Models for the Diastereoselective Synthesis of Indolizidine Alkaloids:

Rui Werner Maçedo Krause

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Degree of Doctor of Philosophy.

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DECLARATION

I declare that the work presented in this thesis was carried out exclusively by me under the supervision of Professor J. P. Michael and Professor H. M. Marques. 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.

Signed

_____

On this first day of December 2004

Dedication

Many wonderful people supported me during this project, and I would like to dedicate this work to them.

Firstly I would like to thank my supervisors Professor H.M. Marques and Professor J.P. Michael, whose reverence for the great chemists was inspirational. Secondly to all the other lecturers I encountered during my studies and introduced me to chemistry, I would like to dedicate the introductory chapters.

To my colleagues and fellow students, who were with me when I wrestled with elusive results, I dedicate the exploratory chapters.

To my friends I dedicate the discussion chapters, in memory of the many hours spent discussing what my work actually means.

To the analysts that assisted me in many ways with the characterisation of numerous compounds, I would like to dedicate the experimental sections.

And finally, I would like to dedicate the concluding chapter to my loving wife Gunda, and parents Joe and Fernanda, who helped me get to the end.

Acknowledgements

I would like to acknowledge the many people who made this project possible. From the three decades of work that precedes this project to people at the NRF and the University of the Witwatersrand, without whose financial contribution these results would certainly not have been possible.

Particular thanks go to Sigi Heiss for running the NMR spectra and for patiently teaching me how to operate the instruments.
Thanks to the staff and students of the structural chemistry group for their assistance in mounting crystals and collecting XRD data.

Abstract

The synthesis of nitrogen containing ring systems has been one of the interests of this research group at the University of the Witwatersrand for a long time. These systems form part of a group of compounds called alkaloids, whose structural diversity is rivalled only by their distribution in nature. A small sub-set of the alkaloids is the fused 5 and 6 membered bicyclic frames with nitrogen at one bridgehead. Having developed a unique method of synthesising these indolizidine alkaloids, we examined various aspects of this methodology and there remained one crucial question – what is the best way to control the stereochemical outcome of the ring-forming steps?

This project looks at this question from the view of a model natural product, the indolizidine alkaloids (+)- and (–)-tashiromine.

The synthesis of tashiromine and related compounds was examined using chiral auxiliaries such as the Oppolzer sultam and the Evans oxazolidinone, as well as the use of chirally modified reductants.

The efficacies of the chiral auxiliaries were studied using molecular modelling techniques, and certain modifications were suggested from these results.

Contents

Declaration
Dedication
Acknowledgements
Abstract
Table of Contents
List of Illustrations

Preface pg 1

1. Introduction
   - 1.1 The Importance and Occurrence of Alkaloids pg 3
   - 1.2 Synthetic Approaches to the Indolizidine Skeleton pg 14
   - 1.3 Project Aims pg 38
   - 1.4 Review of Tashiromine Literature pg 40

2. Results and Discussion of a Model Synthesis of (±)-Tashiromine and (±)-Epitashiromine
   - 2.1 Synthesis of Thiolactams pg 59
   - 2.2 Synthesis of β-Acyl Enaminones pg 68
   - 2.3 Synthesis of the Indolizidine Skeleton pg 69
   - 2.4 Synthesis of (±)-Tashiromine and (±)-Epitashiromine pg 75

3. Introduction to Asymmetric Synthesis
   - 3.1 The Importance of Asymmetric Synthesis pg 85
   - 3.2 Chirality Transfer through Auxiliaries and Reductants pg 94

4. Results and Discussion Asymmetric Syntheses
   - 4.1 Synthesis of Chiral Auxiliaries pg 107
     - 4.1.1 Synthesis of 1,3-Oxazoline [**130**] pg 108
     - 4.1.2 Synthesis of 2-Oxazolidinone [**132**] pg 110
     - 4.1.3 Synthesis of 2-Imidazolidinone [**134**] pg 113
     - 4.1.4 Synthesis of Camphor Sultam [**135**] pg 116
     - 4.1.5 Synthesis of 2-Cumylcyclohexanol [**140**] pg 120

4.2 Synthesis of Chiral Enaminones pg 123
4.2.1 *N*-Alkylpyrrolidinylidenes pg 123
4.2.2 Oxazolidinone-containing Enaminones pg 125
4.2.3 Imidazolidinone-containing Enaminones pg 126
4.2.4 Sultam-containing Enaminones pg 127
4.2.5 *trans*-Cumylcyclohexane-containing Enaminones pg 130
4.2.6 Formation of *N*-3-Propanol Derivatives pg 132
4.2.7 Formation of the Indolizidine Skeleton pg 134
4.3 Synthesis of Alkaloids (–)-Tashiromine, (+)-Tashiromine, and (–)-Epitashiromine via C=C Bond Reduction pg 141
4.3.1 Conditions for Effective Reduction pg 141
4.3.2 Evidence of *cis*/*trans*-Reduction from NMR pg 143
4.3.3 Sultam-containing Octahydroindolizines pg 146
4.3.4 (2-Cumyl)cyclohexyl-containing Octahydroindolizines pg 150
4.4 (–)- and (+)-Tashiromine and (+)-Epitashiromine pg 153

5. Molecular Modelling pg 155
5.1 Computational Techniques pg 155
5.2 Force-Field Parameterisation pg 160

6. Results and Discussion of the Molecular Modelling pg 163
6.1 Crystal Data Mining and Force Field Parameterization pg 163
6.2 Evaluating the Force Field pg 170
6.3 Perspectives from the Molecular Modelling Results pg 174
6.3.1 Bohlmann Bands pg 174
6.3.2 Chiral Auxiliaries pg 176
6.3.3 Chiral Auxiliary Systems pg 178
6.4 Conclusions from the Molecular Modelling Study pg 183

7. Conclusions, Perspectives and Future Work pg 184

8. Experimental pg 188
8.1 General pg 188
8.2 Synthesis of Pyrrolidones pg 194
8.3 Synthesis of Thiolactams pg 199
8.4 Synthesis of Chiral 1,3-Oxazolines pg 205
8.5 Synthesis of Chiral 2-Oxazolidinones pg 213
8.6 Synthesis of Chiral 2-Imidazolidinones pg 217
8.7 Synthesis of Chiral Camphor Sultams pg 218
8.8 Synthesis of Chiral *trans*-Cumylcyclohexanes pg 225
8.9 Acylation of the Chiral Auxiliaries (GP-2) pg 228
8.10 Synthesis of Activated Methylene Compounds pg 236
8.11 Hydrolysis of Acetates pg 251
8.12 Hydrolysis of Propanoate Esters pg 258
8.13 Synthesis of Hexahydroindolizidines pg 261
8.14 Effecting Cyclization via a Tosylate pg 266
8.15 Effecting Cyclization by *in situ* Mesylate Formation pg 268
8.16 Unsuccessful Cyclization Methods pg 269
8.17 Hexahydroindolizines pg 270
8.18 Reduction of C=C Bond pg 276
8.19 Racemic Octahydroindolizines pg 284
8.20 Chiral Pyrrolidinyl Compounds pg 290
8.21 Octahydroindolizines Containing a Chiral Auxiliary pg 297
8.22 Octahydro-indolizin-8-yl-methanol pg 303

References pg 307

Appendix A Data Relating X-ray Crystallography pg 321
Appendix B Excel Macros and Data relating to Molecular Modelling pg 335
Appendix C Selected Spectra and Other Data pg 342

List of Illustrations

Figure 1 The Indolizidine (1-Azabicyclo[4.3.0]nonane) Skeleton showing the Conventional Numbering 4
Figure 2 The Quinolizidine Skeleton Found in Many Lupinine Alkaloids 8
Figure 3 Disconnections to the Indolizidine Skeleton 15
Scheme 1 Synthesis of elaeokanine B via an acyl iminium ion 17
Scheme 2 Synthesis of (±)-coniceine [**28a**] using a [3+3]-annulation process 17
Scheme 3 Synthesis of Daphniphyllum alkaloids 18
Scheme 4 Synthesis of Lupine Alkaloids 18
Scheme 5 Formal Synthesis of Castanospermine Using a Metathesis Step 19
Scheme 6 Synthesis of 5,8-Disubstituted Indolizidine Alkaloids 20
Scheme 7 Formal Synthesis of (–)-Lentiginosine 21
Scheme 8 Completion of the Indolizidines by Nucleophilic Displacement 22
Scheme 9 Alkaloid synthesis by Cyclisation onto Nitrogen 22
Scheme 10 Synthesis of (±)-Ipalbidine [**12**] 23
Scheme 11 Use of Acylpyridinium Salts in the Synthesis of Indolizidines 23
Figure 4 Exocyclic Enaminones 24
Scheme 12 Synthesis of an Exocyclic Urethane 24
Figure 5 Sulfide Contraction in the Synthesis of Vitamin B_{12} 25
Scheme 13 Outline of the Sulfide Contraction Reaction. 26
Figure 6 General Structure of β-Substituted Enamines used in our Laboratories 27
Figure 7 Mechanistic Outline of Sulfide Contraction 28
Scheme 14 Alternative Syntheses of Vinylogous Urethanes 29
Figure 8 Reactive Sites of the Enaminone System 30
Figure 9 Exploiting the Nucleophilicity of Enaminones 31
Scheme 15 Alkylative Cyclisation to Form (±)-Lupinine 31
Scheme 16 Key Cyclisation and Intermediates in the Synthesis of (±) Lamprolobine 31
Scheme 17 Chiral Intermediates in the Synthesis of Indolizidines 32
Scheme 18 Acylative Cyclisation in the Synthesis of Ipalbidine 33
Scheme 19 Alkaloid Synthesis Using a Cycloarylation 34
Scheme 20 Synthesis of (±)-Δ^7-Mesembrenone 34
Scheme 21 Synthesis of 4-QuinoloneAntibacterials 35
Figure 11 Reduction of the C=C Bond in Enaminones 35
Scheme 22 Synthesis of *O*-Methylperipentadenine 36
Scheme 23 Synthetic Strategy for Tashiromine 38
Scheme 24 Tin-Enolate Coupling in the Synthesis of Azabicycles 42
Scheme 25 Synthesis of Bicyclic Ring Systems by Radical Mechanism 43
Figure 12 Proposed Conformations in Radical Cyclisations 44
Figure 13 Lactam Formation from Acyclic Enamines 46
Scheme 26 Synthesis of (±)-5-Epitashiromine 47
Scheme 27 Short Synthesis of Tashiromine 48
Scheme 28 Synthesis of the Indolizidine Skeleton from a Cobaloxime 49
Scheme 29 Completion of the Synthesis of Tashiromine and Epitashiromine 50
Scheme 30 Selective Alkylation of (*S*)-4-Carbethoymethyl-2-oxazolidinone 51

Scheme 31 Synthesis of (+)-Tashiromine via Chiral Carbamates 52
Figure 14 Synthesis of (+)-8-Epitashiromine 52
Scheme 32 Synthesis of (+)-Tashiromine via Protected Lactam 54
Scheme 33 Synthesis of Tashiromine via Bromolactone & Protected Lactam . 55
Scheme 34 Reduction of *N*-Acylaminals for the Synthesis of Indolizidines 56
Scheme 35 Cuprate-Mediated Synthesis of (±)-Tashiromine and Epitashiromine 58
Scheme 36 Model Synthesis of Racemic Tashiromine and Epitashiromine 60
Scheme 37 Enantioselective Synthesis of Precursors to Indolizidine Alkaloids (–)-167B and (–)-209B 61
Scheme 38 Synthesis of *N*-Aryl Lactams 62
Scheme 39 Conjugate Addition in the Synthesis of *N*-Substituted Thiolactams 65
Table 1 Yields of Thiolactams 66
Scheme 40 Formation of a Vinylogous Urethane by Sulfide Contraction 68
Scheme 41 Synthesis of (±)-Lamprolobine [**46**] and (±)-Epilamprolobine 70
Figure 15 Effect of Leaving Group on the Formation of the Indolizidines 71
Scheme 42 Formation of the Indolizidine Core 71
Scheme 43 Selective Reduction of Vinylogous Bond 71
Scheme 44 Proposed Mechanism for the Hydride Reduction of Enones 77
Figure 16 Proposed Fragmentation of Indolizidinyl Molecular Ions 79
Figure 17 Tashiromine [1], showing axial (ax) and equatorial (e) protons 81
Table 2 Comparison of NMR Spectral Data for (±)-Tashiromine 81
Figure 18 Proposed Fragmentation of Tashiromine Molecular Ions 83
Table 3 Comparison of NMR Data for Epitashiromine and Lupinine 85
Scheme 45 Synthesis of Pyrethroids from α-Pinene 88
Figure 19 (–)-Khusimone, (–)-Oestrone, Californian Red Scale Pheromone, and Vitamin B12 Intermediate synthesised from Camphor 89
Scheme 46 A General Synthesis using the Meyers Oxazoline 97
Scheme 47 Proposed Synthesis of Indolizidines using Oxazolines 98
Figure 20 Use of Oxazolidinones in α-Amino Acid Syntheses 99
Scheme 48 Intramolecular Diels–Alder Reaction using the Oppolzer Sultam. 102
Scheme 49 Chiral Esters in Asymmetric Synthesis 103
Figure 21 Three Commonly Used Chiral Ligands 104
Scheme 50 Monsanto Process for the Synthesis of L-DOPA 105
Scheme 51 Synthesis of Isoquinoline Alkaloids (BINAP Reduction) 106
Figure 22 Envisaged Synthesis of Tashiromine and Epitashiromine 109
Figure 23 Unsuccessful Routes to Oxazoline [**130**] 110
Figure 24 Use of a Chiral Imidazolidinone in Aldol Reactions 115
Table 4 Comparison of Physical Data for **143** with Literature Values 117
Scheme 52 Synthesis of Chiral *N*-Methyl-2-pyrrolidinylidenes 125
Table 5 Yields of Sulfide Contraction Products with Chiral Auxiliaries 125
Reaction conditions for the Attempted Formation of Indolizidine [**158**] 125
Table 6 List of Used Reductants and Modified Conditions 143
Figure 25 Computer-modelled Conformation of 8-substituted Indolizidines with a *trans*-Relationship between H-8 and H-8a. 146
Figure 26 Computer-modelled Conformation of 8-substituted Indolizidines with a *cis*-Relationship between H-8 and H-8a 146
Figure 27 Destabilisation of the *s-cis* Conformation 147

Figure 28 Relationship between Diastereomers and the Alkaloids 149
Figure 29 Simplified Spring Representation of Bonds 159
Table 7 Important Missing MM+ Parameters 164
Figure 30 Compounds Modelled to Obtain Missing Parameters 165
ORTEP Plot for Compound **179** 168
ORTEP Plot for Compound **156** 169
ORTEP Plot for Compound **155** 170
Figure 31 Compounds used to Test the Modified Force Field Integrity 171
Figure 32 Comparison of the Crystal Structure of **179** (Dark Lines) with its Computer Generated Model (Light Lines) 172
Table 8 Comparison of the Single-Point Energies between Experimental and Theoretical Models for Compounds **179** and **156** 173
Figure 33 Comparison of the Crystal Structure of Compound **156** (Dark Lines) with its Computer Generated Model (Light Lines) 173
Figure 34 Model of a *Trans*-Fused Indolizidine Conformation for **156** 175
Figure 35 Model of a *Cis*-Fused Indolizidine Conformation for **156** 176
Figure 36 Possible Conformers and Configurational Isomers of Monocyclic Vinylogous Urethanes 178
Graph 1 Variation in Energy as a Function of Torsion Angle C=C–C=O for Compound **147** 180
Figure 37 Model of (*S*)-4-Benzyl-3-[2-(1-methyl-pyrrolidin-2-ylidene)-acetyl]-oxazolidin-2-one [**147**] 181
Graph 2 Variation in Energy as a Functin of Torsion Angle C=C–C=O for Compound **154** 182
Figure 38 Representation of the Minimum Energy Conformation of **158** 183
Graph 3 Variation in Energy as a Function of Torsion Angle C=C–C=O for Compound **158** 183
Figure 39 Two Significantly Different Low-energy Conformers of a Chiral Vinylogous Urethane 184
Scheme 53 Asymmetric Conjugate Addition assisted by $TiCl_4$ Coordination . 186
Scheme 54 Proposed extension of chiral auxiliary-mediated alkylation 186
Scheme 55 Possible use of Chiral Auxiliaries in the Synthesis of Pyrrolizidines 188
Table 10 Summary of General Experimental Procedures 291
Numerical List of Compound Numbers and Experimental Procedure Page Location 291
Table 11 Conditions for the reduction of **147** 291

Preface

The art of organic chemistry has many varied and interesting facets. While some scientists will work on the isolation and characterisation of novel compounds from sources as varied as the compounds they contain, others work on the synthesis of these natural products and their derivatives. A third area of intense activity is the broadening of our knowledge base of reactions, mechanisms and products. This project touches on all these aspects, but focuses primarily on being a methodological study.

The synthesis of certain natural products, primarily alkaloids, has occupied several workers in the Backeberg laboratories at the University of the Witwatersrand for over 3 decades. During this time a modest, yet synthetically useful approach to these alkaloids has been developed, and the group has attempted to make this approach as successful and effective as possible while maintaining it as a general methodology for the synthesis of a variety of alkaloids and other heterocycles containing bridgehead nitrogen atoms. Colloquially we refer to this methodology as the "Wits approach", although the reactions and sequences are by no means restricted to our group.

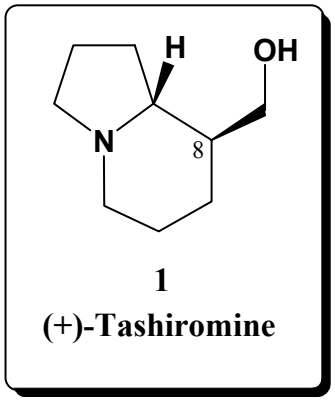
This approach relies on the formation of "enaminones" by employing the Eschenmoser sulfide contraction reaction or related condensation methods, and we have been able to fine-tune the various steps to produce a range of targets. The term enaminone is broadly used to describe any compound containing a conjugated N–C=C–C=O system, although other conjugated systems are often include that fall outside this definition, such as N–C=C–C≡N or N–C=C–NO_2.

The enaminone system can be viewed in several ways: It can be regarded as an enamine with an acyl group attached, as an enone functionalized with an electron-donating amine substituent, or as a vinylogous amide, *i.e.* as an amide with a vinyl group inserted between the nitrogen and the carbonyl. These different ways of examining the system provide alternative insights into their

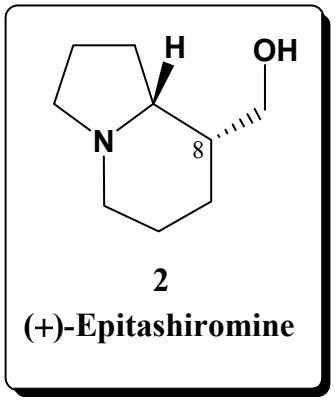
chemical behaviour, some of which will be explored further in the following chapters.

Although I refer to this method as the Wits approach throughout this thesis, we are, as I have mentioned, by no means the only group to use this approach. Related work of other scientists will be expounded on in more detail, although this is not meant to be an exhaustive review of these synthetic methodologies. The Wits approach is often associated with the synthesis of alkaloids, but since the number and types of alkaloid are enormous, the syntheses actually focus on a very small group of structurally related alkaloids, some of which have useful biological properties and others that merely serve to illustrate the synthetic approach. In the following chapters, the background for the project will be set by exploring the field of alkaloids in general followed by a more detailed look at the specific group of alkaloids that has been the focus for the group over the past few years. The synthetic techniques will then be exemplified through one particular natural product, tashiromine [**1**].

It is tashiromine and the C8 epimer (epitashiromine [**2**]) that will be used as a benchmark against which to explore stereoselective modifications of the Wits approach which could give access to an enantioselective generalised method for alkaloid synthesis. This pursuit of enantioselectivity forms the core of this Ph.D. project. Once again, this approach will be illustrated in the successful synthesis of enantiomerically enriched (+)- and (–)-tashiromine, and (+)-epitashiromine.



1
(+)-Tashiromine



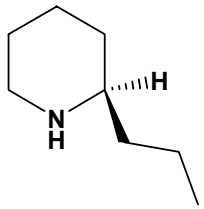
2
(+)-Epitashiromine

Chapter 1 - Introduction

1.1 The Importance and Occurrence of Alkaloids

Organic synthesis is perhaps a little like a murder mystery: The key to solving the mystery is to find the right clues by looking in the right places and asking the right questions. Having done this the mystery may remain partially solved for a long time. The aim of this thesis is to try and get a little closer to solving a mystery that has puzzled the organic chemistry group at Wits for a while, namely the stereospecific syntheses of alkaloids.

Alkaloids are structurally the most diverse class of secondary metabolites currently known. They range from the simple structures like the plant alkaloid coniine [**3**] to complex members such as batrachotoxin [**4**], isolated from the skin of a Colombian frog. They are almost ubiquitous, having been encountered in most orders of organisms from fungi to mammals, although the majority of alkaloids occur in the plant kingdom.



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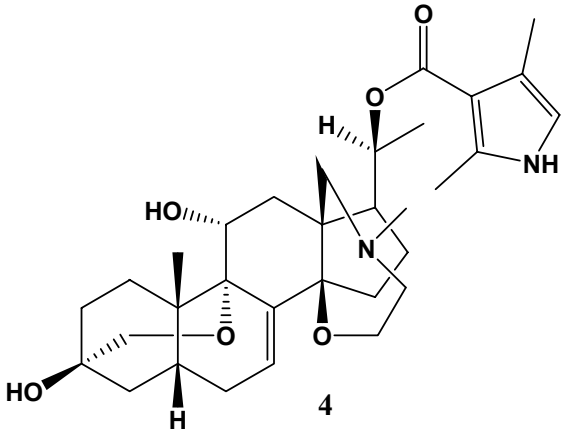

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Many attempts have been made to define alkaloids, including the recent IUPAC definition of an alkaloid as a "…basic nitrogen containing compound (mostly heterocyclic) occurring mostly in the plant kingdom (but not excluding those from animal origin). Amino acids, peptides, nucleotides, nucleic acids, amino sugars and antibiotics are not normally regarded as alkaloids. By extension, certain neutral compounds biogenetically related to basic alkaloids are included."[1] The explicit vagueness of this definition underlines the large

structural diversity of alkaloids, and it is probably fair to say that a definition proposed by Ladenburg in the late 1880s is still valid today. Ladenburg suggested that alkaloids were compounds derived from plants, with a basic character, containing a nitrogen-based heterocyclic ring.[2] In fact the expression "alkaloid" is made from two words 'alkali' and 'ειδοσ' (Greek for having the form or likeness of)[3], and was first proposed by Meissner[4], when he realized that there were compounds belonging to this class that were not strictly alkalis.

The bewildering range of alkaloids, estimated at well over 15000 to date, is sometimes classified according to the amino acids from which the alkaloids arise. This leads to the problem of how to classify alkaloids of polyketide or terpenoid origin, such as coniine [**3**] and batrachotoxin [**4**], above.

To date, no unified systematic code exists to classify alkaloids and all systems used have to accept compromises in certain cases. The most popular criteria used today are biogenesis (what the molecule is made from), structure, biological origin, and spectroscopic similarities. A consideration of the basic carbon skeleton, for example, allows for the subdivision of alkaloids into groups with similar characteristics. One of these groups, alkaloids containing the 1-azabicyclo[4.3.0]nonane skeleton are commonly known as the indolizidine alkaloids (**Figure 1**). This group for example, is well represented in nature and even a discussion confined only to *these* alkaloids could fill several volumes. For the purpose of this text, therefore, the discussions will be confined mainly to alkaloids containing only this simple indolizidine skeleton, as these are the compounds that bear the most relevance to this Ph.D. thesis. Those natural products that contain embedded indolizidine alkaloid skeletons will only be dealt with briefly, where appropriate.

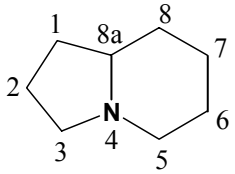
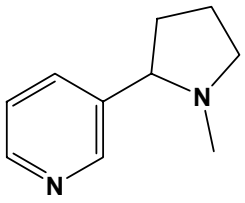


Figure 1 - The Indolizidine (1-Azabicyclo[4.3.0]nonane) Skeleton showing the Conventional Numbering

Although this work is directed to a specific target, a general synthesis should be able to reach a number of different destinations, and so the reader will be taken on a brief survey of the richness of the indolizidine alkaloid natural product chemistry that forms the backdrop to this project. Indolizidines are restricted to plants, apart from a few insect sources, an impressive collection of alkaloids from amphibian origin, a growing collection from marine fauna, and a handful of micro-organism-derived alkaloids, some of which I will talk about a little later in this chapter. With an estimated 10% of all plant species containing some alkaloids, it is not surprising that alkaloids have piqued human interest for many years. Many are familiar compounds such as the tobacco alkaloid nicotine [**5**], the rodenticide strychnine [**6**] (from the *Strychnos* plant species), the analgesic morphine [**7**] (from the opium poppy, *Papaver somniferum* L.), and one of the world's most widely used abusive substances, cocaine [**8**]. Many of our modern drugs contain these alkaloids or their synthetic derivatives, which are immensely important owing to their pharmacological and toxicological properties.



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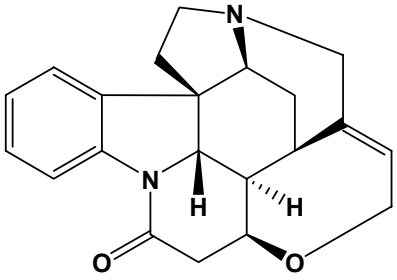

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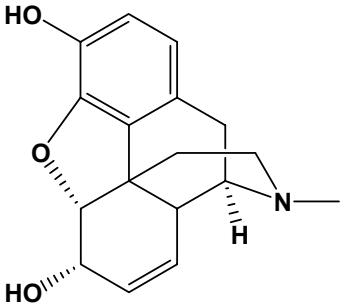

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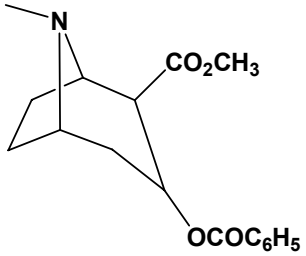
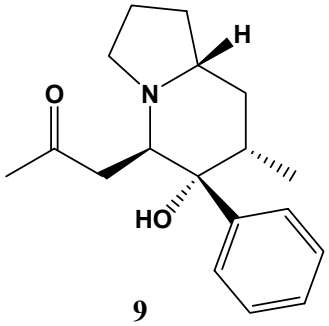


8

Although alkaloids are widely dispersed in the plant kingdom, they are not *evenly* distributed. By way of illustration, there are many examples of alkaloids in

both the *Leguminosae* (lupin) and the *Solanaceae* (tomato, potato, tobacco) families, but they are almost absent in the gymnosperms (conifers), cryptograms (ferns, mosses), and monocotyledons (grasses).[5] Many of the natural plant alkaloids seem to exhibit an allelochemical defence against herbivores, micro-organisms and competing plants,[6] and it is often this expressed bioactivity that has inspired their use as pharmacologically useful compounds for our own utilisation.

The structural diversity found in plant-originated alkaloids is indeed noteworthy. Even within the same family we can find complex structures such as crepidamine [**9**] and simple dimethylated dendroprimine [**10**], both from plants in the Orchidaceae family.



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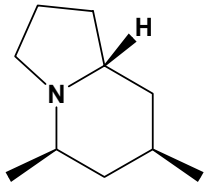

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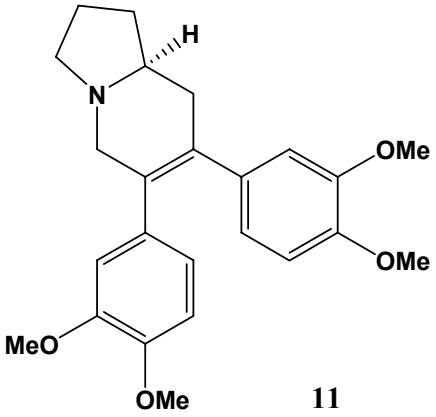
A thorough review of the occurrence of alkaloids in plants would be colossal, and even just simple indolizidines (which are more sparsely distributed among the plant families than most other alkaloids) and their related quinolizidines would fill several pages. Indeed excellent reviews on not only the occurrence, but the isolation, synthesis, and biochemical aspects of simple indolizidines and quinolizidines are published regularly[7][8][9]10 A brief outline of the range of indolizidines and their occurrence in plants is all that follows.

There are several important groups of indolizidines such as: alkyl substituted, aryl substituted, polyhydroxylated, sesquiterpenoid, and lupine indolizidines. These are structurally related alkaloids that are often useful in chemotaxonomy, or are similar in function and application. Some groups appear regularly in members of a plant family and are then associated with that family or species, for example the Elaeocarpus alkaloids from the genus *Elaeocarpus* (family Elaeocarpaceae).

The earliest simple indolizidine to be isolated is believed to be the diaryl-substituted septicine [**11**] in 1963, which was initially isolated from a plant in the Moraceae (fig) family, but subsequently found in another, quite different herb plant from the Asclepiadaceae (milkweed) family.[7][11] This is one of the many aryl indolizidines, including crepidamine [**9**] and members of the Ipalbidine alkaloids, such as ipalbidine itself [**12**]. Ipalbidine was the target of an early formal synthesis using the "Wits approach" developed in our labs, which is discussed in detail in the subsequent chapter.



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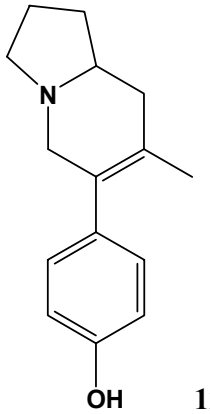
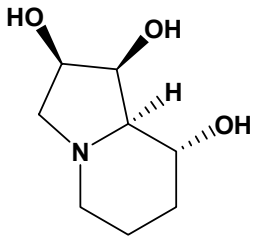
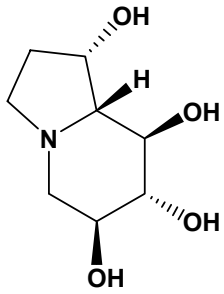


12

The hydroxylated or polyhydroxylated indolizidines have been the targets of several total syntheses, probably due to their presence in a group of agriculturally important plants, the Leguminosae, particularly the subfamily Papilionaceae or Fabaceae (pea family). Not only are these plants important sources of legumes for food and oils, but they are essential in nitrogen fixation, through their root nodules or more commonly bacteria inside the nodules.[6] The alkaloids swainsonine [**13**] and castanospermine [**14**] are possibly the most well-known indolizidines from this group, both isolated from plants in the leguminosae family. Both **13** and **14** are potent glycosidase inhibitors, and hence have been the targets of several syntheses, many of which are pivoted on manipulations of carbohydrate precursors such as glucose and mannose. Swainsonine has also been isolated from micro-organisms *vide infra*.



13 Swainsonine



14 Castanospermine

Related to these hydroxylated molecules are a group of alkaloids of particular importance for this work, known as **lupine alkaloids**. This is a very large set of alkaloids, isolated from the Leguminosae and in particular the Papilionaceae subfamily (the legumes).

Tashiromine and epitashiromine belong to this large group of alkaloids that is dominated by alkaloids with complex structures, which are beyond the scope of this work, but there is a small group of related compounds with a simple quinolizidine structure (**Figure 2**) that show nearly identical structural features to the indolizidines in this study, and it is therefore appropriate to discuss some of them here.

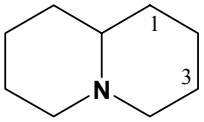
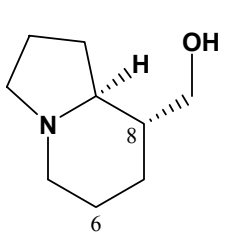
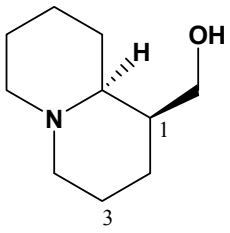


Figure 2 - The Quinolizidine Skeleton Found in Many Lupinine Alkaloids

Most of these alkaloids are 1- or 3-substituted quinolizidines with simple oxygen and nitrogen functional groups, such as lupinine [**15**]. The related indolizidines (such as tashiromine) are similar in structure, having substituents in the 6 or 8 positions (the same relative positions on the six-membered ring), but these are more uncommon, or are at least found in smaller quantities than the quinolizidines. A noteworthy difference in the case of tashiromine and lupinine is the fact that while they have the same relative configurations (CH_2OH *anti* to H), the respective enantiomers of each have opposite absolute configurations.

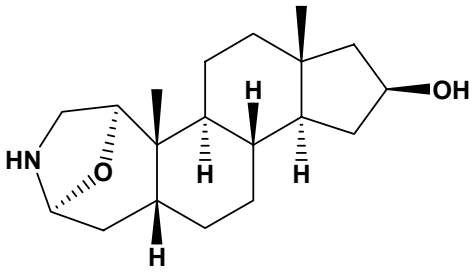


1 (–)Tashiromine



15 (–)-Lupinine

It may be surprising to some to learn of the number of alkaloids isolated from animals, insects, and microorganisms. I have already mentioned batrachotoxin [**6**] as an example of one of the many alkaloids found in the skin secretions of certain African and South American frogs, but there are many other examples such as samandarine [**16**] from the European salamander and the unusual tricyclic *N*-oxide alkaloid conccinelline [**17**] used by the European ladybird (*Exochomus quadripustulatus*) and other Coccinellid beetles as part of their defence arsenal.



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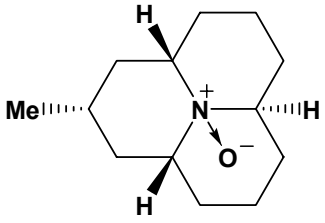
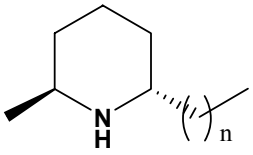


17

As many of the alkaloids in the animal kingdom are considered to be secondary metabolites, it is not always certain of what use they are to the animal concerned. This question has been probed in some detail by several people, especially with respect to the association between insects and plants,[12] and there is general agreement that some of the alkaloids seem to be used for anti-predatory defence, the "allelochemical" response,[13] or for anti-microbial defence, but the vast majority of alkaloids do not appear to have any particular function. In certain cases, the alkaloids appear to come from the diet of the animal. One piece of evidence for this comes from the work of J.W. Daly and his co-workers, who found that hand-reared frogs from Panama (*Dendrobates auratus*) did not produce any alkaloids on their skins, unless they were fed on insects caught from their

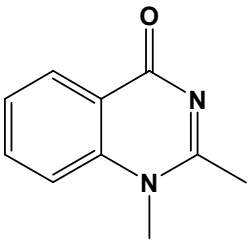
native environment.[14,15] The animals concerned appear to sequester and accumulate the alkaloids. It should be noted, however, that the majority of these anuran-skin alkaloids lack any known counterparts elsewhere in nature, including several indolizidines such as the 5,8-disubstituted and 5,6,8-trisubstituted compounds.

The insect kingdom produces a rich variety of structurally interesting alkaloids, such as the 2,6-dialkylpiperidines [**18**] of the fire ant (*Solenopsis invicta*), the quinazolinones [**19**] of the European millipede, and the dialkyl indolizidine [**20**] used as a trail pheromone by the Pharaoh's ant (*Monomorium pharaonis*).



18

n = 10, 12, or 14



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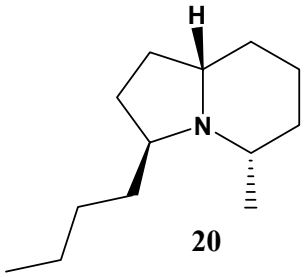
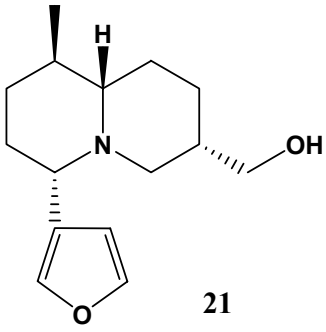


20

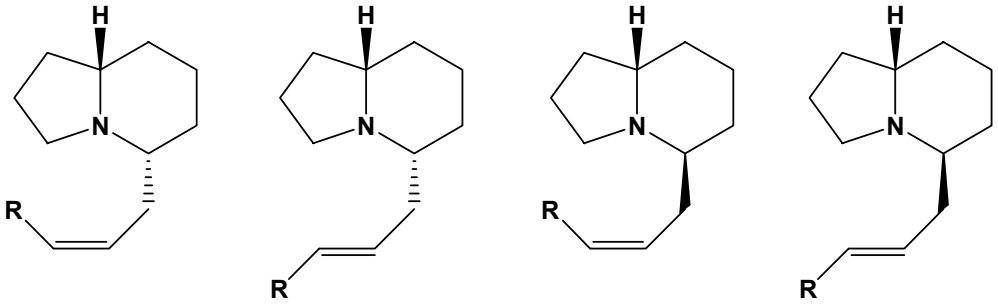
In contrast with the insect world, mammalian alkaloids are rare. One example, however, is the quinolizidine alkaloid (–)-castoramine [**21**] from the scent glands of the Canadian beaver. This Nuphar alkaloid may be acquired from dietary sources, and traces of a related indolizidine have been isolated from the scent glands.



21

Over the past two decades, a plethora of alkaloids have been isolated from two previously relatively unexplored areas, namely marine organisms and microorganisms. A large number of indolizidine and quinolizidine alkaloids are amongst interesting compounds isolated in the past few years, primarily from

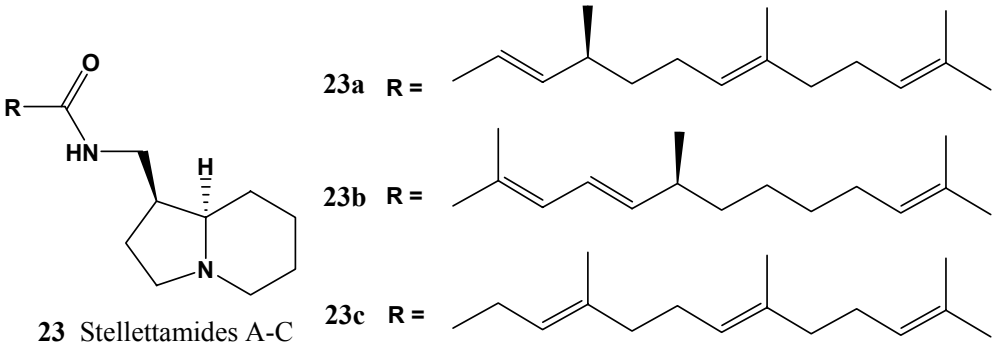
marine sponges, tunicates (sea-squirts), and nudibranchs. The discovery of antimicrobial activity of certain piclavines [**22**] isolated from the sea-squirt *Clavelina picta* have prompted several syntheses of these simple indolizidine alkaloids.[16]



22a **22b** **22c** **22d**

R = $(CH_2)_5CH_3$

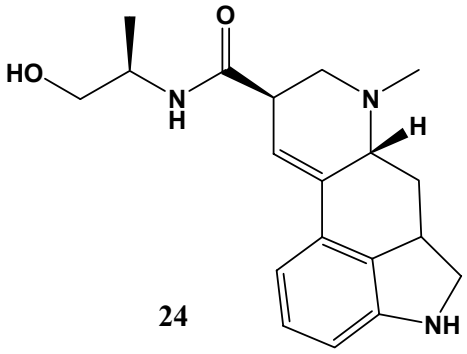
Another group of related indolizine alkaloids that bears mentioning for their simple structure as well as historic significance are the stellettamides [**23**]. These alkaloids were isolated from marine sponges belonging to the genus *Stelletta*, and stellettamide A [**23a**] is credited as being the first simple indolizidine alkaloid to have been found in a marine organism.[17]



23 Stellettamides A-C

Finally, microorganisms have been a rich source of alkaloids for many years. During the Middle Ages, the ergot alkaloids, for example ergometrine [**24**], produced by the fungus *Claviceps purpurea*, were responsible for more misery and death through contamination of grains such as rye, than any other cause except the ravages of bubonic plague. Although hallucinations and mental aberrations were the prime symptoms of the disease called ergotism, the

vasoconstrictive actions of some of these alkaloids (like **24**), led to the more serious manifestation of gangrene. This ergotism resulted in the blackening of limbs, and was given the name St. Anthony's Fire. It is this vasoconstrictive property, however, which makes these alkaloids useful, even today for the control of postpartum bleeding. There are indications in the *Hearst* medical papyrus that crude extracts of ergot have in fact been in use since *ca*. 550 BC.[18]



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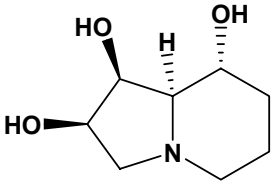
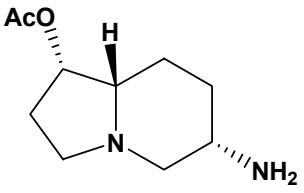
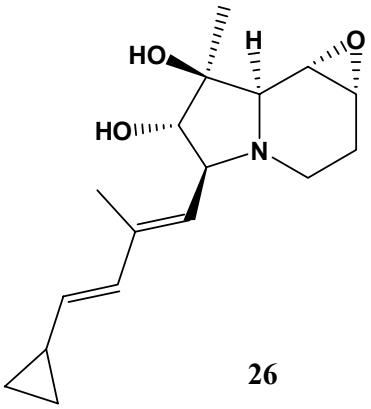
More recently, a number of simple indolizidines that have promising medicinal applications have been isolated from micro-organisms. Two of the most important examples to receive much attention have been swainsonine [**13**] and slaframine [**25**] isolated from the fungus *Rhizoctonia leguminicola*.[19] Various species of *Streptomyces* have also been good sources of many alkaloids, including the interesting indolizidine alkaloid cyclizidine [**26**] isolated, among other sources, from *Streptomyces* NCIB 11649 and *Streptomyces* L-892, [20] and the structurally related, but somewhat remarkable alkaloid indolizomycin [**27**] isolated from *Streptomyces* strain SK2-52.[21][22]



13 (−)-Swainsonine



25 (–)-Slaframine



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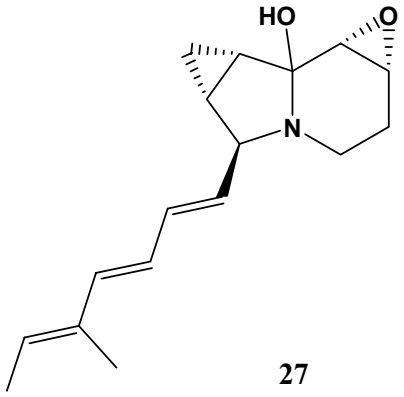


27

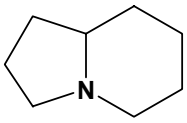
Most known non-plant alkaloids have only been isolated and characterised over the last three or four decades, due to the advent of sensitive modern techniques for structure determination, such as mass spectrometry and ^{1}H- and ^{13}C-NMR techniques. The level of sophistication associated with these techniques is such that it is possible to determine the structure of a compound from a few milligrams of pure compound in a matter of days. This is in stark contrast to the lengthy period required for the elucidation of the structure of morphine (118 years) and strychnine (approximately 125 years).

The complex structures and diverse origins of alkaloids are mirrored in the application of increasingly sophisticated synthetic and analytical techniques that have been attempted in many interesting and varied total or partial syntheses of these compounds. The following chapter will illustrate a few of these developments in some detail.

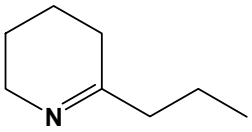
1.2 Synthetic Approaches to the Indolizidine Skeleton

In some way, the goal of the organic chemist is to beat Nature at her own game. We have certainly become remarkably good at mimicking Nature in the diversity and complexity of the molecules whose synthesis we undertake, but we are nowhere near as good when it comes to the efficiency with which we can make the molecules. A major part of the synthetic programme at Wits has been the synthesis of alkaloids. This broad range of compounds with many sources, has found application in much of our daily life. This section presents some of the approaches to the indolizidine (and related quinolizidine) alkaloid framework, together with a brief description of our own synthetic methodology, which forms the background to this project. The simple indolizidines and quinolizidines are exceptionally popular targets for demonstrating synthetic methodologies, and hence this is by no means intended to be a comprehensive review of work in the field, but instead it is merely an exposé of the diverse **range** of approaches to indolizidine and quinolizidine alkaloid synthesis.

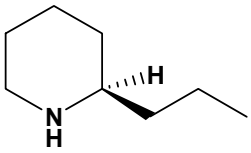
The simplest indolizidine, δ-coniceine [**28a**] is in fact not a known natural alkaloid, but was originally derived (1885)[23] from the poison hemlock (*Conium maculatum* L.) alkaloid (+)-coniine [**3**] by *N*-bromination followed by acid treatment. The belief that **28a** is a natural alkaloid probably stems from the fact that isomers such as γ-coniceine [**28b**] *are* natural products, often found together with coniine. Although several syntheses of δ-coniceine have been published, the molecule is of little use other than as a model for synthetic methodology.



28a δ-coniceine



28b γ-coniceine



3 (+)-coniine

It is likely that every conceivable disconnection of the indolizidine skeleton has been explored at least once. **Figure 3** illustrates some of these disconnections, and indicates a few of the people working on those particular routes. Again, this

is not an exhaustive selection of disconnection schemes, and there are certainly many interesting and elegant syntheses that are not represented, but these few examples serve to illustrate the extent to which the creativity of synthetic organic chemists can solve the same problem in many different ways. Each of these approaches can to some extent be regarded as "general" for the synthesis of bicyclic alkaloids and related nitrogen-bridgehead compounds, but the techniques gained in their development are undoubtedly invaluable to chemistry as a whole.

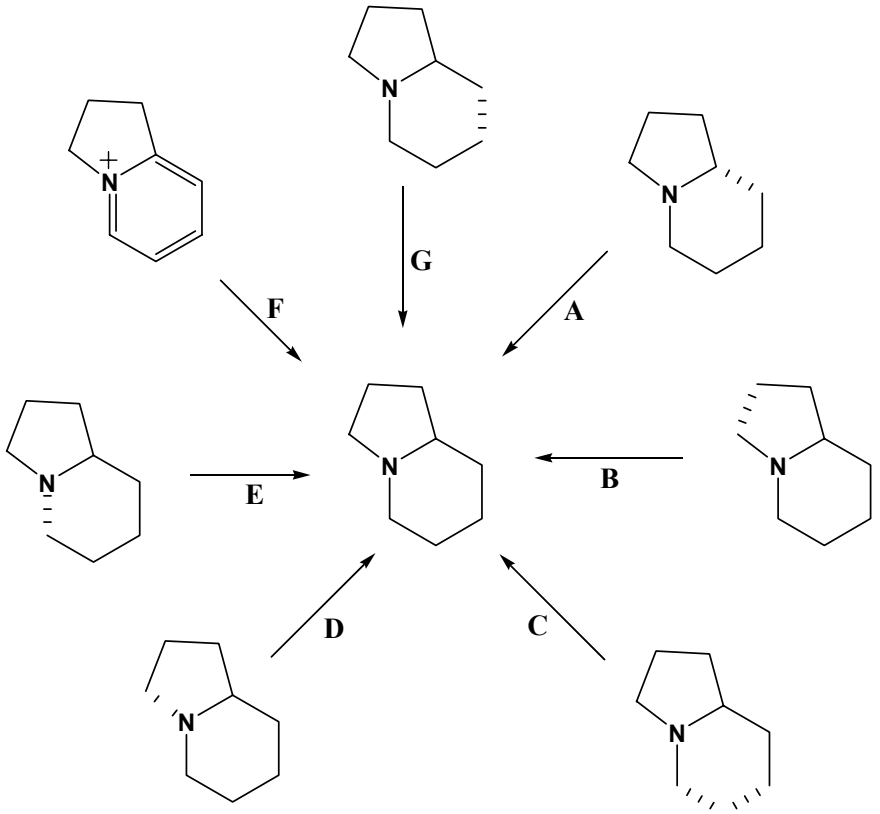


Figure 3 Disconnections to the Indolizidine Skeleton

A: Hiemstra,[24] Hart[25], Heathcock,[26] Speckamp,[27] Overman[28],Gage and Branchaud,[113] Cha,[117] Shono[29][30]

B: Kibayashi[31]

C: Back,[43] Nakajima,[43]

D: Comins,[32] Daly,[33] Padwa,[34] Kibayashi,[35]

E: Lhommet[47], Knight[36], Sibi[37]

F: Bates,[49] Padwa[38]

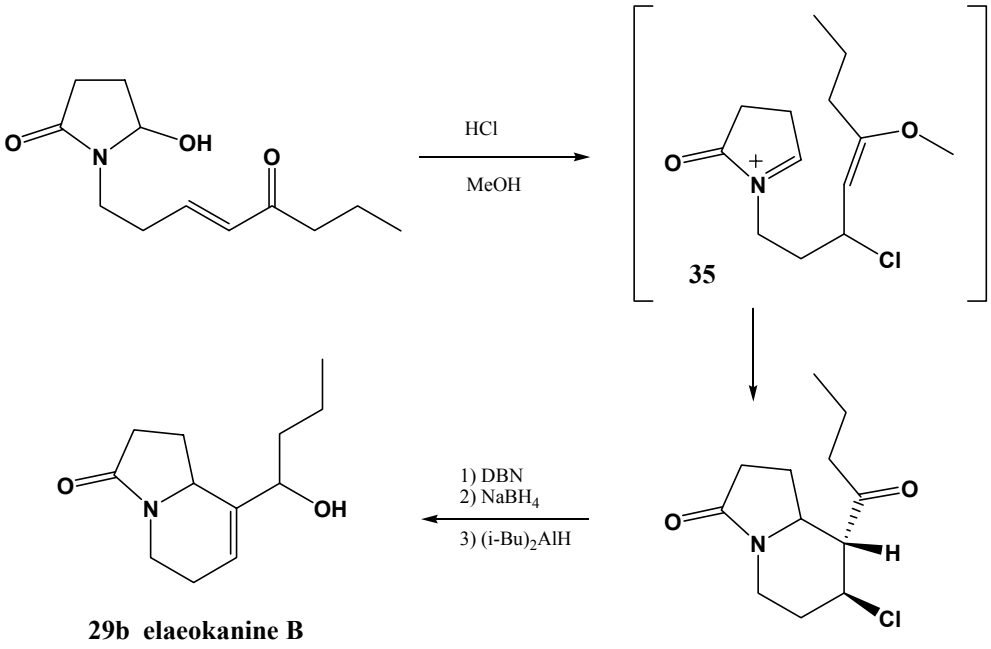
G: Howard & Michael ("Wits" Approach),[39] Russel,[11]

In the following discussion a few examples have been chosen under each disconnection to show how the methodology is applied. The choice is fairly arbitrary, since it would be extremely difficult to single out two or three contributions from the many valuable syntheses in each category.

A: Cyclization onto the carbon of the bridgehead

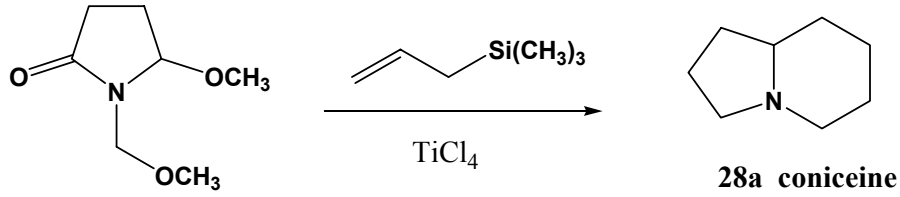
Beginning with this approach is logical since it is one of the most popular yet varied approaches that demonstrate the incredible range of syntheses possible even within a common disconnection. The reactivity of the nitrogen and the α carbons provide logical handles with which to disconnect the indolizidine skeleton. This is also one of the oldest routes to the synthesis of alkaloids.[40] The technique is so diverse that it is difficult to draw any general remarks, but many of the syntheses in this group rely on the use of *N*-acyliminium ions,[41] although other strategies such as Aldol or radical cyclisations exist.

The *N*-acyliminium approach merits attention since the α-carbonyl enhances the electrophilicity of the iminium, allowing for attack of suitably placed nucleophiles in generating the indolizidine skeleton. Elaeocarpus alkaloids have received a fair amount of attention, and the synthesis of elaeokanine B [**29b**] illustrates another reason for the popularity of this disconnection – the general stability of the iminium precursors. It should be noted, however, that the iminium ions themselves are seldom isolated, and many remain as "proposed" intermediates. Hence we can see from **Scheme 1**, the very plausible iminium intermediate **35**, generated by acid-catalysed dehydration of the precursor. Attack of the iminium ion by the enol ether produces the indolizidine skeleton containing the necessary functionality for further elaboration (in this case to the alkaloid elaeokanine B).



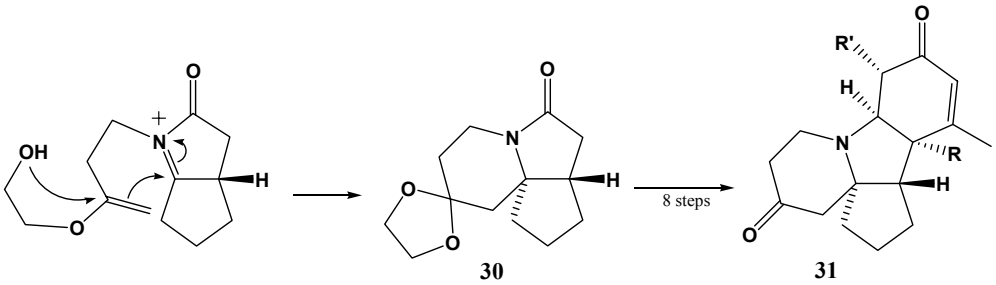
Scheme 1 – Synthesis of elaeokanine B via an acyl iminium ion

An interesting synthesis of δ-coniceine [**28a**] utilizes two such iminium ion reactions. Attack of an allylsilane followed by an intramolecular cyclisation in the presence of titanium tetrachloride gives coniine.



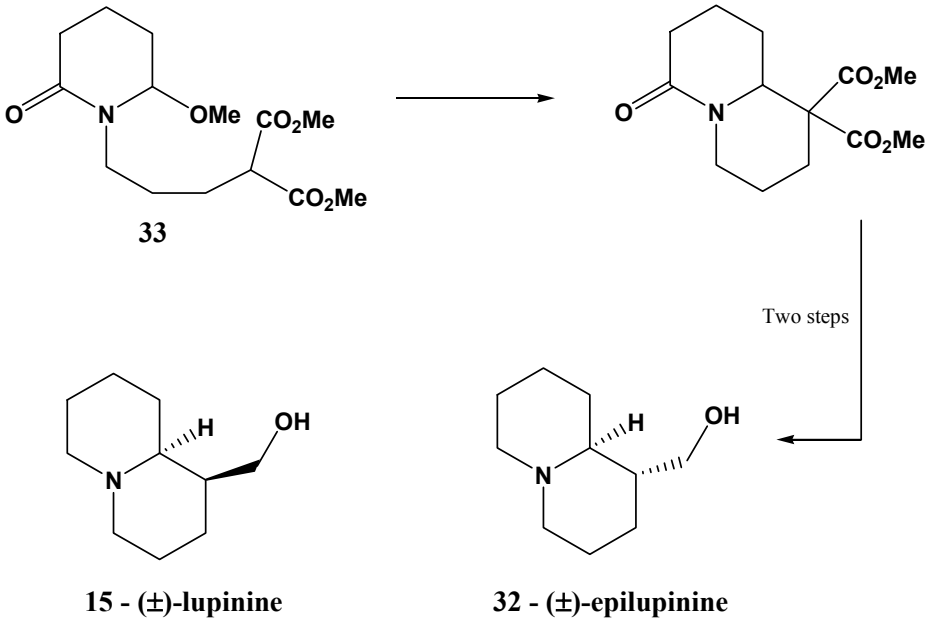
Scheme 2 – Synthesis of (±)-coniceine [**28a**] using a [3 + 3]-annulation process

The availability (or ease of synthesis) of lactams with specific stereochemistry and functionality is a particularly attractive aspect of this tactic, which is illustrated in **Scheme 3** by the synthesis of **30**, an intermediate en route to methyl homodaphniphyllate [**31**], one of the Daphniphyllum alkaloids.



Scheme 3 – Synthesis of Daphniphyllum alkaloids

Finally, lupinine [**15**] and epilupinine [**32**], two related quinolizidine alkaloids, have been popular targets for the "iminium ions" theme. For example, Okita *et al*.[42] obtained both lupinine and epilupinine using the iminium ion generated from methoxy lactam **33** in three steps.

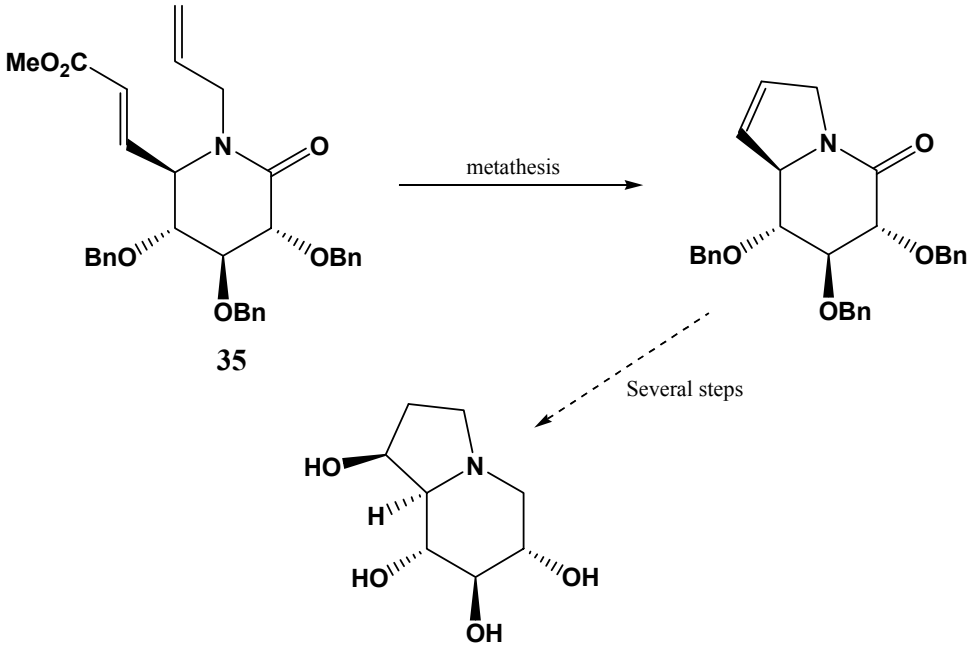


Scheme 4 – Synthesis of Lupine Alkaloids

B: Cyclisation at a remote site in the 5-membered ring

In contrast with the previous disconnection, cyclisations not involving a C–N or C=N bond are not as numerous as those just described for iminium ions, but they usually offer interesting insights into the chemistry of the systems concerned. The following disconnection strategy involves the formation of a C–C bond as the pivotal step in the synthesis of an indolizidine skeleton.

This rather unusual disconnection was used in forming the 5-membered ring via a metathesis reaction. At the time this reaction was unprecedented in these systems, and hence it is quite remarkable that metathesis of dialkene **35** produced the indolizidine skeleton in a yield of 70%. The metathesis step was conducted using Grubbs catalyst {$[(P(C_6H_{11})_3]_2Cl_2Ru{=}CHCH{=}CPh_2$ (5%w/w)}, in toluene and formed part of a formal synthesis of (+)-castanospermine [**14**].[21]



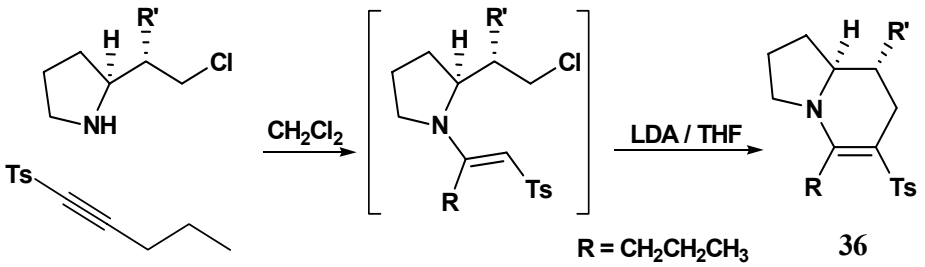
14 (+)-castanospermine

Scheme 5 – Formal Synthesis of Castanospermine Using a Metathesis Step

C: Cyclisation at a remote site in the 6-membered ring

While most disconnections utilise the reactivity of nitrogen or an α-carbon, this is approach, as with the Wits approach (see **G** *vide infra*) accomplishes the final cyclisation at a rather remote site in the molecule. A recent example of this disconnection by Back and Nakajima exploits the nucleophilicity of the enamine moiety by displacing a suitably placed halide (**Scheme 6**). The manner in which the precursor is synthesised allows for the synthesis of a wide range of compounds (such as various indolizidines and quinolizidines) with different substitution patterns.[43] For example, selective reduction of **36**, followed by

cleavage of the sulfone and catalytic hydrogenation of an unsaturated by-product completed a short synthesis of (–)-indolizidine 167B.

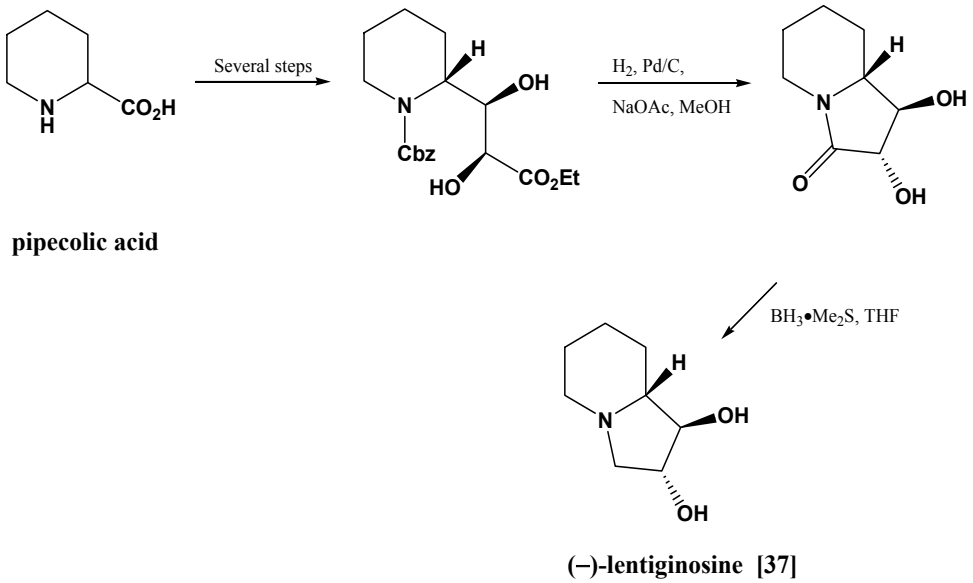


Scheme 6 – Synthesis of 5,8-Disubstituted Indolizidine Alkaloids.

D: Cyclisation onto nitrogen – forming the 5-membered ring

The work of Daly and co-workers has been of great interest to our laboratories for some time, as many of the targets are common to both groups. Certain genera of frogs/toads of the Dendrobatidae, Bufonidae, Mantellinae, and Myobatrachidae families contain a wide variety of alkaloids, especially of the indolizidine and quinolizidine classes. Using a 9-azabicyclo[3.3.1]nonane[44] derivative as a convenient and cheap starting material, Daly and co-workers have been able to synthesise a variety of alkyl substituted indolizidines and quinolizidines present in the skin secretions of these frogs. As was already mentioned in a previous chapter, these alkaloids have been detected in the diet of many of these frogs, and there appears to be an interesting allelochemical interaction.

Another example where the piperidine ring is built up first can be seen in the first published synthesis of (–)-lentiginosine [**37**].[45] Here deprotection of an intermediate, which is synthesised from (*R*)- or (*S*)-pipecolic acid in several steps, results in simultaneous cyclisation to the indolizidine skeleton (Scheme 7). The required target was easily obtained by reduction of the carbonyl using borane. Although this is one of several syntheses of lentiginosine isomers, there is still some debate about the absolute stereochemistry of the natural product.

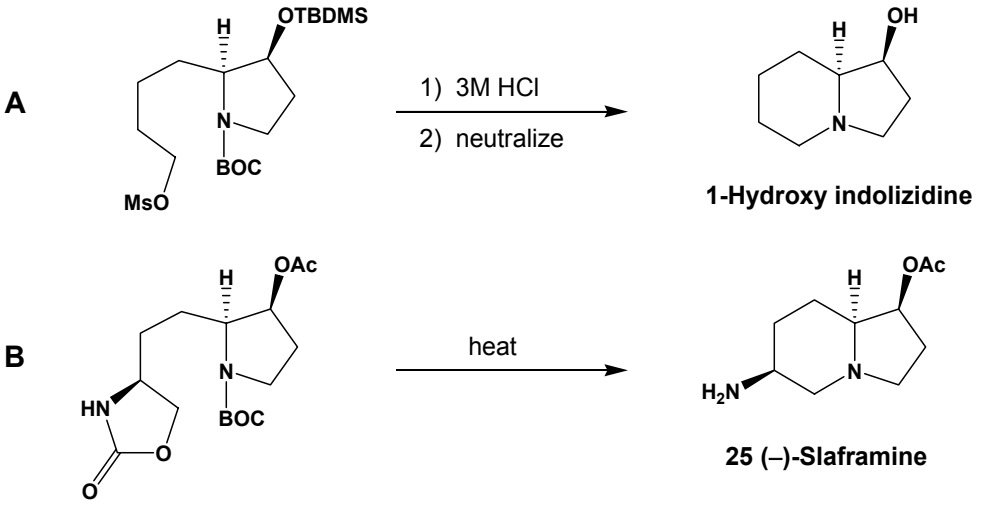


Scheme 7 – Formal Synthesis of (–)-Lentiginosine

E: Cyclisation onto Nitrogen – Forming the 6-Membered Ring

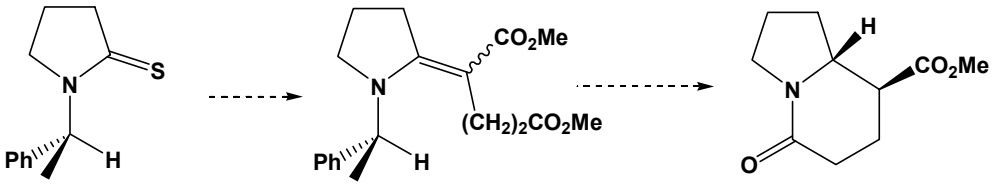
This is a fairly popular disconnection with *tert*-butoxycarbonyl (Boc), benzoyl (Bn), or carbobenzyloxy (Cbz) protecting groups featuring regularly. A common thread through these disconnections (and many of the above described D–disconnection approaches) is that they are often closely allied to biosynthetic pathways for indolizidine and quinolizidine alkaloids. In many natural pathways, one of the rings is built up first by modification and cyclisation of an amino acid, and the indolizidine is then formed by cyclisation onto nitrogen. Many of the synthetic approaches also follow this methodology, using easily available "chiral-pool" precursors in building the pyrrolidine ring with the stereochemistry intact, and then completing the indolizidine system by the displacement of a suitable leaving group on the side-chain.

The completion of the bicyclic ring system is well demonstrated in the work of Sibi and Christensen, who synthesised a number of compounds containing a mesylate as a leaving group in the side chain, and then displaced this to give the corresponding alkaloid (route **A** in **Scheme 8**).[37] Recently this same group has developed a clever cyclisation onto an oxazolidinone ring, in the synthesis of slaframine (route **B** in **Scheme 8**).[46]



Scheme 8 – Completion of the Indolizidines by Nucleophilic Displacement

The synthetic methodology followed by Lhommet and co-workers is interesting to note here in that they use a modified version of the sulfide contraction reaction to form enamino esters with a chiral protecting group on the pyrrolidine nitrogen. This chiral protecting group directs the reduction of the enamino bond, thereby controlling the stereochemistry of the ring junction, as well as that of the position α to this junction, which is a critical position for many functionalised indolizidine and quinolizidines. The indolizidines are revealed simply by deprotection with catalytic hydrogen. This work is discussed in more detail in Section 1.4.[47]

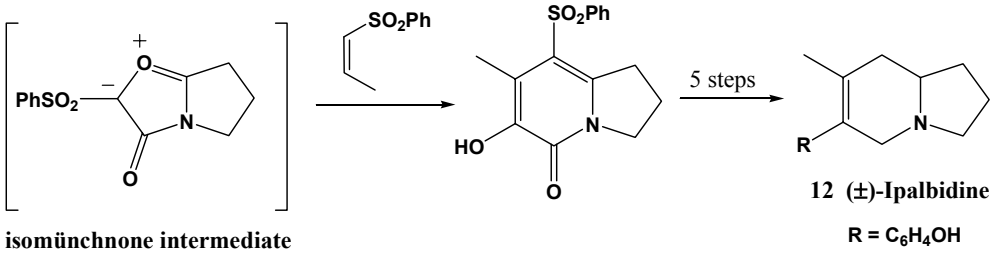


Scheme 9 – Alkaloid Synthesis by Cyclisation onto Nitrogen

F: From Pyridine- or Pyrrole-containing Precursor to Indolizidine

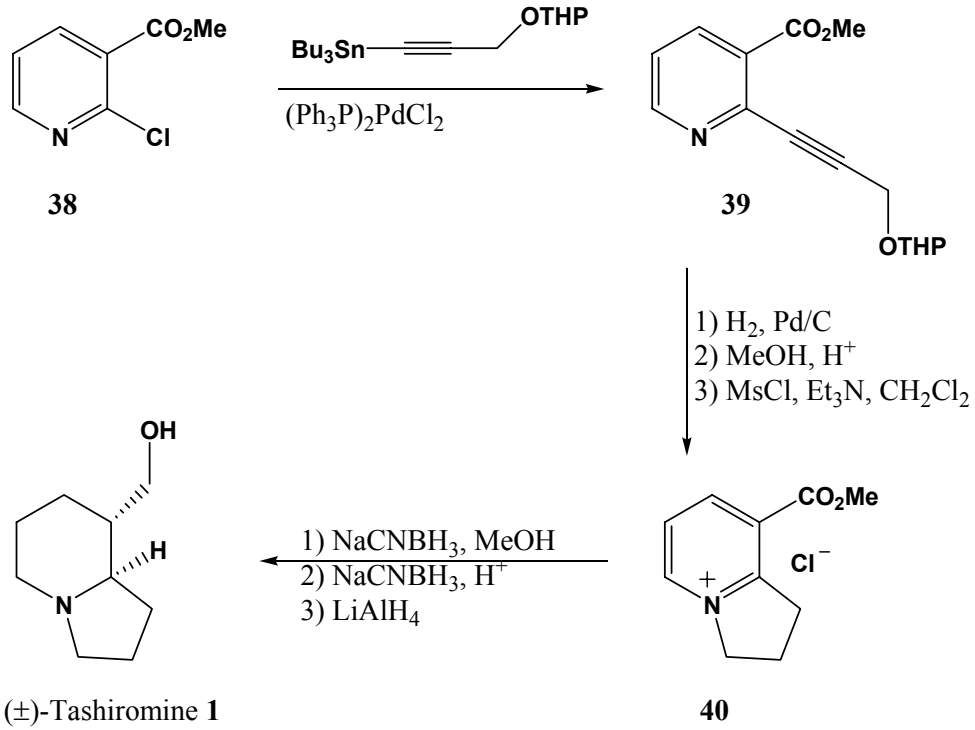
Some of the synthesis described here could be categorised in other disconnections, but they are here because they usually incorporate new and interesting transformations *en route* to the indolizidine skeleton, usually *via* an aromatic precursor.

The first is a dipolar cycloaddition of an isomünchnone with 1-phenylsulfonylprop-1-ene used in the group of Padwa to yield an intermediate that could give (±)-ipalbidine [**12**] after further elaboration and reduction.[48]



Scheme 10 – Synthesis of (±)-Ipalbidine [**12**]

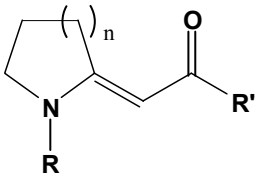
The reduction of a bicyclic alkylated pyridinium salt **40** to give (±)-tashiromine could be seen as a generalised synthesis that fits in this category (**Scheme 11**). Compound **40** was synthesised by radical coupling of a 2-chloronicotinate (**38**) with a protected alcohol using Stille conditions. Although this synthesis produced racemic tashiromine, it could provide an attractive route to other more complex systems since it involves only 5 steps from readily available starting materials, and uses an easily modifiable intermediate (**39**).[49]



Scheme 11 – Use of Acylpyridinium Salts in the Synthesis of Indolizidines

G: The "Wits approach" to alkaloid synthesis

Alkaloid synthesis in the Backeberg Laboratories at the University of the Witwatersrand dates back over three decades. Over this time our efforts have, like those of so many others, concentrated on a generalised synthesis, which could be easily modified to obtain a number of different compounds. Our methodology features the use of exocyclic enaminones (**Figure 4**), especially vinylogous urethanes and amides, which can be considered as β-acylated enamines. This chapter draws on work by previous students in our laboratories,[50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70]71] as well as several papers published from our laboratories.[39][90][91][92][95][121]



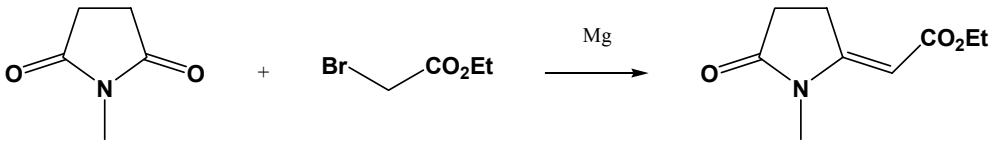
n = 1,2, or 3

R = alkyl or aryl

R' = alkyl, aryl, O-alkyl, or N-alkyl

Figure 4 - Exocyclic Enaminones

Several syntheses of exocyclic enaminones[72][73][74][75][76][77][78][79][80] have been published, including the first reported synthesis by Lukeš in 1932 of an exocyclic vinylogous urethane, [**41**] in 68% yield.[81] His approach of utilising the Reformatsky reaction between *N*-methylsuccinimide and ethyl bromoacetate (**Scheme 12**) has mostly been superseded by other approaches.



41 (68%)

Scheme 12 - Synthesis of an Exocyclic Urethane

In our laboratories, these enaminones are very frequently synthesised by means of the sulfide contraction reaction[82] developed by Eschenmoser and co-workers during their synthesis of Vitamin B_{12}. During this work, a procedure was required for the construction of a vinylogous amide linkage (intermediate **I** in **Figure 5**). The sulfide contraction via alkylative coupling[83] was found to be a

method generally suited to the synthesis of vinylogous amides and enolizable β-dicarbonyl compounds.

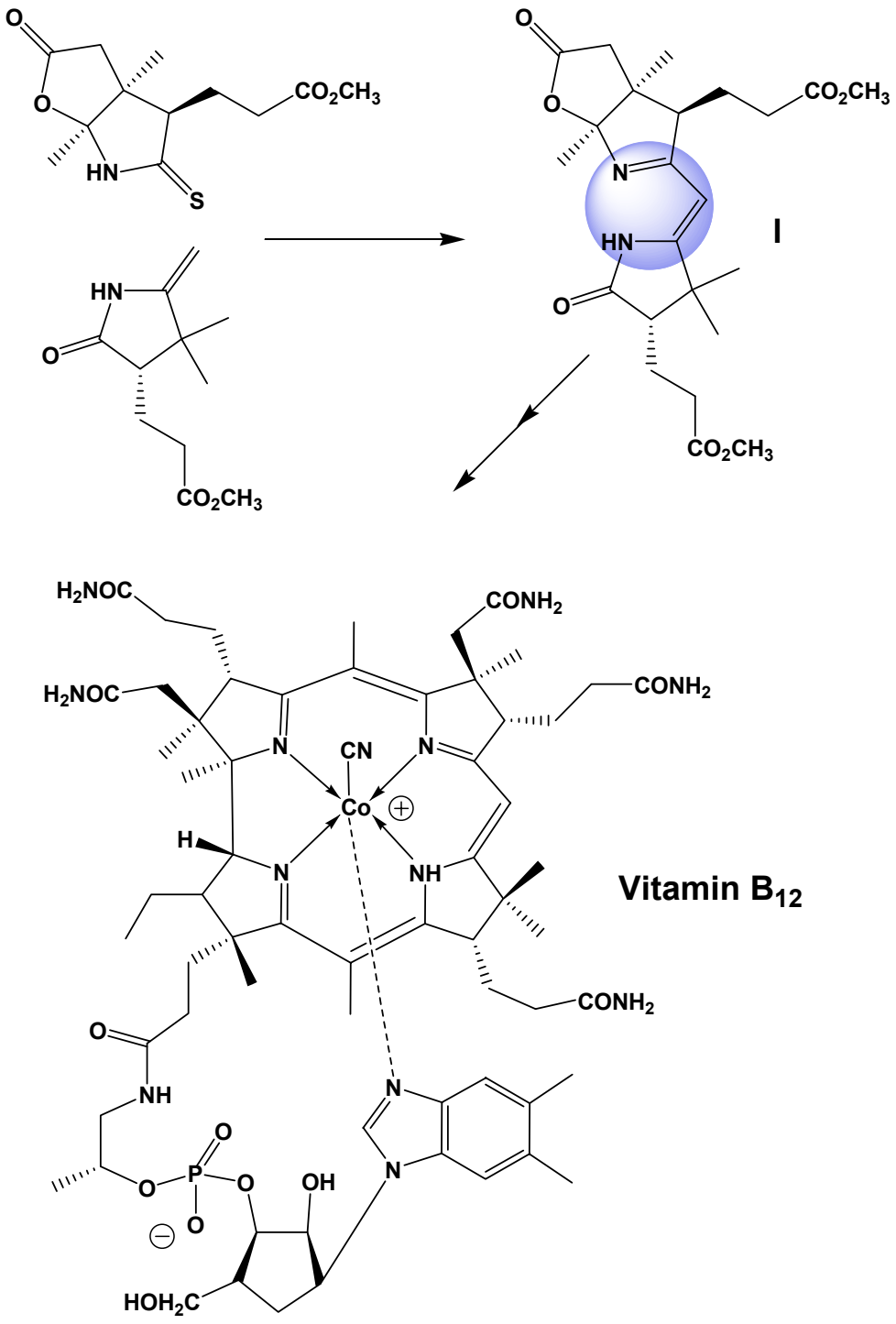
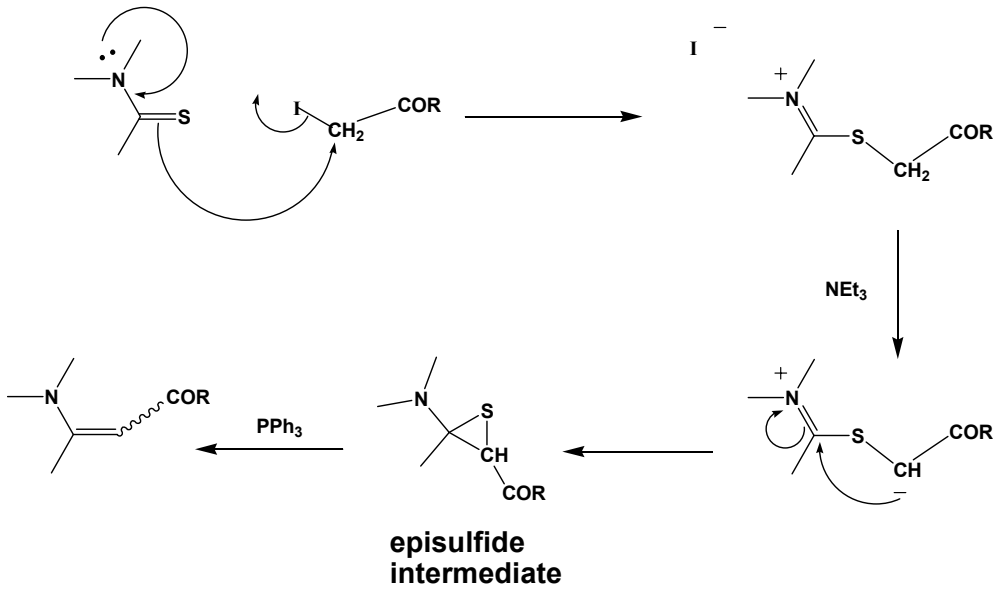


Figure 5 – Sulfide Contraction in the Synthesis of Vitamin B_{12}

This method was later improved during the synthesis of related corrinoid systems,[84] where use was made of an activated methylene (in this case an iodomethylenic compound) instead of the plain methylene compound for the alkylative coupling to the thioamide.



Scheme 13 – Outline of the Sulfide Contraction Reaction

Note: The NEt_3 acts as a base, while PPh_3 is a thiophile to extract the sulfur atom.

This idea of alkylative coupling, followed by sulfur extrusion is by no means a recent development. It was first described by Knott, who "accidentally" performed the reaction on various chromophores in the early 1950's.[85] The reaction has, however, evolved by a series of modifications into the useful procedure it is today. Using enaminones in the synthesis of alkaloids is not unique to our group. Indeed, many examples of the use of enaminones in alkaloid synthesis can be found in the literature, *inter alia* in the work of Comins,[32] Hart,[75] Lhommet,[116] and Stille;[108] however, in most cases the enamines are merely used for homologation, and the C=C bond is reduced out before the final alkaloid skeleton is made.

What can perhaps be considered characteristic of our approach is the use of an enaminone system in a cyclisation step, leading thereby to the formation of

the bicyclic core. By doing this, we are capitalising on the ambident nucleophilic properties of these enaminones, rather than using the sulfide contraction reaction simply as a means of performing a two-carbon homologation α to nitrogen centre.

In our laboratories, we have extensively used the sulfide contraction reaction with great success, in the synthesis not only of vinylogous amides (**A** in **Figure 6**), but all sorts of enaminones such as vinylogous urethanes (**B**) and ureas (**C**). We have also made other related systems such as vinylogous cyanamides (**D**). Included for completion are vinylogous nitramines (**E**) and sulfonamides (**F**), made by a related condensation route (*vide infra*) (see **Scheme 14**). This allows for a great deal of versatility in the functional groups that can be accommodated around the core enaminone system.

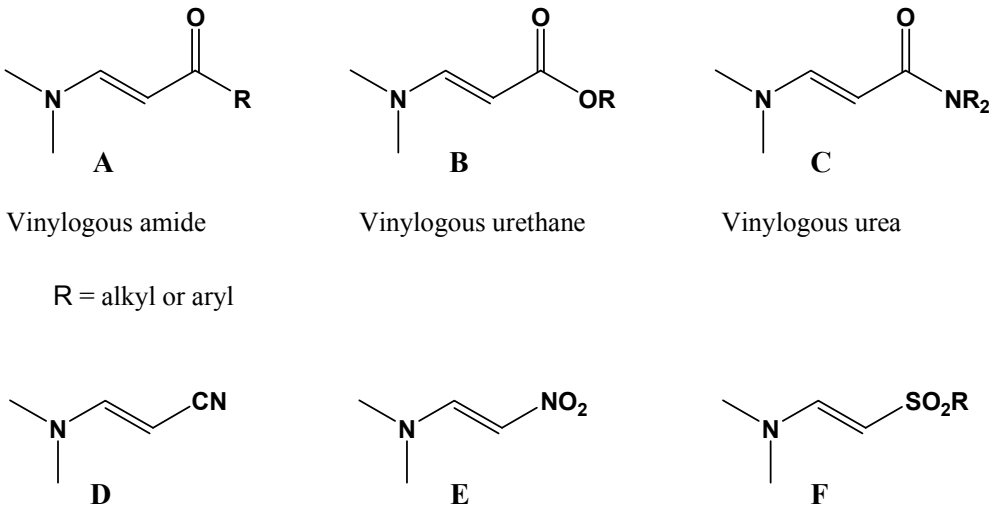


Figure 6 – General Structure of β-Substituted Enamines used in our Laboratories

The preparative execution is wonderfully simple, but the mechanism for the reaction, in contrast, appears to be complex. In essence, however, this mechanism seems to incorporate two key steps (**Figure 7**). The initial step is the alkylation of the nucleophilic sulfur of an α-thioamide (**I** in **Figure 7**) or thiocarboxylic acid derivative with an activated methylenic compound (**II**), such as an α-halocarbonyl compound, to give a thioimino ether salt (**III**). The second

essential step is the conversion of the sulfide intermediate into the vinylogous moiety (**V**) by extrusion or expulsion of sulfur. This second step is usually performed with the addition of a strong base (to remove a proton α to the sulfur atom), and a thiophile to facilitate the extrusion of the sulfur atom. This second step may at first seem a little strange, but on closer investigation is not so; the intermediate sulfide appears to rearrange to form an intermediate thiirane (**IV**). Such compounds have long been known to eliminate sulfur spontaneously.[86][87] In some cases in which the methylene compound is highly activated, for instance in the case of α-halocarbonyl compounds such as diethyl bromomalonate, expulsion of the sulfur takes place spontaneously, or is effected by gentle heating.

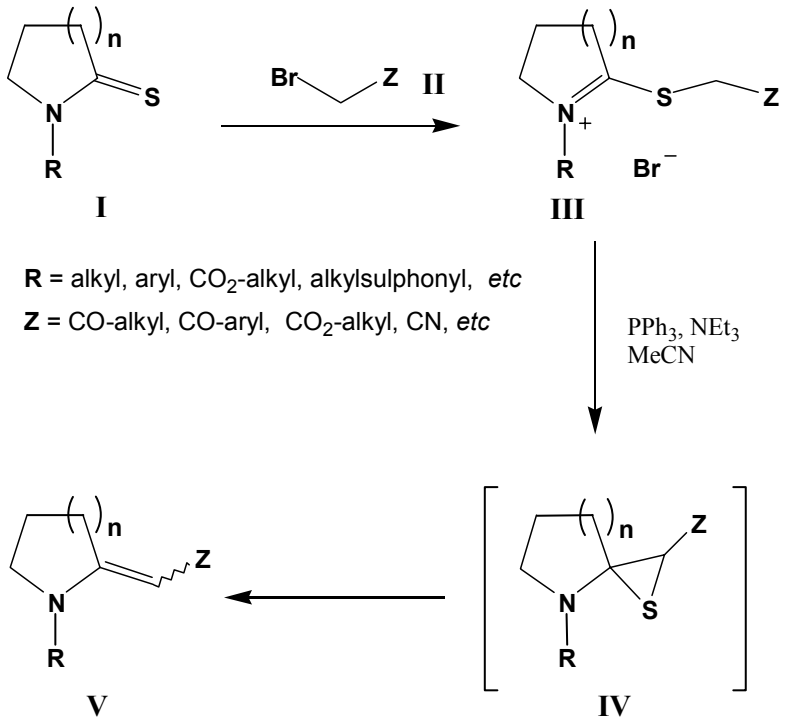
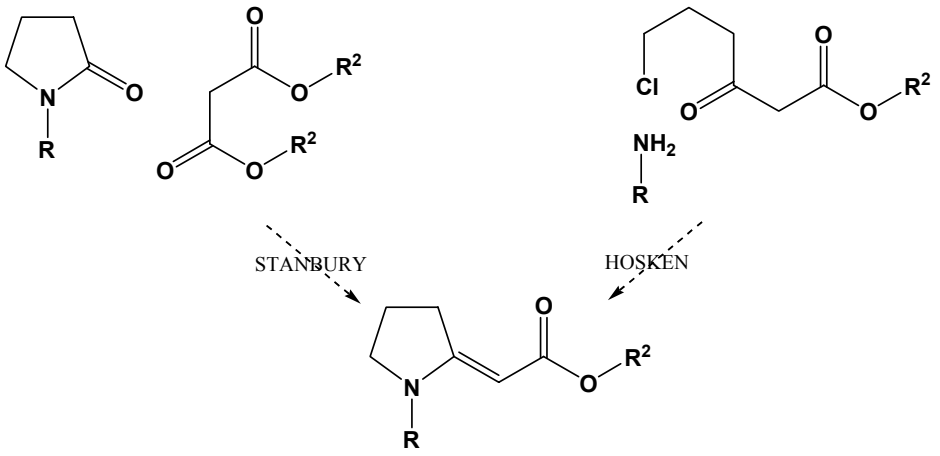


Figure 7 – Mechanistic Outline of Sulfide Contraction

Over the many years of research in our laboratories it has been discovered that it is favourable to carry out the sulfide contraction on tertiary amides (R ≠ H), as these systems are more reactive, and consequently milder reaction conditions can be employed. The tendency for *S*-alkylated secondary thioamides to undergo

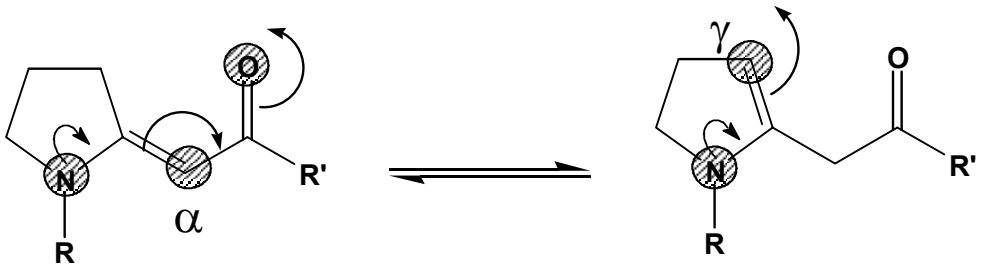
cyclization to thiazolium structures also encourages one to perform the reaction on tertiary rather than secondary amides.

It needs to be pointed out that this is not the only method for producing these β-acyl enamine systems. Probably the most general method for the synthesis of enaminones involves the reaction of an amine and a 1,3-diketone.[88] In fact, even in our laboratories we frequently use other methods such as the condensation of an amine and a chlorinated β-keto ester used by Hosken,[63] or Stanbury's use of a Knoevenagel-type reaction.[59] Addition of suitably activated nucleophiles such as 1,3-dicarbonyl systems or nitromethane to a pyrrolidinium-2-sulfide is also a popular method that has been used extensively.[89]

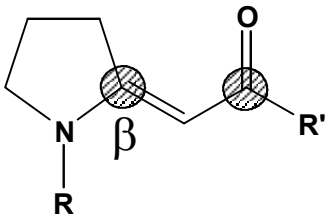


Scheme 14 – Alternative Syntheses of Vinylogous Urethanes

Our use of the sulfide contraction and related reactions as a generalised approach to enaminones allows us access to these versatile intermediates. These intermediates are considered ambident nucleophiles due to their ability to react with electrophiles at either the nitrogen or the enamine α-carbon atom. The oxygen and the γ-carbon are also nucleophilic due to the extended tautomeric delocalization of electron density, and it is possible to exploit this reactivity too. In addition enaminones can be considered as ambident electrophiles (**Figure 8**) as the carbonyl carbon and the carbon atom β to the carbonyl carbon (α to nitrogen) display electrophilic properties when reacted with appropriate nucleophiles.



Sites of Attack on Electrophiles

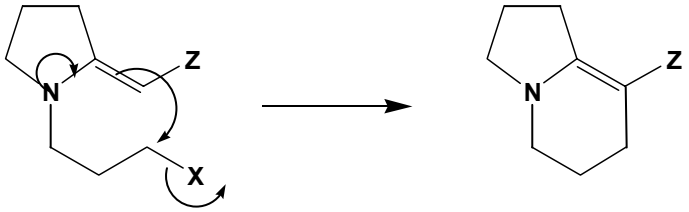


Sites of Attack by Nucleophiles

Figure 8 – Reactive Sites of the Enaminone System

This ambident nucleophilicity and electrophilicity, combined with the large variety of other possible reactions, such as radical and pericyclic reactions, gives us access to a number of different compounds using these enaminones as simple scaffolds to construct more complex ring structures.

In practice, however, the mainstay of our research exploits the nucleophilic reactivity of exocyclic enaminones. By incorporation of a suitable electrophilic partner, we are able to form a new ring, through the formation of a carbon-carbon bond. By way of example, using a suitably functionalised propyl chain attached to the nitrogen of a pyrrolidine moiety, we are able to form the six membered ring of an indolizidine skeleton, by exploiting this nucleophilicity of a vinylogous urethane (**Figure 9**).

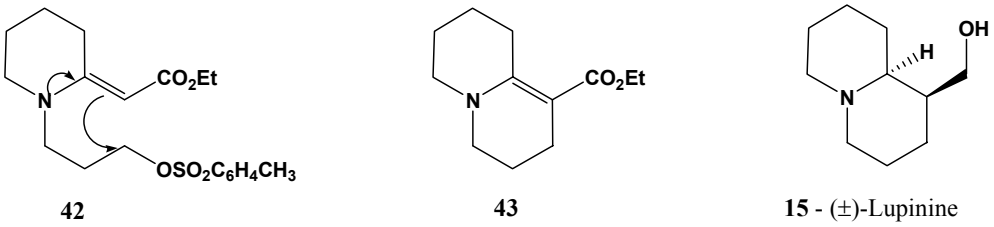


X = good leaving group

Figure 9 – Exploiting the Nucleophilicity of Enaminones

The following examples from our work will more clearly illustrate the versatility of this synthetic methodology in accessing a number of indolizidines, (some related quinolizidines, pyrrolizidines, and perhydroindoles are mentioned for comparison). Once again, these examples focus on the key annulation step of the enaminone, and largely ignore the way in which the system was set up.

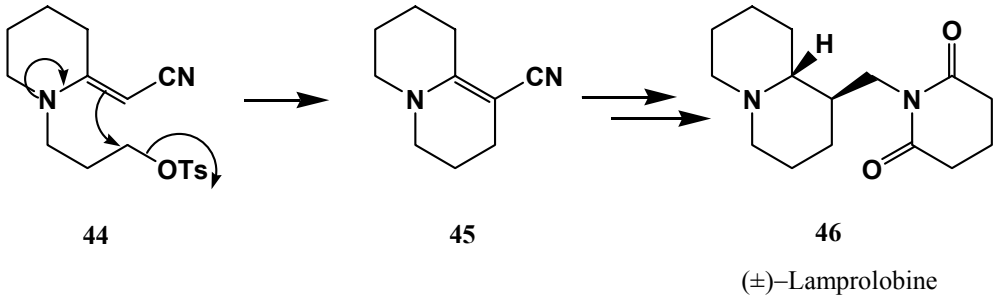
The first example illustrates an early attempt at the synthesis of (±)-lupinine by Orlek in our laboratories.[52] The key cyclisation was accomplished by displacing a suitably placed toluenesulfonyl group from intermediate **42**. Following literature procedures this intermediate was then converted into what was believed to be (±)-lupinine [**15**]. The incomplete characterisation at the time made it difficult to assign the relative stereochemistry with certainty, but Fat has recently repeated the synthesis of lupinine in order to verify the results.[62]



Scheme 15 – Alkylative Cyclisation to Form (±)-Lupinine

The second example is very similar, illustrating the use of the same tosyl leaving group attached to a simple propyl chain on the nitrogen of a piperidyl moiety. In this case, the nitrogen is conjugated to a nitrile, and hence this would strictly be regarded as a vinylogous cyanamide, and not a true enaminone, but the principle underlying the reactivity remains the same. The intramolecular

cycloalkylation of the exocyclic vinylogous cyanamide **44** forms the bicyclic structure [**45**], which is the quinolizidine scaffold. Further transformation of the cyano group provides the necessary functionality required to complete the synthesis of the quinolizidine alkaloid (±)-lamprolobine [**46**] (**Scheme 16**).[90]

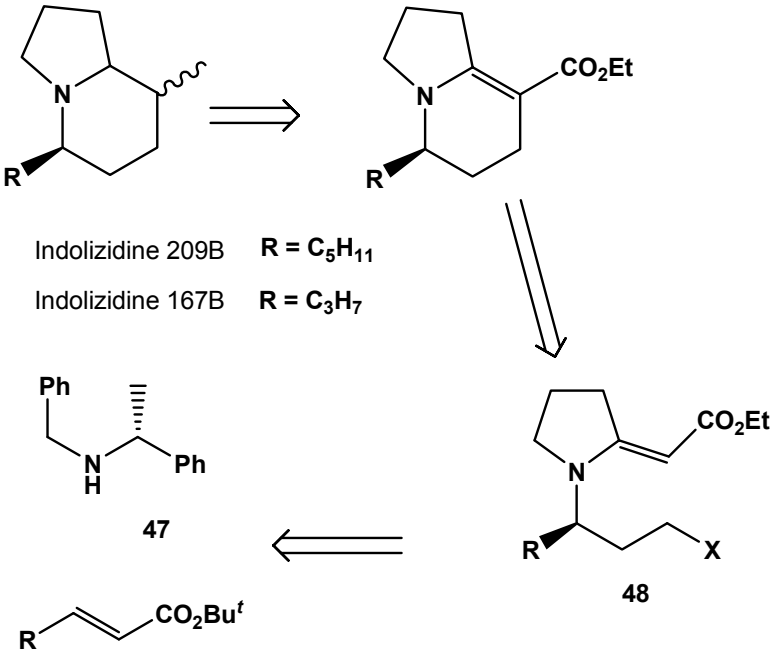


44 **45** **46**

(±)–Lamprolobine

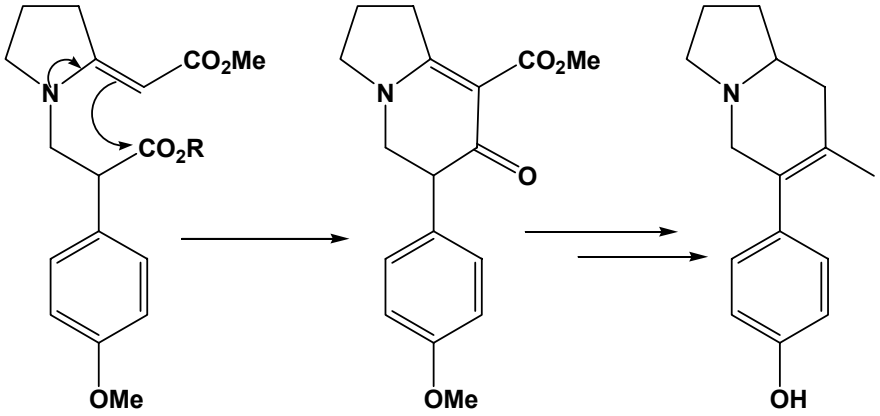
Scheme 16 – Key Cyclisation and Intermediates in the Synthesis of (±) Lamprolobine

In the synthesis of two alkaloids (indolizidine 209B and 167B) found in the skin secretions of dendrobatid frogs, Gravestock used a similar methodology in an intramolecular cycloalkylation of a chiral enaminone [**48**], which was in turn synthesised by Michael addition of chiral amine **47** to an unsaturated ester.[58]



Scheme 17 – Chiral Intermediates in the Synthesis of Indolizidines

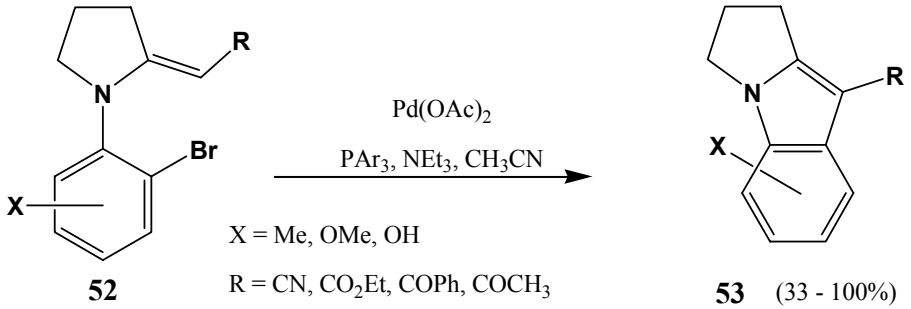
Besides using this nucleophilicity in a *cycloalkylation*, the above reactivity has also been exploited in our laboratories in both *cycloacylation* and *cycloarylation* processes to form various products. One example of the annulation being accomplished by an acylation of a vinylogous urethane can be found in the formal synthesis of (±)-ipalbidine [**12**].[91] Howard and co-workers were able to perform an intramolecular *cycloacylation* of exocyclic vinylogous urethane **50** to prepare the 7-oxoindolizidine [**49**] (**Scheme 18**), via the highly electrophilic mixed anhydride [**51**]. Under these conditions, the cyclization took place spontaneously.



50 R = Me **49** **12** Ipalbidine
51 R = COMe

Scheme 18 – Acylative Cyclisation in the Synthesis of Ipalbidine

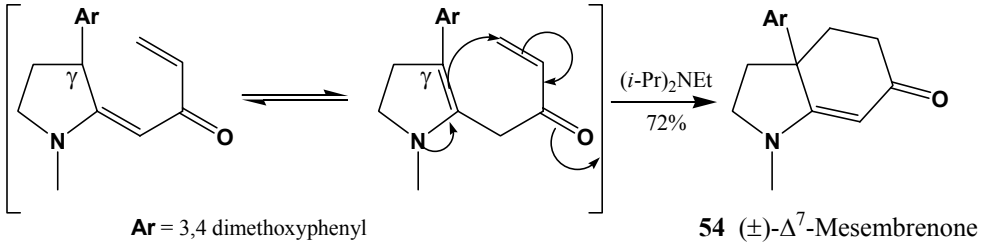
The work of Chang and Wilson gives us several examples of the use of a *cycloarylation* onto the β-position of an enaminone. Although Chang used a palladium-mediated Heck reaction to synthesise the first compounds containing the pyrrolizidine ring system in our laboratories, the principle could be applied to indolizidines.[56] As precursors to the pyrrolo[1,2-*a*]indole derivatives [**53**], Chang and Wilson used a range of *N*-(2-bromoaryl) enaminones [**52**] (**Scheme 19**).[56][65][92]



Scheme 19 – Alkaloid Synthesis Using a Cycloarylation

Although the nucleophilicity of the α position forms the bulk of our work, there are a few examples of synthetic intermediates which we have successfully made by exploiting the other reactivities of β-acylated enamines. These syntheses do not necessarily follow disconnection **G** (**Figure 3**), but are presented here to complement the alkaloid syntheses already demonstrated.

The elegant synthesis of the hexahydroindole alkaloid (±)-Δ^7-mesembrenone [**54**] by Katz[91][93][94] and Zwane,[55][95] exploits the nucleophilicity of the γ position of a substituted pyrrolidine (**Scheme 20**).

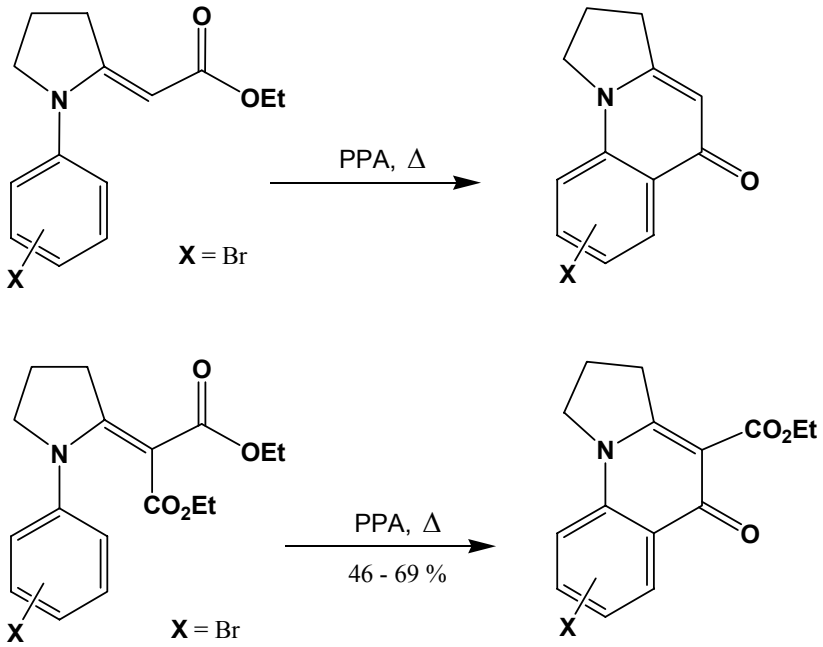


Scheme 20 – Synthesis of (±)-Δ^7-Mesembrenone

The above examples illustrate the effective use of the nucleophilicity of these enaminone systems in our laboratories. The following syntheses make use of the ambident electrophilicity.

During the syntheses of analogues of 4-quinolone antibacterials, we have exploited the carbon electrophilicity at the enaminone carbonyl moiety. The preliminary work in this field was done by Hosken,[63] who found that Conrad–Limpach cyclizations of suitably functionalised *N*-aryl vinylogous urethanes gave the tricyclic 4-quinolinones in moderate to excellent yields (48% – 100%).

Stanbury[59] later extended this methodology by preparing a different series of tricyclic 4-quinolinones possessing an ethoxycarbonyl group, which could subsequently be hydrolysed to give the active carboxylic acids in comparably good yields (**Scheme 21**). Once again, the *N*-aryl vinylogous urethanes were subjected to a Conrad–Limpach cyclization as the key step in the synthesis of the 4-quinolones.



Scheme 21 – Synthesis of 4-QuinoloneAntibacterials

The final example is a very common reaction in our laboratories, and it is a central theme in this project. This also illustrates that we can exploit the electrophilicity for purposes other than ring closure. The reduction of the carbon double bond in the enaminones formally represents an attack of a nucleophilic hydride at the electrophilic β position of the enaminone (**Figure 11**).

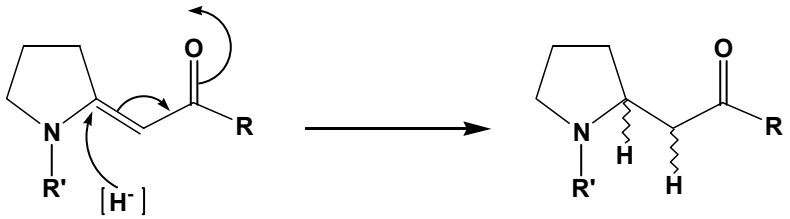
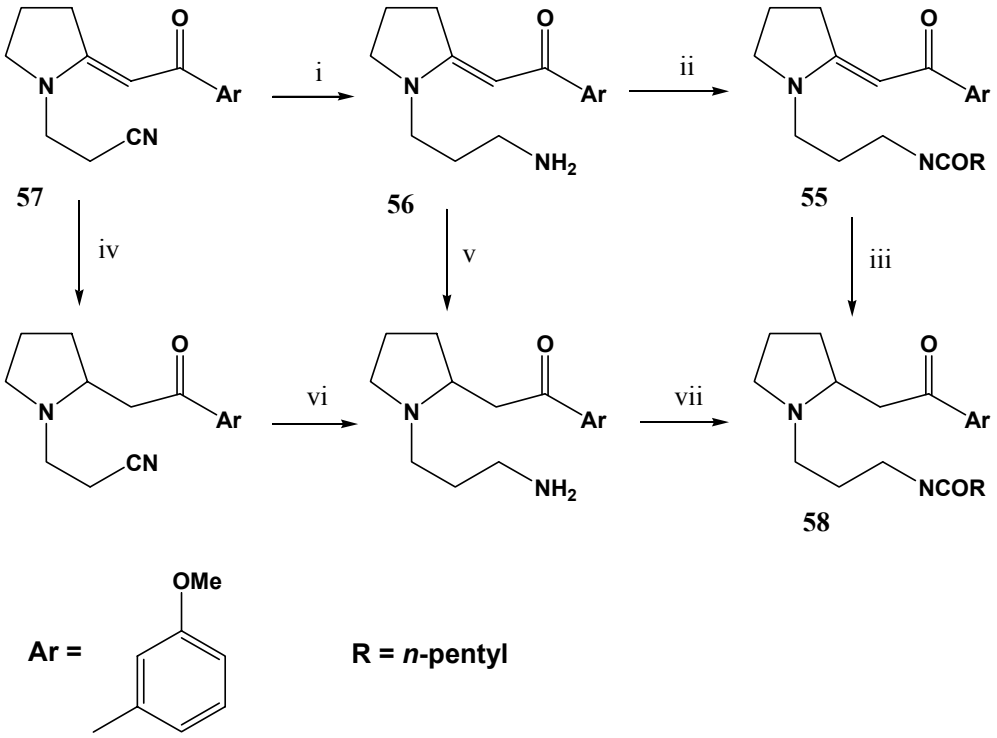


Figure 11 – Reduction of the C=C Bond in Enaminones

In the synthesis of peripentadenine, Parsons was able to reduce vinylogous amide **55** with lithium aluminium hydride ($LiAlH_4$) to give the alkaloid precursor *O*-methylperipentadenine [**58**] in 75% yield.[57] This synthesis also serves to illustrate the flexibility of the vinylogous systems. Although there are several functional groups, which are susceptible to reduction, careful choice of reagents and conditions allows us to explore different routes to the same target by altering the timing of the reactions. Thus, the reductions of vinylogous amides **56** and **57** also represent an attack of a nucleophilic hydride at the β position of the enaminone.



Scheme 22 – Synthesis of *O*-Methylperipentadenine

i), Ni/Al, NaOH, ethanol, (97%), ii) hexanoyl chloride, pyridine, (43%), iii)$LiAlH_4$, (71%), iv) $LiAlH_4$, (87%), v) $NaBH_3CN$, HCl, (89%), vi) [PtO_2/H_2,, (71%)] vii) (hexanoyl chloride), viii) BBr_3, (92%). **Note**: vi) and vii) represent a formal synthesis only.

As can be seen from this chapter, the efforts we have invested in the chemistry of these systems allowed us to achieve the synthesis of many

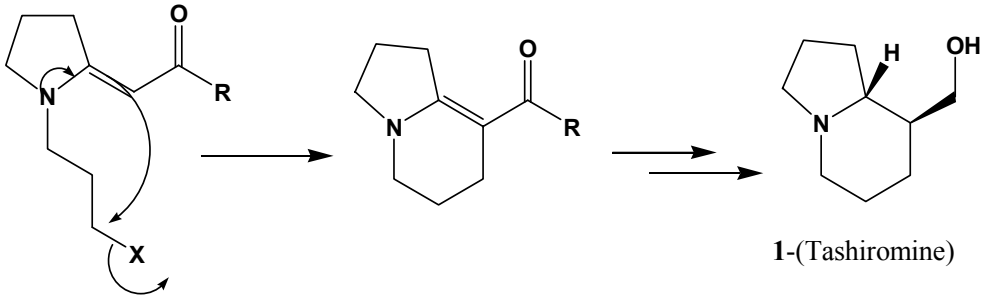
compounds. We believe that we have only begun to scratch the surface of this approach in the synthesis of pyrrolidines, indolizidines, quinolizidines, and certain perhydroindole alkaloids. Perhaps the one disappointment has been the lack of success in preparing bicyclic pyrrolizidine ring systems by cyclising suitable exocyclic enaminones.[51]

One important feature of the bulk of this work is the fact that it has yielded almost exclusively racemic products. The most important goal of this project, therefore, in concentrating on the reduction of the vinylogous bond, was to try to impart to the approach a way of realising enantiomeric products. This will be explained more closely in the following section, where the aims of the project are laid out in full.

1.3 Project Aims

Having outlined some of the work that has been done in what has been called the "Wits Approach" in the previous chapters, and with a short review of the literature in the preceding chapter, we can now clarify the aims of this project.

This project intended to use the same methodology discussed in the preceding chapters, namely the sulfide contraction, to synthesise a variety of 8-substituted indolizidines that could then be transformed into the indolizidine alkaloid, tashiromine [**1**].



1-(Tashiromine)

Scheme 23 – Synthetic Strategy for Tashiromine

As can be seen in **Scheme 23**, this fits in nicely with the use of the nitrogen nucleophilicity through the C=C bond. The alkaloid tashiromine had not yet been synthesised in our laboratories and the limited quantities of the natural product isolated to date leave many questions unanswered about this alkaloid.

The primary focus of this project, however, was not merely to synthesise another target, but rather to investigate whether the use of a small modification in the general strategy could allow us to synthesise the indolizidine skeleton in an enantioselective manner. To do this we envisaged the use of a chiral auxiliary that could be added and removed at a suitable point in the synthesis.

In most of our syntheses of alkaloids the ester or amide moieties are merely convenient appendages that are either removed or altered in yielding the final products (e.g. the R-group in **Scheme 23**). This therefore presented the ideal attachment site for a chiral auxiliary. We hoped these “appendages” would allow for a degree of stereochemical control of at least one step in our approach. Since

the sulfide contraction step had proven to be considerably tolerant of conditions and reagents we were certain of being able to choose a promising auxiliary in the form of a chiral bromoacyl derivative. After this had been used to control the stereochemistry it could be removed to reveal the product alkaloid. In theory, this would require only one or two additional steps in our synthetic methodology, apart from the reactions needed to produce the auxiliary. It should also be general enough to allow for a wide variety of targets.

We eventually considered five different chiral auxiliaries giving chiral vinylogous urethanes and ureas. Due to low yields, poor d.e.'s, and lack of time, only one auxiliary was taken through to the final alkaloids.

A second approach was to look at chiral reductants. Although this would only allow us to control one aspect of the synthesis, namely the reduction of the C=C double bond of the enaminone systems, it should have allowed us to access the alkaloid products in a stereospecific manner. Both of these approaches will be elaborated in chapters 3 and 4.

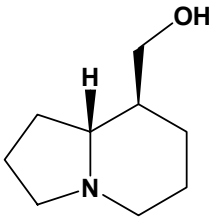
In order to maximise the yields of the tashiromine and epi-tashiromine targets, we undertook a model study of the synthesis of the indolizidine skeleton.

In summary these were the three aims of this project:

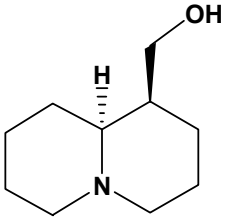
- Compare different chiral auxiliaries in their ability to control the stereochemistry of the reduction of one C=C bond.
- Examine the use of chiral reductants in stereospecifically reducing the C=C bond of the enaminones.
- Synthesise (+)- and (–)-tashiromine.

1.4 Review of Tashiromine Literature

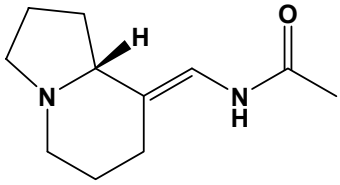
This chapter will survey the current literature on tashiromine, focusing on its synthesis by various scientists. This alkaloid [**1**] is a target of this project, being a model for studying the efficacy of the stereoselective reduction step. It is appropriate, therefore that a chapter is dedicated to a survey of the current literature dealing with tashiromine, focusing on its synthesis by various scientists.



