Novel palladium-catalysed [3+2] cycloadditions towards functionalised aza-bicycles

This item was submitted to Loughborough University’s Institutional Repository by the/an author.

Additional Information:


Metadata Record: [https://dspace.lboro.ac.uk/2134/34391](https://dspace.lboro.ac.uk/2134/34391)

Publisher: © Andrew J. Stott

Rights: This work is made available according to the conditions of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) licence. Full details of this licence are available at: [https://creativecommons.org/licenses/by-nc-nd/4.0/](https://creativecommons.org/licenses/by-nc-nd/4.0/)

Please cite the published version.
University Library

Author/Filing Title: STOTT, A. J.

Class Mark: T

Please note that fines are charged on ALL overdue items.
Novel Palladium Catalysed [3 + 2] Cycloadditions Towards Functionalised Aza-Bicycles

A thesis submitted in fulfilment of the requirements for the award of the degree
Doctor of Philosophy
From
Loughborough University

by
Andrew James Stott, BSc (Hons)

October 2008

Department of Chemistry, Loughborough University,
Loughborough, Leicestershire, LE11 3TU.

© by Andrew J. Stott, 2008
Abstract

Novel pyrrolidine, indolizidine and azepine ring systems have been prepared via the palladium catalysed [3+2] cycloaddition of cyclic imines with vinylcyclopropanes. The reaction of simple cyclic imines with various functionalised vinylcyclopropanes, provided a range of bicyclic systems, as potential scaffolds for further elaboration. The application of functionalised cyclic imines derived from enecarbamates was limited due to difficulties generating the imine bond. The developed methodology was also employed in the formation of pyrrolooxazinone products, as templates for functionalised proline syntheses.

A synthetic sequence based on palladium-catalysed transformations was developed towards the *Stemona* alkaloid (±)-stemoamide. Palladium [3+2] cycloaddition of a suitable acyclic imine, and tert-butyl ester substituted vinylcyclopropane, followed by an intramolecular Heck cyclisation yielded the azepine core present in the natural product. Lactonisation procedures were investigated to install the final ring of the tricyclic core, however due to time restraints, this work remains incomplete.
Contents

Title page i
Abstract ii
Table of contents iii
List of abbreviations vii
Acknowledgments ix

Introduction

Chapter One

1.1 Pyrrolizidine and Indolizidine Alkaloids
   1.1.1 Introduction to the Pyrrolizidine Alkaloids 1
   1.1.2 Syntheses of the Pyrrolizidine and Indolizidine Alkaloids 2

1.2 Stemona Alkaloids
   1.2.1 Introduction to the Stemona Alkaloids 14
   1.2.2 Syntheses of the Stemona Alkaloids 15

1.3 Cyclopropanes in Synthesis
   1.3.1 Bonding in Cyclopropanes 34
   1.3.2 Nucleophilic Addition to Cyclopropanes 35
   1.3.3 Transition Metal-assisted reactions of Cyclopropane derivatives 39
   1.3.4 Palladium Catalysed [3+2] Cycloadditions with Pd-
       Trimethylenemethane complexes 42
   1.3.5 Transition Metal-assisted reactions of Vinylcyclopropanes 44
   1.3.6 Previous work within the Group 51
Results and Discussion

Chapter Two

2.1 Preparation and Reactions of Vinylcyclopropanes
   2.1.1 Synthesis of Vinylcyclopropanes

2.2 Preparation of Cyclic Imines
   2.2.1 Synthesis of 5-membered Cyclic Imines
   2.2.2 Synthesis of 6-membered Cyclic Imines
   2.2.3 Synthesis of 7-membered Cyclic Imines

2.3 Palladium Catalysed [3+2] Cycloadditions with Cyclic Imines
   2.3.1 Formation of novel Pyrrolizidine derivatives
   2.3.2 Formation of novel Indolizidine derivatives
   2.3.3 Formation of novel Azepine derivatives
   2.3.4 Synthesis of Crispine A derivatives
   2.3.5 Optimal conditions for Palladium [3+2] Cycloadditions

2.4 The use of Functionalised Vinylcyclopropanes
   2.4.1 Variation at the vinyl terminus
   2.4.2 Variation at the Malonic position
   2.4.3 Use of Activated Bicyclic Vinlylcyclopropanes

Chapter Three

3.1 Preparation of functionalised imines
   3.1.1 Quartenary Substitution on the Cyclic Imines
   3.1.2 Anti-substituted Cyclic Imines from 3-Pyrroline
   3.1.3 Syn-substituted Cyclic Imines from 3-Pyrroline
   3.1.4 Cyclic Imines from 4-hydroxy piperidine

3.2 New methods towards Imine bond formation
   3.2.1 In situ generation of the Cyclic Imine
   3.2.2 Cyclic Imines from Enecarbamates
   3.2.3 Cyclic Imines from γ,δ- Unsaturated Nitriles

3.3 Conclusion
Chapter Four

4.1 New Routes to Functionalised Prolines
   4.1.1 Proline as a Building block
   4.1.2 Oxazinones in synthesis
   4.1.3 Formation of Oxazinones via Oxazoles
   4.1.4 Alternative Route to Oxazinones using Lead Acetate
   4.1.5 Palladium [3+2] cycloadditions with oxazinones
   4.1.6 Electron deficient quaternary imine bonds
   4.1.7 Controlling the stereochemistry at C-9
   4.1.8 Electron-rich Cyclic Imines

4.2 Conclusion

Chapter Five

5.1 Application to Natural Products
   5.1.1 Retrosynthesis of stemoamide

5.2 Formation of functionalised Pyrrolidine intermediate
   5.2.1 Synthesis of substituted Vinylcyclopropane
   5.2.2 Synthesis of Acyclic Imine
   5.2.3 Palladium Catalysed [3+2] Cycloaddition to functionalised Pyrrolidines

5.3 Investigations into C-ring closure
   5.3.1 Radical methods for C-ring closure
   5.3.2 Halogen-Metal exchange methods for C-ring closure
   5.3.3 Heck coupling methods for C-ring closure
   5.3.4 Tandem Palladium catalysed Azepine formation

5.4 Investigation into direct lactonisation of Z-458b
5.5 Selective reduction of the exocyclic double bond
5.6 Palladium catalysed [3+2] cycloadditions of isocyanates

Chapter Six

6.1 Conclusion and future work
Chapter Seven

7.1 General information

7.1.1 Solvents and reagents 154
7.1.2 Chromatographic procedures 154
7.1.3 FT-IR 155
7.1.4 \(^1\)H NMR 155
7.1.5 \(^{13}\)C NMR 155
7.1.6 Mass spectra 156
7.1.7 Other data 156

7.2 Experimental procedures 157

Chapter Eight

8.1 References 213

Chapter Nine

9.1 Appendix 218
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIBN</td>
<td>Azobis(isobutyronitrile)</td>
</tr>
<tr>
<td>Ar</td>
<td>Aromatic</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>CAN</td>
<td>Ceric ammonium nitrate</td>
</tr>
<tr>
<td>Cbz</td>
<td>Benzylxycarbonyl</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[2.2.2]undecane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarisation Transfer</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N'-Dimethylpropyleneurea</td>
</tr>
<tr>
<td>DMS</td>
<td>Dimethyl sulphide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DMTSF</td>
<td>Dimethylsulphonium tetrafluoroborate</td>
</tr>
<tr>
<td>EI</td>
<td>Electron ionisation</td>
</tr>
<tr>
<td>ES</td>
<td>Electron spray</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast atom bombardment</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylyphosphoramid e</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Coherence</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest occupied molecular orbital</td>
</tr>
<tr>
<td>IR</td>
<td>Infra-red</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant (NMR spectroscopy)</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropyl amide</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid chromatography-Mass spectrometry</td>
</tr>
<tr>
<td>m</td>
<td>Meta</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>MEM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesyl</td>
</tr>
<tr>
<td>m/z</td>
<td>Mass to charge ratio</td>
</tr>
<tr>
<td>NCS</td>
<td>N-Chlorosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>Nuclear Overhauser effect</td>
</tr>
<tr>
<td>o</td>
<td>Ortho</td>
</tr>
<tr>
<td>p</td>
<td>Para</td>
</tr>
<tr>
<td>P.E.</td>
<td>Petroleum ether (40-60)</td>
</tr>
<tr>
<td>PMB</td>
<td>para-Methoxybenzene</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>RAMP</td>
<td>(R)-1-Amino-2-methoxymethylpyrrolidine</td>
</tr>
<tr>
<td>Red-Al</td>
<td>Sodium bis(2-methoxyethoxy)aluminium hydride</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>SAMP</td>
<td>(S)-1-Amino-2-methoxymethylpyrrolidine</td>
</tr>
<tr>
<td>str</td>
<td>Stretch</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-Butylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>Triisobutylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMSCl</td>
<td>Trimethylsilyl chloride</td>
</tr>
</tbody>
</table>
| Ts            | para-Toluenesulfonyle
Acknowledgements

I would like to thank everybody who has contributed towards my PhD experience. Without the help and support of the people around me, these three years would have been endured, rather than enjoyed. Firstly, to all the people I’ve encountered in F001 – Farah, KC, Celine, Poults, Ritz, Lummers, Carole, Prof. X, Yohan, Claire, Wozza, Hayley, Laura – never a dull moment was had!! To other members of the department – Young Paul, Lou, Kate, Tobs, Duffy, Jaime, Amber, Jo, Ben, Sean, Gav, Stanny, Jonker Shaw, Mark – thanks for all your help.

To the Pritchard group past and present – The Prof (for taking me to the board), Chef (I think that was his name), Eric (hey! mate mate), Wenson (for the Barnsdale Close Rumble in the Jungle), Jess (for not letting me sleep in my corner), Curls (uuurrrgh) – thanks for the memories.

A special thank you to Dr. G. J. Pritchard for the opportunity to undertake this project. The steady stream of help, advice and suggestions certainly kept me busy for three years. Also to my industrial supervisor and sponsors, Dr R. E. Rathmell (Eli Lilly), thanks for everything.

Finally - to my family. Explaining ‘Novel Palladium Catalysed [3 + 2] Cycloadditions Towards Functionalised Aza-Bicycles’ over the telephone was always a challenge, but now I have something to physically show you for my troubles! I appreciate the support and encouragement you have given me throughout my life and this thesis is dedicated to you.
Introduction

Chapter One

Alkaloids containing the 1-aza[(2+n).3.0]bicyclic framework have a wide and varied distribution in nature (Figure 1.01). Pyrrolizidine (n=1), indolizidine (n=2) and azepine (n=3) ring systems are the central building blocks to many natural products, and many serve as key synthetic intermediates for more complex molecules. This thesis examines the development of a general method towards these structures, with the ultimate aim of applying this methodology to target synthesis. A brief overview of the therapeutic properties associated with these natural alkaloids, and previous studies in their syntheses follows.

Figure 1.01 The 1-aza[(2+n).3.0]bicyclic framework

1.1 Pyrrolizidine and Indolizidine Alkaloids

1.1.1 Introduction to the Pyrrolizidine Alkaloids

There are a vast number of naturally occurring pyrrolizidine and indolizidine alkaloids, varying from relatively simple polyhydroxylated systems such as retronecine, lentiginosine and swainsonine, to the more complex polycyclic systems such as mitomycin A, tylophorine and alkaloid-205B (Figure 1.02). Amphibians have provided a remarkable array of biologically active compounds, which on secretion from the skin can serve to protect the amphibian from predators and in the case of some peptides, protect from bacterial or protozoan infections.
The glycosidase inhibitory activity of the indolizidine alkaloids has been extensively studied, and together with related alkaloids of the pyrrolizidine, piperidine, pyrrolidine and nortropane families, they are revered as potential therapeutics. The wide-ranging physiological responses associated with these compounds, has generated much interest in their synthetic study, and also elucidation of their mode of action. Glycosidasases are of paramount importance in processes such as intestinal digestion, post-translational treatment of glycoproteins and the lysosomal catabolism of glycoconjugates. For these reasons, this diverse group of alkaloids are highly regarded as possible treatments for diabetes, cancer and viral infections.²

1.1.2 Syntheses of the Pyrrolizidine and Indolizidine Alkaloids

West et al. describe a novel ring expansion of azetidinium ylides to synthesise stereoisomers turneforcidine and platynecine (Scheme 1.01).³ They prepare azitidinecarboxylate esters of type I and effect metal-catalysed decomposition of the diazo-group, to yield transient spirocyclic ylides 2. These in turn undergo a Stevens [1,2]-shift leading to fused ring systems 3.
Reductive debenzylation of azetidinecarboxylate ester 4 using transfer hydrogenation conditions, followed by immediate coupling with 4-bromo-1-diazobutan-2-one 5 lead to key intermediate 6 (Scheme 1.02). Treatment with Cu(acac)$_2$ or Rh$_2$(OAc)$_4$ gave an inseparable mixture of diastereoisomers 7 and 8. Other soluble copper(II) catalysts can be used with comparable rates of turnover, but no improvement of diastereoselectivity was observed. This mixture of isomers was then reduced under standard hydrogenation conditions, to give ester 9 and lactone 10, which were easily separable. The synthesis of racemic turneforcidine and platynecine was completed by LiAlH$_4$ reduction of the ester functionality. Preliminary studies suggest that this protocol can also be applied to the indolizidine alkaloids.

**Scheme 1.02** Reagents: (a) Pd/C, NH$_4$CO$_2$H, MeOH; (b) 5, DIPEA, MeCN (96% 2 steps); (c) 10 mol% Cu(acac)$_2$, toluene, reflux (82%, inseparable mixture 7:8, 3.6:1); (d) PtO$_2$, H$_2$, MeOH (9 (88%), 10 (71%)); (e) LiAlH$_4$, THF (91%); (f) LiAlH$_4$, THF (94%).
Angle et al. exploited the chiral pool in their use of α-amino acids in the synthesis of enantiopure indolizidine 167B, an alkaloid found within the skin secretions of neotropical frogs (Scheme 1.03). The N-benzoyl-protected ethyl ester of D-norvaline was reduced with DIBAL-H before Grignard addition of vinyl magnesium chloride to give alcohol 12 as a mixture of diastereoisomers. Lithium aluminium hydride reduction of the amide followed by N-alkylation with phenyl α-bromoacetate resulted in lactonisation to give tertiary amine 13. Reaction with TIPSOTf and triethylamine generated key intermediate 14. Subsequent Ireland-Claisen rearrangement gave TIPS-ester 15, which was reduced with LiAlH₄ immediately to primary alcohol 16. The minor diastereoisomer of the silyl ketene acetal 14 failed to undergo Ireland-Claisen rearrangement, leading to exclusively one isomer of alcohol 16. Swern oxidation, followed by Horner-Emmons-Wadsworth homologation with triethyl phosphonoacetate, afforded alkene 17 as a mixture of geometrical isomers. The E/Z mixture was subjected to hydrogenolysis using Pearlman's catalyst, and ring closure with trimethyl aluminium lead to lactam 18. Reduction with LiAlH₄ afforded (−)-indolizidine 167B.

Scheme 1.03 Reagents: (a) DIBAL-H, DCM, −78°C; then CH₃CH₂MgBr (53%, 8:1); (b) LiAlH₄, THF, 0°C (82%); (c) BrCH₂CO₂Ph, i-PrNEt₂, MeCN, 0°C (60%); (d) TIPSOTf, NEt₃, benzene, RT; (e) LiAlH₄, 0°C (79% 2 steps); (f) (COCl)₂, DMSO, NEt₃, −78°C; (g) KH, (EtO)₂P(O)(CH₃)₂CO₂Et, THF, −78°C (66% 2 steps); (h) H₂, Pd(OH)₂/C, EtOH, 60°C; (i) Me₃Al, benzene, 0°C to reflux (55% 2 steps); (j) LiAlH₄, Et₂O, 0°C (78%).
Enders et al. made use of (S)/(R)-1-amino-2-methoxymethylpyrrolidine (SAMP/RAMP)-hydrazones in the enantioselective synthesis of dendrobatid alkaloid indolizidine 2091 (Scheme 1.04). This method involved the use of chiral amines arising from the stereoselective reduction of SAMP/RAMP-hydrazone. Reaction of 1-pentanal with RAMP gave chiral hydrazone 20, which was α-alkylated with 21 to give a 90% d.e of the desired acetal 22. Hydrazine 23 was obtained by reaction of an organocerium reagent derived from 3-tert-butyldimethylsiloxypropyl lithium, with complete asymmetric induction. Cleavage of the N-N bond was achieved with borane, followed by N-protection, and silyl deprotection with TBAF. Mesylation of the resulting alcohol was followed by ring-closure with potassium t-butoxide to give compound 24. Hydrogenolysis using Pearlman’s catalyst, removed the N-benzyl ester, and acetal deprotection gave the aldehyde. Subsequent closure of the 6-membered ring was followed by in situ reduction of the imine with potassium cyanide, to give amino nitrile 25. The synthesis of indolizidine 2091 was completed by alkylation with n-propyl bromide and reduction with NaBH₄.

Scheme 1.04 Reagents: (a) RAMP, THF, RT (90-100%); (b) LDA, THF, 0°C; (c) 21, THF, -100°C (81% 2 steps); (d) TBSO(CH₂)₃Li, CeCl₃, THF, -100°C (82%); (e) excess BH₃·THF, reflux; (f) CICO₂Bn, Et₃O, 0°C; (g) TBAF (72% 2 steps); (h) MsCl, NEt₃, THF, 0°C; (i) KO-Bu, THF, 0°C (70% 2 steps); (j) H₂, Pd(OH)₂/C, MeOH; (k) HCl, KCN, pH = 4 (91%); (l) LDA, THF, 0°C; (m) n-propyl bromide, THF, 0°C; (n) NaBH₄, THF, RT (88-89% 3 steps).
Angle et al. have developed a diastereoselective synthesis of highly functionalised 3-hydroxyproline benzyl esters from α-alkoxy N-protected aminoaldehydes and benzyl diazoacetate. Key intermediate 30 was made starting from di-O-isopropylidene-D-mannitol 26 (Scheme 1.05). Stereospecific deoxygenation of the vicinal diol was achieved using mild conditions developed by Hanessian to give alkene 27. Removal of the acetonides using Amberlyst-15™, followed by bis-tosylation of the primary alcohols via a bis(dibutylstannylene acetal) intermediate furnished compound 28. Silyl protection of the secondary alcohols was achieved with TBDMSOTf, and then reaction of the ditosylate with NaNHTs gave 29, which was oxidatively cleaved with ozone to give key intermediate 30. This sequence of reactions was appealing, as one molecule of D-mannitol 26 could be converted into two molecules of chiral aldehyde.

Aldehyde 30 was reacted with benzyl diazoacetate and BF₃.ΟEt₂ and the free hydroxy-group protected with MEMCl to give enantiopure proline derivative 31 (Scheme 1.06). Reduction with NaBH₄ gave a primary alcohol that was displaced with iodide, followed by radical reaction with methyl acrylate to give methyl ester 32. Treatment with magnesium ribbon in MeOH gave lactam 33, with concomitant N-detosylation and

Scheme 1.05 Reagents: (a) CH(OMe)₂NMe₂, DCM, RT; (b) Mel, toluene, RT to reflux (86% 2 steps); (c) Amberlyst-15, MeOH, RT (83%); (d) Bu₂SnO, toluene, reflux; (e) TsCl, RT (66% 2 steps); (f) TBDMSOTf, 2,6-lutidine, DCM, 0°C (92%); (g) NaNHTs, DMSO, 80°C (72%); (h) O₃, DCM, −78°C; then thiourea 0°C (81%).
cyclisation. LiAlH₄ reduction of the lactam and cleavage of the silyl ether, followed by removal of the MEM ether using CBr₄ gave (-)-lentiginosine 34.

\[
\text{OTBDMS} \quad \text{NHTs} \quad \text{N₂=CO₂Bn} \quad \text{a, b} \quad \text{OTBDMS} \quad \text{OMEM} \quad \text{c-e}
\]

\[
\text{OTBDMS} \quad \text{OMEM} \quad \text{a,b} \quad \text{OTBDMS} \quad \text{OMEM} \quad \text{g,h}
\]

Scheme 1.06 Reagents: (a) BF₃.OEt₂, DCM, −78°C (65%); (b) MEMCl, DIPEA, CHCl₃, reflux (78%); (c) NaBH₄, EtOH, RT (88%); (d) PPh₃, I₂, imidazole, DCM, reflux (86%); (e) methyl acrylate, Bu₃SnH, AIBN, benzene, reflux (57%); (f) Mg, MeOH, RT (75%); (g) LiAlH₄, THF, reflux; (h) CBr₄, MeOH, reflux (54% 2 steps).

Montgomery et al. report the stereoselective synthesis of (+)-allopumiliotoxin, by means of a nickel-catalysed, triethylsilane-mediated, reductive cyclisation of ynals (Scheme 1.07). Oxazolidinone 35 was prepared from the methyl ester of L-proline using the Overmann protocol. Hydrolysis of the oxazolidinone ring was achieved with potassium hydroxide, followed by propargylation with enantiopure 36, to give compound 37. Benzylation of the tertiary alcohol followed by deprotection of the primary alcohol and oxidation lead to key intermediate 40. Cyclisation was induced with catalytic Ni(COD)₂, triethylsilane and tributylphosphine, to give exclusively one diastereoisomer of bicycle 41. Deprotection of the silyl ether with HF-pyridine and the benzyl ether with lithium in ammonia afforded (+)-allopumiliotoxin 267A.
Brandi et al. made use of the 1,3-dipole of pyrroline-N-oxide derived from enantiopure malic acid, and reacted this with methylenecyclopropane to form novel indolizidinol 52 (Scheme 1.08).\(^9\) The secondary alcohol of the diethyl ester of \(\text{L-malic acid}\) was protected with 2-methylpropene, and the esters reduced with LiAlH\(_4\), before bis-mesylation of the primary alcohols gave 46. Reaction with hydroxylamine resulted in cyclisation to give compound 47. The key nitron 48 was made after oxidation of the hydroxylamine with mercury(II)oxide. The oxidation reaction provided two regioisomers of the nitron product, but compound 48 was the major isomer (9:1). The key step involved the 1,3-dipolar cycloaddition of nitron 48 with methylenecyclopropane 49, to give a mixture of regioisomers. The major isomer 50 underwent thermal rearrangement in xylenes to give indolizidinone 51. Reduction of the carbonyl group followed by deprotection of the alcohol gave (1S,7S,8aR)-octahydro-1,7-dihydroxyindolizidine 52. This novel and unnatural indolizidine was targeted, due to the common occurrence of hydroxylated indolizidines at the C-1 and C-7 position. Unfortunately the biological activity of this compound was not reported.
Scheme 1.08 Reagents: (a) 2-Methylpropene, Amberlyst-H15, n-hexane (91%); (b) LiAlH₄, Et₂O, reflux (83%); (c) MsCl, NEt₃, DCM (97%); (d) NH₂OH (85%); (e) HgO, DCM, 0°C (90%); (f) 49, benzene, RT (70%); (g) Xylenes, 140°C; (h) NaBH₄, ethanol, 0°C (90%); (i) CF₃COOH, RT (70%).

Cha et al. use the coupling reactions of in situ generated dialkoxytitanacyclopropanes and carbonyl groups (Scheme 1.09), to access novel pyrrolizidine and indolizidine compounds, as well as the core of mitomycin derivatives.¹⁰ The reaction involves the coupling of esters to dialkoxytitanacyclopropanes of type 53, in a formal double alkylation to afford oxygen-substituted cyclopropanes.

Scheme 1.09 Reagents: (a) c-C₅H₉MgCl, CITi(Oi-Pr)₃, DCM, 17 h.
The synthetic potential of the proposed reaction intermediate was unlocked in work towards mitomycin derivatives. Starting from o-imidostyrene 54, obtained from acylation with succinic acid of the o-aminostyrene, reaction with cyclopentane magnesium chloride and triisopropoxy titanium chloride gave the key dialkoxytitanium intermediate 55 (Scheme 1.10). Depending on how the reaction was quenched, the tricyclic cores 56 and 57 were obtained. The crucial primary alcohol required for further elaboration to mitomycin derivatives, was introduced by simply bubbling oxygen through the metallo intermediate. This is a powerful method for accessing a range of mitomycin antibiotics, and also novel bicyclic systems.

\[ \text{Scheme 1.10 Reagents: (a) c-C}_3\text{H}_5\text{MgCl, } \text{ClTi(Oi-Pr)}_3; \text{ (b) O}_2 \text{ (60%); (c) H}_2\text{O (42%).} \]

To date there have been several synthetic routes to the mitomycin antibiotics, however the majority of these have lead to non-racemic products. Sulikowski et al. have described a chemoselective carbon-hydrogen insertion reaction of a metal carbene, to access 1,2-aziridinomitosene products with high levels of optical purity (Scheme 1.11). Pyrrolidine 58 was silylated, then the Boc-protection removed to give azido compound 59 with an enantiomeric excess of 95%. A Buchwald-Hartwig cross-coupling of 2-bromoiodobenzene with 59 gave aryl bromide 61,\textsuperscript{11} which was coupled with silyl ketene acetal 62 in the presence of tributyltin fluoride to give acetate 63. Hydrogenation of the azido group followed by acetylation and desilylation yielded amide alcohol 64. Mesylation followed by treatment with DBU gave oxazoline product 65. They reversed the trans stereochemistry of azido ether 63 to the cis-stereochemistry of oxazoline 65 to theoretically improve the efficiency of the key carbene insertion step. Hydrolysis of 65 followed by tosylation, treatment with phosgene and methanolysis gave carbamate 67.
This in turn underwent diazotransfer using *para*-nitrobenzensulfonyl azide to give diazoester 68. Optimal regioselectivity of the carbene insertion reaction was achieved using the copper(I) complex derived from ligand 69, with a 9:1 ratio in favour of regioisomer 70. The aziridomitosene core 71 was completed by hydrolysis of the oxazinone, mesylation and final aziridine formation with DBU.

Smith *et al.* drew upon the pioneering work carried out by Corey and Seebach on dithiane chemistry,12 in their synthesis of (-)-indolizidine 223AB (Scheme 1.12).13 Dithianes act as important umpolung reagents in organic synthesis, and form one of the components in this convergent strategy. Lithiation of dithiane 72, followed by addition of epoxide 73 and then aziridine 74 containing HMPA, effects a solvent controlled Brook rearrangement to yield compound 75. Bisdesilylation with TBAF, afforded the
diol 76, which was bismesylated, and detosylated in one pot, to effect cyclisation to indolizidine 77. Interestingly the dithiane moiety aids the cyclisation step, presumably via the Thorpe-Ingold effect. Removal of the dithiane group was achieved with Raney-Ni, completing the synthesis of (-)-indolizidine 223AB.

Scheme 1.12 Reagents: (a) t-BuLi, Et₂O, -78°C to -45°C; (b) 73, Et₂O, -78°C to -25°C; (c) 74, HMPA/Et₂O, -78°C to 0°C (56% 3 steps); (d) TBAF (98%); (e) MsCl, Et₃N, THF, RT; (f) K₂CO₃, MeOH, RT, 3 h; then 5% Na-Hg, Na₂HPO₄, RT (95% 2 steps); (g) Raney-Ni, EtOH, H₂, RT (69%).

Katsuki et al. prepared (-)-swainsonine by means of a chiral Mn(III)-salen mediated desymmetrisation of 3-pyrroline 78 (Scheme 1.13). N-Protection via the carbamate followed by dihydroxylation and acetonide protection gave the symmetrical compound 79. The key step in this asymmetric synthesis used a chiral Mn(III)-salen catalysed oxidative desymmetrisation with PhIO, to give an alcohol in 71% ee which was then oxidised to the lactam 80 with PCC. *In situ* generation of the Grignard reagent derived from Cl(CH₂)₄MgBr and reaction with the lactam gave the chloro amine 81, which underwent base mediated deprotection and cyclisation to give chloro imine 82. Heating in toluene effected cyclisation to give a bicyclic iminium salt, which was subjected to base to generate the enamine. This was then hydroborated with an oxidative work up to give a hydroxy group, and final acetonide removal yielded (-)-swainsonine.
Scheme 1.13 Reagents: (a) Boc₂O, Et₃N, DMAP, DCM, RT, 12 h; (b) K₂OsO₄·2H₂O, K₃Fe(CN)₆, K₂CO₃, DABCO, CH₃SO₂NH₂, t-BuOH, H₂O, RT, 15 h; (c) (CH₃)₂C(OMe)₂, p-TsOH, DMF, RT, 20 h (75% 3 steps); (d) Chiral Mn(III)-salen, PhIO, PhCl, -25°C, 25 h; (e) PCC, DCM, RT, 8 h (56% 2 steps); (f) Br(CH₂)₄Cl, Mg, THF, -78°C, 1.5 h (71%); (g) TMSOTf, PhSH, DCM, 0°C, 1.5 h (83%); (h) toluene, reflux, 16 h; (i) t-BuNH₂, KHMS, toluene, 2 h; (j) BH₃·THF, THF, RT, 10 h; then NaOAc, H₂O₂, RT, 12 h (67% 3 steps); (k) PPTS, MeOH, RT, 65 h (45%).
1.2 *Stemona* Alkaloids

1.2.1 Introduction to the *Stemona* Alkaloids

The *Stemona* alkaloids are a structurally diverse class of alkaloids isolated from the roots and rhizomes of the *Stemonaceae* plant family (Figure 1.03). The extracts of several plants of this family (*Stemona* and *Croomia* genera) have been used in traditional Chinese and Japanese folk medicine as treatments for bronchitis, tuberculosis, pertussis and as anti-helmintics.\(^{15,16}\) These alkaloids also show extraordinary insecticidal activity.\(^ {17}\) Although the specific biological activities of the individual members of this alkaloid family are quite limited, it is known that the extracts consist of a series of structurally related alkaloids thought to be responsible for their medicinal properties. The 60 known *Stemona* alkaloids have been classed into six groups depending on structural criteria. The structures of 20 of these, including stenine, stemoamide, stemospironine, croomine, stemoamine, parvistemoline and stemofoline (Figure 1.04) have been confirmed by X-ray analyses whilst the remaining alkaloids have been determined from spectroscopic data and/or by chemical correlation.\(^ {16}\)

![Figure 1.03](image.png)

*Figure 1.03* The foliage of a member of the *Stemonaceae Croomia* genera

Common to five of the six groups is a central 1-azabicyclo[5.3.0]decane system as the most characteristic structural feature. However, \(\gamma\)-butyrolactones are also common occurring as *trans*-, *cis*- and *spiro*-fused systems. The sixth miscellaneous group of the *Stemona* alkaloids arises from cleavage of the basic 1-azabicyclo[5.3.0]decane ring system.
1.2.2 Syntheses of the Stemona Alkaloids

Williams et al. achieved the first synthesis of a Stemona alkaloid in 1989, in the enantiocontrolled synthesis of (+)-croomine (Scheme 1.13). Consecutive ring closures arose from the preliminary construction of a branched acyclic carbon framework. The terminal acetylene was acylated with methyl chloroformate, before copper-catalysed conjugate Grignard addition of \( \text{BnO(CH}_2\text{)}_4\text{MgBr} \), and subsequent Dibal-H reduction gave allylic alcohol. Sharpless asymmetric epoxidation followed by Swern oxidation of the allylic alcohol, allowed homologation following a Wittig protocol with a suitable phosphorous ylide, yielding vinyl epoxide. Reduction of the ester using LiBH₄, followed by hydrogenation of the alkene using rhodium on alumina gave the saturated alcohol, which was protected as the benzoate ester before addition of lithium azide and DMPU to give azido alcohol. Reaction with boron trifluoride etherate generated the saturated dioxepine ring, then ester hydrolysis and Swern oxidation gave an aldehyde which was reacted with the chiral ylide to give alkene exclusively as the \((Z)\)-isomer. Acid hydrolysis of the dioxepine acetal and basic saponification yielded a triol which was oxidised to the lactone ring using Jones’ reagent. Esterification of the terminal carboxylic acid using diazomethane generated butyrolactone 90. Removal of the
benzyl ether followed by oxidation gave an azido aldehyde which was reacted with triphenylphosphine to generate an aza-ylide. Subsequent intramolecular Wittig condensation produced a seven-membered imine, which was reduced to azepine 91 with sodium borohydride. The final two ring-closures were accomplished in a single iodoamination step to give synthetic (+)-croomin.

Scheme 1.14 Reagents: (a) n-BuLi, THF, −78°C to 0°C; then ClCO₂Me, −78°C (63%); (b) BnO(CH₂)₄MgBr, Me₂S.CuBr, TMEDA, Et₂O, −78°C (95%); (c) DIBAL-H, DCM, −78°C (98%); (d) Ti(i-PrO)₄ (cat.), D-DIPT (cat.), t-BuOOH, DMSO, −78°C to 0°C (93%); (e) (COCI)₂, DMSO, NEt₃, DCM, −78°C to 0°C; (f) Ph₃P=CHCOMe, 0°C to RT (89% 2 steps); (g) LiBH₄, Et₂O, MeOH, 0°C (81%); (h) 5% Rh/Al₂O₃, H₂, THF (62%); (i) BzCl, NEt₃, DCM, 0°C to RT (97%); (j) LiN₃, DMPU, 110°C, (94%); (k) BF₃·Et₂O, DCM, 0°C (81%); (l) LiOH, THF, aq. MeOH (97%); (m) (COCI)₂, DMSO, NEt₃, −78°C to RT (91%); (n) 86, THF, −10°C (70-81%); (o) aq. HBF₄, MeOH (74%); (p) LiOH, THF, aq. MeOH, 22°C (86%); (q) Jones’ reagent, THF, 0°C; (r) CH₂N₂, DCM, Et₂O (72% 2 steps). (s) BCl₃, DCM, −78°C to 0°C; then MeOH, −78°C (77%); (t) (COCI)₂, DMSO, NEt₃, −78°C to RT (92%); (u) Ph₃P, THF, 22°C; then NaBH₄, MeOH (90%); (v) I₂, DCM, Et₂O, 22°C (25%).

The first total synthesis of racemic stenine was achieved by Hart et al., utilising an intramolecular Diels-Alder reaction to construct the indolizidine core of the...
molecule. It relies on the synthesis of key intermediate 98 starting from (E)-3,5-hexadienol 92 (Scheme 1.15). Esterification with (E)-2,4-pentadienoyl chloride 93 gave the precursor for the Diels-Alder reaction, which was promoted by Lewis acid to give bicycle 94. Ring-opening of the lactone with hydrazine, followed by exhaustive methylation and acylation of the primary alcohol gave aminimide 95. This underwent an aminimide variant of the Curtius rearrangement in refluxing mesitylene to give an intermediate isocyanate, which was quenched with methanol to give carbamate 96. Hydroboration using sodium perborate as oxidant, and mesylation gave compound 97, which was cyclised using two equivalents of methyl lithium to key intermediate 98.

Scheme 1.15 Reagents: (a) n-BuLi (100%); (b) Et₂AlCl, CHCl₃, 85°C (67%); (c) NH₂NH₂, MeOH (87%); (d) MeI (100%), K₂CO₃; (e) CH₃COCl (100%); (f) mesitylene, reflux, MeOH quench (94%); (g) 9-BBN, NaB(O indeb.)₄H₂O (95%) (h) MsCl, Et₃N (100%); (i) MeLi (2 equiv.) (94%).

The next step in the synthesis involved oxidation of 98 to the acid 99, and iodolactonisation in a biphasic system to give 100. Dehydrohalogenation with DBU, reductive cleavage of the lactone and selective protection of the primary alcohol with TBSCI gave 101. Reaction of the secondary alcohol with amide acetal MeC(OMe)₂NMe₂, lead to an intermediate which underwent a Claisen rearrangement to yield compound 102. Iodolactonisation to form the lactone ring present in stenine, was accompanied by desilylation of the silyl ether. Keck allylation proceeded with excellent diastereoselectivities, presumably because of steric effects to give 105. Methylation of the lactone ring, Swern oxidation of the primary alcohol and Wittig homologation, gave a conjugated diene which was selectively reduced using Red-Al. Removal of the carbamate protection was achieved with trimethylsilyl iodide to give
compound 105. The tetra cyclic core of stenine was completed after refluxing in mesitylene, and the allylic alkene oxidised using Johnson-Lemieux conditions. Finally, to introduce the pendant ethyl group and remove the amide carbonyl, reaction with 1,2-ethanedithiol and Lawesson’s reagent gave thioketal 107, which was desulphurised using Raney-nickel to give racemic stenine (Scheme 1.16).

Scheme 1.16 Reagents: (a) CrO3, H2SO4 (83%); (b) I2, NaHCO3 (95%); (c) DBU (98%); (d) NaBH4 (100%); (e) K2CO3, TBSCI (100%); (f) MeC(OEt)2NMe2 (93%); (g) I2 (75%); (h) n-Bu3SnCH2CH=CH2, AIBN, benzene, reflux (83%); (i) LDA, THF, Mel (87%); (j) Et3N, DMSO, (COCl)2 (99%); (k) Ph3P=CHCO2Et (91%); (l) Red-Al, Cu(l)Br (85%); (m) Me3Si, CH2Cl2, RT (94%); (n) Mesitylene, reflux (91%); (o) OsO4 (cat.), NaIO4 (84%); (p) HSCH2CH2SH, SiO2, SOCl2 (100%); (q) p-MeOC8H4PS2Cl2 (100%); (r) Raney-Ni, EtOH (75%).

In 1998 Rigby et al. reported a novel strategy to the azepinoindole skeleton present in stenine, neotuberostemonine and tuberostemonol (Scheme 1.17). 21 The key step makes use of a [1+4] cycloaddition between vinyl isocyanate 108 and the 1,1-dipole equivalent present in alkyl isocyanide 109, to give hydroindolone 110. Routine enamide alkylation with 1,4-diiodobutane gave alkylated hydroindolone 111, which was cyclised to the tricyclic enamide 112, using ethyl magnesium bromide and diglyme. Hydrolysis of the enamine was achieved using an aqueous solution of oxalic
acid dihydrate to give the hydroisatin derivative 113, existing primarily in the enol form. Oxidation with m-CPBA resulted in functionalisation at the γ-position of the extended enol to give oxidation product 114, containing ring fusion patterns consistent with tuberostemonol.

Scheme 1.17 Reagents: (a) Xylene, reflux (83%); (b) NaH, DMF, 0°C; then I₂(CH₂)₄ (56% 2 steps); (c) EtMgBr, diglyme, 120°C (70%); (d) (COOH)₂, THF/H₂O (60%); (e) m-CPBA, CHCb, -15°C (93%).

Padwa et al. describe the total synthesis of (±)-stenine, which relies on an intramolecular [4+2]-cycloaddition of a 2-methylthio-5-amido furan (IMDAF) to create the azepinoindole skeleton (Scheme 1.18). This approach differs from most, as the azepine ring system was introduced at an early stage, acting as a template for stereochemical manipulation later in the synthesis. Caprolactam 115 was subjected to an aldol reaction with bis-(methylsulfanylacetaldehyde), then acetic anhydride quench to give amide 116. Acylation with trans-5-chlorocarbonyl-pent-3-enoic acid methyl ester gave imide 117. Methyl sulfonilation of one of the methylthio groups of 117 with dimethyl(methylthio)sulfonium (DMTSF) induced thionium-promoted cyclisation. The resulting dihydrofuran readily lost acetate to furnish the desired furan 118. This compound rapidly rearranged at room temperature via the IMDAF mechanism, resulting in azepinoindole 119. Removal of the methylthio group was achieved with Raney nickel, and subsequent Luche reduction of the ketone afforded alcohol 120 as a single diastereoisomer. Stereoselective hydrogenation was achieved by [Ir(cod)pyr(PCy₃)]PF₆/CH₂Cl₂, a catalyst described by Crabtree et al., to give...
exclusively the syn-anti conformation at the ring fusion sites. Regioselective dehydration was achieved by converting the alcohol to the mesylate before treatment with DBU to give compound 121. Hydrolysis of the methyl ester followed by iodolactonisation formed the lactone 122. Final conversion to (±)-stenine was accomplished using a Keck allylation with allyltributyl-stannane. Johnson-Lemieux oxidation afforded the desired aldehyde, which was treated with 1,2-ethanedithiol. Conversion of the amide to the thioamide was done using Lawesson’s reagent, followed by desulfurisation with Raney-Nickel and methylation of the lactone enolate with methyl iodide to give racemic stenine.

Scheme 1.18 Reagents: (a) LDA; (b) (MeS)₂CHCHO; (c) Ac₂O, (80%, 3steps); (d) MeO₂CCCH₂CH=CH₂COCl, (85%); (e) DMTSF, NEt₃, (80%); (f) Raney-Ni, EtOH, (92%); (g) NaBH₄, CeCl₃, MeOH, (77%); (h) Crabtree’s catalyst, H₂, CH₂Cl₂; (i) MeCl, NEt₃, DBU, (64%, 2 steps); (j) LiOH, H₂O; (k) I₂, MeCN; (60%, 2 steps); (l) CH₂=CHCH₂SnBu₃, AIBN, (62%); (m) OsO₄, NaIO₄; (n) HSC(═CH)₂SH, BF₃·Et₂O, (48%, 2 steps); (o) Lawesson’s reagent (73%); (p) Raney-Ni; (q) LDA, HMPA, Mel (93%, 2 steps).

Wipf et al. have developed a general methodology towards the azepinoindole core with Cbz-L-tyrosine 123 acting as the key building block. They have used this
protocol in the synthesis of stenine,25,26 and also (-)-tuberostemonine (Scheme 1.19).27 Bicycle 125 was obtained by treating Cbz-L-tyrosine 123 with iodobenzenediacetate and NaHCO3 in a one-pot procedure before benzylation of the tertiary alcohol, followed by reduction of the enone using Luche conditions. Reaction with Pd2(dba)2.CHCl3 gave a π-allyl intermediate which was reduced in situ using formic acid to give 125. Silylation of the alcohol was followed by deprotection of the carbamate, before cinnamylation and subsequent fluoride-induced desilylation to give alcohol 128. Ruthenium tetroxide oxidation of the secondary alcohol was followed by a stereoselective alkylation of the enolate generated from reaction with KHMDS to give pre-cyclisation compound 129. Ring closing metathesis was carried out using Grubbs catalyst 130 to give azepinoindole 131. Thiophenol was used as a transient protection of the enone double bond to allow reduction of the azepine alkene with Wilkinson’s catalyst. The thiophenol was removed with DBU, and 1,2-reduction of the enone was followed by silyl protection to give 132. The ester was then converted to the Weinreb amide 133 which was added to the lithium anion of ortho ester 134 to give ketone 135. Reduction of the ketone with L-selectride, followed by acidic removal of the ortho ester and silyl ether protecting groups lead to cyclised lactone 136 as a single diastereoisomer.
The introduction of the final lactone ring began by Claisen rearrangement using 1,3-dimethylacetamide dimethyl acetal to give 137 (Scheme 1.20). Selenolactonisation followed by Keck allylation and α-methylation of the fused lactone ring with methyl iodide gave tetracycle 140. Chain contraction of the allyl group was achieved first by isomerisation of the double bond using allyltritylamine and Grubbs 2nd generation catalyst 130, before ethylene cross-metathesis with catalyst.
143 gave compound 142. The synthesis of tuberostemonine was completed by hydrogenation using palladium on carbon.

Scheme 1.20 Reagents: (a) N,N-Dimethylacetamide dimethyl acetal, xylenes, 135°C (78%); (b) PhSeCl, MeCN/H₂O, 0°C (67%); (c) AIBN, allyltriphenyltin (neat), 95°C (70%); (d) LDA, HMPA, THF, −78°C, MeI (76%); (e) 130, allyltrimylamine, DIPEA, toluene, 110°C (85%); (f) TsOH, 143, DCM, reflux, ethylene (81%); (g) Pd/C, H₂ (1 atm), MeOH (97%).

Kende et al. have addressed the structurally demanding spirocyclic core of stemonamide. A fifteen step total synthesis of stemonamide and isostemonamide has been reported. They both contain a characteristic tetra cyclic core, with two contiguous spirocyclic centres differing in relative stereochemistry at the quaternary centres. The heteroatoms are in an anti relationship in stemonamide, but syn in isostemonamide (Figure 1.05).
Their route involved a divergent parallel synthesis from identical starting materials. Grignard addition to PMB protected succinimide 144, resulted in a hemiaminal that was protected as the methoxy derivative 145, then hydrogenolysis of the benzyl group afforded the spiro compound 146. Addition of siloxyfuran 147 to the N-acyliminium ion generated from 146 generated the first quaternary centre as a mixture of diastereomeric alcohols 148. Swern oxidation afforded aldehydes, which were cyclised with DBU to give the tricyclic products, and further oxidised under Swern conditions to a separable mixture of tricyclic ketones 149 and 150. The desired enones were synthesised by first generating the silyl enol ether with tert-butyldimethylsilyl triflate, the oxidation with Pd(OAc)$_2$ produced enones 151 and 152, setting the platform for the parallel synthesis of both stemonamine and isostemonamide (Scheme 1.21).
Scheme 1.21 Reagents: (a) BnO(CH₂)₃MgBr, Et₂O, reflux 30 min; (b) PPTS, MeOH, RT, 30 min (90%, 2 steps); (c) H₂, 5% Pd/C, 3 h (90%); (d) 147, BF₃·Et₂O, CH₂Cl₂, RT, 40 min (82%); (e) (COCl)₂, DMSO, Et₃N, CH₂Cl₂; (f) DBU, CH₂Cl₂, 12 h, RT; (g) (COCl)₂, DMSO, Et₃N, CH₂Cl₂ (70%, 3 steps); (h) TBDSOTf, collidine, toluene, 7 h, 0°C-RT (149, 80% and 150, 68%); (i) Pd(OAc)₂, O₂, DMSO, 80°C, 24-48 h (151, 93% and 152, 89%).

