New Routes to Indolizidine Alkaloids: The Total Synthesis of (−)-Grandisine B

James David Cuthbertson

Thesis submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy

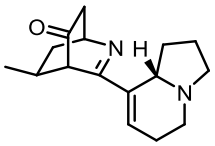
The University of York

Department of Chemistry

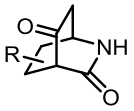
September 2011

Abstract

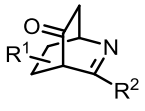
The plant family *Elaeocarpaceae* has been the source of a plethora of structurally related alkaloids isolated over the last 50 years. This Thesis describes our synthetic approaches to (−)-grandisine B **I**, a bioactive indolizidine alkaloid isolated from *Elaocarpus grandis* in 2005. An overview of alkaloids isolated from the family *Elaeocarpaceae* is provided and preliminary studies into the synthesis of grandisine B **I** are described (Chapters **1** and **2**).



I

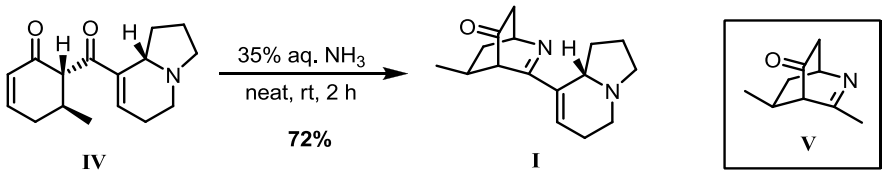


II



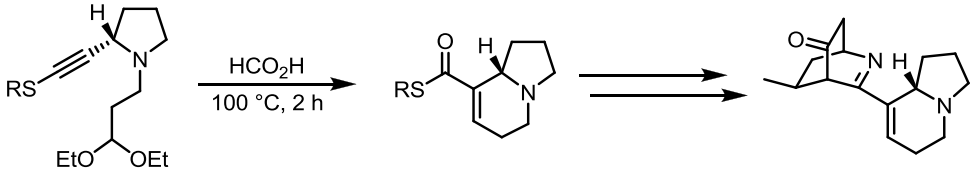
III

Novel routes to bicyclic lactams **II** and isoquinuclidinone frameworks **III** have been developed using aqueous ammonia in a one-pot amination/cyclisation sequence (Chapters **3** and **4**). The scope of the developed methodology was initially demonstrated with a concise synthesis of the alkaloid (−)-mearsine **V**. A biomimetic synthesis of (±)-grandisine B **I**, using the alkaloid grandisine D **IV** as a synthetic precursor, is then described in Chapter **5**.



IV **I** **V**

The development of a formic acid mediated alkyne/acetal cyclisation for the synthesis of heterocyclic scaffolds is also reported. The scope and limitations of the methodology are discussed and applications of the methodology in the synthesis of (−)-grandisine B **I** and structurally related *Elaeocarpus* alkaloids are described (Chapter **6**).



VI **VII** **I**

Contents

List of Figures

List of Tables

Acknowledgements

First and foremost I would like to thank Prof. Richard Taylor for giving me the opportunity to work as part of his research group and for his continuing support and encouragement over the past four years.

I would also like to acknowledge all the members of the Taylor group past and present who have made my time in York so enjoyable. Thanks go to Alan, Alessia, Alexis, Cat, Dan, Dave, David, James, Jana, Johannes, Jon, Katie, Mark, Mary, Mélanie, Mickaël, Mike, Monique, Nicola, Pauline, Phil, René, Reyhan, Rich, Russ, Sandra, Subhrangsu, Vil, Will B and Will U. Particular thanks go to Mike Edwards and Will Unsworth for proof reading this Thesis and to Graeme McAllister for running numerous NMR and CHN samples and doing all the other jobs that benefit the group. Additional thanks go to Dan and Dave for being great flatmates.

Thanks also go to all the technical staff in the chemistry department, in particular, Heather and Amanda (NMR), Trevor, Ben and Karl (Mass Spec), Adrian and Rob (X-ray Crystallography), Phil and Graeme (CHN), Mike, Steve and Val (Stores) and Brian and Abby (Glass Blowing Workshop) whose help and assistance has made the work in this thesis possible.

I would also like to thank my CASE supervisor Andy Godfrey for his help and support over the last four years. Thanks also go to all those at AZ Macclesfield who I had the opportunity to work with whilst on CASE placement. In particular, thanks go to Andy Hard for assistance with chiral HPLC studies.

Finally, I would like to thank my family for their continuing support and encouragement throughout my studies.

Declaration

The research presented in this Thesis was carried out at the University of York between October 2007 and April 2011. The work is, to the best of my knowledge, original except where due reference has been made to other workers.

James Cuthbertson
September 2011

Chapter 1. Introduction

1.1 Alkaloids of Elaeocarpus sp.

1.1.1 *E. polydactylus*

The plant family *elaeocarpaceae* has been the source of a plethora of structurally related alkaloids isolated over the last 50 years.[1] Initial studies by Lamberton and co-workers on extracts from the species *E. polydactylus* revealed two members of a previously undescribed class of indolizidine alkaloids; elaeocarpine **1** and a stereo-isomer isoelaeocarpine **2**.[2]

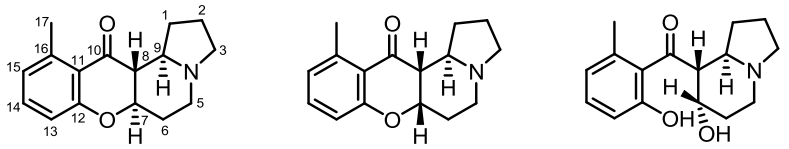


Figure 1.1 Alkaloids isolated from *Elaeocarpus polydactylus*.[2, 3]

Unequivocal evidence for the structure of elaeocarpine **1** was provided by single crystal X-ray diffraction analysis of the hydrobromide salt, with NMR spectroscopic analysis showing the isomeric alkaloid **2** to possess *cis*-stereochemistry at the C-7 and C-8 ring junction (J = 2.1 Hz). Interconversion of the two species in methanolic potassium hydroxide at room temperature was reported to give, at equilibrium, a 1:1 mixture of the two diastereoisomers.[2]

Further studies on extracts from the same species revealed a third alkaloid, isoelaeocarpicine **3**.[3] Whilst the previously isolated alkaloids were found to be racemic, isoelaeocarpicine **3** was optically active, isolated as (+)-**3**. Lamberton reported that heating isoeleaocarpicine **3** in methanolic sodium hydroxide resulted in the rapid formation of elaeocarpine (+)-**1** and racemic isoelaeocarpine **2**.

1.1.2 *E. dolichostylis*

Extracts from *E. dolichostylis* (New Guinea) revealed two additional structurally related indolizidine alkaloids, identified as (+)-elaeocarpiline **4** and (−)-isoelaeocarpiline **5** in which the C-15, C-16 bond is saturated.[4,5]

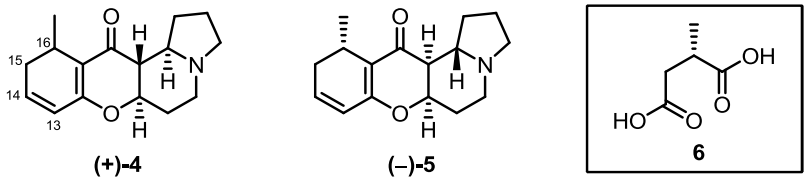


Figure 1.2 Structures of (+)-elaeocarpiline **4** and (−)-isoelaeocarpiline **5**.[4,]

The relative stereochemistry of isoelaeocarpiline **5** at C-16 was determined by sodium borohydride reduction studies. On reduction, the carbonyl group of isoelaeocarpiline **5** was unaffected, however, the C-13, C-14 double bond was reduced quantitatively,[5] an observation Lamberton explained by steric factors. Attack at the carbonyl group is blocked by the C-1 and C-9 hydrogens and also by the C-16 methyl group on the opposite face. Whilst this method proved viable for determining the stereochemistry of isoelaeocarpiline **5**, the relative configuration of elaeocarpiline **4** could not be determined.

Subsequent studies determined the absolute configuration of (−)-isoelaeocarpiline **5** *via* oxidative degradation with $KMnO_4$ to yield the known compound (*S*)-methylsuccinic acid **6**, the absolute configuration of which corresponds to the C-16 stereocentre.[6]

Dehydrogenation of elaeocarpiline **4** and isoelaeocarpiline **5** with Pd/C gave the known alkaloids elaeocarpine **1** and isoelaeocarpine **2** in optically active form, in contrast to those isolated from *E. polydactylus* which were racemic. Gradual racemisation of (+)-elaeocarpine **1** in dilute methanolic sodium hydroxide at 50 ºC was reported to occur over a period of days.[5]

1.1.3 *E. sphaericus*

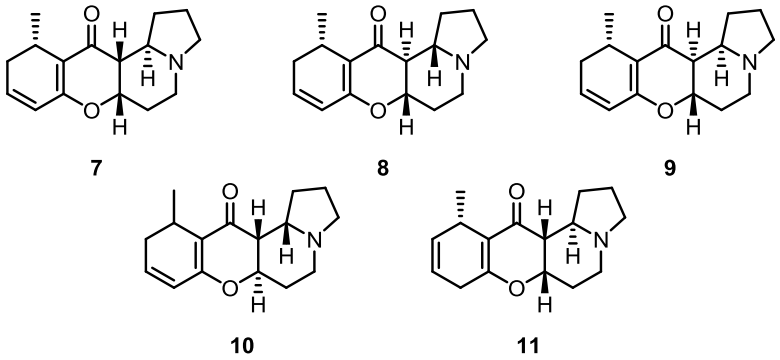


Figure 1.3 Alkaloids isolated from *Elaeocarpus sphaericus*.[6, 7]

Studies by Lamberton on extracts from *E. sphaericus* (Gaertn) K. Schum., revealed 5 further isomeric alkaloids containing the same tetracyclic core, all but one differing only in the relative configurations of the 4 stereocentres.[6, 7] The absolute configurations of the alkaloids were determined by dehydrogenation studies to yield the known compounds elaeocarpine **1** and isoelaeocarpine **2**. Sodium borohydride reduction studies and optical rotatory dispersion studies provided further evidence for the assigned stereochemistry. The isolation of all potential diastereoisomers suggests that the biosynthetic pathway giving rise to such compounds is non-selective or that isomerisation/epimerisation readily occurs upon isolation from the plant material.

The ongoing interest in the family *Elaeocarpacae* continues to reveal novel indolizidine alkaloids. Recent studies by Gan *et al*. described the isolation and structural elucidation of (±)-oxoisoelaeocarpine **12** and (±)-elaeocarpine *N*-oxide **13** from *Elaeocarpus sphaericus*.[8] In parallel with previous work by Lamberton, both alkaloids showed no optical rotation suggesting the compounds were isolated as racemates.

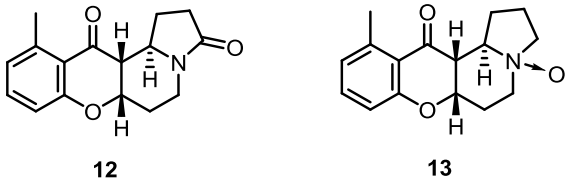
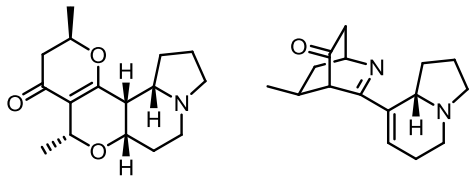


Figure 1.4 Structures of the alkaloids (±)-oxoisoelaeocarpine **12** and (±)-elaeocarpine *N*-oxide **13**.[8]

1.1.4 *E. grandis*

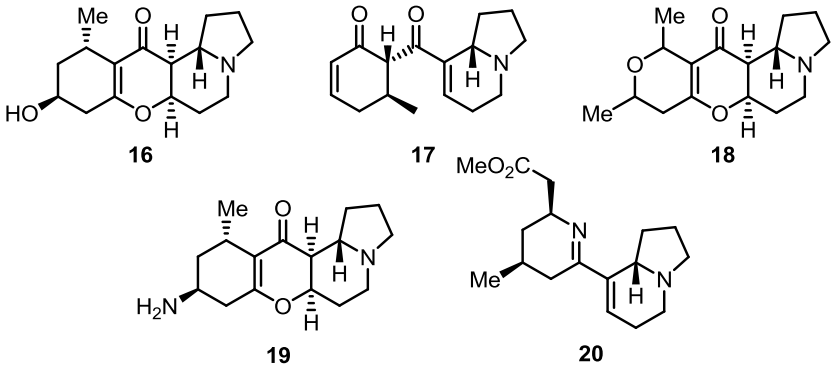
In 2005, Carroll and co-workers reported the isolation and characterisation of two novel indolizidine alkaloids from the leaves of the Australian rainforest species *Elaeocarpus grandis*.[9] As part of an ongoing high throughput screening drug discovery program, extracts from the leaves of *E. grandis* were found to display an affinity for the human δ-opioid recptors. Isolation of the bioactive components revealed the known alkaloid (−)-isoelaeocarpiline **5** along with the novel indolizidine alkaloids grandisine A **14** and grandisine B **15**.



14 **15**

Figure 1.5 Structures of grandisine A **14** and grandisine B **15** isolated from *E. grandis*.[9]

A subsequent paper by Carroll and co-workers disclosed the isolation of 5 further biologically active indolizidine alkaloids from *E. grandis*, assigned the trivial names grandisine C **16**, D **17**, E **18**, F **19** and G **20**, all of which displayed an affinity for the human δ-opioid receptor.[10]



16 **17** **18** **19** **20**

Figure 1.6 Grandisines C-G **16-20** isolated from *E. grandis* by Carroll *et al*.[10]

The relative stereochemistry of all the compounds was established through comprehensive 2D NMR studies, apart from two stereocentres in grandisine E **18**, which remain to be assigned.

1.1.5 *E. habbemensis*

Extracts from the previously uninvestigated species *E. habbemensis* of Papua New Guinea, yielded two novel optically active alkaloids trivially named habbemines A **21** and B **22**.[11]

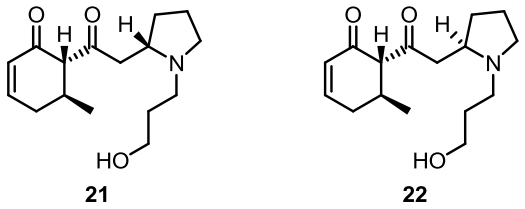
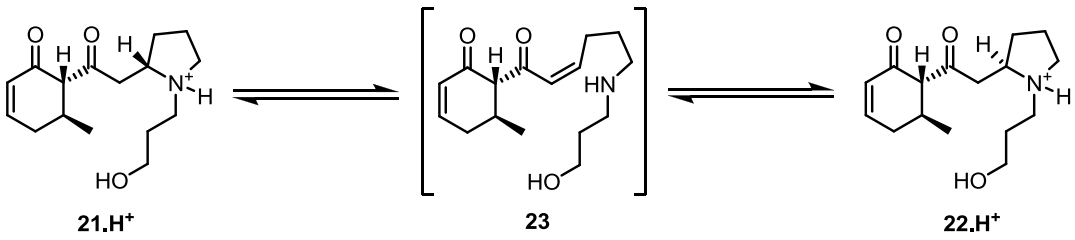


Figure 1.7 Habbemines A **21** and B **22** isolated from *E. habbemensis*.[11]

Isolated as an inseparable mixture, the structure and relative stereochemistry of the habbemines **21** and **22** was established through a combination of HRMS and extensive 2D NMR studies. The closely related compounds were proposed to be diastereoisomers, potentially arising as a result of epimerisation of the C-5 stereocentre. In analogy with the pyrrolidine alkaloids peripentadenine and hygrine,[12] epimerisation is believed to occur *via* the elimination/addition pathway shown in Scheme **1.1**.

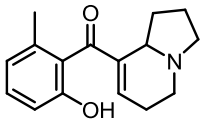


Scheme 1.1 Racemisation of 2-pyrrolidine moiety in habbemines A **21** and B **22**.

Whilst not containing the indolizidine nucleus observed in other *Elaeocarpus* alkaloids isolated to date, it is conceivable the habbemines represent an early intermediate in the *Elaeocarpus* alkaloid biosynthetic pathway.

1.1.6 *E. fuscoides*

Studies by Carroll and co-workers on extracts from the Papua New Guinea species *E. fuscoides* yielded the novel alkaloid elaeocarpenine **24**, along with three previously isolated alkaloids.[13] The analytical data for elaeocarpenine **24** were consistent with a structure closely resembling the previously isolated grandisine D **17**, differing only in the 3-methylphenol moiety. Interestingly, only when Carroll *et al*. avoided the previously used acid/base extraction protocols, instead using a strongly acidic ion exchange method, was the base sensitive alkaloid **24** isolated.



24

Figure 1.8 Elaeocarpenine **24** isolated from *E. fuscoides* by Carroll *et al*.[13]

Carroll reported that on treatment of elaeocarpenine **24** with aqueous ammonia in methanol conversion to the known alkaloids elaeocarpine **1** and isoelaeocarpine **2** was observed,[13] highlighting potential problems associated with the use of ammonia in acid/base extraction procedures.

1.2 Alkaloids of Peripentadenia mearsii

The Australian rainforest species *Peripentadenia mearsii* of the family *Elaeocarpaceae*, has been the source of a range of structurally diverse alkaloids exhibiting similar structures to those isolated from *Elaeocarpus sp*.

Initial studies by Lamberton *et al*. in 1983 revealed the unstable alkaloid peripentadenine **25**.[12] The molecular formula was assigned as $C_{22}H_{34}N_2O_3$ by HRMS, with NMR spectroscopic data suggesting the structure to be pyrrolidine **25**. Conclusive evidence was provided by synthesis of the proposed structure. The compound was isolated as a racemate possibly due to the presence of the β-amino ketone functionality, a motif known to racemise under basic conditions.

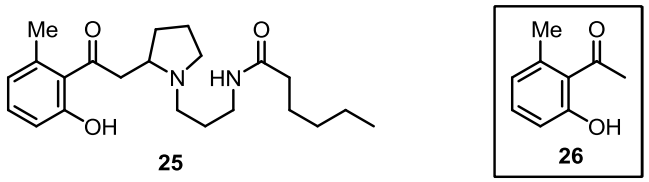
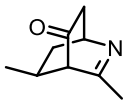


Figure 1.9 Structure of peripentadenine **25** and 2-hydroxy-6-methylacetophenone **26**.[12]

On hydolysis under mild basic conditions, 2-hydroxy-6-methylacetophenone **26** was isolated along with a complex mixture of basic compounds. The isolation of phenol **26** from *E. polydactylus* had previously been reported by Lamberton *et al*.[3]

Mearsine **27**, a minor alkaloid of the North Queensland species *P. mearsii*, was isolated by Robertson *et al*. in 1984.[14] The molecular formula was established by MS and combustion analysis of the crystalline picrate salt, with conclusive evidence obtained from single crystal X-ray diffraction data.[15] To date, mearsine **27** is the only other alkaloid known to possess the isoquinuclidinone core found in grandisine B **15**. Synthetic routes to mearsine **27** will be discussed later.



27

Figure 1.10 Structure of mearsine **27** isolated from *P. mearsii*.[14]

Recently, studies by Carroll and co-workers reported the isolation and characterisation of four additional alkaloids from the leaves of *P. mearsii*.[16] The peripentonines A **28** and B **29**, were found to differ from the previously isolated habbemines **21** and **22** only in the substituent on the pyrrolidine nitrogen.

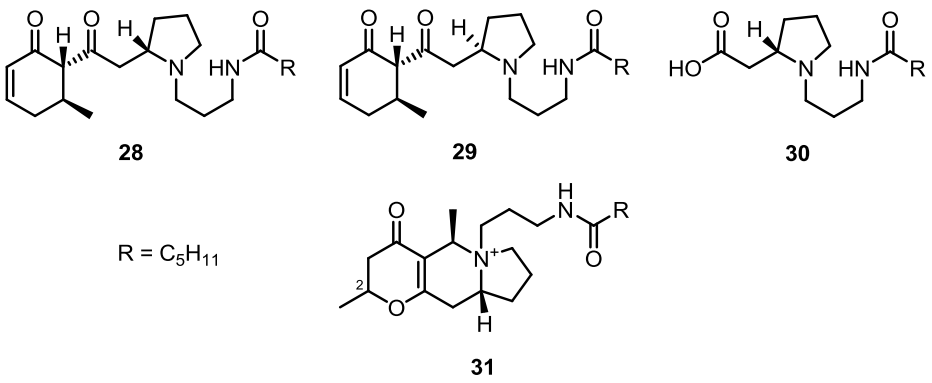


Figure 1.11 Alkaloids isolated from *P. mearsii* by Carroll *et al*.[16]

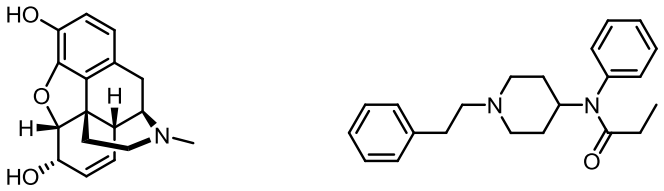
The third compound, peripentonine C **30**, still possessed the pyrrolidine ring, however, signals corresponding to the cyclohexenone ring were absent, consistent with a structure such as **30**. The fourth alkaloid, mearsamine **31**, was found to contain a unique tricyclic skeleton and quaternary amine moiety. The structure was established through 2D NMR spectroscopy, although the relative stereochemistry at C-2 remains to be assigned.

The similar structures exhibited by the *elaeocarpus* and *peripentadenia* alkaloids isolated to date, suggest a closely related biosynthetic pathway. The development of a general synthetic strategy could provide rapid access to a range of biologically active compounds.

1.3 Biological Activity

1.3.1 Opioid Receptor Agonists

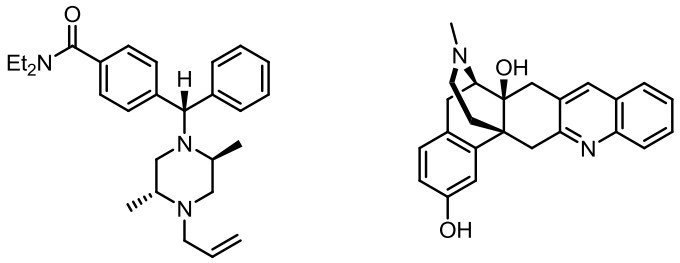
Agonists and antagonists of the opioid receptors are known to modulate pain and therefore represent an important class of pharmaceutical compound.[17] The opioid receptors are a class of G-protein coupled receptors widely distributed in the brain and spinal cord which can be divided into three subclasses (μ, κ and δ). Of the three subclasses, agonists such as morphine **32** and fentanyl **33** act on the μ-opioid receptors.[17, 18]



32 **33**

Figure 1.12 Structures of the selective μ-opioid receptor agonists morphine **32** and fentanyl **33**.

Although agonists of the μ-receptors are highly effective analgesics, activation of the receptors is often accompanied by major side effects, including: dependence, respiratory depression, muscle rigidity and euphoria. As a result, there is currently interest in compounds which display analgesic properties without such side effects. Recently, animal studies have shown that selective agonists of the δ-opioid receptors exhibit antinociceptive activity without the side effects and therefore represent a potential new class of analgesics.[18, 19]



34 **35**

Figure 1.13 Structures of the selective δ-opioid receptor agonists SNC80 **34** and KNT-127 **35**.[20, 21]

Non-peptidic δ-opioid selective agonists, such as SNC80 **34** and KNT-127 **35** have also demonstrated antidepressant-like activity in animal studies.[21] The wide ranging effects displayed by selective δ-opioid agonists could prove to be of both significant scientific and therapeutic benefit.