1 (±)-Tashiromine



15 (±)-Lupinine



59 (–)-Tenuamine

Tashiromine [**1**] is a simple indolizidine alkaloid, isolated from the Asian deciduous shrub *Maackia tashiroï*. Although many indolizidine alkaloids are known, this was, until recently, unique in that it was the only simple indolizidine to occur in the class of lupin alkaloids. Recently (–)-tenuamine [**59**] was isolated from the stems of *Maackia tenuifolia*,[96] as the only other indolizidine in this class of alkaloids. Lupin alkaloids are a group of alkaloids, most of which contain quinolizidine or piperidine ring systems (see chapter 1). Many of them have significant biological activity, and since they are associated with many animal and human foods (legumes in particular), they have been the subject of significant interest. Although other members of the lupin alkaloids are well known, such as the structurally related quinolizidine alkaloid lupinine [**15**], little has been established about tashiromine. In fact, the optical rotation of the natural compound remains unknown due to the shortage of the isolated material.[97]

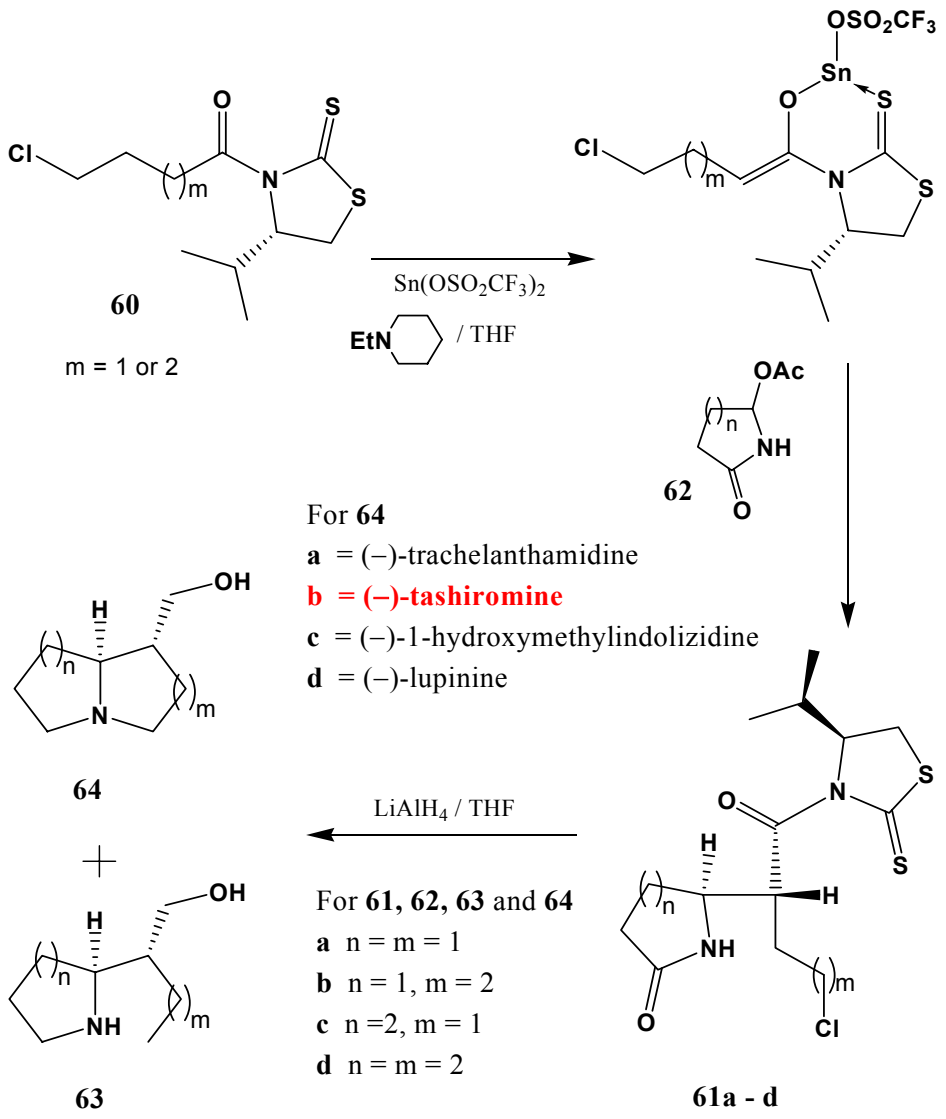
It is interesting to note that although very few plants produce both indolizidines and quinolizidines, many of those that do seem to accumulate

"pairs" of alkaloids with identical or very similar substituents. *Maackia tashiroï*, for example, contains tashiromine and the related quinolizidine alkaloid lupinine.

Despite the lack of structural information, there have been several syntheses of both enantiomers, as well as the epimers. These syntheses are outlined in the rest of this chapter, roughly in chronological order of their appearance in the literature.

Nagao and co-workers; (1988),[98] **(1990)**[99]

An extremely short synthesis of bicyclic alkaloids containing the pyrrolizidine, indolizidine, and quinolizidine skeleta has been developed in the laboratories of Nagao and co-workers. The synthesis (**Scheme 24**) involved a diastereoselective alkylation of a cyclic imide derivative, followed by reductive annulation to give the azabicyclic core. These scientists used a tin(II) enolate of a substituted 1,3-thiazolidine-2-thione [**60**] to control the stereoselectivity of the alkylation of 5-acetoxy-2-pyrrolidine [**62a**] or 6-acetoxy-2-piperidine [**62c**]. Reduction of the active amide moiety and concomitant reductive annulation was accomplished by the treatment of the ω-halolactam [**61a** – **d**] with an excess of $LiAlH_4$. No *O*-cyclisation products were isolated, although hydrogenolysis of the ω-halolactam gave the pyrrolidine [**63a** and **b**] or piperidine [**63c** and **d**] by-products. Comparison of the isolated bicyclic compounds **64a** and **64d** with literature data showed them to be identical to the alkaloids (–)-trachelanthamidine and (–)-lupinine, respectively. Although no direct comparison of the obtained tashiromine [**64b**] was made with the natural product, the authors indicate in the paper that (–)-tashiromine was synthesised in 29.5% overall yield from the 3-ω-chloroacyl-4(*S*)-isopropyl-1,3-thiazolidine-2-thione [**60**]. The remaining alkaloid [**64c**] is (–)-1-hydroxymethylindolizidine, itself an important synthetic target.

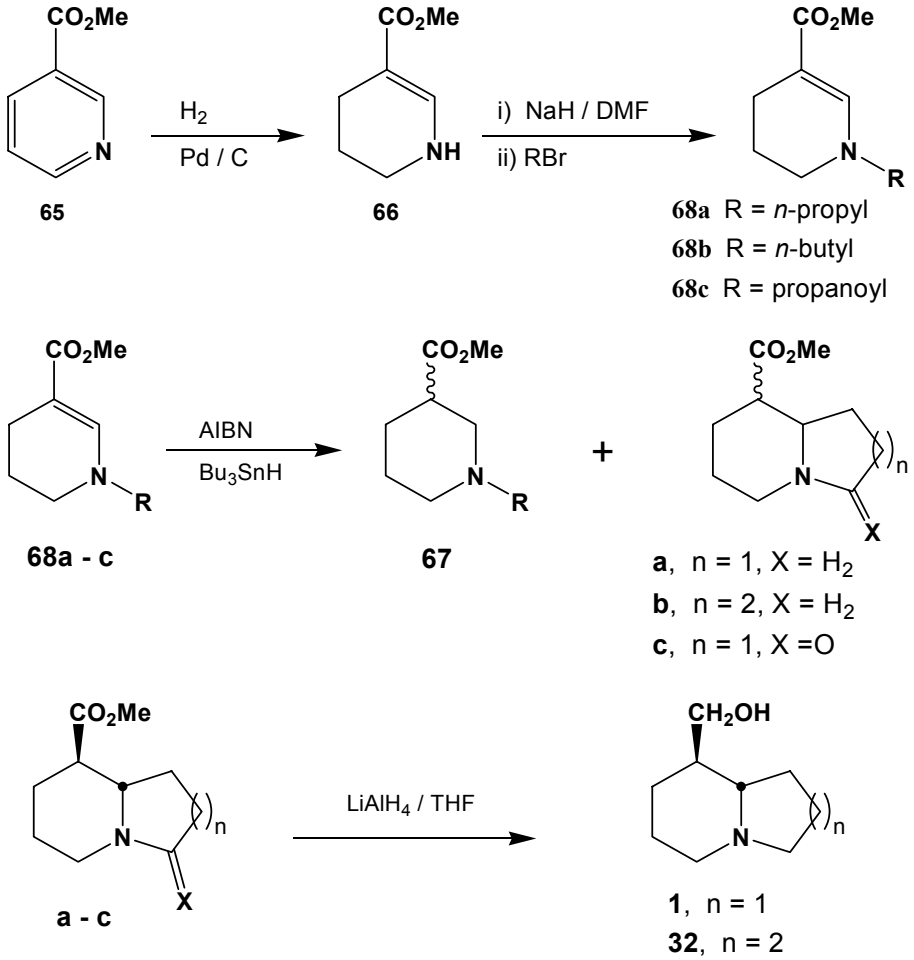


Scheme 24 – Tin-Enolate Coupling in the Synthesis of Azabicycles

Beckwith and Westwood; (1989)[100]

The last few decades have seen a remarkable growth in the use of free radical reactions in organic chemistry for the formation of carbon-carbon bonds.[101] The intramolecular cyclisation of the 5-hexenyl radical to give mainly a cyclopentylmethyl radical by *exo* ring closure has been a particularly useful method for the construction of cyclic compounds.[102] Cyclisations of 1-aza-5-hexenyl radicals,[103] 2-aza-5-hexenyl radicals[104], and 3-aza-5-hexenyl radicals[105] have been used in forming nitrogen-containing heterocyclic systems.

Using an intramolecular radical cyclisation of 4-aza-6-methoxycarbonyl-5-hexenes, Beckwith and Westwood synthesised (±)-epilupinine [**32**] as well as a number of indolizidines, including (±)-tashiromine [**1**], while aiming to examine the ability of 4-aza-5-hexenyl radicals to undergo addition to the *N*-terminus of an enaminic double bond. Apart from the synthetic potential to azabicycles, this cyclisation is also of interest from a mechanistic viewpoint. The nitrogen atom in this case is directly attached to the alkene, and so the electronic properties of the double bond would be very different from other alkene radical cyclisations. The precursors were from methyl nicotinate [**65**] (**Scheme 25**), and cyclisations were carried out in benzene, in the presence of tributylstannane as the radical source. A significant amount (10 – 20%) of the reduction product [**67**] was also isolated.



Scheme 25 – Synthesis of Bicyclic Ring Systems by Radical Mechanism

An interesting point on the stereochemistry of the annulation bears further mention. The cyclisations all afforded predominantly, and sometimes exclusively, *trans*-fused products in which the substituent was *anti* to the fused ring (**D** in **Figure 12**). This is unusual, as it is well known that 5-hexenyl radical cyclisations leading to fused cyclic compounds usually afford the *cis*-fused radicals (**A** in **Figure 12**).[106] Subsequent quenching of the exo radical by hydrogen atom transfer usually occurs from the less hindered exo-face (**A → C)** to give a product in which the substituent is *syn* to the fused ring (**C**). Due to the possibility of nitrogen inversion and the greater stability of *trans*-fused indolizidines,[107] it is presumed that the initially formed *cis*-fused exo-radical (**A**) rapidly isomerises to the more stable *trans*-fused radical (**A → B**). Transfer of a hydrogen atom from the less hindered face (**B → D**) leads to the formation of a *trans*-fused indolizidine product in which the substituent is *anti* to the fused ring (**D**).

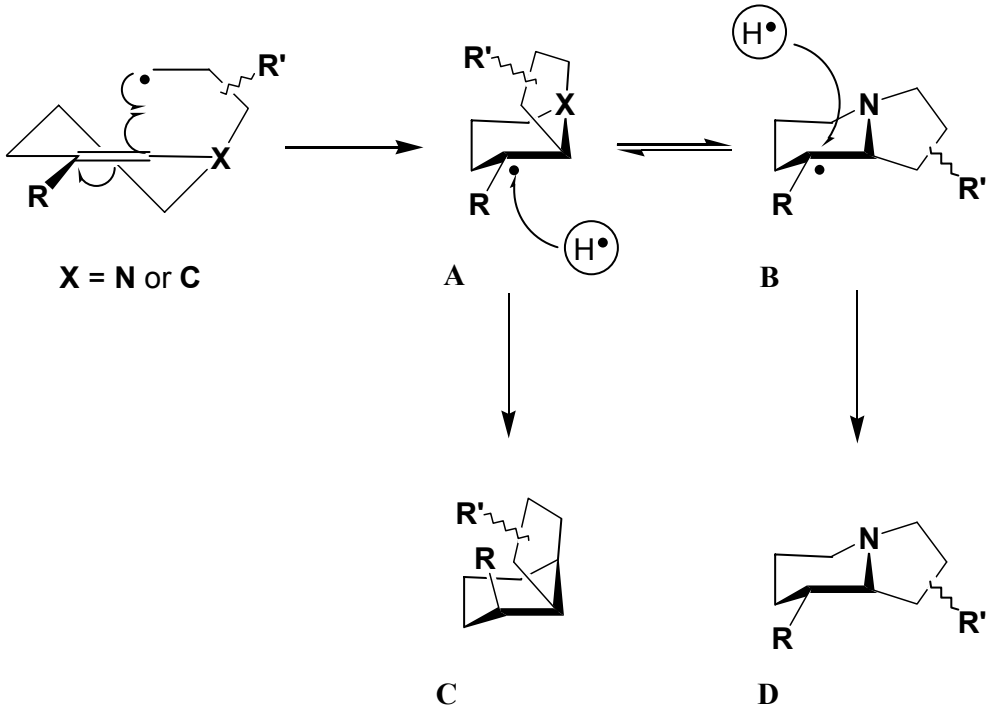
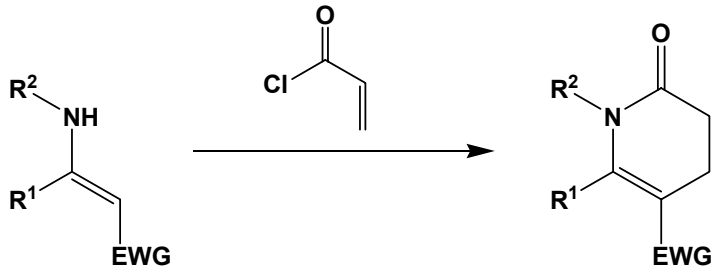


Figure 12 – Proposed Conformations in Radical Cyclisations

Using this radical cyclisation technique, 8-methoxycarbonylindolizidine (**a** in **Scheme 25**) and 1-methoxycarbonylquinolizidine (**b** in **Scheme 25**) were synthesised in good yield. Reduction of the ester moiety furnished (±)-tashiromine [**1**] and (±)-epilupinine [**32**], respectively. (±)-Tashiromine was also obtained by lithium aluminium hydride reduction of 8-methoxycarbonyl-3-oxoindolizidine (**c**), obtained similarly by the radical cyclisation of 3-methoxycarbonyl-1-(1-oxo-3-bromopropyl)-1,4,5,6-tetrahydropyridine [**68c**].

Paulvannan and Stille; (1994)[108]

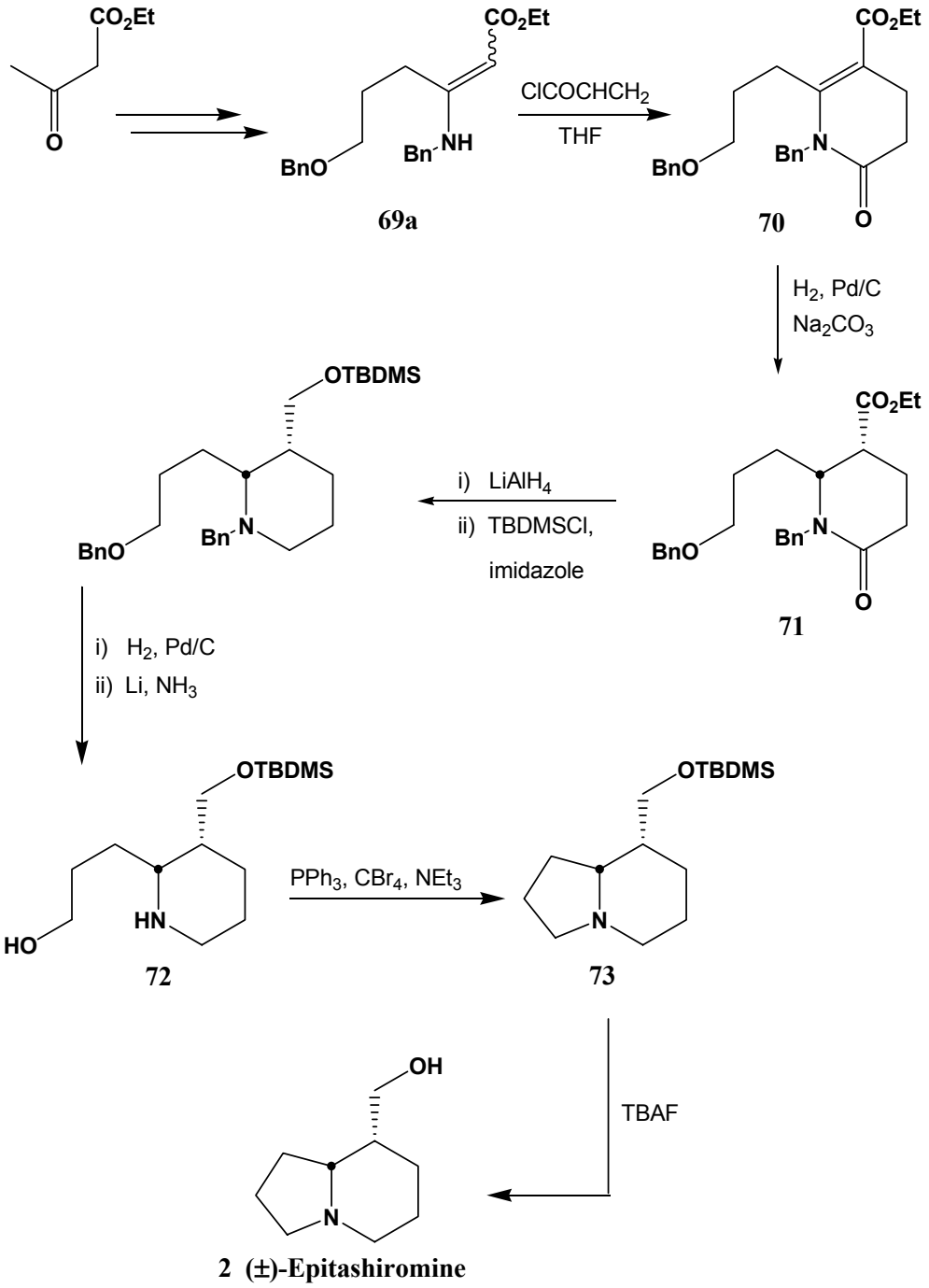
Paulvannan and Stille synthesised both tashiromine [**1**] and its unnatural epimer 8-epitashiromine [**2**] in racemic form by using an aza-annulation of *N*-alkylenamines with acryloyl chloride to form the indolizidine skeleton. As a general synthesis of azabicycles, the use of aza-annulation of imines and various acrylate derivatives has been quite popular,[109] but has in the past suffered from low yields and unwanted side products when acryloyl chlorides were used as the acrylate equivalent.[110] In order to overcome these limitations, enamines which have carbonyl substituents at the nucleophilic enamine carbon have been successfully used.[111][112] Stille and Paulvannan explored the aza-annulation of *acyclic* enamines with acryloyl chlorides to form lactams such those shown in **Figure 13**. This demonstrated the usefulness of this methodology in the synthesis of indolizidine/quinolizidine natural products, since the reaction of acyclic enamine substrates containing a β-electron-withdrawing group, such as ketones, esters, and amides, with acryloyl chloride resulted in the formation of six-membered nitrogen heterocycles.



EWG = **E**lectron **W**ithdrawing **G**roup

Figure 13 – Lactam Formation from Acyclic Enamines

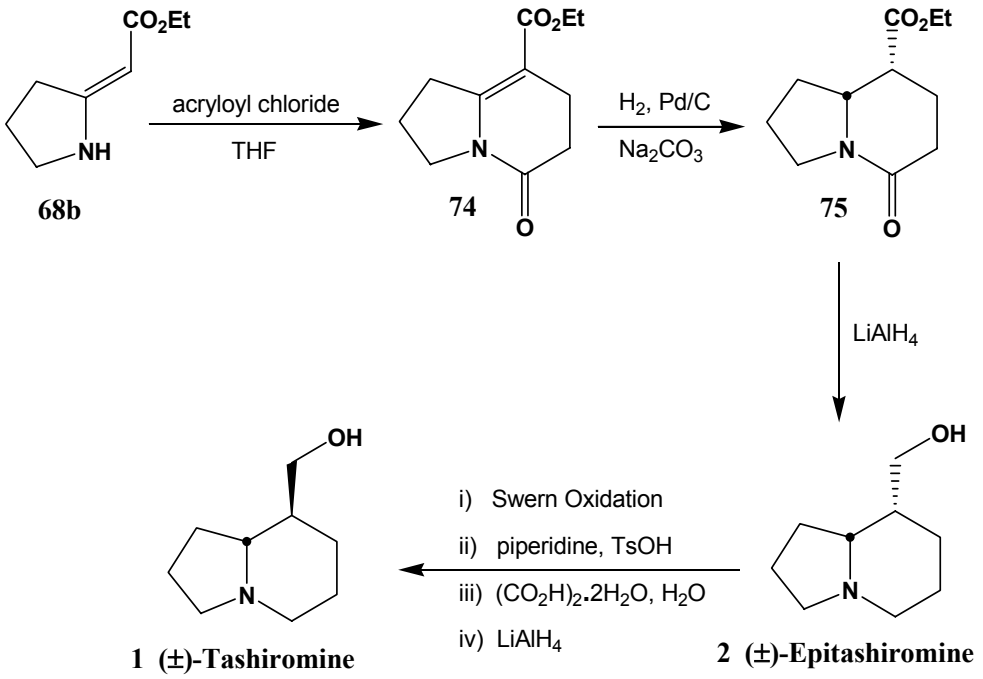
Epitashiromine [**2**] was synthesised from acyclic enamine **69a**, which was synthesised in two steps from ethyl 3-oxobutanoate (**Scheme 26**). Condensation of **69a** with acryloyl chloride gave the unsaturated lactam **70**. Stereoselective hydrogenation of **70** established the relative stereochemistry of the epitashiromine precursor. Reduction of the amide and ester functionalities of **71**, protection of the resulting primary alcohol as a silyl ether, and removal of both the benzyl protecting groups gave a substituted piperidine [**72**]. Annulation with PPh_3 / CBr_4 / NEt_3 gave the indolizidine ring system [**73**], and removal of the TBDMS protecting group completed the synthesis of epitashiromine [**2**].



Scheme 26 - Synthesis of (±)-5-Epitashiromine

For the synthesis of (±)-tashiromine [**1**], the cyclic enamine **68b** was synthesised. This circumvented the necessity for the later formation of the five-membered ring, and so the synthesis of tashiromine was considerably shorter

(Scheme 7). Condensation and accompanying annulation of **68b** with acryloyl chloride gave the indolizidine skeleton directly (i.e. **74**). Hydrogenation of **74** occurred stereoselectively as before to give **75**, which was transformed into epitashiromine [**2**] by reduction with $LiAlH_4$. Epimerisation to give (±)-tashiromine [**1**] was accomplished by an oxidation / epimerisation / reduction sequence.

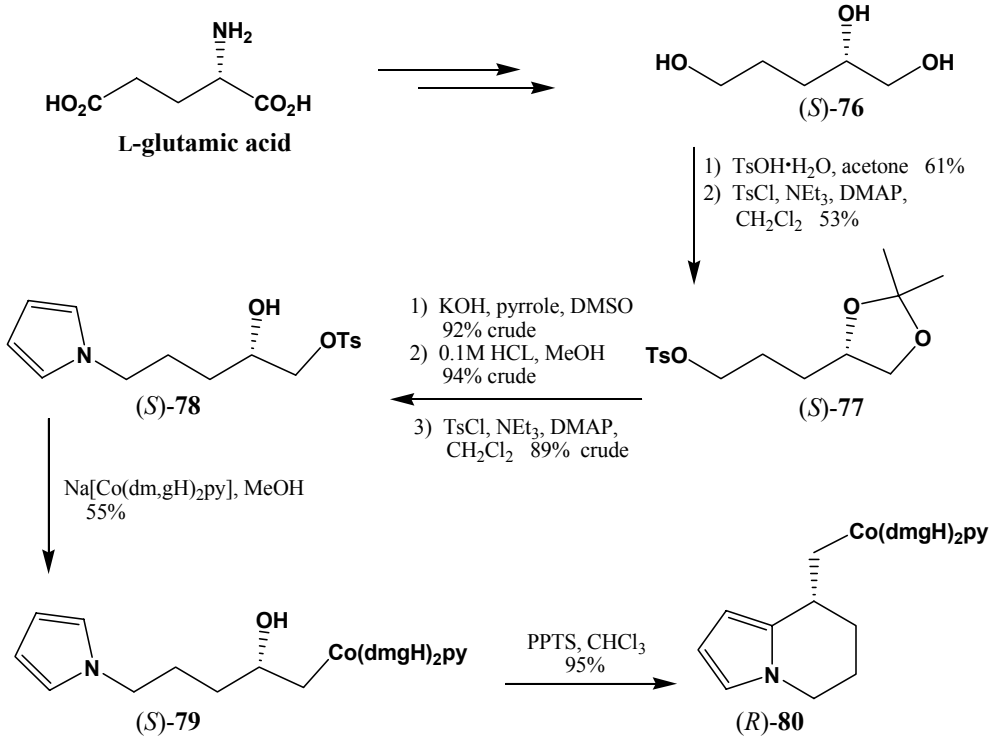


Scheme 27 - Short Synthesis of Tashiromine

Gage and Branchaud; (1997)[113]

The methodology used by Gage and Branchaud was to trap a cobaloxime π-cation with a suitably placed pyrrole to effect cyclisation. This gave a 6-exo cyclisation product that could be further elaborated to give enantiomerically enriched (–)-tashiromine and (+)-epitashiromine. Since the epimerization of racemic epitashiromine at C-8 to give racemic tashiromine is known,[108] this synthesis also completed the formal synthesis of (+)-tashiromine. Gage and Branchaud chose tashiromine to investigate the stereoselectivity of C–C formation in trapping a cobaloxime cation with a carbon nucleophile, since it is well known that trapping the cation with an oxygen nucleophile is highly stereoselective.

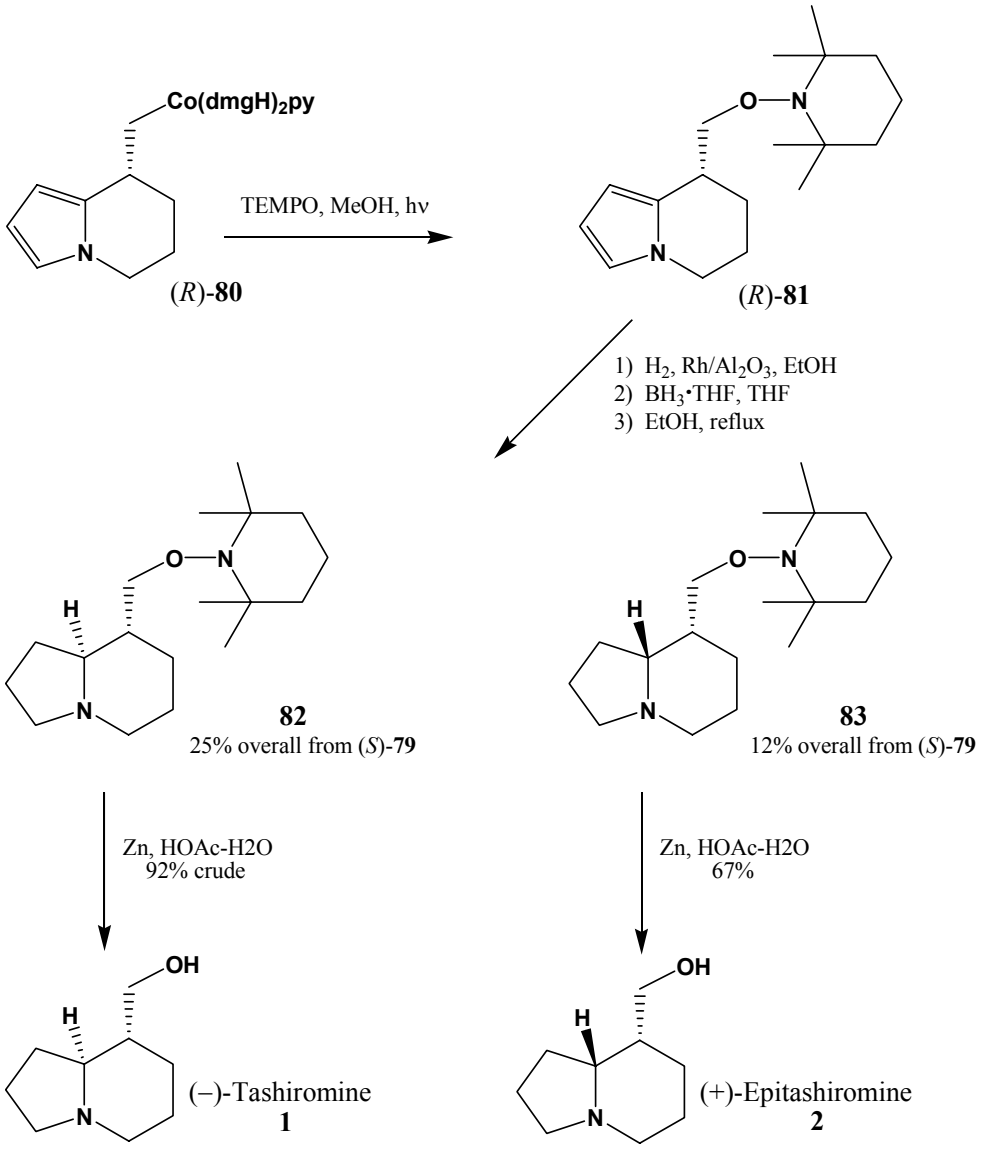
Enantiomerically enriched (*S*)-1,2,5-pentanetriol [**76**] was synthesised from L-glutamic acid in two steps (**Scheme 28**). Introduction of an acetonide group and conversion of the remaining alcohol functionality to a tosylate, gave compound **77**. Alkylation of a pyrrole anion with **(*S*)-77** and removal of the acetonide protecting group gave an *N*-substituted pyrrole from which monotosylate **78** was derived by selective tosylate formation at the primary alcohol in 96% e.e. Displacement of the tosylate with $NaCo(dmgH)_2Py$/MeOH gave the acid sensitive cobaloxime **(*S*)-79**. This key intermediate was cyclised to give exclusively the 6-exo cyclisation product **(*R*)-80**.



Scheme 28 – Synthesis of the Indolizidine Skeleton from a Cobaloxime

Photolysis of thermally unstable cobaloxime **(*R*)-80** with visible light (**Scheme 29**) in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) provided **(R)-81**. Direct transformation of **(R)-81** into the corresponding alcohol was unsuccessful, therefore the pyrrole ring of **(R)-81** was first reduced over 5% Rh/Al_2O_3 to give a mixture of diastereomers, which were separated by careful chromatography and deprotected to give pure **82** and **83**. The alkaloids (–)-

tashiromine [**1**] and (+)-epitashiromine [**2**] were obtained after nitrogen-oxygen bond cleavage. The stereochemistry of (–)-tashiromine [**1**] was confirmed by analysis of the Mosher ester of **1**.

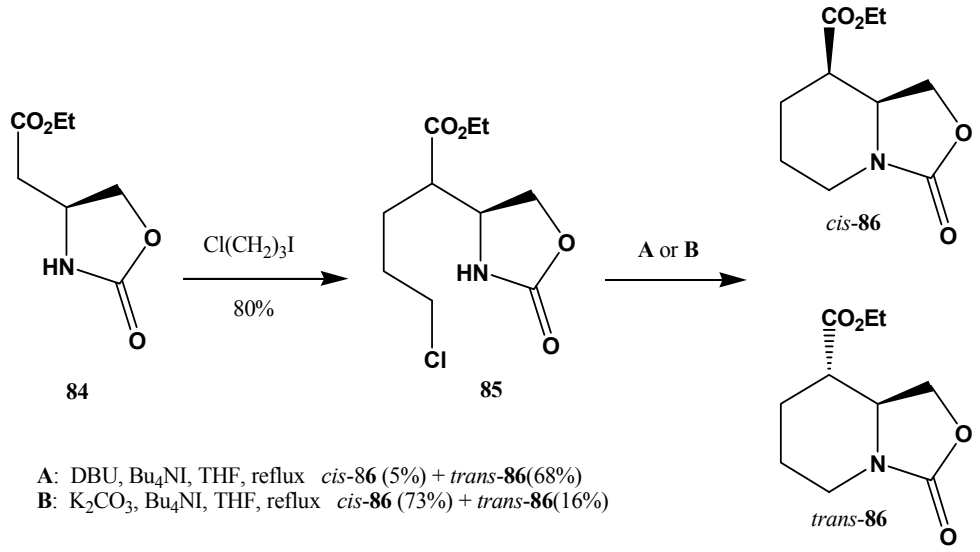


Scheme 29 - Completion of the Synthesis of Tashiromine and Epitashiromine

Deok-Chan Ha; (1998)[114]

Deok-Chan Ha recently published the first total synthesis of (+)-tashiromine by a diastereoselctive alkylation of (*S*)-4-carbethoxymethyl-2-

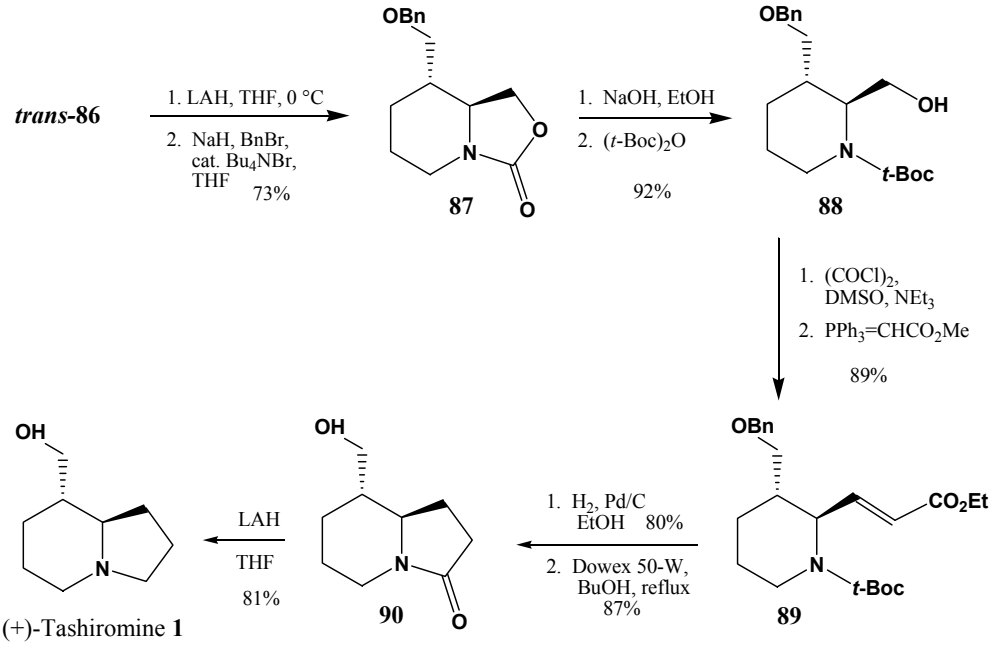
oxazolidinone [115]. Although alkylation of the 2-oxazolidinone [**84**] gave an inseparable mixture of diastereomers [**85**] (d.e. = 94%) cyclisation of **85** under refluxing conditions with a catalytic amount of Bu_4NI and a base gave a separable mixture of the *cis*- and *trans*-bicyclic carbamate **86**. Furthermore, by judicious choice of base, Ha was able to obtain either predominantly *trans*-**86** (using DBU) or *cis*-**86** (using K_2CO_3).



A: DBU, Bu_4NI, THF, reflux *cis*-**86** (5%) + *trans*-**86**(68%)
B: K_2CO_3, Bu_4NI, THF, reflux *cis*-**86** (73%) + *trans*-**86**(16%)

Scheme 30 – Selective Alkylation of (*S*)-4-Carbethoymethyl-2-oxazolidinone

Transformation of *trans*-**86** into (+)-tashiromine was accomplished in 34% overall yield, as shown in **Scheme 31**. Reduction and protection of the ester functionality as a benzyl ether gave **87**. Hydrolysis of this cyclic carbamate followed by protection of the piperidine nitrogen as a *t*-Boc carbamate gave the alcohol **88** in 92% overall yield. Swern oxidation of the alcohol followed by a Wittig reaction of the resulting aldehyde provided the unsaturated ester **89** in 89% yield. Catalytic reduction of the double bond of **89**, together with the concomitant removal of the benzyl protecting group gave a saturated ester that was converted to the indolizidine **90** by removing the *t*-Boc protecting. Finally, $LiAlH_4$ reduction of the carbonyl group of **90** in 81% yield gave (+)-tashiromine.



Scheme 31 – Synthesis of (+)-Tashiromine via Chiral Carbamates

Starting with the *cis*-carbamate *cis*-**86**, and employing the same methodology, Ha synthesised (+)-epitashiromine [**2**] (**Figure 14**), albeit in a lower overall yield of 26%.

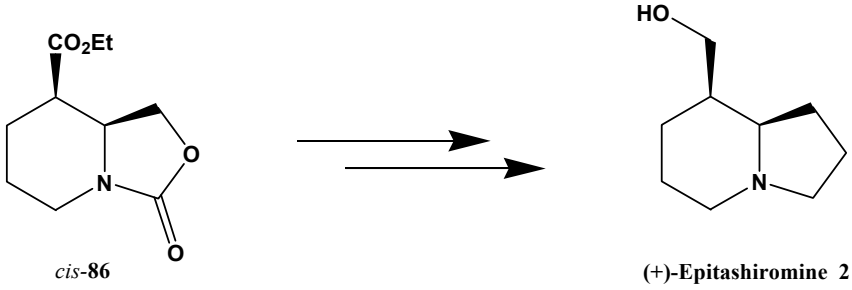
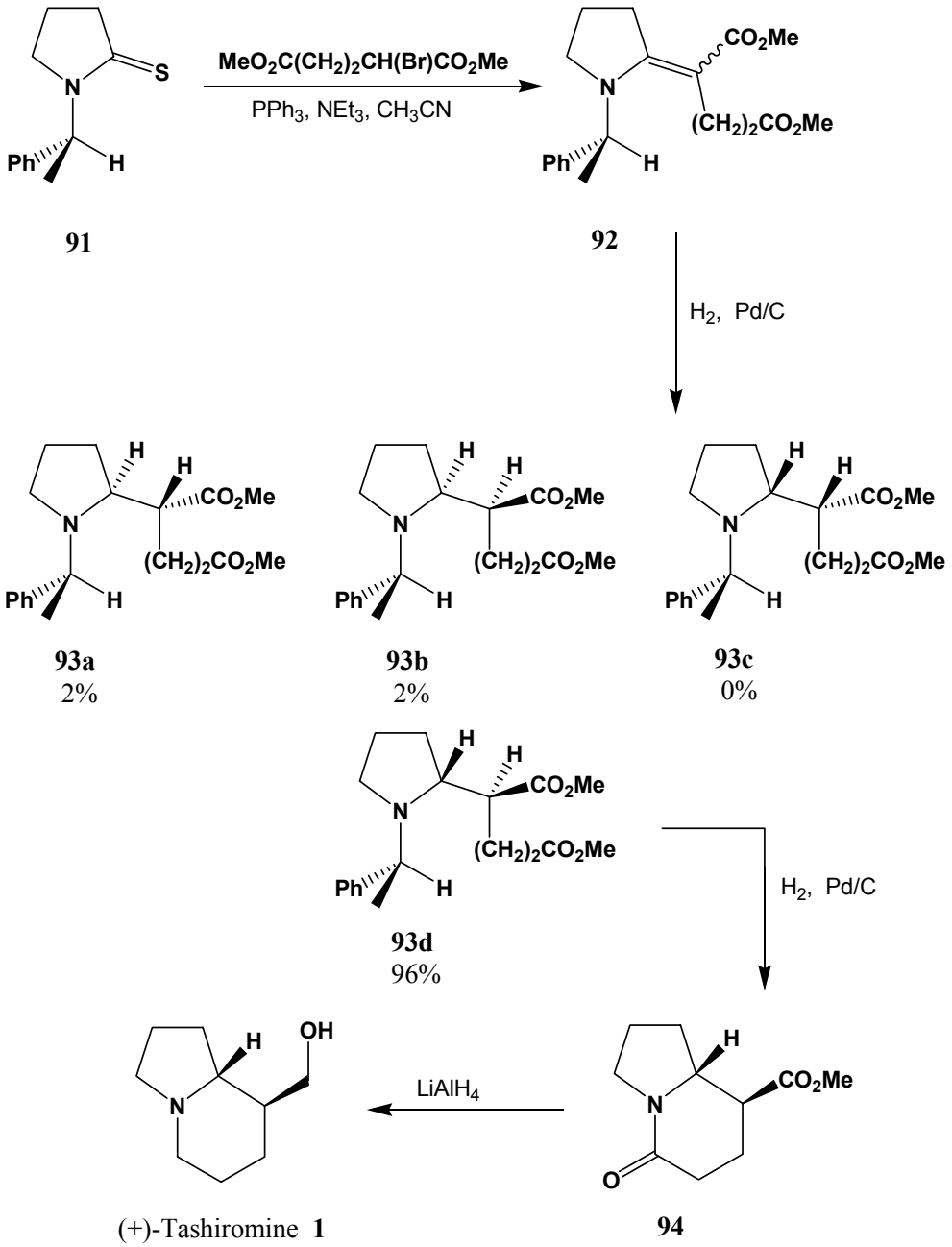


Figure 14 – Synthesis of (+)-8-Epitashiromine

Lhommet; (1999)[47]

The key strategy in the approach by Lhommet and co-workers was to use a chiral protecting group on the nitrogen atom of a pyrrolidine ring to control the stereochemistry of the reduction of various β-enamino esters containing an exocyclic ethylenic moiety. For the synthesis of tashiromine (**Scheme 32**), the

thiolactam 1-[1(*S*)-phenylethyl]pyrrolidine-2-thione [**91**] was synthesised from readily available pyrrolidone in good yield. The α-enamino ester **92**, with an exocyclic double bond, was synthesised from **91** and dimethyl 2-bromopentanedioate by Eschenmoser coupling and was obtained as an inseparable diastereomeric mixture of *E*/*Z* isomers in the ratio of 65:35. Catalytic reduction of the enamino ester furnished a mixture of three or four diastereomers [**93a** – **d**] depending on conditions. Careful control of the reaction conditions (0.04 eq of 10% Pd/C) led to a significant improvement of the diastereoselectivity (yield of major isomer increased from 58% to 96%), and a reduction in the amount of unwanted debenzylation. The stereocenters were now established with the desired configuration, so the α-methylbenzyl group, having served its purpose of stereochemical control, could be removed. Removal of the α-methylbenzyl group in the presence of Pd/C, and subsequent cyclisation gave rise to the bicyclic lactam ester **94**, which was further reduced with lithium aluminium hydride to give (+)-tashiromine [**1**].

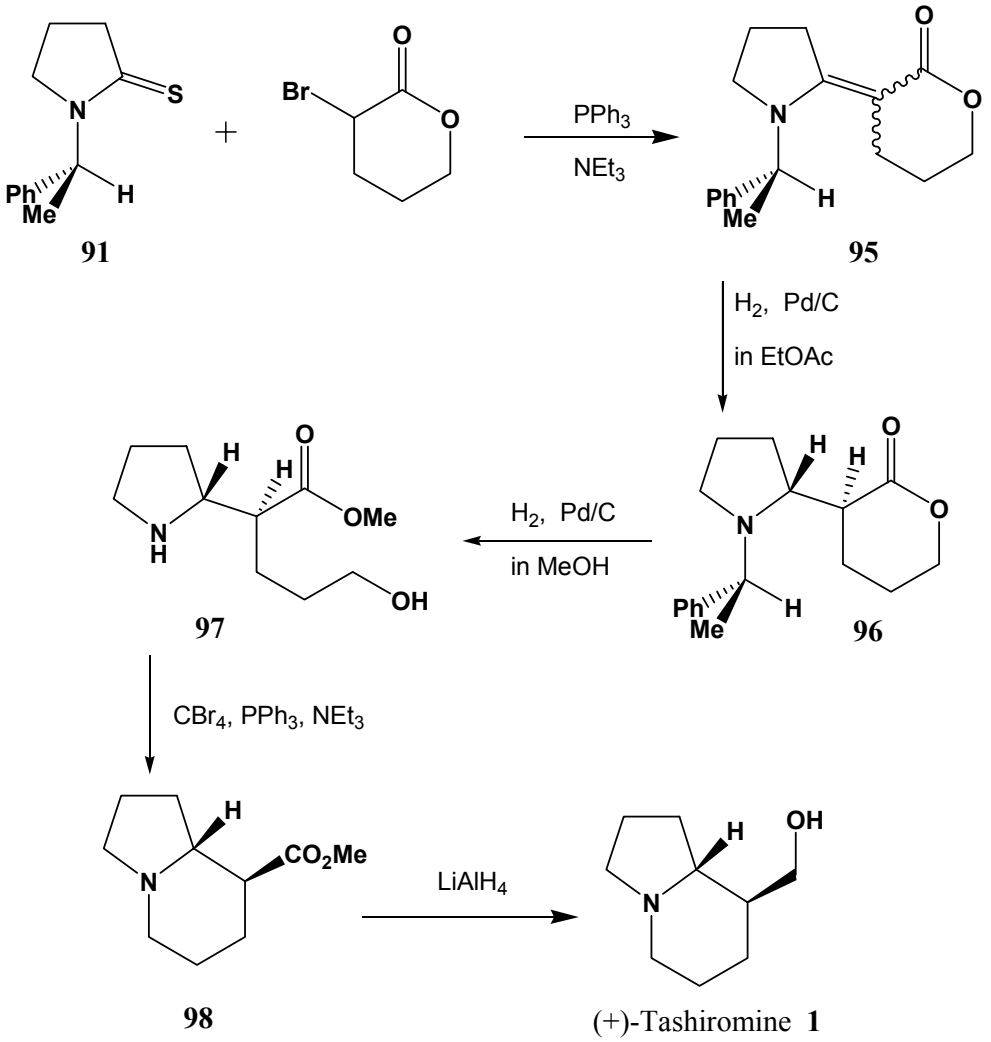


Scheme 32 - Synthesis of (+)-Tashiromine via Protected Lactam

Lhommet; (2001)[116]

In an extension of the previous method, the use of bromo lactones instead of α-substituted bromo esters used above, led to the synthesis of (+)-tashiromine in an enantiomerically pure form.

According to the authors, the use of bromo lactones always led to the formation of the tetra-substituted enamino lactones, while in the case of the esters, condensations were not successful when using six-membered ring thiolactams. As can be seen from **Scheme 33**, the synthetic methodology is similar to that shown above



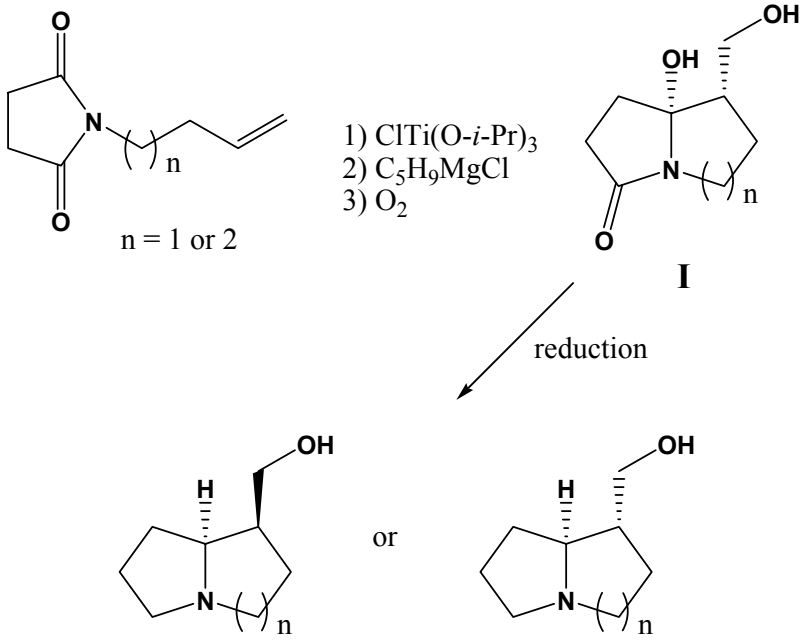
Scheme 33 – Synthesis of Tashiromine via Bromolactone and Protected Lactam

The selected lactams were protected on nitrogen using (*S*)-α-methylbenzylamine and thionated with P_4S_{10} and subjected to Eschenmoser sulfide contraction reactions using a suitable bromo lactone. The resulting chiral β-enamino lactones [**95**] were then reduced under hydrogen to give a number of amino lactone

diastereomers that could be separated. The particular diastereomer of interest to the synthesis of tashiromine [**96**] was obtained in 55% yield and d.e. >99%. The nitrogen protecting group was removed to give **97**, and cyclisation effected via displacement of an alkoxyphosphonium salt. The bicyclic ester **98** was reduced as before in $LiAlH_4$ to yield the (+)-tashiromine in 25% yield. Spectroscopic data and optical rotation for this compound were in good agreement with those data obtained previously for the enantiomerically pure (+)-tashiromine [**1**].

Kim Kim Lai and Cha; (2000)[117]

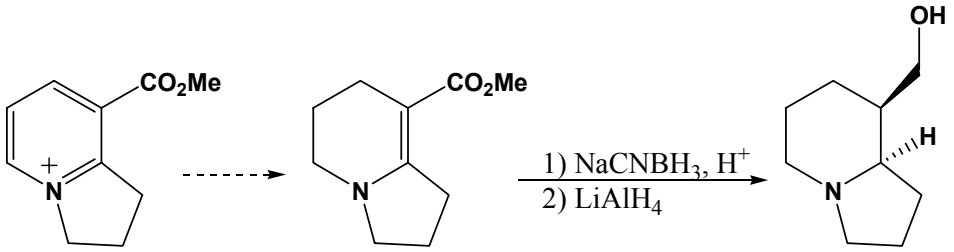
Cha and co-workers probed the stereocontrolled reduction of *N*-acylaminals (**I** in **Scheme 34**) to set up the core of tashiromine and other indolizidines, as well as a number of pyrrolizidines. Since several of these alkaloids are required as both the *trans*-reduced and *cis*-reduced forms this methodology offers an attractive way of obtaining both sets from a common precursor by simply selecting suitable reduction conditions. As with most other syntheses, the catalytic reduction gave access to epitashiromine and borane reduction produced the *trans*-reduced indolizidines such as tashiromine [**1**].



Scheme 34 – Reduction of *N*-Acylaminals for the Synthesis of Indolizidines

Bates and Boonsombat; (2001)[49]

This short synthesis of racemic tashiromine from an acyl pyridinium salt has already been highlighted (see **Scheme 11** Section 1.2) as a valuable contribution to general routes to indolizidines. The use of acidic cyanoborohydride conditions to produce only the *trans*-reduced diastereomers from hexahydroindolizine **98** is identical to the technique we followed in producing racemic tashiromine from various esters or amides.

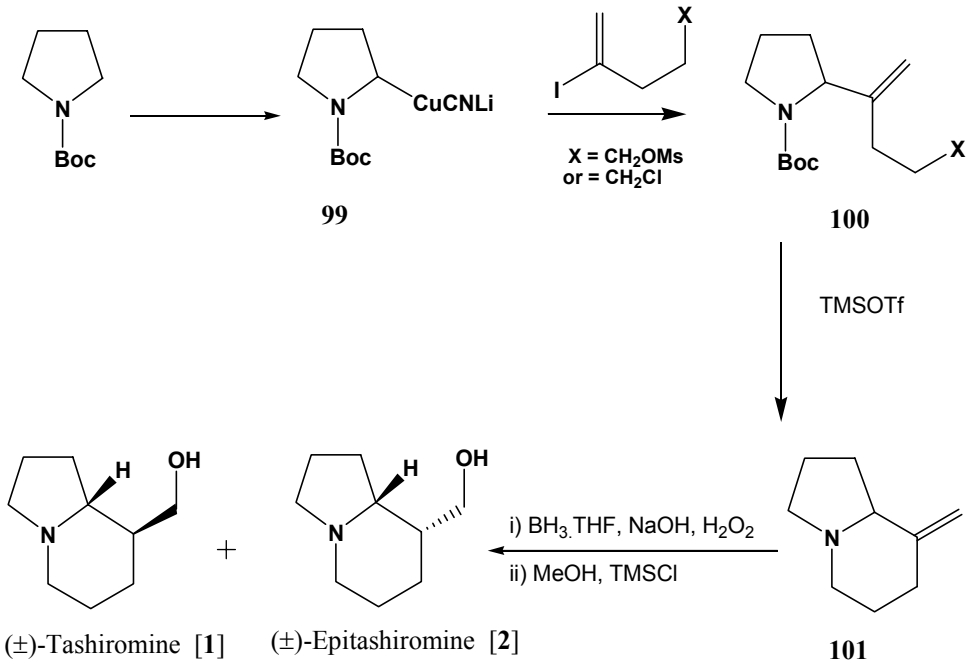


39 **98** (±)-Tashiromine **1**

Dieter and Watson; (2002)[118]

The latest reported synthesis presented here was used as a proof of concept in using α-(*N*-carbamoyl)alkylcuprates and functionalised vinyl iodides to set up systems that could be elaborated to give a range of alkaloids, particularly pyrrolizidine and indolizidines. Tashiromine was synthesised in this manner as the racemate and was isolated together with racemic epitashiromine.

The synthesis involves the short two step route outlined in **Scheme 35**, starting from *N*-Boc protected pyrrolidine. Deprotonation and addition of CuCN resulted in the formation of an organo cuprate [**99**], which was then "vinylated" using various substituted vinyl iodides to give compound **100**. Deprotection and cyclisation was effected in one step to give 8-methylenoctahydroindolizine [**101**], and finally hydroboration/oxidation provided the necessary hydroxyl functionality. The ratio of (±)-tashiromine to (±)-epitashiromine was 7:3, after cleavage of the initially formed amine-boron complexes.



Scheme 35 – Cuprate Mediated Synthesis of (±)-Tashiromine and Epitashiromine

Chapter 2

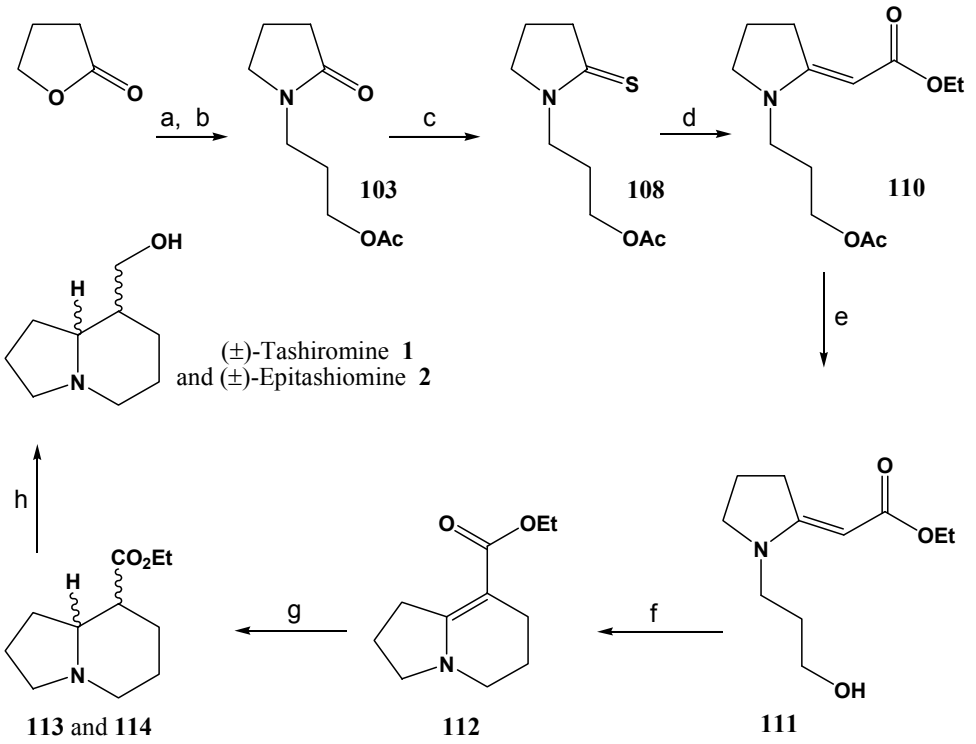
Results and Discussion of a Model Synthesis of (±)-Tashiromine and (±)-Epitashiromine

2.1 Synthesis of Thiolactams

We first undertook a model study of the synthesis of the indolizidine core, experimenting with conditions and reactions in order to maximise the yields for the remainder of the investigations. Both tashiromine and epitashiromine were successfully synthesised in this study in their racemic form. The following discussion explores some of the reactions used to achieve this. Since this is part of a general synthetic approach many of the observations can be extended to the entire project, and these are dealt with together here.

Since the synthesis of both diastereomers of methylindolizidine-8-carboxylate has been accomplished in our laboratories,[67] the purpose of the model study was mainly to attempt to improve the yield of the rather low yielding cyclization step, and secondly to have a "yard-stick" against which we could assess the stereoselective efficacy of the various chiral auxiliaries, by acquiring the data from the racemic alkaloids, neither of which have been synthesised in our laboratories before.

The synthesis of (±)-tashiromine and (±)-8-epitashiromine is outlined in **Scheme 36**, which serves as a reference point from which each step will be discussed in detail.



Scheme 36 – Model Synthesis of Racemic Tashiromine and Epitashiromine

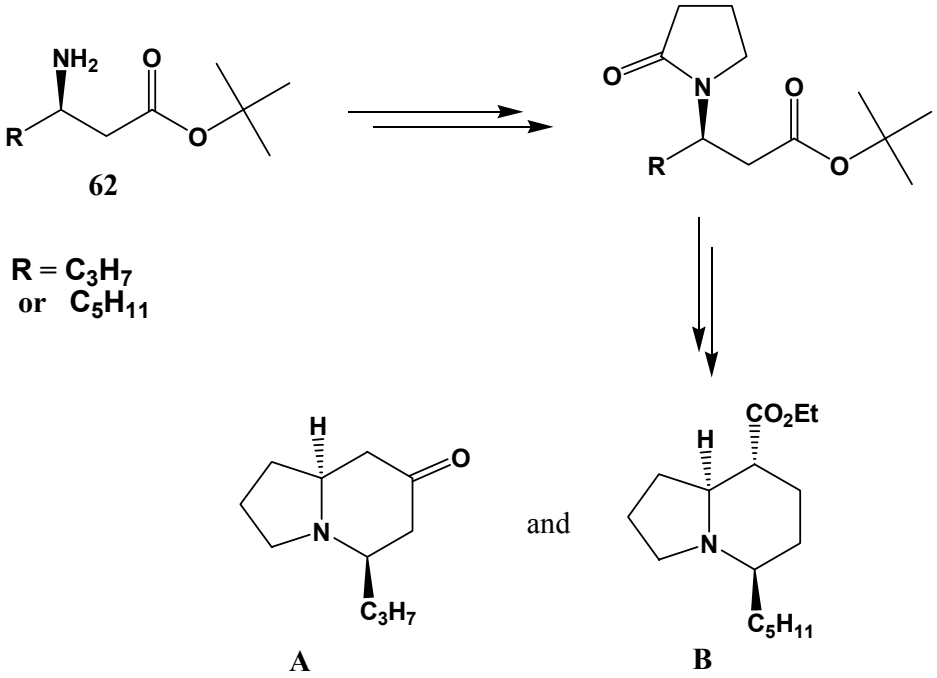
a) $NH_2(CH_2)_3OH$, b) Ac_2O AcOH, c) P_2S_5, d) $BrCH_2CO_2Et$, PPh_3, NEt_3, e) KOH, EtOH f) PPh_3, imidazole, I_2, g), H_2 PtO_2/H_2 h) $LiAlH_4$, ether.

2.1.1 Synthesis of lactam 103

Lactams such as **103** (the acetate ester of **102**) have traditionally been synthesised in our laboratories by one of two general procedures. The first procedure involves the condensation of a lactone and an amine in a Carius tube at ca. 250 °C for several hours. These rather harsh conditions, developed by Reppe[119] for the synthesis of several *N*-substituted lactams, are often not compatible with further functionality in the lactones or the amines. In the synthesis of *N*-aryl lactams for example, Chang[56] reported that the yields for this reaction were variable, and often low. In these cases, the second method, developed by Manhas and Jeng,[120] is usually employed. In this two-step method, the primary amine is first treated with 4-chlorobutanoyl chloride (or the bromide equivalent) to give an amide. The amide is then treated with a base to effect cyclisation by displacement of the second halide. This method has proven useful

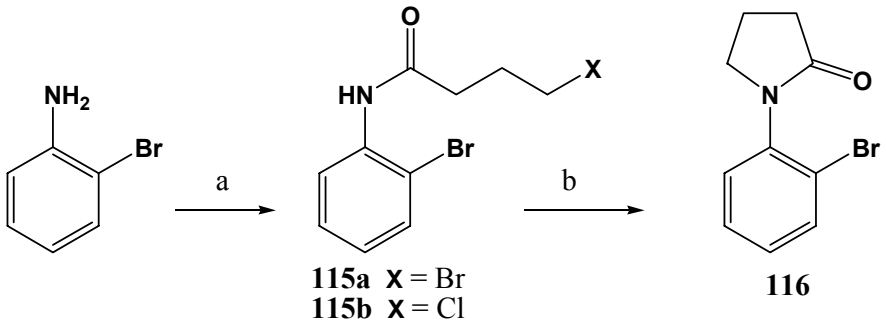
in our laboratories for the synthesis of rather more complex *N*-substituted pyrrolidin-2-ones and related lactams, which might not otherwise survive the harsh conditions of the sealed tube method.

An example of this second method is provided in the work of Gravestock, where in order to maintain the stereochemical integrity of precursor amines **47** (**Scheme 37**), the harsh sealed-tube conditions were avoided. These chiral amines were used in the partial enantioselective synthesis of indolizidine alkaloids (–)-167B (from **A** in **Scheme 37**), and (–)-209B (from **B** in **Scheme 37**). [121][58]



Scheme 37: - Enantioselective Synthesis of Precursors to Indolizidine Alkaloids (–)-167B and (–)-209B

Stanbury also used this two-step procedure for the synthesis of *N*-aryl lactams (**Scheme 38**). The condensation of 4-bromobutyryl bromide with 2-bromoaniline, for example, gave the intermediate bromoamide [**115a**] in 88% yield. Treatment of this product with sodium hydride in DMSO completed the annulation to the desired *N*-(2-bromophenyl)pyrrolidin-2-one [**116**] in 50% yield. Stanbury also found that the use of excess ethylmagnesium chloride as a base led to greatly improved yields.

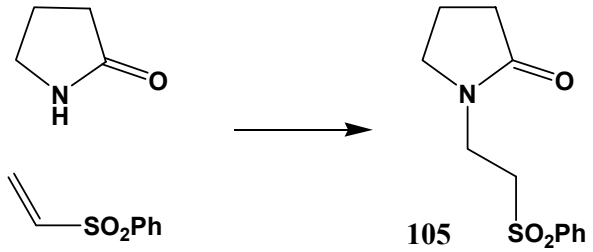


Scheme 38 - Synthesis of *N*-Aryl Lactams

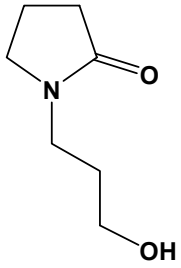
a) $Br(CH_2)_3COBr$, benzene, reflux (88%) or $Cl(CH_2)_3COCl$, Na_2PO_4, $CHCl_3$ (96%); b) NaH / DMSO, 8 h (50%) or NaOEt / EtOH, (98%).

In our laboratories, Wilson found improved reaction yields in the above scheme by using 4-chlorobutyryl chloride in the presence of disodium hydrogen phosphate (2 eq.) in chloroform for the first step of the reaction. This gave the corresponding intermediate *N*-(2-bromophenyl)-4-chlorobutyramide [**115b**] in 96% yield.[65] The use of sodium ethoxide instead of sodium hydride gave the required cyclized *N*-(2-bromophenyl)pyrrolidin-2-one [**116**] in 98% yield.

A third method sometimes used in our laboratories for synthesizing *N*-substituted lactams involves the conjugate addition of a suitable activated alkene precursor to a secondary lactam to give the corresponding *N*-substituted tertiary lactam. This method usually works well on thiolactams (*vide infra*), and hence circumvents the need for protecting groups during the thionation step. In this project by way of example, lactam **105** was synthesised by this method.



For the purpose of this model study, however, we chose to use the sealed-tube method, since it gave high yields of the resulting simple lactams, and does not require any expensive reagents or techniques. The work-up for this reaction also makes it the method of choice, since the major by-product (water) can simply be removed *in vacuo*.



102

Thus, 1-(3-hydroxypropyl)pyrrolidin-2-one [**102**] was formed in 93% yield in several gram quantities from the reaction of pyrrolidin-2-one with 3-aminopropanol, after approximately 18–24 h. Prolonging the reaction did not improve the yields, and led in fact to very dark products, with slightly decreased yields. Both the starting materials for this reaction were used as received, as this reaction seems to be tolerant of several impurities (pyrrolidin-2-one can decompose on standing to the open-chain derivatives, but even old stock of this chemical gave good results). This compound has been widely used in the synthesis of several indolizidines and indolizidine precursors in our laboratories,[67] and hence the spectroscopic data are well documented, and confirm the formation of the product. These data include the characteristic infrared absorptions at $\tilde{\nu}$ = 3400cm^{-1} (br. OH), and 1665 (C=O), as well as a clean ^{1}H NMR spectrum showing the absence of amine protons. The presence of four triplet signals and two triplets of triplets shows the presence of six methylene groups, as does the DEPT spectrum. A slightly broadened signal at δ = 3.8 is consistent with the OH functionality.

During the project the tube furnace used for this reaction broke, and an attempt was made to synthesise this lactam by irradiating a mixture of γ-butyrolactone and 3-amino propanol with microwaves in a conventional microwave oven. Although the reaction did not go to completion, the crude ^{1}H NMR spectrum indicated the formation of the product after only a few minutes. Fractional distillation of the crude residue gave the pure lactam **102** in 38% yield, together with recovered starting materials (30–40%) and a small amount (5%) of an unidentified product. This microwave reaction was not optimised, but may be a useful alternative in the synthesis of lactams.

2.1.2 Synthesis of Thiolactam 108

2.1.2.1 Protection of Hydroxyl Group

The lactams formed by the above methods were converted into the corresponding thiolactams. This again can be accomplished by several methods, but the reaction conditions and those of later steps are not tolerant of free hydroxyl groups, and so these had to be protected first. We chose to protect the hydroxyl as the acetate for ease of protection and deprotection, and the generally high yields associated with these two steps. This was accomplished by treating 1-(3-hydroxypropyl)pyrrolidin-2-one [**102**] with acetic anhydride in the presence of pyridine as a solvent. The reaction was monitored by TLC, and was complete in about 5 hours. Aqueous workup resulted in a colourless oil that was confirmed by spectroscopic analysis to be 3-(2-oxopyrrolidin-1-yl)propyl acetate [**103**]. The disappearance of the hydroxyl absorption in the infra-red spectrum at $\tilde{\nu}$ = 3400, and the presence of two very strong carbonyl absorptions at $\tilde{\nu}$ = 1735 and 1674, due to the acetate carbonyl and pyrrolidin-2-one carbonyl groups, respectively, are clear indications of the identity of the product. ^{1}H NMR and ^{13}C NMR spectra were consistent with previous data reported for this compound. The rather uncomplicated set of triplets and triplet of triplets is easily interpreted. Once again, this was a well-known compound in our laboratories, and no further characterisation was necessary.

2.1.2.2 Thionation

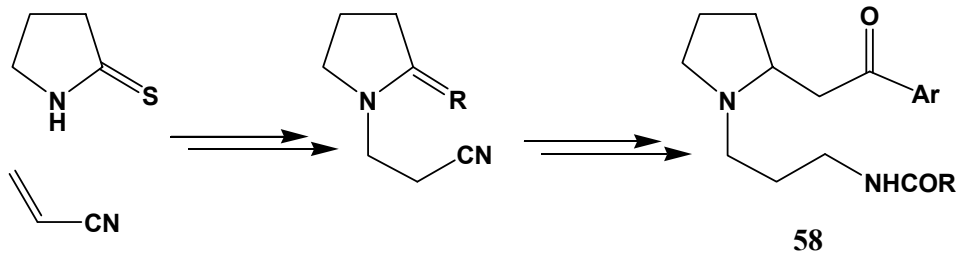
The traditional procedure used in our laboratories for converting an oxygen carbonyl to a sulfur carbonyl (thionyl) is to use the Brillon reagent,[122] which is generated *in situ* by the addition of equimolar quantities of phosphorus pentasulfide and sodium carbonate to tetrahydrofuran (THF) at room temperature. The reagent apparently has the formula $Na_2P_4S_{10}O$. This procedure is, however, impractical and expensive for the large-scale synthesis of thiolactams, owing to the copious amounts of THF required. An attempt was made to recover the THF

for further similar reactions, but this solvent remains extremely odoriferous even after several distillation steps.

Alternative procedures involve the use of either phosphorus pentasulfide or Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] in benzene or toluene under reflux. Hosken used this method in our laboratories for the conversion of *N*-aryl lactams into the corresponding thiolactams.[63] The work of Raucher and Klein showed that thioamides could be synthesised by irradiating a mixture of the amide and phosphorus pentasulfide (1–1.5 eq.) in THF in an ultrasonic cleaning bath at 30–40 °C for 1–2 h.[123] Hosken modified this procedure by using benzene instead of THF to synthesise *N*-aryl pyrrolidine-2-thiones conveniently in a 70–80% yield.[63]

A further modification of this procedure by Stanbury led to improved yields of several *N*-aryl thiolactams.[59] Stanbury used an ultrasound cleaning-bath to irradiate a mixture of the amine and phosphorus pentasulfide in cycles of 15 minutes, followed by 15 minutes without irradiation. This method allowed for prolonged reaction times (up to 2 days), without the disadvantage of excessive heating of the reaction mixture by the ultrasound irradiation, and showed yields of 70–97% for the *N*-aryl thiolactams.

A convenient way of synthesising *N*-substituted thiolactams that are sensitive to the thionation step is to introduce the nitrogen substituent by a Michael addition of a *thiolactam* to a suitable acceptor. This has already been used successfully in our laboratories with both lactams and thiolactams. An example of this reaction in our labs is provided in the Parsons' synthesis of a precursor to *O*-methylperipentadenine [**58**] (**Scheme 39**), where one of the initial steps was the conjugate addition of pyrrolidine-2-thione to vinyl nitrile.

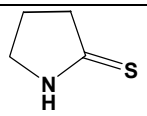
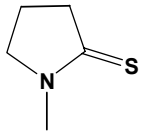
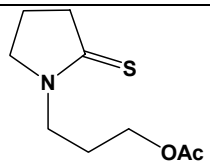
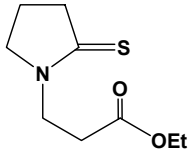
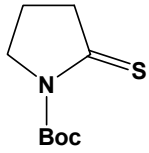
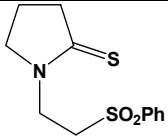


58

Scheme 39 – Conjugate Addition in the Synthesis of *N*-Substituted Thiolactams

In this project, the thiolactams were conveniently synthesised using any one of these general procedures (GP's). Usually the sonication procedure was used for larger quantities (**GP-1C**), due to the convenience of the reaction (room temperature, can be left for prolonged times, low cost), and the Brillon procedure (**GP-1A**), or Lawesson's reagent (**GP-1D**) were reserved for smaller quantities, or for more sensitive substrates. The use of refluxing solvent conditions with P_2S_5 (**GP-1B**) was used as an alternative to sonication. It was possible to synthesise a range of thiolactams (**Table 1**) by employing one of the above methods.

Table 1 – Yields of Thiolactams

Thiolactam		Yield (Method)[*]
106		86% **GP-1A**[a] or **GP-1C**[c]
107		66% **GP-1A** 69% **GP-1B**[b] 70% **GP-1C**
108		72% **GP-1A** 77% **GP-1B** 92% **GP-1C**
109		95% by Michael addition of pyrrolidine-2-thione to ethyl acrylate
117		59% by **GP-1D**[d] 72% by reaction of pyrrolidine-2-thione with $(Boc)_2O$
118		99% by Michael addition of pyrrolidine-2-thione to phenyl vinyl sulfone

[*] GP refers to the General Procedures in the Experimental Section (Chapter 9).
[a] **GP-1A** = standard Brillon protocol, [b] **GP-1B** = in refluxing benzene or toluene in the presence of P_2S_5, [c] **GP-1C** = ultrasonic irradiation with P_2S_5, [d] **GP-1D** = use of Lawesson's reagent in refluxing benzene or toluene.

Apart from the *N*-Boc protected thiolactam [**117**], these thiolactams were not new compounds in our laboratories, and the spectroscopic data provided a good fit with data previously published. A good indication of the presence of the thiocarbonyl carbon is provided in the ^{13}C NMR spectra of these compounds, which shows up in the sparsely populated δ = 200 range, as a typically small signal. For example, thiolactam **108** used in this model study shows this signal at δ = 201. The remaining NMR signals are largely unchanged with respect to the those of the starting material, with the exception of the signals adjacent to the thiocarbonyl, which tend to shift to lower field strengths (by 0.7 ppm for the ^{1}H signal and 14 ppm for the ^{13}C signal).

The IR spectra also indicate the presence of a thiocarbonyl band at between 1110 and 1130 cm^{-1}, (in this compound at $\tilde{\nu}$ = 1121) shifted from the usual carbonyl position at around 1700 cm^{-1}. It should be noted, however, that the position of this band deep in the fingerprint region and the presence of the carbonyl stretch from the acetate group make this spectroscopic evidence unreliable on its own.

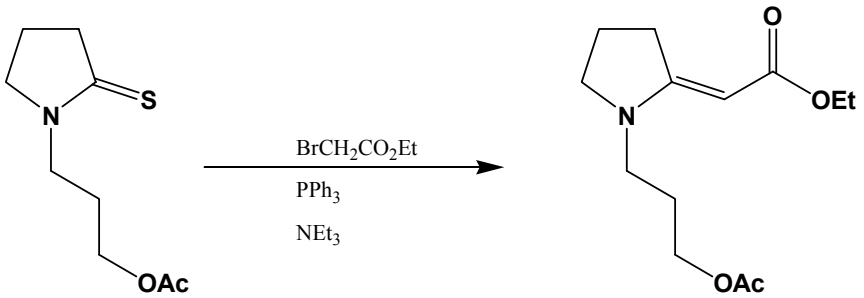
The thiolactams were easily purified, and in this case before further elaboration towards the racemic tashiromine distillation of the product gave a high yield (>90%) of a clear oil. These thiolactams tend to be viscous oils or gums and hence accurate elemental analyses were difficult for us to obtain. We were, however, able to investigate their mass spectra (HRMS) or low resolution spectra using various fragment trapping techniques (MS/MS or SIS), and we are confident that these compounds were successfully produced. In compound **108** the selective storage (SIS) of the molecular ions at m/z = 201 and 203 showed a relative ratio of these ions of 100:4, which is consistent with the natural abundance of ^{34}S of 4.5% relative to that of ^{32}S. In general the presence of this heavier isotope of sulfur provided a further verification of the success of the thionation reactions. The techniques required for the selective ion storage were, however, only available at a very late stage in the project and could unfortunately not be used routinely during the synthesis.

2.2 Synthesis of β-Acyl Enaminones

2.2.1 Synthesis of β-Acyl Enaminones 110

Sulfide Contraction

Synthesis of the enaminones was the next step in the model study. This was accomplished using the well-known Eschenmoser sulfide contraction, already described in detail in the preceding chapter (Section 1.2). When the protected pyrrolidine-2-thione [**108**] was treated with ethyl bromoacetate, it formed an α-thioiminoether salt. This reaction was readily accomplished and monitored in either THF or CH_3CN. Traditionally CH_3CN has been used for these reactions, but the use of THF, besides giving the advantage of being able to observe the salt formation as it precipitates from the solution, improved the overall yield of the sulfide contraction (in this case from around 64% to a maximum of 89%). This improvement is likely to be due to the fact that that the salt formation is an equilibrium reaction, therefore precipitating the salt from the solution drives the equilibrium toward the formation of the product. The salts are not generally isolated, and hence were not characterised. If THF was used, this was removed *in vacuo*, and replaced with acetonitrile. In the case of performing the salt formation in acetonitrile, this was obviously not necessary. The addition of triphenylphosphine as the thiophile, along with triethylamine as a base, resulted in the extrusion of sulfur to give the vinylogous urethane **110**.



108 **110**

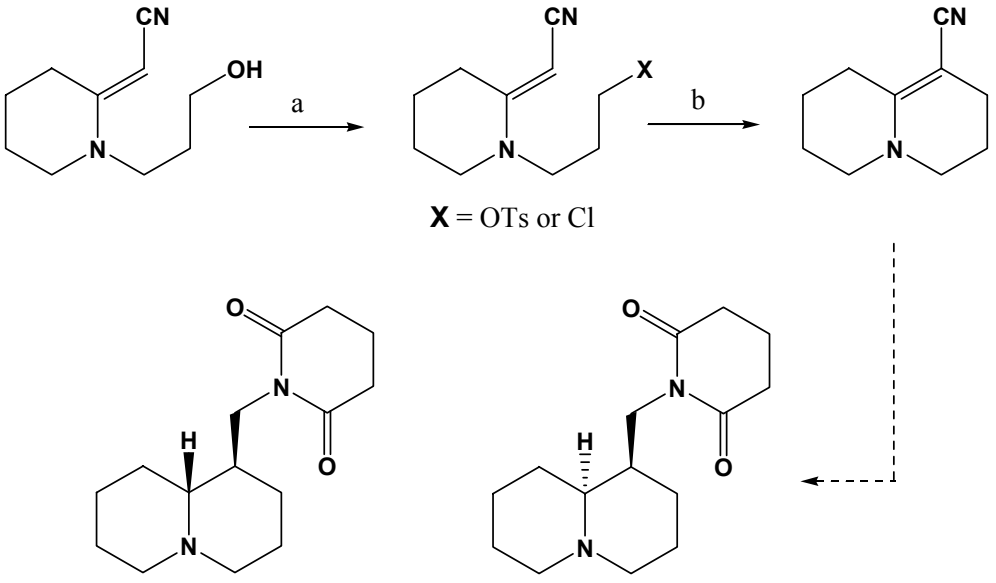
Scheme 40 – Formation of a Vinylogous Urethane by Sulfide Contraction

Again, many of these and other "vinylogous" compounds have been synthesised before in our laboratories and their identification was easily achieved

by comparison of spectral data with those obtained previously. Two key common features are the disappearance of thione signals (especially noticeable in the ^{13}C NMR, and to a lesser extent in the IR spectra), and the appearance of a vinyl hydrogen signal in the ^{1}H NMR spectra. This latter signal usually occurs in a unique part of the spectrum (δ = 4–6), as a singlet, and is thus easily identified. Here this signal is a sharp singlet at δ = 4.53. The shape of the signal seems to depend to some extent on the purity of the compound; with compounds of higher purity generally showing sharper signals, although the origin of this signal broadening is obvious since there are no noticeable impurity signals. There appears to be some evidence of a relationship between the position of the vinyl hydrogen signal and its acidity. No formal study on this phenomenon has been undertaken, but since our laboratories have synthesised a large variety of related compounds, we have been able to examine this informally. This also manifests itself, among other ways, in the ease with which we can accomplish the cyclisation reactions, and this is examined in more detail in chapter 6 (section 6.1).

2.3 Synthesis of the Indolizidine Skeleton

Various routes in our labs have traditionally ensured the formation of the second ring in the indolizidine (and related quinolizidine) skeleton, but they usually rely on one key transformation: the intramolecular nucleophilic displacement of a suitably placed leaving group (Step b in **Scheme 41**). In the synthesis of (±)-lamprolobine [**46**] and (±)-epilamprolobine,[90] Jungman used a tosylate (OTs), formed *in situ* for the cyclization (**Scheme 41**). Small quantities of the chloride were also isolated. It was later discovered that chlorides could be used to accomplish the cyclization by first converting them into the iodide by a halogen exchange reaction such as that developed by Finkelstein.[124]



Scheme 41 - Synthesis of (±)-Lamprolobine [**46**] and (±)-Epilamprolobine

a) NaH, *p*-TsCl / THF, b) CH_3CN, Δ, (70% overall)

Malefetse[67] conducted a study on the effect of different leaving groups (**X**), in relation to the vinylogous moiety (**Z**), and found that the greatest yields were achieved where the leaving group (**X**) was a halide, particularly an iodide (**Figure 15**).

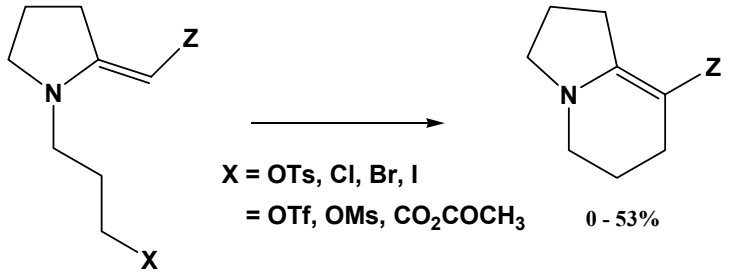
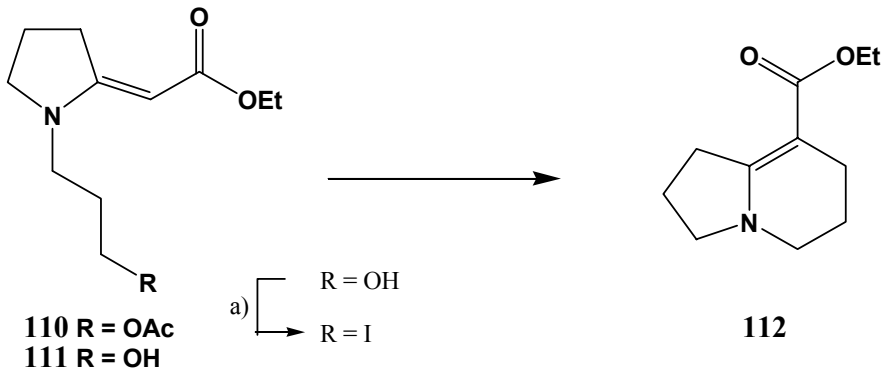


Figure 15 – Effect of Leaving Group on the Formation of the Indolizidine Skeleton

Using these results the indolizidine skeleton for the racemic tashiromine synthesis was constructed by an intramolecular displacement of the iodide. Conversion of the acetate in **110** into a suitable leaving group is accomplished in two steps: hydrolysis of the acetate to the alcohol [**111**], and conversion of the alcohol into a halide or other leaving group. In most cases, the latter compound is not isolated, but immediately cyclises under the reaction conditions to give a compound such as vinylogous urethane **112** (**Scheme 42**).



a) Triphenylphosphine, Imidazole, I_2

Scheme 42 – Formation of the Indolizidine Core

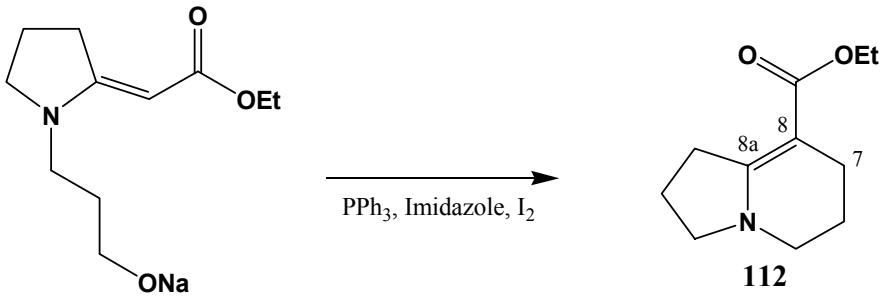
The hydrolysis of the ester was achieved in quantitative yields by stirring the acetate in a basic methanolic solution at room temperature. These alcohols were in general not easily purified, as they retained traces of methanol and moisture (as is evident from NMR studies), and hence tended to remain as viscous oils or gums. Attempts to dry the gums by leaving the material under vacuum

resulted in extensive foaming and loss of material. The alcohol functional group, could, however, be identified from the IR spectra (broad absorption at around $\tilde{\nu}$ = 3300 cm^{-1}), and the NMR spectra (a singlet at about δ = 4 easily exchanged with deuterium in a D_2O wash). Comparison of these data with those reported previously,[67] specifically the OH stretching vibrations at $\tilde{\nu}$ = 3331, the exchangeable proton at δ = 4.45 and the elemental analysis of the pale brown solid, revealed that we had synthesised the alcohol **111** in a good yield of 92%. Chemical-ionisation mass spectrometry using methanol allowed us to observe the strong molecular ion at *m*/*z* = 213, together with the typical loss of water (M^+ – 18).

We first accomplished a conversion of the hydroxy group into an iodo group by using CI_4 and triphenylphosphine, either with or without the addition of an amine base, but found an improved procedure for the conversion, used by Garegg in the synthesis of iodo-carbohydrates[125] that employs a triphenylphosphine, imidazole, iodine combination to rapidly form the iodo compound at room temperature. Under our reaction conditions, the iodo compound was not isolated, but was transformed directly to the cyclized product (**112** in **Scheme 42**). On one occasion we isolated what we believe was an iodide (see chapter 4.2), but it was not stable in air, and rapidly formed the starting alcohol, presumably by exchange with atmospheric moisture. There is some indication that the bicyclic product formed in this reaction may decompose rather rapidly. The presence of a baseline spot on TLC and the darkening of the product from a clear oil to a deep red oil are characteristic of all the $\Delta^{8,8a}$-indolizidines (such as **112**) formed during this project. Attempts to isolate the decomposition products were not successful, but storing the compounds in glass tended to speed up the decomposition, as did prolonged contact with silica gel (during chromatography). A tiny peak in the mass spectrum of **112** at M + 16 indicates that the compound may be oxidising to the *N*-oxide form of the indolizidine. This is well known for indolizidines, but there is no literature precedent of this occurring with dehydroindolizines. Attempts to isolate sufficient amounts of the suspected *N*-oxide by SIS or MS/MS techniques were not successful.

An in *situ* NMR study was performed to try and determine what the degradation products could be by inducing the decomposition during the NMR experiment. In this study, a small amount of silica gel was added to a recently purified sample of $\Delta^{8,8a}$-indolizidine **112**, and the ^{1}H NMR spectrum monitored over the course of 12 hours. Although there was significant broadening of the signals, which can be attributed to the loss of sample homogeneity, and the formation of a bright-red compound on the surface of the silica gel, no other compound or any shifting of the ^{1}H NMR signals was observed. Addition of considerably greater quantities of silica gel did not alter the above result, although more red-surfaced silica gel was formed. Attempts to desorb this red product from the silica gel were also not successful.

In this project, it was found that a slight modification of the conditions used by Garegg led to even better yields (up to 70%) of some cyclized products. The use of CH_3CN as the solvent, instead of toluene, avoided the formation of a messy biphasic reaction mixture. Also, if the alcohol was first converted to the sodium salt (by addition of 1 equivalent of NaH), the reaction was complete in less than two hours.



112

Once again, this product is well documented in our laboratories, and hence no new data were necessary for a complete characterisation of the indolizidine precursor. The $\Delta^{8,8a}$-indolizidine was easily characterised by the absence of OH absorption in the IR spectrum, as well as the missing vinyl hydrogen singlet at δ = 4.5. The remaining signals in the NMR spectrum are largely unaffected, except for those corresponding to nuclei near the C=C bond. The signal for the carbon adjacent to the OH in the starting material (carbon 7 in **112**) shifts upfield by 1.3 ppm from δ = 3.7 to 2.4, as expected, due to the loss of deshielding from the

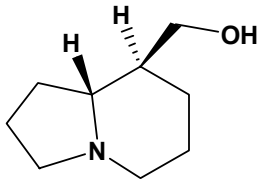
alcohol oxygen. The ^{13}C NMR spectrum shows 11 signals, each well separated. As with the ^{1}H NMR spectrum, the signal positions are similar to those of the starting material, and show good correlation with previous spectra obtained in our labs. Using extensive 2-D NMR techniques we were able to fully assign all the ^{13}C NMR signals (see Experimental Section).

2.4 Synthesis of (±)-Tashiromine and (±)-Epitashiromine

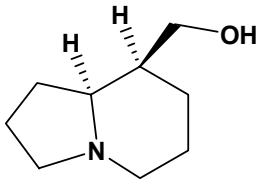
2.4.1 Synthesis of Octahydroindolizines 113 and 114

Reduction of the C=C bond of the enaminone

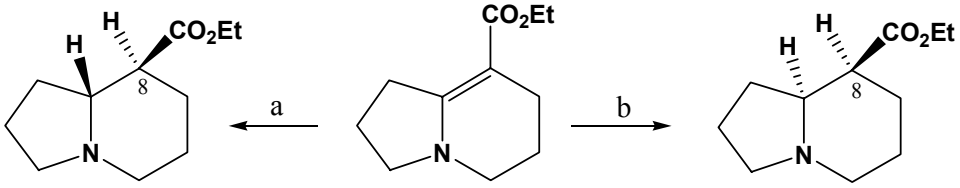
After exploring various reaction conditions, we found two that would allow us to synthesise either the *cis*- or the *trans*-fused indolizidine preferentially. Using sodium cyanoborohydride in acidic medium favoured *trans* reduction of the vinyl bond, while catalytic hydrogenation over platinum dioxide favoured *cis* reduction. Examination of the natural product reveals that tashiromine requires *trans*-located hydrogen atoms, while epitashiromine requires *cis*, noticeably this is the opposite case in the quinolizidine analogues lupinine and epilupinine. We now had access to both the natural product and its 8-epimer, although both of these reduction methods would give mixtures of the *cis*- and *trans*-isomers.



Tashiromine **1**



Epitashiromine **2**



113 - *Trans* reduction **114 - *Cis* reduction**

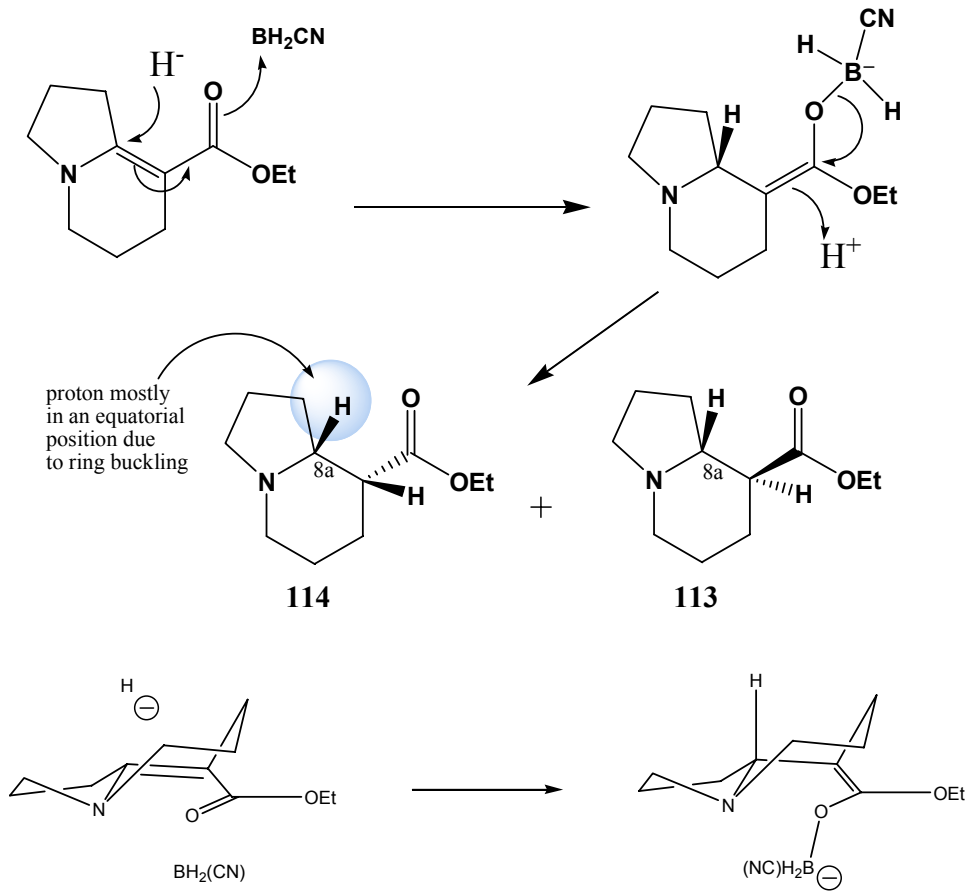
a) $NaBH_3CN$, H_3O^+ b) H_2 / PtO_2, AcOH

Scheme 43 – Selective Reduction of the Vinylogous Bond

These diastereomeric mixtures (**Scheme 43**) were separable by careful repeated flash chromatography to give the racemic 8-ethoxycarbonyl substituted indolizidines in a pure form. It would seem obvious that the reduction on a catalytic surface should deliver both hydrogen atoms to the same face of a double bond, but the same result is not true for the reduction using sodium cyanoborohydride. It is not immediately clear why this should be the case, but a plausible explanation is possible:

Firstly it should be noted that neither of the reductions are completely stereospecific, although an analysis of the ^{1}H NMR signals for the crude products shows that the ratio of major/minor product is approximately 60:40 for the hydride reduction and 85:15 or higher for the platinum reduction. Secondly, the outcome of the hydride reduction could be optimised slightly by careful and slow addition of HCl over several minutes. Together this seems to indicate that the hydride reductions take place in two discrete steps, namely i) the addition of hydride to the electropositive β-centre of the α,β-unsaturated ketone, and ii) displacement of the resulting borate anion by the acid proton. The first step is likely to result in a semi-chair conformation of the indolizidine rings with the pyrrolidine ring occupying a stable equatorial, *trans*-fused conformation (**Scheme 44**). This would allow for delivery of the H^+ either *cis* or *trans* to this newly introduced hydrogen (**Scheme 44**). The *anti* delivery of the second hydrogen with respect to the first one would result in a predominantly *trans*-fused reduction, which would place the ester moiety in a favourable equatorial position. Syn addition of the second hydrogen would result in an energetically less favourable *cis*-fused conformation for the product, and this might explain the experimental observation that this structure was only present in minor quantities. The structure of this anion intermediate was not determined, however, and is therefore the subject of speculation, but it is consistent with the proposed structures from other hydride reductions.[126]

Although it is possible that the order of the two proposed steps could be reversed (i.e protonation of the ester followed by reduction of the iminium species), there is no evidence of the formation of an iminium ion from the *in situ* analysis of the reaction using UV-Visible spectroscopy. A separate analysis of the protonation step also did not show any change in the λ_{max} for the enone.



Scheme 44 – Proposed Mechanism for the Hydride Reduction of Enones and Structure of Borate Intermediate

The spectral data for either **113** (*trans*-fused) or **114** (*cis*-fused) are rather complex compared to the starting materials, since these are now diastereomers. The ethyl moiety is recognisable in the ^{1}H NMR spectrum of either compound as a triplet and quartet at δ = 1.2 and 4.1, respectively. The remainder of the proton signals appear as multiplets between δ = 1.2 and 2.4, with the exception of the non-equivalent (diastereotopic) CH_2 protons α to nitrogen, whose signals are separated by more than 1 δ unit, and are only partly visible at $\delta \sim 3$. These protons are also sensitive to the conformation of the ring, showing a visible downfield shift for protons in an equatorial position. This is discussed in more detail for the attempted synthesis of (–)-tashiromine (Section 4.3), but briefly, the integration of the signals around δ = 2.0 and δ = 3.0 will vary. The *trans*-fused

113 has only two of the five protons adjacent to nitrogen in an equatorial position, so the relative integration of signals at 2 ppm/3 ppm = 3:2, while the *cis*-fused **114** has the inverse ratio of 2:3 due to an extra equatorial proton at C8a (see **Scheme 44**).

The ^{13}C NMR spectra are however more useful, each with 11 clear signals. The absence of the C=C double bond is shown by the absence of the corresponding signals, compared to the spectrum of the starting material. A DEPT experiment shows that these two signals (now sp^3 hybridised carbons) appear significantly upfield from δ = 160 and 87 to around 50 ppm. The signal at δ = 174 could be assigned to the carbonyl signal, but the remaining signals could only be inferred by comparison with the spectrum for the starting material. The IR spectrum also shows no C=C stretching vibration at $\tilde{\nu}$ = 1597.

The mass spectra for these diastereomers are rather similar, and in addition are not very different from the dehydroindolizine compounds. The exact masses for **113** and **114** were found to be 197.1429 $g.mol^{-1}$ and 197.1433 $g.mol^{-1}$, respectively, calculated as 197.1416 $g.mol^{-1}$, which is in excellent agreement with the formula $C_{11}H_{19}NO_2$. These data are in agreement with the proposed structures. In the mass spectra the parent ion is easily discernable at *m*/*z* = 197, together with a peak at *m*/*z* = 196 corresponding to the (M – H) ion. Strong peaks at 168 (M – 29), 152 (M – 45), and 124 (M – 73) could be attributed to the loss of ethyl, ethoxy, and ethoxycarbonyl, respectively (the last mentioned *via* sequential loss of ethyl and CO_2). These losses are typical of ethyl esters under electron impact conditions. The base peak is simply the hexahydroindolizine cation, which does not provide any supporting evidence for the formation of **113** or **114**, and could have arisen from a number of pathways. The remaining significant peaks at *m*/*z* = 96, 83, and 70 are present in most of the mass spectra of the indolizidines examined in this study, as well as many of those from the literature. These are probably formed by C–C bond cleavage α to the nitrogen in the indolizidinyl cation followed by loss of an ethene molecule to give an *N*-methyl piperidinium fragment (*m*/*z* = 96). The loss of an acetylene would give a substituted enaminium cation with *m*/*z* = 70. Alternatively, the fragment with *m*/*z* = 83 could arise from the loss of C_3H_5 radical from an iminium cation. The

structures in the following figure (**Figure 16**) are useful in elucidating the fragmentation and molecular structure (more so than $C_8H_{14}N^+ \rightarrow C_6H_{10}N^+$), but do not necessarily imply known mechanisms.

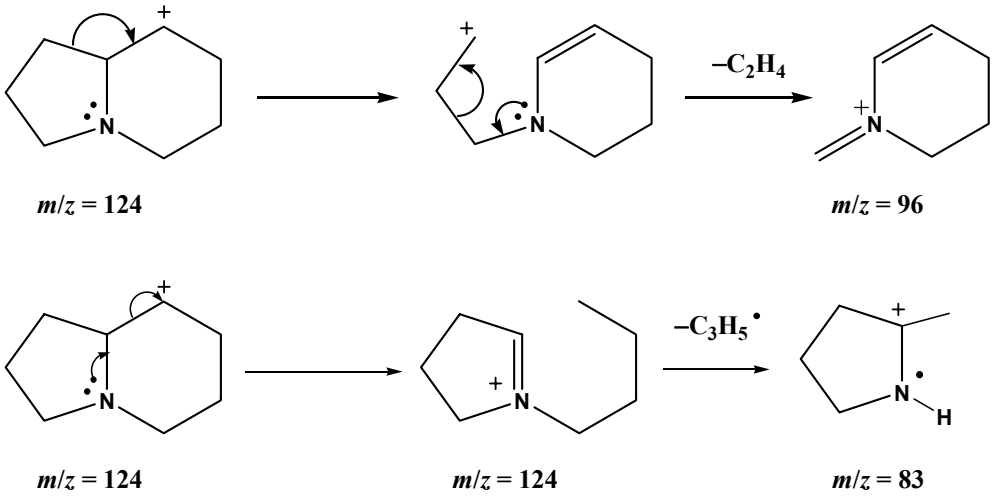
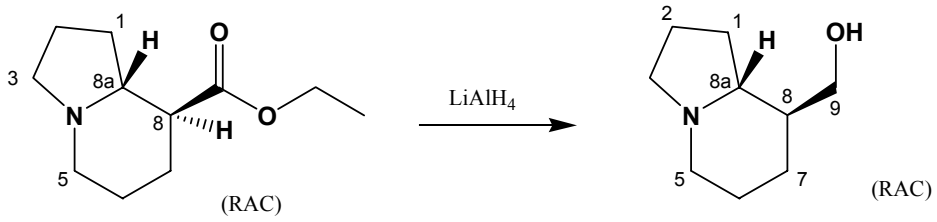


Figure 16– Proposed Fragmentation of Indolizidinyl Molecular Ions

2.4.2 Synthesis of *rac*-tashiromine and *rac*-epitashiromine



113 (±)-Tashiromine **[1]**

Reduction of the ester functionality in was accomplished with $LiAlH_4$, to give the racemic alcohols (±)-tashiromine [**1**] and (±)-epitashiromine [**2**]. Literature suggests that some care is needed during the reduction to epitashiromine, in order to avoid epimerisation at the C8 position. This epimerisation has been deliberately used to synthesise tashiromine [**1**] from epitashiromine [**2**], and probably occurs by deprotonation at C8.[108] This ease of epimerisation may be one of the reasons that the epimer has not been detected as a natural product. The low-energy conformation in tashiromine may make it less susceptible to epimerisation as there no known syntheses of **2** from **1**. Racemic

tashiromine was obtained from the reduction of compound **113**, while the pair of epimers was obtained from **114**.

This was a rather clean reaction, and the resulting products were easily purified by filtering through a short column of silica gel. The obtained gums showed excellent agreement with data from the literature, including IR and NMR. The high resolution mass spectral analysis data are in good agreement with the expected product, and there is a reasonable correlation of data from the literature with the low-resolution spectrum. Elemental analyses were not performed on these compounds due to the fact that they remained as gums, despite several attempts to solidify them.

2.4.2.1 Racemic tashiromine

A broad OH band in the IR spectrum at 3500–3200 shows the successful reduction of the ester functionality, although the ^{1}H NMR signal for this proton is buried within a number of methylene multiplets. The signals from the protons adjacent to this OH are, however discernable as two doublets of doublets, one at $\delta \approx 3.6$ and the other at $\delta \approx 3.4$ppm. Each of these signals shows a large geminal coupling constant of 10Hz, and a slightly smaller coupling constant of 6Hz for the vicinal protons. The ^{13}C NMR signals also match well with those from the literature.[97] This is especially important with carbons 8 and 8a, since these signals are quite different in the epimers. The bridgehead carbon (8a) in the epimer is shifted downfield by 0.3 ppm, with respect to tashiromine, and the adjacent carbon (8) is shifted to 35.3ppm from 44.4, an upfield shift of 9 ppm with respect to tashiromine. The zero optical rotation shows that this product is probably racemic, as expected.

Figure 17 shows the *trans*-fused indolizidine (–)-tashiromine in what was calculated (see Chapter 6.1) to be the most favourable conformation. The rings are conformationally quite labile and do not give signals that can be clearly identified with axial or equatorial protons.

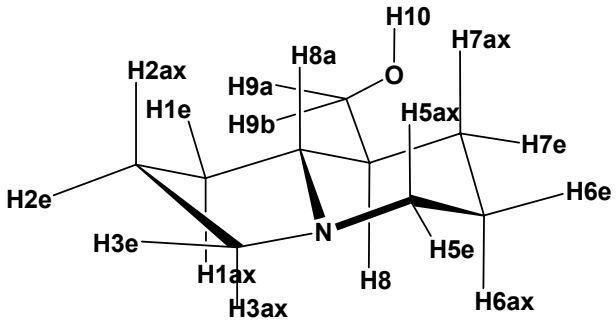


Figure 17 - Tashiromine [1], showing axial (ax) and equatorial (e) protons

Table 2 – Comparison of NMR Spectral Data for (±)-Tashiromine

^{1}H NMR ($CDCl_3$)			^{13}C NMR ($CDCl_3$)		
Proton	RW Krause (δ / ppm)	Literature[97] (δ / ppm)	**Carbon**	RW Krause (δ /ppm)	Literature[97] (δ / ppm)
H-1ax	1.38–1.62		**C-1**	27.6	27.6
H-1e	1.80–2.03				
H-2ax	1.58–2.13		**C-2**	20.6	20.3
H-2eq	1.58-2.13				
H-3ax	1.97–2.13		**C-3**	54.1	54.2
H-3e	2.98–3.17				
H-5ax	1.90–2.00		**C-5**	52.6	52.7
H-5e	2.98–3.17				
H-6ax	1.63–1.83		**C-6**	25.0	25.2
H-6e	1.63–1.83				
H-7ax	1.03		**C-7**	28.9	29.2
H-7e	1.80–2.03				
H-8	1.33–1.61		**C-8**	44.5	44.7
H-8a	1.46–1.80		**C-8a**	66.4	66.4
H-9a	3.42	3.48	**C-9**	65.2	65.9
H-9b	3.61	3.73			
H-10	~3.05	3.02			

It can be seen from the previous table that there is good agreement between the reported spectral data and those obtained in this project, although none of the reported syntheses have assigned ALL of the ^{1}H NMR signals making a direct comparison of ALL the results impossible.

In general it should be noted that the difference between the axial and equatorial proton signals are most pronounced for those protons adjoining the bridge-head nitrogen. The interactions between the nitrogen lone pair and these protons are easily observed in the IR spectra as sharp, weak bands around $\tilde{\nu}$ = 2700, known as Bohlmann bands, and described in more detail below for epitashiromine [**2**] and again in section **4.3** dealing with the diastereoselective synthesis of tashiromine.

The exact mass, obtained from high resolution mass spectrometry was 155.1316 g.mol^{-1} and is in agreement with the calculated value of 155.1310 for $C_9H_{17}NO$. The molecular ion as well as the (M – H) ion (*m*/*z* = 154) were present as high intensity peaks, together with a small peak (15%) for the (M + H) ion. Loss of water from the parent ion was not observed, but can instead be detected as a very intense peak 18 *m*/*z* units lighter than the M+1 peak at 138 (94%). Loss of CH_2OH radical gives a characteristic peak at *m*/*z* = 124, also observed in most of the other indolizidines, together with the peaks at *m*/*z* = 122, 96 (100%), 84(41), 70(31), and 69(44) (*vide supra*). The CH_2OH cation is also observed at *m*/*z* = 31, typical of primary alcohols. The remaining significant peak at *m*/*z* = 110 can be explained by the loss of an ethylene molecule following the loss of water from M+1 and C–C bond cleavage α to the nitrogen.

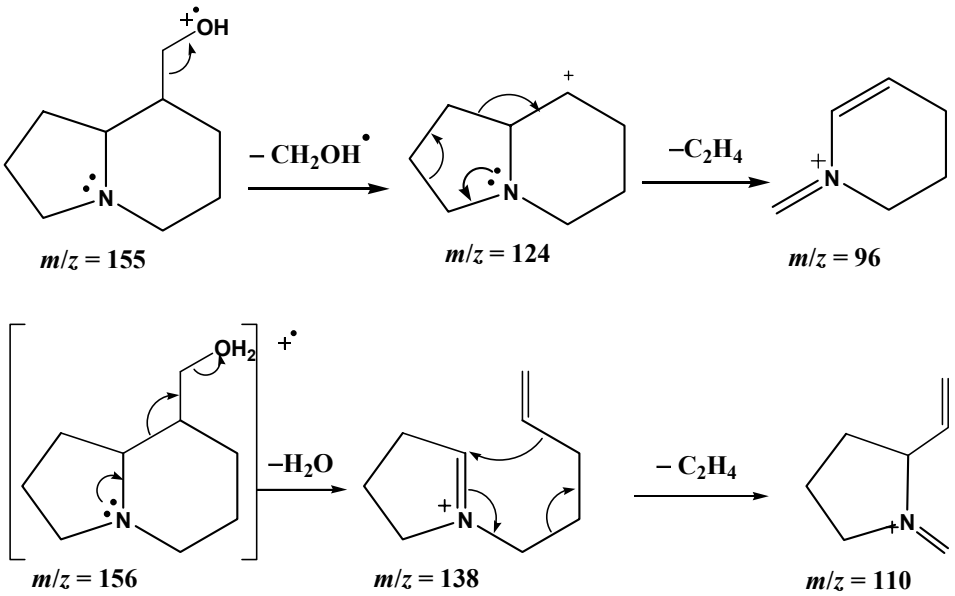


Figure 18 - Proposed Fragmentation of Tashiromine Molecular Ion

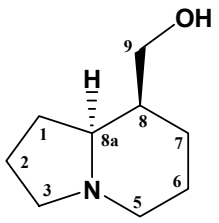
2.4.2.2 Racemic 8-epitashiromine

The IR, ^{1}H NMR and ^{13}C NMR data for this compound are similar to those already discussed above. The distinguishing features are the downfield position of the protons α to the OH group (on C9) (these appear at δ = 4.1 and 3.7, instead of 3.6 and 3.4), and the upfield shift of the ^{13}C NMR signal for C8, *vide supra*. The large geminal coupling of 9.2Hz for the protons at C9 is slightly smaller than the corresponding one found in the case of tashiromine, as is the smaller vicinal coupling constant of 4.3Hz. The reason for these changes is most likely the different conformation of the indolizidine ring as a result of the *syn*-reduction. In section 6.3 on molecular modelling we explore some of these conformations and discovered that there are two conformations with similar energies, one where the indolizidine rings are *cis*-fused, and the other with *trans*-fused rings. In the latter case there is a separation between the hydroxyl group and the nitrogen of between 1.03 and 1.42Å, indicating "hydrogen bond-like" interaction that fixes the indolizidine ring in a *trans*-fused conformation (see **Figure 34**) and would cause a deshielding of the proton H-10. Preference for this conformation is validated by the appearance of Bohlmann bands in the infra-red spectrum of **2** as three sharp weak bands at $\tilde{\nu}$ = 2750, 2733, and 2641.

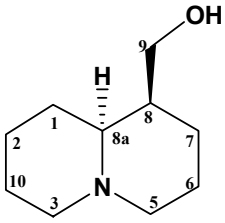
As with the racemic tashiromine, the mass spectrum shows the molecular ion flanked by the (M–1) and (M+1) peaks, which are common for primary alcohols. In the latter case the peaks show abundances (~15 - 20%) greater than what is expected for the heavy isotopes alone (~10%). A peak at 124 corresponds with the loss of CH_2OH radical (cation detected at m/z = 31), and again the substituted piperidine fragments are clearly seen at 84, 83, 70, and 69. A peak at m/z = 85, not seen in the spectrum for tashiromine could be piperidine, formed, for example by elimination of a propyl fragment from one of the precursors.

Lupinine and epitashiromine have similar structures (both have a *cis* arrangement between the hydroxymethyl group and the remaining ring fragment at the bridgehead carbon), and they are therefore expected to show similar spectroscopic data. This comparison has already been made during the isolation of tashiromine from *Maackia tashiroi*.[97] **Table 3** lists the corresponding spectroscopic data for the racemic (±)-epitashiromine produced in this project,

together with that reported in the literature, along with the literature values for lupinine and tashiromine for comparison.



Epitashiromine [2]



Lupinine [15]

Table 3 – Comparison of ^{13}C NMR Data for Epitashiromine and Lupinine

(±)-Epitashiromine				**(±)-Lupinine**		**(±)-Tashiromine**
Carbon [a]	RW Krause	Ohmiya [97]	Paul-vannan[108]	Ohmiya. [97]	Rycroft [127]	RW Krause
C-1	26.3	25.8	25.6	29.5	30.0	27.6
C-2	19.4	20.8	20.7	24.6	25.0	20.6
C-3	53.8	53.5	53.4	56.9	57.3	54.1
C-5	52.4	54.4	54.4	56.9	57.4	52.6
C-6	22.7	23.2	22.9	22.7	23.2	25.0
C-7	27.7	30.5	29.6	30.8	31.6	28.9
C-8	35.2	35.4	35.7	38.5	38.8	44.5
C-8a	65.1	66.8	66.5	65.0	65.2	66.4
C-9	64.0	65.6	64.5	64.7	65.6	65.2
C-10	–			25.5	25.9	

a) Equivalent numbers have been used for lupinine for convenient comparison, and they do not reflect IUPAC numbering.

Once again there is generally acceptable agreement between the spectroscopic data obtained for the (±)-epitashiromine synthesised in this project and other samples reported in the literature. The small (1 ppm) discrepancies may be due to different solvents used.

It is interesting to note that the carbon signal for position 8 in the ^{13}C NMR spectrum of tashiromine shifts ca. 9 ppm upfield relative to epitashiromine.

Chapter 3

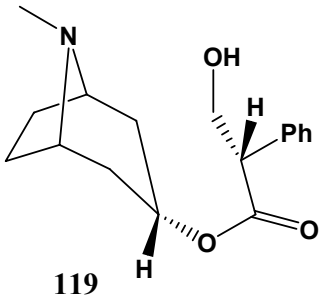
Introduction to Asymmetric Synthesis

3.1 Importance of Asymmetric Synthesis

The increasing demand for non-racemic drugs and pesticides has dramatically changed the prominence of stereoselective synthesis over the past few decades. Modern chemists have at their disposal a bewildering array of methods with which to accomplish, or at least strive for, asymmetric synthesis. The field is served by a steady stream of monographs, reviews,[128][129] specialist conferences,[130] and even dedicated journals.[131][132] This chapter serves as a brief overview of the different methodologies used in synthetic organic chemistry for the synthesis of enantiomerically pure compounds. This brief expose in turn will help to illuminate the need for introducing an aspect of stereocontrol in what I have described already as the generalised Wits approach to alkaloid synthesis.

The term EPC (Enantiomerically Pure Compound) synthesis was introduced in 1980 by Seebach,[133] to include all methods of preparing chiral compounds in enantiomerically pure form. The importance and need for such syntheses is no more apparent than in compounds with high physiological activity such as drugs and pesticides. In these cases, biological activity is often associated with only one enantiomer; alternatively enantiomers may show remarkably different activity. Even a small amount of an unwanted isomer can have dramatic effects. We cannot help but look at the tragedy surrounding the infamous thalidomide cases of the 1960's to realise how dangerous and antiquated it may be to attempt to administer drugs in a racemic form. Although the (*R*)-isomer exhibits desirable analgesic properties, the (*S*)-enantiomer is a powerful teratogenetic, inducing foetal malformations and death. The fact that the shape of a molecule has considerable influence on its physiological activity has been recognised for many years. For example, in the early 1900's Cushney[134] demonstrated that (–)-hyoscyamine [**119**] was approximately twice as potent as the racemate (atropine) in its effect on the nerve endings of the pupils. A more recent example can be found in (–)-carbovir [**120**], the triphosphate of which is a

potent inhibitor of HIV reverse transcriptase, while the antiviral activity of its enantiomer is negligible.



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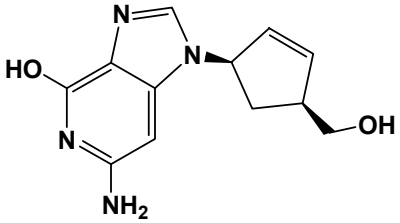

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From examples such as these it is easy to understand why there has been such a big drive for enantiopure substances, and consequently tremendous growth in the methods for achieving this. As a measure of this interest in asymmetric synthesis, it is estimated that at the end of the 20th century 80% of all drugs were administered in an optically pure chiral form, compared to just 12% in 1982.[135] A quick survey of the recent literature will reveal that a significant volume of work in synthetic chemistry is focused on stereoselective work.