The total synthesis of (±)-stemonamide was achieved by conjugate addition of the necessary Grignard reagent to isomer 152 in the presence of CuBr-Me₂S, which gave predominantly anti addition with respect to the C-N bond (Scheme 1.22). The exocyclic double bond was introduced by firstly a Mannich reaction with dimethylmethyleneammonium trifluoroacetate to install the α-methyl group followed by olefination and treatment with KH to give compound 153. Removal of the PMB groups with ceric ammonium nitrate yielded the unprotected lactam, which was treated with RhCl₃ to effect isomerisation of the exo-double bond to an endo position as in 154. Azepine ring closure was achieved by nucleophilic displacement of the mesylate with NaI to afford (±)-stemonamide. An identical approach was used starting from tricyclic ketone 152 in the synthesis of (±)-isostemonamide.
Williams et al. carried out the first synthesis of stemoamide in 25 steps in 1994.\textsuperscript{31} Since then Narasaka, Mori, Jacobi and most recently Somfai in 2007 have attempted to construct the tricyclic core and control the stereochemistry of its four chiral centres.\textsuperscript{32-35} Jacobi et al. have previously prepared racemic stemoamide in an elegant synthesis consisting of only 7 steps.\textsuperscript{34} They have further refined this procedure and describe a novel synthesis of (−)-stemoamide containing a key (Diels-Alder)-(retro-Diels-Alder) sequence to construct the core system (Scheme 1.23). Starting from L-pyroglutamic acid, esterification to the methyl ester followed by reduction with NaBH\textsubscript{4} gave lactam 157. Protection of the primary alcohol with vinyl ethyl ether was followed by alkylation with oxazole 160 and removal of the alcohol protection using TsOH to give compound 161. Swern oxidation gave the unstable aldehyde 162, which was reacted immediately with the Gilbert-Seyferth reagent to give alkyne 163. Methylation of the alkyne terminus lead to key intermediate 164. The (Diels-Alder)-(retro-Diels-Alder) reaction was promoted in refluxing diethyl benzene, with spontaneous loss of acetonitrile to form enantiomerically pure butenolide 165. The

\textbf{Scheme 1.22 Reagents:} (a) PMBO(CH\textsubscript{2})\textsubscript{4}MgBr, 5% CuBr-Me\textsubscript{2}S, TMSCl, HMPA, THF, -78°C, 30 min (74%, 6.4:1, α:β); (b) KH, Me\textsubscript{2}N=CH/CF\textsubscript{3}COO·, THF, 12 h (67%); (c) CAN, CH\textsubscript{3}CN-H\textsubscript{2}O, 2 h (80%); (d) RhCl\textsubscript{3}, H\textsubscript{2}O, EtOH/H\textsubscript{2}O (10:1), reflux, 36 h (66%); (e) MsCl, DMAP, pyridine, CH\textsubscript{2}Cl\textsubscript{2}, 0°C, 1 h; (f) NaH, THF, RT, 30 h (33%, 2 steps).
correct stereochemistry found in (−)-stemoamide was established using the nickel boride catalyst derived from NaBH₄/NiCl₂.³⁶

Olivio et al. report the total synthesis of (−)-stemoamide using a MgBr₂-catalysed stereoselective anti-aldol reaction of a N-acyl thiazolidinethione (Scheme 1.24).³⁷ Addition of the titanium enolate derived from 4R-phenyl thiazolidinethione with the iminium ion formed from a suitable pyrrolidinone precursor, gave the correct diastereomeric product 166 in good yield. Evans has extensively researched the use of chiral thiazolidinethione auxiliaries in diastereoselective aldol reactions, and in this case the anti-aldol product was formed, facilitated by silylation with TMSCl and catalytic amounts of MgBr₂.OEt₂. Crucially, this key intermediate now possessed three of the required stereocentres present in the natural product. The aldol product was protected as the triethylsilyl ether 167 in quantitative yield. All attempts to partially reduce the chiral thiazolidinethione failed, so the auxiliary was removed.
reductively to give the alcohol 168, which was then oxidised to aldehyde 169 with perruthenate. Wittig reaction with the necessary phosphonium ylide, gave an inseparable \( E,Z \)-mixture of methylvinyl ethers. Acidic removal of the silyl protection, hydrolysis of the methylvinyl ether and oxidation of the residual lactol with PCC gave the desired lactone 170. Ring-closing-metathesis was achieved with Grubbs second generation catalyst in refluxing 1,2-dichloroethane. The synthesis was completed by palladium-catalysed hydrogenation of the unsaturated azepine 171, followed by stereoselective methylation\(^\text{32}\) from the least hindered face of the lactone to give \((-\)-stemoamide).

\[
\begin{align*}
\text{Scheme 1.24 Reagents: (a) } & \text{TiCl}_4, \text{ DIPEA, DCM, } -78^\circ\text{C (92%); (b) cinnamaldehyde, cat.} \\
& \text{MgBr_2.OEt_2, RT; then TMSCl, Et_3N, HCl (74%); (c) TESOTf, 2,6-lutidine, 0^\circ\text{C,}} \\
& \text{DCM (99%); (d) NaBH_4, } -50^\circ\text{C, EtOH (96%); (e) TPAP, NMO, DCM (90%); (f) Ph_3P=CHOCH_3, THF, } -78^\circ\text{C (76%); (g) p-TsOH, THF/H_2O, reflux (88%); (h) PCC, NaOAc (87%); (i) 130 (cat.), (ClCH_2)_2, reflux (60%); (j) H_2, Pd/C, MeOH (99%); (k) LiHMDS, THF, MeI, } -78^\circ\text{C (70%).}
\end{align*}
\]
To date there have been far more syntheses of both racemic and natural (−)-stemoamide,1-3,38 but increasingly more attention is being focused on the preparation of analogues of stemoamide. Khim et al. report an efficient synthesis of (−)-9,10-epi-stemoamide via a sequential asymmetric Birch reduction-alkylation, lithium hydroxide-promoted fragmentation and a 7-exo-trig radical cyclisation (Scheme 1.25). Birch reduction of compound 173 provided a chiral enolate, which was then alkylated in situ with methyl iodide to give cyclohexadiene 174 as a single diastereoisomer. The enol ether was hydrolysed using 6 M HCl to give β,γ-enone 175. Iodolactonisation gave the enantiomerically pure carbolactone 176, which was then fragmented with lithium hydroxide monohydrate to give the requisite key intermediate 177. The butenolide carboxylic acid 177 was reduced to the primary alcohol using borane-tetrahydrofuran complex, and subsequent Mitsunobu reaction with succinimide gave imide 178. The carbinol lactam 179 was achieved by NaBH₄ reduction, and this in turn was reacted with PhSH in the presence of p-TSA to give the thiophenyl radical precursor 181. Radical reaction with Bu₃SnH and AIBN (cat.) resulted in ring-closure, to give an inseparable mixture of (−)-9,10-epi-stemoamide and 182 in a 10:1 ratio respectively. The mixture was epimerised using K₂CO₃ in MeOH, resulting in exclusively the more thermodynamically stable (−)-9,10-epi-stemoamide.
Cossy et al. recently reported a similar free-radical approach to the tricyclic core of stoemoamide and its analogues (Scheme 1.26). They utilised the 7-exo-trig radical cyclisation previously seen, in the synthesis of (±)-9,10-bis-epi-stemoamide, which controlled three of the four contiguous stereocentres in one step. Diol 183 was doubly protected with TBSCI, and the primary silyl ether selectively deprotected using ammonium fluoride to give 185. Substitution of the primary hydroxyl with succinimide was carried out using a Mitsunobu-type reaction to give imide 186. This in turn was selectively reduced using Super Hydride®, to give compound 187 which was treated with PhSH in the presence of p-TSA to give the thiophenyl radical precursor 188. These acidic conditions also cleaved the silyl ether, which was subsequently reacted with methylacrylic acid to give ester 189. The lactone ring was

Scheme 1.25 Reagents: (a) K, NH₃, THF, t-BuOH (1 equiv), -78°C, piperylene, Mel; (b) 6 M HCl, MeOH, RT; (c) I₂, THF/H₂O (1:1), RT (81% 3 steps); (d) LiOH.H₂O, THF/H₂O (10:1), RT (41%); (e) BH₃·THF, THF, -30°C (92%); (f) succinimide, Ph₃P, DEAD, THF, RT (92%); (g) NaBH₄, MeOH, -10°C (88%); (h) PhSH, TsOH.H₂O, benzene, 0°C (70%); (i) Bu₃SnH, AIBN (cat.), benzene (3.5 mM), reflux, 24 h; (j) K₂CO₃, MeOH, RT (74% 2 steps).
installed using a ring closing metathesis reaction with second generation Grubbs catalyst, to give the key intermediate 190. The crucial 7-exo-trig radical cyclisation occurred using Bu₃SnH and catalytic AIBN to give (±)-9,10-bis-epi-stemoamide as a single diastereoisomer, in a disappointing final-step yield of an unoptimised 20%.

Scheme 1.26 Reagents: (a) TBSCI, imidazole, DCM (93%); (b) NH₄F, MeOH, 65°C (58%); (c) succinimide, DIAD, Ph₃P, THF (91%); (d) LiBEt₃H, THF, −78°C (96%); (e) p-TSA (cat.), PhSH (87%); (f) methylacrylic acid, DCC, DMAP (cat.), DCM (86%); (g) Grubbs II (10 mol%), DCM, 40°C, 3 h (79%); (h) Bu₃SnH, AIBN, benzene (~5 mM), 80°C (20%).

Gurjar et al. have reported a formal synthesis of (−)-stemoamide using a carbohydrate-based approach.³⁸ Their method involves the elaboration of D-glucose and a stereocontrolled allylation under Barbier conditions. A ring closing metathesis approach forms the integral azepine ring system (Scheme 1.27). Starting material 191, obtainable from D-glucose diacetonide in three steps, was subjected to Swern oxidation conditions to form an unstable aldehyde, which was immediately reacted with allyl bromide in the presence of activated zinc. This Barbier-type reaction yielded exclusively stereoisomer 192, arising from a 7-membered zinc-chelated transition state. Hydroboration-oxidation of 192 followed by a protection-deprotection sequence furnished the mesylate and treatment with NaN₃ afforded the azido alcohol. Swern oxidation followed by reaction of NaClO₂ with the resulting aldehyde gave the azido acid and after esterification. The methyl ester 193 was obtained. Hydrogenation of 193 with palladium on carbon resulted in cyclisation to
give the 2-pyrrolidine ring, and phase transfer N-allylation in a biphasic system gave compound 194. Selective deprotection of the 5,6-acetonide moiety using H$_2$SO$_4$ in MeOH, bismesitylation of the resultant diol and elimination with sodium iodide gave the desired precyclisation intermediate 195. The azepine ring was completed using Grubbs ring closing metathesis. Hydrogenation of the double bond and treatment with Amberlyst-15 afforded the methyl glycoside β-isomer 197. Deoxygenation of the C-2 hydroxyl was achieved using Barton’s radical deoxygenation procedure.$^{40}$ Treatment with thiocarbonyl diimidazole and in situ addition of n-Bu$_3$SnH, AIBN (cat.) afforded 198. Finally the γ-lactone was installed using Grieco’s procedure to give compound 199.$^{41}$ Methylation using LDA and methyl iodide lead to the total synthesis of (-)-stemoamide.

Scheme 1.27 Reagents: (a) (COCl)$_2$, DMSO, Et$_3$N, -78°C, 1 h (80%); (b) allyl bromide, Zn, sat. NH$_4$Cl, THF, 30 min (81%); (c) BH$_3$(CH$_2$)$_2$S, THF, 0°C-RT, 1 h, then NaOAc, H$_2$O$_2$, 30 min (65%); (d) TBSCI, imidazole, CH$_2$Cl$_2$, RT, 1 h (90%) then MsCl, Et$_3$N, CH$_2$Cl$_2$, 0°C-RT, 30 min (85%); (e) NaN$_3$, DMF, 75-85°C, 32 h (77%); (f) (COCl)$_2$, DMSO, Et$_3$N, -78°C, 1 h (80%) then NaClO$_2$, DMSO, NaH$_2$PO$_4$, H$_2$O, 0°C-RT, 1 h (95%) then CH$_2$N$_2$, 50% KOH soln., Et$_2$O, -20°C, 5 min (94%); (g) 10% Pd/C, H$_2$, MeOH, RT, 6 h (87%); (h) allyl bromide, 50% KOH soln, C$_6$H$_6$, TBAI, RT, 2 h (74%); (i) 0.8% H$_2$SO$_4$, MeOH, RT, 8 h (84%); (j) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0°C, 10 min (70%); (k) NaI, ethylmethyl ketone, reflux, 4 h (66%); (l) 130 (cat.), CH$_2$Cl$_2$, reflux, 12 h (83%); (m) 10% Pd/C, H$_2$, MeOH, RT, 6 h (85%); (n) Amberlyst-15, MeOH, reflux, 3 h (70%); (o) Im-CS-Im, toluene, reflux, 6 h; then Bu$_3$SnH, AIBN, toluene, reflux, 12 h (45%, 2 steps); (p) m-CPBA, BF$_3$.OEt$_2$, CH$_2$Cl$_2$, 0°C-RT, 12 h (30%); (q) LDA, HMPA, Mel (93%, 2 steps).
Mori et al. use a novel ruthenium-catalysed enyne metathesis reaction in their synthesis of \((-\text{-stemoamide})\).\(^{33}\) Pyrrolidinone 200, derived from pyroglutamic acid, was N-alkylated with 5-bromo-1-pentene, and the ethoxyethyl protection removed with acidic methanol to give 201. Swern oxidation and Corey-Fuchs homologation with \(\text{CBr}_4\) and \(\text{Ph}_3\text{P}\) in the same pot resulted in the dibromoalkene, which was subjected to butyl lithium to give the enyne 202. Treatment with LDA deprotonated at the terminal alkyne position and subsequent reaction with \(\text{ClCOOMe}\) gave conjugated enyne 203. Ring closing metathesis with ruthenium catalyst 204 gave the cyclised product 205. The important characteristic of this reaction is that the carbon-carbon bond formation between the alkene and alkyne occurs to give the cyclisation product, with concomitant migration of the alkylidene part of the alkyne to the alkyne carbon.

\[
\begin{align*}
\text{O(CH}_2\text{)}_2\text{OEt} \quad & \quad \text{a, b} \quad \text{c-e} \quad \text{g} \\
\text{200} \quad & \quad \text{201} \quad \text{202, } R = H \quad \text{203, } R = \text{CO}_2\text{Me} \\
\text{204} \\
\end{align*}
\]

Scheme 1.28 Reagents: (a) \(\text{NaH, DMF, CH}_2=\text{CH(CH}_2\text{)}_3\text{Br (89%)}\); (b) \(\text{TsOH, MeOH (91%)}\); (c) \(\text{COCl}_2\), DMSO, \(\text{Et}_3\text{N}\); (d) \(\text{CBr}_4, \text{Ph}_3\text{P (87%)}\); (e) \(\text{BuLi, THF, } -98^\circ\text{C (72%)}\); (f) \(\text{LDA, HMPA, ClCOOMe (68%)}\); (g) \(\text{204 (cat.), (4-5 mol%), CH}_2\text{Cl}_2, \text{RT (87%)}\); (h) \(\text{NaBH}_4, \text{MeOH, (85%)}\); (i) \(\text{NaOH, MeOH/H}_2\text{O (85% and 9, 31%)}\); (k) \(\text{NET}_3\); (l) \(\text{NiCl}_2.6\text{H}_2\text{O, NaBH}_4, \text{MeOH, (76%)}\).

1,4-Reduction of the \(\alpha,\beta\)-unsaturated system, followed by hydrolysis of the ester and a bromolactonisation reaction, gave the two products 207 and 208. Compound 207 was easily converted into compound 208 by treatment with \(\text{NET}_3\). The total synthesis was completed via stereoselective reduction using \(\text{NaBH}_4\) and \(\text{NiCl}_2.6\text{H}_2\text{O}\) to give \((-\text{-stemoamide})\).
1.3 Cyclopropanes in Synthesis

1.3.1 Bonding in Cyclopropanes

Cyclopropane derivatives are capable of ring-opening reactions under the influence of many different reacting species, including electrophilic, nucleophilic, and radical reagents, as well as external physical forces such as heat or light. Unlike other aliphatic hydrocarbons, the C–C single bond of the cyclopropane resembles that of a C=C double bond. It is the strained nature of the three-carbon unit and the subsequent relief of the strain during ring opening, which provides the crucial thermodynamic driving force for the reaction.42

The arrangement of carbon atoms in cyclopropanes results in significant angular (Bayer) strain, where the bond angles must deviate to 60° from the ideal 109.5° for sp³-hybridised systems. Additional torsional (Pitzer) strain is observed, as the coplanar nature of the carbon atoms requires the C–H bonds to be eclipsed. However, thermochemical considerations alone are insufficient to explain the remarkable reactivity seen in cyclopropanes, and numerous bonding models have been proposed. The Coulson-Moffit model assumes three sp³-hybridised CH₂-groups results in a reduction of effective orbital overlap, by a deviation of ca. 22° from the imaginary C–C bond, attributing to the angular strain in the system (Figure 1.06).43

![Figure 1.06. The Coulson-Moffitt model](image)

Variations of this model suggest sp², sp³ and sp⁵-hybridised orbitals may explain the greater p-character and similarity to olefin reactivity. Indeed, the Walsh model
suggests three $sp^2$-hybridised carbon nuclei, with the hybrid orbitals orientated radially towards the centre of the ring (Figure 1.07).\cite{44}

Another interesting approach as expressed by Dewar,\cite{45} proposes the notion of “σ-conjugation”, and how a cyclic array of 6 electrons, according to the $4n + 2$ rule, suggests aromaticity in the cyclopropane ring. σ-Aromaticity can explain previously considered anomalies in cyclopropanes, such as; the actual lower strain energy observed in comparison to the theoretical value calculated from bending force constants; the observed upfield shifts of the cyclopropane protons explained by ring current effects; and the reactivity of cyclopropanes towards electrophiles as seen in Freidel-Craft type reactions.

![Figure 1.07 The Walsh model](image)

1.3.2 Nucleophilic Addition to Cyclopropanes

In direct analogy with reactions of olefins, cyclopropanes are susceptible to addition reactions. The major difference is the presence of an extra carbon, the “synthetic wedge”, which improves the number of rearrangement pathways threefold compared to those available to alkenes. Disconnections of similarly functionalised alkenes and cyclopropanes via donor and acceptor interactions, lead to a resonance form in the case of the alkene, and a new compound being formed in the cyclopropane case (Figure 1.08).\cite{42}
In 1895 Bone and Perkin discovered that cleavage of the cyclopropane bond was only possible in the presence of an electron-withdrawing group on the ring.\textsuperscript{46} Best and co-workers found activated cyclopropane \textsuperscript{209} undergoes 1,5 ring opening with diethyl malonate to form the tetraester \textsuperscript{210}, with subsequent intramolecular cyclisation to form the cyclopentanone product \textsuperscript{211} (Scheme 1.29).\textsuperscript{47}

The geminally placed activating groups observed in many nucleophilic openings of this type, help doubly stabilise the anion formed upon ring fission. However, vigorous reaction conditions are still required to effect ring opening with nucleophiles such as amines, mercaptans,\textsuperscript{49} malonate ion,\textsuperscript{46} cuprate\textsuperscript{50} and enamines,\textsuperscript{51} exposing the difficulty in cleaving the strained C–C single bond (Scheme 1.30).

**Scheme 1.29** Best's ring-opening of activated cyclopropanes

**Scheme 1.30** Various nucleophiles for ring-opening
Linstead and co-workers applied this methodology to vinyl analogues and reported both 1,5 and 1,7 modes of ring opening.\textsuperscript{52} The major product of the reaction with diethyl malonate was cyclopentanone 212, with trace amounts of the 1,7-ring opened alkene 213 formed, before suitable treatment of the tetraester gave suberic acid (Scheme 1.31).

\textbf{Scheme 1.31} Linstead's 1,5 and 1,7 modes of ring-opening

The chemical properties of cyclopropanes drastically change upon the incorporation of a neighbouring $\pi$-system. In 1960, Vogel reported the thermal conversion of vinylcyclopropane 214 to cyclopentene 215 (Scheme 1.32).\textsuperscript{53} The mechanism and stereochemistry of this rearrangement has been discussed extensively, and the majority of these are thought to proceed via biradical intermediates, although some concerted processes have been reported. This reaction has become important for the incorporation of cyclopentene structural units into many complex natural products.\textsuperscript{54}
Scheme 1.32 Vogel’s thermal conversion of vinylcyclopropane to cyclopentene

The extension of conjugation seen in vinylcyclopropanes was harnessed by Burgess, who reported a milder and selective ring opening reaction using catalytic amounts of a palladium(0) source (Scheme 1.33). The ratio of mono- and bis-alkylated products 216 and 217, depends not only on the concentration of starting materials, but also the nature of the electron-withdrawing-groups (EWG) present on the vinylcyclopropane and the nucleophile. It was established that the stabilising effect of the EWG on the cyclopropane must be greater or comparable to that of the EWG on the nucleophile.

Scheme 1.33 Burgess’ Palladium catalysed nucleophile addition to vinylcyclopropanes
1.3.3 Transition Metal-assisted reactions of Cyclopropane derivatives

The true potential of these small ring systems, and the plethora of possible structural transformations was only unlocked with the advent of transition metal catalysis. Up until this point, transition metal-assisted transformations of small rings were limited to the synthesis of stoichiometric organometallic complexes. The application of transition metal chemistry in the reactions of cyclopropane derivatives has for a long time been a powerful method for exploiting the versatility of these systems. Three classes of small ring that enjoying a renaissance of exploration were cyclopropenes 218, methylenecyclopropanes 219 and vinylcyclopropanes 220 (Figure 1.09).  

![Figure 1.09 Various cyclopropane derivatives](image)

Each of these derivatives possess significant strain, which increases the potential energy stored within the molecule and explains their unusually high reactivity. The cyclopropene scaffold has increased \( \pi \)-density on its double bond, which makes it an attractive substrate for \( \pi \)-philic transition metals. Cyclopropenes participate in a whole host of reactions of a similar type to olefins, including carbometalation, cycloadditions, cross-coupling, substitution and cycloisomerisation. Meijere et al. demonstrated one example where cyclopropenes were used in a palladium-catalysed allylic alkylation (Scheme 1.34).  

The \( \pi \)-allylpalladium intermediate 223, generated from a variety of primary and secondary cyclopropenylmethyl esters 221, underwent selective alkylation at the \( \alpha \)-position to produce cyclopropenylmethyl derivatives 222. No allylic transposition or ring-opened products were detected during this transformation.
Methylenecyclopropane is the smallest carbocycle with an exo-methylene group. The inherent rigidity and symmetry observed within this molecule confers its unique reactivity. The exocyclic double bond enforces additional strain on the three membered ring by increasing the nearby bond angle and therefore lengthening the opposing bond 225 (Figure 1.10).\textsuperscript{58}

Methylenecyclopropanes participate in reactions that are characteristic of olefins e.g. electrophilic additions, radical additions, addition to carbenes and nitrenes, various thermally activated cycloadditions or in the presence of strong electron withdrawing groups. However, the key to their synthetic versatility is their ability to act as building blocks in [3+2]-cycloaddition reactions catalysed by transition metals such as Ni(0) and Pd(0) under mild conditions.\textsuperscript{59-61}

Initial work by Binger and Noyori describe possible mechanisms for the two reaction pathways in which the metal-catalysed cycloaddition can proceed to afford regioisomeric products (Scheme 1.35).\textsuperscript{59,61}
The transition metal can oxidatively insert into the distal bond 227. Subsequent carbometallation onto the double bond and reductive elimination afford cyclopentane 226, inserting a two-carbon unit in the distal position to the double bond. Alternatively the proximal cleavage leads to isomeric metallacyclobutane 228 with the two-carbon unit being introduced in the proximal position to the exocyclic double bond. Both regioisomeric cyclopentenes 226 and 229 can be isolated in the presence of Ni(0), whereas only type 226 can be isolated when the reaction is catalysed by Pd(0).

The regio-chemical outcome of the reactions is highly dependent on the nature of the metal and its associated ligands. The ability to control both the regio and stereochemical outcome suggests this might provide a powerful cycloaddition process for natural product synthesis.

Although cyclopropenes have a wide-ranging scope of potential transformations, methylenecyclopropanes have enjoyed far more attention in the literature because of their ability to ring-open under transition metal catalysis, forming reactive trimethylenemethane (TMM) complexes.
1.3.4 Palladium Catalysed [3+2] Cycloadditions with Pd-trimethylenemethane complexes

Trost and co-workers report the use of a stabilised trimethylenemethane (TMM) molecule, activated with palladium(0), as a valuable reagent in [3+2] cycloadditions. In 2-[(trimethylsilyl)methyl]-allyl ester 230, the silyl and acetate groups act as carbanionic and carbocationic equivalents respectively. Other more reactive sulfonates or chlorides can be used as well as the acetate leaving group. Formation of a \( \pi \)-allylpalladium complex and subsequent elimination of the silyl group, furnishes a dipolar species 231, reactive enough to attack electron-deficient double bonds (vinyl esters, nitriles, sulfones and any activated alkenes in terms of a conjugate method). Trost showed the formation of the fused cyclopentanoid 232 was possible using an intramolecular version of this reaction (Scheme 1.36).

The Pd-TMM complex generated \textit{in situ} from 230, reacts with a variety of electron deficient alkenes. Interestingly, the [3+2] cycloaddition proves to be stereoselective upon reaction with \textit{trans}-alkenes such as dimethyl fumarate, whereas \textit{cis}-alkene dimethyl maleate produces a \textit{cis/trans} mixture of methylenecyclopentane products 233a and 233b (Scheme 1.37).
Scheme 1.37 Stereoselective addition of electron-deficient alkenes to Pd-TMM complexes

The lack of stereospecificity observed with cis-alkenes, suggests a stepwise mechanism involving an intramolecular nucleophilic addition step, where the reacting intermediate 234 has time to rearrange to the more stable trans conformer (Scheme 1.38).

Scheme 1.38 Proposed mechanism for observed stereochemistry

When the substitution patterns on the TMM compound are considered, some interesting regiochemical information can be deduced. Depending on the position of the methyl-substituent in 235a or 235b, two regioisomeric Pd-complexes 236a and 236b are formed which could undergo subsequent cycloadditions with an electrophile such as cyclopentenone to give cycloadducts 237a-c. However, it is observed that the same ratio of cycloadducts are formed irrespective of the substitution on the Pd-TMM complex, suggesting equilibration of 236a and 236b, occurs faster than the rate of
addition of trapping reagent. Estimation of thermodynamic stability verifies complex 236a as the more stable of the two conformers (Scheme 1.39)."}

---

**Scheme 1.39** Regioselective addition of substituted Pd-TMM complexes

1.3.5 Transition Metal-assisted reactions of Vinylcyclopropanes

Vinylcyclopropanes are yet another versatile strained compound, as the pronounced cyclopropyl Walsh-type "banana-shaped" HOMO can conjugate with the neighbouring π-orbitals of the double bond. Electronic analysis suggests the σ-bond connecting the cyclopropyl and vinyl group has increased double-bond character by 13-15%, significantly shortening the σ-bond. Sarel et al. carried out the first investigations into the field of transition metal-assisted reactions of vinylcyclopropanes in 1965. They used iron carbonyl complexes in stoichiometric
amounts to effect transformations such as (a) creation of π-complexes 238 and 239 via interaction of the double bond with the metal centre; \(^{70}\) (b) isomerisation by ring-opening the cyclopropane 240 to give 1,3-dienes 241; \(^{69}\) (c) photoinduced carbonylative insertion to give cyclohexeneones 242, \(^{71}\) and (d) simultaneous carbonyl insertion and metal interaction to give metal acyl complexes 243 (Figure 1.11). \(^{72}\)

(a) Creation of π-complexes

(b) Isomerisation to 1,3-dienes

(c) Photoinduced 1,5-carbonylation

(d) Metalloacyl complexes

Figure 1.11 The origins of Transition-Metal assisted reactions

After the initial potential of this type of methodology was realised, the scientific community showed a great deal of interest in transition metal catalysed reactions of vinylcyclopropanes. Over the next few decades a range of different catalysts was developed, including iron, cobalt, nickel, rhodium, platinum and most recently palladium based complexes. As the work reported in this thesis is focussed on palladium catalysed ring openings of vinylcyclopropanes, we shall take a systematic look at how the method used within the group evolved.

Vinylcyclopropanes easily form complexes with palladium compounds. The substitution of 244 with ethylene from the palladium complex PdCl₂C₂H₄ results in
a labile intermediate, which under $^1$H NMR analysis showed a broad singlet in the region of 1.5 ppm. The intermediate complex was thought to exist as several species, equilibrating through 2,3-hydride shifts (Scheme 1.40).\textsuperscript{73,74}

\textbf{Scheme 1.40 2,3-Hydride shifts of Palladium on vinylcyclopropane}

Heck \textit{et al.} investigated the effect of palladium salts on vinylcyclopropanes containing electron-withdrawing substituents.\textsuperscript{75} They found that after initial complexation of the olefinic double bond with the metal ion, rearrangements occurred with opening of the cyclopropane ring to give $\pi$-allylic complexes 246. Various products were formed depending on the structure of the vinylcyclopropane derivative (Scheme 1.41).

\textbf{Scheme 1.41 Reagents: (a) Li$_2$PdCl$_3$, Et$_3$N, MeCN, 0°C, RT (37%).}

Mechanistic studies involving deuterium labelled vinylcyclopropane 247, showed migration of one of the benzylic deuterium atoms from C-1 to C-4 to give $\pi$-allylic complex 248 (Scheme 1.42). They proposed a mechanism involving elimination to an alkenylpalladium derivative, followed by a palladium hydride elimination and readdition sequence, which resulted in this intriguing deuterium shift.
Scheme 1.42 Mechanistic studies involving deuterium labelled vinlycyclopropane

Backvall et al. reported a stereochemical and mechanistic diagnosis of the palladium(II)-induced chloro- and oxypalladation reactions of (+)-carene. Reaction of the enantiomerically pure carene with PdCl$_2$(MeCN)$_2$ in non-nucleophilic solvents, lead to chloropalladation and two (π-allyl)palladium complexes 249 and 250. However, upon the incorporation of nucleophilic solvents, a range of oxypalladation reactions occurred to give complexes 251-254, and small amounts of the chloropalladation adduct 249. Interestingly, in the oxypalladation reaction none of the seven-membered ring complex 250 was ever observed.
Scheme 1.43 Palladium(II)-induced chloro- and oxypalladation reactions of (+)-carene

In an attempt to prove the stereochemical configuration of the (π-allyl)palladium complexes, they were reduced with LiAlH₄ and LiAlD₄, to give reduction products 255 and 256 as a 4:1 mixture and 255-d₁ and 256-d₁ in a similar ratio (Scheme 1.44). Reduction with LiAlH₄ showed the methyl group of 256 to be cis to the isopropyl group. Importantly the deuterium in 255-d₁ was found to be trans to the isopropyl group. It was known at the time that LiAlH₄ cleaves (π-allyl)palladium bonds with retention of configuration, so it was deduced that the palladium species inserts with inversion of stereochemistry to place it trans to the chloroisopropyl group.

Scheme 1.44 Reagents: (a) LiAlH₄ or LiAlD₄, THF, −78°C.
Morizawa et al. were the first group to report a palladium(0) catalysed [3+2] cycloaddition of a vinylcyclopropane (Scheme 1.45).\textsuperscript{78} The use of 1,3-dipolar species in the construction of ring systems was accepted as a viable approach, however, at the time there was no simple way to prepare these synthons. They proposed a rearrangement which proceeds through nucleophilic attack of Pd(0) to the dienic group of 257 to form a zwitterion consisting of a π-pentadienylpalladium species and doubly-stabilized anion. The intermediate cyclised to form cyclopentene derivative 259, with the new C-C bond formation exclusively producing a five-membered ring, and not a seven-membered one. They suggest the regioselectivity arises from the preferred W-type conformation of the pentadienyl group in 258.

![Scheme 1.45](image-url)

\textit{Scheme 1.45} Reagents: (a) 10 mol\% Pd(PPh\textsubscript{3})\textsubscript{4}, DMSO, 50°C (87%).

Tsuji et al. also recognised the potential of these types of zwitterionic species in the preparation of functionalised cyclopentanes.\textsuperscript{79} They report an intermolecular reaction between the (π-allyl)palladium zwitterion 260, derived from vinylcyclopropane 259, with methylacrylate to form functionalised 261 (Scheme 1.46).
Similarly to Morizawa, Tsuji believed the palladium to be oxidatively inserting into the vinyl group, with concomitant ring-opening. The 1,3-dipole that results is stabilised by the two electron-withdrawing groups at the malonate centre. Tsuji extended this procedure by recognising the zwitterion to be an intermolecular trapping reagent, and reported the successful trapping of a variety of activated alkenes. The use of aryl isocyanate 262 leads to the generation of a $\gamma$-lactam 263, using similar a similar catalytic system (Scheme 1.47). However the major drawback of this procedure was the use of highly toxic hexamethylphosphoramide (HMPA), and also the fact that two equivalents of isocyanate were required for the reaction to proceed.

Recent work by Polhaus et al. has shown the usefulness of mild Lewis catalysed conditions in the ring opening of aryl-substituted cyclopropanes 264 (Scheme 1.48). Mild conditions using catalytic amounts of Sn(OTf)$_2$ generated a stabilised 1,3-dipole, which was subsequently trapped with a range of electron-rich aldehydes. Excellent diastereoselectivities were observed when using benzaldehyde, with
exclusively the syn-2,5-disubstituted tetrahydrofuran 265 being formed. In the case of other electron-rich aldehydes, mixtures of diastereoisomers were observed, but the syn isomer was always the major product. This method outlines the importance of Lewis acids as potential reagents for ring-opening reactions of cyclopropanes.

Scheme 1.48 Reagents: (a) Sn(OTf)$_2$ (5 mol%), DCM, RT, 2.5 h (100%).

1.3.6 Previous work within the Group

The groundbreaking work carried out by Tsuji has provided our own research group with some valuable insight into the reactions of vinylcyclopropanes. Tang began researching possible variations of Tsuji’s conditions in an attempt to apply it to heterocycle formation, but using milder conditions.

Tang reported a variety of novel palladium catalysed [3+2]-cycloadditions using the versatile doubly activated vinylcyclopropane and a Lewis acid. A variety of trapping agents were explored affording a selection of tetrahydrofurans and pyrrolidines when reacted in conjunction with their respective aldehydes and imines. The respective tetrahydrofurans and pyrrolidines appeared as a pair of diastereoisomers. Careful optimisation led to excellent yields under mild reaction conditions (Scheme 1.49).
Tang concluded that the inclusion of a Lewis acid resulted in a marked increase in yield. The optimum conditions included a stoichiometric amount of the vinylecyclopropane and electrophile, 10 mol% Pd(PPh₃)₄ and two equivalents of ZnBr₂ in THF at room temperature.

It is possible to propose a reaction mechanism that takes into the account the affects of the palladium(O) catalyst, Lewis acid. As the reaction only requires a catalytic (10 mol%) amount of palladium(O) reagent the implication is a catalytic cycle is set up regenerating the palladium(O) species during the [3+2]-stepwise cycloaddition, which results in the formation of the 5-membered heterocyclic product. An oxidative addition of the palladium(O) catalyst to the vinylecyclopropane generates a zwitterion that subsequently undergoes nucleophilic attack on the electrophilic substrate affording a second transient zwitterion. The resultant alkoxide/amide moiety subsequently displaces the palladium reagent from the π-allyl site with concomitant reductive elimination of the transition metal catalyst to give the required heterocycle. It is thought that the Lewis acid sits in between the geminal ester groups, further stabilising the transient zwitterion (Scheme 1.50).
Tang also reported the successful trapping of a cyclic imine with vinylcyclopropane. This is the first and only reported use of a cyclic imine in the above reaction sequence. This thesis will investigate the use of a variety of conformationally locked cyclic cis-imines as potential trapping agents in the palladium catalysed [3+2] cycloaddition step. This would allow a bicyclic ring system to be accessed in one step with the option of functional group elaboration at a later stage. Depending on the ring size of the imine, a range of stereocontrolled, fused nitrogen heterocycles can potentially be synthesised (Scheme 1.51).

This introduction has shown the widespread occurrence of these sorts of bicyclic systems within nature. As such, the development of methods for the asymmetric synthesis of ring-fused derivatives such as pyrrolizidines, indolizidines, and azepines remains an area of current interest. Our ultimate aim was to generate the azepine core
present in the *Stemona* alkaloids, by the successful trapping of a cyclic seven-membered imine. The incorporation of functionality on the cyclic imine substrate was also investigated, as this would act as a handle to gain access to a range of natural compounds (Scheme 1.52). The stereochemical outcome of the reaction may be affected by the size of the cyclic imine ring, making it possible to control two stereogenic centres in one step.

\[ R \quad \text{CO}_2\text{Me} \quad \text{CO}_2\text{Me} \quad n = 1, 2, 3 \]

**Scheme 1.52** Proposed palladium catalysed [3+2] cycloaddition step with functionalised imines
Results and Discussion

Chapter Two

2.1 Preparation and Reactions of Vinylcyclopropanes

2.1.1 Synthesis of Vinylcyclopropanes

Naturally occurring vinylcyclopropanes have attracted considerable interest among organic chemists. Carenes, sesquicarenes, sirenine, dictyopterenes and pyrethroids all contain such functionality, resulting in numerous total syntheses being developed for these compounds (Figure 2.01).\(^{83-85}\) In addition, vinylcyclopropanes are vital synthetic intermediates, justifying the widespread interest shown by the scientific community.

![Chemical Structures](image)

Figure 2.01 Naturally occurring vinylcyclopropanes

There have been various methods for synthesising cyclopropanes documented in the literature. A recognized route to cyclopropanes involves the use of carbene intermediates such as the Simmons–Smith reagent.\(^{86}\) In this reaction, a geminal dihalogen species reacts with reducing zinc metal in solution. The mechanism is not fully clarified, but pure carbenes can be excluded and the existence of a carbenoid is thought to be the reactive intermediate. Reaction of these electrophilic carbenoids with alkenes generates cyclopropanes (Scheme 2.01).
Scheme 2.01 Reagents: (a) Zn/Cu couple, Et₂O.

Paquette et al. reported several methods for generating bifunctional 1-(trimethylsilyl)-substituted cyclopropanes.⁸⁷ The methyl bromide 267 generated from Simmons-Smith cyclopropanation of alkene 266 and bromination with phosphorus tribromide, is shown to be very reactive to SN₂ displacement, and therefore easily transformed into a variety of other derivatives including phenyl sulfides and phenyl sulfones (Scheme 2.02).

Scheme 2.02 Reagents: (a) Mg turnings, CH₂O, Et₂O; (b) CH₂J₂, EtZnl; (c) PBr₃; (d) PhSO₂Na, DMF; (e) PhSH, NaH.

Bäckvall et al. employ a palladium-catalysed route to bicyclic vinylcyclopropanes using 1-acetoxyc-4-chloro-2-alkenes as starting materials.⁸⁸ Reaction of alkenes of the type 268 with base followed by palladium(0) catalyst (Pd(dppe)₂, Pd(dbq)₂/dppe and Pd(OAc)₂/dppe were all used), results in a formal SN₂' cyclisation and formation of the desired vinylcyclopropanes, with high levels of relative stereochemistry between the cyclopropane ring and the double bond being attained. Indeed, bicyclic vinylcyclopropanes can be generated using this method also (Scheme 2.03).
A method used within the Pritchard group to access the above bicyclic vinylcyclopropanes involves the modification of a procedure developed by Livant et al.\textsuperscript{39} Rhodium catalysts such as Rh\textsubscript{2}(OAc)\textsubscript{4} have become the catalyst of choice for many cyclopropanations of aromatic alkenes. It is the ability of rhodium to stabilise carbenes such as that generated from dimethyl diazo malonate, which made the bicyclic vinylcyclopropanes 269, 270, and 271 accessible (Scheme 2.04).

Our method of choice for accessing vinylcyclopropane 259 involved the double displacement of trans-1,4-dibromobut-2-ene with malonic acid dimethyl ester in the presence of sodium methoxide in good yield (82%) (Scheme 2.05).\textsuperscript{55}
The mechanism proceeds via the deprotonation of the activated methylene component of the malonic acid dimethyl ester, followed by an internal $S_N2'$ displacement to form the cyclopropane ring (Scheme 2.06).
2.2 Preparation of Cyclic Imines

2.2.1 Synthesis of 5-membered Cyclic Imines

The 5-membered cyclic imine 1-pyrroline 272, has been proposed as an intermediate in the biosynthesis of phenanthroindolizidine alkaloids such as septicine and tylophorine, and has also been used in the biomimetic syntheses of these alkaloids (Figure 2.07).\textsuperscript{90}

![Chemical structure of 1-pyrroline 272](image)

\[
\text{272} \quad \rightarrow \quad \begin{array}{c}
\text{septicine} \\
\text{tylophorine}
\end{array}
\]

\textbf{Figure 2.07} 1-Pyrroline as a precursor to natural compounds

However, its application in organic synthesis is limited due to its volatility and its tendency to rapidly trimerise at room temperature in neutral or basic solutions. Previous work by Parsons \textit{et al.} describes the cracking of the triazine 273 in boiling THF to give the monomer, which could then be co-distilled with THF and trapped at -78°C. This was trapped with triethylamine and propionyl chloride to obtain the protected enamine 274 as a precursor in their rapid synthesis of racemic brevioxime (Scheme 2.08).\textsuperscript{91}
The problem of trimerisation was easily overcome by Robins et al. who report the stabilisation of 1-pyrroline with zinc iodide, to generate a stable crystalline complex, which can be easily regenerated for the preparation of various pyrrolidine derivatives.\textsuperscript{92} It was with this method we decided to prepare 1-pyrroline-zinc halide complexes 275 and 276 (Scheme 2.09). Addition of a zinc halide to 1-pyrroline was envisaged to enhance its effectiveness as a trapping reagent towards vinylcyclopropane 259. Not only do these complexes introduce an intrinsic Lewis acid into the reaction mixture for the [3+2] cycloaddition, the Lewis acid should draw electron density away from the heteroatom, making the imine bond more susceptible to nucleophilic attack.

This method involved acid hydrolysis of 4-aminobutanal diethylacetal in an intramolecular cyclisation step followed by extraction of the basified solution with ether to give the highly volatile and trimerisable free 1-pyrroline, which was not isolated. This was stabilised by the addition of anhydrous zinc iodide and bromide to form the desired pyrroline zinc halide complexes 275 and 276.
This reaction proved to be problematic with the reaction temperature needing to be carefully monitored at 0°C to minimise losses of the pyrroline by evaporation. Attempts to repeat the 60% yield of zinc iodide complex quoted by Robins,\(^9\) were fruitless, illustrating the capricious nature of the reaction. However, the products 275 and 276, once isolated, proved to be air stable at room temperature, and a convenient precursor for subsequent reactions with vinylcyclopropane 259. Examination of the \(^1\)H NMR spectrum of 275 and 276, taken in CDCl\(_3\), showed all proton signals were shifted downfield 0.1 - 0.4 ppm relative to the signals of the free 1-pyrroline sample.

### 2.2.2 Synthesis of 6-membered Cyclic Imines

Scully et al. reported the use of 1-piperideine 277 as a precursor for the synthesis of complex piperidine alkaloids.\(^9\) Synthesis of 2-substituted piperidines have commonly involved either: (a) cyclisation of an appropriately constructed acyclic precursor and (b) alkylation of a pyridine followed by reduction of the aromatic heterocycle. These methods suffer from too many steps, lack of generality, or low yields. They anticipated C-alkylation of the corresponding cyclic imine precursor, could prove valuable in the synthesis of larger piperidine alkaloids. \(N\)-Chlorination of an ethereal solution of piperidine, followed by reaction with potassium superoxide and a catalytic amount of 18-crown-6, resulted in the free 1-piperideine 277. The reaction was complete when the yellow superoxide colour had faded to beige. The free imine 277, is known to possess similar trimerisation properties as its pyrroline counterpart, so in a modification of Scully’s method, the reaction mixture was filtered, and anhydrous zinc iodide was introduced to the filtrate to form the zinc iodide complex 278 in good yields (Scheme 2.10). Attempts to complex zinc bromide and chloride under the same conditions failed.
Scheme 2.10 Reagents: (a) t-BuOCl, Et₂O, 30 min, RT; (b) KO₂, 18-crown-6, Et₂O, RT, 21 h; (c) ZnI₂, RT, 1 h (80% 3 steps).

The chlorinating reagent t-butyl hypochlorite was generated from the reaction of 2-methyl-propan-2-ol with bleach (Scheme 2.11).

Scheme 2.11 Reagents: (a) NaOCl, CH₃CO₂H, H₂O, RT, 5 min (80%).

Chlorination of piperidine proved to be quite capricious. The chlorinating agent must be added slowly to form a white gelatinous precipitate to signify the formation of the N-chloramine. This free imine precursor can then be formed by elimination of HCl via potassium superoxide in the presence of 18-crown-6. Successful complexation was once again verified by a downfield shift of all proton signals.

2.2.3 Synthesis of 7-membered Cyclic Imines

In a method identical to that used for the synthesis of the 6-membered cyclic imines, homopiperidine, was used to generate the zinc iodide complex 279, in moderate yields (Scheme 2.12).

Scheme 2.12 Reagents: (a) t-BuOCl, Et₂O, 30 min, RT; (b) KO₂, 18-crown-6, Et₂O, RT, 21 h; (c) ZnI₂, RT, 1 h (40% 3 steps).
2.3 Palladium Catalysed [3+2] Cycloadditions with Cyclic Imines

2.3.1 Formation of novel Pyrrolizidine derivatives

Work began on the pyrrolizidine derivatives by reaction of complex 276 with vinylcyclopropane 259 in the presence of 10 mol% tetrakis(triphenylphosphine) palladium(0) in DMF at room temperature for up to 68 hours (Scheme 2.13), conditions outlined by Tang. 81

\[
\begin{array}{ccc}
\text{259} & + & (\text{276})_2 \rightarrow \text{a} \\
\text{280}
\end{array}
\]

Scheme 2.13 Reagents: (a) 10 mol% Pd(PPh₃)₄, DMF, RT, 20 h (27%).

The expected pyrrolizidine 280 was isolated in moderate yield (27%) from the 1-pyrroline zinc iodide complex. 1H NMR analysis of the crude reaction mixture showed a greater proportion of product than was ever isolated after column chromatography. For this reason, water washes were carried out on the crude reaction mixture to remove DMF, before an acid wash extracted the product into the aqueous layer, and subsequent basification and re-extraction into EtOAc gave the desired product. Attempts to perform the same cycloaddition with the zinc bromide complex failed. Significantly, two dimensional 1H NMR and nOe experiments confirmed the pyrrolizidine 280 was isolated as one diastereomer, with the two ring protons adopting a (H,H)-anti relative stereochemistry (Figure 2.08).
A similar mechanism for the [3+2] cycloaddition to vinylcyclopropane can be applied to the cyclic imines as for the acyclic imine substrates. Oxidative addition of palladium(0) into the vinylic double bond effects ring opening of the cyclopropane ring, and generates a zwitterionic species. The zinc iodide may not only help activate the imine bond, but once dissociated from the imine also act as an intrinsic Lewis acid stabilising the zwitterion. Subsequent [3+2] cycloaddition of the imine reductively eliminates the palladium(II) species generating the palladium(0) species in a catalytic cycle and accessing the desired pyrrolizidine (Scheme 2.14).

Scheme 2.14 Proposed catalytic cycle for cyclic imine addition to vinylcyclopropane.
2.3.2 Formation of novel Indolizidine derivatives

Attempts to gain access to the indolidizide core began with reaction of complex 278 with vinylcyclopropane 259 in the presence of 10 mol% palladium(0) under various conditions (Table 2.01). The best conditions were refluxing MeOH, which afforded indolizidine 281 in modest yields (21%). These conditions involved water and brine washes of the crude reaction mixture before column chromatography, instead of acid washes. The importance of column type was not as important as with the pyrrolizidine derivatives, as both silica and neutral alumina gave the desired product. However, crude $^1$H NMR data suggested there is more of the desired product present than purification would indicate, so it can be assumed material is once again being lost on the column. Various palladium catalysts were tried and tested, as catalyst suitability can vary from one system to another. Pd(PPh$_3$)$_4$ is a coordinatively saturated palladium(0) complex, and although the Pritchard group has witnessed much success with this catalyst for simple [3+2] cycloadditions, sometimes overligation can hinder the coordination of some reactants. The highly coordinatively unsaturated Pd(Bu$_3$P)$_2$ was tried as this is a stable palladium(0) complex in solid state and commercially available.$^{94}$ The stability of this unsaturated phosphine complex is certainly due to the bulkiness of its ligands. This complex is a very active catalyst in some reactions, however failed to produce a result in this system.$^{95}$
In all cases where the product was isolated, one diastereomer was formed exclusively from the reaction mixture. Two dimensional $^1$H NMR and nOe experiments confirmed the indolizidine 281 adopts a (H,H)-anti relative stereochemistry with respect to the protons on the newly formed chiral centres (Figure 2.09).
When refluxing in MeOH, a major by-product accounting for ~50% of the crude reaction mixture was alkene 282. Vinylecyclopropane 259 is stable in refluxing methanol, however it is the presence of palladium(0) that causes the unwanted by-product. This is produced by methanol acting as a nucleophile towards the zwitterionic species formed after palladium insertion into the double bond of vinylecyclopropane 259 (Scheme 2.15).

To establish whether the addition of methanol to vinylecyclopropane was reversible, alkene 282 was stirred with the good aldehyde trapping-reagent, 4-nitrobenzaldehyde, in the presence of 10 mol% palladium (0) in an attempt to form the furan 283 (Scheme 2.16). If palladium could re-insert into the alkene bond, eliminate the methoxy group and generate the reactive zwitterion, then it could be possible to form five membered heterocycles directly from the straight chain alkene instead of vinylecyclopropane.
Scheme 2.16 Reagents: (a) 10 mol% Pd(PPh₃)₄, MeOH, RT, 19 h.

The reaction failed to progress, suggesting the alkene 282 was not reversible towards palladium catalysed [3+2] cycloaddition using these conditions.

Although refluxing methanol appeared to give the best yield of indolizidine 281, it also hindered the reaction. This outlined the importance of solvent interaction in this reaction, and suggested the use of non-nucleophilic solvents may prevent this unwanted pathway from occurring.

2.3.3 Formation of novel Azepine derivatives

A cursory glance at the azepine core began with reaction of complex 279 with vinylcyclopropane 259 in the presence of 10 mol% palladium(0) using the most favourable conditions observed for the generation of indolizidine 281 (Scheme 2.17).

Scheme 2.17 Reagents: (a) 10 mol% Pd(PPh₃)₄, MeOH, reflux, 1.5 h (19%).

The desired azepine 284 was synthesised in modest yield. Water and brine washes were carried out before a column was performed. However, by ¹H NMR the washes didn’t seem to have much of an effect on the crude mixture, and a slight reduction to the overall yield could be attributed to this fact. Critically 2D ¹H NMR and nOe data suggested one diastereoisomer was formed exclusively in the reaction, with a (H,H)-
syn relative stereochemistry with respect to the protons on the newly formed chiral centres (Figure 2.11). This is converse to the findings reported for indoloizidine 281 and pyrrolizidine 280. A possible explanation of this result could be attributed to steric factors, arising from ring puckering effects of the incoming cyclic imine. In turn this could determine the axial or equatorial orientation of the bulky vinyl substituent.

\[ \text{CO}_2\text{Me} \]

\[ \text{nOe effects} \]

\[ \text{284} \]

Figure 2.11 NOe interactions of azepine 284

2.3.4 Synthesis of Crispine A derivatives

Extracts of the Carduus crispus plant have been used in Chinese folk medicine for the treatment of cold, stomach ache and rheumatism. Moreover, studies by Zhao and co-workers have revealed significant cytotoxicity in these extracts. Phytochemical studies on C. crispus have isolated the two pyrrolo[2,1-a]isoquinoline alkaloids crispine A and crispine B along with three bicyclic isoquinoline alkaloids (Figure 2.12). 96

\[ \text{Crispine A} \]

\[ \text{Crispine B} \]

Figure 2.12 Extracts of the Carduus crispus plant

Knolker et al. recently reported the total synthesis of the antitumour active pyrrolo[2,1-a]isoquinoline alkaloid (+)-crispine A in three steps (overall yield 24%).
Lewis acid promoted addition of 3-trimethylsilylpropargyl magnesium bromide to 285 revealed that the allene 287 was formed as a by-product (2% yield) along with the propargyl derivative 286 (61% yield). Silver(I)-promoted oxidative cyclisation of 286 provided the tricyclic core 288. The unexpected Grignard product 287 was converted into the same product using slightly different oxidative conditions. Chemoselective hydrogenation of the pyrrole ring was achieved with rhodium on activated charcoal in acetic acid/methanol (1:1) to give crispine A.