1.3.2 Biological Activity

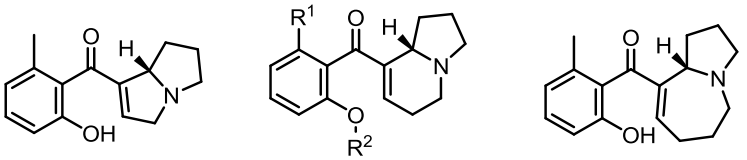
To date, 13 indolizidine alkaloids have been found to inhibit the binding of [^{125}I]-deltorphin II to HEK cell membranes expressing recombinant human δ-opioid receptors, with binding affinities in the micromolar range (1.6-86.4 μM).[8, 10, 11, 13, 16]

A feature common to δ-opioid agonists is a basic nitrogen atom and as such, piperidines bearing aromatic substituents are often encountered.[22] The orientation of the heterocyclic rings coupled to the indolizidine core has been found to play a role in determining activity, with more active compounds showing an orthogonal relationship between the piperidine ring and the coupled heterocycle. Conversely, in less active compounds, the piperidine ring is in the same plane as the attached heterocycle.

Comparison of the habbemines and peripentonines also provides insight into the biological activity. Replacing the propyl alcohol *N*-substituent with a propylhexamide group has been shown to halve the binding affinity, whilst replacing the cyclohexenone group with a carboxylic acid or phenolic group was found to significantly increase the binding affinity. Interestingly, mearsamine **31** showed no affinity for the δ-opioid selective agonists, suggesting that steric crowding of the pyrrolidine nitrogen or quaternisation of the amine is not tolerated.[16]

1.3.3 SAR Studies

A recent publication by Tamura, detailed the synthesis of elaeocarpenine **24**, and a range of structural analogues. Whilst, the compounds were shown to display weak binding affinities for the δ-opioid receptor, all were found to be non-selective, displaying increased affinity for both the μ and κ receptor subtypes.[23]

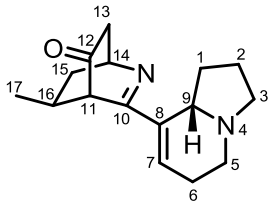


36 **24** R^1 = Me, R^2 = H **39**
37 R^1 = Me, R^2 = Me
38 R^1 = H, R^2 = H

Figure 1.14 Elaeocarpenine analogues prepared by Tamura and co-workers.[23]

Structure activity relationship studies showed that replacing the piperidine ring with a pyrrolidine **36** or stemona alkaloid skeleton **39** altered the affinity for the three receptor subtypes, potentially providing a method for modulating receptor selectivity. The stereochemistry of the indolizidine core was also reported to play a critical role in receptor binding, with 9*R*-**23** found to be more active than the 9*S*-**23** enantiomer although a decreased selectivity for receptor subtypes was observed.[23]

1.4 Grandisine B (15) – Structure Elucidation



15

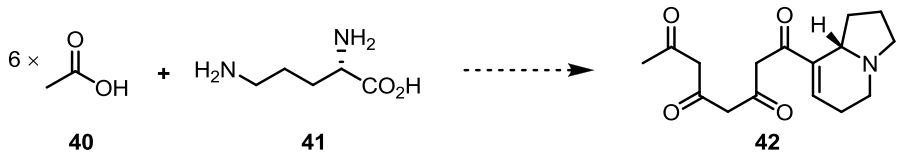
Figure 1.15 Grandisine B **15**.[9]

Grandisine B **15** was assigned the molecular formula $C_{16}H_{22}N_2O$ by high resolution mass spectrometry, with 2D NMR spectroscopy (COSY/HMBC) revealing a unique combination of unsaturated indolizidine and isoquinuclidinone moieties within the molecule. Correlations between H-7 and C-10 revealed the two cores were linked by a Csp^2-Csp^2 bond. The relative stereochemistry of the isoquinuclidinone core unit was established through coupling constant analysis. The large (12 Hz) coupling constant between H-15b and H-16 suggested the protons were in an eclipsed conformation. A W-coupling between H-13b and H-15b was also evident in the COSY spectrum. The data were consistent with a structure in which the methyl substituent was on the same face as the ketone.[9]

Although the stereochemistry of the isoquinuclidinone core unit was determined, the stereochemistry of the indolizidine core unit relative to the isoquinuclidinone core could not be established using NMR techniques.[9]

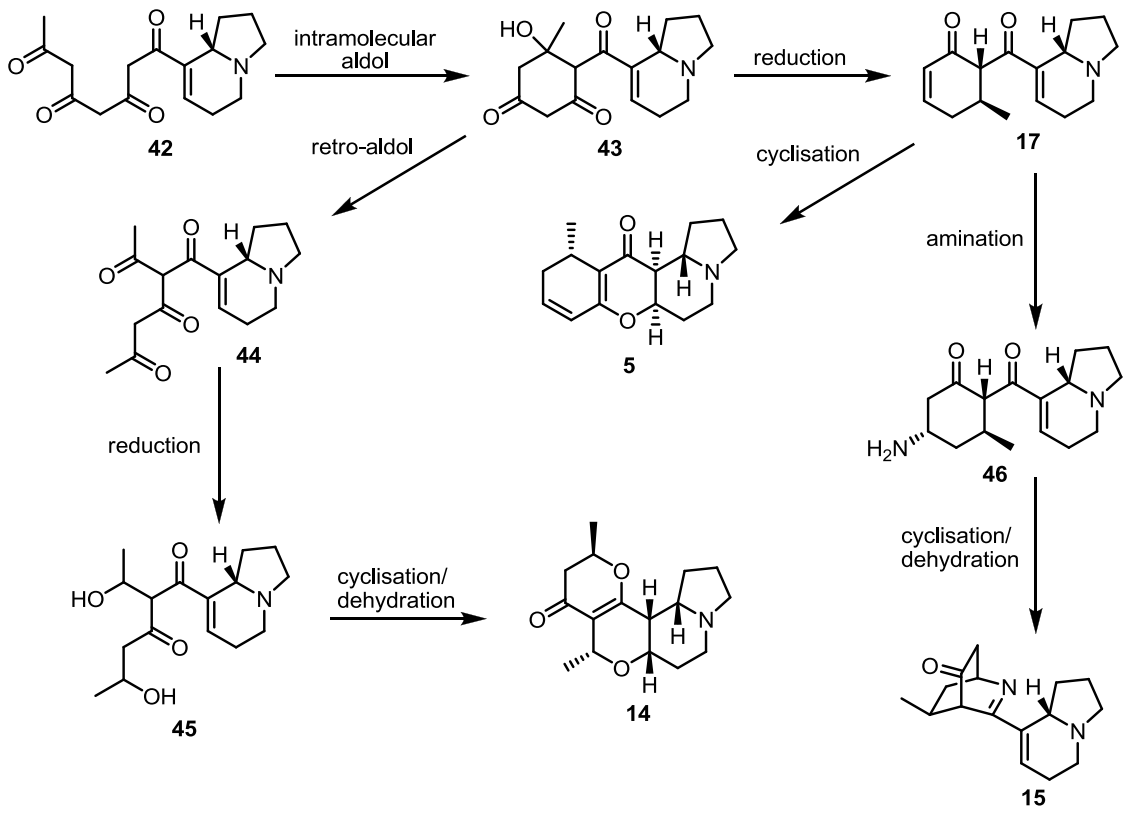
1.5 Elaeocarpus Alkaloid Biosynthesis

In early studies on the family *Elaeocarpaceae*, Johns *et al*. proposed that the *Elaeocarpus* alkaloids are biosynthesised from a polyketomethylene chain derived from 6 acetate units **40** and *L*-ornithine **41**, Scheme **1.2**.[5]



Scheme 1.2 Johns‟ proposed biosysnthesis of *Elaeocarpus* alkaloids.[5]

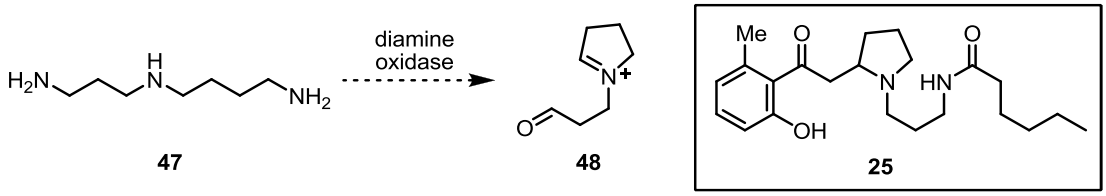
On the basis of Johns‟ biosynthetic proposal,[5] Carroll *et al*. later hypothesised that the grandisine alkaloids could be derived from a common precursor **42**, Scheme **1.3**.[9]



Scheme 1.3 Carroll's proposed biosynthesis of the elaeocarpus alkaloids **5**, **14**, **15** and **17**.[9]

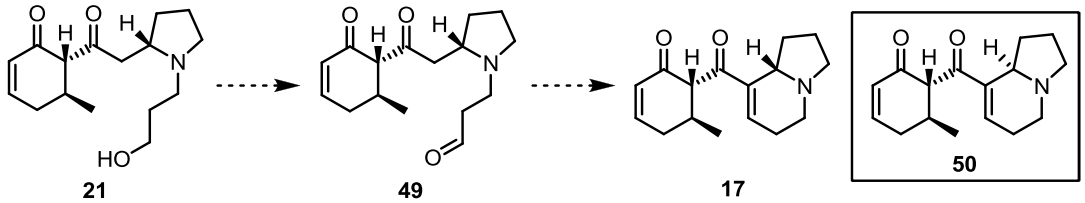
Carroll proposed that the presence of a common intermediate in the biosynthetic pathway would suggest that the stereochemistry of the grandisine alkaloids would be the same as that of the known compound isoelaeocarpiline **5**,[6] a proposal that was later confirmed by Danishefsky and Tamura.[24,25]

Alternatively, Onaka proposed that the *Elaeocarpus* alkaloids are derived from the common intermediate **48**,[26] which could be obtained *via* the enzymatic oxidation of spermidine **47**, Scheme **1.4**. Gribble proposed that the alkaloid peripentadenine **25** isolated from *P. mearsii* could also be derived from spermidine **47**,[27] providing evidence to support Onaka's biosynthetic proposal.



Scheme 1.4 Onaka's proposed biosynthetic intermediate **48**.[26]

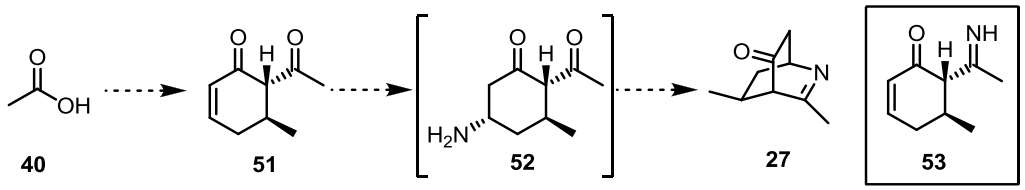
The recent isolation of compounds such as habbemines A **21** and B **22** have raised further questions about the biosynthetic origins of the grandisine alkaloids. In particular, Carroll proposed that the habbemines could also represent an early intermediate in the biosynthesis of grandisine D **17** *via* the sequence shown in Scheme **1.5**.[11] However, whilst grandisine D **17** was isolated as a single enantiomer, the habbemines were isolated as a diastereomeric mixture and as such this pathway should also give rise to the diastereoisomer of grandisine D **50**. Further studies are therefore required to determine the biosynthetic origins of the grandisine alkaloids.



Scheme 1.5 Proposed biosynthesis of grandisine D **17** from habbemine A **21**.[11]

1.5.1 Biosynthesis of Mearsine (27)

Robertson postulated that mearsine **27**, isolated from *P. mearsii* is also biosynthesised from acetate units *via* the intermediate diketone **51**, a partial structure also common to certain *Elaeocarpus*/*Peripentadenia* alkaloids, Scheme **1.6**.[14] The final steps in the biosynthesis are also consistent with those proposed for grandisine B **15**.



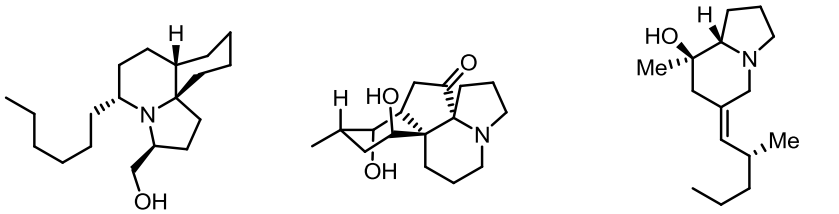
Scheme 1.6 Robertson"s proposed biosynthesis of mearsine **27**.[14]

With respect to the amination/cyclisation sequence, which is analogous to that proposed by Carroll for the synthesis of grandisine B **15**, it is thought that an initial amination of the enone occurs to give the intermediate amine **52**. An intramolecular cyclisation/dehydration sequence then occurs to furnish the isoquinuclidinone **27**.

Alternatively, it is conceivable that the initial step in the sequence is imine formation on the exocyclic ketone, to give an intermediate such as **53**, which can adopt a conformation allowing intramolecular conjugate addition of the imine into the enone.

1.6 Indolizidine Alkaloids

The indolizidine alkaloids represent an abundant and diverse family of natural products which have been isolated from myriad of sources including amphibians, fungi and trees.[28] The compounds have been shown to possess interesting biological activities such as phytotoxicity, antibacterial and fungicidal properties. Representative examples include lepadiformine **54**, isolated from sea squirt of the families *Clavelina* and *Polycitoridae*.[29] Other members include the *Lycopodium* alkaloid serratinine **55**,[30] and the pumiliotoxins **56** isolated from the poison dart frog family *Dendrobatidae*.[31]



Lepadiformine **54** Serratinine **55** Pumiliotoxin 237A **56**

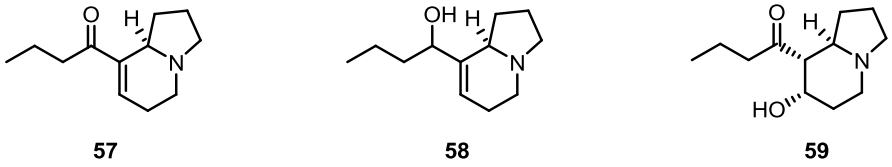
Figure 1.16 A selection of indolizidine alkaloids.

As a result of the varied structures exhibited by the indolizidine alkaloids, they have received sustained interest from the synthetic community. Accordingly, a brief overview of selected methodologies applied to the synthesis of the indolizidine alkaloids most closely resembling the unsaturated nucleus in grandisine B **15**, is included. A more comprehensive review on the synthesis of indolzidine alkaloids was recently reported by Michael.[32]

1.6.1 Elaeokanine A (57)

The indolizidine alkaloid elaeokanine A **57** was isolated along with elaeokanines B **58** and C **59** from the New Guinea rainforest species *Elaeocarpus kainesis* by Lamberton and co-workers.[33] The compound has been the subject of numerous racemic syntheses,

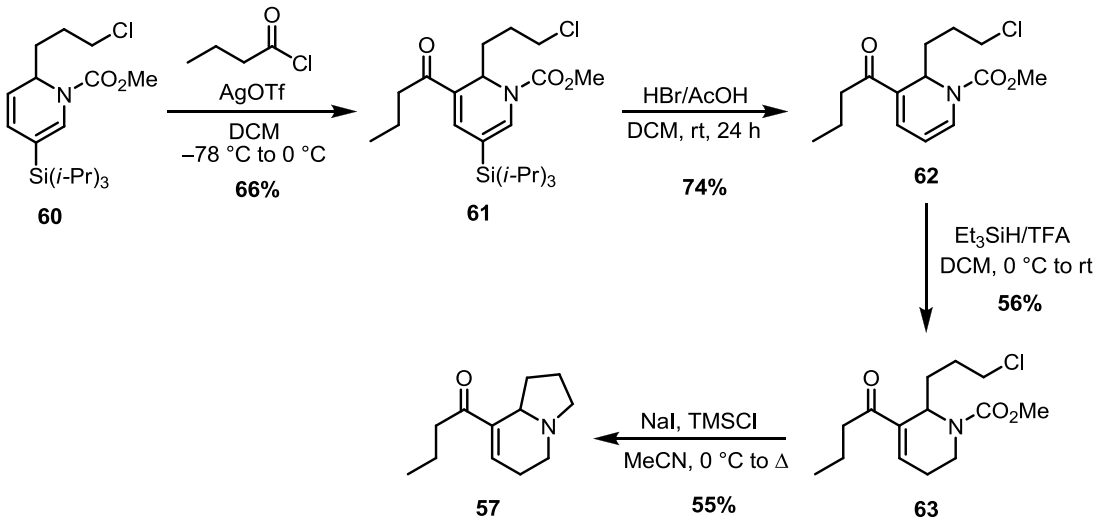
however, to date, only a few syntheses of the naturally occurring (+)-**57** have been reported.



57 **58** **59**

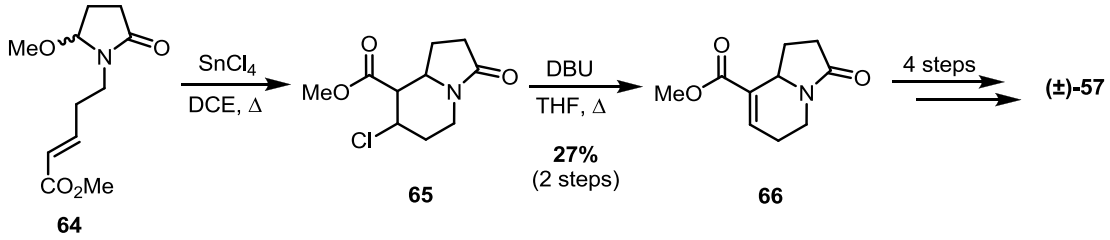
Figure 1.17 Indolizidine alkaloids isolated from *Elaeocarpus kaniensis*.[33]

Comins *et al*. utilised 1-acyl-5-(trialkylsilyl)-1,2-dihydropyridines in the synthesis of *rac*-**57**, Scheme **1.7**.[34] The presence of the silyl group promoted the regioselective addition of a Grignard reagent at the least sterically hindered C-6 position to afford the alkylated dihydropyridine **60**. Installation of the side chain was achieved through regioselective Friedel–Crafts acylation at the C-3 position, to give ketone **61** in 66% yield. Protodesilylation in the presence of HBr/AcOH and subsequent reduction with triethylsilane furnished tetrahydropyridine **63**, which was readily converted into (±)-elaeokanine A **57** on treatment with NaI/TMSCl.



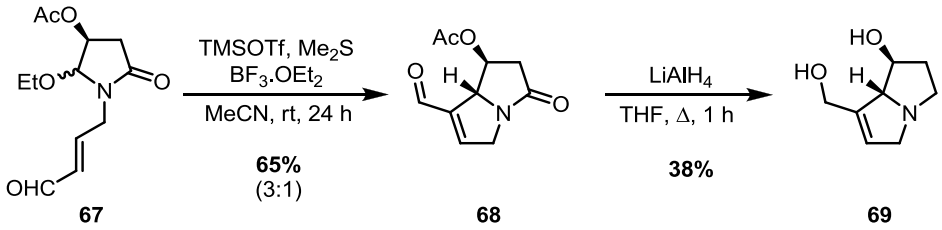
Scheme 1.7 Comins' total synthesis of (±)-elaeokanine A **57**.[34]

A more practical synthesis of *rac*-**57** was reported by Taber and co-workers *via* a tin(IV) chloride mediated *N*-acyliminium ion cyclisation, Scheme **1.8**.[35] Treatment of intermediate **65** with DBU gave the α,β-unsaturated ester **66** which was readily converted into (±)-elaeokanine A **57**, in four steps.



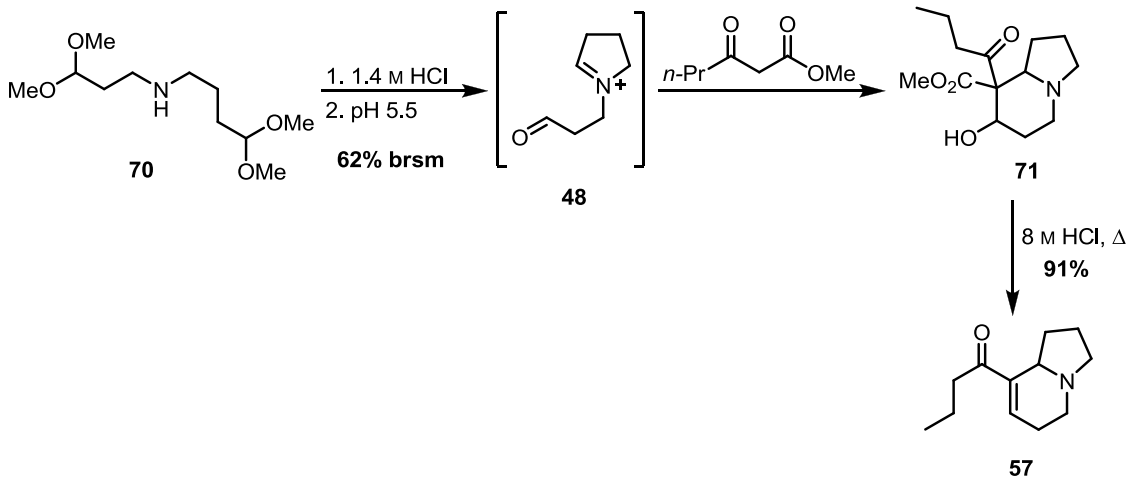
Scheme 1.8 $SnCl_4$ mediated cyclisation in Taber's synthesis of (±)-**57**.[35]

A similar *N*-acyliminium ion approach was recently reported by Aggarwal for the synthesis of pyrrolizidine alkaloids, which was used to prepare the necine base (+)-heliotridine **69**.[36] On subjecting intermediate **67** to non-classical Morita-Baylis-Hillman conditions, pyrrolizidine **68** was isolated in 65% yield as a 3:1 mixture of diastereoisomers, Scheme **1.9**. Subsequent treatment with lithium aluminium hydride gave (+)-heliotridine **69** in 38% yield.



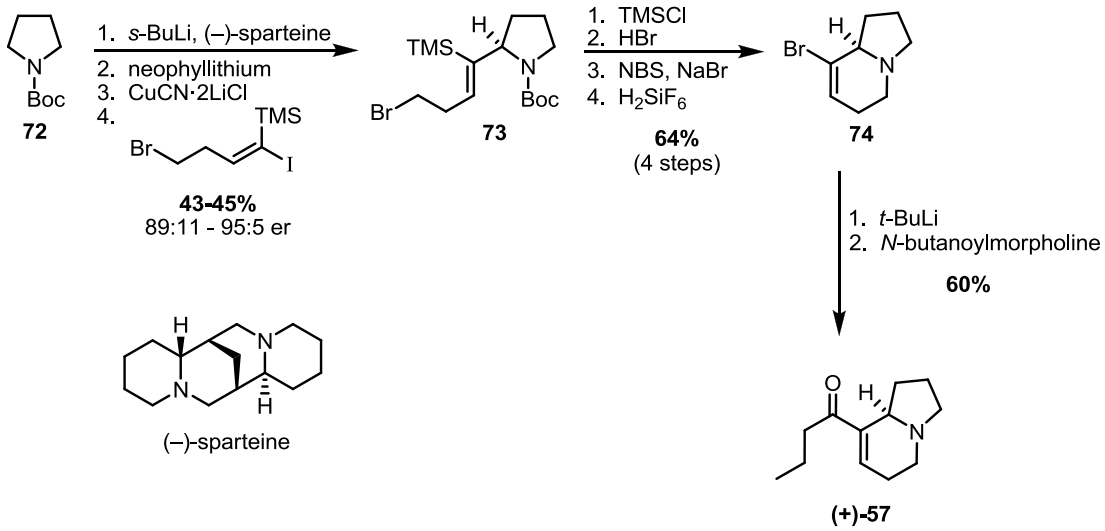
Scheme 1.9 Concluding steps in Aggarwal's synthesis of (+)-heliotridine **69**.[36]

Gribble *et al*. proposed a general strategy for the synthesis of *Elaeocarpus* alkaloids,[27] based on a common intermediate **48** identified in Onaka"s biosynthetic hypothesis.[26] Synthesis of intermediate **48** *via* treatment of the *bis*-acetal amine **70** with 1.4 M aqueous hydrochloric acid and subsequent buffering of the reaction mixture in the presence of 3-oxohexanoate ester gave indolizidine **71**, Scheme **1.10**. Conversion to elaeokanine A **57** was achieved in good yield on heating ester **71** at reflux in 8 M HCl.