Different Methods

There are three principal strategies used in obtaining compounds in a stereoselective form, namely:

3.1.1 Use of chirally pure starting materials

3.1.2. Resolution of a mixture of enantiomers

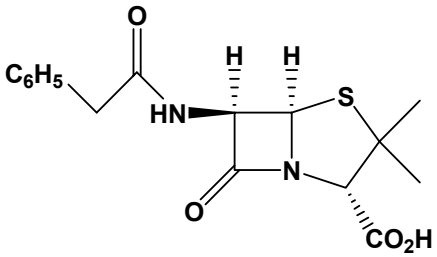
3.1.3 Transfer of chirality to a prochiral precursor

Each of these methods has limitations and advantages, and these will be outlined briefly below. Finally, we could look at the possibility of chiral reactions that do not fall into any of these categories.

In this project we will make use of the first two methods in the synthesis of the chiral auxiliaries, and then concentrate on the transfer of chirality to a prochiral precursor for the remainder of the project.

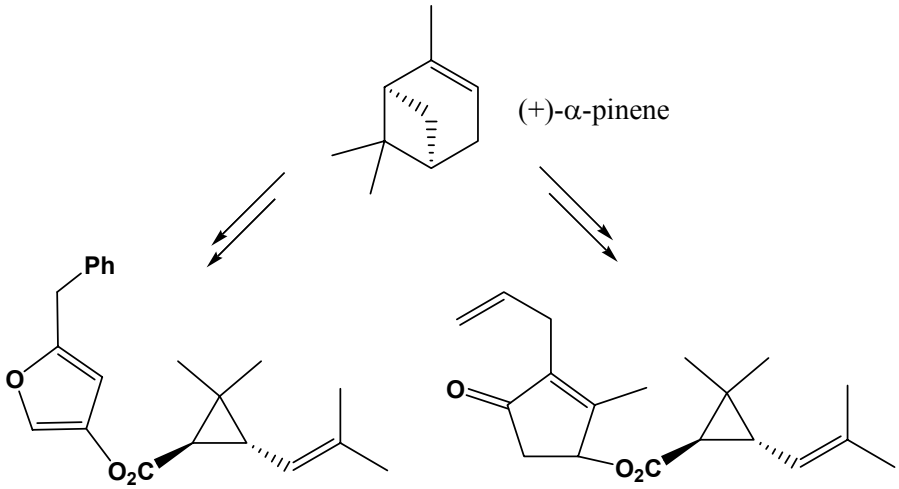
3.1.1. Use of chirally pure substrates

This is perhaps the oldest method of achieving a stereoselective synthesis. It relies on the technique of modifying optically pure, mainly bio-derived starting materials, to give a new product. A term that is often used to describe this type of synthesis is "ex-chiral-pool synthesis", and refers to the use of readily available optically active natural products. These chiral substrates (chirons) are in general, derived by careful manipulation of readily accessible optically pure chiral starting materials such as carbohydrates, amino acids, alkaloids, and terpenoids.[136]



121

Terpenes have been a rich source of chiral building blocks. Since many terpenes are isolated form natural oils, however, the main disadvantage of using terpenes is that they are usually not available in high chemical or enantiomeric purity. These materials often require costly and lengthy purification before they are suitable for use in asymmetric synthesis. The other disadvantage is that many terpenes lack any functionality apart from double bonds. Nonetheless, the presence of geminal dimethyl groups in conjunction with optical activity stimulated their use in synthetic pyrethroid insecticides (e.g. [**122**] and [**123**] from (+)-α-pinene).

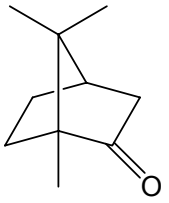


BIORESMETHRIN **122** BIOALLETHRIN **123**

Scheme 45– Synthesis of Pyrethroids from α-Pinene

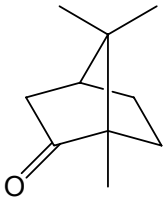
The unusual ring structures of some of these terpenes have piqued the interest of many synthetic chemists. As an example, in this project we make use of (+)- or (–)-camphor [**124**]. Interest in camphor and its derivatives is evident in the whole history of natural product synthesis. The availability of both enantiomers in a pure form and in large quantities, together with the fact that it undergoes a wide variety of transformations make it a very versatile material in the enantioselective synthesis of natural products.

The versatility of camphor [**124**] in the synthesis of natural products is clearly illustrated in the diverse products formed (**Figure 19**).

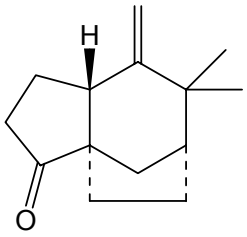


(+)-camphor

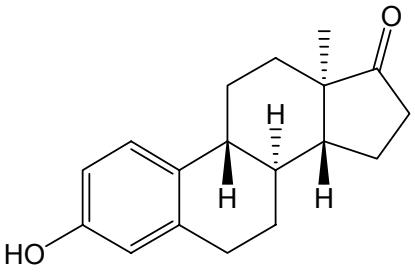
124



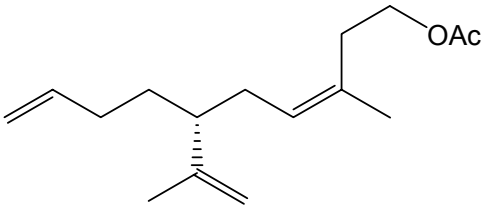
(–)-camphor



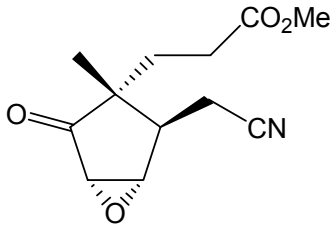
(-)-Khusimone



(-)-Oestrone



Californian Red Scale Pheromone



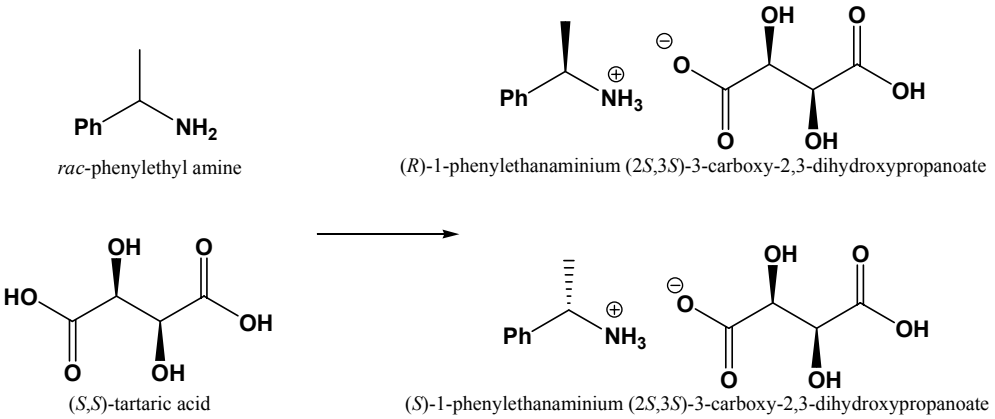
Vitamin B_{12} Intermediate

Figure 19 – (–)-Khusimone,[137][138] (–)-Oestrone,[139] Californian Red Scale Pheromone,[140] and Vitamin B12 Intermediate[141] synthesised from Camphor.[142]

The general drawback of this method of stereoselective synthesis is the lack of suitable starting materials, and the fact that the materials usually have to be significantly manipulated before they even remotely resemble the required product.

3.1.2. Resolution of a mixture of enantiomers

This cannot be considered a synthesis, but rather a separation technique used to obtain enantiopure materials. The use of resolution to obtain enantiomerically enriched products is perhaps almost as old and as widely accepted as the use of chiral starting materials. Resolution has come a long way from the days of Pasteur, who painstakingly separated enantiomorphous crystals of (+)- and (–)-sodium ammonium tartrate by hand. The principles, however are very similar, and rely on one enantiomer or diastereomer having either different reactivity toward certain substrates (kinetic resolution), or having a different physical property (classical resolution). By far the most common method employed is classical resolution, where a racemate is reacted with a chiral resolving agent, forming diastereomers whose properties are sufficiently different that they can be separated by crystallisation or chromatography. The purified diastereomer is then converted back into the desired enantiomer, and the remaining diastereomer is either recycled or discarded. This is illustrated below in the resolution of phenylethylamine with (***S***,***S***)-tartaric acid. The (**1*S***)(**2*S*,3*S***) salt is more soluble in methanol and can be separated from the (**1*R***)(**2*S*,3*S***) salt.



Classical methods are frequently applied on a large scale, giving precursors that can be used in the synthesis of more complex molecules.[135]

More modern examples of classical resolution, which are gaining in popularity, are techniques such as the resolution of enantiomers by clathrate formation. In certain cases, compounds form crystal lattice inclusion compounds (clathrates), with different solubilities for each diastereomer. The clathrates are therefore easily separated by crystallisation, and the optically pure guest obtained by simple vacuum distillation of the separated isomer

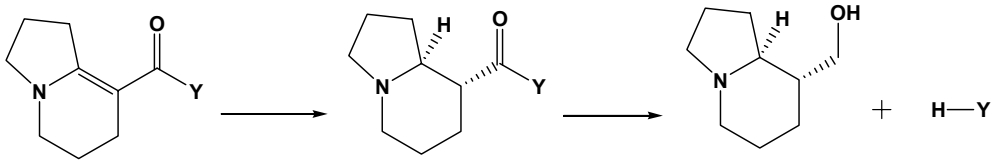
Some racemates may be separated by chromatographic methods, using chirally modified stationary phases. Although a variety of such stationary phases have been developed recently, a predictable and generally applicable method has not yet been found.

The kinetic resolution of racemates is also often used. These methods of resolution capitalise on the different reactivities of the enantiomers with optically active reagents. A weapon that is being used with increasing frequency is the use of enzymes. Certain enzymes, such as the lipases of *Candida cylindricia*, or pig liver esterases, are capable of selectively transforming one enantiomer faster or even at the exclusion of the other.[143] In this project kinetic resolution using enzymes is used in the synthesis of one of the chiral auxiliaries, cyclohexanol **140**.

Perhaps the biggest drawback of this method in general, besides the time spent in separation of the enantiomers and derivatives, is the fact that at some point in the synthesis, one enantiomer, and hence 50% of the material is usually discarded. Although certain methods often are available to convert the unwanted enantiomer into the required enantiomer within a few cycles of racemization of the unwanted enantiomer and resolution of the racemate, these methods introduce extra steps into the synthesis.

3.1.3. Transfer of chirality to a prochiral precursor

Transferring chirality to a prochiral centre by association in some way with a reagent, which is itself either chiral, or contains some "chiral disposition" is the topic of this section. These associations are often temporary and are usually removed once the transformations are complete. These methods, collectively known as chirality transfer, are becoming increasingly popular, due to the availability of suitable transfer reagents. Biochemically, the asymmetric synthesis can be achieved with enzymes, and chemically using chiral auxiliaries, reagents, or catalysts. In this project we made use of this technique to synthesise (+)- and (–)-tashiromine.



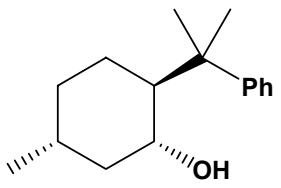
Y = chrial auxiliary tashiromine [**1**]

Older reactions are constantly being modified to improve selectivity, including stereoselectivity in many cases. The other attractive feature of this method is that although the chiral transfer reagents are in general quite expensive, they are usually recoverable to some extent. This makes the method economical in the long run, but the drawback is of course the time spent in developing the reagents in the first place.

After decades of exploratory studies, this field of asymmetric synthesis by chirality transfer attained a great deal of respect when several scientists succeeded in synthesising efficient and practical chiral auxiliaries. A chiral auxiliary is quite simply a chiral adjunct that can be attached (usually temporarily) to the substrate.

In this way it usually directs the reagent to act at one face of a prochiral substrate. Having transferred the chirality, the auxiliary can then be removed, leaving the enantiopure product. This idea is one of the key concepts of this project. By attaching a chiral auxiliary to the indolizidine precursors, we hoped to be able to control the enantioselective formation of the core indolizidine skeleton. One advantage of this approach over the other two already discussed is the prospect of using the same auxiliary-reagent combination on different substrates. The following chapter will explore this idea in more detail.

Perhaps the first general auxiliary to be used with any great deal of efficacy was (–)-8-phenylmenthol [**125**], developed by Corey and Ensley in the mid 1970's.[144] The higher levels of asymmetric induction associated with (–)-8-phenylmenthol in comparison with menthol itself allowed Corey and others to use this auxiliary in a large variety of different condensation reactions. Scientists soon realised that the bulky phenyl substituent acted as a steric barrier, and resulted in controlling the syntheses to give products with high diastereoselectivities. Many modifications of this system were undertaken as scientists around the world tried to improve the efficacy of the auxiliary. d'Angelo and Maddaluno showed that replacing the phenyl group in 8-phenylmenthol [**125**] or *trans*-2-phenyl cyclohexanol [**126**] with other more bulky aromatic substituents led to a notable enhancement in the degree of diastereo-differentiation.[145]



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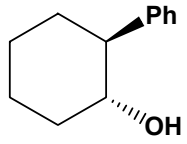

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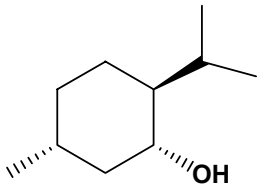


(–)-Menthol

The chiral auxiliaries used in this project will be discussed in more detail in the next chapter, but before I do this I need to mention the second component of chirality transfer - that of chirally modified reagents. In this area, an important breakthrough in the late 1980's allowed chemists to perform a number of reactions using only catalytic amounts of the chiral reagent along with a stoichiometric

amount of a less reactive achiral co-reagent. A good example of these types of reactions is the epoxidation of allylic alcohols pioneered by Sharpless in the 1980's and 1990's. Originally developed using stoichiometric amounts of tartrate catalysts, it is usually performed today using catalytic amounts of $Ti(O\textit{i}\text{-}Pr)_4$ and diisopropyl tartrate as the co-reagent. Another important development is the phenomenon of chiral amplification, where a moderately enantio-enriched reagent can lead to highly enantiopure products.[146] These catalytic systems are attractive because they save money by limiting the costly reagents, but they also save chemical waste – an issue that is becoming increasingly important.

"True" asymmetric reactions – a dream or future reality

Certain aspects of asymmetric synthesis, currently on the fringe of contemporary thinking will perhaps be the ultimate tools of the future. Of the most controversial of these tools is the possibility of using polarised light, strong magnetic fields, or other regions of the electromagnetic spectrum to influence the outcome of reactions. Reactions of this genre would rely on neither the reagents, nor the substrate for the chirality. These are perhaps the most attractive methods of all - the ability to transform a prochiral substrate selectively, without the disadvantage of wasted chemicals will continue to attract attention. Sadly, at the moment these truly stereoselective reactions are strongly contested. For this reason, I offer the possibility of this method, but I will not discuss any examples.

3.2 Chirality Transfer through Auxiliaries and Reductants

The use of chiral auxiliaries can perhaps be termed a "second-generation" asymmetric synthesis. Whereas in a first generation or "ex chiral pool" synthesis an enantiomerically pure compound is incorporated into the final product, in the second generation synthesis a chiral auxiliary is attached to a prochiral molecule, and having served its purpose it is removed. The first part of this chapter will examine some of the aspects of the use of these second-generation syntheses, focusing in particular on the five auxiliaries that were used in this project. The remainder of the chapter will look at the increasingly popular intermolecular chirality transfer, which was attempted without much success at the end of this project.

3.2.1 Chiral Auxiliaries

As was pointed out in the previous chapter, the enantiomerically pure auxiliary is not incorporated into the final product, as it would in the "first-generation" methods. The advantage is that although the final product can usually be obtained with high enantiomeric purity, these methods suffer the disadvantage that at least two extra steps are needed; attachment of the auxiliary and its removal. Nonetheless, since diastereomers are being formed, any loss on enantioselectivity can usually be corrected, and, as was pointed out in the previous chapter the cost advantage usually outweighs any disadvantage.

The principles of this approach are simple: 1) A chiral auxiliary is manufactured in an enantiomerically pure state, 2) The auxiliary is deliberately attached to an achiral substrate, in order to "direct" the outcome of the following reactions, 3) Chirality is induced in that part of the molecule that was not originally the auxiliary, 4) Any unwanted diastereomer is separated and removed, and 5) The auxiliary is removed, leaving the product – a pure enantiomer.

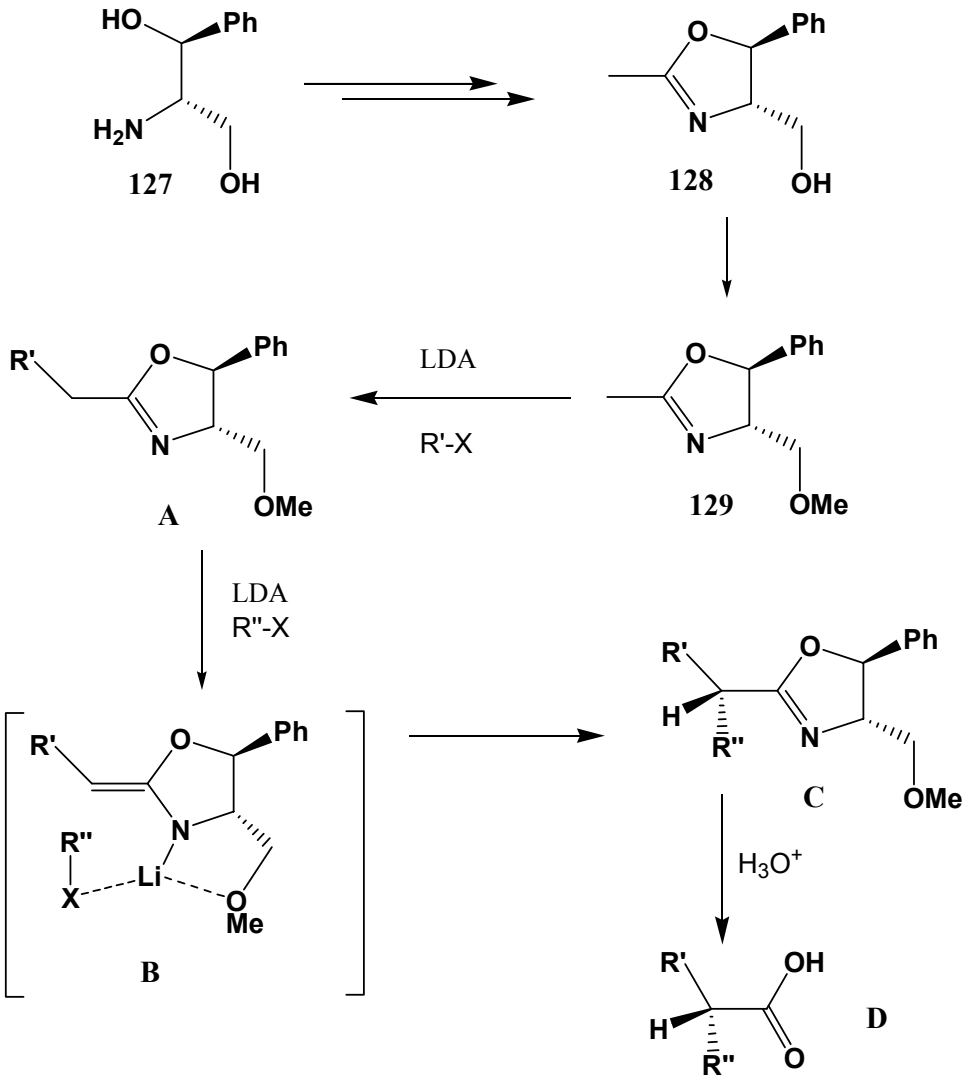
In reality, however, things are not so easy. In order to make the synthesis economically viable (and overcome the cost of the extra steps used), the

attachment and removal of the auxiliary has to be done in high yields. The auxiliary itself may need to be synthesised, and this will have to be done in an enantiomerically pure manner. Even the choice of auxiliary needs some judicious thought, since it may interfere with subsequent steps, or may be consumed under certain reaction conditions.

3.2.1.1 Meyers Oxazoline[231]

Chiral enolates and aza-enolate equivalents lend themselves to asymmetric synthesis by the use of chiral auxiliaries. There are several points of attachment of the auxiliary to an enolate system, but since this is not a review of enolate chemistry, only one will be considered; attachment on the nitrogen atom of the aza-enolate. This is perhaps the most common attachment point, and it serves to introduce the first auxiliary, an amino alcohol protected as the Meyers oxazoline. Believably one of the most versatile auxiliaries, the 2-amino alcohol [**127**] can be transformed into an oxazoline [**128**] (**Scheme 46**) by a variety of reactions. The most common approach involves the condensation of an amino alcohol with the hydrochloride salt of ethyl acetimidate. Surprisingly, the majority of these syntheses give only the one oxazoline, e.g. **128** from **127**. The alternative oxazoline, with a free benzyl alcohol substituent is not formed, or is formed in only trace quantities.

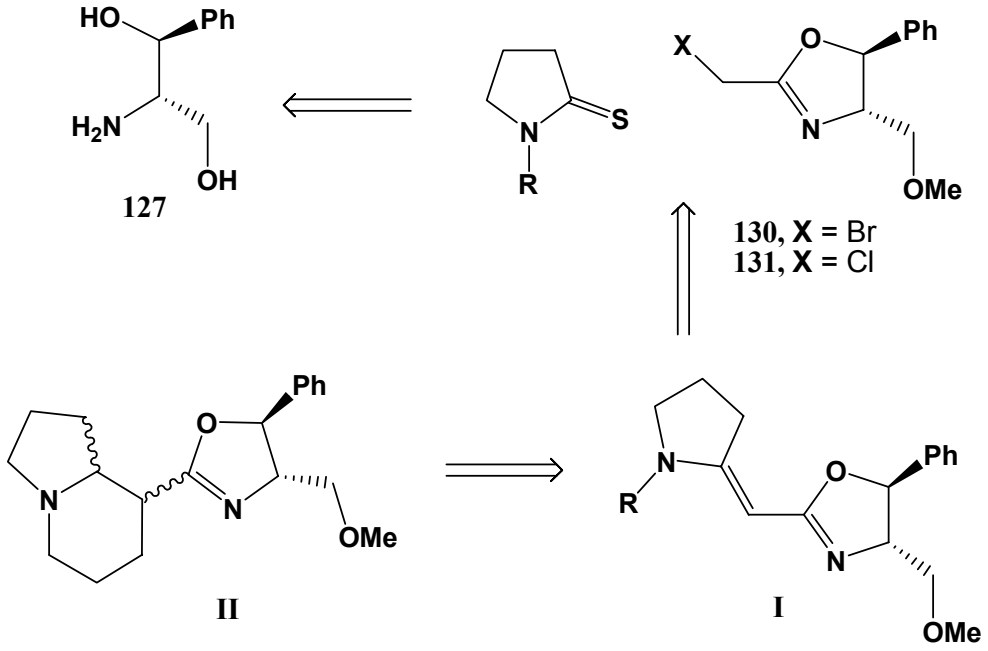
In this synthesis, the remaining hydroxy group is protected as the methyl ether. The chiral oxazoline can then be alkylated using a suitable lithium base to give the alkyl oxazoline **A** in **Scheme 46**. A second alkylation can be carried out to produce exclusively one diastereomeric product via the *Z*-enolate anion (intermediate **B** in **Scheme 46**). Removal of the auxiliary by acid hydrolysis yields the enantiomerically pure carboxylic acids (**D**). The stereocontrol essentially relies on the selective complexation of the second alkyl group on the same face as the methyl ether (intermediate **B** in **Scheme 46**). This is the favoured location for the lithium atom since it is coordinated to both an oxygen and a nitrogen on the oxazoline ring.



Scheme 46 – A General Synthesis using the Meyers Oxazoline

In this project, we had hoped to make use of this directing effect by synthesising the bromo oxazoline **130** (**Scheme 47**) or chloro analogue **131**. Suitable sulfide contraction with a thiolactam would in theory allow us to access a prochiral enaminic system such as **I** in **Scheme 47**. We would then have two options for completing the synthesis of our target alkaloids: 1) reduction followed by alkylative cyclisation, or 2) cyclisation followed by reduction. We expected in either case, that the oxazoline would act as a directing group for the reduction of the enaminic double bond, leading to a single diastereomer. If, however, we only managed a moderate diastereoselectivity, we should still have been able to isolate

one pure diastereomer by careful separation. Although we wanted to use the ambident nucleophilicity of the enamine system to effect the cyclisation, we could instead utilize the selective alkylation shown by the oxazoline systems to obtain the indolizidine core (**II**), containing a suitable functional group at the 8 position that could easily be converted into the necessary alcohol to yield tashiromine.



Scheme 47 – Proposed Synthesis of Indolizidines using Oxazolines

Unfortunately we were not able to form intermediate **I** or **II**, either by sulfide contraction reactions or by direct synthesis of the oxazoline from suitable pyrrolidinyl- or indolizidinyl-precursors. We were therefore forced to abandon this auxiliary in favour of other options.

Evans Oxazolidinone

The occurrence of chiral α-amino acids in many biologically active compounds makes them important targets in asymmetric syntheses.[147] As with the Meyers oxazoline above, the Evans oxazolidinone is a versatile auxiliary for the synthesis of these amino acids. In fact, it is useful for the synthesis of carboxylic acids, substituted at the alpha position by not only nitrogen, but also oxygen or carbon, as can be seen in **Figure 20** below.

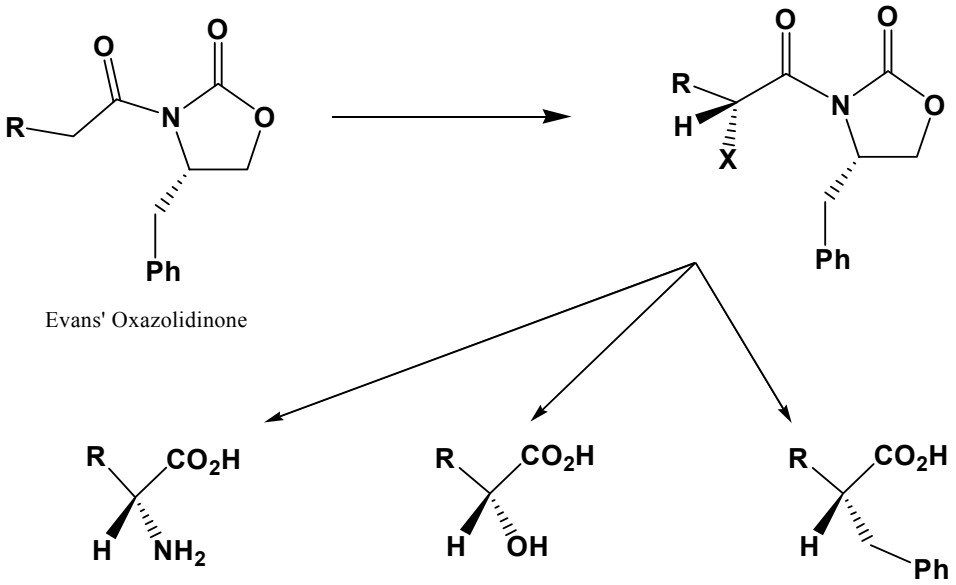
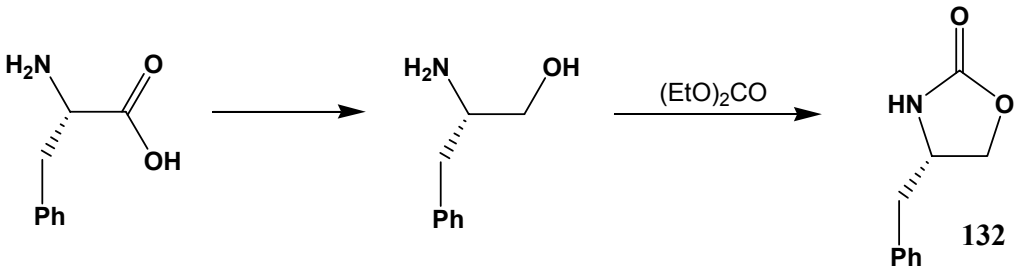


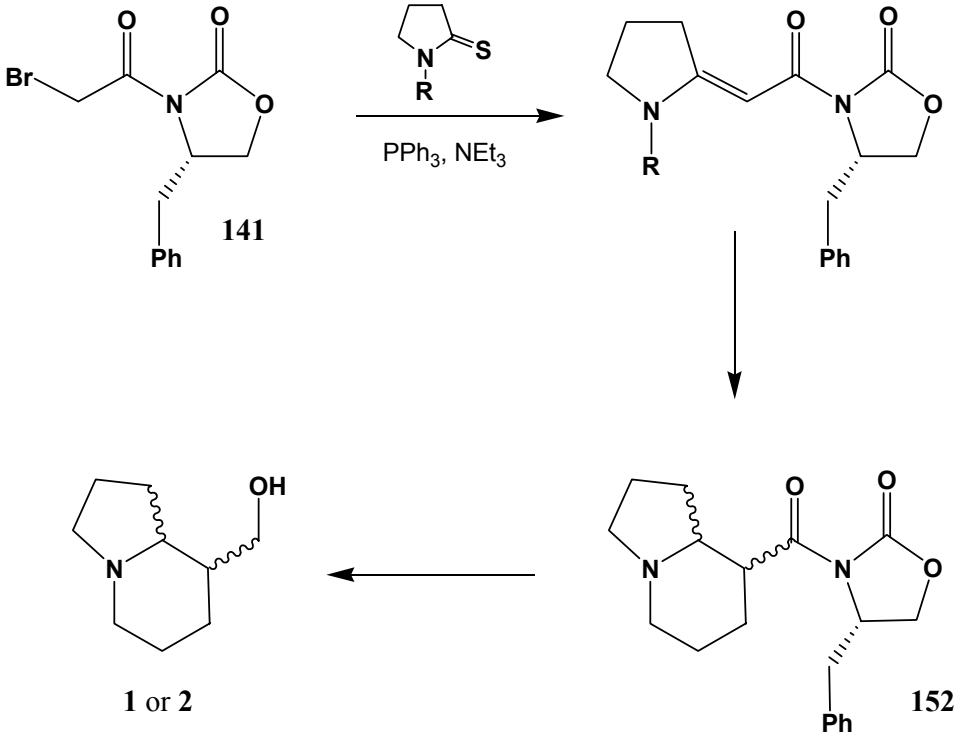
Figure 20 – Use of Oxazolidinones in α-Amino Acid Syntheses

Evans and co-workers initially developed the oxazolidinone auxiliary for diastereofacially selective aldol reactions.[160] The amino acid phenylalanine was converted into the corresponding amino alcohol, and then condensed with either an ortho ester, or a carbonate to give the auxiliary **132**. Synthesis of a number of auxiliaries is possible, simply by variation of the starting amino acid.



In our synthesis we hoped, once again to rely on the steric control of the auxiliary to enable us to perform a diastereoselective reduction of the enaminone double bond. By simply acylating the chiral auxiliary with bromoacetyl bromide, we would have access to an activated methylenic compound [**141**], which after sulfide contraction would lead to the active methylene systems. This chiral bromoacyl derivative [**141**] was synthesised in a good overall yield of 70%, which

is a primary requirement for effective use of chiral auxiliaries. Alkylative ring closure, followed by reduction would give **152**, from which the indolizidine skeleton [**1** or **2**] could be accessed by hydrolysis of the auxiliary and reduction of the carbonyl moiety.

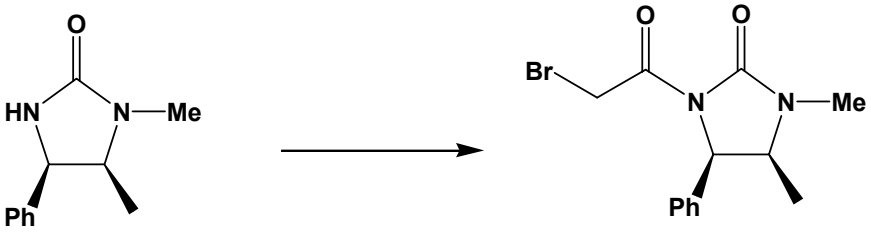


This route was only partly successful since we were not able to cleanly form the indolizidine ring or conduct the reduction steps in a high yield without significant loss of the auxiliary. These frustrations led to the development of the sultam chiral auxiliary (*vide infra*).

3.2.1.2 Imidazolidinone

While working on the Evans oxazolidinone we encountered some difficulty with the reduction of the amino acid to the amino alcohol. In the event that we would not successfully be able to resolve this problem we decided to try a similar auxiliary, the imidazolidinone. Made in a similar manner, from the diamine, rather than the amino alcohol, the imidazolidinone strategy was in other ways identical to the above oxazolidinone one, and therefore the rationale for choosing this route is the same.

The hydrochloride salt of ephedrine was fused with urea, to give compound **134**.[178] This was treated with a base and bromoacetyl bromide, to give *N*-acyl derivative **143**.

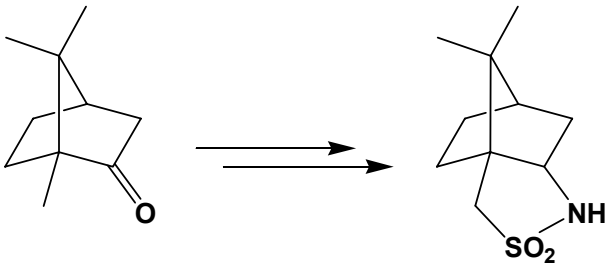


134 **143**

We also hoped that the greater proximity of the phenyl group in this auxiliary, compared to the oxazolidinone would result in enhanced diastereoselectivity.

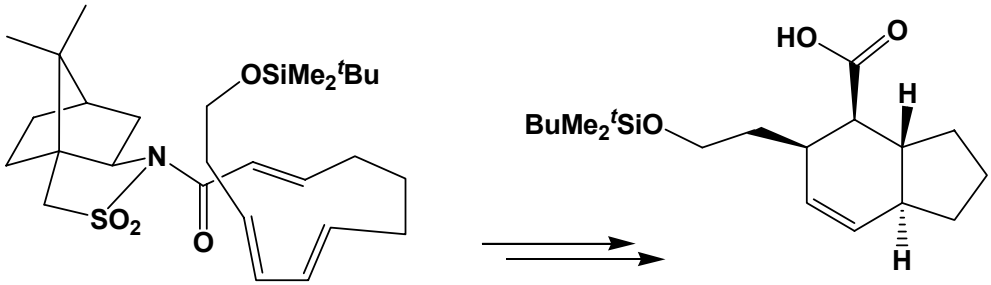
3.2.1.3 Oppolzer Sultam

The camphor moiety has attracted the interests of synthetic chemists throughout the history of organic chemistry. Among the many features that make it so attractive a molecule are its abundance in enantiopure form, crystallinity, and ease of transformation into a variety of useful compounds. Oppolzer has pioneered the use of the camphor sultam auxiliary in asymmetric reactions. By a series of transformations, either enantiomer of camphor can be transformed into its corresponding sultam [e.g. **135**], and then acylated with a suitable dienophile, such as a crotonyl moiety.[187]



camphor **135**

The real power of the method becomes apparent when we consider the use of these auxiliaries in intramolecular Diels–Alder reactions such as in **Scheme 48**.[148] In this case, four new stereogenic centres are formed in a single step, each with completely defined relative and absolute configuration.



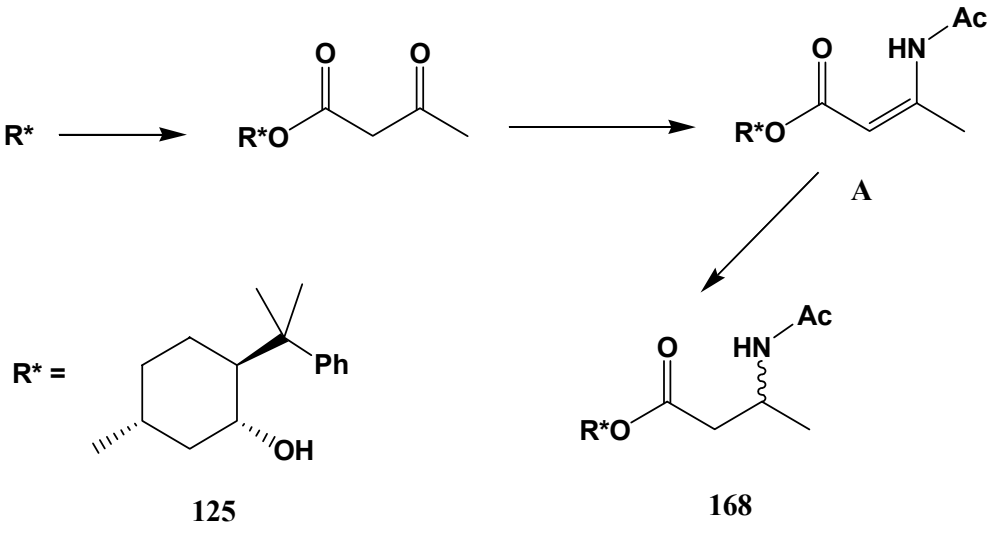
Scheme 48 – An Intramolecular Diels–Alder Reaction using the Oppolzer Sultam

Once again, in our systems, we intended to use the auxiliary to synthesise a vinylogous urea, with a chiral auxiliary attached. We anticipated that the auxiliary would selectively block one face of the double bond, and thereby present only the other face to the reductant.

This auxiliary was most successful, but one further auxiliary was attempted in order to get a chiral vinylogous urethane.

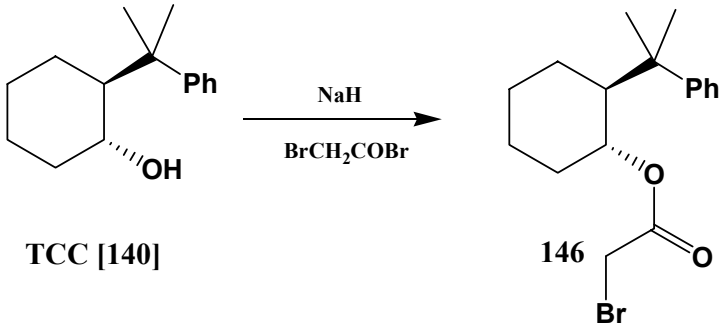
3.2.1.4 Comins Cyclohexyl Auxiliary

The successful reduction of β-acetamidocrotonates (**A** in **Scheme 49**) in the synthesis of chiral β-amido esters [**168**] by d'Angelo and co-workers[149] prompted us to look at the arylcyclohexyl chiral auxiliaries. Although these systems had been used successfully for many years, they suffered, until recently, from one major drawback: the limited availability, especially of the 8-phenylmenthol [**125**] type of auxiliary, originally developed by Corey and co-workers.[144]



Scheme 49 – Chiral Esters in Asymmetric Synthesis

A review by Comins and Guera-Weltzein[150] in 1996 suggested that the cumyl based auxiliaries might be more effective than other auxiliaries in the synthesis of alkaloids. This, coupled with their ease of synthesis, and the fact that in our laboratories we had not achieved much success with the synthesis of the 8-phenylmenthol auxiliaries, inspired us to look into the related *trans*-2-(α-cumyl)cyclohexanol (**TCC**). Esterification of this alcohol with bromoacetyl bromide would provide us with ester **146** that we could use in our generalised alkaloid synthesis. Once we had performed the sulfide contraction on this ester, we would have a system very similar to that used by d'Angelo and co-workers.



TCC [140] **146**

3.2.2 Chiral Reductants[151]

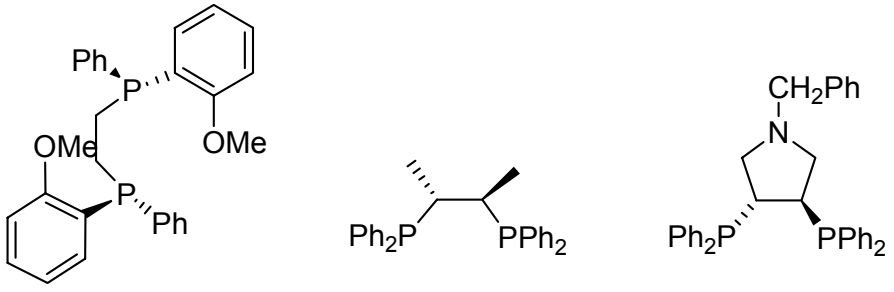
Finally, as a completely different approach we decided to make use of chiral reductants. Their use, especially in sub-stoichiometric amounts, is a rather elegant and relatively new development in asymmetric synthesis. The

distinguishing feature of these methods is the fact that the control of chirality no longer lies with the substrate, but with the reagent. These methods can be regarded as "third generation" asymmetric syntheses. Although the second generation methods are very useful, these increasingly popular third generation methods are attractive for two reasons: firstly, there is no longer a need to scour the chiral pool for suitable starting materials, and secondly, we can do away with the unattractive extra steps of attaching and removing the chiral auxiliary.

There are many possible transformations within this field of asymmetric reagents and catalysts, but the focus here will be on a few of the developments in reductions, since this is the area that was explored in this project. Even then, only a brief overview can be given of a few of the most important methods, since this is certainly one of the most widely explored areas of asymmetric synthesis. The idea was to begin probing the possibility of applying this step to our general method.

The first soluble chiral metal complexes used for asymmetric hydrogenations were designed and studied in the early 1970's. Since then, tremendous advances have been made in the range of possible substrates and the usefulness (in terms of selectivity and catalyst turnover), and yet the field of catalytic stereoselective reduction continues to expand at an impressive pace.[151]

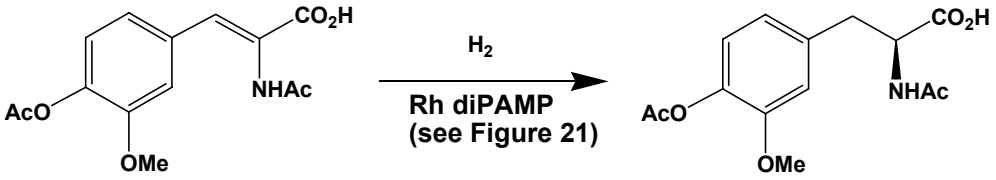
Although there are many important reports from the 1970's and before, this chapter focuses only on recent advances in catalytic asymmetric reactions promoted by transition metal complexes, especially ruthenium complexes with phosphine ligands, and their related predecessor rhodium complexes.



diPAMP Chiraphos Degaphos

Figure 21 – Three Commonly Used Chiral Ligands

A survey of the literature will reveal what is probably the first soluble chiral transition-metal complex for a catalytic asymmetric reaction to be a copper(II) complex.[151] This complex was found to catalyze the enantioselective formation of *cis*- and *trans*-2-phenylcyclopropane carboxylates from styrene and ethyl diazoacetate. Asymmetric hydrogenation of multiple bonds to form stereo-defined carbon centres is one of the most important reactions. It is not surprising, therefore that these are of the most well studied catalytic asymmetric hydrogenations. The versatility of phosphine ligands, together with seminal contributions by many scientists has resulted in a numerous such complexes. This focus on catalytic hydrogenation is due, in large part, to the commercialisation of Monsanto's L-DOPA synthesis (**Scheme 50**) in 1972.[152]

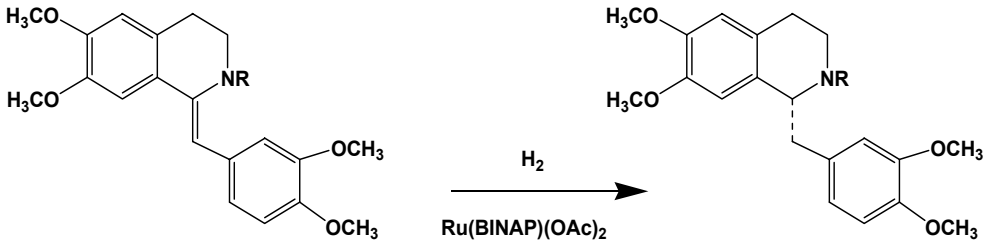


Scheme 50 – Monsanto Process for the Synthesis of L-DOPA

These achievements spurred many developments in this field, and although ruthenium has largely replaced rhodium, due to the broader group of substrates to which the latter is suited, the ligands that were developed in the early stages of this research have remained largely unchanged. Almost all of the ligands have two diphenyl phosphine moieties that are tethered to each other by a rigid bridge. This link, often in the form of a carbo- or heterocycle, or a biphenyl atropisomer, holds the phosphines in a specified configuration. **Figure 21** shows some of the popular ligands used, particularly in rhodium complexes.

One of the most remarkable developments that took place during the late 1980's and early 1990's, besides the advances in ligand design, was the synthesis of ruthenium- as opposed to rhodium-based chiral catalysts. The ruthenium BINAP [BINAP = 2,2'-bis(diarylphosphino)-1,1'-binaphthyl] catalysts in

particular have been very successful, and have been referred to as "second generation chiral catalysts".[153] BINAP ligands are formed as a pair of atropisomers, each accommodating a wide variety of transition metals to form a highly skewed seven-membered chelate ring whose geometry provides a chirally-distinct environment for reactions at the metal center. These characteristics seem to render these catalyst systems extremely efficient. Noyori *et al*[155] successfully applied these systems to the asymmetric reduction of prochiral olefins other than dehydroamino acid compounds and BINAP-mediated reductions have become synonymous with this research group. One application of BINAP-Ru(II) complexes in alkaloid synthesis is illustrated below. These carboxylate-containing ligands were easily synthesised and used in the hydrogenation of isoquinoline alkaloid precursors (**Scheme 51**).[154]



R = $COCH_3$, CH_3, H, $COCF_3$, etc. ***ee* = 95 - 99.5%**

Scheme 51 – Synthesis of Isoquinoline Alkaloids using Catalytic BINAP Reduction

Although this reaction is commonly sluggish (often requiring >48 hours and high pressures of hydrogen), it gives remarkably high enantioselectivities,[155] and we hoped this reduction of an enamine bond would be as effective with our enamine compounds. The one drawback, which we believe could have been the downfall of this approach for us, was that in the initial studies most of the (*E*)-enamide substrates were inert to these reduction conditions. This could have been due to the sterically more demanding (*E*)-substrates that contained a pivaloyl group on nitrogen. However, it has also been noted that these reductions are extremely sensitive to the reaction conditions, and changing the pressure, for example, from 2atm to 100 atm of hydrogen can change the reaction outcome

from no selectivity to *ee*'s of 90%. There was therefore a good chance of success, assuming we could find suitable conditions.

Although the ruthenium catalytic cycle is not as well understood as the rhodium equivalent, which was elegantly deciphered through the work of Halpern and Brown,[156][157], it is nonetheless believed to have certain common characteristics. One of the most important of these, for effective hydrogenation, appears to be the attractive interaction between the transition metal and the carbonyl and/or amide groups of the substrate, which appears to involve a ruthenium monohydride species. The fact that our alkaloid precursors also contained at least one carbonyl group in close proximity to the prochiral atoms was a further motivation to attempt these reductions.

Chapter 4

Results and Discussion – Asymmetric Syntheses

4.1 Synthesis of Chiral Auxiliaries

A number of model 2-pyrrolidinylidenes containing the various chiral auxiliaries were synthesised in order to try to implement a "chiral auxiliary" strategy successfully. These auxiliary-containing 2-pyrrolidinylidene compounds were subjected to various reductions to investigate the diastereoselectivity induced by the chiral auxiliary. The most promising compounds were further elaborated to the corresponding 8-substituted indolizidines, which by further transformation could yield the natural products tashiromine and epitashiromine. The following three chapters expand on these aspects in succession, namely the synthesis of chiral auxiliaries followed by the reduction studies and then the syntheses of the natural products using this approach.

Synthesis of chiral auxiliaries

These are described essentially in chronological order of their development, although we worked on several systems simultaneously. It is difficult to evaluate the overall success of using each chiral auxiliary since problems and successes encountered were often quite distinct, but we can consider that a series of successful reactions should lead to a high yield (and high enantioselectivity) of the natural product concerned. The most "successful" chiral auxiliary in this regard was the camphor sultam, since we were able to produce the two natural products tashiromine and epitashiromine from indolizidines containing this chiral auxiliary. The remaining auxiliaries were all synthesised in high yields, but in each case we encountered a problematic step in the production of the natural products. Nevertheless, these systems are easy to set up, and may be more useful in other alkaloid skeletons or under different conditions.

4.1.1 Synthesis of 1,3-Oxazoline [130]

The frequent use of an ester functionality in our vinylogous urethane systems, together with the immense versatility of the 2-oxazoline ring system as a protected carboxylic acid, lead us to believe that this might be a useful chiral auxiliary. We envisaged that it would be possible to "unmask" the carboxylic acid (**IV** in **Figure 22**) and reduce this, or indeed even reduce the oxazoline moiety (**III**) directly, to give the desired alcohol in the target indolizidine (**1** in **Figure 22**).

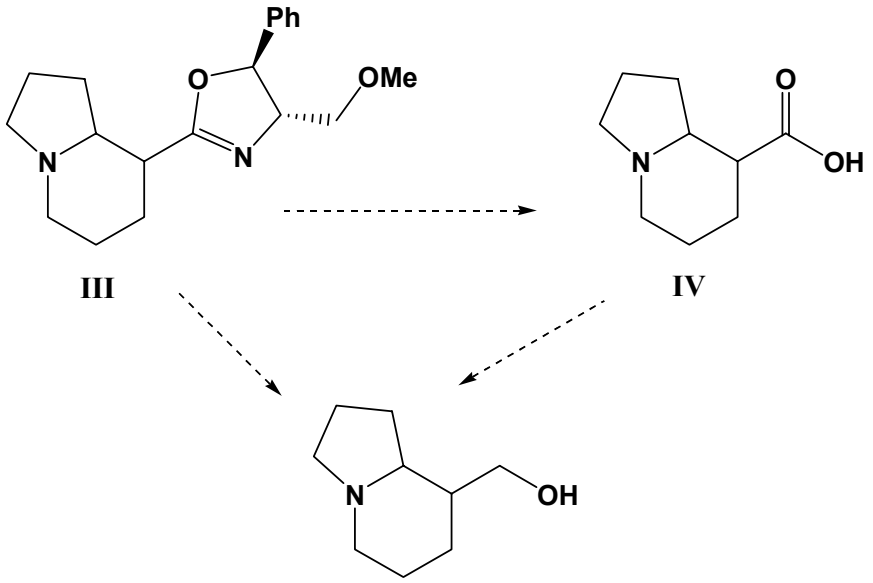


Figure 22 – Envisaged Synthesis of Tashiromine and Epitashiromine

The 2-oxazoline ring system, effectively a cyclic imino ether, has been known since 1884.[158] Methods for the preparation of these 2-oxazolines are varied, and include almost everything from the harsh cyclodehydration of carboxylic acids, to the mild opening of strained epoxides and aziridines. A traditional method often used with acid-stable substrates is the condensation of an imino ether with an amino alcohol. This method was used by Hajdu in the synthesis of an antitumor phospholipid.[159]. Our attempts to synthesize **130** by bromination of **129** were disppointing, as were attempts to protect the free hydroxyl in **169** (or the bromo equivalent). Although we were easily able to synthesize the protected chloro analogue **131**, we were unable to get this

compound to undergo sulfide contraction, and were not successful at *in situ* halogen substitution to give the more reactive bromo or iodo compounds.

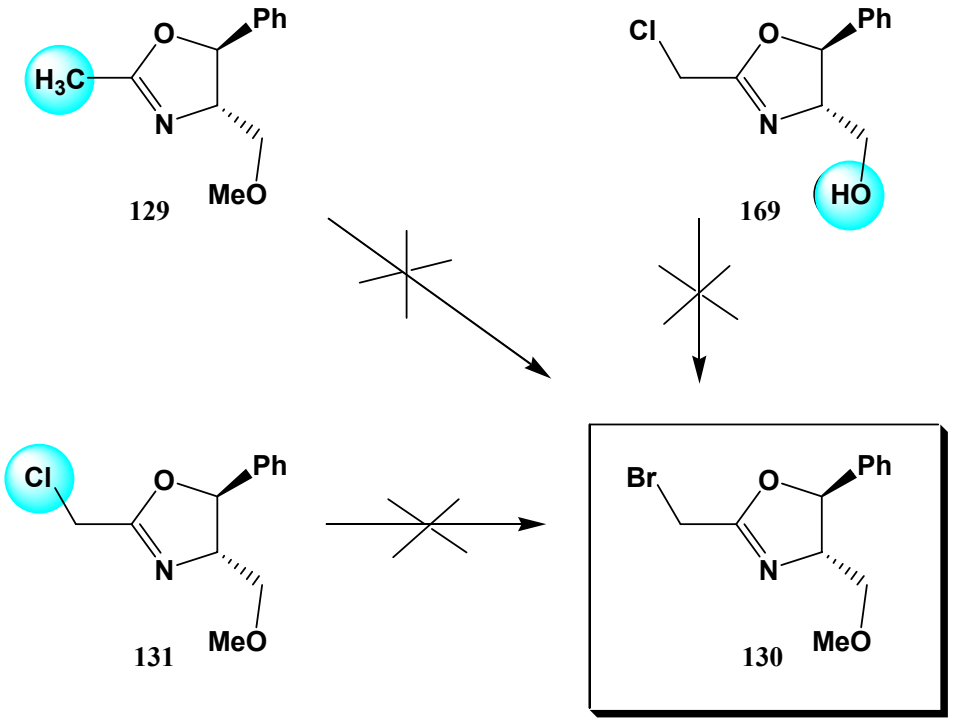
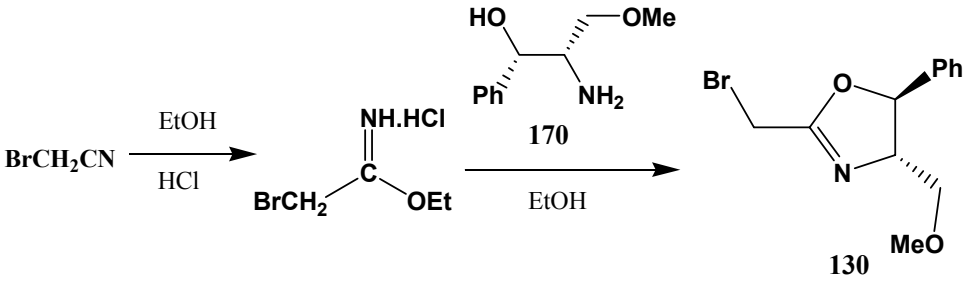


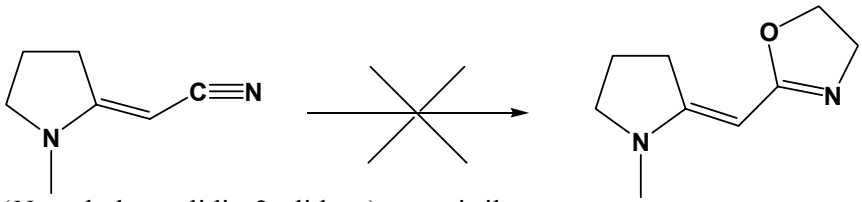
Figure 23 - Unsuccessful Routes to Oxazoline [**130**]

We were eventually successful in synthesizing **130** by condensing the imino ether derived from bromoacetonitrile with the chiral amino alcohol 2-amino-3-methoxy-1-phenylpropanol [**170**].



The overall yield for this auxiliary was only 20%, but the NMR spectra correspond well with the literature data for the chloro analogue. The oxazoline **130** is not reported in the literature, however, even with the chiral auxiliary in hand the synthesis had to be abandoned since we could not effect the sulfide contraction under any circumstances. We also attempted to synthesise the

oxazoline directly on the indolizidine ring by treatment of *N*-substituted (*E*)-2-(pyrrolidin-2-ylidene)acetonitriles under conditions that should produce an oxazoline, but these did not produce any new product.

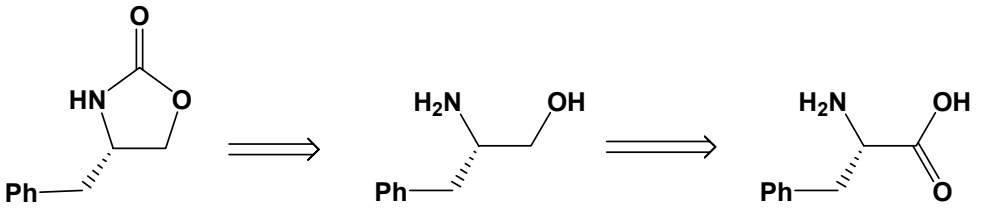


(*E*)-2-(*N*-methylpyrrolidin-2-ylidene)acetonitrile

4.1.2 Synthesis of 2-Oxazolidinone [132]

A conceptually simpler approach than the one adopted above was to synthesise a chiral bromoacetic acid derivative. The remaining chiral auxiliaries, namely three "amides" and one ester were made using this tactic.

This next auxiliary was chosen mainly because of the ease with which ***either*** enantiomer can be prepared in high purity from readily available amino acids.

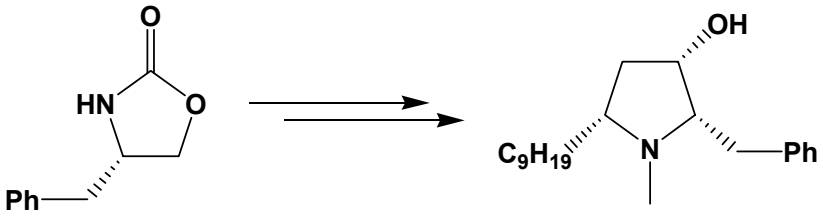


132 **133** **L-phenylalanine**

Originally developed by Evans for use in asymmetric Lewis acid-catalysed Diels–Alder reactions of chiral α,β-unsaturated *N*-acyloxazolidinones,[160][161] and for the asymmetric synthesis of *anti*-β-hydroxy-α-amino acids,[162] oxazolidinone **132** has since gained immense popularity for a wide variety of synthetic uses. In a recent report, Sibi and Ji used oxazolidinones in conjunction with various Lewis acids to effect enantioselective conjugate radical additions,[163] and in another report, Phoon and Abell used the Evans' oxazolidinone to accomplish solid-phase Aldol and conjugate addition reactions.[164] A further reason for choosing this auxiliary is the ease with which it can be removed using lithium aluminium hydride in THF at 0 °C,[165] or simply using sodium methoxide in methanol.[166

Early work on quinolizidine lupine alkaloids utilised similar reductions of achiral systems, and hence there was some precedent for this methodology. Unfortunately, this initially-perceived benefit proved to be the downfall of this auxiliary for our synthetic methodology, since we found that under all tested reaction conditions the auxiliary was cleaved during the reduction step, leaving a complex mixture of products.

Oxazolidinone **132** has recently been used by Verma and Ghosh in the stereocontrolled total synthesis of a novel pyrrolidine alkaloid antibiotic (+)-preussin, isolated from the fermentation broth of *Aspergillus ochraceus*.[167]



132 (±)-preussin

As a derivative of the amino acid L-phenylalanine, oxazolidinone **132** is easily synthesised in two steps: reduction to L-phenylalaninol [**133**] and condensation with diethyl carbonate in the presence of potassium carbonate, according to the method developed by Gage and Evans.[168] Reduction of the carboxylic acid was accomplished in high yield using the synthesis described by Abiko and Masamune,[169] which not only uses inexpensive reagents ($NaBH_4$ and H_2SO_4), but also avoids the need for the careful control of reaction conditions that plague some of the other hydride and borane methods.[170][168][171][172]

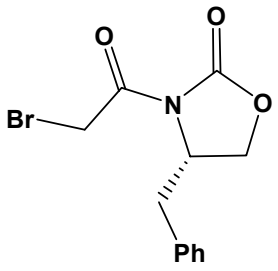
Using this method, L-phenylalanine was added to sodium borohydride and fresh concentrated sulfuric acid in tetrahydrofuran at 0°C (the use of old, presumably impure sulfuric acid or higher reaction temperatures resulted, in our hands, in considerably lower yields). Once the addition was complete, the mixture was stirred overnight at room temperature. Since this method generates borane *in situ*, methanol was added to destroy any unreacted borane, and the solution was concentrated *in vacuo*. The solution was basified with 5 M NaOH solution, and heated under reflux for three hours in order to decompose the

borane-phenylalaninol complex. Work-up and extraction afforded a white solid, which was recrystallised from hexane/ethyl acetate mixtures to give phenylalaninol [**133**] in 97% yield as white needle-like crystals, whose physical data (m.p., $[\alpha]_D^{23}$, and ^{1}H NMR data) are in close agreement with the literature values.[168] The ^{13}C NMR data are not quoted in this reference, but agree well with expected values, showing, besides the four aromatic carbons, a benzylic carbon at $\delta = 40.9$, together with two peaks at $\delta = 54.1$ and 66.3 corresponding to the C–NH_2 and C–OH nuclei, respectively. The reduction of phenylalanine directly with borane dimethyl sulfide complex and boron trifluoride diethyl etherate gave similar yields (93%), but the generation of hydrogen and dimethyl sulfide as by-products of this procedure make it a more dangerous and inconvenient procedure. The product from this direct reduction gave identical spectroscopic data to that already mentioned.

The formation of the oxazolidinone is accomplished by reaction with the ortho ester, tetraethyl orthocarbonate, or diethyl carbonate and potassium carbonate. In our case, we found excellent results (89% yield) using freshly distilled diethyl carbonate and anhydrous potassium carbonate. If the diethyl carbonate was not distilled before use, the yields dropped to around 67%. The oxazolidinone obtained had physical characteristics in close agreement with the literature data.[168] Again there were no ^{13}C NMR data given in this reference, but the appearance of a carbonyl signal at $\delta = 159.6$ in an otherwise relatively unchanged spectrum serves to confirm the formation of the product.

Preparation of (4*S*)-3-bromoacetoxy-4-phenylmethyl-1,3-oxazolidin-2-one [141]

The reaction of **132** and bromoacetyl bromide in toluene using either sodium hydride or *n*-butyl lithium as base, under vigorous stirring, gave the desired bromoacetamide **141** in 81% yield as a viscous pale yellow oil. The formation of a by-product, as a result of a double addition of the oxazolidinone to the bromoacetyl bromide, caused a decrease in yield. Vigorous stirring was required in order to minimise the yield of this double adduct **142**.



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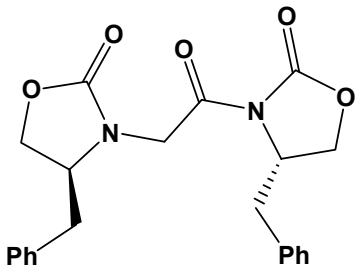


142

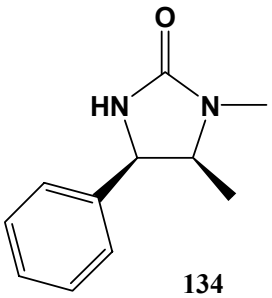
The *N*-bromoacyl oxazolidinone **141** has been used in a total synthesis of a sphingosine derivative from *Anemonia sulcata*[173]as well as in the asymmetric synthesis of several *anti*-β-hydroxy-α-amino acids.[162] Unfortunately, no spectral data were given for this compound so no comparisons could be made. We were, however confident about the formation of the *N*-bromoacetyl oxazolidinone, from the data collected. Two new signals at δ = 165.8 and 28.3 in the ^{13}C NMR spectrum, resulting from the two new carbon atoms on the molecule, attested to the success of the reaction. The absence of the NH signal of the starting material in the ^{1}H NMR spectrum of the product, and the presence of two doublets at δ = 4.57 and 4.50, as an "AB quartet", in the expected region for the methylene protons alpha to bromine provided further corroborative evidence. These signals were observed in all the chiral bromoacetyl derivatives and arise from diastereotopic α-methylene protons each giving a double at slightly different chemical shifts. Finally, there is also a new C=O band in the FTIR spectrum at 1710 cm^{-1} in addition to that for the oxazolidinone ring carbonyl at 1780 cm^{-1}.

This chiral auxiliary was synthesised in a high overall yield of 70%, readily underwent sulfide contraction reactions with a range of thiolactams, and was easily purified and recovered from unsuccessful reactions. It would therefore have been an ideal candidate for the synthesis of indolizidines if it were not for the fact that it was easily cleaved in later steps.

4.1.3 Synthesis of 2-Imidazolidinone [134]

We next turned out attention to the chiral imidazolidinone **134**, because of its similarity with oxazolidinone **132** and also the greater proximity of the bulky phenyl group to the nitrogen of the auxiliary. Once incorporated as a chiral

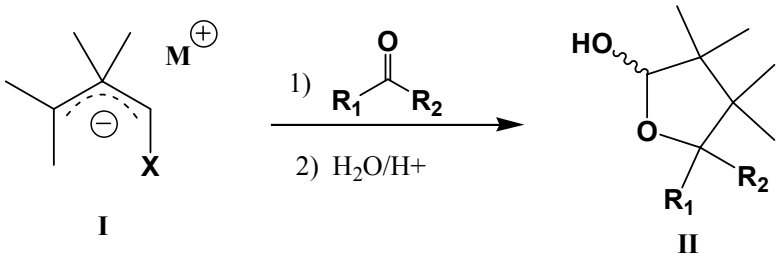
auxiliary in our synthetic scheme, the phenyl group would be closer to the double bond whose reduction we are trying to control, and hence we hoped that this would lead to improved diastereoselectivities.



134

An additional reason for examining this auxiliary was the difficulty we were experiencing with the reduction of amino acids required for the synthesis of oxazolidinones, discussed above. This problem was eventually traced to the use of old reagents and excessive temperature, but in the interim we managed to produce significant quantities of imidazolidinone **134**.

Helmchen and co-workers developed the cyclic urea derivative for use in the first enantioselective homoaldol reaction involving a chiral allyl system of type **I** (see **Figure 24**).[174] The one-step fusion of ephedrinium chloride [$PhCH(NH_2)CHCH_3NHCH_3$], with urea was developed by Close[175] in 1950 for the synthesis of racemic **154**. Heating these two reactants for two hours at between 170 and 200 °C gave the desired product as white needles, although in a disappointingly low yield of 28%. The physical characteristics of this compound were in close agreement with that reported in the literature.[175]



I **II**

X = Imidazolidinone **134**

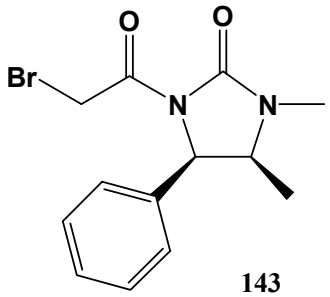
Figure 24 – Use of a Chiral Imidazolidinone in Aldol Reactions

Although not as popular as the oxazolidinone derivatives, this compound has been used in several synthetically useful reactions. For example, a recent

review by Wulff[176] describes the formation of several imidazolidinone Fischer carbene complexes, and their utility in asymmetric synthesis.

Preparation of (–)-(4*R*,5*S*)-3-bromoacetoxy-1,5-dimethyl-4-phenyl-1,3-imidazolidin-2-one [143]

Using the same procedure as for oxazolidinone **132**, the imidazolidinone was converted into the bromoacetyl derivative **143**. In this case, however, no bis adduct was isolated.



143

This appears to be a novel compound, although the NMR and other data for this compound offer strong evidence for its formation. The diastereotopic α-methylene protons appear in the ^{1}H NMR at δ = 4.63, in same region as the previous compounds with α-methylene protons, and are the only new signals when compared to the spectrum of the starting material. In addition, the broad NH signal from the starting material is no longer observed in the spectrum of the product. In the ^{13}C NMR spectrum, two new signals are observed: one at δ = 28.6 in the region expected for the methylene α to the bromine atom, and the other at 171.0 is attributed to the carbonyl group. The FTIR shows two strong carbonyl absorptions in the region 1700–1730cm^{-1}. Comparison of these data with the data obtained by Clark and Bender for the corresponding chloro analogue[177] is further evidence for its formation (**Table 4**).

Table 4 – Comparison of Physical Data for **143** with Literature Values

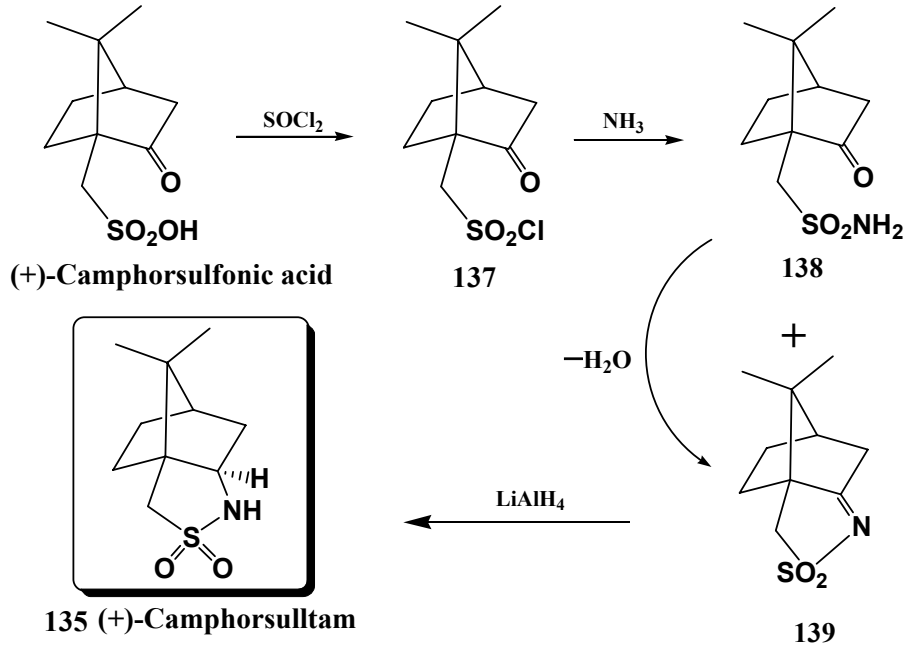
	Clark and Bender[177] Chloroacyl imidazolidinone	**Krause Bromoacyl imidazolidinone**
FTIR **C=O absorptions**	1725 $^{cm-1}$ 1700 $^{cm-1}$	1726 cm^{-1} 1700 cm^{-1}
^{1}H NMR **"AB quartet" (double doublet)**	$\delta = 4.75$	$\delta = 4.63$
^{13}C NMR acyl group signals	$\delta = 28.1$ $\delta = 165.2$	$\delta = 28.6$ $\delta = 171.0$

In our hands, however, this auxiliary suffered from the same drawbacks as the oxazolidinone, namely loss of auxiliary during the reduction step. The initial synthesis of the chiral auxiliary was also very low yielding, resulting in a poor overall strategy that was abandoned for the sultam described hereafter.

4.1.4 Synthesis of Camphor Sultam [135]

The next chiral auxiliary we looked at was the extremely popular sultam (1*R*,5*R*,7*S*)-10,10-dimethyl-3,3-dioxo-3-thia-4-azatricyclo[5.2.1.0^{1,5}]decane [**135**]. This compound was developed by Oppolzer and co-workers, initially for enantioselective Diels–Alder reactions,[159] and hence it has since become known simply as the Oppolzer sultam. The availability of both enantiomers of camphor (as well as many of its derivatives) together with its crystallinity make it one of the most popular starting materials for the synthesis of chiral auxiliaries, for a wide variety of reactions. The amide bond that connects the auxiliary is also very easily cleaved, giving complete recovery of the auxiliary.

Although both (–)-(1*R*)- and (+)-(1*S*)-camphor-10-sulfonic acid are available commercially, they can be easily prepared from the respective enantiomer of camphor by treatment with a mixture of sulfuric and acetic acid, using the procedure by discovered by Reychler as early as 1898.[178]



There are several reported preparations of sultam (–)-(**135**)[179][180][181][182][183][184] as well as (+)-(**135**),[185] starting from the camphor-10-sulfonic acid. We followed the procedure of Davis and co-workers,[183] as in our hands, the other procedures, such as that of Vanderwalle and co-workers suffered from slightly lower yields, due to the necessity of isolating the (+)-(1*S*)-10-camphorsulfonyl chloride [**137**].[185] The acid chloride easily and rapidly hydrolyses back to the starting sulfonic acid unless care is taken to avoid moisture.

In the procedure by Davis the (+)-(1*S*)-10-camphorsulfonyl chloride is synthesised from (+)-camphorsulfonic acid by heating it in the presence of thionyl chloride in chloroform under reflux for several hours. The reaction progress was monitored by the evolution of SO_2 and HCl. The resultant (+)-(1*S*)-10-camphorsulfonyl chloride was not isolated, but converted directly into the (+)-(1*S*)-camphorsulfonamide by dropping the chloroform solution into a cold (0 °C) solution of NH_4OH over 1 hr. The reaction mixture was warmed to room temperature, the organic layer separated and the aqueous layer extracted with dichloromethane. Removal of the solvent yielded the (+)-(1*S*)-camphorsulfonamide (90%) together with a small amount (5–10%) of the (–)-(1*S*)-camphorsulfonylimine as a pale yellow crystalline powder. The sulfonamide

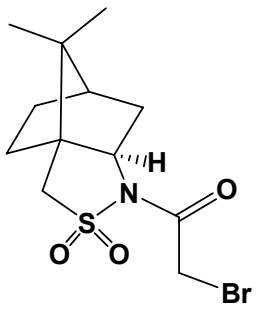
slowly dehydrates on standing to give greater amounts of the imine. In order to confirm the presence of the (+)-(1*S*)-10-camphorsulfonamide, a small portion of the chloroform solution was removed, and the solvent evaporated to give a pale yellow solid, which was subjected to recrystallisation from hexane in an anhydrous environment to give the (+)-(1*S*)-10-camphorsulfonyl chloride as white plates, m.p. 65–66°C (lit.[185] m.p. 65–66°C). The ^{1}H NMR data and other physical data were in agreement with literature values. A small portion of the sulfonamide [**138**] was also further purified by chromatography to yield pure (+)-(1*S*)-camphorsulfonyl amide as a white crystalline powder with m.p. 130–132 °C (lit.[185] m.p. 133–134°C). There was close agreement between the NMR data for this compound and literature values.[183][185]

The bulk of the camphorsulfonyl amide was not purified, however, but was dissolved in toluene and stirred over a strongly acidic ion-exchange resin, while simultaneously removing the water azeotropically. After 4 hr the solution was cooled slightly, and dichloromethane added to dissolve the (+)-(1*S*)-camphorsulfonamide as it crystallised. The ion-exchange resin was removed by filtration, and the solvent was evaporated to give the crude product, which was purified by recrystallisation from absolute ethanol. The resulting white crystalline product, obtained in quantitative yield, was confirmed as the imine **139** by comparison with literature data,[183][185] m.p. 223–225°C, $[\alpha]_D^{25}$ = –34.3 (c 1.82, $CHCl_3$); (lit.[183] 90–95%, m.p. 225–228 °C, $[\alpha]_D^{22}$ = –32.3 (c 1.8, $CHCl_3$).

There are several methods to reduce the imine to give the sultam, including catalytic hydrogenation over Raney Nickel[182] and reduction with lithium aluminium hydride. The low solubility of the imine in THF meant that large volumes of THF would be needed to perform the reduction by this method. Davis[183][186] has overcome this problem by using a Soxhlet extraction procedure to slowly siphon the imine into the reducing lithium aluminium hydride slurry. Using this method, we obtained a yellowish solid after work-up, which was recrystallised from absolute ethanol to give the desired sultam chiral auxiliary **135** as a white solid in 98% yield, m.p. 182–183°C, $[\alpha]_D^{22}$ = –34.2 (c 1.03, EtOH); lit.[183] 92%, m.p. 182–183°C, $[\alpha]_D$ = –30.7 (c 2.3, $CHCl_3$). There was good

agreement of the NMR spectral data of this compound with literature values. [183][185]

Preparation of (1*R*,5*R*,7*S*)-4-bromoacetoxy-10,10-dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0^{1,5}]decane [144]

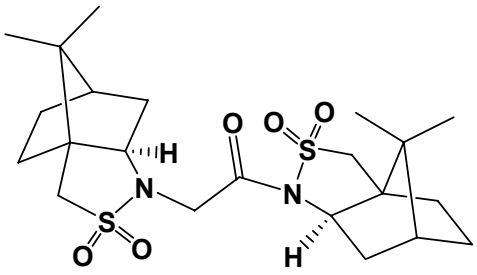


144

The bromoacetamide **144** was easily synthesised by using the same procedures as before, namely treatment of a basic solution of the sultam **135** with bromoacetyl bromide. Using either sodium hydride or butyllithium to abstract the *N*-proton from the sultam, and then reaction of this anion with bromoacetyl bromide gave the desired product. The resulting acetamide was purified by recrystallisation from hexane/ethyl acetate mixtures to give white needles. Although the analogous chloroacetamide was prepared by Oppolzer[148] by the reaction of the sultam with vinyl chloroacetate, there was no indication that the bromoacetamide had ever been prepared before, so we had no literature values for the physical data. The presence of two sets of doublets at δ = 4.34 and 4.20 in the ^{1}H NMR spectrum, sharing a geminal coupling constant of J = 13.1 Hz, and the absence of the NH signal was strong evidence for the presence of a methylene group alpha to bromine. Further evidence for the product was obtained from the ^{13}C NMR spectrum, where the carbonyl carbon resonated at δ = 164.4. A new signal at δ = 27.5 was assigned to the carbon atom alpha to bromine. Absorptions in the FTIR at 1708 cm^{-1} (C=O), 1338, and 1168 cm^{-1} (S=O) are in the region expected for those stretches. This compound also gave excellent microanalysis results, consistent with the molecular formula $C_{12}H_{18}NO_3SBr$.

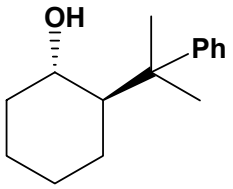
As was the case with the bromination of 2-oxazolidinone **132**, the sultam bis adduct **145** was isolated in 1–15%, and tended to be formed in greater quantities if the stirring was not vigorous during the addition of bromoacetyl bromide to the sultam anion. This dimer was not characterised fully and was easily removed by chromatography or recrystallisation. The bromoacetic acid

formed from the excess bromoacetyl bromide was more problematic, and traces could be found in most NMR spectra.



145

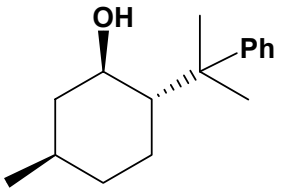
4.1.5 Synthesis of 2-Cumylcyclohexanol [140]



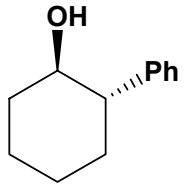
140

Finally, the ease with which the amide based chiral auxiliaries hydrolyzed from the vinylogous urethanes during the reduction of those compounds led to the exploration of a different chiral auxiliary altogether. We were looking for a chiral ester functionality, as this had worked well with exocyclic vinylogous ethyl urethane compounds in previous studies, as well as the model-study section of this project.

Enantiopure (–)-8-phenylmenthol [**125**] is a highly effective chiral auxiliary which has been known for a long time, and has been used in several types of reactions as a powerful stereodirecting group.[187][188] Although **125** is commercially available, or can be prepared from (+)-pulegone in 5 steps,[189] the (+) enantiomer is very expensive, or requires 8 steps to synthesize from (–)-citronellol.[190] Whitesell developed two *trans*-2-cyclohexanols, as alternatives to 8-phenylmenthol.[191][192][193] T*rans*-2-phenylcyclohexanol [**126**] can be easily prepared as either enantiomer, but it is generally not as effective a chiral auxiliary as *trans*-2-(α-cumyl)cyclohexanol (TCC) [**140**]. The procedure used by Whitesell is complicated by a



125



126

chromatography step needed to remove the unwanted epimer, so Comins developed a simpler and inexpensive route to both enantiomers using enzymatic resolution.[194] We decided to use this Comins route in order to have access to both enantiomers of the chiral auxiliary.

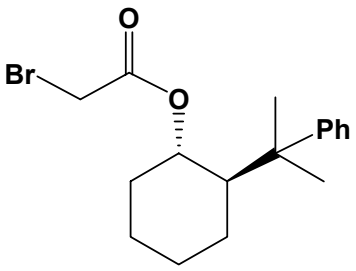
The synthesis is a two step procedure, firstly requiring the formation of α-cumylpotassium, which was accomplished in 2 days at room temperature by stirring a solution of α-cumene with butyllithium and potassium *tert*-butoxide. Although Comins used potassium *tert*-pentoxide, we found that reasonable results were obtained with the *tert*-butoxide. The racemic TCC [**140**] was then easily obtained by slowly adding cyclohexene oxide to this dark purple solution. After workup, white crystals were obtained by distillation of the residue and cooling the resulting oil at –5 °C for several days with a seed crystal of racemic TCC.[1] After further recrystallisation from petroleum ether (b.p. 30–60 °C), the white crystals obtained had m.p. 47.5–49.0 °C, which compared favourably with the literature values [lit.[193] 45.5–47.5°C and 49.5–51.5°C.[194]. Although this auxiliary was initially used in its racemic form in our synthesis, we later resolved the compound by employing a modification of the procedure developed by Triantaphylides and co-workers.[195] The enzymatic esterification procedure was carried out with lauric acid and lipase from *Candida rugosa*. The progress of lauryl ester formation was monitored by chiral-column HPLC. Comins found that the best separation of enantiomers was achieved if the enzymatic resolution was performed twice with only 45% conversion to the ester. Initially we struggled to obtain a good rate of reaction, but eventually traced the problem to two inactive batches of enzyme, and solved the problem by utilizing 1000 fold excess of the enzyme. The recovered enzyme could, however be reused without any further loss of activity. Since the (–)-TCC is esterified preferentially, the remaining (+)-TCC is easily separated by distillation.

The physical characteristics including optical rotation of the two enantiomers were once again comparable to the literature values. Ideally this resolution process should be conducted several times until a suitable e.e. is

[1] We are grateful to Prof. Comins for the seed crystals supplied.

obtained, but as we were merely trying to demonstrate a "proof of concept" we only required a slightly enriched enantiomer.

Synthesis of 1-Bromoacetoxy-(1*R,2*R**)-2-(1-methyl-1-phenyl)ethyl cyclohexanol [146]**



146

Conversion of **140** into the bromoacyl ester was accomplished in good yield by treating the alcohol with sodium hydride in toluene, and adding a solution of bromoacetyl bromide in toluene. The compounds obtained in this manner were pale yellow oils. These appear to be new compounds, so there are no literature values with which to compare our data; however the absence of the strong OH band in the FTIR spectrum, together with the appearance of the carbonyl band at $\tilde{\nu}$ = 1731 lead us to believe that the correct compound was indeed formed. The ^{13}C NMR spectra of **146** and **140** are very similar, except for the addition of a carbonyl signal at δ = 166 and methylene carbon signal at δ = 33. In the ^{1}H NMR spectrum the appearance of the signals for the diastereotopic protons as two doublets at δ = 3 is once again typical of all the bromoacyl chiral auxiliaries. In addition, the high-resolution mass spectrum shows a characteristic doublet molecular mass fragment at *m*/*z* = 338.0877 and 340.0858. These molecular ions showed very low abundances, but do give the molecular formulae of $C_{17}H_{23}O_2{}^{79}Br$ (*m*/*z* calculated at 338.0881). The molecular ion was confirmed by using a "softer" ionisation technique, although this chemical ionisation mass-spectrometer was only available for low-resolution detection.

Chapter 4

4.2 Synthesis of Chiral Enaminones

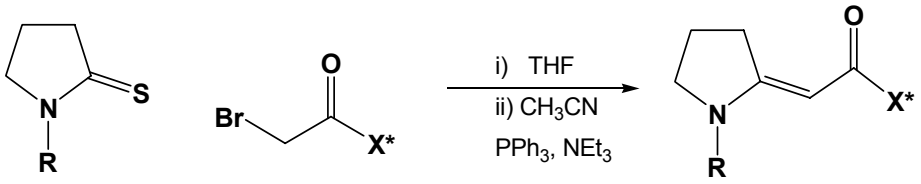
With sufficient quantities of the chiral auxiliaries in hand, we were now in a position to form the enaminones and to test the efficacy of the chiral auxiliaries at inducing stereoselectivity. *N*-methyl-2-pyrrolidinylidenes were first synthesised, and then a group of compounds containing an *N*-3-acetoxypropyl moiety instead of the methyl on the nitrogen of the pyrrolidine. This second set of compounds could be elaborated to yield chiral 8-substituted indolizidines, which in turn would give us access to the natural products tashiromine and epitashiromine. This latter synthesis of indolizidine alkaloid targets is dealt with in the following section (Section 4.3).

Thiolactams used in these sulfide contractions have already been described in the section on the model study (Section 2.1), but we found with the more bulky bromoacetyl reagents that extended reaction times were needed in order to complete the salt formation (the first step in the sulfide contraction procedure). As in the model study, we found the ideal conditions required the salt formation to be performed in tetrahydrofuran (THF) rather than the more traditional acetonitrile (CH_3CN), since the low solubility of the salts in THF forced the reaction to completion. Each of the combinations of thiolactam and bromoacyl-chiral auxiliaries were dissolved in THF and stirred for several hours to 3 days, until TLC analysis showed consumption of the reactants. The solvent was then removed *in vacuo* and replaced with freshly distilled CH_3CN. Triphenylphosphine and triethylamine were added, and the workup was carried out in the usual manner. The obtained compounds were purified by chromatography, followed, in the case of solid samples, by recrystallisation.

4.2.1 *N*-Alkylpyrrolidinylidenes

Each of the chiral auxiliaries was used to synthesise either an *N*-methyl-2-pyrrolidinylidene or an *N*-(3-acetoxypropyl)-2-pyrrolidinylidene according to **Scheme 52**. Only the oxazoline **130** failed to give any product, even after a week

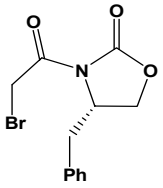
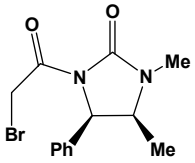
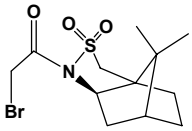
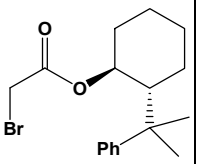
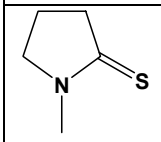
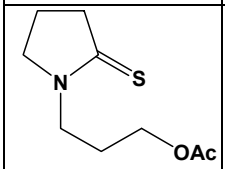
under reflux conditions; the remainder of the reactions were successful to varying extents and the product yields are summarised in **Table 5**.



Where **X*** = chiral auxiliary

Scheme 52 – Synthesis of Chiral *N*-Alkyl-2-pyrrolidinylidenes

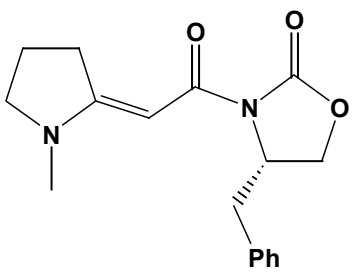
Table 5 – Percentage Yields of Sulfide Contraction Products Containing Chiral Auxiliaries (product numbers given in parentheses)

	Substrate with Attached Chiral Auxiliary			
				
Thiolactam	**141**	**143**	**144**	**146**
 **107**	78% solid [**147**]	52% solid [**153**]	22% solid [**154**]	Not attempted
 **108**	77% oil [**148**]	Not isolated, only recovered starting material	36% semi-solid [**155**]	86% semi-solid [**163**]

The main reason for the synthesis of the *N*-methyl series was to test the reduction step on readily synthesised material. The other series could be elaborated towards alkaloid targets, and would eventually be much more useful, but these would require at least two more steps (including a low-yielding cyclisation step) before they could be reduced.

4.2.2 Oxazolidinone-Containing Enaminones

(*S*)-4-Benzyl-3-[2-(1-methylpyrrolidin-2-ylidene)acetyl]oxazolidin-2-one [147]

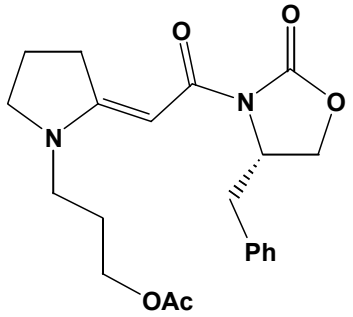


It was expected that the synthesis of this compound [**147**], which was accomplished in a high yield (78%) as fine pale yellow leaves after recrystallisation from hexane/ethyl acetate mixtures would allow us to examine the reduction methodology. The excellent microanalysis results were complemented by the NMR data, which showed a characteristic singlet for the *N*-methyl protons in the ^{1}H NMR spectrum at $\delta = 2.94$, as well as a singlet for the vinyl proton at 6.04. Three other signals: a triplet at $\delta = 3.47$, a multiplet at 2.02, and a doublet of triplets at 3.33 were assigned to the pyrrolidine ring protons. The disappearance of the two doublets for the protons α to the bromine in the starting material was also observed. In the ^{13}C NMR spectrum, the signals for the vinylic carbons are clearly observed at $\delta = 79.2$ and 154.3, which are typical values for such carbons. The FTIR spectrum is similar to that of the starting material, with the exception that the C=S signal at 1118cm^{-1} is absent. In addition to these data, excellent microanalysis data were obtained for this compound, which is consistent with the molecular formula $C_{17}H_{20}N_2O_3$. The high-resolution mass spectrum shows an *m*/*z* peak of 300.1459 that requires a molecular mass of 300.1474 g.mol^{-1} for the parent molecular ion. The base peak at *m*/*z* = 176 is very likely due to the chiral auxiliary and was perhaps an omen for later reactions.

Synthesis of 3-{2-[2-(*S*)-(4-Benzyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propyl acetate [148]

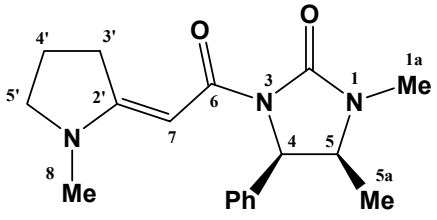
Using the same sulfide contraction methodology, vinylogous urea **148** was synthesised from *N*-(acetoxypropyl)pyrrolidin-2-thione and the *N*-bromoacetamide derivative of the Evan's oxazolidinone in 77% yield as a viscous yellow oil. No microanalysis results were obtained on this compound due to the difficulty of analysing liquid samples at the time, but there are close similarities in

the ^{1}H NMR data when compared to the *N*-methyl derivative: the vinyl proton signal is shifted slightly by 0.1 ppm to δ = 6.14, while the proton signals from the oxazolidinone as well as the pyrrolidine ring are located at almost identical positions. A singlet at δ = 2.09 integrates for 3 protons and is typical of the protons of an acetyl moiety. This signal is significantly shifted down-field when compared to that of the *N*-methyl protons of the previous compound. The signals for the protons of the propyl chain are partially obscured by the other signals and hence are difficult to assign accurately, however, their presence is clearly indicated in the ^{13}C NMR spectrum by 3 signals at δ = 20.8, 43.3, and 61.4. A DEPT spectrum shows that these carbon signals are not present in the ^{13}C NMR spectrum of the *N*-methyl derivative above, are all due to methylene carbons and appear in similar positions to the already identified carbons from the *N*-propyl chain of the thiolactam *N*-acetoxypropylpyrrolidin-2-thione. The carbon-13 spectrum also shows three carbonyl signals, at δ = 165.3, 167.6, and 171.1, but the characteristic thiocarbonyl signal (at *ca* 200 ppm) is absent. The vinyl carbon signals are virtually unchanged at δ = 79.28 and 154.11. This product resisted all attempts at crystallisation.



4.2.3 Imidazolidinone-containing Enaminones

(4*R*,5*S*)-1,5-Dimethyl-3-[2-(1-methylpyrrolidin-2-ylidene)acetyl]-4-phenylimidazolidin-2-one [153]



This compound was initially isolated as a pale brown solid in 60% yield. TLC analysis showed that there were several unidentified contaminants. Recrystallisation of the solid from a solution of ethyl acetate in an atmosphere of hexane gave white, hexagonal-shaped crystals. The microanalysis was

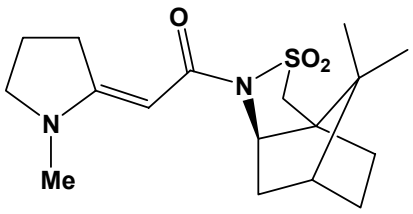
consistent with the formula $C_{18}H_{23}N_3O_2$. The other spectroscopic data confirm the formation of the C=C bond, for example, the vinylic proton signal at $\delta = 6.31$ and the vinylic carbon signal at 80.5, are in the expected region for this functional group. Again, the disappearance of the C=S signal in the IR spectrum is also an indication of the success of the reaction.

Only the *N*-methyl derivative was made since we later found that the reduction step was not diastereoselective using this system, and it suffered the same fate as the previous (oxazolidinone) auxiliary – namely concomitant hydrolysis during reduction. Due to the much lower overall yield of making the acylated imidazolidinone **143** in comparison to oxazolidinone **141**, it was decided not to pursue this route further.

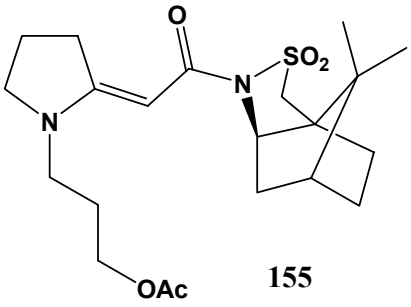
4.2.4 Sultam-containing Enaminones

(1*R*,5*R*,7*S*)-1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-(1-methylpyrrolidin-2-ylidene)ethanone [154]

and 3-{2-[2-(1*R*,5*R*,7*S*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propyl acetate [155].



154



155

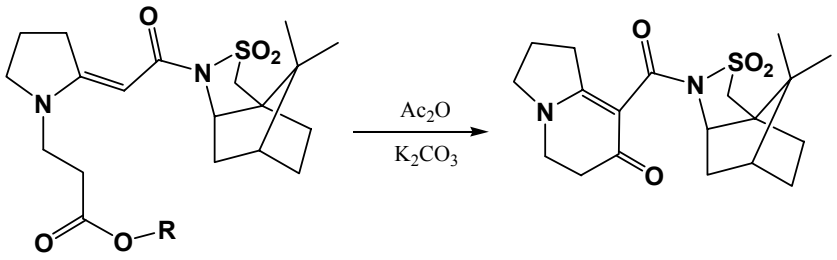
These pyrrolidinylidene compounds containing the sultam chiral auxiliary were made by the reaction of the bromoacetyl-substituted sultam with *N*-methyl- or *N*-(acetoxypropyl)pyrrolidine-2-thione, in 22% and 36% yield, respectively. It should be noted that all the compounds made with the *N*-acetoxypropyl chain were thick gums or semi-solids, while the *N*-methyl analogues were solids. In the case of compound **155**, a small amount of solid was eventually obtained by

careful recrystallisation in a Teflon test-tube at low temperature. Storage of this solid at room temperature, however, resulted in observable decomposition to a yellow semi-solid. Unreacted bromoacetyl sultam was always recovered from these reactions, regardless of the reaction times. In fact, prolonged salt formation (prior to the addition of PPh_3) led to the isolation of significant (ca. 30%) quantities of pure sultam. We were not able to verify the reasons for this poor yield, nor the reasons for the hydrolysis of the bromoacyl group from the sultam.

The *N*-methyl derivative [**154**] was isolated as a red viscous gum. Chromatography on silica, followed by recrystallisation in ethanol gave pale brown needles. The complexity of signals from the sultam auxiliary makes the NMR spectra difficult to assign completely, but the characteristic signals are present and identifiable in positions not very different to other *N*-methylpyrrolidinylidene compounds. The *N*-methyl ^1H NMR signal, for example at $\delta = 2.89$ and the vinyl proton signal at $\delta = 5.18$, both singlets, integrate for 3 and 1 proton, respectively. Microanalysis was problematic since the compound reportedly arrived slightly decomposed, but we eventually managed to get reasonable results (e.g. C found 60.55%, requires 60.33%) consistent with the formula $C_{17}H_{26}N_2O_3S$.

Compound **155** was also initially isolated as a red gum, and required two chromatographic purifications with CH_2Cl_2, and then with ethyl acetate/hexane mixtures, followed by recrystallisation from ethyl acetate/hexane to yield white orthorhombic crystals. Again the complexity of ^1H NMR signals makes assignment very difficult, but the vinyl proton is discernible as a singlet at $\delta = 5.26$ and the acetate CH_3 protons as a singlet at $\delta = 2.1$. The ^{13}C NMR shows an absence of a thiocarbonyl signal, but instead has two alkene signals at $\delta = 79.6$ and 164.6, the former signal correlates with the vinyl proton signal under 2-dimensional NMR experiments. Again the sample decomposed en route to the microanalysis laboratory, and in this case no reliable analysis could be performed.

Ethyl 3-{2-[2-(1*R*,5*R*,7*S*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propanoate [156]



156 **R** = CH_2CH_3
165 **R** = H
KOH / EtOH

During the synthesis of sultam-containing indolizidines (i.e. the cyclisation step) we encountered some problems in finding suitable reaction conditions, and we decided to try to utilise a slightly different cyclisation, namely acylative instead of alkylative cyclisation. For this purpose we required the ethyl ester **156**. This was made by sulfide contraction of ethyl 3-(2-thioxopyrrolidinyl)propanoate [**109**] with (1*R*,5*R*,7*S*)-2-bromo-1-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)ethanone [**144**] in an overall yield of 70%. This is a great improvement on the yields, compared to those described above, which suggests that it should be possible to improve the low yields obtained for the sulfide contraction of the other sultam-containing compounds.

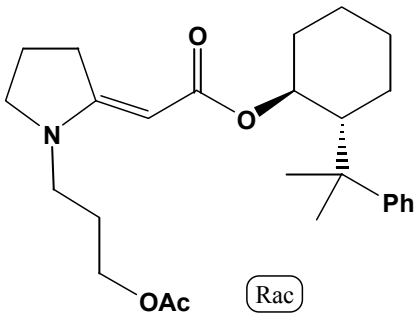
Compound **156** readily recrystallised from ethyl acetate/hexane mixtures at low temperature to give white orthorhombic flakes that were suitable for X-ray analysis. This structure refined quite well with a final R(int) of 6.4%, and was useful in testing the accuracy of the molecular modelling force-field developed separately (see Chapter 5 and 6). Although a final R factor of 9.94% was obtained, most of this "uncertainty" can be linked to the ester moiety occupying two positions. If these positions are fixed with equal populations the final R-factor and weighted values (w*R*2) become 2.61% and 6.14%, respectively. This analysis confirmed what was interpreted from the spectroscopic data, namely that the compound (with formula $C_{21}H_{32}N_2O_5S$) was synthesised successfully. A narrow melting point range (144–144.5°C) and good stability allowed us to obtain high-resolution mass spectral data to further substantiate the structure of this new

compound. It should be noted that the mass spectra of most of the sultam derivatives have a strong peak (usually the base peak) at m/z = 150. This can be attributed to the loss of SO_2 from the unsubstituted sultam **135**.

The ^{1}H NMR is again very complex due to the sultam proton signals, and assignment was largely based on comparison with other spectra. The IR spectrum shows two distinct carbonyl bands, consistent with 2 signals in the carbonyl region of the ^{13}C NMR spectrum.

4.2.5 *trans*-Cumylcyclohexane-containing Enaminones

[1-(3-Acetoxypropyl)pyrrolidin-2-ylidene]-(1*S,2*S**)-2-(1-methyl-1-phenylethyl)cyclohexyl acetate [163]**



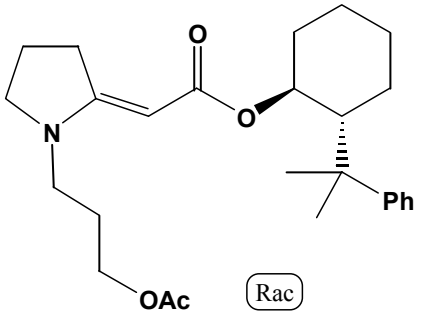
One attempt to form the *N*-methyl pyrrolidine enaminone was disappointing, and only traces of product were examined in the spectrum of the crude product, but since we had already established a protocol for the reduction of the enaminones that would give either *trans* or *cis* reduction there was no need to synthesise this model compound. Instead vinylogous urethane **163** was made by the reaction of 3-(2-thioxopyrrolidin-1-yl)propyl acetate [**108**] and racemic (1*S**,2*S**)-2-(2-phenylpropan-2-yl)bromoacetate [**146**]. The yields for this reaction were more varied than for any other sulfide contraction conducted during the project, and averaged only 38%. Significant amounts of unreacted starting material were always recovered, even if the reaction was left for several days. Even attempts to conduct the reaction under reflux resulted in a yield of only 40% after recovery of starting material.

All attempts to force this compound to crystallise failed and we were not able to obtain good analytical data. This was only a minor set-back, however, since the corresponding alcohol [**164**] (after hydrolysis of acetate **163**) gave excellent high-resolution mass spectral data, which should indicate that this acetate was also synthesised correctly. Noticeably, the presence of an OH

stretching signal in the IR spectrum at $\tilde{\nu}$ = 3450 may indicate that the acetate **163** is isolated as a mixture with the hydrolysed compound, alcohol **164**, which may explain the lack of accurate data, but all attempts to determine or isolate the "impurity" were not successful.

The ^{1}H NMR spectrum shows evidence of a successful sulfide-contraction in the vinyl proton signal at 4.05 ppm. This is considerably upfield compared to other similar compounds. Apart from obvious signals due to aromatic protons, and the methyl singlets, the remainder of the spectral signals are only tentatively assigned from double-resonance experiments and comparison with the spectra of the starting material.

[1-(3-Acetoxypropyl)pyrrolidin-2-ylidene]-(1*S*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexyl acetate (–)-[163]

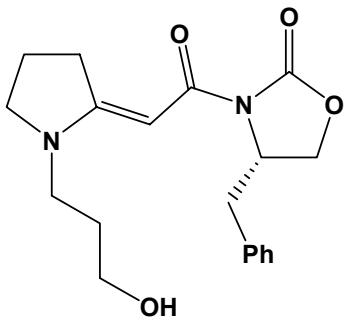


The reaction of (–)-**146** proceeded in a similar manner to that just described for the racemate, except that the product was isolated as a clear pale yellow gum (in 45% yield). Again attempts to crystallise the product failed to give a solid. The ^{1}H NMR and the ^{13}C NMR data for this compound are identical to those obtained for the racemic **163**. The optical rotation was determined at –4.8°, and careful analysis by chiral-phase HPLC showed the presence of both enantiomers in a ratio of 75:25, which suggests an optical rotation of almost –10° for the pure enantiomer. Since the reaction conditions are unlikely to result in the racemization of the enantiomerically enriched (–)-**146**, the optical rotation obtained is a good indication that the product was indeed formed, although some caution is needed in examining these data since we found large margins of error in some of the specific rotation data.

4.2.6 Formation of *N*-3-Propanol Derivatives

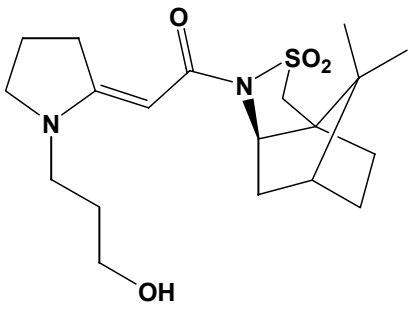
The model *N*-methylpyrrolidinylidene compounds could be used directly in the reduction studies, but they were of little value for the synthesis of indolizidines, and hence the *N*-propyl derivatives were afforded more attention. For each of these latter compounds, the acetate protecting group needed to be removed before cyclisation could be effected. This was generally performed in high yield by basic methanolysis using potassium carbonate in methanol for several hours at room temperature. Harsher conditions (reflux or sodium hydroxide) resulted in some loss of chiral auxiliary and were therefore avoided unless necessary.

(4*S*)-4-Benzyl-3-{2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]acetyl}oxazolidin-2-one [149]



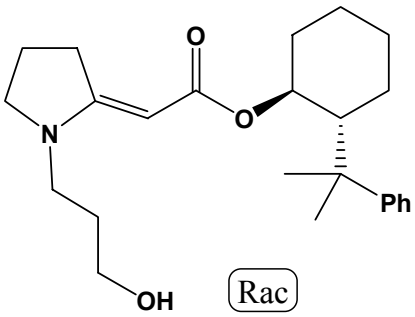
This was isolated as a pale-yellow oil in 82–87% yield after chromatography. Since neither elemental analyses nor HRMS data could be obtained, we relied on the spectroscopic data to verify the success of the reaction. The presence of the alcohol functional group is clearly shown in the IR spectrum by a broad –OH stretch at 3415 cm^{-1}, as well as by a multiplet in the ^1H NMR spectrum at $\delta = 3.4$, which initially integrates for 3 protons, but reduces by one when the solution is re-run after addition of D_2O. A small peak in the low-resolution mass spectrum at $m/z = 344$ (<5%) corresponds with the molecular ion. The remaining spectroscopic data is almost identical with the acetate. TLC analysis of this alcohol showed an indeterminable impurity with almost identical polarity, even after repeated chromatography and distillation. The optical rotation was determined to be +57.9 in ethanol, which is only slightly higher than the +50.1 obtained for the acetate, although it should be noted that the latter value was obtained in a different solvent since the acetate was not soluble in ethanol.

(1*R*,5*R*,7*S*)-1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]ethanone [157]



Isolated as a clear oil in varying yield (52-63%), after short-column chromatography on silica gel, this compound was also difficult to characterise, but a careful examination of the spectroscopic data shows that the reaction was successful. The IR spectrum shows a broad OH band at 3445 cm^{-1}. A multiplet in the ^{1}H NMR spectrum at δ = 1.8-2.5 integrated for 9 protons before D_2O shake, and only 8 afterwards. The remaining ^{1}H and ^{13}C NMR signals appear in virtually identical positions to those of the acetate-protected precursor, but the complexity of multiplets from the sultam moiety do not allow for extrication of individual signals. The only discernible differences are in the ^{13}C NMR, where one carbonyl signal at ca. δ = 166 is missing when compared to the precursor, together with the acetate methyl signal. In the precursor this methyl signal from the acetate coincided with one of the sultam methyl signals, hence it is not possible to determine accurately if there are any changes in the number of methyl carbons, although this signal decreases in intensity. No elemental or mass spectroscopy data were obtained for this compound, firstly because of decomposition, secondly due to the product retaining traces of solvent, even after distillation under reduced pressure.

[(1S,2*R*)-2-(2-phenylpropan-2-yl)cyclohexyl]-2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]acetate [164]



Methanolysis of acetate **163** or (–)-**163** in basic methanol solutions resulted in extremely poor yields of 5% and 23% for (±)-**164** and (+)-**164**, respectively. The ^{1}H and ^{13}C NMR spectra of this alcohol were almost identical to those of the acetate from

which it was derived, and hence a full assignment was not carried out. The extremely low yield of the racemic alcohol restricted further significant purification and analysis steps, although a cursory survey of the spectroscopic data shows it is similar but not identical to the enantiomerically enriched (+)-**164**. The following changes in the spectra of the acetate and suspected alcohol allude to the success of the reaction:

i) In the ^{1}H NMR spectrum the absence of an acetate singlet (CH_3) signal at $\delta = 2.08$ and the absence of both a carbonyl signal (δ = ca. 170) and a methyl signal (δ = ca. 20) in the carbon spectrum indicate the hydrolysis of the acetate. It should be noted that the signal for the hydroxyl proton lies hidden beneath a set of methylene multiplets at around 2 ppm, and could not be identified directly from this spectrum. Its presence was inferred from the decrease observed in the integral trace after the addition of D_2O.

ii) In the ^{13}C NMR spectrum the middle methylene signal from the pendant propyl chain shifts to lower field by 15 ppm. This is consistent with the value obtained from formulae for the estimation of ^{13}C NMR signals such as $\delta = -2.3 + \Sigma Zi$, where Zi are correction factors for substituents in α, β, and γ positions.[196]

iii) In the IR spectrum there is a broad OH stretching band at $\tilde{\nu} = 3452$, which is absent in the spectrum of the starting material.

iv) The optical rotation changes from a negative value (–4.7) to a positive value (+12.2)

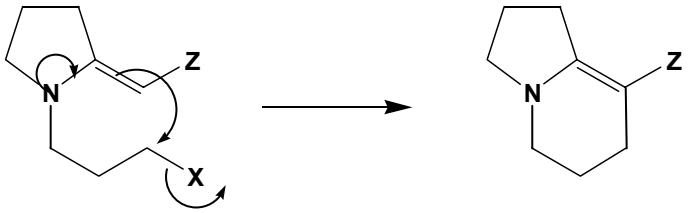
v) Finally, the low-resolution APCI/MS spectrum shows a molecular ion of m/z = 511, corresponding to (M + 1).

4.2.7 Formation of the Indolizidine Skeleton

The purpose of producing the above-mentioned *N*-3-hydroxypropyl derivatives was to allow the cyclisation and hence formation of the second ring in the indolizidine skeleton. Besides the obvious need for two rings (the indolizidines), the reduction studies on the *N*-methyl derivatives were not very promising and we hoped that the greater steric bulk of the indolizidine system

would improve the stereoselectivity of the reduction steps (see next section: Chapter 4.3).

Similar previous cyclisations in our laboratories were often low yielding, however,[67] and hence several cyclisation reactions were studied with the aim of improving the yields. Each of these cyclisation reactions essentially relied on two key points: i) replacing the hydroxy functional group with a suitable leaving group and ii) the nucleophilic displacement of the leaving group by attack via the vinylogous amide. This second point has already been discussed in some detail (Chapter 1, Section 1.2), and is depicted by the diagram below. The nature of the leaving group seemed to be less important, but in our experience, halides, particularly iodides provide for a more facile reaction. Indeed, it is often impossible to isolate the iodide compounds, since they spontaneously react under the reaction conditions to give the indolizidine systems.



X = good leaving group

To this end, several methods of converting hydroxyl to iodide (also to bromide, chloride, tosylate, mesylate or triflate) were investigated, drawing mostly on carbohydrate chemistry to avoid any unnecessarily harsh conditions. Finally, a modification of a literature procedure gave the best results via an *in situ*-generate iodide.[125] In this procedure, triphenylphosphine and iodine are added to the alcohol precursor in the presence of a suitable base. In our labs we have made extensive use of this reaction, utilising triethylamine as the base in most cases.

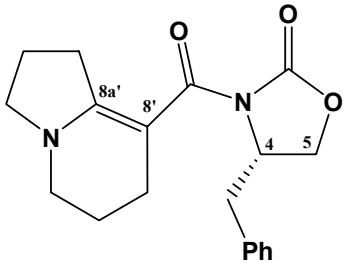
Slight modifications allow for the introduction of other halides, but iodine was likely to be the most successful here. In our hands, this literature procedure gave only traces of indolizidines, regardless of the halide. In the case of the chlorides there was some evidence for the formation of traces of an *N*-3-chloropropyl derivative, but this was not investigated further.

The use of imidazole gave reasonable results, however, and a further slight improvement was realized by reacting this mixture of PPh_3, I_2, and imidazole with the sodium alkoxide (made by reaction of sodium hydride with the alcohol).

Finally, the use of a mixed solvent system avoided the necessity to work with a biphasic system, which resulted in a cleaner reaction.

Formation of the 1,2,3,5,6,7-hexahydroindolizine-8-carboxylic acid ethyl ester [**132**] using this method in 69% yield has already been discussed in Section 2.1, so I will now examine some of the evidence for the formation of chiral 8-substituted indolizidines.

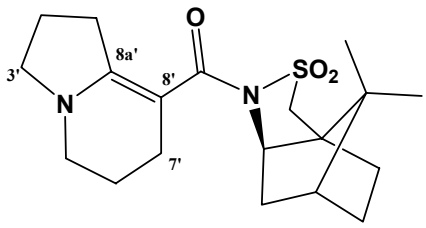
(*S*)-4-Benzyl-3-[1,2,3,5,6,7-hexahydroindolizin-8-ylcarbonyl]oxazolidin-2-one [150]



This product was not isolated, despite repeated attempts using several reaction conditions. On one occasion, a small amount of clear oil was isolated from the reaction of the alcohol precursor with carbon tetrachloride and triphenylphosphine. The ^1H NMR spectrum of this product is almost identical to the starting material, except that there appears to be no hydroxyl group. The broad –OH stretch in the IR spectrum of the starting material is also absent in the product. We believe this compound was the *N*-3-chloropropyl derivative. This is further supported by two peaks in the low-resolution GC-MS of this compound, where two peaks at 362 and 364 correspond with the molecular formula $C_{19}H_{23}ClN_2O_3$ (i.e. the ^{35}Cl and ^{37}Cl species). We then attempted a few halogen displacement reactions (better known as Finkelstein reactions), by treating the suspected chloride with sodium iodide in CH_3CN. Sodium chloride is not very soluble in acetonitrile, so the idea is that the iodide would displace the chloride, and this sodium chloride would therefore precipitate forcing the equilibrium towards the production of the iodoalkane. If this occurred, then simply heating the resulting iodidoalkane in acetonitrile should result in the formation of the indolizidine skeleton. This was not observed, and neither was any evidence of NaCl precipitation observed. Although there appears to be some

evidence (presented above) for the formation of this indolizidine product, the complexity of the mixtures obained did not allow us to isolate it.

(1*S*,5*R*,7*R*)-4-[(1,2,3,5,6,7-Hexahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane [158]



This dehydroindolizine was isolated as a pale-brown powder after rapid chromatographic purification over silica gel. The elemental analyses show an excellent correlation with the expected formula of $C_{19}H_{28}N_2O_3S$. Also, the exact mass was found to be 364.1832 g.mol^{-1} and calculated at 364.1821 g.mol^{-1}, an insignificant difference of 0.0003%. The mass spectra also show a base peak at m/z = 150, as with other sultam derivatives.

As has been described above, the yields for the cyclisation procedures were generally quite low, and initially we were not able to isolate any indolizidine-containing products using the traditional cyclisation techniques (such as the use of carbon tetrabromide or chloride). Several modifications involving the base, the relative amounts of reagents, and the solvents did not improve the yields significantly.

The table overleaf shows some of the traditional reaction conditions that were attempted. In each case several combinations of different amounts of reagents were also examined, and reaction times varied from a few hours to several days. The reactions were all monitored by TLC, and in cases where no reaction was noticed at room temperature, or where there was evidence of significant amounts of starting material, the reaction was heated to reflux. In addition to these conditions, we tried to effect the cyclisation via tosylates, mesylates, and triflates, to name but a few, but these were also not significantly successful.

Reaction Conditions for the Attempted Formation of Indolizidine [158]

Reagents and Conditions	Solvents	Yield[a]
CBr_4, PPh_3, reflux up to 2 days	CH_3CN/NEt_3	0–2%
CBr_4, PPh_3, reflux up to 2 days	CH_3CN/Pyridine	0–2%
CBr_4, PPh_3, Imidazole	CH_3CN/Toluene	1–2%
CBr_4, PPh_3, with and without Imidazole	Pyridine	0–3%
CCl_4, PPh_3, NEt_3, catalytic pyridine	CH_3CN	0–5%
CI_4, PPh_3, with pyridine or imidazole or both	NEt_3	1–4%
CI_4, PPh_3, with and without pyridine	Toluene/pyridine	1–4%
1–4 eq. PPh_3, 2–6 eq. Imidazole, 0.5–3 eq. I_2	Toluene or CH_3CN or mixtures of these	1–20%
2.6 eq.PPh_3, 2.7 eq. Imidazole, 1.78 eq.I_2, NaH	Toluene/CH_3CN	40–48%

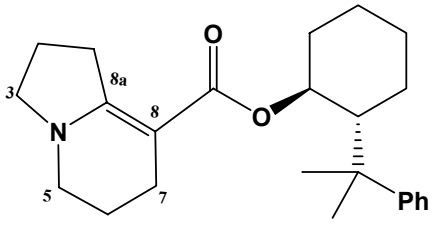
a) Low yields estimated from NMR analysis of the crude product

Further evidence for the formation of this product was obtained by extensive 2-D NMR analyses. The complexity of signals and the overlapping sets of multiples make it difficult to assign these signals unequivocally, but the vinylic proton signal (present in the spectrum of the precursor) is noticeably absenct in the ^{1}H NMR spectrum, as is the OH proton signal, although the latter is not as reliable due to its often broad nature. The remaining signals appear at virtually unchanged positions when compared to the ^{1}H- and ^{13}C-NMR of the starting material, and they therefore offer little extra evidence for the formation of the product.