**Scheme 2.18**

Reagents: (a) Et$_2$O.BF$_3$, THF, -23°C, 30 min; (b) Me$_3$SiCCCH$_2$MgBr, Et$_2$O, -23°C, 15 h (286 (61%) and 287 (2%)); (c) AgOAc, DCM, RT, 14 h (58%); (d) AgOAc, Me$_2$CO, 56°C, 6-14 h (43%); (e) 5% Rh/C, H$_2$, HOAc/MeOH (1:1), RT, 8 d (66%).

It was reasoned that our palladium catalysed [3+2] cycloaddition methodology could be used to generate the tricyclic parent framework of crispine A in one step. It would also be an opportunity to try the cycloaddition of another conformationally locked 6-membered cis-imine.

Commercially available 6,7-dimethoxy-3,4-dihydro isoquinoline, HCl hydrate 289 was reacted with vinylcyclopropane 259 in the presence of 10mol% palladium(0) and Lewis acid under different conditions (**Table 2.02**), failing to give the desired isoquinoline 290.
Previous work within the Pritchard group has shown cyclisations worked in DCM, in the absence of palladium(0) catalyst, and rely solely on Lewis acid interactions.\textsuperscript{98} These conditions were tried without success.

In light of the successful cyclisations using zinc iodide complexes, the zinc halide isoquinoline complex 291 was formed by complexation of zinc iodide to 6,7-dimethoxy-3,4-dihydro isoquinoline, HCl hydrate 289 in diethyl ether in excellent yield (81\%) (Scheme 2.19).

Complexation was unsuccessful when ZnBr\textsubscript{2} and ZnCl\textsubscript{2} were used as Lewis acid.\textsuperscript{1}H NMR can easily verify a successful complexation, as a switch in the peak positions of the 10-CH\textsubscript{2} and methoxy protons occurs.
The isoquinoline complex 291 was then reacted with vinylcyclopropane 259 in the presence of 10 mol% palladium(0), using different conditions (Table 2.03).

![Chemical structure]

<table>
<thead>
<tr>
<th>Pd Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>RT</td>
<td>63</td>
<td>8</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>DMF</td>
<td>RT</td>
<td>19</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 2.03

The cyclised isoquinoline 290 was isolated in modest yields (22%) as an inseparable mixture of diastereoisomers. The importance of workup on the reaction mixture was paramount, as column chromatography failed to isolate any product if no reaction workup was performed. It was thought that residual Lewis acid interfered with purification by column chromatography. For this reason, the crude reaction mixture was extracted into aqueous HCl, before basification and re-extraction into ethyl acetate to give a crude material suitable for column chromatography. Despite the modest yield, it was pleasing to construct the tricyclic core of the crispine alkaloids using our methodology.
2.3.5 Optimal conditions for Palladium [3+2] Cycloadditions.

It was pleasing to isolate various novel compounds using our methodology, however poor yields limited the synthetic utility of the reaction. One final solvent study made use of dimethylsulfoxide, a solvent known to greatly enhance the reactivity of ionic reagents due to its excellent solvating power. An improvement in yield was observed for all cycloadducts 280, 281, 284 and 290, with conversion occurring within an hour. (Table 2.04).

![Cyclised product](image)

Table 2.04 | Cyclic imine | Cyclised Product | Yield (%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>276</td>
<td><img src="image" alt="Cyclic imine" /></td>
<td>65</td>
</tr>
<tr>
<td>278</td>
<td><img src="image" alt="Cyclic imine" /></td>
<td>42</td>
</tr>
<tr>
<td>279</td>
<td><img src="image" alt="Cyclic imine" /></td>
<td>90</td>
</tr>
<tr>
<td>289</td>
<td><img src="image" alt="Cyclic imine" /></td>
<td>59</td>
</tr>
</tbody>
</table>

Table 2.04 Reagents: (a) 10 mol% Pd(PPh₃)₄, DMSO, 80°C, 1 h.
Once again, compounds 280, 281 and 284 were all isolated exclusively as one diastereoisomer, confirmed by nOe experiments. In the case of the pyrrolizidine and indolizidine compounds, the relative stereochemistry of the protons on the newly formed chiral centres was (H, H)-anti. However, conversely to this, the azepine ring system sets up a (H, H)-syn relationship. The cyclised product 290 was formed as a mixture of syn and anti products. Reaction workup was key with water washes carried out on the crude reaction mixtures to remove DMSO, before acid washes extracted the product into the aqueous layer, and subsequent basification and re-extraction into EtOAc gave the desired products. Purification of the aza-bicycles 280, 281, 284 and 290 with silica or alumina lead to the majority of the compound being lost on the column, presumably due to the presence of the highly basic tertiary amine functionality. Yields reported in the table are therefore without column chromatography.

Interestingly, the commercially available isoquinoline hydrochloride salt used to generate compound 290 did not require any Lewis acid for the reaction to work. The zinc iodide is essential for the stabilisation of the readily trimerisable simple cyclic imines, but may not necessarily play a further role in the cycloaddition reaction.

### 2.4 The use of Functionalised Vinylcyclopropanes

#### 2.4.1 Variation at the vinyl terminus

In an attempt to improve the scope of the reaction, the introduction of an electron-withdrawing group on the vinyl terminus of the vinylcyclopropane was explored. This would create a handle for further elaboration of the molecule at a later stage if required. It would also give some insight into the palladium-catalysed insertion reaction, by gauging the effect of substitution on the alkene bond. Ethyl ester substituted vinylcyclopropane 294 was synthesised (Scheme 2.20). The first step involved stirring acrolein with dimethyl bromomalonate in the presence of potassium carbonate in a high boiling solvent such as dimethoxyethane for 17 hours. The reaction proved to be quite problematic, with initially very sluggish yields recorded. Dimethoxyethane was tried as an alternative solvent, but to no avail. It was found that the order in which the reagents were added, was crucial to the success of the reaction.
The dimethyl bromomalonate must be added to a stirred solution of acrolein and potassium carbonate for the reaction to form the aldehyde 292 in temperamental yields ranging from 5-60%. Stirring the dimethyl bromomalonate with base prior to the addition of acrolein, lead to dimerisation to give unwanted tetra-ester by-products.

Scheme 2.20 Reagents: (a) DMF, K$_2$CO$_3$, RT, 17 h (5-60%); (b) n-BuLi, THF, 0°C, 10 min (90%).

The temperamental nature of the reaction leading to aldehyde 292 resulted in other routes being investigated. It was found that ozonolysis of vinylcyclopropane 259 worked far more effectively and reproducibly to give aldehyde 292 (Scheme 2.21).

Scheme 2.21 Reagents: (a) O$_3$, DCM, −78°C, 1 h; then DMS quench (90%).

The aldehyde 292 in turn underwent a Wittig reaction, with commercially available (carbethoxymethyl)triphenylphosphonium bromide, to form the substituted vinylcyclopropane 294 in good yield exclusively as the E-isomer. We hoped to discover whether the electron deficient alkene would have an effect on the cyclisation of simple cyclic imines, using our recently developed palladium cyclisation conditions. Cyclisations worked with consistently good yields to give the pyrrolizidine, indolizidine and azepine products 295, 296, 297 and 298 (Table 2.05). It was observed that the pyrrolizidine and indolizidine products were isolated as mixtures of ring diastereoisomers. NOe experiments confirmed the same relative stereochemistry of the 7-membered cyclisation product, as for the unsubstituted product 284. In later work it was discovered that the problem of ring diastereoisomer formation could be circumvented by modifying the order in which reagents were
added (pg. 134). This was unknown at the time this stage of the research was being carried out. It is therefore not unreasonable to assume that such a modification could lead to improved stereocontrol for the compounds isolated as diastereoisomers.

![Image of chemical reaction](https://example.com/chemistry.png)

\[ \text{EtO}_2\text{C} + \text{Cyclic imine} \xrightarrow{a} \text{Cyclised product} \]

<table>
<thead>
<tr>
<th>Cyclic imine</th>
<th>Cyclised Product</th>
<th>Yield (%)</th>
<th>d.r</th>
</tr>
</thead>
<tbody>
<tr>
<td>276</td>
<td>295</td>
<td>60</td>
<td>1:1</td>
</tr>
<tr>
<td>278</td>
<td>296</td>
<td>55</td>
<td>1:1</td>
</tr>
<tr>
<td>279</td>
<td>297</td>
<td>65</td>
<td>-</td>
</tr>
<tr>
<td>289</td>
<td>298</td>
<td>69</td>
<td>1:1</td>
</tr>
</tbody>
</table>

Table 2.05 Reagents: (a) 10 mol% Pd(PPh\(_3\))\(_4\), DMSO, 80°C, 1 h.

Once again \(^1\)H NMR analysis of the crude reaction mixtures showed a greater proportion of product than was ever isolated after column chromatography. Water washes were carried out on the crude reaction mixtures to remove DMSO, before acid washes extracted the product into the aqueous layer, and subsequent basification and re-extraction into EtOAc gave the desired products. Purification of the aza-bicycles 295-298 with silica or alumina lead to the majority of the compound being lost on the column, presumably due to the presence of the highly basic tertiary amine
functionality. Yields reported in the table are therefore without column chromatography.

This result of an electron-withdrawing group at the vinyl terminus appeared to have no detrimental effect on the efficiency of the reaction, with an improvement in yield observed in some cases. It was considered whether an aromatic ring in the same position would affect the reaction. Attempts to form the phenyl-substituted vinylcyclopropane 299 from the Wittig reagent benzyl triphenylphosphonium bromide, failed using the standard Wittig reaction conditions and no further work was carried out in this area (Scheme 2.22).

Scheme 2.22 Reagents: (a) Ph₃P⁺CH₂PhBr⁻, n-BuLi, THF, RT, 17 h.

2.4.2 Variation at the Malonic position

To establish whether different electron-withdrawing substituents attached to the cyclopropane ring have any effect on its ring opening, the dicyano vinylcyclopropane 300 was synthesised (Scheme 2.23). The superior electron-withdrawing nature of the cyano groups would theoretically aid ring opening and make the molecule more reactive. Formation of vinylcyclopropane 300 proved to be very capricious, with two different routes being investigated. The first, a procedure utilised by Tang,⁸¹ involved adding malononitrile to a stirred solution of trans-bromobut-2-ene and sodium hydride in THF. The reaction was extremely exothermic with a vigorous reaction taking place. The reaction mixture was then poured into EtOAc and ice water, followed by an unpleasant extraction, in which a very poor separation was observed. This resulted in poor yields of the desired vinylcyclopropane. The alternative route as used by Ali involved the use of potassium tert-butoxide as the base, in a methanolic solution.¹⁰¹ Once again, a difficult extraction followed by column chromatography resulted in poor yields. In both cases the desired product was not stored for longer than 2 days, as it degraded quite readily.
The reaction was performed on a large enough scale to yield enough vinylcyclopropane 300 for a few attempted cyclisations (Scheme 2.24).

Although the reactions were only performed using 25 mg of vinylcyclopropane 300, $^1$H NMR data clearly showed the formation of the desired aza-bicycles 301 and 302. However since such small amounts of the products were isolated, full characterisation was not possible. The stability of the cyclised products was also very poor. Further work needs to be carried out on the reaction work-up in the generation of vinylcyclopropane 300, to generate enough material for cyclisation.

2.4.3 Use of Activated Bicyclic Vinylcyclopropanes

Previous work within the group has investigated the rhodium-stabilised carbenoid reaction of diazo-carbonyl compounds and 1,3-cyclodienes, to form activated bicyclic vinylcyclopropanes 303 of varying ring size (Scheme 2.25). These types of compound are known to undergo palladium catalysed [3+2] cycloadditions with a variety of imine and aldehyde trapping reagents, furnishing bicyclic heterocycles 304.
The bicyclic vinylcyclopropane compounds are known to be less reactive than the simpler vinylcyclopropanes 259 and 294.\textsuperscript{98} To improve the scope of our reaction, the [4.1.0] activated bicyclic vinylcyclopropane 307 was reacted with a range of cyclic imines, to hopefully access a range of novel tricyclic compounds. Regitz et al. have reported the use of diazo transfer groups such as mesyl azide in the formation of dimethyl diazomalonate.\textsuperscript{102,103} Preparation of the diazo transfer compound 305, introduces the diazo functionality in a single step. Mesyl azide was therefore synthesised in excellent yields form mesyl chloride and sodium azide in acetone (Scheme 2.26).\textsuperscript{104} The diazo group is transferred by a donor (mesyl azide) to an acceptor (acidic malonate centre).

\begin{equation}
\text{Scheme 2.26 Reagents: (a) Acetone/water, reflux, 2 h (99\%)}
\end{equation}

Diazoo dimethylmalonate 306 was synthesised by reacting dimethyl malonate, mesyl azide 305 and triethylamine in acetonitrile, in a moderate yield (Scheme 2.27).

\begin{equation}
\text{Scheme 2.27 Reagents: (a) Et}_3\text{N, MeCN, RT, 4 h (54\%)}
\end{equation}
With the dimethyl diazomalonate 306 in hand, rhodium(II) catalysed thermal decomposition with 1,3-cyclohexadiene gave the [4.1.0]-activated bicyclic vinylcyclopropane 307 (Scheme 2.28). The schematic shows how thermal decomposition of the diazo compound leads to a carbene at the malonate centre, which can be stabilised by the rhodium. Aware that diazo carbonyl compounds can be potentially explosive, the reaction mixture was kept reasonably dilute (0.1 M of diazo dimethylmalonate 306 in CH$_3$CN, 5 ml).

![Scheme 2.28 Reagents: (a) Rh$_2$(OAc)$_4$ (10 mol%), MeCN, reflux, 3 h (41%)](image)

The reaction progressed in moderate yield, yielding the bicyclic vinylcyclopropane 307, which was reacted with a variety of cyclic imines. It was hoped tricyclic ring systems could be set up in one step. Bicyclic vinylcyclopropane 307 was reacted with zinc complexes 276 and 278 under palladium catalysis (Scheme 2.29).

![Scheme 2.29 Reagents (a) Pd(PPh$_3$)$_4$ (10 mol%), DMSO, 80°C, 24 h](image)
In each case, an unidentified product was isolated, but \(^1\)H NMR and IR spectra did not suggest any of the desired heterocycles had been made. Bicyclic vinylcyclopropane 307 was stirred with \(\text{Pd(PPh}_3\text{)}_4\) in DMSO at 80°C, to ascertain whether a rearrangement of the vinylcyclopropane was occurring. However, only starting material was recovered, suggesting the cyclic imines do play a role in the reaction.
Chapter Three

3.1 Preparation of functionalised imines

3.1.1 Quarternary Substitution on the Cyclic Imines

Commercially available 2-methyl-1-pyrroline was used as the cyclic imine substrate, to ascertain whether a quarternary centre in the α-position poses any steric restraints upon reaction with vinylcyclopropane 259. The methyl-substituted imine is less prone to trimerisation than its unsubstituted 1-pyrroline counterpart, meaning the free imine could be reacted directly with the vinylcyclopropane. Various conditions were explored (Table 3.01).

![Diagram of reaction between vinylcyclopropane and imine]

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Pd Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnCl₂</td>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>RT</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>ZnCl₂</td>
<td>Pd(PPh₃)₄</td>
<td>DMF</td>
<td>RT</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>ZnCl₂</td>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>Reflux</td>
<td>16</td>
<td>No product isolated</td>
</tr>
<tr>
<td>-</td>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>RT</td>
<td>60</td>
<td>SM</td>
</tr>
<tr>
<td>-</td>
<td>Pd(PPh₃)₄</td>
<td>DMF</td>
<td>RT</td>
<td>21</td>
<td>No product isolated</td>
</tr>
<tr>
<td>ZnBr₂</td>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>RT</td>
<td>19</td>
<td>No product isolated</td>
</tr>
<tr>
<td>ZnCl₂</td>
<td>Pd₂(dba)₃</td>
<td>THF</td>
<td>RT</td>
<td>19</td>
<td>SM</td>
</tr>
</tbody>
</table>

Table 3.01

Despite doubling the equivalents of Lewis acid, the yield of the desired pyrrolizidine 308 remained unchanged. This reaction proved to be quite problematic as only small amounts of the cyclised product were present in the crude reaction mixture by ¹H NMR, the majority of which was vinylcyclopropane 259. It is possible the presence of the quarternary C-centre on the imine may cause a steric restraint on the nucleophilic addition of the zwitterionic species. Closer inspection of ¹H NMR data.
for the crude reaction mixtures clearly showed the unreacted imine peaks are broadened, possibly because of its complexation to the Lewis acid, suggesting the affinity of the imine for the Lewis acid may hinder the reaction.

The basic tertiary amine constituent of pyrrolizine 308 made this compound difficult to purify through silica flash chromatography, and mobile phase modifiers such as triethylamine were required. Neutral alumina was used in an attempt to isolate the desired product, but yields were still very poor. Interestingly, 2D $^1$H NMR and nOe experiments confirmed one diastereomer was formed exclusively in this reaction.

2-Methyl-1-pyrroline was complexed with zinc iodide successfully to form the complex 309 as a cream powder in good yields (Scheme 3.01). Successful complexation can be confirmed by an upfield shift (~0.1ppm) in the proton shifts of protons adjacent to the nitrogen atom.

![Scheme 3.01](image)

Scheme 3.01 Reagents: (a) ZnI$_2$, Et$_2$O, 0°C, 1 h (85%).

Vapour diffusion from DCM and hexane gave crystals, which X-ray crystallographic data showed to be tetrahedral about the zinc metal centre, with the imines sitting in orthogonal planes to one another (Figure 3.01).

![Figure 3.01](image)
The zinc iodide complex 309 was subsequently reacted with vinylcyclopropane 259 and 10 mol% palladium(0), using various conditions (Table 3.02).

\[
\text{CO}_2\text{Me} + \text{Zn} \quad \text{Pd(0)} \quad \text{Solvent} \quad \text{CO}_2\text{Me} \quad \text{Complex 309 present (y/n)} \quad \text{Time (h)} \quad \text{Product yield (%)}
\]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Pd Catalyst</th>
<th>Temperature</th>
<th>Complex 309 present (y/n)</th>
<th>Time (h)</th>
<th>Product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>Pd(PPh₃)₄</td>
<td>RT</td>
<td>Y</td>
<td>68</td>
<td>None isolated</td>
</tr>
<tr>
<td>THF</td>
<td>Pd(PPh₃)₄</td>
<td>RT</td>
<td>Y</td>
<td>18</td>
<td>None isolated</td>
</tr>
<tr>
<td>MeCN</td>
<td>Pd(PPh₃)₄</td>
<td>RT</td>
<td>Y</td>
<td>18</td>
<td>None isolated</td>
</tr>
<tr>
<td>MeCN</td>
<td>Pd(PPh₃)₄</td>
<td>RT</td>
<td>N</td>
<td>22</td>
<td>SM</td>
</tr>
</tbody>
</table>

Table 3.02

The small amounts of cyclised product apparently present in the crude reaction mixture were lost in the purification process. The use of acetonitrile as solvent appears to give numerous by-products by TLC, with one product appearing to account for 50% of the crude material. However, it was difficult to determine a single compound by \(^1\)H NMR data. Interestingly, for the complex mixture of products to be observed, the imine complex 309 must be present.

3.1.2 *Anti*-substituted Cyclic Imines from 3-Pyrroline

After the success observed with simple cyclic imines our attention was drawn to imines containing a degree of functionalisation. Davis et al. recently reported the use of novel cyclic sugar imines as carbohydrate mimics for the creation of aza-sugars. Polyhydroxylated nitrogen heterocycle aza-sugars are considered to be sugar mimics, by virtue of the ring oxygen being substituted for a nitrogen atom. These compounds possess potent inhibitory activity towards carbohydrate-processing enzymes and can be applied to a wide range of therapies including the treatment of viral infections,
cancer, diabetes, tuberculosis, lysosomal storage diseases and parasitic protazoa. In their method, simple or polyhydroxylated pyrrolidine or piperidine imines are used as scaffolds to diversely functionalised aza-sugars through highly diastereoselective organometallic additions (Scheme 3.02).

Interestingly, in the few cases that sugar imines have been formed, they have shown enhanced inhibitory properties over their fully reduced counterparts. The introduction of hydrophobic substituents onto these cyclic sugar mimics, leads to an enhanced potency and bioavailability in carbohydrate-processing systems. Typically, the introduction of such groups has taken place at an early stage in the synthesis of sugar mimics, however Davis et al. have developed a late stage diversification using regioselective C=N imine formation, followed by organometallic addition to these late stage cyclic imine intermediates.

It was decided to construct one of these five membered, dihydroxylated imine intermediates, whose preparation involved 7 steps (Scheme 3.03). The synthesis of imine 315 began with benzyl chloroformate protection of the secondary amine of commercially available 3-pyrroline. Epoxidation using m-CPBA proceeded only after addition of two separate portions of peracid. Acid-catalysed ring opening of the epoxide proved to be very problematic. Vigorous stirring was required to mix the biphasic system, but the epoxide proved difficult to break, with the reported yield for this step calculated from recovered starting material. The concentration of acid was increased to 3 M with no effect, and any attempt to further increase the concentration was avoided, as cleavage of the benzyl protecting group was possible. The reaction was repeated several times to acquire enough of the protected diol 312 for the remaining steps. tert-Butyldimethylsilyltrifluoromethanesulfonate was used as the silicon-protecting group and was introduced with no problems.
Scheme 3.03 Reagents: (a) Benzyl chloroformate, 3M aq. NaOH, toluene, RT, 1 h (83%); (b) m-CPBA, DCM, RT, 25 h (44%); (c) 2M aq. H₂SO₄, Et₂O, RT, 2.5 d (62%); (d) TBDMSOTf, pyr, DCM, RT, 2 h (69%); (e) H₂, Pd/C, MeOH, RT, 5 h (83%); (f) NCS, Et₂O, RT, 19 h; (g) DBU, Et₂O, RT, 5 h (34% for two steps).

Palladium on carbon hydrogenolysis, deprotected the nitrogen atom in good yields to give the silicon protected amine 314, before N-chlorination using N-chlorosuccinimide and elimination with diazabicycloundecane gave the target anti-imine 315 in 4.4% overall yield.

After this process only a small amount of the imine was isolated, and only one reaction was attempted with vinylcyclopropane 259. The free imine was complexed to zinc iodide in ethereal solution, and unlike the zinc complexes 276, 278 and 279, which precipitated out of solution; the zinc iodide appeared to dissolve, suggesting the zinc iodide complex 316 was soluble in ether (Scheme 3.04). This enhanced solubility in an aprotic solvent such as Et₂O, could potentially increase the reactivity of the imine with the vinylcyclopropane reactant.

Scheme 3.04 Reagents: (a) ZnI₂, Et₂O, RT, 1 h (87%).
The complex 316 was added to a solution of vinylcyclopropane 259 in both THF and DMSO with 10 mol% palladium(0) (Table 3.03). No desired product was formed, and both the vinylcyclopropane and imine were recovered after purification with silica gel.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Pd Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>RT</td>
<td>20</td>
<td>SM</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>RT</td>
<td>21</td>
<td>SM</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>DMSO</td>
<td>RT→reflux</td>
<td>20</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Table 3.03

3.1.3 *Syn*-substituted Cyclic Imines from 3-Pyrroline

It was hypothesized that substituents at the C-3 and C-4 position on the 5-membered cyclic imine, may have a directing effect on the [3+2] cycloaddition step, and hence control the sterechemical outcome of the indolizidine product. It was reasoned that the *syn*-imine derivative 320 could be synthesised using an osmium-catalysed dihydroxlation step in a modification of Davis’ procedure (Scheme 3.05).
Scheme 3.05 Reagents: (a) Benzyl chlorofonnate, 3M aq. NaOH, toluene, RT, 1 h (83%); (b) AD-mix-β, methane sulfonamide, t-BuOH:H₂O (1:1), 0°C, 19 h (73%); (c) TBDMSOTf, pyr, DCM, RT, 2 h (70%); (d) H₂, Pd/C, MeOH, RT, 5 h (82%); (e) NCS, Et₂O, RT, 19 h; (f) DBU, Et₂O, RT, 5 h (33% for two steps).

Poor yields were initially observed in the dihydroxylation step. The addition of AD-mix-β to a solution of N-protected-3-pyrroline in tert-butanol:water (1:1) gave an unacceptable 29% yield of diol 317. The step had to be optimised for this to be a viable route toward the syn-imine 320. The AD-mix formulation consists of 0.6% by weight of (DHQD)₂-PHAL ligand and OsO₄, blended into the bulk ingredients ferricyanide and carbonate, providing a convenient yellow powder. Sharpless and co-workers found that addition of methane sulfonamide to this mixture is recommended for all non-terminal olefins, as an enhanced rate of ester hydrolysis is thought to occur.¹⁰⁹

With this in mind, the N-protected-3-pyrroline was reacted with AD-mix-β in tert-butanol:water (1:1) at 0°C, and methane sulfonamide added to the slurring mixture. The workup involved the addition of sodium sulfite and extraction into DCM. The eventual yield of the dihydroxylation step increased to 73%, making this early stage in the process a lot more efficient. Subsequent silicon-protection, hydrogenation, N-chlorination and elimination steps were performed with no problems to give the target syn-imine 320 in 11% overall yield.
As a greater quantity of the *syn*-imine 320 was prepared a few different conditions were tried in the cycloaddition reaction with vinylcyclopropane 259. Firstly, the free imine was reacted with vinylcyclopropane, using different conditions (Table 3.04).

![Chemical structures](Image)

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Pd Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnCl₂</td>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>RT</td>
<td>20</td>
<td>SM</td>
</tr>
<tr>
<td>ZnBr₂</td>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>RT</td>
<td>21</td>
<td>SM</td>
</tr>
<tr>
<td>-</td>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>RT→reflux</td>
<td>20</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>ZnCl₂</td>
<td>Pd(PPh₃)₄</td>
<td>DMF</td>
<td>Reflux</td>
<td>19</td>
<td>SM</td>
</tr>
<tr>
<td>ZnCl₂</td>
<td>Pd(PPh₃)₄</td>
<td>DMSO</td>
<td>RT→reflux</td>
<td>19</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Table 3.04

Analysis of the crude reaction mixtures suggested the presence of only starting materials in most cases. However, when no Lewis acid was used, the reaction mixture was stirred for 18 hours at room temperature, and TLC suggested no reaction had occurred. The mixture was then heated to reflux for 2 hours resulting in a complex mixture of products, which appeared to contain a cyclisation product due to the characteristic proton peaks at 6.00 ppm. Purification by column chromatography appeared to isolate one spot by TLC, but complicated ¹H NMR data suggested a mixture of compounds, one of which a possible cyclisation product.

The free imine 320 was complexed to zinc iodide to give the zinc iodide complex 321 in good yield (Scheme 3.06).
Complex 321 was subsequently reacted with vinylcyclopropane 259 in DMSO at room temperature with 10 mol% tetrakis(triphenylphosphine) palladium(0) but again no desired pyrollizidine was observed and the starting materials were recovered (Scheme 3.07).

This was quite a disheartening stage of the research, as a better result was envisaged with the use of these functionalised imines. For this reason, an alternate protecting group was investigated. It was decided 2,2-dimethoxypropane would be used to protect the cbz-protected syn-diol 317, as it would be able to withstand the hydrogenation conditions needed to cleave the cbz-group later in the synthesis of the imine, and would also alleviate the problem of C—Si bond lability (Scheme 3.08).

---

**Scheme 3.06** Reagents: (a) ZnI₂, Et₂O, RT, 1 h (70%).

**Scheme 3.07** Reagents: (a) Pd(PPh₃)₄ (10 mol%), DMSO, 80°C, 24 h.

**Scheme 3.08** Reagents: (a) Acetone, 2,2-dimethoxypropane, PTSA, RT, 19 h (77%); (b) H₂, Pd/C, MeOH, RT, 20 h (90%); (c) NCS, Et₂O, RT, 19 h; (d) DBU, Et₂O, RT, 5 h (15%, 2 steps).
The DMP protection progressed well, as well as hydrogenation of the cbz-group. However, the last step to form the imine with NCS and DBU was very disappointing, with only 15% of the product possibly being the desired imine 322, by $^1$H NMR data. It was decided to use this crude product in a cyclisation with vinylcyclopropane 259. The reaction was carried out on the free imine with Lewis acid in THF at room temperature with 10 mol% tetrakis(triphenylphosphine) palladium(0) (Scheme 3.09). No desired cyclised pyrrolizidine product was observed, and only unreacted vinylcyclopropane was present in crude $^1$H NMR spectra.

Scheme 3.09 Reagents: (a) Pd(PPh$_3$)$_4$, THF, ZnBr$_2$, RT, 19 h.

3.1.4 Cyclic Imines from 4-hydroxy piperidine

Having exerted much time and effort in the unsuccessful trapping of functionalised imines 315 and 320 it was decided to try alternative functionalised imines. Possible reasons for this lack of reactivity of the aforementioned imines could be attributed to steric or stereoelectronic influences of the proximal silyl ether functionality, hindering the attack of an incoming nucleophile on the imine bond. For this reason, it was envisaged that a 6-membered cyclic imine, with para-substitution, would eliminate the possibility of steric/stereoelectronic interference. 4-Hydroxy piperidine was protected with TBDMSOTf and pyridine in DCM. The reaction progressed smoothly with the silyl ether 323 being isolated in good yield (Scheme 3.10).

Scheme 3.10 Reagents: (a) TBDMSOTf, pyr, DCM, RT, 24 h (71%).
The silyl ether 323 could then be N-chlorinated using NCS, then DBU used to eliminate HCl to form the cyclic imine 324. However, real problems were encountered with this reaction. $^1$H NMR data clearly showed the presence of the downfield imine proton, but this rapidly disappeared, possibly due to trimerisation. Potassium superoxide was also used as an alternative reagent, as once the reaction had finished, the remaining solid potassium superoxide could be filtered off, removing the majority of impurities. Once again the characteristic imine proton quickly disappeared with time (Scheme 3.11).

![Scheme 3.11 Reagents: (a) NCS, Et$_2$O, RT, 19 h; (b) DBU or KO$_2$, 18-crown-6.](image)

By introducing a Lewis acid, such as ZnI$_2$, it was hoped the imine complex 325 could be isolated as a stable powder, suitable for use in cyclisation reactions. Upon addition of the Lewis acid to the colourless solution, a deep red colour was observed. The reaction mixture was filtered, leaving a pale yellow solid, in poor yield. $^1$H NMR and IR data proved to be inconclusive as to whether the complex formation was a success. The material obtained from the complexation reaction was reacted with vinylcyclopropane 259, under palladium catalysis, using a variety of conditions (Table 3.05). However, in each case unreacted vinylcyclopropane was recovered. The poor yields and uncertainty as to whether the cyclic imine had been formed at all, was certainly a contributing factor to the failure of this reaction.
3.2 New methods towards imine bond formation

3.2.1 In situ generation of the Cyclic Imine

The application of cyclic imines in organic synthesis is limited due to their volatility and tendency to rapidly trimerise at room temperature in neutral or basic solution. As a possible solution to this, other than introducing a Lewis acid, we hoped generating the imine directly from its N-chloramine derivative in the presence of a palladium(0) source, would bypass the problem of trimerisation.

Homopiperidine was used, as the azepine ring system forms more readily than its pyrrolizidine and indolizidine counterparts. *N*-Chlorination of homopiperidine was carried out with NCS in ethereal solution, with the reaction being stirred overnight (Scheme 3.12).
Scheme 3.12 *Reagents:* (a) NCS, Et₂O, RT, 24 h.

The reaction was monitored by TLC, with the majority of starting material being consumed. Water and brine washes were performed, and the organic fractions dried over MgSO₄. IR spectroscopy confirmed the absence of a N-H stretch in the region 3400-3100 cm⁻¹. The N-chloramine 326 was used immediately upon its formation, and reacted with vinylcyclopropane 259, in the presence of base and 10 mol% tetrakis(triphenylphosphine) palladium(0) (Scheme 3.13).

Scheme 3.13 *Reagents:* (a) Pd(PPh₃)₄, DBU, DMSO, 80°C, 1.5 h (19%).

Encouragingly, the azepine 284 was formed in modest yield, as exclusively one diastereoisomer. This showed that *in situ* generation of the imine could be a viable route towards these sorts of compounds. The reaction was carried out just one time, so there is possibly some scope for further optimisation of the reported yield.

### 3.2.2 Cyclic Imines from Enecarbamates

Carreira *et al.* report the first total synthesis of (±)-strychnofoline, a class of natural product isolated from the leaves of *Strychnos usambarensis*, which displays antimitotic activity in cultures of mouse melanoma and Ehrlich tumour cells. The prominent structural feature of this group of alkaloids is the spiro[pyrrolidin-3,3'-oxindole] nucleus, which they construct with a ring-expansion reaction of a spiro[cyclopropan-1,3'-oxindole] and a cyclic imine (Scheme 3.14). The cyclisation step occurs via a MgI₂ mediated process.
They reported a mild and convenient synthesis of cyclic imines from Boc-protected enamine 327, upon treatment with TMSOTf/NEt3 at −20°C, with aqueous workup (Scheme 3.15). They refer to the cyclic imines lack of stability, and for this reason no purification was carried out before its subsequent cyclisation.

For this route to be viable, a range of functionalised enecarbamates 327 must be easily accessible from cheap and readily available starting materials. Accordingly we turned our attention to a protocol by Yu et al., in which they report a general one-pot synthesis of cyclic enecarbamates. 112 Their approach in the preparation of a drug candidate involved the reduction of lactam carbamate 328 with Super Hydride to lactamol derivative 329, which without quench or isolation was treated directly with trifluoroacetic anhydride, diisopropylethylamine and a catalytic amount of DMAP. The dehydration occurred in good yield at room temperature, to give the enecarbamate 330 (Scheme 3.16).
Four different enecarbamates were synthesised from the respective carbamates 328, 331, 332 and 333 following the described procedure, to explore the possibility of whether this synthetic route could be applied to our research. The unfunctionalised enecarbamate 334, after imine formation, would hopefully give a direct comparison with our own method for the preparation of pyrrolizidine 280. The methyl, and ethyl ester versions 328, 332 and aromatic 333 were chosen in an effort to introduce some simple functionality onto the ring (Table 3.06).
With this selection of enecarbamates at hand, we decided to apply Carreira’s protocol to form the cyclic imines \(272, 338, 339\) and \(340\) (Table 3.07)

![Chemical structure diagram](image)

<table>
<thead>
<tr>
<th>Enecarbamate</th>
<th>Cyclic imine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boc, (\text{N} \equiv \text{N})</td>
<td>(\text{N} \equiv \text{N})</td>
</tr>
<tr>
<td>(334)</td>
<td>(272)</td>
</tr>
<tr>
<td>Boc, MeO(_2\text{C})</td>
<td>MeO(_2\text{C})</td>
</tr>
<tr>
<td>(335)</td>
<td>(338)</td>
</tr>
<tr>
<td>Boc, EtO(_2\text{C})</td>
<td>EtO(_2\text{C})</td>
</tr>
<tr>
<td>(336)</td>
<td>(339)</td>
</tr>
<tr>
<td>Boc, 2H(_2\text{O})</td>
<td>2H(_2\text{O})</td>
</tr>
<tr>
<td>(337)</td>
<td>(340)</td>
</tr>
</tbody>
</table>

Table 3.07 Reagents: (a) TMSOTf, Et\(_3\text{N}\), DCM, \(-78^\circ\text{C} \rightarrow -20^\circ\text{C}\); (b) aq. NaHCO\(_3\) quench, \(-78^\circ\text{C}\).

It is important to note that no yields were reported, as the material taken through for cyclisations was always crude, due to the general instability of the cyclic imines. \(^1\text{H}\) NMR data of the crude imines showed the characteristic imine proton to be present, and was a key indication of a successful reaction. In the case of the simple cyclic imine \(272\), the crude reaction material was immediately reacted with vinylcyclopropane \(259\), under palladium catalysis to give the previously synthesised pyrrolizidine \(280\) exclusively as one diastereoisomer, in a lower yield of 19% (Scheme 3.17).
This was quite a promising result, as no attempt had been made to stabilise the readily trimerisable cyclic imine prior to its cyclisation, and it illustrates Carreira's chemistry could possibly be applied to our own. However, attempts to cyclise functionalised versions 338-340 were unsuccessful under identical conditions. In fact, the only product isolated from the reaction was, surprisingly, the enecarbamates 335-337. Heating the crude imines in DMSO for one hour was enough to convert them back to their respective enecarbamate precursors. This unwanted reaction occurs due to the impure nature of the cyclic imines. Different solvents were used in an attempt to stop this reaction occurring and to isolate the desired cyclised products (Table 3.08). Trace amounts of pyrrolizidine 341 were observed using THF as solvent.
Cyclised Product

<table>
<thead>
<tr>
<th>Cyclic imine</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Cyclised product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>DMSO</td>
<td>80°C</td>
<td>![image]</td>
<td>19</td>
</tr>
<tr>
<td>MeO₂C N</td>
<td>DMSO</td>
<td>80°C</td>
<td>![image]</td>
<td>none</td>
</tr>
<tr>
<td>MeO₂C</td>
<td>DCM</td>
<td>Reflux</td>
<td></td>
<td>isolated</td>
</tr>
<tr>
<td>EtO₂C</td>
<td>THF</td>
<td>Reflux</td>
<td>![image]</td>
<td>trace</td>
</tr>
<tr>
<td>MeO₂C</td>
<td>THF</td>
<td>Reflux</td>
<td></td>
<td>none</td>
</tr>
</tbody>
</table>

Table 3.08

Two major side-products observed when using DCM and THF, were straight chain alkenes 342 and 343 (Figure 3.02).

![image]

Figure 3.02

The bis-alkene 342 is thought to arise via an oxidation pathway, whereas the tris-alkene 343 is the by-product arising from Et₃N reacting with vinylcyclopropane 259 in a dimerisation reaction. The presence of surplus Et₃N in the crude imine caused
real problems with the subsequent cyclisation reaction. When isolating the imine, saturated aqueous NaHCO₃ and brine washes were performed, but prolonged contact with aqueous solvent lead to a reduction in the yield of the imine, presumably through hydrolysis of the imine bond. However carefully the work-up was performed, significant quantities of Et₂N were left in the imine residue. Attempts to purify the imine by column chromatography failed, with nothing being isolated from the column. Polymer bound diethylamine was used in an attempt to eliminate the problem, with the intention of filtering off the polymer to leave the clean imine. However, solid-supported reagents can behave very differently under similar reaction conditions, and the reaction failed to work.

Lewis acids such as zinc iodide have previously been used to stabilise simple cyclic imines, so upon isolation of the crude imine, zinc iodide was introduced into an ethereal solution of the imine 339. A precipitate initially appeared to form in solution, however, as soon as the precipitate was filtered appeared to become wet. It can be assumed the complex 344 is much more hygroscopic than previously isolated zinc complexes. The wet solid isolated from this reaction was still reacted with vinylcyclopropane 259, under palladium catalysis in DMSO (Scheme 3.18).

![Scheme 3.18](image)

Scheme 3.18 Reagents: (a) TMSOTf, Et₃N, DCM, -78°C → -20°C; then aq. NaHCO₃ quench, -78°C; (b) ZnI₂, Et₂O, RT, 1 h; (c) 259, Pd(PPh₃)₄ (10 mol%), DMSO, 80°C, 24 h (10% 3 steps).

The reaction was only attempted one time, with crude ¹H NMR data showing the presence of a possible cyclisation product resembling compound 341. After column chromatography, cyclised product 341 was isolated in modest yield (10%), with nOe data suggesting the one diastereoisomer being formed. This avenue needs to be revisited with an aim to modifying the complexation procedure, possibly with more stringent, anhydrous conditions in place.
3.2.3 Cyclic Imines from $\gamma,\delta$-Unsaturated Nitriles

Fry et al report the addition of Grignard reagents to $\omega$-bromonitriles and $\gamma,\delta$-unsaturated nitriles to effect ring closure, forming cyclic imines 345 and 346 in good overall yields (Scheme 3.19).\cite{113}

\[
\begin{align*}
\text{OTMS} & \quad \begin{array}{c}
\text{CN} \\
\text{Br}
\end{array} \\
\text{RMgX} & \quad \text{TMSO} \\
\text{N} & \quad \text{R}
\end{align*}
\]

Scheme 3.19 Grignard additions to $\omega$-bromonitriles and $\gamma,\delta$-unsaturated nitriles

Previous work has failed in the cyclisation of imine bonds bearing quartemary centres, due to steric hindrance. In a modification of Fry's procedure, it was envisaged the Grignard reagent could be replaced by a hydride source to give unsubstituted, functionalised imines 347 (Scheme 3.20).

\[
\begin{align*}
\text{OTMS} & \quad \begin{array}{c}
\text{CN} \\
\text{Br}
\end{array} \\
\text{Super Hydride} & \quad \text{TMSO} \\
\text{THF} & \quad \text{N} & \quad \text{R}
\end{align*}
\]

Scheme 3.20 Proposed modification of Fry's procedure

Fry reports the synthesis of the bromonitrile precursor following a synthetic sequence involving alkylation of acetonitrile with allyl bromide followed by epoxidation and subsequent ring cleavage of the 2-cyanoethyl epoxide with trimethylsilyl bromide (Scheme 3.21).

101
Attempts to synthesise the bromonitrile failed with problems encountered with the initial alkylation step. Although the desired alkylation product appeared to be present in the crude reaction mixture, upon careful purification with column chromatography, a close running impurity could not be removed. This in turn hindered the epoxidation step, and none of the desired epoxide could be isolated. It was decided to terminate this section of research at this stage.

### 3.3 Conclusion

Good progress has been made in the reaction of simple and functionalised vinylcyclopropane derivatives with a variety of simple cyclic imines (Scheme 3.22).

Although the introduction of di-cyano functionality onto the cyclopropane ring was difficult, initial experiments suggested, the cyclisation reaction works well with the superior electron-withdrawing nature of the cyano group. Introduction of functionality onto the double bond still gave a compound susceptible to palladium insertion and subsequent ring formation. It has been shown that there is scope for wide variation of the vinylcyclopropane derivative in its reaction with simple cyclic imines.

Major problems have been encountered in the use of more functionalised cyclic imines with simple vinylcyclopropane (Scheme 3.23). The generation of a whole host
of functionalised cyclic imines has lead to problems with their isolation, due to the reactivity of the imine bond. For this reason, numerous different reaction sequences have been explored in an attempt to gain access to functionalised imines. Trace amounts of cyclised products have been isolated suggesting the reactions have the potential to work, but a more robust method for the stabilisation of the cyclic imines is required for future success.

Scheme 3.23 Failed reactions of functionalised cyclic imines
Chapter Four

4.1 New Routes to Functionalised Prolines

4.1.1 Proline as a Building block

Peptide-derived chemotherapeutics have attracted a great deal of interest in recent years and has heightened the importance of viable synthetic routes towards rare and nonproteinogenic enantiomerically pure amino acids. Consequently, expeditious preparations of these types of compound have become increasingly prevalent in the literature. The importance of making enantiomerically pure compounds cannot be emphasized enough and the current interest in this field has been brought about by (a) the enantioespecificity shown by most biological systems in their responses to drugs, (b) the regulatory pressure on the pharmaceutical industry to market chiral drugs as single enantiomers, and (c) the strong drive for synthetic efficiency.

Particular attention has been devoted to asymmetric syntheses of heterocyclic compounds, due to their presence in nature and specific biological activities. Researchers in this field have relied heavily on enantiospecific processes proceeding from the chiral pool to gain access to this broad class of compounds. The most significant contribution from the chiral pool arises from amino acids, due to their versatility and have been the most extensively used for the synthesis of chiral, enantiomerically pure heterocycles. The proteinogenic amino acids possess a limited but significant number of diverse functional groups, which help facilitate numerous synthetic transformations; their protection-deprotection and activation chemistry is thoroughly documented and they are readily available commercially, usually in both enantiomeric forms.

Proline continues to be a favorite starting material for the construction of the pyrrolizidine alkaloids. Mulzer et al. recently reported a synthesis of the necine base (-)-petasinecine using the highly stereoselective Ireland-Claisen rearrangement to create two of the three chiral centers present in the molecule (Scheme 4.01). The required allyl ester 349 was rapidly prepared from allyl alcohol 348, in turn obtained via Horner-Emmons homologation of Boc-prolinal. Reaction of 349 with lithium
hexamethyldisilazide and trimethylsilyl chloride gave the Ireland-Claisen precursor, which after rearrangement was cyclised to 350. Ozonolysis and reduction gave the primary alcohol 351 which was reduced using borane-THF complex and debenzylated using hydrogenolysis conditions.

Scheme 4.01 Reagents: (a) BnOCH₂COCl, pyr, RT, 5 h (98%); (b) LiHMDS, TMSCI, THF, -110°C, 2 h, then 5 h at 0°C; (c) F₃CCO₂H, BuOH, -20°C, 1 h, RT, 16 h, 60°C, 48 h (82%); (d) O₃, MeOH, -78°C, 10 min; (e) NaBH₄, MeOH, -78°C, 16 h (92%); (f) BH₃·THF, THF, 60°C, 48 h; (g) 10% Pd/C, H₂, MeOH, RT, 1 bar, 48 h (98%).

In a further example that extends the usefulness of the anodic methoxylation of prolines, alkynylsubstituted proline ester 355 (prepared by acylation of prolinol 353, followed by oxidation and esterification) was submitted to an anodic oxidation-iminium ion cyclization sequence to afford indolizinedione 357, which was ultimately transformed into the angiotensin-converting enzyme inhibitor A58365A (Scheme 4.02).¹¹⁸
Jacobi et al. have used an intramolecular Diels-Alder cycloaddition of an acetylenic oxazole derived from proline dipeptide 359 to synthesise the complex tetracyclic alkaloid (-)-norsecurinine (Scheme 4.03). Dipeptide 359 was converted to the oxazole pyrrolidine derivative 360 by cyclodehydration followed by catalytic hydrogenation. The protected enynone 361 underwent rapid 1,4-addition with the secondary amine to give acetylenic ketone 362, which without purification was converted to the furanoketone 363, by brief thermolysis in mesitylene. Reduction with sodium borohydride and elimination using Martin’s reagent ([(PhC(CF₃)₂O)₂SPh₂]) led to the introduction of the double bond in the seven-membered ring. Deprotection of 363, followed by hydrolysis with NaI/TiCl₄, afforded the butenolide alcohol 364 as a single isomer. Finally, mesylation and subsequent transannular alkylation with potassium hexamethyldisilazide gave (-)-norsecurinine.¹¹⁹
Scheme 4.03 Reagents: (a) POC13, reflux, 4 h; (b) Pd/C, H2, MeOH, RT, 19 h (65% 2 steps); (c) 361, MeCN, 50°C, 2 h; (d) Reflux, mesitylene, 6 h (50% 2 steps); (e) NaBH4, THF, -30°C; (f) [PhC(CF3)2]2O]2SPb2, DCM, RT (60% 2 steps); (g) TBAF, THF, RT (90%) (h) NaI, TiCl4, H2O, 65°C (75%); (i) MsCl, DMAP cat., Et3N, RT, 2 h (98%); (j) KHMDs, THF, -78°C, 1 h (69%)

These are all examples of protocols taking advantage of proline as a building block towards more complex molecules. Synthetic sequences towards more complex proline templates are becoming increasingly commonplace, as precursors for more diverse molecule formation. An example of this is the synthesis of trans-(2S,4R)-4-hydroxy-L-proline 369 (L-Hyp), a non-essential amino acid found in a number of secondary metabolites such as echinocandins and etamycin. With its two chiral centers, L-Hyp is the molecule of choice for access to numerous multifunctionalised pyrrolidine ring compounds.120 Takano et al recently prepared L-Hyp in a ten-step sequence starting from (S)-O-benzylglycidol (Scheme 4.04). Acetylenic substitution of epoxide 365 and subsequent reduction of the resulting pentynol compound, then Mitsunobu reaction with phthalimide gave derivative 366. Reaction with hydrazine and benzoylation gave compound 367, which cyclised in the presence of iodine to obtain 4-benzoate-2-prolinol 368, which was Boc-protected, oxidized, and further deprotected to give 369 in 25% overall yield.121
Scheme 4.04 Reagents: (a) C₂H₂, NaH, DMSO; (b) H₂, Pd/CaCO₃ cat.; (c) Phthalimide, PPh₃, DEAD (61% 3 steps); (d) N₂H₄, EtOH; (e) BzCl, Et₃N (87% 2 steps); (f) I₂, H₂O/THF (78%); (g) Boc₂O, Et₃N, DCM; (h) K₂CO₃; (i) H₂, Pd(OH)₂; (j) RuCl₃, NaIO₄; (k) TFA (61% 5 steps).

L-Hyp acts as a more functionalised analogue of proline, and allows access to a large variety of chiral molecules such as glutamic acids analogues, kainic acids, arginine analogues, carbapenems, natural products such as lycoperdic acid, bulgecins, echinochandins or didemmins, and also fully synthetic piperidines and pyrrolidines, benzodiazepins, puromycin analogues, baclofen, quinolones and naphthyridones (Figure 4.01).¹²⁰,¹²²

Figure 4.01 Examples of natural products based on L-Hyp
The pursuit for general methodology towards various functionalised proline derivatives can only enhance the efficiency with which complex molecules can be constructed. As such, we decided to expand the potential synthetic utility of the palladium [3+2] cycloaddition, in an attempt to form novel proline compounds as templates for further elaboration.