Scheme 1.10 Gribble's synthesis of (±)-**57**.[27]

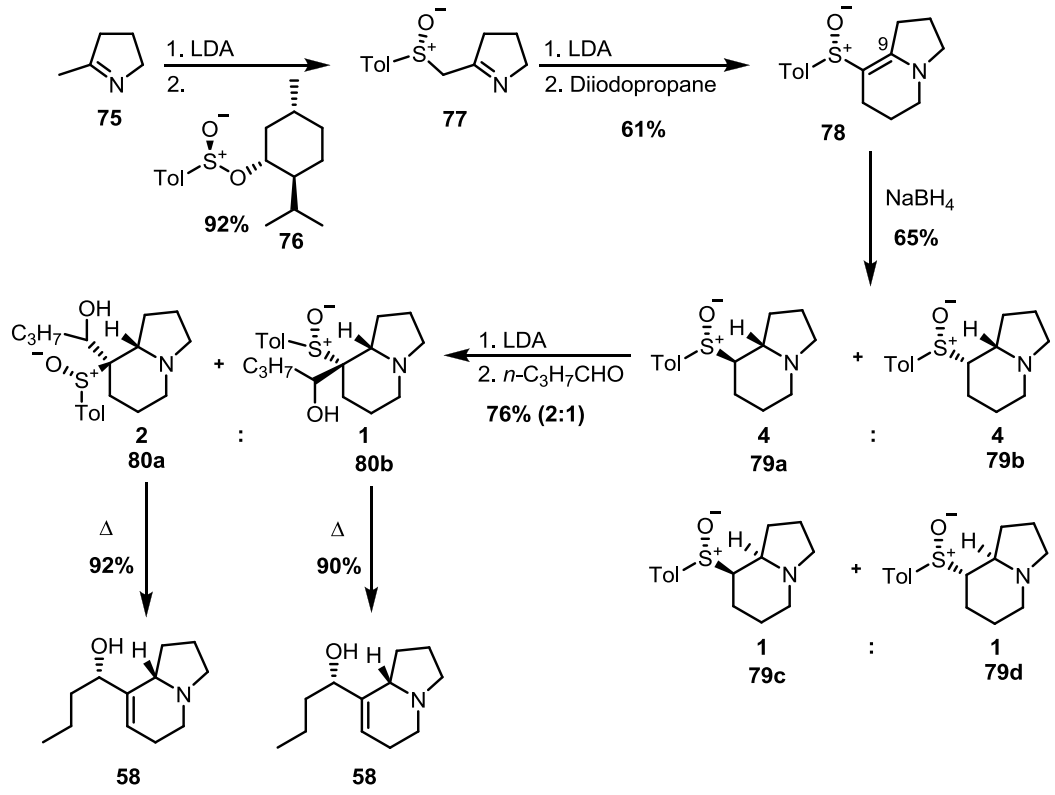
In 2006, Dieter *et al*. reported an asymmetric synthesis of (+)-**57** in which the stereocentre was installed *via* the asymmetric deprotonation of *N*-Boc pyrrolidine **72**,[37] followed by *in situ* trapping with (*E*)-4-bromo-1-iodo-1-trimethylsilyl-1-butene. Subsequent one-pot olefin isomerisation and intramolecular alkylation furnished vinyl bromide **74**. Halogen-lithium exchange and trapping of the resulting organolithium species with *N*-butanoylmorpholine gave (+)-**57** in 10-16% overall yield and 81% ee, Scheme **1.11**.



Scheme 1.11 Dieter's synthesis of (+)-**57** *via* the asymmetric deprotonation of Boc-pyrrolidine **72**.[37]

1.6.2 Elaeokanine B (58)

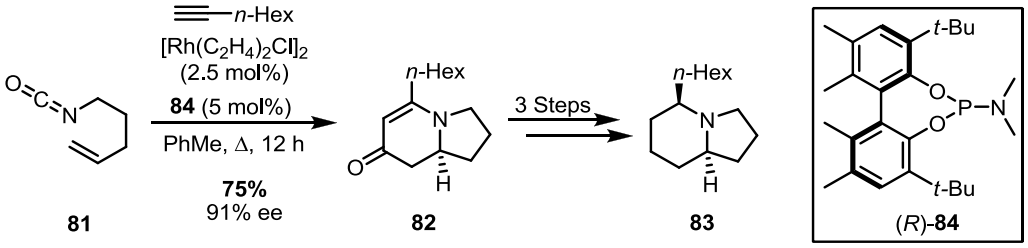
A total synthesis of elaeokanine B **58** was reported by Hua *et al*. who determined the absolute configuration of **57** and **58** through single crystal X-ray diffraction analysis of the intermediate sulfoxide **80b**.[38] Sulfinyl ketimine **77** was obtained in excellent yield on treatment of lithiated ketimine **75** with (−)-(*S*)-1-menthyl-*p*-toluenesulfinate **76**. Deprotonation of sulfoxide **77** with LDA, followed by addition of 1,3-diiodopropane furnished the β-enamino sulfoxide **78** in 61% yield. Transfer of chirality from the sulfoxide to the indolizidine on reduction of enamine **77** with sodium borohydride gave a 4:4:1:1 ratio of diastereomeric sulfoxides **79** which were readily separable by chromatography. Treatment of sulfoxides **79a** or **79b** with LDA, then butyraldehyde gave a 2:1 ratio of alcohols **80a** and **80b**, which readily underwent dehydrosulfinylation in toluene at reflux to give (−)-elaeokanine B **58** in excellent yield, Scheme **1.12**.



Scheme 1.12 Hua's total synthesis of elaeokaine B **58** *via* α-sulfinyl ketimine **77**.[38]

1.6.3 Indolizidine 209D (83)

Rovis recently reported a novel synthesis of indolizidine frameworks *via* a rhodium-catalysed [2+2+2]-cycloaddition between alkenyl isocyanates and terminal alkynes.[39] The use of phosphoramidite ligand **84** yielded indolizidine frameworks in good yield and excellent enantioselectivity, Scheme **1.13**. The methodology was applied to a concise synthesis of indolizidine 209D **83** in 5 steps from commercially available hexenoic acid.



Scheme 1.13 Rovis' Rh-catalysed synthesis of indolizidine architectures.[39]

1.7 Isoquinuclidinones

Whilst the saturated isoquinuclidine nucleus is incorporated into alkaloids from the species *Daphniphyllum*,[40] such as methyl homosecodaphniphyllate **85** and Iboga alkaloids such as ibogaine **86**,[41] it is only mearsine **27**,[14] isolated from *P. mearsii* which shares the same structure and relative stereochemistry as the isoquinuclidinone core unit in grandisine B **15**. A brief overview of literature detailing the synthesis of isoquinuclidinones is provided.

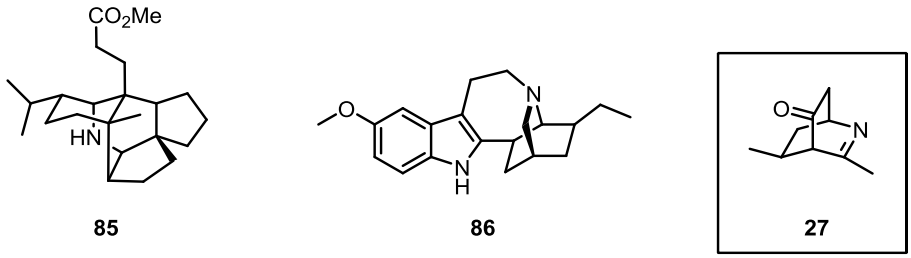
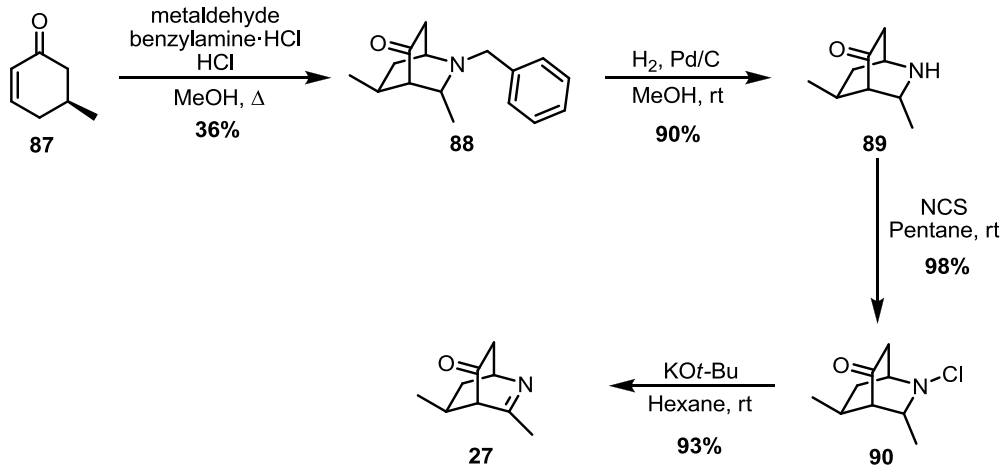


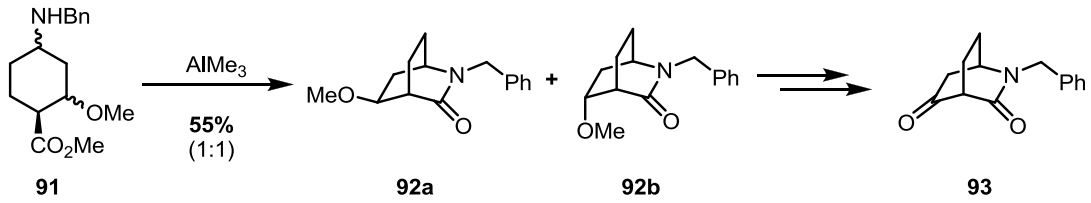
Figure 1.18 A selection of isoquinuclidine/isoquinuclidinone alkaloids.

In 1989, Pinder *et al*. reported the total synthesis of (+)-mearsine **27**, using a Mannich/conjugate addition sequence to rapidly assemble the isoquinuclidinone core **88**, Scheme **1.14**.[42] Subsequent debenzylation and chlorination/elimination furnished (+)-mearsine **27** in 30% overall yield.



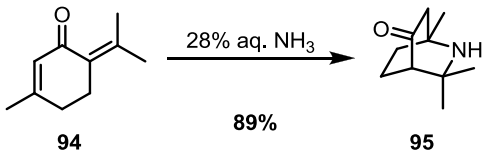
Scheme 1.14 Pinder's synthesis of (+)-**27** *via* an intramolecular conjugate addtion.[42]

An alternative synthesis of isoquinuclidinones reported by Bonjoch *et al*. utilised a trimethylaluminium-promoted lactamisation of the substituted cyclohexane derivative **91**,[43] readily available in two steps from Danishefsky's diene and methyl acrylate. Subsequent demethylation and oxidation steps furnished the isoquinuclidinone **93**, Scheme **1.15**.



Scheme 1.15 Synthesis of isoquinuclidinone **93** *via* a trimethylaluminium-promoted epimerisation-lactamisation sequence.[43]

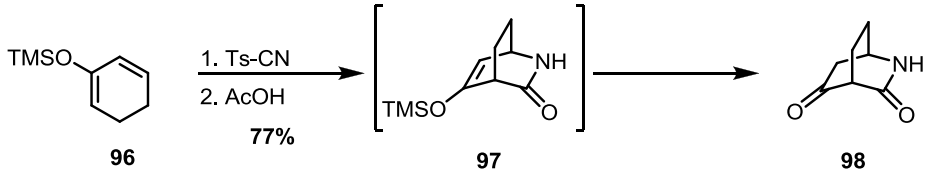
An early synthesis of simple isoquinuclidinone structures was reported by Rassat, using a double conjugate addition of ammonia to construct the bicyclic framework.[44] The *bis*-enone **94** was found to react with aqueous ammonia at ambient temperature to yield the corresponding isoquinuclidinone **95** in good yield, Scheme **1.16**.



Scheme 1.16 Rassat's synthesis of isoquinuclidinones **95** *via* a double conjugate addition of ammonia.[44]

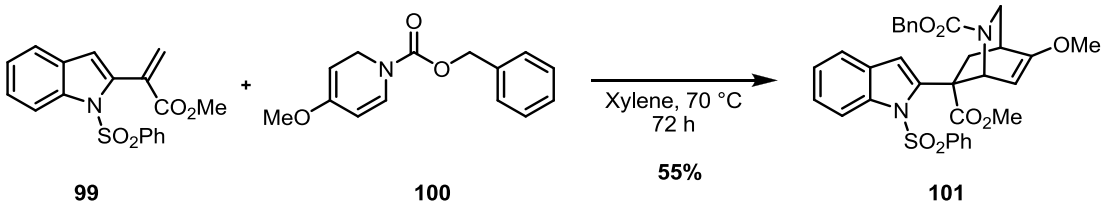
1.7.1. Diels-Alder Approaches to Isoquinuclidinones

The Diels-Alder reaction is also well precedented for the synthesis of isoquinuclidinone frameworks. McClure *et al*. reported the Diels-Alder reaction of tosyl cyanide with the cyclohexadiene derivative **96** to give the bicyclic silyl enol ether **97**,[45] which upon acidic hydrolysis with acetic acid furnished the unsubstituted bicyclic lactam **98**, Scheme **1.17**.



Scheme 1.17 Synthesis of isoquinuclidinone **98** *via* a nitrile Diels-Alder reaction.[45]

Methoxy-dihydropyridine derivatives have also been used as dienes in Diels-Alder reactions. Sundberg *et al*. reported the reaction of 1-carbobenzyloxy-4-methoxy-1,2-dihydropyridine **100** with the electron-deficient dienophile **99**, Scheme **1.18**.[46] Hydrolysis of enol ether **101** provided access to the corresponding isoquinuclidinone.



Scheme 1.18 1,2-Dihydropyridine Diels-Alder reaction.[46]

The strategy was successfully applied to the synthesis of the racemic iboga alkaloid analogues **102** and **103**.[46]

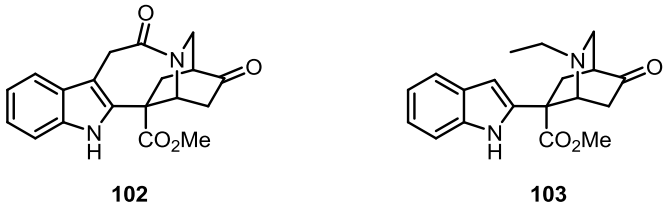
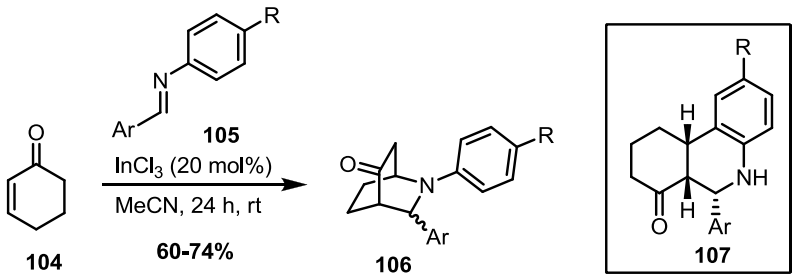


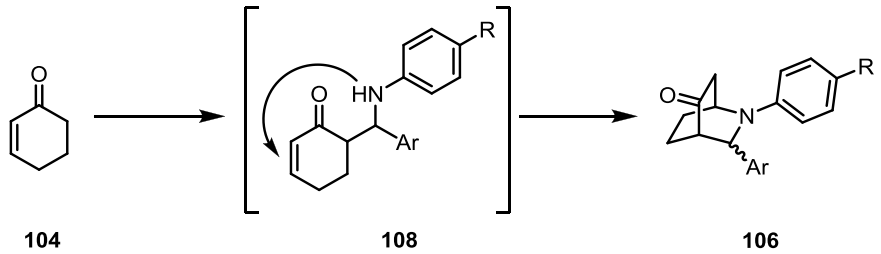
Figure 1.19 Iboga alkaloids synthesised *via* a dihydropyridine Diels-Alder reaction.[46]

Alternative approaches to isoquinuclidinone frameworks include the *aza*-Diels-Alder reaction. In 1998, Perumal and co-workers reported the unexpected synthesis of aryl-substituted isoquinuclidinones **106** while attempting to prepare phenanthridone derivatives **107**, Scheme **1.19**.[47] In the presence of indium(III) chloride, 2-cyclohexenone **104**, was found to react with aryl substituted imines **105** to give isoquinuclidinones **106** in moderate yield.



Scheme 1.19 Indium(III) chloride mediated synthesis of isoquinuclidinones **106**.[47]

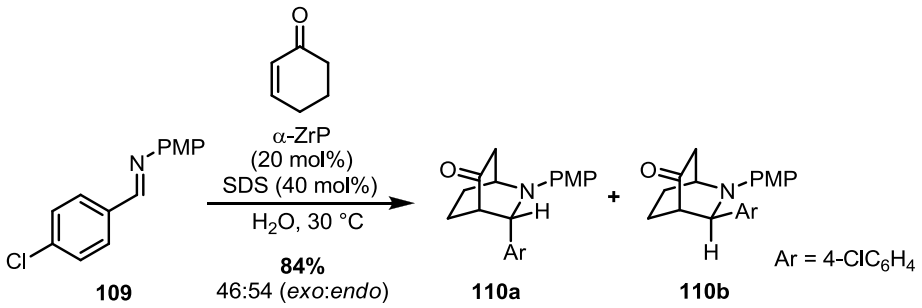
Mechanistically, the reaction is believed to proceed *via* the Mannich product **108** which then undergoes an intramolecular cyclisation to form the bicyclic core **106**, Scheme **1.20**.



Scheme 1.20 Mechanism proposed for Perumal's synthesis of isoquinuclidinones.

A similar approach to isoquinuclidinones was reported by Peirmatti *et al*., using an *aza*-Diels-Alder reaction in aqueous media.[48] Reaction of cyclohexenone **104** with a range of preformed imines in the presence of α-zirconium hydrogen phosphate (α-ZrP) (20

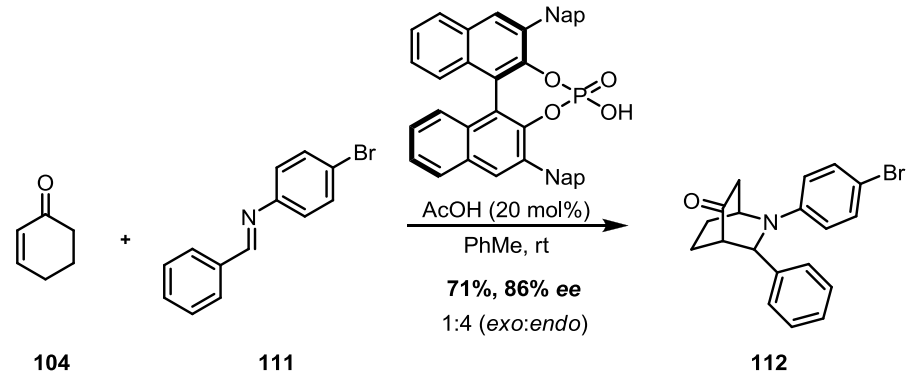
mol%) and catalytic sodium dodecyl sulfate (40 mol%) furnished isoquinuclidinone frameworks **110** in good yield, although diastereoselectivities were generally poor. Recycling of the α-ZrP was also found to be possible, with no appreciable loss of yield after three cycles, Scheme **1.21**.



Scheme 1.21 Piermatti's *aza*-Diels-Alder approach to isoquinuclidinones **110**.[48]

1.7.3. Asymmetric Syntheses of Isoquinuclidinones

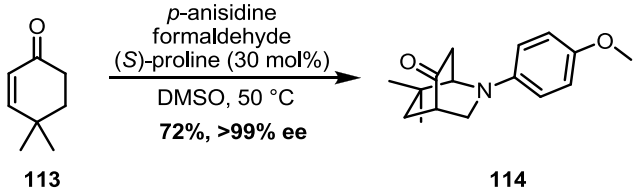
A number of methods have recently emerged for the asymmetric synthesis of isoquinuclidinone frameworks. Rueping *et al*. utilised the co-operative effect between two Brønsted acids to simultaneously activate cyclohexenones and imines to prepare isoquinuclidinones in reasonable yields and enantioselectivity, Scheme **1.22**.[49] Mechanistically the reaction can be described as a Mannich/*aza*-Michael sequence.



Scheme 1.22 Rueping's Brønsted acid catalysed synthesis of isoquinuclidinones.[49]

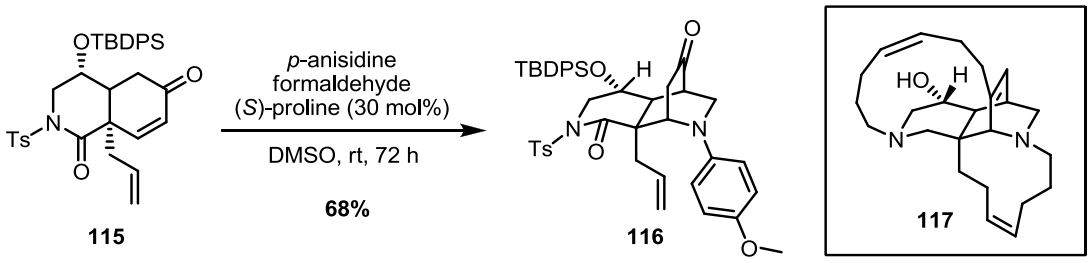
Córdova and co-workers reported an organocatalytic enantioselective *aza*-Diels-Alder reaction between an imine generated *in situ* and a cyclohexenone derived diene, to give

isoquinuclidinone products in moderate to high yield and excellent enantioselectivity, Scheme **1.23**.[50]



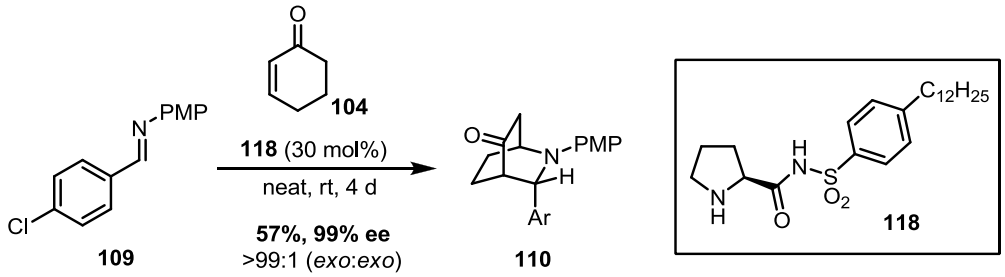
Scheme 1.23 Proline catalysed enantioselective *aza*-Diels-Alder reaction.[50]

Danishefsky *et al*. recently utilised the methodology in studies towards xestocyclamine A **117**, a protein kinase inhibitor isolated from marine sponges of the genus *Xestospongia*.[51] On subjecting intermediate **115** to the conditions reported by Cordova, the substituted isoquinuclidinone **116** was isolated in 68% yield, Scheme **1.24**.



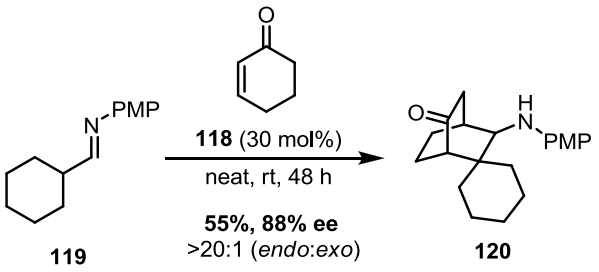
Scheme 1.24 Application of Cordova's proline catalysed *aza*-Diels-Alder reaction in studies towards the synthesis of xestocyclamine A **117**.[51]

Carter and Yang also reported an organocatalytic approach to isoquinuclidinones using proline-derived catalysts.[52] The reaction of cyclohexenone **104** and aryl imine **109** in the presence of sulfonamide catalyst **118**, gave the isoquinuclidinone **110** in moderate yield but also excellent enantioselectivity, Scheme **1.25**.



