75 cm^3). The residue was extracted with dichloromethane (3 × 75 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography using 5% ethyl acetate:hexane as eluent, and *tert*-butyl 3-(dibenzylamino)octanoate **[379]** (6.92 g, 17.5 mmol, 78%) was obtained as a light yellow oil. $\mathbf{R}_f$ 0.38 (1:19 ethyl acetate:hexane); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3062 (ArC-H str, w), 2928 (C-H str, s), 2862 (C-H str, s), 2730 (w), 1726 (C=O, vs), 1461 (s), 1368 (S), 1289 (w), 1253 (w), 1153 (s), 1028 (w), 963 (m); **^{1}H** 7.35-7.20 (10H, m, Ar-H's), 3.68 (2H, d, *J* 13.6 Hz, 2 × $CH_{2a}Ph$), 3.39 (2H, d, *J* 13.6 Hz, 2 × $CH_{2b}Ph$), 3.06 (1H, m, H-3), 2.62 (1H, dd, *J* 5.0 and 13.7 Hz, H-2a), 2.11 (1H, dd, *J* 8.5 and 13.7 Hz, H-2b), 1.44-0.88 (8H, m, H-4, H-5, H-6 and H-7), 1.42 (9H, s, $C(CH_3)_3$), 0.82 (3H, t, *J* 7.2 Hz, H-8); **^{13}C** 172.4 (C-1), 140.0 (C-1'), 129.0 (C-2' and C-6'), 128.0 (C-3' and C-5'), 126.8 (C-4'), 80.0 ($\underline{C}(CH_3)_3$), 55.3 (2 × $\underline{C}H_2Ph$), 53.5 (C-3), 36.2 (C-2), 31.5 (C-4), 31.1 (C-6), 28.1 ($C(\underline{C}H_3)_3$), 26.1 (C-5), 22.6 (C-7), 14.0 (C-8); **HRMS m/z (EI)** 395.28300 (M^+ 10%, $C_{26}H_{37}NO_2$ requires 395.28243), 325 (72), 324 (51), 304 (52), 281 (100), 269 (70), 133 (67), 132 (76), 92 (90), 65 (76), 56 (68), 43 (82), 39 (87), 29 (65).

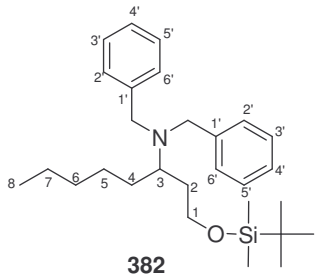
14.8 3-(Dibenzylamino)-1-octanol [381]



381

tert-Butyl 3-(dibenzylamino)octanoate **[379]** (1.51 g, 3.82 mmol) in diethyl ether (8.00 cm^3, 2.00 $cm^3.mmol^{-1}$) was added dropwise to a slurry of lithium aluminium hydride (0.290 g, 7.65 mmol, 2.0 eq.) in diethyl ether (16.0 cm^3, 4.00 $cm^3.mmol^{-1}$) at 0 °C. The reaction mixture was stirred for 3 h. The solution was allowed to warm to rt and was quenched by the sequential addition of water (0.8 cm^3, 0.2 $cm^3.mmol^{-1}$), aqueous sodium hydroxide (0.8 cm^3, 15% w/v, 0.2 $cm^3.mmol^{-1}$) and finally water (2.4 cm^3, 0.6 $cm^3.mmol^{-1}$). The solids were removed by filtering the mixture through a thin celite pad. The filtrate was dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield a light yellow oil. The crude oil was purified by column chromatography using 15% ethyl acetate:hexane as eluent to yield 3-(dibenzylamino)-1-octanol **[381]** as a yellow oil (0.873 g, 2.32 mmol, 70%). $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3065 (ArC-H str, w), 3029 (ArC-H str, w), 2930 (C-H str, m), 2862 (C-H str, m), 1726 (s), 1506 (s), 1460 (C-H bend, s), 1368 (C-H bend, s), 1294 (s), 1250 (s), 1158 (vs); **^{1}H** 7.57-7.21 (10H, m, ArH's), 4.60 (1H, s broad, OH), 3.87 (2H, d, *J* 13.6 Hz, 2 × CH_{2a}Ph), 3.76-3.72 (1H, m, H-1a), 3.53-3.46 (1H, m, H-1b), 3.34 (2H, d, *J* 13.6 Hz, 2 × CH_{2b}Ph), 2.74 (1H, m, H-3), 1.84-1.78 (2H, m, H-2), 1.53-1.47 (1H, m, H*), 1.32-1.16 (7H, m, H*), 0.90 (3H, t, *J* 7.2 Hz, H-8); **^{13}C** 139.1 (C-1'), 129.2 (C-2' and C-6'), 128.4 (C-3' and C-5'), 127.2 (C-4'), 63.2 (C-3), 58.5 (C-1), 53.3 (2 × $\underline{C}H_2$Ph), 32.0 (C-4), 31.5 (C-6), 27.1 (C-2 and C-5), 22.6 (C-7), 14.0 (C-8); **HRMS m/z (EI)** 325.24060 (M^+ 52%, $C_{22}H_{31}NO$ requires 325.24056) 282 (81), 280 (77), 256 (81), 254 (100), 181 (37), 91 (94), 65 (41), 41 (31).