We turned our attention to the use of oxazinones 370 within the reaction. Oxazinones offer an alternative form of cyclic imine, with a highly electrophilic imine bond, caused by the electron-withdrawing lactone portion of the ring. This improved environment is conducive towards nucleophilic attack from vinylcyclopropane 259, to give intermediary bicycles 371 as templates for functionalised proline syntheses (Scheme 4.05). The relatively simple preparation of oxazinones from amino alcohols, allows us the opportunity to screen numerous different substrates, and also take advantage of the chiral pool presented by amino acid derivatives. The ultimate aim of this project was to gain total control of the two stereogenic centres created in the cycloaddition step, leading to an enantioselective route towards functionalised prolines.

\[
\begin{align*}
\text{259} & \quad \text{Pd(0)} & \quad \text{370} & \quad \text{371}
\end{align*}
\]

Scheme 4.05 Proposed route to novel functionalised prolines

4.1.2 Oxazinones in synthesis

The use of oxazinones (or glyoxylate imines) is widespread in the literature, particularly as electrophilic chiral glycine equivalents.\(^{123}\) Molinski \textit{et al} reported an unexpected rearrangement route towards these types of compounds.\(^{124}\) Starting from 2-substituted oxazolines, a novel reverse-Beckmann type rearrangement occurred after oxidation of the \(\alpha\)-carbon by selenium dioxide, followed by \(\beta\)-cleavage by 1,2-migration and concomitant ring expansion (Scheme 4.06).
The proposed reaction mechanism proceeds through a Lewis acid-catalysed rearrangement of a 2-acyloxazoline intermediate (Scheme 4.07). Allylic oxidations are known to occur in the presence of SeO$_2$ and for this reason it was considered that 2-acyloxazoline 372 was a reasonable intermediate. In the presence of Lewis acid, compound 372 is unstable and undergoes rapid ring opening leading to a conjugated nitrilium ion. It was reasoned that sources of Lewis acid in this reaction might arise from selenium-containing by-products formed in the reduction of SeO$_2$. The cationic nitrilium intermediate then rearranges via a 1,2-shift to an acylium ion, followed by ring closure to give oxazinone 373.
Chen et al. were one of the first groups to harness this reaction in their diastereoselective synthesis of arylglycine derivatives, via TFA-promoted Freidel-Crafts reactions of phenols with cyclic glyoxylate imines. They report the use of a diphenyl substituted glyoxylate imine \(374\) as an electrophile in the reaction with phenol \(375\), to give a mixture of ortho and para adducts. These adducts were subsequently treated with Pearlman’s catalyst \([\text{Pd(OH)}_2/C]\) and TFA in a hydrogenolysis reaction to remove the chiral template and form the free amino acid without notable racemisation (Scheme 4.08).

![Scheme 4.08](image)

Scheme 4.08 **Reagents:** (a) TFA, DCM, 0°C; (b) Pd(OH)$_2$/C, TFA H$_2$ (1 atm), MeOH:H$_2$O (20:1).

### 4.1.3 Formation of Oxazinones via Oxazoles

Oxazoles \(376-380\) were prepared following the protocol of Meyers et al., in which a selection of racemic and chiral amino alcohols were condensed with commercially available ethyl iminoacetate hydrochloride. The oxazoles were then subjected to SeO$_2$ forming the corresponding oxazinones (Scheme 4.09).
Oxazoles 376-380 were synthesised in average to good yields (40-85%) from phenylalaninol, valinol, leucinol, phenylglycinol and 2-amino-butanol. Kuglerohr distillation of the oxazole products was necessary to obtain optical purities comparable to those reported in the literature, however, water washes were sufficient to isolate oxazole products in good yields, suitable for the oxidative rearrangement reaction. In most cases the commercially available amino alcohol was purchased directly, however, (S)-phenylalaninol 386 was prepared via the reduction of (S)-phenylalanine with lithium borohydride/TMSCl (Scheme 4.10).
The best yield obtained in the SeO₂ promoted rearrangement reaction was for benzyl-substituted oxazole 376, affording oxazinone 381 in 60% yield. The reaction appeared to be sensitive to the quality of SeO₂ used, and the reduction in yield for oxazinones 383-385 was a possible indication of this. The oxazinones were isolated as viscous oils after column chromatography, and showed no signs of degradation on silica. Surprisingly, these types of imines were also stable to hydrolysis through aqueous work-up. The inherent stability of these compounds removed the requirement for any stabilisers (such as Lewis acid). Previous work with simple cyclic imines has shown the incorporation of zinc iodide to be crucial to inhibit trimerisation.

4.1.4 Alternative Route to Oxazinones using Lead Acetate

An alternative route to access oxazinones involved the double displacement of phenyl α-bromoacetate with amino alcohols using Hüning's base, to form secondary amines 387 and 388 (Scheme 4.11). Oxidation of the secondary amines with lead tetraacetate, directly lead to the formation of an imine bond. Phenyl and benzyl substituted oxazinones 381 and 384 were synthesised from phenylalaninol and phenylglycinol in moderate yields. Temperatures were kept below 40°C to avoid the formation of a dimeric species. Once oxazinones 381 and 384 were prepared, they were reacted in the next step immediately.
Scheme 4.11 Reagents: (a) DIPEA, MeCN, RT, 17 h (387 (27%), 388 (56%)).

The oxidation reaction with lead tetraacetate was then carried out to form oxidised oxazinones 387 and 388 in good yields (Scheme 4.12). The convenient synthesis involved stirring the secondary amine and lead tetraacetate in acetonitrile. The reaction mixtures turned bright orange upon addition of the lead reagent and went to completion once this colour faded to pale yellow. The reaction mixture could then be filtered through celite, and reduced in vacuo, to give the oxidised products. The only other contaminant present was acetic acid arising as a by-product of lead tetraacetate oxidation. Surprisingly, the oxazinones isolated were very stable to aqueous work-up and column chromatography, and were purified by the latter method in good yield.

Scheme 4.12 Reagents: (a) Pb(OAc)$_4$, MeCN, 14 h (381 (85%), 384 (92%)).

The inherent drawback involved with this route was the use of the heavy metal lead and the associated health and safety implications. As numerous different oxazinones were required on a frequent basis, it was decided to avoid this method and use Molinski’s oxidative rearrangement methodology.
4.1.5 Palladium [3+2] cycloadditions with oxazinones

The varying degrees of substitution on the oxazinone products were chosen to assess the effect of both straight and branched chain substituents and also phenyllic/benzylic functionalisation on the eventual cycloaddition reaction. The various substituents could potentially direct the approach of the incoming imine on vinylcyclopropane 259 and hence determine the stereoselectivity of the reaction. To further increase the level of stereocontrol, it was envisaged the use of chiral starting materials would make for an enantioselective process.

With these oxazinones in hand, we attempted the palladium catalysed [3+2] cycloadditions under a variety of conditions initially on benzyl-substituted oxazinone 384 (Table 4.01). In all cases where product was isolated, a mixture of inseparable diastereoisomers 389a and 389b was observed, the relative stereochemistry confirmed by nOe experiments. Surprisingly, the syn-conformer 389a (in relation to the ring protons) was the major isomer in all cases, suggesting formation of the kinetic product was favoured over the more thermodynamically stable anti-conformer 389b, under this set of conditions. THF appeared to give the best yield of cycloadducts (78%) used in conjunction with Pd(PPh3)4, although superior d.e.'s were observed using Pd[P(2-furyl)3]2 generated in situ from palladium acetate. In the examples where the palladium catalyst was generated in situ, 10 mol% palladium acetate and 20 mol% of the corresponding ligand were allowed to preform in THF at 50°C for 10 minutes before addition of vinylcyclopropane 259.
A further set of experiments was carried out at higher temperatures to see if any improvement in yield could be obtained. A range of solvents was explored including ionic liquids, which have attracted increasing interest as an environmentally benign reaction media, suitable for a range of palladium reactions. However, in the majority of cases, the oxazoline was being recovered at the end of the reaction, with trace amounts of the desired cyclised product (Table 4.02).
At high temperatures vinylcyclopropane 259 was not recovered from the reaction mixture. To ascertain what side reaction was happening, the reaction was followed by LC-MS, and revealed a strong [M+H]^+ peak at 369, and a smaller peak at 553. These peaks indicate the formation of a dimer and trimer of vinylcyclopropane 259.

Tentative ^1H NMR analysis of the isolated compounds suggested the formation of dimer 390 and trimer 391 (Figure 4.02).
The best results at high temperature were observed using THF as solvent, giving a mixture of diastereoisomers 389a and 389b. An optimum d.r of 4:1 (389a: 389b) was observed when the reaction was heated thermally to reflux temperature. When microwave energy was used to surpass the natural reflux temperature of THF, a gradual decrease in d.e was observed. In conclusion, the yields of the desired cycloadducts were poor when the reaction temperatures were raised, presumably due to the increased rate of dimerisation and trimerisation of vinylcyclopropane 259. This unwanted side reaction hindered the cyclisation of oxazinone 384 and outlined the importance of using lower temperatures to avoid this phenomenon.

Having obtained promising results with benzyl-oxazinone 384, isopropyl-oxazinone 382 was investigated (Table 4.03). Interestingly, pyrrolo-oxazinone 392 was isolated exclusively as the theoretically more stable thermodynamic anti-product, under one set of conditions. A more acceptable yield was observed using THF at room temperature, giving a 5:4 d.r in favour of the syn diastereoisomer.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Lewis Acid</th>
<th>T</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>d.r (392a : 392b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td></td>
<td>reflux</td>
<td>17</td>
<td>SM</td>
<td></td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>Toluene</td>
<td></td>
<td>reflux</td>
<td>17</td>
<td>SM</td>
<td></td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>THF/DMF (3 : 1)</td>
<td>ZnCl₂</td>
<td>110°C</td>
<td>17</td>
<td>15</td>
<td>1:0</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td></td>
<td>RT</td>
<td>48</td>
<td>54</td>
<td>5:4</td>
</tr>
</tbody>
</table>

Table 4.03
Leucinol-oxazinone 383 was then investigated, to explore the effect of an additional methylene group spacer between the i-Pr substituent and the ring, on the stereochemical outcome of the reaction (Scheme 4.13). Pyrrolo-oxazinone 393, was clearly made in the reaction (approx. 15% yield by NMR), however after column chromatography, TLC and LC-MS experiments confirmed the desired product was co-eluting with unwanted by-product dimer 390. Preparative HPLC was carried out on the 20 mg sample obtained after column chromatography. The separation proved to be quite difficult, and most of the sample was lost on the HPLC column. As a result, full data for the desired cycloadduct 393 has not been reported. $^1$H NMR data of the mixture clearly showed the cycloadduct had been formed in a 1:1 mixture of diastereoisomers, evidently showing the stereochemical outcome of the cyclisation to be substrate dependant, as well as temperature dependant.

Scheme 4.13 Reagents: (a) Pd(PPh$_3$)$_4$, THF, RT, 18 h.

(±)-2-Amino-1-butanol was used as the amino alcohol to introduce an ethyl group in oxazinone 385. This was successfully cyclised with vinylcyclopropane 259 using microwave conditions, yielding the cycloadduct 394 as a 1:1 mixture of diastereoisomers in poor yield (17%) (Scheme 4.14). The reaction has still to be attempted at room temperature, and we would hope that an improvement in yield would be observed, due to reduced rate of by-product formation, and also greater control over the stereochemical outcome.
Finally, (R)-phenylglycinol was used to access phenyl-oxazinone 384. This was successfully cyclised yielding pyrrolo-oxazinone 395a and 395b as an inseparable mixture of diastereoisomers (1:1, 395a: 395b) (Scheme 4.15). The ultimate aim of this project was to remove the chiral auxiliary, furnishing the functionalised proline amino acid. We were hopeful that the phenyl-oxazinone 384 would work well in the cyclisation, as hydrogenolysis to remove the benzyl protection and hydrolysis to cleave the lactone would provide a two-step deprotection route to our desired proline derivative. Unfortunately, low yields thwarted the potential synthetic applicability of this reaction.

**Scheme 4.15** Reagents: (a) Pd(PPh₃)₄, THF, RT, 18 h (25%, 1:1 (syn:anti)).

4.1.6 Electron deficient quaternary imine bonds

To understand the stereochemical course of these cycloadditions, it was reasoned that the introduction of additional substitution on the imine bond, such as in 3,5-diphenyl-oxazinone 396, could possibly increase stereocontrol. A relatively bulky phenyl substituent could affect the direction of the incoming nucleophile, and in essence “lock out” any epimers seen at C-9 in the compound 397 (Scheme 4.16).
Previous work has unsuccessfully evaluated the use of quaternary centres on simpler cyclic imines. An explanation of this result is the sterically demanding environment associated with the formation of two adjacent quaternary centres. Although 3,5-diphenyl-oxazonine 396 still had the unfavourable steric environment to contend with, we were hopeful that the electron-withdrawing lactone group would render the imine bond electrophilic enough to overcome this problem. Work began by generating 2-phenylethyl acetimidate hydrochloride salt 398 following a procedure by Wenker.\textsuperscript{128} This involved bubbling HCl gas through an ethanolic solution of benzyl cyanide and cooling, giving crystals of the desired product in excellent yield (90\%) (Scheme 4.17).

\begin{center}
\begin{align*}
\text{Scheme 4.16 Locking out epimers at C-9}
\end{align*}
\end{center}

Acetimidate 398 was reacted with (\textit{R})-phenylglycinol, to give diphenyl oxazole 399 in good yield, followed by selenium dioxide-promoted oxidative rearrangement to the required diphenyl-oxazoline 396 (Scheme 4.18).
Oxazinone 396 was then subjected to our palladium catalysed cyclisation reaction with vinylcyclopropane 259 (Scheme 4.19). Unfortunately none of the desired product was formed, but another product was isolated in almost stoichiometric amounts.

The reaction was monitored by LC-MS and indicated total consumption of starting materials, and the presence of a [M+H]+ peak at 436 indicating the two reactants had combined via an alternative pathway. Further analysis suggested the formation of alkylated product 400 had occurred (Scheme 4.20). A possible mechanistic explanation of this is the abstraction the benzylic proton from oxazonine 396, by the nucleophilic end of the vinylcyclopropane zwitterion, forming a stabilised anion capable of entering into conjugation with the remainder of the molecule. This anion can then react with the π-allyl portion of the zwitterion giving unexpected compound 400.
4.1.7 Controlling the stereochemistry at C-9

The palladium catalysed cyclisation reaction of oxazinones with vinylcyclopropane 259, has so far lead to the generation of a mixture of diastereoisomers, with i-Pr oxazinone 382 being the only exception. Where an excess of one diastereomer was observed, it was surprisingly the more strained syn kinetic product. Scheme 68 shows the configurational difference between the two diastereomers of benzyl-pyrrolo-oxazinone 389 (Figure 4.03).129

The syn product was formed preferentially over the anti product, even though when all the ring protons are on the same face, the bicyclic ring system is forced into a strained “boat” arrangement. Epimerisation at C-9 would give the anti-product, clearly alleviating the strain in the ring system (Scheme 4.21).
It was our intention to control the stereochemical outcome of the reaction during the cycloaddition step, but in the cases where mixtures of diastereomers were observed, we planned to exploit the enolisable nature of C-9 to switch between epimers. After trying bases such as sodium hydroxide and DBU, it was found that potassium hexamethyldisilazide deprotonated pyrrollo-oxazinone 389 at -78°C, forming the enolate, which was subsequently re-protonated upon aqueous work-up, giving almost complete conversion to the more thermodynamically stable anti-isomer in good yield (Scheme 4.22).

Scheme 4.21 Controlling the C-9 stereochemistry

This was a pleasing result, as the nature of the cyclised product allowed interconversion between the two diastereoisomers formed in the reaction.

4.1.8 Electron-rich Cyclic Imines

With the limited success observed for electron-deficient imine bonds such as those found in oxazinones 389, 392, 393, 394 and 395, we briefly turned our attention to the use of electron rich systems. We considered whether the electron-rich quaternary imine bond of oxazole 379 would cyclise. However, no product was isolated,
suggesting the steric and electronic environment of the imine bond hampered the progress of the reaction (Scheme 4.23).

Scheme 4.23 Reagents: (a) 10 mol% Pd(PPh₃)₄, THF, RT → reflux, 20 h.

Other more sterically accessible electron-rich systems include those found in 2-oxazoline 401 and 2-imidazoline 402 (Figure 4.04). Imidazoline 402 was commercially available, and oxazoline 401 was synthesised in two steps.¹³⁰

Figure 4.04 2-Oxazoline and 2-imidazoline

2-Oxazolines have previously been prepared in the literature by Wenker, from N-acetyl-2-aminoethanols.¹²⁸ N-Formyl-2-aminoethanol 403 was formed conveniently by heating equimolar proportions of formic acid and 2-aminoethanol to 200°C, followed by vacuum distillation. Compound 403 was subsequently reacted with thionyl chloride in a cyclisation reaction to form 2-oxazoline 401 (Scheme 4.24).

Scheme 4.24 Reagents: (a) 200°C, 4 h (59%); (b) SOCl₂, 0°C→RT (56%).
With our electron-rich imines in hand, the cyclisation reaction was attempted with vinylcyclopropane 259. However, no reaction occurred using tetrakis(triphenylphosphine) palladium(0) in THF at room or reflux temperature (Scheme 4.25).

Scheme 4.25 Reagents: (a) Pd(PPh₃)₄ (10 mol%), THF, RT or reflux, 18 h.
4.2 Conclusion

Preliminary work assessed the use of functionalised oxazinones as trapping reagents in the palladium catalysed [3+2] cyclisation reaction with vinylcyclopropane 259. Starting from various amino alcohol substrates, a selection of oxazoles was made, which were then transformed into oxazinones and reacted with vinylcyclopropane 259 to form pyrrolo-oxazinone products (Table 4.04).

![Chemical structure]

$$\text{Oxazinone} + \text{Product} \rightarrow 10 \text{ mol}\% \text{Pd(PPh}_3\text{)}_4$$

<table>
<thead>
<tr>
<th>Oxazinone</th>
<th>A</th>
<th>B</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>d.r A:B</th>
</tr>
</thead>
<tbody>
<tr>
<td>381</td>
<td></td>
<td></td>
<td>THF, RT, 48 h</td>
<td>72</td>
<td>2:1</td>
</tr>
<tr>
<td>381</td>
<td></td>
<td></td>
<td>THF, reflux, 24 h</td>
<td>19</td>
<td>4:1</td>
</tr>
<tr>
<td>381</td>
<td></td>
<td></td>
<td>THF, µ-wave, 90°C, 10 min</td>
<td>30</td>
<td>7:5</td>
</tr>
<tr>
<td>381</td>
<td></td>
<td></td>
<td>THF, µ-wave, 100°C, 16 min</td>
<td>19</td>
<td>1:1</td>
</tr>
<tr>
<td>382</td>
<td></td>
<td></td>
<td>THF/DMF, 80°C, 24 h</td>
<td>15</td>
<td>1:0</td>
</tr>
<tr>
<td>384</td>
<td></td>
<td></td>
<td>THF, RT, 48 h</td>
<td>54</td>
<td>5:4</td>
</tr>
<tr>
<td>384</td>
<td></td>
<td></td>
<td>THF, RT, 32 h</td>
<td>25</td>
<td>1:1</td>
</tr>
<tr>
<td>385</td>
<td></td>
<td></td>
<td>THF, µ-wave, 90°C, 10 min</td>
<td>17</td>
<td>1:1</td>
</tr>
</tbody>
</table>

Table 4.04

The best cyclisation yield was observed for benzyl-substituted oxazinone 381, with different diastereomeric ratios reported for different reaction temperatures. This outlined the importance of temperature on the stereoselectivity of the reaction. The best diastereomeric ratio observed in these experiments was for i-Pr-substituted oxazinone 382, with exclusively one diastereoisomer produced. This suggested the
stereoselectivity to be dependant on substrate, and the steric influence of the \textit{i}-Pr had a directing effect on the reaction.

We have also shown that quaternary imines and electron rich imines suffer from reduced reactivity, and fail to cyclise under the reaction conditions explored (Scheme 4.26).

\begin{scheme}
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{Ph} \quad \text{N} \quad \text{Ph} & \quad \text{Pd}(\text{PPh}_3)_4 \\
\xrightarrow{\text{THF}} & \\
\text{X} & \quad \text{X}
\end{align*}
\end{scheme}

\textbf{Scheme 4.26 Failed cyclisation attempts}
Chapter Five

5.1 Application to natural products

5.1.1 Retrosynthesis of stemoamide

The next stage of this project involved the application of the recently developed palladium [3+2] cycloaddition process to the natural product stemoamide. A brief introduction to the physiological properties and previous syntheses of this compound has been covered in the introduction, and will not be detailed any further at this stage. Stemoamide is based on a tricyclic system, which after retrosynthetic analysis can be disconnected back to two synthons amenable to our methodology (Scheme 5.01).

[Diagram of stemoamide retrosynthesis]

Cleavage of the lactone ring gives a functionalised azepine system. This could potentially arise from Heck coupling of a suitable vinyl halide tether to an α,β-unsaturated group. The functionalised pyrrolidine precursor could be derived from a suitable substituted vinylcyclopropane, and an acyclic imine. Previous work within the group has investigated the use of simple acyclic imine substrates, and found phenyl substituted imines to be easily prepared and also relatively stable. For this
reason, preliminary studies towards stemoamide used an acyclic imine where R = phenyl. However, it was noted at this early stage that variation of the R-group could act as a handle to access closely related analogues of the Stemona alkaloids, such as stemoamide, stemonine and didehydroparvistemonine (Figure 5.01).

![Diagram of stemonine, stemoamide, and didehydroparvistemonine](image)

**Figure 5.01** Synthetically versatile imine building block

### 5.2 Formation of functionalised Pyrrolidine intermediate

#### 5.2.1 Synthesis of substituted Vinylcyclopropane

The first objective was to synthesise the appropriate substituted vinylcyclopropane. From earlier work reported within this thesis, it is known that substitution at the vinyl terminus with electron-withdrawing groups is possible, with no appreciable drop in reactivity during the [3+2] cycloaddition. It was decided to introduce the t-butyl ester at this position using a similar method to that used previously. Ozonolysis of vinylcyclopropane 259 gave aldehyde 292, which was subjected to Wittig homologation with (tert-butoxycarbonylmethyl)triphenylphosphonium bromide, to give the substituted compound 405 (Scheme 5.02).
Scheme 5.02 Reagents: (a) \( \text{O}_3, -78^\circ\text{C}, 2\) h; then quench with DMS, RT, 12 h (80%); (b) 404, BuLi, THF, 0°C, 10 min (89%).

The introduction of the \( \text{t-butoxy ester} \) at this early stage would hopefully help in the lactonisation step later in the synthesis. We envisaged carrying out an iodolactonisation to close the final lactone ring of stemoamide, and \( \text{t-butoxy esters} \) are known to carry out this transformation in one step, without the need to hydrolyse the ester first.\(^{131}\) It was reasoned that this could save a step in the synthesis (Scheme 5.03).

5.2.2 Synthesis of Acyclic Imine

An investigation into the preparation of acyclic imine 412 had already been carried out within the group.\(^{100}\) A linear approach was used starting from 3-butyn-1-ol 406, and involved bromination at the alkyne terminus, followed by selective reduction using diimide to give exclusively the \( \text{cis-isomer} \) 408. This in turn was mesylated, and transformed into the iodo-adduct 410 by Finklestein reaction with sodium iodide. The most problematic step involved displacement of iodine with phthalimide, to install a masked amine in the correct position on the acyclic chain. This was a temperamental step, with yields never surpassing 56%. Finally phthalimide 411 was hydrolysed using hydrazine monohydrate to give the free amine, which was not isolated. The crucial element in the amine formation was the reaction workup. Complete reaction
of the phthalimide group with the hydrazine monohydrate was signified by the generation of a white precipitate in the reaction mixture. The key stage in the work-up involved addition of aqueous 2 M HCl and refluxing of the reaction mixture for a further 10 minutes. The reaction was then cooled to room temperature and the residual solids were filtered and washed with water. The aqueous ethanol filtrate was concentrated under reduced pressure before basifying with NaOH and extracting into diethyl ether. Any variations of the reaction workup led to only small quantities of amine being generated. The amine itself was relatively volatile, so removal of diethyl ether was done at low temperature, to give a concentrated solution to be used in the imine formation reaction with benzaldehyde. (Scheme 5.04).

\[
\begin{array}{c}
\text{OH} \\
406 \\
\rightarrow a \\
\rightarrow \begin{array}{c}
\text{Br} \\
407 \\
\rightarrow b \\
\rightarrow \begin{array}{c}
\text{Br} \\
408 \\
\rightarrow c \\
\end{array}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\text{OMs} \\
409 \\
\rightarrow d \\
\rightarrow \begin{array}{c}
\text{I} \\
410 \\
\rightarrow e \\
\rightarrow \begin{array}{c}
\text{NPhth} \\
411 \\
\rightarrow f, g \\
\end{array}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\text{N}_{\text{Ph}} \\
412
\end{array}
\]

Scheme 5.04 Reagents: (a) KOH, Br₂, H₂O, dark, 0°C→RT, 24 h (92%); (b) p-TolSO₂NH₂, NaOAc, THF:H₂O (1:1), 4 h (93%); (c) MsCl, Et₃N, DCM, 0°C, 4 h (94%); (d) NaI, acetone, reflux, 18 h (82%); (e) KNPhth, 2-butanol, reflux, 24 h (54%); (f) N₂H₄·H₂O, EtOH, reflux, 2 h; (g) PhCHO, 4 Å molecular sieves, Et₂O, RT, 18 h (74% 2 steps).

Attempts to shorten the synthesis were investigated, with some success observed converting mesylate 409 directly to the phthalimide 411. Conditions were developed using potassium phthalimide and a catalytic amount of potassium iodide (Scheme 5.05). The reaction worked in an improved yield of 69% for the one step in comparison to 68% for the two-step method. However, these conditions only ever worked on a scale less than 200 mg, so this route was rejected.
Another route was also investigated starting from the commercially available phthalimide protected alkyne 413. Attempts to form the free phthalimide 411 failed, however the bromination reaction worked well, only when the product was isolated as the hydrochloride salt 414. The selective diimide reduction of the alkyne worked on the hydrochloride salt in a reduced yield of 54% (Scheme 5.06). The synthesis of imine 412 was completed as described above in an overall yield of 28% for 4 steps, as opposed to 26% for 7 steps. A combination of both routes was used to synthesise reasonable quantities of the desired imine.

\[
\text{Scheme 5.05 Reagents: (a) KNPhth, KI (10 mol%), 18-crown-6, DMF, 80^\circ C, 18 h (69%).}
\]

5.2.3 Palladium Catalysed [3+2] Cycloaddition to functionalised Pyrrolidines.

The first key-step in the synthesis involved the cycloaddition of vinylcyclopropane 405, with acyclic imine 412. $^1$H NMR analysis of the imine usually showed varying amounts of unreacted benzaldehyde, from the imine formation step, to be present. For a successful [3+2] cycloaddition to take place, it was vital to adjust the number of equivalents of vinylcyclopropane 405 used, as benzaldehyde itself is an excellent trapping reagent that forms the unwanted furan by-product.

The cyclisation occurred in excellent yields to form the two geometric isomers 415a and 415b, which could be easily separated by column chromatography (Scheme 5.07). It was deduced that after the palladium had inserted into the double bond, reductive elimination, coupled with bond rotation lead to the generation of these
isomers. Interestingly, exclusively one diastereoisomer was formed with respect to the ring protons, with a \textit{syn} relative stereochemistry observed. This was confirmed by \textit{nOe} experiments.

\begin{center}
\begin{tikzpicture}

\node (405) at (0,0) {
  \begin{tikzpicture}
   \node (a) at (0,0) {
      \begin{tikzpicture}
       \draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
       \node at (0.5,0.5) {$\text{Br}$};
       \node at (0.5,0.75) {$\text{N}$};
       \node at (0.5,0.25) {$\text{Ph}$};
      \end{tikzpicture}
   \end{tikzpicture}
  \end{tikzpicture}
};

\node (412) at (3.5,0) {
  \begin{tikzpicture}
   \node (a) at (0,0) {
      \begin{tikzpicture}
       \draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
       \node at (0.5,0.5) {$\text{Br}$};
       \node at (0.5,0.75) {$\text{N}$};
       \node at (0.5,0.25) {$\text{Ph}$};
      \end{tikzpicture}
   \end{tikzpicture}
};

\node (415a) at (7,0) {
  \begin{tikzpicture}
   \node (a) at (0,0) {
      \begin{tikzpicture}
       \draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
       \node at (0.5,0.5) {$\text{Br}$};
       \node at (0.5,0.75) {$\text{N}$};
       \node at (0.5,0.25) {$\text{Ph}$};
      \end{tikzpicture}
   \end{tikzpicture}
};

\node (415b) at (10.5,0) {
  \begin{tikzpicture}
   \node (a) at (0,0) {
      \begin{tikzpicture}
       \draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
       \node at (0.5,0.5) {$\text{Br}$};
       \node at (0.5,0.75) {$\text{N}$};
       \node at (0.5,0.25) {$\text{Ph}$};
      \end{tikzpicture}
   \end{tikzpicture}
};

\node (a) at (5,0) {$\rightarrow$}
\end{tikzpicture}
\end{center}

Scheme 5.07 \textit{Reagents:} (a) \textit{Pd(PPh$_3$)$_4$} (10 mol%), ZnBr$_2$ (2 equivs), THF, RT, 18 h (90%).

Another crucial factor for a successful cyclisation was the order in which the reagents were introduced to the reaction mixture. To a solution of the vinylcyclopropane 405, must be added the imine 412, and then the zinc bromide. These must then be stirred at room temperature for 15 minutes before addition of the palladium catalyst. Any variation in this sequence of events, lead to both ring diastereoisomers and geometrical isomers being formed.

\section*{5.3 Investigations into C-ring closure}

Even though two geometrical isomers had been formed in the cycloaddition reaction, it was hoped that both compounds would still be suitable for the seven-membered ring closure. Initially it was reasoned that a reductive ring-closing procedure would be beneficial, as this would simultaneously close the ring and reduce the alkene of the $\alpha,\beta$-unsaturated system. This exocyclic carbon-carbon single bond mimics the arrangement found in stemoamide. Radical and halogen-metal exchange methods would theoretically carry out this transformation, so these were first examined (Scheme 5.08).
5.3.1 Radical methods for C-ring closure.

A variety of radical conditions were explored, using either Et<sub>3</sub>B or AIBN as the radical initiator (Table 5.01). In all cases starting material was recovered. The only curious result arose from reaction of cis-isomer 415b with Et<sub>3</sub>B in benzene. This lead to apparent isomerisation of the alkene double bond, and resulted in the trans-isomer 415a being formed in good yield.

<table>
<thead>
<tr>
<th>Pyrrolidine</th>
<th>Initiator</th>
<th>Propagator</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>415a</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Benzene</td>
<td>RT</td>
<td>17</td>
<td>SM</td>
</tr>
<tr>
<td>415a</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Toluene</td>
<td>RT</td>
<td>17</td>
<td>SM</td>
</tr>
<tr>
<td>415a</td>
<td>AIBN</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>CCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>100°C</td>
<td>17</td>
<td>SM</td>
</tr>
<tr>
<td>415a</td>
<td>AIBN</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Benzene</td>
<td>RT</td>
<td>17</td>
<td>SM</td>
</tr>
<tr>
<td>415b</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Benzene</td>
<td>RT</td>
<td>17</td>
<td>SM + 415a (85%)</td>
</tr>
<tr>
<td>415b</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Toluene</td>
<td>RT</td>
<td>17</td>
<td>SM</td>
</tr>
<tr>
<td>415b</td>
<td>AIBN</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>CCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>100°C</td>
<td>17</td>
<td>SM</td>
</tr>
<tr>
<td>415b</td>
<td>AIBN</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Benzene</td>
<td>RT</td>
<td>17</td>
<td>SM</td>
</tr>
</tbody>
</table>

Table 5.01
5.3.2 Halogen-Metal exchange methods for C-ring closure.

With no signs of the desired transformation occurring using radical means, halogen-metal protocols were next investigated (Table 5.02). Organolithium reagents were first examined, with the various isomers of butyl lithium. When n-BuLi was used, there was a new product isolated from the reaction. However, rigorous analysis of this compound suggested the vinyl halide to still be present, and the t-butyl group of the ester had disappeared. LC-MS experiments showed the [M+H]⁺ peak at 564, suggesting the double 1,2-addition of the butyl anion to the α,β-unsaturated system, to give the unwanted tertiary alcohol 416. In an attempt to prevent the formation of this by-product, the more sterically demanding t-BuLi was used. However, once again the apparent loss of the t-butyl group of the ester was observed, suggested compatibility issues with this functionality. Spectral analysis was unable to determine the exact structure of the product. The addition of CuI in an effort to soften any nucleophilic attack, and stimulate 1,4 addition to the Michael acceptor also failed. To ascertain if the t-butyl ester was in fact at the heart of the problem, the ethyl ester derivative 417 was synthesised, but similar compatibility issues were encountered.

The possibility of using a Grignard type addition was investigated, first by simply stirring the pyrrolidine E-415a with magnesium turnings. This only yielded starting material, and prompted a look at the literature for similar Grignard-type additions. Knochel et al. have recently reported the stereoselective addition of alkenylmagnesium reagents using i-PrMgCl.LiCl.³² This reagent dramatically increased the efficiency of the halogen-magnesium exchange process. However, attempts to apply this to our own system failed.
One final attempt to effect halogen-metal exchange was explored using a procedure by Mori et al., using a stannyl anion generated from Me$_3$SiSnBu$_3$ and CsF (Scheme 5.09). This method was used for 5-membered ring formation between a vinyl halide and an ester. It was hoped that this could be applied to carry out the same type of addition onto an $\alpha,\beta$-unsaturated system. Unfortunately, starting material was only ever recovered from the reaction mixture.

### Table 5.02 Conditions:
- $^a$ THF/H$_2$O quench;
- $^b$ THF/MeOH quench;
- $^c$ 2 M HCl quench.

<table>
<thead>
<tr>
<th>Entry</th>
<th>SM</th>
<th>R</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>415a</td>
<td>$t$-Bu</td>
<td>$n$-BuLi</td>
<td>THF</td>
<td>$-78^\circ$C</td>
<td>15 min</td>
<td>SM</td>
</tr>
<tr>
<td>2$^a$</td>
<td>415b</td>
<td>$t$-Bu</td>
<td>$n$-BuLi</td>
<td>THF</td>
<td>$-78^\circ$C</td>
<td>15 min</td>
<td>SM</td>
</tr>
<tr>
<td>3$^a$</td>
<td>415a</td>
<td>$t$-Bu</td>
<td>$n$-BuLi</td>
<td>THF</td>
<td>$-78^\circ$C $\rightarrow$ $-20^\circ$C</td>
<td>15 min</td>
<td>SM + 416 (54%)</td>
</tr>
<tr>
<td>4$^a$</td>
<td>415b</td>
<td>$t$-Bu</td>
<td>$n$-BuLi</td>
<td>THF</td>
<td>$-78^\circ$C $\rightarrow$ RT</td>
<td>2 h</td>
<td>SM + 416 (40%)</td>
</tr>
<tr>
<td>5$^a$</td>
<td>415a</td>
<td>$t$-Bu</td>
<td>$t$-BuLi</td>
<td>THF</td>
<td>$-78^\circ$C $\rightarrow$ $-20^\circ$C</td>
<td>15 min</td>
<td>Unknown By-product</td>
</tr>
<tr>
<td>6$^a$</td>
<td>415b</td>
<td>$t$-Bu</td>
<td>$t$-BuLi</td>
<td>THF</td>
<td>$-78^\circ$C $\rightarrow$ $-20^\circ$C</td>
<td>2 h</td>
<td>Unknown By-product</td>
</tr>
<tr>
<td>7$^b$</td>
<td>417</td>
<td>Et</td>
<td>$n$-BuLi</td>
<td>THF</td>
<td>$-78^\circ$C $\rightarrow$ RT</td>
<td>15 min</td>
<td>SM + 416 (67%)</td>
</tr>
<tr>
<td>8$^c$</td>
<td>415a</td>
<td>$t$-Bu</td>
<td>$t$-BuLi, CuI</td>
<td>THF</td>
<td>$-78^\circ$C $\rightarrow$ RT</td>
<td>1 h</td>
<td>Unknown By-product</td>
</tr>
<tr>
<td>9$^a$</td>
<td>415a</td>
<td>$t$-Bu</td>
<td>LDA</td>
<td>THF</td>
<td>$-78^\circ$C $\rightarrow$ reflux</td>
<td>3 h</td>
<td>Unknown By-product</td>
</tr>
<tr>
<td>10</td>
<td>415a</td>
<td>$t$-Bu</td>
<td>Mg turnings</td>
<td>Et$_2$O</td>
<td>Reflux</td>
<td>18 h</td>
<td>SM</td>
</tr>
<tr>
<td>11</td>
<td>415a</td>
<td>$t$-Bu</td>
<td>$i$-PrMgCl/LiCl</td>
<td>THF</td>
<td>$-40^\circ$C $\rightarrow$ RT</td>
<td>12 h</td>
<td>SM</td>
</tr>
<tr>
<td>12</td>
<td>415a</td>
<td>$t$-Bu</td>
<td>Me$_3$SiSnBu$_3$, CsF</td>
<td>DMF</td>
<td>0$^\circ$C $\rightarrow$ RT $\rightarrow$ 100$^\circ$C</td>
<td>12 h</td>
<td>SM</td>
</tr>
</tbody>
</table>
What was clear from these findings was the complete lack of insertion into the vinyl halide bond. Chemoselectivity issues lead to unwanted side reactions occurring on the ester group. This fruitless stage of the research meant other avenues had to be explored.

5.3.3 Heck coupling methods for C-ring closure.

Alternative routes were explored to close the seven-membered ring, involving palladium catalysed Heck couplings. This method would theoretically close the ring, leaving an exocyclic double bond, which would require selective reduction at a later stage in the synthesis (Scheme 5.09).

Previous work within the group had isolated Heck product \textit{E-418a} in an average yield of 42\%. Repetition of these conditions gave 39\% of the desired product. This was a disappointingly low yield at a critical stage of the synthesis, so in light of the success observed using palladium catalysts with \textit{DMSO} previously within this thesis, attempts were made to improve this yield. Satisfyingly, the Heck reaction worked in excellent yields using either triethylamine or sodium hydrogen carbonate as base.
(Table 5.03). Modifications were made to the reaction conditions in an attempt to effect a reductive Heck cyclisation. The powerful method of reductive Heck couplings has been previously studied within the literature, but efforts to apply similar conditions to our own system failed, with only starting material being isolated.

Interestingly, when the E-isomer 415a was subjected to these Heck conditions, geometrical isomerisation of the double bond was observed, leading to E-isomer 418a. It is important to note that the priorities around the alkene have changed during this transformation. For the opposite isomer Z-415b, similar isomerisation of the double bond occurs. It was reasoned that after oxidative insertion of palladium into the vinyl halide, carbometallation occurs to give the seven-membered ring. In the β-hydride elimination step that follows, the palladium and hydride must be coplanar for the reaction to take place, as this is a syn elimination process. Bond rotation must therefore dictate the stereochemical outcome of this reaction (Scheme 5.10).

<table>
<thead>
<tr>
<th>Pyrrolidine</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>415a</td>
<td>Pd(OAc)₂, PPh₃</td>
<td>DIPEA</td>
<td>DMF</td>
<td>RT</td>
<td>17</td>
<td>418a (39%)</td>
</tr>
<tr>
<td>415a</td>
<td>Pd(PPh₃)₄</td>
<td>Et₃N</td>
<td>DMSO</td>
<td>80°C</td>
<td>2</td>
<td>418a (95%)</td>
</tr>
<tr>
<td>415b</td>
<td>Pd(PPh₃)₄</td>
<td>Et₃N</td>
<td>DMSO</td>
<td>80°C</td>
<td>2</td>
<td>418b (90%)</td>
</tr>
<tr>
<td>415a</td>
<td>Pd(PPh₃)₄</td>
<td>NaHCO₃</td>
<td>DMSO</td>
<td>80°C</td>
<td>2</td>
<td>418a (92%)</td>
</tr>
<tr>
<td>415b</td>
<td>Pd(PPh₃)₄</td>
<td>NaHCO₃</td>
<td>DMSO</td>
<td>80°C</td>
<td>2</td>
<td>418b (96%)</td>
</tr>
<tr>
<td>415a¹³¹</td>
<td>Pd(PPh₃)₄</td>
<td>piperidine; HCOOH</td>
<td>DMF</td>
<td>80°C</td>
<td>24</td>
<td>SM</td>
</tr>
<tr>
<td>415a</td>
<td>Pd(PPh₃)₄</td>
<td>NaHCO₃; HCOOH</td>
<td>DMSO</td>
<td>80°C</td>
<td>18</td>
<td>SM</td>
</tr>
</tbody>
</table>

Table 5.03
Crystals of $E$-418a have previously been grown simply by evaporation of diethyl ether, and the configuration confirmed by X-ray crystallographic analysis (Figure 5.02). Various different conditions were tested to grow suitable crystals of $Z$-418b, however no crystals were ever isolated. NOe experiments confirmed the relative stereochemistry of both isomers of the Heck products.
$^1$H NMR analysis of both 418a and 418b showed some significant differences in proton environments. In 418a, H-3 is deshielded by the proximal carbonyl of the tert-butyl ester, and as such 0.91 ppm further downfield than H-3 in 418b. Conversely, H-5 in 418b sees an even larger shift downfield because of this deshielding effect, and is 1.20 ppm further downfield than H-5 in 418a (Figure 5.03).

![Figure 5.03 Deshielding effect as observed by $^1$H NMR](image)

At this stage, both Heck products 418a and 418b were recognised to be potential precursors to the tricyclic core of stemoamide. The arrangement of the tert-butyl ester in 418a meant a selective reduction of the exocyclic double bond was necessary before free rotation of this group would set the compound up for a lactonisation step. It was reasoned that the reverse stereochemistry observed in 418b, could allow the lactonisation to occur without the need to selectively reduce the exocyclic double bond. If the lactonisation were to work, an easier, non-selective alkene reduction would yield the desired product. The convergence of both synthetic pathways from different isomers to a single compound was very appealing (Scheme 5.11).
5.3.4 Tandem Palladium catalysed Azepine formation

At this stage it was recognised that to form azepine ring systems 418a and 418b, consecutive palladium catalysed processes had been employed. A short period of time was spent examining the possibility of carrying out a tandem [3+2] cycloaddition and Heck coupling process. This would in effect "zip up" the two halves of the molecule, forming three new C–C bonds, and defining two stereocentres in a single step. The first experiment simply combined all reagents for the two separate steps using 20 mol% of the palladium catalyst (Scheme 5.12).
None of the desired product was formed, with only the vinylcyclopropane 405 being recovered. Importantly, the cyclisation had failed to work prompting the question whether the cyclisation reaction actually works in DMSO, as previously this step had been carried out in THF. The cyclisation reaction was attempted in DMSO, however the cyclisation appeared to fail at 80°C and needed to be heated to 100°C before any cyclisation occurred. Unfortunately the pyrrolidine isolated, existed as an inseperable mixture of ring diastereoisomers, in modest yield (Scheme 5.13).

The lack of stereoselectivity and apparent reduction in reaction turnover, lead to a switching of solvent systems during the reaction (Scheme 5.14). The cyclisation was carried out in THF, before evaporating off the solvent and replacing it with DMSO for the Heck reaction. As expected, the cyclisation worked, but Heck coupling failed to progress, even upon the further addition of fresh palladium catalyst. This suggested a possible byproduct or remnant from the cyclisation reaction was interfering with the progress of the Heck reaction.
Another study simply added NaHCO₃ to the reaction mixture of the completed cyclisation reaction, but once again the Heck reaction failed to work. Closer scrutiny of the catalytic cycle is required to explore the range of additives or scavengers that could be introduced to the reaction, to make the transformation viable.

### 5.4 Investigation into direct lactonisation of Z-418b

Over the years there have been many protocols for lactone ring formation, the most common being halolactonisation methods. Previous syntheses of the *Stemona Alkaloids* have employed iodolactonisation and selenolactonisation methods for the incorporation of the crucial lactone ring, however, these methods require at least two steps for the transformation. The tert-butyl ester functionality present within our system was designed from an early stage to carry out the iodolactonisation step, without the need to hydrolyse the ester first.

The favourable conformation of the tert-butyl ester in Z-418b, led to efforts to form the final lactone ring of stemoamide prior to the reduction of the exocyclic double bond. The shorter bond length associated with the C=C double bond compared to that of a C=C single bond was considered to be a potential pitfall in the iodolactonisation. It was recognised that the transformation would probably be energetically less favourable than an iodolactonisation on a more conventional precursor, and as such harsher conditions may have been required. The tert-butyl ester group is known to carry out iodolactonisations directly, with the driving force behind the reaction being the loss of the stable tert-butyl cation, as proposed by Bartlett, who studied its
mechanism. Antonioletti et al. have recently developed iodolactonisation methodology in the diastereoselective synthesis of tetrastubstituted dihydrofurans, and it was with their conditions we decided to study our own system (Table 5.04). However, none of the desired product was formed, with the products isolated being difficult to unambiguously elucidate. The presence of the tert-butyl group by NMR was a key indicator that the reaction had failed to work, and as such with time restraints, this avenue of research was terminated.

Table 5.04

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, Na₂CO₃, dark¹³¹</td>
<td>DCM</td>
<td>RT</td>
<td>17</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>C, Na₂CO₃, dark</td>
<td>THF</td>
<td>RT</td>
<td>17</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>C, Na₂CO₃, dark</td>
<td>DCM</td>
<td>Reflux</td>
<td>17</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>C, Na₂CO₃, dark</td>
<td>THF</td>
<td>Reflux</td>
<td>17</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>


5.5 Selective reduction of the exocyclic double bond

With the failure of the iodolactonisation of Z-418b, investigations began on the selective reduction of the exocyclic double bond present in the other isomer E-418a. A successful reduction on this isomer would also be expected to work on the isomer Z-418b. There is a plethora of research within the literature concentrating on chemoselective reduction of α,β-unsaturated carbonyl compounds. Reagents which have previously been used for this conversion include CuI/LiAlH₄, homogenous metal hydride catalysts, Mg/MeOH, Li/EtNH₂, LDA, zinc-copper couple, LiAlH₄ in the presence of lanthanide salts, aqueous Zn-NiCl₂ under ultrasonication and Al-NiCl₂.¹³⁷

There is however far less research into α,β,γ,δ-unsaturated carbonyl compounds and their selective reduction, such as the system found in E-418a. The challenging problem associated with the selective reduction of these systems is enhanced because of three reducible positions. Birch reduction with lithium and ammonia produces β,γ-unsaturated carbonyl compounds. Hydrogenation with Ni-Al₂O₃ targets the γ,δ-unsaturated double bond, while the presence of Pb or Cd reduces the α,β-enone. Reduction of the α,β-double bond is also observed using a triallylsilane in the presence of either rhodium or platinum catalysts. The reduction of α,β,γ,δ-unsaturated carboxylic esters by trialkylsilane reagents in the presence of Wilkinson’s catalyst provides β,γ-unsaturated esters from acyclic molecules, whereas strained cyclic compounds, the α,β-double bond is reduced.¹³⁸ The number of different possible reduction pathways increases the complexity of the reaction, and the effect of the substrate on the chemoselectivity could potentially undermine any trend previously observed. A variety of selective reducing conditions were tested (Table 5.05).¹³⁸-¹⁴²
Entries 1-4 show metal-catalysed methods to reduce conjugated systems. The basis of these methods relies on a relatively unreactive source of hydride, coupled with a catalytic amount of a transfer reagent, to selectively reduce various electrophilic functionalities. Unfortunately regioselectivity problems were encountered in the case of entries 1 and 3, with the γ,δ-unsaturated double bond being reduced to give compound 419. The use of Stryker's reagent (entry 5) appeared to have no effect whatsoever. In light of the relative lack of reactivity observed with metal-catalysed reduction systems, it was decided to subject E-418a to slightly harsher dissolving metal conditions.