During an attempt to form the indolizidine moiety via a tosylate an impure orange oil was isolated in about 12% yield. The spectroscopic data is not easy to interpret since the *p*-toluenesulfonyl group has similar atom connectivities (e.g. S=O) as those already present in the alcohol precursor. Twinned bands (at $\tilde{\nu}$ = 1342, 1316 and 1180, 1176) in the IR spectrum, however, indicate the possibility of two sets of S=O bonds in different environments. There are also indications of a 1,4-disubstituted aromatic ring at 3059 (C–H), 1912, 1823 (overtone bands), and 919 (C–H bend). This compound was significantly contaminated with several other compounds, and purification on silica gel was not successful. The ^{1}H NMR

spectrum of the crude product indicates the presence of aromatic protons (as two doublets at above 7 ppm. The carbon signals for this aromatic moiety are also seen in the ^{13}C NMR spectrum at around 130 ppm. The low yield of this reaction, however, made this an unattractive option, especially since cyclisation via the iodide was successful, and no further characterisation was conducted.

(1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate [166]



The use of similar conditions to those used for the synthesis of **158** gave **166** in a low yield of only 5%.

In the IR spectrum the weak cyclohexane skeletal vibration bands (CH_2 γ) are overshadowed at $\tilde{\nu}$ = 909 and 733 by rather sharp and strong bands, probably from aromatic CH vibrations, but the absence of an OH stretch is consistent with the formation of the indolizidine. Most of the ^{1}H NMR spectrum appears as a set of multiplets, except for the methyl singlets at δ = 1.24 and 1.35, and a triplet at δ = 3.22, but the vinyl singlet from the starting material is missing. The signals from the double bond, are, however still present in the ^{13}C NMR, at almost identical positions as those of the starting material.

It can be seen from the above results that the most successful synthesis of an indolizidine system containing a chiral auxiliary was that of sultam derivative **158**. This product was reduced to give the natural products tashiromine and epitashiromine, but first we had to explore some aspects of the reduction step, which are discussed in the following section.

Chapter 4

4.3 Synthesis of Alkaloids (–)-Tashiromine, (+)-Tashiromine, and (–)-Epitashiromine via C=C Bond Reduction

The reduction of the C=C bond adjacent to nitrogen was by far the most challenging aspect of this project. Part of the reason that the "Wits approach" to alkaloids is so attractive is the stability of the enaminone systems. Unfortunately very few alkaloid targets have this double bond in place, and hence its transformation into other functional groups is vital. In this section the various approaches used to reduce the alkene to an alkane will be explored.

4.3.1 Conditions for Effective Reduction

Initially we decided we would have to focus on two "types" of reductant, namely hydrides and metal catalysts. Experimental evidence from similar systems clearly shows that hydride reagents tend to effect a *trans* reduction, where hydrogen atoms are delivered to opposite faces of the double bond. This delivery appears to be sequential, so the possibility exists for some *cis* reduction to occur. In fact, one might expect an equal distribution between *cis*- and *trans*-reduced products, but this is not usually observed. Catalytic metallic reductants, on the other hand, would be expected to give almost 100% *cis* reduction due to the activation of the metal surface with hydrogen and subsequent adsorption of the substrate. This state results in the nearly simultaneous delivery of hydrogen atoms to the same face of the C=C bond. We expected these systems to provide good stereoselectivity due to the need to accommodate the chiral auxiliary on or near the metal surface. The reduction of enamine, enones, and even enaminones is not new, and previous successful attempts, especially from our laboratories guided our choice of reductants to these two types.

Sodium borohydride and sodium cyanoborohydride are two of the most commonly used reductants for these systems. The selectivity for the carbon double bond over the carbonyl or other oxidised functional groups is quite high, while the mild nature of the reactions makes these routes attractive for a general

synthetic approach where sensitive groups might be present. Sodium cyanoborohydride is a particularly useful reagent in this respect, since its selectivity is partly pH dependent.[197]

Finally there is one consideration that is often overlooked in the choice of suitable reagents, that of commercial availability. The plethora of synthetic reagents available to the practising chemist is almost overwhelming, but their preparation is often not straightforward. More importantly, the characterisation and purification of these chemicals as well as the optimisation of the reduction conditions require significant resources. Luckily many of the most common reagents are easily accessible through reputable commercial outlets, and we concentrated on modifying the reduction conditions as a means of influencing the outcome of the reactions.

Table 6 lists the most commonly attempted reductants together with the reaction conditions we chose to investigate. In the field of reductions (especially ligand-directed catalysis) there are few general reaction conditions or even trends, and hence we were forced to modify selected parameters such as pressure, solvent, temperature and even order of addition in order to optimise the reactions.

Table 6 – List of Used Reductants and Modified Conditions

Reductant	**Conditions and Modifications**
$LiAlH_4$	Solvents: diethyl ether, THF, CH_2Cl_2, methanol, ethanol, acetic acid, trifluoroacetic acid Order: normal and reverse order of addition Additives: lanthanide salts ($CeCl_3$), transition metal salts ($TiCl_4$, $NiCl_2$, $CoCl_2$), others (MgI_2) Temperature and Reaction Times
$NaBH_4$	Solvents: methanol, ethanol, acetic acid, trifluoroacetic acid Additives: lanthanide salts ($CeCl_3$), transition metal salts ($NiCl_2$, $CoCl_2$), others (MgI_2) Temperature and Reaction Times

Table 6 continued – List of Used Reductants and Modified Conditions

Reductant	**Conditions and Modifications**
$NaCNBH_3$	Solvents: methanol, ethanol, acetic acid pH: acidic, neutral Additives: lanthanide salts ($CeCl_3$), transition metal salts ($NiCl_2$, $CoCl_2$), others (MgI_2) Temperature and Reaction Times
Pd/C	Pressure: 1 atm, 10 atm H_2 Reaction Times Additives: acids (acetic acid, HCl), bases (Na_2CO_3), lanthanide salts ($CeCl_3$)
Pt_2O	Pressure: 1 atm, 10 atm H_2 Solvents: methanol, ethanol, acetic acid Temperature and Reaction Times
Ru(BINAP)	Pressure: 1 atm, 10 atm, 110 atm H_2 Solvents: ethanol, acetic acid Temperature and Reaction Times
Diisobutyl aluminium hydride (DIBAL)	Amount: 1eq, 6 eq Solvents: methanol, ethanol, CH_2Cl_2 Temperature and Reaction Times
Boranes	Various boranes generated *in situ* or added separately Solvents, Temperature and Reaction Times
L-Selectride	Only one set of conditions used
Triethyl silane	Various addition sequences and co-reductants
Metals	Sodium, Lithium in suitable solvents

4.3.2 Evidence of *cis*/*trans* Reduction from NMR

In a study on Orchidaceae alkaloids, Lüning and Lundin examined the effect of the relative configuration of protons alpha to nitrogen on the IR and ^1H NMR spectra.[198] They found, as would be expected that there was a difference in the positions of the ^1H NMR signals for the protons in the axial and the equatorial positions. Equatorial protons were shifted downfield by about 0.8 ppm

(in the τ scale)[2]. It is not clear from the article, however, which reference was used, and we must assume that the quoted NMR chemical shifts are similar to those obtained relative to TMS. This appears to be a valid assumption, since the methyl signals are quoted at τ = 8.5–9.0, which would correspond with a δ value of between 1.0 and 1.5, the expected range for methyl protons. In our case the indolizidine six-membered ring would most likely adopt a chair conformation, with the substituent at C-8 in an equatorial position. In the *trans*-reduced indolizidines a *trans*-fused ring system is easily accommodated, which places H-8a axial to the nitrogen lone pair. In this conformation three α-hydrogen atoms would appear axial to the nitrogen lone pair and two would be equatorial. This has two important consequences for the spectroscopic data. The first is that the Bohlmann bands should be rather pronounced (since these bands occur with the nitrogen lone pair anti-periplanar to an α-hydrogen), and the second is that H-8a should appear upfield relative to the other α-protons (at C-3 and C-5).

Bohlmann bands occur as one or two sharp bands between 2800 and 2700 cm^{-1} in the IR spectrum. These bands occur as a result of the interaction of the p-orbital of nitrogen with the σ-orbitals of the C–H bonds in antiperiplanar arrangements. They were discovered by Ferdinand Bohlmann during the study of Lupinine quinolizidine alkaloids,[199] where he proposed that the hyperconjugation in these systems would lead to a weakening of the C–H bonds, and the observed shift to lower wavenumbers. The bands are visible in systems with bridgehead nitrogen atoms and at least one 6-membered heterocycle such as indolizidines and quinolizidines. The most stable ring conformation is where the nitrogen lone-pairs are in an axial position and the rings are *trans*-fused (see **Figure 25**). When the reduction of the $\Delta^{8,8a}$-indolizidine system occurs in an *anti* fashion, the C-8 substituent (R) is easily accommodated in an equatorial position, as is shown in **Figure 25**. As can be seen from this diagram, this arrangement would result in three axial α-protons in an antiperiplanar arrangement with the nitrogen lone pair therefore give rise to strong Bohlmann bands. Indeed these bands are observed in all the diastereomers with a major component consisting of *anti*- or *trans*-reduced C=C bond, such as tashiromine [**1**].

[2] The τ scale is an older scale, no longer in regular use in modern NMR, and is defined as τ = 10–δ.

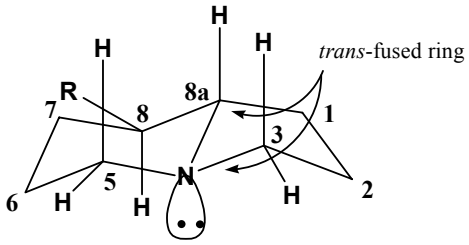


Figure 25 – Computer-modelled Conformation of 8-Substituted Indolizidines with a *trans*-Relationship between H-8 and H-8a.

The three α-hydrogen atoms above the plane of the molecule are antiperiplanar with the nitrogen lone pair, giving rise to Bohlmann bands in the IR spectra.

The *syn*- or *cis*-reduced indolizidines, on the other hand, would either need to have the 8-substituent in an axial arrangement, or part of the pyrrolidine ring in an axial (*cis*-fused) position. Molecular modelling (*vide infra*) and NMR studies[200] seem to indicate that the *cis*-fused indolizidine skeleton with no other substituent is only slightly more energetic than the *trans*-fused system, and it can be shown that the interconversion is accomplished by the facile inversion of the pyramidal nitrogen group. In this *cis*-fused conformation a C-8 substituent would be in an energetically favourable equatorial orientation (**Figure 26**). The Bohlmann bands would be almost absent, however, since only one α-proton (on C-5) would be antiperiplanar with the nitrogen lone pair.

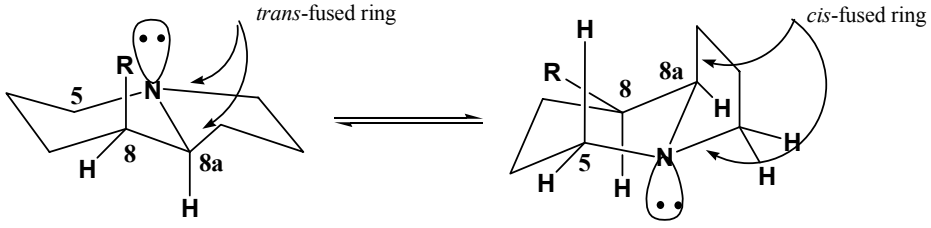


Figure 26 – Computer-modelled Conformation of 8-Substituted Indolizidines with a *cis*-Relationship between H-8 and H-8a

With the smaller substituents at C-8, there are Bohlmann bands in the IR spectra, although not as prominent as those for the *trans*-fused system, but this effectively means that we cannot discount at least some contribution from the *trans*-fused conformer. Molecular modelling of the two conformations from this *cis*-reduced isomer shows that they have almost identical energy, and hence the contributions to the IR spectra are probably fairly equal. Note that in the *trans*-reduced isomers a *cis* ring fusion is much less favourable resulting in a much smaller contribution from this high energy conformation to the IR spectra, and therefore much more prominent Bohlmann bands.

4.3.3 Sultam-containing Octahydroindolizines

Oppolzer discovered that the hydrogenation of prochiral enoyl sultams with H_2 in the presence of Pd/C takes place with high diastereofacial discrimination,[179][201][202] providing the enoyl adopts an *s-cis* conformation. This is suspected to result in the coordination of the carbonyl and SO_2 groups to the surface of the catalyst, thereby assisting in the delivery of the hydrogen preferentially to one face of the double bond. Several data support this assumption, for example the crystal structures of titanium coordinated to β,β-disubstituted sultams show the clear coordination of the carbonyl and SO_2 groups to the metal.[148] More convincing is the fact that if the *s-cis* conformation is destabilised, for example where the substituent in the α-position interacts unfavourably with the sultam, the selectivity of the hydrogenation is lowered (**Figure 27**).

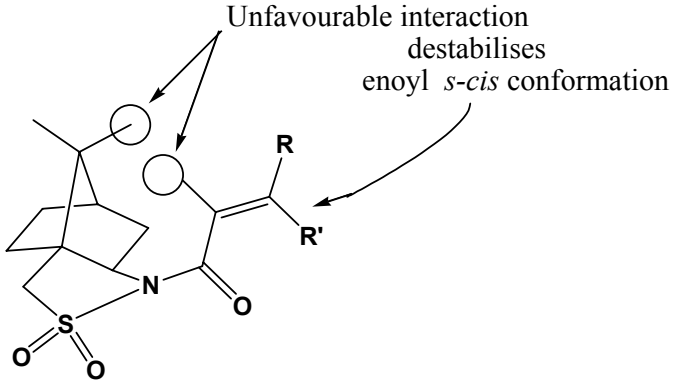
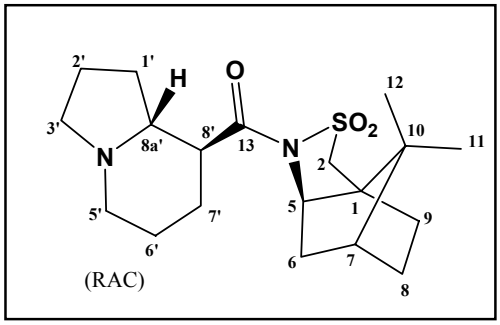


Figure 27 – Destabilisation of the *s-cis* Conformation

We would therefore expect a high stereoselectivity for the reduction of the sultam-containing hexahydroindolizine **158**.

All the reduction procedures suffered from three drawbacks: loss of chiral auxiliary, low yields, difficulty in monitoring reaction to completion.

Under sufficiently mild conditions to maintain the integrity of the chiral auxiliary we would not find any reduction, while under more vigorous conditions, which allowed us to obtain the octahydroindolizine, we always isolated significant quantities of the chiral auxiliary. The sultam material that was isolated in this way could be recycled by subjecting it once more to the bromoacylation procedures, following a simple clean-up operation such as recrystallisation without any noticeable difference in yields.



(RAC)

The remainder of the reaction mixture (after reduction) presented a very complex set of products from which we were only able to isolate small quantities of the alkaloids tashiromine and epitashiromine. The problem with these was that we could not separate the diastereomers to identify them sufficiently.

A final complicating factor in most of the reduction reactions was the presence of minor quantities of starting material. Again this material could generally be recovered by careful chromatography. There appeared to be no difference in the recovered material when compared to the freshly synthesised material.

To characterise the materials, as well as allow a reasonable chance of separation of diastereomers, we performed the reduction reactions for shorter periods of time (until approximately 50% conversion) and under the mildest possible conditions that would still allow reduction, such as the use of room temperature for the reactions.

We were able to transform the hexahydroindolizine **158** into the octahydroindolizine equivalent [**162**] by using either sodium cyanoborohydride or hydrogen over a catalyst.

In the hydrogenations (using metal catalysts) we obtained predominantly the *cis*-reduced isomers, with the stereochemistry of the two new stereogenic centres both having either the *R*- or the *S*-configuration. In the case of the hydride reductions, the major diastereomers had the opposite configurations. In both cases we were able to detect small quantities of the remaining diastereomers. This was especially problematic in the isolation of the *cis*-reduced diastereomers since these had an R_f slightly lower than those of the *trans*-reduced isomers. We were able to isolate some of the *trans*-reduced diastereomers as white powders after careful and repeated chromatography, but the *cis*-isomers were always contaminated with the *trans*-isomers. The relationship between the isomers and the alkaloids is shown in **Figure 28** below, together with the isolated yields after reduction and chromatography. The best diastereoselectivity we obtained was 5:2 in favour of the (8*R*, 8a*S*) isomer, using the sodium cyanoborohydride reduction (**GP-7A**).

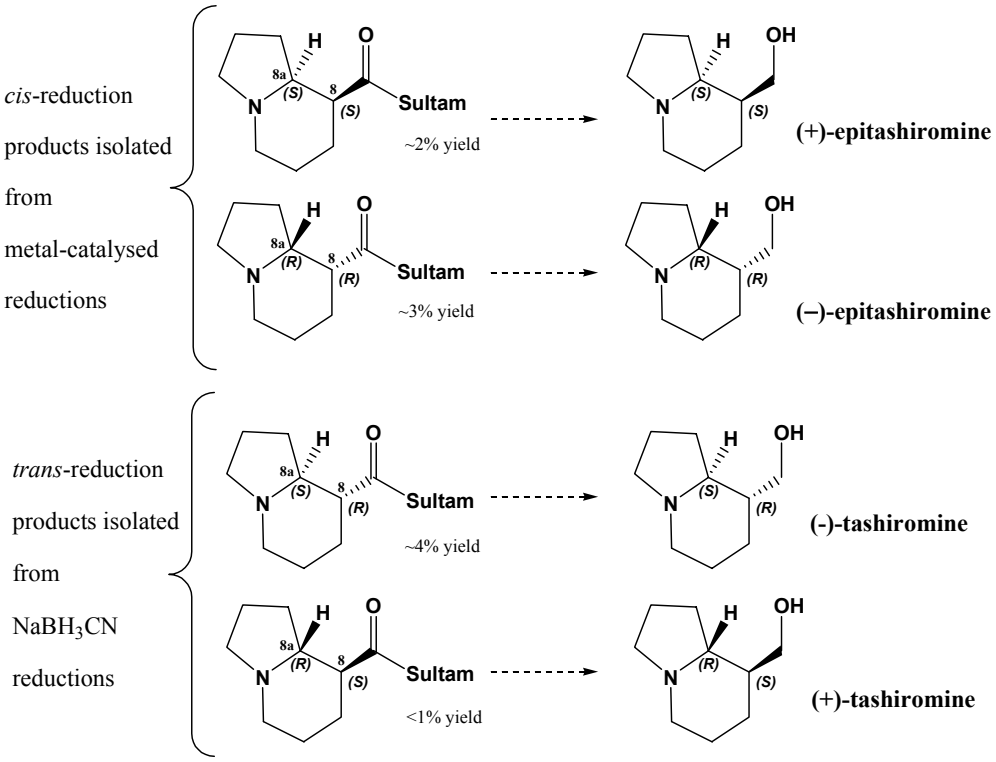
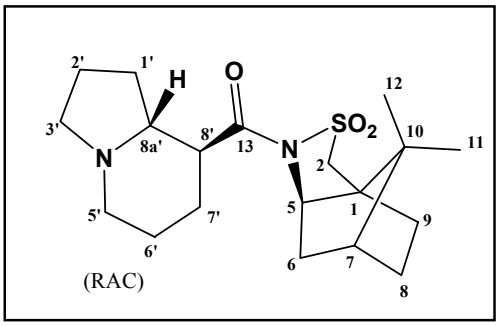


Figure 28 – Relationship between Diastereomers and the Alkaloids

We were not able to completely isolate the *cis*-diastereomers since they had retention factors too similar to each other and to the *trans*-reduced isomers. Even the HPLC analysis of the diastereomers was not conclusive since the peaks were poorly resolved.

The following interpretation of the data for the (8*S*,8a*R*) diastereomer of **161** is typical of all the diastereomers. This particular diastereomer was further reduced (see next section – 4.4), to obtain (+)-tashiromine.

(1*S*,5*R*,7*R*,8*S*,8a*R*)-4-[(Octahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane [161]



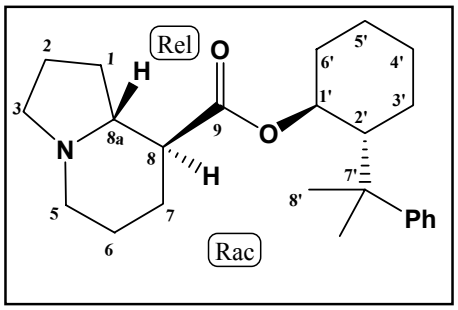
This product was isolated in a poor overall yield of 4% after chromatography. The NMR spectra are exceedingly complex, and it was not possible to determine or assign all the data. Many of the NMR signals, especially for the ^{13}C NMR spectrum, occur in identical or similar positions to the starting material, but the complexity of multiplets in the ^{1}H NMR spectrum do not allow for accurate double resonance experiments. Another factor that complicated the ^{1}H NMR spectrum is the geminal coupling, which now becomes overwhelming. Several attempts were made to obtain X-ray data by carefully recrystallising the sample from ethanol and ethyl acetate mixtures by evaporation, but the crystals were not suitable for analysis. The presence of only one carbonyl signal in the ^{13}C NMR spectrum together with an absence of the vinylic carbon signals is evidence that the reduction was successful. Also in the IR spectrum there is no longer an absorption for the C=C stretch at ca. 1640, while a strong signal at $\tilde{\nu}$ = 1686 reveals the presence of the carbonyl group. In the carbon-13 spectrum the signals for C-8 and C-8a now appear at δ = 77.2 and 64.8, while previously these were found at ca. 92 and 163 ppm, respectively. The remainder of the spectrum is quite similar to that of the starting material.

The accurate mass determination confirmed that the product very likely has a molecular formula of $C_{19}H_{30}N_2O_3S$, with a calculated molecular mass of 366.1977 g.mol^{-1}, while the parent ion was found at m/z = 366.1963. The mass spectrum itself is again not very different from that of the didehydro starting material, and shows the characteristic base peak at m/z = 150.

We believe this evidence strongly supports isolation of this product, although in a very poor yield. The remaining *trans*-reduced isomer was isolated as the major component of a mixed fraction and was only analysed by IR and NMR spectroscopy. Only minor changes can be noticed between this product and its precursor, especially in the ^{13}C NMR spectrum where the crude reaction product shows a doubling of nearly all signals.

As was mentioned before, the *cis*-reduced isomers were not isolated cleanly, and so even the NMR spectra cannot be interpreted completely. The characteristic absence of alkene signals is, however, evidence for the success of the reaction.

4.3.4 (2-Cumyl)cyclohexyl-containing Octahydroindolizines



In this case the low yields of the indolizidine systems, particularly of the racemic structures forced us to use the enantiomerically enriched dehydroindolizine (+)-**166**. All the reduction reactions attempted were very low yielding, and hence this was not an attractive route. The reductions using sodium cyanoborohydride or sodium borohydride gave predominantly what we assume is the *trans*-reduced diastereomer pairs, consistent with our observation that sodium cyanoborohydride results in mostly tans-reduced products. Since the starting material was only enantiomerically enriched, the product (*trans*-reduced indolizidine) would potentially be a complex mixture of four diastereomers as two sets of enantiomers. A further complication could be the presence of the four diastereomers resulting from the *cis*-reduced indolizidines, although these are expected to be minor

products from the hydride reductions. Indeed, all the ^{1}H- and the ^{13}C-NMR spectra taken directly from the reactions are very complex, and difficult to assign with any confidence. The diastereomers present as a single spot on TLC and were not separable. There is, however strong evidence that the reductions were successful, and some supporting evidence from the NMR and IR spectra for the presence of *trans*-reduced indolizidines. In the ^{13}C NMR spectrum, the signals assigned to carbons 8 and 8a are missing from δ = ca. 90 and 164, respectively. These signals are characteristic of the dehydroindolizines, and usually appear in parts of the spectra with few or no other signals; hence their presence or absence is conspicuous. A new set of signals at δ ~ 65 could be attributed to the carbon 8a, while a set at δ ~ 41 can be assigned to carbon 8. These positions are not only consistent with theoretical calculations of signal positions, but they present two of the few changes in the spectrum of the starting material.

The ^{13}C NMR spectrum has almost twice the number of signals (43) as the number of carbons in the products (24). Considering the degeneracy of the phenyl carbons, we would expect each diastereomer to show 22 signals. The carbonyl signal appears slightly downfield at 173.5 ppm, and is the only signal that does not appear to be twinned. The remaining signals are largely present as what appears to be two closely spaced signals with intensity ratios of around 1:3. For example, there are 8 signals in the aromatic region of the spectra, namely at:

δ = 124.88(1.6), 125.20(3.5), Δδ = 0.32 ppm
125.34(3.8), 125.72(0.7), Δδ = 0.38 ppm
127.81(9.4), 127.95(3.6), Δδ = 0.14 ppm
151.11(0.7), and 151.39(1.3), Δδ = 0.28 ppm (intensities given in parentheses as arbitrary units).

In the ^{1}H NMR spectrum the many methylene protons result in overlapping multiplets that are not resolved, and make the spectrum difficult to interpret.

Finally, the appearance of two rather sharp Bohlmann Bands at $\tilde{\nu}$ = 2784 and 2702 cm^{-1} in the IR spectra indicate the presence of protons *trans*-diaxial with the nitrogen lone-pair.

While each set of data presented here is not overwhelming, the "balance of evidence" indicates that the indolizidine system was indeed reduced, predominantly in the *trans*-reduced precursor to tashiromine, and insignificant amounts of the *cis*-reduced analogues.

4.4 (–)- and (+)-Tashiromine and (+)-Epitashiromine

The final step in the synthesis of the 8-hydroxymethyl-indolizidines is the removal of the chiral auxiliary. Traditionally this is done by hydrolysis in aqueous lithium hydroxide, but during one of the reductions of the hexahydroindolizine (1*S*,5*R*,7*R*)-4-[(1,2,3,5,6,7-hexahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane [**158**] with $LiEt_3BH$ we noticed that the NMR spectrum contained evidence of the reduced indolizidines without any chiral auxiliary. We were not able to isolate this product to determine if it was tashiromine or epitashiromine, but it has a retention time very similar to that for tashiromine using HPLC. We therefore decided to try using conditions similar to those used by Goldberg and Ragade for the reductive cleavage of their chiral auxiliaries during the synthesis of lupinine.[237]

Using this procedure a sample of the isolated (1*S*,5*R*,7*R*,8*S*,8a*R*)-4-[(octahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane was subjected to $LiAlH_4$ reduction giving (–)-tashiromine as a clear oil in 50% yield. The optical rotation for this oil was near impossible to determine since the concentration was very low, but we obtained an average value of $[\alpha]_D^{23} = -16$ for three determinations. This is very different to the $[\alpha]_D^{23} = -26$ given in the literature, but shows at least the correct isomer is dominant. There was insufficient product to allow derivatisation in order to determine the enantiomeric excess, but the IR, NMR, and mass spectra are nearly identical to those obtained previously for the racemic sample, and those quoted in the literature.[114]

The (+)-tashiromine was obtained in an identical manner from the diastereomer (1*S*,5*R*,7*R*,**8*R*,8a*S***)-4-[(octahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane. In this case, however, the even smaller amount of starting material, coupled to the fact that this starting material was used as a mixture with a smaller d.e. gave us a product whose properties could not be determined accurately. The ^{1}H NMR spectrum was identical to that obtained for the (–)-tashiromine, and indeed identical to the (±)-

tashiromine. The optical rotation could not be determined with any degree of certainty due to the extremely low concentration we were forced to use. We did however obtain a rotation value of $[\alpha]_D^{23} = +1$ (compared to $[\alpha]_D^{23} = +42$) given in the literature.[115]

(+)-Epitashiromine

As with the isolation of tashiromine, treatment of the *cis*-reduced isomers of **162**, with $LiAlH_4$ gave a product whose data were very similar to the isolated racemic epitashiromine. Analysis of the optical rotation gave a value of $[\alpha]_D^{23} = +1.4$ which indicates that the major isomer is that of (+)-epitashiromine. The presence of other impurities, in particular that of tashiromine isomers does not allow further analysis of this product. In the literature the optical rotation of in ethanol is given as +1.1, but the authors indicate that they had difficulty in obtaining this since the product showed a slow change in the optical rotation from positive to negative, suggesting the formation of the *N*-oxide.[114] These scientists were able to get an optical rotation of $[\alpha]_D^{23} = +29.1$ for HCl salt, but in our case the small amount of sample prevented us from attempting this.

Chapter 5
Molecular Modelling

Computers have pervaded every corner of society in the last few decades, and chemistry has not escaped the "electronic age". Computers and computational techniques have become important in progressing our understanding of certain aspects of chemistry that would otherwise be almost impossible to visualise: aspects such as what is occurring at a molecular level in a reaction, or what are the processes which lead to the dissolution of one compound and not another. One of the most successful computational techniques used in chemistry today is conformational analysis. The ability to visualise a molecule or set of molecules in 3-D space, how they interact, and how their conformation influences their properties and behaviour has led to many advances in chemistry. The conformations of a molecule can be defined as a set of arrangements of its atoms in space, which can be interconverted solely by rotation about single bonds.[203] It is helpful in computational chemistry to relax this definition somewhat, to acknowledge that many conformations require only small distortions in bond lengths and angles, and also to recognise that it is often possible to make small rotations (twists) in bonds which have a bond order higher than one.

5.1 Computational Techniques

Although conformational analysis has its roots in the late nineteenth century, it was not until the twentieth century that these ideas began to become important. It is thanks to people like Andrews (1930), who noticed that there was a relationship between Raman spectra and structure of organic molecules, that we have the idea that a molecule could have a "natural" shape, and that this shape could be related to certain physical and chemical properties.[211] Still, it was not until the 1950's that this work started to gain momentum, through the work of Dostrovsky, Fowden, Hughes, and Ingold,[204][205] among others (who were attempting to understand the rates of S_N2 reactions in haloalkanes) and also

through the pioneering work of Barton (trying to explain how axial and equatorial substituents on cyclohexane rings show different reactivity) that we have the idea of molecular conformation being important in reactivity.[211] Perhaps one of the most significant developments in this area was in a series of papers published by Westheimer,[206][207][208] whose calculations regarding the rates of racemization of optically active halo-substituted biphenyls laid the groundwork for modern computational modelling techniques. Modern conformational analysis has grown extensively from those observations and through the use of techniques such as NMR and IR spectroscopy, and especially the development of X-ray diffraction methods. The advent of computational techniques able to handle and quickly manipulate large volumes of data has put the use of conformational analysis in the hands of every chemist.

One of the most important aspects of conformational analyses is the potential energy surface (PES). The PES is a remarkable graphical representation of a set of mathematical functions known as the force field. The Born–Oppenheimer (BO) approximation states that the nuclear and electronic motions can be uncoupled from one another, and considered separately. This allows one to solve the Schrödinger equation for an individual molecule or set of molecules, by assuming that the nuclei of the atoms ***are fixed in space***. In other words, we can assume that the electrons will find their own optimal distribution, and approach chemical problems by optimising the position of the nuclei in 3D space. Although this approach of capturing atoms in a fixed position in space clearly violates the Heisenberg Uncertainty Principle, the errors generated in this manner are negligible for most chemical purposes. The important features of the PES are easily linked to key chemical concepts. Minima on the surface are particularly important as they correspond to low energy conformations of molecules. Saddle points in the PES are also important as they are often correlated with transition states, and provide the lowest energy path for interconversion between conformational minima. The PES is not perfect, however, as it incorporates a number of approximations. The force fields behind the PES are generally divided into two categories: those derived primarily from quantum mechanical

considerations (QM force fields), and those derived from empirical evidence, which became known as molecular mechanics (MM force fields). In general, although QM derived force fields are more accurate, they require much greater computing power; they are therefore impractical for most molecules, and are thus used much less frequently. The MM derived force fields are analogous (as a first approximation) to a set of weights joined by springs. In reality most force fields are more complicated than this, and today there are a number of different force fields, which have been designed to suit particular needs, e.g. force fields for hydrocarbons and small organic molecules or for peptides and nucleic acids.

Perhaps the most fundamental principle in molecular mechanics is the idea that the total energy of a system can be divided into various constituent parts (equation **1**), which can then in turn be handled by an appropriate potential energy function. Thus, the total steric energy (E_{TOT}) can be divided into a bond stretching component (E_S), a bond angle bending component (E_B), a van der Waals term (E_{VDW}), a torsion energy term (E_{TOR}), an electrostatic component (E_{ELEC}), and other, smaller, cross terms (E_{CROSS}).[215]

$$E_{TOT} = E_S + E_B + E_{VDW} + E_{TOR} + E_{ELEC} + E_{CROSS} \qquad \text{(equation 1)}$$

The first term in the above equation, the bond stretching term, can be regarded, as a first approximation, as a Hooke's law harmonic (equation **2**), where the energy is expressed as a function of the bond length (b), compared to a reference, or strain-free bond length b^o. Within this expression is an inherent approximation – the reference bond length is usually taken from empirical evidence such as the bond lengths of all similar bonds taken from X-ray crystallographic data.

$$E = \tfrac{1}{2}k_s (b - b^o)^2 \qquad \text{(equation 2)}$$

In reality, a bond is much better represented by a Morse potential, as a harmonic does not allow for dissociation.[209] A complete Morse function is

however, computationally demanding, and hence in MM2 there is a compromise; the bond is treated as a simple harmonic, but the cubic term from the Morse function is retained (equation **3**), to account for energy in the region where a bond is being pulled apart.

$$E_S^{MM2} = 143.88\ ½k_s(b - b_0)^2[1 - 2(b - b_0)] \qquad \text{(equation 3)}$$

Similar Hooke's law type potentials are used to describe the angle bending terms. We could envisage a spring holding together atoms 1 and 3 (see **Figure 29**). When the ideal length Θ^0 of the spring is changed, the angle between 1, 2, and 3 would increase or decrease.

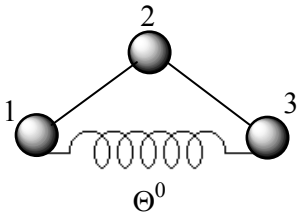


Figure 29 – Simplified Spring Representation of Bonds

The van der Waals interactions are usually handled by a Lennard-Jones 12-6 potential, as a function of distance between interacting centres. Research has shown that the 12 potential is too steep, and is often replaced by a smaller term. In MM2, a modified Hill equation[210] is used, which is essentially a 6-potential:

$$E_{vdw}^{MM2} = \varepsilon\left\{-2.25\left(\frac{r_0}{r}\right)^6 + 2.90.10^{-5}\exp\left[-12.50\left(\frac{r}{r_0}\right)\right]\right\} \qquad \text{(equation 4)}$$

The electrostatic interactions are treated as point charges, and Coulomb's law is used to calculate the energies.

In MM2, the energy contribution from the intramolecular rotation (torsional strain) of a molecule is function of the torsion angle (ω), and exists between all atoms having a 1,4 relationship. The energy is calculated by the first three terms of a Fourier series. By convention, a positive angle indicates a counter-clockwise rotation of bond 1–2 relative to 3–4.

$$E_{TOR}^{MM2} = \frac{V_1}{2}(1 + \cos\omega) + \frac{V_2}{2}(1 - \cos 2\omega) + \frac{V_3}{2}(1 - \cos 3\omega) \qquad \text{(equation 5)}$$

The remaining terms are usually small in comparison to these, but they add to the accuracy of the results obtained, and help reduce most of the errors generated by the inherent assumptions made in order to simplify the computational power required. These remaining terms are often called cross terms, because they incorporate behaviour from more than one component. As an example, it is well known from empirical evidence that when a bond angle is reduced, the two bonds forming the angle will stretch in order to alleviate some of the strain. This type of interaction involves movement in two directions at the same time, and hence a term is needed which will calculate the energy used or gained in this stretch-bend motion. This might, for example, be called E_{SB}.

When all these terms are taken into account, the resultant energy equation forms a potential energy "hypersurface" that describes the dependence of a molecule's energy on the geometrical coordinates of its atoms.

5.2 Force-Field Parameterisation

The accuracy and reliability of the results obtained from any calculation depend on the parameters (such as k_s, b_0, and Θ_0, *vide supra*) used in the force field. It is important therefore that these parameters are as complete and as accurate as possible. Since the number of possible atom combinations far outweighs the number of experimentally observed combinations, it is often necessary to add or modify certain parameters in a given force field. This is, however, not a simple task, as the parameters rely on experimentally observed results, often from a variety of different sources, and measured by a variety of different experiments. They therefore require some subjective ranking of importance. As force fields develop,[211] scientists are finding new ways to improve the accuracy and reliability of the results, but for now we have to rely on the somewhat trial and error approach of looking for suitable parameters from the experimental data available, and allowing the errors to be absorbed by the other parameters. Much of this experimental data is collected in certain databases, such as the Cambridge Structural Database (CSD),[212] which contains data from X-ray crystallographic studies. By searching these data for fragments or molecules of similar connectivity to the ones we wish to study, we are often able to extract the relevant parameters required for the force field. Other methods for obtaining this information include manipulation of the parameters by a trial and error approach, or *ab initio* calculations of the parameters. Once the force field has been established, parameterised and tested by various means, it is ready for use in molecular modelling calculations.

5.2.1 Energy Minimisation

The most popular use for the force field is to find the minimum energy conformation of a particular molecule, or set of molecules. Various methods or algorithms exist for finding the minimum energy, including steepest descent, conjugate gradient, and block diagonal.[213] The steepest descent method is perhaps the simplest method, and therefore requires very little computational resources. This method relies on finding the first derivative of the PES with

respect to the Cartesian coordinates, and then moving in the direction of the negative gradient of the potential energy. When the molecule is far away from the energy minimum, this is the most useful algorithm. The conjugate gradient method is slightly different to the steepest descent method, in that it relies on both the current gradient, and the previous gradient to find the minimum in the PES. In this way, the method takes into account the history of the minimisation, and converges much more rapidly on the minimum. The block diagonal method or Newton-Raphson method is computationally the most taxing, as it calculates both the first and second derivatives of the PES with respect to the Cartesian coordinates and thus gives information on both the slope and curvature of the PES. It is therefore most useful near the minimum conformation. As new optimisation methods are developed, the ability to find the global minimum accurately and reliably also improves. One question still remains, no matter how good the optimisation is; "how can we be certain that the global minimum is reached, and not just a local minimum?" This too is no trivial question to answer, and here we have to rely on another technique known as Simulated Annealing.

5.2.2 Simulated Annealing

Simulated annealing is a molecular dynamics technique, that is, it aims to reproduce the time-dependent motion of a molecule. In simulated annealing, a molecule is suspended within a force field, and a small amount of energy is incrementally added to the molecule. Newton's law (F = ma) is then solved for all atoms and for all degrees of freedom. New atomic velocities are calculated, and the atoms are moved to these new positions. This simulated increase in temperature causes an increase in the internal energy of the system, and should enable higher potential barriers to be overcome and therefore prevent the molecule from getting caught in a local minimum on the PES. Once the maximum temperature has been reached, the cycle is then reversed, and small amounts of energy are slowly removed from the system, to allow the molecule to "anneal" into a low energy state once more. Once this has been done, the resulting molecule is again subjected to a geometry optimisation process. In this manner, a molecule that is in a local minimum geometry will be jarred out of it by the

simulated annealing process. Repeating this process a few times should eventually lead to a reliable global minimum conformation.

So what information can be gained from this process of molecular modelling?

5.2.3 Comparing the results

Throughout this introduction, reference has been made to the modelling process as being able to give energy minima for molecules, which could then be used to generate idealised conformations. It must be remembered, however, that the molecules are compared to hypothetical "ideal" molecules, and hence molecular modelling cannot give the actual energy of a real molecule. It is therefore often impossible to compare energies between molecules directly. It is often necessary to compare only certain sections of molecule in order to get an idea of the *relative* energies of different molecules. In this manner, a series of molecules can be compared for the most favourable conformation about a double bond, for example, by comparing the energy of the double bond in each of the molecules, or by looking at the amount of steric interaction around the bond. This kind of technique of optimising a small portion of a molecular conformation is often used in drug design. By modelling the active site of a drug or a drug target, it is often possible to examine and even improve aspects of the drug such as the affinity of the binding pockets for the receptors.[214] Although drug design and drug research has made the most use of molecular modelling, there are a great number of other uses such as reaction-mechanism elucidation and attempts to further understand system reactivity. The area of physical chemistry is also a very intense user of molecular modelling in order to study physical characteristics of surfaces, solvation effects, thermodynamics, and many other areas which are difficult or indeed impossible to study by traditional wet chemistry.

Chapter 6

Results and Discussion of the Molecular Modelling

6.1 Crystal Data Mining and Force Field Parameterisation

Model compounds used

We determined the missing parameters in the HyperChem®[215] MM+ force field[216] by taking the single point energy of a small set of compounds whose molecular connectivities were representative of those we wished to model (**Figure 30**). These molecules were not initially subjected to any optimisation of the molecular structure but were used to generate log-files of the computation process that contained information such as errors encountered and default parameter values used. This gave an indication of which parameters had been accurately calculated. In this particular version of the MM2 program, Hyperchem® will try to substitute the inaccurate or missing parameters with other similar parameters. For example, if a bond length for C–N doesn't exist, the program will try to substitute another C–X bond length (where X is another atom).

The entries in **Table 7** show the most important parameters that were missing from the MM2 force field. Some other missing parameters such as the N–S=O angle are less important in modelling the position of the chiral auxiliary relative to the C=C bonds and in these cases the default parameters were used.

Table 7 – Important Missing MM+ Parameters

Parameter	**Parameter Type**	**Calculated values used**
C_{sp3}–C_{sp3}–C_{sp2}–N_{amide}	Torsion	V1 = V2 = 0, V3 = 0.4
C_{sp3}–C_{sp2}–N_{amide}–C_{sp3}	Torsion	V1 = V3 = 0, V2 = 5.0
C_{sp3}–C_{sp2}–N_{amide}–H	Torsion	V1 = V3 = 0, V2 = 5.0
H–C_{sp3}–C_{sp2}–N_{amide}	Torsion	V1 = V2 = 0, V3 = 0.4
$C_{carbonyl}$–C_{sp2}–C_{sp2}–N_{amide}	Torsion	V1 = V3 = 0, V2 = 10.0
O–$C_{carbonyl}$–C_{sp2}–H	Torsion	V1 = V3 = 0, V2 = 11.1
C_{sp3}–C_{sp2}–N_{amide}	Angle	Bond constant k = 0.550, Bond angle (Θ) = 117°

The choice and number of compounds used for these calculations is fairly arbitrary, but should include all the combinations of 4-atom bonds likely to be encountered in the modelling study. Compound **172** for example contains the basic pyrrolidine ring, together with the exocyclic vinylogous urethane, present in many of the alkaloid precursors. Compound **173** was included to correlate the structure obtained with that obtained by a previous study of an *N*-aryl compound by an honours student in our laboratories.[217] The remaining compounds in **Figure 30** have various other aspects of the achiral molecules we would later model, such as the *N*-acetoxypropyl moiety, the complete indolizidine ring, and the chiral auxiliaries used most frequently in this project.

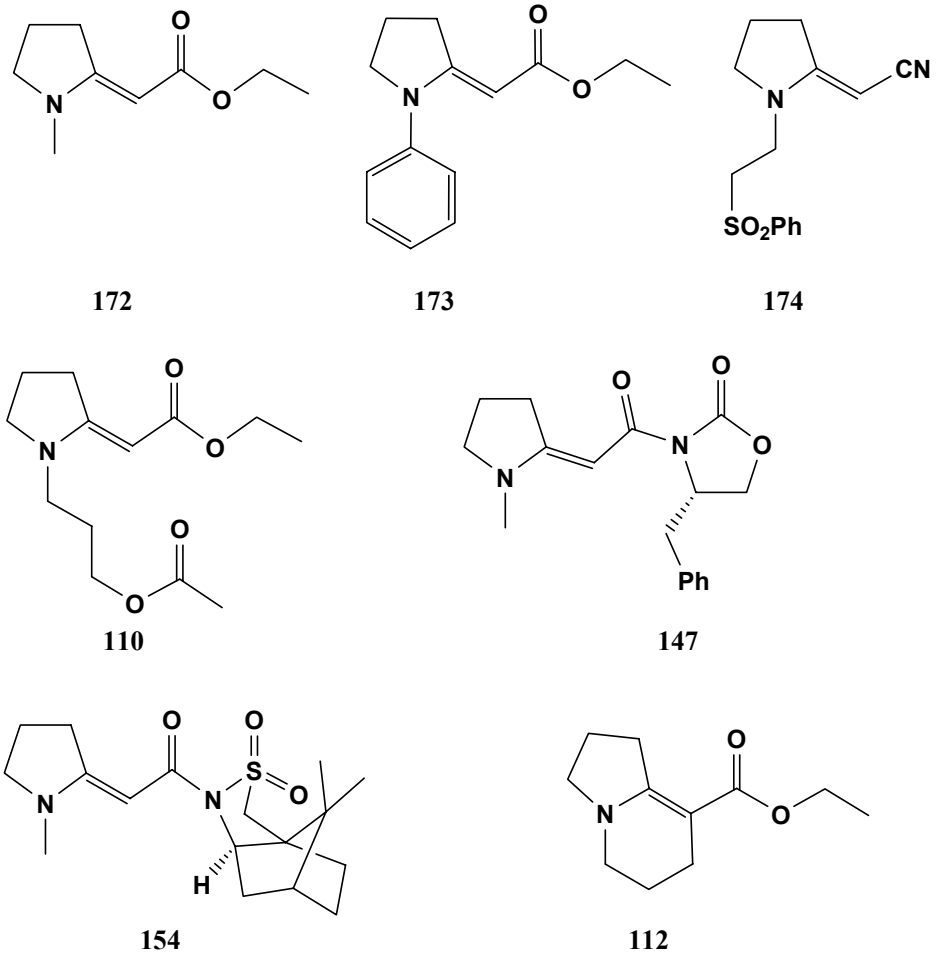
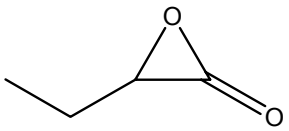
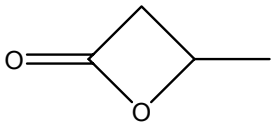


Figure 30 – Compounds Modelled to Obtain Missing Parameters

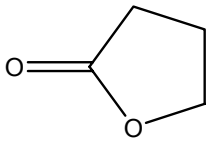
Those parameters that are important to the system under investigation needed to be corrected accurately. Two procedures were followed in order to achieve this: Firstly, the Cambridge Crystallographic Database was searched for several fragments containing the missing parameters. The data obtained by this method came from all the compounds that contain the specific fragment, whose crystal structures have been determined. A statistical plot of individual bond lengths, angles, or torsions allowed us to obtain a range for each of the missing parameters. Any outlying parameters, such as unusually long bonds or angles obtained from unusual conformations were disregarded in the calculation of the mean value for that parameter. These decisions were largely arbitrary, and for convenience any value within approximately one standard deviation of the mean was accepted in the calculation. This is an acceptable practice, since a bond could easily be distorted from the ideal value by ring strain or by the crystal packing. As an illustration, the O–(C=O)–C bond in lactones is very different when comparing alpha-, beta-, and gamma-butyrolactone. If we were interested in only the 5-memebered ring, the others would not be valuable in the calculations, but would be returned from the database as valid compounds containing a cyclic O–(C=O)–C bond.



alpha butyrolactone



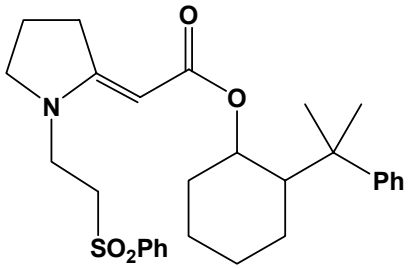
beta butyrolactone



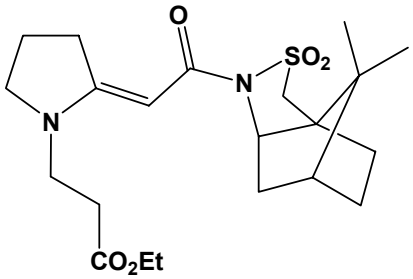
gamma butyrolactone

The mean bond lengths and angles obtained by this method were used directly in the modified force field by simply entering these values as part of the data-set used by the program. The torsion angles, however, required further calculation, since they contain terms responsible for van der Waals interactions, hyperconjugation, and steric strain, among other effects. These terms are known simply as the V_1, V_2, and V_3 terms for the Fourier series. These V terms can be obtained by optimising the quadratic Fourier-series equation for three degrees of freedom, using the obtained torsional values as inputs. This was done using a simple iterative program for solving quadratic equations.

A second much smaller set of parameters was obtained from our own synthesised systems. To this end we tried to form enaminone systems that might be solid and therefore have the potential of forming crystals for X-ray analysis. Most of the compounds listed hereunder were not sufficiently crystalline or did not form suitable crystals for X-ray analysis. These molecules had no other use for this project and we did not characterise them further, but they are listed here for completion.

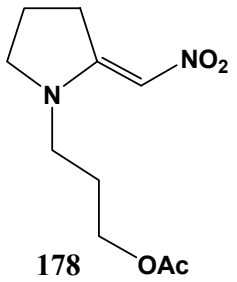


177



156

The first set of compounds contained the phenylsulfonyl moiety (e.g. **177**). These were easy to synthesise and usually gave solids, but were frustratingly difficult to purify and only the nitro-substituted version, 2-(nitromethylene)-1-[2-(phenylsulfonyl)ethyl]pyrrolidine gave useful data. Similarly, ethyl 3-{2-[2-(1*R*,5*R*,7*S*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propanoate [**156**] formed a solid, but crystallised as a ribbon difficult to mount on the sample holder.

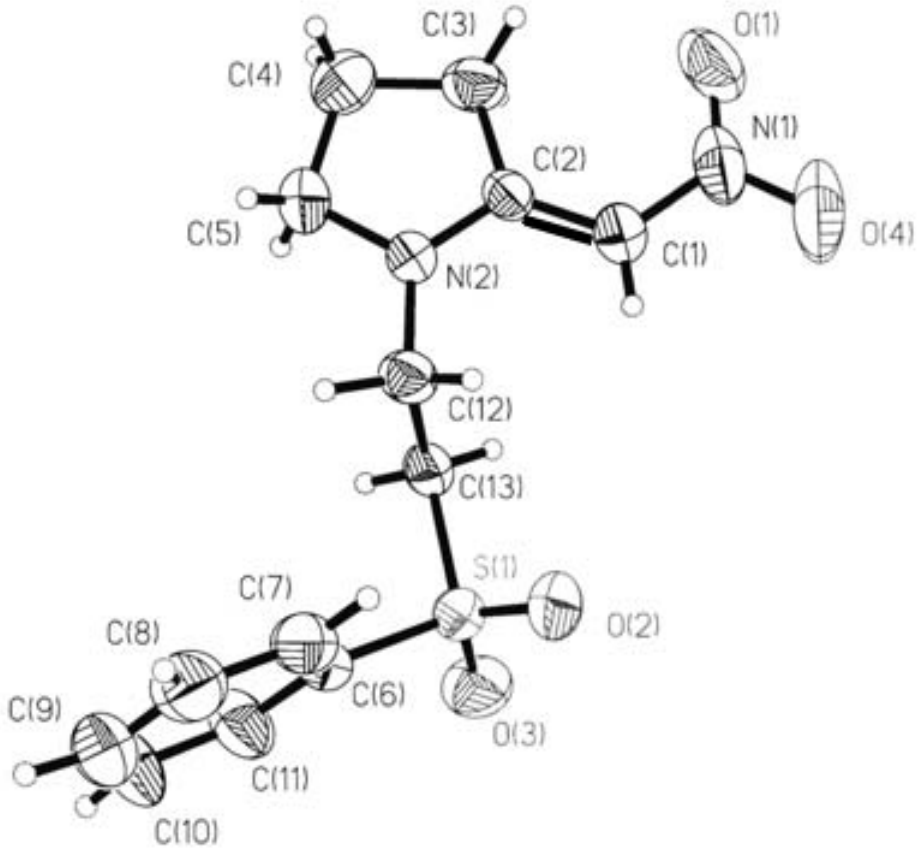


178

Some simple compounds such as 3-(2-nitromethylenepyrrolidin-1-yl)propyl acetate [**178**] previously synthesised in our laboratories tended to be amorphous powders, while others such as those containing an *N*-Boc protected pyrrolidine were liquids. This was largely an exercise conducted on the "sidelines" and the lack of suitable crystals was not detrimental to the project, so while every effort was made to obtain suitable crystals, the unsuccessful compounds were simply abandoned.

The following three compounds were the only ones to give useful crystal structures (the ORTEP plots for each crystal is shown below): 2-(nitromethylene)-1-[2-(phenylsulfonyl)ethyl]pyrrolidine [**179**], 3-{2-[2-

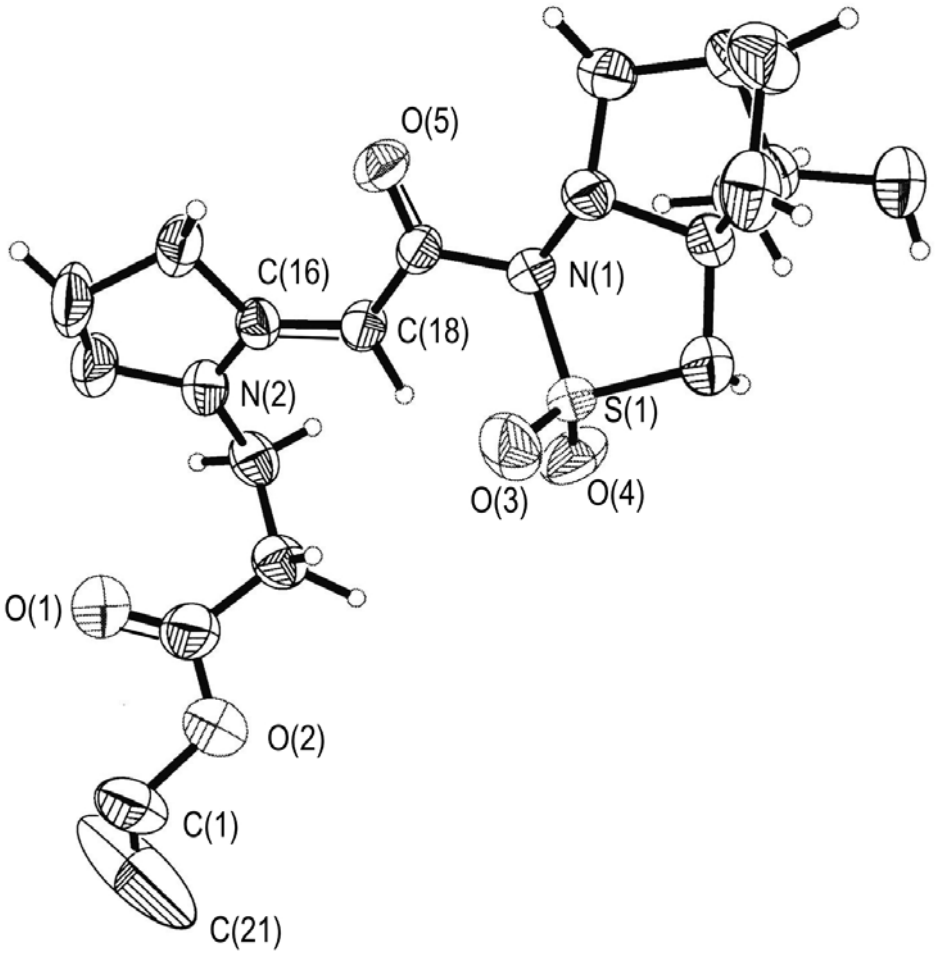
(1*R*,5*R*,7*S*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propyl acetate [**155**], and ethyl 3-{2-[2-(1*R*,5*R*,7*S*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propanoate [**156**].



ORTEP Plot for compound 179

This molecular structure was useful for confirming some of the bond angles and bond lengths that were missing in the computational force-field. Some of these parameters, such as the angles in the pyrrolidine ring were irrelevant to the geometry of the chiral auxiliary, but by making certain that even these angles were accurate allowed us greater confidence in our predictions. All the missing parameters were the same (within experimental errors) as the default values used by the modelling program, so there was no need to modify these parameters.

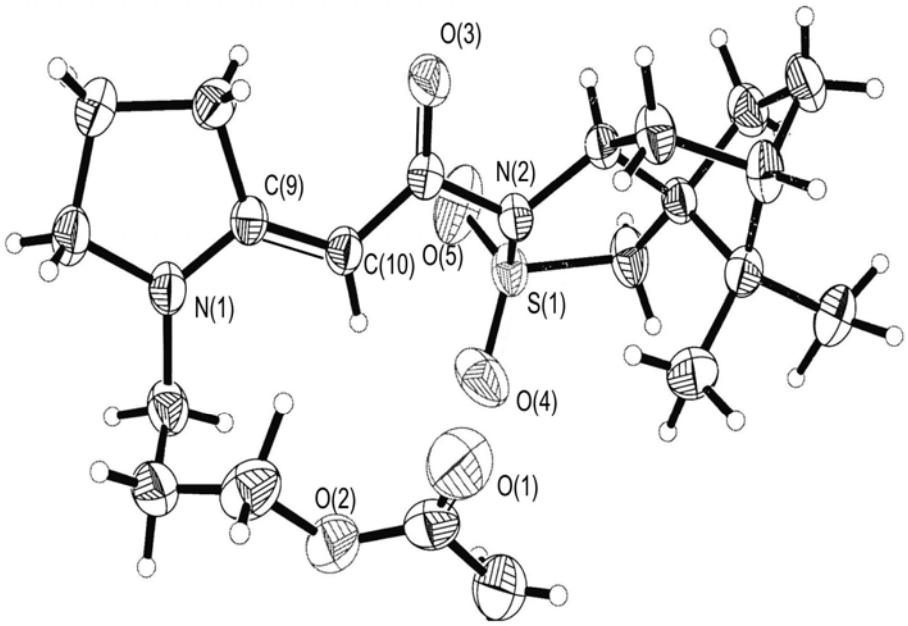
It should also be noted that all the crystal structures show an (*E*)-double bond configuration, such as the C(1)=C(2) bond in the above ORTEP plot. This is consistent with the results obtained in the early modelling studies.



ORTEP Plot for compound 156

As with the previous crystal structure, this molecule was used to confirm the values for bond angles and bond lengths that might have been missing in the force field (**Table 7**). This structure had some disorder in the ethyl ester moiety, and this can be seen by the large thermal ellipsoids for carbons C(21) and C(1) This resulted in rather large refinement factors of 9.9%. This disorder is not significant and may simply represent two conformations of the ethyl chain in the crystal structure. Indeed if the ester moiety is ignored in the calculations the final R factors are much smaller (around 2%). Again it should be noted that the double

bond (C16=C18) was in the energetically favourable *trans*- or (*E*)-configuration. Finally, as will be shown in the modelling results later in this chapter, the sultam moiety (the right-hand side of the ORTEP diagram) is pointing away from the C=C bond, and would not provide any stereo-facial differentiation, although in the solid state this could be simply due to lattice constraints.



ORTEP Plot for compound 155

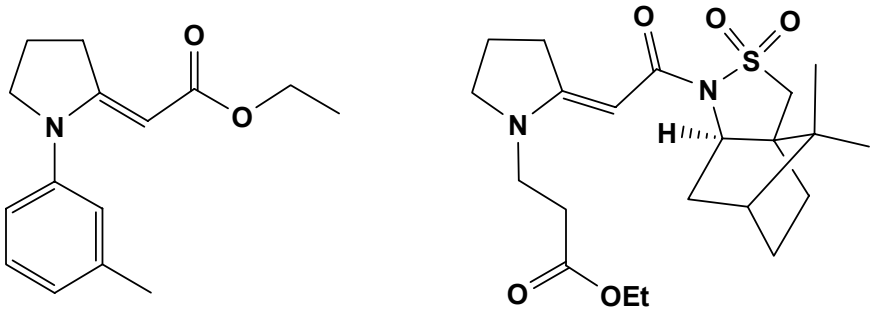
The crystal structure for this molecule refined to an R factor of 4.36% in the orthorhombic lattice space group $P2_12_12_1$. Although the angles and bond-lengths in this molecule are nearly identical to those in the previous molecule (**156**), these parameters were not used in refining the force-field. The reason for this is that we chose this structure to verify the predictive accuracy of the final, adjusted force-field.

The complete set of parameters for these crystal structures, including measured bond-lengths and bond-angles can be found in Appendix A

Once all the missing parameters (**Table 7**) were added to the force field, its validity had to be tested by comparing known experimental molecular geometries with those produced by the program.

6.2 Evaluating the Force Field

To test the force-field we chose two compounds, whose crystal structures were not previously known in the general literature, and compared them with the models generated by the modified force field. The two compounds were the *N*-tolyl pyrrolidine **179**, synthesised by van Heerden during a study of the theoretical energies of enaminones,[217] and the sultam-containing ester **156** (**Figure 31**).



179 **156**

Figure 31 – Compounds used to Test the Modified Force Field Integrity

The crystal structures for these compounds were used to determine how well the calculated parameters would fit with experimental data. Using a small Visual Basic program called CrysToHyp (**Appendix B**) to convert the crystallographic coordinates to Cartesian coordinates, the X-ray data were used to form a copy of the crystal image in HyperChem. This image was compared with the energy-minimised structure obtained directly from the modelling process (this process included both molecular dynamics and simulated annealing steps in order to try and obtain the global minimum). It is important to note that neither compound **156** nor **179** were used during the optimisation of torsion angles, and could therefore serve as useful tests for how true the energy-minimised models are to the real molecular structures. We should also bear in mind the fact that certain crystal packing confinements may distort bonds and angles; this is especially true of conformations with small differences in energy. The similarity between the two models (experimental and theoretical) can be seen from **Figure 32**. Apart

from the obvious differences in the conformation of the ethyl chain and the aromatic ring, the images fit reasonably closely.

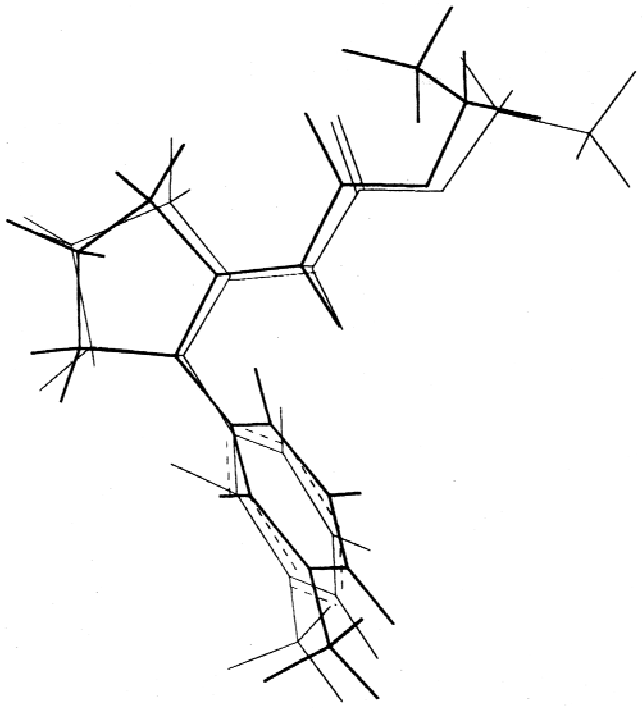


Figure 32 – Comparison of the Crystal Structure of **179** (Dark Lines) with its Computer Generated Model (Light Lines).
Note, the double bonds and aromatic ring (dashed lines) are only shown in the molecular model for clarity.

This visual confirmation of the validity of the force field was supported by the similarity in the single point energy of both the theoretical and experimental models, which are shown in **Table 8**. These single-point energies represent a single location on the energy contour where the geometry of the molecule is optimised, and therefore the energy minimised. The fact that the program can accurately predict the geometry and energy of an experimentally determined system is an indication of the accuracy of the parameters used in the prediction.

Table 8 – Comparison of the Single-Point Energies between Experimental and Theoretical Models for Compounds **179** and **156**

Compound	Theoretical Model	X-ray crystal model
179	15.08 kJ/mol	15.06 kJ/mol
156	60.82 kJ/mol	62.10 kJ/mol

Compound **156** was treated similarly to **179**. A suitable single crystal of this compound was grown from ethyl acetate, by vapour diffusion of hexane at room temperature over 9 days. The X-ray crystallographic data were collected, and the atomic coordinates of all atoms, except the hydrogen atoms were converted by the program CrysToHyp (appendix B) into Cartesian coordinates. The image generated in this manner was compared both visually and computationally with the model of compound **156**. The results of this comparison are shown in **Figure 33** and **Table 8**, respectively.

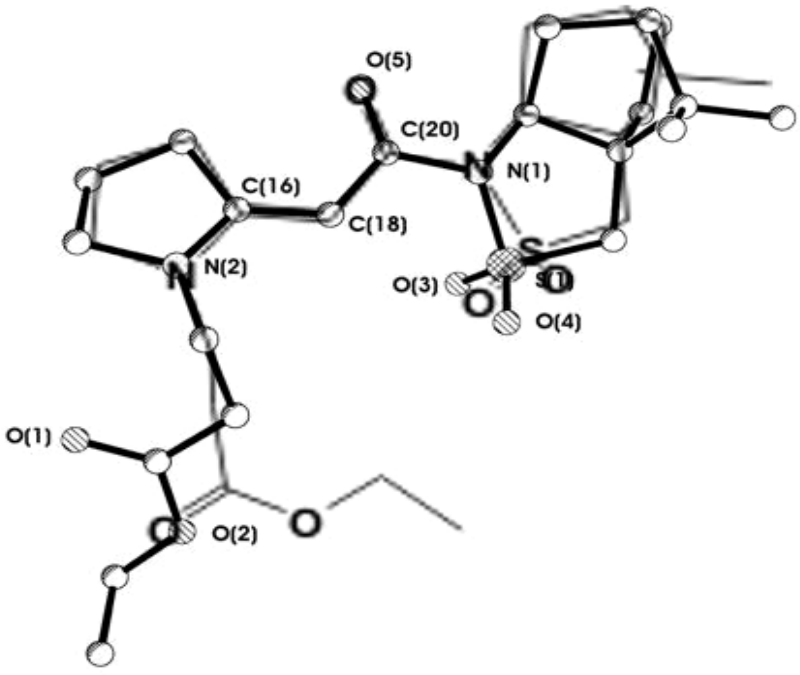


Figure 33 – Comparison of the Crystal Structure of Compound **156** (dark lines) with its Computer Generated Model (Light Lines)
Note, the double bonds are only shown in the molecular model for clarity.

Again it is clear that there is good agreement between experimental values and calculated values. In the case of **156** the greater complexity of the molecule and the inclusion of some non-critical but not optimised parameters (such as the O=S=O bond angle) results in a greater discrepancy in the single-point energies shown in **Table 8**, but there is good agreement with the general orientation of the chiral auxiliary with respect to the C=C bond. If we examine the individual bond angles and bond lengths we find identical values (within experimental limits). For example, the bond length for the C=C bond of **156** is 1.362(± 0.006) Å from the crystal data and 1.366 Å from the molecular model.

Finally it should be reiterated that there is no significance in the absolute energy values shown in **Table 8**. The one drawback of empirical molecular modelling methods is that direct comparison of energies of different molecules or systems cannot be made. The aim in this project, however, was to examine conformations of the same molecule in order to determine the efficacy of the chiral auxiliaries conformation locking.

6.3 Perspectives from the Molecular Modelling Results

6.3.1 Bohlmann Bands

Once the modified force-field had been tested we could confidently use it to examine some aspects of the project that were puzzling. The first of these was the variation in Bohlmann bands in the infrared spectra of the indolizidines (after reduction of the C=C bond). In particular, some of the simply-substituted indolizidine systems with a *syn*-reduced double bond had unusually prominent bands in comparison to more complex substituents. By modelling the various indolizidine conformations we were able to suggest a reason for this observation: There are two possible conformations of the bicyclic core in *syn*-reduced indolizidines, one where the two rings are fused at the same face (called *cis*-fused) and the other with the rings fused across both faces (*trans*-fused). The barrier to inversion of the nitrogen atom is not significant, but there is a slight disadvantage, energetically, to the *cis*-fused conformer. The loss of stability resulting from an axial C-8 substituent is therefore compensated by the equatorial arrangement of the *trans*-fused indolizidine rings (**Figure 34**). The converse holds for the equatorial substituent and axial (*cis*-fused) ring system (**Figure 35**).

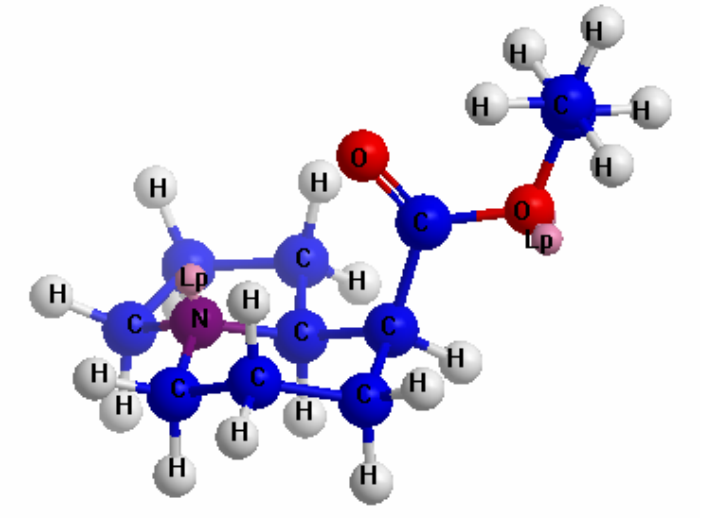


Figure 34 – Model of a *Trans*-Fused Indolizidine Conformation for **156**

The previous model is showing an energetically favoured (*trans*-fused) pyrrolidine ring forcing the ester group (CO_2Et) at position 8 into an unfavourable axial position. The energy of this system was calculated at 31.8 kcal·mol^{-1}, almost 1 kcal·mol^{-1} more than the next conformer (**Figure 35**).

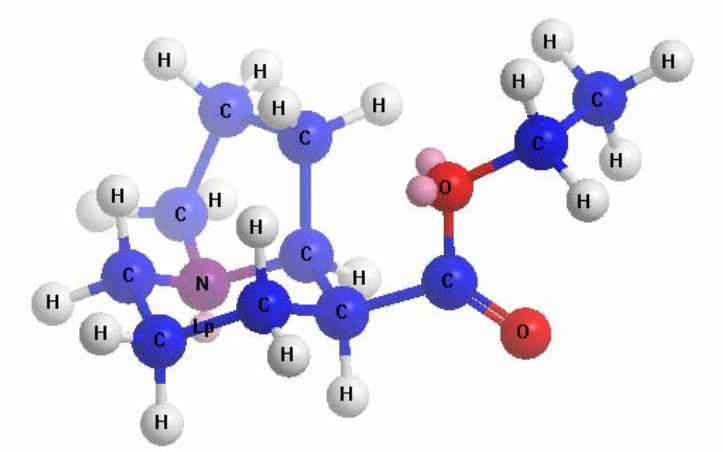


Figure 35 – Model of a *Cis*-Fused Indolizidine Conformation for **156**

In the case of a (*cis*-fused) pyrrolidine ring the ester group (CO_2Et) is now in an energetically favoured equatorial position, which is reflected in the lower system energy calculated at 31.0 kcal.mol^{-1}. The ester moiety adopted slightly different conformations in replicate calculations, but this did not have a significant influence on the energy of the system.

The energy contribution of the axial C-8 substituent increases, however, with larger substituents such as the camphor sultam, and hence we would expect the relative contributions of the two conformers to change in favour of the *cis*-fused indolizidine. The Bohlmann bands observed in the IR spectra are a result of the anti-periplanar overlap of vicinal axial hydrogen atoms with the nitrogen lone-pair. With small C8 substituents the small difference in energies between *cis*-fused and *trans*-fused conformations allows for a greater contribution of the latter where three axial protons show good anti-periplanar overlap and therefore strong Bohlmann bands.

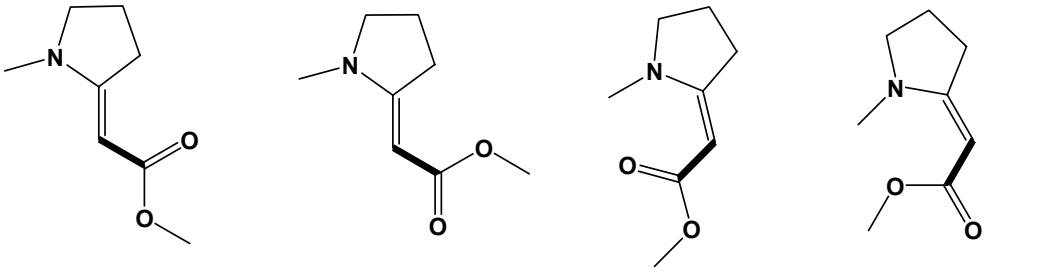
In the case of epitashiromine [**2**], the *trans*-fused conformation is further stabilised by a short H-bonding interaction between the hydroxyl proton (H-10)

and the nitrogen. The exact value of this bond length was not determinable using the MM+ force-field, and varied between 1.03 and 1.42Å. Against expectation, therefore, the IR spectra of epitashiromine showed much stronger Bohlmann bands than did tashiromine.

These models also help to explain the downfield shift in the signal position of proton H-8. In the anti-reduced systems the proton would be in an axial position (both the ring and the C8 substituent are in an equatorial position), with the *trans*-fused conformer dominating. Experimentally the ^{1}H NMR signal for the proton at C8 appears at $\delta < 2.1$, but in the syn-reduced indolizidines this proton appears downfield by ca. 0.9 ppm, together with two or three other protons (the other equatorial N-C*H* protons at C-3 and C-5).

6.3.2 Chiral Auxiliaries

The second aspect we hoped to explain was the lack of diastereoselectivity shown by both the sultam and the oxazolidinone chiral auxiliaries. In choosing these auxiliaries we had anticipated that their steric bulk would result in some "shielding" of one face of the double bond, which would result in the selective delivery of hydrogen to the remaining "vulnerable" face. This was not observed experimentally and we hoped molecular modelling would provide some reasons. Before we examine the bicyclic systems, we need to look at the monocyclic *N*-methyl pyrrolidine compounds. In these systems there are two possible arrangements about the C=C double bond (namely *E* or *Z*), and two arrangements of the carbonyl relative to the C=C bond, these being termed s-*cis* and s-*trans* by the arrangement around the single bond (highlighted in **Figure 36**) between the C=C and C=O bonds. It is therefore possible to examine the four conformations that are shown in **Figure 36** using methyl 2-(1-methylpyrrolidin-2-ylidene)acetate as an example.



I (*E*)-s-*cis* **II** (*E*)-s-*trans* **III** (*Z*)-s-*cis* **IV** (*Z*)-s-*trans*

Figure 36 – Possible Conformers and Configurational Isomers of Monocyclic Vinylogous Urethanes

We modelled each of these conformations by artificially "fixing" the C=C–C=O torsion at either 0° or 180° and allowing the rest of the system to move. Once again for each conformation found we tried to make certain that this was the global minimum energy conformation by simulating a number (usually 5) heating/cooling/energy-minimisation cycles. As expected, the *Z* conformers **III** and **IV** are significantly higher in energy than the corresponding *E* isomers (by at least 5 kcal.mol^{-1}). The energy difference is much smaller, only 0.4 kcal.mol^{-1}, between the s-*cis* and s-*trans* conformers **I** and **II**. Surprisingly the most favoured conformation is **II**, and this is confirmed by the fact that a completely unrestrained system always tended to a geometry almost identical to **II** (only a small deviation of the C=C–C=O torsion could be detected). It should be noted that this conformation would not be possible for larger groups attached to the carbonyl; such is the case with the chiral auxiliaries.

For the remaining modelling exercises we used only the *E* conformations **I** and **II**. The reasons for this are two-fold: firstly as is shown above the other configurational isomers are significantly higher in energy and this difference in energy increases when we consider larger substituents such as the chiral auxiliaries in place of the methyl group, and secondly in the bicyclic systems **III** and **IV** are not possible since the double bond is fixed, and this would allow us to keep most of the system constant when we investigated the indolizidine systems.

6.3.3 Chiral Auxiliary Systems

In order to consider the effect of the chiral auxiliaries on the C=C double bond we needed to know both the relative energies and the ease of conformational change between the s-*cis* and s-*trans* conformations. To do this we used an incremental iterative process of changing the central torsion from 0° through 180° and back to 0° (360°). After each change the molecule was allowed to perturb until an energy minimum was found, a cycle of simulated heating and annealing was carried out followed by another energy minimisation step. After this second energy minimisation the single-point energy was calculated and recorded. Details of the Microsoft Excel program used for this process can be found in Appendix B.

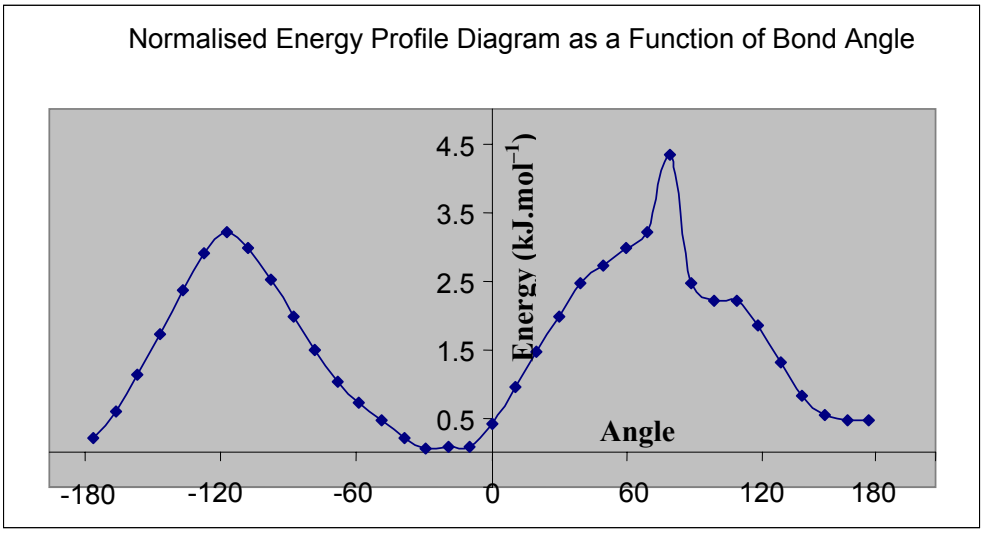
6.3.3.1 Evans Chiral Auxiliary System

All the minimised structures with this chiral auxiliary attached had the benzyl group as far away from the C=C double bond as possible. **Figure 37** shows the energy-minimised s-*cis* structure with both faces of the C=C bond apparently readily accessible to a reductant. In this case, the extra carbonyl group in the oxazolidinone causes a 1.5 $kJ \cdot mol^{-1}$ interaction with the pyrrolidine ring in the s-*trans* conformation. Significantly, however the barrier to rotation about the adjacent C–C bond (i.e. the barrier to conformational change) is only 2 $kJ \cdot mol^{-1}$.

In order to determine the effect of the chiral auxiliary the torsion angle for the bond O=C–N–C was varied from –180° to +180° using a Microsoft Excel™ macro written for the purpose (Appendix B). The choice of angle to vary was not important, as long as the chiral auxiliary was slowly "rotated" with respect to the enamine C=C bond. This macro allowed us to change the torsion, complete a full energy minimisation until the root mean square (RMS) gradient showed that the energy of the system had minimised, and then determine the overall energy using a single-point energy calculation. In order to ensure rapid convergence of the gradient three gradient optimisation algorithms were used; namely the Fletcher-Reeves (a simple conjugate gradient method), Polak-Ribiere (a more complex conjugate gradient algorithm), and the Newton-Raphson block-diagonal method. The optimisation was performed for up to 1000 cycles using each algorithm until the RMS gradient dropped below 0.01 $kcal.mol^{-1}$. An exit flag in the macro

allowed for the termination of this process after 10 complete sets of optimisations if no convergence was reached. In general this occurred for three or four values of the torsion angle, but in each case the RMS gradient was always less than 0.03 kcal.mol^{-1}. The energies obtained in this manner were then converted to kJ.mol^{-1} and plotted using the same Excel™ package.

The graph below shows the energy obtained by this process by varying the angle for the O=C–N–C bond. Note the sharp peak at 80° is a result of the benzyl group on the chiral auxiliary getting "caught" in an unnatural position as a result of the iterative process and is not representative of a significant energy barrier. We can see (from **Graph 1**) that the lowest energy conformer has the two carbonyl groups in an almost antiperiplanar arrangement (torsion angle of 180°).



Graph 1 - – Variation in Energy as a Function of Torsion Angle C=C–C=O for compound **147**

The small barrier means that it should be quite easy for the chiral auxiliary to freely rotate into different conformations. In addition, the fact that the bulky phenyl ring on the oxazolidinone points away from the double bond explains why we did not observe any stereo-differentiation during the reduction of these

systems. The two lowest-energy states are also very similar in energy, suggesting a 50/50 distribution between these two conformers.

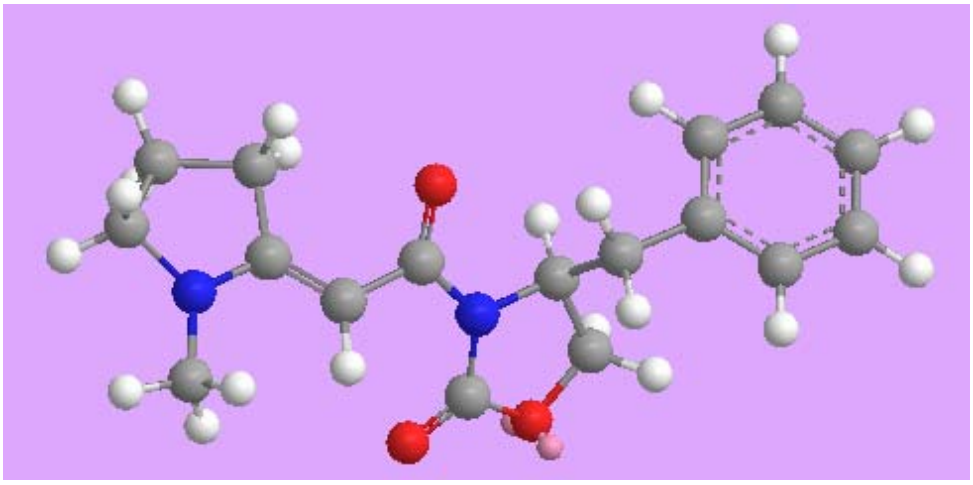
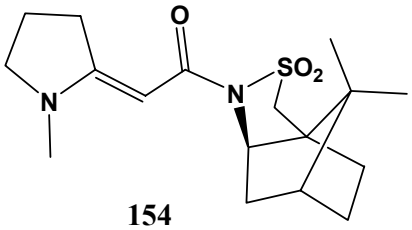
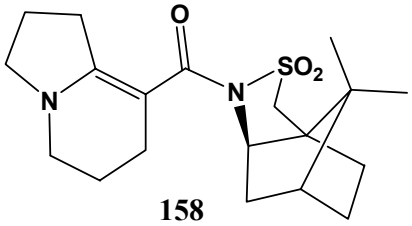


Figure 37 - Model of (*S*)-4-Benzyl-3-[2-(1-methyl-pyrrolidin-2-ylidene)-acetyl]-oxazolidin-2-one [**147**]

6.3.3.2 Sultam Chiral Auxiliary System



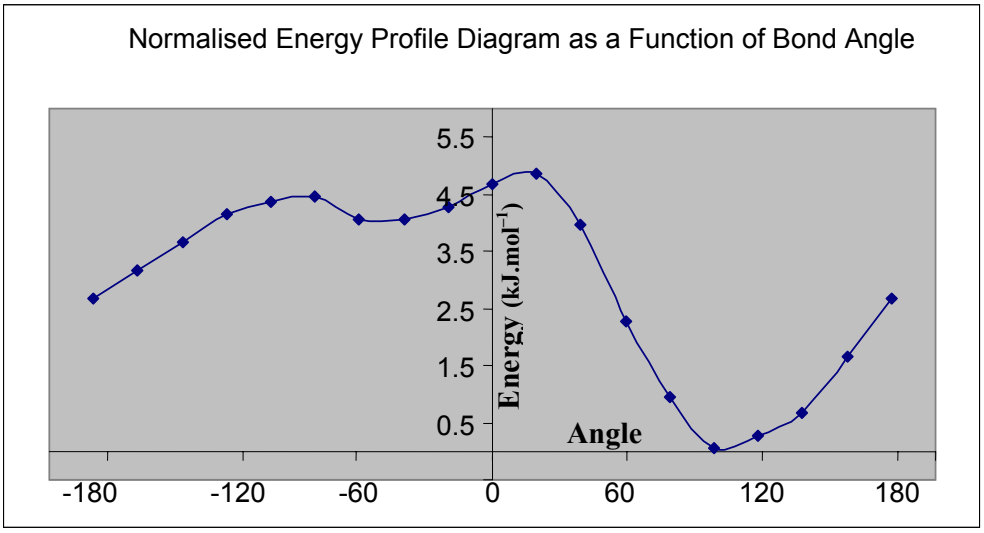
154



158

Whether we consider the monocyclic or bicyclic systems the situation is not much better in the sultam-containing molecules. In both molecules **154** and **158** the s-*cis* conformation is favoured, with an ideal angle of ca. 30° for the C=C–C=O torsion. In **154** a total energy of 59.84 kcal.mol^{-1} was calculated for the energy-minimised structure. Once again, as with the Evans chiral auxiliary, there is a small barrier to conformation change and even smaller energy difference between s-*cis* and s-*trans* conformations. The equivalent s-*trans* minimum conformation, for example, with a C=C–C=O torsion of 143° has a total energy of 61.40 kcal.mol^{-1}, around 1.5 kcal.mol^{-1} higher than the most favoured s-*cis* conformation.

Graph 2 shows the tiny energy barrier between conformations at 4.8 $kJ.mol^{-1}$ for **154**, and **Graph 3** the corresponding value of 6.5 $kJ.mol^{-1}$ for molecule **158**.



Graph 2 – Variation in Energy as a Function of Torsion Angle C=C–C=O for Compound **154**

The indolizidine system shows four lowest energy conformations with O=C–N–S torsion angles of 16°, 137°, -163°, and -39° (**Graph 3**). The first and last conformation are distorted s-*trans* conformations with the SO_2 moiety partially blocking either the anterior or posterior face of the C=C bond (as seen in **Figure 38**). The remaining conformations have the "bicyclodecane" part of the chiral auxiliary closest to the double bond, each closer to one face. These conformations are the lowest energy conformations and one is depicted in **Figure 38**. It should be noted from these conformations that the "blocking" effect mentioned is not significant, firstly because the chiral auxiliary can rotate quite freely, and secondly because the bulky groups are predicted to be far away from the double bond.

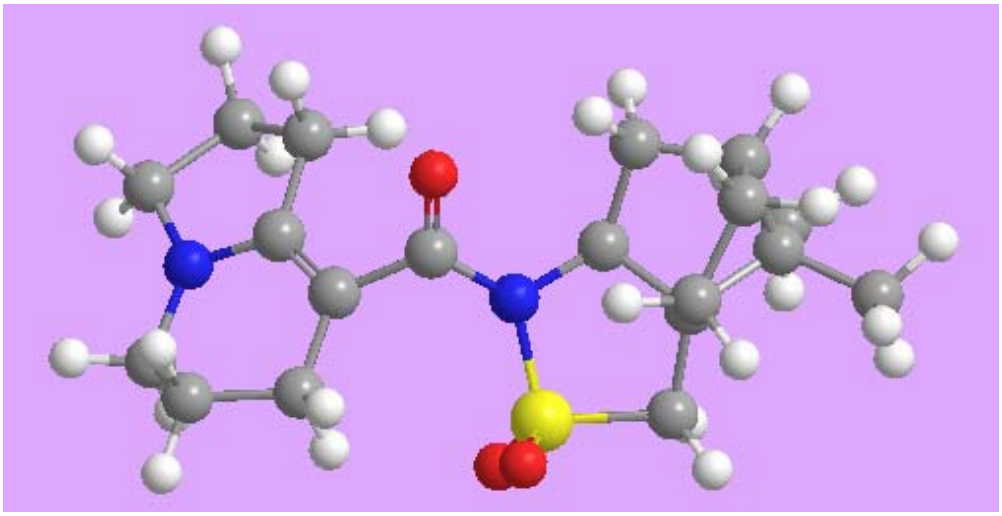
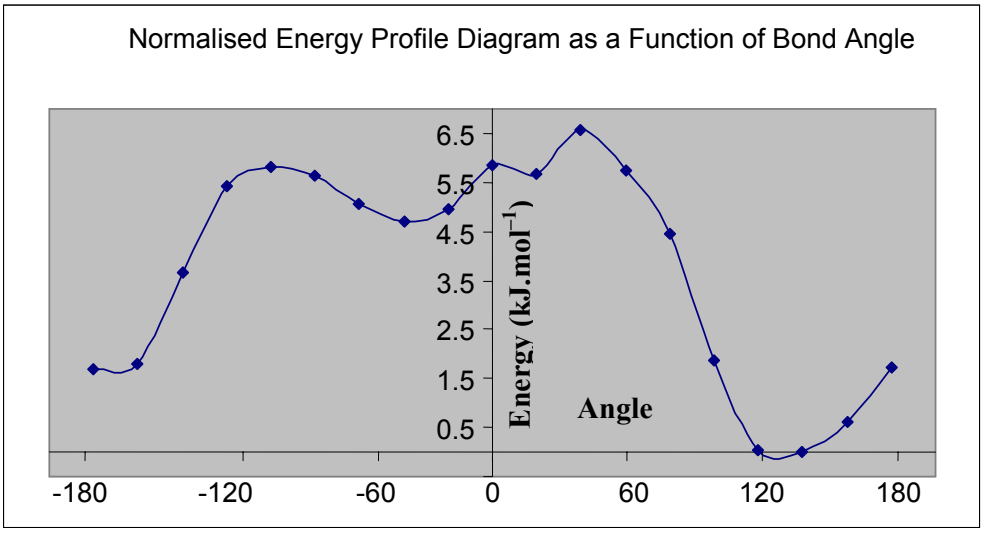


Figure 38 – Representation of the Minimum Energy Conformation of **158**

Although these are very different shielding effects, there is little difference between any of the conformations (in terms of energy), and hence once again there would be an almost statistical distribution of molecules in these conformations. This is reflected in the poor diastereoselectivity observed in the reduction of **158** to give tashiromine. There appears to be a small selectivity d.e. = 9% towards the (–)-tashiromine which would either indicate that the SO_2 group is not as effective at blocking the C=C bond, or that the conformation leading to the (8*R*,8a*S*) diastereomer of **162** is favoured.



Graph 3 - – Variation in Energy as a Function of Torsion Angle C=C–C=O for Compound **158**

6.4 Conclusions from the Molecular Modelling Study

The lack of significant stereocontrol in either of the chiral auxiliaries used can be traced to two factors:

1) The probable hydrolysis or cleavage of the chiral auxiliary during the reduction reactions as evidenced by the large amounts of auxiliary that were recovered during most of the reduction steps.
2) The relative ease with which the chiral auxiliary can adopt different conformations.

In contrast to this, the work of Lhommet *et. al.*[47][116] shows that a chiral phenyl group attached directly to the nitrogen has conformations with significantly different energies (calculated at almost 18 kJ.mol^{-1} between low-energy conformers **I** and **II** in **Figure 39**), and that the barrier to rotation is almost 50 kJ.mol^{-1}.

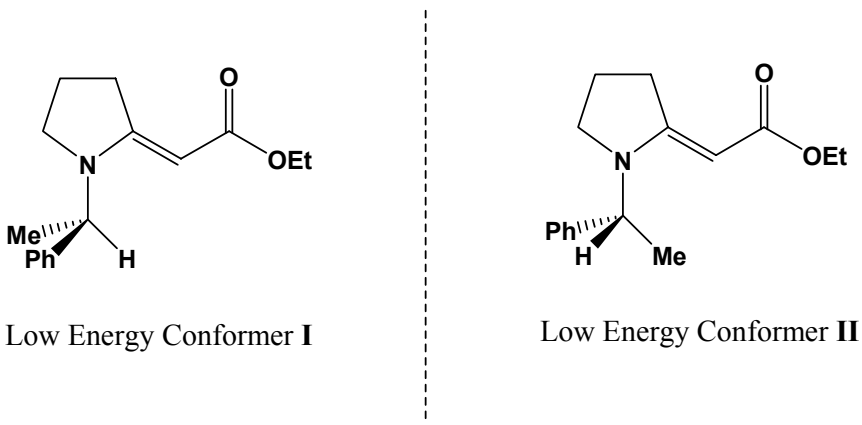


Figure 39 – Two Significantly Different Low-energy Conformers of a Chiral Vinylogous Urethane

Chapter 7

Conclusions, Perspectives and Future Work

This project has taken the first step in determining the viability of using chiral auxiliaries as part of the general methodology on alkaloid synthesis within the laboratories of the University of the Witwatersrand. Despite the problems, none of which were insurmountable, we were able to synthesise both tashiromine and epitashiromine from the same precursor by merely varying the reduction conditions.

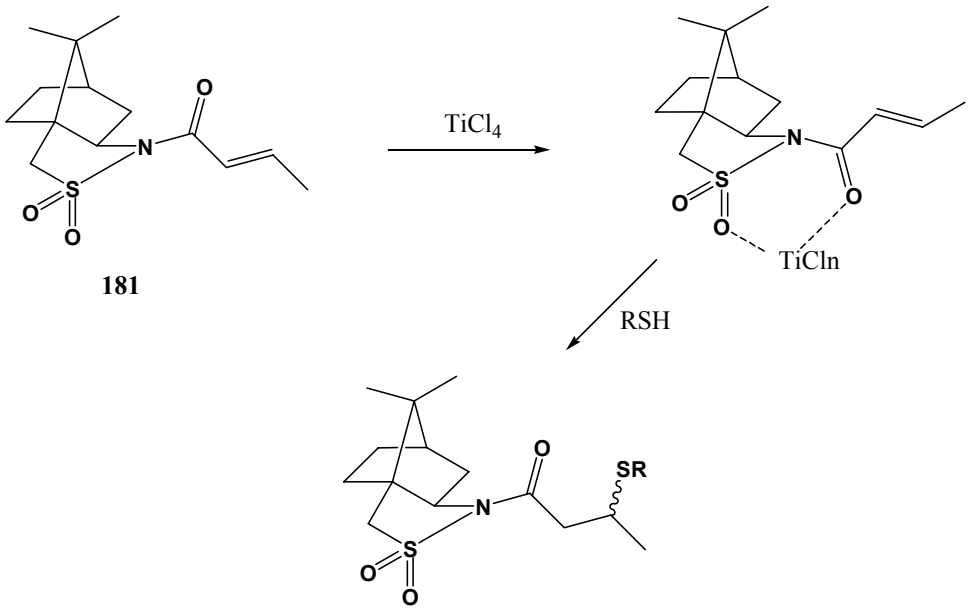
The successful synthesis of a number of chiral auxiliaries with fairly high overall yields is a motivating factor in implementing this strategy further, but two critical factors need to be addressed;

1) More effective shielding from the chiral auxiliary.
2) Better stability under the chosen reaction conditions.

The conformational lability of the chosen chiral auxiliaries (allowing both faces of the double bond to be equally vulnerable to attack by the reductant) and the susceptibility of the *N*-acyl bond to cleavage are two of the biggest challenges emanating from this project. We have, however only started to scratch the surface as far as choice of auxiliary is concerned. The introduction of other chiral auxiliaries may contribute to a solution to these problems. Perhaps the use of chiral ethers instead of amines would impart greater stability to the system.

There are also strong precedents for selectively coordinating the auxiliary using a Lewis acid such as $TiCl_4$ or a simple metal ion such as magnesium. Using the current chiral auxiliaries it should be possible to improve the stereocontrol by employing small modifications in the reaction conditions.

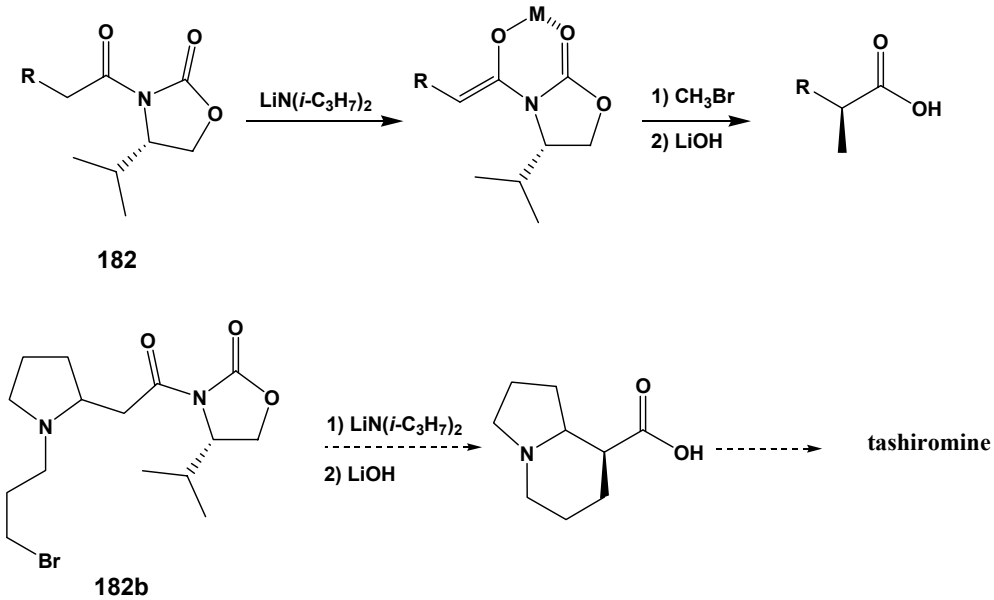
Titanium has, for example, been used successfully in conjunction with camphor to influence the outcome of the conjugate addition of thiols to enoyl-sultams such as **181**.[218][219]



Scheme 53 – Asymmetric Conjugate Addition assisted by $TiCl_4$ Coordination

In this project we briefly tried the addition of titanium, caesium, and magnesium salts to the reduction reactions, but were without success since time did not allow us to optimise this strategy.

A similar strategy would be to transform a chiral precursor such as **182** into its enolate by reaction with a base, and use this to stereoselectively alkylate the position α to the auxiliary.

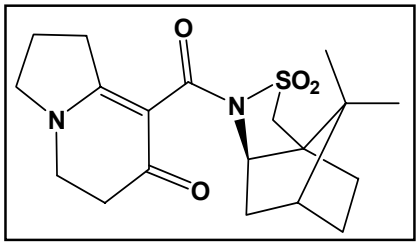


Scheme 54 – Proposed extension of chiral auxiliary-mediated alkylation

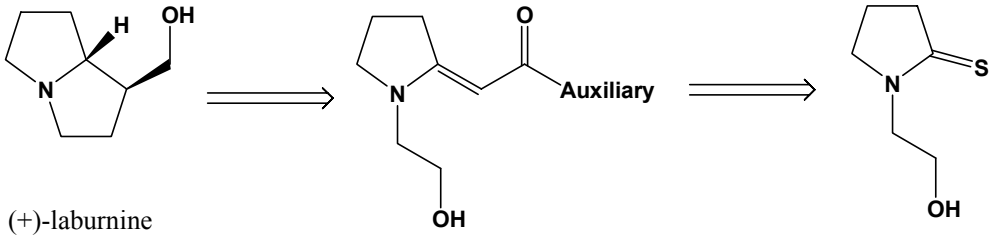
This strategy has been successfully employed by Evans and co-workers in the enantioselective synthesis of α-substituted carboxylic acids.[220] Thus it may be possible to extend this strategy to targets such as tashiromine.

The early loss of the chiral auxiliary is a problem that merits further investigation. It may be possible to find more robust auxiliaries or other reducing techniques that are more effective. Milder techniques may provide a way to control the diastereoselectivity without loss of the chiral auxiliary. For example, a trace amount of chloroform has been used during catalytic reductions as a source of HCl instead of conducting the reaction in acetic acid.[221][222] This strategy may limit the extent of cleavage by providing only a small amount of acid. Alternatively it should be possible to use the chiral auxiliaries to control other aspects of the synthesis. Most of the chiral auxiliaries used in this project have been used successfully in the alkylation of the position α to the carbonyl. Although this would detract from the chemistry of enaminones, it may for example be possible to reduce the enaminone first and effect the cyclisation in a second step via a chiral enolate.

Another drawback to the synthesis of indolizidines presented here is the often low and variable yield of the alkylative cyclisation step. It should be possible to optimise the cyclisation through the judicious choice of reagents, but this project has shown that this would have to be done for each substrate in turn since a strategy considered "ideal" in one case may not apply to others. Alternatively the acylative cyclisation (such as the synthesis of compound **159**) may provide not only a higher yield of the indolizidine core, but also more conformational control of the chiral auxiliary. The presence of an extra carbonyl group on the indolizidine ring may force the sultam into a conformation that would better block the double bond. This could then be used for further functionalisation if needed, or could be removed.



The successful synthesis of the set of 8-hydroxymethylindolizidines should allow us to explore similar indolizidine targets such as the popular polyhydroxylated alkaloid slaframine, or even the synthesis of quinolizidine and pyrrolizidine alkaloids. This statement comes from an awareness of the varying reactivities of these ring systems in our labs. Thus the synthesis of the quinolizidines lupinine and epilupinine might be more facile than the corresponding indolizidine syntheses shown here. Similarly, it should be possible to synthesise the pyrrolizidines isoretronecanol and laburnine by starting with an *N*-hydroxyethyl pyrrolidine instead of the *N*-hydroxypropyl version.



Scheme 55 – Possible use of Chiral Auxiliaries in the Synthesis of Pyrrolizidines

A methodology study such as this one often raises as many questions and possibilities as it answers, but I believe this approach of using chiral auxiliaries could be applied to many of the targets in our laboratories. It might be interesting, for example to try and attach the chiral auxiliary at other positions along the alkaloid core, or at a later stage in the synthesis. There has been much interest in polyhydroxylated indolizidines and quinolizidines, and the presence of other functional groups would allow for a greater choice of attachment site, perhaps closer to the required pro-stereogenic centres. This may have another advantage in that the more complex system should present greater conformational stability and thereby improve the stereoselectivity of the chosen reactions.

Finally I believe greater use could be made of molecular modelling techniques, not only to explain some of the problems encountered during a reaction (as was the case in this project), but ideally as a predictive tool. The molecular mechanics and dynamics simulations should allow us to predict the success or failure of a chosen chiral auxiliary even before it is synthesised.

Chapter 8

Experimental Section

8.1 General

Purification of solvents and reagents

All solvents used in reactions, and most of the liquid reagents were pre-dried over an appropriate desiccant, and distilled prior to use according to literature procedures.[223]. Eluents used for chromatography were distilled prior to use.
Most of the reagents were purchased from commercial sources and used without further purification, unless otherwise stated.

Chromatographic Separations

Thin layer chromatography (TLC) was performed on aluminium-backed Machery–Nagel ALUGRAM Sil G / UV_{254} plates pre-coated with 0.25 mm silica gel 60. Compounds were by examining with ultraviolet light at 254 and 366 nm and visualised with iodine vapour. Where necessary a spray reagent was also used. The R_f values quoted (followed in parentheses by the solvent mixture to which they refer) are for thin layer chromatography.

Preparative, centrifugally-accelerated, radial, TLC (radial chromatography) was performed using a Chromatotron on Machery–Nagel Kieselgel G / UV_{254} silica gel (particle size ≤ 0.02 mm).

Column chromatography was routinely employed for the separation and purification of products, using silica gel 60 (Machery–Nagel Kieselgel 60 with particle size 0.063 – 0.200 mm) as the adsorbent. Silica gel 30–40 times the mass of the product was packed into a column such that the ratio of the diameter of the column (in cm) to the mass of silica (in g) 1:7.
Whatman Partisil Prep 40 silica gel or Machery–Nagel Kieselgel 60 (particle size 0.040 – 0.063 mm) was used for preparative flash chromatography.

HPLC experiments were performed using a Spectrasystem UV3000 P4000 HPLC system, and compounds were detected by a split beam PMT from the irradiation of a deuterium or tungsten lamp (the detection wavelengths are indicated where

appropriate, or at default were set to 254 and 366nm). The columns used for routine reverse-phase HPLC were C_{18}-bonded 5μm silica columns of either 4.6 or 10 mm ID and 250 mm length. Determinations of enantiomeric purity and "chiral" separations were conducted using a Daicel CHIRALCEL OJ column of 4.6 mm ID and 250 mm length. Solvents used were HPLC grade, and were sonicated for 5 minutes prior to use. Samples were first purified by column chromatography, and then filtered through an MSI Cameo 0.45 μm PTFE filter before injection.

Spectroscopic and Physical Data

Yields: are quoted after purification, unless otherwise specified.

Melting points: were determined on a Reichert hot-stage melting-point apparatus and are uncorrected. The solvents used for crystallization are given in parentheses where necessary.

Optical rotation values: were obtained on a Jasco DIP-370 Digital Polarimeter, measured on the sodium D line. The values reported represent an average of several consistent measurements, and are expressed in units of 10^{-1} deg.cm^2.g^{-1}. Values are shown in the form $[\alpha]_D^{23}$ = 123.5 (c = 1.34 in ethanol), where the temperature is given in superscript and the value is followed in parenthesis by the concentration (g/100ml) and solvent.

Elemental analyses: were performed on solid samples where possible, using a Perkin–Elmer 2400 CHN Elemental Analyser. The combustion temperature used was 980°C, and the carrier gas was research grade helium.

Ultra-violet and visible spectroscopy (UV-Vis): UV-Vis experiments were run on a Cary 3E UV/Vis spectrophotometer as solutions in quartz cells of 10mm diameter. Where appropriate, data are reported in the form λ_{max}(solvent)/nm (ε/dm^3.mol^{-1}.cm^{-1} values in parentheses).

Infrared (IR) data: Infrared spectra were recorded on a Bruker IFS 25, or a Bruker Vector 22 Fourier-Transform spectrophotometer. Liquid samples were recorded as a thin film between sodium chloride plates, and solid samples were recorded either as a thin pellet of finely crushed sample and anhydrous KBr, or as a chloroform solution between sodium chloride plates. All absorption maxima are

quoted in cm^{-1} for the range 400–4000cm^{-1}. The terms (s) and (w) indicate strong and weak bands, respectively, and (γ) is a skeletal vibration.

Nuclear Magnetic Resonance (NMR): Unless otherwise stated, all products were characterised routinely by interpretation of proton (^1H) and decoupled carbon (^{13}C) nuclear magnetic resonance spectra, recorded in deuteriated chloroform ($CDCl_3$) with tetramethyl silane (TMS) or $CHCl_3$ as internal references. The ^1H spectra were run on either a Bruker AC-200 or Bruker DRX 400 spectrometer at 200.13 MHz or 400.132 MHz respectively. The chemical shifts are reported as follows: value (δ), reported in parts per million relative to TMS, [multiplicity of signal, number of equivalent hydrogen nucleii (by integration), coupling constant(s) (*J*) in Hz where applicable, and assignment where possible). Signal multiplicity patterns are abbreviated by: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app. = apparent. Combinations of the above are also used, for example dd = doublet-of-a-doublet.

^{13}C spectra were obtained on either a Bruker AC-200 or Bruker DRX 400 spectrometer at 50.32 MHz or 100.625 MHz respectively. The chemical shifts are reported as follows: value (δ) reported in parts per million relative to the central signal of $CHCl_3$ (taken as 77.0 ppm) (assignment where possible).

Additional NMR experiments such as DEPT and ^{13}C–^1H correlated spectra were used to complement the ^1H and ^{13}C spectra, and confirm assignments.

Note: Signals with identical assignments, or with an asterisk are interchangeable. Numerals next to the asterisks were used to distinguish between sets of interchangeable assignments.

Mass Spectrometry data: Samples were analysed by high resolution mass spectrometry on a Kratos MS902/50 (Cape Technikon) spectrometer at 70eV and 200μA or on a VG 70E MS with a mass spectrum CC Pyramid data system, or on a VG 70 SEQ mass spectrometer with either a VG 11-250J data system or a Marc II data system. Data are quoted: *m*/*z* value (relative % abundance, assignment if possible).

Low resolution mass spectra were recorded on a Finnigan TSQ-7000 GC-MS system, utilising a Finnigan MAT GCQ gas chromatograph and Finnigan GCQ quadrupole ion trap mass analyser with direct insert probe. The system uses a

rhenium metal electron source at 70 eV, and the ion trap was operated in positive EI detection mode at 1.03 MHz (with a 15 kV conversion diode). Alternatively a Varian Saturn 2000 GC-MS equipped with an ion trap was used with a 30 m × 0.25 mm DB5MS column for low-resolution GC-MS work. This system could perform Atmospheric Pressure Chemical Ionization (APCI), and was run with either liquid methanol or gaseous methane. Data are quoted as for high resolution data.

X-ray crystallographic data and general procedures pertaining thereto are quoted in Appendix A.

Other General procedures

In general, ***work-up*** refers to the extraction of an aqueous phase with an organic solvent, followed by drying of the combined organic phases over anhydrous sodium or magnesium sulfate.

Evaporation of the solvent ***in vacuo*** [referring to the removal of the solvent under reduced pressure (approximately 40 Torr, 50–60 °C) on a rotary evaporator] followed by removal of residual solvent at an oil pump (pressure approximately 1 Torr at room temperature).

Bulb-to-bulb distillations were performed under reduced pressure (0.5–2 Torr) in a Kügelrohr apparatus.

Ultrasound irradiation or sonication was performed in a UMC2 ultrasound cleaning bath at 43 kHz and 0.2 A. All ultrasound experiments were performed on an on/off cycle of 15 minutes for the duration of the experiment, to avoid excess heating of either the solvent or the reaction.

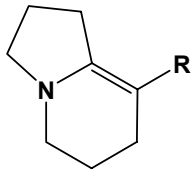
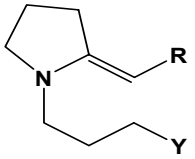
General experimental procedures are summarised in **Table 10** below.

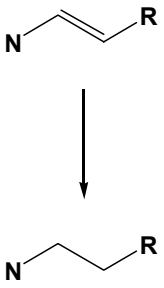
Nomenclature and numbering of compounds

The compounds prepared during the course of this project are named in the experimental sections according to IUPAC systematic nomenclature, however, the numbering system used to illustrate the diagrams of these compounds is one adopted for convenience and does not necessarily reflect their systematic numbering.

Names given in parenthesis and double underlined, immediately below the IUPAC name are convenient abbreviated alternatives, eg.*(camphor sultam)* is used in place of (1*S*,5*R*,7*R*)-10,10-dimethyl-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane-3,3-dioxide.

Table 10- Summary of General Experimental Procedures

Procedure Number	General Description	Details on page	Products Formed
GP-1A	Brillion Procedure for thionation		-C=O → -C=S
GP-1B	Thionation with P_2S_5 in benzene under reflux		-C=O → -C=S
GP-1C	Thionation with P_2S_5 under ultrasonic irradiation		-C=O → -C=S
GP-1D	Thionation using Laweson's Reagent		-C=O → -C=S
GP-2A	Acylation using NaH as the base		-NH → -NCOCH$_2$Br and -OH → -NCOCH$_2$Br
GP-2B	Acylation using *n*-BuLi as a base		-NH → -NCOCH$_2$Br
GP-3A	Sulfide Contraction		-N-C=S → -N-C=C-R
GP-3B	Knoevenagel Modification		-N-C=S → -N-C=C-NO$_2$
GP-4	Hydrolysis of Acetate Compounds		-CH$_2$OAc → -CH$_2$OH
GP-5	Hydrolysis of Propanoates		-CH$_2$CO$_2$Et → -CH$_2$CO$_2$H
GP-6A	Cyclisation of alcohols using PPh_3, I_2, and Imidazole		 **R** = CO_2-chiral auxiliary, CO_2Et, NO_2, CN, etc
GP-6B	Cyclisation of alcohols using PPh_3, I_2, and Imidazole *and NaH*		
GP-6C	Cyclisation of alcohols using **CI_4**, PPh_3, and catalytic Py		
GP-6D	Cyclisation of alcohols using **CI_4** and PPh_3, with or without NEt_3.		
GP-6E	Cyclisation of alcohols using **CBr_4**, PPh_3 (including modifications).		
GP-6F	Cyclisation of alcohols using **CCl_4** and PPh_3 (including modifications).		
GP-6G	Tosylate formation with *p*-TsCl and a base (**NaH**, **BuLi**, or **NEt_3**)		 **Y** = leaving group
GP-6H	Mesyate formation with MsCl and a base (**NEt_3**)		
GP-6I	Triflate formation using triflic anhydride.		