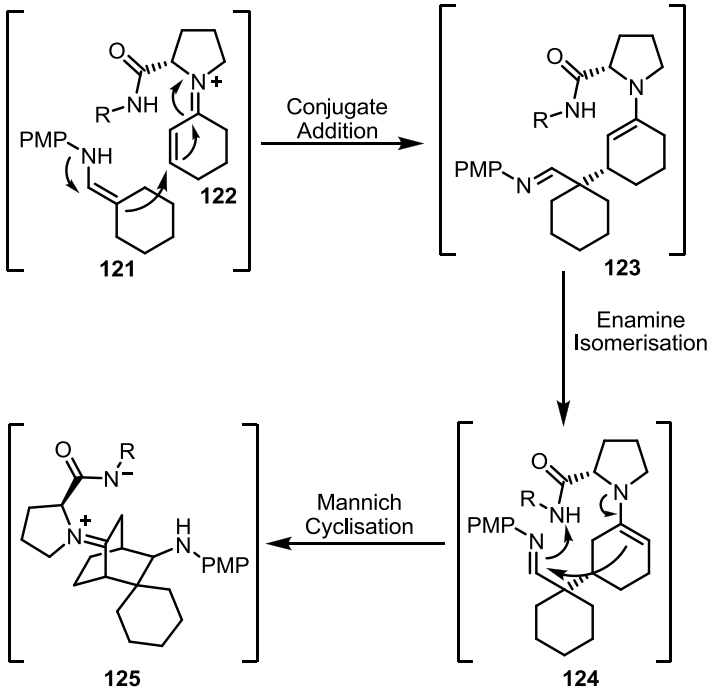
Scheme 1.25 Carter's organocatalytic *aza*-Diels-Alder approach to isoquinuclidinones **110**.[52]

Whilst yields for the transformation were generally modest, the reaction proceeded with a high degree of enantioselectivity, for a range of substrates. Interestingly, when aliphatic imines such as the cyclohexyl derivative **119** were used in the reaction, bicyclo[2.2.2]octane **120** products were obtained, Scheme **1.26**.[52]



Scheme 1.26 Alternative reaction pathway for aliphatic imines reported by Carter.[52]

Carter's proposed mechanistic explanation for the observed transformation, shown in Scheme **1.27**, involved an initial conjugate addition of enamine **121** into the activated enone **122**. Enamine isomerisation and intramolecular Mannich reaction gave the bicyclo[2.2.2] framework **125**, which was readily converted into isoquinuclidinone **120** upon hydrolysis.[52]

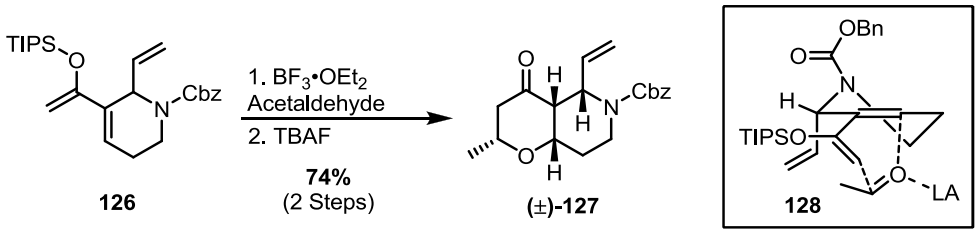


Scheme 1.27 Carter's proposed mechanism for bicyclo[2.2.2]octane formation.[52]

1.8 Previous Syntheses of Grandisine Alkaloids

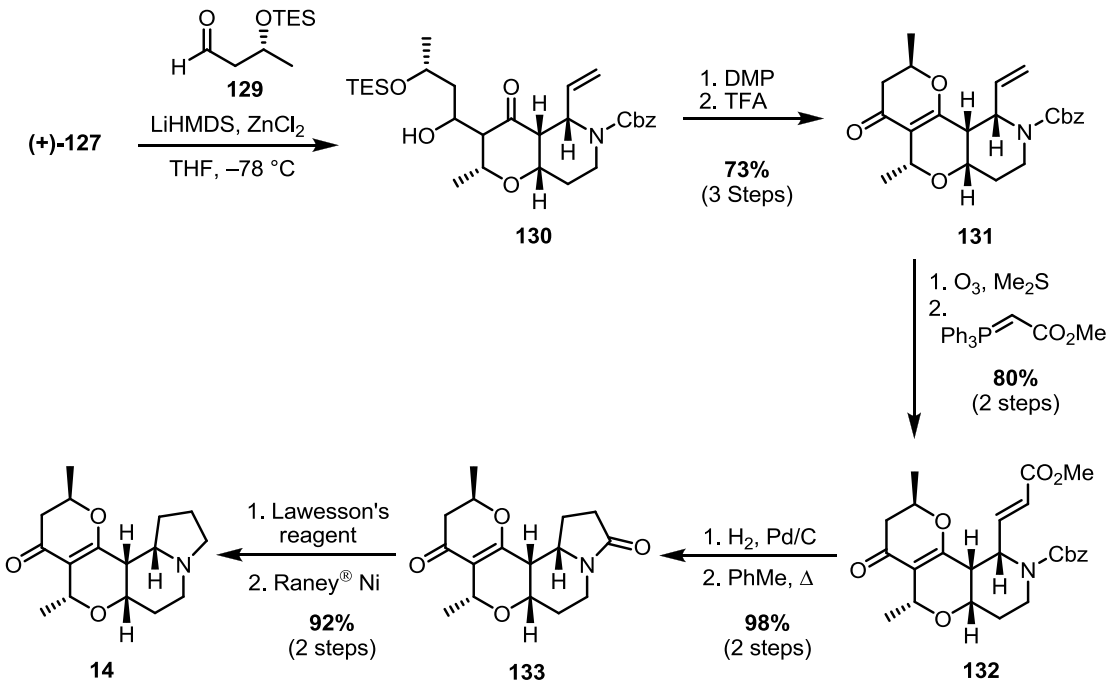
1.8.1 Grandisine A (14)

As a result of unique structural features and intriguing biological activity, the grandisine alkaloids have attracted considerable interest since they were isolated in 2005/06. In 2007, Danishefsky and Maloney reported the first total synthesis of a grandisine alkaloid, (+)-grandisine A **14**.[24,53] The approach centred on a Lewis acid catalysed diene aldehyde cyclisation to construct the tetrahydropyranone core **127**. In the presence of boron trifluoride etherate and acetaldehyde, diene **126** underwent a selective cycloaddition reaction to afford the bicyclic pyranone **127**, *via* transition state **128**, Scheme **1.28**.



Scheme 1.28 Construction of the tetrahydropyranone core unit of grandisine A **14**.[24]

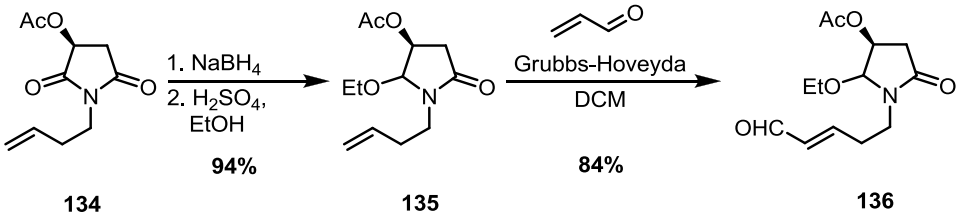
After resolution of *rac*-**127** by chiral HPLC, alkylation of the lithium enolate of **127** with aldehyde **129**, and subsequent oxidation/deprotection gave the functionalised enantiopure tricyclic core **131**. Homologation of the vinyl chain was achieved *via* ozonolysis and Wittig condensation to give the α,β-unsaturated ester **132**. In the concluding steps of the synthesis, simultaneous reduction of the unsaturated ester and cleavage of the CBz group gave, after heating, the tetracyclic intermediate **133**. Conversion into the corresponding thiolactam and reduction with Raney® nickel furnished grandisine A **14** in 92% yield, Scheme **1.29**.



Scheme 1.29 Concluding steps in Danishefsky's synthesis of grandisine A **14**.[24]

1.8.2 Grandisine D (17)

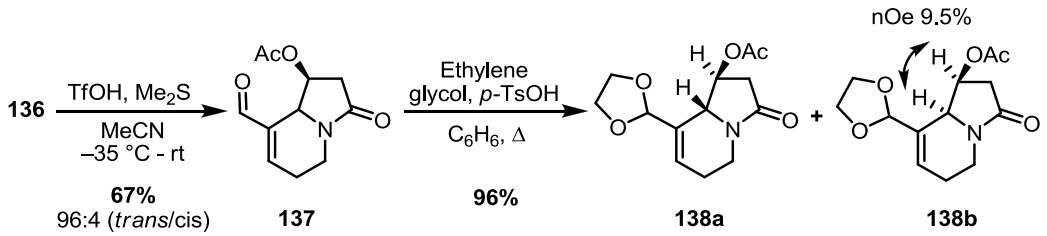
In 2009, during the research described in this thesis, Tamura and co-workers reported the first total synthesis of grandisine D **17**.[25] Tamura's approach utilised Aggarwal's Brønsted acid mediated Morita-Baylis-Hillman (MBH) ring closure to construct the indolizidine ring.[36] Imide **134**, prepared from (*S*)-malic acid using Lee's method,[54] was subjected to regioselective reduction with $NaBH_4$, furnishing aminal **135** in 94% yield. Installation of the unsaturated aldehyde *via* cross metathesis gave the MBH precursor **136** in 84% yield, Scheme **1.30**.



Scheme 1.30 Initial steps in Tamura's synthesis of grandisine D **17**.[25]

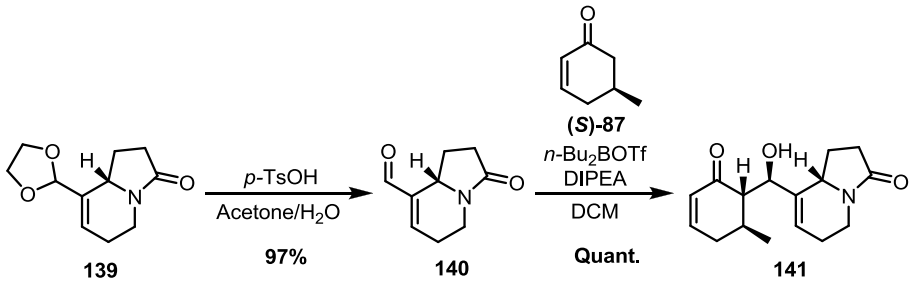
Treatment of aldehyde **136** with trifluoromethanesulfonic acid and dimethyl sulfide in acetonitrile, afforded the cyclised product **137** as a 96:4 mixture of diastereoisomers,

Scheme **1.31**. Significant nOe effects observed on conversion to acetal **138a** and **138b** confirmed the major product to be the desired *trans*-isomer.



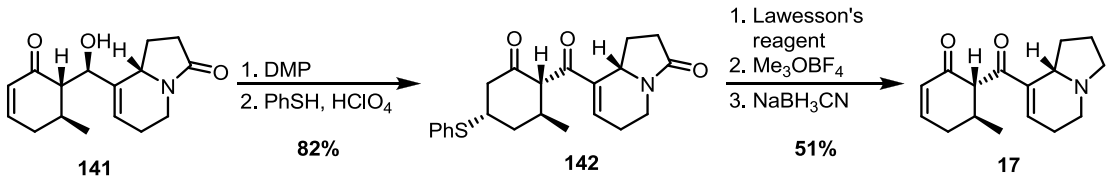
Scheme 1.31 Stereochemical outcome of the *N*-acyliminium MBH reaction.[25]

Deacetylation and subsequent Barton-McCombie deoxygenation gave the indolizidine **139** in 66% yield over three steps. Aldehyde **140**, obtained on acidic hydrolysis of the acetal protecting group was coupled to (*S*)-5-methylcyclohexenone **87** using boron-aldol methodology, to furnish alcohol **141** in quantitative yield as a single diastereoisomer, Scheme **1.32**.



Scheme 1.32 Tamura's synthesis of the grandisine D carbon skeleton **141**.[25]

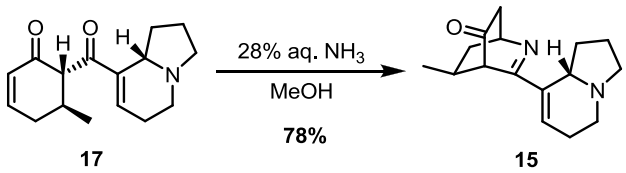
Oxidation of alcohol **141** with Dess-Martin periodinane and protection of the enone moiety afforded thiophenyl adduct **142**, which was converted into grandisine D **17**, in 51% yield over 3 steps, Scheme **1.33**.



Scheme 1.33 Concluding steps in Tamura's synthesis of grandisine D **17**.[25]

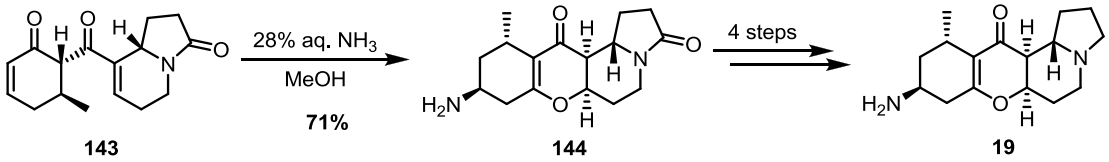
1.8.3 Grandisine B (15) and F (19)

More recently, Tamura and co-workers also reported the conversion of grandisine D **17** into grandisines B **15** and F **19**.[55] On treatment of grandisine D **17** with aqueous ammonia, the compound was found to undergo a 1,4-addition of ammonia and intramolecular cyclisation to construct the isoquinuclidinone core unit, Scheme **1.34**.



Scheme 1.34 Conversion of grandisine D **17** into grandisine B **15**.[55]

Alternatively, treatment of amide **143** with aqueous ammonia yielded amine **144**, which was readily converted into grandisine F **19** in 50% over four steps, Scheme **1.35**.



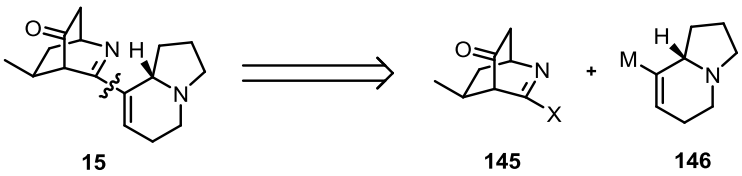
Scheme 1.35 Conversion of diketone **143** into grandisine F **19**.[55]

1.9 Aims and Objectives: Retrosynthetic Analysis

Following on from worked carried out by Geyelin,[56] our initial aim was to complete the total synthesis of grandisine B **15**. Despite grandisine B **15** exhibiting one of the highest IC_{50} values of the *Elaeocarpus* alkaloids isolated to date, the unique structure, exemplified by a previously unknown combination of isoquinuclidinone and indolizidine cores made the total synthesis of grandisine B **15** an interesting synthetic challenge. It should be noted that at the time this project commenced, there were no published syntheses of grandisines B **15** or D **17**.

On the basis that grandisine B **15** is composed of two distinct *N*-heterocyclic frameworks, namely, the indolizidine and isoquinuclidinone cores, a convergent

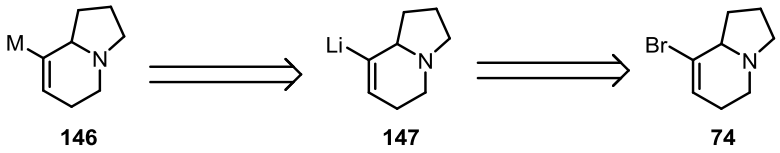
strategy involving a carbon-carbon bond formation as outlined retrosynthetically in Scheme **1.36** was initially proposed.



Scheme 1.36 Retrosynthetic analysis of grandisine B **15**.

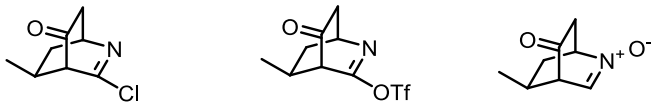
When work began on the project the relative stereochemistry of grandisine B **15** was unknown; the strategy would therefore provide access to both diastereoisomers of grandisine B **15** by switching the stereochemistry of the coupling partners. From a biological screening point of view, the route is also attractive, as analogue formation could be achieved by preparing libraries of indolizidine and isoquinuclidinone frameworks.

Initially, we planned to prepare a racemic model of the indolizidine core unit using the synthesis reported by Overman *et al*.[57] Through lithium-halogen exchange, vinyl bromide **74** would provide access to a range of potential organometallic coupling partners, for use in cross-coupling studies.



Scheme 1.37 Retrosynthetic analysis of indolizidine coupling partners.

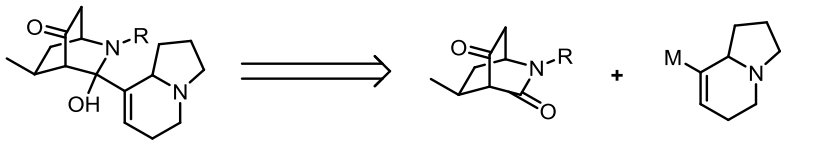
Alternatively, vinyllithium **147** could be trapped with an isoquinuclidinone-derived electrophile such as an imidoyl chloride **148**, imidoyl triflate **149** or nitrone **150** (Figure **1.20**).



148 149 150

Figure 1.20 Electrophilic isoquinuclidinone coupling partners.

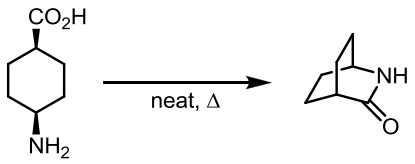
Direct addition of an organometallic reagent **146** to lactam derivatives of the isoquinuclidinone core unit **152** as outlined in Scheme **1.38** could also be investigated as a potential method for coupling the two core units.



151 152 146

Scheme 1.38 Synthesis of the grandisine B core unit **151** *via* addition of an organometallic reagent to bicyclic lactam **152**.

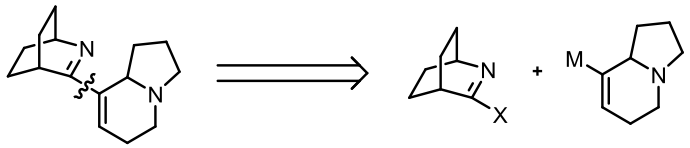
It was envisaged that a simple model isoquinuclidinone core unit **154** would be prepared *via* the thermal cyclisation of 4-aminocyclohexane carboxylic acid **153** (Scheme **1.39**),[58] providing an ideal substrate for initially investigating the formation of coupling partners. The synthesis of a functionalised isoquinuclidinone core unit constitutes an important challenge of the project.



153 154

Scheme 1.39 Synthesis of a model isoquinuclidinone core **154**.[58]

The first objective of the project was to investigate routes towards an unfunctionalised model of grandisine B **155** *via* the proposed coupling strategy, Scheme **1.40**.



155 156 146

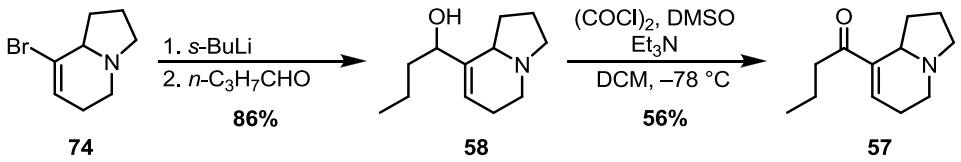
Scheme 1.40 Retrosynthesis of the grandisine B model **155**.

With an established route in hand, the synthesis of a functionalised isoquinuclidinone core unit would be required in order to investigate the viability of the developed route. If successful, an asymmetric synthesis of grandisine B **15** was to be undertaken, with the intention of also developing routes to other grandisine alkaloids.

Chapter 2. A Potential Cross-Coupling Approach to Grandisine B (15)

2.1 Synthesis of 8-Bromo-1,2,3,5,6,8a-hexahydroindolizidine (74)

Initial studies towards the synthesis of grandisine B **15** commenced with the preparation of a racemic indolizidine core unit for use in cross-coupling investigations. The requirement for a racemic indolizidine core providing a suitable handle for further functionalisation, led us to prepare bromo-indolizidine **74**, an intermediate reported previously by Overman *et al*. in their synthesis of the *Elaeocarpus* alkaloids (±)-elaeokanine A **57** and B **58**, Scheme **2.1**.[57]

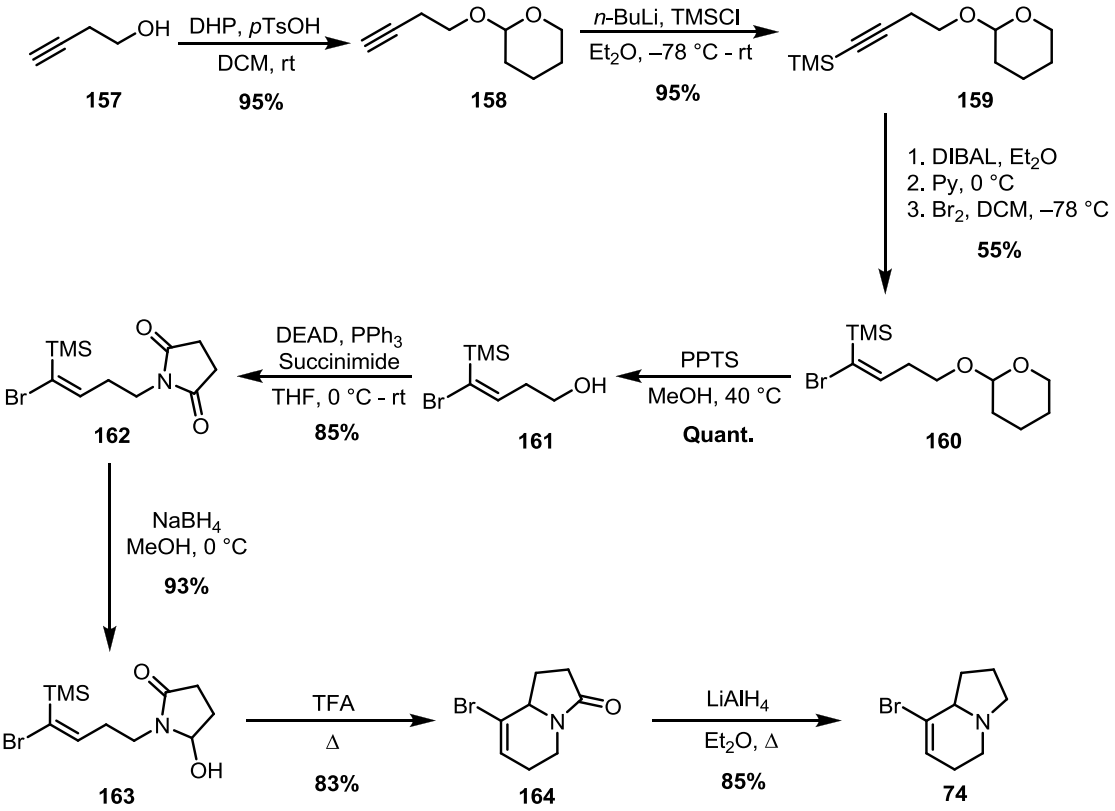


Scheme 2.1 Selected steps in Overman's synthesis of elaeokanines A **57** and B **58**.[57]

Although not as concise as other reported syntheses of indolizidine frameworks,[35,37] compound **74** provided an ideal substrate with which to investigate halogen/lithium exchange and the subsequent synthesis of organometallic reagents for use in cross-coupling studies.