It is important to note that these reactions were carried out on a small scale (~0.1 mmol), and initial experiments using lithium metal in ammonia, suffered from lack of precision in measuring such small amounts of the metal solution. An excess of lithium was no doubt added, and this would potentially affect the course of the

---

**Table 5.05**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₂SiH₂, Pd(PP₃)₄, ZnCl₂</td>
<td>CHCl₃</td>
<td>RT</td>
<td>17</td>
<td>SM + 419 (60%)</td>
</tr>
<tr>
<td>2</td>
<td>InCl₃/NaBH₄</td>
<td>MeCN</td>
<td>RT</td>
<td>17</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>Rh(PP₃)₃Cl, PhMe₂SiH</td>
<td>THF</td>
<td>50°C</td>
<td>16</td>
<td>SM + 419 (33%)</td>
</tr>
<tr>
<td>4</td>
<td>Rh(PP₃)₃Cl, Et₃SiH</td>
<td>Benzene</td>
<td>RT</td>
<td>17</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>[PPh₃CuH]₆</td>
<td>Benzene</td>
<td>RT</td>
<td>17</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>Li/NH₃, t-BuOH</td>
<td>THF</td>
<td>−78°C</td>
<td>1</td>
<td>SM + 420 (40%)</td>
</tr>
<tr>
<td>7</td>
<td>Li/anthracene</td>
<td>THF</td>
<td>−78°C to RT</td>
<td>2</td>
<td>421 (80%)</td>
</tr>
</tbody>
</table>

---

SM refers to the starting material.
reaction. Interestingly, entry 6 appeared to reduce the conjugated system leaving a \( \beta,\gamma \)-unsaturated ester. However, closer examination of the new product by NMR showed the CH\(_2\) of the pyrrolidine ring had lost its characteristic diastereotopic proton signals. Further analysis confirmed the cleavage of the pyrrolidine ring to form compound 420 (Figure 5.04). This was a particularly frustrating stage of the research, as reduction of the conjugated system only to give a \( \beta,\gamma \)-unsaturated ester would nevertheless unveil a compound capable of being transformed into the lactone, via a method previously used by Mori (see Scheme 1.28). \(^{33}\)

![Figure 5.04 Isolated by-products from attempted selective reduction experiments](image)

It was decided to substitute the ammonia in the Li/NH\(_3\) system for anthracene in THF. These are a set of dissolving metal conditions, where lithium and anthracene are stirred in THF for 1-2 days, or until a deep green/blue colour is observed.\(^{142}\) The benefit of this system was that a measured solution of lithium anthacenide could be prepared, and stored for a couple of weeks, allowing far easier handling. Reaction of the lithium anthracenide with \( E-418a \) was complete after 1-2 hours, with a new spot by TLC forming at half the \( R_f \) value of the starting material. This was initially dubious, as the desired product should theoretically have a similar \( R_f \) value to that of the closely related starting material. Once again conjugate reduction had occurred, however, mass spectrometry confirmed a dimerisation process had occurred, leading to compound 421. Attempts were made to keep the reaction solution very dilute to avoid this problem, however recombination of two molecules was always observed. Due to time restraints, work was halted at this stage, but further work is necessary in order to gain more control over the course of the reaction.
5.6 Palladium catalysed [3+2] cycloadditions of isocyanates

The introduction of isocyanates into the palladium catalysed [3+2] cycloaddition methodology would incorporate the characteristic amide group found in stemoamide. To assess the tolerance of the palladium catalysed [3+2] cycloaddition to isocyanates, a range of substrates were examined (Table 5.06). Tsuji et al have previously observed the reaction of isocyanates with vinylcyclopropanes, however the use of highly toxic HMPA as reaction solvent was a major drawback.\textsuperscript{143}

\[
\text{Ph} \text{CO}_2\text{Me} + R - \text{N} = \text{C} = \text{O} \rightarrow \text{Ph} \text{CO}_2\text{Me} + R\text{N}=\text{C}=\text{O}
\]

\[
\text{Ph} \text{CO}_2\text{Me} + R - \text{N} = \text{C} = \text{O} \rightarrow \text{Ph} \text{CO}_2\text{Me} + R\text{N}=\text{C}=\text{O}
\]

Table 5.06

<table>
<thead>
<tr>
<th>R</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Pd(PPh(_3))(_4)</td>
<td>DMSO</td>
<td>2</td>
<td>422 (59%) + 342</td>
</tr>
<tr>
<td>Ph</td>
<td>Pd(PPh(_3))(_4)</td>
<td>THF</td>
<td>2</td>
<td>SM + 342</td>
</tr>
<tr>
<td>Bn</td>
<td>Pd(PPh(_3))(_4)</td>
<td>DMSO</td>
<td>2</td>
<td>SM + 342</td>
</tr>
<tr>
<td>Bn</td>
<td>Pd(PPh(_3))(_4), ZnBr(_2)</td>
<td>THF</td>
<td>2</td>
<td>SM + 342</td>
</tr>
<tr>
<td>Et</td>
<td>Pd(PPh(_3))(_4)</td>
<td>DMSO</td>
<td>2</td>
<td>SM + 342</td>
</tr>
</tbody>
</table>

Phenyl isocyanate was the only substrate that was successfully cyclised. The desired compound was stable to aqueous workup and column chromatography. In all cases, between 5-50\% of the reaction mixture was accounted for by the oxidised vinylcyclopropane adduct 342. Even though this was an isolated example of the application of isocyanates, it was a promising result. It indicated that the introduction of the amide portion of the pyrrolidinone ring in the cyclisation step was a real possibility.
Chapter Six

6.1 Conclusion and Future Work

Good progress has been made towards a general strategy for the construction of closely related analogues of the *Stemona Alkaloids*. The palladium catalysed [3+2] cycloaddition of functionalised vinylcyclopropane 405 and acyclic imine 412 proceeded in good yields, to form exclusively one diastereoisomer with respect to the ring protons, and a mixture of geometric alkene isomers. Two avenues of research focussed on reductive cyclisation and Heck methods were pursued to close the seven-membered ring. No success was seen with the reductive methods examined, however, this is an area of research which would benefit from more study, as this would be a more efficient and elegant route to the desired stemona skeleton. The Heck coupling worked extremely well to give 418a and 418b, which were both studied as intermediates for the same target molecule (Scheme 6.01).

Initial work on the selective reduction of the exocyclic double bond has proved problematic, with unwanted reduction pathways occurring. However, some success
has been seen in the conjugate reduction of the \( \alpha,\beta,\gamma,\delta \)-unsaturated ester, to give a \( \beta,\gamma \)-unsaturated dimer. Other single electron transfer processes and conditions must be examined to try and impede this dimerisation process, as the resultant \( \beta,\gamma \)-unsaturated carboxylic acid would be expected to ring-close in a bromolactonisation step outlined by Mori et al (Scheme 6.02).\(^{33}\)

![Scheme 6.02 Possible bromolactonisation procedure](image)

If problems were to persist with the selective reduction of the exocyclic double bond, it would be theoretically possible to exploit the more accessible and reactive nature of the endocyclic double bond in a dihydroxylation step. The lactone ring could then be formed under acid catalysis (Scheme 6.03).

![Scheme 6.03 Functionalisation of the endocyclic double bond](image)

Until now, it can be assumed that the \( \alpha \)-methyl group on the lactone ring, as found in stemoamide, could be introduced in a late stage alkylation step. However, it is possible that this methyl group could be introduced at a much earlier stage, and incorporated into the functionalised vinylcyclopropane, using a suitable Wittig reagent (Scheme 6.04).
With the promise shown by isocyanates as trapping reagents in the palladium catalysed [3+2] cycloaddition, it is envisaged that a suitable acyclic isocyanate could be synthesised and this reacted with the methyl-substituted functionalised vinylcyclopropane. After further manipulation, a compound such as 423 could be accessed, with the possibility of carrying out a double decarbonylation of the original diester functionality, by virtue of the adjacent carbonyl of the amide group (Scheme 6.05).

Further work needs to be carried out into the various groups which can be introduced onto the acyclic imine. Work towards stemonine would need an acyclic imine precursor with either the lactone ring already present, or a masked lactone, such as a furan, which could be readily oxidised to the desired lactone oxidation level (Scheme 6.06).
Scheme 6.06 Varying the acyclic imine substrate
Chapter Seven

7.1 General information

7.1.1. Solvents and Reagents

All solvents and reagents were purified by standard techniques as reported in Perrin. D.D.; Armarego, W. L. F., Purification of Laboratory Chemicals, 3rd edition. Pergamon Press, Oxford, 1998 or as used as supplied from commercial sources as appropriate.

Reagent chemicals were purchased from Aldrich Chemical Company Ltd., Lancaster Chemical Synthesis Ltd., Acros (Fischer) Chemicals Ltd. and Avocado. Commercially available reagents were used as supplied, without further purification unless otherwise stated. Air- and moisture-sensitive reactions were carried out using glassware that had been dried overnight in an oven at 240°C. The reactions were carried out under a slight positive static pressure of nitrogen unless otherwise stated.

Solvents where necessary, were dried and stored over 4Å molecular sieves prior to use. Molecular sieves were activated at 240°C over a period of 3 days. 40-60 petroleum ether (P.E. 40-60) refers to the fraction of the light petroleum ether which boils between 40-60°C. DCM, Et₂O, MeOH, EtOH and THF refer to dichloromethane, diethyl ether, methanol, ethanol and tetrahydrofuran respectively.

7.1.2. Chromatographic Procedures

Analytical thin layer chromatography (TLC) was conducted using aluminium or glass backed plates coated with 0.25 mm silica containing fluorescer. Plates were visualised by quenching of UV light (254 nm) as well as through staining with 1% vv/v potassium permanganate in aqueous alkaline solution followed by heat where appropriate. Flash chromatography was conducted using Merck Kieslgel (70-230 Mesh ASTM) as the stationary phase unless otherwise stated. Samples were applied
as saturated solutions in the appropriate solvent. Pressure was applied to the column by use of hand bellows.

7.1.3. FT-IR

Infra-red spectroscopy (IR) was conducted in the range of 4000-600 cm\(^{-1}\), using a Perkin-Elmer Fourier Transform Paragon 1000 spectrophotometer (with internal calibration). Samples were dissolved in appropriate solvent and applied as thin film to the NaCl plates. Liquid samples were applied neat to the plate and run as thin films. Only major absorbencies have been quoted.

7.1.4. \(^1\)H NMR

Proton magnetic resonance spectra (\(^1\)H NMR) were recorded at 250, 400 or 500 MHz using a Brüker AC-250, Brüker DPX-400 or Brüker DPX-500 spectrometer as solutions of deuterated CDCl\(_3\) unless otherwise specified. Chemical shifts (\(\delta_{HH}\)) were quoted as parts per million (ppm) and are referenced to the residual solvent peak tetramethylsilane (TMS) as the internal standard. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q) multiplet (m) and broad (br). Assignment of individual proton signals was assisted by analysis of \(^1\)H COSY spectra and nOe data. Coupling constants (\(J\) values) are reported in Hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the \(^1\)H NMR spectra.

7.1.5. \(^{13}\)C NMR

Carbon magnetic resonance spectra (\(^{13}\)C NMR) at 100 MHz using a DPX-400 spectrometer were recorded as solutions of deuterated CDCl\(_3\) unless otherwise specified. (\(\delta_{CH}\)) were quoted as parts per million (ppm) and are referenced to the residual solvent peak tetramethylsilane (TMS) as the internal standard. Assignment of individual carbon signals was assisted by DEPT and HMQC data.
7.1.6. Mass Spectra

Mass spectra (high/low resolution) were recorded using a Fisons VG Quattro II SQ instrument, with modes of ionisation being indicated as electron impact (EI) and fast atom bombardment (FAB) and electron spray (ES) with only the molecular ion, molecular ion fragments and major peaks being reported. Accurate masses were recorded using a Kratos MS-80 instrument. Elemental analysis was performed by Mr J. Kershaw, Department of Chemistry, Loughborough University and by the ESPRC National mass spectrometry service in Swansea.

7.1.7. Other Data

Melting points where appropriate were determined using an electrical 9100 Thermal Melting point instrument and are uncorrected. Yields (unless otherwise stated) are quoted for isolated pure products.
7.2 Experimental procedures

2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (259)\textsuperscript{55}

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{array}
\]

To a solution of sodium methoxide prepared from sodium (2.30 g, 100 mmol) in methanol (40 ml) was added dimethyl malonate (11.42 ml, 100 mmol) and a methanolic solution of trans-1,4-dibromobut-2-ene (10.70 g, 50 mmol in 40 ml methanol). The mixture was refluxed for 19 h to give a colourless solution. The mixture was cooled to room temperature, and the white precipitate formed (NaBr), filtered and discarded, before reducing the filtrate in vacuo. The residue was dissolved in ethyl acetate (60 ml) and washed with distilled water (3 x 60 ml) and saturated brine solution (20 ml), dried over MgSO\textsubscript{4} and evaporated under reduced pressure to give a pale yellow oil. Purification by column chromatography (SiO\textsubscript{2}, 40-60 P.E: ethyl acetate; 6:1) afforded vinyl cyclopropane 259 (8.29 g, 82%) as a colourless oil. \(\nu_{\text{max}}\) (thin film)/cm\textsuperscript{-1} 2954 s (C-H str), 1732 s (C=O str), 1614 m (C=C str), 1434 s, 1334 s, 1274 s, 1210 s, 1132 s, 991 m, 920 m; \(\delta_H\) (250 MHz, CDCl\textsubscript{3}) 5.40-5.30 (1H, m, 4-CH), 5.23 (1H, d, \(J=16.0\) Hz, 5-C(H)H), 5.08 (1H, d, \(J=10.0\) Hz, 5-C(H)H), 3.73 (6H, s, 2 x OCH\textsubscript{3}), 2.53-2.62 (1H, m, 2-CH), 1.71 (1H, dd, \(J=5.0\) and 7.5 Hz, 3-C(H)H), 1.57 (1H, dd, \(J=5.0\) and 9.0 Hz, 3-(H)H); \(\delta_c\) (100 MHz, CDCl\textsubscript{3}) 170.06, 167.83 (2 x C=O), 132.96 (4-C), 118.75 (5-C), 52.77 (OCH\textsubscript{3}), 52.64 (OCH\textsubscript{3}), 35.74 (1-C), 31.53 (2-C), 20.64 (3-C).
Bis(1-pyrroline)diiodozinc (276)

\[
\begin{array}{c}
\text{I} \\
\text{Zn} \\
\text{I}
\end{array}
\]

4-Aminobutanal diethylacetal (2.34 g, 14.5 mmol) was dissolved in 2 M HCl (20 ml) and diethyl ether (50 ml) was added. The mixture was stirred at 0 °C for 20 min, and then basified with K$_2$CO$_3$. The aqueous layer was extracted with cold diethyl ether (3 x 50 ml). The combined diethyl ether extracts were dried and filtered at 0 °C, and anhydrous zinc iodide (2.08 g, 7.2 mmol) was added. The mixture was stirred at 0 °C under nitrogen for 30 min. The precipitate was filtered off and washed with cold diethyl ether to give a cream powder (0.83 g, 26%). mp 120-124°C [lit mp 120-122°C]; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1636 s (C=N str), 961 m; $\delta_{\text{H}}$ (400 MHz, DMSO-d$_6$) 7.77 (1H, br s, 2-CH), 3.77-3.72 (2H, m, 5-CH$_2$), 2.61 (2H, br t, $J$ 8.5 Hz, 3-CH$_2$), 1.78 (2H, quintet, $J$ 8.5 and 15.6 Hz, 4-CH$_2$); $\delta_{\text{c}}$ (100 MHz, DMSO-d$_6$) 171.12 (2-C), 59.93 (5-C), 36.31 (3-C), 19.84 (4-C).

Bis (1-piperideine)diiodozinc (278)

\[
\begin{array}{c}
\text{I} \\
\text{Zn} \\
\text{I}
\end{array}
\]

To a stirred solution of piperidine (1.00 g, 11.8 mmol) in dry diethyl ether (30 ml) was added tert-butyl hypochlorite (1.17 g, 11.8 mmol) to give a colourless solution with small amounts of a white suspension. This was stirred for 30 min under a nitrogen atmosphere. 18-Crown-6 (30 mg, 0.11 mmol) in diethyl ether (1 ml) and potassium superoxide (1.79 g, 25 mmol) were added to give a yellow slurry. This was stirred for 21 h resulting in a beige coloured mixture that was filtered using diethyl ether washings (2 x 15 ml) and to the filtrate was added zinc iodide (1.88 g, 5.89
mmol). The filtrate was vigorously stirred for 1 h under a nitrogen atmosphere yielding the zinc complex 278 (2.26 g, 80%) as a white precipitate. mp 125-129°C; υ\text{max} (thin film)/cm\textsuperscript{-1}: 2943m, 1653s (C=N str), 1445m, 1389m, 1108m, 1041m; δ\textsubscript{H} (250 MHz, CDCl\textsubscript{3}) 8.45 (1H, s, 2-CH), 3.82-3.69 (2H, m, 6-CH\textsubscript{2}), 2.55-2.45 (2H, m, 3-CH\textsubscript{2}), 1.79-1.50 (4H, m, 4 and 5-CH\textsubscript{2}).

tert-Butyl hypochlorite

\[ \text{OC}l \]

Sodium hypochlorite (200 ml) was placed in a silver-foil covered RBF. The reaction vessel temperature was kept below 10°C with rapid stirring before a solution of t-butyl alcohol (14.8 ml, 0.16 mmol) and glacial acetic acid (9.8 ml, 0.17 mmol) was added in a single portion. The mixture was stirred for 5 min, poured into a separating funnel and the aqueous layer discarded. The oily yellow layer was washed with 10% Na\textsubscript{2}CO\textsubscript{3} (50 ml) aqueous solution and then distilled water (50 ml). The resultant yellow oil was dried over CaCl\textsubscript{2}, filtered into a dark glass container with glass stopper (12.3 g, 80%), and used without further purification. δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.35 (9H, s, 3 x CH\textsubscript{3}); δ\textsubscript{c} (100 MHz, CDCl\textsubscript{3}) 83.93 (C(CH\textsubscript{3})), 26.80 (C(CH\textsubscript{3})).

Bis (1-piperideine)diiodozinc (279)

To a stirred solution of homopiperidine (1.00 g, 10.1 mmol) in dry diethyl ether (30 ml) was added tert-butyl hypochlorite (1.00 g, 10.1 mmol) to give a colourless solution with a small amount of a white suspension. This was stirred for 30 min under a nitrogen atmosphere. 18-Crown-6 (30 mg, 0.11 mmol) in diethyl ether (1 ml) and potassium superoxide (1.80 g, 25.0 mmol) were added to give a slurring yellow
mixture. This was stirred for 21 h resulting in a beige coloured mixture which was filtered and washed with diethyl ether (2 x 15 ml) and to the filtrate was added zinc iodide (1.88 g, 5.89 mmol). The filtrate was vigorously stirred for 1 h under a nitrogen atmosphere yielding the zinc iodide complex 279 as a cream precipitate (2.00 g, 40%). The product was used directly in the next step without further purification. mp = 141-144°C.

3-Vinylhexahydropyrrolizine-1,1-dicarboxylic acid dimethyl ester (280)

Vinylcyclopropane 259 (100 mg, 0.54 mmol) and tetrakis(triphenylphosphine) palladium(0) (64 mg, 0.054 mmol) in anhydrous DMSO (2 ml) were stirred at room temperature under nitrogen for 10 min before adding zinc complex 276 (147 mg, 0.32 mmol). The mixture was heated to 80°C for 1 h before cooling to room temperature. ethyl acetate (10 ml) was added to the mixture and this washed with distilled water (5 x 10 ml) and brine (2 x 10 ml). The organic layer was separated and then partitioned with aqueous 2 M HCl (15 ml). The aqueous layer was basified with saturated NaHCO₃ (15 ml). Ethyl acetate (3x10 ml) was used to extract the product and the combined extracts were dried over MgSO₄ and concentrated to give pyrolizidine 280 (90 mg, 65%) as an orange oil. υ max (thin film)/cm⁻¹: 2950m, 2870m (C-H str), 1736m (C=O str), 1430m, 1269s, 1241s, 1200s, 1140m, 1100m, 994w, 922m; δH (400 MHz, CDCl₃) 5.62 (1H, ddd, J 7.5, 10.0 and 17.2 Hz, 9-CH), 5.15 (1H, ddd, J 1.0, 1.7 and 17.2 Hz, 10-C(H)H), 4.81 (1H, ddd, J 1.0, 1.7 and 10.0 Hz, 10-C(H)H), 4.18 (1H, dd, J 6.8 and 9.1 Hz, 8-CH), 3.67 (6H, s, 2 x OCH₃), 3.37-3.28 (1H, m, 3-CH), 2.92-2.80 (1H, m, 5-C(H)H), 2.73-2.68 (1H, dd, J 6.0 and 12.5 Hz, 2-(C(H)H), 2.61-2.58 (1H, m, 5-C(H)H), 2.02-1.97 (1H, dd, J 10.0 and 12.5 Hz, 2-(C(H)H), 1.90-1.69 (3H, m, 7-C(H)H and 6-CH₂), 1.38-1.35 (1H, m, 7-C(H)H); δc (100 MHz, CDCl₃) 171.46, 171.00 (2 x C=O), 140.11 (10-C), 116.12 (11-C), 69.39 (8-C), 68.08 (3-C), 61.40 (1-C), 52.45, 52.82 (2 x OCH₃), 52.15 (5-C), 41.59 (2-C), 28.09 (7-C), 26.06 (6-C); m/z
Vinylecyclopropane 259 (100 mg, 0.54 mmol) and tetrakis(triphenylphosphine) palladium(0) (64 mg, 0.054 mmol) in anhydrous DMSO (2 ml) were stirred at room temperature under nitrogen for 10 min before adding zinc complex 310 (144 mg, 0.32 mmol). The mixture was heated to 80°C for 1 h before cooling to room temperature. Ethyl acetate (10 ml) was added to the mixture and this washed with distilled water (5 x 10 ml) and brine (2 x 10 ml). The organic layer was separated and then partitioned with aqueous 2 M HCl (15 ml). The aqueous layer was basified with saturated aqueous NaHCO₃ (15 ml). Ethyl acetate (3x10 ml) was used to extract the product and the combined extracts were dried over MgSO₄ and concentrated to give indolizidine 281 (61 mg, 42%) as an orange oil. 

\[
\begin{align*}
\text{max}^* (\text{thin film})/\text{cm}^{-1} & \quad 2949s, 2855w, 1736m (\text{C=O str}), 1648w (\text{C=C str}), 1434s, 1382m, 1275s, 1245s, 1202m, 1147m, 994m; \\
\delta_{\text{H}} & \quad (400 \text{ MHz, } \text{CDCl}_3) 6.00 (1\text{H}, \text{ddd}, J=8.4, 10.0 \text{ and } 17.2 \text{ Hz}, 10-\text{C}), 5.14 (1\text{H}, \text{dd}, J=1.6 \text{ and } 17.2 \text{ Hz}, 11\text{-C(H)H}), 5.09 (1\text{H}, \text{dd}, J=1.6 \text{ and } 10 \text{ Hz}, 11\text{-C(H)H}), 3.46, 3.43 (6\text{H}, \text{s}, \text{2 x OCH}_3), 3.15 (1\text{H}, \text{br d}, J=10.8 \text{ Hz}, 5\text{-C(H)H}), 2.99 (1\text{H}, \text{dd}, J=2.4 \text{ and } 10.8 \text{ Hz}, 9\text{-CH}), 2.70 (1\text{H}, \text{dd}, J=8.4 \text{ and } 13.4 \text{ Hz}, 2\text{-C(H)H}), 2.67 (1\text{H}, \text{q}, J=8.4 \text{ Hz}, 3\text{-CH}), 2.32 (1\text{H}, \text{dd}, J=8.4 \text{ and } 13.4 \text{ Hz}, 2\text{-C(H)H}), 2.32-2.26 (1\text{H}, \text{m}, 8\text{-C(H)H}), 1.83-1.70 (2\text{H}, \text{m}, 5\text{-C(H)H} \text{ and } 6\text{-C(H)H}), 1.60-1.20 (4\text{H}, \text{m}, 6\text{-C(H)H}, 7\text{-CH}_2 \text{ and } 8\text{-C(H)H}); \\
\delta_{\text{C}} & \quad (100 \text{ MHz, } \text{CDCl}_3) 171.48, 170.27 (2 \times \text{C=O}), 139.83 (10\text{-C}), 116.88 (11\text{-C}), 69.18 (9\text{-C}), 68.04 (3\text{-C}), 61.01 (1\text{-C}), 51.76 (5\text{-C}), 51.68, 51.57 (2 \times \text{OCH}_3), 38.48 (2\text{-C}), 28.68 (6\text{-C}), 24.99 (8\text{-C}), 24.43 (7\text{-C}); m/z (FAB+) 267 (52), 236 (36), 208 (31), 148 (20), 123 (57), 95 (21), 83 (22), 81 (28), 69 (33), 67 (24), 57 (33); \text{HRMS} \text{ found } 267.1468 [\text{M}^+]^*, [\text{C}_{14}\text{H}_{25}\text{NO}_4]^+ \text{ requires } 267.1471.
\end{align*}
\]
3-Vinyl octahydropyrrolo[1,2-a]azepine-1,1-dicarboxylic acid dimethyl ester (284)

Vinylcyclopropane 259 (100 mg, 0.54 mmol) and tetrakis(triphenylphosphine)palladium(0) (64 mg, 0.054 mmol) in anhydrous DMSO (2 ml) were stirred at room temperature under nitrogen for 10 min before adding zinc complex 312 (167 mg, 0.32 mmol). The mixture was heated to 80°C for 1 h before cooling to room temperature. Ethyl acetate (10 ml) was added to the mixture and this was washed with distilled water (5 x 10 ml) and brine (2 x 10 ml). The organic layer was separated and then partitioned with aqueous 2 M HCl (15 ml). The aqueous layer was basified with saturated aqueous NaHCO₃ (15 ml). Portions of ethyl acetate (3x10 ml) were then used to extract the product and the combined extracts were dried over MgSO₄ and concentrated to give azepine 284 (137 mg, 90%) as an orange oil. δH (400 MHz, CDCl₃) 5.65-5.52 (1H, ddd, J 8.0, 10.0 and 17.0 Hz, 11-CH), 5.08 (1H, ddd, J 1.0, 2.0 and 17.0 Hz, 12-C(Η)H), 5.02 (1H, dd, J 2.0 and 10.0 Hz, 12-C(Η)H), 3.68, 3.65 (6H, 2 x s, 2 x OCH₃), 3.30-3.27 (1H, m, 10-CH), 2.85-2.75 (1H, m, 5-C(Η)H), 2.75-2.65 (1H, m, 3-CH), 2.41-2.31 (1H, dd, J 10.0 and 14.0 Hz, 2-C(Η)H), 2.20-2.10 (2H, m, 2-C(Η)H and 5-C(Η)H), 1.69-1.39 (7H, m, 6-CH₂, 8-CH₂, 9-CH₂ and 7-C(Η)H), 1.37-1.25 (1H, m, 7-C(Η)H); δc (100 MHz, CDCl₃) 172.30, 170.50 (2 x C=O), 140.24 (11-C), 116.99 (12-C), 68.62 (10-C), 67.18 (3-C), 62.33 (1-C), 52.76, 52.37 (2 x OCH₃), 51.49 (5-C), 38.86 (2-C), 31.35, 28.66, 26.04, 25.60 (6-C, 7-C, 8-C and 9-C); m/z (Cl+) 282 (100), 180 (48), 134 (26), 100 (27), 98 (49); HRMS found 282.1699 [M+H]⁺, [C₁₅H₂₃NO₄+H]⁺ requires 282.1700.
Vinylcyclopropane 259 (100 mg, 0.54 mmol) and tetrakis(triphenylphosphine) palladium(0) (64 mg, 0.054 mmol) in anhydrous DMSO (2 ml) were stirred at room temperature under nitrogen for 10 min before adding 6,7-dimethoxy-3,4-dihydroisoquinoline•HCl (136 mg, 0.60 mmol). The mixture was heated to 80°C for 1 h before cooling to room temperature. Ethyl acetate (10 ml) was added to the mixture and this washed with distilled water (5 x 10 ml) and brine (2 x 10 ml). The organic layer was separated and then partitioned with 2 M HCl (15 ml). The aqueous layer was basified with saturated NaHCO₃ (15 ml). Portions of ethyl acetate (3 x 10 ml) were then used to extract the product and the combined extracts were dried over MgSO₄ and concentrated to give an orange oil. Purification by column chromatography (SiO₂, 40-60 P.E:ethyl acetate, 6:1) gave indolizidine 290 (120 mg, 59%, 5:4) as an inseparable mixture of diastereoisomers. νmax (thin film)/cm⁻¹ 2999w, 2950w, 2836w (C-H str), 1737m (C=O str), 1651m (C=C str), 1602m, 1513s, 1434s, 1342s, 1275s, 1138m, 930w; δH (400 MHz, CDCl₃) 6.95 (1H, s, 7-CH), 6.92 (1H, s, 7-CH'), 6.50 (1H, s, 10-CH'), 6.48 (1H, s, 10-CH), 5.76 (1H, ddd, J 8.0, 10.0 and 17.0 Hz, 14-CH'), 5.69-5.61 (1H, ddd, J 8.0, 10.0 and 17.0 Hz, 14-CH'), 5.24 (1H, s, 5-CH), 5.22-5.10 (4H, m, 15-CH₂ and 15-CH₂'), 4.06 (1H, s, 5-CH'), 3.98-3.90 (1H, m, 3-CH), 3.79-3.74 (6 x s, CO₂CH₃, CO₂CH₃'), 2 x OCH₃ and 2 x OCH₃'), 3.37 (3H, s, CO₂CH₃'), 3.11 (3H, s, CO₂CH₃), 3.18-3.09 (1H, m, 13-C(H)H), 3.08-3.00 (1H, m, 13-C(H)H'), 3.00-2.88 (2H, m, 13-C(H)H and 3-CH'), 2.76-2.64 (2H, m, 13-C(H)H' and 12-C(H)H'), 2.63-2.55 (2H, m, 12-C(H)H and 2-C(H)H'), 2.50 (2H, d, J 8.0 Hz, 2-CH₂'), 2.37-2.22 (2H, m, 12-C(H)H and 12-C(H)H'), 2.09 (1H, dd, J 8.0 and 13.0 Hz, 2-C(H)H); δc (100 MHz, CDCl₃) 172.81, 172.15, 171.05, 171.02 (2 x C=O and 2 x C=O'), 147.43, 147.28 (9-C and 9-C'), 146.80, 146.25 (8-C and 8-C'), 139.89 (14-C') 138.08 (14-C), 128.89, 127.76, 126.
30, 126.10 (6-C, 11-C, 6-C' and 11-C'), 118.66 (15-C), 117.60 (15-C'), 110.95 (10-
C'), 110.83 (7-C), 110.77 (10-C), 109.92 (7-C'), 69.65 (5-C'), 65.90 (3-C'), 65.43 (1-
C), 65.12 (5-C), 64.89 (3-C), 62.24 (1C'), 55.84, 55.69 (2 x OMe and 2 x OMe'),
52.89, 52.85, 52.38, 52.07 (2 x CO₂Me and 2 x CO₂Me'), 45.76 (13-C), 44.19 (13-
C'), 40.34 (2-C'), 39.75 (2-C), 24.41 (12-C and 12-C'); m/z (FAB+) 376 (66), 375
(23), 374 (58), 344 (40), 279 (27), 231 (100), 230 (48), 192 (27); HRMS found
375.1687 [M]+, [C₂₀H₂₅NO₆Zn]+ requires 375.1760.

Bis (6,7-dimethoxy-3,4-dihydroisoquinoline)dilodinozinc (291)

To a stirred solution of 6,7-dimethoxy-3,4-dihydroisoquinoline HCl hydrate (200 mg,
0.88 mol) in diethyl ether (10 ml) was added zinc iodide (140 mg, 0.44 mmol) and the
mixture vigorously stirred at room temperature for 30 min under a nitrogen
atmosphere. The precipitate was filtered under suction and washed with diethyl ether
to give zinc complex 291 (211 mg, 81%) as a pale yellow powder. mp 180-182°C; δ_H
(250 MHz, DMSO-d₆) 8.95 (1H, s, 2-CH), 7.52 (1H, s, 4-CH), 7.18 (1H, s, 7-CH),
3.93 (3H, s, OMe), 3.86 (2H, t, J 8.2 Hz, 10-CH₂), 3.81 (3H, s, OMe), 3.07 (2H, t, J
8.2 Hz, 9-CH₂); δ_C (100 MHz, DMSO-d₆) 164.33 (2-C), 156.39 (5-C), 147.84 (6-C),
133.42 (3-C), 116.70 (8-C), 115.25 (4-C), 111.52 (7-C), 56.40 (OMe), 55.86 (OMe),
40.75 (10-C), 23.65 (9-C).
2-Formyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (292). (Method A)

To a stirred solution of acrolein (356 mg, 6.36 mmol) and potassium carbonate (1.32 g, 9.53 mmol) in anhydrous DMF (20 ml), was added dimethyl bromomalonate (1.00 g, 4.76 mmol). The reaction mixture was stirred for 2 h at room temperature, under an atmosphere of nitrogen to give a yellow solution. Aqueous 2 M HCl was added to neutralise the reaction mixture, and this extracted into diethyl ether (2 x 20 ml). The combined organic fractions were washed with distilled water (4 x 20 ml) and brine (4 x 20 ml), dried over MgSO₄, and evaporated under reduced pressure to give the cyclopropane 292 (709 mg, 60%) as a yellow oil, suitable for use without need for further purification.

\[
\begin{align*}
&\text{O}^4 \\
&\text{C}^2 & \text{O}_2\text{Me} \\
&\text{C}^3 & \text{C}^2 \text{Me}_2
\end{align*}
\]

\[\text{O}_2\text{Me} \]

\[\text{U}_{\text{max}} \ (\text{thin film})/\text{cm}^{-1} \ 3012m, 2956m, 2850m \ (\text{C-H str}), 1734s \ (\text{C}=\text{O} \ \text{str}), 1437m, 1270s \ (\text{C}-\text{O}), 1211m, 1133m; \ \delta_{\text{H}} \ (400 \text{ MHz, CDCl}_3) 9.30 \ (1\text{H, d, } J 5.4 \text{ Hz, 4-CH}), 3.71 \ (6\text{H, s, } 2 \ \times \ \text{OMe}), 2.04-2.01 \ (1\text{H, dd, } J 5.4 \text{ and } 8.8 \text{ Hz, 2-C(H)H}), 1.76-1.75 \ (1\text{H, dd, } J 5.4 \text{ and } 8.8 \text{ Hz, 2-C(H)H}); \ \delta_{\text{C}} \ (100 \text{ MHz, CDCl}_3) 196.32 \ (4-\text{C}), 168.37, 166.44 \ (2 \ \times \ \text{C}O_2\text{Me}), 53.22 \ (2 \ \times \ \text{OMe}), 37.58 \ (1-\text{C}), 34.88 \ (3-\text{C}), 19.71 \ (2-\text{C}).
\]

2-Formyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (292). (Method B)

Vinylcyclopropane 259 (6.40 g, 34.8 mmol) in DCM (50 ml) was treated with ozone at -78°C for 2 h, or until the reaction mixture turned blue. The reaction was quenched with dimethylsulfoxide (13.5 g, 217 mmol), and allowed to stir open to the air, at room temperature overnight. The colourless oil was then dissolved in ethyl acetate (30 ml) and washed with water (30 ml) and brine solution (2 x 30 ml). The organic portion was dried over MgSO₄ and evaporated under reduced pressure to give the cyclopropane 292 (5.00 g, 77%). Data as for Method A.
2-(2-Ethoxycarbonylvinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (294)¹⁰⁰

![Diagram of 2-(2-Ethoxycarbonylvinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester]

To a stirred solution of carbethoxymethyl triphenylphosphonium bromide (1.60 g, 3.72 mmol) in anhydrous THF (20 ml) at 0°C, was added n-BuLi (1.48 ml, 3.72 mmol, 2.5 M in THF). The yellow reaction mixture was stirred under a nitrogen atmosphere for 10 min, before the addition of 2-formyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester 292 (350 mg, 1.86 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for a further 2 h. The reaction was quenched with saturated aqueous NaHCO₃ (15 ml) at 0°C. Ethyl acetate (20 ml) was added to the biphasic system, and the organic layer extracted with distilled water (3 x 20 ml) and brine (3 x 20 ml). The combined aqueous fractions were back-extracted into ethyl acetate (20 ml), and the combined organic fractions dried over MgSO₄ and evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (SiO₂, 40-60 P.E:ethyl acetate; 7:1) afforded the vinylcyclopropane 294 (290 mg, 61%) as a colourless oil. \( \nu_{\text{max}} \) (thin film)/cm⁻¹: 2982w, 2955w, 2904w, 2848w (C–H str), 1731s (C=O), 1649m (C=O str), 1437s, 1380s, 1331s (C–O), 1254m, 1199s, 1131s; \( \delta_d \) (400 MHz, CDCl₃) 6.41-6.34 (1H, dd, J 7.4 and 9.0 Hz, 4-CH), 6.00 (1H, d, J 9.0 Hz, 5-CH), 4.13-4.08 (2H, t, J 7.0 Hz, OCH₂CH₃), 3.70 (6H, s, 2 x OMe), 2.62-2.57 (1H, m, 2-CH), 1.77-1.73 (1H, dd, J 7.4 and 12.0 Hz, 3-C(H)H), 1.68-1.64 (1H, dd, J 7.4 and 12.0 Hz, 3-C(H)H), 1.90 (3H, t, J 7.0 Hz, OCH₂CH₃); \( \delta_c \) (100 MHz, CDCl₃) 169.3, 167.2, 165.6 (3 x C=O), 143.1 (4-C), 124.4 (5-C), 60.4 (OCH₂CH₃), 52.9, 52.9 (2 x OMe), 36.5 (1-C), 29.8 (2-C), 21.5 (3-C), 14.3 (OCH₂CH₃); HRMS found (256.0947 C₁₂H₁₆O₆ requires 256.0946).
3-(2-Ethoxycarbonylvinyl)hexahydro pyrrolizine-1,1-dicarboxylic acid dimethyl ester (295)

Vinylcyclopropane 294 (50 mg, 0.195 mmol) and tetrakis(triphenylphosphine)palladium(0) (32 mg, 0.027 mmol) in anhydrous DMSO (2 ml) were stirred at room temperature under nitrogen for 10 min before adding bis-(1-pyrroline)diiodozinc 276 (89 mg, 0.195 mmol). The mixture was heated to 80°C for 1 h before cooling to room temperature. Ethyl acetate (10 ml) was added to the mixture and this washed with distilled water (5 x 10 ml) and brine (2 x 10 ml). The organic layer was separated and then partitioned with aqueous 2 M HCl (15 ml). The aqueous layer was basified with saturated aqueous NaHCO₃ (15 ml). Ethyl acetate (3 x 10 ml) was used to extract the product and the combined extracts were dried over MgSO₄ and concentrated to give pyrolizidine 295 (39 mg, 61%, d.r 1:1) as an orange oil. νₘₐₓ (thin film)/cm⁻¹ 2953m (C-H str), 1731s (C=O str), 1660w (C=C str), 1435m, 1367w, 1249m (C-O); δH (400 MHz, CDCl₃) 6.81-6.72 (2H, m, 9-CH and 9-CH'), 5.92 (1H, d, J 15.2 Hz, 10-CH'), 5.91 (1H, d, J 15.2 Hz, 10-CH), 4.23-4.17 (2H, m, 8-CH and 8-CH'), 3.68, 3.67, 3.67, 3.66 (12H, 4 x s, 2 x OMe and 2 x OMe'), 3.60-3.52 (2H, m, 3-CH), 3.43-3.31 (2H, dd, J 6.4 and 13.6 Hz, 2-CH (H)H and 2-CH (H')H'), 2.73 (2H, dd, J 6.4 and 13.6 Hz, 2-CH (H)H and 2-CH (H')H'), 2.54-2.48 (2H, m, 5-C(H)H and 5-C(H)H'), 2.05 (2H, m, 2-C(H)H and 2-C(H)H'), 1.90-1.71 (6H, m, 6-CH₂, 6-CH₂', 7-C(H)H and 7-C(H)H'), 1.44-1.31 (2H, m, 7-C(H)H and 7-C(H)H'), 1.22 (6H, 2 x t, J 7.0 Hz, OCH₂CH₃ and OCH₂CH₃'), δC (100 MHz, CDCl₃) 171.22, 170.98, 170.98, 170.85, 166.45, 166.33 (3 x C=O and 3 x C=O'), 149.00 (9-C'), 148.54 (9-C), 122.06 (10-C), 121.58 (10-C'), 69.52 (8-C'), 69.41 (8-C), 66.25 (3-C), 66.13 (3-C'), 61.51 (1-C), 61.48 (1-C'), 60.43 (OCH₂CH₃ and OCH₂CH₃'), 52.90 (2 x OMe), 52.86 (5-C'), 52.85 (5-C), 52.60 (OMe'), 52.50 (OMe'), 41.16 (2-C and 2-C'), 28.18 (6-C), 28.07 (6-C'), 26.56 (7-C), 26.52 (7-C), 14.10 (OCH₃CH₃), 13.97 (OCH₂CH₃'); m/z: (FAB+) 326 (100), 325 (18), 324 (46); HRMS found 325.15254 [M]+, [C₁₆H₂₃NO₆]⁺ requires 325.3577.)
3-(2-Ethoxycarbonylvinyl)hexahydro indolizine-1,1-dicarboxylic acid dimethyl ester (296)

Vinylcyclopropane 294 (50 mg, 0.195 mmol) and tetrakis(triphenylphosphine) palladium(0) (32 mg, 0.027 mmol) in anhydrous DMSO (2 ml) were stirred at room temperature under nitrogen for 10 min before adding zinc complex 278 (95 mg, 0.195 mmol). The mixture was heated to 80°C for 1 h before cooling to room temperature. Ethyl acetate (10 ml) was added to the mixture and this washed with distilled water (5 x 10 ml) and brine (2 x 10 ml). The organic layer was separated and then partitioned with aqueous 2 M HCl (15 ml). The aqueous layer was basified with saturated aqueous NaHCO₃ (15 ml). Ethyl acetate (3x10 ml) was used to extract the product and the combined extracts were dried over MgSO₄ and concentrated to give indolizidine 296 (40 mg, 60%, d.r 1:1) as an orange oil. ν_max (thin film)/cm⁻¹ 2935w (C-H str), 1730s (C=O str), 1650m (C=C str), 1437m, 1368w, 1266m (C-O); δ_H (400 MHz, CDCl₃) 6.86 (1H, dd, J 5.3 and 16.0 Hz, 10-CH'), 6.82 (1H, dd, J 5.3 and 16.0 Hz, 10-CH'), 5.80 (1H, d, J 16.0 Hz, 11-CH'), 5.79 (1H, d, J 16.0 Hz, 11-CH), 4.12 (4H, 2 x q, J 7.2 Hz, OCH₂CH₃ and OCH₂CH₃'), 3.66, 3.66, 3.65, 3.65 (12H, 4 x s, 2 x OMe and 2 x OMe'), 3.50-3.45 (2H, m, 3-CH and 3-CH'), 3.01-2.91 (2H, m, 9-CH and 9-CH'), 2.51-2.40 (2H, m, 5-C(H)H and 5-C(H)H'), 2.31-2.18 (4H, m, 5-C(H)H₅-C(H)H'), 2-C(H)H and 2-C(H)H'), 2.00-1.88 (2H, m, 2-C(H)H and 2-C(H)H'), 1.60-1.45 (8H, m, 6-CH₂, 6-CH₂', 8-CH₂ and 8-CH₂'), 1.42-1.30 (4H, m, 7-CH₂ and 7-CH₂'), 1.23 (4H, 2 x t, J 7.2 Hz, OCH₂CH₃ and OCH₂CH₃'); δ_C (100 MHz, CDCl₃) 170.01, 169.87, 168.54, 168.41, 166.35, 165.94 (3 x C=O and 3 x C=O'), 146.94 (10-C), 146.04 (10-C'), 123.71 (11-C), 123.05 (11-C'), 64.23 (9-C and 9-C'), 61.51 (OCH₂CH₃), 61.43 (OCH₂CH₃'), (1-C not observed), 52.59, 52.53, 51.66 (2 x OMe and 2 x OMe'), 50.23 (5-C and 5-C'), 49.10 (3-C), 49.07 (3-C'), 30.01 (2-C and 2-C'), 26.30 (6-C, 6-C', 8-C' and 8-C), 24.58 7-C and 7-C'), 14.26 (OCH₂CH₃), 14.26 (OCH₂CH₃'); m/z (FAB+) 340 (100), 339 (33), 338 (62), 310 (54), 308 (23), 168
240 (22), 196 (80), 154 (29), 136 (25), 122 (35); HRMS found 339.1681 [M]$^+$, [C$_{17}$H$_{25}$NO$_6$]$^+$ requires 339.3845).

3-(2-Ethoxycarbonylvinyl)octahydro pyrrolo[1,2-a]azepine-1,1-dicarboxylic acid dimethyl ester (297)

\[
\text{EtO}_2\text{C} \quad \begin{array}{c}
\text{H} \\
\text{2} \\
\text{1} \\
\text{3} \\
\text{4} \\
\text{11} \\
\text{12} \\
\text{10} \\
\text{9} \\
\text{8} \\
\text{7} \\
\text{6} \\
\text{5}
\end{array} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\]

Vinylcyclopropane 294 (70 mg, 0.273 mmol) and tetrakis(triphenylphosphine) palladium(0) (40 mg, 0.034 mmol) in anhydrous DMSO (2 ml) were stirred at room temperature under nitrogen for 10 min before adding zinc complex 279 (140 mg, 0.273 mmol). The mixture was heated to 80°C for 1 h before cooling to room temperature. Ethyl acetate (10 ml) was added to the mixture and this washed with distilled water (5 x 10 ml) and brine (2 x 10 ml). The organic layer was separated and then partitioned with aqueous 2 M HCl (15 ml). The aqueous layer was basified with saturated aqueous NaHCO$_3$ (15 ml). Ethyl acetate (3 x 10 ml) was used to extract the product and the combined extracts were dried over MgSO$_4$ and concentrated to give azepine 297 (58 mg, 60%) as an orange oil. $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1732s (C=O str), 1656w (C=C str), 1436m, 1370w, 1262m, 1175m; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 6.76-6.70 (1H, dd, J 7.6 and 15.5 Hz, 11-CH), 5.88 (1H, d, J 15.5 Hz, 12-CH), 4.15-4.10 (2H, q, $J$ 7 Hz, OCH$_3$CH$_3$), 3.68, 3.65 (6H, 2 x s, 2 x OMe), 3.43-3.38 (1H, m, 10-CH), 3.01-2.92 (1H, m, 3-CH), 2.71-2.62 (1H, m, 5-C(H)H), 2.44-2.38 (1H, dd, J 10.0 and 13.0 Hz, 2-C(H)H), 2.35-2.24 (1H, m, 5-C(H)H), 2.23-2.17 (1H, dd, J 6.6 and 13.0 Hz, 2-C(H)H), 1.75-1.26 (8H, m, 6, 7, 8, 9-CH$_2$), 1.22 (3H, t, J 7 Hz, OCH$_3$CH$_3$); $\delta_{c}$ (100 MHz, CDCl$_3$) 171.98, 169.93, 166.40 (3 x C=O), 149.50 (11-C), 122.58 (12-C), 67.94 (10-C), 64.44 (3-C), 62.57 (1-C), 60.42 (OCH$_3$CH$_3$), 52.94, 52.49 (2 x OMe), 51.77 (5-C), 38.36 (2-C), 31.43, 28.95, 26.35, 25.37 (6, 7, 8, 9-C), 14.27 (OCH$_3$CH$_3$); m/z (FAB+) 354 (100), 353 (46), 352 (93), 324 (79), 294 (41), 254 (46), 154 (82), 138 (35), 137 (49), 136 (86), 107 (48), 91 (44), 89 (42), 81 (41), 77 (58), 69 (61), 55 (86); HRMS found 354.19132 [M+H]$^+$, [C$_{18}$H$_{27}$NO$_6$+H]$^+$ requires 354.19166.
3-(2-Ethoxycarbonylvinyl)-8,9-dimethoxy-2,3,6,10b-tetrahydro-5H-pyrrolo[2,1-a]isoquinoline-1,1-dicarboxylic acid dimethyl ester (298)

Vinylcyclopropane 294 (100 mg, 0.39 mmol) and tetrakis(triphenylphosphine) palladium(0) (44 mg, 0.034 mmol) in anhydrous DMSO (2 ml) were stirred at room temperature under nitrogen for 10 min before adding 6,7-dimethoxy-3,4-dihydroisoquinoline.HCl (81 mg, 0.35 mmol). The mixture was heated to 80°C for 1 h before cooling to room temperature. Ethyl acetate (10 ml) was added to the mixture and this washed with distilled water (5 x 10 ml) and brine (2 x 10 ml). The organic layer was separated and then partitioned with aqueous 2 M HCl (15 ml). The aqueous layer was basified with saturated aqueous NaHCO₃ (15 ml). Ethyl acetate (3x10 ml) was used to extract the product and the combined extracts were dried over MgSO₄ and concentrated to give an orange oil. Purification by column chromatography (SiO₂, 40-60 P.E:ethyl acetate, 6:1) gave indolizidine 298 (130 mg, 83%, 2:1) as an inseparable mixture of diastereoisomers. \( \nu_{\text{max}} \) (thin film)/cm⁻¹ 2999w, 2950w, 2836w (C-H str), 1737m (C=O str), 1651m (C=C str), 1541s, 1434s, 1346s, 1275s, 1138m, 930w; \( \delta_H \) (400 MHz, CDCl₃) 6.98 (1H, s, 7-CH), 6.91 (1H, s, 7-CH'), 6.88 (1H, dd, J 9.6 and 17.2 Hz, 14-CH'), 6.74 (1H, dd, J 6.8 and 15.6 Hz, 14-CH), 6.50 (1H, s, 10-CH'), 6.47 (1H, s, 10-CH), 6.00 (1H, d, J 15.6 Hz, 15-CH), 5.95 (1H, d, J 15.6 Hz, 15-CH'), 5.23 (1H, s, 5-CH), 4.06 (1H, s, 5'-CH'), 4.20-4.01 (6H, m, OCH₂CH₃, OCH₂CH₃', 3-CH and 5-CH'), 3.84, 3.79, 3.77, 3.76, 3.74 (18H, 6 x s, CO₂CH₃, CO₂CH₃', 2 x OCH₃ and 2 x OCH₃'), 3.37 (3H, s, CO₂CH₂), 3.11 (3H, s, CO₂CH₃), 3.19-3.09 (1H, m, 3-CH'), 3.09-3.00 (1H, m, 13-CH(H)H'), 2.99 (1H, m, 13-CH(H)H), 2.80-2.65 (2H, m, 13-CH(H)H and 12-CH(H)H), 2.62 (1H, dd, J 5.6 and 12.8 Hz, 2-CH(H)), 2.60-2.48 (2H, m, 2-CH₂'), 2.35-2.25 (2H, m, 13-CH(H)H' and 12-CH(H)H), 2.08 (1H, dd, J 8.8 and 12.8 Hz, 2'-CH(HH)), 1.29-1.18 (6H, m, OCH₂CH₃ and OCH₂CH₃'); \( \delta_C \) (100 MHz, CDCl₃) 171.74, 171.20, 170.77, 170.47 (2 x CO₂Me and 2 x CO₂Me'), 166.28 (CO₂Et), 166.05 (CO₂Et'), 149.41 (14-C), 147.52 (14-C'), 147.37
To a stirred solution of 2-methyl-1-pyrroline (2.00 g, 24.1 mol) in diethyl ether (50 ml) was added zinc iodide (3.84 g, 12.1 mol) and the mixture vigorously stirred at 0 °C under nitrogen for 30 min. The precipitate was filtered under suction and washed with cold diethyl ether to give zinc complex 309 (5.18 g, 89%) as a cream powder. A portion of the complex was recrystallised from DCM/hexane vapour diffusion experiments and X-ray crystallographic data obtained (See Appendix). mp 145-147°C; ν<sub>max</sub> (thin film)/cm<sup>-1</sup> 1635s (C=N str), 965m; δ<sub>H</sub> (250 MHz, DMSO-d<sub>6</sub>) 3.80-3.72 (2H, m, 5-CH<sub>2</sub>), 2.69 (2H, t, J 8.4 Hz, 3-CH<sub>2</sub>), 2.14 (3H, s, 6-CH<sub>3</sub>), 1.87 (2H, quintet, J 8.4 and 15.6 Hz, 4-CH<sub>2</sub>); δ<sub>c</sub> (100 MHz, DMSO-d<sub>6</sub>) 182.99 (2-C), 60.16 (5-C), 39.26 (3-C), 21.26 (4-C), 19.56 (6-C).
1-Carboxybenzyl-3-pyrroline (310)¹⁰⁶

\[
\text{O} \quad \text{O} \quad \text{Ph} \\
\quad 6 \quad 7 \\
\quad 1 \\
\quad 2 \\
\quad 3 \\
\quad 4 \\
\quad 5
\]

To a stirred solution (5°C) of 3-pyrroline (4.00 g, 54.0 mmol) in toluene (100 ml) and 3 M NaOH (72 ml) was added benzyl chloroformate (10.6 ml, 75.0 mmol). After 1 h TLC (1:1 ethyl acetate:hexane) showed all starting material had been consumed. The layers were separated and the organic layer washed with distilled water (50 ml), dried over MgSO₄ and evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (SiO₂, Hexane:ethyl acetate; 7:3) afforded 1-carboxybenzyl-3-pyrroline 310 (9.80 g, 83%) as a pale yellow oil. \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3064w, 3031w (Ar C-H str), 2952s, 2860s (C-H str), 1701s (C=O str), 1623m (C=C str); \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 7.39-7.26 (5H, m, 5 x Ar-CH), 5.80-5.73 (2H, m, 3 and 4-CH), 5.16 (2H, s, 7-CH₂), 4.21-4.10 (4H, m, 2 and 5-CH₂); \( \delta_{\text{c}} \) (100 MHz, CDCl₃) 154.66 (6-C), 136.95 (iAr-C), 128.48, 127.95, 127.88 (5 x Ar-C), 125.79, 125.66 (3 and 4-C), 66.79 (7-C), 53.43, 52.96 (2 and 5-C).