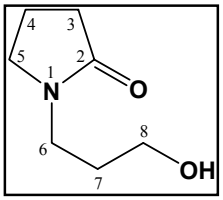
GP-7A	Reduction of vinyl bond using $NaBH_3CN$		
GP-7B	Reduction using PtO_2 / H_2		
GP-7C	Reduction using Pd/C / H_2		
GP-7D	Reduction $NaBH_4$ in Ethanol/Methanol		
GP-7E	Reduction using $Ru(BINAP)_2$ / H_2		
GP-7F	Reduction using $LiAlH_4$		

Numerical List of Compound Numbers and Experimental Procedure Page Location

Compound Number	Page	Compound Number	Page
1	287, 289	**146**	235
2	288, 289	**147**	239
		148	240
102	196	**149**	253
103	196	**150**	273
104	197	**151**	291
105	198	**152**	298
106	201	**153**	241
107	202	**154**	242
108	202	**155**	243
109	203	**156**	245
110	238	**157**	255
111	252	**158**	274
112	271	**159**	260
113	285	**160**	294
114	286	**161**	298
117	204	**162**	301
118	205	**163**	246
128	206	**164**	256
129	207	**165**	259
130	209	**166**	275
131	211	**167**	292
132	216	**169**	210
133	214	**170**	208
134	218	**171**	302
135	224	**174**	249
136	219	**175**	258
137	220	**176**	267
138	221	**177**	250
139	222	**178**	248
140	226	**179**	251
141	230		
142	231		
143	232		
144	232		
145	234		

Section 8.2 Synthesis of Pyrrolidones

8.2.1 1-(3-Hydroxypropyl)pyrrolidin-2-one [102]



A mixture of 3-aminopropan-1-ol (0.9 – 2.0 mol) and γ-butyrolactone (1.01 eq.) was placed in a thick-walled Carius tube. The tube was sealed and thereafter heated at 250°C for between 16 and 30h. After cooling to RT, the tube was opened and the water that had formed was evaporated *in vacuo* to give a yellow-brown oil. Distillation (155 – 160 °C / 0.5mmHg) yielded pure 1-(3-hydroxypropyl)pyrrolidin-2-one as a clear, pale yellow oil (93%).[67]

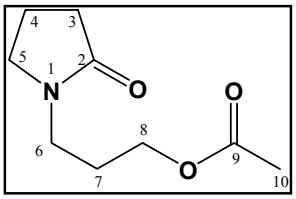
R_f = 0.22 (1:1 ethyl acetate/hexane), 0.23 (1:1 acetone/hexane)

IR Absorptions υ_{max}/cm^{-1} (thin film) = 3398 (O–H), 1666 (C=O), 1428, 1368 (C–N), 1264 (C–O)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) = 1.73 (tt, 2 H, J_1 = 6.4, J_2 = 6.0, $CH_2C\underline{H_2}CH_2OH$, H-7), 2.06 (tt, 2 H, J_1 = 7.5, J_2 = 7.4, $NCH_2C\underline{H_2}$ H-4), 2.41 (t, 2 H, J = 7.5, $NCOC\underline{H_2}$ H-3), 3.40, (t, 2 H, J = 6.4, $C\underline{H_2}CH_2CH_2OH$ H-6), 3.44 (t, 2 H, J = 7.4, $NC\underline{H_2}CH_2$ H-5), 3.55 (t, 2 H, J = 6.0, $CH_2CH_2C\underline{H_2}OH$ H-8), 4.20 (br s, 1 H, $O\underline{H}$ H-9)

δ_C (400 MHz; $CDCl_3$) = 17.88 (C-4), 29.77 (C-7), 30.93 (C-3), 39.23 (C-6), 47.62 (C-5), 58.61 (C-8), 175.94 (C-2)

8.2.2 3-(2-Oxopyrrolidin-1-yl)propyl acetate [103]



The acetylation of **102** was achieved by adding a solution of freshly distilled acetic anhydride (1.00 eq., 90.0 mmol) and pyridine (1.01 eq., 90.9 mmol) drop-wise at 0 °C to a solution of 1-(3-hydroxypropyl)pyrrolidine-2-one (**102**, 0.66 eq., 59.4 mmol) in pyridine (5 cm^3), over 10 minutes. After addition, the solution was allowed to warm to RT over 5h. Ethyl acetate (17 cm^3) was added, and the solution washed with sat'd NaCl (3 × 40 cm^3). The aqueous phase was extracted with CH_2Cl_2 (3 ×

40 cm^3), and the combined organic fractions washed with 30 cm^3 of a solution of NH_4Cl and NH_3 (2 cm^3 NH_3 in 28 cm^3 sat'd NH_4Cl) to remove any excess pyridine. The combined organic layers were dried with Na_2SO_4, filtered and evaporated to give a pale yellow oil, which was distilled under vacuum to give the desired product, as a clear, pale yellow oil (84%).[67]

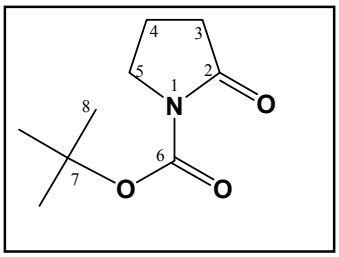
R_f = 0.48 (1:1 acetone/hexane), 0.22 (1:1 acetone/hexane)

IR Absorptions υ_{max}/cm^{-1} (thin film) = 3009(s), 2943 (m), 1735 (vs, O–*C*=O), 1674 (vs, N–*C*=O), 1368 (C–N), 1296 (s), 1244 (vs, *C*–O)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) = 1.89 (m, 2 H, $NCOCH_2CH_2$ H-4), 2.01 (s, 3 H, $COCH_3$ H-10), 2.0–2.1 (m, 2 H, $CH_2CH_2CH_2OAc$ H-7), 2.37 (t, *J* = 8.3, 2 H, $NCOCH_2$ H-3), 3.37 (t, *J* = 6.9, 2 H, $CH_2CH_2CH_2OAc$ H-6), 3.4 (t, *J* = 6.9, 2 H, $NCOCH_2CH_2CH_2$ H-5), 4.1 (t, *J* = 6.4, 2 H, $CH_2CH_2CH_2OAc$ H-8)

δ_C (400 MHz; $CDCl_3$) = 17.66 (C-4), 20.6 (C-10), 26.1 (C-7), 30.6 (C-3), 39.1 (C-6), 46.8 (C-5), 61.5 (C-8), 170.6 (C-9), 174.7 (C-2).

8.2.3 2-Oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester [104] (*N*-BOC-pyrrolidin-2-one)



The protection of pyrrolidin-2-one as a *tert*-butoxycarbonyl (BOC) urethane was achieved in 98% yield following a literature procedure:[224][225]

To a 0.50 M solution of pyrrolidin-2-one (1.0 eq., 1.70 g, 20.0 mmol), in dichloromethane was added triethylamine (1.0 eq., 2.78 cm^3), di-*tert*-butyl pyrocarbonate (also known as di-*tert*-butyl dicarbonate or DIBOC) (2.0 eq., 8.72 g), and 4-(dimethylamino)-pyridine (DMAP) (1.0 eq., 2.46 g). The solution was stirred for 6 h under

nitrogen. The volatile substances were removed and the residue was purified by chromatography (ethyl acetate/hexane) to give a clear oil.

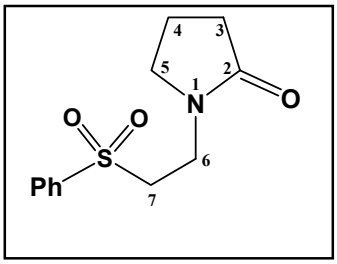
R_f = 0.47 (1:1 ethyl acetate/hexane)

IR Absorptions υ_{max}/cm^{-1} (thin film) = 3015(s), 2942 (m), 1725 (vs, O–C=O), 1671 (vs, N–C=O), 1366 (C–N), 1295 (s), 1244 (vs, C–O)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.53 (s, 9 H, -CH_3, H-8), 2.05 (app. pent, J_1 = 7.4 2 H, $NCOCH_2CH_2$, H-4), 2.52 (t, J_1 = 8.1, 2 H, $NCOCH_2$, H-3), 7.76 (t, J_1 = 7.0, 2 H, $NCOCH_2CH_2CH_2$, H-5)

δ_C (200 MHz; $CDCl_3$) 17.04 ($NCOCH_2CH_2$, C-4), 27.65 (CH_3, C-8), 32.57 ($NCOCH_2$, C-3), 46.15 ($NCOCH_2CH_2CH_2$, C-5), 82.26 [$OC(CH_3)_3$, C-7], 149.83 (COO, C-6), 174.01 (NC=O, C-2)

8.2.4 1-(-2-Phenylsulfonylethyl)pyrrolidine-2-one [105]



A solution of phenyl vinyl sulfone (1.500 g, 8.917 10^{-3} mol) and pyrrolidine-2-one (1.1 eq, 0.833 g, 9.809 10^{-3} mol) in wet THF (10 cm^3) was stirred in the presence of catalytic NaOH for 48 h. TLC indicated complete consumption of the starting materials. Water (20 cm^3) was added and the reaction extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic fractions were dried (Na_2SO_4), filtered and evaporated to give a yellow oil (1.030 g, 45%). This product was not purified further since a more advanced intermediate (the protected pyrrolidine2-thione **118**) was made in higher yield.[226]

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.97, (app. pent, 2 H, J_1 = 7.3, -$NCOCH_2C\underline{H_2}$, H-4), 2.28 (t, 2 H, J_1 = 8.3, -$NCOC\underline{H_2}$, H-3), 3.40 [t, 2 H, J_1 = 6.8, -$NC\underline{H_{2(ring)}}$, H-5], 3.44 (t, 2 H, J_1 = 7.0, -$SO_2C\underline{H_2}$, H-7), 3.68 (t, 2 H, J_1 = 6.6, -$NC\underline{H_2}CH_2SO_2$, H-6), 7.5–8.0 (m, 5 H, Ar-*H*)

δ_C (200 MHz; $CDCl_3$) 17.91 (C-4), 30.51 (C-3), 36.92 (C-5), 47.71 (C-7), 53.00 (C-6), 127.78, 129.32, 133.90, and 139.00 (Ar-*C*), 175.39 (C-2)

8.3 Synthesis of Thiolactams

General Procedures (GP) for the Thionation of Lactams:

8.3.1 Brillon Procedure (GP-1A)[64][122][227]

Sodium carbonate (1.3 eq., typically *ca.* 2 g) was added in portions to a stirred suspension of phosphorus pentasulfide (1.3eq.) in THF (*ca.* 10cm^3 per 1 g of sodium carbonate). The initial addition was highly exothermic, and caused significant effervescence. Once dissolution was complete, a solution of the requisite lactam (1 eq., typically *ca.* 13 mmol) in THF (*ca.* 1cm^3 per 1 mmol of lactam) was added, and the reaction left to stir at room temperature. On completion of the reaction (5 h), the reaction was quenched by the careful sequential addition of the following three components: i) a solution of sodium carbonate (10% m/v, 1.5 cm^3 per mmol of lactam), ii) ethyl acetate (volume equal to ¾ that of the just-added sodium carbonate solution), and iii) hexane (¼ the volume of the sodium carbonate solution). The aqueous layer was extracted with dichloromethane (3 × 20cm^3) and the combined organic phases washed with sat'd NaCl solution (20 cm^3), dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the crude thiolactam. These were purified by chromatography on silica gel, using mixtures of ethyl acetate and hexane as eluents.

8.3.2 Reflux in Benzene/Toluene (GP-1B)[228][229]

The lactam (9 – 35 mmol scale) was added to a stirred suspension of P_2S_5 (*ca*. 0.6 eq) in benzene (*ca.* 10 cm^3 per 1 g of lactam) in a dry round bottomed flask equipped with a reflux condenser. The reaction was maintained at reflux until complete as indicated by TLC (between 4 and 16h). After cooling, the benzene was decanted from the P_2S_5 residues, and the malodorous gummy residues were digested in aqueous ammonia (50 cm^3). The dark yellow brown ammonia solution was then extracted with dichloromethane (2 × 20cm^3). The combined organic fractions were dried (Na_2SO_4), and evaporated *in vacuo* to give the crude thiolactams as dark yellow/brown oils. These oils were partially purified by passing through a short column of silica and eluting with a 20:80 ethyl acetate/hexane solution.

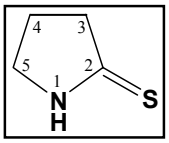
8.3.3 Ultrasonic irradiation in benzene or toluene (GP-1C)[59][63][123]

The requisite lactam (10 – 30 mmol) was added either neat, or as a solution in toluene to a suspension of P_2S_5 (*ca.* 0.6 eq.) in benzene or toluene (*ca.* 10 cm^3 per 1 g of lactam) in a dry round-bottomed flask. The flask was maintained under an inert atmosphere, and all adapters are kept in place by "Bibby" clips or springs. The reaction mixture was then subjected to ultrasonic radiation in an ultrasonic cleaning bath (see general remarks) during a 15 minute cycle followed by an equal amount of time at rest, for a total of 2 to 19 hours. On completion of the reaction, the organic phase was decanted, and the gummy residues washed with copious amounts of boiling benzene (*ca.* 200cm^3). The combined organic fractions were evaporated *in vacuo* to give the crude thiolactams as yellow oils or gums, which were purified by column chromatography.

8.3.4 Using Lawesson's Reagent - [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] (GP-1D)[229]

The lactam (9 – 35 mmol scale) was added to a stirred suspension of Lawesson's reagent (*ca*. 0.6 eq) in benzene (*ca.* 10 cm^3 per 1 g of lactam) in a dry round bottomed flask equipped with a reflux condenser. The reaction was maintained at reflux for approximately 6 h, or until the reaction was complete as indicated by TLC. Workup was performed as above, by decanting the organic phase from the residue, washing with benzene. The crude thiolactams were purified by chromatography or distillation.

8.3.5 Pyrrolidine-2-thione [106]



This product was easily isolated from procedure **GP-1A**, after recrystallisation (ethyl acetate/hexane) as a white solid (86%, m.p. 111–112°C, lit.[67]) 109–110°C). All data are consistent with those in the literature.

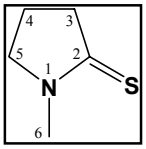
R_f = 0.37 (1:1 ethyl acetate/hexane)

IR Absorptions υ_{max}/cm^{-1} (KBr disk) = 3414, 3184, 3052, 2976, 2890, 1544, 1518, 1476, 1458, 1424, 1310, 1294, 1114 (C=S), 970, 794, 722

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) = 2.22 (tt, 2H, J_1 = 6.8Hz, J_2 = 7.8, $CH_2C\underline{H_2}$, H-4). 2.92 (t, 2 H, J = 6.8Hz, $CSC\underline{H_2}$, H-3), 3.68 (t, 2 H, J 7.7Hz, $CH_2C\underline{H_2}NH$, H-5), 9.32 (s, 1H, $N\underline{H}$, H-1)

δ_C (400 MHz; $CDCl_3$) 22.59 (C-4), 43.21 (C-3), 49.54 ppm (C-5), 205.15ppm (C-2)

8.3.6 *N*-methylpyrrolidine-2-thione [107]



This clear oil was isolated from **GP-1A**, **GP-1B**, or **GP-1C**, in 66%, 69%, and 70%, respectively, after thionation of *N*-methylpyrrolidin-2-one. Again the data correspond to those from the literature.[67]

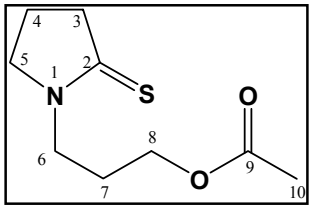
R_f = 0.59 (1:1 EtOAc/hexane)

IR Absorptions υ_{max}/cm^{-1} (Thin Film) = 3144, 2989, 2887, 1544, 1511, 1414, 1321, 1110 (C=S), 976

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 2.0–2.2 (m, 2H, $-CH_2C\underline{H_2}CH_2$, H-4), 3.04 (t, 2 H, J = 8.3Hz, $CSC\underline{H_2}$, H-3), 3.28 (s, 3 H, $C\underline{H_3}$, H-6), 3.77 (t, 2 H, J = 7.2Hz, $CH_2C\underline{H_2}NH$, H-5)

δ_C (200 MHz; $CDCl_3$) 19.13 (C-4), 35.22 (C-3), 44.42 (C-6), 56.91 ppm (C-5), 200.81ppm (C-2)

8.3.7 3-(2-Thioxopyrrolidin-1-yl)propyl acetate [108]



Thionation of the acetyl protected lactam **103** gave a yellow oil (72% from procedure **GP-1A**; 77% from **GP-1B**; 82% from procedure **GP-1C**), which on purification by column chromatography (hexane/ethyl acetate or hexane/acetone) yielded the thiolactam

as a pale yellow oil. The slight yellow discolouration could be removed by dissolving the oil in dichloromethane and stirring the solution over activated charcoal for 10 minutes. Evaporation of the solvent after filtration gave a clear oil, however the product was normally not subjected to this process, as the colour had no effect on later reactions. Data corresponds well with literature values.[67]

R_f = 0.36 (1:1 EtOAc/hexane) and 0.34 (2:1 hexane/acetone)

Elemental Analysis Found: C, 53.75; H, 7.66; N, 6.94 Calculated for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96; O, 15.90; S, 15.93

IR Absorptions υ_{max}/cm^{-1} (thin film) = 2976(s), 1735 (vs, O–C=O), 1518 (vs), 1472 (s), 1370 (s), 1331 (s), 1295 (s), 1244 (vs, C–O), 1121 (s, C=S).

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.97–2.17 (m, 4 H, $NCSCH_2CH_2$ & $CH_2CH_2CH_2OAc$ H-4, H-7), 2.07 (s, 3 H, $COCH_3$ H-10), 3.03 (t, *J* = 7.9, 2 H, $NCSCH_2$ H-3), 3.76 (t, *J* = 7.3, 2 H, $NCSCH_2CH_2CH_2$ H-5), 3.86 (t, *J* = 7.3, 2 H, $CH_2CH_2CH_2OAc$ H-6), 4.12 (t, *J* = 6.3, 2 H, $CH_2CH_2CH_2OAc$ H-8).

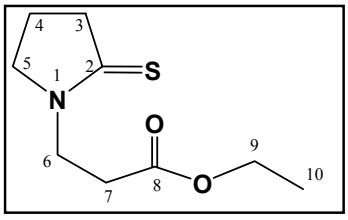
δ_C (200 MHz; $CDCl_3$) 19.34 (C-4), 20.60 (C-10), 25.16 (C-7), 44.60 (C-3 & C-6), 54.63 (C-5), 61.42 (C-8), 170.51 (C-9), 201.06 (C=S C-2).

Mass Spec. Data *m/z* = 201 (M^+, relative abundance 100%), 203 (M^+ + 2, relative abundance 4.1%)

SIS storage of ions 200–204

8.3.8 Ethyl 3-(2-thioxopyrrolidin-1-yl)propionate [109]

[1-(2-Ethoxycarbonylethyl)pyrrolidine-2-thione]



A solution of pyrrolidine-2-thione ([**106**], 2.710g, 27.69mmol, 1.1eq.) and ethyl acrylate (2.503g, 24.75mmol) in tetrahydrofuran (40 cm^3) was stirred for 2 days with a catalytic amount of sodium hydroxide and a drop of water.[66] Note: Completely anhydrous conditions result

in very poor yields for this reaction. On completion of the Michael addition, the solvent was removed *in vacuo* and the residue dissolved in dichloromethane ($60cm^3$) and washed with water ($2 \times 20cm^3$) before drying ($MgSO_4$). Distillation of the crude product led to the isolation of ethyl 3-(2-thioxopyrrolidin-1-yl)-propionate as a viscous yellow oil (4.733g, 23.5mmol, 95%). Data matches those obtained previously in our laboratories.[66]

R_f = 0.60 (1:1 ethyl acetate/hexane)

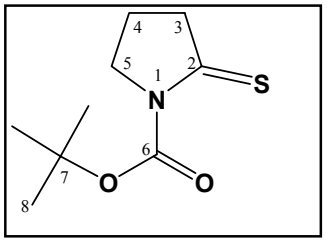
IR Absorptions υ_{max}/cm^{-1} (thin film) = 1733 cm^{-1} (C=O), 1512, 1463, 1374, 1292, 1250 (C–O), 1221, 1189, 1119 (C=S), 1056, 490

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.27 (t, 3 H, J = 7.2 Hz, $CO_2CH_2C\underline{H}_3$, H-10), 2.07 (tt, 2 H, J_1 = 7.8 Hz, J_2 = 7.3Hz, $NCSCH_2C\underline{H}_2CH_2$, H-4), 2.77 (t, 2 H, J = 6.8 Hz, $CH_2C\underline{H}_2CO_2$, H-7), 3.02 (t, 2 H, J = 7.8 Hz, $NCSC\underline{H}_2$, H-3), 3.82 (t, 2 H, J = 7.3 Hz, $NCSCH_2CH_2C\underline{H}_2$, H-5), 4.01 (t, 2 H, J = 6.8 Hz, $C\underline{H}_2CH_2CO_2$, H-6), 4.15 (q, 2 H, q, J = 7.2 Hz, $CO_2C\underline{H}_2CH_3$, H-9),

δ_C (400 MHz; $CDCl_3$) 14.17 (C-10), 19.90 (C-4), 31.02 (C-7), 43.77 (C-6), 44.93 (C-3), 55.85 (C-5), 60.83 (C-9), 171.42 (C-8), 201.52 (C-2)

8.3.9 2-Thioxopyrrolidine-1-carboxylic acid *tert*-butyl ester [117]

(*N*-Boc-pyrrolidine-2-thione)



To a solution of pyrrolidine-2-thione (**106**, 1.0 eq., 1.01 g, 10.0 mmol), in dichloromethane (20 cm^3) was added triethylamine (1.0 eq.), di-*tert*-butyl pyrocarbonate (DIBOC, 2.0 eq., 4.36 g), and 4-(dimethylamino)pyridine (~1.0 eq., 2.00 g). The solution was stirred for 12 h under nitrogen. The volatile substances were removed and the residue was purified by chromatography (ethyl acetate/hexane) to give a clear oil (72%).

An identical product was isolated by procedure **GP-1C** after sonication of 2-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (0.5g) for 7 hours, followed by the

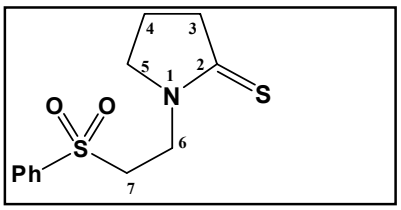
usual workup, but the yields in this case were significantly reduced (~40%). No product was isolated that showed thionation of the ester carbonyl.

R_f = 0.77 in 1:1 ethyl acetate/hexane

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.51 (s, 9 H, -C<u>*H*</u>$_3$, H-8), 2.00 (app. pent, J_1 = 7.1, 2 H, NCSCH$_2$C<u>*H*</u>$_2$, H-4), 3.02 (t, J_1 = 7.8, 2 H, NCSC<u>*H*</u>$_2$, H-3), 4.02 (t, J_1 = 7.1, NC<u>*H*</u>$_2$, H-5)

δ_C (200 MHz; $CDCl_3$) 19.85 (NCSCH$_2$<u>*C*</u>H$_2$, C-4), 27.71 (<u>*C*</u>H$_3$, C-8), 48.78 (NCS<u>*C*</u>H$_2$, C-3), 53.62 (N<u>*C*</u>H$_2$, C-5), 83.69 [O<u>*C*</u>(CH$_3$)$_3$, C-7], 150.14 (<u>*C*</u>OO, C-6), 207.60 (<u>*C*</u>=S, C-2)

8.3.10 <u>1-(-2-Phenylsulfonylethyl)pyrrolidine-2-thione [118]</u>



A solution of phenyl vinyl sulfone (1.500 g, 8.917 10^3 mol) and pyrrolidine-2-thione (**106**, 1.1 eq, 0.990 g, 9.809 10^3 mol) in wet THF (10 cm^3) was stirred in the presence of catalytic NaOH for 48 h. TLC indicated complete consumption of the starting materials. Water (20 cm^3) was added and the reaction extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic fractions were dried (Na_2SO_4), filtered and evaporated to give a pale red oil (2.186 g) which solidified on standing. Recrystallisation (EtOAc/Hexane) gave a pale yellow amorphous solid (1.78 g) in 96% yield. M.p. = 96-98°C

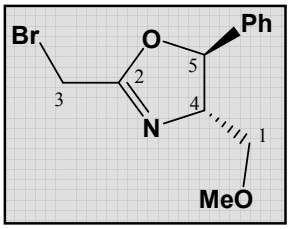
R_f =0.71 (ethyl acetate)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 2.04, (app. sept, 2 H, J_1 = 7.1, -NCSCH$_2$C<u>*H*</u>$_2$, H-4), 2.33 (t, 2 H, J_1 = 7.9, -NCSC<u>*H*</u>$_2$, H-3), 3.60 (t, 2 H, J_1 = 6.8, -NCH$_2$C<u>*H*</u>$_2$SO$_2$, H-7), 3.88 (m, 2 H, -NC<u>*H*</u>$_{2(ring)}$ H-5), 4.11 (t, 2 H, -NC<u>*H*</u>$_2$CH$_2$SO$_2$, H-6), 7.5–8.0 (m, 5 H, Ar-<u>*H*</u>)

(400 MHz; $CDCl_3$) 19.95 (C-4), 41.72 (C-6), 44.61 (C-3), 51.85 (C-7), 56.30 (C-5), 77.64, 127.34, 129.43, and 134.07 (Ar-<u>*C*</u>), 202.55 (C-2)

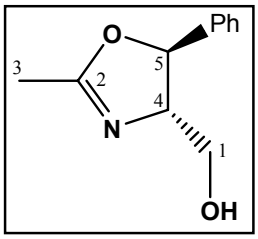
8.4 – Synthesis of Chiral 1,3-Oxazolidones

8.4.1 (4*S*,5*S*)-2-(Bromomethyl)-4-(methoxymethyl)-5-phenyl-4,5-dihydrooxazole [130]



These products were synthesised by reacting various amino-alcohols with an iminoacetate hydrohalide.[230][231][232]

8.4.2 (4*S*,5*S*)-(2-Methyl-5-phenyl-4,5-dihydro-oxazol-4-yl)methanol [128]



Acetonitrile (20.00 g, 25.45 cm^3, 0.4880 mol) and ethanol (22.6 g, 28.6 cm^3, 0.500 mol) were stirred together at 0 °C, and HCl gas bubbled through the solution until it increased in weight by 19.0 g (O.520 mol HCl).[232] The flask was allowed to warm to RT, and on standing overnight it solidified to give ethyl iminoacetate hydrochloride (m.p. 64–65 °C). This was not purified or characterised further, but stirred together (4.24 g, $3.30.10^{-2}$ mol) with (1*S*,2*S*)-2-amino-1-phenylpropan-1,3-diol (3.50 g, $2.09.10^{-2}$ mol) in CH_2Cl_2 (70 cm^3) for 24 hours. The solution was poured into ice water (100 cm^3), and the organic layer removed. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 cm^3), and the combined organic extracts were washed with sat'd aq. NaCl (30 cm^3), dried with Na_2SO_4, filtered and evaporated to give a clear oil, which solidified after several hours at room temperature to give 4.09 g of the crude oxazoline, which yielded white crystals (3.2 g, 80% in two crops) after recrystallisation from diethyl ether.

R_f = 0.30 (2:3 ethyl acetate/hexane)

Optical Rotation $[\alpha]_D^{23} = -162$ (c 10 in $CHCl_3$) [lit.[232] = –174.6 (c 10.5 in $CHCl_3$)]

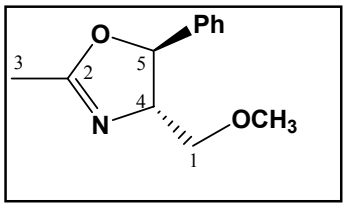
IR Absorptions υ_{max}/cm^{-1} (thin film) = 3319 (br, OH), 3050 (m), 2926 (s),

2824 (s), 1711 (s), 1671 (s, C=N), 1098 (s), 704

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 2.09 (d, J_1 = 1.20, 3 H, C<u>*H*</u>$_3$C, H-3), 3.65 and 3.95 (ABX system ddd J_{AB} = 11.83, J_{AX} = 3.85, J_{BX} = 3.33, 2 H, C<u>*H*</u>$_2$OH, H-1), 4.00 (m, 1 H, C<u>*H*</u>CH_2OH, H-4), 4.70 (br. s, 1 H, O<u>*H*</u> – signal disappears on shaking the solution with D_2O), 5.36 (d, J_1 = 7.67, 1 H, C<u>*H*</u>–Ar, H-5), 7.33 (m, 5 H, Ar-<u>*H*</u>)

δ_C (200 MHz; $CDCl_3$) 14.93 (C-3), 74.04 (C-1*), 74.32 (C-5*), 83.34 (C-4), 125.31, 127.91, 128.52, 140.62 (Ar-<u>*C*</u>), 165.04 (C-2)

8.4.3 <u>(4*S*,5*S*)-4-Methoxymethyl-2-methyl-5-phenyl-4,5-dihydro-oxazole [129]</u>



The dry (4*S*,5*S*)-(2-methyl-5-phenyl-4,5-dihydro-oxazol-4-yl)methanol (**128**, 5.00 g, $2.60.10^{-2}$ mol, 1.0 eq) in THF (45 cm^3), was added dropwise at RT to a suspension of NaH (1.50 g, 31.2 mmol, 1.2 eq of a 50% suspension in oil) in THF (10 cm^3) at a rate sufficient to maintain a mild evolution of hydrogen.[233] MeI (4.80 g, 33.8 mmol) in THF (10 cm^3) was added dropwise, and the reaction stirred for 2 hours. The pale yellow solution was poured into 100 cm^3 of ice water, and extracted with diethyl ether (3 × 70 cm^3). The combined organic extracts were dried with Na_2SO_4, filtered and evaporated to give a pale-yellow oil (5.10 g, 95 %). This was distilled under vacuum by bulb-to-bulb distillation (122 °C at 3 mm Hg), to give a clear liquid (3.48 g, 65 %).

B.p 122 °C (3 mm Hg) [lit.[232] = 85–87°C (0.20 Torr)]

R_f = 0.34 (2:3 ethyl acetate/hexane)

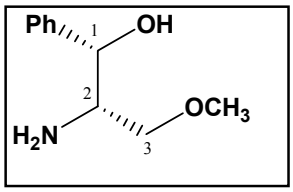
Optical Rotation $[\alpha]_D^{23}$ = –117 (c 10.5 in $CHCl_3$) [lit. [231] = –114 (c 10 in $CHCl_3$)]

IR Absorptions υ_{max}/cm^{-1} (thin film) = 3049 (m),3033, 2929 (s), 2829 (s), 1714 (s), 1676 (s, C=N), 1129, 1096 (s), 703

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 2.09 (d, J_1 = 1.36, 3 H, C<u>*H*</u>$_3$C, H-3), 3.40 (s, 3 H, C<u>*H*</u>$_3$O), 3.51 and 3.60 (ABX system ddd J_{AB} = 9.61, J_{AX} = 6.01, J_{BX} = 4.52, 2 H, C<u>*H*</u>$_2$OCH$_3$, H-1), 4.00 (ddq, J_1 = 6.01, J_2 = 2.75, J_3 = 1.36, 1 H, C<u>*H*</u>CH$_2$OCH$_3$, H-5), 5.27 (d, J_1 = 6.98, 1 H, C<u>*H*</u>–Ar, H-4), 7.30 (m, 5 H, Ar-<u>*H*</u>)

δ_C (200 MHz; $CDCl_3$) 13.93 (C-3), 59.06 (<u>*C*</u>H$_3$O-), 74.04 (C-4*), 74.32 (C-5*), 83.34 (C-1), 125.31, 127.91, 128.52, 140.62 (Ar-<u>*C*</u>), 165.04 (C-2)

8.4.4 <u>(1*S*, 2*S*)-2-Amino -3-methoxy-1-phenylpropanol [170]</u>



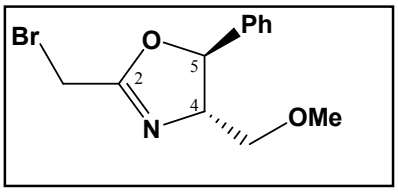
(4*S*,5*S*)-2-Methyl-4-phenyl-5-methoxymethyl oxazoline (**129**, 1.5 g, 7.8.10^3 mol) was heated under reflux in 3 M HCl (50 cm^3) for 12 hours to hydrolyse the oxazoline.[231] Note: any of the 5-methoxymethyl oxazolines could have been used in the same manner. The solution was cooled, and made basic (pH 10) with NaOH solution. Extraction with ether (3 × 40 cm^3), drying with $MgSO_4$, and evaporation of the solvent gave an oil, which solidified upon standing (0.92 g 82%). The solid was not purified further, but was used immediately in the following reaction. Characterisation was merely to confirm the completion of the hydrolysis.

M.p 49–51 °C (lit.[232] = 49–51°C)

Optical Rotation $[\alpha]_D^{23}$ = +24.1 (c 1.01 in $CHCl_3$) [lit.[232] = 24.2 (c 10 in $CHCl_3$)]

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 2.33–2.67 (br s, 3 H, O<u>*H*</u> and N<u>*H*</u>$_2$), 2.87–3.23 (m, 2 H, CH$_3$OC<u>*H*</u>$_2$, H-3), 3.23–3.50 (m, 1 H, NH$_2$C<u>*H*</u>, H-2), 4.60 (d, J_1 = 6.0, PhC<u>*H*</u>-, H-1), 7.2–7.4 (m, 5 H, Ar<u>*H*</u>)

8.4.5 (4*S*,5*S*)-2-Bromomethyl-4-methoxymethyl-5-phenyl-4,5-dihydro-oxazole [130]



Dry HCl (g) was passed through a rapidly stirred solution of bromoacetonitrile (3.0 g, 25 mmol, 1.0 eq) in abs. ethanol (1.19 g, 1.51 cm^3, 25.8 mmol, 1.03 eq) at –5 °C, until the weight of the flask increased by 950 mg. The solvent was removed *in vacuo* and the resulting liquid was allowed to stand overnight at –5 °C during which time it solidified (m.p. 77-81°C). The ethyl iminobromoacetate hydrochloride was used without further purification or characterization.

Ethyl iminobromoacetate hydrochloride (0.11 g, $5.4.10^{-4}$ mol, 1.0 eq) was stirred together with (1*S*, 2*S*)-2-amino-3-methoxy-1-phenylpropanol (**170**, 0.10 g, $5.5.10^{-4}$ mol) in CH_2Cl_2 (25 cm^3) for 24 hours. The solution was poured into ice-water (50 cm^3), and the organic layer removed. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 cm^3), and the combined organic extracts were dried with Na_2SO_4, filtered and evaporated to give a dark oil (30 mg, 20%). This oil was distilled in a bulb-to-bulb distillation unit to give 10 mg of a clear orange oil.

R_f = 0.18 (30:70 ethyl acetate/hexane)

Optical Rotation $[\alpha]_D^{23} = -65$ (c 1.01 in $CHCl_3$)

IR Absorptions υ_{max}/cm^{-1} (thin film) = 3047 (m),3033, 2927 (s), 2827 (s), 1714 (s), 1666 (s, C=N), 1129, 1096 (s), 915, 703

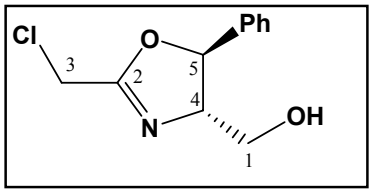
NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 3.35 (s, 3 H, C*H*$_3$O), 3.45 and 3.60 (ABX system ddd J_{AB} = 9.72, J_{AX} = 5.91, J_{BX} = 5.13, 2 H, C*H*$_2$OCH$_3$, H-1), 3.96 (d, J_1 = 2.77, 2 H, BrC*H*$_2$C, H-3), 4.19 (m, 1 H, C*H*CH$_2$OCH$_3$, H-4), 5.01 (d, J_1 = 4.11, 1 H, C*H*–Ar, H-5), 7.33 (m, 5 H, Ar-*H*)

δ_C (200 MHz; $CDCl_3$) 42.50 (C-3), 59.10 (*C*H$_3$O-), 72.66 (C-5*), 73.42 (C-4*), 83.34 (C-1), 125.88, 127.66, 128.23, 140.73 (Ar-*C*), 166.44 (C-2)

8.4.5.1 Attempted synthesis of (4S,5S)-2-bromomethyl-4-methoxymethyl-5-phenyl-4,5-dihydro-oxazole [130b] by direct bromination of (4S,5S)-4-methoxymethyl-2-methyl-5-phenyl-4,5-dihydro-oxazole:

N-Bromosuccinimide (0.836 g, $4.70.10^{3}$ mol, 1.1 eq) was dissolved in methanol (20 cm^3) in a darkened vessel, and (4*S*,5*S*)-4-methoxymethyl-2-methyl-5-phenyl-4,5-dihydro-oxazole (**129**, 0.560 g, $4.27.10^{-2}$ mol, 1.0 eq) in methanol (3 cm^3) was added to the stirring solution. The reaction was stirred at RT for 5 hours. Water (30 cm^3) was added, and the dark yellow solution extracted with CH_2Cl_2 (4 × 25 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting yellow solid was purified by chromatography with EtOAc/hexane 3:7 to remove succinimide, and other impurities, but no other products or un-reacted starting material was recovered.

8.4.6 (4S,5S)-(2-Chloromethyl-5-phenyl-4,5-dihydro-oxazol-4-yl)methanol [169]



Dry HCl(g) was passed through a rapidly stirring solution at of chloroacetonitrile (1.13 g, 15 mmol, 1.0 eq) in abs. ethanol (0.72 g, 9.06 cm^3, 15.5 mmol, 1.03 eq) –5 °C until the weight of the flask increased by 570 mg.[230][231] The solvent was removed *in vacuo* and the resulting liquid allowed to stand for 2 days at –5 °C during which time it solidified to give the product as a white solid m.p. 85 °C. The ethyl iminochloroacetate hydrochloride was used without further purification or characterisation, although it could be stored successfully for several weeks in a desiccator. (1*S*,2*S*)-2-Amino-1-phenylpropan-1,3-diol (0.454 g, $2.72.10^{3}$ mol) was stirred together with ethyl iminochloroacetate hydrochloride (0.452 g, $3.14.10^{3}$ mol, 1.15 eq) in CH_2Cl_2 (20 cm^3) for 26 hours. The solution was poured into ice water (50 cm^3), and the organic layer removed. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 cm^3), and the combined organic extracts were dried with Na_2SO_4, filtered and evaporated to give a white solid (0.315 g, 70%)

R_f = 0.22 (50:50 ethyl acetate/hexane)

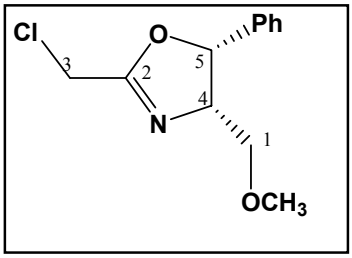
Optical Rotation $[\alpha]_D^{23} = -25$ (c = 1 in $CHCl_3$)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 3.69 and 3.94 (ABX system ddd J_{AB} = 11.83, J_{AX} = 4.27, , J_{BX} = 3.66, 2 H, C*H*$_2$OH, H-1), 3.83 (br. s, 1 H, O*H* – signal disappears on shaking the solution with D_2O, signal also shifted slightly in different samples), 4.12 (m, 1 H, C*H*CH_2OH, H-4), 4.21 (s, 2 H, ClC*H*$_2$C, H-3), 5.45 (d, J_1 = 7.73, 1 H, C*H*–Ar, H-5), 7.33 (m, 5 H, Ar-*H*)

δ_C (200 MHz; $CDCl_3$) 33.16 (C-3), 62.89 (C-1), 76.27 (C-5), 83.96 (C-4), 125.57, 128.56, 128.84, 139.45 (Ar-*C*), 164.07 (C-2)

Mass Spec. Data *m*/*z*: 225 (M+ ^{35}Cl 9%), 227 (M+ ^{37}Cl 2.9%)

8.4.7 (4*S*,5*S*)-2-Chloromethyl-4-methoxymethyl-5-phenyl-4,5-dihydro-oxazole [131]



Dry HCl(g) was passed through a rapidly stirring solution at –5 °C of chloroacetonitrile (1.13 g, 15 mmol, 1.0 eq) in abs. ethanol (0.72 g, 9.06 cm^3, 15.5 mmol, 1.03 eq) until the weight of the flask increased by 570 mg. The solvent was removed *in vacuo* and the resulting liquid allowed to stand for 2 days at –5 °C during which time it solidified to give the product as a white solid m.p. 85 °C. The ethyl iminochloroacetate hydrochloride was used without further purification or characterization. (1*S*,2*S*)-2-Amino-3-methoxy-1-phenylpropanol (**170**, 0.478 g, 2.86.10^3 mol) was stirred together with ethyl iminochloroacetate hydrochloride (0.452 g, 3.14.10^3 mol, 1.0 eq) just formed in CH_2Cl_2 (15 cm^3) for 28 hours. The solution was poured into ice water (50 cm^3), and the organic layer removed. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 cm^3), and the combined organic extracts were dried with Na_2SO_4, filtered and evaporated to give a very viscous yellow-brown gum (0.336 g, 47.3%). This gum was composed of several

products. Chromatography on silica gel (ethyl acetate/hexane mixtures) yielded 32mg of a yellow solid.

M.p. = 38-41°C

R_f = 0.14 (30:70 ethyl acetate/hexane)

Optical Rotation $[\alpha]_D^{23}$ = –80.2 (c 1.5 in $CHCl_3$) [lit.[231] = –84.1 (c 11 in $CHCl_3$)

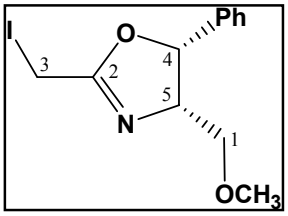
NMR Data δ_H (200 MHz; $CDCl_3$; TMS) = 3.71 and 3.92 (ABX system ddd, J_{AB} = 11.82, J_{AX} = 4.32, J_{BX} = 3.73, 2 H, -CHC<u>*H*</u>$_2$OH, H1), 3.8 (br s, 1 H, O<u>*H*</u>, signal exchanges with D_2O), 4.1 (m, 1 H, C<u>*H*</u>CH_2OH, H-4), 4.2 (s, 2 H, ClC<u>*H*</u>$_2$C, H-3), 5.4 (d, *J* = 7.7, 1 H, C<u>*H*</u>C_6H_5, H-5), 7.2–7.4 (m, 5 H, Ar<u>*H*</u>)

δ_C (200 MHz; $CDCl_3$) 36.1 (C-3), 62.9 (<u>*C*</u>H_3O-), 73.42 (C-5*), 76.3(C-4*), 84.0(C-1), 125.6, 128.6, 128.8 and 139.4 (Ar <u>*C*</u>), 164.1 ($ClCH_2$<u>*C*</u>, C-2).

8.4.7.2 Attempted synthesis by methylation of (4S,5S)-(2-chloromethyl-5-phenyl-4,5-dihydro-oxazol-4-yl)methanol

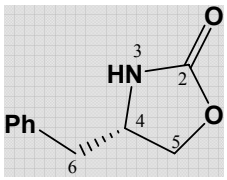
(4*S*,5*S*)-(2-Chloromethyl-5-phenyl-4,5-dihydro-oxazol-4-yl)methanol (**131**, 1.00 g, $6.04.10^{-3}$ mol, 1.0 eq) in THF (20 cm^3), was added dropwise at RT to a suspension of NaH (0.348 g, $7.3.10^{-3}$ mol, 1.2 eq of a 50% suspension in oil) in THF (10 cm^3) at a rate sufficient to maintain a mild evolution of hydrogen. MeI (1.06 g, 0.70 cm^3, $7.5.10^{-3}$ mol) in THF (3 cm^3) was added dropwise, and the reaction stirred for 2 hours. The solution was poured into 40 cm^3 of ice water, and extracted with ether (3 x 30 cm^3). The combined organic extracts were dried with Na_2SO_4, filtered and evaporated to give a yellow oil (0.857 g, 79 %). NMR analysis of the crude sample as well as TLC indicated a severe mixture of products consisting of mostly un-reacted starting material. Attempted purification by radial chromatography (ethyl acetate/hexane mixtures) gave only traces of a product with identical spectroscopic characteristics to the desired product already synthesised by a different route.

8.4.8 (4*S*,5*S*)-2-Iodomethyl-4-methoxymethyl-5-phenyl-4,5-dihydro-oxazole [130c]



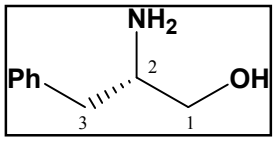
(4*S*,5*S*)-2-Bromomethyl-4-methoxymethyl-5-phenyl-4,5-dihydro-oxazole (**130**, 20 mg, $7.04.10^{-5}$ mol) was dissolved in acetonitrile (5 cm^3), and stirred under nitrogen at room temperature together with sodium iodide (ca. 11 mg, 1.05 eq) for 2 hours in an attempted Finkelstein halogen exchange reaction.[124] A milky solution indicated the presence of sodium chloride and consumption of sodium iodide. The solution was filtered through a small pad of Celite, and the solvent evaporated to give a pale yellow oil (20 mg). NMR analysis of the crude oil indicated the presence of mostly two compounds, namely the starting material and what could be the expected product, in a ratio of 1:3. The product was not characterised further, but was used directly in an attempted sulfide contraction reaction.

8.5 Synthesis of Chiral 2-Oxazolidinones



Synthesised in a two-step process from the amino acid phenylalanine, namely reduction followed by condensation of the amino propanol with a carbonate.

8.5.1 (*S*)-(–)-2-Amino-3-phenylpropan-1-ol [133] (Phenylalaninol)



8.5.1.1 Reduction of (S)-phenylalanine with borane[170]

Dry THF (20 cm^3) was added to a 100 cm^3 3-necked flask containing (*S*)-(–)-phenylalanine (1.652g, 0.0100 mol), and equipped with a nitrogen inlet, a condenser (attached to a paraffin bubbler vented to a fume-hood), and a pressure equalising dropping funnel with a rubber septum. The dropping funnel was charged with freshly distilled boron trifluoride diethyl etherate (1.25 cm^3, 0.0101 mol), and this was then added drop-wise over 20 minutes to the phenylalanine. When addition was complete, the reaction was heated at reflux for 2 hours. Borane dimethyl sulfide complex (1.05 cm^3, 0.0110 mol) was added to the vigorously refluxing solution over 30 minutes. Vigorous bubbling during the first 10 minutes of addition was a result of the steady evolution of hydrogen and dimethyl sulfide. When addition of the borane dimethyl sulfide complex was complete, the reaction was heated under reflux for 6 hours. After cooling to RT the excess borane was destroyed by the slow addition of 1.25 cm^3 of a 1:1 mixture of THF/water. 5M NaOH (7.5 cm^3) was added, and the two-phase mixture again heated under reflux for 13 hours. After once again cooling the reaction to RT, it was filtered and washed with 2 × 5 cm^3 THF. The bulk of the THF was evaporated, and the slurry extracted with CH_2CH_2 (3 × 10 cm^3). The organic phase was dried over sodium sulfate, filtered and evaporated to give a pale yellow liquid, which solidifies to a pale yellow crystalline solid (1.745g) upon standing for an hour. Recrystallisation from EtOAc and hexane in two crops gave white crystalline needles (1.426g, 93%, m.p. 88.5–90.5 °C). An analytical sample was further purified by vapour diffusion of

hexane into a saturated solution of phenylalaninol in EtOAc, to give white needles with m.p. 90–90.5 °C (lit. =. 90–91°C[169]; lit. = 89–91°C[168]). This sample was also used to obtain the other physical data.

R_f = 0.81 ($CHCl_3$/MeOH/NH_3 10:10:1)

Optical Rotation $[\alpha]_D^{23}$ = –21.40 (c = 1.075 in ethanol), –22.57 (c = 0.315 in CH_2Cl_2) [lit. = –24.7 (c = 1.03 in ethanol)][168]

IR Absorptions υ_{max}/cm^{-1} = 3625 (br. OH & NH), 3360, 3035, 2930, 2855, 1497, 1456, 1032

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.88 [br. s, 3 H, -N<u>*H*</u>$_2$, -O<u>*H*</u> (spinning side-bands at 1.77 and 2.17)]; 2.54 (dd, 1 H, J_1 = 13.4, J_2 = 8.6, -C<u>*H*</u>$_2$Ph, H3a), 2.82 (dd, 1 H, J_1 = 13.4, J_2 = 5.2, -C<u>*H*</u>$_2$Ph, H3b), 3.13 (m, 1 H, -C<u>*H*</u>NH_2, H2), 3.40 (dd, 1 H, J_1 = 10.6, J_2 = 7.2, -C<u>*H*</u>$_2$OH, H1a), 3.66 (dd, 1 H, J_1 = 10.6, J_2 = 3.9, -C<u>*H*</u>$_2$OH, H1b), 7.1–7.4 (m, 5 H, -Ar<u>*H*</u>)

δ_C (200 MHz; $CDCl_3$) 40.91 (-<u>*C*</u>H_2Ph, C3), 54.14 (<u>*C*</u>HNH_2, C2), 66.33 (<u>*C*</u>H_2OH, C1), 126.42, 128.57, 129.19, and 138.62 (Ar<u>*C*</u>)

8.5.1.2 Reduction with lithium aluminium hydride:[170]

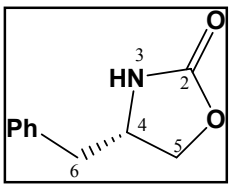
$LiAlH_4$ (0.341g, $8.97.10^3$ mol) and THF (8.5 cm^3) was added to a 250 cm^3 3-necked flask, equipped with a condenser and a nitrogen inlet. The flask was cooled in an ice bath, and (*S*)-(–)-phenylalanine (1.00g, $6.05.10^3$ mol) was added over 10 minutes. CAUTION must be taken during this addition, as hydrogen gas is evolved. When the addition was complete, the reaction was allowed to warm to room temperature. The reaction bubbled vigorously as it approached room temperature, and stopped after about 10 minutes. The reaction was then heated at reflux for 6 hours, and then cooled in ice once more, and diluted with 7 cm^3 diethyl ether. Work-up involved adding 0.34 cm^3 water over 30 minutes, followed by 0.34 cm^3 15% NaOH solution over 20 minutes, followed by a further 1.02 cm^3 water over 30 minutes (these volumes were calculated on the amount of added $LiAlH_4$ to be approximately 1:1:3 cm^3 water/NaOH/water per gram

$LiAlH_4$). The slurry was then stirred for a further 50 minutes, filtered and washed with 3×1 cm^3 diethyl ether. The organic filtrates were collected and concentrated *in vacuo* to yield a viscous yellow liquid (0.362g) that gives a white crystalline product (0.136g, 14.7%) on distillation (150 °C at 3 mm Hg). This product was identical to that obtained before.

8.5.1.3 Reduction with $NaBH_4$ and H_2SO_4 [169]

$NaBH_4$ (10.0 g, 250 mmol) was suspended in THF (100 cm^3), in a 250 cm^3 round-bottomed flask equipped with a 50 cm^3 dropping funnel, and cooled to 0°C. Phenylalanine (16.5 g, 0.100 mol) was added, and stirred together with the $NaBH_4$ suspension. A solution of fresh conc. H_2SO_4 (6.60 cm^3, 125 mmol) in ether (total volume 20 cm^3), was added dropwise, at a rate sufficient to maintain the temperature of the reaction below 10°C. When addition was complete (approx. 80 minutes), the reaction was allowed to warm to RT, and then stirred for 14 hours. MeOH (15 cm^3) was added carefully to destroy excess BH_3, and the mixture concentrated *in vacuo* to *ca*. 60 cm^3. NaOH (110 cm^3 of 5M solution) was added, and the mixture distilled, to remove any solvent that distilled below 100 °C. The resulting mixture was heated under flux for 3 hours, before it was cooled, filtered through a pad of Celite, and washed with water (100 cm^3). The filtrate and the washings were combined, extracted with CH_2Cl_2 (3×80 cm^3), dried with Na_2SO_4 and evaporated to give the desired amino alcohol as a white solid, which was recrystallized from EtOAc / hexane to yield, in two crops, the required phenylalaninol (15.99 g, 97%). The product was identical with that obtained previously.

8.5.2 Preparation of (*S*)-4-benzyl-2-oxazolidinone [132]



A dry 25cm^3 2-necked flask was equipped with a nitrogen inlet and a K-condenser (containing a vigreux column and a cold finger) attached to a 10 cm^3 receiver flask and an outlet to a paraffin bubbler.[234]] (*S*)-(–)-2-Amino-3-phenyl-1-propanol (**133**, 0.453g, $3.00.10^{-3}$ mol), potassium carbonate (anhydrous) (0.0415g, $0.300.10^{-3}$ mol) and freshly distilled

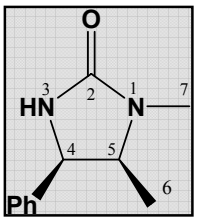
diethyl carbonate (0.75 cm^3, $6.18.10^3$ mol) were added to the flask, and stirred. The mixture was lowered into a preheated oil bath (135–140°C), the receiver flask was cooled to 0°C and ethanol (0.3 cm^3) was collected over 2 hours. When the ethanol stopped distilling, the pale yellow mixture was cooled to room temperature, diluted with dichloromethane (10 cm^3) and washed with water (10 cm^3). The organic phase was removed, dried over anhydrous sodium sulfate, filtered, and evaporated to give a light yellow crystalline solid (0.532g, 100% yield). The solid was taken up in 7 cm^3 of a hot mixture of 2:1 ethyl acetate/hexane, and filtered while hot. Upon evaporation of the solvent, small needle-like crystals were obtained [0.475 g, 89% yield, m.p. = 84°C (lit. = 84.5–86.5°C).[234]

R_f = 0.41 (1:1 ethyl acetate/hexane)

Optical Rotation		$[\alpha]_D^{21}$ = 5.32 (c = 1.10 in EtOH); [lit. = +4.9 (c 1.10 in EtOH)][168]
IR Absorptions		υ_{max}/cm^{-1} = 3460 (NH), 3020, 1760, 1480, 1405, 1220
NMR Data	δ_H	(200 MHz; $CDCl_3$; TMS) 2.88 (dd, 2 H, J_1 = 6.3, J_2 = 5.0, C<u>*H*</u>$_2$Ph, H1), 4.0–4.2 (m, 2 H, CHC<u>*H*</u>$_2$O, H5), 4.3–4.5 (m, 1 H, C<u>*H*</u>CH_2O, H4), 6.25 (br. d, 1 H, J_1 = 25.4, N<u>*H*</u>), 7.1–7.4 (m, 5 H, Ar<u>*H*</u>)
	δ_C	(200 MHz; $CDCl_3$) 41.24 (Ph<u>*C*</u>H_2, C1), 53.66 (<u>*C*</u>HNH, C4), 69.44 (<u>*C*</u>H_2O, C5), 127.09, 128.84, 128.95, and 135.84 (Ar<u>*C*</u>), 159.56 (NH<u>*C*</u>O, C2)

8.6 Synthesis of Chiral 2-Imidazolidinones

8.6.1 (–)-(4*R*,5*S*)-1,5-Dimethyl-4-phenyl-imidazolidin-2-one [134]



(–) Ephedrine hydrochloride (10.0 g, $4.96.10^{-2}$ mol) and urea (8.93 g, $1.49.10^{-1}$ mol, 3 eq) were mixed together in a 100 cm^3 2-necked flask equipped with a gas bubbler, and heated to between 170 and 175 °C for 30 minutes.[177] The reaction was then stirred at 200°C for a further 1 hour, and allowed to cool to RT. Water (~90 cm^3) was added, and stirred to break up the sticky solid. The resulting precipitate was filtered, washed with 5% HCl solution (50 cm^3), followed by water (50 cm^3), dried and recrystallized from ethanol to give the desired product as white crystals (2.65 g, 28%).

M.p. 173–176°C (lit. = 144.5–145 °C for the racemate,[175] 177–179 °C for this enantiomer.[174])

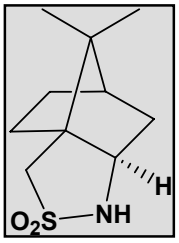
R_f = 0.13 (1:1 ethyl acetate/hexane)

Optical Rotation $[\alpha]_D^{23}$ = –44° to –46° (c = 3.01 in MeOH) [lit. = –44.5 (c = 3 in MeOH)][174]

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.74 (d, 3 H, J = 6.5, -NCHC<u>*H*</u>$_3$, H-6), 2.73 (s, 3 H, C<u>*H*</u>$_3$NCH-, H-7), 3.87 (dq, J_1 = 8.5, J_2 = 6.5, 1 H, -NC<u>*H*</u>CH_3, H-5), 4.78 (d, J = 8.5, 1 H, -NHC<u>*H*</u>C_6H_5, H-4), 5.44 (br s, 1 H, -N<u>*H*</u>, H-3), 7.2–7.4 (m, 5 H, Ar<u>*H*</u>)

δ_C (200 MHz; $CDCl_3$) 14.10 (-NCH<u>*C*</u>H_3, C6), 27.99 (<u>*C*</u>H_3NCH, C1), 57.48 (-N<u>*C*</u>HCH_3, C5*), 58.01 (-NH<u>*C*</u>HC_6H_5, C4*), 127.02, 127.79, 128.28, and 138.08 (Ar<u>*C*</u>), 162.47 (-N<u>*C*</u>ON-, C2)

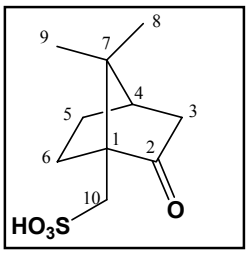
8.7 Synthesis of Chiral Camphor Sultams



This product was synthesised in several steps from camphor. Several of the intermediates, such as camphor sulfonyl chloride are available commercially, which could shorten the synthesis:

8.7.1 (1*S*,4*R*)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid [136]

[(1S)-(+)-10-Camphorsulfonic acid]



In a 100 cm^3 3-necked flask, fitted with an overhead stirrer (with Teflon blades), 20 cm^3 dropping funnel, and thermometer, was placed conc. H_2SO_4 (0.20 mol, 19.6 g, 12.2 cm^3).[234] The flask was surrounded by an ice-salt bath, and acetic anhydride (2.0 eq, 0.40 mol, 40.5 g, 39.0 cm^3) was added via the dropping funnel at such a rate that the temperature remained below 20 °C (addition was very slow at first). D-Camphor (1.0 eq, 0.2 mol, 30.4 g) was added in portions, and stirred slowly until dissolved (~2 h.). The overhead stirrer was replaced with a magnetic stirrer and the reaction was allowed to warm to room temperature and then stirred for a total of 68h. The white solid that forms was filtered and washed with copious amounts of ether (which had been dried over 4Å molecular sieves). Drying under vacuum for 5 h gave 18.8 g of pure (1*S*)-(+)-camphorsulfonic acid (41% yield). This is a well known commercial product that was not fully characterised.

M.p. = 201–202 °C (dec.)

Optical Rotation $[\alpha]_D^{20} = 19.9$ (c 2.00 in H_2O) lit.[174] = 20.0 (c 2.00 in H_2O)

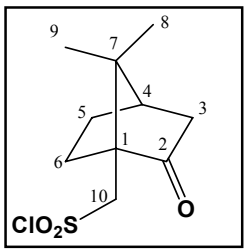
IR Absorptions υ_{max}/cm^{-1} = 3030, 2966, 1742, 1704, 1392, 1372, 1168, 1158, 916, 890, and 428

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.00 (s, 3 H, CC*H*$_3$, H8*), 1.03 (s, 3 H CC*H*$_3$, H-9*), 1.40–2.50 (m, 7 H, H-3, H-4, H-5, H-6), 3.15 and 3.48 (AB quartet, J = 15.1, 2 H, C*H*$_2$SO$_2$, H-10), 12.48 (s, 1 H, O*H*)

δ_C (200 MHz; $CDCl_3$) 19.97 and 20.15 (C-8* and C-9*), 25.70, 27.61, 43.39, 43.87, 48.43, and 49.42 (C1 and C3 – C7), 59.20 (C10), 225.23 (C=O, C-2)

8.7.2 (1*S*,4*R*)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonyl chloride [137]

(Camphorsulfonyl chloride)



(1*S*)-(+)-10-Camphorsulfonic acid (10.00 g, $4.3.10^{-2}$ mol) and phosphorus pentachloride (12.50 g, $6.0.10^{-2}$ mol) were stirred together at 0 °C until homogeneous.[185] The reaction was allowed to warm to room temperature over 2 h. The solution was poured into crushed ice, and the insoluble precipitate rapidly filtered, and washed with 50 cm^3 of ice water. Rapid drying of the solid *in vacuo* gave a white solid (7.38 g, 68%). NMR analysis of this crude product revealed that it contained some of the camphorsulfonic acid (presumably from the hydrolysis of the acid chloride).

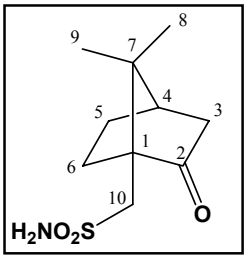
M.p. = 55–65 °C (impure), 65–66 °C (pure in inert dry atmosphere) (Lit.[185] = 65–66°C)

The product was not characterised further, as it rapidly hydrolysed in air, and is commercially available. An IR spectrum was, however recorded to confirm the presence of the desired product.

IR Absorptions υ_{max}/cm^{-1} = 3404, 3348, 3028, 2964, 2892, 1738, 1652, 1342, 1278, 1166, 1150, and 808.

8.7.3 (1*S*,4*R*)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonamide [138]

(Camphorsulfonamide)



8.7.3.1 Produced from camphorsulfonyl chloride [137] and ammonia:[185]

Camphorsulfonyl chloride (10.0 g, $3.99.10^{-2}$ mol) was dissolved in chloroform (20 cm^3), and cooled to 0 °C in an ice-bath. Ammonia gas was slowly bubbled through the reaction for 15 minutes, until the reaction formed a thick slurry. The reaction was filtered, and the product dried *in vacuo* and recrystallised from ethanol to give the required camphor sulfonamide (4.34 g, 47 %). The sulfonamide was not purified or characterised further, as it appears (from NMR studies of the crude product) to contain a substantial amount of camphorsulfonyl imine, which is required in the next step. This is likely to come from a self-condensation of the amide. This view is supported by the fact that the amount of camphor sulfonyl imine increased on standing from about 5–20% (depending on the method of preparation), to well over 30% within a week.

An analytically pure sample was obtained by from the reaction of commercial camphor sulfonic acid and ammonia in dioxane by procedure ***8.7.4.2.*** The following data are typical of the products obtained.

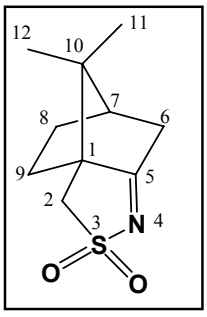
Optical Rotation		$[\alpha]_D^{23}$ = 23.10 (c 0.1.53 EtOH)
IR Absorptions		υ_{max}/cm^{-1} = 3410 (br, NH_2), 3028, 2964, 2892, 1738 (C=O), 1650, 1550, 1346, 1164, 562, 528, and 490
NMR Data	δ_H	(200 MHz; $CDCl_3$; TMS) 0.93 (s, 3 H, CC$\underline{H}_3$, H-8*), 1.01 (s, 3 H CC$\underline{H}_3$, H-9*), 1.40–2.50 (m, 7 H, H1 and H3 – H6), 3.13 and 3.54 (AB quartet, *J* = 15.2, 2 H, C$\underline{H}_2SO_2$, H-10), 5.60 (br s, 2 H, N$\underline{H}_2$)
	δ_C	(200 MHz; $CDCl_3$) 18.72 and 19.20 (C-8* and C-9*), 26.50, 28.15, 35.67, 44.37, 49.21, 59.12, (C1 and C3 – C7), 64.38 (C), 195.65 (C=O, C-1)

8.7.3.2 Produced from camphorsulfonic acid using thionyl chloride and ammonium hydroxide

Camphorsulfonic acid (20 g, $8.6.10^{-2}$ mol) was added to $CHCl_3$ (130 cm^3) in a 2-necked 500 cm^3 round-bottomed flask, equipped with a condenser attached to a paraffin bubbler vented to a fume-hood. The solution was heated to reflux and $SOCl_2$ (12.3 g, 0.104 mol, 7.6 cm^3, 1.2 eq) was added drop wise to the refluxing suspension over 40 minutes. The reaction was heated under reflux for a further 20 minutes, and then cooled to RT. The resulting reaction mixture was carefully poured into a 1000 cm^3 flask surrounded with ice and containing concentrated aq. NH_4OH solution (275 cm^3) at 0 °C. The rate of addition was controlled to maintain the NH_4OH solution below 10 °C. When addition was complete, the reaction was warmed to RT, and stirred for 4 hours. The organic layer was removed, and the aqueous fraction extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organic fractions were washed with sat'd NaCl, dried with Na_2SO_4, filtered and evaporated to give crude sulfonamide (13.40 g, 63 %). The sulfonamide was not purified further since it was found to be sufficiently pure for the following reaction.

8.7.4 Preparation of (1*S*,7*R*)-10,10-dimethyl-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-ene 3,3-dioxide [139]

(Camphorsulfonyl imine)



8.7.4.1 Produced by dehydration of camphorsulfonamide [138] over an acid catalyst:

The sulfonamide (**138**, 13.4 g) was dehydrated by azeotrope with toluene (200 cm^3) in a 250 cm^3 round-bottomed flask equipped with a Dean–Stark apparatus and condenser. Amberlyst 15 - acidic resin (1.5 g) was added to speed up the dehydration. The reaction was stirred under reflux until the water stopped collecting in the Dean–Stark apparatus (approximately 4 hours). The Amberlyst

was removed by filtration, and the toluene removed *in vacuo* to give the crude product (11.5 g, 99%).

M.p. 225–228 °C (lit. 230°C)[183]

Optical Rotation $[\alpha]_D^{23} = -34.3$ (c = 1.8 in $CHCl_3$) [lit. = –32.7 (c = 1.9 in $CHCl_3$)][183]

IR Absorptions υ_{max}/cm^{-1} = 3028, 2968, 2924, 1738, 1652, 1454, 1414, 1376, 1340, 1228, 1210, 1192, 1168, 1134, 1098, and 806

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.98 (s, 3 H, CC*H*$_3$, H11*), 1.16 (s, 3 H, CC*H*$_3$, H12*), 1.4–2.5 (m, 5 H, N=C-C*H*$_2$, -C*H*$_2$C*H*$_2$-, H6a*[1], H8, H9), 2.37 (d, *J* = 15.3, 1 H, N=C-C*H*$_2$, H6b*[1]), 2.73 (m, 1 H, -C*H*-, H7), 2.98 and 3.17 (AB quartet, *J* = 11.9, 2 H, C*H*$_2$SO$_2$, H2).

δ_C (400 MHz; $CDCl_3$) 18.8 (C*C*H$_3$, C11*), 19.3 (C*C*H$_3$, C12*), 26.5, 28.3, 35.7, 44.5, 47.8, 49.3, 64.4, 195.5 (*C*=N, C1)

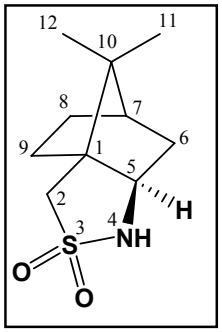
8.7.4.2 From camphorsulfonic acid using thionyl chloride and ammonia in dioxane:[184]

An identical product to that described above was obtained directly from the sulfonic acid by the following short procedure: Freshly distilled thionyl chloride ($SOCl_2$; 60 cm3, 0.88 mol, 2eq) was added dropwise to camphorsulfonic acid (**136**, 102g, 0.44 mol) in a round-bottom flask equipped with a magnetic stirrer, a reflux condenser and a gas trap. The reaction was heated to 110°C for four hours, during which time a vigorous evolution of HCl and SO_2 is observed. DMF (2 drops was then added to ensure completion of the reaction, and excess $SOCl_2$ was removed by distillation. Traces of thionyl chloride were removed by co-distillation with toluene (50 cm^3). The resulting yellow semi-solid was dissolved in 1,4-dioxane (200 cm^3) and slowly poured into cold (5°C) ammonium hydroxide solution which had previously been saturated with ammonia gas at 5°C. The literature suggests a density of 0.866 $g.cm^{-3}$, but the strong pungent odour of ammonia makes this determination difficult and we did not find much difference in using solutions with greater or smaller densities. The reaction was then left to

warm to room temperature and stirred for 2 h, followed by a further 4 h at 90°C. The mixture was then cooled, filtered and washed with water (2 × 50 cm^3) to give the camphorsulfonyl imine in 81% yield (lit. value 83%).

8.7.5 Preparation of (1*S*,5*R*,7*R*)-10,10-dimethyl-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane-3,3-dioxide [135]

(Camphor sultam)



8.7.5.1 Selective reduction using $LiAlH_4$:[185]

Camphorsulfonyl imine (**139**, 8.50 g, 3.98.10^{-2} mol) was suspended at 0 °C in THF (160 cm^3) while $LiAlH_4$ (1.52 g, 0.0400 mol) was added over 15 minutes. Once addition was complete, it was stirred at 0 °C for 75 minutes. 1M HCl (50 cm^3) was added dropwise over 40 minutes to quench the reaction. The insoluble residue was filtered and washed with $CHCl_3$ (50 cm^3). The aqueous fraction was extracted with CH_2Cl_2 (2 × 50 cm^3) and the combined organic layers dried with $MgSO_4$, filtered and evaporated to give a white crystalline solid (5.5 g, 64%).

M.p. 171–181 °C [lit.[184] = 190–191°C)

R_f = 0.78 in 1:1 ethyl acetate/hexane

Optical Rotation $[\alpha]_D^{23}$ = –34.15 (c 1.025 in ethanol) [lit.[184] =–31.3 (c 5 in $CHCl_3$)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.88 (s, 3 H, CC*H*$_3$, H-11*), 1.09 (s, 3 H, CC*H*$_3$, H-12*), 1.28 (m, 1H), 1.44 (m, 1 H), 1.6–2.1 (m, 5 H), 3.07 (AB doublet, 2 H, J_1 = 14.2, C*H*$_2$$SO_2$, H-2), 3.35 (m, 1 H, C*H*N, H-5), 4.9 [(variable position) br d, 1 H, J = 6.5, 1 H, N*H*, H-4]

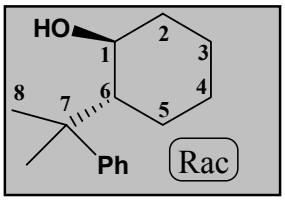
δ_C (400 MHz; $CDCl_3$) 20.3 (C*C*H$_3$, C11 and C12 superimposed), 26.7 (*C*H$_2$, C-8), 31.7 (*C*H$_2$, C-9), 35.9 (*C*H, C-7), 44.5 (*C*H$_2$, C-6), 47.3 [*C*(CH$_3$)$_2$, C-10], 50.3 (SO_2*C*H$_2$, C-2), 54.8 (SO_2CH_2*C*, C-1), 62.7 (*C*HNH, C-5)

8.7.5.2 Improved reduction procedure using $LiAlH_4$:

A three-necked 500 cm^3 round-bottom flask was equipped with a soxhlet extraction thimble and 50 cm^3 dropping funnel. Camphorsulfonyl imine (**139**, 9.00 g, 4.22 10^{-2} mol) was placed in the thimble and $LiAlH_4$ (6.2 g) was suspended in THF (150 cm^3) in the flask. After heating under reflux for 2 h, all of the imine had siphoned into the flask. The reaction was heated for a further 1 h under reflux and cooled to room temperature. 1 M HCl (50 cm^3) was added to quench the reaction. The organic layer was separated, and the aqueous fraction extracted with CH_2Cl_2 (2 × 50 cm^3). The combined organic fractions were dried with Na_2SO_4, filtered and evaporated to give a white crystalline solid (8.08 g, 89%).

8.8 Synthesis of Chiral *trans*-Cumylcyclohexanes

8.8.1 (1*S**,2*R**)-2-(2-Phenylpropan-2-yl)cyclohexanol [140]



Potassium *t*-butoxide (12.3 g, 0.11 mol, 1.1eq) was added to a solution of cumene (isopropyl benzene; 48.1 g, 55.6 cm^3, 0.4 mol, 1eq) in cyclohexane (60 cm^3).[194] BuLi (10 cm^3 of a 1.16 M solution and 80 cm^3 of a 1.107 M solution in hexane, 0.1 mol, 1.0eq) was added to the above mixture and the anion allowed form by stirring at RT for 4 days. Cyclohexene oxide (9.82 g, 10.12 cm^3, 0.1 mol, 1.0eq) was added dropwise to the solution over 30 min, while maintaining the temperature below 20°C. When the addition was complete, the deep purple suspension was allowed to warm to RT and stirred for 5 h. Work-up involved cooling the reaction in ice, followed by the dropwise addition of saturated NH_4Cl (30 cm^3), extraction with ether (100 cm^3) and evaporation of the solvent. The pale-yellow oil (22 g) was distilled in vacuo to give a very viscous clear oil (17 g, 78% yield) that solidified overnight. This was recrystallised in petroleum ether (b.p. 60°C) at –5°C to give a white crystalline product (6.5 g in two crops, 30% yield). HPLC in a chiral column revealed the expected racemic mixture.

M.p. 47.5–49.0°C, (lit.[193] = 45.5–47.5°C, and 49.5–51.5°C).[194]

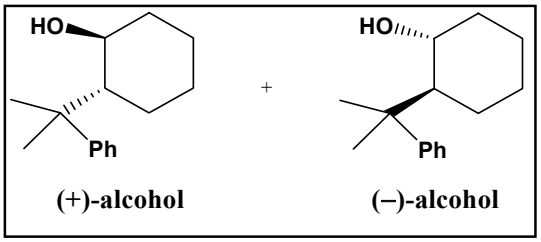
IR Absorptions υ_{max}/cm^{-1} = 3460 (br, -OH), 2928, 2857, 1448, 1289, 1109, 1019, 980, 699

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.97–1.31 (m, 4 H,), 1.29 and 1.43 (s, 3 H, -C*H*$_3$), 1.64–1.79 (m, 5 H), 1.84–1.88 (m, 1 H, -OCHC*H*), 3.47–3.51 (m, 1 H, -OC*H*CH), 7.15–7.41 (m, 5 H, Ar-*H*)

δ_H An attempt was made to resolve the diastereomers using shift reagents, but this was not successful due to the complex nature of the signals.

δ_C (400 MHz; $CDCl_3$) 24.19 (-<u>C</u>H_2, C-3*), 25.04 (-<u>C</u>H_2, C-4), 26.28 (-<u>C</u>H_3, C-8), 26.88 (-<u>C</u>H_3, C-8), 28.71 (-<u>C</u>H_2, C-5), 36.75 (-<u>C</u>H_2, C-2), 39.93 (-<u>C</u>CH_3, C-7), 54.66 (-<u>C</u>H, C-6), 73.44 (-<u>C</u>H-OH, C-1), 125.76, 125.78, 128.44 and 151.34 (-Ar-<u>C</u>)

8.8.2 Resolution of (1*S**,2*R**)-2-(2-phenylpropan-2-yl)cyclohexanol



Enantiomerically enriched (+)-(1*S*,2*R*)-2-(2-phenylpropan-2-yl)cyclohexanol **(+)-140** and (–)-(1*R*,2*S*)-2-(2-phenylpropan-2-yl)cyclohexanol **(-)-140** were obtained by the following enzymatic resolution procedure:[235] Racemic alcohol (**140**, 2.18 g, 0.01 mol, 1.0eq) and lauric acid (2.0 g, 0.01 mol, 1.0eq) were stirred together in 40 cm^3 of cyclohexane, together with 280 mg *Candida rugosa* enzyme (activity 13.9 u/mg) for 24 h. A further portion of enzyme (2.5 g) was added and the reaction stirred for a further 20 h at 40°C. HPLC analysis shows a decrease of one enantiomer and the appearance of a new peak attributed to the lauryl ester. After a further 28 hours the HPLC analysis shows 42% conversion of one enantiomer to the lauryl ester, and the reaction was stopped. The optical rotation of this reaction solution shows a strong positive rotation of approximately 22 (c ≈ 5.5% in cyclohexane). The lipase was filtered and air-dried for 2 days (99% recovery). The cyclohexane was removed from the remaining solution and the resulting oil purified by bulb-to-bulb distillation under reduced pressure (90–180°C at 2 mm Hg) to give a mixture of lauric acid enriched with (+) alcohol. This mixture was subjected to a second resolution step (4.00 g of enzyme for 50 h at 40°C). HPLC analysis at this point showed that the remaining (–) alcohol was less than 1% of the (+) isomer. The enzyme was again filtered and air dried for 4 days (99% recovery). The filtrate was evaporated to give a viscous oil that was again purified by bulb to bulb distillation.

The distillate contained enantiomerically enriched (+) alcohol (50%ee), while the residue contained the enantiomerically enriched lauryl ester of the (–)-alcohol, which could be hydrolysed by treatment with ethanolic potassium hydroxide for 3 hrs at RT to give the (–)-alcohol (32%ee).

Apart from the optical rotations, given below, the remaining spectroscopic data was identical to that shown above for the racemic mixture.

Optical Rotation $[\alpha]_D^{23} = 15.7$ (c 1.7 in MeOH) [lit.[194] $[\alpha]_D^{23} = 29.6$ (c = 1.7 in MeOH), or $[\alpha]_D^{23} = 26.3$ (c = 2.05 in MeOH)[193]]

8.9 Acylation of the Chiral Auxiliaries (GP-2)

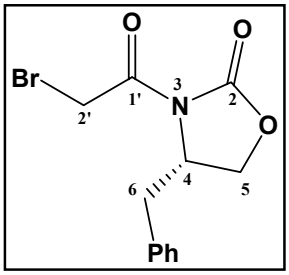
8.9.1 Using Sodium Hydride as base (GP-2A)

A solution of the appropriate chiral auxiliary in dry freshly distilled toluene (5 $cm^3.mmol^{-1}$) was added dropwise at room temperature to a stirred suspension of sodium hydride (50–60% suspension in mineral oil, 1.5 equivalents) in dry toluene (0.2 $cm^3.mmol^{-1}$). After 1 hour, a solution of freshly distilled bromoacetyl bromide (2 equivalents) in dry toluene (2.5 $cm^3.mmol^{-1}$) was added dropwise to the above mixture, with vigorous stirring, at room temperature. After addition, the mixture was stirred for 3 hours at room temperature. Water was carefully added to quench the reaction. The organic phase was washed with brine, separated, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude products were purified by column chromatography using appropriate ethyl acetate/hexane mixtures and solid products were further purified by recrystallisation.

8.9.2 Using BuLi solutions (GP-2B)

A solution of the chiral auxiliary in THF was cooled to –78°C, and *n*-BuLi (1.10 mole equivalents) was added with stirring over 10 minutes, and the reaction was stirred for 20 minutes at –78 °C. The reaction was warmed slightly to –40°C, and bromoacetyl bromide (1.02 – 2.00 mol equivalents) was added as quickly as possible to a vigorously stirred solution. The solution was stirred for a further 30 minutes and then allowed to warm to room temperature with continued stirring. Excess bromoacetyl bromide was destroyed by the addition of saturated ammonium chloride solution. The bulk of the solvent was then removed and the remaining slurry extracted with CH_2CH_2. The combined organic phase was washed with 1M NaOH (5 cm^3) followed by saturated NaCl solution (5 cm^3). The organic phase was then dried over anhydrous Na_2SO_4 or $MgSO_4$, filtered and evaporated. The crude products obtained were purified by column chromatography and solid samples were further purified by recrystallisation.

8.9.3 (*S*)-4-Benzyl-3-(2-bromoacetyl)oxazolidin-2-one [141]



Both **GP-2A** and **GP-2B** worked well, but the use of butyl lithium resulted in larger amounts of bromoacetic acid and other by-products.

During a typical procedure (+)-(*S*)-4-benzyloxazolidin-2-one (**132**, 1.773 g, 10.0 mmol), sodium hydride (1.5 eq, 733 mg, 15 mmol), and bromoacetyl bromide (1.80 cm^3, 20.0 mmol), were reacted together to give an orange oil that was purified by chromatography using 30%–40% ethyl acetate/hexane mixtures. This afforded the product (*S*)-4-benzyl-3-(2-bromoacetyl)oxazolidin-2-one as a viscous pale yellow oil (2.354 g, 79%).

R_f = 0.62 (50% ethyl acetate/hexane).

IR Absorptions υ_{max}/cm^{-1} (thin film) 3062 (Ar C–H), 3028 (Ar C–H), 3004 (Ar C–H), 2970 (C–H), 2922 (C–H), 1780 (OC=O), 1710 (NC=OO), 1604 (C=C), 1454 (CH_2 asymmetric bend), 1052 (C–O), 799, 720 (C–Br)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 2.81 (dd, 1 H, J_1 = 13.4, J_2 = 9.5, C$\underline{H}_2$Ph H-6a), 3.32 (dd, 1 H, J_1 = 13.4, J_2 = 3.3, C$\underline{H}_2$Ph H-6b), 4.18 – 4.32 (m, 2 H, CHC$\underline{H}_2$O H-5), 4.54 (AB quartet, 2 H, J_1 = 13.8 , BrCH_2-, H-2'), 4.64 – 4.76 (m, 1 H, C$\underline{H}$CH_2O H-4), 7.19 – 7.39 (m, 5 H, Ar *H*).

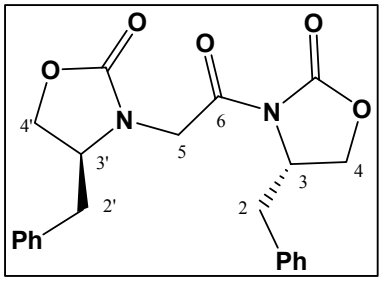
δ_H (400 MHz; $CDCl_3$; TMS) *J* resolved spectrum, decoupled at 4.25 ppm showed 4.66 – 4.77 (dd, 1 H, J_1 = 9.3, J_2 = 3.3 C$\underline{H}$CH_2O H-4)

δ_C ^{13}C NMR (400 MHz; $CDCl_3$) 28.28 (Br$\underline{C}H_2$ C-2'), 37.34 ($\underline{C}H_2$Ph C-6), 55.32 ($\underline{C}$HCH_2O C-4), 66.58 (CH$\underline{C}H_2$O C-5), 127.40, 128.93, 129.31, 134.65 (Ar-C), 152.88 (BrC$H_2\underline{C}$=O C-2), 165.82 (N$\underline{C}$=OO C-1').

By-products of the previous reaction: Bromoacetic acid (40 – 50%) and dimer [**142**].

8.9.3.1 1,2-Bis-[(4*S*)-4-benzyl-1,3-oxazolidin-2-on-3-yl]ethanone [142]

(Oxazolidinone Dimer)



Inefficient stirring of the reaction during the addition of the bromoacetyl bromide led to increased yields of this viscous yellow oil.

The use of BuLi as a base (**GP-2B**) also appeared to increase the yields of this by-product. Nonetheless, it was easily remove from the product by chromatography, as it was substantially more polar than the required product. Yields of this by-product were estimated at *2–10%* by mass and ^{13}C NMR, since it was difficult to isolate the product completely.

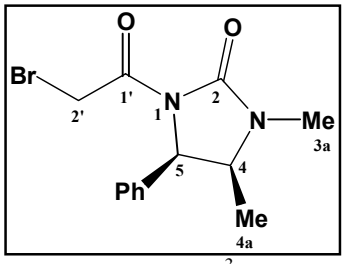
R_f = .28 (1:1 ethyl acetate/hexane)

IR Absorptions υ_{max}/cm^{-1} = 3112–2850, 1778 (br. s C=O) 1752 (br. s C=O) 1710 (s C=O) 1428, 1398, 1268, 1216, 1104

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 2.77 (dd, 1 H, J_1 = 13.5, J_2 = 4.4, Ph-C<u>*H*</u>$_2$, H-2a*), 2.81 (dd, 1 H, J_1 = 13.5, J_2 = 2.5, Ph-C<u>*H*</u>$_2$, H-2b*), 3.02 (dd, 1 H, J_1 = 13.7, J_2 = 5.7, Ph-C<u>*H*</u>$_2$, H-2'a*), 3.25 (dd, 1 H, J_1 = 13.5, J_2 = 3.2, Ph-C<u>*H*</u>$_2$, H-2'b*), 4.05 (dd, 1 H, J_1 = 7.2, J_2 = 5.9, O-C<u>*H*</u>$_2$, H-4a*1), 4.05 (dd, 1 H, J_1 = 7.2, J_2 = 5.9, O-C<u>*H*</u>$_2$, H-4a*1), 4.2-4.4 (m, 3 H, O-C<u>*H*</u>$_2$C-, H-4b*1, H-4a'*1, H-4b'*1) (note: these signals give dd that are only partially visible due to overlapping signals J_1 = 8.0, J_2 = 5.4), 4.15-4.35 (m, 1 H, C<u>*H*</u>, H-3'), 4.56-4.63 (m, 1 H, C<u>*H*</u>, H-3), 4.62 (AB system quartet, 2 H, J_1 = 77.6, J_2 = 18.9, NC<u>*H*</u>$_2$CO, H-5), 7.1-7.4 (m, 10 H, Ar-<u>*H*</u>)

δ_C (400 MHz; $CDCl_3$) 37.4 and 38.7 (Ph-<u>*C*</u>H_2, C-2* and C-2'*), 46.2 (N<u>*C*</u>H_2CO, C-5), 54.8 and 56.3 (<u>*C*</u>H, C-3*1 and C-3'*1), 67.0 and 67.5 (O-<u>*C*</u>H_2C-, C-4*2 and C-4a'*2), 127.0, 127.3, 128.8, 128.9, 129.3, 134.6, and 135.4 (Ar-<u>*C*</u>), 153.2 (<u>*C*</u>=O), 158.6 (<u>*C*</u>=O), 167.8 (<u>*C*</u>=O),

8.9.4 (4*R*,5*S*)-1-(2-Bromo-acetyl)-3,4-dimethyl-5-phenyl-1,3-imidazolidin-2-one [143]



Obtained from (–)-(4*R*,5*S*)-1,5-dimethyl-4-phenyl-1,3-imidazolidin-2-one (**134**, 1.00 g, 5.26×10^{-3} mol, 1eq.), sodium hydride (231 mg, washed free of oil, 5.78×10^{-3} mol, 1.1eq.), and bromoacetyl bromide (3.01 g, 1.2 cm^3, 1.29×10^{-3} mol, 2.5 eq.), using **GP-2A** as an orange, viscous oil, which was purified by chromatography (ethyl acetate/hexane). This afforded *(4R,5S)-1-(2-bromo-acetyl) -3,4-dimethyl-5-phenyl-1,3-imidazolidin-2-one* [**163**] as a viscous pale yellow oil.

R_f = 0.47 (1:1 ethyl acetate/hexane)

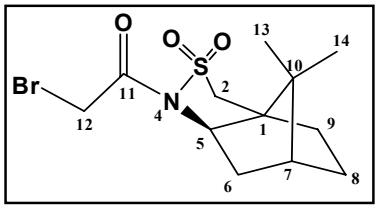
Optical Rotation $[\alpha]_D^{23}$ = –99.3 (c 2.0 in EtOH)

IR Absorptions υ_{max}/cm^{-1} = 2978, 2938, 1730 (vs C=O), 1694 (vsC=O), 1426, 1400, 1372, 1358, 1292, 1154, 758, 702, 606, and 414

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.81 (d, 3 H, J_1 = 6.6, -CHC$\underline{H}_3$ H4a), 2.86 (s, 3 H, -NC$\underline{H}_3$, H3a), 3.91–4.07 (m, 1 H, -C$\underline{H}$$CH_3$, H4), 4.57 (AB quartet, 2 H, J_1 = 18.6, J_2 = 11.9, -C$\underline{H}_2$Br, H2'), 5.31 (d, 1 H, J_1 = 8.6, -C$\underline{H}$Ph, H5), 7.1–7.4 (M, 5 H, Ar-$\underline{H}$)

δ_C (200 MHz; $CDCl_3$) 14.81 (-CH$\underline{C}H_3$, C4a), 28.16 (-N$\underline{C}H_3$, C3a), 28.61 (-$\underline{C}H_2$Br, C2'), 54.10 (-$\underline{C}$$CHCH_3$, C4), 59.52 (-$\underline{C}$HPh, C5), 126.88, 128.28, 128.52, 135.53 (Ar-C)

8.9.5 (1*R*,5*R*,7*S*)-2-Bromo-1-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)ethanone [144]



For a typical procedure using **GP-2A**, the reaction of (1*R*,5*R*,7*S*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane (**135**, 31.0

mmol, 6.67 g), NaH (1.2 eq, 37.1 mmol, 892 mg – oil removed by centrifugation several times in toluene), and bromoacetyl bromide (2.0 eq, 62.0 mmol, 12.6 g, 5.43 cm^3) gave an orange oil, which was purified by chromatography using 5–20% EtOAc/hexane as the eluent.[177] This afforded *(1S,5R,7R)-2-bromo-1-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)ethanone* as a pale yellow oil (9.69 g, 93%), which subsequently solidified on standing overnight. Recrystallisation from hexane/EtOAc afforded long, colourless, needles (9.12 g, 89%).

Using **GP-2B**, (1*R*,5*R*,7*S*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane (**135**, 23.3 mmol, 5.00 g) was dissolved in 35 cm^3 THF, and *n*-BuLi (1.10 eq, 12.6 mmol, 26.2 cm^3 of a 0.98 M solution in hexane) added over 1 hr., followed by bromoacetyl bromide (1.50 eq, 35.0 mmol, 7.06 g, 3.05 cm^3) at –78 °C, to give an identical product to that obtained by **GP-2A** in 67% yield, after purification.

M.p. 118,5–119,5°

R_f 0.38 (20% ethyl acetate/hexane), 0.79 (50% ethyl acetate/hexane)

Optical Rotation $[\alpha]_D^{25} = -105.2$ (c 1.35, abs. ethanol)

Elemental Analysis Found: C, 42.88; H, 5.46; N, 4.18%, Required for $C_{12}H_{18}NO_3SBr$: C, 42.87; H, 5.40; N, 4.17%

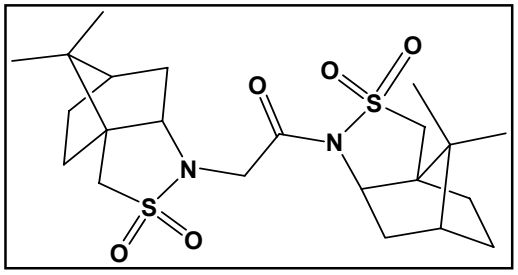
IR Absorptions υ_{max}/cm^{-1} = 2966 (C–H); 2920 (C–H); 2888 (C–H); 1708 (vs, br., C=O); 1338 (asymmetric S=O); 1316; 1304; 1168 (symmetric S=O)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.98 [s, 3 H, -C(C$\underline{H}_3$)$_2$, H-13*], 1.16 [s, 3 H, -C(C$\underline{H}_3$)$_2$, H-14*], 1.49–1.27 (m, 2 H), 2.22–1.82 (m, 5 H), 3.51 (AB quartet, 2 H, J_1 = 13.9, J_2 = 8.9, -C$\underline{H}_2$SO$_2$-, H-2), 3.92 (dd, 1 H, J_1 = 7.3, J_2 = 5.4, -NC$\underline{H}$-, H-5), 4.26 (AB quartet, 2 H, J_1 = 18.9, J_2 = 13.1, -C$\underline{H}_2$Br, H-12)

δ_C (400 MHz; $CDCl_3$) 19.8 [-C(<u>C</u>H_3)$_2$, C-13*], 20.6 [-C(<u>C</u>H_3)$_2$, C-14*], 26.3 (C-8[*1]), 27.5 (C-9[*1]), 32.7 (C-6), 37.8 (C-7), 44.4 (C-10), 47.8 (C-12), 48.9 (C-1), 52.59 (C-5), 65.3 (C-2), 164.4 (C=O, C-11)

8.9.5.1 *By-product 1,2-Bis-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)ethanone [145]*

<u>(Sultam Dimer)</u>



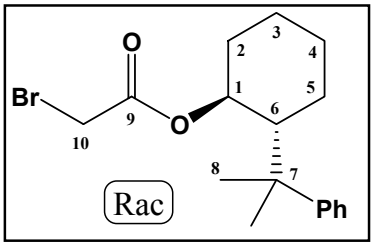
This was isolated in small quantities as a by-product of the reaction after chromatography in estimated yields of about 3%. This is a known by-product of no interest to us, so the purification and characterisation were not completed. In general all the NMR signals appear twinned, and severe overlapping of multiplets prevents the assignment of the signals. Listed below are selected data.

$R_{\underline{f}}$ = 0.21 (50% ethyl acetate/hexane)

IR Absorptions υ_{max}/cm^{-1} = 1711 (br., C=O); 1336 (asymmetric S=O); 1316; 1302; 1166 (symmetric S=O)

NMR Data **Selected assignments** δ_H (200 MHz; $CDCl_3$; TMS) 0.96, 1.03, 1.11, and 1.16 [4 sets s, 3 H, -C(C<u>H</u>$_3$)$_2$], 1.27–1.92 (m, 14 H), 3.51 (AB quartet, 2 H, J_1 = 13.7, J_2 = 8.5, -C<u>H</u>$_2$SO$_2$), 3.72 (AB quartet, 2 H, J_1 = 13.8, J_2 = 9.0, -C<u>H</u>$_2$SO$_2$), 3.7-4.1 (m, 2 H, -NC<u>H</u>), 4.71 (AB quartet, 2 H, J_1 = 70.2, J_2 = 17.9, NC<u>H</u>$_2$CO)

8.9.6 (1*S**,2*R**)-2-(2-Phenylpropan-2-yl)cyclohexyl 2-bromoacetate [146]



The reaction of (1*S**,2*S**)-2-(2-phenylpropan-2-yl)cyclohexanol (**140**, 4.02 g, 18.4 mmol, 1eq.), BuLi (17.5 cm^3 of a 1.16M solution in hexane, 20.3 mmol, 1.1eq.) and bromoacetyl bromide (7.80 g, 3.37 cm^3, 38.6 mmol, 2.1 eq.) by **GP-2B** gave a red oil. The use of NaH (**GP-2A**) caused significant product degradation. Purification of the product was achieved by column chromatography (benzene, then acetone/hexane), to give the pure, racemic product in 68% yield, as a pale yellow oil.

R_f = 0.52 (50% EtOAc/hexane)

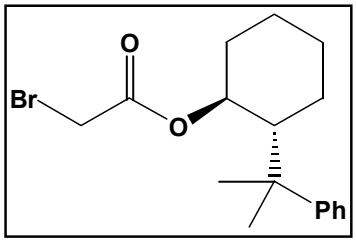
IR Absorptions υ_{max}/cm^{-1} = 2929, 2859, 1731 (C=O), 1447, 1280, 1169, 1020, 981, 765, 701 (C–Br), 562

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.83–0.98 (m, 2 H, -C*H*$_2$-, H-4*), 1.09–1.32 (m, 2 H, -C*H*$_2$-, H-3*), 1.20 and 1.31 (s, 3 H, -C*H*$_3$-, H-8), 1.63–1.73 (m, 2 H, -C*H*$_2$-, H-5), 1.82–1.91 (m, 2 H, -C*H*$_2$-, H-2), 2.07–2.13 (m, 1 H, -C*H*C-, H-6), 3.00 (AB q, 2 H, J_1 = 12.4, J_2 = 23.8, -C*H*$_2$*Br*, H-10), 4.75–4.84 (m, 1 H, -C*H*O-, H-1), 7.04–7.30 (m, 5 H, -Ar-*H*)

δ_C (400 MHz; $CDCl_3$) 22.95 (-*C*H$_2$, C-2*), 24.55 (-*C*H$_2$, C-3*), 25.79 (-*C*H$_2$, C-4*), 26.39 (-*C*H$_2$, C-5*), 26.66 (-*C*H$_2$, C-8*), 32.83 (-*C*H$_2$Br, C-10), 39.59 [-*C*(CH$_3$)$_2$, C-7], 50.71 (-*C*HC-, C-6), 76.25 (-*C*H–O–C-, C-1), 125.08, 125.28, 127.94, and 151.67, (Ar-*C*) 166.26 (*C*=O)

Mass Spec. Data *m*/*z* found: 338.0877, calculated for $C_{17}H_{23}O_2{}^{79}Br$, = 338.0881 (M^+, <5%), 340.0858, calculated for $C_{17}H_{23}O_2{}^{81}Br$, = 338.0861 (M^+ + 2, <5%), 200.16 (M+ – $BrCH_2CO_2H$, 8%), 136.99 ($BrCH_2CO_2$+, 10%), 119.09, [$PhC(CH_3)_2{}^+$, 100%], 91.05 ($C_6H_6CH^+$, 18%), 83 ($C_6H_{10}{}^+$3%)

8.9.7 (1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl-2-bromoacetate (–)-[146]



Diastereomerically ***enriched*** bromoacetic acid-(1*S*,2*S*)-2-(2-phenylpropan-2-yl)cyclohexyl ester (d.e. = 50%, confirmed by chiral-phase HPLC) was obtained as a clear oil (186 mg, 40% yield) from the equally enriched (1*S*,2*S*)-2-(2-phenylpropan-2-yl) cyclohexanol [(+)(-**140**] using the same procedure as for the racemic compound (above), after chromatography with ethyl acetate/hexane mixtures.

R_f = 0.51 (50% ethyl acetate/hexane)

Optical Rotation $[\alpha]_D^{23}$ = –30.0 (c 1.50 in abs. ethanol)

IR Absorptions υ_{max}/cm^{-1} = 2934, 2860, 1729, 1455, 1377, 1281, 1170, 1114, 1025, 981, 765, 703, 564

NMR Data δ_H Listed above under **8.9.7**

The addition of 0.2 M chiral shift reagent showed a splitting of all signals. The ratio of diastereomers could be determined from the methyl signals at δ = –0.17, 0.10, 0.19, and 0.37 at approximately 25:75

δ_C Listed above under **8.9.7**

8.10 Synthesis of Activated Methylene Compounds

General Procedure for the Preparation of 2-methylenepyrrolidines. (GP-3)

General procedures for the preparation of iminium salts from pyrrolidin-2-thiones and bromoacylated chiral auxiliaries (or other activated methylenes):

8.10.1 Using thiolactams in THF or CH_3CN GP-3A:

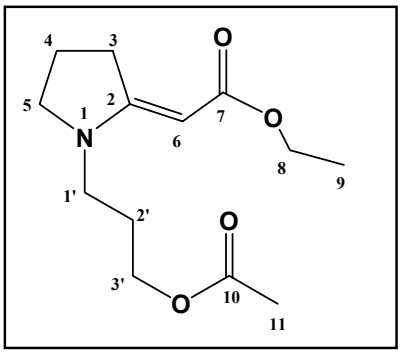
A small excess (1.05 –1.2 eq.) of the required pyrrolidine-2-thione and the corresponding bromoacylated chiral auxiliary (or other activated methylene compound) were dissolved in a small amount of either dry THF or CH_3CN (to give concentrations of 0.3 M to 1.2 M), and stirred together at room temperature for 12 – 72 hours, or until salt formation was completed. Salt formation was observed as a base-line spot by TLC (EtOAc as the eluent). In THF, salt could usually be seen precipitating from the solution as a pale solid or oil. The reaction was taken as completed when one of the reactants (usually the bromoacylated chiral auxiliary) no longer showed up on TLC. If THF was used, the solvent was removed and the salts dried *in vacuo*. If CH_3CN was used, the solution of the salt was used without further manipulations. The salts were not characterised.

The salt was dissolved in acetonitrile, and triphenylphosphine (1.2 eq.) in a small amount of acetonitrile was then added, followed by triethylamine (2.2 eq.). After 30min to 3h stirring at RT, the reaction was complete. The reaction mixture was triturated with Et_2O to precipitate excess PPh_3S, which was removed by filtration. The product was isolated by evaporation of the solvent.

8.10.2 Using (methylthio)pyrrolidinium salts GP-3B:

Iodomethane (3.0 eq.) was added to a solution of the appropriate thiolactam in THF, and the reaction mixture stirred under nitrogen. After 16 hours, complete formation of the (methylthio)-Δ^1-pyrrolinium iodide was indicated by a baseline spot on the TLC plate, and consumption of the thiolactam. The solvent was then evaporated *in vacuo* and replaced with DMF or CH_3CN. Equimolar amounts of the activated methylene compound, together with anhydrous potassium carbonate (2.0 eq.) were added to the solution. The reaction mixture was left stirring overnight. Evaporation of the organic solvent led to the isolation of the crude products, which were further purified as necessary.

8.10.3 [1-(3-Acetoxy-propyl)pyrrolidin-2-ylidene]acetic acid ethyl ester [110]



The reaction of 3-(2-thioxopyrrolidin-1-yl)propyl acetate (**108**, 5.00 g, 24.8 mmol, 1.0eq.) with ethyl bromoacetate (4.98 g, 3.31 cm^3, 29.8 mmol, 1.2eq.) according to **GP-3A** in THF (20 cm^3) gave *ethyl [1-(3-acetoxypropyl)pyrrolidin-2-ylidene]acetate* as a yellow oil after work-up and column chromatography (ethyl acetate/hexane) in 64–89% yield.

Note: The same reaction in CH_3CN gave a yield of 52–64%

R_f = 0.52 (50% EtOAc/hexane)

Elemental Analysis Found: 255.1487, Calculated for $C_{13}H_{21}NO_4$:255.1471

IR Absorptions υ_{max}/cm^{-1} = 2976, 2948, 1740 (C=O), 1682, 1592, 1484, 1462, 1428, 1378, 1298, 1242 (O–*C*=O), 1204, 1140, 1112, 1098, 1058, 786.

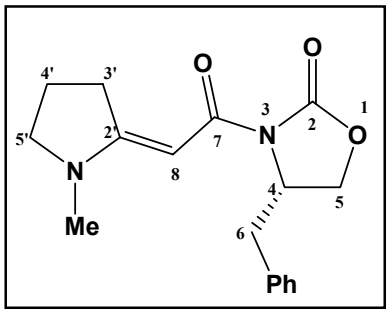
NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.25 (t, 3 H, *J* = 7.2, -OCH$_2$C*H*$_3$, H-9), 1.99–1.88 (m, 4 H, -NCH$_2$C*H*$_2$-, H-2' & H-4), 2.08 (s, 3 H, -C=OC*H*$_3$, H-11), 3.15 (t, 2 H, *J* = 7.8, =CC*H*$_2$-, H-3), 3.27 [t, 2 H, *J* = 7.2, -N-C*H*$_{2(ring)}$-, H-5], 3.38 (t, 2 H, *J* = 7.1, -NC*H*$_2$-, H-1'), 4.07 (t, 2 H, *J* = 6.2, -C*H*$_2$CO-, H-3'), 4.08 (q, 2 H, *J* = 7.2, -OC*H*$_2$CH$_3$, H-8), 4.53 (s, 1 H, -C*H*-, H-6)

δ_C (400 MHz; $CDCl_3$): 14.93 (-OCH$_2$*C*H$_3$, C-9), 20.70 (-C=O*C*H$_3$, C-11), 20.95 (-NCH$_2$*C*H$_2$-, C-2'), 25.23 (=C*C*H$_2$-, C-3), 32.42 (-NCH$_2$*C*H$_2$-, C-4), 42.86 (-N*C*H$_2$-, C-1'), 52.48 (C-8), 58.06 (-*C*H$_2$CO-, C-3'), 61.58 [-N-*C*H$_{2(ring)}$-, C-5], 77.77 (-*C*H-, C-6), 164.65 (N*C*=, C-2*), 169.20 (-O*C*H$_2$CH$_3$, C-8*), 170.76 (*C*=O, C-10*[1]), 172.34 (*C*=O, C-7*[1])

Mass Spec. Data *m*/*z* 255 (M^+, 17%), 210(48), 197(10), 196(100), 169(61), 168(88), 140(19), 124(12), 122(42), 110(42), 108(22), 101(43), 97(66), 96(50), 94(10), 83(14), 80(40)

Compounds Containing the Evan Auxiliary

8.10.4 (*S*)-4-Benzyl-3-[2-(1-methylpyrrolidin-2-ylidene)acetyl]oxazolidin-2-one [147]



The addition of (4*S*)-4-benzyl-3-(2-bromoacetyl)-1,3-oxazolidin-2-one (**135**, 326 mg, 1.16×10^{-3} mol, 1eq.) in THF (10 cm^3) to a solution of *N*-methylpyrrolidine-2-thione (**107**, 133 mg, 1.16×10^{-3} mol, 1eq. in 20 cm^3 of THF) according to **GP-3A** gave *(4S)-4-benzyl-3-[2-(1-methylpyrrolidin-2-ylidene)acetyl]oxazolidin-2-one* [**147**] as a brown solid (yield: 78%). This was recrystallised from ethyl acetate/hexane to give pale yellow leaves.

R_f: 0.63 (ethyl acetate)

Elemental Analysis Found: C, 67.99; H, 6.73; N, 9.35%, Required for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33%

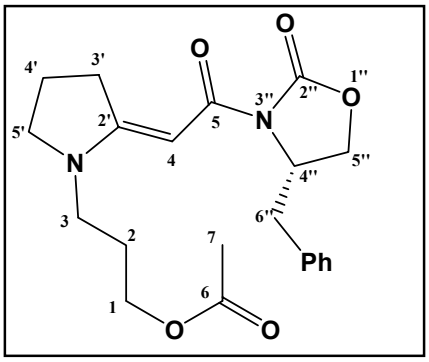
IR Absorptions υ_{max}/cm^{-1} = 3008, 1758 (vs C=O), 1646, 1568 (vs C=O), 1486, 1416, 1384, 1348, 1300, 1188 (vs C–O), 966, 826, and 706

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 2.02 (app. quintet, J_1 = 7.4, 2 H, $NCH_2C\underline{H}_2$, H-4'), 2.76 (dd, J_1 = 13.3 J_2 = 9.6, 1 H, PhC$\underline{H}$aHb, H-6a), 2.94 (s, 3 H, C$\underline{H}_3$N), 3.27 (dt, J_1 = 7.4 J_2 = 6.2, 2 H, NCC$\underline{H}_2$, H-3'), 3.47 (dd, J_1 = 13.3 J_2 = 3.3, 1 H, PhCHa$\underline{H}$b, H-6b), 3.45 (t, J_1 = 7.4, 2 H, NC$\underline{H}_2CH_2$, H-5'), 4.09 (m, 2 H, NCHC$\underline{H}_2$O, H-5), 4.76 (dddd, 1 H, J_1 = 9.6 , J_2 = 4.4, J_3 = 2.4 and J_4 = 2.4, $PhCH_2C\underline{H}$, H-4), 6.04 (s, 1 H, C=C$\underline{H}$C=O, H-8), 7.20–7.35 (m, 5 H, Ar-$\underline{H}$)

δ_C (200 MHz; $CDCl_3$) 20.74 (-$NCH_2\underline{C}H_2$, C-4'), 33.47 (-NCH_3), 33.83 [-NC(CH)$\underline{C}H_2$, C-3'], 54.65 (-N$\underline{C}H_2$, C-5'), 55.29 ($PhCH_2CH$, C-4), 65.30, (NCH$\underline{C}H_2O$, C-5), 79.16 (-$\underline{C}HC{=}O$, C-8), 126.89, 128.66, 129.52 and 136.26 (Ar-$\underline{C}$), 154.31 (N$\underline{C}CH_2$, C-2'*), 165.19 (C=O*), 168.28 (C=O)

Mass Spec. Data *m/z* found: 300.1459, calculated for $C_{17}H_{20}N_2O_3$ = 300.1474 (M^+, 11%), 301 (M^+ + H, <5%), 176 (chiral auxiliary, 100%), 97 (25), 96 (29), 91 ($C_6H_6CH_2^+$, 48%), 72 (12)

8.10.5 3-{2-[2-(*S*)-(4-Benzyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propyl acetate [148]



A mixture of 3-(2-thioxopyrrolidin-1-yl)propyl acetate (**108**, 1.35 g, 6.71×10^{-3} mol) and (4*S*)-4-benzyl-3-(2-bromo-acetyl)-1,3-oxazolidin-2-one (**132**, 2.00 g, 6.71×10^{-3} mol) were stirred together in THF for two days following **GP-3A** to give the product as a viscous yellow to dark orange oil after work-up. Purification by column chromatography (CH_2Cl_2 then ethyl acetate/hexane) *gave* the *3-{2-[2-(4S)-(4-benzyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propyl acetate* [**148**] as a very thick yellow oil in 77% yield. Repeated attempts to crystallise the product, even at low temperatures, failed to produce any solid material.

R_f = 0.39 (3:2 ethyl acetate/hexane)

Optical Rotation $[\alpha]_D^{23}$ = 50.1 (c 1.09 in ethyl acetate)

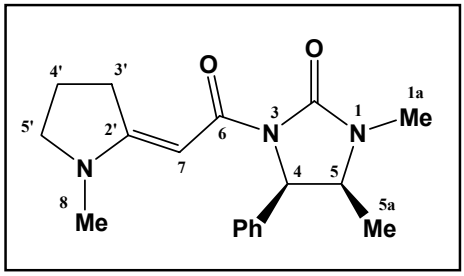
IR Absorptions υ_{max}/cm^{-1} = 2970, 1760 (vs C=O), 1738 (vs C=O), 1648, 1566 (vs), 1484, 1386, 1348, 1238 (vs C–O), 1186 (vs C–O), 824, 788, 746, and 704

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 2.0 (m, 4 H, $NCH_2C\underline{H}_2$ & $C\underline{H}_2CH_2OAc$, H-4' and H-2), 2.09 (s, 3 H, $COC\underline{H}_3$, H-7), 2.75 (dd, 1 H, J_1 = 13.3, J_2 =9.6, $C\underline{H}aCHbC_6H_5$, H-6a"), 3.35 (m, 2 H, $NCC\underline{H}_2$, H-3'), 3.38 (dd, J_1 = 9.6, J_2 = 3.5, 1 H, $CHaC\underline{H}bC_6H_5$, H-6b"), 3.45 (t, J_1 = 7.2, 2 H, $NC\underline{H}_2CH_2CH_2OAc$, H-3), 3.47 (t, J_1 = 7.2, 2 H, $NC\underline{H}_2CH_2CH_2C$, H-5'), 4.0–4.2 (m, 4 H, $C\underline{H}_2OAc$ & $NCHC\underline{H}_2O$, H-1 and H-5"), 4.75 (ddt, J_1 = 9.7, J_2 = 7.6, J_3 = 3.5, 1 H, $NC\underline{H}CH_2O$, H-4"), 6.14 (s, 1 H, $NCC\underline{H}C{=}O$, H-4), 7.3 (m, 5 H, Ar-$\underline{H}$).

δ_C (400 MHz; $CDCl_3$) 20.91 ($NCH_2\underline{C}H_2CH_2OAc$ &$CO\underline{C}H_3$, C-2 and C-7), 25.40 ($NCH_2\underline{C}H_2CH_2C$, C-4'), 33.78 ($NCH_2CH_2\underline{C}H_2C$, C-3'), 38.61 ($\underline{C}H_2C_6H_5$, C-6"), 43.43 ($N\underline{C}H_2CH_2CH_2OAc$, C-3), 52.95 ($N\underline{C}H_2CH_2CH_2C$, C-5'), 55.30 ($N\underline{C}HCH_2O$, C-4"), 61.55 ($NCH_2CH_2\underline{C}H_2OAc$, C-1), 65.32 ($NCH\underline{C}H_2O$, C-5"), 79.48 ($NC\underline{C}HC{=}O$, C-4), 126.87, 128.68, 129.52 and 136.27 (Ar-$\underline{C}$), 154.26 ($N\underline{C}CHC{=}O$, C-2'), 165.25 ($\underline{C}{=}O$, C-5*), 167.59 ($\underline{C}{=}O$, C-6*), 171.11 ($\underline{C}{=}O$, C-2"*).

Methylene compounds containing the imidazolidinone auxiliary.

8.10.6 (4*R*,5*S*)-1,5-Dimethyl-3-[2-(1-methylpyrrolidin-2-ylidene)acetyl]-4-phenylimidazolidin-2-one [153]



N-Methylpyrrolidine-2-thione (**107**, 63 mg, 5.46×10^{-4} mol, 1eq.) and (4*R*,5*S*)-1-(2-bromoacetyl)-3,4-dimethyl-5-phenyl-1,3-imidazolidin-2-one (**143**, 170 mg, 5.46×10^{-4} mol, 1eq.) were stirred together in THF (12 cm^3) by **GP-3A** to give the product as a pale brown solid. Recrystallisation (ethyl acetate/hexane) gave white hexagonal shaped crystals.

Yield = 159 crude, 52% (after recrystallisation).

Optical Rotation Value was close to zero and did not give a significant result.

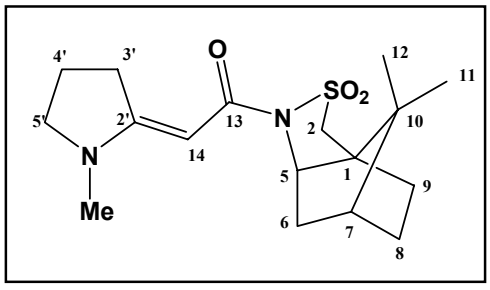
Elemental Analysis Found: C, 69.01; H, 7.46; N, 13.38%, Required for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41%

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.77 (d, J_1 = 6.6, 3 H, NCHC$\underline{H}_3$, H-5a), 1.88 (app. pent, 2 H, J_1 = 7.4, $NCH_2CH_2C\underline{H}_2C$, H-3'), 2.79 (s, 3 H, CONC$\underline{H}_3$, H-1a*), 2.91 (s, 3 H, $CH_2NC\underline{H}_3$, H-8*), 3.09 (dt, J_1 = 4.2, J_2 = 7.8, 2 H, $NCH_2C\underline{H}_2$, H-4'), 3.35 (t, J_1 = 7.2, 2 H, $NC\underline{H}_2CH_2CH_2C$, H-5'), 3.81 (dq, J_1 = 6.6, J_2 = 8.6, 1 H, NCHC$\underline{H}$NCH$_3$, H-5), 5.39 (d, J_1 = 8.6, NC$\underline{H}$CHNCH$_3$, H-4), 6.31 (s, 1 H, NCC$\underline{H}$CON, H-7), 7.2–7.5 (m, 5 H, Ar $\underline{H}$)

δ_C (200 MHz; $CDCl_3$) 14.99 ($\underline{C}H_3CHNCH_3$, C-5a), 20.93 ($NCH_2\underline{C}H_2CH_2C$, C-4'), 28.27 ($CH_3CHN\underline{C}H_3$, C-1a), 33.36 ($NCH_2CH_2\underline{C}H_2C$ and $\underline{C}H_3NCH_2CH_2CH_2C$, C-3' and C-8), 54.04 (NCH$\underline{C}$HNCH$_3$, C-5), 54.36 ($N\underline{C}H_2CH_2CH_2C$, C-5'), 59.28 (N$\underline{C}$HCHNCH$_3$, C-4), 80.49 (C$\underline{C}$HCON, C-7), 126.97, 127.43, 128.36 and 131.49 (Ar $\underline{C}$), 138.09 (N$\underline{C}$CHCON, C-2'), 157.01 ($\underline{C}$O, C-2*), 166.82 ($\underline{C}$O, C-6*).

Methylene compounds containing the sultam auxiliary.

8.10.7 (1*R*,5*R*,7*S*)-1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-(1-methylpyrrolidin-2-ylidene)ethanone [154]



The reaction of *N*-methylpyrrolidine-2-thione (**107**) with (1*R*,5*R*,7*S*)-2-bromo-1-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)ethanone [**144**] by **GP-3A**, gave a reddish, viscous gum, (23%), which was purified by repeated flash column

chromatography to give a pale brown amorphous solid. Recrystallisation of this solid in EtOH gave small, pale brown needles, but these were not suitable for crystallographic analysis despite several attempts.

Rf = 0.42 (2:3 hexane/ethyl acetate)

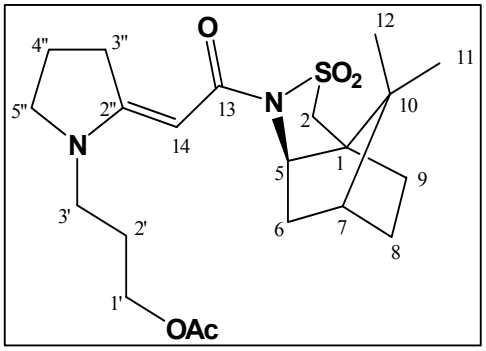
Optical Rotation $[\alpha]_D^{23} = -4.5$ (c = 1.10 in methanol)

Elemental Analysis Found: C, 60.55%; H, 7.84%; N, 8.21% Calculated for $C_{17}H_{26}N_2O_3S$: C, 60.33%; H, 7.74%; N, 8.28%

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.95 (s, 3 H, CC<u>*H*</u>$_3$, H-11*), 1.20 (s, CC<u>*H*</u>$_3$, H-12*), 1.25-1.49 (m, 2 H), 1.82 – 2.20 (m, 7 H), 2.89 (s, 3 H, NC<u>*H*</u>$_3$), 3.18 (dt, J_1 = 22.0 J_2 = 8.1, 2 H, NCC<u>*H*</u>$_2$, H-3'), 3.41 (m, 4 H, C<u>*H*</u>$_2$SO$_2$ and NC<u>*H*</u>$_2$, H-2 and H-5'), 3.91 (dd, 1 H, J_1 = 7.8, J_2 = 4.8, SO$_2$NC<u>*H*</u>, H-5), 5.18 (s, 1 H, NC=C<u>*H*</u>, H-14).