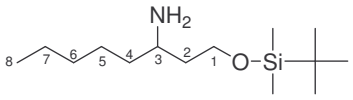
14.9 *N*,*N*-Dibenzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-3-octanamine [382]



382

3-(Dibenzylamino)-1-octanol **[381]** (2.78 g, 8.53 mmol) and imidazole (1.16 g, 17.1 mmol, 2.0 eq.) were stirred in dimethylformamide (10.0 cm^3, 1.20 $cm^3.mmol^{-1}$). To this was mixture was added *tert*-butyldimethylsilyl chloride (1.41 g, 9.38 mmol, 1.1 eq.) in dimethylformamide (5 cm^3, 0.6 $cm^3.mmol^{-1}$) dropwise over 10 min. The mixture was stirred for 24 h. Thereafter reaction mixture was washed with ice/water (100 cm^3), and the aqueous residues were extracted with dichloromethane (5 × 100 cm^3). The combined organic residues were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo*. The residue was re-dissolved in dichloromethane (100 cm^3) and washed with water (4 × 100 cm^3). The organic extract was dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to yield a crude yellow oil. Purification by column chromatography using 10% ethyl acetate:hexane as eluent afforded *N*,*N*-dibenzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-3-octanamine **[382]** (2.6746 g, 6.08 mmol, 71%) as a clear oil. ν_{max} **(film)/cm^{-1}** 2930 (C-H str, s), 2860 (C-H str, s), 1644 (w), 1568 (s) 1464 (C-H bend, s), 1386 (C-H bend, s), 1308 (w), 1254 (s), 1096 (C-O str, vs), 1010 (w); **^{1}H** 7.33-7.18 (10H, m, ArH's), 3.72-3.49 (2H, m, H-1), 3.54 (2H, s, C$\underline{H}_2$Ph), 3.53 (2H, s, C$\underline{H}_2$Ph), 2.56 (1H, quintet, H-3), 1.88 (1H, m, H-2a), 1.60-1.11 (9H, m, H-2b, H-4, H-5, H-6 and H-7), 0.86 (3H, t, *J* 7.3, H-8), 0.85 [6H, s, Si$(CH_3)_2$], 0.08 [C$(CH_3)_3$]; **^{13}C** 140.7 (C-1'), 128.9 (C-2' and C-6'), 128.0 (C-3' and C-5'), 126.2 (C-4'), 61.9 (C-3), 54.3 (C-1), 53.4 (2 × $\underline{C}H_2$Ph), 33.0 (C-2), 31.9 (C-4), 29.8 (C-6), 26.6 (C-5), 26.0 [C($\underline{C}H_3)_3$], 22.7 (C-7), 18.3 [$\underline{C}(CH_3)_3$], 14.1 (C-8), –5.3 [Si$(CH_3)_2$]; **HRMS m/z (EI)** 439.3268 (M^+ 12%, $C_{28}H_{45}NOSi$ requires 439.32704) 369 (100), 368 (53), 281 (77), 280 (51), 220 (43), 91 (53), 73 (53), 57 (55), 41 (56).