Following the reported procedure,[57] synthesis of vinyl bromide **74**, commenced with THP protection of 3-butyn-1-ol to afford the protected alcohol **158** in near-quantitative yield, Scheme **2.2**. Deprotonation of alkyne **158** with *n*-butyllithium and trapping with chlorotrimethylsilane at −78 ºC gave alkyne **159** in 95% yield. Using Zweifel's hydroalumination protocol,[59] followed by treatment with bromine in pyridine, the desired ((*E*)-1-bromo-alkenyl)silane **160** was obtained in a disappointing 55% yield (Lit.[57] 83%). Cleavage of the THP protecting group using catalytic pyridinium *p*-toluenesulfonate (PPTS) proceeded readily, giving alcohol **161** in quantitative yield. Mitsunobu coupling of alcohol **161** with succinimide, gave imide **162** in 85% yield; however, in our hands the reaction was not amenable to scale-up due to difficulties with

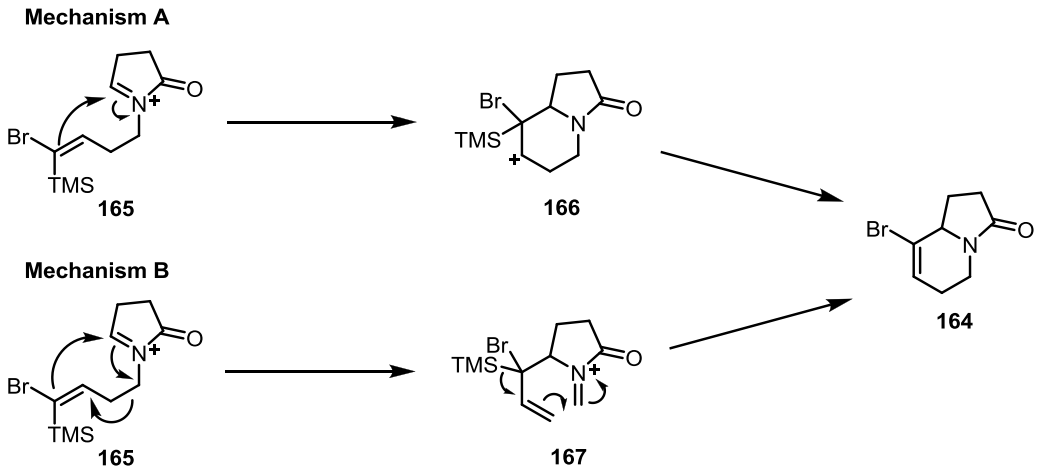
the isolation and purification of imide **162**. Reduction of imide **162** using sodium borohydride gave the hydroxylactam **163** in 93% yield. Cyclisation of hydroxylactam **163** proceeded cleanly in trifluoroacetic acid at reflux to furnish indolizidine **164** in 83% yield, with no evidence of the corresponding protodesilylation product. Finally, reduction of lactam **164** with lithium aluminium hydride gave bromo-indolizidine **74** in 85% yield (Lit.[57] 67%), the data for which were consistent with those reported by Overman.[57]



Scheme 2.2 Overman's synthesis of vinyl bromide **74**.[57]

2.1.1 Proposed Mechanism for the *N*-Acyliminium Ion Cyclisation

Although no conclusive evidence for the mechanism of the *N*-acyliminium cyclisation was reported, Overman *et al*. proposed two viable pathways,[57] Scheme **2.3**. Mechanism A involved direct cyclisation onto iminium ion **165** to give the intermediate β-silyl cation **166**, which yields vinyl bromide **164** on loss of the trimethylsilyl group.

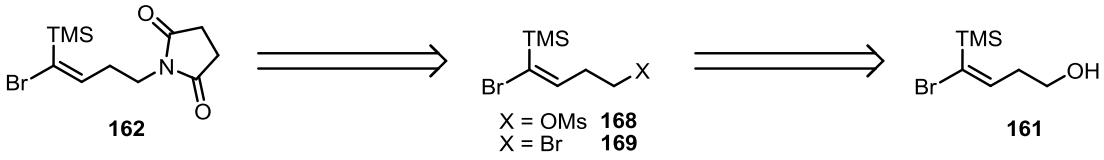


Scheme 2.3 Mechanisms proposed for the *N*-acyliminium ion cyclisation.[57]

Alternatively, iminium ion **165**, may undergo a cationic *aza*-Cope rearrangement to give an allylsilane iminium ion **167** which cyclises to furnish the vinyl bromide **164**. Additional studies by Overman *et al*. suggested that the vinylsilane **165** and allylsilane **167** intermediates equilibrate more rapidly than cyclisation occurs. It was therefore proposed that bromide **164** results from cyclisation of the more nucleophilic allylsilane, in accordance with mechanism B.

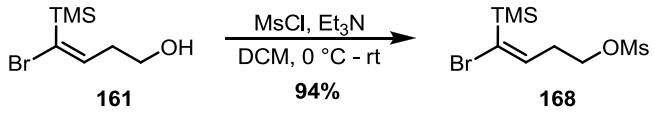
2.1.2 Challenges of Overman's Route

Whilst the yields for the indolizidine synthesis sequence were generally good, in our hands, the Mitsunobu coupling did not prove amenable to scale-up as a result of difficulties encountered with the purification of imide **162**. Alternative routes to imide **162**, were therefore investigated. We proposed that conversion of alcohol **161** into the corresponding mesylate **168** or bromo **169** derivatives and displacement with sodium succinimide would provide a scalable route to imide **162**, as shown retrosynthetically in scheme **2.4**.



Scheme 2.4 Alternative routes to imide **162**.

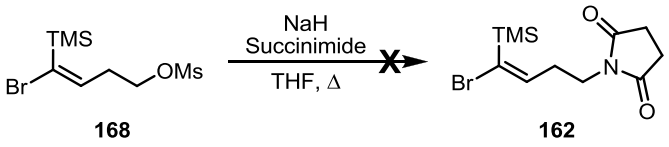
Treament of alcohol **161** with methanesulfonyl chloride and triethylamine in DCM, furnished mesylate **168** in 94% yield after 1 h at room temperature, Scheme **2.5**. Furthermore, the material was found to be homogeneous by ^{1}H NMR spectroscopic analysis and could be used in subsequent chemistry without purification.



161 **168**

Scheme 2.5 Synthesis of mesylate **168**.

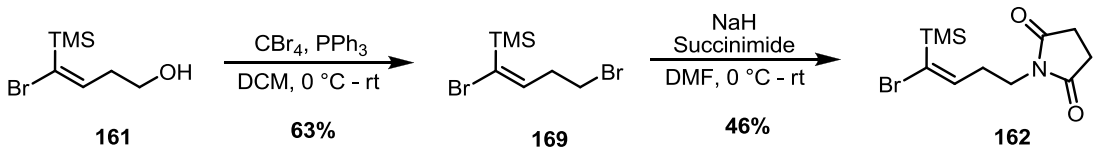
With mesylate in hand, we were in a position to investigate the displacement with succinimide-derived nucleophiles. Thus, mesylate **168** was added to a preformed solution of sodium succinimide in THF. Disappointingly, after 24 h at reflux, TLC analysis of the reaction mixture showed only starting material to be present, Scheme **2.6**. Further heating in the presence of 10 mol% sodium iodide also failed to promote the reaction.



168 **162**

Scheme 2.6 Attempted synthesis of imide **162** from mesylate **168**.

With no success in the displacement of mesylate **168**, alcohol **161** was converted into the bromo-derivative **169** under standard Appel conditions.[60] Following the procedure of Marsden,[61] addition of bromide **169** to a preformed solution of sodium succinimide in DMF resulted in clean conversion into imide **162**. Disappointingly, after purification, imide **162** was isolated in only 46% yield, Scheme **2.7**.



161 **169** **162**

Scheme 2.7 Attempted synthesis of imide **162** via bromide **162**.

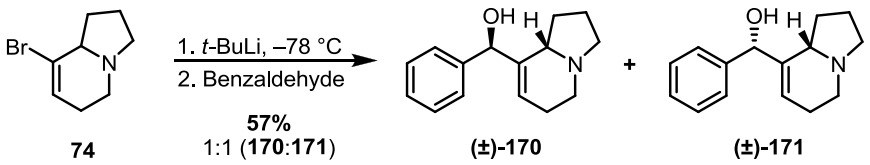
Although attempts to displace the mesylate in refluxing THF were unsuccessful, displacement of the bromo group in **169** proceeded cleanly in DMF at room temperature. Whilst the mesylate is a better leaving group, the difference in reactivity was attributed to the change in solvent, the polar aprotic solvent DMF favouring the S_N2 displacement.

Despite partial success with the modified route, due to the low yield for the displacement, we felt it would be counter-productive to spend further time optimising the sequence, and the Mitsunobu coupling reported by Overman was therefore used in subsequent reactions.[57]

2.1.3 Halogen-Lithium Exchange

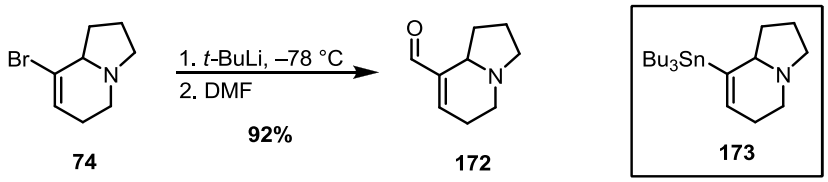
With vinyl bromide **74** in hand we were in a position to investigate the synthesis of cross-coupling partners. In order to confirm that halogen-lithium exchange proceeded cleanly, the reaction was investigated *via* trapping with simple electrophiles.

Following the procedure of Geyelin,[56] treatment of vinyl bromide **74** with *t*-butyllithium in THF at −78 ºC and subsequent trapping with benzaldehyde, gave the alcohols **170** and **171** in an unoptimised 57% yield, isolated as a 1:1 mixture of diastereoisomers, Scheme **2.8**.



Scheme 2.8 Halogen-lithium exchange reaction on vinyl bromide **74**.

The reaction was also repeated using DMF as electrophile to give the volatile indolizidine aldehyde **172**, in 92% yield, Scheme **2.9**. It was subsequently found that the lithiation could be successfully effected using *s*-butyllithium with no appreciable loss of yield.

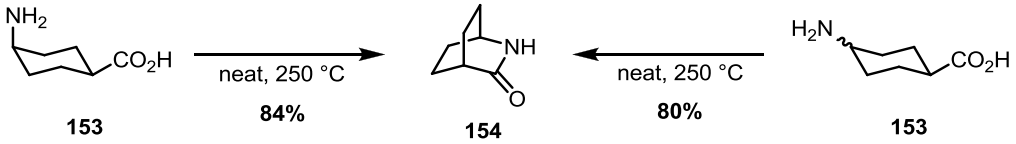


Scheme 2.9 Synthesis of aldehyde **172** from vinyl bromide **74**.

Previous work in the Taylor group had shown that the corresponding vinyl stannane **173** could be accessed *via* trapping with tributyltin chloride.[56] We also envisaged that trapping with tri*iso*propyl borate would provide access to the boronate/boronic acid derivative. At this point in time attention was turned to the synthesis of a model isoquinuclidinone core unit, for use in initial coupling studies.

2.2 Synthesis of a Model Bicyclic Lactam (154)

For the purposes of initial studies, an unfunctionalised bicyclic lactam **154** was required. Following the procedure reported by Werner,[58] bicyclic lactam **154** was prepared in 84% yield *via* a thermally induced cyclisation of commercially available *cis*-aminocyclohexane carboxylic acid **153**, Scheme **2.10**.

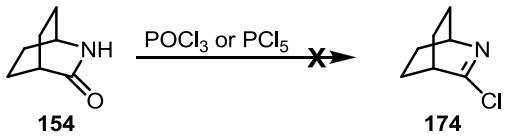


Scheme 2.10 Thermally induced cyclisation of 4-aminocyclohexene carboxylic acid **153**.[58]

Due to the high cost of *cis*-aminocyclohexane carboxylic acid, we felt it would be instructive to attempt the reaction using the cheaper *cis*/*trans*-mixture. On subjecting the *cis*/*trans*-mixture to the thermal cyclisation conditions, bicyclic lactam **154** was isolated in 80% yield; the *trans*-isomer clearly epimerises when subjected to the high temperatures. Although lacking the ketone functionality present in the isoquinuclidinone core unit of grandisine B **15**, we felt the bicyclic lactam **154** would provide an ideal model for initial coupling studies.

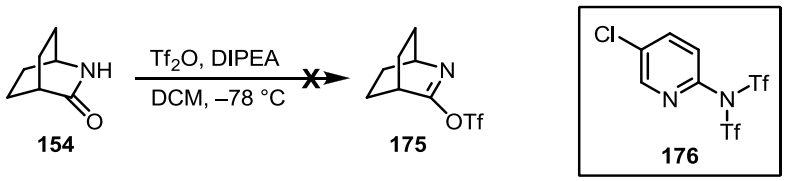
2.3 Synthesis of a Bicyclic Imidoyl Chloride/Triflate Cross-Coupling Partner

As a continuation of early studies by Geyelin,[56] attempts were made to prepare the novel imidoyl chloride **174** for use in cross-coupling studies. Treatment of lactam **154** with phosphoryl(V) oxychloride at reflux resulted in complete consumption of the starting material, Scheme **2.11**. However, the ^{1}H NMR spectrum of the unpurified reaction mixture showed no evidence of the desired imidoyl chloride **174**. Repeating the reaction using conditions reported by Olsson,[62] in which lactam **154** was treated with PCl_5 in toluene at reflux, was also unsuccessful.



Scheme 2.11 Attempted synthesis of imidoyl chloride **174**.

Due to failed efforts to prepare imidoyl chloride **174**, attention was turned to the synthesis of the corresponding imidoyl triflate **175**, which we envisaged could also be used in cross-coupling studies. Treatment of lactam **154** with Tf_2O and DIPEA in DCM at −78 ºC, failed to give any of the desired imidoyl triflate **175**, Scheme **2.12**.

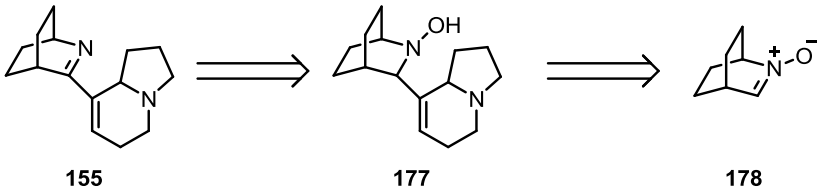


Scheme 2.12 Attempted synthesis of imidoyl triflate **175**.

Alternative conditions reported by Donohoe were also investigated.[63] Disappointingly, treatment of lactam **154** with NaHMDS and Comins' reagent **176** in anhydrous THF was also unsuccessful. The unsuccessful attempts were attributed to the instability of both the imidoyl chloride **174** and imidoyl triflate **175** which we proposed rapidly hydrolysed/decomposed on isolation.

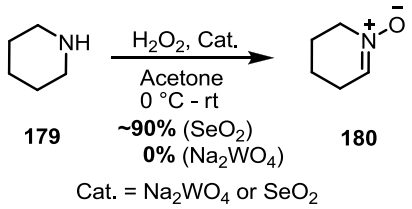
2.4 Nitrone Chemistry

Whilst attention had initially focussed on a transition metal catalysed cross-coupling strategy, we proposed that direct addition of a metallated indolizidine core unit to an electrophilic isoquinuclidinone derivative could also prove a viable method for coupling of the two core units. A paper by Murahashi was brought to our attention, detailing the synthesis of imines from *N*,*N*-disubstituted hydroxylamines on treatment with $TiCl_3$,[64] providing a potential route to the model grandisine B skeleton **155**, as outlined retrosynthetically in Scheme **2.13**.



Scheme 2.13 Retrosynthetic analysis of the grandisine B model **155**.

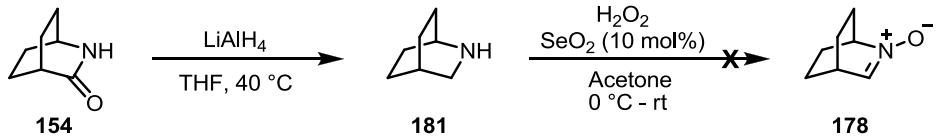
The required *N*,*N*-disubstituted hydroxylamine **177** could be obtained from nitrone **178** *via* the addition of an organolithium or Grignard reagent.[64] In order to investigate this strategy, the known nitrone **180** was initially prepared.



Scheme 2.14 Synthesis of nitrone **180** using the procedure of Murahashi.[65,66]

Initial attempts to prepare nitrone **180** using Murahashi's sodium tungstate-mediated oxidation proved unsuccessful.[65] The reaction was found to be highly exothermic, giving only trace amounts of product after work-up (Lit.[65] 42% yield). An alternative procedure also reported by Murahashi using catalytic selenium dioxide was found to be more reproducible,[66] yielding nitrone **180** in ~90% yield after work-up, the material of sufficient purity to be used without purification. Disappointingly, attempts to further purify the product on silica or alumina were unsuccessful, resulting in complete

decomposition. In the knowledge that nitrone **180** could be prepared, attempts were made to prepare the corresponding bicyclic nitrone **178**. Although not commercially available, amine **181** was readily accessed from lactam **154**. Reduction of lactam **154** with lithium aluminium hydride in THF gave the volatile amine **181**, which was immediately subjected to nitrone formation without purification, Scheme **2.15**.

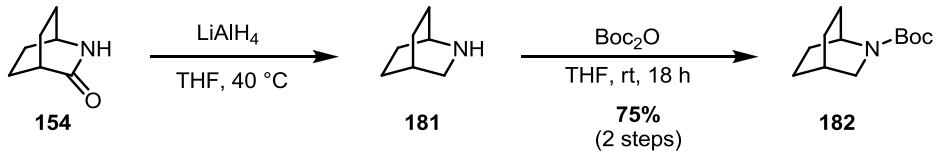


154 **181** **178**

Scheme 2.15 Attempted synthesis of nitrone **178**.

Addition of hydrogen peroxide to a solution of amine **181** in the presence of catalytic selenium dioxide in acetone resulted in complete consumption of the starting material. Unfortunately, ^{1}H NMR spectroscopic analysis of the unpurified mixture showed no signals corresponding to the desired product **178**.

In order to confirm that the reduction of lactam **154** was proceeding, the unpurified amine **181** was treated with Boc_2O, which gave after purification the Boc-protected amine **182** in 75% yield, Scheme **2.16**. The result provided evidence to suggest that nitrone formation was the problematic step in the sequence.



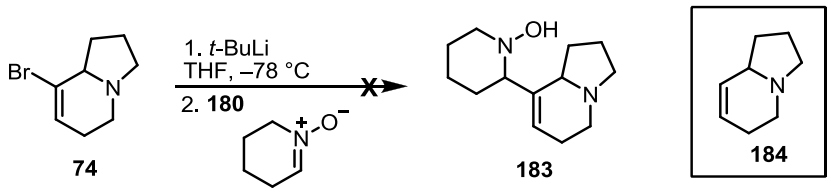
154 **181** **182**

Scheme 2.16 Trapping of amine **181** with Boc_2O.

2.4.1 Addition of Organolithium Reagents to Cyclic Nitrones

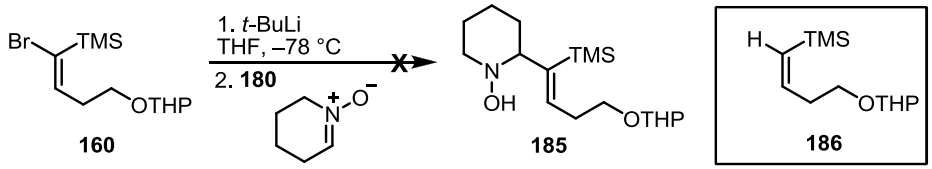
In parallel to the synthesis of bicyclic nitrone **178**, attempts were made to couple the racemic indolizidine core unit **74** with model nitrone **180**, to test the viability of this strategy.

Lithiation of vinyl bromide **74** with *t*-butyllithium in THF at −78 ºC followed by addition of nitrone **180** resulted in complete consumption of the starting material, evident by TLC analysis, Scheme **2.17**.



Scheme 2.17 Attempted coupling of indolizidine **74** with nitrone **180**.

Disappointingly, no evidence of the desired hydroxylamine **183** was observed upon inspection of the ^{1}H NMR spectrum of the unpurifed reaction mixture, or peaks corresponding to an indolizidine species. It was therefore proposed that vinyllithium intermediate was protonated during work-up and lost as the volatile indolizidine **184**. Further evidence for this was provided when lithiation of bromide **160** under identical conditions, gave only the protonated alkene **186**, after work-up, Scheme **2.18**.

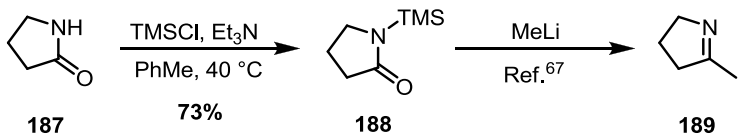


Scheme 2.18 Attempted coupling of vinyl bromide **160** with nitrone **180**.

Due to unsuccessful attempts to prepare the model bicyclic nitrone **178** and failed attempts to couple lithiated species with nitrone **180**, further worker on this approach was suspended.

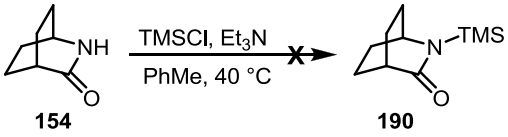
2.5 Addition of Organolithium Reagents to N-Silylated Lactams

An alternative route to cyclic imines was reported by Hua and co-workers *via* the addition of organolithium reagents to *N*-TMS lactams, Scheme **2.19**.[67] Following Hua's procedure, treatment of 2-pyrrolidinone **187** with trimethylsilyl chloride and triethylamine gave the known silylated lactam **188** in 73% yield.



Scheme 2.19 Hua's procedure for the synthesis of cyclic ketimine **189**.[67]

Disappointingly, attempts to utilise this procedure in the synthesis of silylated bicyclic lactam **190** gave only recovered starting material **154**, Scheme **2.20**. Similarly, only starting material was recovered when the reaction was repeated using the procedure of Menezes.[68] Repeating the reaction in the presence of stronger bases such as *n*-butyllithium and sodium hydride also failed to yield any of the silylated lactam **190**.



Scheme 2.20 Attempted synthesis of TMS-Lactam **190** using Hua's procedure.[67]

The difficulties encountered were initially attributed to the instability of the TMS-lactam **190**, and a one-pot procedure was therefore attempted in order to negate the possibility that silyl lactam **190** was decomposing during work-up. Thus, attempts were made to trap the silylated species *in situ* with MeLi to give the corresponding cyclic imine **191**. Disappointingly, treatment of lactam **154** with *n*-butyllithium and trimethylsilyl chloride, followed by addition of methyllithium, gave after work-up only recovered lactam **154**, Scheme **2.21**.

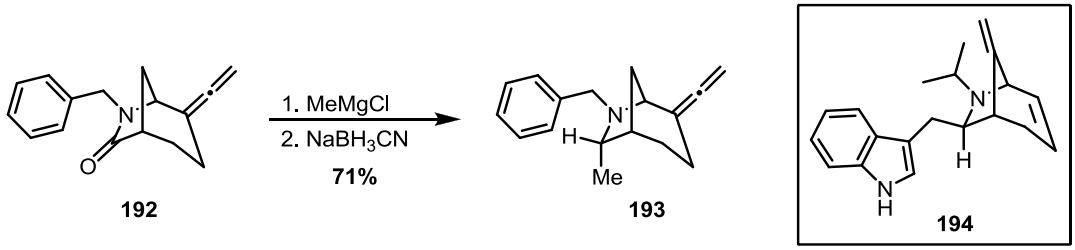
Scheme 2.21 Attempted *in situ* trapping on TMS-lactam **190**.

Using a similar procedure reported by Romo *et al.*;[69] lactam **154** was treated with *n*-butyllithium and TMSOTf in DME; subsequent addition of methyllithium gave only recovered starting material on work-up. These further experiments suggested that initial

formation of the TMS-lactam **190** was not occurring, as a result, an alternative coupling strategy was sought.

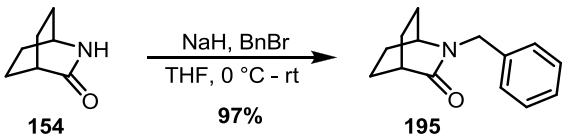
2.6 Addition of Organometallic Reagent to Amides

In the search for alternative strategies, a particularly relevant paper by Speckamp and co-workers reporting the synthesis of the alkaloid peduncularine **194**,[70] was brought to our attention. A key transformation in the paper was the addition of a Grignard reagent to the bicyclic lactam **192** and subsequent reduction of the iminium ion to give amine **193**, Scheme **2.22**.