δ_C (400 MHz; $CDCl_3$) 19.8 (C<u>*C*</u>H$_3$, C-11*), 20.6 (C<u>*C*</u>H$_3$ and NCCH$_2$<u>*C*</u>H$_2$, C-12* and C-4'), 26.6 (<u>*C*</u>H$_2$, C-8*[1]), 32.5 (<u>*C*</u>H$_2$, C-9*[1]), 33.2 (N-<u>*C*</u>H$_3$), 33.3 (NC<u>*C*</u>H$_2$, C-3'), 38.7 (CH$_2$<u>*C*</u>H, C-7), 44.6 (<u>*C*</u>H$_2$, C-6), 47.5 (), 47.6 (SO$_2$CH$_2$<u>*C*</u>, C-1), 52.8 (NCCH$_2$<u>*C*</u>H$_2$, C-5'), 54.5 (SO$_2$<u>*C*</u>H$_2$, C-2), 64.9 (N<u>*C*</u>H, C-5), 79.3 (NC=<u>*C*</u>H, C-14), 164.7 (C=O, C-13), 167.2 (N<u>*C*</u>=CH, C-2').

8.10.8 <u>3-{2-[2-(1*R*,5*R*,7*S*)-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propyl acetate [155]</u>



The crude product was obtained as either a deep red or a yellow semi-solid by reacting ethyl 3-(2-thioxopyrrolidin-1-yl)propionate (**108**, 144 mg, 7.17×10^{-4} mol, 1.1eq.) with (1*R*,5*R*,7*S*)-2-bromo-1-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)ethanone (**144**, 210

mg, 6.52×10^{-4} mol, 1eq.) according to procedure **GP-3A** in 10 cm^3 of solvent. The use of either THF or CH_3CN during the reaction did not seem to change the outcome of the reaction much. The reaction took up to 4 days to reach completion, but this could be halved by the addition of a few grains of NaI to the initial solution. The isolated white orthorhombic crystals (36%), after purification by chromatography (CH_2Cl_2 then ethyl acetate/hexane) and subsequent recrystallisation (ethyl acetate/hexane) at 5°C, were stored in Teflon test-tubes. Storage of the white crystalline product in contact with glass resulted in a significant yellowing of some of the product within days. It was not possible to obtain accurate mass spectral data or elemental analysis of this product due to its decomposition.

M.p. = 112–114°C

R_f = 0.41 in 1:1 ethyl acetate/hexane

Optical Rotation $[\alpha]_D^{23}$ = +29.5 (c = 2.5 in ethanol)

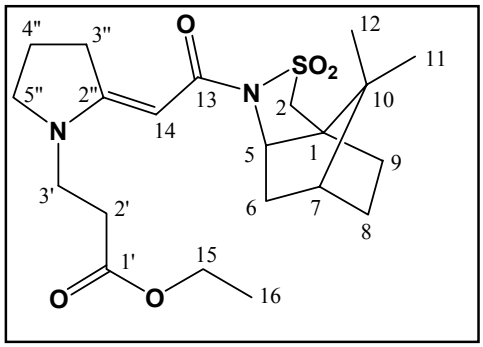
Elemental Analysis Sample decomposed

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.95 (s, 3 H, CC<u>*H*</u>$_3$, H-11*), 1.19 (s, 3 H, CC<u>*H*</u>$_3$, H-12*), 1.2 – 1.5 (m, 2 H), 1.8 – 2.2 (m, 9 H), 2.08 (s, 3 H, COC<u>*H*</u>$_3$), 3.19 (apparent q, 2 H, J_1 = 7.0, NCC<u>*H*</u>$_2$, H-3''), 3.2 – 3.5 (m, 4 H), 3.40 (d, J_1 = 1.6, 2 H, C<u>*H*</u>$_2SO_2$, H-2), 3.90 (dd, 1 H, J_1 = 7.8, J_2 = 4.8, SO_2NC<u>*H*</u>, H-5), 4.09 (t, 2 H, J_1 = 6.3, C<u>*H*</u>$_2$OAc, H-1'), 5.26 (s, 1 H, NC=C<u>*H*</u>, H-14)

δ_C (400 MHz; $CDCl_3$) 19.7 (C<u>*C*</u>H_3, C-11*), 20.5 (NCCH$_2$<u>*C*</u>H_2, C-4''), 20.6 (C<u>*C*</u>H_3 and CO<u>*C*</u>H_3, C-12* and C-15), 26.5 [<u>*C*</u>$H_{2(sultam)}$, C-8*1], 32.4 [<u>*C*</u>$H_{2(sultam)}$, C-9*1], 33.3 (NC<u>*C*</u>H_2, C-3''), 38.6 (CH_2<u>*C*</u>HCH_2, C-7), 43.1 (N<u>*C*</u>$H_2CH_2CH_2O$, C-3'), 44.4 [<u>*C*</u>$H_{2(sultam)}$, C-6], 47.4 (NCH$_2$<u>*C*</u>H_2CH_2O, C-2'), 47.5 (<u>*C*</u>CH_2SO_2, C-1), 52.6 [N<u>*C*</u>$H_2CH_2CH_2C$=CH, C-5''], 52.7 (<u>*C*</u>H_2SO_2, C-2), 61.2 (<u>*C*</u>H_2O, C-1'), 64.7 (N<u>*C*</u>H, C-5), 79.6 (NC=<u>*C*</u>H, C-14), 164.6 (N<u>*C*</u>=O, C-13), 166.2 (C=O), 170.7 (N<u>*C*</u>=CH, C-2'')

Mass Spec. Sample decomposed and no reliable data available

8.10.9 Ethyl 3-{2-[2-(1*R*,5*R*,7*S*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propanoate [156]



The reaction of ethyl 3-(2-thioxopyrrolidinyl) propanoate with (1*R*,5*R*,7*S*)-2-bromo-1-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)ethanone (**144**, 3.15 g, 9.41×10^{-3} mol, 1.01 eq) with ethyl 3-(2-thioxopyrrolidinyl)propanoate (**109**, 2.0 g, 9.4×10^{-3} mol, 1eq.) by **GP-3A**, first in THF (35 cm^3) followed by CH_3CN (30 cm^3) gave a pale yellow solid (2.80 g, 70%). This solid could be recrystallised repeatedly in ethyl acetate/hexane at low temperature (<10°C) to give white orthorhombic flakes.

Yield: 70% crude 66% pure.

M.p. = 144–144.5°C

R_f = 0.72 (1:1 ethyl acetate/hexane)

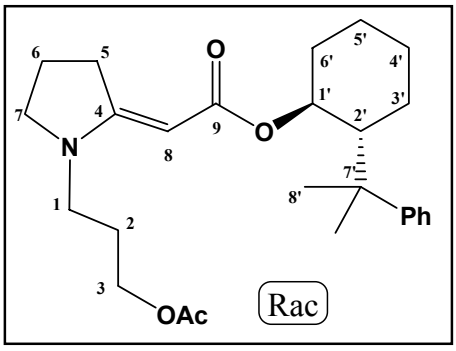
Elemental Analysis Found: C, 59.49%; H, 7.62%; N, 6.65% Calculated for $C_{21}H_{32}N_2O_5S$: C, 59.41%; H, 7.60%; N, 6.60%

δ_H (200 MHz; $CDCl_3$; TMS) 0.95 (s, 3 H, CC$\underline{H}_3$, H-11*), 1.19 (s, 3 H, CC$\underline{H}_3$, H-12*), 1.2 – 1.5 (m, 2 H), 1.26 (q, 3 H, J_1 = 7.1, $CH_2C\underline{H}_3$, H-16), 1.8 – 2.2 (m, 8 H), 2.64 (t, 2 H, C=OC$\underline{H}_2$, H-2'), 3.17 (apparent q, 2 H, J_1 = 6.7, NCC$\underline{H}_2$, H-3''), 3.4 – 3.6 (m, 3 H), 3.41 (s, 2 H, C$\underline{H}_2SO_2$, H-2), 3.90 (dd, 1 H, J_1 = 7.4, J_2 = 5.0, $SO_2NC\underline{H}$, H-5), 4.14 (q, 2 H, J_1 = 7.1, C$\underline{H}_2CH_3$, H-15), 5.21 (s, 1 H, NC=C$\underline{H}$, H-14)

δ_C	(400 MHz; $CDCl_3$) 14.0 ($CH_2\underline{C}H_3$, C-16), 19.9 ($C\underline{C}H_3$, C-11*), 20.7 ($NCCH_2\underline{C}H_2$, C-4"), 20.9 ($C\underline{C}H_3$, C-12*), 26.6 [$\underline{C}H_{2(sultam)}$, C-8*1], 32.6 [$\underline{C}H_{2(sultam)}$, C-9*1], 33.4 ($NC\underline{C}H_2$, C-3"), 38.7 ($CH_2\underline{C}HCH_2$, C-7), 39.6 ($NCH_2\underline{C}H_2C{=}O$, C-2'), 42.1 ($N\underline{C}H_2CH_2C{=}O$, C-3'), 44.7 [$\underline{C}H_{2(sultam)}$, C-6], 47.6 ($\underline{C}CH_2SO_2$, C-1), 47.7 [$N\underline{C}H_2CH_2CH_2C{=}CH$, C-5"], 52.8 ($\underline{C}H_2SO_2$, C-2), 60.7 ($\underline{C}H_2CH_3$, C-15), 64.9 ($N\underline{C}H$, C-5), 80.0 ($NC{=}\underline{C}H$, C-14), 164.8 ($N\underline{C}{=}O$, C-13), 166.4 (C=O, C-1'), 171.6 ($N\underline{C}{=}CH$, C-2"),
Mass Spec. Data	*m/z* found: 424.2030, calculated for $C_{17}H_{23}O_2{}^{79}Br$, = 424.2032 (M^+, 9%), 425(2), 182(13), 151(23), 150(100), 148(2), 123(11)
X-ray Crystallography	R (int.) = 6.40%, Space Group $P2_12_12_1$ a = 8.9607 b = 11.7839 c = 21.3871 $\alpha = \beta = \gamma = 90°$

Substituted Methylene Compounds Containing Cyclohexyl Auxiliary

8.10.10 [(1*S**,2*R**)-2-(2-Phenylpropan-2-yl)cyclohexyl]-[1-(3-acetoxy-propyl)pyrrolidin-2-ylidene] acetate [163]



A mixture of 3-(2-thioxopyrrolidin-1-yl)propylacetate (**108**, 46 mg, 2.3×10^{-4}, 1eq.) and the (1*S**,2*S**)-2-(2-phenylpropan-2-yl)bromoacetate (**146**, 70 mg, 2.3×10^{-4} mol, 1eq.) in CH_3CN (10 cm^3) were reacted for 48h. The compound could not be detected by TLC, but the addition of NEt_3 (0.07 cm^3, 4.8×10^{-4} mol, 2.1eq.) and PPh_3 (65 mg, 2.5×10^{-4} mol, 1.1eq.) gave the expected product as a clear liquid. The compound was purified by column chromatography using CH_2Cl_2 as eluent (to remove phosphines), followed by mixtures of ethyl

acetate/hexane in a gradient from 20% to 60% with respect to the ethyl acetate. This gave a white semi-solid, which could not be forced to solidify despite several attempts.

This reaction was never complete, and significant amounts of starting materials were always isolated, even under prolonged reaction conditions of up to 5 days at room temperature. The yields for this reaction were also extremely varied, from 12% to 63% (40% to 86%, based on recovered starting material). An average yield of 38% was calculated for 12 reactions.

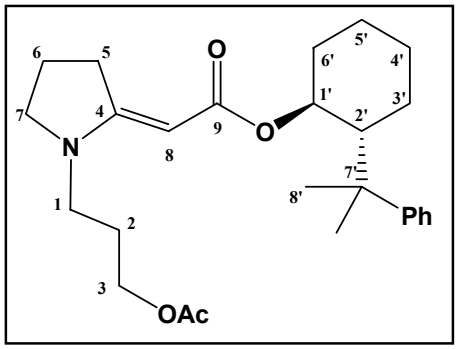
R_f = 0.57 in 1:1 ethyl acetate/hexane

IR Absorptions υ_{max}/cm^{-1} = 3452 (br –OH), 2933, 2858, 1740 (s, C=O), 1673, 1591, 1238, 1140, 1050, 788, 766, 732, 701

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.93–1.11 (m, 1 H, -C<u>*H*</u>$_2$-, H-4'a), 1.2–1.4 (m, 2 H, -C<u>*H*</u>$_2$-, H-5'), 1.23 and 1.26 (s, 3 H, -C<u>*H*</u>$_3$, H-8'), 1.42–1.60 (m, 1 H, -C<u>*H*</u>$_2$-, H-4'b), 1.46–1.68 (m, 4 H, -C<u>*H*</u>$_2$-, H-3' and H-6'), 1.90 (app. sept. 2 H, J_1 = 7.6, -C<u>*H*</u>$_2$-, H-2), 1.93–2.05 [m, 3 H, -C<u>*H*</u>C$(CH_3)_2$-, H-2' and H-6], 2.08 (s, 3 H, -COC<u>*H*</u>$_3$), 2.80–3.15 (m, 2 H, -NCC<u>*H*</u>$_2$-, H-5), 3.15–3.22 [t, 2 H, J_1 = 9.3, -NC<u>*H*</u>$_{2(ring)}$-, H-7], 3.29–3.36 (t, 2 H, J_1 = 7.1, -NC<u>*H*</u>$_2$-, H-1), 4.07 (t, 2 H, J_1 = 6.2, -C<u>*H*</u>$_2$O-, H-3), 4.07 (s, 1 H, -C<u>*H*</u>C=O-, H-8), 4.69–4.80 (ddd, 1 H, *J* indeterminate, -C<u>*H*</u>-O-, H1'), 7.0–7.3 (m, 5 H, Ar-<u>*H*</u>)

δ_C (400 MHz; $CDCl_3$), 20.85 (-C=O-<u>C</u>H_3), 21.01 (-<u>C</u>H_2-, C-6), 24.83 (-<u>C</u>H_2-, C-3'*), 25.29 (-<u>C</u>H_2-, C-2), 25.89 (-<u>C</u>H_3, C-8'), 26.11 (-<u>C</u>H_2-, C-6'*), 26.95 (-<u>C</u>H_3, C-8'), 27.42 (-<u>C</u>H_2-, C-4'), 29.17 (-<u>C</u>H_2-, C-5'), 31.67 (impurity), 32.34 (-<u>C</u>H2-, C-5), 34.01 [-<u>C</u>$(CH_3)_2$-, C-7], 42.88 (-N<u>C</u>H_2-, C-1), 51.32 (-<u>C</u>H-, C-2'), 52.54 (-<u>C</u>H_2-, C-7), 53.72 (impurity), 61.25 (-<u>C</u>H_2-, C-3), 72.44 (-<u>C</u>H-O-, C-1'), 78.70 (-<u>C</u>H-C=O, C-8), 124.52, 125.53, 127.65, and 152.05 (Ar-<u>C</u>), 165.16 (<u>C</u>=O), 168.09 (-N-<u>C</u>=), 170.22 (<u>C</u>=OCH_3)

8.10.11 3-(2-[(1*S*,2*S*)-2-(1-methyl-1-phenyl)ethylcyclohexyl]carbonylmethylene)pyrrolidin-1-ylpropyl acetate (–)-[163]



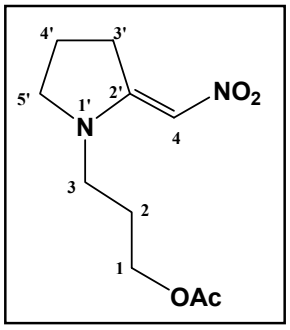
This acetate was isolated as a pale yellow oil from the reaction, according to **GP-3A**, of 3-(2-thioxopyrrolidin-1-yl)propyl acetate (**108**) and bromoacetic acid-(1*S*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexyl ester [(–)-**146**] in CH_3CN. The compound was purified by column chromatography to give a clear gum in 35% yield. The spectroscopic data were the same as for the racemic compound and are not repeated here.

R_f = 0.42 in 1:2 ethyl acetate/hexane

Optical Rotation $[\alpha]_D^{23}$ = –4.8 (c 2.2 in EtOH)

Miscellaneous Compounds with a Pyrrolidinylidene Moiety

8.10.12 3-(2-Nitromethylenepyrrolidin-1-yl)propyl acetate [178]



This compound was obtained by the reaction of 3-(2-thioxopyrrolidin-1-yl)propyl acetate (**108**) with nitromethane according to **GP-3B** as a chromatographically pure (CH_2Cl_2 then EtOAc/hexane) light brown solid. An analytically pure sample was isolated by recrystallisation from ethyl acetate/hexane; yield, 60%, m.p. 75 – 76 °C. Crystals were agglomerates and not suitable for X-ray analysis.

R_f = 0.47 (ethyl acetate)

IR Absorptions υ_{max}/cm^{-1} = 3022, 3011, 2976, 1740, 1588, 1501, 1470, 1436, 1429, 1364, 1335, 1301, 1244, 1221, 1202, 1162,

1079, 1049, 798, 686, 682.

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.89-2.04 (m, 2 H, -C$\underline{H}_2$-, H-2), 2.15 (s, 3 H, C$\underline{H}_3$), 2.07-2.19 (m, 2 H, -NCCH$_2$C$\underline{H}_2$-, H-4'), 3.35 [t, 2 H, J = 7.1, -NC$\underline{H}_{2(ring)}$, H-5'], 3.48 (t, 2 H, J = 7.5, -NC$\underline{H}_2$, H-3), 3.58 (t, 2 H, J = 7.1, -NCC$\underline{H}_2$, H-3'), 4.14 (t, 2 H, J = 6.8, -OC$\underline{H}_2$, H-1), 6.68 (s, 1 H, C$\underline{H}$, H-4)

δ_C (400 MHz; $CDCl_3$) 20.48 ($\underline{C}H_3$), 20.84 (C-3'), 25.34 (-$\underline{C}H_2$-, C-2), 34.49 (-NCCH$_2\underline{C}$H$_2$-, C-4'), 44.13 (-N$\underline{C}$H$_2$, C-3), 54.08 [N$\underline{C}$H$_{2(ring)}$, C-5'], 61.14 (-O$\underline{C}$H$_2$, C-1), 109.09 (-$\underline{C}$H, C-4), 163.79 (-N$\underline{C}$=, C-2'), 170.82 ($\underline{C}$=O)

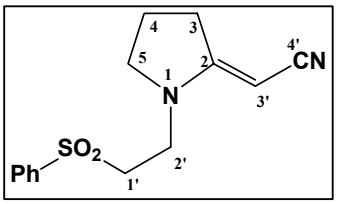
8.10.13 *N*-Boc protected enaminones

Several attempts at producing any compound from the sulfide contraction of 2-thioxopyrrolidine-1-carboxylic acid *tert*-butyl ester [**117**] with a range of activated methylene compounds did not produce sufficient material to characterise. The materials tended to be sticky red gums, and TLC analysis showed complex mixtures that always included starting materials, even after several days of reaction. Our only interest in these products was as potential solids for obtaining crystal structures. Hence this route was abandoned.

Pyrrolidin-2-ylidene compounds with an *N*-phenylsulfonyl ethyl group.

A number of attempts were made to synthesise this class of compound in order to provide crystal structures for measurement of key bond angles and lengths. Only the product that gave satisfactory crystals were characterised significantly.

8.10.14 (*E*)-2-{1-[2-(Phenylsulfonyl)ethyl]pyrrolidin-2-ylidene}acetonitrile [174]



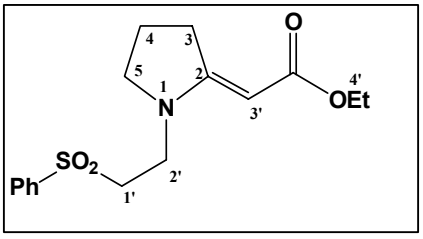
A very fluid clear oil was obtained from the reaction of compound **118** with bromoacetonitrile. The following spectroscopic data were obtained. Further

analysis was not done since this product was not solid.

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.88 [app. pent, 2 H, J_1 = 7.3, -NC(=CH)$CH_2C\underline{H_2}$], 2.75 [t, 2 H,J_1 = 6.9, -NC(=CH)$C\underline{H_2}$], 3.32 (t, 2 H, J_1 = 6.4, -$NC\underline{H_2}$), 3.42 (t, 2 H, J_1 =7.0, -$NC\underline{H_2}$), 3.55 (s, 1 H, -NC=C$\underline{H}$), 3.58 (t, 2 H, J_1 = 6.8, -$SO_2C\underline{H_2}$), 7.5–8.0 (m, 4 H, Ar-$\underline{H}$)

δ_C (400 MHz; CDCl3) 20.59 [-NC(=CH)$\underline{C}H_2$], 32.31 [-NC(=CH)$CH_2\underline{C}H_2$], 39.68 (-$N\underline{C}H_2CH_2S$), 51.43 (-$NCH_2\underline{C}H_2S$*), 53.67 (-$N\underline{C}H_2$*), 55.31 (-NC=$\underline{C}$H*), 121.55 (-$\underline{C}\equiv$N), 127.68, 129.36, and 138.72 (Ar-$\underline{C}$), 164.82 (-N$\underline{C}$=CH)

8.10.15 (1*S**,2*R**)-2-(2-Phenylpropan-2-yl)cyclohexyl 2-{1-[2-(phenylsulfonyl)ethyl]pyrrolidin-2-ylidene}acetate [177]



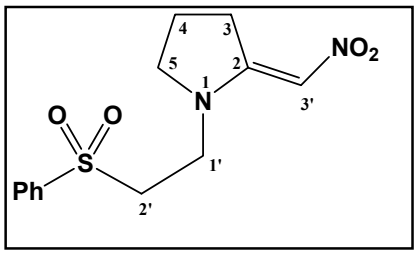
Isolated from the reaction of ethyl bromoacetate and 1-(-2-phenylsulfonylethyl)pyrrolidine-2-thione [**118**] by **GP-2B**:

The following data were collected for this product, which was isolated as a yellow solid, but no suitable X-ray quality crystals were grown.

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.01–1.41 (m, 5 H, -$C\underline{H_2}$-), 1.21 and 1.32 (two s, 3 H, -CH_3), 1.51–1.72 (m, 3 H, -$C\underline{H_2}$-), 1.79 [app. pent, 2 H, J_1 = 7.7, -NC(=CH)$CH_2C\underline{H_2}$], 1.8–2.1 (m, 1 H, -OCHC$\underline{H}$), 2.80-2.91 [m, 2 H, -NC(=CH)$C\underline{H_2}$*], 1.2.95–3.10 (m, 2 H, -$NC\underline{H_2}$*), 3.24–3.34 (m, 2 H, -$NC\underline{H_2}$*), 3.55 (t, 1 H, J_1 = 6.7, $SO_2C\underline{H_2}$), 3.88 (s, 1 H, -NC=C$\underline{H}$), 4.65–4.70 (m, 1 H, -OC$\underline{H}$-), 7.1–8.0 (m, 10 H, Ar-$\underline{H}$)

Unassigned δC (400 MHz; CDCl3) 20.86, 24.71, 25.99, 26.24, 26.51, 27.25, 31.92, 33.86, 39.56, 39.93, 51.14, 51.71, 52.57, 72.52, 79.96, 124.52, 125.44, 127.52, 127.58, 129.32, 133.91, 138.98, 151.82, 163.24, 167.72

8.10.15 2-(Nitromethylene)-1-[2-(phenylsulfonyl)ethyl]pyrrolidine [179]



Isolated as a pale-orange solid in a yield of 48% from the reaction of nitromethane and 1-(2-phenylsulfonylethyl)pyrrolidine-2-thione [**118**] by **GP-2B**.

The product was purified by a short silica column followed by recrystallisation from ethyl acetate. A suitable single crystal was grown by from ethanol/acetone/water mixtures.

The following data were obtained for the product, which was usually contaminated with some PPh_3O or PPh_3S.

R_f = 0.43 in 1:1 ethyl acetate/hexane

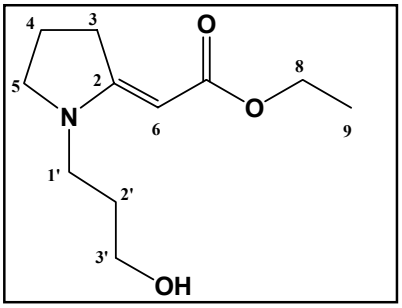
NMR Data	δ_H	(200 MHz; $CDCl_3$; TMS) 2.03 [app. pent, 2 H, J_1 = 7.4, -NC(=CH)$CH_2C\underline{H_2}$], 3.36 (app. q, 4 H, J_1 = 6.5, -NC(=CH)$C\underline{H_2}$* and -$NC\underline{H_2}$*), 3.69 (app. pent, 4 H, J_1 = 6.8, -$NC\underline{H_2}$* and -$SO_2C\underline{H_2}$*), 6.54 (s, 1 H, -NC=C$\underline{H}$), 7.58–8.00 (m, 6 H, Ar-$\underline{H}$ – including some PPh_3O impurity)
	δC	(400 MHz; CDCl3) 20.54 [-NC(=CH)$\underline{C}H_2$], 34.22 [-NC(=CH)$CH_2\underline{C}H_2$], 40.43 (-$N\underline{C}H_2CH_2S$), 51.65 (-$NCH_2\underline{C}H_2S$*), 54.44 (-$N\underline{C}H_2$*), 109.50 (-NC=$\underline{C}$H*), 127.76, 129.50, and 134.49, (Ar-$\underline{C}$), 138.66 (impurity Ar-$\underline{C}$), 163.10 (-N$\underline{C}$=CH)
X-ray		R_1 = 6.04%, Space Group $P2_1/n$
Crystallography		a = 8.1770
		b = 9.0528
		c = 19.2072
		$\alpha = \gamma = 90°$
		β = 98.068°

8.11 Hydrolysis of Acetates

General Procedure for the Hydrolysis of Acetates (GP-4)

The acetate was dissolved in methanol (3 cm^3 per mmol of acetate), and K_2CO_3 (0.1–1.1 eq) was added. The reaction was stirred at RT until the reaction was complete by TLC (1–4 hours). The solution was then filtered through a bed of celite, and the solvent evaporated to give the crude product. The residue was dissolved in chloroform and washed with saturated NaCl. The aqueous phase was extracted with $CHCl_3$ and the combined organic layers dried with Na_2SO_4, filtered and evaporated to give the following products:

8.11.1 Ethyl [1-(3-hydroxy-propyl)-pyrrolidin-2-ylidene] acetate [111]



[1-(3-Acetoxypropyl)pyrrolidin-2-ylidene]acetic acid ethyl ester (**110**, 1.5 g) was dissolved in methanol (10 cm^3) and K_2CO_3 (1 g) added. The reaction was left for 3-5 h. and workup gave of 92–98% of the desired product as an oil. The material foamed significantly under vacuum. An analytical sample was purified by crystallisation from ethyl acetate/hexane to give pale yellow plates.

R_f = 0.14 (50% ethyl acetate/hexane),

R_f = 0.54 in 90:9:1 CH_2Cl_2/methanol/NH_4OH

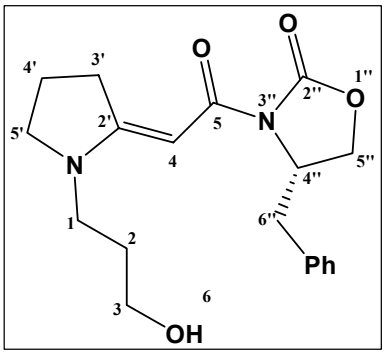
IR Absorptions υ_{max}/cm^{-1} = 3331 (OH), 2982, 2950, 2882, 2702, 1734, 1653, 1558, 1466, 1428, 1373, 1298, 1252, 1194, 1132, 1041, 856

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.25 (t, 3 H, J = 7.1, -OCH_2CH_3, H-9) 1.79 (s, 1 H, -O*H* – signal disappears with D_2O wash), 1.82 (app. pent, 2 H, J_1 = 7.5, -NCH_2CH_2-, H-2'), 1.95 (app. pent, 2 H, J_1 = 6.6, -$NCH_2CH_{2(ring)}$-, H-4), 3.14 (t, 2 H, J = 7.8, =CCH_2-, H-3), 3.31 (t, 2 H, J = 7.1, -N-$CH_{2(ring)}$-, H-5), 3.40 (t, 2 H, J = 7.1, -NCH_2-, H-1') 3.66 (t, 2 H, J = 6.4, -CH_2CO-, H-3'), 4.08 (q, 2 H, J = 7.1, -OCH_2CH_3, H-8), 4.55 (s, 1 H, -C*H*-, H-6, signal shifts to δ = 4.75 after D2O wash, and merges with a broad HDO signal)

δ_C (400 MHz; $CDCl_3$) 14.63 (CH_2CH_3, C-9) 20.95 ($NCCH_2CH_2$, C-4), 28.85 ($HOCH_2CH_2$, C-2'), 32.66 ($NCCH_2$, C-3), 43.01 (NCH_2, C-6), 52.69 (NCH_2, C-1'), 58.24 (CH_2CH_3, C-8), 59.78 ($HOCH_2$, C-3'), 77.29 (CH, C-6), 165.07 (NC=CH, C-2), 169.67 (C=O)

Mass Spec. Data APCI-MS (MeOH) *m/z* 213 (40%, M^+), 196 (15%), 195 (38%), 182 (13%), 169 (100%), 168 (75%), 128 (29%), 110 (24%), 97 (58%), 96 (75%), 41 (13%).

8.11.2 (4*S*)-4-Benzyl-3-{2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]acetyl}oxazolidin-2-one [149]



The alcohol was isolated as a pale-yellow sticky gum after short-column or radial-chromatography (90:9:1 CH_2Cl_2/methanol/NH_4OH) in 87% yield. This reaction was complete in 3 h at RT. The product was contaminated with an unknown impurity, even after repeated chromatography. The polarity of this impurity was so similar to that of the product (as can be seen by the R_f values), that they were not separable. A typical procedure saw the reaction of 3-{2-[2-(*S*)-(4-benzyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propyl acetate (**148**, 100 mg, 2.59×10^{-4} mol, 1eq.) with anhydrous K_2CO_3 (39 mg 2.85×10^{-4} mol, 1.1eq.) in methanol (2 cm^3).

R_f = 0.08 in 1:1 ethyl acetate/hexane

R_f (impurity) = 0.06 in 1:1 ethyl acetate/hexane

R_f = 0.14 in 3:2 ethyl acetate/hexane

R_f = 0.39 in 90:9:1 CH_2Cl_2/methanol/NH_4OH

R_f (impurity) = 0.37 in 90:9:1 CH_2Cl_2/methanol/NH_4OH

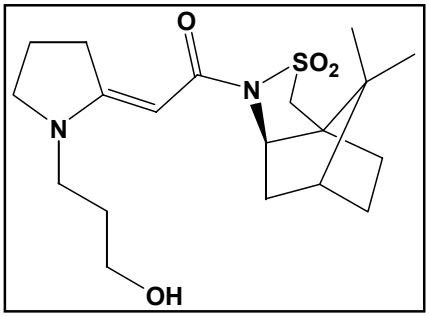
Optical Rotation $[\alpha]_D^{23}$ = 57.9 (c 1.06 in ethanol)

IR Absorptions υ_{max}/cm^{-1} = 3417 (br, OH), 2943, 2876, 1760 (v.s C=O), 1646, 1562, 1483, 1387, 1349, 1296, 1187 (s C–O), 1066, 824, 783, 744, and 704

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.87 (app. pent, 2 H, $NCH_2C\underline{H_2}CH_2C$ H-4') 2.02 (app. pent, 2 H, $NCH_2C\underline{H_2}CH_2OH$, H-2), 2.75 (dd, 1 H, J_1 = 13.3, J_2 = 9.7, $PhC\underline{H_2}$, H-6"a), 3.28 (dt, 2 H, J_1 = 20.4, J_2 = 7.9, $NC\underline{H_2}CH_2CH_2OH$, H-1*), 3.35 (dd, 2 H, J_1 = 13.6, J_2 = 3.5, $NC\underline{H_2}CH_2CH_2C$, H-5'*), 3.48 (m, 1 H, $PhC\underline{H_2}$, H-6"b), 3.2–3.5 [m, 3 H (reduces to 2 H with a D_2O shake), $NCH_2CH_2C\underline{H_2}C$ and $NCH_2CH_2CH_2O\underline{H}$, H-3' and H-6], 3.69 (broad t, 2 H, J = 5.6, $NCH_2CH_2C\underline{H_2}OH$, H-3), 4.1–4.3 (m, 2 H, $NCHC\underline{H_2}O$, H-5"), 4.7–4.8 (m, 1 H, $NC\underline{H}CH_2O$, H-4"), 6.05 (s, 1 H, $CC\underline{H}CON$, H-4), 7.2–7.3 (m, 5 H, Ar-$\underline{H}$)

δ_C (400 MHz; $CDCl_3$) 20.82 ($NCH_2\underline{C}H_2CH_2OH$, C-2), 29.29 ($NCH_2\underline{C}H_2CH_2C$, C-4'), 33.77 ($NCH_2CH_2\underline{C}H_2C$, C-3'), 38.57 ($\underline{C}H_2C_6H_5$, C-6"), 43.14 ($NCH_2CH_2\underline{C}H_2OH$, C-3), 52.93 ($N\underline{C}H_2CH_2CH_2C$, C-5'), 55.29 ($N\underline{C}HCH_2O$, C-4"), 59.33 ($N\underline{C}H_2CH_2CH_2OH$, C-1), 65.45 ($NCH\underline{C}H_2O$, C-5"), 79.15 ($NC\underline{C}HC{=}O$, C-4), 126.85, 128.38, 129.45 and 136.13 (Ar-$\underline{C}$), 154.56 ($N\underline{C}CHC{=}O$, C-2'), 165.08 ($\underline{C}{=}O$, C-5*), 171.11 ($\underline{C}{=}O$, C-2"*).

8.11.3 *(1R,5R,7S)*-1-(-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]ethanone [157]



Alcohol **157** was isolated as a very viscous pale-orange gum from procedure **GP-4** after three hours at RT, by mixing 3-{2-[2-(1*R*,5*R*,7*S*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propyl acetate (**155**, 380 mg, 8.95×10^{-4} mol, 1eq.) with K_2CO_3 (14 mg, 1×10^{-4} mol, 0.1eq.) in methanol (4 cm^3). Attempts to purify the product by chromatography did not result in any significant changes in the spectroscopic properties, and the product remained as a gum. An attempt to distil this product resulted in charring and significant loss of material. The material has an unusual odour of honey.

Yield: 52 – 63 %

Purified by short-column chromatography on silica gel in ethyl acetate, to remove any residual carbonate.

R_f = 0.22 in 1:1 ethyl acetate/hexane

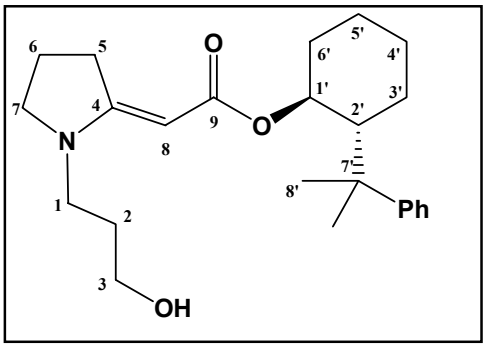
M.p. = 125–129°C

IR Absorptions υ_{max}/cm^{-1} = 3445 (br, OH)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.95 (s, 3 H, CC*H*$_3$, H-11*), 1.19 (s, 3 H, CC*H*$_3$, H-12*), 1.2 – 1.5 (m, 2 H), 1.8 – 2.5 (m, 9 H)(reduces to 8 protons after D_2O shake), 3.1-3.5 (m, 8 H), 3.40 (d, 2 H, J_1 = 5.8, C*H*$_2$SO$_2$, H-2), 3.90 (dd, 1 H, J_1 = 7.1, J_2 = 5.0, SO$_2$NC*H*, H-5), 5.21 (s, 1 H, NC=C*H*, H-14)

δ_C (400 MHz; $CDCl_3$) 19.6 (C<u>C</u>H$_3$, C-11*), 20.0 (NCCH$_2$<u>C</u>H$_2$, C-4”), 20.6 (C<u>C</u>H$_3$, C-12*), 28.8 [<u>C</u>H$_{2(sultam)}$, C-8^{*1}], 31.5 [<u>C</u>H$_{2(sultam)}$, C-9^{*1}], 33.3 (NC<u>C</u>H$_2$, C-3”), 38.4 (CH$_2$<u>C</u>HCH$_2$, C-7), 42.8 (N<u>C</u>H$_2$CH$_2$CH$_2$O, C-3’), 44.3 [<u>C</u>H$_{2(sultam)}$, C-6], 47.2 (NCH$_2$<u>C</u>H$_2$CH$_2$O, C-2’), 47.4 (<u>C</u>CH$_2$SO$_2$, C-1), 52.5 [NCH$_2$CH$_2$CH$_2$<u>C</u>=CH, C-5”], 52.6 (<u>C</u>H$_2$SO$_2$, C-2), 58.8 (<u>C</u>H$_2$O, C-1’), 64.6 (N<u>C</u>H, C-5), 79.0 (NC=<u>C</u>H, C-14), 164.4 (N<u>C</u>=O, C-13), 166.6 (N<u>C</u>=CH, C-2”)

8.11.4 <u>(+)-(1*S*,2*R*)-2-[(2-Phenylpropan-2-yl)cyclohexyl]-2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]acetate (+)-[164]</u>



Isolated as a clear oil from the corresponding acetate (**163**) in 23% yield. Bulb-to-bulb distillation at reduced pressure provided a clean sample for analysis. The corresponding racemate (±)-[**164**] was isolated from racemic acetate **163** in only 5% yield and was not purified or characterised further.

R_f = 0.32 in 1:1 ethyl acetate/hexane (stains yellow in iodine)

Optical Rotation $[\alpha]_D^{23}$ = 12.2 (c 0.9 in methanol)

IR Absorptions υ_{max}/cm^{-1} = 3397 (br –OH), 2928, 2858, 1668 (C=O), 1586 (C=C), 1447, 1142, 1064 (C–O), 911, 731, 700

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.95–1.0 (m, 2 H, -C*H*$_2$-, H-4'a), 1.1–1.6 (m, 2 H, -C*H*$_2$-, H-5'), 1.24 and 1.35 (s, 3 H, -C*H*$_3$, H-8'), 1.40–1.51 (m, 3 H, -C*H*$_2$- and -C*H*$_2$O-, H-4'b and H-3), 1.58–1.68 (m, 4 H, -C*H*$_2$-, H-3' and H-6'), 1.90 (app. sept. 2 H, J_1 = 3.7, -C*H*$_2$-, H-2), 1.92–2.18 [m, 3 H, -C*H*C$(CH_3)_2$-, H-2' and H-6], 2.96–3.13 [m, 2 H, -N(C=)C*H*$_2$-, H-5], 3.23 [t, 2 H, J_1 = 7.3, -NC*H*$_{2(ring)}$-, H-7], 3.35 (t, 2 H, J_1 = 7.1, -NC*H*$_2$-, H-1), 4.05 (br s, 1 H, -C*H*C=O-, H-8), 4.72–4.8 (m, 1 H, -C*H*-O-, H1'), 7.10–7.31 (m, 5 H, Ar-*H*)

Partial assignment based on spectral comparison δ_C (400 MHz; $CDCl_3$) 21.05 (-*C*H$_2$-, C-6), 24.90 (-*C*H$_2$-, C-3'*), 25.88 (-*C*H$_3$, C-8'), 26.18 (-*C*H$_2$-, C-6'*), 27.14 (-*C*H$_3$, C-8'), 27.52 (-*C*H$_2$-, C-4'), 29.01 (-*C*H$_2$-, C-5'), 32.53 (-*C*H2-, C-5), 34.01 [-*C*$(CH_3)_2$-, C-7], 40.17 (-*C*H$_2$-, C-2), 42.99 (-N*C*H$_2$-, C-1), 51.40 (-*C*H-, C-2'), 52.66 (-*C*H$_2$-, C-7), 60.09 (-*C*H$_2$-, C-3), 72.54 (-*C*H-O-, C-1'), 78.39 (-*C*H-C=O, C-8), 124.61, 125.64, 127.71, and 152.05 (Ar-*C*), 164.60 (*C*=O), 168.59 (-N-*C*=)

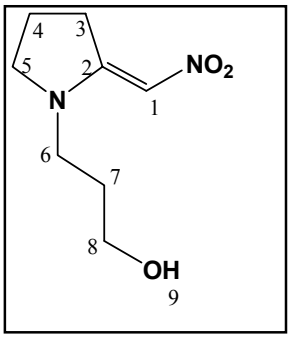
Mass Spec. Data

APCI-MS (MeOH) *m*/*z* 386 (M^+ + 1, 41%) (obtained as a low-resolution APCI-MS)

Exact mass found 385.2616 $g.mol^{-1}$, calculated 385.2617 $g.mol^{-1}$ for $C_{24}H_{35}NO_3$

m/*z* = 385 (11%, M+), 341(21), 266[12, M^+ – $PhCHCH_3)_2$], 186(51), 168(64), 142 (38), 141 (100), 126(36), 119[38, $PhCHCH_3)_2^+$], 97(38), 91(20, $C_7H_7^+$)

8.11.5 3-(2-Nitromethylene-pyrrolidin-1-yl)propan-1-ol [175]



This compound was isolated as brown crystals (recrystallized from EtOAc) from the corresponding acetate, 3-(2-nitromethylenepyrrolidin-1-yl)propyl acetate in a yield of 89%, m.p. 65.0 – 66.5°C. This product had been synthesised in our labs and was known to be solid. Attempts to isolate single crystals suitable for analysis were not successful. The remaining data are only confirmatory of the product.

R_f = 0.23 (50% ethyl acetate-hexane)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.85 (tt, 2 H, *J* = 6.2, H-7), 2.09 (tt, 2 H, *J* = 7.7, H-4), 2.45 (br s, 1 H, H-9), 3.38 (t, 2 H, *J* = 7.3, H-5), 3.45 (t, 2 H, *J* = 8.1, H-6), 3.62 (t, 2 H, *J* = 7.7, H-3), 3.69 (t, 2 H, *J* = 5.9, H-8), 6.85 (s, 1 H, H-1)

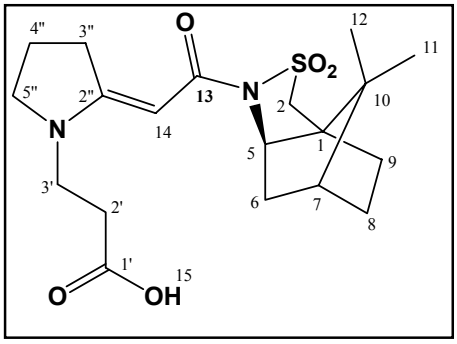
δ_C (400 MHz; $CDCl_3$) 20.20 (C-4), 28.78 (C-7), 34.79 (C-3), 44.29 (C-6), 54.32 (C-5), 58.99 (C-8), 108.41 (C-1), 164.82 (C-2)

8.12 Hydrolysis of Propanoate Esters

General Procedure for the Ester Hydrolysis (GP-5) and Cyclisation via a Mixed Anhydride

The propanoate was dissolved in ethanol (3 cm^3 per mmol of ester), and NaOH (1.0 eq) was added. The reaction was heated under reflux until the reaction was complete by TLC (20 min–2 hours). The solution was then filtered through a bed of celite, and the solvent evaporated to give a crude residue. The residue was dissolved in chloroform and shaken up with an equal volume of water. HCl (~ 1 M) was carefully added until the aqueous layer was neutral. The aqueous phase was separated and extracted with further portions of $CHCl_3$ or by continuous extraction with ether overnight. The combined organic layers were then thoroughly dried with Na_2SO_4, filtered and evaporated to give the following products:

8.12.1. 3-(2-{[(1*R*,5*R*,7*S*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl]-2-oxo-ethylidene}pyrrolidin-1-yl) propanoic acid [165]



This carboxylic acid was obtained by hydrolysis of the corresponding ester (**156**, 1.00 g, 2.36×10^{-3} mol) in ethanol (20 cm^3) using KOH (132 mg, 1eq) at reflux for 90 min. Careful recrystallisation in a desiccator ($CaCl_2$) gave fine white ribbons. An attempt was made to obtain X-ray crystallographic data, but it was not possible to successfully mount the crystals due to the extremely fine nature of the leaves. This product was not fully characterised since it was always contaminated with traces of the starting material and solvent of recrystallisation. In addition to the low yield, the need for subsequent functional group manipulation made this route to tashiromine unattractive.

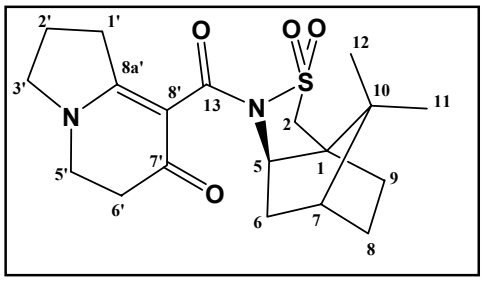
Yield: 21%

R_f = 0.18 in 1:1 ethyl acetate/hexane (compound streaks on TLC)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.90 (s, 3 H, CC*H*$_3$, H-11*), 1.14 (s, 3 H, CC*H*$_3$, H-12*), 1.2 – 1.6 (m, 2 H), 1.8 – 2.1 (m, 5.4 H, 0.4 H = ethyl ester impurity), 2.5–2.74 (t, 2 H, J_1 = 6.5, C=OC*H*$_2$, H-2'), 3.0–3.2 (m, 2 H, NCC*H*$_2$, H-3''), 3.5 (d, 2 H, J_1 = 2.2, C*H*$_2$SO$_2$, H-2), 3.44 (t, 2 H, J_1 = 7.0), 3.52 (t, 2 H, J_1 = 7.2), 3.85 (apparent q, 1 H, J_1 = 6.9 J_2 = 5.0, SO$_2$NC*H*, H-5), 4.14 (q, 0.3 H, J_1 = 7.0, ethyl ester impurity), 5.17 (s, 1 H, NC=C*H*, H-14), 5.87 (br. s, 1 H, O*H*, H-15, this signal disappears with D_2O shake)

δ_C (400 MHz; $CDCl_3$) 19C-1.9 (C*C*H$_3$, C-11*), 20.6 (NCCH$_2$*C*H$_2$, C-4"), 20.9 (C*C*H$_3$, C-12*), 26.6 [*C*H$_{2(sultam)}$, C-8*[1]], 30.7 (NCH$_2$*C*H$_2$C=O, C-2'), 32.6 [*C*H$_{2(sultam)}$, C-9*[1]], 33.4 (NC*C*H$_2$, C-3"), 38.7 (CH$_2$*C*HCH$_2$, C-7), 42.0 (N*C*H$_2$CH$_2$C=O, C-3'), 44.7 [*C*H$_{2(sultam)}$, C-6], 47.6 (*C*CH$_2$SO$_2$, C-1), 47.7 [N*C*H$_2$CH$_2$CH$_2$C=CH, C-5"], 52.8 (*C*H$_2$SO$_2$, C-2), 53.3 [*C*(CH$_3$)$_2$, C-10], 64.9 (N*C*H, C-5), 80.0 (NC=*C*H, C-14), 164.9 (N*C*=O, C-13), 175.0 (N*C*=CH, C-2"), 192.8 (C=O, C-1')

8.12.2 8-(1*R*,5*R*,7*S*)-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane-4-carbonyl)-2,3,5,6-tetrahydro-1H-indolizidin-7-one [159]



The carboxylic acid (**165**, 1.47 g, 3.69×10^{-3} mol, 1eq) was dissolved in acetonitrile (20 cm^3). Acetic anhydride (753 mg, 0.696 cm^3, 7.38×10^{-3} mol, 2eq) and potassium carbonate (1.02 g, 7.38×10^{-3} mol, 2eq) were added to form the mixed anhydride at RT for 16 h. Washing with water (20 cm^3) and extraction of the aqueous phase with CH_2Cl_2

(2×20 cm^3), followed by drying of the combined organic phase and evaporation of the solvent, gave a white crystalline powder (950 mg). This powder was recrystallised from ethanol (to which a few drops of ethyl acetate had been added) to give 859 mg of mustard-coloured leaves (62% yield).

R_f = 0.12 in 1:1 ethyl acetate/hexane (an almost identical R_f to the starting material makes reaction monitoring difficult, but this compound does not streak, while in this solvent system the starting material does.)

Optical Rotation		$[\alpha]_D^{23}$ = –4.5 (c 1.9 in methanol)
Elemental Analysis		Found: C, 60.61 ; H, 7.44 ; N, 7.59 Calculated for $C_{19}H_{26}N_2O_4S$: C, 60.29; H, 6.92; N, 7.40
IR Absorptions KBr		υ_{max}/cm^{-1} = 2975 (C–H), 1703 (C=O), 1669 (C=O), 1635 (C=C), 1584, 1523, 1455, 1378 (S=O), 1290 (C–N), 1199 (S=O), 1087, 1050, 1010, 906, 857, 721, 513,
NMR Data	δ_H	(200 MHz; $CDCl_3$; TMS) 0.95 (s, 3 H, -CC<u>*H*</u>$_3$, H11*), 1.2–1.5 (m, 2 H), 1.32 (s, 3 H, -CC<u>*H*</u>$_3$, H12*), 1.8–1.9 (m, 3 H), 2.0–2.2 (m, 3 H), 2.02 (dd, 1 H, J_1 = 13.4, J_2 = 7.8), 2.45 (dt, 1 H, J_1 = 16.1, J_2 = 6.7, C=OC<u>*H*</u>$_2$, H-6a'), 2.7–2.8 (m, 2 H), 3.12 (dt, 1 H, J_1 = 17.9, J_2 = 8.8, NCC<u>*H*</u>$_2$, H-1a'), 3.36 (AB quartet, 2 H, J_1 = 32.4, J_2 = 13.7, C<u>*H*</u>$_2$$SO_2$, H-2), 3.47–3.59 (m, 4 H), 3.94 (br. q, 1 H, $J_1 \approx 6$, SO_2NC<u>*H*</u>, H-5)
	δ_C	(400 MHz; $CDCl_3$) 20.1 (C<u>*C*</u>H_3, C-11*), 20.3 (NCCH_2<u>*C*</u>H_2, C-2'), 21.1 (C<u>*C*</u>H_3, C-12*), 26.8 [<u>*C*</u>$H_{2(sultam)}$, C-8*1], 31.5 (NCH_2<u>*C*</u>H_2C=O, C-6'), 32.7 [<u>*C*</u>$H_{2(sultam)}$, C-9*1], 34.6 (NC<u>*C*</u>H_2, C-1'), 37.9 (CH_2<u>*C*</u>HCH_2, C-7), 44.4 (N<u>*C*</u>H_2CH_2C=O, C-5'), 44.7 [<u>*C*</u>$H_{2(sultam)}$, C-6], 47.75 (<u>*C*</u>C$H_2$$SO_2$, C-1), 47.76 [N<u>*C*</u>H_2CH_2CH_2C=CH, C-3'], 52.8 (<u>*C*</u>$H_2$$SO_2$, C-2), 54.1 [<u>*C*</u>$(CH_3)_2$, C-10], 64.4 (N<u>*C*</u>H, C-5), 84.4 (NC=<u>*C*</u>, C-8'), 166.2 (N<u>*C*</u>=O, C-13), 169.0 (N<u>*C*</u>=CH and C=O, C-8a' and C-7')

8.13 Synthesis of Hexahydroindolizines

General Procedures for Effecting Cyclization by in situ Conversion of the Alcohol into an Alkylhalide

8.13.1 Via the iodide - using triphenylphosphine, imidazole, and iodine GP-6A:[125]

The required hydroxypropylpyrrolidine (0.5 – 1 mmol scale, 1.0 eq), was added to either toluene or a 1:1 mixture of toluene and acetonitrile (total volume 100 cm^3 per mole of pyrrolidine compound), and the following reagents added in strict sequence; triphenylphosphine (2.6 eq), imidazole (2.7 eq) and iodine (1.78 eq). These reagents were allowed to dissolve, and then heated together under reflux for 3–12 hours. The reaction was cooled to RT, and sat'd $NaHCO_3$ (50 cm^3) added. The mixture was stirred for 5 minutes. Iodine was then added in portions until the toluene phase remained yellow, and the reaction stirred for 10 minutes. Excess iodine was destroyed by the addition of sodium thiosulfate (10 % aq. solution), and the mixture transferred to a separating funnel using a small amount of acetone to transfer all the products. The toluene layer was separated, extracted with water (2 × 40 cm^3) and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a brown product, purified further by chromatography.

8.13.2 Via the iodide utilising an alkoxide - a modification of GP-6A: - using triphenylphosphine, imidazole, iodine, and sodium hydride GP-6B:

An improved yield was obtained with the above procedure by using the sodium alkoxide instead of the alcohol. Thus, for example, 8-ethoxycarbonyl-$\Delta^{8,8a}$-indolizidine was isolated in a yield of almost 70% from sodium; 3-(2-ethoxycarbonylmethylenepyrrolidin-1-yl)propan-1-olate.

The alkoxide was generated in a separate dry flask as follows: The hydroxypropylpyrrolidine was dissolved or suspended in toluene (~10 cm^3 per mole of pyrrolidine compound). Sodium hydride (1.0 eq was then added in portions at room temperature and stirred under an inert atmosphere until evolution of hydrogen ceased (ca 15 min). The sodium salts were usually insoluble in

toluene. Additional toluene and acetonitrile were then introduced to give a total volume of about 100 cm^3 (approximate ratio of toluene/acetonitrile = 1:1).
The remainder of the procedure is as above in **GP-6A**: addition in strict sequence of triphenylphosphine (2.6 eq), imidazole (2.7 eq) and iodine (1.78 eq), heating under reflux for 3–12 hours, and the usual workup procedure.

8.13.3. Via the iodode – using carbontetraiodide, triphenylphosphine and catalytic pyridine GP-6C:

The required hydroxypropylpyrrolidine (0.5 – 1 mmol scale) was dissolved in pyridine (to give approximately a 0.1 M solution) and cooled to 0°C under an inert atmosphere. A sequential addition of triphenylphosphine (2.0 eq.) and carbon tetra-iodide (1.2eq.) gave a biphasic mixture, which was stirred at room temperature for 18–24hours. The mixture was then cooled to below 15°C and methanol was added to decompose the excess reagent. The solvent was removed *in vacuo* and the resulting crude gum partitioned between water (20cm^3) basified with 25% ammonia solution and dichloromethane (40cm^3). Further extraction of the aqueous layer followed by drying ($MgSO_4$) of the organic phase led to the isolation of the dehydroindolizines. All of these compounds appeared to decompose rapidly in contact with silica gel, as indicated by the presence of a baseline spot on the TLC plate.

8.13.4 Modifications of GP-6C

Procedure **GP-6C** was modified sequentially to try and improve the yield of indolizidine products. Modifications made included:

1) use of triethylamine instead of pyridine,

2) addition of imidazole (up to 1.2 eq) instead of pyridine or in addition to pyridine,

3) no pyridine or other amine,

4) warming the reaction to 65°C and,

5) prolonged reaction – up to 48 hours at room temperature.

These modifications did not result in any improvements in the reaction when judged by TLC, and were therefore abandoned in favour of the more successful procedures described earlier.

8.13.5 Via the bromide – using triphenylphosphine and carbon tetrabromide GP-6E

The relevant 3-hydroxypropyl starting material (1–2 mmol) was dissolved in acetonitrile (10 cm^3 per mmol) in a suitable dry flask. Triphenylphosphine (1.2eq.) was then added and allowed to dissolve under stirring. A gummy substance often separated from the acetonitrile after a few minutes. After 30 minutes at room temperature, carbon tetrabromide (1.2eq.) was added and stirring was continued under nitrogen at for 24hours, or at reflux for 5 hours.

The biphasic mixture was then cooled to below room temperature and any excess reagent was destroyed by addition of methanol. The solvent was removed *in vacuo* to give a dark gum in each case. TLC analysis of the gums showed both unconverted starting material and product dehydroindolizines, but never any traces of intermediate bromide compounds. The product yields appeared to low from TLC, even under extended reaction times at elevated temperatures. The starting material could be recovered by chromatography, but once again the products tended to decompose in contact with silica gel.

8.13.5.1 Using carbon tetrabromide and triphenylphosphine in pyridine.

An attempt was made to modify this procedure by dissolving 2-{[4-(phenylmethyl)-2-oxazolidinone]carbonylmethylenepyrrolidin-1-yl}propanol (120.0 mg, $3.484.10^{-4}$ mol) in pyridine (2 cm^3), and cooling to 0°C before addition of PPh_3 (183.0 mg, $6.968.10^{-4}$ mol, 2 eq) and CBr_4 (115.5 mg, $3.484.10^{-4}$ mol, 1 eq). When the reaction had subsided, the solution was heated to reflux (60 °C) for 6 hours. The usual workup with methanol (10 cm^3), followed by filtering and evaporation of the solvent gave a dark yellow solid (123 mg). Purification of this solid by chromatography resulted in a pale yellow solid (12 mg), which was found to contain mostly unreacted starting material, and triphenylphosphine oxide (98 mg).

8.13.5.2 Using carbon tetrabromide and triphenylphosphine.

A similar attempt at cyclisation of 3-(2-[(1*S*,5*R*,7*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decan-4-yl]carbonylmethylene)pyrrolidin-1-ylpropanol (40.0 mg) using CBr_4 (41.5 mg, $1.25.10^{-4}$ mol, 1.2 eq) in acetonitrile (0.2 cm^3), PPh_3 (41,0 mg, $1.57.10^{-4}$ mol, 1.5 eq), and NEt_3 (15.8 mg, 0.22 cm^3, $1.57.10^{-4}$ mol, 1.5 eq) was conducted at 0°C. After 30 minutes the reaction was allowed to warm to RT and stirred for 50 hours, during which time it changed colour from an initial pale yellow to a deep orange.

The solvent was removed *in* vacuo and CH_2Cl_2 (10 cm^3) was added. This solution was washed with water (15 cm^3), and the aqueous fraction re-extracted with CH_2Cl_2 (2 × 10 cm^3) and ethyl acetate (10 cm^3).

The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give a dark orange oil (101 mg).

Purification of this oil using chromatography (ethyl acetate/hexane mixtures) gave 4 mg (10% yield) of a pale-red oil, whose NMR indicates the presence of the desired product. This procedure, however, was abandoned in favour of other more successful procedures.

8.13.6 – Via chloride - using carbon tetrachloride and triphenylphosphine GP-6F

This procedure is similar to others already mentioned using tetrahalomethanes. To a solution at of 2-[(4-(phenylmethyl)-2-oxazolidinone)carbonylmethylenepyrrolidin–1-yl]propanol (**149**, 100 mg, $2.99.10^{-4}$ mol) and CCl_4 (55.2 mg, 0.035 cm^3, $3.59.10^{-4}$ mol, 1.2 eq) in acetonitrile (0.5 cm^3) at 0 °C, was added PPh_3 (118 mg, $4.50.10^{-4}$ mol, 1.5 eq) and NEt_3 (45.5 mg, 0.063 cm^3, $4.50.10^{-4}$ mol, 1.5 eq).

The solution was stirred at 0 °C for 10 minutes, then allowed to warm to RT, and stirred for 14 hours.

The solvent was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (10 cm^3). This solution was washed with water (30 cm^3), and the aqueous fraction extracted with CH_2Cl_2 (2 × 10 cm^3) and ethyl acetate (20 cm^3).

The combined organic layers were then dried with Na_2SO_4, filtered and evaporated *in vacuo* to give a pale yellow semi-solid (240 mg), which was

purified by chromatography (using a 1:2:2 benzene:CH_2Cl_2:hexane solution to separate the product from triphenylphosphine residues). The isolated oil weighed 53 mg, but NMR studies show significant phosphine contamination and other unidentifiable products.

8.14 Effecting Cyclization via a Tosylate

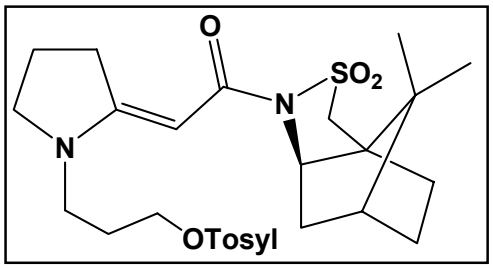
8.14.1 Using tosyl chloride and a base (sodium hydride, butyllithium, or triethylamine/dimethylaminopyridine as a base GP-6G:[236]

A solution of the alcohol (1–4 mmol) in THF, CH_2Cl_2, or acetonitrile (5 cm^3 per mmol alcohol) was cooled to –5°C in an ice/salt bath under nitrogen. The chosen base was then added in excess (1.2eq of a 60% mineral oil suspension of sodium hydride, or 1.1eq of a 1.6 M hexane solution of butyllithium, or 9.4eq of neat triethylamine) under stirring. Note, dimethylaminopyridine (DMAP, 0.1eq) was often added with the triethylamine reactions. The *p*-toluenesulfonyl chloride (1.1 eq) was the added, and the mixture left to stir under nitrogen at 0°C or at RT for several hours, until TLC analysis showed the reaction to be near complete. A white precipitate usually formed within minutes, but TLC showed that the *p*-toluenesulfonyl chloride was never exhausted.

No attempt was made to isolate the tosylate, but rather, any THF or CH_2Cl_2 was removed and replaced with acetonitrile (10 cm^3), and the reaction heated to reflux in an attempt to force cyclization to the indolizidine products.

Evaporation of the solvent and chromatographic separation failed to isolate any characterisable indolizidine product, but often resulted in traces of the starting material as well as some *p*-toluenesulfonic acid. Although no direct attempt was made to isolate the tosyl esters, data often suggests their presence in crude materials. These data also indicate the presence of chloride substitution products.

8.14.2 *(1S,5R,7R)*-3-{2-[2-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propyl-4-toluenesulfonate [176]



Isolated from the reaction of (1*R*,5*R*,7*S*)-1-(-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-[1-(3-hydroxypropyl)pyrrolidin-2-

ylidene]ethanone [**157**] with tosyl chloride via procedure **GP-6G**:

The base used in this reaction was triethylamine with a catalytic amount of dimethylaminopyridine (DMAP). This product, isolated as an orange oil in 12% yield was not characterised fully, but was used directly in the cyclisation procedure. Attempts to purify this oil by distillation or chromatography resulted in complete loss of material.

R_f = 0.24 in 1:1 ethyl acetate/hexane

IR Absorptions (neat): υ_{max}/cm^{-1} = 3447 (br, OH), 3059 (C–H aromatic), 2958, 2696, 2509, 2234, 1975 (and 1912 and 1823, aromatic overtones), 1733 (C=O), 1650 (C=C), 1567, 1342 (S=O), 1176 (S=O and C–O), 1033, 1011, 919, 729

8.15 Effecting Cyclization by *in situ* Mesylate Formation

8.15.1 By employing triethylamine as a base GP-6H

Reaction of the alcohol (~1 mmol) with *p*-methanesulfonyl chloride (1 eq.), and triethylamine (4.0 eq.) in acetonitrile at 0°C gave a white or pale yellow precipitate within minutes. After three hours when the reaction was complete by TLC, the temperature was raised to reflux. TLC analysis of the reaction after several hours showed very faint spots with similar R_f values to the desired indolizidine products. The complex mixture of products, however, deterred further investigation of this method.

8.16 Unsuccessful Cyclization Methods

8.16.1 Using triphosgene and triphenyphosphine:

To a stirred solution of PPh_3 (158 mg, $6.04.10^{-4}$ mol, 2.6 eq) in CH_2Cl_2 (3 cm^3) at 0°C, was added $(CCl_3O)_2CO$ (69.0 mg, $2.32.10^{-4}$ mol, 1.0 eq). The reaction bubbled vigorously, and when the bubbling had stopped, it was stirred for 5 minutes. The solvent was removed *in vacuo*, and 3-(2-[(1*S*,5*R*,7*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decan-4-yl]carbonylmethylene)pyrrolidin-1-ylpropanol (**157**, 10.0 mg, 2.32.10-4 mol, 1.0 eq) in CH_2Cl_2 (1.25 cm^3) was added to the remaining white solid. The resulting yellow solution was stirred at RT for 28 minutes, and the solvent removed once more *in vacuo* to give a pale yellow semi-solid.

Column chromatography of the product gave only triphenylphosphine oxide, and (1*S*,5*R*,7*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane.

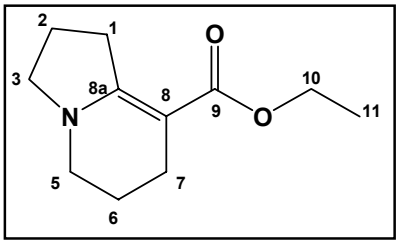
8.16.2 Using triflic anhydride GP-6I

Triflic anhydride (200 mg, 0.12 cm^3, $7.13.10^{-4}$ mol) was placed in a Schlenk tube together with CH_2Cl_2 (1 cm^3), kept under an atmosphere of argon, and cooled to 0 °C. A solution of the required alcohol {2-[(4-(phenylmethyl)-2-oxazolidinone)carbonylmethylenepyrrolidin-1-yl]propanol (**149**, 240 mg, 7.10^{-4} mol) or 3-(2-[(1*S*,5*R*,7*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decan-4-yl]carbonylmethylene)pyrrolidin-1-ylpropanol (**157**, 100 mg, $2.79.10^{-4}$ mol)} in CH_2Cl_2 (3 cm^3). was added via a cannula with stirring. Once the solution had cooled to 0 °C, pyridine (10 eq), was added, and the reaction stirred at 0 °C for 1 hour. The solvent was removed *in vacuo*, and the resulting slurry diluted with CH_2Cl_2 (20 cm^3), washed with water (10 cm^3), neutralized with Na_2CO_3 and washed with sat'd NaCl solution (10 cm^3). The remaining organic phase was dried with Na_2SO_4, and evaporated. TLC analysis always showed several spots, and these products were difficult to isolate and characterise

8.17 Hexahydroindolizines

8.17.1 1,2,3,5,6,7-Hexahydroindolizine-8-carboxylic acid ethyl ester [112]

(8-Ethoxycarbonyl-$\Delta^{8,8a}$-indolizidine)



8-Ethoxycarbonyl-$\Delta^{8,8a}$-indolizidine was isolated as a dark brown gum from 1-(3-hydroxypropyl)-2-ethoxycarbonylmethylenepyrrolidine (**111**), using procedure **GP-6A** (45%), **GP-6B** (69% yield), or **GP-6C** (yields varied from 10 to 31%). The product could be purified by chromatography on silica gel to give a pale red-brown oil. This oil solidified, but also darkened rapidly on standing or in contact with silica gel or even in glass sample vials. Washing the sample vials with a base prior to storage did not reduce this effect.

Several attempts were made to try and identify the decomposition products without success. A fresh sample (500 mg) was rapidly purified by radial chromatography and immediately subjected to spectroscopic analysis, giving the values in the table below. Half of this sample was then left for several days in contact with silica gel. The sample darkened visibly within hours, and was almost black within two weeks. Spectroscopic analysis of this decomposing sample was conducted at regular intervals, but no difference was apparent. IR shows some splitting of two bands; the band at 1597 splits into two at 1603 and 1587, and the band at 1101 splits into two at 1109 and 1100. The rest of the bands are identical. NMR analysis shows some signal broadening, which could be due to suspended silica gel particles, but no new signals were detected. Low resolution MS shows some slight changes, including a small peak at m/z = M+16, indicating the possibility of an oxidation product, possibly the N-oxide, however, no confirming evidence was obtained by UV-Vis spectroscopy. This product is, however, significantly more polar than the other products and can be clearly seen as a red baseline spot on all TLC analyses. This spot could not be removed from the silica gel, even using very polar solvents.

The most successful reaction could be summarised as follows: Using **GP-6B**, 1-(3-hydroxypropyl)-2-ethoxycarbonylmethylenepyrrolidine (**111**, 1.00 g, 4.83×10^{-3} mol, 1.0eq.) in toluene (50 cm^3), was reacted with NaH (127 mg of a suspension in oil, 1.1eq.). In a separate flask containing toluene (5 cm^3) and acetonitrile (5 cm^3) was prepared the iodination reagent using PPh_3 (3.79 g), imidazole (1.64 g), and iodine (2.69 g). The two solutions were mixed at 0°C and warmed to R.T. while stirring for an hour. Work-up gave the expected product.

R_f = 0.61 in 50% ethyl acetate/hexane (previous 0.72 in the same solvent)[67]
R_f (impurity) = 0 in 50% ethyl acetate/hexane

Elemental Analysis: No satisfactory results were obtained for this compound.

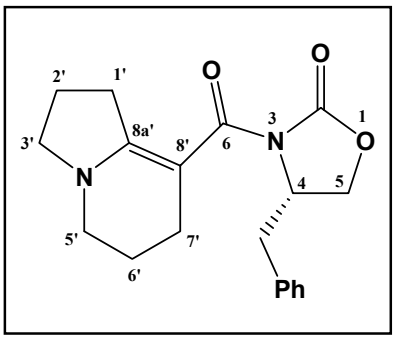
IR Absorptions Thin film from $CDCl_3$ solution.: υ_{max}/cm^{-1} = 2946, 2854, 2361 (chloroform impurity), 1655, 1592, 1285, 1259, 1184, 1104, 943, 721, 543

NMR Data δ_H: (200 MHz; $CDCl_3$; TMS) 1.25 (3H, t, J_1 = 7.1, -$CH_2C\underline{H}_3$, H-11), 1.76 [2H, tt, J_1 = 7.1, J_2 = 5.8, -NC(=C)$CH_2C\underline{H}_2$-, H-2], 1.91(2H, tt, J_1 = 7.6, J_2 = 6.2, -C=C(CO)$CH_2C\underline{H}_2$-, H-6), 2.35 (2H, t, J = 6.2, -C=C(CO)C$\underline{H}_2$-, H-7), 3.05 (2H, t, J = 7.6, -NC$\underline{H}_2$-, H-5), 3.14 (2H, t, J = 5.8, -NC$\underline{H}_2$-, H-3), 3.27 [2H, t, J = 7.1, -NC(=C)C$\underline{H}_2$-, H-1], 4.11 (2H, q, J = 7.1, -C$\underline{H}_2CH_3$, H-10)

δ_C: (400 MHz; $CDCl_3$) 14,68 (-$CH_2\underline{C}H_3$, C-11), 20.80 [-NC(=C)$CH_2\underline{C}H_2$-, C-2], 21.25 [-C=C(CO)$CH_2\underline{C}H_2$-, C-6], 21.41 [-C=C(CO)$\underline{C}H_2$-, C-7), 32.54 [-NC(=C)CH_2-, C-1], 44.84 (-N$\underline{C}H_2$, C-5), 52.78 (-N$\underline{C}H_2$, C-3), 58.24 (-$\underline{C}H_2CH_3$, C-10), 87.29 (-C=$\underline{C}$CO, C-8), 159.04 (-$\underline{C}$=CCO, C-8a), 168.66 (-C=O, C-9)

Mass Spec. Data: Exact mass 195.1262 calculated 195.1259 for $C_{11}H_{17}NO_2$
m/z = 195 (63%, M^+), 166(71%, $M^+ - C_2H_5$), 150(99%, $M^+ - C_2H_5O$), 123(50), 122(100%, $M^+ - C_2H_5O - CO$), 120(27)

8.17.2 (*S*)-4-Benzyl-3-[1,2,3,5,6,7-hexahydroindolizin-8-ylcarbonyl]oxazolidin-2-one [150]



All attempts to produce this product from (4*S*)-4-benzyl-3-{2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]acetyl}oxazolidin-2-one [**149**] gave extremely complex mixtures that did not produce significant isolated quantities of the expected indolizidine.

Some of the data were obtained on these crude mixtures or the best purified fractions we were able to obtain. For example, **GP-6F** gave an oil (53 mg) with the following properties:

Rf: 0.66 in 1:1:2:2 acetone/hexane/benzene/CH_2Cl_2

NMR of this product shows signs of both an oxazolidinone skeleton and a pyrrolidine section, but is also heavily contaminated with triphenylphosphine or triphenylphosphine oxide residues. Low resolution MS of the oil shows a small peak at m/z = 362, together with a corresponding peak at 364.

8.17.2.1 Attempted formation of chloride and subsequent cyclization via halogen exchange:

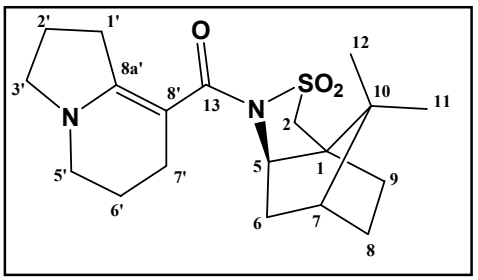
The above procedure was repeated with 6 equivalents of NEt_3, to give a brown oil (21 mg) that was dissolved in acetonitrile (1 cm^3), and NaI (9.0 mg, 5.0.10–5 mol) added, together with $NEt(iPr)_2$ (0.01 cm^3, 6.10^{-5} mol).

The reaction was stirred at RT for 23 hours, but TLC showed no new product, and no NaCl was visible as a precipitate.

R_f = 0.36 in 1:1 ethyl acetate:hexane

R_f = 0.47 in ethyl acetate

8.17.3 (1*S*,5*R*,7*R*)-4-[(1,2,3,5,6,7-Hexahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane [158]



(1*R*,5*R*,7*S*)-1-(-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]ethanone (**157**, 350 mg, $9.15.10^{-4}$ mol, 1.0 eq), triphenylphosphine (640 mg, $2.4.10^{3}$ mol, 2.6 eq), imidazole (166 mg, $2.47.10^{3}$ mol, 2.7 eq) and iodine (413 mg, $1.63.10^{3}$ mol, 1.78 eq) under reflux in toluene (35 cm^3) and acetonitrile (15 cm^3) for 3 hours. The crude gum was purified by rapid chromatography on silica gel (using 50:50 ethyl acetate/hexane as eluent) to give the $\Delta^{8,8a}$-indolizidine in a modest yield of 48% (160 mg).

This product darkened on storage or in contact with silica gel, and hence even rapid chromatography did not produce extremely pure material. A small sample was purified by sublimation in an attempt to obtain accurate mass and elemental data.

M.p. = 193–198°C (dec.)

M.p. (sublimed material) = 218–220°C (dec.)

R_f = 0.51 (1:1 ethyl acetate/hexane)

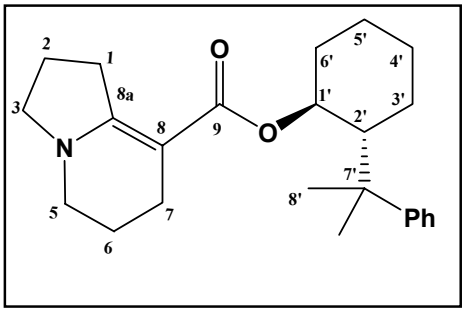
Elemental Analysis	Found: C, 62.63 ; H, 7.75 ; N, 7.69 Calculated for $C_{19}H_{28}N_2O_3S$: C, 62.61; H, 7.74; N, 7.69; O, 13.17; S, 8.80
IR Absorptions Thin film evaporated on NaCl	υ_{max}/cm^{-1} = 2955 (C–H), 1637 (C=O), 1558 (C=C), 1484, 1373 (S=O), 1292 (C–N), 1189 (S=O), 1093, 1049, 1026, 908, 731, 513
NMR Data δ_H	(200 MHz; $CDCl_3$; TMS) 0.95 (s, 3 H, -CC*H*$_3$, H11*), 1.13–2.05 (m, 12 H), 1.25 (s, 3 H, -CC*H*$_3$, H12*), 2.39 (dt, J_1 = 15.3, J_2 = 4.6, 1 H,), 2.72 (ddd, J_1 = 14.6, J_2 = 9.6, J_3 = 4.3, 1 H), 3.0 (ddd, J_1 = 8.6, J_2 = 5.7, J_3 = 5.4, 1 H,), 3.11–3.42 (m, 4 H,), 4.15 (t, 1 H, J_1 = 5.4,)

δ_C	(400 MHz; $CDCl_3$) 20.01 (C-2), 20.77 (C<u>C</u>H$_3$, C11*), 21.01 (C<u>C</u>H$_3$, C12*), 21.51, 23.16, 26.81 (C-8), 32.90 (C-1'), 32.93 (C-7'), 37.49 (C-6'), 45.01, 45.38, 47.63 (C-1*[1]), 47.80 (C-10*[1]), 52.75 (C-4'), 53.44 (C-2), 65.16 (C-5), 92.31(C-8'), 163.13 (C-8a'), 167.27 (C-13)
Mass Spec. Data	Exact mass found 364.1832 g.mol^{-1} calculated 364.1821 g.mol^{-1} for $C_{19}H_{28}N_2O_3S$ *m/z* = 364 (12%, M+), 151 (10%), 150 (100%), 122 (4%), 120 (4%).

Attempted formation via the tosyl ester

The in situ formation of the tosyl ester was not very successful, but a small amount of the suspected *(1S,5R,7R)-3-{2-[2-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]-pyrrolidin-1-yl}-propyl-4-toluenesulfonate* [**176**] was heated in acetonitrile at reflux in an attempt to force the S_N2 displacement of the tosyl leaving group. No indolizidine product was detected by TLC.

8.17.4 <u>(1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate [166]</u>



Successfully isolated in very low yield of 5% (7mg) from (+)-(1*S*,2*R*)-2-[(2-phenylpropan-2-yl)cyclohexyl]-2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]acetate (+)-[**164**] using procedure **GP-6B**. The product was not fully characterised.

IR Absorptions Thin film	υ_{max}/cm^{-1} = 2933 (C–H), 2856, 1654 (C=O), 1589 (C=C), 1284, 1259, 1184, 1108, 1035, 909 (s) (CH_2 γ in cyclohexanes), 760 (w), 733 (s), 701 (w)

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.15–1.3 (m, 3 H, -C<u>*H*</u>$_2$-, H-5', H3'a), 1.24 and 1.35 (s, 3 H, -C<u>*H*</u>$_3$, H-8'), 1.40–2.20 (m, 12H, -C<u>*H*</u>$_2$-, -C<u>*H*</u>-, H-2, H-2', H-3'b, H-4', H-6, H-6', and H-7), 2.88 [app. septet, 2H, J_1 = 7.4, -N(C=)C<u>*H*</u>$_2$-, H-1], 3.08 (t, 2 H, J_1 = 5.6, -NC<u>*H*</u>$_2$, H-5), 3.22 (t, 2H, J_1 = 7.0, H-3), 4.82–4.95 (m, 1H, -O-C<u>*H*</u>, H-1'), 7.0–7.4 (m, 5H, Ar-<u>*H*</u>)

δ_C (200 MHz; $CDCl_3$) 20.91 (-<u>C</u>H$_2$-, C-6*), 21.11 (-<u>C</u>H$_2$-, C-3'*), 21.40 [-C=C(CO)<u>C</u>H$_2$-, C-7*], 24.91 (-<u>C</u>H$_3$, C-8'), 25.75 (-<u>C</u>H$_2$-, C-4'*[1]), 26.16 (-<u>C</u>H$_2$-, C-6'*[1]), 27.54 (-<u>C</u>H$_3$, C-8' and -<u>C</u>H$_2$-, C-5'), 32.43 [-NC(=C)CH$_2$-, C-1], 34.34 [-NC(=C)CH$_2$<u>C</u>H$_2$-, C-2], 40.26 [-<u>C</u>(CH$_3$)$_2$-, C-7'], 44.93 (-N<u>C</u>H$_2$, C-5), 51.51 (-<u>C</u>H-, C-2'), 52.84 (-N<u>C</u>H$_2$, C-3), 72.15 (-<u>C</u>H-O-, C-1'), 88.16 (-C=<u>C</u>CO, C-8), 124.67, 125.62, 127.66, and 152.03 (Ar-<u>C</u>), 159.06 (-<u>C</u>=CCO, C-8a), 167.65 (<u>C</u>=O, C-9)

8.18 Reduction of the C=C Bond

Many reducing agents and variations of conditions were attempted in order to find suitable reducing conditions for the systems under study. The reagents included hydrides, metal catalysis, and boranes, while the variations included time, temperature, addition order, solvents, and co-reagents. Below are listed only the most commonly used methods and some modifications, or those that met with the most success.

8.18.1 Reduction with Sodium Cyanoborohydride GP-7A

The compound to be reduced was dissolved in absolute ethanol to give a very dilute solution of approximately 0.01 M. This was stirred under an inert atmosphere and sodium cyanoborohydride (0.8 mol eq) was added, followed immediately by 1 drop of bromocresol green (0.5 % in ethanol). HCl conc. was then added dropwise to maintain the reaction solution acidic (indicated by a yellow colour). This addition was best done with a micro-syringe, to minimise the drop size. The reaction was stirred for 2 hours, and was then worked-up by the addition of water (about 20% of the reaction volume) and the solution made basic (pH 8) by the addition of NH_3 (aq.).

The solution was extracted with ether (3 × 20 cm^3) and the combined organic phases washed with sat'd. NaCl (10 cm^3). The organic layer was dried with $MgSO_4$, filtered and evaporated to give the crude products as pale oils or brown solids. These were purified by chromatography.

8.18.2 Reduction with Platinum Dioxide GP-7B:

Platinum dioxide (15 mg) was added to glacial acetic acid (3 cm^3) (or methanol 6 cm^3) in a hydrogenation bomb. The bomb was purged with hydrogen for several minutes and pre-hydrogenated for 15 minutes under a slight positive pressure of hydrogen. The compound to be reduced (10–50 times the mass of catalyst) was quickly added, and the reaction stirred at room temperature. The reaction was monitored by TLC and was complete when the starting material had been consumed, or after 48 hours. In most cases these reactions were complete within 2 hours at room temperature.

The catalyst was quickly filtered off, washed with several volumes of acetic acid and kept moist (**DANGER**, the spent catalyst is pyrophoric when dry!). The filtrate was carefully neutralised with 1 M NaOH solution and extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Purification involved recrystallisation and column chromatography.

8.18.3 Using Palladium on Charcoal under an Atmosphere of Hydrogen GP-7C:

This procedure is identical to the one above, except that palladium on charcoal was used instead of platinum dioxide. This procedure was also performed in ethanol in a high-pressure hydrogen bomb at between 2 and 10 atmospheres of hydrogen (by default 3 atm H_2 were used). Work-up was performed as with **GP-7B**, but this catalyst was not found to be as pyrophoric.

8.18.4 Using Sodium Borohydride in Alcoholic Solvent GP-7D:

The relevant precursor (0.1 to 3 mmol) was dissolved either in dry methanol or ethanol (10 – 50 cm^3), and cooled to 0°C. Sodium borohydride (1.5 eq.) was added in one go. The heterogeneous solution was stirred for 4 hours, or until TLC showed the reaction to be complete. A further 1 eq. of sodium borohydride was added in cases where TLC showed unreacted starting material, and the reaction stirred for a further 2 hours at RT. The reaction was worked-up by adding water (5 cm^3) and neutralizing to a pH of 7 with a few drops of dilute (1 M) HCl. $NaHCO_3$ (1 M, 5 cm^3) was then added, and the solution extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic layers were dried with Na_2SO_4, filtered and evaporated to give the crude product, usually as a white or pale yellow solid.

8.18.5 Using Ruthenium BINAP Catalyst under an Atmosphere of Hydrogen GP-7E:

The starting material (50 mg) was dissolved in super-dry ethanol (50 cm^3) in a steel bomb (high pressure autoclave). (–)Ru(BINAP)Cl_2 (15 mg) was added and the bomb flushed with hydrogen gas (using several pump-fill cycles). The bomb was heated to 70°C and pressurised with high-purity hydrogen to 50 atm. The reaction was left to stir for 60hrs. This long time was used because of the difficulty of monitoring the reaction, although an early experiment indicated that 24hrs was not sufficient for the reaction to reach completion. Work-up of this reaction involved cooling the bomb to RT followed by a slow depressurisation. The reaction mixture was filtered through a bed of celite to remove the catalyst, and the solvent evaporated *in vacuo*.

8.18.6 Using Lithium Aluminium Hydride[237]

The starting material (typically 60-600 mg) was dissolved in THF (20 cm^3), and cooled to –40 °C. $LiAlH_4$ (1.5 eq) was added to the reaction in portions of about 20 mg, and then stirred for 1 h at –40 °C. The reaction was monitored by TLC and if incomplete was allowed to warm to 0 °C and stirred for 2 h, and then stirred for a further 12 hours at RT. On several occasions no reaction was observed even after a further 12 h at RT. In these cases more $LiAlH_4$ (0.5 eq) was added, and the reaction stirred at 50 °C for 2–6 hours. This was especially true when aged $LiAlH_4$ was used.

Various procedures were used to worked-up the reaction, including:

i) addition of methanol drop-wise, then filtering through celite and evaporating the solvent.

ii) addition of water or moistened ether, followed by drying (Na_2SO_4) filtering and evaporation.

iii) sequential addition of water (1 cm^3 per gram $LiAlH_4$ used), 15% (w/w) NaOH solution (1 cm^3 per gram $LiAlH_4$ used), and water (3 cm^3 per gram $LiAlH_4$ used), followed by drying, filtering and evaporation of solvent.

Modification 1

Ether was used instead of THF for the reaction. In general not much difference was observed between the use of THF and ether, but the reaction yields were often slightly lower in the latter solvent.

Modification 2 – Reverse Addition

In reverse addition reactions, the compound to be reduced was added to a suspension of $LiAlH_4$ in THF (or ether) previously cooled to between 0 and 5°C in ice. This modification seemed to give slightly improved yields (by about 10%) over the other methods.

Modification 3 – Chelation with magnesium

In an attempt to constrain the chiral auxiliary by chelation was made by the addition of magnesium iodide (generated *in situ* by mixing magnesium and iodine in ether), but there was no improvement in the overall stereoselectivity.

8.18.7 Other attempted reduction methods

8.18.7.1 Using Diisobutylaluminium hydride

The $\Delta^{8,8a}$-indolizidinyl compound (1eq) was dissolved in toluene (50 cm^3) in a dry flask equipped with a septum. The flask was cooled in an ice bath to 0°C and DIBAL (0.14 cm^3 of a 1 M solution in hexane, 1.4×10^{-4} mol, 1eq) was added via syringe. The reaction was warmed to RT and stirred for 12 h, then a heated at reflux for a further 1 h. No evidence of reduction was collected, and the starting material was recovered in 60–80% yield.

8.18.7.2 Using Raney Nickel[238]

The $\Delta^{8,8a}$-indolizidine (200 mg, 1eq) was dissolved in abs. ethanol (50 cm^3) and Raney nickel (15 mg) was added. The reaction was placed in a bomb and flushed under a slow steam of hydrogen gas for 3 minutes. The bomb was sealed and the pressure was raised to 7 atm with hydrogen, while heating to 100°C. The reaction was stirred for 68 h, cooled to RT, filtered over a pad of celite and evaporated *in vacuo*.

8.18.7.3 Using Raney Nickel at high pressure

A pressure of 150 atm was used and a much shorter reaction time of 5 h. The rest of the procedure was the same as described above.

Using Modified Borohydrides

8.18.7.4 Sodium borohydride with cerium(III) chloride[239]

(4*S*)-4-Benzyl-3-[2-(1-methyl-pyrrolidin-2-ylidene)-acetyl]-oxazolidin-2-one (**147**, 40.0 mg, $1.33.10^{-4}$ mol) was dissolved in THF (6 cm^3), and $CeCl_3$ (33.5 mg, $1.26.10^{-4}$ mol, 1.04 eq) was added, and stirred at RT until homogeneous (15 minutes).

$NaBH_4$ (5.5 mg, $1.47.10^{-4}$ mol, 1.1 eq) was added, and the reaction stirred for 18 hours at RT.

The reaction was poured into sat'd NaCl, extracted with ether (2 × 10 cm^3) and CH_2Cl_2 (2 × 10 cm^3), and the combined organic layers dried with Na_2SO_4, filtered and evaporated to give a pale yellow solid (33mg). This was separated using radial chromatography to yield 28 mg of a white solid, which was found by NMR to be unreacted starting material.

8.18.7.5 Sodium cyanoborohydride in the presence of cerium(III) chloride

$CeCl_3$ (90 mg, $3.65.10^{-4}$ mol, 1.1 eq) was added to abs. ethanol (5 cm^3), and stirred at RT for 30 minutes. (4*S*)-4-Benzyl-3-[2-(1-methyl-pyrrolidin-2-ylidene)-acetyl]-oxazolidin-2-one (**147**, 100.0 mg, $3.329.10^{-4}$ mol) was added and allowed to dissolve. $NaBH_3CN$ (23.0 mg, $3.66.10^{-4}$ mol, 1.1 eq) was added, followed by a drop of bromocresol green solution (0.5 % in ethanol), and then conc. HCl was added drop-wise to keep the solution acidic (indicated by a yellow colour). The reaction was stirred until the colour faded to a pale grey.

Water (10 cm^3) was added, followed by enough NH_3 solution to basify the solution.

Extraction of the solution with CH_2Cl_2 (3 × 20 cm^3), drying with Na_2SO_4, filtering and evaporation gave a clear oil (110 mg).

8.18.7.6 Sodium triacetoxyborohydride

$NaBH_4$ (38 mg, 1 mmol) was added to glacial acetic acid (1.15 g, 19.2 mmol, 1.10 cm^3) at RT and stirred until hydrogen evolution had ceased (15 minutes). The white $NaBH(OAc)_3$ could be isolated and stored for several weeks by heating the above solution to 40°C for several hours *in vacuo* to remove residual solvent, but was generally used *in situ* without further purification. In cases of poor solubility of the starting material a co-solvent such as THF or methanol was added. A typical reduction continues as follows: (4*S*)-4-Benzyl-3-[2-(1-methyl-pyrrolidin-2-ylidene)-acetyl]-oxazolidin-2-one (**147**, 100 mg, $3.33.10^{-4}$ mol) was added to the $NaBH(OAc)_3$ solution prepared above, and the reaction stirred at RT for 4 hours. The solvent was evaporated, and CH_2Cl_2 (10 cm^3) added. This was washed with aq. Na_2CO_3, dried with Na_2SO_4 and evaporated to give a clear oil (156 mg, 157%). Crude NMR of this product mixture shows evidence of a reduced product, but even extensive chromatography could not isolate the desired material. Instead only small amounts of chiral auxiliary [**152**] were isolated.

A further modification was attempted, where magnesium iodide (generated *in situ* as the diethyl etherate by reacting magnesium and iodine in ether) was added to the (4*S*)-4-benzyl-3-[2-(1-methyl-pyrrolidin-2-ylidene)-acetyl]-oxazolidin-2-one prior to the addition of $NaBH_4$. The reaction did not show any evidence of reduction of the C=C bond.

8.18.7.7 Sodium borohydride in trifluoroacetic acid

A variation of this method was to use trifluoroacetic acid instead of acetic acid. Again the intermediate sodium tris(trifluoro-acetoxy)borohydride was not isolated, but a strong signal in the IR spectrum of the crude mixture at $\tilde{\nu}$ = 1371 indicates the formation of at least one B–O bond, and the release of hydrogen gas during the reaction is consistent with the formation of this product.

8.18.7.8 Sodium cyanoborohydride in acetic acid

$NaBH_3CN$ (628 mg, 1 mmol) was added to a solution of THF (5 cm^3), methanol (1 cm^3) and glacial acetic acid (1 cm^3), at RT, and stirred until hydrogen evolution had ceased, and the solution was homogeneous (5 minutes)

(4*S*)-4-benzyl-3-[2-(1-methyl-pyrrolidin-2-ylidene)-acetyl]-oxazolidin-2-one (150 mg, $4.99.10^{-4}$ mol) was added in THF (1 cm^3). When effervescence had ceased, (10 minutes), water (5 cm^3) was added, and the solution basified with K_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (3 ×15 cm^3), and the combined organic layers were dried with Na_2SO_4, filtered and evaporated to dryness.

8.18.7.9 Sodium borohydride with nickel(II) chloride

(4*S*)-4-Benzyl-3-[2-(1-methylpyrrolidin-2-ylidene)acetyl]oxazolidin-2-one (**147**, 60 mg, 2.0×10^{-4} mol, 1eq) was dissolved in methanol (5 cm^3) and cooled to –40°C. $NiCl_2{\cdot}6H_2O$ (95.0 mg, 4.0×10^{-4} mol, 2eq) was added, followed by $NaBH_4$ (76 mg, 2.0×10^{-3} mol, 10eq). The initially pale-green solution turned black immediately and was stirred for 1.5 h at this temperature and a further 4 h at RT. No change in the starting material was observable by TLC, so the reaction was stirred for 4 d at RT, during which the reaction became pale green once more, and the starting material was consumed. Workup was done by adding sufficient HCl to neutralise the reaction and then 10 cm^3 of water. The mixture was extracted with ether (2×20 cm^3), CH_2Cl_2 (20 cm^3) and ethyl acetate (20 cm^3). The combined organic fractions were dried (Na_2SO_4), filtered and evaporated to give an opaque white oil (46 mg). ^{13}C NMR indicated some new product with no C=C bond, but this product could not be isolated either by chromatography or by distillation. Attempts to do so resulted in loss of material.

8.18.7.10 Sodium borohydride with cobalt(II) chloride

Similarly to modification 5 above, the reduction was attempted with the addition of cobalt(II) chloride (2.4eq). The initially blue reaction turns black, as with the previous modification. No evidence of reduction was seen from TLC, even after prolonged reaction times. The spectroscopic data shows only recovered starting material (80%).

8.18.7.11 L-Selectride (lithium tri-sec-butylborohydride)

The vinyl compound was treated with L-selectride (1.2 eq) in THF at –78°C over 15 minutes. After the addition was complete the reaction was left to

stir for 30 minutes and saturated ammonium chloride added (2eq). The reaction was allowed to warm to room temperature over 30 minutes and extracted with ether. The NMR analysis and TLC analysis of the crude showed only starting material present, together with traces of cleaved chiral auxiliary (presumably by saponification).

Using Silane

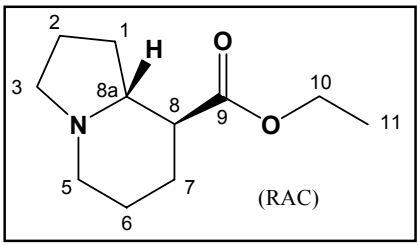
8.18.7.12 Triethylsilane

Triethyl silane (11.6 mg, 1×10^{-4} mol) and trifluoroacetic acid (ca. 0.2 cm^3, 20 fold excess) were mixed together and slowly added to (4*S*)-4-benzyl-3-[2-(1-methyl-pyrrolidin-2-ylidene)-acetyl]-oxazolidin-2-one (**147**, 30 mg, 1×10^{-4} mol, 1eq). The reaction was heated to 50°C for 14 h, but TLC analysis showed no change in the starting material. The reaction was terminated and starting material recovered.

8.19 Racemic Octahydroindolizines

8.19.1 Reductions of 8-ethoxycarbonyl-$\Delta^{8,8a}$-indolizidine to give the *trans*-reduced product (8*S**,8a*R**)-Octahydro-indolizine-8-carboxylic acid ethyl ester [113]

(±)-(trans-8-ethoxycarbonylindolizidine)



*All the diastereomers of 8-ethoxycarbonylindolizidine were initially isolated as an oil from 8-ethoxycarbonyl-$\Delta^{8,8a}$-indolizidine using procedures **GP-7A** to **GP-7E**:*

The product was found as a set of diastereomeric pairs, in major and minor quantities. The *trans*-reduced isomer pair [(8*S*, 8a*R*) or (8*R*, 8a*S*)], was the major product from the reduction with sodium cyanoborohydride (**GP-7A**) (yield of major isomer 60–90%). Traces of the *cis*-reduced product were always present. None of the attempted modifications significantly changed the outcome of this reaction. The major and minor diastereomer pairs could be separated by careful and repeated chromatography on preparative TLC, or flash silica columns.

R_f = *trans* diastereomers = 0.09 (1:1 ethyl acetate/hexane

R_f = *cis* diastereomers = 0.06 (1:1 ethyl acetate/hexane

IR Absorptions υ_{max}/cm^{-1} = 2939, 2782 and 2487 (Bohlmann bands), 2363 (B–H impurity from reductant), 1733 (C=O), 1560, 1540, 1507, 1156, 910.

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.19 (t, 3 H, *J* = 7.1, -$CH_2C\underline{H}_3$, H-11), 1.41–1.51 [m, 2 H, -NCHC$\underline{H}_2$- and -CH(CO)C$\underline{H}_2$-, H-1a and H-7a], 1.59–1.71 (m, 2 H, -$NCHCH_2C\underline{H}_2$-, H-2), 1.71–1.82 [m, 2 H, -$CH(CO)CH_2C\underline{H}_2$-, H-6], 1.92–2.18 (m, 4 H, -C$\underline{H}_2$N(C$\underline{H}_2$)C$\underline{H}$C$\underline{H}_2$-, H-5_{axial}, H-3_{axial}, H-8a, and H-1b), 2.11–2.18 [dd (appears as q), 1 H, J_1 = 18.0, J_2 = 9.1, -CH(CO)C$\underline{H}_2$-, H-7a], 2.23–2.30 (ddd, 1 H, -C$\underline{H}$CO-, H-8), 3.05–3.11 (m, 2 H, -NC$\underline{H}_2$-, H-$3_{equatorial}$ and H-$5_{equatorial}$), 4.16 (q, 2 H, *J* = 7.1, -C$\underline{H}_2CH_3$, H-10)

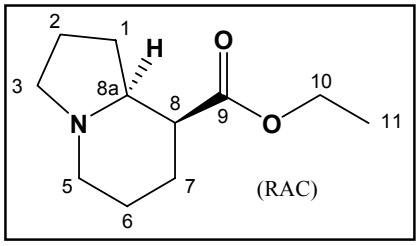
δ_C (200 MHz; $CDCl_3$) 14.15 (-CH_2<u>C</u>H_3, C-11), 20.40 (-NCHCH$_2$<u>C</u>H_2-, C-2), 24.66 [-CH(CO)CH_2<u>C</u>H_2-, C-6], 28.04 [-CH(CO)<u>C</u>H_2-, C-7], 29.07 (-NCH<u>C</u>H_2-, C-1), 48.04 (-<u>C</u>HCO-, C-8), 52.15 (-N<u>C</u>H_2-, C-3*), 53.94 (-N<u>C</u>H_2-, C-5*), 60.08 (-<u>C</u>H_2CH_3, C-10), 65.03 (-N<u>C</u>H, C-8a), 174.26 (<u>C</u>=O)

Mass Spec. Data Exact mass found 197.1429 g.mol^{-1} calculated 197.1416 g.mol^{-1} for $C_{11}H_{19}NO_2$

m/*z* = 197 (48%, M^+), 196(40, M^+ – H), 168(90, M^+ – C_2H_5), 166(50), 152(60, M^+ – OC_2H_5), 150(70), 124(43, M^+ – OC_2H_5 – CO), 122(100), 96(90), 83(45), 70(33), 69(48)

8.19.2 *Cis*-reduced product: (8*R**,8a*R**)-Octahydro-indolizine-8-carboxylic acid ethyl ester [114]

<u>± *(cis-8-ethoxycarbonylindolizidine)*</u>



Procedure **GP-7B** (PtO_2) was most commonly used, since it resulted in a clean reaction with only about 15% of the minor diastereomer pair present. As with the *trans*-8-ethoxycarbonylindolizidine above, these minor diastereomers could be removed from the major product by careful and repeated chromatography, but in this case the lower R_f made complete isolation impossible. The use of **GP-7C** (Pd/C) gave unsatisfactory yields of less than 12%, although the NMR of the crude indicates only small amounts of *trans*-reduced diastereomers are present (estimated 5%).

Procedure **GP-7E** (Ruthenium BINAP) was used with some success, but the product was contaminated with the fully-reduced epitashiromine diastereomers, which were difficult to remove successfully, as well as unreacted starting material, even after 24 hours under 100 atm H_2 at 100°C. The approximate ratio of *cis*- to *trans*-8-ethoxycarbonyl indolizidine (from ^{13}C NMR and HPLC on a chiral column) was found to be 8:1 in favour of the former.

The following data were obtained for the product as a clear oil:

R_f = 0.16 (90:9:1 CH_2Cl_2/methanol/NH_4OH)

IR Absorptions υ_{max}/cm^{-1} = 2938, 2787, 1734, 1462, 1373, 1311, 1197, 1155, 1126, 1047, 915, 782

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.26 (t, 3 H, *J* = 7.1, -CH_2CH_3, H-11), 1.42–1.59 [m, 2 H, -NCHCH_2- and -CH(CO)CH_2-, H-1a and H-7a], 1.62–1.83 [m, 4 H, -NCHCH_2CH_2-, -CH(CO)CH_2CH_2-, H-2, H-6], 1.97–2.20 [m, 4 H, -CH_2N(CH_2)CHCH_2- and -CH(CO)CH_2-, H-5_{axial}, H-3_{axial}, H-1b, and H-7a], 2.75–2.79 (app. q, 1 H, J_1 = 3.3, -CHCO-, H-8), 3.02–3.12 (m, 3 H, -NCH_2-, and -NCH, H-$3_{equatorial}$, H-$5_{equatorial}$, and H-8a), 4.14 (q, 2 H, *J* = 7.1, -C$H_2$$CH_3$, H-10)

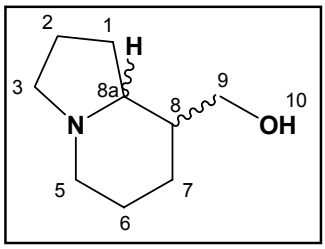
δ_C (200 MHz; $CDCl_3$) 14.24 (-$CH_2$$CH_3$, C-11), 20.53 (-NCHC$H_2CH_2$-, C-2), 22.34 [-CH(CO)C$H_2CH_2$-, C-6], 26.19 [-CH(CO)C$H_2$-, C-7*], 26.54 (-NCHC$H_2$-, C-1*), 41.63 (-C$H$CO-, C-8), 52.93 (-NC$H_2$-, C-3*[1]), 54.77 (-NC$H_2$-, C-5*[1]), 59.76 (-C$H_2$$CH_3$, C-10), 64.42 (-NC$H$, C-8a), 173.15 (C=O)

Mass Spec. Data Exact mass found 197.1433 calculated 197.1416 for $C_{11}H_{19}NO_2$

m/*z* = 197 (38%, M^+), 196(40, $M^+ - H$), 195(22), 168(72, $M^+ - C_2H_5$), 166(52), 152(22, $M^+ - OC_2H_5$), 150(100), 124 (35, $M^+ - OC_2H_5 - CO$), 122(71), 96(55), 83(40), 70(35)

8.19.3 ***(Octahydro-indolizin-8-yl)-methanol [1] and [2]***

(Mixture of racemic tashiromine and racemic epitashiromine)



*Isolated from various procedures, including vigorous reduction of 8-ethoxycarbonyl-$\Delta^{8,8a}$-indolizidine with lithium aluminium hydride (**GP-7F**):*

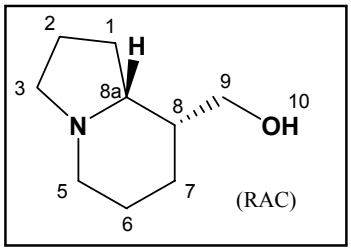
The isolation of all four diastereomers of (octahydro-indolizin-8-yl)-methanol in combined yields of between 23% and 43% was achieved after purification by flash chromatography (using ethyl acetate/hexane mixtures as eluents). The reaction was stopped after 3 h, and the best results were obtained by reverse addition (modification 2), using moist ether work-up. The reaction contained a complex mixture of starting material and product, together with what appears to be an intermediate 8-ethoxycarbonyl indolizidine. This facilitated the decision to not characterise this product fully, especially since both the *syn*- and *anti*-reduced diastereomer pairs were isolated by other procedures.

R_f = 0.08 (ethyl acetate)

IR Absorptions υ_{max}/cm^{-1} = 3354, 2931, 2795, 2722, 2650, 1734, 1652, 1446, 1382, 1330, 1218, 1198, 1164, 1131, 1088, 1042, 913, 892, and 609

8.19.4 (8*R**,8a*R**)(Octahydro-indolizin-8-yl)-methanol [1]

(Racemic tashiromine)



In general reverse addition methods in THF **GP-7F** (modification 2) gave the best results and allowed for the isolation of a clear oil (51 mg, 64%) in under two hours starting from ethyl (8*S**,8a*R**)-octahydro-indolizine-8-carboxylate (**133**, 100 mg). The extremely small R_f of this product makes it difficult to determine when the reaction is complete.

R_f = 0.08 (ethyl acetate)

R_f = 0.14 (90:9:1 CH_2Cl_2/methanol/NH_4OH)

IR Absorptions υ_{max}/cm^{-1} = 3354, 2931, 2795, 2722, 2650, 1652, 1446, 1382, 1330, 1218, 1164, 1088, 1042, 892, and 609

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 1.03 (ddd, 1 H, J_1 = 23.8, J_2 = 12.5, J_3 = 5.2, H-7a), 1.38–1.62 (m, 1 H, H-1a), 1.80–2.03 (m, 2 H, H-1b and H-7b), 1.33–1.61 (m, 1 H, H-8), 1.46–1.80 (m, 1 H, H-8a), 1.58–2.13 (m, 2 H, H-2), 1.63–1.83 (m, 2 H, H-6), 1.90–2.00 (m, 1 H, H-5_{axial}), 2.05 (apparent q, 1 H, J_1 = 15.2, H-3_{axial}), 2.98–3.17 (m, 2 H, H-$3_{equatorial}$ and H-$5_{equatorial}$), 3.42 (dd, 1 H, J_1 = 10.8, J_2 = 6.3, H-9a)(lit.[97] = dd, 1 H, J_1 = 10.0, J_2 = 6.0), 3.61 (dd, 1 H, J_1 = 10.8, J_2 = 4.5, H-9b)(lit.[97] = dd, 1 H, J_1 = 10.0, J_2 = 4.0), ~3.05 (variable) (br. s, 1 H, -O*H*, H-10, disappears when sample is re-run after a D_2O shake)

Note: these multiplets overlap and ranges were determined by double resonance experiments

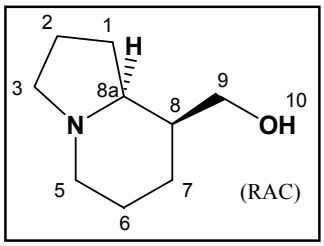
δ_C (400 MHz; $CDCl_3$) 20.6 (C-2), 25.0 (C-6), 27.6 (C-1), 28.9 (C-7), 44.5 (C-8), 52.6 (C-5), 54.1 (C-3), 65.2 (C-9), 66.4 (C-8a)

Mass Spec. Data Low resolution data APEI-MS

m/*z* =156 (7%, $M^+ + H$), 155(61, M^+), 154(64, $M^+ - H$), 138(94 $M^+ - OH$), 124(60, $M^+ - CH_3O$), 122(13), 110(19), 97(67), 96(100), 84(41), 83(48), 70(31), 69(44)

8.19.5 (8*S**,8a*R**)(Octahydro-indolizin-8-yl)-methanol [2]

(*Racemic 8-epitashiromine)*



Isolated from (8*R**,8a*R**)-octahydroindolizine-8-carboxylic acid ethyl ester (**114**, 50 mg) by treatment with lithium aluminium hydride in ether using procedure **GP-7F**.

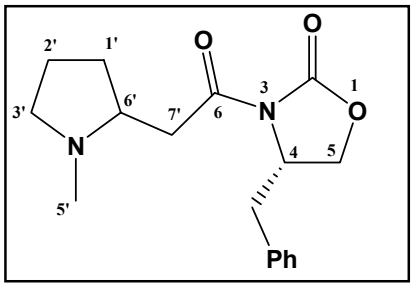
R_f = 0.08 (ethyl acetate)

IR Absorptions υ_{max}/cm^{-1} = 3367(br. OH, lit.[108] = 3370), 2933, 2791, 2750(w), 2733(w), 2641(w), 1664, 1462, 1380, 1326, 1262, 1217, 1158, 1091, 1036, 908, and 731

NMR Data	δ_H	(400 MHz; $CDCl_3$; TMS) 1.02–1.15 (m, 2H, H-1), 1.4–2.0 (m, 2H, H-7), 1.6 (m, 1H, H-8a), 1.6–2.2 (m, 2 H, H-2), 1.7–2.2 (m, 2 H, H-6), 2.0 and 3.0 (m, 4 H, H-3 and H-5), 3.70 (dd, 1 H, J_1 = 8.9, J_2 = 1.9, C$\underline{H}_2$OH, C-9a)(lit.[97] = dd, 1 H, J_1 = 9.2, J_2 = 1.1), 4.18 (dd, 1 H, J_1 = 9.1, J_2 = 4.1, C$\underline{H}_2$OH, C-9b)(lit.[97] = ddd, 1 H, J_1 = 9.2, J_2 = 4.3, J_3 = 1.2), 5.3 (s, 1 H, H-10)
Identification of signals from double resonance experiments	δ_H	(400 MHz; $CDCl_3$; TMS) **H-1ax**, 1.38–1.62, **H-1e**, 1.80–2.03, **H-2ax**, 1.58–2.13, **H-2eq**, 1.58-2.13, **H-3ax**, 1.97–2.13, **H-3e**, 2.98–3.17, **H-5ax**, 1.90–2.00, **H-5e**, 2.98–3.17, **H-6ax**, 1.63–1.83, **H-6e**, 1.63–1.83, **H-7ax**, 1.03, **H-7e**, 1.80–2.03, **H-8**, 1.33–1.61, **H-8a**, 1.46–1.80, **H-9a**, 3.42, **H-9b**, 3.61, **H-10**, 3.01
{} = related Lit.[97] values	δ_C	(400 MHz; $CDCl_3$) 19.4 (C-2){20.8}, 22.7 (C-6){23.2}, 26.3 (C-1){25.8}, 27.7 (C-7){ 30.5}, 35.2 (C-8){35.4}, 52.4 (C-5){53.5}, 53.8 (C-3){54.8}, 64.0 (C-9){65.6}, 65.1 (C-8a){66.8}

8.20 Chiral Pyrrolidinyl Compounds

8.20.1 (4*S*)-4-Benzyl-3-[2-(1-methylpyrrolidin-2-yl)acetyl)oxazolidin-2-one [151]



Several attempts at isolating this compound led only to recovered starting material or mixtures of diastereomers, shown in **Table 11** for the attempted reduction of 1-methyl-2-[(4*S*)-4-(phenylmethyl)-2-oxazolidinone]carbonylmethylenepyrrolidine [**147**].

Table 11 – Conditions for the reduction of **147**

147 **mass, mmol**	Procedure (reductant)	Solvent (volume), time	Temp, pressure	Products (yield) and Comments
200 mg, 0.665 mmol	**GP-7B** (PtO_2/H_2)	glacial acetic acid (3 cm^3), 90 min	R.T., 1 atm.	auxiliary [**132**] (30-40%)
200 mg, 0.665 mmol	**GP-7B** (PtO_2/H_2)	glacial acetic acid (3 cm^3), 40 min	R.T., 1 atm.	auxiliary [**132**] (10%) starting material (70%)
200 mg, 0.665 mmol	**GP-7B** (PtO_2/H_2)	methanol (3 cm^3), 2 h	R.T., 1 atm.	auxiliary [**132**] (20%) starting material (60%)
200 mg, 0.665 mmol	**GP-7B** (PtO_2/H_2)	methanol (10 cm^3), 4 h	R.T., 1 atm.	auxiliary [**132**] (18%) starting material (65%)
200 mg, 0.665 mmol	**GP-7B** (PtO_2/H_2)	methanol (10 cm^3), 8 h	R.T., 1 atm.	auxiliary [**132**] (55%)
100 mg, 0.333 mmol	**GP-7C** (Pd/C)	ethanol (10 cm^3), 6 h	40°C., 3 atm.	starting material (87%) Note 1
35.6 mg, 0.118 mol	**GP-7D** $NaBH_4$	methanol (10 cm^3) 8 h or 21 h	R.T. up to 50°C	starting material (73-84%) Note 2, Note 3
110 mg, 0.367 mmol	**GP-7A** $NaCNBH_3$	ethanol (5 cm^3) with HCl (1 drop)	R.T.	Several products. Also [**132**] (12%)
150 mg 0.199 mmol	***8.19.7.6*** $NaBH(OAc)_3$	THF (10 cm^3) 4 h	R.T.	Several products including [**132**], Note 4

Note 1 - Addition of 1 eq. $NaHCO_3$ did not improve the result

Note 2 - The addition of $CeCl_3$ (33 mg) gave a complex mix of products, from which a 28 mg (70%) of unreacted starting material was recovered.

Note 3 – The reaction was also carried out in THF without further improvement in yield.

Note 4 – This product gave the best evidence of (4*S*)-4-Benzyl-3-[2-(1-methylpyrrolidin-2-yl)acetyl)oxazolidin-2-one [**151**] and was used for the following spectroscopic data, but no product was isolated from either chromatography or other techniques.

The most successful synthesis of [**151**] is summarised as follows:

$NaBH_4$ (38 mg, 1 mmol) was added to a mixture of THF (5 cm^3) and glacial acetic acid (1.15 g, 19.2 mmol, 1.10 cm^3) at RT and stirred for 15 min. until hydrogen evolution had stopped. (4*S*)-4-Benzyl-3-[2-(1-methylpyrrolidin-2-ylidene)acetyl]oxazolidin-2-one (**147**, 100 mg, $3.33.10^{-4}$ mol) was added and the reaction stirred at RT for 4 h. Work-up and evaporation of the solvent gave a clear oil (56 mg, 57%).

The following spectroscopic data were obtained:

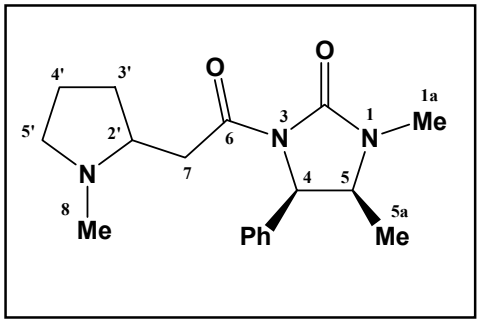
R_f = 0.03 (80:19:1 ethyl acetate/methanol/ammonia) – suspected product

NMR Data These NMR data were obtained by difference from [**152**] and starting material

δ_H (200 MHz; $CDCl_3$; TMS) 1.8–2.2 (s, 3 H, -N-C<u>*H*</u>$_3$, H-5'), 2.3-2.5 (m, 1 H), 2.7-2.9 (m, 3 H), 2.82 (d, 2 H, J_1 = 4.8 Hz), 3.2-3.4 (m, 2 H), 3.6-3.8 (m, 2 H), 4.1-4.4 (m, 2 H, NCHC<u>*H*</u>$_2$O, H-5), 4.6-4.8 (m, 1 H, $PhCH_2C$<u>*H*</u>, H-4), 7.2-7.4 (m, 6 H, Ar-<u>*H*</u>)

δ_C (200 MHz; $CDCl_3$) 21.26, 22.24, 22.65, 22.75, 30.05, 30.16, 37.14, 37.64, 37.75, 38.02, 41.21, 42.11, 55.19 ($PhCH_2$<u>*C*</u>H, C-4), 56.59, 56.73, 65.09 and 65.18, (NCH<u>*C*</u>H_2O, C-5), 66.87, 66.99, 127.32 and 128.94 and 129.35 and 135.00 and 135.17 (Ar-<u>*C*</u>), 153.57 and 153.65 (C=O*), 169.40 and 169.54 (C=O*)

8.20.2 <u>(4*R*,5*S*)-1,5-Dimethyl-3-[2-(1-methylpyrrolidin-2-yl)acetyl]-4-phenylimidazolidin-2-one [167]</u>



8.21.2.1 *Reduction with $NaBH_3CN$ in acetic acid*

A modification of **GP-7A** in acetic acid was performed as follows: THF (1.7 cm^3), glacial acetic acid (0.3 cm^3), and methanol (0.3 cm^3) were stirred together and sodium cyanoborohydride (0.209 g, 0.300 mmol) was added and

allowed to dissolve completely at RT. 1-Methyl-2-[(4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one-3-carbonylmethylene]pyrrolidine (**153**, 52 mg, $1.67.10^{-4}$ mol) was added and the reaction stirred at RT for 10 minutes.