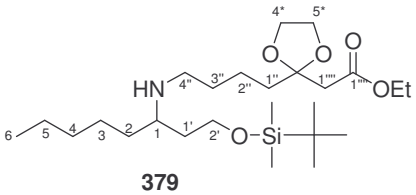
14.10 1-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-octanamine [378]



378

N,*N*-Dibenzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-3-octanamine **[382]** (2.67 g, 6.08 mmol) and 10% palladium on carbon (0.912 g, 0.150 g.mmol^{-1}) were dissolved in absolute ethanol (55.0 cm^3, 9.00 cm^3.mmol^{-1}) and placed in an autoclave. The reaction mixture was subjected to 7 atmospheres of hydrogen gas at rt for 24 h. The reaction mixture was filtered through celite, washed several times with ethanol and evaporated *in vacuo* to afford a crude grey oil. The crude oil was purified by column chromatography using 10% ethyl acetate:hexane as eluent to afford 1-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-octanamine **[378]** as a yellow oil (1.48 g, 5.71 mmol, 94%). $\mathbf{R}_f$ 0.15 (10% methanol:ethyl acetate); $\boldsymbol{\nu}_{\mathbf{max}}$ **(film)/cm^{-1}** 3155 (N-H str, w), 2930 (C-H str, s), 2858 (C-H str, s), 2359 (w), 2253 (s), 1794 (w), 1714 (m), 1649 (m), 1469 (s), 1380 (s), 1256 (s), 1216 (w), 1095 (s), 1006 (w), 910 (s); **^{1}H** 3.68 (2H, t, *J* 7.3 Hz, H-1), 2.85-2.78 (1H, m, H-3), 1.62-1.56 (1H, m, H-2a), 1.45-1.34 (5H, m, H-2b, H-5 and NH_2), 1.33-1.20 (6H, m, H-4, H-6 and H-7), 0.90-0.81 (3H, m, H-8) 0.83 (9H, s, $C(CH_3)_3$), 0.01 (6H, s, $Si(CH_3)_2$); **^{13}C** 61.1 (C-1), 48.9 (C-3), 40.5 (C-2), 38.4 (C-4), 31.7 (C-5), 25.8 ($C(\underline{C}H_3)_3$), 22.3 (C-7), 18.2 ($\underline{C}(CH_3)_3$), 14.1 (C-8), 0.0 ($Si(CH_3)_2$); **HRMS m/z (EI)** Inconsistent results were obtained.

14.11 Ethyl [2-(4-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)hexyl]amino}butyl)-1,3-dioxolan-2-yl]acetate [379]

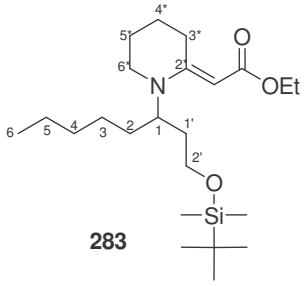


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To a stirred solution of ethyl [2-(4-chlorobutyl)-1,3-dioxolan-2-yl]acetate **[371]** (0.103 g, 0.411 mmol, 1.1 eq.) in acetonitrile (10.0 cm^3, 24.0 cm^3.mmol^{-1}) was added sodium iodide (0.065 g, 0.411 mmol, 1.1 eq.), potassium carbonate (0.0700 g, 0.411 mmol, 1.1 eq.) and 1-