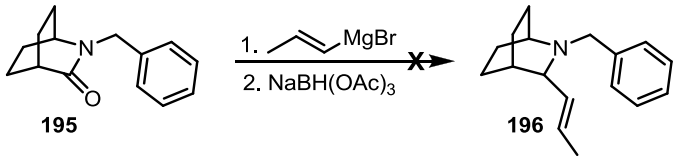
Scheme 2.22 Addition of a Grignard reagent to bicyclic lactam **192**.[70]

Whilst not providing direct access to the required imine, there is literature precedent for the conversion of secondary amines into imines.[42] In order to investigate this approach, benzyl lactam **195** was prepared in 97% yield from lactam **154** *via* deprotonation with sodium hydride and alkylation with benzyl bromide.



Scheme 2.23 *N*-Benzylation of lactam **154**.

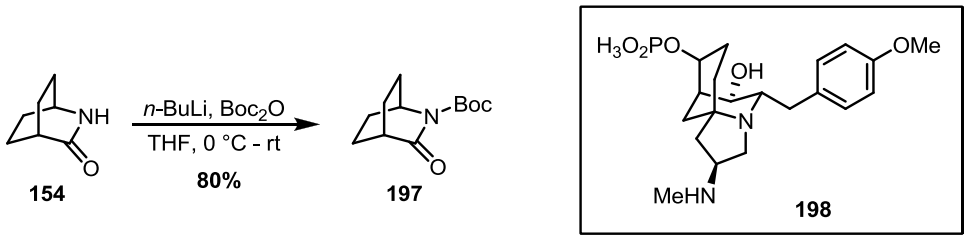
With benzyl lactam **195** in hand, the addition of simple Grignard and organolithium reagents was investigated. Treatment of **195** with propenyl magnesium bromide in THF at 0 ºC followed by sodium triacetoxyborohydride gave only recovered starting material after work-up, Scheme **2.24**.



Scheme 2.24 Attempted coupling of Grignard reagents with benzyl lactam **195**.

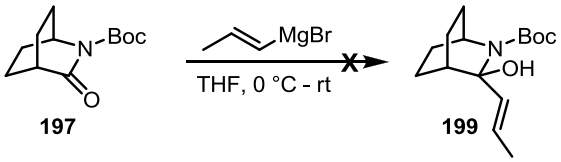
Alternative reaction conditions using *n*-butyllithium as the nucleophile and lithium aluminium hydride as the reductant under a variety of conditions, also failed to give the substituted amine.

Due to unsuccessful attempts to add organometallic reagents into the *N*-benzyl bicyclic lactam **195**, the corresponding *N*-Boc derivative **197** was considered. Addition of organometallic reagents to Boc-amides has recently been utilised by Martin and Weinreb in two differing approaches to the immunosuppressant FR901483 **198**.[71,72] In order to investigate this approach, the model Boc-protected lactam **197** was prepared *via* treatment of lactam **154** with *n*-butyllithium and Boc_2O, to give after purification, the novel Boc-lactam **197** in 80% yield, Scheme **2.25**.



Scheme 2.25 Synthesis of Boc-lactam **197** from bicyclic lactam **154**.

Following the general procedure reported by Weinreb,[72] addition of propenylmagnesium bromide to Boc-lactam **197** in THF resulted in complete consumption of starting material evident by TLC analysis, Scheme **2.26**.

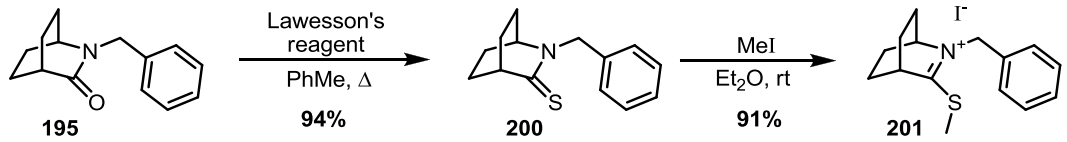


Scheme 2.26 Attempted addition of propenyl magnesium bromide to Boc-lactam **197**.

Pleasingly, upon inspection of the ^{1}H NMR spectrum of the crude product, trace signals potentially corresponding to the expected product **199** were observed. Unfortunately, none of the desired product was recovered after attempted purification on silica. Subsequent attempts to repeat the reaction also failed to give the alkylated product **199**.

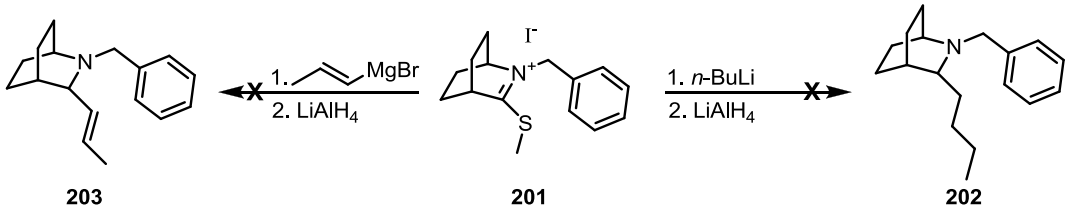
2.7 Grignard Addition to Thioimidates

An alternative coupling approach reported by Speckamp involved the addition of Grignard reagents to thioiminium ions.[70] Thus, thioiminium ion **201** was prepared from benzyl lactam **195** in two steps. Treatment of lactam **195** with Lawesson's reagent in toluene gave the novel thioamide **200** in 94% yield, which upon treatment with methyl iodide gave thioiminium ion **201** in 91% yield, Scheme **2.27**.



Scheme 2.27 Synthesis of thioiminium ion **201** using the procedure of Speckamp.[70]

With thioiminium ion **201** in hand, we were in a position to investigate the addition of organometallic reagents. Upon addition of *n*-butyllithium to iminium ion **201** in THF and subsequent reduction with lithium aluminium hydride consumption of the starting material was evident by TLC analysis, however, all attempts to isolate the polar products from the crude mixture were unsuccessful. Attempts to repeat the reaction using propenyl magnesium bromide also gave complex mixtures of products, with no evidence of the bicyclic amine **203** observed in the ^{1}H NMR spectrum of the crude reaction mixture, Scheme **2.28**.



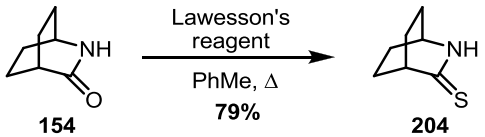
Scheme 2.28 Attempted addition of Grignard and organolithium reagents to thioiminium ion **201**.

Despite the literature precedent for the addition of organometallic reagents to amides/thioiminium ions, it became quickly apparent during initial studies on the model system, that the strategy was not viable for the synthesis of grandisine B **15**.

2.8 A Liebeskind-Srogl Cross-Coupling Strategy

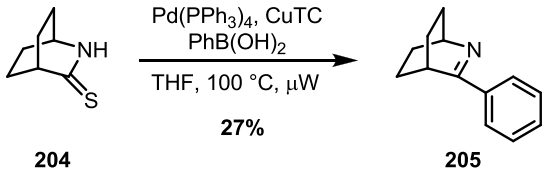
Despite unsuccessful attempts to react organometallic reagents directly with thioiminium ions, we felt the thioamide derivatives could still be utilised as a potential coupling partner.

Returning to the originally proposed cross-coupling strategy, we were keen to investigate metal-catalysed coupling reactions such as the Kumada coupling of Grignard reagents with thioimidates using nickel catalysts or the copper-mediated Liebeskind-Srogl coupling. A recent publication by Kappe *et al*. reported the palladium-catalysed, copper-mediated coupling of thioamides with aryl boronic acids.[73] The Liebeskind-Srogl type reaction was reported to give imine products in moderate to excellent yield. In order to investigate this approach the required isoquinuclidinone coupling partner **204** was prepared in 79% yield *via* treatment of lactam **154** with Lawesson's reagent in toluene, Scheme **2.29**.



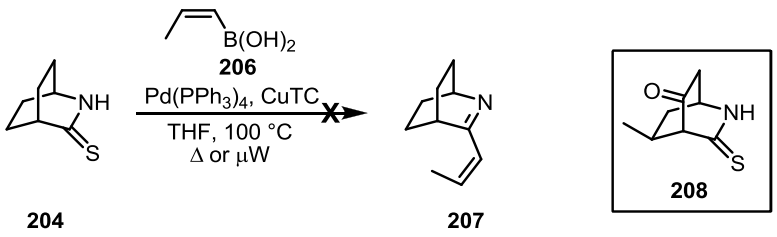
Scheme 2.29 Synthesis of thiolactam **204** from bicyclic lactam **154**.

The publication by Kappe focused on the coupling of aromatic boronic acids,[73] and we therefore initially examined the coupling reaction using commercially available phenyl boronic acid. Upon subjecting thiolactam to the reported microwave conditions we were pleased to observe the formation of bicyclic imine **205**, evident from characteristic bridgehead signals at 4.3 ppm and 3.3 ppm apparent in the ^{1}H NMR spectrum of the unpurified reaction mixture, Scheme **2.30**. Although the bicyclic imine **205** was only isolated in 27% yield, we felt this could be optimised at a later stage.



Scheme 2.30 Liebeskind-Srogl type cross-coupling of thiolactam **204** with phenyl boronic acid.

In order for the methodology to be applied to the synthesis of grandisine B **15**, it would be necessary to couple a vinyl boronic acid coupling partner with a thioamide. However, initial attempts to couple thiolactam **204** with *cis*-propenyl boronic acid **206** under microwave or sealed-tube conditions failed to give any of the desired imine **207**, Scheme **2.31**.



Scheme 2.31 Attempted cross-coupling of thiolactam **204** with propenyl boronic acid **206**.

Despite the disappointing result with the vinyl boronic acid, we felt the route warranted further investigation. The synthesis of a functionalised isoquinuclidinone coupling partner **208** was therefore investigated in order to further study the Liebeskind-Srogl-type cross-coupling.

2.9 Summary

A number of strategies for the coupling of model indolizidine and isoquinuclidinone core units have been investigated. A Liebeskind-Srogl-type approach has shown promising results on simple model systems; a functionalised isoquinuclidinone coupling partner **208** will therefore be prepared in order to test the viability of the strategy for the synthesis of grandisine B **15**. The results of these studies are described in Chapter 3.

Chapter 3. Synthesis of a Functionalised Bicyclic Lactam

3.1 Introduction

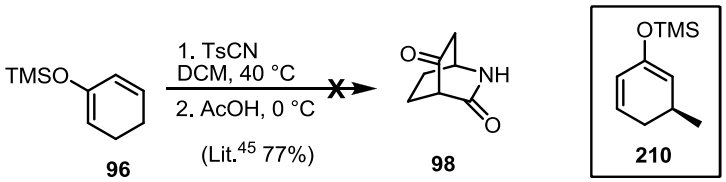
In the previous chapter, a potential route to grandisine B **15** was reported, *via* a Liebeskind-Srogl-type coupling of a thioamide derived from bicyclic lactam **154** with a boronic acid. A route to the functionalised bicyclic lactam **209** (Figure **3.1**) was therefore required in order to further investigate the cross-coupling approach.

154 **209**

Figure 3.1 Bicyclic lactam **154** and functionalised bicyclic lactam **209**.

3.2 A Nitrile Diels-Alder Approach

A paper by McClure *et al*. reported the synthesis of isoquinuclidinone **98** *via* an *aza*-Diels-Alder reaction between *p*-toluenesulfonyl cyanide and diene **96**, Scheme **3.1**.[45]



96 **98** **210**

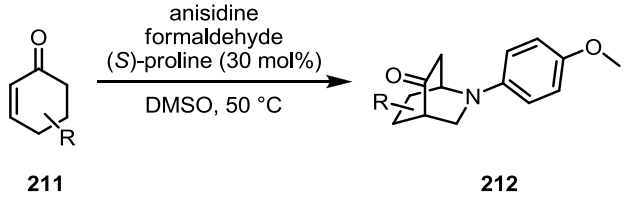
Scheme 3.1 Attempted synthesis of bicyclic lactam **98** using the procedure of McClure.[45]

Although only providing racemic material, we felt the brevity of the route justified the use of the sequence in the synthesis of a model isoquinuclidinone core unit. Whilst lacking the required methyl substituent, it was envisaged that the methodology could be extended to the synthesis of a methyl substituted isoquinuclidinone *via* the use of the silyl enol ether **210**. Following the procedure of Shibasaki,[74] diene **96** was prepared in 88% yield from commercially available cyclohexenone *via* deprotonation with LiHMDS in THF at 0 ºC and subsequent trapping with chlorotrimethyl silane.

Subjecting diene **96** to the conditions reported by McClure gave, after work-up, a pale yellow solid, the analytical data for which showed a number of unidentified products. Attempts to isolate the bicyclic lactam **98** from the mixture were unsuccessful, yielding only trace amounts of the desired product **98** (Lit.[45] 77%). Due to the relatively high cost of *p*-toluenesulfonyl cyanide and unsuccessful attempts to repeat the literature procedure, alternative routes to the functionalised isoquinuclidinone core unit were sought.

3.3 Cordova Diels-Alder Chemistry

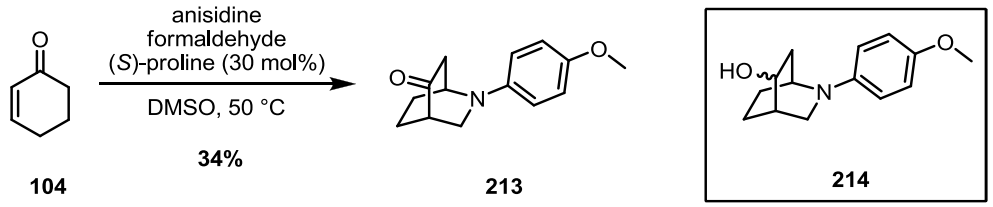
A recent paper by Cordova *et al*. came to our attention detailing the enantioselective synthesis of isoquinuclidinones **212** using proline catalysis, Scheme **3.2**.[50] Although lacking the amide functionality required, it was envisaged that this could be subsequently installed by oxidation of isoquinuclidinone **212**.



211 **212**

Scheme 3.2 Cordova's enantioselective synthesis of isoquinuclidinones **212**.[50]

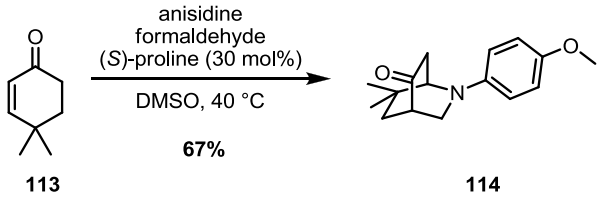
Following the reported procedure,[50] isoquinuclidinone **213** was prepared in a moderate 34% yield (Lit.[50] 82% after reduction to the corresponding alcohol), Scheme **3.3**. In accordance with the literature, isoquinuclidinone **213** proved to be unstable in our hands, readily decomposing on silica resulting in low recovery of the product. Under acidic conditions, Cordova reported that isoquinuclidinone **213** undergoes a retro-*aza*-Michael reaction, although no evidence was found to support this; analysis of the material showed only decomposition products.



Scheme 3.3 Synthesis of isoquinuclidinone **213** using the procedure of Cordova.[50]

In situ reduction of isoquinuclidinone **213** using $NaBH_4$ and subsequent isolation of the diastereomeric alcohols **214** was also attempted. Addition of excess $NaBH_4$ to the reaction mixture gave, after work-up, a brown oil which contained a number of components as evident by TLC analysis. Attempts to purify the mixture were unsuccessful with none of the desired alcohol **214** isolated. Reduction of the unpurified isoquinuclidinone **213**, obtained after an aqueous work-up, also failed to give alcohol **214**.

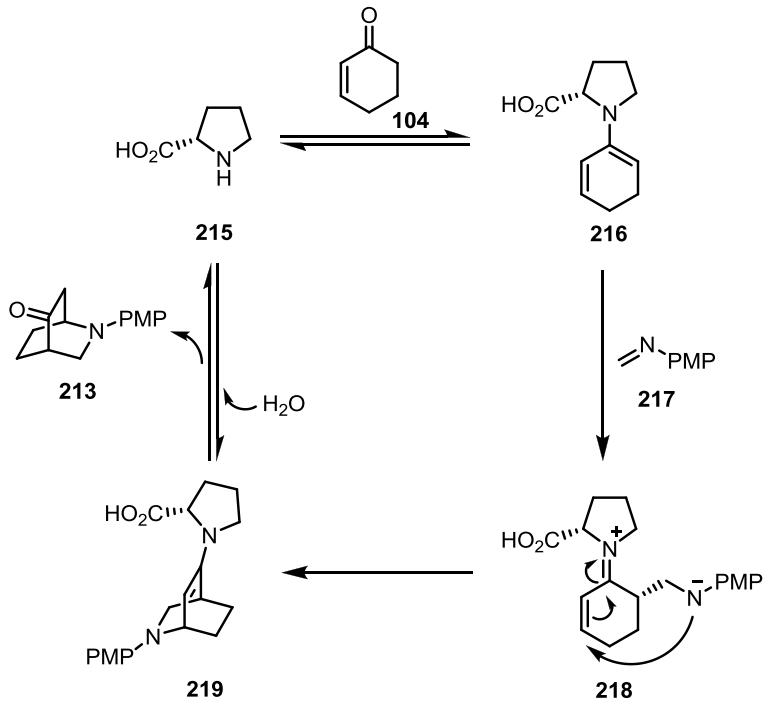
Due to the low stability and poor yields encountered during the synthesis of isoquinuclidinone **213**, the reportedly more stable isoquinuclidinone **114** was prepared in 67% yield (Lit.[50] 70%), Scheme **3.4**.



Scheme 3.4 Synthesis of isoquinuclidinone **114** using the procedure of Cordova.[50]

Analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy showed the reaction proceeded cleanly to give isoquinuclidinone **114**, with unreacted 4,4-dimethylcyclohexenone **113** the only impurity present. The problems previously encountered with stability were not found with isoquinuclidinone **114**, which could be purified by silica gel chromatography.

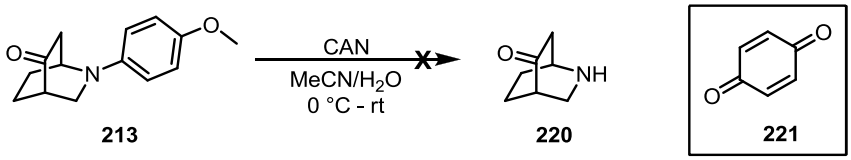
Whilst the reaction is described as an *aza*-Diels-Alder reaction, mechanistically, Cordova proposed a stepwise process involving an initial Mannich reaction to yield amine **218**, Scheme **3.5**. The secondary amine subsequently adds into the activated enone to furnish the isoquinuclidinone **213**.



Scheme 3.5 Proposed mechanism of Cordova's *aza*-Diels-Alder reaction.[50]

3.3.1 PMP Deprotection

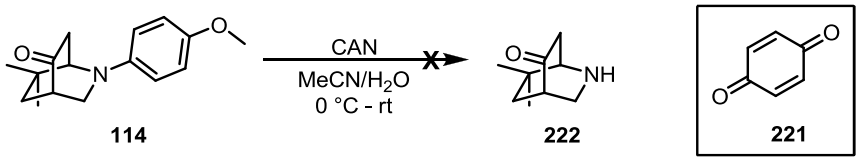
Before investigating potential coupling strategies, the removal of the PMP group and installation of the amide function had to be addressed. Initially, we chose to investigate the removal of the PMP group. Although removal of the PMP group from primary amines is widely precedented in the literature, the removal of PMP groups from secondary amines has received less attention. Initially, isoquinuclidinone **213** was subjected to standard deprotection conditions using excess ceric ammonium nitrate in aqueous acetonitrile.[75] After 1 h at 0 ºC, TLC analysis showed complete consumption of the starting material, with the formation of two products, one baseline species and the other more lipophilic than the starting material, Scheme **3.6**. The more lipophilic species was thought to be *p*-benzoquinone **221**, the by-product of the PMP deprotection.



Scheme 3.6 Attempted cleavage of the PMP group using CAN.

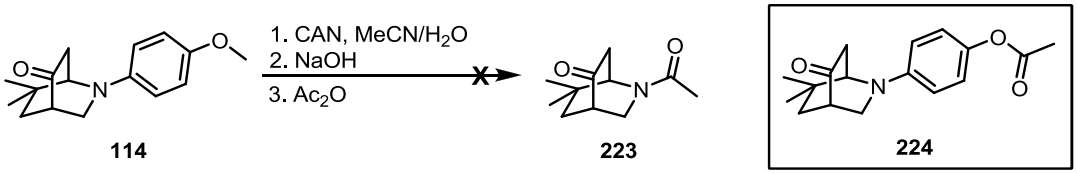
Inspection of the ^{1}H NMR spectrum of the unpurified material showed no evidence of the expected bicyclic amine **220**, although the presence of *p*-benzoquinone **221** was suggested by a singlet at ~6.8 ppm. Due to the low stability of isoquinuclidinone **213**, further investigations were carried out using the more stable isoquinuclidinone **114**.

Initially, isoquinuclidinone **114** was subjected to the standard conditions used previously, Scheme **3.8**. Analysis of the reaction mixture by ^{1}H NMR spectroscopy, showed an absence of signals corresponding to the PMP group, but no signals corresponding to amine **222** were observed. The formation of *p*-benzoquinone **221** in both reactions was consistent with the removal of the PMP group, suggesting the products were decomposing under the reaction conditions.



Scheme 3.8 Attempted cleavage of the PMP group with CAN.

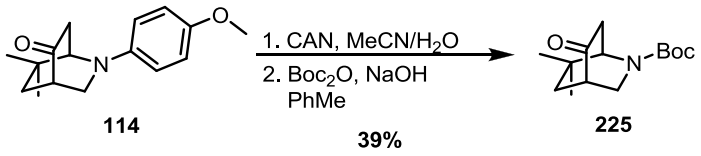
A one-pot deprotection/acetate protection procedure reported by Tomioka caught our attention as it would negate the need to isolate amine **222**.[76] Thus, following the reported procedure, a solution of isoquinuclidinone **114** in acetonitrile was treated with CAN, Scheme **3.9**. After 5 min., the reaction was quenched with aqueous sodium hydroxide and excess acetic anhydride was added.



Scheme 3.9 Attempted deprotection/acetate protection strategy.[76]

Disappointingly, analysis of the ^{1}H NMR spectrum of the crude reaction mixture, showed signals corresponding to a *p*-substituted aromatic group were still present, but, no signals corresponding to the methoxy group were observed. The ^{1}H NMR spectroscopic data were consistent with a product such as the acetate derivative **224**, however, insufficient material was obtained to allow full characterisation.

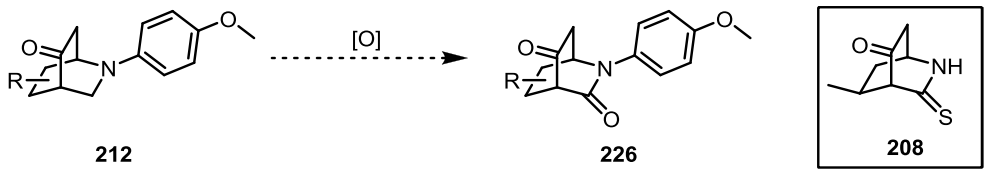
Due to the unsuccessful attempt to isolate acetate-protected isoquinuclidinone **223** an alternative deprotection/Boc-protection strategy reported by Buchwald was investigated.[77] Treatment of isoquinuclidinone **114** with CAN in acetonitrile and subsequent protection with Boc_2O in aqueous toluene, gave after purification, the novel Boc-protected isoquinuclidinone **225** in an unoptimised 39% yield, Scheme **3.10**



Scheme 3.10 Synthesis of isoquinuclidinone **225** *via* a deprotection/Boc-protection strategy.[77]

3.4 Oxidation of Isoquinuclidinones

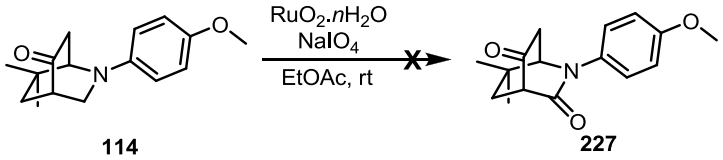
In order to investigate the synthesis of grandisine B **15** *via* the proposed coupling strategy, a route to thioamide **208** was required, which we envisaged could be obtained from the corresponding bicyclic lactam. A method for the oxidation of isoquinuclidinones **212** to give bicyclic lactams **226** was therefore required, Scheme **3.11**.