1-Carboxybenzyl-3,4-epoxy-pyrrolidine (311)¹⁰⁶

\[
\text{O} \quad \text{O} \quad \text{Ph} \\
\quad 6 \quad 7 \\
\quad 1 \\
\quad 2 \\
\quad 3 \\
\quad 4 \\
\quad 5
\]

To 1-carboxybenzyl-3-pyrroline 310 (4.90 g, 24.1 mmol) in dry DCM (90 ml) was added a solution of meta-chloroperoxybenzoic acid (mCPBA) (55%, 15.1 g) in DCM (90 ml). The mixture was left to stir under nitrogen for 19 h before addition of a second portion of mCPBA (55%, 15.0 g) in DCM (90 ml). After a total of 38 h, TLC (1:1 diethyl ether:hexane) showed consumption of starting material and formation of a major product (Rₜ 0.5). The solvent was evaporated under reduced pressure and the
resultant white solid dissolved in diethyl ether (50 ml) and washed with aqueous NaHCO₃ (50 ml) followed by brine (3 x 50 ml). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to give a white solid. Purification by column chromatography (SiO₂, Hexane:ethyl acetate; 1:1) yielded 1-carboxybenzyl-3,4-epoxy-pyrrolidine 311 (2.30 g, 44%) as a colourless oil. νmax (thin film)/cm⁻¹ 2950w, 2875w (C-H str), 1704s (C=O str);  δH (400 MHz, CDCl₃) 7.35-7.29 (5H, m, 5 x Ar-CH), 5.09 (2H, s, 7-CH₂), 3.80 (1H, d, J 12.8 Hz, 5-C(H)H), 3.76 (1H, J 12.8 Hz, 2-C(H)H), 3.61 (2H, dt, J 1.4 and 3.1 Hz, 3-CH and 4-CH), 3.32 (1H, dd, J 1.4 Hz and 12.8 Hz, 5-C(H)H); δe (100 MHz, CDCl₃) 155.32 (6-C), 136.55 (iAr-C), 128.24, 128.07, 127.96 (5 x Ar-C), 67.05 (7-C), 55.54, 54.98 (2 and 5-C), 47.45, 47.18 (3 and 4-C).

(±)-(3S,4S)-1-Carboxybenzyl-3,4-dihydroxypyrrolidine (312)¹⁰⁶

1-Carboxybenzyl-3,4-epoxy-pyrrolidine 311 (1.80 g, 8.22 mmol) was dissolved in 2 M aqueous H₂SO₄ (150 ml) and diethyl ether (150 ml). This was left to stir under nitrogen at room temperature for 21 h. diethyl ether (50 ml) was added and the layers separated. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure giving a colourless oil. The aqueous layer was back-extracted with ethyl acetate (50 ml), and the organic extract dried over MgSO₄, filtered and evaporated under reduced pressure to give a colourless oil. Both products were shown by ¹H NMR to be the diol. Purification by column chromatography (SiO₂, ethyl acetate) yielded (±)-(3S,4R)-1-carboxybenzyl-3,4-dihydroxypyrrolidine 312 (678 mg, 62%) as a colourless oil. νmax (thin film)/cm⁻¹ 3400br (OH str), 3064m, 3040m (Ar C-H str), 2949w, 2886w (C-H str), 1675s (C=O str);  δH (400 MHz, CDCl₃) 7.31-7.23 (5H, m, 5 x Ar-C), 5.01 (2H, s, 7-CH₂), 4.05 (2H, s, 3 and 4-CH), 3.62-3.59 (2H, m, 2 and 5-C(H)H), 3.36-3.31 (2H, m, 2 and 5-C(H)H); δe (100 MHz, CDCl₃) 155.67 (6-
C), 136.35 (iAr-C), 128.52, 128.11, 127.79 (5 x Ar-C), 75.19, 74.55 (3 and 4-C), 67.21 (7-C), 51.77, 51.44 (2 and 5-C).

(±)-(3S,4S)-3,4-di-O-tert-Butyldimethylsilyl-1-carboxybenzyl-3,4-dihydroxy-pyrrolidine (313)

\[
\begin{align*}
&\text{O} \\
&\text{O} \\
&\text{Ph} \\
&\text{N} \\
&\text{TBDMS} \quad \text{OTBDMS}
\end{align*}
\]

To a solution of 312 (678 mg, 2.86 mmol) and dry pyridine (1.40 ml, 17.3 mmol) in dry DCM (40 ml) was added tert-butyldimethylsilyltrifluoro methanesulphonate (1.97 ml, 8.60 mmol) at 0 °C. The reaction mixture was stirred under nitrogen for 75 min before TLC (100% ethyl acetate) showed consumption of starting material. The reaction mixture was washed with distilled water (20 ml) followed by 1 M aqueous HCl (20 ml) and again by distilled water (20 ml). The aqueous extracts were back-extracted with DCM (20 ml) and the combined organic layers dried over MgSO₄, filtered and evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (SiO₂, Hexane:ethyl acetate; 17:3) afforded (±)-(3S,4S)-3,4-di-O-tert-butyldimethylsilyl-1-carboxybenzyl-3,4-dihydroxy-pyrrolidine 313 (922 mg, 69%) as a colourless oil. \( \nu_{\text{max}} \) (thin film)/cm⁻¹ 2952w, 2856w (Ar C-H str), 1710s (C=O str); \( \delta_H \) (400 MHz, CDCl₃) 7.35-7.30 (5H, m, 5 x Ar-C), 5.14 (2H, s, 7-CH₂), 3.97-3.95 (2H, m, 3 and 4-CH), 3.59-3.50 (2H, m, 2 and 5-C(H)H), 3.30-3.21 (2H, m, 2 and 5-C(H)H), 0.85 (18H, s, 2 x SiC(CH₃)₃), 0.06 (12H, s, 2 x Si(CH₃)₂); \( \delta_c \) (100 MHz, CDCl₃) 155.32 (6-C), 137.10 (iAr-C), 128.44, 127.84, 127.71 (5 x Ar-C), 76.51, 75.75 (3 and 4-C), 66.68 (7-C), 52.37, 52.09 (2 and 5-C), 25.73, 25.71 (SiC(CH₃)₃), 17.97, 17.94 (SiC(CH₃)₃), -4.69, -4.75, -4.78, 4.83 (OSi(CH₃)₂).
To a solution of (±)-(3S,4S)-3,4-di-O-tert-butyldimethylsilyl-1-carboxybenzyl-3,4-dihydroxy-pyrrolidine 313 (922 mg, 1.98 mmol) in dry MeOH (35 ml) was added palladium on carbon (10% wt Pd, 10 mg). The reaction mixture was stirred under a hydrogen atmosphere for 19 h. TLC (1:4 ethyl acetate:hexane) showed complete consumption of starting material. The mixture was filtered through a pad of Celite and the filtrate evaporated under reduced pressure to yield (±)-(3S,4S)-3,4-di-O-tert-butyldimethylsilyl-3,4-dihydroxy-pyrrolidine 314 (545 mg, 83%) as a colourless oil. 

\[
\text{\(v_{\text{max}}\) (thin film)/cm\(^{-1}\) 3342br (br N-H str), 2954w, 2982w, 2886w (C-H str); \(\delta_H\) (400 MHz, CDCl\(_3\)) 3.90-3.82 (2H, dd, J 1.6 and 3.2 Hz, 3 and 4-CH), 3.03 (2H, dd, J 3.2 and 12.0 Hz, 2 and 5-C(H)H), 2.60 (2H, dd, J 1.6 and 12.0 Hz, 2 and 5-C(H)H), 0.82, (18H, s, SiC(CH\(_3\)\(_3\))), 0.01 (12H, s, Si(CH\(_3\)\(_2\))); \(\delta_c\) (100 MHz, CDCl\(_3\)) 79.28 (3 and 4-C), 54.08 (2 and 5-C), 25.85 (SiC(CH\(_3\)\(_3\))), 25.78 (SiC(CH\(_3\)\(_3\))), -4.69 (OSi(CH\(_3\)\(_2\))).}
\]

(±)-(3S,4S)-3,4-di-O-tert-butyldimethylsilyl-3,4-dihydroxy-1-pyrroline (315)\(^{106}\)

To a solution of 314 (545 mg, 1.65 mmol) in dry diethyl ether (30 ml) was added N-chlorosuccinimide (241 mg, 1.80 mmol). The reaction mixture was stirred under nitrogen for 19 h. TLC (1:4 ethyl acetate:hexane) showed consumption of starting material. The reaction mixture was diluted with diethyl ether (30 ml) and washed with water (3 x 20 ml). The aqueous fractions were back-extracted with diethyl ether (2 x 20 ml) and the combined organic fractions dried over Na\(_2\)SO\(_4\) and filtered to give a solution of (±)-(3S,4S)-3,4-di-O-tert-butyldimethylsilyl-1-chloro-3,4-
dihydroxypyrrolidine. To this solution was added DBU (273 mg, 1.82 mmol). The reaction mixture was stirred under nitrogen for 4 h. The reaction mixture was filtered through a glass sinter funnel and the solvent removed in vacuo to yield an orange oil. Purification by column chromatography (SiO₂, Hexane:ethyl acetate; 17:3) afforded (±)-(3S,4S)-3,4-di-O-tert-butyldimethylsilyl-3,4-dihydroxy-1-pyrroline 315 (182 mg, 34%) as an orange oil. νmax (thin film)/cm⁻¹ 2954s, 2856s (C-H str), 1650m (C=N str); δH (400 MHz, CDCl₃) 7.38 (1H, d, J 5.0 Hz, 2-CH), 4.42-4.45 (1H, dd, J 5.0 and 3.0 Hz, 3-CH), 4.09-4.00 (1H, m, 4-CH), 3.87 (1H, dd, J 3.2 and 12.0 Hz, 5-C(H)H), 3.45-3.37 (1H, m, 5-C(H)H), 0.78 (18H, s, 2 x Si(C(H₃))₃), 0.00 (12H, s, 4 x Si(C(H₃))₂); δc (100 MHz, CDCl₃) 168.57 (2-C), 85.56 (3-C), 79.21 (4-C), 67.00 (5-C), 25.77, 25.75 (2 x Si(C(H₃))₃), 18.08, 17.98 (2 x Si(C(H₃))₂), -4.59, -4.61, -4.66, -4.879 (4 x Si(C(H₃))₂).

(±)-(3S,4R)-1-Carboxybenzyl-3,4-dihydroxypyrrolidine (317)\(^{106}\)

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{Ph} \\
\text{N} & \quad \text{O} & \quad \text{O} \\
\text{HO} & \quad \text{H} & \quad \text{HO} \\
\end{align*}
\]

To a solution of tert-butyl alcohol and distilled water (1:1; 30 ml) was added AD-mix-β (1.40 g) and the two phase mixture stirred at room temperature for 5 min. Methane sulphonamide (250 mg, 2.63 mmol) was added and the mixture cooled to 0 °C. To this solution was added 1-carboxybenzyl-3-pyrroline 310 (500 mg, 2.46 mmol) and the reaction mixture stirred for 19 h. Sodium sulfite (1.50 g, 14.6 mmol) was added to give a brown solution and the reaction mixture warmed to room temperature. The mixture was partitioned with DCM (30 ml) and the aqueous layer re-extracted with DCM (3 x 15 ml). The organic layers were combined and washed with aqueous 2 M KOH (30 ml) and the organic layer dried over MgSO₄ and evaporated under reduced pressure to give a colourless oil. Purification by column chromatography (SiO₂, 100% ethyl acetate) gave (±)-(3S,4R)-1-carboxybenzyl-3,4-dihydroxypyrrolidine 317 (229 mg, 73%) as a colourless oil. νmax (thin film)/cm⁻¹ 3405br (O-H str), 3032w (C-H str), 2951w, 2887w (C-H str), 1683s (C=O str); δH
(400 MHz, CDCl$_3$) 7.33-7.27 (5H, m, 5 x Ar-CH), 5.08 (2H, 2 x s, 7-CH$_2$), 4.14 (2H, s, br, 3 and 4-CH), 4.00 (1H, br s, OH), 3.77 (1H, br s, OH), 3.58-3.55 (2H, m, 2 and 5-C(H)H), 3.41-3.36 (2H, m, 2 and 5-C(H)H); $\delta_c$ (100 MHz, CDCl$_3$) 155.24 (6-C), 136.48 (iAr-C), 128.50, 128.08, 127.84 (5 x Ar-C), 71.11, 70.39 (3 and 4-C), 67.09 (7-C), 50.48, 50.34 (2 and 5-C).

(±)-(3S,4R)-3,4-di-O-tert-Butyldimethylsilyl-1-carboxybenzyl-3,4-dihydroxypyrrolidine (318)$^{106}$

![structure](image)

To a solution of 317 (1.50 g, 6.33 mmol) and dry pyridine (3.07 ml, 37.9 mmol) in dry DCM (90 ml) was added tert-butyldimethylsilyl trifluoro methanesulphonate (4.35 ml, 19.0 mmol) at 0 °C. The reaction mixture was stirred under nitrogen for 75 min. TLC (100% ethyl acetate) showed consumption of starting material. The reaction mixture was washed with distilled water (30 ml) followed by 1 M aqueous HCl (30 ml) and again by distilled water (30 ml). The aqueous fractions were back-extracted with DCM (30 ml) and the combined organic layers dried over MgSO$_4$ filtered and evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (SiO$_2$, Hexane:ethyl acetate; 17:3) afforded (±)-(3S,4R)-3,4-di-O-tert-butyldimethylsilyl-1-carboxybenzyl-3,4-dihydroxypyrrolidine 318 (2.04 g, 70%) as a colourless oil. $\nu_{\text{max}}$ (thin film)/cm$^{-1}$: 2955w, 2851w (Ar C-H str), 1711s (C=O str); $\delta_h$ (400 MHz, CDCl$_3$) 7.29-7.18 (5H, m, 5 x Ar-CH), 5.06 (2H, s, 7-CH$_2$), 4.02-4.00 (2H, m, 3 and 4-CH), 3.41-3.39 (2H, m, 2 and 5-C(H)H), 3.30-3.25 (2H, m, 2 and 5-C(H)H), 0.84 (18H, s, 2 x SiC(CH$_3$)$_3$), 0.02 (6H, s, Si(CH$_3$)$_2$), 0.01 (6H, s, Si(CH$_3$)$_2$); $\delta_c$ (100 MHz, CDCl$_3$) 155.15 (6-C), 136.98 (iAr-C), 128.45, 127.90, 127.84 (5 x Ar-C), 72.64, 72.05 (3 and 4-C), 66.73 (7-C), 50.80, 50.64 (2 and 5-C), 25.84, 25.70, 25.66 (2 x SiC(CH$_3$)$_3$), 18.23, 18.22 (2 x SiC(CH$_3$)$_3$), -4.55, -4.59, -4.83, -4.99 (4 x OSi(CH$_3$)$_2$).
To a solution of $(\pm)$-(3S,4R)-3,4-di-O-tert-butyldimethylsilyl-1-carboxybenzyl-3,4-dihydroxy-pyrroline 318 (1.02 g, 2.19 mmol) in dry MeOH (30 ml) was added palladium on carbon (10% wt Pd, 100 mg). The reaction mixture was stirred under a hydrogen atmosphere for 19 h. TLC (1:4 ethyl acetate:hexane) showed complete consumption of starting material. The mixture was filtered through a pad of Celite and the filtrate evaporated under reduced pressure to yield $(\pm)$-(3S,4R)-3,4-di-O-tert-butyldimethylsilyl-3,4-dihydroxy-pyrroline 319 (595 mg, 82%) as a colourless oil.

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3403br (br N-H str), 2926w, 2855w, 2882w (C-H str);

OH (400 MHz, CDCl$_3$) 3.97-3.95 (2H, m, 3 and 4-CH), 2.90-2.81 (2H, m, 2 and 5-C(H)H), 2.79-2.75 (2H, m, 2 and 5-C(H)H), 0.84 (18H, s, 2 x SiC(CH$_3$)$_3$), 0.02 (6H, s, (Si(CH$_3$)$_2$), 0.01 (6H, s, (Si(CH$_3$)$_2$); $\delta$$_c$ (100 MHz, CDCl$_3$) 74.06 (3 and 4-C), 51.57 (2 and 5-C), 26.09, 25.98, 25.94, 25.87, 25.78, 25.74 (2 x SiC(CH$_3$)$_3$), 18.32, 18.28 (2 x SiC(CH$_3$)$_3$), -4.51, -4.80, -4.85, -5.08 (4 x OSi(CH$_3$)$_3$).

$(\pm)$-(3S,4R)-3,4-di-O-tert-Butyldimethylsilyl-3,4-dihydroxy-1-pyrroline (320)$^{106}$

To a solution of 344 (1.13 g, 3.41 mmol) in dry diethyl ether (60 ml) was added N-chlorosuccinamide (566 mg, 1.99 mmol). The reaction mixture was stirred under nitrogen for 19 h. TLC (1:4 ethyl acetate:hexane) showed consumption of starting material. The reaction mixture was diluted with diethyl ether (30 ml) and washed with water (3 x 20 ml). The aqueous fractions were back-extracted with diethyl ether (2 x 20 ml) and the combined organic fractions dried over Na$_2$SO$_4$ and filtered to give a
solution of (±)-(3S,4R)-3,4-di-0-tert-butyldimethylsilyl-1-chloro-3,4-dihydroxypyrrrolidine. To this solution was added DBU (0.74 ml, 4.93 mmol). The reaction mixture was stirred under nitrogen for 4 h. The reaction mixture was filtered through a glass sinter funnel and the solvent removed in vacuo to yield an orange oil. Purification by column chromatography (SiO₂, Hexane:ethyl acetate; 17:3) afforded (±)-(3S,4R)-3,4-di-0-tert-butyldimethylsilyl-3,4-dihydroxy-1-pyrroline 320 (373 mg, 33%) as an orange oil. \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\): 2952 w, 2853 w (C-H str), 1652 m (C=N str); \( \delta_{\text{H}} \) (400 MHz, CDCl₃): 7.50 (1H, d, \( J = 5.0 \) Hz, 2-CH), 4.40-4.37 (1H, m, 3-CH), 4.14-4.11 (1H, m, 4-CH), 3.81-3.75 (1H, m, 5-C(H)H), 3.69-3.60 (1H, m, 5-C(H)H), 0.82 (9H, s, (SiC(CH₃)₃), 0.80 (9H, s, (SiC(CH₃)₃), 0.09 (12H, s, 4 x Si(CH₃)₂); \( \delta_{\text{C}} \) (100 MHz, CDCl₃): 169.13 (2-C), 81.53 (3-C), 71.87 (4-C), 67.49 (5-C), 26.07, 25.99, 25.97, 25.92, 25.85, 25.68 (2 x SiC(CH₃)₃), 18.23, 18.15 (2 x SiC(CH₃)₃).

4-(tert-Butyl-dimethyl-silanyloxy)-piperidine (323)

\[
\begin{align*}
\text{H} & \quad \text{N} \\
\text{5} & \quad \text{4} \\
\text{6} & \quad \text{3} \\
& \quad \text{OTBDMS}
\end{align*}
\]

To a stirred solution of 4-hydroxypiperidine (1.00 g, 9.89 mmol) in DCM (50 ml), was added pyridine (2.4 ml, 29.6 mmol) and TBDMSOTf (3.5 ml, 14.8 mmol). The reaction mixture was stirred at 0°C for 24 h under a nitrogen atmosphere. The solvent was evaporated under reduced pressure to give a pale yellow oil. Purification by column chromatography (SiO₂, 40-60 P.E:ethyl acetate; 2:1) afforded the protected piperidine 323 (1.5 g, 71%) as a colourless oil. \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\): 3499 s (N-H str), 2955 m, 1615 m (N-H bend), 1471 m, 1259 s, 1169 s, 1030 s; \( \delta_{\text{H}} \) (CDCl₃, 400 MHz): 4.05-4.00 (1H, m, 4-CH), 3.35-3.27 (2H, m, 6-C(H)H and 2-C(H)H), 3.22-3.16 (2H, m, 6-C(H)H and 2-C(H)H), 2.00-1.89 (2H, 5-C(H)H and 3-C(H)H), 1.72-1.61 (2H, m, 5-C(H)H and 3-C(H)H), 0.82 (9H, s, SiC(CH₃)₃), 0.00 (6H, s, Si(CH₃)₂); \( \delta_{\text{C}} \) (100 MHz, CDCl₃): 62.51 (4-C), 40.43 (2-C and 6-C), 30.32 (3-C and 5-C), 25.69 (SiC(CH₃)₃), 17.90 (SiC(CH₃)₃), -4.72, -5.06 (Si(CH₃)₂); \( m/z \) (El+) HRMS found 216.1777 [M+H]^+, [C₁₁H₂₃NOSi+H]^+ requires 216.1778.
5-Oxopyrrolidine-1,2-dicarboxylic acid-1-tert-butyl ester-2-ethyl ester (328)

To a stirred solution of ethyl-(s)-(+)2-pyrrolidinone-5-carboxylate (1.25 g, 7.95 mmol) in DCM (25 ml) was added di-tert-butyl dicarbamate (2.09 g, 9.54 mmol) and DMAP (100 mg). The reaction mixture was stirred for 24 h under a nitrogen atmosphere resulting in a yellow solution. This was evaporated under reduced pressure and the yellow oil filtered through a plug of silica (100% ethyl acetate) affording the lactam carbamate 328 (1.85 g, 91%) as a colourless oil. \([\alpha]_D^{20} +27.5\) (c 0.0112 in CHCl₃); \(\nu_{\text{max}}\) (thin film)/cm⁻¹ 2978w, 2940w (C=H str), 1792s, 1750s, 1712s (C=O str), 1340m, 1312s (C–O), 1157s; \(\delta_H\) (400 MHz, CDCl₃) 4.54-4.51 (1H, dd, \(J 3.3\) and 10.0 Hz, 5-CH), 4.16 (2H, q, \(J 7\) Hz, OCH₂CH₃), 2.57-2.52 (1H, m, 3-C(H)H), 2.45-2.39 (1H, m, 3-C(H)H), 2.30-2.26 (1H, m, 4-C(H)H), 1.98-1.89 (1H, m, 4-C(H)H), 1.49 (9H, s, C(CH₃)₃), 1.22 (3H, t, \(J 7\) Hz, OCH₂CH₃); \(\delta_c\) (100 MHz, CDCl₃) 173.4 (O(C=O)N), 171.3 (C=O ester), 149.2 (2-C=O), 83.4 (C(CH₃)₃), 61.6 (OCH₂CH₃), 58.9 (5-C), 33.0 (3-C), 28.0, 27.8, 27.6 (C(CH₃)₃), 21.4 (4-C), 14.1 (OCH₂CH₃).
5-Oxopyrrolidine-1,2-dicarboxylic acid-1-tert-butyl ester-2-methyl ester (332)\textsuperscript{112}

\[ \text{Boc} \]

To a stirred solution of methyl-\((s)-(+)-2\)-pyrrolidinone-5-carboxylate (1.00 g, 6.99 mmol) in DCM (25 ml) was added di-tert-butyl dicarbamate (1.83 g, 8.38 mmol) and DMAP (100 mg). The reaction mixture was stirred for 24 h under a nitrogen atmosphere resulting in a yellow solution. This was evaporated under reduced pressure and the yellow oil filtered through a plug of silica (100% ethyl acetate) affording the lactam carbamate \(332\) (1.65 g, 95%) as a white, waxy solid. mp 70.8-71.4°C [lit mp 71-73°C]; \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 1792s, 1748s, 1714s (C=O str), 1370m, 1314s (C-O), 1257m, 1211m, 1152s; \(\delta_H\) (400 MHz, CDCl\(_3\)) 4.65-4.62 (1H, dd, \(J\) 3.0 and 9.5 Hz, 5-CH), 3.79 (3H, s, OMe), 2.66-2.59 (1H, m, 3-C(H)H), 2.54-2.51 (1H, m, 3-C(H)H), 2.38-2.32 (1H, m, 4-C(H)H), 2.07-2.04 (1H, m, 4-C(H)H), 1.49 (9H, s, C(CH\(_3\))\(_3\)); \(\delta_e\) (100 MHz, CDCl\(_3\)) 173.4 (O(C=O)N), 171.9 (C=O ester), 149.2 (2-C=O), 83.6 (C(CH\(_3\))\(_3\)), 58.8 (5-C), 52.6 (OCH\(_3\)), 31.1 (3-C), 27.9 (C(CH\(_3\))\(_3\)).

2-Oxo-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester (333)\textsuperscript{112}

\[ \text{Boc} \]

To a stirred solution of 3,4-dihydro-2(1H)-quinolinone (500 mg, 3.40 mmol) in DCM (20 ml) was added di-tert-butyl dicarbamate (891 mg, 4.08 mmol) and DMAP (50 mg). The reaction mixture was stirred for 24 h under a nitrogen atmosphere resulting in a yellow solution. This was evaporated under reduced pressure and the yellow oil filtered through a plug of silica (100% ethyl acetate) affording the lactam carbamate \(333\) (900 mg, 100%) as a colourless oil. \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 2976w, 2938w (C–H
str), 1791 s, 1751 s, 1718 s (C=O str), 1336 m, 1313 s (C−O), 1157 s; δ_H (400 MHz, CDCl₃) 7.18-7.08 (2H, m, 9-CH and 6-CH), 7.02-6.96 (1H, m, 8-CH), 6.89-6.85 (1H, d, J 7 Hz, 7-CH), 2.90-2.85 (2H, m, 3-CH₂), 2.61-2.57 (2H, m, 4-CH₂), 1.53 (9H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 169.3 (2-C), 151.8 (C=O ester), 137.1 (10-C), 128.0 (6-C), 127.3 (8-C), 125.9 (5-C), 124.1 (7-C), 117.0 (9-C), 85.0 (C(CH₃)₃), 32.3 (3-C), 27.7 (C(CH₃)₃), 25.5 (4-C).

2,3-Dihydropyrrole-1-carboxylic acid tert-butyl ester (334)¹¹²

\[
\text{Boc-N}^1\text{CH}^2\text{CH}^3\text{CH}^4\text{CH}^5
\]

To a stirred solution of 1-(tert-butoxycarbonyl)-2-pyrrolidinone (500 mg, 2.80 mmol) in dry toluene (20 ml) at -78°C, was carefully added Super Hydride (3.11 ml, 3.10 mmol, 1 M in THF). After stirring under a nitrogen atmosphere for 1 h, diisopropylethylamine (2.81 ml, 16.0 mmol), a catalytic amount of DMAP (6 mg, 0.04 mmol) and trifluoroacetic anhydride (0.48 ml, 3.36 mmol) were sequentially added. The reaction mixture was allowed to warm up to room temperature, and stirred for 2 h. Distilled water (20 ml) was added to the reaction, the organic layer separated, and washed with further portions of distilled water (2 x 20 ml). The organic fraction was dried over MgSO₄ and evaporated under reduced pressure to give a yellow oil.

Purification by column chromatography (SiO₂, 40-60 P.E:ethyl acetate; 6:1) afforded the enecarbamate 334 (300 mg, 66%) as a colourless oil. ν_max (thin film)/cm⁻¹ 2974 m, 2930 m, 2863 m (C−H str), 1702 s, (C=O str), 1617 m (C=C str), 1477 m, 1450 m, 1134 s (C−O); δ_H (400 MHz, DMSO, 100 °C) 6.45 (1H, m, 3-CH), 4.91 (1H, m, 2-CH), 3.68-3.57 (2H, m, 4-CH₂), 2.62-2.50 (2H, m, 5-CH₂), 1.41 (9H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 151.6 (C=O), 129.8 (2-C), 107.5 (3-C), 80.0 (C(CH₃)₃), 44.7 (5-C), 28.7 (4-C), 28.4 (C(CH₃)₃).
2,3-Dihydropyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (335)

To a stirred solution of lactam carbamate 332 (2.91 g, 12.6 mmol) in dry toluene (50 ml) at -78°C, was carefully added Super Hydride™ (13.9 ml, 13.9 mmol, 1.0 M in THF). After stirring under a nitrogen atmosphere for 1 h, diisopropylethylamine (12.5 ml, 71.8 mmol), a catalytic amount of DMAP (30 mg, 0.20 mmol) and trifluoroacetic anhydride (2.15 ml, 15.1 mmol) were sequentially added. The reaction mixture was allowed to warm up to room temperature, and stirred for 2 h. Distilled water (30 ml) was added to the reaction, the organic layer separated, and washed with further portions of distilled water (2 x 30 ml). The organic fraction was dried over MgSO₄ and evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (SiO₂, 40-60 P.E:ethyl acetate; 10:1) afforded the enecarbamate 335 (2.00 g, 70%) as a colourless oil. [α]D²⁰ +81.2 (c 0.0104 in CHCl₃); νmax (thin film)/cm⁻¹ 2976m, 2932m, 2876m (C–H str), 1755s, 1703s (C=O str), 1623m (C=C str), 1402s, 1367s, 1204s, 1180s, 1137s; δH (400 MHz, DMSO, 100°C) 6.53 (1H, m, 2-CH), 5.00 (1H, m, 3-CH), 4.62-4.57 (1H, dd, J 4.6 and 11.7 Hz, 5-CH), 3.70 (3H, s, OMe), 3.10-3.02 (1H, m, 4-C(H)H), 2.62-2.55 (1H, m, 4-C(H)H), 1.43 (9H, s, C(CH₃)₃); δC (100 MHz, CDCl₃) 172.1 (O(C=O)N), 151.0 (C=O ester), 130.1 (2-C), 105.9 (3-C), 80.7 (C(CH₃)₃), 58.5 (5-C), 52.2 (OCH₃), 34.9 (4-C), 28.4 (C(CH₃)₃).
To a stirred solution of lactam carbamate 328 (1.70 g, 6.90 mmol) in dry toluene (30 ml) at \(-78^\circ\text{C}\), was carefully added Super Hydride\textsuperscript{TM} (7.60 ml, 7.60 mmol, 1 M in THF). After stirring under a nitrogen atmosphere for 1 h, diisopropylethylamine (6.90 ml, 39.6 mmol), a catalytic amount of DMAP (20 mg, 0.13 mmol) and trifluoroacetic anhydride (1.20 ml, 8.43 mmol) were sequentially added. The reaction mixture was allowed to warm up to room temperature, and stirred for 2 h. Distilled water (30 ml) was added to the reaction, the organic layer separated, and washed with further portions of distilled water (2 x 30 ml). The organic fraction was dried over MgSO\textsubscript{4} and evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (SiO\textsubscript{2}, 40-60 P.E:ethyl acetate; 10:1) afforded the enecarbamate 336 (1.13 g, 72%) as a colourless oil. $[\alpha]_D^{20} +109.1$ (c 0.011 in CHCl\textsubscript{3}); $\nu_{\text{max}}$ (thin film)/cm\textsuperscript{-1} 2977m, 2933m, 2867m (C-H str), 1753s, 1707s (C=O str), 1623m (C=C str), 1478m, 1456m, 1404s, 1386m, 1133s, 1193s, 1135s; $\delta_H$ (400 MHz, DMSO-d\textsubscript{6}, 100 °C) 6.54 (1H, m, 2-CH), 5.00 (1H, m, 3-CH), 4.59-4.55 (1H, dd, $J$ 4.7 and 11.8 Hz, 5-CH), 4.20-4.14 (2H, q, $J$ 7 Hz, OCH\textsubscript{2}CH\textsubscript{3}), 3.11-3.02 (1H, m, 4-C(H)H), 2.61-2.54 (1H, m, 4-C(H)H), 1.45 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.24 (3H, t, $J$ 7 Hz, OCH\textsubscript{2}CH\textsubscript{3}); $\delta_C$ (100 MHz, CDCl\textsubscript{3}) 171.6 (O(C=O)N), 151.3 (C=O ester), 130.1 (2-C), 105.8 (3-C), 80.6 (C(CH\textsubscript{3})\textsubscript{3}), 61.0 (OCH\textsubscript{2}CH\textsubscript{3}), 58.5 (5-C), 35.0 (4-C), 28.4 (C(CH\textsubscript{3})\textsubscript{3}), 14.3 (OCH\textsubscript{2}CH\textsubscript{3}).
4H-Quinoline-1-carboxylic acid tert-butyl ester (337)

To a stirred solution of lactam carbamate 333 (1.70 g, 6.90 mmol) in dry toluene (30 ml) at −78°C, was carefully added Super Hydride™ (7.60 ml, 7.60 mmol, 1 M in THF). After stirring under a nitrogen atmosphere for 1 h, diisopropylethylamine (6.90 ml, 39.6 mmol), a catalytic amount of DMAP (20 mg, 0.13 mmol) and trifluoroacetic anhydride (1.20 ml, 8.43 mmol) were sequentially added. The reaction mixture was allowed to warm up to room temperature, and stirred for 2 h. Distilled water (30 ml) was added to the reaction, the organic layer separated, and washed with further portions of distilled water (2 x 30 ml). The organic fraction was dried over MgSO4 and evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (SiO2, 40-60 P.E:ethyl acetate; 10:1) afforded the enecarbamate 337 (1.13 g, 72%) as a colourless oil. v_{max} (thin film)/cm\(^{-1}\) 2975w, 2929w (C-H str), 1714s (C=O str), 1664 (C=C str), 1488m, 1368s, 1340s (C-O); δ_{H} (400 MHz, CDCl3) 7.82 (1H, d, 17Hz, 9-C), 7.15-7.08 (1H, m, 7-CH), 7.00-6.96 (2H, m, 6-CH and 8-CH), 6.84-6.80 (1H, dt, 17Hz and 0.8 Hz 2-CH), 5.21-5.18 (1H, m, 3-CH), 3.26-3.23 (2H, m, 4-CH2), 1.53 (9H, s, C(CH3)3); δ_{c} (100 MHz, CDCl3) 151.7 (C=O ester), 137.0 (10-C), 128.2 (6-C), 128.0 (5-C), 127.3 (2-C), 126.1 (8-C), 124.5 (7-C), 121.8 (9-C), 108.6 (3-C), 81.9 (C(CH3)3), 28.3 (C(CH3)3), 27.6 (4-C).

Formation of imines 272, 338, 339 and 340 from enecarbamates 334, 335, 336 and 337.

To a stirred solution of enecarbamate 334, 335, 336 or 337 (2.16 mmol) and triethylamine (21.6 mmol) in DCM (10 ml) at −78°C was added TMSOTf (15.1 mmol) dropwise. The reaction was warmed to −20°C and stirred under an atmosphere of nitrogen for 2 h. The reaction was quenched with saturated NaHCO3(aq) (2 ml) at −78°C. The reaction mixture was allowed to warm to room temperature and the organic layer separated. The organic layer was washed with saturated aqueous...
NaHCO₃ (2 ml) and brine (2 ml), dried over Na₂SO₄, evaporated under reduced pressure to give a yellow residue containing the cyclic imine, which was used without further purification.

3-Vinylhexahydropyrrolizine-1,1,5-tricarboxylic acid 5-ethyl ester 1,1-dimethyl ester (341)

![Chemical Structure](image)

To a stirred solution of imine 339 (132 mg, 0.94 mmol) in DCM (10 ml) was added zinc bromide (106 mg, 0.47 mmol). The reaction mixture was stirred for 10 min in which time the zinc bromide dissolved. The solvent was evaporated under reduced pressure to give the imine complex as an oily residue. This residue was dissolved in anhydrous DMSO (2 ml) and added to a stirred solution of vinylcyclopropane 291 (86 mg, 0.47 mmol) and tetrakis(triphenylphosphine) palladium(0) (32 mg, 0.027 mmol) in anhydrous DMSO (2 ml). The reaction was stirred for 17 h at 80°C under a nitrogen atmosphere. The reaction mixture was diluted with distilled water (10 ml) and extracted with ethyl acetate (2 x 15 ml). The combined organic fractions were washed with water (3 x 20 ml) and brine (3 x 20 ml), the organic was then dried over MgSO₄, and the solvent evaporated under reduced pressure to give an orange oil. Purification by column chromatography (SiO₂, 40-60 P.E:ethyl acetate; 6:1) afforded the pyrrolizine 341 (15 mg, 10%) as an orange oil. \( v_{\text{max}} \) (thin film)/cm⁻¹ 2917w, 2848w (C=H str), 1732s (C=O str), 1682 (C=C str); \( \delta_H \) (400 MHz, CDCl₃) 5.68-5.62 (1H, m, 9-CH), 5.13-5.09 (1H, m, 10-C(H)H), 4.97-4.92 (1H, m, 10-C(H)H), 4.42-4.39 (1H, m, 5-CH), 4.10-4.00 (2H, q, J 7.0 Hz, OCH₂CH₃), 3.67, 3.66 (6H, 2 x s, 2 x OCH₃), 3.57-3.49 (1H, m, 3-CH), 3.42-3.37 (1H, t, J 12.7 Hz, 8-CH), 2.65-2.57 (1H, dd, J 5.8 and 13.6 Hz, 2-C(H)H), 2.22-2.10 (2H, m, 2-C(H)H and 7-C(H)H), 2.02-1.90 (2H, m, 7-C(H)H and 6-C(H)H), 1.45-1.39 (1H, m, 6-C(H)H); \( \delta_C \) (100 MHz, CDCl₃) 178.3, 178.0 (2 x C=O), 165.5 (C=O), 138.3 (9-C), 116.6 (10-C), 70.1 (1-C), 68.7 (5-C), 66.9 (8-C), 61.9 (CH₃CH₂O), 54.1 (3-C), 53.9, 53.8 (2 x OCH₃), 41.2 (2-C), 31.5 (6-C), 29.8 (7-C), 13.5 (CH₃CH₂O); m/z (FAB+) 326 (86), 252 (92), 186
154 (37), 149 (38), 136 (34), 109 (31), 97 (34), 95 (48), 91 (36), 83 (44), 81 (51), 71 (40), 69 (76), 67 (44), 57 (97), 55 (100), 43 (38), 41 (32); HRMS found 326.1606 [M+H]\(^+\), [C\(_{16}\)H\(_{23}\)NO\(_6\)+H]\(^+\) requires 326.1604; \([\alpha]\)\(_D\)^{20} +6.8 (c 0.011 in CHCl\(_3\)).

**General Procedure for the preparation of 2-methyl-4,5-dihydro-1,3-oxazoles 376, 377, 378, 379, 380 and 399.**

A solution of the appropriate amino alcohol (1.0 equiv.) in DCM (50 ml) was added dropwise to a stirred solution of ethyl iminoacetate hydrochloride (1.1 equiv.) or α-phenylacetimidate hydrochloride 398 (1.1 equiv.) in DCM at 0°C. After complete addition, the mixture was stirred at room temperature for 24 h and then washed with water, dried and the solvent evaporated under reduced pressure. Oxazoles were obtained as viscous oils.

**(4S)-4-Benzyl-2-methyl-4,5-dihydro-1,3-oxazole (376)**

![Chemical Structure](image)

From (2S)-2-amino-3-phenylpropan-1-ol (phenylalaninol) (2.93 g, 19.4 mmol). Oxazole 376 was isolated as a colourless oil (2.34 g, 69%). IR (neat/cm\(^{-1}\)) 1673s (C=N), 1497w, 1454w, 1229s; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 7.32-7.19 (5H, m, Ar-CH), 4.40-4.32 (IH, m, 4-CH), 4.19-4.15 (1H, t, J 8.4 Hz, 5-C(H)H), 3.95-3.91 (1H, dd, J 8.2 and 8.4 Hz, 5-C(H)H), 3.08 (1H, dd, J 5.4 and 13.7 Hz, PhC(H)H), 2.65 (1H, dd, J 8.3 and 13.7 Hz, PhC(H)H), 1.97 (s, 3H); \(\delta\)\(_C\) (75 MHz, CDCl\(_3\))): 165.00 (2-C), 138.03 (iAr-C), 129.16 (oAr-C), 128.52 (mAr-C), 126.46 (pAr-C), 71.82 (5-C), 67.44 (4-C), 41.80 (6-C), 13.93 (7C); \([\alpha]\)\(_D\)^{20} -44.0 (c 5.6 in CHCl\(_3\)) [lit. \([\alpha]\)\(_D\)^{20} -47.9 (c 5.6 in CHCl\(_3\))].
4-Isopropyl-2-methyl-4,5-dihydro-1,3-oxazole (377)\textsuperscript{126}

From 2-amino-3-methylbutan-1-ol (valinol) (2.0 g, 19.4 mmol). Oxazole 377 was isolated as a colourless oil (1.48 g, 60\%). IR (neat/cm\textsuperscript{-1}) 1677 (C=N), 1386, 1230; $\delta_H$ (400 MHz, CDCl\textsubscript{3}) 4.22 (1H, dd, $J$ 7.8 and 9.3 Hz, 5-C(H)H), 3.93-3.82 (2H, m, 5-C(H)H and 4-CH), 1.97 (3H, d, $J$ 1.5 Hz, 6-CH\textsubscript{3}), 1.72 (1H, dt, $J$ 13.2, 6.8 Hz, 7-CH), 0.97 (3H, d, $J$ 6.8 Hz, 8-CH\textsubscript{3}), 0.88 (3H, d, $J$ 6.8 Hz, 9-CH\textsubscript{3}). $\delta_c$ (75 MHz, CDCl\textsubscript{3}) 164.3 (2-C), 72.4 (5-C), 70.3 (4-C), 32.7 (6-C), 18.8 (8-C), 18.3 (9-C), 13.8 (7-C).

(4S)-4-(2-methylpropyl)-2-methyl-4,5-dihydro-1,3-oxazole (378)\textsuperscript{126}

From (R)-leucinol (2.27 g, 19.4 mmol). Oxazole 378 was isolated as a colourless oil (1.09 g, 40\%). IR (neat/cm\textsuperscript{-1}) 2958\textsuperscript{m} (C-H), 1676\textsuperscript{s} (C=N), 1386\textsuperspace{(C-O)}, 1226\textsuperspace{s}, 1044\textsuperspace{m}, 984\textsuperspace{s}, 905\textsuperspace{m}; $\delta_H$ (300 MHz, CDCl\textsubscript{3}) 4.31 (1H, dd, $J$ 8.0, 9.3 Hz, 5-C(H)H), 4.15-4.09 (1H, m, 4-CH), 3.77 (1H, t, $J$ 8.0 Hz, 5-C(H)H), 1.96 (3H, d, $J$ 1.3 Hz, 6-CH\textsubscript{3}), 1.84-1.71 (1H, m, 8-CH), 1.62-1.53 (1H, quintet, $J$ 8.8 and 9.3 Hz, 7-C(H)H), 1.27 (1H, dt, $J$ 13.4 and 7.3 Hz, 7-C(H)H), 0.94 (6H, 2 x d, $J$ 4.6 and 6.7 Hz, 9-CH\textsubscript{3} and 10-CH\textsubscript{3}); $\delta_c$ (75 MHz, CDCl\textsubscript{3}) 164.24 (2-C), 73.12 (5-C), 64.68 (4-C), 45.66 (6-C), 25.41 (7-C), 22.88 (9-C), 22.55 (10-C), 13.96 (8-C); [$\alpha$]\textsubscript{D}$\textsuperscript{20} -103.8 (c 1.04 in CHCl\textsubscript{3}).
(4R)-4-Phenyl-2-methyl-4,5-dihydro-1,3-oxazole (379)\textsuperscript{126}

![Chemical structure of (4R)-4-Phenyl-2-methyl-4,5-dihydro-1,3-oxazole (379)](image)

From (R)-phenylglycinol (2.66 g, 19.4 mmol). Oxazole 379 was isolated as a colourless oil (2.65 g, 85%). IR (neat/cm\textsuperscript{-1}) 1684s (C=N); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.36-7.25 (5H, m, Ar-CH), 5.18-5.14 (1H, m, 4-CH), 4.60 (1H, dd, J 8.3, 10.3 Hz, 5-C(H)H), 4.08 (1H, t, J 8.3 Hz, 5-C(H)H), 2.09 (3H, d, J 1.5 Hz, 6-CH\textsubscript{3}); δ\textsubscript{C} (75 MHz, CDCl\textsubscript{3}): 165.79 (2-C), 142.40 (7-C), 128.71 (8-C), 127.51 (10-C), 126.53 (9-C), 74.66 (4-C), 69.78 (5-C), 13.91 (6-C); [α]\textsubscript{D}\textsuperscript{20} +85.2 (c 1.60 in CHCl\textsubscript{3}) [lit. [α]\textsubscript{D}\textsuperscript{20} +98.2 (c 1.66 in CHCl\textsubscript{3})].

(±)-4-Ethyl-2-methyl-4,5-dihydro-1,3-oxazole (380)\textsuperscript{126}

![Chemical structure of (±)-4-Ethyl-2-methyl-4,5-dihydro-1,3-oxazole (380)](image)

From 2-aminobutan-1-ol (2.19 g, 19.4 mmol). Oxazole 380 was isolated as a colourless oil (0.78 g, 45%). IR (neat/cm\textsuperscript{-1}) 1670s (C=N); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 4.31-4.26 (1H, dd, J 8.0 and 8.2 Hz, 5-C(H)H), 4.03-3.95 (1H, m, 4-CH), 3.83 (1H, t, J 8.1 Hz, 5-C(H)H), 1.97 (3H, d, J 1.5 Hz, 6-CH\textsubscript{3}), 1.69-1.58 (1H, m, 7-C(H)H), 1.55-1.44 (1H, m, 7-C(H)H), 0.95 (3H, t, J 7.3 Hz, 8-CH\textsubscript{3}); δ\textsubscript{C} (75 MHz, CDCl\textsubscript{3}) 164.43 (2-C), 72.19 (5-C), 67.72 (4-C), 28.65 (6-C), 13.89 (7-C), 10.06 (8-C).