{[*tert*-butyl(dimethyl)silyl]oxy}-3-octanamine **[378]** (0.0970 g, 0.374 mmol). The reaction mixture was refluxed for 12 h, cooled to rt and the solvent was removed *in vacuo*. The residue was taken up in water (20 cm^3) and extracted with diethyl ether (3 × 20 cm^3). The combined organic fractions were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give ethyl [2-(4-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)hexyl]-amino}butyl)-1,3-dioxolan-2-yl]acetate **[379]** as a pure yellow oil (0.129 g, 0.272 mmol, 73%). $\boldsymbol{\nu_{max}}$ **(film)/cm^{-1}** 3427 (N-H str, m), 2930 (C-H str, s), 2859 (C-H str, s), 1731 (C=O, s), 1469, (C-H bend, m), 1372 (C-H bend, m), 1256 (m), 1216 (m), 1096 (C-O str, m), 910 (s); **^{1}H** 4.11 (2H, q, *J* 7.1 Hz, $OC\underline{H}_2CH_3$), 3.94-3.90 (4H, m, H-4* and H-5*), 3.73-3.68 (2H, m, H-4''), 3.50 (2H, t, *J* 6.7 Hz, H-2'), 2.86 (1H, m, H-1), 2.61 (2H, s, H-1'''), 1.84-1.72 (4H, m, H-1' and H-1''), 1.63-1.20 (12H, m, H$^\$$), 1.23 (3H, t, *J* 7.2 Hz, $OCH_2C\underline{H}_3$), 0.86 (12H, s broad, $C(CH_3)_3$ and H-6), 0.03 ($Si(CH_3)_2$); **^{13}C** 169.4 (C=O), 109.0 (C-2*), 65.0 (C-4* and C-5*), 61.1 ($O\underline{C}H_2CH_3$), 60.4 (C-2'), 49.2 (C-1), 44.9 (C-4''), 42.6 (C-1'''), 40.1 (C-1'), 38.1 (C-2), 36.7 (C-1''), 32.5 (C-4), 31.9 (C-3''), 25.9 ($C(\underline{C}H_3)_3$), 25.7 (C-3), 22.6 (C-5), 20.8 (C-2''), 18.1 ($\underline{C}(CH_3)_3$), 14.1 ($OCH_2\underline{C}H_3$)$^\#$, 14.0 (C-6)$^\#$, −5.5 ($Si(CH_3)_2$), **HRMS m/z (EI)** Inconsistent results were obtained. $^\$$ Remaining hydrogens, $^\#$ These signals are interchangeable.

14.12 Ethyl (2*E*)-{1-[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)hexyl]-2-piperidinylidene}ethanoate [287]



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Attempt 1

Ethyl [2-(4-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)hexyl]amino}butyl)-1,3-dioxolan-2-yl]acetate **[379]** (0.389 g, 0.945 mmol) in dichloromethane (20.0 cm^3, 2.00 $cm^3.mmol^{-1}$) was cooled to 0 °C and treated with freshly distilled boron trifluoride etherate (1.34 g, 1.20 cm^3, 9.45 mmol, 10.0 eq.). The reaction mixture was stirred at 0 °C for 24 h, and then quenched

with saturated aqueous sodium hydrogen carbonate (38 cm^3). The mixture was warmed to rt and extracted with dichloromethane (3 × 21 cm^3). The combined organic fractions were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a yellow oil. The crude yellow oil was purified by column chromatography to yield an unidentified product which showed the loss of the silyl group.

Attempt 2

Ethyl [2-(4-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)hexyl]amino}butyl)-1,3-dioxolan-2-yl]acetate **[379]** (0.100 g, 0.211 mmol) was dissolved in acetonitrile (5.00 cm^3, 24.0 $cm^3.mmol^{-1}$). To the reaction mixture was added sodium iodide (5 × 10^{-3} g, 15 mol%) and cerium trichloride heptahydrate (0.118 g, 0.317 mmol). The reaction mixture was refluxed for 3 h, and then quenched with 0.5 M hydrochloric acid (1 cm^3). The aqueous fractions were extracted with diethyl ether (3 × 10 cm^3). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (10 cm^3) and brine (10 cm^3), dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give an orange oil. The crude orange oil was purified by column chromatography to yield recovered ethyl [2-(4-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-hexyl]amino}butyl)-1,3-dioxolan-2-yl]acetate **[379]** as a yellow oil (0.0910 g, 91% recovery of starting material).