Scheme 3.11 Proposed oxidation of isoquinuclidinones **212** to give bicyclic lactams **226**.

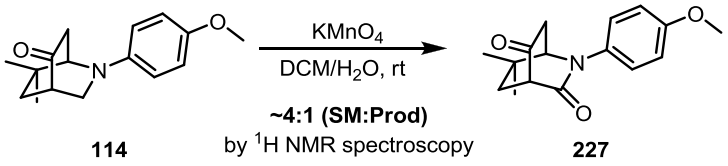
With limited quantities of the Boc-protected compound **225** obtained after deprotection, oxidation of the PMP derivative **114** was initially considered.

Although ruthenium-based oxidations of secondary amines are precedented in the literature,[78] to our knowledge, there are only limited reported oxidations of tertiary amines bearing aromatic substituents.[79] Initial studies were undertaken using conditions reported by Arakawa.[80] Disappointingly, treatment of isoquinuclidinone **114** with catalytic ruthenium(IV) oxide hydrate and aqueous sodium periodate resulted in complete decomposition of the starting material after 4 h at room temperature, Scheme **3.12**.



Scheme 3.12 Attempted ruthenium-mediated oxidation of isoquinuclidinone **227**.[80]

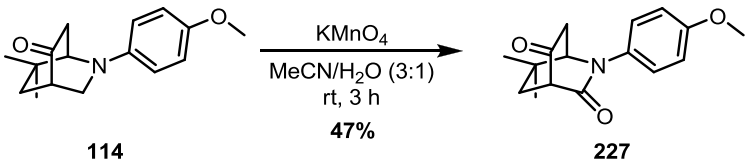
A particularly relevant paper by Benn *et al.*, reported the oxidation of the alkaloid lycoctonine using potassium permanganate in aqueous solvent systems to yield the corresponding tertiary amide.[81] Following the reported procedure, on addition of a slight excess of aqueous potassium permanganate to a solution of amine **114** in DCM, the appearance of a more polar species was observed by TLC analysis, Scheme **3.13**. Pleasingly, ^{1}H NMR spectroscopic analysis of the unpurified product, revealed signals corresponding to residual starting material **114** and the desired bicyclic lactam **227** (evident from the loss of the C-3 proton signals at 3.47 ppm and a downfield shift of the C-4 bridgehead proton from 2.61 ppm to 3.37 ppm).



Scheme 3.13 Oxidation of isoquinuclidinone **114** using the conditions reported by Benn.[81]

A paper published by Suginome, reported the oxidation of tertiary amines with $KMnO_4$ in aqueous acetone.[82] The reaction of amine **114** with $KMnO_4$ was therefore repeated in both aqueous acetone and acetonitrile, to establish whether complete oxidation of amine **114** could be achieved. After 5 h, TLC analysis of the reactions showed the presence of both starting material and product. Additional $KMnO_4$ was added to both reactions until

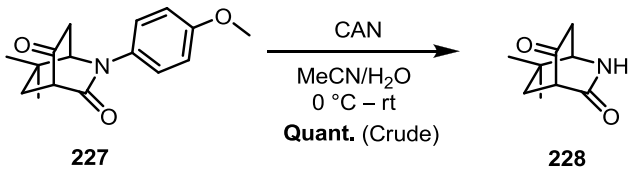
complete consumption of the starting material was observed. In both instances, it was found that 5 equivalents of $KMnO_4$ were required to achieve complete conversion into lactam **227**. Upon work-up of the reaction carried out in aqueous acetonitrile, lactam **227** was obtained in 48% isolated yield. Analysis of the unpurified material by ^1H NMR spectroscopy showed the product to be homogeneous, requiring no purification. When repeated on a larger scale, the reaction went to completion in 3 h using only 3 equivalents of $KMnO_4$, to give bicyclic lactam **227** in 47% yield, Scheme **3.14**.



Scheme 3.14 Oxidation of isoquinuclidinone **114** using $KMnO_4$ in aqueous acetonitrile.

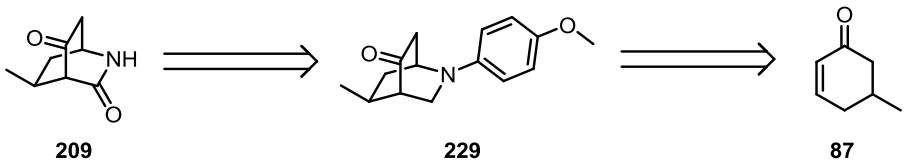
Disappointingly, attempts to optimise the reaction and work-up conditions failed to give yields higher than 50%, with yields reproducibly between 45% and 50%. Concentration of the aqueous phase *in vacuo* and subsequent analysis of the residue failed to show any organic products, providing no explanation to account for the poor mass balance.

Despite the moderate yield for the oxidation, the removal of the PMP group was briefly investigated on small-scale. Treatment of lactam **227** with ceric ammonium nitrate in aqueous acetonitrile, resulted in clean conversion to a single product **228**, Scheme **3.15**. Analysis of the unpurified material by ^1H NMR spectroscopy showed the desired bicyclic lactam **228** contaminated with minor traces of *p*-benzoquinone **221**.



Scheme 3.15 Synthesis of bicyclic lactam **228** *via* PMP deprotection.

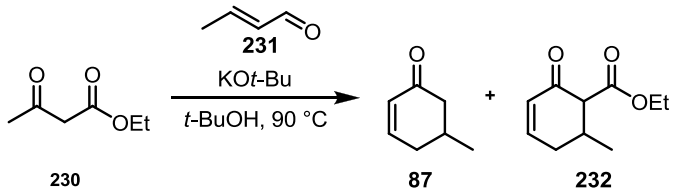
With these pleasing results in hand, we were keen to explore the use of the sequence in the synthesis of the grandisine B isoquinuclidinone core unit **209**. Disconnection *via* the *aza*-Diels-Alder strategy reveals the known cyclohexenone **87**, bearing the methyl substituent found in grandisine B **15**, Scheme **3.16**.



Scheme 3.16 Retrosynthesis of functionalised bicyclic lactam **209**.

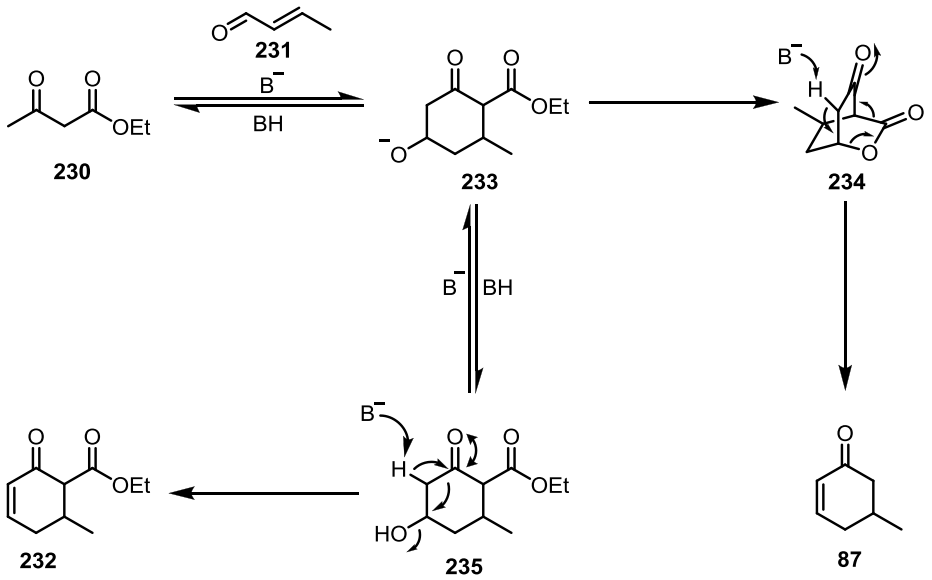
3.5 Synthesis of 5-Methylcyclohexenone (87)

For initial investigations we chose to prepare racemic 5-methylcyclohexenone **87** using the procedure reported by Koo *et al*.;[83] the low cost of the starting materials and brevity of the route appeared to be ideal. However, upon treatment of ethyl acetoacetate **230** and crotonaldehyde **231** with potassium *tert*-butoxide in *tert*-butanol, following the reported procedure, a 1:1 mixture of enones **87** and **232** was obtained, Scheme **3.17**. Disappointingly, attempts to separate the products chromatographically were unsuccessful, giving only trace amounts of the desired cyclohexenone **87**.



Scheme 3.17 Attempted synthesis of cyclohexenone **87** using Koo's procedure.[83]

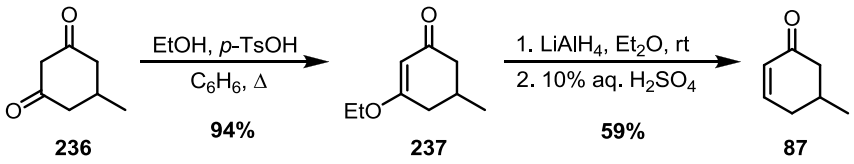
Mechanistically, the formation of enone **87** is reported to proceed *via* a base-catalysed Michael addition of ethyl acetoacetate into crotonaldehyde, Scheme **3.18**. Cyclisation of the resulting intermediate **233** gives a bicyclic lactone **234**, which collapses with concomitant loss of CO_2 to yield enone **87**. It was proposed that the presence of water may result in the protonation of intermediate **233** before cyclisation occurs, giving rise to the alternative enone **232** *via* an elimination pathway.[83]



Scheme 3.18 Koo's proposed mechanism for the formation of enone **87** and **232**.[83]

Repeating the reaction in *tert*-butanol, freshly distilled from sodium, also gave enone **87** in a disappointing 15% yield (Lit.[83] 78%).

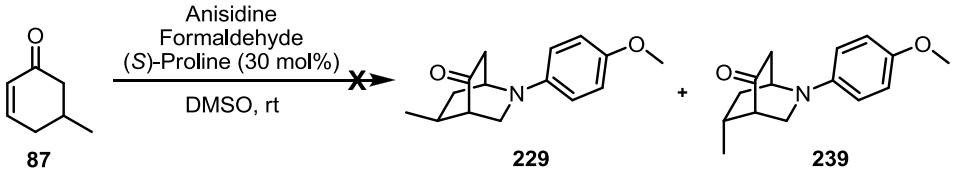
An alternative synthesis reported by Fuchs *et al*. *via* reduction of ethoxy enone **237** came to our attention, Scheme **3.19**.[84] Synthesis of ethoxy enone **237**, was accomplished using the procedure of Pattenden *et al*.;[85] treatment of commercially available 5-methyl-1,3-cyclohexanedione **236** with *p*-TsOH in ethanol and benzene at reflux under Dean-Stark conditions gave, after work-up, β-ethoxy enone **237** in 94% yield. On subjecting enone **237** to the reductive transposition sequence reported by Fuchs *et al*.,[84] methyl cyclohexenone **87** was isolated in 59% yield after distillation (Lit.[84] 84%).



Scheme 3.19 Synthesis of cyclohexenone **87** using the procedure reported by Fuchs.[84]

With cyclohexenone **87** in hand we were in a position to investigate the synthesis of isoquinuclidinone **229** using Cordova's "*aza*-Diels-Alder" methodology. Subjecting enone **87** to the (*S*)-proline-catalysed Diels-Alder conditions gave, after work-up, a brown oil, Scheme **3.20**. Upon inspection of the ^{1}H NMR spectrum of the unpurified

material, minor peaks corresponding to the diastereomeric isoquinuclidinones **229** and **239** were apparent, but, attempts to isolate the compounds by flash column chromatography gave none of the desired product **229**.

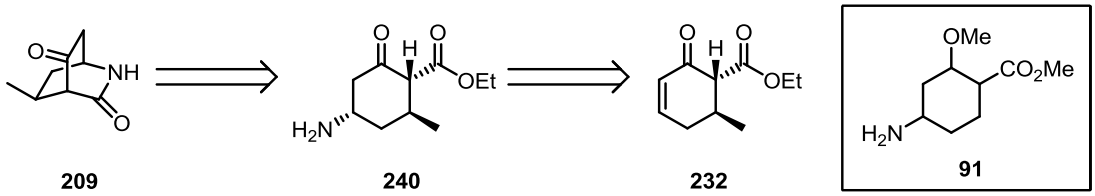


Scheme 3.20 Aza-Diels-Alder reaction using cyclohexenone **87**.

On repeating the reaction at 50 ºC traces of the desired product were apparent in the ^{1}H NMR spectrum of the crude material, but isolation attempts again proved unsuccessful. Due to the difficulties encountered with the preparation of the methyl-substituted isoquinuclidinone **229** and the known instability of previously prepared isoquinuclidinones **213**, an alternative approach to a functionalised isoquinuclidinone core unit **209** was sought.

3.6 An Alternative Strategy for the Synthesis of Isoquinuclidinones

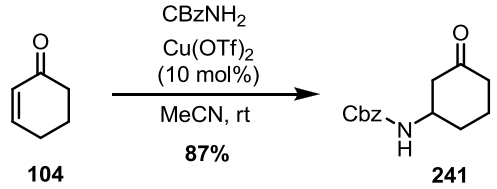
Owing to the difficulties encountered with the preparation of a functionalised bicyclic lactam using precedented procedures, an alternative route to the isoquinuclidinone core unit **209** was proposed, Scheme **3.21**. We envisaged that disconnection of the amide bond would reveal the 4-amino cyclohexane carboxylate derivative **240**; a structure resembling the intermediate **91** used by Bonjoch in the synthesis of isoquinuclidinones.[43]



Scheme 3.21 Retrosynthesis of isoquinuclidinone **209**.

The required amine could be potentially installed *via* a Lewis acid-catalysed conjugate addition of benzyl carbamate to enone **232** following a number of reported procedures,

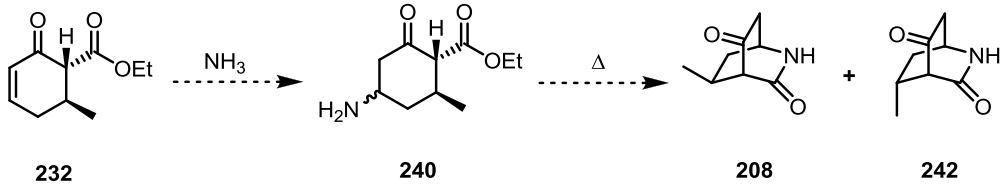
Scheme **3.22**.[86,87] Recent reports on the asymmetric addition of carbamates to unsaturated carbonyl compounds using chiral Lewis acid catalysts,[88] could provide an enantioselective route to the isoquinuclidinone core.



Scheme 3.22 Spencer's copper-catalysed conjugate addition of benzyl carbamate.[86]

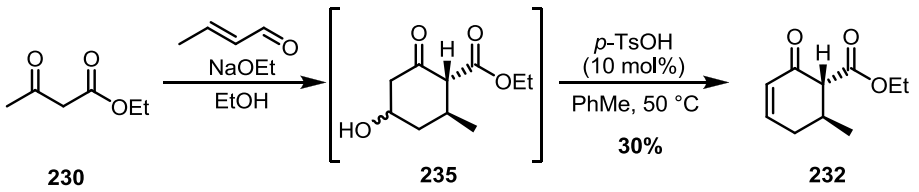
Alternatively, the conjugate addition of aqueous ammonia into unsaturated ketones was previously used by Rassat in the synthesis of isoquinuclidinones,[44] and by Snider in the synthesis of the cyclindricine alkaloids.[89]

A speculative strategy was proposed, using aqueous ammonia to install the required nitrogen functionality, Scheme **3.23**. Previous research by Bonjoch had shown that structurally related compounds undergo lactamisation on heating to afford the corresponding bicyclic lactam as a mixture of diastereoisomers.[43]



Scheme 3.23 Proposed synthesis of bicyclic lactams **209** and **242**.

Synthesis of the racemic β-ketoester **232** was accomplished using a modification of the procedure reported by Hamada.[90] Treatment of ethyl acetoacetate and crotonaldehyde with freshly prepared sodium ethoxide gave the β-hydroxy ketone **235**, which yielded the desired enone **232** on treatment with *p*-TsOH in toluene, Scheme **3.24**. Whilst the yield for the transformation was moderate, the low cost of the starting materials and brevity of the route allowed multi-gram quantities of enone **232** to be prepared.

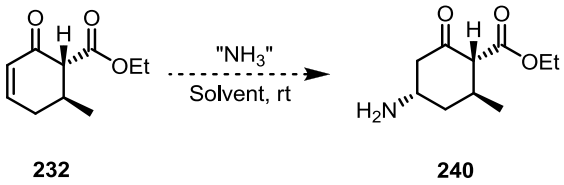


Scheme 3.24 Synthesis of β-ketoester **232** using a modification of Hamada's procedure.[90]

The relative stereochemistry was determined by ^{1}H NMR spectroscopy; the large (11.7 Hz) coupling constant between the adjacent protons was consistent with a *trans*-equatorial relationship between the methyl substituent and ester group.

3.6.1 Initial Studies

Following the proposed synthesis, the addition of ammonia into the enone was investigated, Scheme **3.25**, Table **3.1**.



Scheme 3.25 Attempted synthesis of β-amino ketone **240**.

Table 3.1 Conditions screened for the amination of enone **232**.[a]

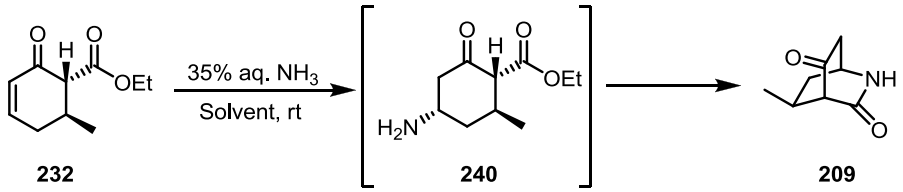
Entry	NH_3 Source	Co-solvent	Time (h)	Conversion[b]
1	2.0 M in IPA	-	24	<5%
2	35% aq.	DCM	24	100%
3	35% aq.	THF	24	100%
4	35% aq.	MeCN	6	100%
5	35% aq.	MeOH	2	100%
6	35% aq.	-	1	100%

[a] All reactions were performed on a 0.1 mmol scale; entries 2-6 were carried out using 35% aq. NH_3 (0.25 mL) and solvent (0.5 mL).

[b] Conversion estimated by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture.

An initial amination attempt using ammonia in *iso*propanol resulted in the formation of a number of products as evident by TLC analysis, which were also seen in the ^{1}H NMR spectrum of the unpurified material (entry 1). Enone peaks at 6.1 and 7.0 ppm suggested significant amounts of starting material were still present; however, the identities of the other products could not be established.

On treatment of enone **232** with 35% aqueous ammonia in a range of co-solvents, conversion of the starting material to a single, more polar species was evident by TLC analysis. Using THF or DCM as solvent, complete consumption of starting material was observed after 24 h at room temperature (entries 2 and 3), however, when water-miscible solvents such as acetonitrile or methanol were used, reaction times were reduced to a few hours (entries 4 and 5). In the absence of a co-solvent, rapid consumption of the starting material was observed giving rise to a single product in 1 h. On inspection of the ^{1}H NMR spectra for all the reaction, signals corresponding to the expected ethyl ester **240** were absent. Further analysis suggested the isolated product in all reactions was the novel bicyclic lactam **209**, presumed to form as a result of *in situ* cyclisation of the intermediate amine **240**, Scheme **3.26**.



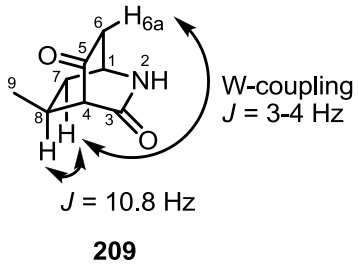
232 **240** **209**

Scheme 3.26 *In situ* cyclisation of amine **240**.

3.6.2 Structure Elucidation

The isolated product was assigned the molecular formula $C_8H_{12}NO_2$ based on HRMS and elemental analysis. Analysis of the material by ^{1}H/^{13}C NMR spectroscopy revealed characteristic bridgehead signals at δ 4.0 and 3.1 ppm and two quaternary signals in the ^{13}C NMR spectrum corresponding to the bridging ketone and lactam (205.1 ppm and 171.8 ppm respectively). Although not conlusive, evidence for the stereochemistry of the methyl group was established *via* coupling constant analysis in analogy with that used to determine the relative stereochemistry of the isoquinuclidinone core unit in

grandisine B **15**.[9] The large coupling (10.8 Hz) between H-7a and H-8 suggested the protons were in an eclipsed conformation. An additional coupling (3-4 Hz) to H-7a was consistent with a W-coupling, which could only arise from a coupling with H-6a (Figure **3.2**).



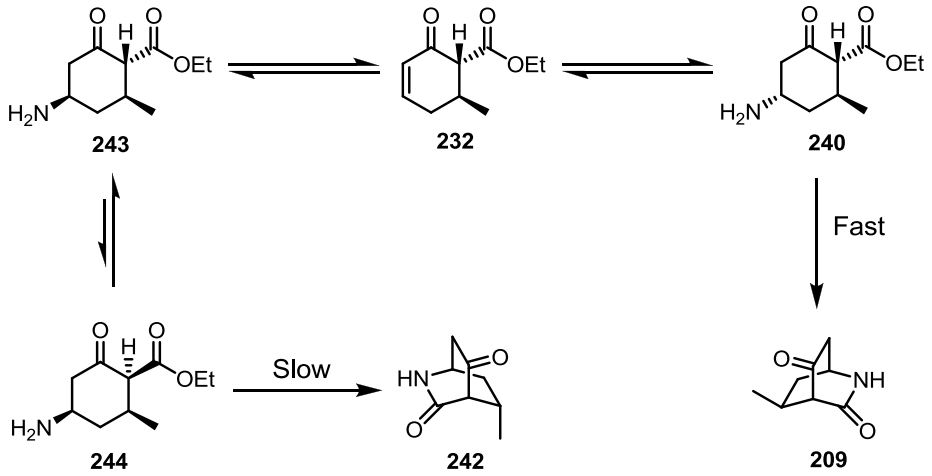
209

Figure 3.2 Evidence for the stereochemistry of bicyclic lactam **209**.

The ^{1}H NMR spectroscopic data were conclusive with a bicyclic structure in which the methyl substituent was on the same face as the bridging ketone.

3.6.3 Mechanism of the Amination/Cyclisation Sequence

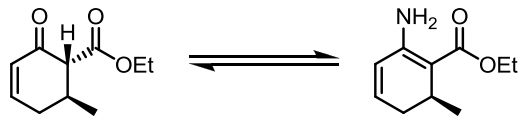
Mechanistically, the reaction is believed to proceed *via* an initial conjugate addition of ammonia to give the intermediate β-amino ketone **240** which cyclises *in situ* to yield a single diastereoisomer of the bicyclic lactam **209**.



Scheme 3.27 Proposed mechanism for the amination/cyclisation sequence.

We proposed that the formation of a single diastereoisomer could be rationalised by the reversible nature of the initial conjugate addition of ammonia. Under the reaction conditions, the conjugate addition of aqueous ammonia could give rise to two diastereomeric β-amino ketones **240** and **243**, Scheme **3.27**. The addition of ammonia *syn* to the methyl substituent gives rise to the cyclohexanone derivative **243** in which there is an *anti* relationship between the amine and ester. In order for the cyclisation to occur, the ester must initially epimerise to establish the *syn*-stereochemistry required for cyclisation. A slow cyclisation on the sterically hindered face of the cyclohexanone **244** would yield isoquinuclidinone **242**. Alternatively, addition of ammonia, *anti* to the methyl group would give rise to cyclohexanone **240** in which a *syn*-relationship between the amine and ester is already established. Rapid cyclisation on the less hindered face of the cyclohexane **240** proceeds to give lactam **209**.

Under the reaction conditions, it is also conceivable that β-keto ester **232** is in equilibrium with β-enamino ester **245**, Scheme **3.28**. The low conversion observed when ammonia in isopropanol was used in the reaction could possibly be attributed to the absence of water, which prevents hydrolysis of the β-enamino ester intermediate **245**.