General Procedure for the SeO\textsubscript{2}-Promoted Oxidative Rearrangement to oxazinones 381, 382, 383, 384, and 385.\textsuperscript{124}

A solution of oxazoline (1.0 equiv.) in dry dioxane (50 ml) was added to a suspension of selenium dioxide (1.2 equiv.) in dioxane (50 ml), and the mixture was
heated at reflux for 2 h. The mixture was cooled, and the yellow reaction mixture
decanted from the selenium residue. The mixture was evaporated under reduced
pressure, to give a yellow oil. Purification by column chromatography (SiO₂, iso-
hexane:ethyl acetate, 4:1) afforded oxazinones 381, 382, 383, 384, 385 and 396 (20-
65%) as colourless oils.

(5S)-5-Benzyl-5,6-dihydro-2H-1,4-oxazin-2-one (381)\(^{124}\)

From (4S)-4-benzyl-2-methyl-4,5-dihydro-1,3-oxazole 376 (1.80 g, 10.5 mmol).
Oxazinone 381 was isolated as an orange oil (1.19 g, 60%). IR (neat/cm\(^{-1}\)) 2987, 2972
(C-H str), 1742 (C=O), 1651 (C=N); δ\(_{\text{H}}\) (300 MHz, CDCl₃) 7.88 (1H, d, J 2.4 Hz, 3-
CH), 7.38-7.30 (6H, m, Ar-CH), 4.37 (1H, dd, J 4.4 and 11.7 Hz, 6-C(H)H), 4.18
(1H, dd, J 7.8 and 11.7 Hz, 6-C(H)H), 4.08-4.02 (1H, m, 5-CH), 3.17 (1H, dd, J 5.9
and 14.2 Hz, 7-C(H)H), 2.77 (1H, dd, J 8.8 and 14.2 Hz, 7-C(H)H); δ\(_{c}\) (75 MHz,
CDCl₃): 154.35 (2C), 152.57 (3C), 136.58 (iAr-C), 129.18 (oAr-C), 128.86 (mAr-C),
127.18 (pAr-C), 68.59 (5C), 57.77 (6C), 37.76 (7C); [α]\(_{D}\)\(^{20}\) +116 (c 0.15 in CHCl₃)
[lit. [α]\(_{D}\)\(^{20}\) +112 (c 0.15 in CHCl₃)].

(±)-5-Isopropyl-5,6-dihydro-2H-1,4-oxazin-2-one (382)\(^{124}\)

From 4-isopropyl-2-methyl-4,5-dihydro-1,3-oxazole 377 (1.33 g, 10.5 mmol).
Oxazinone 382 was isolated as an orange oil (0.88 g, 60%). IR (neat/cm\(^{-1}\)) 1746
(C=O), 1630 (C=N); δ\(_{\text{H}}\) (400 MHz, CDCl₃) 7.90 (1H, d, J 2.9 Hz, 3-CH), 4.47 (1H,
dd, J 4.4 and 11.7 Hz,), 4.26 (dd, J 9.5 and 11.7 Hz, 1H), 3.53-3.48 (1H m, 5-CH),
190
1.95 (1H, td, $J$ 13.6 and 7.3 Hz, 7-CH), 1.07 (6H, t, $J$ 7.3 Hz, 8 and 9-CH$_3$); $\delta_c$ (75 MHz, CDCl$_3$): 154.57 (2-C), 152.31 (3-C), 68.35 (6-C), 61.54 (5-C), 30.44 (7-C), 19.27 (8-C), 18.74 (9-C).

(5S)-5-(2-methylpropyl)-5,6-dihydro-2H-1,4-oxazin-2-one (383)$^{124}$

From (4S)-4-(2-methylpropyl)-2-methyl-4,5-dihydro-1,3-oxazole 378 (1.48 g, 10.5 mmol). Oxazinone 383 was isolated as an orange oil (0.52 g, 32%). IR (neat/cm$^{-1}$) 1745s (C=O), 1645w (C=N), 1457w; $\delta_{1H}$ (300 MHz, CDCl$_3$) 7.86 (1H, d, $J$ 2.6 Hz, 3-CH), 4.46-4.41 (1H, dd, $J$ 4.0 and 11.5 Hz, 6-C(H)H), 4.18-4.11 (1H, dd, $J$ 8.3 and 11.5 Hz, 6-C(H)H), 3.87-3.81 (1H, m, 5-CH), 1.99-1.85 (1H, m, 8-CH), 1.64-1.54 (1H, m, 7-C(H)H), 1.39-1.26 (1H, m, 7-C(H)H), 1.00 (6H, dd, $J$ 1.4 and 6.7 Hz, 9 and 10-CH$_3$); $\delta_c$ (75 MHz, CDCl$_3$) 154.48 (2-C), 152.12 (3-C), 69.75 (6-C), 54.64 (5-C), 40.49 (8-C), 24.76 (7-C), 22.73 (9-C), 22.30 (10-C); $[\alpha]_b^{20}+146$ (c 0.11 in CHCl$_3$).

(5R)-5-Phenyl-5,6-dihydro-2H-1,4-oxazin-2-one (384)$^{124}$

From (4R)-4-phenyl-2-methyl-4,5-dihydro-1,3-oxazole 379 (1.69 g, 10.5 mmol). Oxazinone 384 was isolated as an orange oil (0.28 g, 15%). IR (neat/cm$^{-1}$) 2971, 2901 (C-H str), 1746 (C=O), 1670 (C=N), 1455; $\delta_{1H}$ (300 MHz, CDCl$_3$) 8.07 (1H, d, $J$ 3.0 Hz, 3-CH), 7.46-7.40 (5H, m, Ar-CH), 4.92 (1H, ddd, $J$ 10.6, 4.5 and 3.0 Hz, 5-CH), 4.62 (1H, dd, $J$ 4.5 and 11.8 Hz, 6-C(H)H), 4.29 (1H, dd, $J$ 10.6 and 11.8 Hz, 6-C(H)H); $\delta_c$ (75 MHz, CDCl$_3$): 154.05 (2-C), 153.29 (3-C), 136.09 (iAr-C), 129.05 (oAr-C), 128.53 (pAr-C), 127.07 (mAr-C), 71.11 (5-C), 59.99 (6-C); $[\alpha]_b^{20}+249.2$ (c 0.12 in CHCl$_3$) [lit. $[\alpha]_b^{20}$-252 (c 5.23 in CHCl$_3$)].
(±)-5-Ethyl-5,6-dihydro-2H-1,4-oxazin-2-one (385)\textsuperscript{124}

From 4-ethyl-2-methyl-4,5-dihydro-1,3-oxazole 380 (1.18 g, 10.5 mmol). Oxazinone 385 was isolated as an orange oil (0.40 g, 30%). IR (neat/cm\textsuperscript{-1}) 1732 (C=O), 1651 (C=N); $\delta_{H}$ (400 MHz, CDCl\textsubscript{3}) 7.86 (1H, d, J 2.4 Hz, 3-CH), 4.46 (1H, dd, J 3.9 and 11.7 Hz, 6-C(H)H), 4.20 (1H, dd, J 8.3 and 11.7 Hz, 6-C(H)H), 3.70-3.65 (1H, m, 5-CH), 1.77-1.65 (2H, m, 7-CH\textsubscript{2}), 1.11 (3H, t, J 7.3 Hz, 8-CH\textsubscript{3}). $\delta_{c}$ (75 MHz, CDCl\textsubscript{3}) 154.32 (2-C), 153.19 (3-C), 69.50 (6-C), 54.01 (5-C), 42.32 (8-C), 24.90 (7-C).

5-Phenyl-morpholin-2-one (387)\textsuperscript{127}

A solution of (R)-phenylglycinol (2.00 g, 14.6 mmol) and diisopropylethylamine (5 ml, 29.2 mmol) in acetonitrile (70 ml) were stirred at room temperature under a nitrogen atmosphere for 15 min. Phenyl-$\alpha$-bromoacetate (2.84 g, 13.1 mmol) was dissolved in acetonitrile (30 ml) and added to the reaction mixture via a side arm pressure equalised addition funnel over a 20 min period. The colourless solution was stirred at room temperature for 17 h. The solvent was evaporated under reduced pressure keeping temperatures below 40°C. The oil was redissolved in DCM (10 ml) and loaded onto a silica column with a sodium carbonate pre-column. Purification by column chromatography (SiO\textsubscript{2}, 40-60 P.E:ethyl acetate; 1:1) afforded the morpholinone 387 (700 mg, 27%) as a colourless oil. $\nu_{\text{max}}$ (thin film)/cm\textsuperscript{-1} 3320m (N-H str), 1738s (C=O str), 1456m, 1405s, 1212s; $\delta_{H}$ (400 MHz, CDCl\textsubscript{3}) 7.33-7.26 (5H, m, Ar-CH), 4.32 (1H, dd, J 4.5 and 11.5 Hz, 6-C(H)H), 4.22 (1H, t, J 11.5 Hz, 6-C(H)H), 4.08 (1H, dd, J 10.7 and 11.5 Hz, 5-CH\textsubscript{2}), 3.93 (1H, d, J 17.9 Hz, 3-C(H)H), 3.84 (1H, d, J 17.9 Hz, 3-C(H)H), 1.96 (1H, br, NH); $\delta_{c}$ (100 MHz, CDCl\textsubscript{3}) 167.7
A solution of (R)-phenylalaninol (1.25 g, 8.28 mmol) and diisopropylethylamine (3.60 ml, 20.7 mmol) in acetonitrile (50 ml) was stirred at room temperature under a nitrogen atmosphere for 15 mins. Phenyl-α-bromoacetate (1.60 g, 13.1 mmol) was dissolved in acetonitrile (20 ml) and added to the reaction mixture via a side arm pressure equalised addition funnel over a 20 min period. The colourless solution was stirred at room temperature for 17 h. The solvent was evaporated under reduced pressure keeping temperatures below 40°C. The oil was redissolved in DCM (10 ml) and loaded onto a silica column with a sodium carbonate pre-column. Purification by column chromatography (SiO₂, 40-60 P.E:ethyl acetate; 1:1) afforded the morpholinone 388 (800 mg, 56%) as a colourless oil. \( \nu_{\max} \) (thin film)/cm⁻¹ 3325m (N-H str), 1740s (C=O str), 1455m, 1415m, 1203s; \( \delta_H \) (400 MHz, CDCl₃) 7.27-7.11 (5H, m, Ar-CH), 4.29-4.26 (1H, dd, \( J = 3.5 \) and 10.8 Hz, 6-C(H)H), 4.06 (1H, t, \( J = 11.5 \) Hz, 6-C(H)H), 3.68 (1H, d, \( J = 18.0 \) Hz, 3-C(H)H), 3.52 (1H, d, \( J = 18.0 \) Hz, 3-C(H)H), 3.22-3.18 (1H, m, 5-CH), 2.73-2.68 (1H, dd, \( J = 5.5 \) and 13.6 Hz, PhC(H)H), 2.59-2.54 (1H, dd, \( J = 8.2 \) and 13.6 Hz, PhC(H)H), 1.65 (1H, br, NH); \( \delta_c \) (100 MHz, CDCl₃) 168.02 (C=O), 136.68 (iA-rC), 129.16 (oAr-C), 128.95 (mAr-C), 127.13 (pAr-C), 73.87 (6-C), 52.70 (5-C), 48.00 (3-C), 37.80 (PhCH₂); m/z (El) 192 (88), 101 (32), 65 (45); HRMS found 192.1027 [M+H]+, [C₁₁H₁₃NO₂+H]+ requires 192.1024.
General procedure for the pyrrolo-oxazinones 389, 392, 394 and 395

To a stirred solution of vinylcyclopropane 259 (100 mg, 0.54 mmol, 1 eq.) and tetrakistriphenylphosphine palladium(0) (10 mol%) in THF (5 ml), was added oxazinone (0.49 mmol, 0.9 eq.). The reaction mixture was stirred at room temperature for 20 h. The solvent was removed in vacuo, redissolved in ethyl acetate and washed with water and brine (2 x 10 ml). The organic extract was dried over MgSO₄ and evaporated under reduced pressure to give an orange oil. Purification by column chromatography (SiO₂: iso-hexane:ethyl acetate, 5:1) afforded pyrrolo-oxazinones 389, 392, 394 and 395 (15-75%) as an inseparable mixture of diastereoisomers.

5-Benzyl-8-oxo-3-vinyl-hexahydro-pyrrolo[2,1-c][1,4]oxazine-1,1-dicarboxylic acid dimethyl ester (389a:389b, syn:anti, 2:1)

From (5S)-5-benzyl-5,6-dihydro-2H-1,4-oxazin-2-one 381 (102 mg, 0.54 mmol). The pyrrolooxazinone was isolated as a yellow oil as an inseparable mixture of diastereoisomers (151 mg, 75%, 2:1 syn:anti, 389a:389b). IR (neat/cm⁻¹) 1742s (C=O), 1603w (C=C), 1454w, 1435w, 1267m; δH (400 MHz, CDCl₃) 7.31-7.14 (1OH, m, Ar-CH), 5.59-5.47 (2H, m, 10-C and 10-C'), 5.23-5.14 (4H, m, 11-CH₂ and 11-CH₂'), 4.71 (1H, s, 9-CH'), 4.33-4.28 (2H, m, 6-C(H)H and 6-C(H)H'), 4.18-4.13 (1H, dd, J 3.4 and 11.2 Hz, 6-C(H)H'), 4.04 (2H, m, 9-CH and 6-C(H)H'), 3.84 (3H, s, OCH₃), 3.82 (3H, s, OCH₃'), 3.78 (2H, s, OCH₃), 3.76 (3H, s, OCH₃'), 3.47-3.41 (2H, m, 3-CH and 3-CH'), 3.32-3.27 (1H, m, 5-CH'), 3.11-3.04 (1H, m, 5-CH'), 2.94-2.84 (2H, m, 12-C(H)H and 12-C(H)H'), 2.75-2.67 (3H, m, 12-C(H)H', 12-C(H)H', 2-C(H)H and 2-C(H)H'), 2.41 (1H, dd, J 6.4 and 13.4 Hz, 2-C(H)H), 2.23 (1H, dd, J 8.6 and 13.4 Hz, 2-C(H)H'), δC (75 MHz, CDCl₃): 170.11 (C=OOMe), 169.74 (C=OOMe), 167.49 (8-C), 139.33 (10-C'), 137.72 (10-C), 129.33-126.67 (6 x Ar-C and 6 x Ar-C'), 119.08 (11-C), 117.63 (11-C'), 70.87 (6-C), 68.20 (6-C'), 67.55 (3-
5-Isopropyl-8-oxo-3-vinyl-hexahydro-pyrrolo[2,1-c][1,4]oxazine-1,1-dicarboxylic acid dimethyl ester (392a : 392b, syn:anti, 5:4)

From 5-Isopropyl-5,6-dihydro-2H-1,4-oxazin-2-one 382 (76 mg, 0.54 mmol). The pyrrolooxazinone was isolated as a yellow oil as a separable mixture of diastereoisomers (94 mg, 54%, 5:4 syn:anti, 392a : 392b). **Anti isomer:** IR (neat/cm⁻¹) 1741s (C=O), 1435m, 1265s, 1204m; δH (400 MHz, CDCl₃): 5.63-5.54 (1H, m, 10- C), 5.20-5.08 (2H, m, 11-C), 4.65 (1H, s, 9-CH), 4.45 (1H, dd, J 4.6 and 12.0 Hz, 6-C(H)H), 4.24 (1H, dd, J 8.3 and 12.0 Hz, 6-C(H)H), 3.80 (3H, s, OCH₃), 3.39-3.33 (IH, q, J 7.8 Hz, 5-CH), 2.77-2.72 (1H, dd, J 7.3 and 13.7 Hz, 2-C(H)H), 2.60-2.55 (1H, m, 5-CH), 2.25 (1H, dd, J 7.3 and 13.7 Hz, 2-C(H)H), 1.81 (1H, td, J 13.7 and 6.8 Hz, 12-C), 0.95-0.90 (6H, 2 x d, J 12.0 Hz, 13 and 14-C); δC (75 MHz, CDCl₃) 170.03, 169.87 (2 x C=O(OMe)), 169.23 (C=O), 139.66 (10-C), 117.70 (11-C), 67.33 (3-C), 66.09 (6-C), 63.57 (9-C), 61.15 (1-C), 59.17 (5-C), 53.35, 53.17 (2 x OMe), 37.79 (2-C), 29.71 (12-C), 19.22 (13-C), 18.20 (14-C); **Syn isomer:** IR (neat/cm⁻¹) 1741s (C=O), 1435m, 1265s, 1204m; δH (400 MHz, CDCl₃): 5.42-5.31 (1H, m, 10-C'), 5.14 (1H, dd, J 1.4 and 10.0 Hz, 11-C(H)H'), 5.05 (1H, dd, J 1.4 and 17.0 Hz, 11-C(H)H'), 4.46 (1H, s, 9-CH'), 4.28 (1H, dd, J 6.1 and 11.2 Hz, 6-C(H)H'), 4.06 (1H, t, J 11.2 Hz, 6-C(H)H'), 3.74 (3H, s, OCH₃), 3.70 (3H, s, OCH₃), 3.75-3.70 (1H, m, 5-CH'), 3.04 (1H, quintet, J 5.6 and 11.0 Hz, 3-CH'), 2.75 (1H, dd, J 8.3 and 14.0 Hz, 2-C(H)H), 2.33 (1H, dd, J 5.8 and 13.8 Hz, 2-C(H)H),
1.81 (1H, m, (CH₃)₂CH), 0.86-0.81 (6H, 2 x d, J 12.0 Hz, 2 x CH₃); δc (75 MHz, CDCl₃) 171.25, 169.64 (2 x C=O(OMe) '), 168.04 (C=O'), 138.64 (10-C'), 119.49 (11-C'), 68.28 (6-C'), 64.95 (5-C'), 62.05 (9-C'), 60.26 (1-C'), 56.00 (3-C'), 53.48, 53.07 (2 x OMe'), 36.52 (2-C'), 31.03 (12-C'), 19.30 (13-C'), 18.40 (14-C'); m/z (FAB+) 326 (35), 109 (22), 97 (29), 95 (38), 93 (22), 91 (30), 85 (22), 83 (39), 81 (44), 79 (29), 77 (26), 73 (23), 71 (35), 69 (69), 67 (46), 57 (62), 55 (100), 43 (42), 41 (43); HRMS found 326.1604 [M+H]+, [C₁₆H₂₃N₀₆+H]+ requires 326.1604.

5-Ethyl-8-oxo-3-vinyl-hexahydro-pyrrolo[2,1-c][1,4]oxazine-1,1-dicarboxylic acid dimethyl ester (394a : 394b, syn:anti, 1:1)

![Diagram of 394a (syn) and 394b (anti)]

From 5-Ethyl-5,6-dihydro-2H-1,4-oxazin-2-one 385 (67 mg, 0.54 mmol). The pyrrolooxazinone was isolated as a yellow oil as an inseparable mixture of diastereoisomers (29 mg, 17%, 1:1 syn:anti, 394a : 394b); IR (neat/cm⁻¹) 1746s (C=O str), 1651m (C=C str), 1604w, 1496m; δt (400 MHz, CDCl₃): 5.66-5.56 (2H, m, 10-CH and 10-CH'), 5.21-5.09 (4H, m, 11-CH₂ and 11-CH₂'), 4.66 (1H, s, 9-CH'), 4.47 (1H, dd, J 4.2 and 11.5 Hz, 7-C(H)H'), 4.38 (1H, dd, J 3.9 and 10.8 Hz, 7-(CH)H), 4.27 (1H, dd, J 3.9 and 10.8 Hz, 7-(CH)H'), 4.14-4.09 (1H, dd, J 7.8 and 11.5 Hz, 7-(CH)H'), 3.96 (1H, s, 9-CH), 3.81 (3H, s, OCH₃), 3.80 (3H, s, OCH₃'), 3.77 (3H, s, OCH₃), 3.76 (3H, s, OCH₃'), 3.53-3.43 (2H, m, 3-CH and 3-CH'), 2.99-2.94 (1H, m, 6-CH), 2.80-2.74 (1H, m, 6-CH'), 2.72-2.65 (2H, m, 2-(CH)H and 2-(CH)H'), 2.41 (1H, dd, J 5.9 and 13.7 Hz, 2-(CH)H), 2.23 (1H, dd, J 8.6 and 13.7 Hz, 2-(CH)H'), 1.59-1.48 (4H, m, 12-CH₂ and 12-CH₂'), 0.96-0.88 (6H, m, 13-CH₃ and 13-CH₃'); δc (75 MHz, CDCl₃) 170.18, 170.02, 169.73, 169.64 (C=O), 168.79 (C=O), 139.67 (10-C'), 137.97 (10-C), 130.51 (1-C), 118.74 (11-C), 117.46 (11-C'), 71.04 (6-C), 68.58 (6-C'), 66.92 (3-C'), 63.69 (9-C'), 63.64 (9-C), 61.49 (1-(C') 60.68 (3-C), 60.46 (1-C), 55.46 (5-C'), 53.38, 53.35, 53.21, 52.97 (2 x OMe and 2 x OMe'), 52.47 (5-C), 196
From (5R)-5-phenyl-5,6-dihydro-2H-1,4-oxazin-2-one 384 (95 mg, 0.54 mmol). The pyrrolooxazinone was isolated as a yellow oil as an inseparable mixture of diastereoisomers (48 mg, 25%, 1:1 syn:anti, 395a : 395b). IR (neat/cm\textsuperscript{-1}) 1749s (C=O), 1605w (C=C), 1450w, 1441w, 1124m; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 7.38-7.31 (m, 10H, 5 x Ar-CH and 5 x Ar-CH'), 5.70-5.59 (1H, m, 10-C'), 5.45-5.37 (1H, m, 10-C), 5.26 (1H, dd, J 10.0 and 1.2 Hz, 11-C(H)\textsuperscript{+}H'), 5.18 (1H, dd, J 17.1 and 1.2 Hz, 11-C(H)\textsuperscript{+}H), 4.90 (1H, d, J 17.1 Hz, 11-C(H)H), 4.89 (1H, s, 9'-CH), 4.75 (1H, d, J 10.0 Hz, 11-C(H)H), 4.65 (1H, dd, J 5.1 and 11.5 Hz, 6'-CH(H)), 4.45 (1H, dd, J 5.9 and 11.1 Hz, 6-CH(H)), 4.35 (1H, dd, J 5.1 and 11.1 Hz, 6-CH(H)), 4.28-4.23 (2H, m, 5-CH and 5-CH'), 4.10 (1H, s, 9-CH), 4.00 (1H, dd, J 4.6 and 10.5 Hz, 6-CH(H)), 3.83 (3H, s, OCH\textsubscript{3}), 3.81-3.80 (9H, 2 x s, O CH\textsubscript{3}' and 2 x OCH\textsubscript{3}), 3.74-3.72 (3H, m, OCH\textsubscript{3}), 3.49 (1H, q, J 7.7 Hz, 3-CH), 3.39-3.33 (1H, m, 3-CH'), 2.80-2.75 (1H, dd, J 7.8 and 14.2 Hz, 2-C(H)\textsuperscript{+}H'), 2.64-2.54 (1H, dd, J 7.8 and 14.2 Hz, 2-C(H)H), 2.43 (1H, dd, J 6.4 and 13.7 Hz, 2-C(H)\textsuperscript{+}H), 2.32-2.25 (1H, dd, J 7.8 and 13.7 Hz, 2-C(H)\textsuperscript{+}H); δ\textsubscript{C} (75 MHz, CDCl\textsubscript{3}): 170.16, 170.07, 169.73, 169.37, 169.16, 168.48 (6 x C=O), 138.62 (10-C), 137.65 (10-C'), 135.55 (iAr-C), 128.85 (oAr-C), 128.56 (oAr-C'), 128.27 (pAr-C), 128.15 (pAr-C'), 127.92 (mAr-C), 127.67 (mAr-C'), 119.52 (11-C'), 116.52 (11-C), 72.76 (6-C'), 71.59 (5-C'), 68.30 (6-C), 64.69 (3-C), 62.96 (9-C'), 61.73 (9-C), 60.89 (3-C'), 60.16 (1-C), 55.22 (5-C), 53.43, 53.39, 53.29, 53.07 (4 x OCH\textsubscript{3}), 38.49 (2-C'), 38.41 (2-C); m/z (FAB+) 361 (21), 360 (100), 359 (61), 358

8-Oxo-5-phenyl-3-vinyl-hexahydro-pyrrolo[2,1-c][1,4]oxazine-1,1-dicarboxylic acid dimethyl ester (395a : 395b, syn:anti, 1:1)
(32), 153 (22), 136 (23), 121 (28), 105 (26), 104 (70), 91 (41), 77 (26), 69 (30), 67 (20), 57 (41), 55 (44), 43 (26), 41 (28); HRMS found 360.1441 [M+H]+, [C19H21NO6+H]+ requires 360.1447.

α-Phenylacetimidate hydrochloride (398)\textsuperscript{128}

![α-Phenylacetimidate hydrochloride](image)

Hydrogen chloride gas was bubbled through a stirred solution of benzyl cyanide (9.85 ml, 83.8 mmol) in ethanol (5.38 ml, 92.2 mmol) at 0 °C, until the reaction mixture had gained 3.37 g in mass. The resulting solution was then allowed to stand in the freezer for 17 h before diethyl ether (75 ml) was added, and additional cooling in an ice bath yielded the hydrochloride salt 398 (14.2 g, 85%) as white crystals. IR (neat/cm\textsuperscript{-1}) 3397m (N-H str), 1659 (C=N), 1448m, 1097m; δ\textsubscript{H} (300.07 MHz, CDCl\textsubscript{3}) 7.46-7.36 (5H, m, Ar-CH), 4.62 (2H, q, J 7.0 Hz, CH\textsubscript{2}CH\textsubscript{3}), 4.05 (2H, s, PhCH\textsubscript{2}), 1.98-1.95 (1H, br, NH), 1.44 (3H, t, J 7.0 Hz, CH\textsubscript{2}CH\textsubscript{3}); δ\textsubscript{C} (75.45 MHz, CDCl\textsubscript{3}): 177.17 (C=N), 131.27 (iAr-C), 129.55 (oAr-C), 129.13 (mAr-C), 128.34 (pAr-C), 71.09 (PhCH\textsubscript{2}), 39.33 (CH\textsubscript{2}CH\textsubscript{3}), 13.53 (CH\textsubscript{2}CH\textsubscript{3}).

\textit{(4R)-4-Phenyl-2-benzyl-4,5-dihydro-1,3-oxazole (399)}\textsuperscript{126}

From (R)-phenylglycinol (2.66 g, 19.4 mmol) and α-phenylacetimidate hydrochloride 398 (4.25 g, 21.3 mmol) Oxazole 399 was isolated as a colourless oil (2.76 g, 60%). IR (neat/cm\textsuperscript{-1}) 1689s (C=N); δ\textsubscript{H} (300 MHz, CDCl\textsubscript{3}) 7.39-7.31 (10H, m, Aromatic-CH), 5.22-5.16 (1H, t, J 9.2 Hz, 4-CH), 4.60 (1H, dd, J 8.5 and 10.2 Hz, 5-C(H)H), 4.08 (1H, t, J 8.5 Hz, 5-C(H)H), 3.74 (2H, s, 6-CH\textsubscript{2}); δ\textsubscript{C} (75 MHz, CDCl\textsubscript{3}): 167.18 (2-C), 142.35 (i-Ar-C), 135.19 (iAr-C), 129.01 (oAr-C), 128.70 (oAr-C), 128.67 (mAr-
C), 127.52 (pAr-C), 127.08 (pAr-C), 126.56 (mAr-C), 74.93 (4-C), 69.66 (5-C), 34.91 (6-C); \[\alpha\]_D^{\circ} +53.2 (c 2.83 in CHCl_3) [lit., +50.7 (c 2.83 in CHCl_3)].

2-Oxazoline (401)^{130}

Thionyl chloride (2.08 ml, 28.7 mmol) was added dropwise to N-formyl-ethanolamine 403 (1.50 g, 16.9 mmol) at 0°C, resulting in a vigorous exothermic reaction. The reaction mixture was allowed to warm to room temperature over 1 h. The reaction mixture was then evaporated under reduced pressure to remove excess thionyl chloride, resulting in a colourless oil which was neutralised with aqueous sodium carbonate (35 ml), extracted with dichloromethane (3 x 40 ml), dried over sodium sulphate and evaporated so the temperature remained below 40°C. The resulting colourless oil was 2-oxazoline 401 (720 mg, 60%) with no need for further purification. IR (neat/cm\(^{-1}\)) 1640m (C=N); \delta_H (400 MHz, CDCl_3) 8.21 (1H, s, 2-CH), 3.72-3.50 (4H, m, 4-CH_2 and S-CH_2); \delta_C NMR (75 MHz, CDCl_3) 161.37 (2-C), 43.68 (4-C), 39.85 (5-C).

N-formyl ethanolamine (403)^{128}

Ethanolamine (5.00 g, 82.0 mmol) and formic acid (3.77 g, 82.0 mmol) were combined and heated in an open flask 4 h until the loss of weight corresponded with 1 mol of water. Boiling began at 160°C and ceased at 200°C, indicating the end of the reaction. Kuglerohr distillation of the viscous oil gave N-formyl ethanolamine 403 (4.30 g, 59%) as a colourless oil, bp 225-227°C (8.3 mbar). IR (neat/cm\(^{-1}\)) 3387, 3630 (NH and OH str) 1756s (C=O); \delta_H (400 MHz, DMSO-d_6) 7.98 (1H, s, NCHO), 4.70 (1H, br, NH), 3.46-3.38 (2H, m, 2-CH_2), 3.15-3.06 (2H, m, 1-CH_2); \delta_C (75 MHz, CDCl_3) 165.64 (C=O), 61.23 (2C), 43.98 (1C).
2-(2-tert-Butoxycarbonylvinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (405)

A 100 ml round bottom flask was charged with (tert-butoxycarbonylmethyl)-triphenylphosphonium bromide (6.15 g, 13.5 mmol) in THF (50 ml) under a nitrogen atmosphere. n-Butyllithium (5.39 ml of a 2.5 M solution in hexanes) was added dropwise at 0°C and the mixture stirred for 10 min. The aldehyde 292 (2.09 g, 11.2 mmol) was added to the reaction, and the mixture was stirred for a further 10 min, upon which it was quenched with H₂O (10 ml), and extracted into DCM (3 × 15 ml). The organic layer was dried over MgSO₄ and evaporated under reduced pressure to give the crude product as an orange oil which was further purified via flash chromatography on silica gel (petrol:ethyl acetate, 6:1) to give the product as a colourless oil (2.27 g, 71%). νₚₚₑₓₙ( neat)/cm⁻¹ 1731s (C=O str), 1651s (C=C str), 1435s, 1367s, 1257s, 1142s; δₜₜ (400 MHz, CDCl₃) 6.28 (1H, dd, J 9.6 & 15.2 Hz, 4-CH), 5.91 (1H, d, J 15.2 Hz, 5-CH), 3.70 (3H, s, OCH₃), 3.69 (3H, s, OCH₃), 2.61-2.54 (1H, m, 3-CH), 1.73 (1H, dd, J 5.2 & 7.6 Hz, 2-(CH=H), 1.63 (1H, dd, J 5.2 & 9.2 Hz, 2-(CH=H)), 1.39 (9H, s, OC(CH₃))₃; δₜ (100 MHz, CDCl₃) 169.44 (C=O), 167.27 (C=O), 164.98 (C=O), 141.77 (4-C), 126.25 (5-C), 80.54 (1-C), 53.01 (OCH₃), 52.89 (OCH₃), 36.41 (OC(CH₃))₃, 29.81 (3C), 28.18 (OC(CH₃))₃, 21.46 (2-C); m/z: (CI) 302 ([M+(NH₄)]⁺, 98%), 246 (79), 211 (33), 145 (80), 120 (54), 113 (61), 98 (40), 65 (37), 57 (100) and 41 (72); HRMS found 302.1598 [M+(NH₄)]⁺; [C₁₄H₂₀O₆+(NH₄)]⁺ requires 302.1598.
4-Bromobut-3-yn-1-ol (407)\(^{100}\)

\[
\begin{array}{c}
\text{Br} \\
1 \\
\text{OH} \\
3 \\
2 \\
4
\end{array}
\]

To a solution of potassium hydroxide (32.0 g, 576 mmol) in H\(_2\)O (300 ml) was added bromine (8.16 ml, 158 mmol), and the solution was cooled to 0 °C. The flask was covered with aluminium foil and then 3-butyne-1-ol (10.0 g, 143 mmol) was added. The mixture was stirred for 24 h after warming to room temperature. The mixture was extracted with diethyl ether (2 \times 50 ml), and the organic layer was dried over Na\(_2\)SO\(_4\), and evaporated under reduced pressure to give the desired product as a colourless oil (19.5 g, 92%). \(\nu\)\(_{\text{max}}\) (neat)/cm\(^{-1}\): 3355br (O-H str), 1417w, 1034s and 845m; \(\delta\)\(_{\text{H}}\) (400 MHz, CDCl\(_3\)) 3.76 (2H, t, \(J\ 3.2\ Hz\), 4-CH\(_2\)), 2.49 (2H, t, \(J\ 3.2\ Hz\), 3-CH\(_2\)), 2.08-2.02 (1H, s, OH); \(\delta\)\(_{\text{C}}\) (100 MHz. CDCl\(_3\)) 60.80 (4-C), 40.08 (1-C), 15.26 (2-C); \(m/z\): (EI) 150 ([M+H]\(^+\), Br\(^{81}\), 5%), 148 ([M+H]\(^+\), Br\(^{79}\), 5%), 120 (95), 118 (100) and 69 (25); HRMS found 147.9527 [M]\(^+\), [C\(_4\)H\(_5\)OBr\(^{79}\)+H]\(^+\), requires 147.9523.

4-Bromobut-3-en-1-ol (408)\(^{100}\)

\[
\begin{array}{c}
\text{Br} \\
1 \\
\text{OH} \\
3 \\
2 \\
4
\end{array}
\]

A dry 10 ml round bottomed flask was charged with 4-bromo-but-3-yn-1-ol 407 (9.00 g, 60.6 mmol) and THF/H\(_2\)O (1:1, 300 ml). To this was added \(p\)-toluenesulfonylhydrazide (22.5 g, 121 mmol) and sodium acetate (15.0 g, 182 mmol). This mixture was stirred under reflux for 4 h, after which the reaction was allowed to cool, and then extracted with DCM (2 \times 50 ml). The organics were dried over MgSO\(_4\), then evaporated under reduced pressure to give the desired product as a colourless oil (8.5 g, 93%). \(\nu\)\(_{\text{max}}\) (neat)/cm\(^{-1}\): 3335br (O-H str), 1623m (C=O str); \(\delta\)\(_{\text{H}}\) (400 MHz, CDCl\(_3\)) 6.22 (1H, \(J\ 1.2\) and 7.2 Hz, 1-CH), 6.12 (1H, q, \(J\ 7.2\ Hz\), 2-CH), 3.65 (2H, t, \(J\ 6.8\ Hz\), 4-CH\(_2\)), 2.46-2.38 (2H, m, 3-CH\(_2\)); \(\delta\)\(_{\text{C}}\) (100 MHz. CDCl\(_3\)) 131.21 (2-C), 109.93 (3-C), 60.94 (4-C), 33.22 (3-C); \(m/z\): (EI) 152 ([M]\(^+\), Br\(^{81}\), 8%).
150, ([M]⁺, Br⁷⁹, 8%), 122 (49), 120 (52) and 71 (100); HRMS found 149.9678 [MBr⁷⁹⁺], [C₄H₇OBr⁷⁹⁺] requires 149.9680.

Methanesulfonic acid 4-bromobut-3-enyl ester (409)¹⁰⁰

\[
\begin{array}{c}
\text{Br} \\
1 \quad 2 \\
\hline
3 \\
\text{O} \\
4 \\
\text{S} \\
5
\end{array}
\]

A 10 ml round bottomed flask was charged with 4-bromobut-3-en-1-ol 408 (6.00 g, 39.7 mmol) dissolved in DCM (3 ml). To this mixture was added triethylamine (4.40 g, 43.7 mmol) and the reaction mixture was cooled to 0 °C. Methanesulfonyl chloride (5.00 g, 43.7 mmol) was added dropwise, and the reaction was stirred whilst allowed to warm to room temperature overnight. The reaction was quenched with H₂O (30 ml) followed by a saturated sodium bicarbonate solution (20 ml). The organics were extracted into DCM (3 × 20 ml), dried over MgSO₄ and evaporated under reduced pressure to give the crude product which was further purified via flash chromatography (P.E 60-40:ethyl acetate, 6:1) to give the desired product as an orange oil (8.51 g, 94%). v_{\text{max}}(\text{neat})/\text{cm}^{-1} 3087w, 3026w, 2939w (C-H aliphatic str), 1625m (C=C str), 1470w, 1416w, 1359s, 1171s, 965s, 920s; δH (400 MHz, CDCl₃) 6.30 (1H, dt, J 1.2 and 6.8 Hz, 1-CH), 6.12 (1H, q, J 6.8 Hz, 2-CH), 4.23 (2H, t, J 6.4 Hz, 4-CH₂), 2.97 (3H, s, 5-CH₃), 2.64-2.58 (2H, m, 3-CH₂); δC (100 MHz, CDCl₃) 128.99 (2-C), 111.45 (1-C), 67.64 (4-C), 37.68 (5-C), 29.86 (3-C); m/z: (EI) 248 ([M+(NH₄)⁺], Br⁸¹, 98%), 246 ([M+(NH₄)⁺], Br⁷⁹, 98%), 134 (90), 118 (52), 109 (56), 91 (48), 79 (100) and 53 (80); HRMS found 245.9791 [M+(NH₄)Br⁷⁹⁺], [C₃H₆O₃SBr⁷⁹+(NH₄)⁺] requires 245.9794.
1-Bromo-4-iodo-but-1-ene (410)

Methanesulfonic acid 4-bromobut-3-enyl ester 409 (8.51 g, 37.2 mmol) and sodium iodide (83.5 g, 557 mmol) were added to anhydrous acetone (1000 ml) and heated under reflux for 24 h. The resulting precipitate was removed by filtration through a Celite pad, and the filtrate was evaporated under reduced pressure. The white solid was washed with diethyl ether (5 x 20 ml) and the solution was evaporated under reduced pressure a second time to give the desired product as an orange oil (8.00 g, 82%).

\[ \text{\( \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} 1621\text{m} (\text{C=C str}), 1422\text{m}, 1285\text{s}, 1171\text{s}; \delta_{\text{H}} (400 \text{ MHz, CDCl}_3) 6.28 (1\text{H, dt, } J 1.6 \& 6.8 \text{ Hz 1-CH}), 6.08 (1\text{H, q, } J 6.8 \text{ Hz, 2-CH}), 3.14 (2\text{H, t, } J 6.8 \text{ Hz, 4-CH}_2), 2.75 (2\text{H, dt, } J 1.6, 6.8 \text{ and } 7.5 \text{ Hz, 3-CH}_2); \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) 132.92 (2-C), 109.62 (1-C), 33.09 (4-C), 2.16 (3-C); m/z: (EI) 262 ( [M]+, Br^81, 98%), 260 ( [M]+, Br^79, 98%), 209 (35), 139 (39), 91 (100), 65 (52), 55 (61) and 43 (91); HRMS found 259.8694 [MBr^79]+, [C4H6Br^79]+ requires 259.8697. \]

4-Bromobut-3-enylisoindole-1, 3-dione (411) Method A

A solution of methanesulfonic acid 4-bromobut-3-enyl ester 409 (500 mg, 2.35 mmol), potassium phthalimide (477 mg, 2.58 mmol), potassium iodide (38 mg, 0.23 mmol) and 18-crown-6 (55 mg, 0.21 mmol) in DMF (20 ml) was heated under reflux for 24 h under a nitrogen atmosphere. After cooling to room temperature, the resulting residue was diluted with ethyl acetate, and the solids filtered. The organic phase was washed with H2O (3 x 30 ml), dried over MgSO4 and evaporated under reduced pressure to give the crude product which was further purified by flash chromatography on silica gel (P.E 60-40:ethyl acetate, 6:1) to give the phthalimide.
product as a yellow crystalline solid (300 mg, 46%). $\nu_{\text{max}}$(neat)/cm$^{-1}$: 3460w, 1771s, 1712s (C=O str), 1623m (C=C str), 1467m, 1436m, 1396s, 1360s; $\delta$H (400 MHz, CDCl$_3$) 7.79-7.76 (2H, m, 9 and 10-CH), 7.67-7.65 (2H, m, 11 and 12-CH), 6.16 (1H, dt, $J$ 1.6 & 7.2 Hz, 1-CH), 6.08 (1H, q, $J$ 7.2 Hz, 2-CH), 3.76 (2H, t, $J$ 6.8 Hz, 4-CH$_2$), 2.55 (2H, dd, 1.6 and 7.2 Hz 3-CH$_2$); $\delta$C (100 MHz, CDCl$_3$) 168.34 (5 and 6-C), 134.00 (11 and 12-C), 132.02 (7 and 8-C), 130.81 (2-C), 123.29 (9 and 10-C), 110.65 (1-C), 36.10 (4-C), 29.22 (3-C); mp: 61.5-63.8°C; mlz: (FAB+) 282 ([M+H]$^+$, Br 81, 2%), 280 ([M+H]$^+$, Br 79, 2%), 160 (39), 95 (30), 81 (.8), 69 (570, 57 (67), 55 (100) and 41 (40); HRMS found 279.9977 [M+H]$^+$, Br$^{79}$, [C$_{12}$H$_{10}$O$_2$NBr$_{79}$+H]$^+$ requires 279.9973.

4-Bromobut-3-enylisoindole-1, 3-dione (411)$^{100}$ Method B

A solution of 1-bromo-4-iodobut-1-ene 410 (2.60 g, 9.98 mmol) and potassium phthalamide (3.70 g, 20.0 mmol) in 2-butanone (50 ml) was heated under reflux for 24 h under a nitrogen atmosphere. After cooling to room temperature, the resulting residue was diluted with ethyl acetate, and the solids filtered. The organic phase was washed with H$_2$O (3 x 30 ml), dried over MgSO$_4$ and evaporated under reduced pressure to give the crude product which was further purified by flash chromatography on silica gel (P.E 60-40:ethyl acetate, 1:1) to give the phthalamide product as a white crystalline solid (1.50 g, 54%). Data as shown in Method A.

4-(Bromobut-3-enyl)-[1-phenylmethylidene]-amine (412)

![Structural formula](image)

Phthalamide 411 (600 mg, 2.15 mmol) in EtOH (30 ml) was treated with hydrazine monohydrate (120 mg, 2.15 mmol). The reaction mixture was refluxed for 2 h. The reaction was complete upon formation of a white precipitate. To this was added aqueous 2 M HCl (10 ml) and the reaction refluxed for a further 10 min. The reaction was allowed to cool to room temperature, and the solids were filtered and washed with water (2 x 10 ml). The aqueous ethanol filtrate was evaporated under reduced
pressure, and re-dissolved in aqueous 2 M NaOH, and extracted into diethyl ether (2 x 20 ml). The organic fractions were combined and dried over MgSO₄ before concentrating to ~10 ml in vacuo, using a cool water bath. To this solution were added molecular sieves (2.50 g 4 Å) and benzaldehyde (212 mg, 2.00 mmol). The reaction mixture was left to stir overnight, after which time it was filtered under suction and washed several times with diethyl ether (3 x 5 ml). The filtrate was evaporated under reduced pressure to give the imine as an orange oil (380 mg, 74%).

\( \nu_{\max\text{(neat)}}/\text{cm}^{-1} \): 2925, 2359, 1289, 1055, 772 and 689; \( \delta_H\text{ (CDCl}_3, 400 \text{ MHz)} \): 8.29 (1H, s, 5-CH), 7.78-7.72 (2H, m, Ar-H), 7.49-7.43 (2H, m, Ar-H), 7.42-7.40 (1H, m, Ar-H), 6.30-6.22 (1H, m, 1-CH), 6.19-6.10 (1H, m, 2-CH), 3.74-3.70 (2H, m, 4-CH₂), 2.62 (2H, q, J 6.6 Hz, 3-CH₂); \( \delta_C\text{ (CDCl}_3, 100 \text{ MHz)} \): 161.58 (C-12), 136.03 (C-1), 132.27 (C-7), 130.65 (C-4), 128.56 (C-2 and C-6), 128.08 (C-3 and C-5), 109.09 (C-11), 59.64 (C-10) and 31.29 (C-9), m/z: (FAB+) 240 ([M+H⁺], Br³¹, 10%), 238 ([M+H⁺], Br⁷⁹, 10%), 136 (27), 118 (28), 95 (37), 91 (38), 81 (38), 69 (55), 57 (50) and 55 (100); HRMS found 238.0234 [M+H⁺], Br⁷⁹, [C₁₁H₁₂NBr⁷⁹+H⁺] requires 238.0231.

4-(4-Bromobut-3-enyl)-3-(2-tert-butoxycarbonylvinyl)-5-phenylpyrrolidine-1,1-dicarboxylic acid dimethyl ester (415)

![Diagram](image)

To a stirred solution of 2-(2-tert-butoxycarbonyl-vinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester 405 (1.16 g, 4.09 mmol) in THF (20 ml) was added 4-(bromobut-3-enyl)-[1-phenylmethylidene]-amine 412 (1.07 g, [91% imine 9% benzaldehyde], 4.09 mmol imine) then ZnBr₂ (2.30 g, 10.2 mmol) at room temperature. This was left to stir under a nitrogen atmosphere for 10 min before addition of tetrakistriphenylphosphine palladium(0) (236 mg, 0.204 mmol). The

205
reaction mixture was stirred for 24 h. The solvent was then removed in vacuo, and the residue dissolved in ethyl acetate (10 ml) and washed with water (2 x 20 ml). The organic fraction was then dried over MgSO₄ and evaporated under reduced pressure to give an orange oil. Purification by column chromatography (SiO₂; 40-60 P.E:ethyl acetate; 20:1) afforded pyrrolidines 415a and 415b as a separable mixture of isomers (415a [1.24 g, 58%], 415b [0.50 g, 23%]) as yellow oils. E-isomer 415a:

$v_{\text{max( neat)}}/\text{cm}^{-1}$ 2951 m, 2840 m (C-H aliphatic), 1732 s, 1712 s (C=O str), 1651 m (C=C str), 1621 w (C=C-Br), 1493 w, 1455 m, 1434 m, 1367 s, 1151 s; $\delta_{\text{H}}$ (400 MHz, CDCl₃) 7.31 (2H, d, $J$ 8.4 Hz, 2 x oAr-CH), 7.23-7.15 (3H, m, 2 x mAr-CH and 1 x pAr-CH), 6.76 (1H, dd, $J$ 7.6 Hz and 15.6 Hz, 6-CH), 5.98 (1H, d, $J$ 6.9 Hz, 16-CH), (1H, d, $J$ 15.6 Hz, 7-CH), 5.82 (1H, q, $J$ 6.9 Hz, 15-CH), 4.71 (1H, s, 5-CH), 3.72 (3H, s, OMe), 3.30-3.21 (1H, m, 3-CH), 3.04 (3H, s, OMe), 2.70-2.65 (2H, m, 13-C(H)H and 2-C(H)H), 2.64-2.59 (1H, m, 13-C(H)H), 2.22 (1H, dd, $J$ 5.7 and 13.2 Hz, 2-C(H)H), 2.10-1.98 (2H, m, 14-CH₂); $\delta_{\text{C}}$ (100 MHz, CDCl₃) 171.81, 168.67, 165.55 (3 x C=O), 147.54 (6-C), 140.28 (iAr-C), 132.48 (15-C), 128.52, 127.84 (5 x Ar-C), 124.76 (7-C), 108.72 (16-C), 80.61 (9-C), 71.60 (5-C), 64.74 (1-C), 63.24 (3-C), 53.16 (OMe), 52.10 (OMe), 50.46 (13-C), 38.58 (2-C), 28.16 (10, 11 and 12-C), 28.05 (14-C); m/z (FAB+) 524 ([M+H]⁺, Br81, 11%), 522 ([M+H]⁺, Br79, 17%), 466 (27), 402 (100), 346 (38); HRMS found 522.1498 ([M+H]⁺, Br79), [C25H32NO6Br79+H⁺ requires 522.1491). Z-isomer 415b:

$v_{\text{max( neat)}}/\text{cm}^{-1}$ 2976 m, 2950 m (C-H aliphatic), 1733 s, 1667, 165.55 (3 x C=O), 147.54 (6-C), 140.28 (iAr-C), 132.48 (15-C), 128.52, 127.84 (5 x Ar-C), 124.76 (7-C), 108.72 (16-C), 80.61 (9-C), 71.60 (5-C), 64.74 (1-C), 63.24 (3-C), 53.16 (OMe), 52.10 (OMe), 50.46 (13-C), 38.58 (2-C), 28.16 (10, 11 and 12-C), 28.05 (14-C); m/z (FAB+) 524 ([M+H]⁺, Br81, 13%), 522 ([M+H]⁺, Br79, 19%), 466 (100), 464 (89), 346 (57); HRMS found 522.1485 [M+H]⁺, Br79; [C25H32NO6Br79+H⁺ requires 522.1491.
2-Amino-3-phenyl-propan-1-ol (417)

Chlorotrimethylsilane (15.2 ml, 120 mmol) was added to a suspension of lithium borohydride (1.32 g, 60.1 mmol) in dry THF (85 ml) under a nitrogen atmosphere over a 5 min period at room temperature. (R)-Phenylalanine (5.00 g, 30.0 mmol) was then added over 5 mins. The mixture was allowed to stir for 24 h before being quenched with methanol until there was no effervescence visible. The solvent was evaporated under reduced pressure, and the residue treated with 20% potassium hydroxide solution and extracted with DCM (3 x 30 ml). The combined organic phase was dried over sodium sulphate and evaporated under reduced pressure to give the β-aminoalcohol 417 (4.30 g, 95%) as a pale yellow solid, which was used without further purification. \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3659s (O-H), 3355s (N-H), 1578w, 1122m; \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.32-7.18 (5H, m, Ar-CH), 3.62 (1H, dd, J 4.00 and 10.8 Hz, 1-C(H)H), 3.39 (1H, dd, J 7.2 and 10.8 Hz, 1-C(H)H), 3.10 (1H, m, 2-CH), 2.79 (1H, dd, J 5.2 and 13.6 Hz, 3-C(H)H), 2.50 (1H, dd, J 8.8 and 13.6 Hz, 3-C(H)H); \( \delta_C \) (100 MHz, CDCl\(_3\)) 139.1 (iAr-C), 129.6 (oAr-C), 129.0 (mAr-C), 126.8 (pAr-C), 66.5 (1-C), 54.6 (2-C), 41.1 (3-C).
To a stirred solution of 1-(4-bromo-but-3-enyl)-5-(2-tert-butoxycarbonyl-vinyl)-2-phenyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester 415a (100 mg, 0.181 mmol) in DMSO (5 ml) was added tetrakistriphenylphosphine palladium(0) (22 mg, 19.0 μmol). This was stirred under a nitrogen atmosphere for 10 min before addition of NaHCO₃ (80 mg, 0.952 mmol). The reaction mixture was heated to 80°C for 1 h, then cooled to room temperature. Water (10 ml) was added and the aqueous mixture extracted with ethyl acetate (10 ml). The aqueous fraction was re-extracted with a further portion of ethyl acetate (10 ml), and the organic fractions combined and washed with water (2 x 10 ml) and saturated brine solution (3 x 10 ml). The organic layer was dried over MgSO₄ and evaporated under reduced pressure to give an orange oil. Purification by column chromatography (SiO₂, 40-60 P.E.; ethyl acetate; 20:1) afforded the pyrrolidine 418a (72 mg, 92%) as a white crystalline solid. mp 131-134°C; νmax(neat)/cm⁻¹: 2951m, 1731s (C=O str), 1631m (C=C str), 1584w, 1434m, 1146s; δH (400 MHz, CDCl₃) 7.38 (2H, d, J 8.0 Hz, 2 x Ar-CH), 7.23-7.15 (3H, m, 3 x Ar-CH), 6.05 (1H, br d, J 12.4 Hz, 5-CH), 5.73 (1H, dt, J 5.3 and 12.4 Hz, 6-CH), 5.60 (1H, s, 11-CH), 4.64 (1H, s, 10-CH), 4.40-4.34 (1H, m, 3-CH), 3.72 (3H, s, OMe), 2.93 (3H, s, OMe), 2.73(1H, dd, J 5.3 and 10.2 Hz, 2-C(H)H), 2.70-2.62 (1H, m, 8-C(H)H), 2.60-2.52 (2H, m, 8-C(H)H and 2-C(H)H), 2.28-2.15 (1H, m, 7-C(H)H), 2.04-1.96 (1H, m, 7-C(H)H), 1.40 (9H, s, 14-CH₃, 15-CH₃ and 16-CH₃); δc (100 MHz, CDCl₃) 172.08, 169.67, 165.70 (3 x C=O), 156.87 (4-C), 139.69 (iAr-C), 135.54 (6-C), 128.43 (5-C), 128.43 (pAr-C), 127.83 (2 x mAr-C), 127.79 (2 x oAr-C), 120.99 (11-C), 79.95 (13-C), 72.87 (10-C), 66.35 (3-C), 63.81 (1-C), 52.77, 51.97 (2 x OMe), 47.56 (8-C), 38.99 (2-C), 33.25 (7-C), 28.16 (14, 15 and 16-C); m/z (FAB+).
442 (9), 385 (27), 384 (100); HRMS found 442.2237 [M+H]^+; [C_{23}H_{31}NO_6+H]^+ requires 442.2230.