Attempt 3

To a stirred solution of ethyl [2-(4-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)hexyl]amino}butyl)-1,3-dioxolan-2-yl]acetate **[379]** (0.100 g, 0.211 mmol) in water:acetone (0.500 cm^3:4.50 cm^3, 2.40 $cm^3.mmol^{-1}$:21.0 $cm^3.mmol^{-1}$) was added a catalytic amount of *para*-pyridinyl toluene sulfonic acid. The reaction mixture was stirred at rt for 24 h, and then refluxed for a further 24 h. The reaction mixture was cooled to rt and quenched with saturated aqueous sodium hydrogen carbonate (20 cm^3). The mixture was extracted with dichloromethane (3 × 20 cm^3). The combined organic fractions were dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give an unidentifiable yellow oil.

Attempt 4

Ethyl [2-(4-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)hexyl]amino}butyl)-1,3-dioxolan-2-yl]acetate **[379]** (0.107 g, 0.211 mmol) was dissolved in acetic acid:tetrahydrofuran:water (0.600 cm^3:0.150 cm^3:0.250 cm^3, 3.00 $cm^3.mmol^{-1}$:0.700 $cm^3.mmol^{-1}$:1.20 $cm^3.mmol^{-1}$) and stirred for 48 h at 40-45 °C. The solvent was removed *in vacuo*, and the reside was re-dissolved in water (10 cm^3) and extracted with dichlromethane (3 × 10 cm^3) The organic fractions were combined, dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography afforded unreacted ethyl [2-(4-{[1-(2-{[*tert*-butyl(dimethyl)silyl]-oxy}-ethyl)hexyl]amino}butyl)-1,3-dioxolan-2-yl]acetate **[379]** as a yellow oil (0.0750 g, 0.183 mmol, 75% recovery of starting material).

Attempt 5

To a solution of ethyl [2-(4-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)hexyl]amino}butyl)-1,3-dioxolan-2-yl]acetate **[379]** (0.102 g, 0.211 mmol) in dry acetone (2.1 cm^3, 10 cm^3) was added palladium chloride (0.002 g, 0.0106 mmol, 5 mol%). The mixture was stirred at rt for 24 h. The solvent was removed *in vacuo*, the residue was re-dissolved in water (10 cm^3) and extracted with ethyl acetate (3 × 10 cm^3). The organic fractions were combined, dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo* to give a crude yellow oil. Purification by column chromatography yielded recovered ethyl [2-(4-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)hexyl]amino}butyl)-1,3-dioxolan-2-yl]acetate (0.0691 g, 0.168 mmol, 68% recovery of starting material).

CHAPTER 15

REFERENCES



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CHAPTER 15

APPENDIX A: SELECTED ^{1}H AND ^{13}C NMR SPECTRA



APPENDIX A: SELECTED ^{1}H AND ^{13}C NMR SPECTRA

The ^{1}H and ^{13}C nuclear magnetic resonance spectra of selected compounds synthesized during the course of this project are given below in.