The reaction was worked-up by adding water (3 cm^3) and basifying with NH_3 solution. The solution was then extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined organic layers dried with $MgSO_4$, filtered and evaporated to give a small amount of opaque liquid (12mg, 23%), which was identified as the required product as a mixture of two closely-related isomers. The ratio of isomers was estimated from ^{13}C NMR to be 1:1

8.20.2.2 Reduction with hydrogen over platinum catalyst in methanol.

Procedure **GP-7B** performed with platinum dioxide (15 mg), in methanol (5 cm^3), pre-hydrogenated for 30 minutes in 1 atm. of hydrogen, followed by the addition of 1-methyl-2-[(4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one-3-carbonylmethylene]pyrrolidine (**153**, 50 mg, 1.60×10^{-4} mol), gave no new product, even after 48 hours at RT. The reaction set-up did not allow for safe heating of the solution, but addition of a catalytic amount of acetic acid gave a mixture of compounds that was not purified further.

8.20.2.3 Reduction with sodium cyanoborohydride (GP-7A)

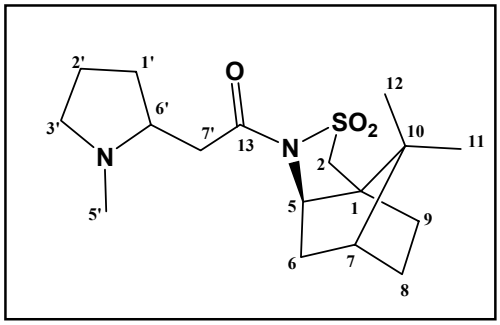
1-Methyl-2-[(4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one-3-carbonylmethylene]pyrrolidine (**153**, 70 mg, $2.23.10^{-4}$ mol) was dissolved in abs. ethanol (1.5 cm^3). $NaBH_3CN$ (15.0 mg, $2.46.10^{-4}$ mol, 1.1 eq) was added followed immediately by one drop of bromocresol green solution (0.5% in ethanol), and enough conc. HCl drop-wise to keep the solution acidic (indicated by a yellow colour). The reaction was stirred for 2 hours, and then worked-up by adding water (3 cm^3) and basifying with NH_3 solution. The solution was then extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined organic layers dried with $MgSO_4$, filtered and evaporated to give a clear oil (40 mg) that foamed excessively under vacuum. This product was revealed to be an almost 1:1 ratio of (**2*R***,4*R*,5*S*)- and (**2*S***,4*R*,5*S*)-1,5-dimethyl-3-[2-(1-methylpyrrolidin-2-yl)acetyl]-4-

phenylimidazolidin-2-one [**167**] (determined from the spectroscopic data). These isomers could not be separated, and were not characterised fully.

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) 0.87 (d, J_1 = 6.6, 3 H, NCHC$\underline{H}_3$, H-5a), 1.4–2.0 (m, 2 H, $NCH_2CH_2C\underline{H}_2C$, H-3'), 2.34 (d, 3 H, J_1 = 0.8, H-8), 2.83 (s, 3 H, CONC$\underline{H}_3$, H-1a), 2.9–3.1 (m, 2 H, $NCH_2C\underline{H}_2$, H-4'), 3.40 and 3.52 (2 sets dd, J_1 = 15.4, J_2 = 4.5, 2 H, NC$\underline{H}_2CH_2CH_2C$, H-5'), 3.90 (dq, J_1 = 8.5, J_2 = 6.6, 1 H, NCHC$\underline{H}NCH_3$, H-5), 5.29 (d, J_1 = 8.5, NC$\underline{H}CHNCH_3$, H-4), 7.0–7.8 (m, 5 H, Ar $\underline{H}$)

δ_C (200 MHz; $CDCl_3$) 14.90 ($\underline{C}H_3CHNCH_3$, C-5a), 22.02 and 22.15 (intensity 5:6, $NCH_2\underline{C}H_2CH_2C$, C-4'), 28.14 ($CH_3CHN\underline{C}H_3$, C-1a), 30.84 and 31.09 (intensity 1:1, $NCH_2CH_2\underline{C}H_2C$, C-3'), 40.28 and 40.58 (intensity 1:1, $\underline{C}H_3NCH_2CH_2CH_2C$, C-8), 53.18 ($NCH\underline{C}HNCH_3$, C-5*), 56.72 ($N\underline{C}H_2CH_2CH_2C$, C-5'), 59.17 and 59.30 (intensity 7:8, $N\underline{C}HCHNCH_3$, C-4*), 62.04 and 62.39 (intensity 7:11, $C\underline{C}HCON$, C-7), 128–133 (8 signals, Ar $\underline{C}$), 136.63 ($N\underline{C}CHCON$, C-2'), ~155 ($\underline{C}O$, C-2*[1]), 171.16 and 171.25 (intensity 9:10, $\underline{C}O$, C-6*[1]).

8.20.3 (1*S*,5*R*,7*R*)-1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-(1-methylpyrrolidin-2-yl)ethanone [160]



Reductions of the pyrrolidinylidene gave mostly recovered starting material, or gave very poor yields of the required pyrrolidinyl ethanone together with an unidentified substance with very high polarity (baseline spot by TLC in ethyl acetate/methanol mixtures).

8.20.3.1 Reduction with sodium cyanoborohydride

(1*S*,5*R*,7*R*)-1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-(1-methylpyrrolidin-2-ylidene)ethanone (**154**, 50.0 mg, 1.63.10^{-4} mol) was dissolved in superdry ethanol (~0.5 cm^3) to give an approximately 0.4M solution. Sodium cyanoborohydride (11.2 mg, 1.78.10^{-4} mol, 1.10 eq) was added at RT, followed immediately by 1 drop of bromocresol green solution (0.5% in ethanol). Conc. HCl was then added drop-wise to the solution to keep it acidic (indicated by a yellow colour).

When the reaction was complete, the solution was stirred for 1 hour at RT, and then worked up as usual to give a clear oil (47.3 mg, 93% yield), which was composed of two diastereomers (observable by doubling of signals in the NMR spectra). These diastereomers could not be separated, and were estimated from the ^{13}C NMR spectrum to be present in a ratio of 45:55%.

IR Absorptions υ_{max}/cm^{-1} = 2957, 2801 (NCH_3 δ sym), 1684, 1454, 1365, 1332, 1233, 1168, 1162, 1063, 905, 781

NMR Data δ_H (200 MHz; $CDCl_3$; TMS) (400 MHz; $CDCl_3$; TMS) 0.97 [s, 3 H, –C(C$\underline{H}_3$)$_2$, H-11*], 1.16 [s, 3 H, –C(C$\underline{H}_3$)$_2$, H-12*], 1.3–1.5 (m, 2 H), 1.5–2.4 (m, 10 H), 2.37 (apparent d, 3 H, J_1 = 2.4, N-C$\underline{H}_3$), 2.6–2.8 (m, 2 H), 2.9-3.2 (m, 2 H), 3.47 (two overlapping AB quartets as 8 signals, note 1, 2 H, J_1 = 3.2, -C$\underline{H}_2$SO$_2$-, H-2), 3.88 (t, 1 H, J_1 = 6.4, -NC$\underline{H}$-, H-1).

Note 1: The quartets present as 8 signals, the middle 4 signals have the same intensity, and occur in a ratio of 8:1 with respect to the outer signals, almost giving the impression of spinning side-bands.

δ_C (400 MHz; $CDCl_3$) 19.8 ($C\underline{C}H_3$, C-11*), 20.7 and 20.8 ($C\underline{C}H3$, C-12*), 22.0 and 22.1 ($NCHCH_2\underline{C}H_2$, C-4'), 26.4 ($\underline{C}H_2$, C-8[*1]), 30.9 ($\underline{C}H_2$, C-9[*1]) 32.75 and 32.78 ($N\underline{C}H$, C2'), 38.4 and 38.5 ($CH_2\underline{C}HCH_2$, C-7), 39.8 ($N\underline{C}H$), 40.3 and 40.4 ($N\text{-}\underline{C}H_3$), 44.56 and 44.62 ($\underline{C}H_2$, C-6), 47.7 (), 48.28 and 48.31 ($SO_2CH_2\underline{C}$, C-1), 52.87 and 52.91 ($NCHCH_2\underline{C}H_2$, C-5'), 56.5 and 56.6 ($SO_2\underline{C}H_2$, C-2), 62.0 and 62.5 ($N\text{-}\underline{C}H_3$), 65.0 and 65.1 ($N\underline{C}H$, C-5), 170.4 (C=O, C-13)

8.20.3.2 Attempted Reduction with Lithium Aluminium Hydride (GP-7F)

(1*R*,5*R*,7*S*)-1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-(1-methylpyrrolidin-2-ylidene)ethanone (**154**, 60.0 mg, $1.95.10^{-4}$ mol) was dissolved in THF (20 cm^3), and cooled to -40 °C. $LiAlH_4$ (11.1 mg, $2.93.10^{-4}$ mol, 1.5 eq) was added to the reaction, and then stirred for 1 hour at -40 °C. No change was observed with TLC, so the reaction was allowed to warm to 0 °C and stirred for two hours, and then stirred for a further 12 hours at RT. Still no reaction was observed, so more $LiAlH_4$ (3.7 mg, $9.75.10^{-5}$ mol, 0.5 eq) was added, and the reaction stirred at 50 °C for 2 hours.
The reaction was worked-up by adding methanol drop-wise, then filtering through celite, and evaporating the solvent.
Starting material (50 mg) was recovered, and no other product was detected by NMR spectroscopy.

8.20.3.3 Reduction with Hydrogen at 1 atm. over Platinum Metal

Platinum dioxide (11.0 mg) was added to superdry methanol (15 cm^3), and pre-hydrogenated in 1 atm. of hydrogen for 60 minutes. (1*R*,5*R*,7*S*)-1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-(1-methylpyrrolidin-2-ylidene)ethanone (**154**, 50 mg, $1.63.10^{-4}$ mol)in methanol (2 cm^3) was added, and stirred overnight at RT. TLC showed no remaining starting material, and two new spots (a baseline spot and a very weak spot with an R_f of

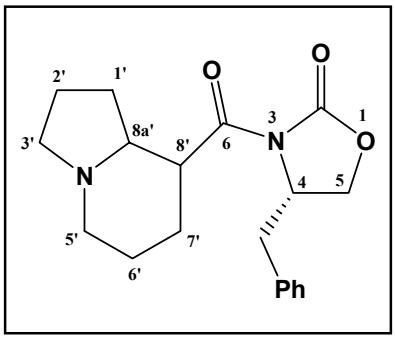
0.66 in 40:60 hexane/ethyl acetate). Work-up revealed a clear oil (41 mg, 81% yield) of the required product, again as a pair of diastereomers that could not be separated. ^{13}C NMR analysis allowed us to estimate the ratio of isomers as 45:55.

8.20.3.4 Other Attempted Reductions with Poor Yields

154 mass, mmol	Procedure (reductant)	Conditions / Variations	Products (yield) and Comments
60.0 mg, $1.77.10^{-4}$ mol	$LiAlH_4$	$CeCl_3$ (48.9 mg, $1.98.10^{-4}$, 1.12 eq). Temperature (–40°C to 50°C.) Normal and reverse addition of $LiAlH_4$.	Starting material (50 mg)
60.0 mg, $1.77.10^{-4}$ mol	$NaBH_4$	$CeCl_3$ (48.9 mg, $1.98.10^{-4}$, 1.12 eq). Ether or THF solvent.	Starting material (25 mg), mixture of isomers [**160**] (10 mg, 24%)
60.0 mg, $1.77.10^{-4}$ mol	$NaBH_4$	$CeCl_3$ (48.9 mg, $1.98.10^{-4}$, 1.12 eq). Superdry ethanol solvent. Temperature 50°C (80 min)	Mixture of isomers [**160**] (48.8 mg, 98% yield). Poor d.e. ratio by ^{13}C NMR.

8.21 Octahydroindolizines Containing a Chiral Auxiliary

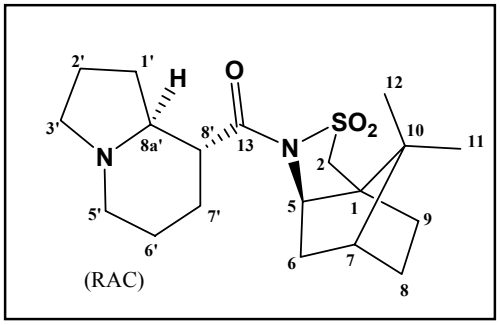
8.21.1 (4*S*)-4-Benzyl-3-(octahydroindolizine-8-carbonyl)oxazolidin-2-one [152]



An impure sample of (*S*)-4-benzyl-3-[1,2,3,5,6,7-hexahydroindolizin-8-ylcarbonyl]oxazolidin-2-one [**150**] was reduced using metal-catalyst reductions **GP-7B** or **GP-7C** in an attempt to isolate a more tractable product, but we were only able to isolate even more complex mixtures or small amounts (representing approximately 25% of the initial mass) of the chiral auxiliary in the *N*-H form [**132**].

Reductions with hydrides, even at low temperature gave pale brown viscous oils that showed complex mixtures of products with near-identical R_f values. No starting material could be detected in the case of reduction with sodium cyanoborohydride (**GP-7A**) and the ^{1}H NMR of the crude extract shows complex multiplet signals characteristic of other 8-substituted indolizidines, but these could not be separated satisfactorily, even under repeated flash-silica chromatography.

8.21.2 Formation of (1*S*,5*R*,7*R*,8*R**,8a*S**)-4-[(octahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]decane [161]



Using **GP-7A**, 800 mg starting material (**158**, 2.23×10^{-3} mol) was reduced in 40 min. to give 928 mg of a blue foam (114% crude yield, blue contaminant is most likely bromocresol green).

This product was purified by chromatography (ethyl acetate then methanol/ethyl acetate mixtures, then CH_2Cl_2/methanol/NH_4OH = 90:9:1), to give 132 mg of a white solid (16% yield). NMR analysis of this product shows that it consists of two diastereomers in a 5:2 ratio. Chiral-phase HPLC showed the presence of two other isomers, later identified as the *cis*-reduced isomers. The ratio of diastereomers was determined to be 50:20:6:1 from this process. Careful flash chromatography of 80 mg of this mixture using hexane/ethyl acetate/CH_2Cl_2 (2:2:1) followed by CH_2Cl_2/methanol mixtures (up to 10%methanol) gave two products, product 1 = 54 mg (which represents an overall yield of 4.0% for this diastereomer over the reduction step) and product 2 = 9 mg (an overall yield of 0.7%), together with 16 mg of mixed fractions. These diastereomers could also be separated by radial chromatography using the same solvent described above.

The major isomer (product 1) was later identified as the (8*R*,8a*S*) isomer (1*S*,5*R*,7*R*,8*R*,8a*S*)-4-[(octahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.$0^{1,5}$]decane [**161**] since it led to (–)-tashiromine after hydrolytic reduction of the chiral auxiliary.

M.p. (rac) = 169–173°C, M.p. = 180–181°C (material appears to sublime and change crystal morphology at 150°C)

R_f = 0.14 in 1:1 ethyl acetate/hexane

R_f = 0.52 (product 1) or 0.49 (product 2) in CH_2Cl_2/methanol/NH_4OH = 90:9:1

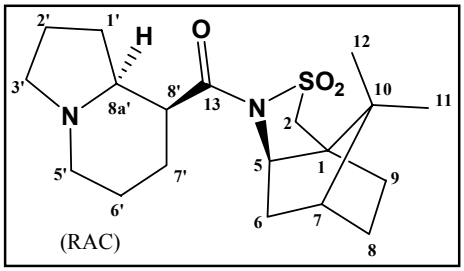
IR Absorptions υ_{max}/cm^{-1} = 2959, 2800, 2721(w), 1686, 1454, 1389, 1334, 1264, 1223, 1172, 1124, 1063, 908, 780, 731, and 543

NMR Data δ_H (400 MHz; $CDCl_3$; TMS) 0.97 [s, 3 H, –C(C<u>*H*</u>$_3$)$_2$, H-11*], 1.18 [s, 3 H, –C(C<u>*H*</u>$_3$)$_2$, H-12*], 1.32–1.47 (m, 2 H), 1.49–1.60 (m, 2 H, H-7'), 1.61–1.83 (m, 5 H, H-8a + sultam), 1.86–2.01 (m, 3 H, H-7 and H-6'), 2.03–2.17 (m, 6 H, H-6 and others), 2.93–2.99 (ddd, 1 H, J_1 = 12.4, J_2 = 7.1, J_3 = 3.6, C=OC<u>*H*</u>, H-8'), 3.03–3.10 (m, 2 H), 3.41–3.44 (d, 1 H, J_1 = 13.8, -C<u>*H*</u>$_2$SO$_2$-, H-2a), 3.50–3.53 (d, 1 H, J_1 = 13.8, -C<u>*H*</u>$_2$SO$_2$-, H-2b), 3.87–3.90 (dd, 1 H, J_1 = 7.3, J_2 = 5.3, -NC<u>*H*</u>-, H-1).

Product 1 (8*R*,8a*S*) isomer	δ_C	(400 MHz; $CDCl_3$) 19.84 [–C(<u>*C*</u>$H_3)_2$, C-11*], 20.56 (–<u>*C*</u>H_2–, C-2'), 20.72 [–C(<u>*C*</u>$H_3)_2$, C-12*], 24.89 (–<u>*C*</u>H_2–, C-6'), 26.41 (–<u>*C*</u>H_2CHC=O–, C-7'), 28.33 (–<u>*C*</u>H_2–, C-6), 29.86 (–NCH<u>*C*</u>H_2–, C-1'), 32.70 (–<u>*C*</u>H_2–, C-9), 38.33 (–<u>*C*</u>H_2–, C-8), 44.54 (–<u>*C*</u>H–, C-7), 47.67 (–SO_2CH_2<u>*C*</u>–, C-1[*1]), 48.53 (–<u>*C*</u>$(CH_3)_2$, C -10[*1]), 51.99 (–N<u>*C*</u>H_2–, C3'[*2]), 53.14 (–SO_2<u>*C*</u>H_2–, C-2), 53.80 (–N<u>*C*</u>H_2– C-5'[*2]), 64.15 (–SO_2N<u>*C*</u>H, C-5), 64.75 (–N<u>*C*</u>HCHC=O, C-8a'), 77.2 (–<u>*C*</u>HC=O, C-8'), 173.22 (<u>*C*</u>=O, C-13)
Product 2 (8*S*,8a*R*) isomer	δ_C	(400 MHz; $CDCl_3$) 19.82 [–C(<u>*C*</u>$H_3)_2$, C11*], 20.42 (–<u>*C*</u>H_2–, C-2'), 20.83 [–C(<u>*C*</u>$H_3)_2$, C-12*], 24.22 (–<u>*C*</u>H_2–, C-6'), 26.36 (–<u>*C*</u>H_2CHC=O–, C-7'), 27.22 (–<u>*C*</u>H_2–, C-6), 27.94 (–NCH<u>*C*</u>H_2–, C-1'), 32.90 (–<u>*C*</u>H_2–, C-9), 38.55 (–<u>*C*</u>H_2–, C-8), 44.70 (–<u>*C*</u>H–, C-7), 47.67 (–SO_2CH_2<u>*C*</u>–, C-1[*1]), 48.23 (–<u>*C*</u>$(CH_3)_2$, C-10[*1]), 48.38 (–<u>*C*</u>HC=O, C-8'), 52.16 (–N<u>*C*</u>H_2–, C-3[*2]), 53.16 (–SO_2<u>*C*</u>H_2–, C-2), 53.64 (–N<u>*C*</u>H_2–, C-5'[*2]), 65.12 (–SO_2N<u>*C*</u>H, C-5), 66.47 (–N<u>*C*</u>HCHC=O, C-8a') 173.85 (<u>*C*</u>=O, C-13)
Mass Spec. Data		Exact mass found 366.1963 calculated 366.1977 for $C_{19}H_{30}N_2O_3S$ *m*/*z* = 366(1.3%, M+), 365(2, M^+ – H), 302(13, M^+ –SO_2), 287(6), 193(9), 152(11), 150(100%, $C_9H_{12}NO^+$), 122(28), 120(3), 97(18), 96(21)

Using **GP-7E**, TLC shows complete consumption of the starting material, and a new spot at R_f = 0.53 (methanol/CH_2Cl_2/NH_4OH = 9:9:1). Surprisingly this spot does not show a positive reaction to ninhydrin nor phosphomolybdic acid. It is only visible as a very faint spot under treatment with chromic acid and heat. ^1H NMR of this crude product indicates the presence of a mixture of diastereomers (in a ratio of 4:5) and the IR is almost identical to that obtained previously.

8.21.3 (1*S*,5*R*,7*R*,8*S**,8a*S**)-4-[(Octahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane [162]



These were the major isomers from all the reduction procedures using metal catalysts; **GP-7B**, **GP-7C**, and **GP-7E**. They were also the minor isomers from all the remaining reduction procedures. Surprisingly these isomers were always contaminated with the *trans*-reduced isomers described above, and it was, very difficult to isolate this isomer in a pure form due to its slightly lower R_f value. This meant that all samples of this product were contaminated with the less polar *trans*-reduced product. The quantities isolated were sufficient for IR and NMR analyses, but the optical rotation measurements were not successful due to a large range of values obtained as a result of low solution concentrations. The obtained data are given below. The highest-yielding reduction reaction in this class was the use of PtO_2 in methanol at room temperature, together with a catalytic amount of acetic acid (0.1 eq.) to reduce compound **158**. The reaction was left for 5 hours at room temperature until the reaction was deemed to be approximately 50% complete (by TLC). Work-up gave the required product as a grey powder in an isolated yield of 5%. HPLC analysis showed the major diastereomers are present in a ratio of 5:4, with approximately 20% of the *trans*-reduced diastereomers present as trace quantities. The exact amount of these trace impurities is difficult to calculate since the chromatographic peaks are very poorly separated.

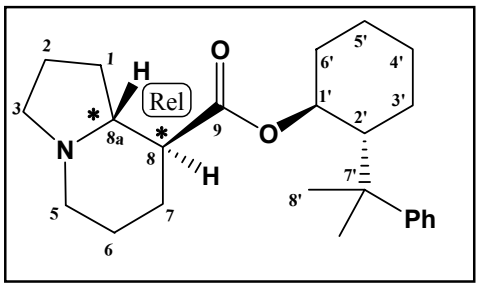
R_f = 0.49 (diastereomer 2) in CH_2Cl_2/methanol/NH_4OH = 90:9:1

IR Absorptions υ_{max}/cm^{-1} = 2963, 2888, 2800, 2737(w), 1686, 1458, 1392, 1332, 1264, 1232, 1166, 1133, 1114, 1062, 908, 787, 726, and 543

NMR Data δ_H (400 MHz; $CDCl_3$; TMS) 0.97 [s, 3 H, –C(C<u>*H*</u>$_3)_2$, H11*], 1.18 [s, 3 H, –C(C<u>*H*</u>$_3)_2$, H12*], 1.32–1.47 (m, 2 H), 1.49–1.60 (m, 2H H7'), 1.61–1.83 (m, 5H, H8 +others), 1.86–2.01 (m, 3H, H7 + H6'), 2.03–2.17 (m, 6H, H6 + others), 2.93–2.99 (ddd, 1H, H8'), 3.03–3.10 (m, 2H), 3.41–3.44 (d, 1 H, J_1 = 13.8, -C<u>*H*</u>$_2$SO$_2$-, H2a), 3.50–3.53 (d, 1 H, J_1 = 13.8, -C<u>*H*</u>$_2$SO$_2$-, H2b), 3.87–3.90 (dd, 1 H, J_1 = 7.3, J_2 = 5.3, -NC<u>*H*</u>-, H1).

δ_C (400 MHz; $CDCl_3$) 19.97 [–C(<u>C</u>H$_3)_2$, C-11*], 20.41 (–<u>C</u>H$_2$–, C-2'), 20.81 [–C(<u>C</u>H$_3)_2$, C-12*], 24.22 (–<u>C</u>H$_2$–, C-6'), 26.35 (–<u>C</u>H$_2$CHC=O–, C-7'), 27.22 (–<u>C</u>H$_2$–, C6), 27.94 (–NCH<u>C</u>H$_2$–, C-1'), 32.82 (–<u>C</u>H$_2$–, C-9), 38.53 (–<u>C</u>H$_2$–, C-8), 44.69 (–<u>C</u>H– , C-7), 47.65 (–SO$_2$CH$_2$<u>C</u>– C-1[*1]), 48.15 (–<u>C</u>(CH$_3)_2$ C-10[*1]), 48.35 (–<u>C</u>HC=O, C-8'), 52.16 (–N<u>C</u>H$_2$–, C-3'[*2]), 53.19 (–SO$_2$<u>C</u>H$_2$–, C-2), 53.64 (–N<u>C</u>H$_2$–, C-5'[*2]), 65.11 (–SO$_2$N<u>C</u>H, C-5), 66.56 (–N<u>C</u>HCHC=O, C-8a') 173.85 (<u>C</u>=O, C-13)

8.21.4 (8*S**,8a*R**)-[(1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl]octahydroindolizine-8-carboxylate [171]



Both *cis*- and *trans*-reduced indolizidine diastereomers (i.e. those containing either the **(8*S**,8a*R**)** or **(8*S**,8a*S**)** relative stereochemistry [but both having only the (+)OTCC chiral auxiliary] were isolated from procedure **GP-7A** as follows: (1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (**166**, 53 mg, 1.4×10^{-4} mol, 1eq.) and $NaCNBH_3$ (10.0 mg, 1.58×10^{-4} mol, 1.1eq.) were stirred together in methanol (3 cm^3) containing a tiny drop of bromocresol green. HCl was added to maintain the reaction at pH ~ 4 for 20 minutes. Work-up and chromatography (ethyl

acetate/hexane mixtures) gave two fractions, the first a yellow oil of 10 mg and the second similar oil of 11 mg. The first product was tentatively identified as the *trans*-reduced product (major isomer) and the second as a mixture of the *cis*- and *trans*-reduced isomers. These isomers streaked significantly using a variety of solvents, and neither was isolated in a very pure form. Distillation of the oil was not successful and resulted in charring of the product.

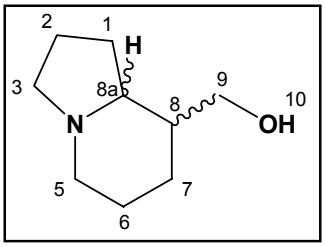
First fraction R_f = 0.33 (1:1 ethyl acetate/hexane)

Second fraction R_f = 0.10 (1:1 ethyl acetate/hexane)

IR Absorptions		υ_{max}/cm^{-1} = 2936 (C–H), 2859, 2784 and 2702 (Bohlmann bands) 1720 (C=O), 1587, 1219,1197, 1156, 1125, 1024, 910 (w CH_2 γ in cyclohexanes), 764 (s), 700 (s)
NMR Data	δ_H	(200 MHz; $CDCl_3$; TMS) 1.0–2.2 (m, 27H), 1.21 and 1.22 (two s, 3H, -C*H*$_3$, H-8'), 1.26 (s solvent impurity), 1.31 and 1.32 (two s, 3H, -C*H*$_3$, H-8'), 2.9–3.1 (m, 2H, -$NCH_{axial}H_{equatorial}$, H-$3_{eq}$ and H-5_{eq}), 4.12 (q, 1 H, solvent impurity), 4.7–4.85 (m, 1H, -O-C*H*, H-1'), 7.0–7.4 (m, 5H, Ar-*H*)
Incomplete ASSIGNMENT due to complexity of signals	δ_C	(200 MHz; $CDCl_3$) 20.36, 20.55, 20.90, 22.88, 24.30, 24.60, 24.95, 25.46, 25.88, 26.50, 26.87, 27.04, 27.29, 28.32, 29.00, 29.28, 33.19, 33.30, 39.92, 41.38, 47.72, 48.19, 50.61, 50.72, 52.01, 52.18, 54.73, 60.33, 64.01, 64.36, 65.47, 73.88, 74.65, 74.79, 124.88, 125.20, 125.34, 125.72, 127.81, 127.95, 151.11, 151.39, 173.53 (C=O)

8.22 Octahydro-indolizin-8-yl-methanol

(Tashiromine and epitashiromine)



8.22.1.1 Reduction with $LiEt_3BH$:

An impure mixture (**161 and 162**, 52 mg, 1.44×10^{-4} mol) of the previous products (both the *cis*- and *trans*-reduced products were used), was dissolved in THF (1 cm^3) and cooled to 0°C. $LiEt_3BH$ (1.0eq, 1.44×10^{-4} mol, 0.144 cm^3 of a 1M solution in THF) was carefully added via syringe. The reaction was allowed to warm to RT over 30 min and stirred for 1 hr. TLC analysis showed no change, so the reaction was stirred under reflux for 6 hrs, then overnight at RT. Radial chromatography of the crude reaction mixture (ethyl acetate with 1% ammonium hydroxide) gave 15 mg of a product with identical R_f to the previously obtained racemic tashiromine/epitashiromine mixtures, which reacted positively to ninhydrin spray reagent. The ^{1}H-NMR indicates the presence of significant amounts of sultam, as well as signals corresponding to tashiromine.

This reaction was also performed on the substrate (1*S*,5*R*,7*R*)-4-[(1,2,3,5,6,7-hexahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.$0^{1,5}$]decane (**158**, 50 mg), using the same conditions and reagents to give a grey powder (10 mg), which showed evidence (NMR) of an 8-hydroxymethyloctahydroindolizine, but we were not able to isolate it from this mixture.

R_f = 0.08 (ethyl acetate)

8.22.1.2 By reduction with $LiAlH_4$.:[237]

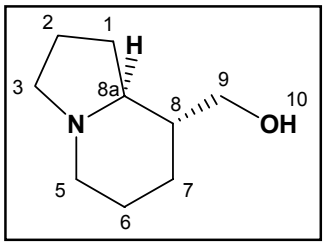
A sample of mixed diastereomers of (1*S*,5*R*,7*R*)-4-[(octahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.$0^{1,5}$]decane (**162** and **163**, 50 mg, 1.39×10^{-4} mol, 1.0eq) in THF (0.5 cm^3) was added to a stirred suspension of $LiAlH_4$ (5.3 mg, 1.39×10^{-4} mol, 1.0eq) in THF (0.2 cm^3) at RT and stirred for 1 h. To stop the reaction two drops of a saturated Na_2SO_4 solution were added. THF (4 cm^3) was then added and the reaction dried with

MgSO4, filtered and evaporated to give a pale yellow oil (35.9 mg, 166% crude yield). Flash chromatography (90:9:1 CH_2Cl_2/methanol/NH_4OH) yielded a clear oil (15.5 mg, 72% yield based on tashiromine). NMR indicates the presence of the camphor sultam, but also the presence of mixed fractions of tashiromine and epitashiromine.

R_f = 0.17 (90:9:1 CH_2Cl_2/methanol/NH_4OH) – spot is positive to ninhydrin spray.

NMR Data (**SELECT assignments**)	δ_H	(200 MHz; $CDCl_3$; TMS) 0.97 and 1.14 (two s, sultam C$\underline{H}_3$) 0.74-2.26 (several m, unassigned), 2.94–3.00 (m, unassigned), 3.04–3.12 (m, tashiromine or epitashiromine H-3 and H5), 3.41–3.53 (m, tashiromine or epitashiromine H-9), ~4.4 (1H, br. s, sultam –N$\underline{H}$ and tashiromine/epitashiromine –O$\underline{H}$, H-10)

8.22.2 (–)-Tashiromine



An enantiomerically enriched sample of (–) tashiromine was obtained from the $LiAlH_4$ reduction of (1*S*,5*R*,7*R*,8*R*,8a*S*)-4-[(octahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decane [**161**]. This starting material was contaminated with some of the (8*S*,8a*R*) minor isomer since these two diastereomers could not be separated. An identical procedure to the one given above used for obtaining the mixtures of tashiromine/epitashiromine was followed. In this case, the product was isolated as a pale-yellow oil in 31.6 mg (146% crude yield), which gave 10.9 mg of a clear oil (50.6% yield based on tashiromine).

R_f = 0.08 (ethyl acetate)

Optical Rotation	$[\alpha]_D^{23}$ = –16.1 (c 0.4 in ethanol), (lit.[117] = –25.9 (c 1.03 in ethanol)
IR Absorptions	υ_{max}/cm^{-1} = 3380(Lit.[47] = 3600–3100), 2953, 2781, 2733(w), 2641(w), 1698, 1454, 1413, 1380, 1330, 1270,

		1209, 1166, 1123, 1069, 985, 769, 730, 615, and 538
NMR Data	δ_H	(200 MHz; $CDCl_3$; TMS) 1.05 (ddd, 1 H, J_1 = 20.7, J_2 =
See **8.20.4**		11.3, J_3 = 4.8, H-7a), 1.4–2.0 (m, 4 H, H-1, H-7b, H-8), 1.6 (m, 1 H, H-8a), 1.6–2.2 (m, 2 H, H-2), 1.7–2.2 (m, 2 H, H-6), 2.0 and 3.0 (m, 4 H, H-3 and H-5), 3.42 (dd, 1 H, J_1 = 10.3, J_2 = 6.1, C$\underline{H_2}$OH, H-9a), 3.61 (dd, 1 H, J_1 = 10.3, J_2 = 3.9, C$\underline{H_2}$OH, H-9b), m, H-9), 5.3 (1H, s, H-10)
	δ_C	(400 MHz; $CDCl_3$) 20.6 (C-2), 25.1 (C-6), 27.7 (C-1), 29.0 (C-7), 44.6 (C-8), 52.6 (C-5), 54.2 (C-3), 65.3 (C-9), 66.4 (C-8a)
Mass Spec. Data		Exact mass found 366.1963 calculated 366.1977 for $C_{19}H_{30}N_2O_3S$ *m*/*z* = 366(1.3%, M+), 365(2, $M^+ - H$), 302(13, $M^+ - SO_2$), 287(6), 193(9), 152(11), 150(100%, $C_9H_{12}NO^+$), 122(28), 120(3), 97(18), 96(21)

8.22.3 (+)-Tashiromine

This product was isolated from the reduction (in $LiAlH_4$) of (1*S*,5*R*,7*R*, 8*S*, 8a*R*)-4-[(octahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.$0^{1,5}$]decane (5 mg) using the same procedure described above for (–)-tashiromine. The product was isolated in a yield of 0.6 mg, which only allowed us to obtain a ^{1}H NMR spectrum the optical rotation. The ^{1}H NMR is identical to that given above for (–)-tashiromine, but the signal to noise ratio was much lower in this case.

Optical Rotation $[\alpha]_D^{23}$ = +1.2 (c =0.1 in ethanol), (lit.[114] = +42.9 (c 1.03 in ethanol)

8.22.4 (+)-Epitashiromine

This product was isolated from the reduction (in $LiAlH_4$) of (1*S*,5*R*,7*R*,8*R*,8a*R*)-4-[(octahydroindolizin-8-ylcarbonyl)]-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.$0^{1,5}$]decane (**162**, 15 mg) using the same procedure described above for (–)-tashiromine. The product was isolated in a

yield of 1.2 mg, which again only allowed us to obtain a ^{1}H NMR spectrum the optical rotation.

Optical Rotation		$[\alpha]_D^{23}$ = +1.4 (c =0.1 in ethanol), [lit.[114] = +1.1 (c 1.03 in ethanol]
NMR Data	δ_H	(400 MHz; $CDCl_3$; TMS) 1.02–1.15 (m, 2 H, H-1), 1.4–2.0 (m, 2 H, H-7), 1.6 (m, 1 H, H-8a), 1.6–2.2 (m, 2 H, H-2), 1.7–2.2 (m, 2 H, H-6), 2.0 and 3.0 (m, 5 H, H-3, H-5, and H8), 3.70 (dd, 1 H, J_1 = 8.9, J_2 = 1.9, C$\underline{H_2}$OH, C-9a), 4.18 (dd, 1 H, J_1 = 9.1, J_2 = 4.1, C$\underline{H_2}$OH, C-9b), 5.3 (s, 1 H, H-10)
See **8.20.5**	δ_C	(400 MHz; $CDCl_3$) 19.6 (C-2) 22.9 (C-6), 25.3 (C-1), 28.7 (C-7), 35.8 (C-8), 44.0 (impurity C-8 from *trans*-reduced isomers), 52.4 (C-5), 53.3 (C-3), 61.2 (C-9), 65.6 (C-8a)

References

1 G. Moss, P. Smith, and D. Tavernier, *Pure and Applied Chemistry*, 1995, **67**, p 1309

2 I.L. Finar, *Organic Chemistry*, 4th Ed. Longmann Press, London, UK, 1965, Vol.**2**, p 601

3 Oxford English Dictionary, online second edition, http://www.dictionary.com

4 W Meissner, *J. Chem. Phys*., 1819, **25**, p 379

5 K. W.A. Remers, R.T. Dorr, in "*Alkaloids: Chemical and Biological Perspectives*" (S.W. Pelletier, ed.), Wiley, New York, 1988, Vol **6**

6 M. Wink, in "*The Alkaloids. Chemistry and Pharmacology*", (G.A. Cordell, ed.) Academic Press, San Diego, USA, 1993, Vol. **43**, Chapter 1, pp 1–118

7 A.S. Howard and J.P. Michael, in "*The Alkaloids*" (A.Brossi, ed.), Academic Press, New York, USA, 1986, Vol. **28**, Chapter 3, pp 189-308

8 H. Takahata and T. Momose, in "*The Alkaloids*", (G.A. Cordell, ed.) Academic Press, San Diego, USA, 1993, Vol. **44**, Chapter 3, pp 189-256

9 a) J.P. Michael, "Indolizidine and quinolizidine alkaloids", *Natural Product Reports*, 2003, **20**, 458–475

b) J.P. Michael, "Indolizidine and quinolizidine alkaloids", *Natural Product Reports,* 2002, **19**, 719-741

c) J.P. Michael, "Indolizidine and quinolizidine alkaloids", *Natural Product Reports,* 2001, **18**, 520-542

d) J.P. Michael, "Indolizidine and quinolizidine alkaloids", *Natural Product Reports,* 2000, **17**, 579-602

e) J.P. Michael, "Indolizidine and quinolizidine alkaloids", *Natural Product Reports,* 1999, **16**, 675 and references therein

f) J.P. Michael, "Indolizidine and quinolizidine alkaloids", *Natural Product Reports,* 1998, **15**, 571-594 and references therein

10 J.P. Michael, “Simple Indolizidine and Quinolizidine Alkaloids”, in *The Alkaloids: Chemistry and Biology* (G.A. Cordell, ed.), Academic Press, San Diego, USA 2001, Volume **57**, Chapter 2, , pp 91-258

11 J.H. Russel, *Naturwiss*. 1963, **50**, 443

12 For example see the following review by Brown and Trigo; K.S. Brown Jr. and J.R. Trigo "Ecological activity of alkaloids" in “*The Alkaloids*” (G. Cordell ed.), (1995) volume **47**, Academic Press, NY, 227-354

13 M. Wink “Allelochemical properties or Raison d’Être of Alkaloids” in *The Alkaloids: Chemistry and Biology*”, (Cordell, G. A. ed.), Academic Press, New York, 2001; Vol. **55**, Chapter 1, pp. 1–118.

14 J.W. Daly, H.M. Garraffo, T.F. Spande, C. Jaramillo and A.S. Rand, J. *Chem*. *Ecol*.,1994, **20**, 943.

15 J.W. Daly, S.I. Secunda, H.M. Garraffo, T.F. Spande, A. Wisnieski and J.F. Cover, Jr., *Toxicon*,1994, **32**, 657.

16 D.J. Faulkner, *Nat*. *Prod*. *Rep*., 2002, **19** (1), 1–48

17 H. Hirota, S. Matsunaga, and N. Fusetani, *Tetrahedron Lett*., 1990, **31**, 4163-4164

18 S. Aaronson, *Antiquity*, 1989, **63**, p 247

19 For a general reference on these alkaloids, including their isolation and toxilogic effects, see S.M. Colegate and P.R. Doring, in "*Handbook of Plant and Fungal Toxins*" (J.P.F. D'Mello, ed.), CRC Press, Boca Raton, 1997, 1-18,

20 A.A. Freer, D. Gardner, D. Greatbanks, J.P. Poyser, and G.A. Sim, *J. Chem. Soc*., *Chem*. *Commun*. 1982, 1160

21 S.Gomi, D. Ikeda, H. Nakamura, H. Naganawa, F. Yamashita, K. Hotta, S. Kondo, Y. Okami, H. Umezawa and Y. Iitaka: *J. Antibiot*. (Tokyo). 1984, **37**(11), 1491–1494.

22 See also Ref [7] for an excellent account of the isolation, structural elucidation, and biological activity of this alkaloid.

23 A.W. Hofmann, “Zur Kenntnis des Coniin-Gruppe”, *Ber*. *Dtsch*. *Chem*. *Ges*., 1885, **18**, 109

24 F.P.J.T. Rutjies, J.J.N. Veerman, W.J.N. Meester, H. Hiemstra, and H.E. Schoemaker, *Eur. J. Org. Chem.*, 1999, 1127

25 D.J. Hart, *J. Am. Chem. Soc.*, 1980, **102**, 397–398

26 C. H. Heathcock, S.K. Davidsen, S.Mills and M.A. Sanner, *J. Am. Chem. Soc.*, 1986, **108**, 5650–5651

27 B.P. Wijnberg and W. N. Speckamp, *Tetrahedron Lett.*, 1981, **22**, 5079–5082

28 L.E. Overman, T.C. Malone, G.P. Meier, *J. Am. Chem. Soc.*, 1983, **105**, 6993–6994

29 T.Shono, Y. Matsumura, K.Uchida, K. Tsubata, and A. Makino, *J. Org. Chem.*, 1984, **49**, 300–304

30 T.Shono, Y. Matsumura, K.Uchida, and H. Kobayashi, *J. Org. Chem.*, 1985, **50**, 3243–3254

31 S. Aoyagi, T. –C. Wang, C. Kibayashi, *J. Am. Chem. Soc.*, 1992, 114, 10653–10654

32 D.L. Comins and E. Zeller, *Tetrahedron Lett.*, 1991, **32**, 5889–5892

33 P. Michel, A. Rassat, J.W. Daly, and T.F. Spande, *J. Org. Chem.*, 2000, **65**(26), 8908–8918

34 J.M. Harris and A. Padwa, *J. Org. Chem.*, 2003, **68**, 4371–4381

35 Y. Watanabe, H. Iida, and C. Kibayashi, *J. Org. Chem.*, 1989, **54**, 4088–4097

36 D.W. Knight and A.W. Sibley, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2179–2188

37 M.P. Sibi and J.W. Christensen, *J. Org. Chem.*, 1999, **64**, 6434–6442

38 A. Padwa and J.M. Harris, *J. Org. Chem.*, 2003, **68**, 4371–4380

39 J.P. Michael, C.B. de Koning, C. San Fat and G.L. Nattrass, *ARKIVOC*, 2002, (**ix**), 62–77 (http://www.arkat-usa.org/ark/journal/2002/Bull/JB-604J/604J.pdf).

40 H. Böhme and H.G. Viehe, eds., “Iminium Salts in Organic Chemistry”, Parts 1 and 2, Wiley, New York, USA, 1979

41 H. Hiemstra and W.N. Speckamp, "*N*-Acyliminium Ions as Intermediates in Alkaloid Synthesis", in "*The Alkaloids: Chemistry and Pharmacology*" (A. Brossi, ed.), 1988, Academic Press, San Diego, USA 1988, Volume **32**, Chapter 4, pp 271–339

42 M. Okita, T. Wakamatsu, and Y. Ban, *Heterocycles*, 1983, **20**, 401–404

43 T.G. Back and K. Nakajima, *J. Org. Chem*., 2000, **65**, 4543–4552

44 P. Michel, A. Rassat, J.W. Daly and T.F. Spande, *J. Org. Chem.,* 2000, **65**(26), 8908–8918

45 M.K. Gurjar, L.Ghosh, M. Syamala, and V. Jayasree, *Tetrahedron Lett*., 1994, **35**, 8871–8872

46 M.P. Sibi and J.W. Christensen, *J. Org. Chem*., 1992, **57**, 4329–4330

47 O. David, J. Blot, C. Bellec, M-C. Fargeau-Bellassoued, G. Haviari, J-P. Célérier, G. Lhommet, J. C. Gramain, and D. Gardette, *J. Org. Chem*., 1999, **64**, 3122–3131

48 S.M. Sheehan and A. Padwa, *J. Org. Chem*., 1997, **62**, 438–439

49 R.W. Bates and J. Boonsombat, *J. Chem. Soc. Perkin Trans*. 1, 2001, 654–656

50 D. M.J. Nattrass, Ph.D. Thesis, University of the Witwatersrand, 1973

51 J.P. Michael, Ph.D. Thesis, University of the Witwatersrand, 1975

52 B.S. Orlek, Ph.D. Thesis, University of the Witwatersrand, 1976

53 C.A. Meerholz, Ph.D. Thesis, University of the Witwatersrand, 1977

54 R.B. Katz, Ph.D. Thesis, University of the Witwatersrand, 1983

55 M.I. Zwane, Ph.D. Thesis, University of the Witwatersrand, 1991

56 S.S.-F. Chang, Ph.D. Thesis, University of the Witwatersrand, 1991

57 A.S. Parsons, Ph.D. Thesis, University of the Witwatersrand, 1992

58 D. Gravestock, Ph.D. Thesis, University of the Witwatersrand, 1993

59 T.V. Stanbury, Ph.D. Thesis, University of the Witwatersrand, 1999

60 C.W. van der Westhuyzen, Ph.D. Thesis, University of the Witwatersrand, 2001

61 I. Yillah, Ph.D. Thesis, University of the Witwatersrand, 2002

62 C.S. Fat, Ph.D. Thesis, University of the Witwatersrand, 2002

63 G.D. Hosken, M.Sc. Dissertation, University of the Witwatersrand, 1988.

64 C.M. Jungmann, M.Sc. Dissertation, University of the Witwatersrand, 1992.

65 C. Wilson, M.Sc. Dissertation, University of the Witwatersrand, 1993.

66 G.T. Brankin, M.Sc. Dissertation, University of the Witwatersrand, 1993

67 T. Malefetse, M.Sc. Dissertation, University of the Witwatersrand, 1996

68 P.S. Cheesman, M.Sc. Dissertation, University of the Witwatersrand, 1996

69 S.C. Pelly M.Sc. Dissertation, University of the Witwatersrand, 1997

70 G.L. Nattrass M.Sc. Dissertation, University of the Witwatersrand 2001

71 R.L. Petersen, Ph.D. Thesis, University of the Witwatersrand, 2004

72 M. Natsume, M. Takahashi, K. Kiuchi and H. Sugaya, *Chem. Pharm. Bull.*, 1971, 19, 2648–2651

73 J.P. Célérier, E. Deloisy, G. Lhommet and P. Maitte, *J. Org. Chem.*, 1979, **44**, 3089–3089

74 J.P. Célérier, M.G. Richand and G. Lhommet, *Synthesis*, 1983, 195

75 M.M. Gugelchuk, D.J. Hart and Y. Tsai, *J. Org. Chem.*, 1981. **46**, 3671–3675

76 M. Yamaguchi and I. Hirao, *J. Org. Chem.*, 1985, **50**, 1975–1977

77 K. Kobayashi and H. Suginome, *Bull. Chem. Soc. Japan.*, 1986, **59**, 2635–2636

78 A. Brandi, S. Carli and A. Goti, *Heterocycles*, 1988, **27**, 17

79 E.G. Occhiato, A. Guarna, A. Brandi, A. Goti and F. De Sarlo, *J. Org. Chem.*, 1992, **57**, 4206–4211

80 H.M.C. Ferraz, E.O. de Oliveira, M.E. Payret-Arrua and C.A. Brandt, *J. Org. Chem.*, 1995, **60**, 7357–7359

81 E. R. Lukeš, *Coll. Czech. Chem. Commun.*, 1932, **4**, 81; *Chem. Abstr.*,1932, **25**, 3252

82 C. K. Shiosaki, "The Eschenmoser Coupling Reaction", in "*Comprehensive Organic Synthesis*" (B.M. Trost, ed.), 1991, Vol. **2**, p. 865. Pergamon Press, Oxford.

83 F. M Roth, P. Dubs, E. Götschi, and A. Eschenmoser, *Helv. Chim. Acta*,1971, **54** , 710–734

84 G. E. Götschi, W. Hunkeler, H. Wild, P. Schneider, W. Fuhrer, J. Gleason, and A. Eschenmoser, *Angew. Chem. Int. Ed.*,1973, **12**(11), 910–916

85 E. Knott, *J. Chem. Soc.*, 1995, 916

86 E. Lutz e and JF. Biellmann *Tetrahedron Lett.*, 1985 **26**(23), 2789–2792

87 RB Woodward and R Hoffman, *Angew. Chem. Int. Ed.*, 1969, **8**(11): 781

88 J.V. Greenhill, *Chem. Soc. Rev.*, 1977, Vol **6**, 277–294

89 K.Shiosaki, G. Fels, and H. Rapoport, *J. Org. Chem.*, 1981, **46**, 3230–3234

90 J.P. Michael and C.M. Jungmann, *Tetrahedron*,1992, **48**, 10211–10220.

91 L. A.S. Howard, G.C. Gerrans and J.P. Michael, *J. Org. Chem.*, 1980, **45**, 1713–1715

92 J.P. Michael, S.S.-F. Chang and C. Wilson, *Tetrahedron Lett.*,1993, **34**, 8365–8368

93 A.S. Howard, R.B. Katz and J.P. Michael, *Tetrahedron Lett.*,1983, **24**, 829–830

94 J.P. Michael, A.S. Howard, R.B. Katz and M.I. Zwane, *Tetrahedron Lett.*,1992, **33**, 6023–6024

95 J.P. Michael and M.I. Zwane, *Tetrahedron Lett.*,1992, **33**, 4755–4758

96 Y-H. Wang, K. Higashiyama, H. Kubo, J-S. Li, . Li, and S. Ohmiya, *Heterocycles*, 1999, Vol. **51**, 3001–3004

97 S. Ohmiya, H. Kubo, H. Otomasu, K. Saito, and I. Murakoshi, *Heterocycles*, 1990, **30**, 537–542

98 Y. Nagao, W-M. Dai, M. Ochiai, S. Tsukagoshi, and E. Fujita, *J. Am. Chem. Soc.*, 1988, **110**, 289–291

99 Y. Nagao, W-M. Dai, M. Ochiai, S. Tsukagoshi, and E. Fujita, *J. Org. Chem.*, 1990, **55**(4), 1148–1156

100 A. L. J. Beckwith and S. W. Westwood, *Tetrahedron*, 1989, **45**(16), 5269–5282

101 a) B. Giese, in "*Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*" (J. E. Baldwin ed.); 1986, Pergamon Press: New York,
b) D. P. Curran, *Synthesis* 1988, 489–491

102 A. L. J. Beckwith, A. K. Serelis, and C. Easton, *J. Chem. Soc., Chem. Commun.*,1980, 482–493

103 R M. Newcomb and T. M. Deeb, *J. Am. Chem. Soc.*, 1987, **109**, 3163–3165

104 D. A. Burnett, J. K. Choi, D. J. Hart, and Y. M. Tsai, *J. Am. Chem. Soc.*, 1984, **106**, 8201–8207

105 D. H. R. Barton, J. Guilhem, Y. Herve, P. Potier, and J. Thierry, *Tetrahedron Lett.*, 1987, **28**, 1413–1418

106 Y. A. Mohammed and D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 1986, 588–593

107 H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, 1968, **9**, 6191–6199

108 K. Paulvannan and J. R. Stille, *J. Org. Chem.*, 1994, **59**, 1613–1620

109 K. Paulvannan and J. R. Stille, *J. Org. Chem.*, 1992, **57**, 5319–5332, and references cited therein

110 P. W. Hickmott and G. Sheppard, *J. Chem. Soc., Chem. Commun.*, 1971, 1358–1360

111 K. Wiesner, I. Jirkovsky, M. Fisherman, and C. A. J. Williams, *Tetrahedron Lett.*, 1967, **8**, 1523–1526

112 W. Shen, C. A. Coburn, W. G. Bornmann, S. J. Danishefsky, *J. Org. Chem.*, 1993, **58**, 611–623

113 J. L. Gage and B. P. Branchaud, *Tetrahedron Lett.*, 1997, **38**(40), 7007–7010

114 D.-C. Ha, S.-H. Park, K.-S. Choi, and C.-S. Yun, *Bull. Korean Chim. Soc.*, 1998, **19**(17), 728–730

115 D.-C. Ha, K. -E. Kil, K.-S. Choi, S.-H. Park, *Tetrahedron Lett.*, 1996, **37**, 5723–5727

116 O. David, C. Bellec, M-C. Fargeau-Bellassoued, G. Lhommet *Heterocycles*, 2001, **55**, 1689–1702

117 S.-H. Kim, S.-I. Kim, S.Lai, and J.K. Cha, *J. Org. Chem.*, 1999, **64**, 6771–6775

118 R.K. Dieter and R. Watson *Tetrahedron Lett.*, 2002, **43**, 7725–7728

119 C. W. Reppe, *Liebigs Ann. Chem.*, 1955, **596**, 158–213

120 B. M. S. Manhas and S. J. Jeng, *J. Org. Chem*., 1967, **32**, 1246–1248

121 J.P. Michael and D. Gravestock, *Eur. J. Org. Chem*., 1998, 865–870

122 E. D. Brillon, *Synth. Commun*., 1990, **20**, 3085–3095

123 S. Raucher and P. Klein, *J. Org. Chem*., 1981, **46**, 3558–3559.

124 N. Finkelstein, *Chem. Ber*., 1910, **43**, 1528

125 P.J. Garegg and B. Samuelsson, *J. Chem. Soc*., *Perkin Trans. 1*., 1980, 2866–2869

126 C. Hehr, *Angew. Chem*., *Int. Ed*., 1996, **35**, 2566–2587

127 D.S. Rycroft and D.J. Robins, *Magn. Reson. Chem*., 1992, **30**, S15–S17

128 R. A. Shedon, P. A. Porskamp, and W. ten Hoeve, in "*Biocatalysts in Organic Synthesis*"; (J. Tamper, H. C. van Plas, and P. Linko eds.) 1985; Elsevier: Amsterdam, pg 59

129 *Asymmetric Synthesis*; (J. D. Morrison and J. W. Scott, ed.); 1983–1985, Academic Press: Orlando, Vols **1–5**, various pages

130 The International Conference on Chirality; Cancun, Mexico; 6–9 June 1990

131 *Chirality* 1989, **1**

132 *Tetrahedron Asymmetry*, 1990, **1**

133 D. Seebach, V. Prelog, *Angew. Chem*., *Int. Ed*., 1982, **21**, 654

134 A. W. Stewart, "*Stereochemistry*", 2nd Ed.; 1919, Longmans Green and Co.: London, p. 248

135 J. Crosby, *Tetrahedron*, 1991, **47**, 4789–4846

136 S. Hanessian, "*Total synthesis of Natural Products: The Chiron Approach*", 1983, Pergamon Press New York

137 H.-J.Liu and W.H. Chan, *Can. J. Chem*., 1979, **57**, 708

138 H.-J.Liu and W.H. Chan, *Can. J. Chem*., 1982, **60**, 1081

139 M.S. Allen, N.Lamb, and T. Money, *Can. J. Chem*., 1979, **57**, 742

140 J.H. Hutchinson and T. Money, *Can. J. Chem*., 1985

141 R.V. Stevens, J.H. Chong, R. Lapalme, S. Schow, M.G. Schlageter, R. Shapiro, and H.N. Weller, *J. Am. Chem. Soc*., 1983, **105**, 7719–7729

142 T. Money, *Natural Products Reports*, 1985, 253–289

143 C-H Wong and G.M. Whitesides, "Enzymes in synthetic organic chemistry", *Tetrahedron Organic Chemistry Series,* vol. **12**, 1994, Elsevier Science Ltd, Oxford

144 E.J. Corey and H.E. Ensley, *J. Am. Chem. Soc.*, 1975, **97**, 6908–6909

145 J. d'Angelo and J. Maddaluno, *J. Am. Chem. Soc.*, 1986, **108**, 8112–8114

146 H.B. Kagan and J.C. Fiaud, "*Topics in Stereochemistry*", (Eliel and S. Wilen, ed.), 1988, Vol 18, various pages

147 R. M. Williams, "*Synthesis of Optically active a-Amino Acids*", 1989, Pergamon Press, Oxford

148 W. Oppolzer, D. Dupuis, G. Poli, T.M. Raynham and G. Bernardinelli, *Tetrahedron Lett.*,1988, **29**, 5885–5888

149 D. Potin, F. Dumas, and J. d'Angelo, *J. Am. Chem. Soc.*, 1990, **112**, 3483–3486

150 D. L. Comins and L. Guerra-Weltzein, *Tetrahedron Lett.*, 1996, **37**, 3807–3810

151 Brunner and W Zettlmeier, "*Handbook of Enantioselective Catalysis*", 1993, VCH, Weinheim

152 For a review of recent advances in asymmetric synthesis on an industrial scale see G. Parshall and W. Nugent, *Chemtech*, 1988, **18**, 194

153 I. Ojima, N. Clos, and C. Bastos, *Tetrahedron*, 1989, **45**, 6901–6939

154 M. Kitamura, Y. Hsiao, M. Ohta, M. Tsukamato, T. Ohta, H. Takaya, and R. Noyori, *J. Org. Chem.*, 1994, **59**, 297–310

155 R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, and H. Takaya, *J. Am. Chem. Soc.*, 1986, **108**, 7117–7119

156 J. Halpern, Chapt 2 in "*Asymmetric Synthesis*", (J.D. Morrison, ed.), 1985, Academic Press, New York, Vol **5**

157 J.M. Brown, *Angew. Chem., Int. Ed.*, 1987, **26**, 190

158 R. Andreasch, *Monatsh. Chem.*, 1884, 5, 33–35

159 W. Oppolzer, *Angew. Chem., Int. Ed.*,1984, **23**, 876

160 D.A. Evans, K.T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, 1984, **106**, 4261–4263

161 D.A. Evans, K.T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238–1256

162 D.A. Evans, E.B. Sjogren, A.E. Weber and R.E. Conn, *Tetrahedron Lett.*, 1987, **28**, 39–42

163 M.P. Sibi and J. Ji, *J. Am. Chem. Soc.*, 1996, **118**, 9200–9201

164 C.W. Phoon and C. Abell, *Tetrahedron Lett.*, 1998, **39**, 2655–2658

165 T. Saito, T. Karakasa, H. Fujii, E. Furuno, H. Suda and K. Kobayashi, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1359–1362

166 D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737–1739

167 R. Verma and S.K. Ghosh, *J. Chem. Soc., Perkin Trans.* 1, 1999, 265–270

168 J.R. Gage and D.A. Evans, *Org. Synth.*, Coll. Vol. **VII**,1990, 68, 77-

169 A. Abiko and S. Masamune, *Tetrahedron Lett.*,1992, **33**, 5517–5518.

170 D.A. Dickman, A.I. Meyers, G.A. Smith and R.E. Gawley, *Org. Synth.*, Coll. Vol. **VII**,1990, 530–533.

171 L.N. Pridgen, J. Prol Jr., B. Alexander and L. Gillyard, *J. Org. Chem.*,1989, **54**, 3231–3233

172 A. Giannis and K. Sandhoff, *Angew. Chem., Int. Ed.*,1989, 28, 218-

173 M. Nakagawa, A. Tsuruoka, J. Yoshida and T. Hino, *J. Chem. Soc., Chem. Commun.*, 1990, 603–605

174 H. Roder, G. Helmchen, E-M. Peters, K. Peters, and H-G. von Schnering, *Angew. Chem., Int. Ed.*, 1984, **23**, 898–899

175 W.J. Close, *J. Org. Chem.*, 1950, **15**, 1131–1134

176 W.D. Wulff, *Organometallics*, 1998, **17**, 3116–3134

177 W.M. Clark and C. Bender, *J. Org. Chem.*, 1998, **63**, 6732–6734

178 G. Reychler, *Bull. Soc. Chim.*, 1898, **19**(3), 120

179 W. Oppolzer, *Tetrahedron*,1987, **43**, 1969–2004

180 W. Oppolzer, C. Chapuis and G. Bernardinelli, *Helv. Chim. Acta*,1984, **67**, 1397

181 P. Binger, A. Brinkmann, P. Roefke and B. Schäfer, *Liebigs Ann. Chem.*,1989, 739

182 R.L. Schriner, J.A. Shotton and H. Sutherland, *J. Am. Chem. Soc*., 1938, **60**, 2794–2796

183 J.C. Towson, M.C. Weismiller, G.S. Lal, A.C. Sheppard, A. Kumar and F.A. Davis, *Org. Synth*., Coll. Vol. **VIII**, 1993, 104–112.

184 M. Capet, F. David, L. Bertin and J.C. Hardy, *Synth. Commun*.,1995, 25, 3323–3327

185 M. Vandewalle, J. Van der Eycken, W. Oppolzer and C. Vullioud, *Tetrahedron*,1986, **42**, 4035–4043

186 F. A. Davis, J. C. Towson, M. C. Weismiller, G. Lal, and P. J. Carroll, *J. Am. Chem. Soc*., 1988, **110**, 8477–8482

187 W. Oppolzer, C. Robbiani, and K. Bätig, *Helv. Chim. Acta*, 1980, **63**, 2015

188 J.K. Whitesell, *Acc. Chem. Res*., 1985, 18, 280-

189 O. Ort, *Org. Synth*., Coll. Vol. **VI**, 1987, 65, 203-

190 E.J. Corey, H.E. Ensley, and J.W. Suggs, *J. Org. Chem*., 1976, **41**, 380–381

191 A. Schwartz, P. Madan, J.K Whitesell, and R.M. Lawrence, *Org. Synth*., Coll. Vol. **VII**, 1990, 69, 1-6

192 J.K. Whitesell, A. Bhattacharya, and K. Henke, *J. Chem. Soc*., *Chem. Commun*., 1982, 988-

193 J.K. Whitesell and R.M. Lawrence, *Chimia*, 1986, 40, 318

194 D.L. Comins and J.M Salvador, *Tetrahedron Lett*., 1993, **34**, 801–804

195 G. Langrand, J. Baratti, G. Buono, C. Triantaphylides, *Tetrahedron Lett*., 1986, **27**, 29–32

196 E. Pretsch, P. Buhlmann, and C. Affolter, "*Structure Determination of Organic Compounds*", 3rd Ed, 2000, Springer-Verlag, Berlin Heidelberg

197 C.F. Lane, *Synthesis*, 1975, 135–146

198 B.Lüning and C. Lundin, *Acta Chem. Scand*., 1967, **21**, 2136–2142

199 F. Bohlmann, *Chem. Ber*., 1958, **91**, 2157–2167

200 L. Jackmann, "*Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*", 1959, Oxford University Press, Oxford, 112–117

201 B.H. Kim and D.P. Curran, *Tetrahedron*, 1993, **49**, 293–318

202 W. Oppolzer, G. Poli, C. Startkann, and G. Bernardinelli, *Tetrahedron Lett*., 1988, **29**, 3559–3562

203 IUPAC International Union of Pure and Applied Chemistry Nomenclature of Organic Chemistry, Section E (Stereochemistry). Pergamon, New York, (1979)

204 I. Dostrovsky, E. D. Hughes, C. K. Ingold, *J. Chem. Soc*., 1946, 143

205 P. de la Mare, L. Fowden, E.D. Hughes, C.K. Ingold, and J. Mackie, *J. Chem. Soc*., 1955, 3200–3205

206 F. H. Westheimer and J. E. Mayer, *J. Chem. Phys*, 1946, **14**, 733

207 F. H. Westheimer, *J. Chem. Phys*, 1947, **15**, 252

208 M. Reiger and F. H. Westheimer, *J. Am. Chem. Soc*., 1950, **72**, 19–28

209 P. M. Morse, *Phys. Rev*., 1929, **34**, 57

210 T. L. Hill, *J. Chem*, *Phys*., 1946, **14,** 465

211 U. Dinur and A.T. Hagler, Chapter 4 in "*Reviews in Computational Chemistry*", (K.B. Lipkowitz and D.B. Boyd ed.), 1991, VCH Publishers. Vol **2**

212 F. N. Allen, J. E. Davies, J. J. Galloy, O. Johnson, O. Kennard, C. F. Macrae, E. M. Mitchell, G. F. Mitchell J. M. Smith, D. G. Watson, *J. Chem. Inf. Comput. Sci*. 1991, **31**, 187–204; CCDC Version 5.18, October 1999.

213 For a review of the different optimization methods see T. Schlick Chapter 1 in "*Reviews in Computational Chemistry*", K.B. Lipkowitz and D.B. Boyd. ed.), 1991, VCH Publishers, Vol **3**

214 L.M. Balbes, S.W. Mascarella, and D.B. Boyd Chapter 7 in "*Reviews in Computational Chemistry*", K.B. Lipkowitz and D.B. Boyd ed.), 1991, VCH Publishers, Vol **5**

215 Hyperchem® Release 5.1 for Windows®, Hypercube Inc. and ALCHEMY® III, Triphos Associates, Inc.

216 MM+ Force Field, N. L. Allinger, *J. Am. Chem. Soc*., 1977, **99**, 8127–8134

217 P. van Eeden, Honours Project, University of the Witwatersrand, 1998

218 W. Oppolzer, I. Rodriguez, J. Blagg, and G. Bernardinelli, *Helv. Chim. Acta*,1989, **72**, 123–130

219 M. -J. Wu, C. –C. Wu, and T. –C. Tseng, *J. Org. Chem*. 1994, **59**, 7188–7189

220 D.A. Evans, M.D. Ennis, and D.J. Mathre, *J. Am. Chem. Soc*. 1982, **104**, 1737–1739

221 J. A. Secrist and M. W. Logue, *J. Org. Chem*. 1972, **37**, 335–336

222 See for example: (a) N. J. Leonard and T. Sato, *J. Org. Chem*., 1969, **34**, 1066–1070 (b) S. Miyano, S. Fujii, O. Yamashita, N. Toraishi, and K. Sumoto, *J. Org. Chem*., 1981, **46**, 1737–1738

223 D.D. Perrin, W.L.F Amarego, and D.R. Perrin, "*Purification of Laboratory Chemicals*", 3rd ed, Pergamon Press Oxford, 1988

224 L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", vol **15,** p 94 and references cited therein

225 D.L. Flynn, R.E. Zelle, and P.A. Grieco, *J. Org. Chem*., 1983, **48**, 2424–2426

226 L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", vol **13**, p 335 and references cited therein

227 W. Walter and J. Voss, "*The Chemistry of Amides*", (J. Zabicky, ed.), 1970, J. Wiley and Sons, New York, 383–475

228 S. Scheibye, B. Pedersen, and S.O. Lawesson, *Bull. Soc. Chim. Belg*., 1978, **87**, 229–231

229 S. Scheibye, J. Kristensen, and S.O. Lawesson, *Tetrahedron*, 1979, **35**, 1339–1343

230 A.W. Dox, *Org.Synth*. Collected Vol. **III**, pg 5–7

231 A.I. Meyers, G. Knaus, and P.M. Kendall, *Tetrahedron Lett*., 1974, **39**, 3495–3498

232 A.I. Meyers, G. Knaus, K. Kamata, and M.E. Ford, *J. Am. Chem. Soc*., 1976, **98**, 567–576

233 A.I. Meyers, G. Knaus, and K. Kamata, *J. Am. Chem. Soc*., 1974, **96**, 268–270

234 P.D. Bartlett and L.H. Knox, *Org. Synth*. Collected Vol. **V**, pg 194–195

235 A. Ursini, P. Maragni, C. Bismara, and B. Tamburini, *Synth*. *Commun*., 1999, **29**(8), 1369–1377

236 A.B. Holmes, A.L. Smith, S.F. William, L.R. Hughes, Z. Lidert, and C. Swithenbank *J*. *Org*. *Chem*., 1991, **56**, 1393–1405

237 S.I. Goldberg and I. Ragade, *J*. *Org*. *Chem*., 1967, **32**, 1046–1050

238 J.P. Célérier, M. Haddad, C. Saliou, G. Lhommet, *Tetrahedron*, 1989, **45**(19), 6161–6170

239 J-L. Luche, L. Rodriguez-Hahn, P. Crabbé, *J*. *Chem*. *Soc*., *Chem*. *Commu*., 1978, 601–602

240 Siemens (1995) SHELXTL Version 5.0 - Structure determination program. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA

241 Siemens (1995) ASTRO and SAINT - Data collection and processing software for the SMART system. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA

242 Siemens (1996) SMART Reference Manual. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA

Appendix A:

x-Ray Crystallography Data

The X-ray data were collected on either an Enraf–Nonius CAD-4 diffractometer or the novel 1K SMART Siemens CCD area detector system using Mo radiation. X-rays were generated using a regular sealed tube and an X-ray generator operating at 50 kV and 30mA. The 9 cm wide CCD area detector was mounted 4. cm from the crystal and the dataset collected at room temperature (unless otherwise). A graphite monochromator followed by a 0.5 mm collimator was used. The selected crystals were individually mounted on a glass fibre.

In order to obtain an initial set of cell parameters and an orientation matrix for data collection, a number of reflections (usually 150) from 3 sets of 15 frames each were collected covering 3 perpendicular sectors of space.

The data collection nominally covered over a full sphere/hemisphere of reciprocal space, by a combination of 3 sets of exposures. Each set had a different φ angle for the crystal and each exposure covered 0.3° in ω.

In order to monitor crystal and instrument stability, and to enable crystal decay corrections, the first 50 frames of the first set were measured again at the end of the data collection. Unless otherwise stated, crystal decay was found to be negligible after analysing duplicate reflections.

The structures were solved using the Patterson method or direct methods, followed by normal difference Fourier techniques. The H atoms were placed geometrically and refined with a riding model, and with U_{iso} constrained to 0.08 Å, and fixed C–H distances (C–H = 0.95 Å; B_{iso} = 4 Å^2). The structures were refined by the full-matrix least-squares method (anisotropically for the non-H atoms). Atomic scattering factors were those included in SHELX93.[240][241][242] Other programs used were SHELX76 and, ORTEP.

The determination of the unit cell parameters, crystal orientation, and data collection were performed with the SMART system.[242] The crystallographic raw data frames were integrated, all reflections extracted, reduced, and Lp-corrected using the program SAINT.[241] The program SHELXTL ver. 5.0 was used for structure solution, refinement, molecular graphics, and publication preparation.[240]

The following tabulated data were obtained for the crystal structures of sultam-containing compounds **155** and **156**, as well as **179**. Values in parentheses are error margins where appropriate.

Table 12 – Crystal structure refinement data for **155**

Compound (File)	**155** (LC16_s)
IUPAC Name	3-{2-[2-(1*S*,5*R*,7*R*)-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propyl acetate
Empirical formula	$C_{21}H_{32}N_2O_5S$
Formula weight	424.5542
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	9.2964 (0.0005)
b(Å)	11.8847 (0.0007)
c(Å)	19.5268 (0.0011)
α(°)	90
β(°)	90
γ(°)	90
Volume (Å^3)	2157.42
Z	4
D_{calc} (g cm^3)	1.307
Absorption coefficient. (mm^{-1})	0.18
F(000)	912
Index ranges	–10≤h≤11; –15≤k≤15; –17≤l≤25
Reflections collected	13945
Independent reflections	4953
R_{int}	0.0282
Reflections Observed (>4σ)	4702
Final *R* indices (I>2σ (I)	*R*1 = 0.0436 and w*R*2 = 0.1280
Electron density synthesis (Fo-Fc)	Max = 0.23 and min = –0.43 e.Å^{-3}

Appendix A

ORTEP Diagram for Compound 155

Note: The numbering used is the same as for the tables of co-ordinates, bond angles, and bond lengths, but differs from the numbering used in the NMR assignments.

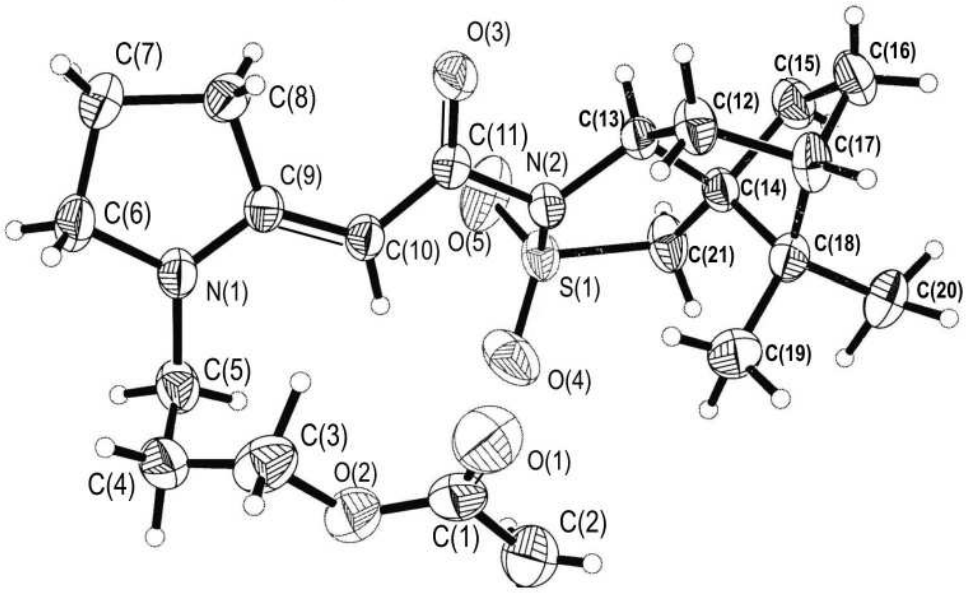


Table 13 – Atomic co-ordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\times 10^4$) for compound **155**, with errors given in parentheses.

Atom	**x**	**y**	**z**	**U(eq) / A^2**
S1	725(1)	3704(1)	7165(1)	365(1)
N1	4185(2)	5501(1)	–99(1)	343(3)
N2	230(2)	4986(1)	1491(1)	299(3)
01	–830(2)	5184(2)	–617(1)	660(5)
02	994(2)	4075(1)	–926(1)	508(4)
03	1275(2)	6716(1)	1413(1)	432(3)
04	789(3)	2941(1)	1202(1)	658(6)
05	1977(2)	3784(2)	2190(1)	685(6)
Cl	–329(3)	4275(2)	–672(1)	471(5)
C2	–1035(4)	3191(3)	–480(2)	618(7)
C3	1807(3)	5037(2)	–1156(1)	524(5)
C4	3367(3)	4669(2)	–1190(1)	514(5)
C5	4022(2)	4466(2)	–492(1)	419(4)
C6	5251(3)	6327(2)	–327(1)	489(5)
C7	5235(2)	7205(2)	234(1)	456(5)
C8	3793(2)	7039(2)	598(1)	365(4)
C9	3327(2)	5860(2)	410(1)	288(3)
C10	2215(2)	5262(2)	696(1)	325(4)
C11	1303(2)	5737(2)	1213(1)	305(3)
C12	–1915(2)	6300(2)	1671(1)	399(4)
C13	–798(2)	5486(1)	1981(1)	298(3)
C14	–1723(2)	4510(2)	2268(1)	320(3)
C15	–2341(2)	4956(2)	2948(1)	433(4)
C16	–3421(3)	5865(2)	2691(1)	487(5)
C17	–3347(2)	5765(2)	1904(1)	429(5)
C18	–3077(2)	4497(2)	1798(1)	403(4)
C19	–2822(3)	4164	1051(1)	557(6)
C20	–4287(3)	3727	2068(2)	665(7)
C21	–819(3)	3449(2)	2291(1)	456(5)

Table 14 – Atomic co-ordinates ($\times 10^4$) of placed hydrogen atoms for compound **155** with errors given in parentheses.

Atom	x	y	z
H2A	–38(10)	260(8)	–26(5)
H2B	–191(5)	327(3)	–43(2)
H2C	–93(5)	258(3)	–75(2)
H3A	144(4)	531(2)	–157(2)
H3B	157(4)	567(3)	–78(2)
H4A	382(3)	519(2)	–142(1)
H4B	341(4)	398(3)	–145(2)
H5A	506(4)	409(3)	–49(2)
H5B	350(3)	397(2)	–24(1)
H6A	629(4)	601(3)	–34(2)
H6B	489(3)	667(2)	–81(2)
H7A	540(3)	789(3)	5(2)
H7B	614(3)	702(2)	54(2)
H8A	385(3)	709(3)	102(2)
H8B	309(3)	753(2)	45(1)
H10	200(3)	450(2)	56(1)
H12A	–179(3)	633(2)	120(2)
H12B	–171(3)	707(2)	178(1)
H13A	–33(2)	585(2)	232(1)
H15A	–166(4)	540(3)	325(2)
H15B	–269(3)	435(2)	322(1)
H16A	–333(2)	653(3)	282(2)
H16B	–434(3)	572(2)	288(1)
H17	–427(4)	610(3)	164(1)
H19A	–214(3)	465(2)	80(1)
H19B	–247(4)	330(3)	100(2)
H19C	–367(5)	412(3)	81(2)
H2OA	–467(4)	380(3)	257(2)
H2OB	–375(5)	287(4)	195(2)
H20C	–529(6)	397(4)	189(3)
H21A	–42(4)	330(3)	269(2)
H21B	–133(3)	280(3)	208(2)

Table 15 – Bond Lengths (Å) and Bond Angles (°) for Compound **155**

Bond Lengths		**Bond Angles**	
Bond	**Length**	**Bond**	**Angle**
C(1)–C(2)	1.494(4)	C(2)-C(1)-O(1)	126.31(27)
C(1)–O(1)	1.182(3)	O(1)-C(1)-O(2)	123.69(24)
O(2)–C(3)	1.441(3)	C(1)-O(2)-C(3)	116.96(20)
C(3)–C(4)	1.516(4)	O(2)-C(3)-C(4)	106.63(20)
C(4)–C(5)	1.512(3)	C(3)-C(4)-C(5)	113.07(19)
C(5)–N(1)	1.457(3)	C(4)-C(5)-N(1)	112.40(17)
C(6)–N(1)	1.465(2)	C(5)-N(1)-C(6)	118.49(16)
C(9)–N(1)	1.344(2)	C(5)-N(1)-C(9)	126.52(16)
C(6)–C(7)	1.514(3)	N(1)-C(6)-C(7)	103.62(16)
C(7)–C(8)	1.529(3)	C(6)-C(7)-C(8)	104.81(16)
C(8)–C(9)	1.511(3)	C(7)-C(8)-C(9)	104.99(16)
C(9)–C(10)	1.374(2)	C(8)-C(9)-C(10)	126.62(16)
C(10)–C(11)	1.434(2)	C(9)-C(10)-C(11)	121.85(16)
C(11)–O(3)	1.227(2)	C(10)-C(11)-O(3)	127.57(17)
C(11)–N(2)	1.445(2)	C(10)-C(11)-N(2)	115.44(15)
N(2)-S(1)	1.679(1)	C(11)-N(2)-S(1)	119.42(12)
C(13)-N(2)	1.475(2)	C(11)-N(2)-C(13)	116.19(14)
S(1)-O(4)	1.426(2)	N(2)-S(1)-O(4)	102.02(10)
S(1)-O(5)	1.432(2)	N(2)-S(1)-O(5)	110.31(11)
C(1)–O(2)	1.347(3)	O(4)-S(1)-O(5)	117.08(14)
C(21)-S(1)	1.791(2)	O(5)-S(1)-C(21)	109.29(12)
		N(2)-S(1)-C(21)	96.70(8)
C(14)-C(21)	1.517(3)	S(1)-C(21)-C(14)	106.63(12)
C(13)-C(14)	1.549(2)	C(21)-C(14)-C(13)	109.01(15)
C(14)-C(15)	1.542(2)	C(21)-C(14)-C(15)	117.81(17)
C(14)-C(18)	1.557(3)	C(21)-C(14)-C(18)	117.23(17)
C(12)-C(13)	1.543(2)	N(2)-C(13)-C(12)	115.74(14)
C(12)-C(17)	1.545(3)	N(2)-C(13)-C(14)	106.97(13)
C(15)-C(16)	1.557(3)	C(14)-C(15)-C(16)	101.63(16)
C(16)-C(17)	1.543(3)	C(15)-C(16)-C(17)	103.81(16)
C(17)-C(18)	1.542(3)	C(12)-C(17)-C(18)	102.82(16)
		C(16)-C(17)-C(18)	102.54(18)
		C(12)-C(17)-C(16)	107.48(18)
C(18)-C(19)	1.528(3)	C(14)-C(18)-C(17)	92.42(15)
C(18)-C(20)	1.543(3)	C(14)-C(18)-C(19)	116.05(17)
		C(14)-C(18)-C(20)	113.17(20)
		C(17)-C(18)-C(20)	114.49(19)

Table 16– Crystal structure refinement data for **156**

Compound (File)	**156** (LC14_s)
IUPAC Name	Ethyl 3-{2-[2-(1*S*,5*R*,7*R*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-oxo-ethylidene]pyrrolidin-1-yl}propanoate
Empirical formula	$C_{21}H_{32}N_2O_5S$
Formula weight	424.5542
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	8.9607 (0.0005)
b(Å)	11.7839 (0.0007)
c(Å)	21.3871 (0.0013)
α(°)	90
β(°)	90
γ(°)	90
Volume (Å^3)	2258.31
Z	4
D_{calc} (g cm^3)	1.225
Absorption coefficient. (mm^{-1})	0.18
F(000)	880
Index ranges	–11≤h≤11; –15≤k≤15; –14≤l≤28
Reflections collected	13774
Independent reflections	5038
R_{int}	0.0640
Reflections Observed (>4σ)	3289
Final *R* indices (I>2σ (I)	*R*1 = 0.0994 and w*R*2 = 0.2268
Indices without C1, C2, and O1	*R*1 = 0.0261 and w*R*2 = 0.0614
Electron density synthesis (Fo-Fc)	Max = 0.36 and min = –0.40 e.Å^{-3}

ORTEP Diagram for Compound 156

Note: The numbering used is the same as for the tables of co-ordinates, bond angles, and bond lengths, but differs from the numbering used in the NMR assignments.

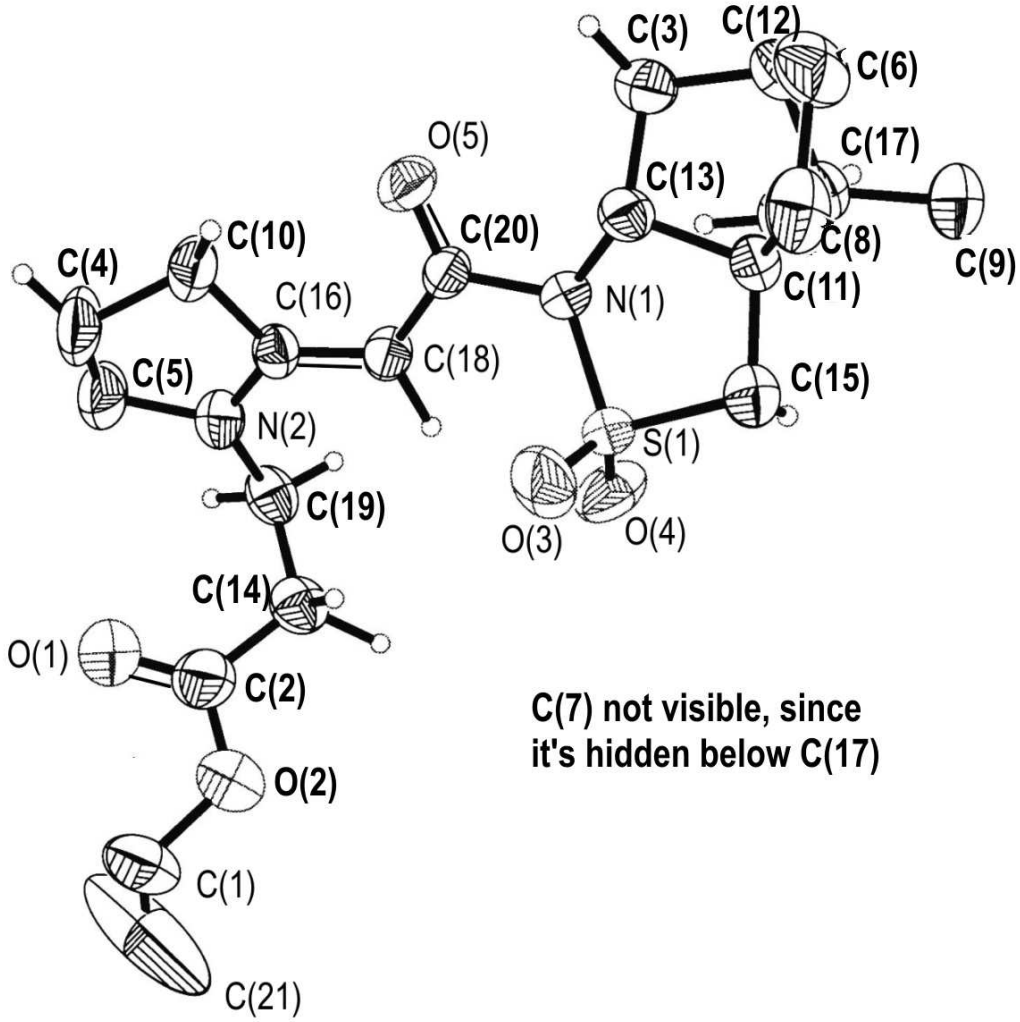


Table 17– Atomic co-ordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\times 10^4$) for compound **156** with errors given in parentheses.

Atom	**x**	**y**	**z**	**U(eq) / A^2**
S1	416(0)	197(0)	251(1)	43(0)
N1	349(0)	84(0)	290(0)	39(1)
N2	-93(0)	66(0)	160(0)	50(1)
O1	-191(1)	200(1)	37(0)	-58(5)
O2	-54(1)	354(0)	30(0)	93(2)
O3	463(1)	165(0)	190(0)	-30(3)
O4	313(0)	290(0)	256(0)	-1(2)
O5	248(0)	-87(0)	268(0)	54(1)
Cl	-87(1)	359(1)	-38(0)	105(3)
C2	-102(1)	267(1)	60(0)	-4(4)
C3	447(1)	-50(1)	377(0)	0(3)
C4	-85(1)	-117(1)	121(0)	-10(4)
C5	-187(1)	-15(1)	126(0)	-13(3)
C6	721(1)	-38(1)	393(0)	21(3)
C7	413(1)	181(1)	427(0)	13(4)
C8	740(1)	46(1)	336(0)	63(2)
C9	688(1)	188(1)	445(0)	73(2)
C10	16(1)	-108(0)	179(0)	57(1)
C11	593(1)	113(0)	339(0)	41(1)
C12	568(1)	-5(0)	421(0)	3(3)
C13	479(1)	21(0)	316(0)	2(2)
C14	-51(1)	267(0)	127(0)	9(3)
C15	577(1)	217(1)	299(0)	-8(3)
C16	19(1)	18(0)	192(0)	-3(2)
C17	562(1)	126(0)	410(0)	-1(2)
C18	118(1)	74(0)	229(0)	40(1)
C19	-138(1)	186(1)	168(0)	50(1)
C20	237(1)	15(0)	262(0)	38(1)
C21	-164(2)	454(1)	-51(0)	223(9)

Table 18 – Atomic co-ordinates ($\times 10^4$) of placed hydrogen atoms for compound **156** with errors given in parentheses.

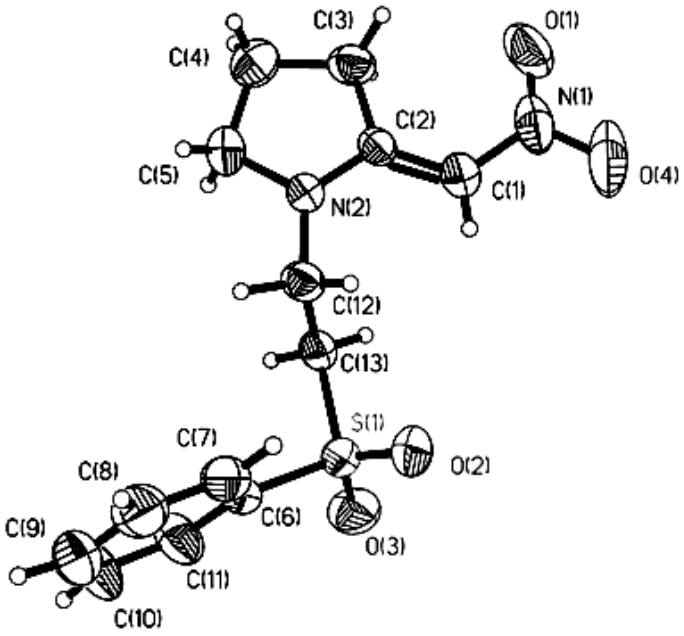
Atom	x	y	z
H3A	449(5)	-138(4)	364(2)
H3B	364(5)	-38(4)	388(2)
H4	-112(8)	-191(6)	116(3)
H6A	791(6)	-29(4)	433(3)
H7A	415(7)	197(5)	477(3)
H7B	324(5)	149(3)	398(2)
H7C	439(6)	264(5)	418(3)
H8	798(6)	81(4)	340(2)
H9A	698(6)	258(4)	431(2)
Hl0	137(8)	-159(6)	176(3)
H14A	-9(7)	352(5)	148(3)
H14B	48(6)	253(4)	129(2)
H15A	547(5)	276(4)	320(2)
H18	105(7)	172(6)	230(3)
H19A	-252(6)	178(4)	156(2)
H19B	-119(5)	202(4)	210(2)

Table 19 – Bond Lengths (Å) and Bond Angles (°) for Compound **156**

Bond Lengths		**Bond Angles**	
Bond	**Length**	**Bond**	**Angle**
C(1)–C(21)	1.338(14)	C(21)-C(1)-O(2)	109.38(78)
C(1)–O(2)	1.487(9)	C(1)-O(2)-C(2)	117.72(57)
C(2)–O(1)	1.225(8)	O(2)-C(2)-O(1)	121.34(63)
C(2)–C(14)	1.492(9)	O(2)-C(2)-C(14)	112.50(59)
C(14)-C(19)	1.523(9)	C(2)-C(14)-C(19)	113.44(53)
C(19)-N(2)	1.479(7)	C(14)-C(19)-N(2)-	113.60(46)
C(5)–N(2)	1.470(7)	C(19)-N(2)-C(5)	121.22(45)
C(16)-N(2)	1.332(6)	C(19)-N(2)-C(16)	123.27(43)
C(4)–C(5)	1.515(10)	N(2)-C(5)-C(4)	101.46(44)
C(4)–C(10)	1.527(8)	C(5)-C(4)-C(10)	104.32(51)
C(2)-O(2)	1.289(7)	C(4)-C(10)-C(16)	103.35(49)
C(10)-C(16)	1.517(8)	C(10)-C(16)-N(2)	107.52(43)
C(16)–C(18)	1.362(6)	C(10)-C(16)-C(18)	126.70(47)
C(18)–C(20)	1.443(7)	C(16)-C(18)-C(20)	121.78(43)
C(20)–O(5)	1.212(6)	C(18)-C(20)-O(5)	126.20(43)
C(20)–N(1)	1.431(6)	C(18)-C(20)-N(1)	116.56(40)
N(1)-S(1)	1.682(4)	C(20)-N(1)-S(1)	119.27(31)
C(13)-N(1)	1.490(6)	C(20)-N(1)-C(13)	114.83(37)
S(1)-O(3)	1.427(4)	N(1)-S(1)-O(3)	110.17(24)
S(1)-O(4)	1.435(4)	N(1)-S(1)-O(4)	109.71(21)
		O(3)-S(1)-O(4)	117.82(28)
C(15)-S(1)	1.780(6)	O(4)-S(1)-C(15)	112.22(27)
		N(1)-S(1)-C(15)	96.44(23)
C(11)-C(15)	1.517(8)	S(1)-C(15)-C(11)	107.08(37)
C(11)-C(13)	1.569(7)	C(15)-C(11)-C(13)	108.61(39)
C(3)-C(13)	1.568(8)	C(11)-C(13)-C(3)	102.68(40)
		N(1)-C(13)-C(3)	115.51(43)
		N(1)-C(13)-C(11)	106.22(37)
C(3)-C(12)	1.535(8)	C(13)-C(3)-C(12)	102.09(44)
C(12)-C(17)	1.556(7)	C(3)-C(12)-C(17)	102.66(42)
C(6)-C(12)	1.555(9)	C(3)-C(12)-C(6)	106.70(49)
		C(17)-C(12)-C(6)	102.47(48)
C(6)-C(8)	1.568(10)	C(12)-C(6)-C(8)	103.81(47)
C(8)-C(11)	1.530(7)	C(6)-C(8)-C(11)	101.72(48)
C(11)-C(17)	1.552(6)	C(8)-C(11)-C(17)	104.00(44)
C(9)-C(17)	1.538(8)	C(13)-C(11)-C(17)	105.09(39)
		C(8)-C(11)-C(13)	101.20(43)
		C(15)-C(11)-C(17)	117.62(44)
C(7)-C(17)	1.531(8)	C(12)-C(17)-C(7)	114.68(46)
C(9)-C(17)	1.538(8)	C(12)-C(17)-C(9)	112.10(48)
		C(7)-C(17)-C(9)	114.49(19)
		C(11)-C(17)-C(9)	

Table 20– Crystal structure refinement data for **199**

Compound (File)	**179** (LC17_s)
IUPAC Name	2-(Nitromethylene)-1-[2-(phenylsulfonyl)ethyl]pyrrolidine
Empirical formula	$C_{13}H_{16}N_2O_4S$
Formula weight	296.3421
Crystal system	Monoclinic
Space Group	$P2_1/n$
a (Å)	8.1770 (0.0005)
b(Å)	9.0528 (0.0006)
c(Å)	19.2072 (0.0012)
α(°)	90
β(°)	98.068(1)
γ(°)	90
Volume (Å^3)	1407.74
Z	4
D_{calc} (g cm^3)	1.398
Absortion coeffic. (mm^{-1})	0.24
F(000)	624
Index ranges	$-10 \le h \le 10$; $-11 \le k \le 11$; $-25 \le l \le 19$
Reflections collected	8744
Independent reflections	3171
R_{int}	0.0275
Reflections Observed (>4σ)	2548
Final *R* indices (I>2σ (I)	*R*1 = 0.0604 and w*R*2 = 0.1899
Electron density synthesis (Fo-Fc)	Max = 0.29 and min = –0.28 e.Å^{-3}



ORTEP Plot for compound **179**

Table 21– Atomic co-ordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\times 10^4$) for compound **179** with errors given in parentheses.

Atom	x	y	z	U(eq) / A^2
C1	501(0)	611(0)	80(0)	47(1)
C2	366(0)	700(0)	61(0)	37(1)
C3	344(0)	816(0)	4(0)	52(1)
C4	181(0)	889(0)	12(0)	66(1)
C5	99(0)	794(0)	60(0)	59(1)
C6	6(0)	356(0)	237(0)	41(1)
C7	60(0)	446(0)	293(0)	50(1)
C8	-52(1)	489(0)	337(0)	68(1)
C9	-210(1)	442(0)	326(0)	81(1)
C10	-265(0)	353(1)	270(0)	84(1)
C11	-156(0)	310(0)	224(0)	64(1)
C12	200(0)	589(0)	145(0)	44(1)
C13	138(0)	440(0)	115(0)	41(1)
N1	647(0)	624(0)	52(0)	62(1)
N2	229(0)	692(0)	90(0)	40(0)
O1	666(0)	719(0)	7(0)	79(1)
O2	311(0)	304(0)	219(0)	60(1)
O3	89(0)	165(0)	147(0)	66(1)
O4	758(0)	533(0)	71(0)	99(1)
S1	147(0)	301(0)	180(0)	43(0)

Table 22 – Atomic co-ordinates ($\times 10^4$) of placed hydrogen atoms for compound **179** with errors given in parentheses.

Atom	x	y	z	Atom	x	y	z
H1	498(4)	542(3)	112(2)	H12A	111(3)	631(3)	169(1)
H3A	439(4)	875(3)	6(1)	H12B	304(4)	577(3)	173(1)
H3B	336(5)	764(5)	-39(2)	H13A	29(4)	440(3)	98(1)
H4A	202(7)	980(6)	36(3)	H13B	205(4)	407(3)	83(1)
H4B	127(6)	916(5)	-28(2)				
H5A	20(6)	740(5)	42(2)				
H5B	67(5)	849(5)	100(2)				
H7	174(4)	479(3)	302(1)				
H8	-25(6)	550(5)	373(2)				
H9	-285(6)	474(5)	352(2)				
H10	-362(7)	318(5)	262(3)				
H11	-189(5)	253(4)	182(2)				

Table 23 - Bond Lengths (Å) and Bond Angles (°) for Compound **179**

Bond Lengths		**Bond Angles**	
Bond	**Length**	**Bond**	**Angle**
C(6)–S(1)	1.768(2)	C(7)-C(6)-S(1)	119.10(20)
		C(11)-C(6)-S(1)	119.80(23)
S(1)-O(2)	1.436(2)	C(6)-S(1)-O(2)	108.45(12)
S(1)-O(3)	1.438(2)	C(6)-S(1)-O(3)	108.10(12)
		O(2)-S(1)-O(3)	118.21(13)
C(13)-S(1)	1.770(2)	C(6)-S(1)-C(13)	105.64(11)
C(12)-C(13)	1.529(3)	S(1)-C(13)-C(12)	112.11(17)
C(12)-N(2)	1.453(3)	C(13)-C(12)-N(2)	111.44(20)
C(5)-N(2)	1.462(3)	C(12)-N(2)-C(5)	120.70(21)
C(2)-N(2)	1.327(3)	C(12)-N(2)-C(2)	124.88(21)
		C(2)-N(2)-C(5)	114.38(21)
C(4)-C(5)	1.493(5)	N(2)-C(5)-C(4)	104.31(24)
C(3)-C(4)	1.519(4)	C(5)-C(4)-C(3)	106.33(25)
C(2)-C(3)	1.503(3)	C(4)-C(3)-C(2)	104.99(23)
C(1)-C(2)	1.371(3)	C(3)-C(2)-N(2)	108.52(21)
		C(3)-C(2)-C(1)	128.03(23)
C(1)-N(1)	1.390(3)	C(2)-C(1)-N(1)	123.07(26)
N(1)-O(1)	1.235(4)	C(1)-N(1)-O(1)	121.86(26)
N(1)-O(4)	1.240(4)	C(1)-N(1)-O(4)	117.33(31)
		O(1)-N(1)-O(4)	120.80(27)

Appendix B

Excel Macros and Data relating to Molecular Modelling

All calculations were performed using HyperChem version 5.0[215] and the MM+ force field.[216] Some of the force field parameters were not available for our system, and hence were added from calculations and from mean values obtained from crystal structures obtain in turn from the Cambridge Crystallographic Data Base.[212] Once all the missing parameters had been added, the accuracy of the force field was tested against the crystal structure of two of the compounds which were not part of the original parameterisation step.

The co-ordinates of the two crystal structures were converted into coordinates for HyperChem, and compared with the structure obtained by a complete energy minimisation of the same molecule using only the HyperChem parameters.