4-tert-Butoxycarbonyl-(Z)-methylene-10-phenyl-2,7,8-tetrahydro-1H-pyrrolo[1,2-a]azepine-1,1-dicarboxylic acid dimethyl ester (418b)

To a stirred solution of 4-(4-bromo-but-3-enyl)-3-(2-tert-butoxycarbonylvinyl)-5-phenylpyrrolidine-1,1-dicarboxylic acid dimethyl ester 415b (100 mg, 0.181 mmol) in DMSO (5 ml) was added tetrakistriphenylphosphine palladium(0) (22 mg, 19.0 μmol). This was stirred under a nitrogen atmosphere for 10 min before addition of NaHCO₃ (80 mg, 0.952 mmol). The reaction mixture was heated to 80°C for 1 h, then cooled to room temperature. Water (10 ml) was added and the aqueous mixture extracted with ethyl acetate (10 ml). The aqueous fraction was re-extracted with a further portion of ethyl acetate (10 ml), and the organic fractions combined and washed with water (2 x 10 ml) and saturated brine solution (3 x 10 ml). The organic layer was dried over MgSO₄ and evaporated under reduced pressure to give an orange oil. Purification by column chromatography (SiO₂, 40-60 P.E:ethyl acetate; 20:1) afforded the pyrrolidine 418b (75 mg, 94%) as a white crystalline solid. mp 132-135°C; ν_{max}(neat)/cm⁻¹:2951m, 1731s (C=O str), 1632m, 1434m, 1146s; δ_{H} (400 MHz, CDCl₃) 7.32 (2H, d, J 8.0 Hz, 2 x Ar-CH), 7.23-7.15 (4H, m, 3 x Ar-CH and 5-CH), 5.94 (1H, dt, J 5.2 and 12.4 Hz, 6-CH), 5.64 (1H, s, 11-CH), 4.61 (1H, s, 10-CH), 3.71 (3H, s, OMe), 3.49-3.43 (1H, br q, 3-CH), 2.99 (3H, s, OMe), 2.92 (1H, dd, J 11.2 and 13.2 Hz, 8-C(H)H), 2.58 (1H, ddd, J 6.4, 10.0 and 13.2 Hz, 8-C(H)H), 2.39 (1H, dd, J 5.2 and 13.2 Hz, 2-C(H)H), 2.20-2.12 (2H, m, 7-CH₂), 1.43 (9H, s, 14, 15 and 16-CH₃); δ_{C} (100 MHz, CDCl₃) 172.05, 169.12, 165.76 (3 x C=O), 154.60 (4-C), 139.54 (iAr-C), 135.57 (6-C), 128.72 (2 x oAr-C), 127.85 (2 x mAr-C), 127.81 (5-C), 126.11 (pAr-C),
Azepeine 418a or 418b in THF (1.0 ml) and t-BuOH (7.0 µl) was added dropwise to a stirred solution of lithium metal (5 mg, 0.14 mmol) in ammonia (5 ml) at −78°C. This was stirred for 20 min before addition of saturated aqueous ammonium chloride (1 ml). The reaction mixture was allowed to warm to room temperature, then partitioned between ethyl acetate (10 ml) and distilled water (10 ml). The organic layer was then washed with brine (10 ml), and dried over MgSO4. Purification by column chromatography (SiO2, 40-60 P.E:ethyl acetate; 20:1) afforded compound 420 (16 mg, 40%) yellow oil. δH (400 MHz, CDCl3) 7.25-7.14 (5H, m, 5 x Ar-CH), 5.68 (1H, t, J 5.8 Hz, 5-CH), 3.76-3.72 (2H, m, 3-CH and 10-C(H)H), 3.65 (3H, s, OMe), 3.65-3.62 (1H, m, 10-C(H)H), 3.59 (3H, s, OMe), 3.11-3.02 (1H, m, 1-CH), 3.00-2.91 (1H, m, 8-C(H)H), 2.82-2.73 (3H, m, 8-C(H)H and 11-CH2), 2.38-2.27 (1H, m, 2-C(H)H), 2.20-2.10 (2H, m, 6-CH2), 1.81-1.70 (1H, m, 7-C(H)H), 1.38-1.29 (1H, m, 7-C(H)H); δC (100 MHz, CDCl3) 171.27, 170.57, 169.67 (3 x C=O), 140.06 (4-C), 137.63 (iAr-C), 130.03 (5-C), 128.81 (2 x oAr-C), 128.12 (2 x mAr-C), 126.73 (pAr-C), 80.58 (13-C), 63.44 (11-C), 58.80 (10-C), 52.37, 52.37 (OMe), 48.84 (3-C), 48.80 (8-C), 44.62 (11-C), 28.73 (2-C), 28.12 (6-C), 28.08 (14,15 and 16-CH3), 21.84 (7-C); m/z (FAB+) 445 (24), 372 (21), 301 (21), 300 (100), 244 (65); HRMS found 445.2460 [M]+, [C25H33NO8]+ requires 445.2464.
Azepine 418a or 418b (50 mg, 0.13 mmol) in THF (2 ml) was cooled to −78°C under a nitrogen atmosphere. To this solution was added lithium anthracenide (0.10 ml, 100 mg Li and 2.58 g anthracene in 20 ml THF), or enough to turn the reaction mixture deep green. The reaction was stirred for 30 min until TLC experiments confirmed the consumption of starting material. The reaction was then exposed to the air for 10 min, before concentrating under reduced pressure to give a yellow solid. Purification by column chromatography (SiO₂, 40-60 P.E:ethyl acetate; 6:1) afforded the dimer 421 (40 mg, 80%) as a yellow oil. δH (400 MHz, CDCl₃) 7.32-7.14 (10H, m, 10 x Ar-CH), 5.38 (2H, br s, 2 x 5-CH), 4.52 (2H, s, 2 x 10-CH), 3.68 (6H, s, 4 x OMe), 3.42-3.34 (2H, br m, 2 x 3-CH), 3.03 (6H, s, 4 x OMe), 3.02-2.82 (6H, m, 2 x 6-CH and 2 x 11-CH₂), 2.72-2.58 (6H, m, 2 x 2-C(H)H and 2 x 8-CH₂), 2.43 (2H, dd, J 6.0 and 12.8 Hz, 2 x 2-C(H)H), 1.65-1.47 (4H, m, 2 x 7-CH₂), 1.38 (18H, s, 2 x [14,15 and 16 CH₃]); δC (100 MHz, CDCl₃) 171.98, 171.14, 169.16 (6 x C=O), 140.21 (4-C), 134.98 (5-C), 128.51 (4 x oAr-C), 128.16 (2 x iAr-C), 127.83 (4 x mAr-C), 127.60 (2 x pAr-C), 80.51 (13-C), 73.68 (10-C), 64.45 (1-C), 63.76 (3-C), 52.92, 52.00 (8 x OMe), 51.04 (8-C), 43.84 (11-C), 40.07 (6-C), 38.58 (2-C), 30.55 (7-C), 27.97 (14, 15 and 16-C); m/z (FAB+) 886 (46), 885 (60), 884 (49), 883 (36), 443 (40), 442 (22), 441 (25), 387 (32), 386 (95), 385 (37), 384 (47), 342 (71), 341 (31), 340 (100).
To a stirred solution of vinylcyclopropane 259 (100 mg, 0.54 mmol) in DMSO (5 ml), was added tetrakistriphenylphosphine palladium(0) (62 mg, 0.054 mmol), under an atmosphere of nitrogen. This was stirred for 10 min at room temperature before adding phenyl isocyanate (129 mg, 1.08 mmol). The reaction mixture was heated to 80°C for 2 h, giving a deep red solution. The mixture was allowed to cool to room temperature, diluted with water (20 ml), then extracted with ethyl acetate (10 ml). The aqueous fraction was re-extracted with a further portion of ethyl acetate (10 ml), and the organic fractions combined and washed with water (2 x 10 ml) and saturated brine solution (3 x 10 ml). The organic layer was dried over MgSO4 and evaporated under reduced pressure to give an orange oil. Purification by column chromatography (SiO2, 40-60 P.E:ethyl acetate; 6:1) afforded the pyrrolidinone 422 (89 mg, 54%) as a colourless oil. νmax(neat)/cm⁻¹ 3063w, 2953w, 1734s, 1700s (C=O str), 1595m (C=C str), 1491s, 1420s, 1264s; δH (400 MHz, CDCl3) 7.41-7.28 (5H, m, 5 x Ar-C), 5.72-5.60 (1H, ddd, J 17.6 and 10.4 and 17.6 Hz, 6-CH), 5.17 (1H, d, J 17.6 Hz, 7-C(H)H), 5.11 (1H, d, J 10.4 Hz, 7-C(H)H), 4.65 (1H, q, J 7.6 Hz, 4-CH), 3.76 (3H, s, OMe), 3.75 (3H, s, OMe), 3.00 (1H, dd, J 7.6 Hz, 5-C(H)H), 2.54 (1H, dd, J 6.0 Hz, 5-C(H)H); δC (100 MHz, CDCl3) 167.93, 167.50, 165.92 (C=O), 137.03 (iAr-C), 136.28 (6-C), 129.39 (2 x oAr-C), 128.86 (pAr-C), 119.17 (7-C), 63.49 (1-C), 60.05 (4-C), 53.79 (OMe), 53.65 (OMe), 35.07 (5-C); m/z (FAB+) 303 (35), 212 (100), 130 (33), 77 (25); HRMS found 303.1111 [M]+, [C19H21NO6]+ requires 303.1106.
Chapter Eight

8.1 References

(70) Sarel, S. Ace. Chem. Res. 1978, 11, 204-211.
(91) Parsons, P. J.; Karadogan, B.; Macritchie, A. Synlett 2001, 2, 257-259.
(96) Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. Tetrahedron 2002, 58, 6795-6798.
(105) X-ray data produced courtesy of Dr. Mark Elsegood, Loughborough University, 2006.


(141) Liu, H.-J.; Ramani, B. Synthetic Commun. 1985, 15, 965-971.


Chapter Nine

9.1 Appendix
Bis(2-methyl-1-pyrolidine)diiodocaine (343) [pp5].
<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>gp5</td>
</tr>
<tr>
<td>Chemical formula</td>
<td>C_{16}H_{34}N_{2}Zn</td>
</tr>
<tr>
<td>Formula weight</td>
<td>485.43</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2_1/c</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td></td>
</tr>
<tr>
<td>a = 8.2835(8) Å</td>
<td>α = 90°</td>
</tr>
<tr>
<td>b = 11.0457(10) Å</td>
<td>β = 96.772(9)°</td>
</tr>
<tr>
<td>c = 16.1971(19) Å</td>
<td>γ = 90°</td>
</tr>
<tr>
<td>Calculated density</td>
<td>2.191 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient μ</td>
<td>5.840 mm(^{-1})</td>
</tr>
<tr>
<td>F(000)</td>
<td>912</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>pale yellow, 0.90 x 0.78 x 0.68 mm(^2)</td>
</tr>
<tr>
<td>Reflections for cell refinement</td>
<td>7843 (θ range 2.23 to 28.66°)</td>
</tr>
<tr>
<td>Data collection method</td>
<td>Bruker SMART 1000 CCD diffractometer</td>
</tr>
<tr>
<td>0 range for data collection</td>
<td>2.24 to 28.86°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>h −10 to 10, k −14 to 14, l −21 to 21</td>
</tr>
<tr>
<td>Completeness to θ = 26.00°</td>
<td>99.9%</td>
</tr>
<tr>
<td>Intensity decay</td>
<td>0%</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>12336</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3500 (R_{int} = 0.0346)</td>
</tr>
<tr>
<td>Reflections with F^2&gt;2σ</td>
<td>3090</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>semi-empirical from equivalents</td>
</tr>
<tr>
<td>Min. and max. transmission</td>
<td>0.077 and 0.109</td>
</tr>
<tr>
<td>Structure solution</td>
<td>direct methods</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
</tr>
<tr>
<td>Weighting parameters a, b</td>
<td>0.0165, 2.5157</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3500 / 0 / 139</td>
</tr>
<tr>
<td>Final R indices [F^2&gt;2σ]</td>
<td>R_1 = 0.0262, wR2 = 0.0560</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R_1 = 0.0315, wR2 = 0.0575</td>
</tr>
<tr>
<td>Goodness-of-fit on F^2</td>
<td>1.083</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.00171(13)</td>
</tr>
<tr>
<td>Largest and mean shift/su</td>
<td>0.001 and 0.060</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>1.267 and −1.276 e Å(^{-1})</td>
</tr>
</tbody>
</table>
Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å²) for gp5. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^i$ tensor.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$U_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn(1)</td>
<td>0.13588(5)</td>
<td>0.51251(3)</td>
<td>0.18827(2)</td>
<td>0.01673(9)</td>
</tr>
<tr>
<td>I(1)</td>
<td>-0.16910(3)</td>
<td>0.56907(2)</td>
<td>0.156297(15)</td>
<td>0.02601(8)</td>
</tr>
<tr>
<td>I(2)</td>
<td>0.24132(3)</td>
<td>0.52660(2)</td>
<td>0.344346(14)</td>
<td>0.02422(8)</td>
</tr>
<tr>
<td>N(1)</td>
<td>0.2627(3)</td>
<td>0.6264(3)</td>
<td>0.12145(17)</td>
<td>0.0186(6)</td>
</tr>
<tr>
<td>C(1)</td>
<td>0.2636(4)</td>
<td>0.7424(3)</td>
<td>0.1217(2)</td>
<td>0.0226(7)</td>
</tr>
<tr>
<td>C(2)</td>
<td>0.3671(5)</td>
<td>0.7963(4)</td>
<td>0.0621(2)</td>
<td>0.0325(9)</td>
</tr>
<tr>
<td>C(3)</td>
<td>0.4230(3)</td>
<td>0.6885(4)</td>
<td>0.0147(3)</td>
<td>0.0356(10)</td>
</tr>
<tr>
<td>C(4)</td>
<td>0.3681(4)</td>
<td>0.5792(3)</td>
<td>0.0609(2)</td>
<td>0.0251(8)</td>
</tr>
<tr>
<td>C(5)</td>
<td>0.1718(5)</td>
<td>0.8168(4)</td>
<td>0.1760(3)</td>
<td>0.0342(9)</td>
</tr>
<tr>
<td>N(2)</td>
<td>0.1677(3)</td>
<td>0.3488(3)</td>
<td>0.13496(17)</td>
<td>0.0186(6)</td>
</tr>
<tr>
<td>C(6)</td>
<td>0.2830(4)</td>
<td>0.2722(3)</td>
<td>0.1487(2)</td>
<td>0.0218(7)</td>
</tr>
<tr>
<td>C(7)</td>
<td>0.2536(5)</td>
<td>0.1563(3)</td>
<td>0.1016(2)</td>
<td>0.0297(8)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.1107(5)</td>
<td>0.1873(3)</td>
<td>0.0369(2)</td>
<td>0.0297(8)</td>
</tr>
<tr>
<td>C(9)</td>
<td>0.0366(4)</td>
<td>0.2999(3)</td>
<td>0.0736(2)</td>
<td>0.0264(8)</td>
</tr>
<tr>
<td>C(10)</td>
<td>0.4317(3)</td>
<td>0.2923(4)</td>
<td>0.2076(2)</td>
<td>0.0291(8)</td>
</tr>
</tbody>
</table>

Table 3. Bond lengths [Å] and angles [°] for gp5.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
<th>Bond</th>
<th>Length [Å]</th>
<th>Bond</th>
<th>Length [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn(1)-N(1)</td>
<td>2.031(3)</td>
<td>Zn(1)-N(2)</td>
<td>2.035(3)</td>
<td>Zn(1)-I(1)</td>
<td>2.5947(5)</td>
</tr>
<tr>
<td>Zn(1)-I(2)</td>
<td>2.5801(5)</td>
<td>N(1)-C(1)</td>
<td>1.282(4)</td>
<td>N(1)-C(4)</td>
<td>1.482(4)</td>
</tr>
<tr>
<td>N(1)-C(5)</td>
<td>1.477(5)</td>
<td>C(1)-C(2)</td>
<td>1.489(5)</td>
<td>C(3)-C(4)</td>
<td>1.519(5)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.518(6)</td>
<td>C(3)-C(4)</td>
<td>1.485(4)</td>
<td>N(2)-C(9)</td>
<td>1.495(5)</td>
</tr>
<tr>
<td>N(2)-C(6)</td>
<td>1.276(5)</td>
<td>C(6)-C(7)</td>
<td>1.537(5)</td>
<td>C(6)-C(10)</td>
<td>1.524(5)</td>
</tr>
<tr>
<td>C(6)-C(10)</td>
<td>1.482(5)</td>
<td>N(1)-Zn(1)-N(2)</td>
<td>102.89(11)</td>
<td>N(1)-Zn(1)-I(2)</td>
<td>110.38(8)</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.524(5)</td>
<td>N(2)-Zn(1)-I(2)</td>
<td>115.06(8)</td>
<td>N(1)-Zn(1)-I(1)</td>
<td>107.29(8)</td>
</tr>
<tr>
<td>N(1)-Zn(1)-N(2)</td>
<td>107.53(8)</td>
<td>N(2)-Zn(1)-I(1)</td>
<td>112.965(18)</td>
<td>I(2)-Zn(1)-I(1)</td>
<td>128.4(3)</td>
</tr>
<tr>
<td>C(1)-N(1)-C(4)</td>
<td>110.5(3)</td>
<td>C(1)-N(1)-I(1)</td>
<td>123.7(4)</td>
<td>C(1)-C(1)-C(2)</td>
<td>122.7(3)</td>
</tr>
<tr>
<td>C(4)-N(1)-Zn(1)</td>
<td>121.1(2)</td>
<td>C(1)-C(1)-C(2)</td>
<td>104.3(3)</td>
<td>C(2)-C(1)-C(2)</td>
<td>101.5(3)</td>
</tr>
<tr>
<td>N(1)-C(1)-C(4)</td>
<td>113.6(3)</td>
<td>C(2)-C(1)-C(2)</td>
<td>104.3(3)</td>
<td>C(6)-N(2)-C(9)</td>
<td>119.1(2)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)</td>
<td>104.4(3)</td>
<td>C(6)-N(2)-Zn(1)</td>
<td>124.1(3)</td>
<td>N(2)-C(6)-C(7)</td>
<td>115.9(3)</td>
</tr>
<tr>
<td>N(1)-C(4)-C(3)</td>
<td>106.3(3)</td>
<td>N(2)-C(6)-C(10)</td>
<td>122.0(3)</td>
<td>C(6)-C(7)-C(8)</td>
<td>103.0(3)</td>
</tr>
<tr>
<td>C(6)-N(2)-Zn(1)</td>
<td>130.3(2)</td>
<td>C(6)-C(7)-C(8)</td>
<td>105.0(3)</td>
<td>C(7)-C(8)-C(9)</td>
<td>103.0(3)</td>
</tr>
</tbody>
</table>
Table 4. Hydrogen coordinates and isotropic displacement parameters ($\AA^2$) for gp5.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(2A)</td>
<td>0.4611</td>
<td>0.8396</td>
<td>0.0919</td>
<td>0.039</td>
</tr>
<tr>
<td>H(2B)</td>
<td>0.3037</td>
<td>0.8535</td>
<td>0.0240</td>
<td>0.039</td>
</tr>
<tr>
<td>H(3A)</td>
<td>0.5427</td>
<td>0.6889</td>
<td>0.0153</td>
<td>0.043</td>
</tr>
<tr>
<td>H(3B)</td>
<td>0.3718</td>
<td>0.6891</td>
<td>-0.0437</td>
<td>0.043</td>
</tr>
<tr>
<td>H(4A)</td>
<td>0.3068</td>
<td>0.5223</td>
<td>0.0218</td>
<td>0.030</td>
</tr>
<tr>
<td>H(4B)</td>
<td>0.4630</td>
<td>0.5362</td>
<td>0.0901</td>
<td>0.030</td>
</tr>
<tr>
<td>H(5A)</td>
<td>0.1296</td>
<td>0.7648</td>
<td>0.2175</td>
<td>0.051</td>
</tr>
<tr>
<td>H(5B)</td>
<td>0.0811</td>
<td>0.8567</td>
<td>0.1423</td>
<td>0.051</td>
</tr>
<tr>
<td>H(5C)</td>
<td>0.2439</td>
<td>0.3872</td>
<td>0.2041</td>
<td>0.051</td>
</tr>
<tr>
<td>H(7A)</td>
<td>0.2254</td>
<td>0.0900</td>
<td>0.1384</td>
<td>0.036</td>
</tr>
<tr>
<td>H(7B)</td>
<td>0.3502</td>
<td>0.1324</td>
<td>0.0748</td>
<td>0.036</td>
</tr>
<tr>
<td>H(8A)</td>
<td>0.0313</td>
<td>0.1201</td>
<td>0.0301</td>
<td>0.036</td>
</tr>
<tr>
<td>H(8B)</td>
<td>0.1479</td>
<td>0.2057</td>
<td>-0.0176</td>
<td>0.036</td>
</tr>
<tr>
<td>H(9A)</td>
<td>0.0038</td>
<td>0.3603</td>
<td>0.0296</td>
<td>0.032</td>
</tr>
<tr>
<td>H(9B)</td>
<td>-0.0599</td>
<td>0.2778</td>
<td>0.1011</td>
<td>0.032</td>
</tr>
<tr>
<td>H(10A)</td>
<td>0.4377</td>
<td>0.3776</td>
<td>0.2243</td>
<td>0.044</td>
</tr>
<tr>
<td>H(10B)</td>
<td>0.5277</td>
<td>0.2713</td>
<td>0.1805</td>
<td>0.044</td>
</tr>
<tr>
<td>H(10C)</td>
<td>0.4279</td>
<td>0.2413</td>
<td>0.2568</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Table 5. Torsion angles [°] for gp5.

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N(2)–Zn(1)–N(1)–C(1)</td>
<td>169.2(3)</td>
<td>I(2)–Zn(1)–N(1)–C(1)</td>
<td>-67.5(3)</td>
<td></td>
</tr>
<tr>
<td>I(1)–Zn(1)–N(1)–C(1)</td>
<td>55.9(3)</td>
<td>N(2)–Zn(1)–N(1)–C(4)</td>
<td>-8.9(3)</td>
<td></td>
</tr>
<tr>
<td>I(2)–Zn(1)–N(1)–C(4)</td>
<td>114.4(2)</td>
<td>I(1)–Zn(1)–N(1)–C(4)</td>
<td>-122.1(2)</td>
<td></td>
</tr>
<tr>
<td>C(4)–N(1)–C(1)–C(5)</td>
<td>-179.4(3)</td>
<td>Zn(1)–N(1)–C(1)–C(5)</td>
<td>2.4(5)</td>
<td></td>
</tr>
<tr>
<td>C(4)–N(1)–C(1)–C(2)</td>
<td>0.4(4)</td>
<td>Zn(1)–N(1)–C(1)–C(2)</td>
<td>-177.9(2)</td>
<td></td>
</tr>
<tr>
<td>N(1)–C(1)–C(2)–C(3)</td>
<td>5.6(4)</td>
<td>Zn(1)–N(1)–C(1)–C(3)</td>
<td>-174.7(3)</td>
<td></td>
</tr>
<tr>
<td>C(1)–C(2)–C(3)–C(4)</td>
<td>-8.8(4)</td>
<td>C(5)–C(1)–C(2)–C(3)</td>
<td>-6.2(4)</td>
<td></td>
</tr>
<tr>
<td>Zn(1)–N(1)–C(1)–C(3)</td>
<td>172.1(2)</td>
<td>C(1)–N(1)–C(4)–C(3)</td>
<td>9.2(4)</td>
<td></td>
</tr>
<tr>
<td>N(1)–Zn(1)–N(2)–C(6)</td>
<td>85.1(3)</td>
<td>C(2)–C(3)–C(4)–N(1)</td>
<td>-35.0(3)</td>
<td></td>
</tr>
<tr>
<td>I(1)–Zn(1)–N(2)–C(6)</td>
<td>-161.9(3)</td>
<td>I(2)–Zn(1)–N(2)–C(6)</td>
<td>-99.7(2)</td>
<td></td>
</tr>
<tr>
<td>I(2)–Zn(1)–N(2)–C(9)</td>
<td>140.2(2)</td>
<td>N(1)–Zn(1)–N(2)–C(9)</td>
<td>13.4(3)</td>
<td></td>
</tr>
<tr>
<td>C(9)–N(2)–C(6)–C(10)</td>
<td>-179.3(3)</td>
<td>Zn(1)–N(2)–C(6)–C(10)</td>
<td>-3.8(3)</td>
<td></td>
</tr>
<tr>
<td>C(9)–N(2)–C(6)–C(7)</td>
<td>-1.0(4)</td>
<td>Zn(1)–N(2)–C(6)–C(7)</td>
<td>174.6(2)</td>
<td></td>
</tr>
<tr>
<td>N(2)–C(6)–C(7)–C(8)</td>
<td>13.8(4)</td>
<td>Zn(1)–N(2)–C(6)–C(7)</td>
<td>-167.8(3)</td>
<td></td>
</tr>
<tr>
<td>C(6)–C(7)–C(8)–C(9)</td>
<td>-19.7(4)</td>
<td>C(10)–C(6)–C(7)–C(8)</td>
<td>-12.3(4)</td>
<td></td>
</tr>
<tr>
<td>Zn(1)–N(2)–C(9)–C(8)</td>
<td>171.6(2)</td>
<td>C(6)–N(2)–C(9)–C(8)</td>
<td>19.7(4)</td>
<td></td>
</tr>
</tbody>
</table>
4-tert-Butoxycarbonyl-(E)-methylene-10-phenyl-2,3,7,8-tetrahydro-1H-pyrrolo[1,2-a]azepine-1,1-dicarboxylic acid dimethyl ester (458a) [gp7].
Table 1. Crystal data and structure refinement for gp7

<table>
<thead>
<tr>
<th>Identification code</th>
<th>gp7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C_{21}H_{13}NO_{6}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>441.51</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2₁</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>a = 9.3057(8) Å, α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 13.1079(11) Å, β = 95.186(2)°</td>
</tr>
<tr>
<td></td>
<td>c = 9.5560(8) Å, γ = 90°</td>
</tr>
<tr>
<td>Cell volume</td>
<td>1160.85(17) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Calculated density</td>
<td>1.263 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient μ</td>
<td>0.090 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>472</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>pale yellow, 0.31 x 0.15 x 0.14 mm³</td>
</tr>
<tr>
<td>Reflections for cell refinement</td>
<td>3096 (0 range 2.65 to 26.34°)</td>
</tr>
<tr>
<td>Data collection method</td>
<td>Bruker APEX 2 CCD diffractometer, ω rotation with narrow frames</td>
</tr>
<tr>
<td>0 range for data collection</td>
<td>2.14 to 26.41°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>h -11 to 11, k -16 to 16, l -11 to 11</td>
</tr>
<tr>
<td>Completeness to 0 = 26.00°</td>
<td>100.0%</td>
</tr>
<tr>
<td>Intensity decay</td>
<td>0%</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>10450</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2488 (R_{int} = 0.0471)</td>
</tr>
<tr>
<td>Reflections with F³&gt;2σ</td>
<td>2094</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>semi-empirical from equivalents</td>
</tr>
<tr>
<td>Min. and max. transmission</td>
<td>0.973 and 0.988</td>
</tr>
<tr>
<td>Structure solution</td>
<td>direct methods</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Weighting parameters a, b</td>
<td>0.0389, 0.1009</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2488 / 1 / 294</td>
</tr>
<tr>
<td>Final R indices [F³&gt;2σ]</td>
<td>R₁ = 0.0343, wR₂ = 0.0715</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R₁ = 0.0502, wR₂ = 0.0796</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.037</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>10(10), Friedel's merged; absolute structure unknown</td>
</tr>
<tr>
<td>Largest and mean shift/su</td>
<td>0.040 and 0.000</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.173 and -0.179 e Å⁻³</td>
</tr>
</tbody>
</table>
Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å²) for gp7. \(U_{eq}\) is defined as one third of the trace of the orthogonalized \(U^t\) tensor.

<table>
<thead>
<tr>
<th></th>
<th>(x)</th>
<th>(y)</th>
<th>(z)</th>
<th>(U_{eq})</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)</td>
<td>0.2733(2)</td>
<td>0.73848(15)</td>
<td>-0.0190(2)</td>
<td>0.0205(4)</td>
</tr>
<tr>
<td>C(1)</td>
<td>0.3343(3)</td>
<td>0.69201(19)</td>
<td>0.1119(3)</td>
<td>0.0207(5)</td>
</tr>
<tr>
<td>C(2)</td>
<td>0.4970(3)</td>
<td>0.70097(19)</td>
<td>0.1377(3)</td>
<td>0.0223(5)</td>
</tr>
<tr>
<td>C(3)</td>
<td>0.5862(3)</td>
<td>0.7501(2)</td>
<td>0.0372(3)</td>
<td>0.0274(6)</td>
</tr>
<tr>
<td>C(4)</td>
<td>0.5550(3)</td>
<td>0.8205(2)</td>
<td>-0.0627(3)</td>
<td>0.0316(6)</td>
</tr>
<tr>
<td>C(5)</td>
<td>0.4180(3)</td>
<td>0.8738(2)</td>
<td>-0.1087(3)</td>
<td>0.0310(6)</td>
</tr>
<tr>
<td>C(6)</td>
<td>0.2922(3)</td>
<td>0.84917(19)</td>
<td>-0.0255(3)</td>
<td>0.0248(6)</td>
</tr>
<tr>
<td>C(7)</td>
<td>0.1216(2)</td>
<td>0.70588(19)</td>
<td>-0.0371(3)</td>
<td>0.0206(5)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.1250(3)</td>
<td>0.59516(18)</td>
<td>0.0283(2)</td>
<td>0.0202(5)</td>
</tr>
<tr>
<td>C(9)</td>
<td>0.2833(3)</td>
<td>0.58198(19)</td>
<td>0.0885(3)</td>
<td>0.0233(5)</td>
</tr>
<tr>
<td>C(10)</td>
<td>0.5694(3)</td>
<td>0.6603(2)</td>
<td>0.2534(3)</td>
<td>0.0245(5)</td>
</tr>
<tr>
<td>C(11)</td>
<td>0.5062(3)</td>
<td>0.6100(2)</td>
<td>0.3715(3)</td>
<td>0.0272(6)</td>
</tr>
<tr>
<td>O(1)</td>
<td>0.3833(2)</td>
<td>0.61989(18)</td>
<td>0.4025(2)</td>
<td>0.0411(5)</td>
</tr>
<tr>
<td>O(2)</td>
<td>0.60640(18)</td>
<td>0.55093(15)</td>
<td>0.44140(19)</td>
<td>0.0283(4)</td>
</tr>
<tr>
<td>C(12)</td>
<td>0.5695(3)</td>
<td>0.4829(2)</td>
<td>0.5567(3)</td>
<td>0.0326(7)</td>
</tr>
<tr>
<td>C(13)</td>
<td>0.7114(4)</td>
<td>0.4289(3)</td>
<td>0.5942(4)</td>
<td>0.0560(10)</td>
</tr>
<tr>
<td>C(14)</td>
<td>0.5259(4)</td>
<td>0.5446(3)</td>
<td>0.6802(3)</td>
<td>0.0448(8)</td>
</tr>
<tr>
<td>C(15)</td>
<td>0.4542(4)</td>
<td>0.4083(3)</td>
<td>0.5017(4)</td>
<td>0.0513(9)</td>
</tr>
<tr>
<td>C(16)</td>
<td>0.0588(3)</td>
<td>0.71297(18)</td>
<td>-0.1882(3)</td>
<td>0.0210(5)</td>
</tr>
<tr>
<td>C(17)</td>
<td>0.1432(3)</td>
<td>0.69730(19)</td>
<td>-0.2993(3)</td>
<td>0.0246(6)</td>
</tr>
<tr>
<td>C(18)</td>
<td>0.0813(3)</td>
<td>0.7003(2)</td>
<td>-0.4370(3)</td>
<td>0.0295(6)</td>
</tr>
<tr>
<td>C(19)</td>
<td>-0.0641(3)</td>
<td>0.7178(2)</td>
<td>-0.4653(3)</td>
<td>0.0331(7)</td>
</tr>
<tr>
<td>C(20)</td>
<td>-0.1484(3)</td>
<td>0.7344(2)</td>
<td>-0.3557(3)</td>
<td>0.0350(7)</td>
</tr>
<tr>
<td>C(21)</td>
<td>-0.0875(3)</td>
<td>0.7317(2)</td>
<td>-0.2182(3)</td>
<td>0.0275(6)</td>
</tr>
<tr>
<td>C(22)</td>
<td>0.0237(3)</td>
<td>0.58842(19)</td>
<td>0.1465(3)</td>
<td>0.0222(5)</td>
</tr>
<tr>
<td>O(3)</td>
<td>-0.0544(2)</td>
<td>0.65473(14)</td>
<td>0.18068(19)</td>
<td>0.0326(5)</td>
</tr>
<tr>
<td>O(4)</td>
<td>0.03545(19)</td>
<td>0.49691(14)</td>
<td>0.20727(19)</td>
<td>0.0287(4)</td>
</tr>
<tr>
<td>C(23)</td>
<td>-0.0539(3)</td>
<td>0.4800(2)</td>
<td>0.3213(3)</td>
<td>0.0315(6)</td>
</tr>
<tr>
<td>C(24)</td>
<td>0.0706(3)</td>
<td>0.51604(18)</td>
<td>-0.0806(3)</td>
<td>0.0224(5)</td>
</tr>
<tr>
<td>O(5)</td>
<td>-0.0548(2)</td>
<td>0.49393(16)</td>
<td>-0.1037(2)</td>
<td>0.0356(5)</td>
</tr>
<tr>
<td>O(6)</td>
<td>0.17617(19)</td>
<td>0.47742(14)</td>
<td>-0.14906(19)</td>
<td>0.0289(4)</td>
</tr>
<tr>
<td>C(25)</td>
<td>0.1299(4)</td>
<td>0.4078(2)</td>
<td>-0.2623(3)</td>
<td>0.0404(8)</td>
</tr>
</tbody>
</table>
### Table 3. Bond lengths [Å] and angles [°] for gp7.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length/Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)–C(1)</td>
<td>1.459(3)</td>
</tr>
<tr>
<td>N(1)–C(7)</td>
<td>1.470(3)</td>
</tr>
<tr>
<td>C(1)–C(9)</td>
<td>1.528(4)</td>
</tr>
<tr>
<td>C(2)–C(3)</td>
<td>1.473(4)</td>
</tr>
<tr>
<td>C(4)–C(5)</td>
<td>1.485(4)</td>
</tr>
<tr>
<td>C(7)–C(16)</td>
<td>1.511(3)</td>
</tr>
<tr>
<td>C(8)–C(24)</td>
<td>1.523(3)</td>
</tr>
<tr>
<td>C(8)–C(9)</td>
<td>1.542(3)</td>
</tr>
<tr>
<td>C(11)–O(1)</td>
<td>1.214(3)</td>
</tr>
<tr>
<td>C(12)–C(13)</td>
<td>1.512(4)</td>
</tr>
<tr>
<td>C(16)–C(21)</td>
<td>1.387(3)</td>
</tr>
<tr>
<td>C(17)–C(18)</td>
<td>1.389(4)</td>
</tr>
<tr>
<td>C(19)–C(20)</td>
<td>1.381(4)</td>
</tr>
<tr>
<td>C(22)–O(3)</td>
<td>1.197(3)</td>
</tr>
<tr>
<td>O(4)–C(23)</td>
<td>1.446(3)</td>
</tr>
<tr>
<td>C(24)–O(6)</td>
<td>1.329(3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length/Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)–N(1)–C(6)</td>
<td>114.3(2)</td>
</tr>
<tr>
<td>C(6)–N(1)–C(7)</td>
<td>113.61(19)</td>
</tr>
<tr>
<td>N(1)–C(1)–C(9)</td>
<td>100.20(19)</td>
</tr>
<tr>
<td>C(10)–C(2)–C(3)</td>
<td>115.9(2)</td>
</tr>
<tr>
<td>C(3)–C(2)–C(1)</td>
<td>122.8(2)</td>
</tr>
<tr>
<td>C(3)–C(4)–C(5)</td>
<td>131.3(3)</td>
</tr>
<tr>
<td>N(1)–C(6)–C(5)</td>
<td>109.6(2)</td>
</tr>
<tr>
<td>N(1)–C(7)–C(8)</td>
<td>103.64(18)</td>
</tr>
<tr>
<td>C(24)–C(8)–C(22)</td>
<td>105.95(19)</td>
</tr>
<tr>
<td>C(22)–C(8)–C(9)</td>
<td>110.4(2)</td>
</tr>
<tr>
<td>C(22)–C(8)–C(7)</td>
<td>110.59(19)</td>
</tr>
<tr>
<td>C(1)–C(9)–C(8)</td>
<td>102.84(19)</td>
</tr>
<tr>
<td>O(1)–C(11)–O(2)</td>
<td>124.5(2)</td>
</tr>
<tr>
<td>O(2)–C(11)–C(10)</td>
<td>109.3(2)</td>
</tr>
<tr>
<td>O(2)–C(12)–C(15)</td>
<td>109.7(2)</td>
</tr>
<tr>
<td>C(15)–C(12)–C(13)</td>
<td>110.9(3)</td>
</tr>
<tr>
<td>C(15)–C(12)–C(14)</td>
<td>112.6(3)</td>
</tr>
<tr>
<td>C(21)–C(16)–C(17)</td>
<td>118.6(3)</td>
</tr>
<tr>
<td>C(17)–C(16)–C(7)</td>
<td>121.6(2)</td>
</tr>
<tr>
<td>C(19)–C(18)–C(17)</td>
<td>120.5(3)</td>
</tr>
<tr>
<td>C(19)–C(20)–C(21)</td>
<td>120.3(3)</td>
</tr>
<tr>
<td>O(3)–C(22)–O(4)</td>
<td>124.2(2)</td>
</tr>
<tr>
<td>O(4)–C(22)–C(8)</td>
<td>109.9(2)</td>
</tr>
<tr>
<td>O(5)–C(24)–O(6)</td>
<td>124.4(2)</td>
</tr>
<tr>
<td>O(6)–C(24)–C(8)</td>
<td>112.4(2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length/Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)–C(1)–C(2)</td>
<td>1.463(3)</td>
</tr>
<tr>
<td>C(1)–C(2)–C(10)</td>
<td>1.517(3)</td>
</tr>
<tr>
<td>C(2)–C(10)–C(11)</td>
<td>1.352(4)</td>
</tr>
<tr>
<td>C(3)–C(4)–C(5)</td>
<td>1.341(4)</td>
</tr>
<tr>
<td>C(5)–C(6)–C(7)</td>
<td>1.509(4)</td>
</tr>
<tr>
<td>C(7)–C(8)–C(9)</td>
<td>1.579(3)</td>
</tr>
<tr>
<td>C(8)–C(22)–C(21)</td>
<td>1.538(3)</td>
</tr>
<tr>
<td>C(10)–C(11)–C(12)</td>
<td>1.472(4)</td>
</tr>
<tr>
<td>C(12)–C(11)–C(13)</td>
<td>1.343(3)</td>
</tr>
<tr>
<td>C(16)–C(17)–C(18)</td>
<td>1.511(4)</td>
</tr>
<tr>
<td>C(19)–C(20)–C(21)</td>
<td>1.516(4)</td>
</tr>
<tr>
<td>C(22)–O(3)–C(23)</td>
<td>1.392(3)</td>
</tr>
<tr>
<td>C(24)–O(6)–C(25)</td>
<td>1.374(4)</td>
</tr>
<tr>
<td>C(24)–O(6)–C(25)</td>
<td>1.383(4)</td>
</tr>
<tr>
<td>C(24)–O(6)–C(25)</td>
<td>1.333(3)</td>
</tr>
<tr>
<td>C(24)–O(6)–C(25)</td>
<td>1.203(3)</td>
</tr>
<tr>
<td>C(24)–O(6)–C(25)</td>
<td>1.451(3)</td>
</tr>
</tbody>
</table>
Table 4. Hydrogen coordinates and isotropic displacement parameters (Å^2) for gp7.

<table>
<thead>
<tr>
<th></th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1)</td>
<td>0.2880</td>
<td>0.7222</td>
<td>0.1928</td>
<td>0.025</td>
</tr>
<tr>
<td>H(3)</td>
<td>0.6838</td>
<td>0.7278</td>
<td>0.0446</td>
<td>0.033</td>
</tr>
<tr>
<td>H(4)</td>
<td>0.6244</td>
<td>0.8396</td>
<td>-0.1129</td>
<td>0.038</td>
</tr>
<tr>
<td>H(5A)</td>
<td>0.3908</td>
<td>0.8566</td>
<td>-0.2085</td>
<td>0.037</td>
</tr>
<tr>
<td>H(5B)</td>
<td>0.4355</td>
<td>0.9482</td>
<td>-0.1034</td>
<td>0.037</td>
</tr>
<tr>
<td>H(6A)</td>
<td>0.3100</td>
<td>0.8771</td>
<td>0.0708</td>
<td>0.030</td>
</tr>
<tr>
<td>H(6B)</td>
<td>0.2033</td>
<td>0.8810</td>
<td>-0.0707</td>
<td>0.030</td>
</tr>
<tr>
<td>H(7)</td>
<td>0.0643</td>
<td>0.7511</td>
<td>0.0213</td>
<td>0.025</td>
</tr>
<tr>
<td>H(9A)</td>
<td>0.2899</td>
<td>0.5434</td>
<td>0.1779</td>
<td>0.028</td>
</tr>
<tr>
<td>H(9B)</td>
<td>0.3405</td>
<td>0.5464</td>
<td>0.0209</td>
<td>0.028</td>
</tr>
<tr>
<td>H(10)</td>
<td>0.6717</td>
<td>0.6645</td>
<td>0.2593</td>
<td>0.029</td>
</tr>
<tr>
<td>H(13A)</td>
<td>0.7411</td>
<td>0.3935</td>
<td>0.5112</td>
<td>0.084</td>
</tr>
<tr>
<td>H(13B)</td>
<td>-0.6999</td>
<td>0.3793</td>
<td>0.6691</td>
<td>0.084</td>
</tr>
<tr>
<td>H(13C)</td>
<td>0.7852</td>
<td>0.4791</td>
<td>0.6267</td>
<td>0.084</td>
</tr>
<tr>
<td>H(14A)</td>
<td>0.6032</td>
<td>0.5926</td>
<td>0.7106</td>
<td>0.067</td>
</tr>
<tr>
<td>H(14B)</td>
<td>0.5092</td>
<td>0.4986</td>
<td>0.7579</td>
<td>0.067</td>
</tr>
<tr>
<td>H(14C)</td>
<td>0.4372</td>
<td>0.5824</td>
<td>0.6519</td>
<td>0.067</td>
</tr>
<tr>
<td>H(15A)</td>
<td>0.3621</td>
<td>0.4442</td>
<td>0.4832</td>
<td>0.077</td>
</tr>
<tr>
<td>H(15B)</td>
<td>0.4443</td>
<td>0.3547</td>
<td>0.5718</td>
<td>0.077</td>
</tr>
<tr>
<td>H(15C)</td>
<td>0.4813</td>
<td>0.3774</td>
<td>0.4145</td>
<td>0.077</td>
</tr>
<tr>
<td>H(17)</td>
<td>0.2436</td>
<td>0.6845</td>
<td>-0.2808</td>
<td>0.030</td>
</tr>
<tr>
<td>H(18)</td>
<td>0.1398</td>
<td>0.6902</td>
<td>-0.5123</td>
<td>0.035</td>
</tr>
<tr>
<td>H(19)</td>
<td>-0.1063</td>
<td>0.7185</td>
<td>-0.5596</td>
<td>0.040</td>
</tr>
<tr>
<td>H(20)</td>
<td>-0.2486</td>
<td>0.7477</td>
<td>-0.3748</td>
<td>0.042</td>
</tr>
<tr>
<td>H(21)</td>
<td>-0.1464</td>
<td>0.7429</td>
<td>-0.1435</td>
<td>0.033</td>
</tr>
<tr>
<td>H(23A)</td>
<td>-0.0216</td>
<td>0.5245</td>
<td>0.4004</td>
<td>0.047</td>
</tr>
<tr>
<td>H(23B)</td>
<td>-0.0461</td>
<td>0.4086</td>
<td>0.3512</td>
<td>0.047</td>
</tr>
<tr>
<td>H(23C)</td>
<td>-0.1546</td>
<td>0.4956</td>
<td>0.2895</td>
<td>0.047</td>
</tr>
<tr>
<td>H(25A)</td>
<td>0.0713</td>
<td>0.3533</td>
<td>-0.2262</td>
<td>0.061</td>
</tr>
<tr>
<td>H(25B)</td>
<td>0.2148</td>
<td>0.3780</td>
<td>-0.3004</td>
<td>0.061</td>
</tr>
<tr>
<td>H(25C)</td>
<td>0.0725</td>
<td>0.4450</td>
<td>-0.3367</td>
<td>0.061</td>
</tr>
</tbody>
</table>