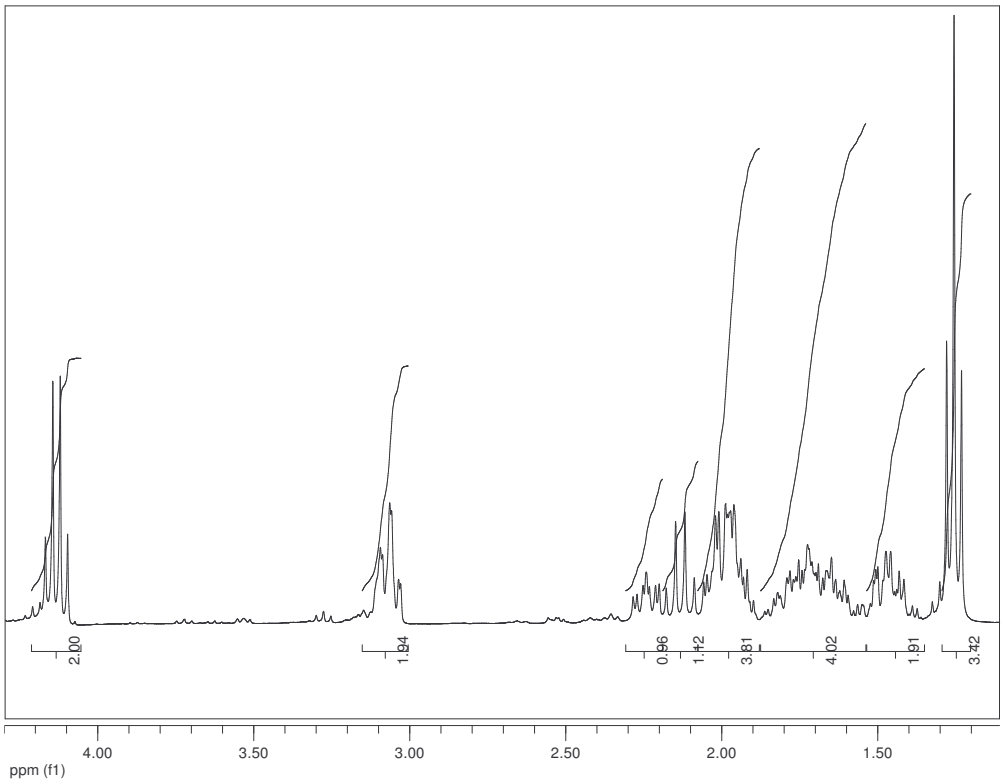
Compound Name and Number	Page
Ethyl (8*S*,8a*R*)-octahydro-8-indolizinecarboxylate **[301a]**	320
Ethyl (8*R*,8a*R*)-octahydro-8-indolizinecarboxylate **[301b]**	321
(±)-Tashiromine **[330a]**	322
(±)-5-Epitashiromine **[330b]**	323
tert-Butyl (3*R*)-3-{benzyl[(1*S*)-1-phenylethyl]amino}hexanoate **[268]**	324
tert-Butyl (3*R*)-3-aminohexanoate **[336]**	325
tert-Butyl (3*R*)-3-[(4-chlorobutanoyl)amino]hexanoate **[341]**	326
tert-Butyl (3*R*)-3-(2-oxo-1-pyrrolidinyl)hexanoate **[269]**	327
tert-Butyl (3*R*)-3-(2-thioxo-1-pyrrolidinyl)hexanoate **[270]**	328
tert-Butyl (3*R*)-3-((2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)hexanoate **[272]**	329
(2*E*)-2-{1-[(1*R*)-1-(2-Hydroxyethyl)butyl]-2-pyrrolidinylidene}-*N*-methoxy-*N*-methylethanamide **[273]**	330
(3*R*)-3-{Benzyl[(1*S*)-1-phenylethyl]amino}-1-hexanol **[343]**	331
(3*R*)-*N*-Benzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-[(1*S*)-1-phenylethyl]-3-hexanamine **[344]**	332
(3*R*)-1-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-hexanamine **[346]**	333
N-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)butyl]-4-chlorobutanamide **[348]**	333
1-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)butyl]-2-pyrrolidinone **[347]**	334
1-[(1*R*)-1-(2-Hydroxyethyl)butyl]-2-pyrrolidinone **[350]**	335
(3*R*)-3-(2-Oxo-1-pyrrolidinyl)hexyl acetate **[349]**	336
(3*R*)-3-(2-Thioxo-1-pyrrolidinyl)hexyl acetate **[351]**	337
(3*R*)-3-((2*E*)-2-{2-[Methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)hexyl acetate **[352]**	338
(5*R*)-*N*-Methoxy-*N*-methyl-5-propyl-1,2,3,5,6,7-hexahydro-8-indolizinecarbox-	

amide **[274]** 339

(5*R*,8*S*,8a*S*)-*N*-Methoxy-*N*-methyl-5-propyloctahydro-8-indolizinecarboxamide **[275]** 340

1-[(5*R*,8*S*,8a*S*)-5-Propyloctahydro-8-indolizinyl]-1-propanone **[353]** 341

1-[(5*R*,8*R*,8a*S*)-5-Propyloctahydro-8-indolizinyl]-1-propanone **[191]** 342


2.00
1.94
0.96
1.42
3.81
4.02
1.91
3.42
4.00
3.50
3.00
2.50
2.00
1.50
ppm (f1)

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OFFENDING COMMAND: .buildcmap

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/CMap
-dictionary-
/WinCharSetFFFF-V2TT9BF4ACCAt
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