Excel Macro for Running HYPERCHEM® Energy Minimizations as a Function of Torsional Angle. — Written by R. Krause

Comments in italics following an apostrophe

```
'Start of Module
   'Declare all Module Variables
   'Option Explicit
   Dim LowAngle
   Dim HighAngle
   Dim StepAngle
   Dim TEnergy
   Dimx
   Dimc

'Sub Calculate is the main module
Sub Calculate()
   Channel DDElnitiate("HyperChem", "System") 'Open Hyperchem
      Param
      NameD
      RotatE

  'Close Open Channel
      DDETerminate (Channel)
End Sub
```

```
'Set Optimization Parameters, and open Hyperchem file
Sub Param()
   DDEExecute Channel, "query-response-has-tag(no)"
   DDEExecute Channel, "calculation-method = molecularmechanics"
   DDEExecute Channel, "molecular-mechanics-method = mm+"
   DDEExecute Channel, "mechanics-mmp-electrostatics = BondDipoles"
   DDEExecute Channel, "optim-algorithm = polakribiere" 'Or other algorithm
   DDEExecute Channel, "optim-convergence = 0.01" 'Convergence limit
   DDEExecute Channel, "optim-max-cycles = 400" 'Number of cycles to try
      LowAngle = InputBox("Starting Torsion Angle? (Between -180 and +180)",
"Low Angle", 0) 'Opens an input box requesting the starting angle – default 0°
      HighAngle = InputBox("Last Torsion Angle? (Between -180 and +180)",
"High Angle", 180) 'Input for the final angle – default 180°
      StepAngle = InputBox("Angle Increments?", "Step Angle", 10)
End Sub


'NameD Defines all the Named Selections used regularly
Sub NameD()
   DDEExecute Channel, "selection-target(atoms)"
   DDEExecute Channel, "select-none"
   DDEExecute Channel, "select-atom(1,1)" 'This is atom 1 in molecule 1
   DDEExecute Channel, "select-atom(2,1)" 'This selects atom 2 in molecule 1
   DDEExecute Channel, "select-atom(3,1)" 'This selects atom 3 in molecule 1
   DDEExecute Channel, "select-atom(4,1)" 'This selects atom 4 in molecule 1
   DDEExecute Channel, "name-selection = Torsionl"
End Sub

'RotatE() Generates values for a Rotational Energy Profile
Sub RotatE()
      x    LowAngle
      Cells(1,1).Formula = "Angle"
      Cells(1,2).Formula = "Total Energy"
      Cells(1,3).Formula = "RMS Gradient"
      Cells(1,4).Formula = "Kill Counter"

   For x = LowAngle To HighAngle Step StepAngle
      Cells(y,1).Value = x
      SelectTorsion
         DDEExecute Channel, "optim-max-cycles = 200"
         DDEExecute Channel, "do-optimization"
```

```
        Converge = DDERequest(Channel, "rms-gradient")
          Cells(y, 3).Value = Converge
          c = Cells(y, 3).Value

          KillCounter = 1 'A counter to terminate the calculation if it does not
          converge
          Do While c> 0.02
'Next swap to Newton-Raphson algorithm
        DDEExecute Channel, "optim-algorithm = newtonraphson"
        DDEExecute Channel, "optim-convergence = 0.02"
        DDEExecute Channel, "optim-max-cycles = 200"
        DDEExecute Channel, "do-optimization"
'Next swap to Polak-Ribiere algorithm
        DDEExecute Channel, "optim-algorithm = polakribiere"
        DDEExecute Channel, "optim-convergence = 0.02"
        DDEExecute Channel, "optim-max-cycles 100"
        DDEExecute Channel, "do-optimization"

        Converge DDERequest(Channel, "rms-gradient")
                Cells(y, 3).Value = Converge
                Cells(y, 4).Value  =KillCounter
                c = Cells(y, 3).Value

      KillCounter = KillCounter + 1
      If KillCounter = 10 Then Cells(y, 4).Value = KillCounter
      If KillCounter = 10 Then Exit Do

          Loop

'Now calculate the single-point energy of the optimized structure and enter it in
the next available cell in the Excel spreadsheet
     DDEExecute Channel, "do-single-point"
        TEnergy = DDERequest(Channel, "total-energy")
        Cells(y, 2).Value = TEnergy
'Save the hyperchem hin file of the optimized structure
        DDEExecute Channel, "write-file c:\hyper\rui\molecule175\torsion1.j" + y
          + ".hin"

        y = y+ 1
   Next x
End Sub

'Sub SelectTorsion constrains the bond mentioned in Sub NameD
Sub SelectTorsion()
   DDEExecute Channel, "select-name Torsionl"
```

```
    DDEExecute Channel, “set-bond-torsion “+ x
    DDEExecute Channel, “restraint Torsionl, “+ x + “, 99999”
    DDEExecute Channel, “select-none”

End Sub
```

Program Crys-to-Hyp also known as xray2hin

```
/* Program xray2hin -- converts xyz atomic data and x-ray data to .HIN
   format.  Written by Joel Polowin.  Last mod 19:45 Dec 14, 1996.
*/

#include <ctype.h>
#include <math.h>
#include <stdlib.h>
#include <stdio.h>
#include <string.h>

void syntax()
    {
    fprintf(stderr,

"Program xray2hin converts xyz atomic data to .HIN format.\n\n"
"  Syntax: xray2hin [infile] [> outfile]\n\n"
"Data on input lines should be separated by spaces or commas.\n"
"If the first line contains six numbers, the file is\n"
"interpreted as crystal data beginning with a, b, c,\n"
"alpha, beta, gamma values.  Otherwise lines contain\n"
"x,y,z coordinates with an atom type preceding or\n"
"following them.  Lines which can't be parsed as above\n"
"are converted to comment lines in the output.\n\n"
"To assign bonds, read this program's output into HyperChem,\n"
"save in Z-matrix format, and read that file back in.\n\n"
");

    exit(1);
    }

void main(argc,argv)
int   argc;
char *argv[];
{
    void syntax();

    char  line[85],atom[85],atomtype[5],element[4];
    FILE *infile;
    int   atomno=0,crystal=0;
    float a,b,c,alpha,beta,gamma;
    float sina,cosa,cosb,sing,cosg,pirad,fact1,fact2;
    float xin,yin,zin,xout,yout,zout;

    if(argc>2)
       syntax();
```

```
   if(argc==2)
      {
      if(!(infile=fopen(argv[1],"r")))
         {
         fprintf(stderr,"Can't open file %s.\n",argv[1]);
         syntax();
         }
      }
   else infile=stdin;

   printf("sys 0\n");  /* opening comments for .HIN file */
   element[3]=NULL;

   for(;;)
      {
      if(NULL==fgets(line,85,infile)) break;
      if(84==strlen(line))
         fprintf(stderr,"* Warning: truncated line.\n%s\n",line);

      if((atomno==0) && !crystal && (crystal=
        ((6==sscanf(line,"%f %f %f %f %f
%f",&a,&b,&c,&alpha,&beta,&gamma))||

(6==sscanf(line,"%f,%f,%f,%f,%f,%f",&a,&b,&c,&alpha,&beta,&gamma)))
        ))  /* found a crystal header */
         {
         pirad=180./3.14159265;
         sina=sin(alpha/pirad);
         cosa=cos(alpha/pirad);
         cosb=cos(beta/pirad);
         sing=sin(gamma/pirad);
         cosg=cos(gamma/pirad);
         fact1=(cosb-cosa*cosg)/sing;
         fact2=sqrt(sina*sing-fact1*fact1);
         continue;
         }
      if((4!=sscanf(line,"%s %f %f %f",atom,&xout,&yout,&zout)) &&
        (4!=sscanf(line,"%f %f %f %s",&xout,&yout,&zout,atom)) &&
        (4!=sscanf(line,"%f,%f,%f,%s",&xout,&yout,&zout,atom)) &&
        (4!=sscanf(line,"%[^,],%f,%f,%f",atom,&xout,&yout,&zout)))
         {
         printf(";%s",line);
         continue;
         }

      sscanf(atom,"%4s",atomtype);
      atomno++;
      element[0]=toupper(atomtype[0]);
```

```
      element[1]=(isalpha(atomtype[1]))?tolower(atomtype[1]):'\0';
      element[2]=(isalpha(atomtype[2]))?tolower(atomtype[2]):'\0';
      if(crystal)
         {
         xin=a*xout;
         yin=b*yout;
         zin=c*zout;
         xout=xin*sing+zin*fact1;
         yout=yin+xin*cosg+zin*cosa;
         zout=zin*fact2;
         }

      printf("mol %d\natom 1 %s %s ** - 0 %f %f %f 0\nendmol %d\n",
        atomno,atomtype,element,xout,yout,zout,atomno);

      }
   if(infile!=stdin)
      fclose(infile);
   exit(0);

}
```

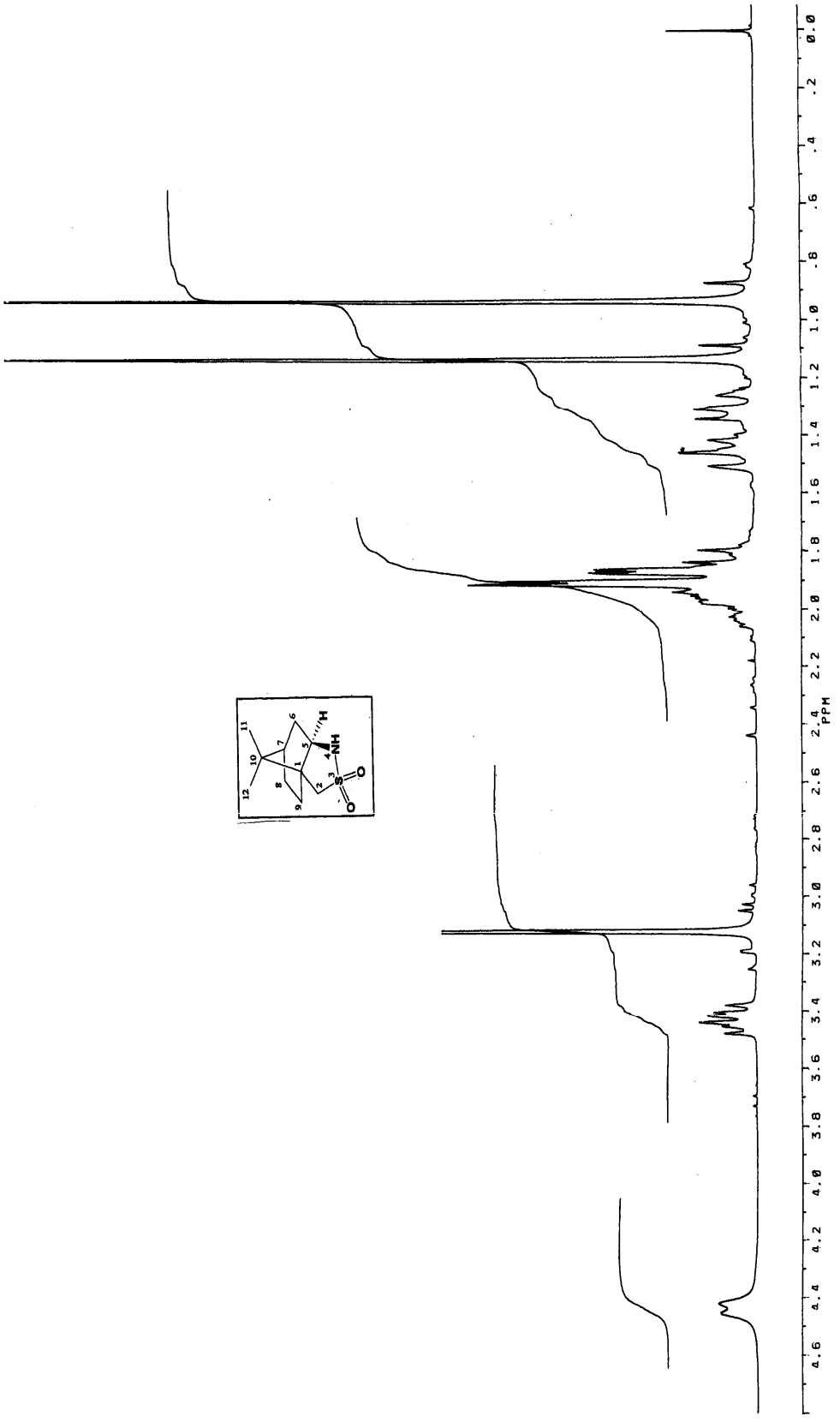
Appendix C

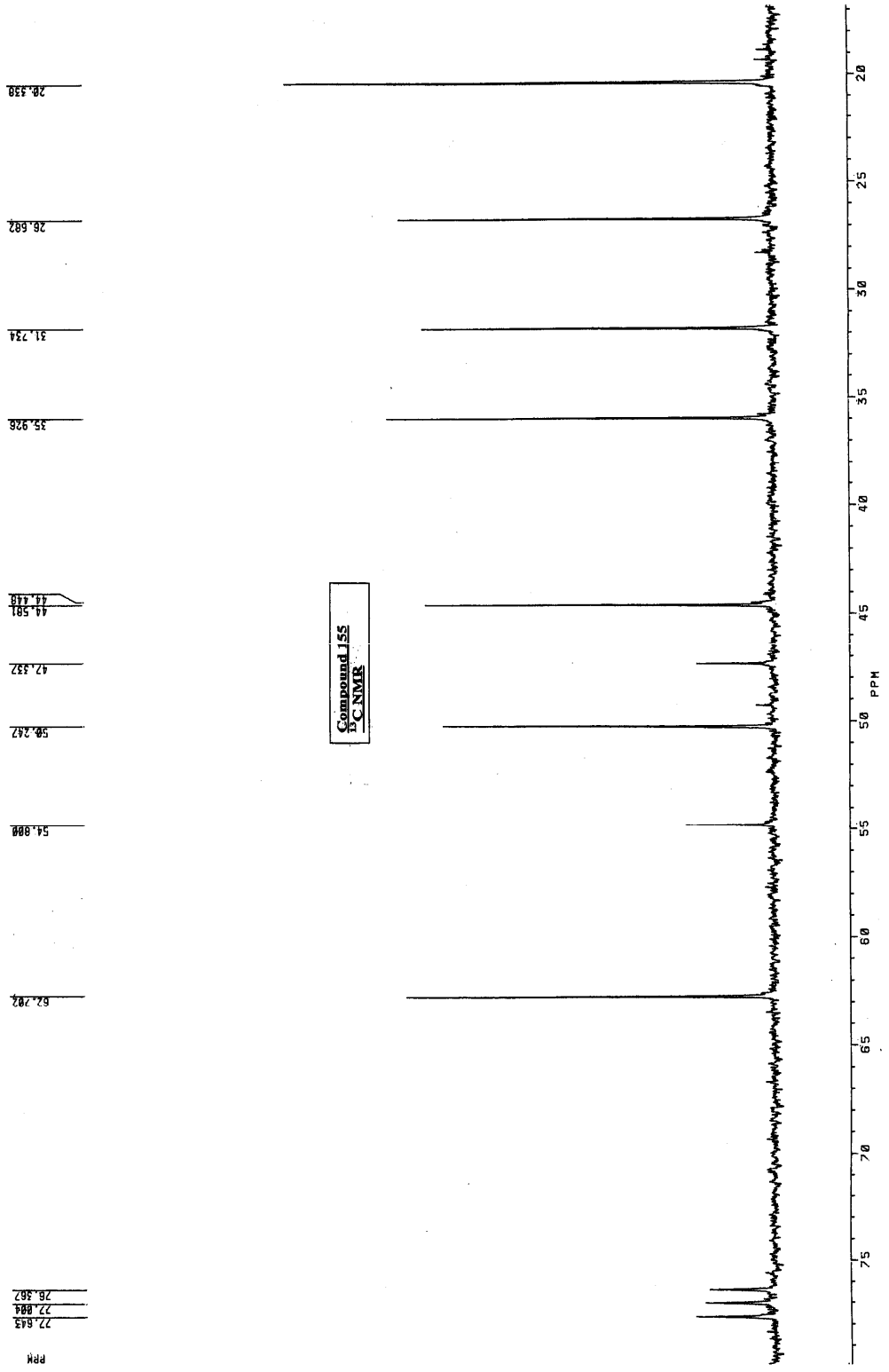
Selected Spectra

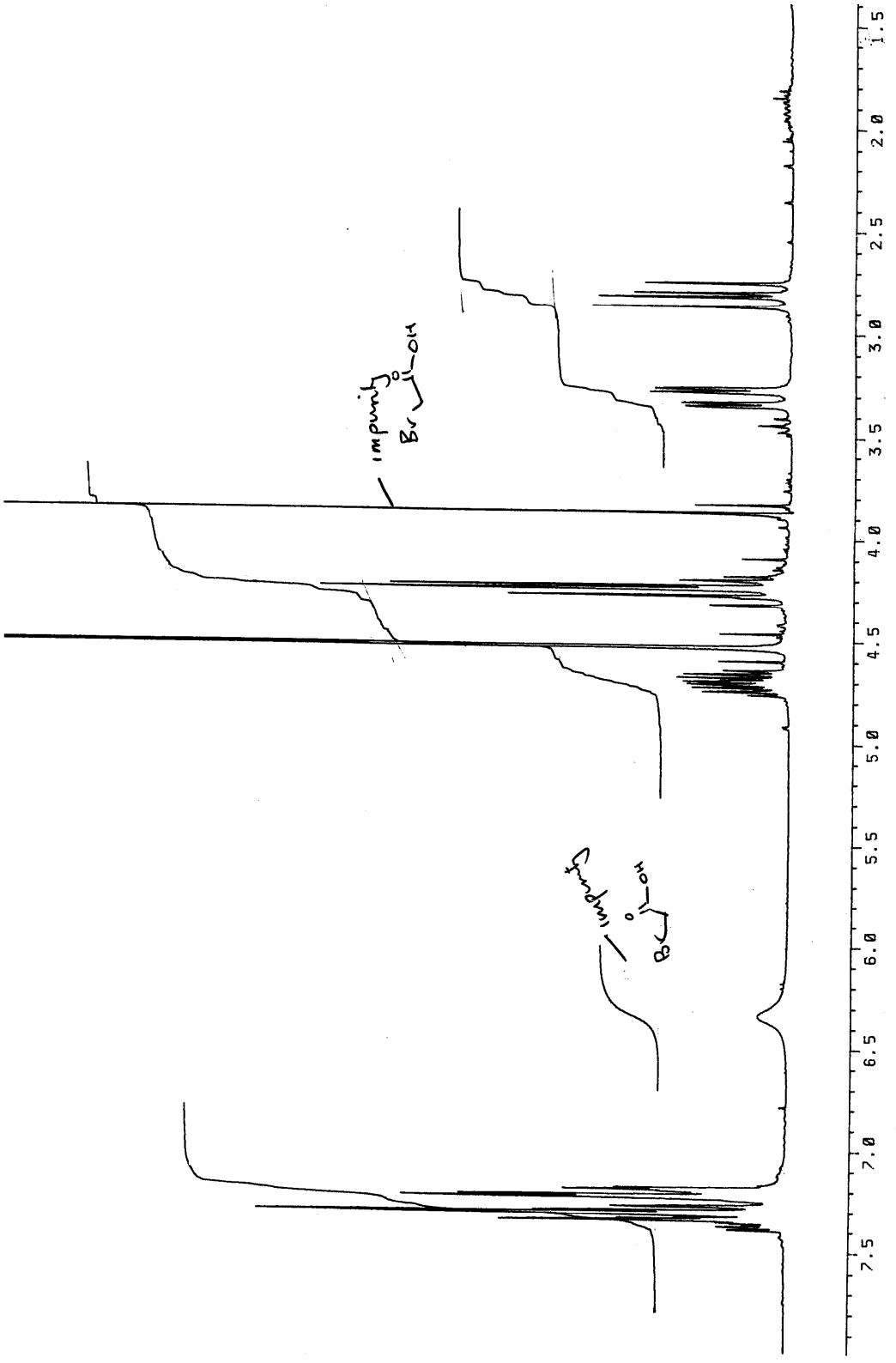
The following copies of original spectra are provided here for reference:

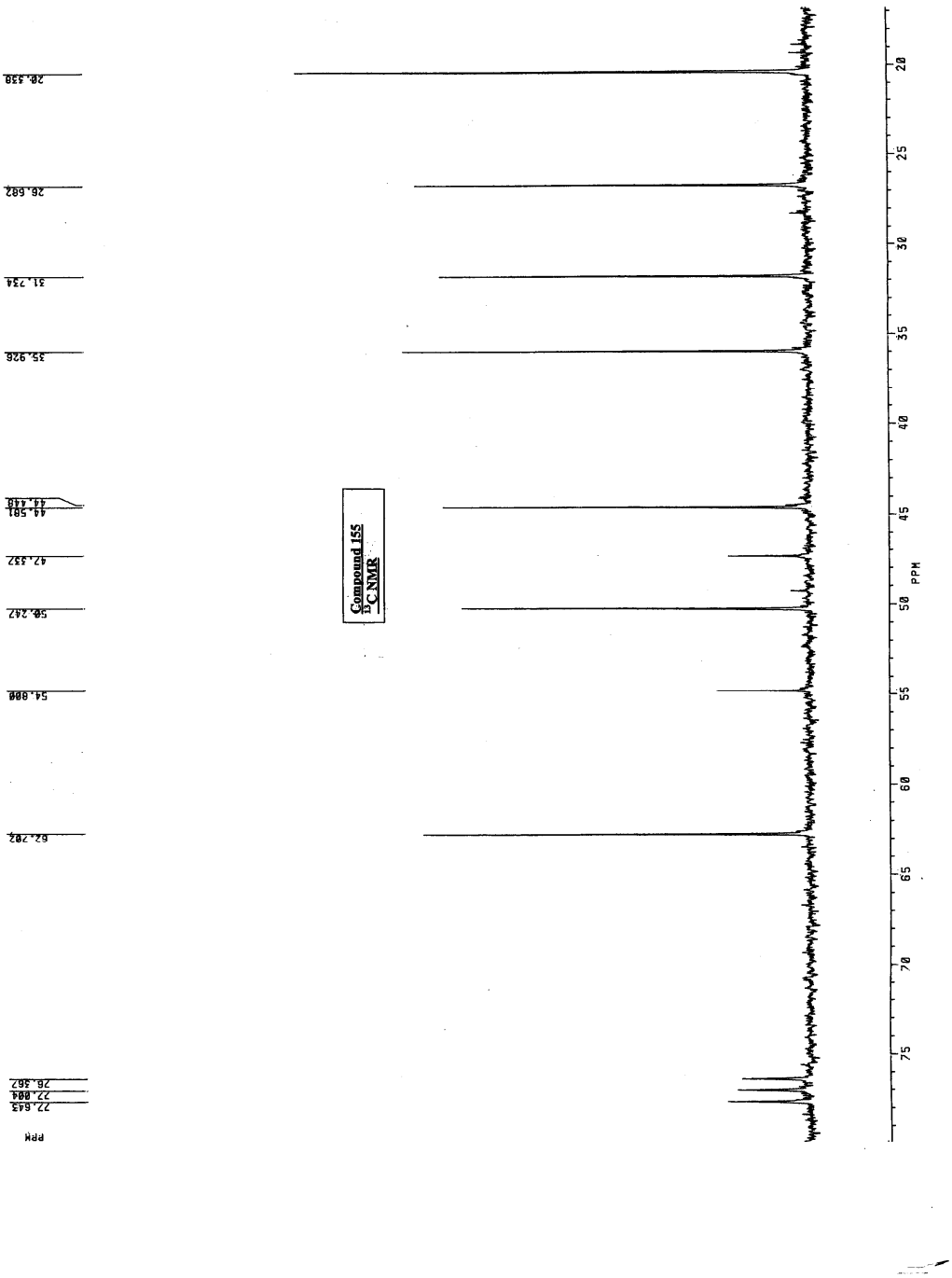
Page **Spectrum**

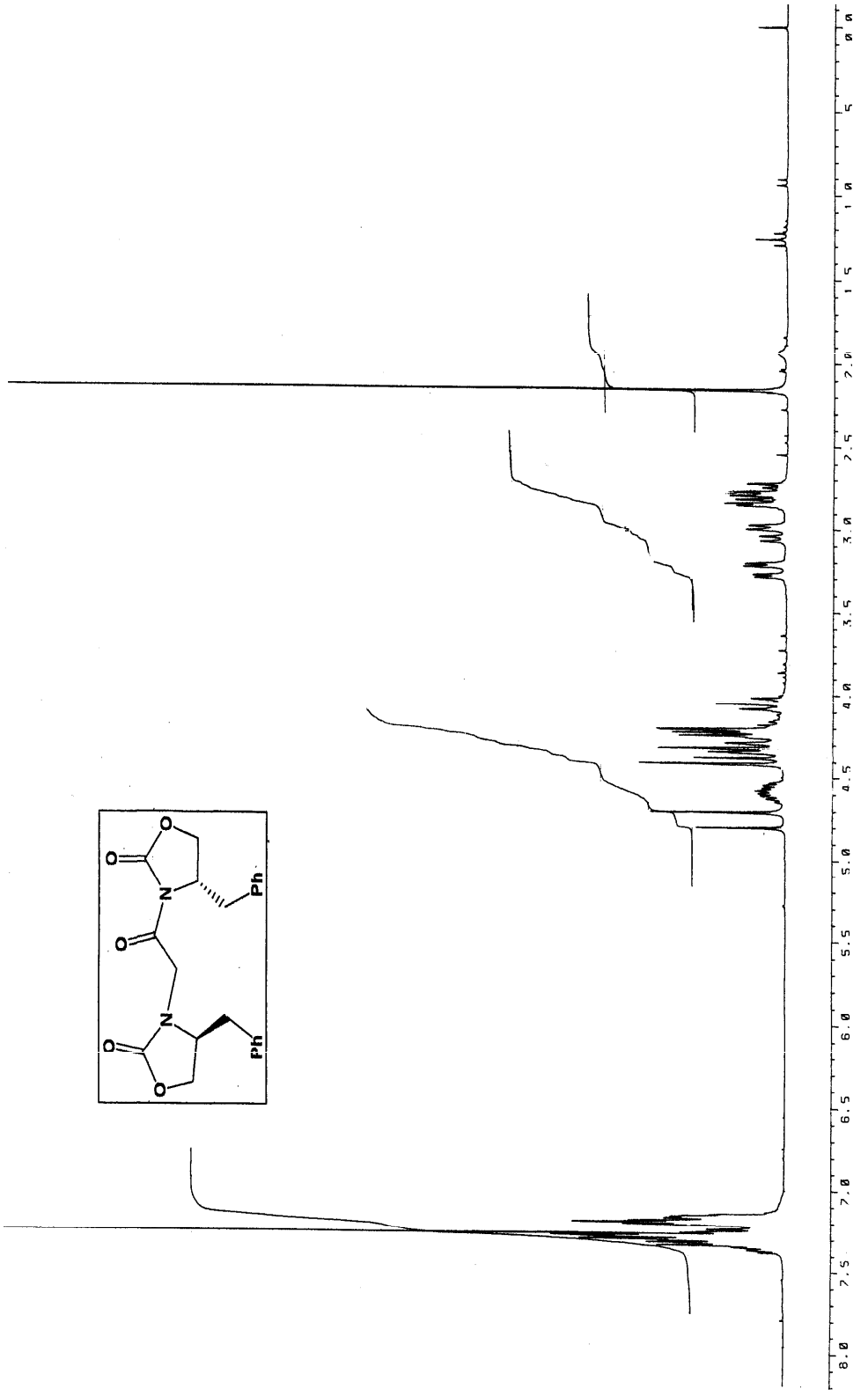
344) ^{1}H NMR spectrum of sultam **135**
345) ^{13}C NMR spectrum of sultam **135**
346) ^{1}H NMR spectrum of bromoacyloxazolidinone **141**
347) ^{13}C NMR spectrum of bromoacyloxazolidinone **141**
348) ^{1}H NMR spectrum of oxazolidinone dimer **142**
349) ^{1}H NMR spectrum of bromoacylated cyclohexanol **163**
350) Mass spectrum of **163**
351) HMBC spectrum of trans-reduced sultam-containing indolizidine **161**
352) ^{1}H NMR spectrum of sultam-containing acetate **155**
353) ^{13}C NMR spectrum of sultam-containing acetate **155**
354) ^{1}H NMR spectrum of TCC-containing pyrrolidinyl alcohol **164**
355) IR spectrum of **164**
356) ^{13}C NMR spectrum of **164**
357) ^{1}H NMR spectrum of 7-oxoindolizidine **159** from acylative cyclisation
358) HMQC spectrum of **159**
359) IR spectrum of sultam-containing didehydroindolizidine **158**
360) HMQC spectrum of **158**
361) ^{1}H spectrum of sultam-containing *N*-methyl compound **154**
362) ^{13}C NMR of reduced sultam-containing *N*-methyl compound **160**
363) Mass spectrum of *trans*-reduced sultam-containing indolizidine **161**
364) ^{1}H NMR spectrum of **161**
365) ^{13}C NMR spectrum of **161**
366) ^{1}H NMR spectrum of *trans*-reduced 8-ethoxycarbonylindolizidine **113**
367) ^{13}C NMR of **113**
368) ^{13}C NMR of reduction of sultam compound **158** showing tashiromine
369) ^{1}H and ^{13}C NMR spectrum of *cis*-8-ethoxycarbonylindolizidine **114**
370) ^{1}H NMR of epitashiromine **2**
371) ^{13}C NMR of **2**
372) mass spectrum of (±)tashiromine **1**
373) HMQC spectrum of **1**
374) ^{1}H NMR of (–)-**1**
375) ^{13}C NMR of (–)-**1**

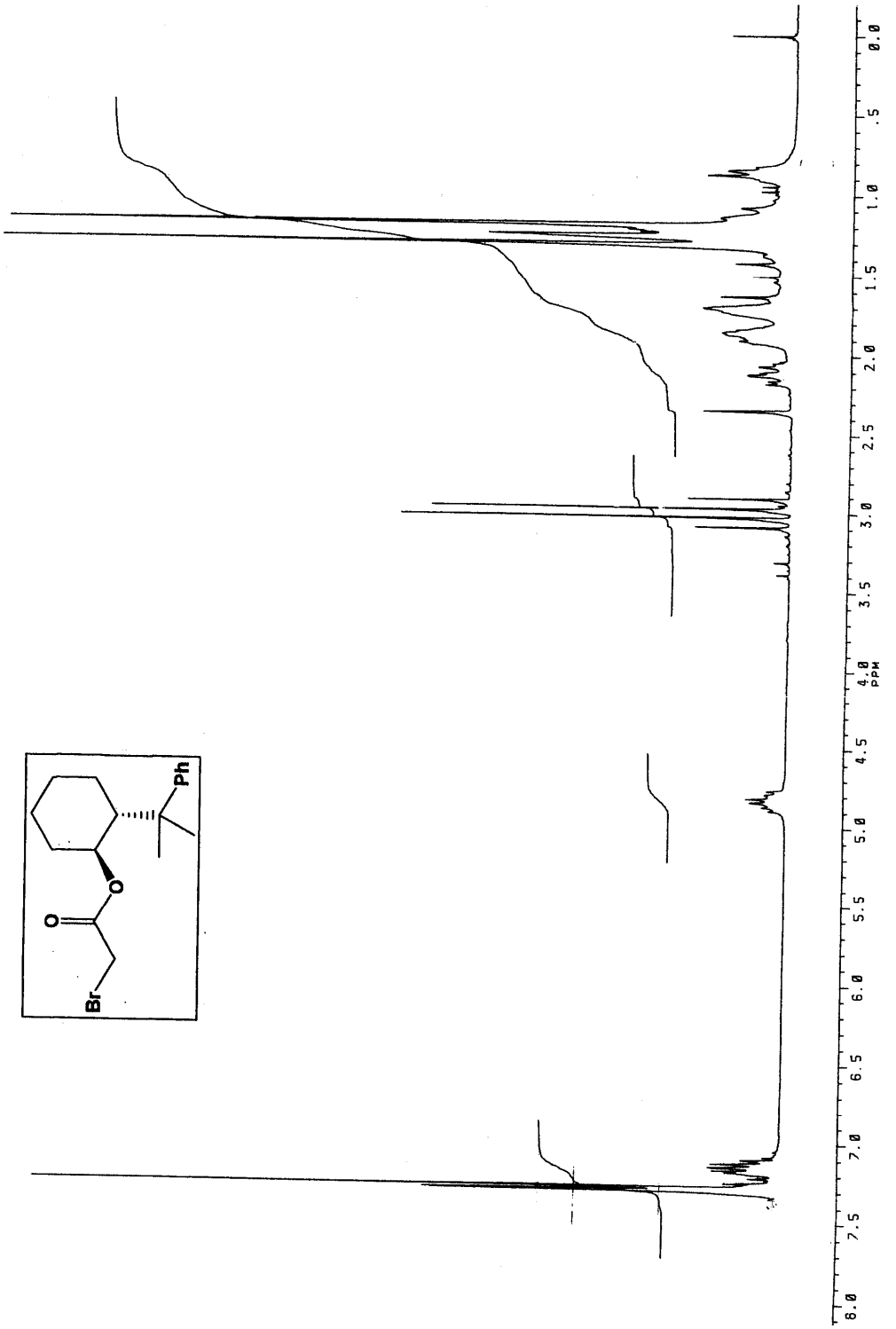

PPM

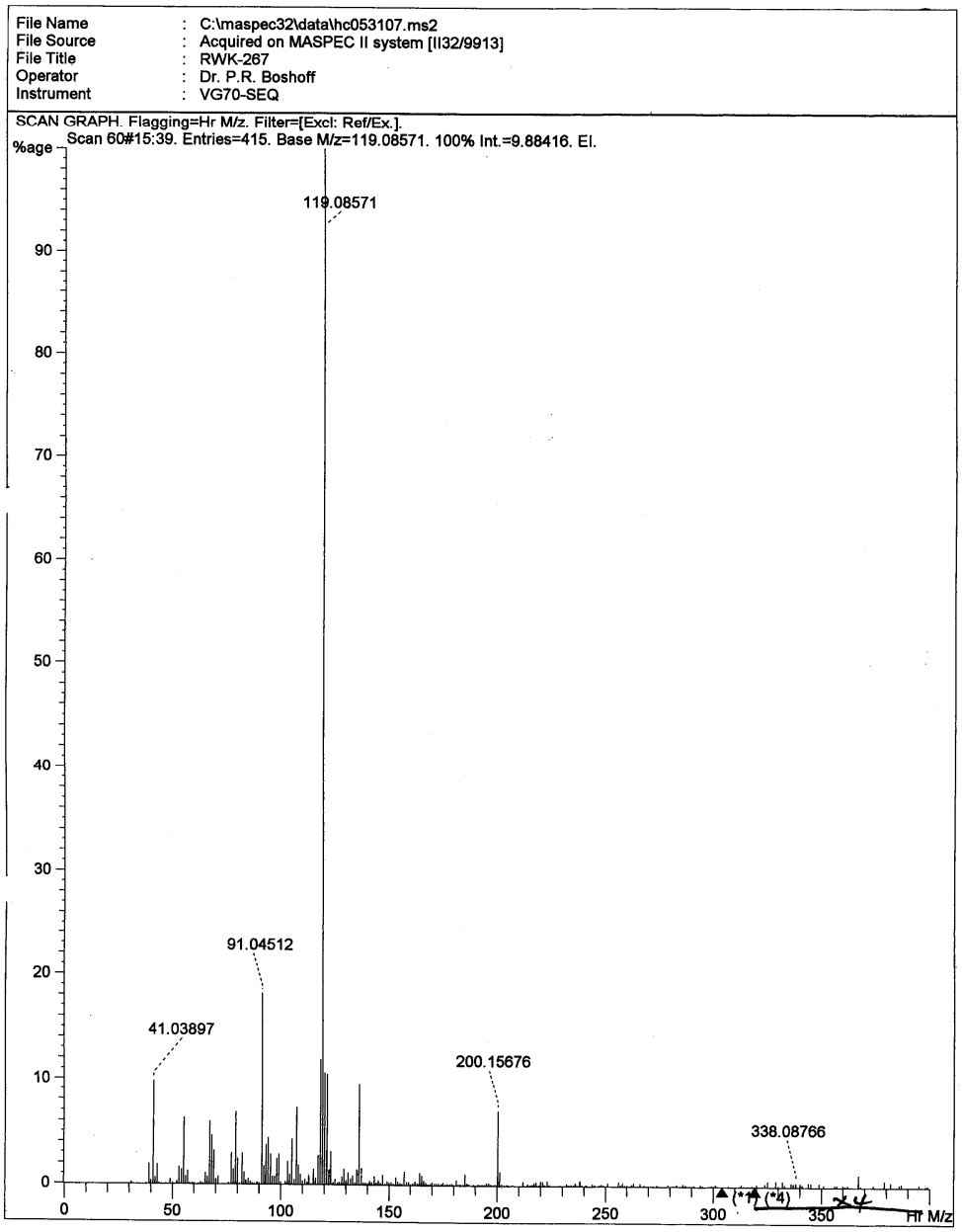

Compound 155
13C NMR
20.338
26.682
31.734
35.926
44.581
44.448
42.332
50.247
54.000
62.202
76.367
77.004
77.643
PPM

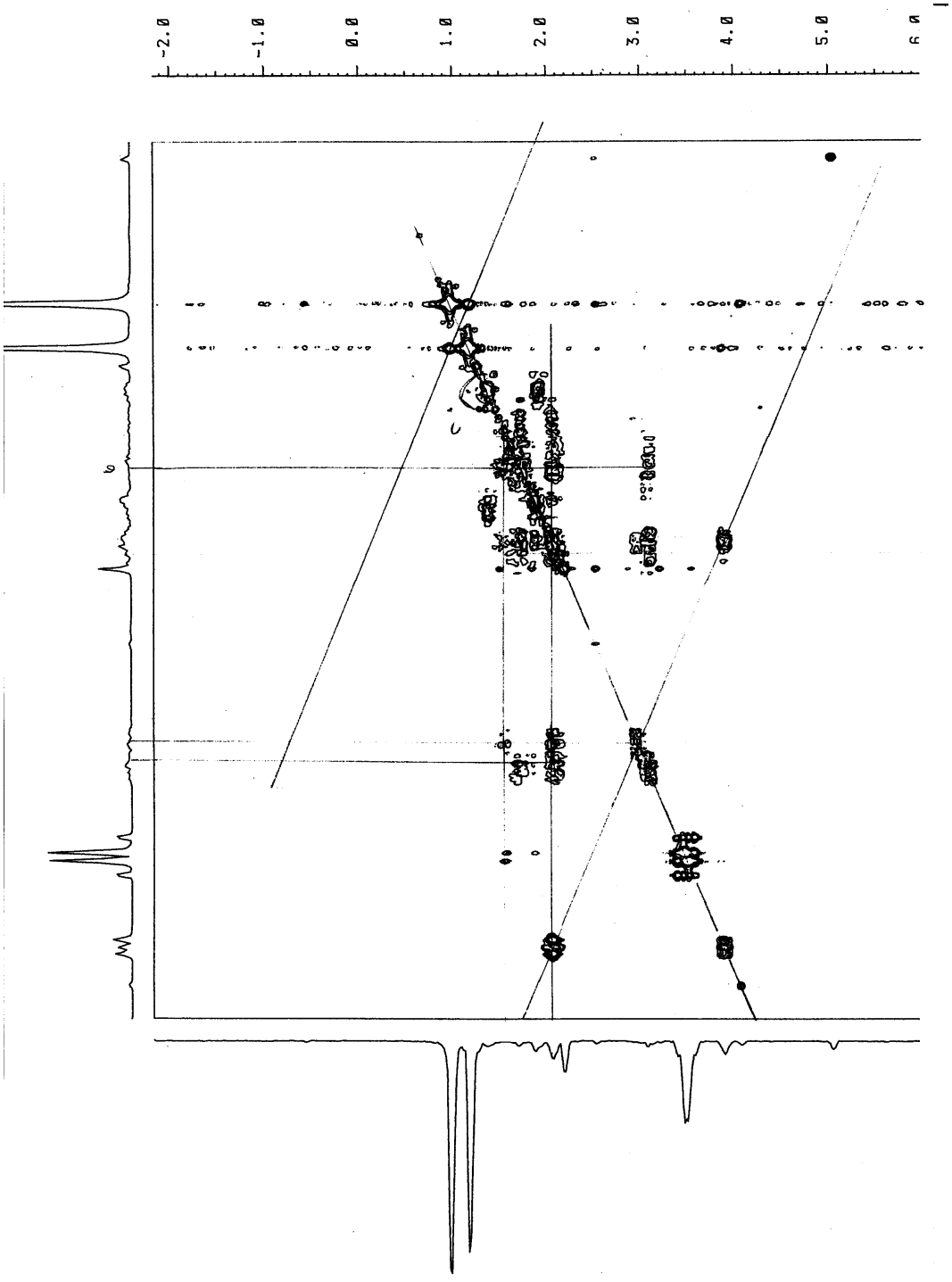

impurity
Br
impurity
Br
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

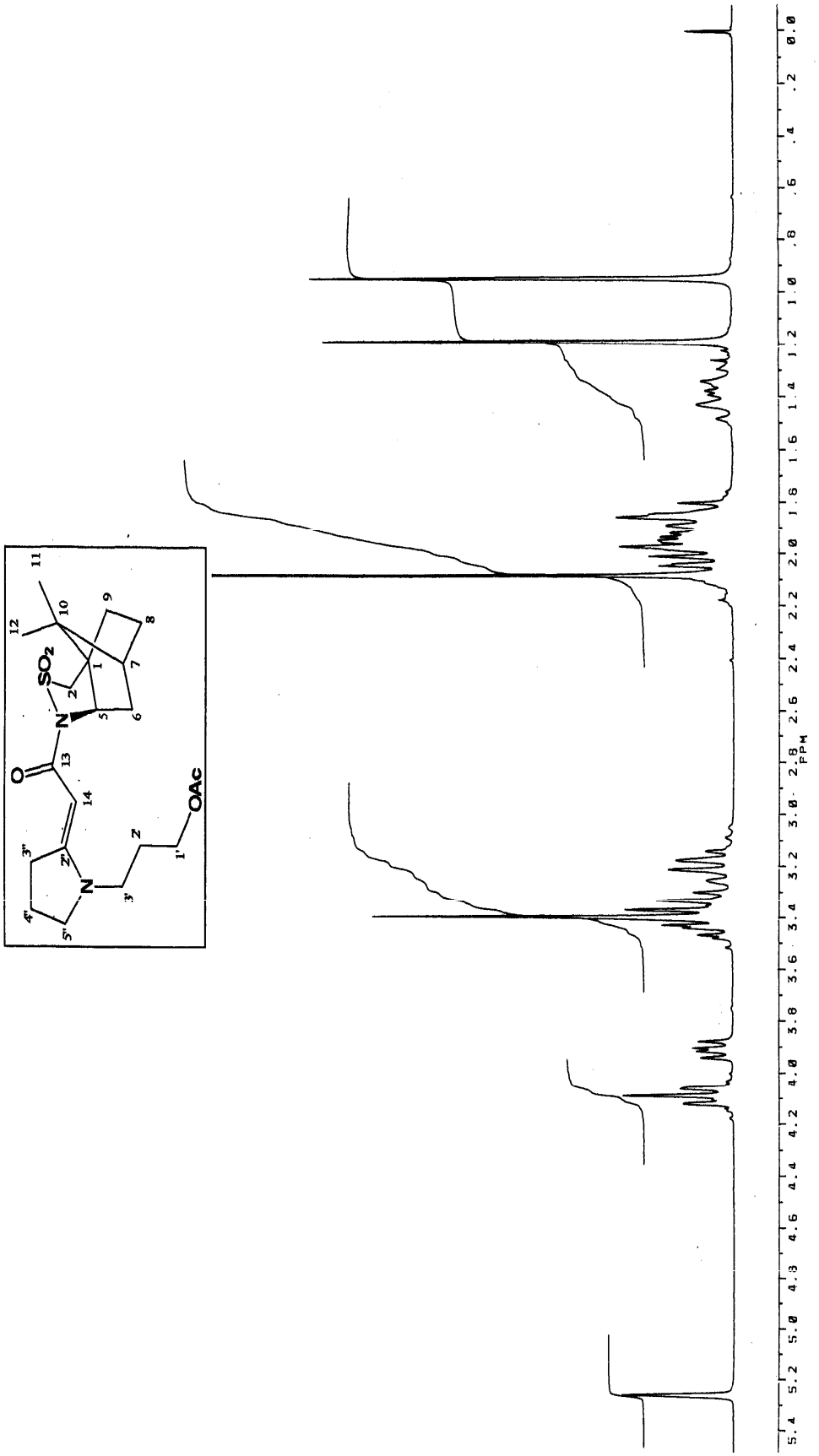

Compound 155
13C NMR
20.338
26.682
31.234
35.926
44.148
44.581
47.332
50.242
54.808
62.202
22.643
22.804
26.367
PPM
20
25
30
35
40
45
50
55
60
65
70
75
PPM

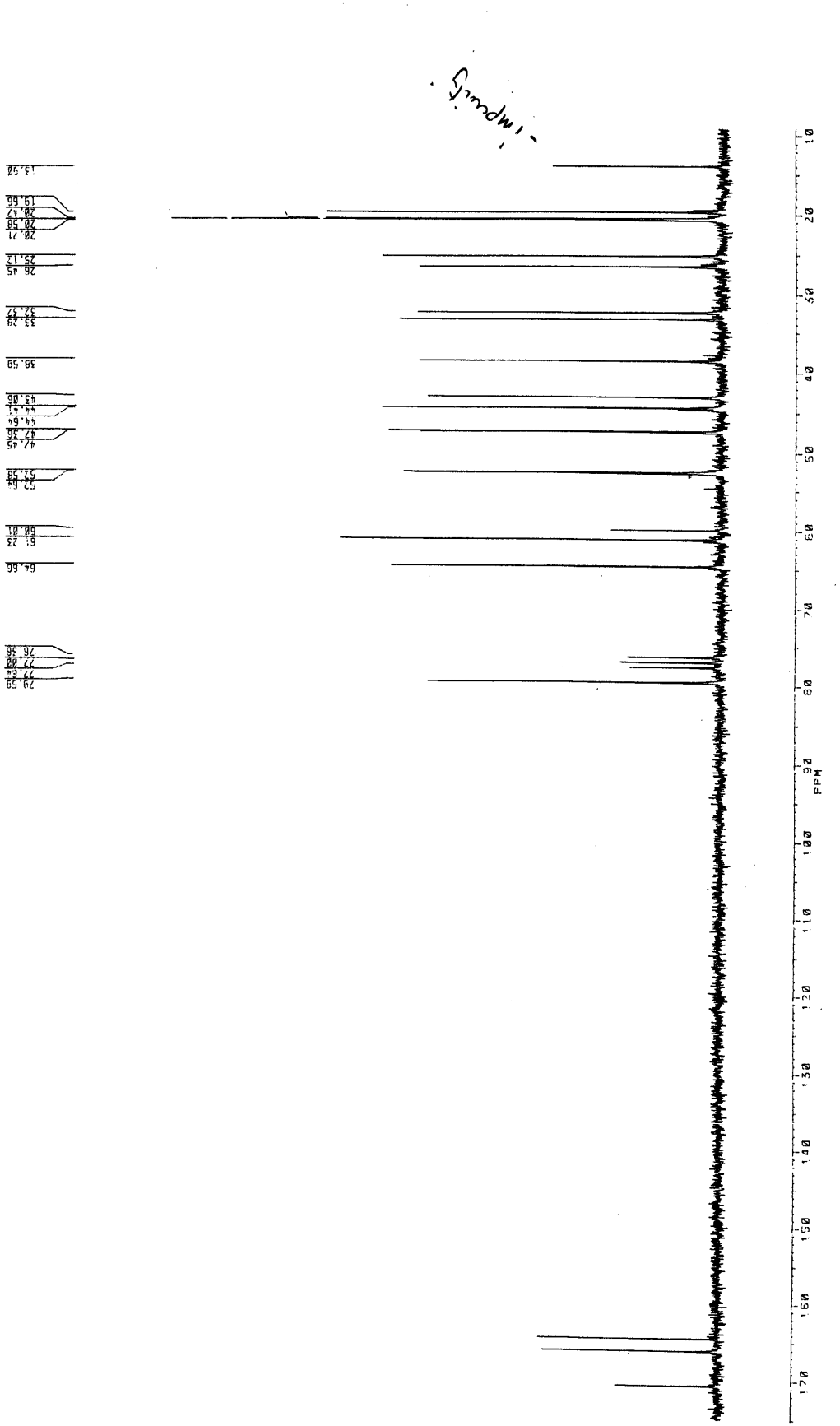

O
O
N
Ph
O
N
O
Ph
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

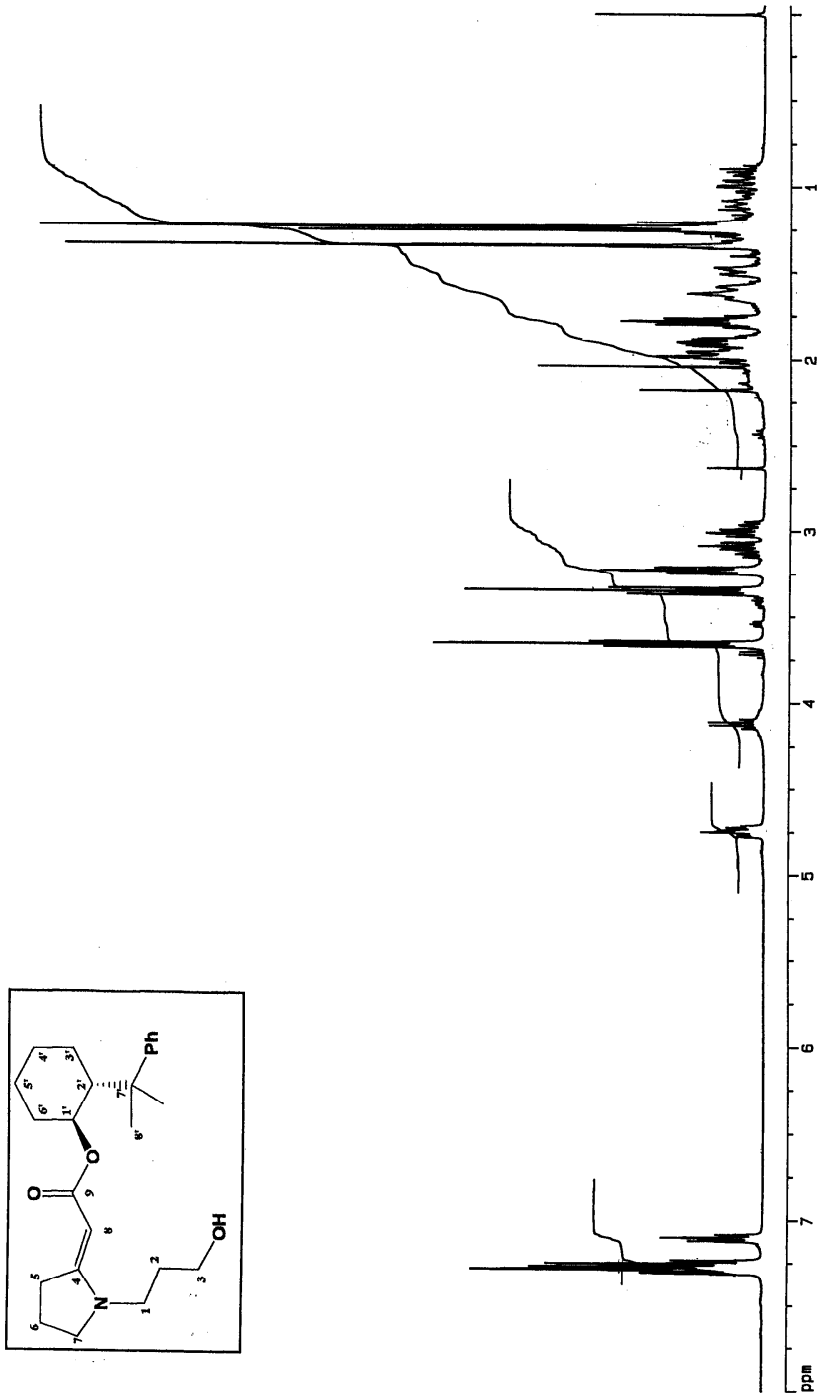

Ph
O
O
Br
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
PPM
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

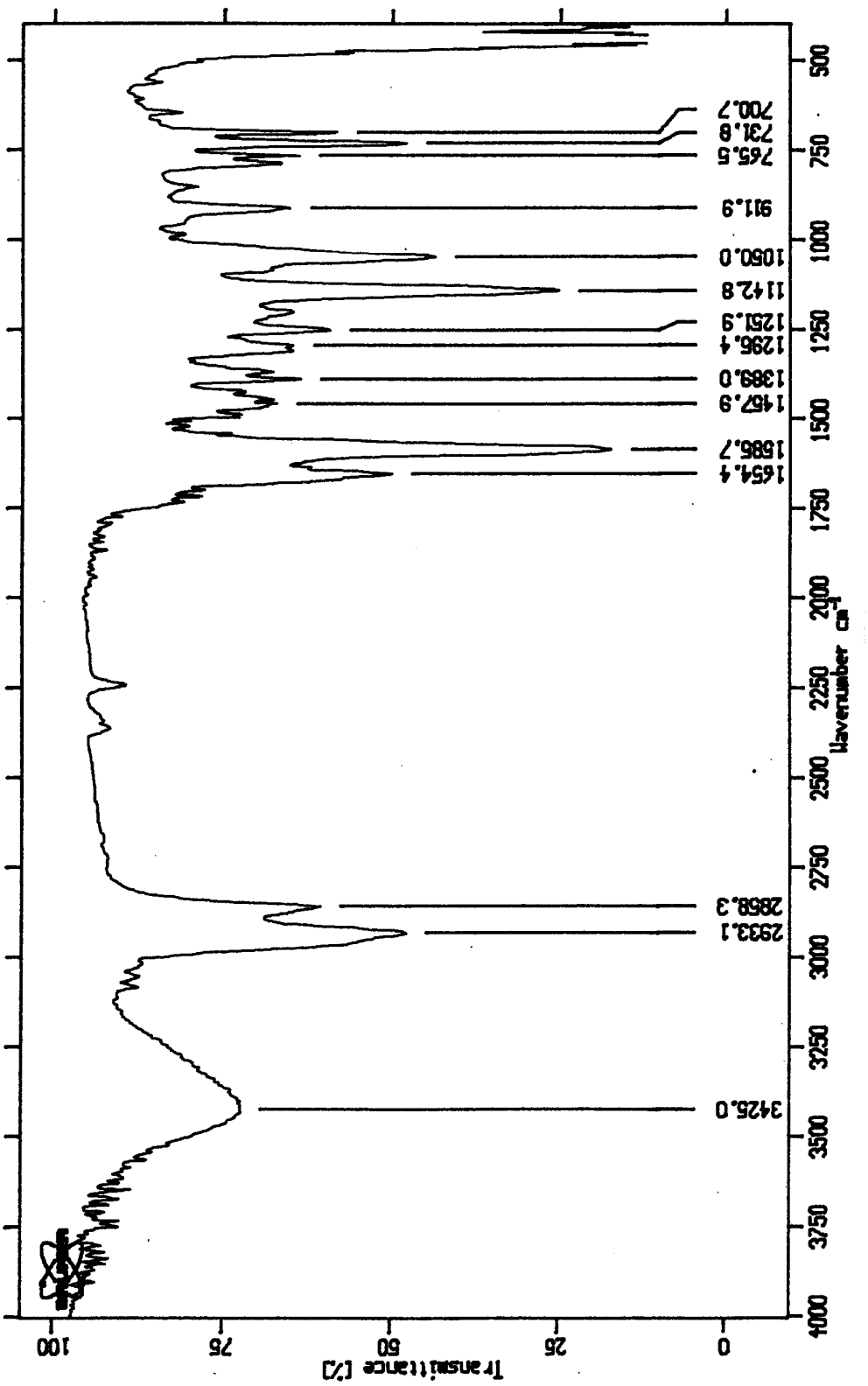

File Name : C:\maspec32\data\hc053107.ms2
File Source : Acquired on MASPEC II system [II32/9913]
File Title : RWK-267
Operator : Dr. P.R. Boshoff
Instrument : VG70-SEQ
SCAN GRAPH. Flagging=Hr M/z. Filter=[Excl: Ref/Ex.].
Scan 60#15:39. Entries=415. Base M/z=119.08571. 100% Int.=9.88416. EI.
%age
119.08571
91.04512
41.03897
200.15676
338.08766
0
10
20
30
40
50
60
70
80
90
0
50
100
150
200
250
300
350
Hr M/z

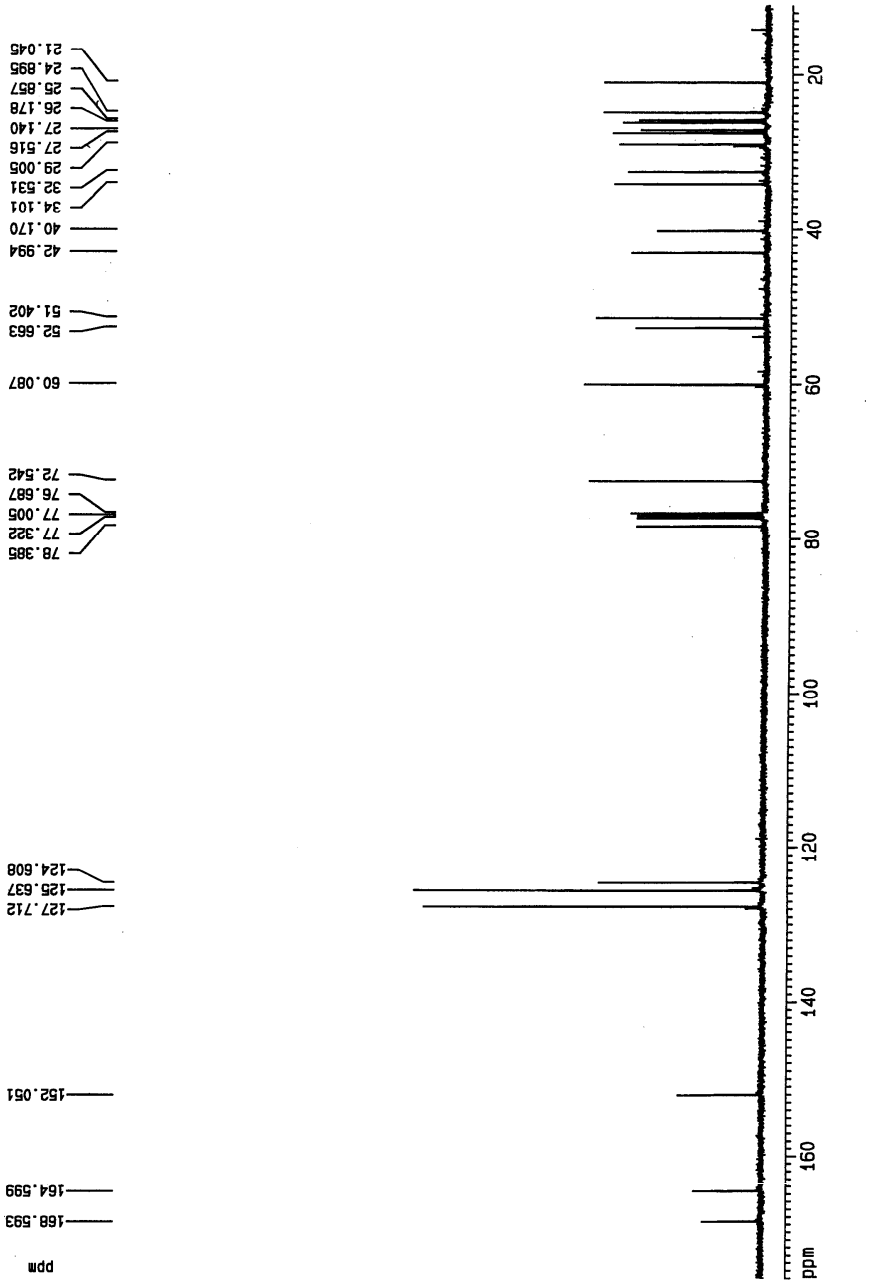

-2.0
-1.0
0.0
1.0
2.0
3.0
4.0
5.0


OAc
PPM


13.90
19.66
20.17
20.58
28.71
25.13
26.45
32.37
33.29
38.59
43.06
44.61
47.36
47.45
52.58
52.64
64.01
64.23
64.66
76.56
77.00
77.42
79.59
PPM


Ph
O
O
OH
N
ppm
1
2
3
4
5
6
7


3425.0
2933.1
2868.3
1654.4
1586.7
1467.9
1389.0
1296.4
1251.9
1142.8
1050.0
911.9
765.5
731.8
700.7
Wavenumber cm-1
Transmittance [%]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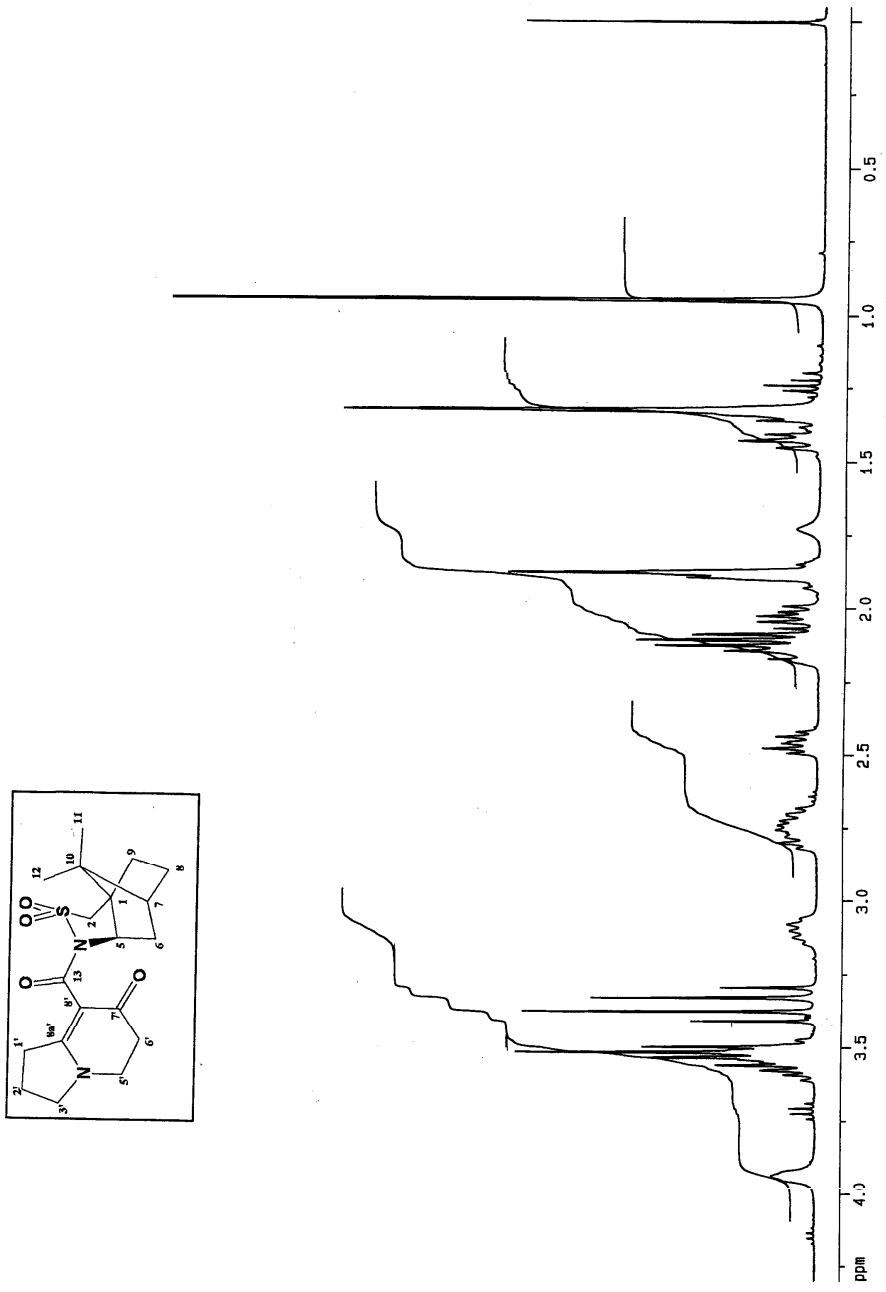
24.895
25.857
26.178
27.140
27.516
29.005
32.531
34.101
40.170
42.994
51.402
52.663
60.087
72.542
76.687
77.005
77.322
78.385
124.608
125.637
127.712
152.051
164.599
168.593
ppm
20
40
60
80
100
120
140
160
ppm


ppm
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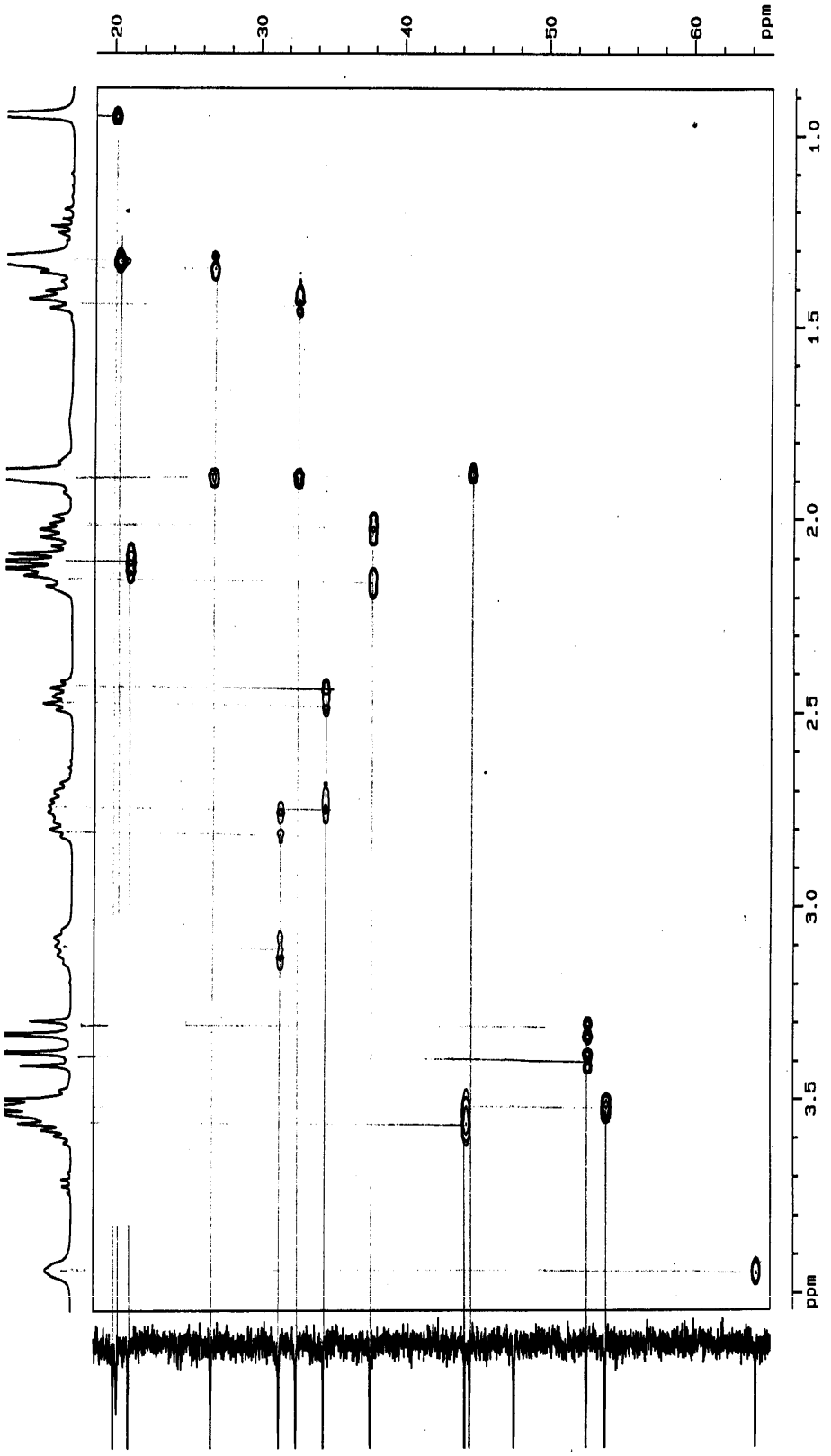
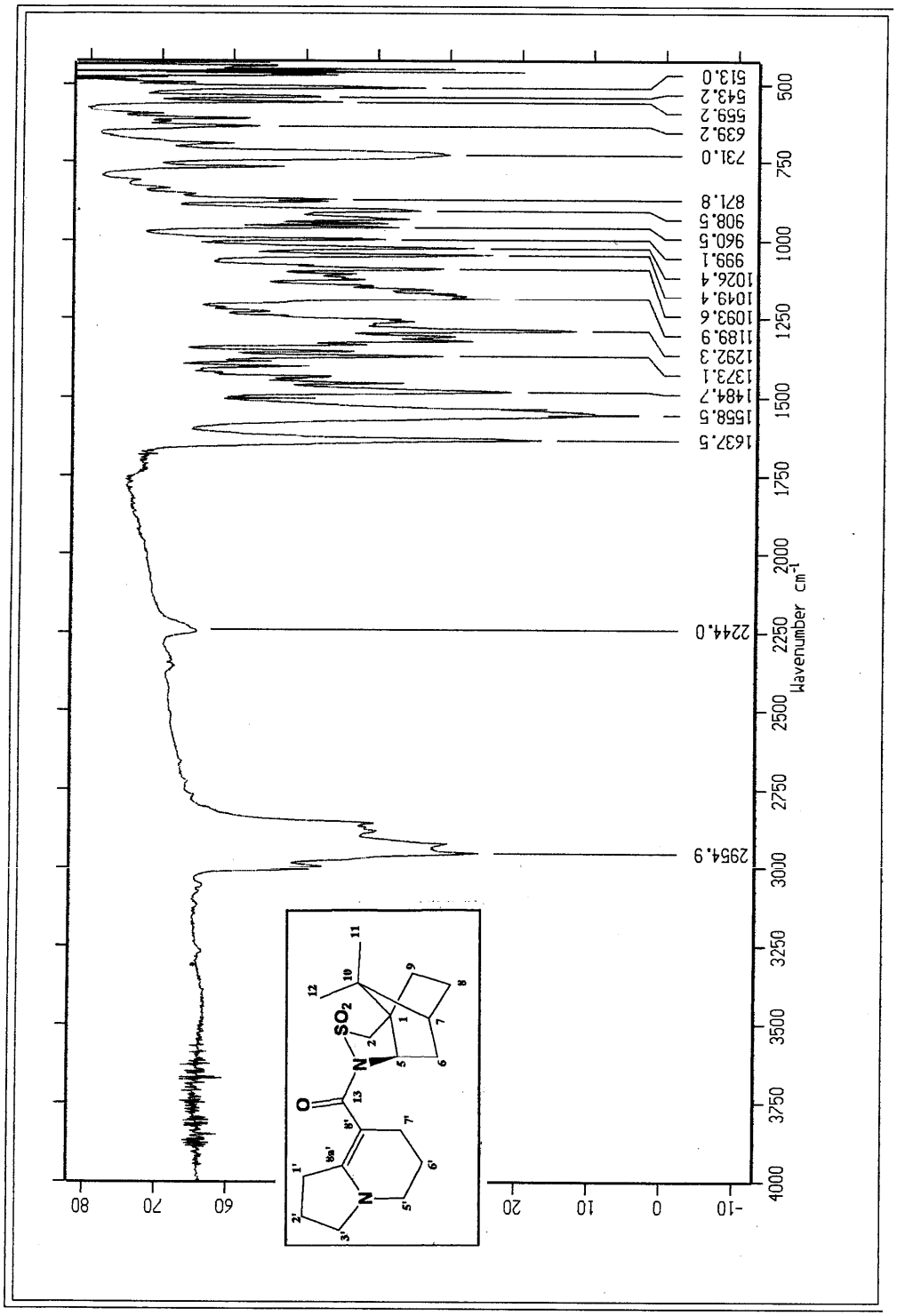
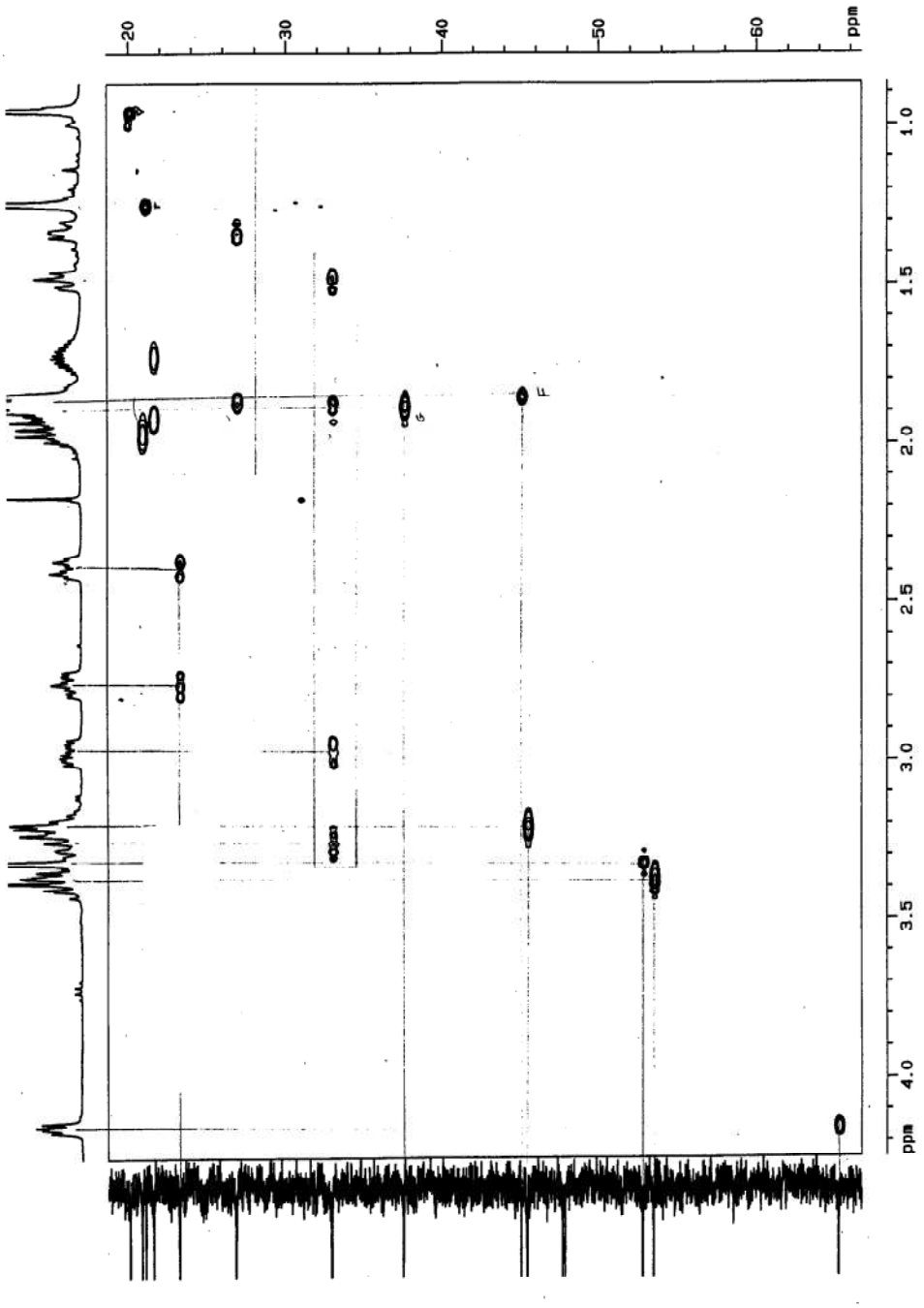
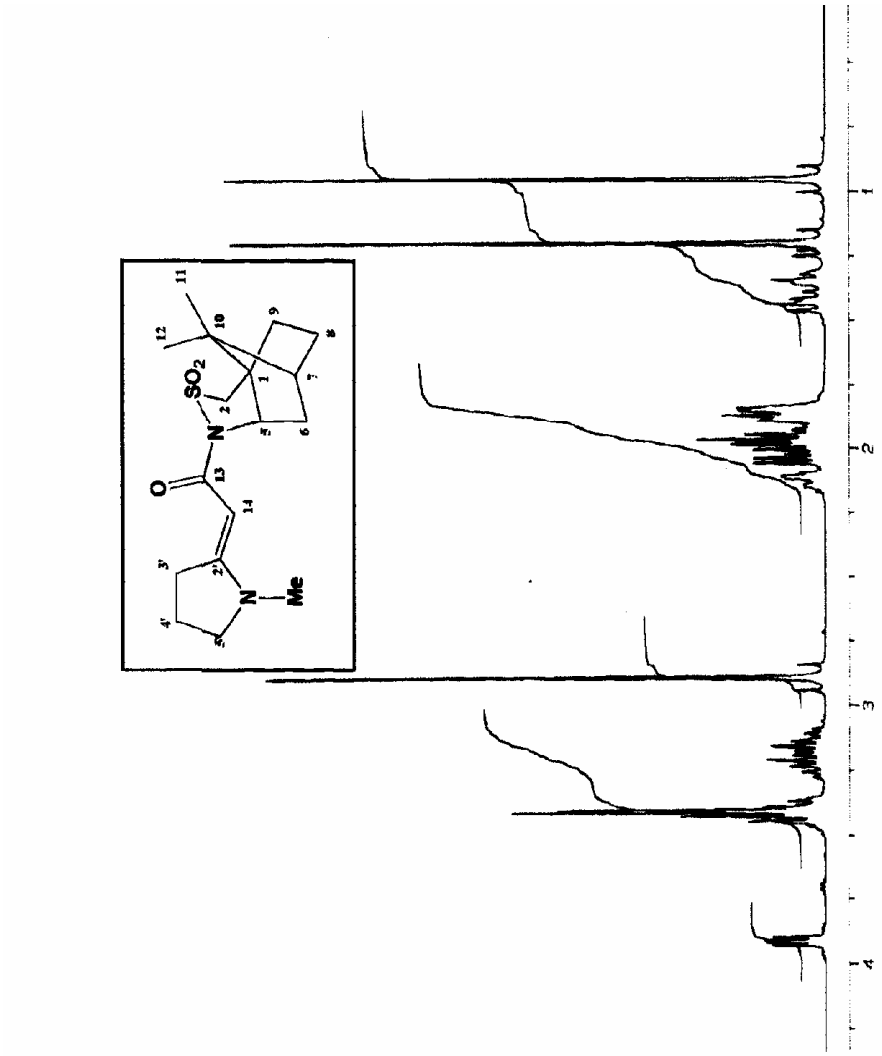
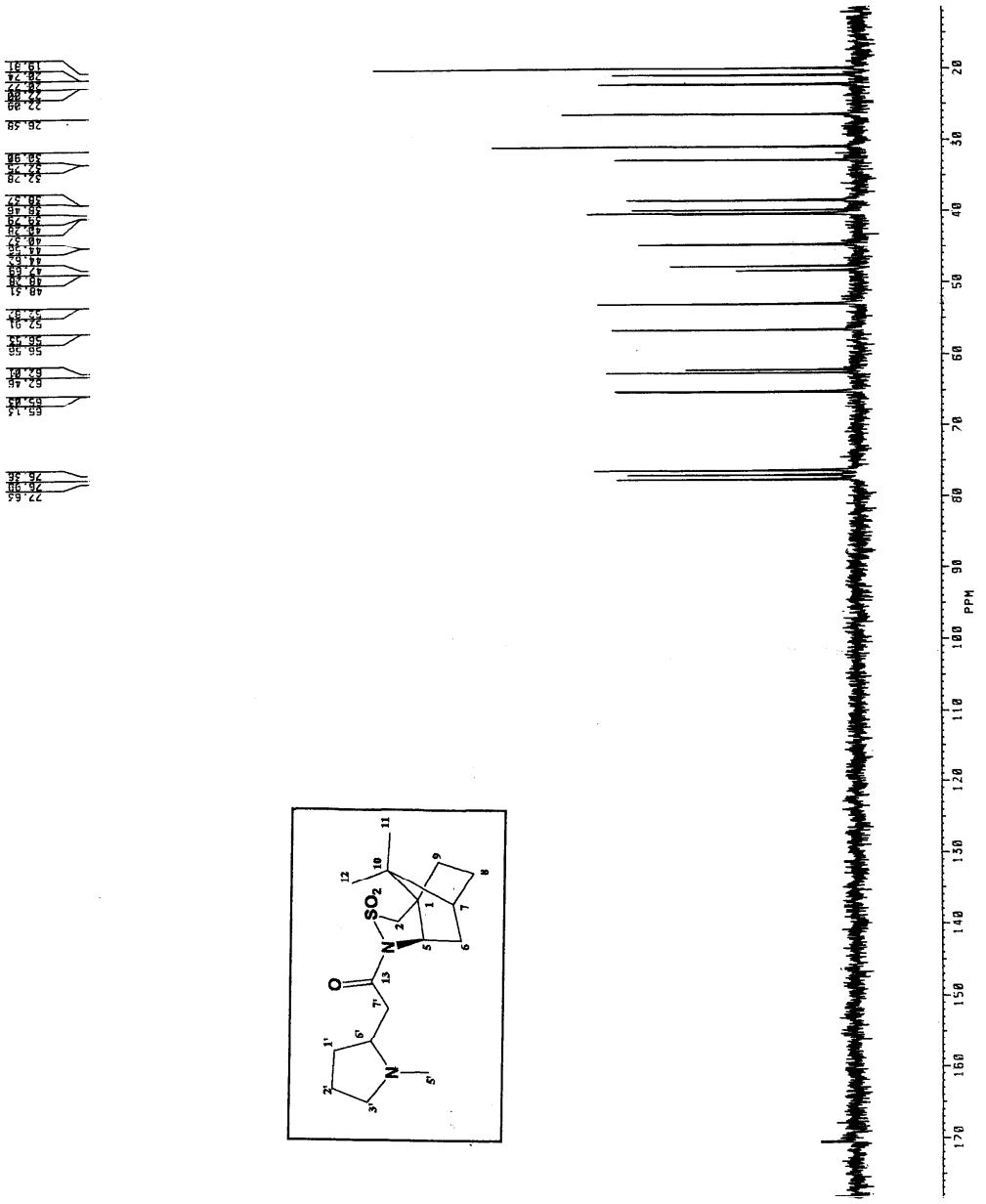
1.0
1.5
2.0
2.5
3.0
3.5

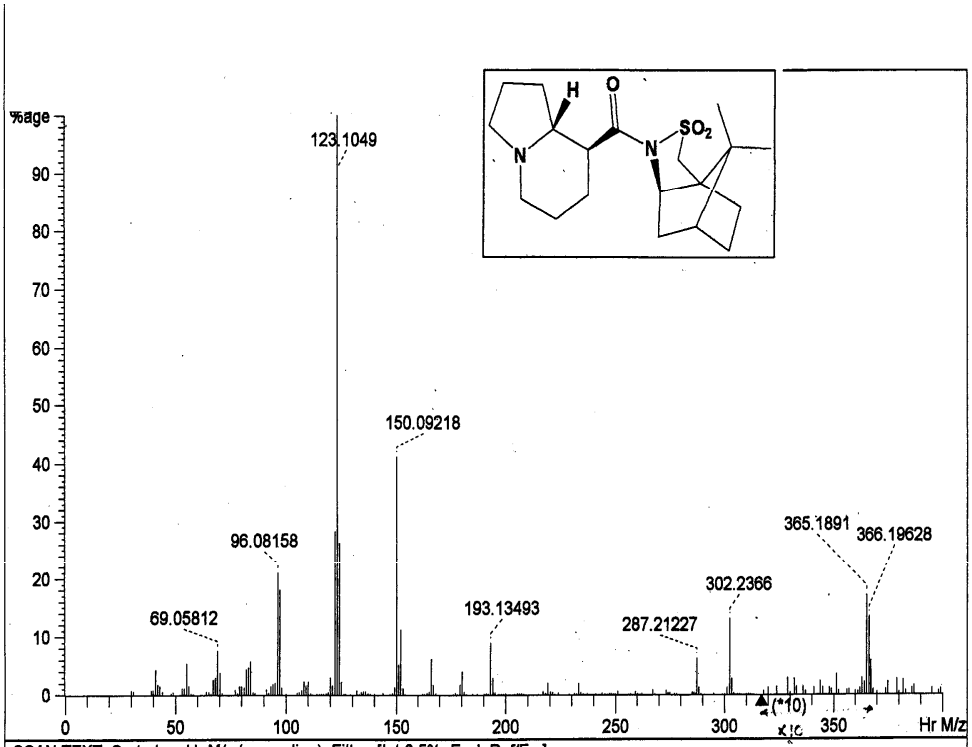

20
30
40
50
60
ppm
1.0
1.5
2.0
2.5
3.0
3.5
ppm


513.0
543.2
559.2
639.2
731.0
871.8
908.5
960.5
999.1
1026.4
1049.4
1093.6
1189.9
1292.3
1373.1
1484.7
1558.5
1637.5
2244.0
2954.9
Wavenumber cm-1
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
-10
0
10
20
60
70
80
O
SO2
N
N


20
30
40
50
60
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
ppm

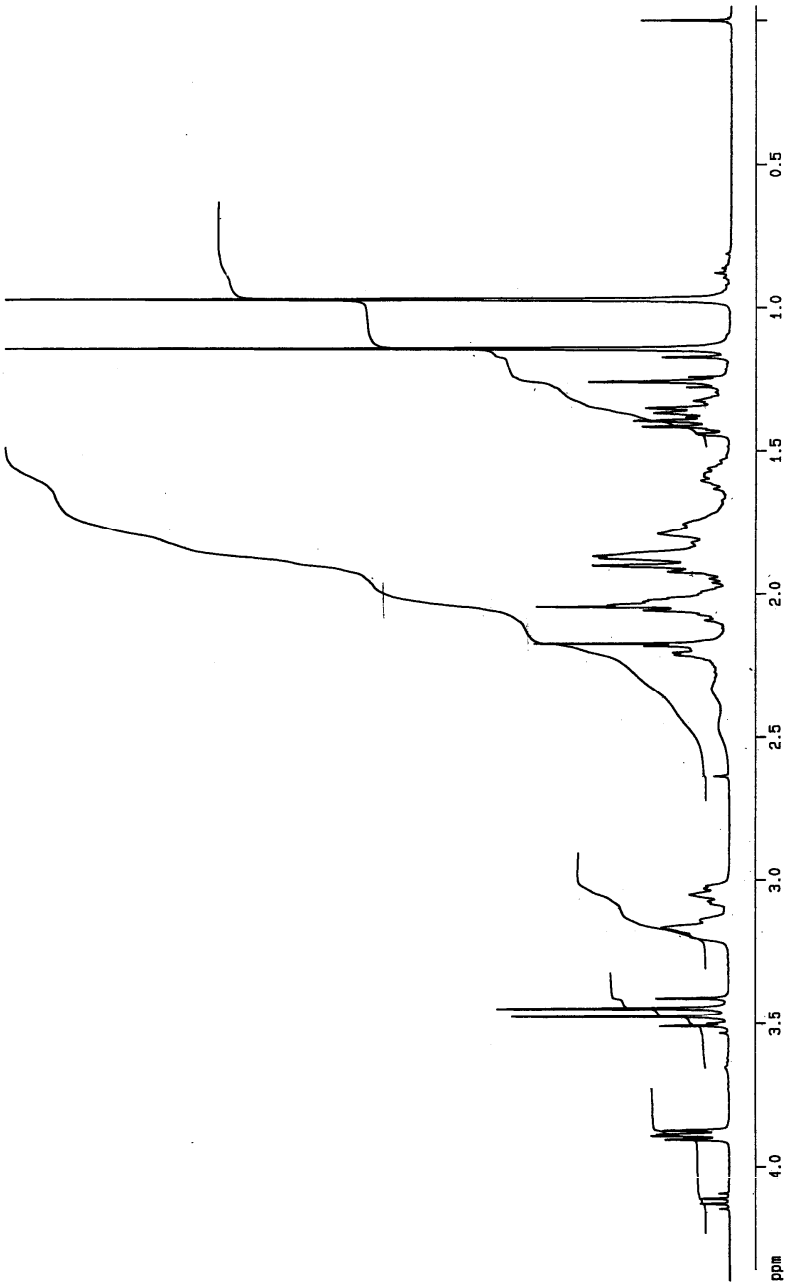

SO2
N
O
Me
1
2
3
4

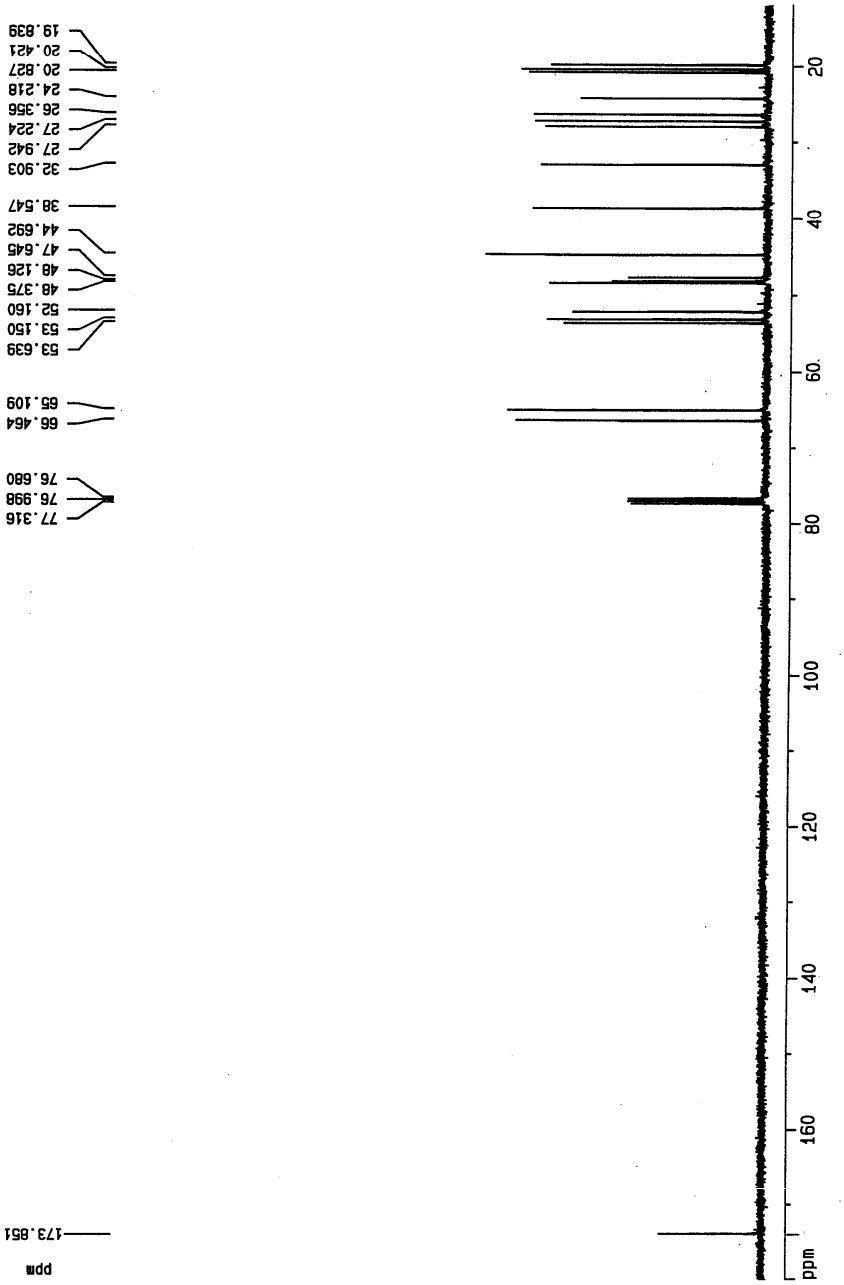

PPM

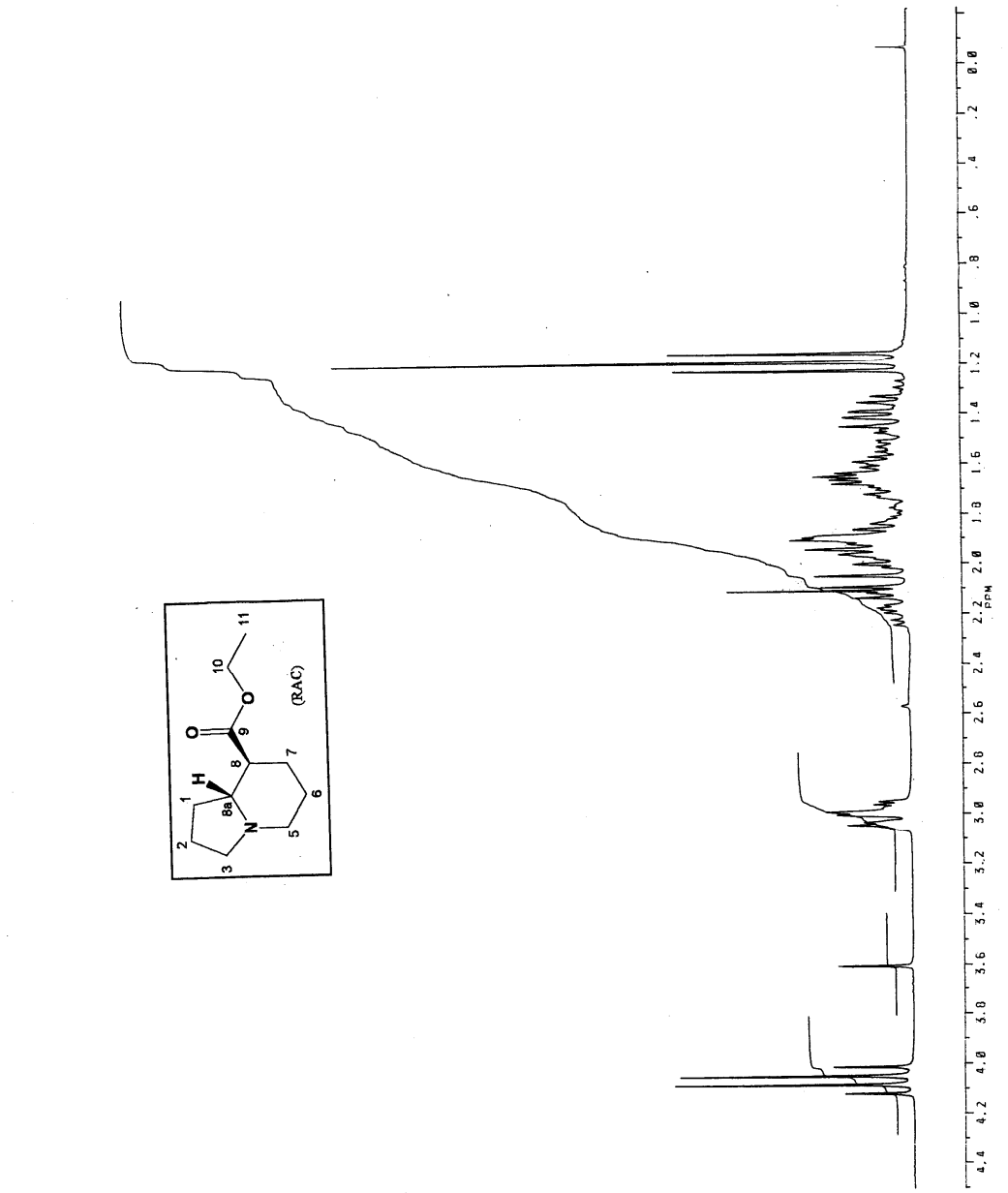


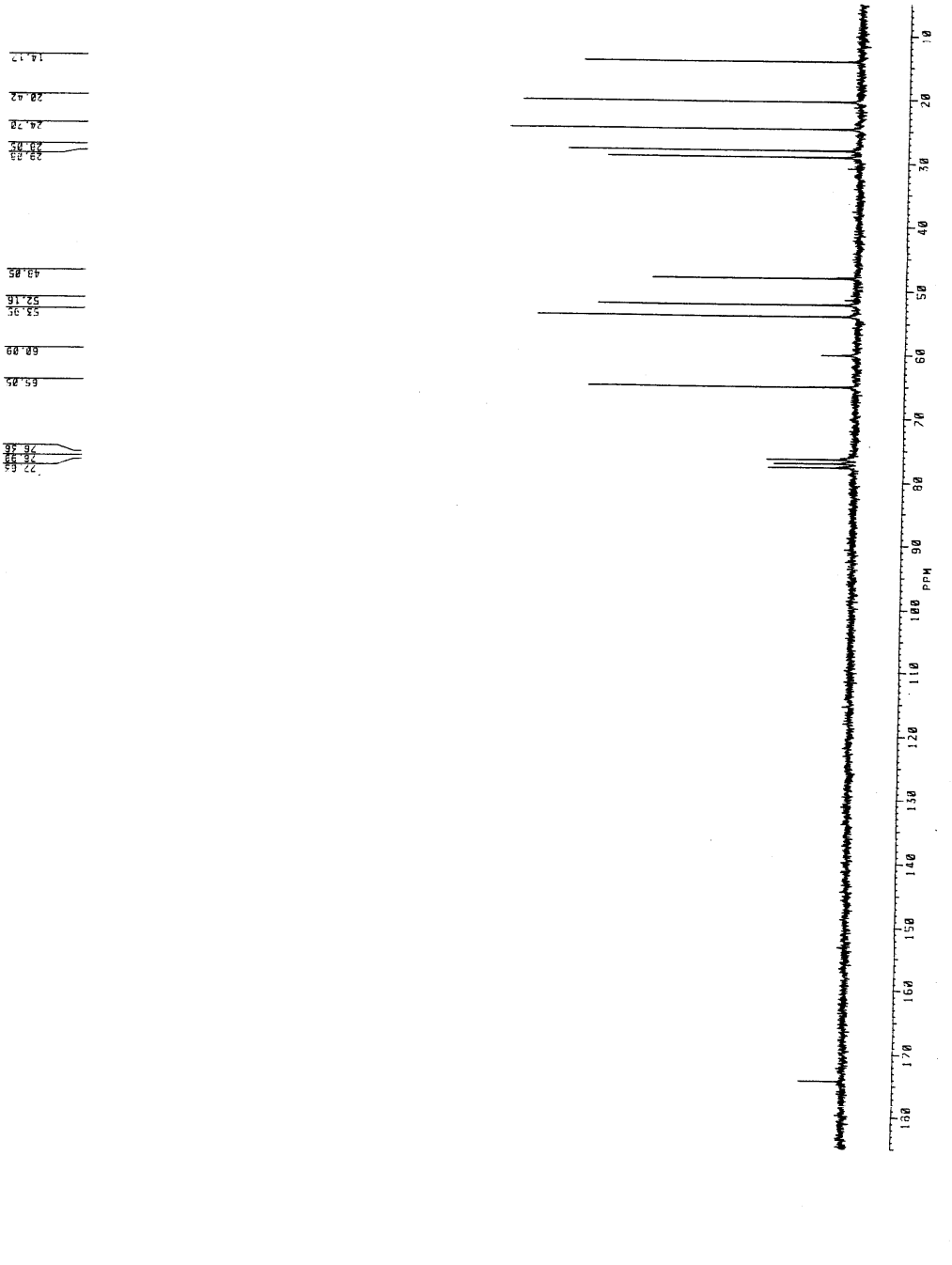
SCAN TEXT. Sorted on Hr M/z (ascending). Filter=[Int:0.5%. Excl: Ref/Ex.].
Scan 26#6:55 - 29#7:41. Entries=67. Base M/z=123.1049. 100% Int.=6.00448. EI.

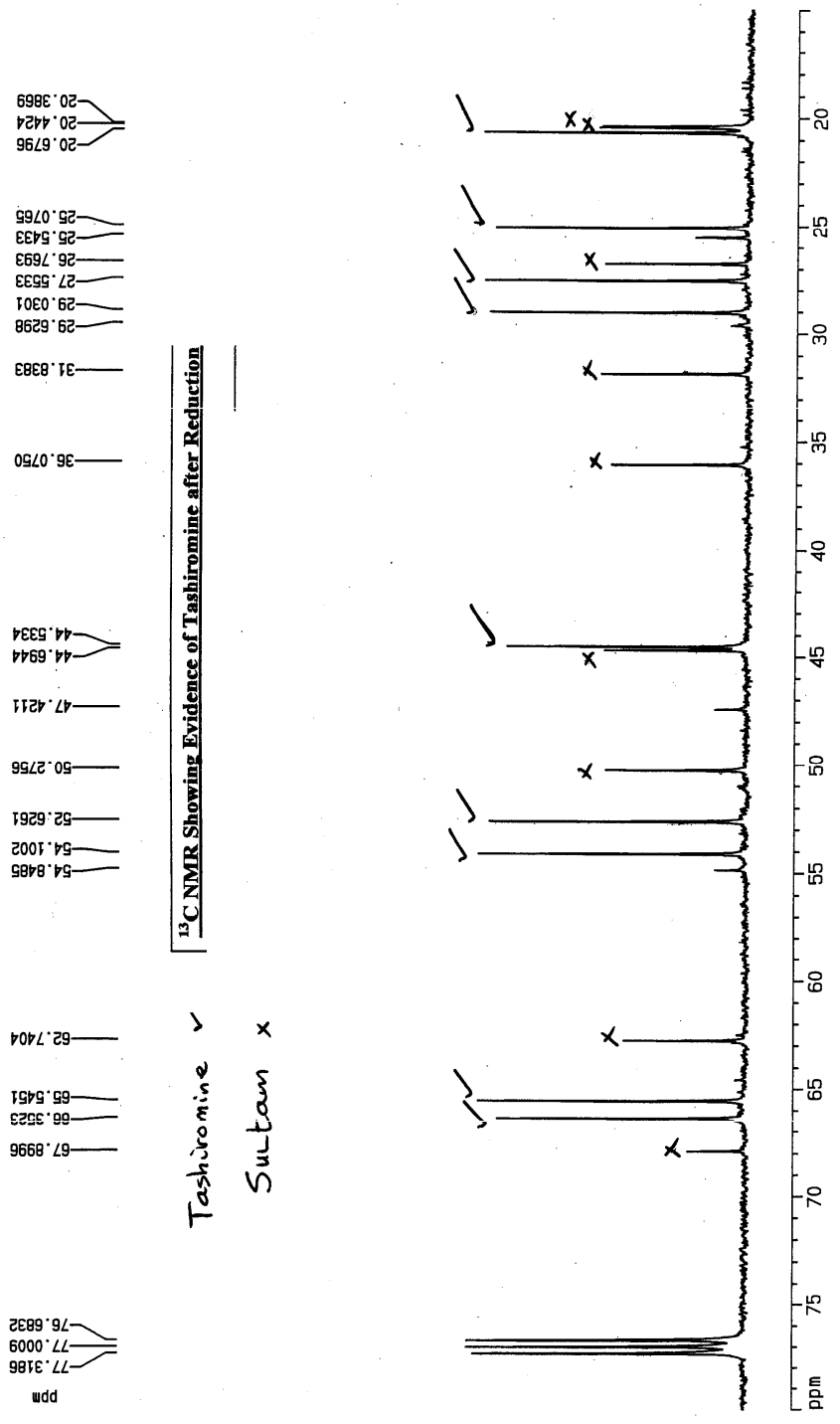
Hr M/z	%age	Hr M/z	%age	Hr M/z	%age
30.03008	0.66	97.08899	18.02	250.99303	0.55
39.02389	0.79	98.09226	1.23	266.98442	0.77
39.96293	0.80	107.08209	0.77	273.19757	0.67
41.03964	4.26	108.08223	2.29	287.21227	6.26
42.04203	1.68	109.08986	1.51	288.21575	1.26
43.05499	1.45	110.09689	2.25	301.22873	1.16
44.05065	0.54	120.08113	3.01	302.23660	13.03
53.03885	1.13	121.09020	1.56	303.24033	2.74
54.03663	1.14	122.09700	28.23	365.18910	1.70
55.01827	2.30	123.10490	100.00	366.19628	1.34
55.05425	5.34	124.11126	26.25	366.98074	0.58
56.05077	1.43	125.11554	2.21		
67.05241	2.53	131.99728	0.66		
68.05011	2.92	135.11373	0.52		
69.05812	7.55	149.10301	1.28		
70.06511	3.79	150.09218	41.17		
77.03881	0.84	151.09676	5.11		
79.05462	1.42	152.10809	11.18		
80.05074	1.34	153.11136	1.15		
81.06328	1.18	166.11074	6.14		
82.06579	4.36	167.11671	1.59		
83.07333	4.58	179.11782	1.68		
84.08105	5.75	180.12644	3.92		
91.05465	0.98	193.13493	8.88		
93.06887	1.46	194.14075	2.79		
94.06648	1.75	216.98771	0.54		
95.07544	2.04	219.14921	2.00		
96.08158	21.02	233.16611	1.84		

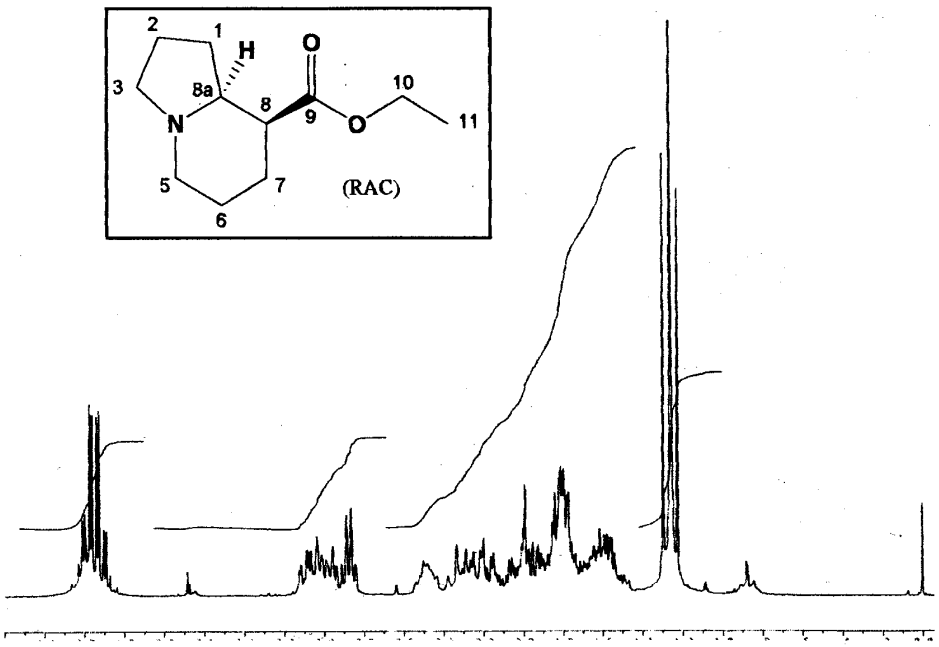

0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
ppm

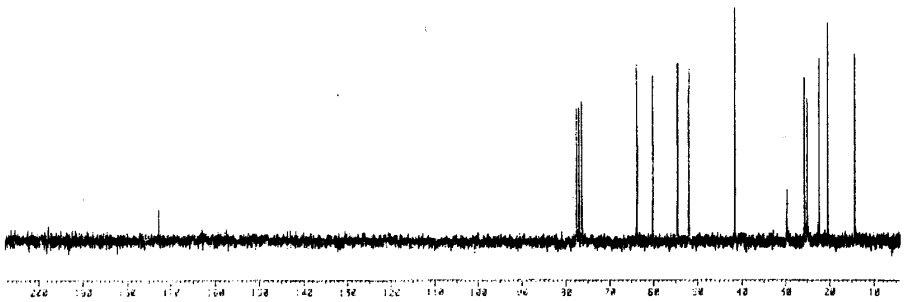

19.839
20.421
20.827
24.218
26.356
27.224
27.942
32.903
38.547
44.692
47.645
48.126
48.375
52.160
53.150
53.639
65.109
66.464
76.680
76.998
77.316
173.851
ppm
20
40
60
80
100
120
140
160
ppm

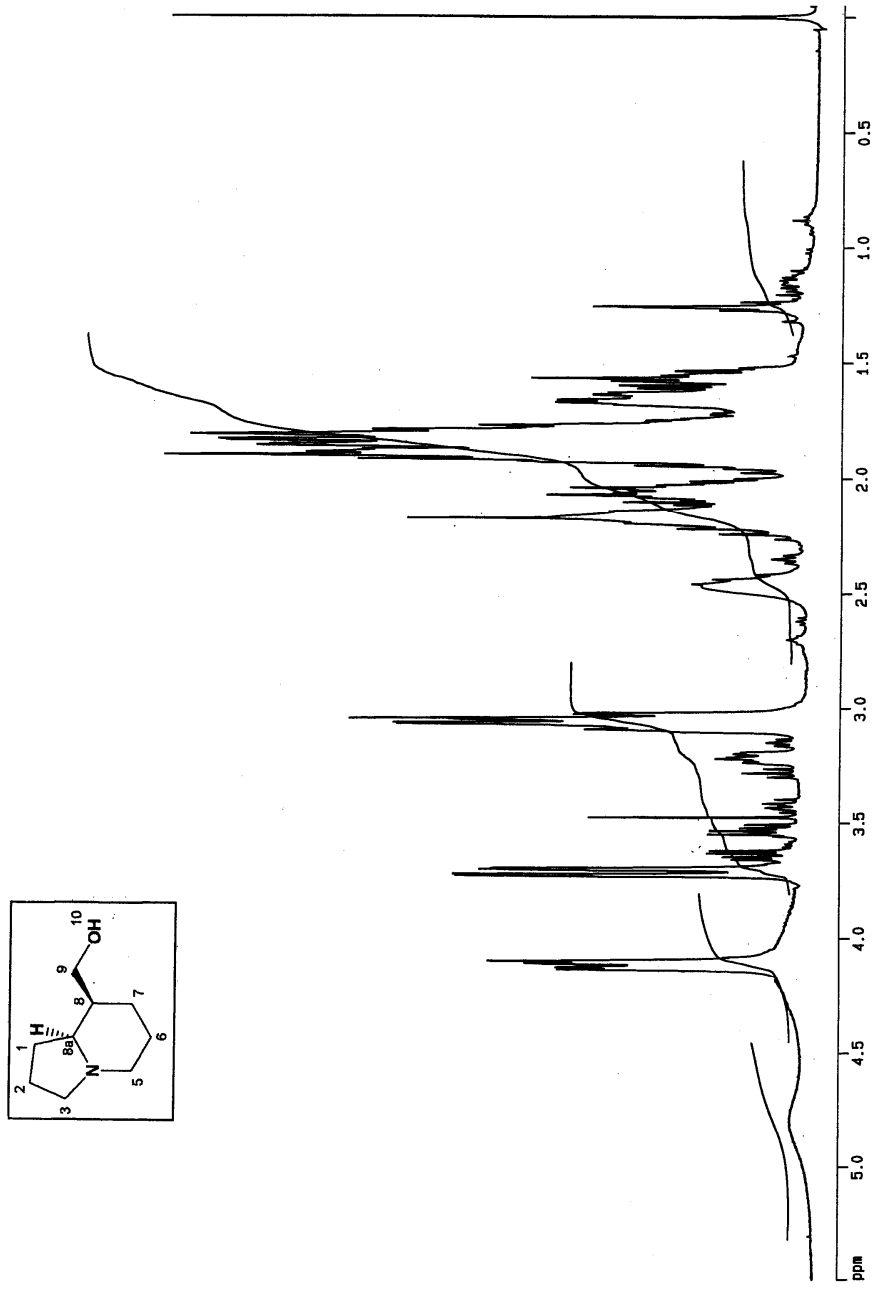

(RAC)
PPM

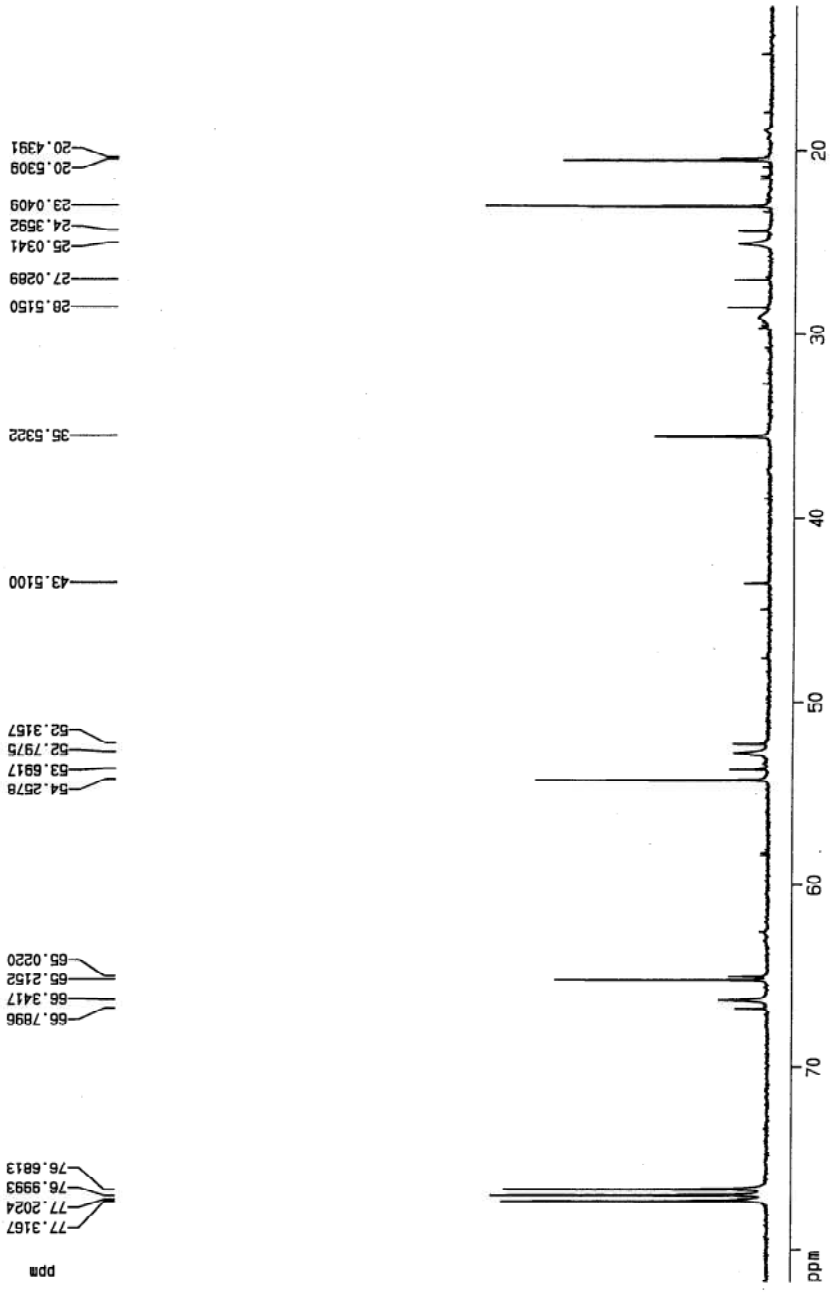

14.17
20.42
24.78
29.25
29.85
43.85
52.16
53.95
60.09
65.09
76.26
76.99
77.65
PPM

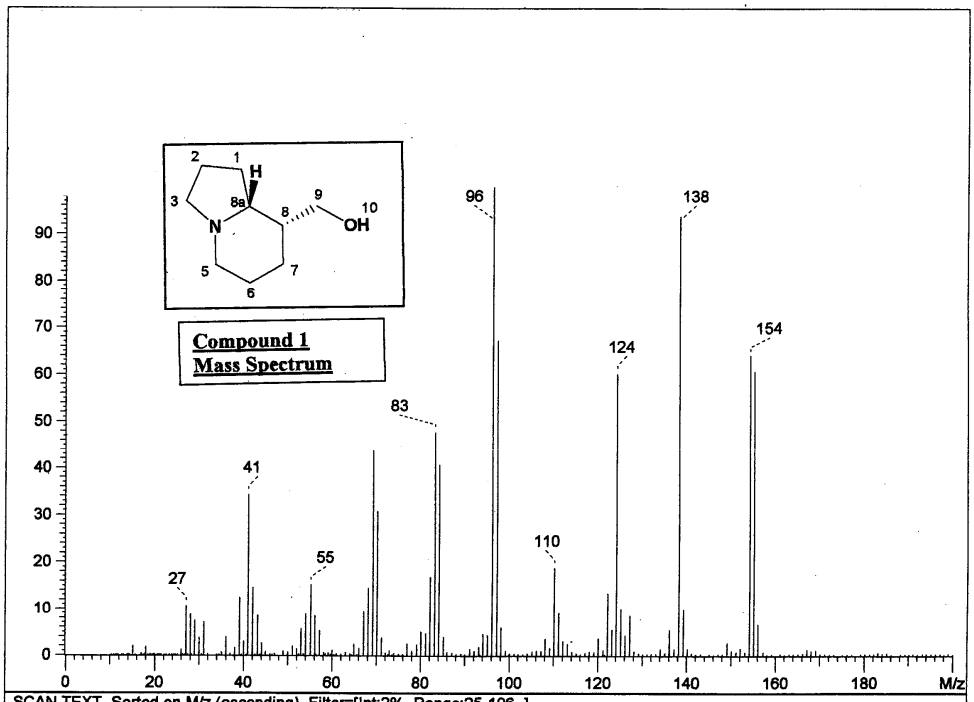

13C NMR Showing Evidence of Tashiromine after Reduction
Tashiromine √
Sultam x
77.3186
77.0009
76.6832
67.8996
66.3523
65.5451
62.7404
54.8485
54.1002
52.6261
50.2756
47.4211
44.6944
44.5334
36.0750
31.8383
29.6298
29.0301
27.5533
26.7693
25.5433
25.0765
20.6796
20.4424
20.3869
ppm
ppm


2
1
H
O
3
8a
8
10
N
9
O
11
5
7
(RAC)
6



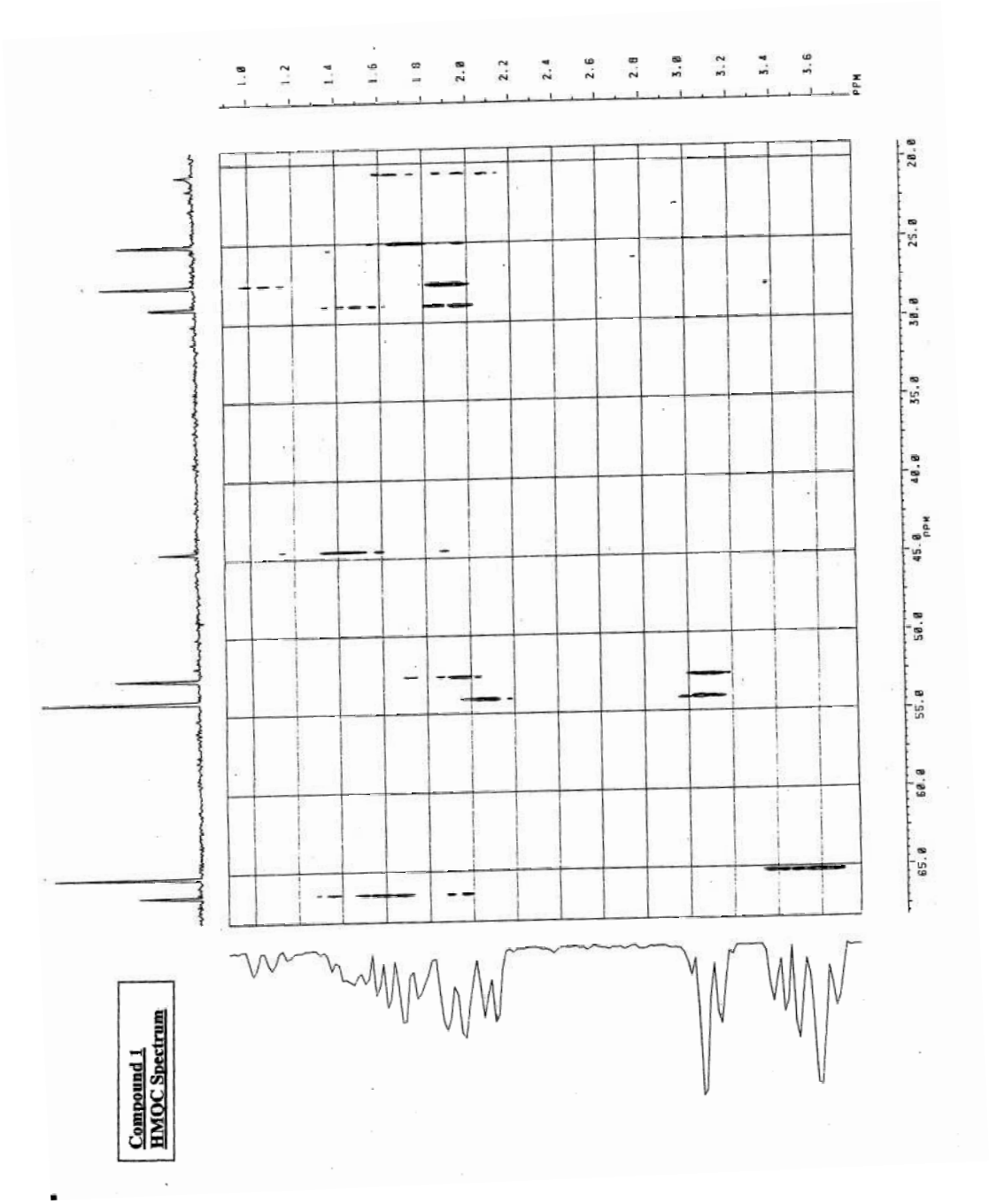

OH
10
9
8
7
6
5
N
8a
H
1
2
3
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
ppm

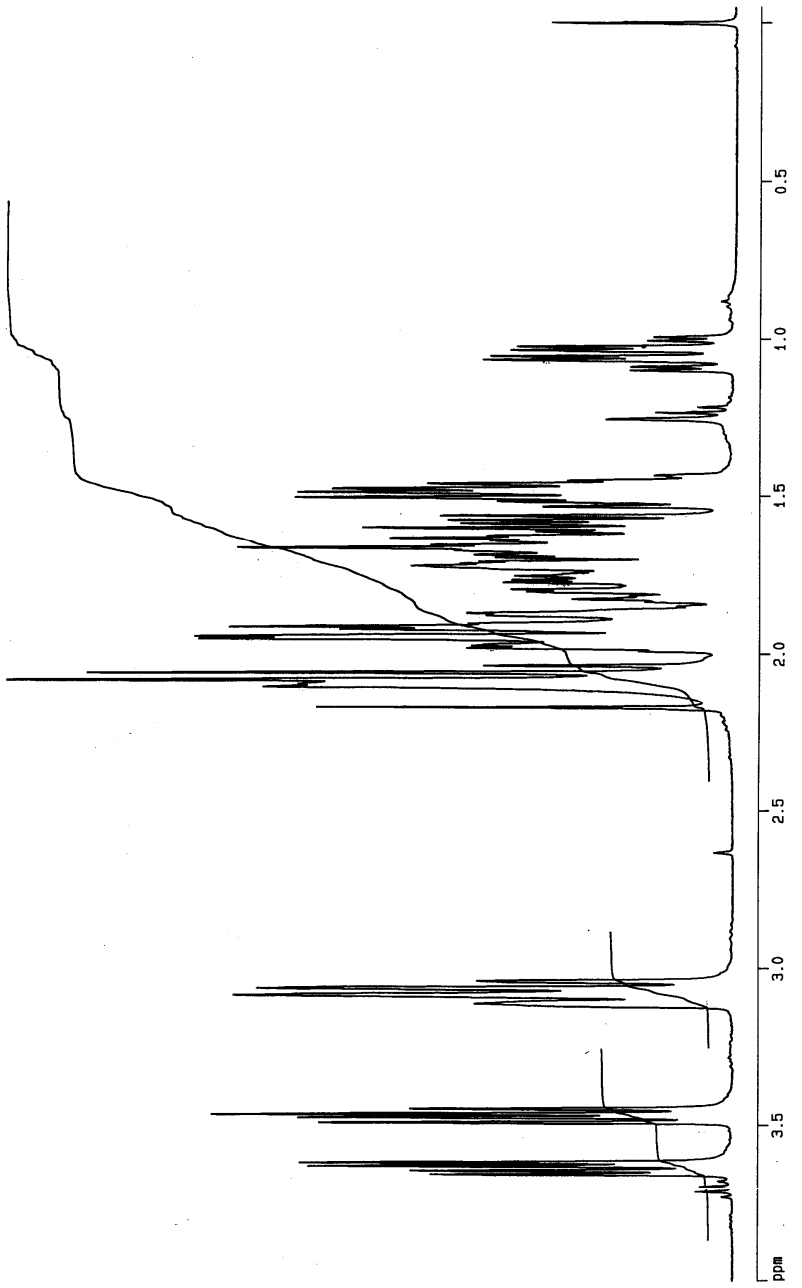

20.4391
20.5309
23.0409
24.3592
25.0341
27.0289
28.5150
35.5322
43.5100
52.3157
52.7975
53.6917
54.2578
65.0220
65.2152
66.3417
66.7896
76.6813
76.9993
77.2024
77.3167
ppm
20
30
40
50
60
70
ppm

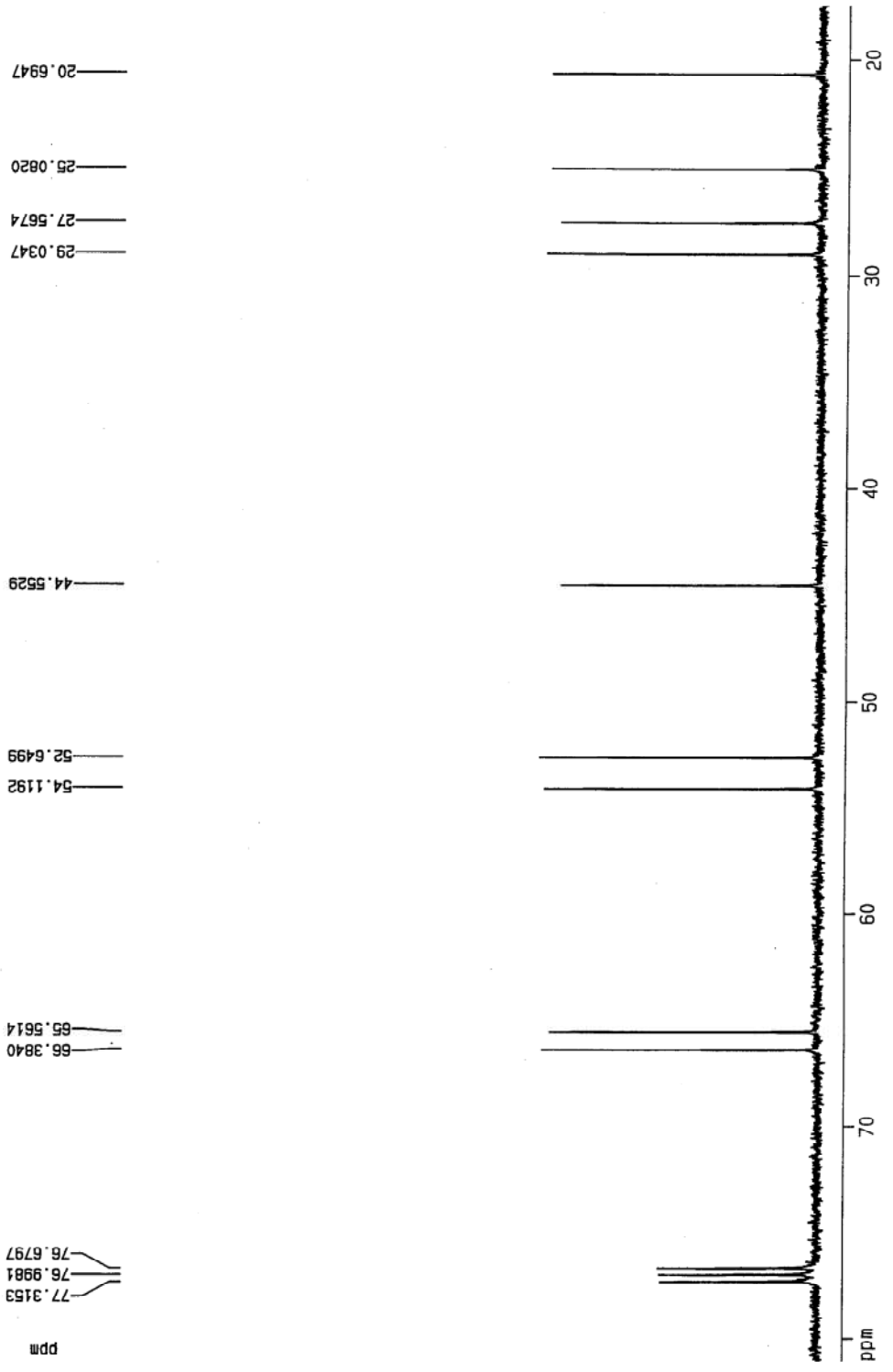


SCAN TEXT. Sorted on M/z (ascending). Filter=[Int:2%. Range:25-196.].
Scan 5#0:50 - 7#1:11. Entries=55. Base M/z=96.1. 100% Int.=4.40235.

om.M/z	%age	Width	om.M/z	%age	Width	om.M/z	%age	Width
27	10.62	52	82	16.84	51	156	6.65	50
28	8.69	77	83	47.66	50			
29	7.38	55	84	40.73	51			
30	3.72	56	85	3.93	64			
31	7.03	51	94	4.53	51			
36	3.91	408	95	4.31	62			
39	12.41	51	96	100.00	50			
40	2.92	60	97	67.28	50			
41	34.26	59	98	5.95	62			
42	14.50	64	108	3.57	52			
43	8.52	90	110	18.79	50			
44	2.60	79	111	9.04	52			
53	5.66	52	112	3.05	67			
54	8.75	56	113	2.41	69			
55	15.16	63	120	3.63	51			
56	8.46	56	122	13.43	50			
57	5.22	83	123	5.52	52			
65	2.42	52	124	60.21	50			
67	9.28	56	125	10.07	51			
68	14.41	52	126	4.23	60			
69	43.67	52	127	8.49	52			
70	30.81	51	136	5.39	52			
71	3.74	67	138	93.78	49			
77	2.46	52	139	10.06	51			
79	2.26	53	149	2.65	66			
80	5.02	51	154	64.14	50			
81	4.68	56	155	60.69	50			


1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
PPM
20.0
25.0
30.0
35.0
40.0
45.0
PPM
50.0
55.0
60.0
65.0
Compound 1
HMQC Spectrum


0.5
1.0
1.5
2.0
2.5
3.0
3.5
ppm


20.6947
25.0820
27.5674
29.0347
44.5529
52.6499
54.1192
65.5614
66.3840
76.6797
76.9981
77.3153
ppm
20
30
40
50
60
70
ppm