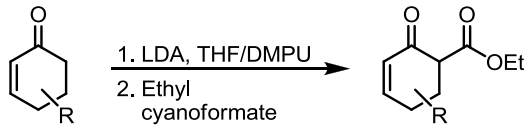


232 **245**

Scheme 3.28 Possible equilibrium established under the reaction conditions.

3.6.4 Scope of the Amination/Cyclisation Sequence

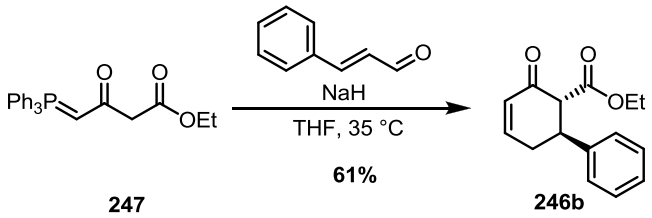
Having established a viable process for the synthesis of isoquinuclidinones *via* a one-pot amination/lactamisation sequence, the scope of the transformation was investigated. Following the procedure of Shing,[91] the substrates **246** were prepared from the corresponding cyclohexenones **211** on treatment with LDA in THF/DMPU and subsequent trapping of the lithium enolate with ethyl cyanoformate, Scheme **3.29**.



211 **246**

Scheme 3.29 Synthesis of β-ketoester substrates **246** from cyclohexenones **211**.[91]

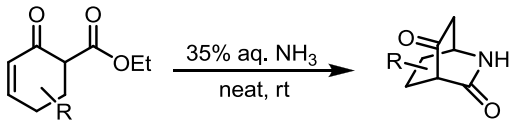
The phenyl substituted derivative **246b** was prepared in 61% yield using the procedure reported by Pietrusiewicz,[92] Scheme **3.30**.



247 **246b**

Scheme 3.30 Synthesis of substrate **246b** using the procedure of Pietrusiewicz.[92]

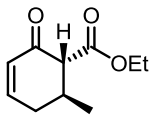
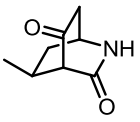
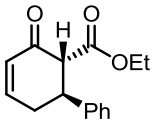
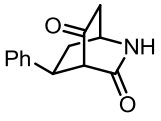
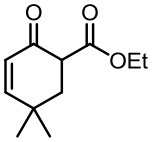
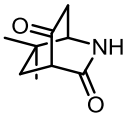
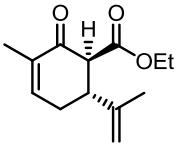
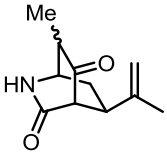
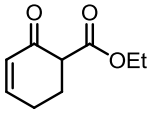
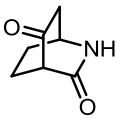
As seen in Table **3.2**, the developed amination/cyclisation sequence was applicable to a range of substrates, Scheme **3.31**.



246 **248**

Scheme 3.31 Scope of the amination/cyclisation sequence.

Table 3.2 Scope of amination/cyclisation sequence for the synthesis of bicyclic lactams **248**.[a]

Entry	Substrate (246)	Product (248)	Time (h)	Yield[b] (%)
1	 **246a**	 **248a**	2	93%
2	 **246b**	 **248b**	2	76%
3	 **246c**	 **248c**	2	83%
4	 **246d**	 **248d**	24	98%[c]
5	 **246e**	 **248e**	4	60%

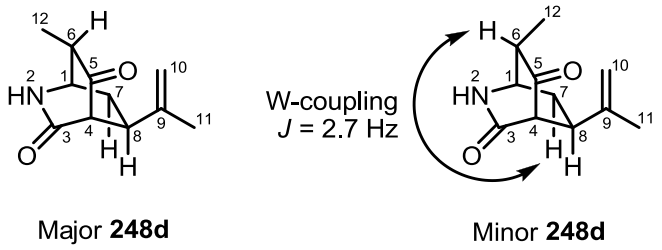
[a] All reactions were performed on a 0.25 mmol scale using 35% aq. NH_3 (1.0 mL) at rt.

[b] Isolated yields.

[c] Diastereomeric ratio ~4:1.

The model substrate **246a** used in initial studies cleanly cyclised to afford the methyl substituted lactam **248a** in 93% yield and the corresponding phenyl substituted lactam **248b** was also prepared as a single diastereoisomer in good yield (entries 1 and 2). The process was also found to be applicable to disubstituted enones, the dimethyl substrate **246c** cyclised in good yield to afford the 7,7-substituted isoquinuclidinone **248c** (entry 3). The carvone-derived substrate **246d** was also found to cyclise, giving rise to a mixture of two diastereomeric lactams **248d**, in excellent yield, however, the reaction time was extended, which was attributed to steric effects (entry 4). Attempts to separate the carvone-derived bicyclic lactams **248d** by chromatography or fractional crystallisation proved to be unsuccessful and we were therefore unable to conclusively determine the structure by X-ray analysis. The relative stereochemistry was speculatively assigned from analysis of the ^{1}H NMR spectroscopy coupling constants, Scheme **3.32**. The C-6 proton in the major product showed couplings only to the methyl

substituent (C-12) and bridgehead proton (H-1), whereas the minor product showed an additional coupling (2.7 Hz), consistent with a W-coupling to H-7a.



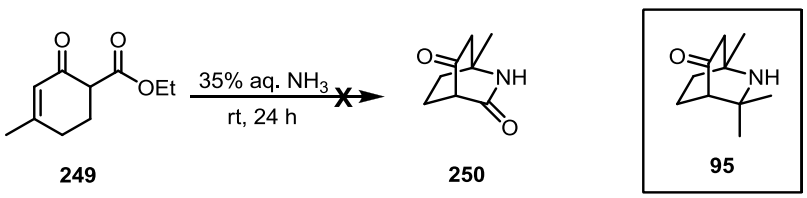
Major **248d** Minor **248d**

Scheme 3.32 Stereochemistry proposed for bicyclic lactams **248d**.

Finally, the cyclisation of the parent unsubstituted enone **246e** was examined. On subjecting enone **246e** to the optimised conditions, the formation of a number of products was observed by TLC analysis of the reaction mixture. Although the crude mixture was more complex than previous examples, the known isoquinuclidinone **248e** was isolated in 60% yield (entry 5). The NMR spectroscopic data for the unsubstituted isoquinuclidinone **248e** were consistent with those reported,[45] but, a significant difference in the melting point was noted; 207-209 ºC (Lit.[45] 143-144 ºC).

3.6.5 Synthesis of Bridgehead Substituted Isoquinuclidinones

The synthesis of isoquinuclidinones bearing substituents at the bridgedhead positions was also investigated. On subjecting the β-substituted enone **249** to the optimised reaction conditions, Scheme **3.33**, no cyclisation to the corresponding isoquinuclidinone **250** was observed even after extended reaction times.



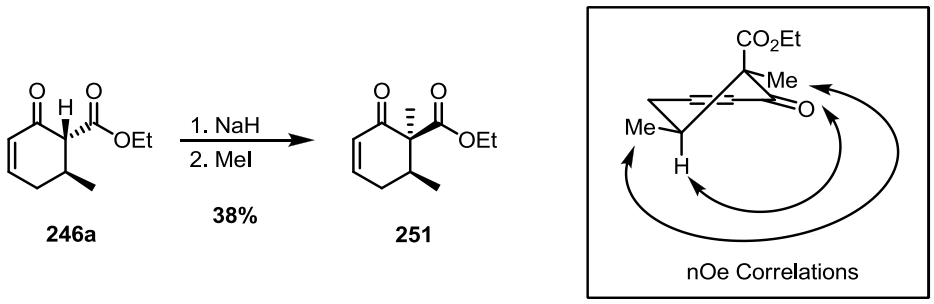
249 **250** **95**

Scheme 3.33 Attempted cyclisation of bridgehead substituted enone **249**.

The result suggests that substitution at the β-position of the enone disfavours the initial 1,4-addition of ammonia preventing cyclisation. However, the bridgehead substituted

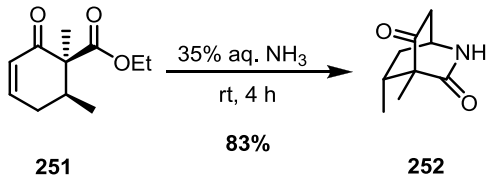
isoquinuclidinone **95** was previously prepared by Rassat, suggesting that 1,4-addition of ammonia into β-substituted enones can occur under similar conditions.[44]

Despite the unsuccessful attempts to prepare the C-1 substituted isoquinuclidinone **250**, the synthesis of C-4 substituted isoquinuclidinones was investigated. Treatment of β-keto ester **246a** with sodium hydride in THF and subsequent trapping of the enolate with methyl iodide gave substrate **251** in 38% yield. The stereochemistry of the product was assumed to be that depicted in Scheme **3.34**, formed *via* approach of the electrophile on the opposite face to the methyl substituent. Attempts to confirm the stereochemistry of ester **251** by nOe studies proved inconclusive; the C-6 methyl group showed correlations to both the C-5 proton and C-5 methyl substituent.



Scheme 3.34 Synthesis of substrate **251**.

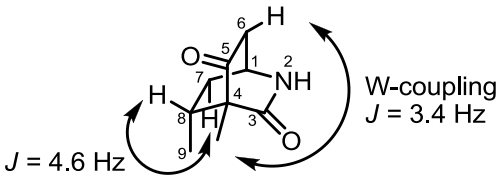
On subjecting enone **251** to the optimised reaction conditions, isoquinuclidinone **252** was successfully prepared in 83% yield, with a slight increase in reaction time, which was attributed to cyclisation occurring on the sterically hindered face of the enone, Scheme **3.35**.



Scheme 3.35 Synthesis of isoquinuclidinone **251** from enone **252**.

^{1}H NMR spectroscopic analysis of the purified product provided evidence for the stereochemistry. A small coupling (3.4 Hz) between H-6a and H-7a was attributed to a W-coupling, however, in contrast to isoquinuclidinones isolated previously, the small

(4.6 Hz) coupling between H-7a and H-8 was consistent with an axial-equatorial coupling (Figure **3.3)**. The data were consistent with a structure in which the methyl substituent was on the opposite face to the bridging ketone.



252

Figure 3.3 Stereochemistry of isoquinuclidinone **252**.

Conclusive evidence for the structure was obtained by single crystal X-ray diffraction analysis of the product, which confirmed the methyl group was on the opposite face to the bridging ketone (Figure **3.4**).

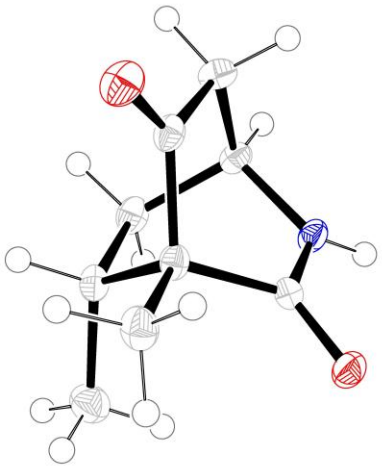
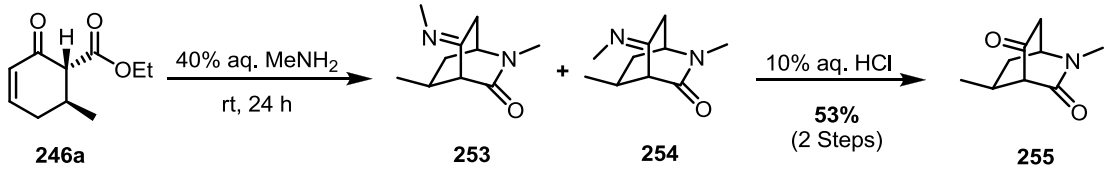


Figure 3.4 X-ray strucutre of compound **252** depicted using ORTEP-3 (CCDC 789903).

The result confirms that cyclisation can occur on the hindered face of the cyclohexanone substrate if epimerisation of the ester is not possible.

3.7 Synthesis of N-Substituted Bicyclic Lactams

Having demonstrated the scope of the amination/cyclisation sequence using aqueous ammonia, alternative nitrogen sources were considered. Initially, the reaction of enone **246a** with methylamine was investigated. On treatment of enone **246a** with excess aqueous methylamine, consumption of the starting material was observed, with the formation of a single product apparent by TLC analysis. However, on inspection of the ^{1}H NMR spectrum of the unpurified material, signals corresponding to two structurally related products were evident, with additional methyl signals also apparent. The NMR spectroscopic and HRMS data were consistent with structures **253** and **254** corresponding to the methyl imine derivatives of the expected product **255**, Scheme **3.36**.



Scheme 3.36 Formation of *N*-methyl lactam **255** *via* hydrolysis of imine **253** and **254**.

Further evidence for the structures **253** and **254** was obtained on treatment of the imine with 10% aqueous HCl, which gave the expected isoquinuclidinone **255** in 53% yield. Gradual hydrolysis of imines **253** and **254** was also observed when a sample was left to stand in chloroform.

In an attempt to negate the formation of imines **253** and **254**, the reaction was repeated using stoichiometric amine. Pleasingly, on treatment of enone **246a** with 1 equivalent of methylamine in water, the *N*-methyl isoquinuclidinone **255a** was isolated in 62% yield, without the need for an additional hydrolysis step. Conclusive evidence for the structure of *N*-methyl lactam **255a** was obtained by single crystal X-ray diffraction analysis, which confirmed the relative stereochemistry, Figure **3.5**.

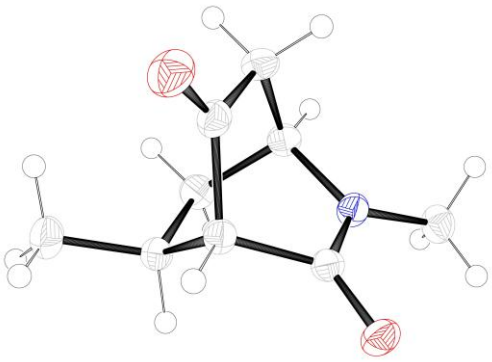
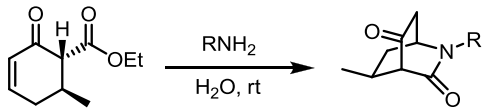


Figure 3.5 X-ray strucutre of compound 255a depicted using ORTEP-3 (CCDC 789904).

Having demonstrated that primary amines could also be successfully employed in the cyclisation sequence, the use of other amines was investigated, Scheme **3.37**, Table **3.3**.



246a **255**

Scheme 3.37 Synthesis of *N*-substituted bicyclic lactams **255**.

Table 3.3 Synthesis of *N*-substituted bicyclic lactams **255**.[a]

Entry	Amine	Time	Yield[b]
1	Methylamine	24 h	62%
2	*n*-Propylamine	48 h	49% (49%)[c]
3	Allylamine	48 h	43%
4	Hexylamine	48 h	0%
5	Benzylamine	48 h	0%
6	Tryptamine	48 h	0%
7	*tert*-Butylamine	48 h	0%

[a] All reactions performed on 0.25 mmol scale using amine (0.25 mmol) in H_2O (1 mL).

[b] Isolated yields after purification by column chromatography.

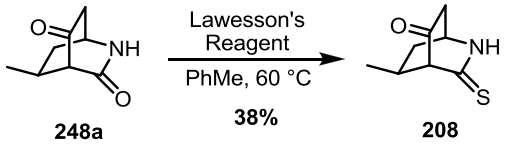
[c] Reaction complete in 18 h at 80 ºC.

As seen in Table **3.3**, propyl and allyllamine gave the corresponding *N*-substituted isoquinuclidinones in **255b** and **255c** in 49% and 43% yield respectively (entries 2 and

3). Disappointingly, lactam formation was not observed when hexylamine, benzylamine tryptamine or *tert*-butylamine were employed (entries 4-7), which gave complex mixtures of unidentified products. The unsuccessful cyclisations were attributed to steric effects, however, it is also conceivable that poor solubility of the reaction intermediates in the aqueous solvent system could prevent the cyclisation.

3.8 Synthesis of a Thiolactam Cross-Coupling Partner

Having established a viable procedure for the synthesis of a functionalised isoquinuclidinone core, conversion into the corresponding thiolactam was investigated in order to prepare a suitable cross-coupling partner for use in the Liebeskind-Srogl-type coupling. Pleasingly, on treatment with Lawesson's reagent in toluene at reflux, thiolactam **208** was isolated in an unoptimised 38% yield, the low yield partially attributed to purification on a small-scale, Scheme **3.38**.



248a **208**

Scheme 3.38 Conversion of bicyclic lactam **248a** to the thiolactam **208**.

3.9 Summary

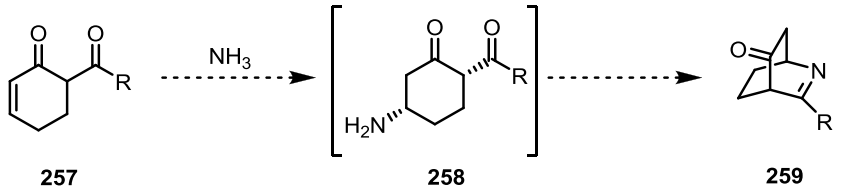
A one-pot procedure for the synthesis of bicyclic lactams **248** from cyclohexenone derivatives **246**, *via* an amination/cyclisation sequence has been successfully developed. The methodology was extended to enable the synthesis *N*-substituted bicyclic lactams **255**. A suitable partner **208** for use in cross-coupling studies has also been prepared *via* conversion of a functionalised bicyclic lactam into the corresponding thioamide. A further extension of the amination/cyclisation sequence, with potential applications in the synthesis of grandisine B **15**, is described in Chapter 4.

The work described in this Chapter was the subject of a recent publication.[93]

Chapter 4. An Amination/Cyclisation Approach to Isoquinuclidinones

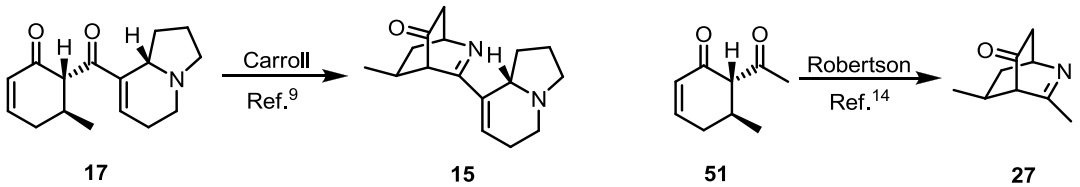
4.1 Initial Cyclisation Studies

In the previous chapter the development of a one-pot synthesis of bicyclic lactams *via* an amination/lactamisation sequence was described. Although in a position to investigate the synthesis of grandisine B **15** *via* the proposed cross-coupling strategy, we were keen to further explore the utility of the amination/cyclisation sequence in the synthesis of other *aza*-bicyclic systems. We proposed that replacement of the ester functionality with a ketone would afford the corresponding imine on cyclisation, Scheme **4.1**. Such a route would provide rapid access to isoquinuclidinone structures similar to that found in grandisine B **15**.



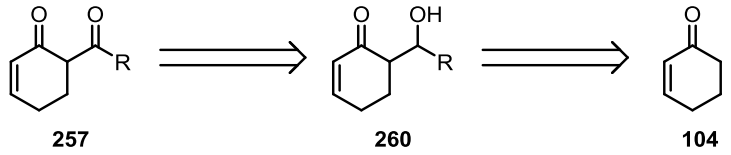
Scheme 4.1 Proposed synthesis of isoquinuclidinone **259** *via* an amination/cyclisation sequence.

The proposed sequence would constitute a biomimetic synthesis of isoquinuclidinones, in accordance with the final step in Carroll's proposed synthesis of grandisine B **15** and Robertson's proposed synthesis of mearsine **27**.[9,14]



Scheme 4.2 Selected steps in the synthesis of grandisine B **15** and mearsine **27**.[9,14]

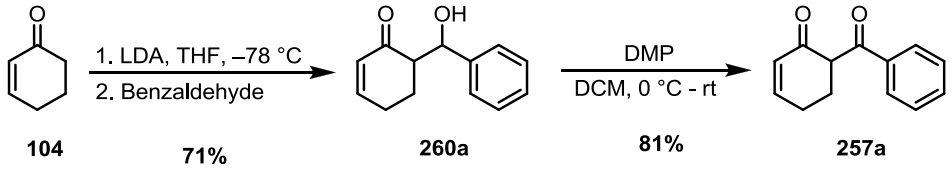
Retrosynthetically, it was envisaged that the 1,3-diketone substrates **257** could be readily prepared from cyclohexenone **104** *via* an aldol/oxidation sequence as shown in Scheme **4.3**.



Scheme 4.3 Retrosynthesis of 1,3-diketone substrates **257**.

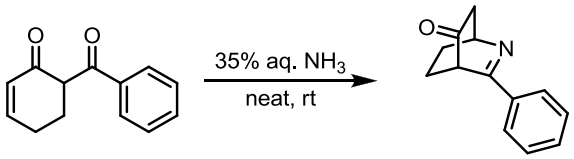
4.1.2 A Phenyl-Substituted Model Substrate

Initially we chose to prepare diketone **257a**, which was accomplished in 2 steps from commercially available cyclohexenone **104**. Deprotonation of cyclohexenone **104** with lithium di*iso*propylamide at −78 ºC and subsequent trapping with benzaldehyde, gave the aldol product **260a** in 71% yield, Scheme **4.4**. Oxidation of benzylic alcohol **260a** under modified Swern conditions[94] using trifluoroacetic anhydride furnished the diketone **257a** in 81% yield, which was found to exist as a mixture of keto/enol tautomers.



Scheme 4.4 Synthesis of substrate **257a** *via* aldol/oxidation sequence.

With diketone **257a** in hand, we were in a position to investigate the amination/cyclisation sequence. Using the conditions previously optimised for the amination/lactamisation sequence, treatment of diketone **257a** with 35% aqueous ammonia, resulted in the rapid consumption of the starting material with the concomitant formation of a number of species apparent by TLC analysis, Scheme **4.5**.



257a **259a**

Scheme 4.5 Attempted cyclisation of 1,3-diketone **257a**.

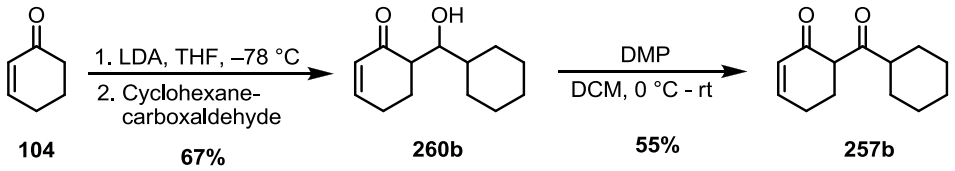
Pleasingly, ^{1}H NMR spectroscopic analysis of the unpurified material showed signals corresponding to the desired bicyclic imine **259a**, along with a number of minor impurities. However, attempts to purify the material proved unsuccessful, with no product recovered after silica gel chromatography. It was proposed that the isoquinuclidinone product **259a** was unstable, or susceptible to hydrolysis, in the presence of acid. In the initial reaction we were therefore unable to fully characterise isoquinuclidinone **259a** and conclusively confirm the structure. Disappointingly, on scale-up, TLC analysis showed the formation of a number of species. Analysis of the unpurified material by ^{1}H NMR spectroscopy revealed a complex mixture of compounds containing only minor amounts of the desired bicyclic imine **259a**.

Due to the difficulties encountered with purification, a screen of reaction conditions was undertaken to determine whether bicyclic imine **259a** could be formed exclusively, without the need for purification. Whereas previously the reaction had been carried out neat, it was proposed that addition of aqueous ammonia to a solution of diketone **257a** in a water miscible solvent would ensure the reaction mixture was homogeneous. Repeating the reaction in aqueous acetonitrile, however, failed to offer any improvement on the previously observed product distribution. A further screen of reaction conditions (temperature, concentration) also failed to improve the product distribution, with isoquinuclidinone **259a** generally a minor product observed by ^{1}H NMR spectroscopy. The addition of NH_4Cl to buffer the aqueous ammonia, as reported by Snider and co-workers in their synthesis of cylindricine A, also proved unsuccessful.[89]

Due to limited success in preparing the model isoquinuclidinone **259a** using the amination/cyclisation sequence, the analogous cyclohexyl substituted diketone **257b** was prepared, to determine whether this would cyclise on treatment with ammonia.

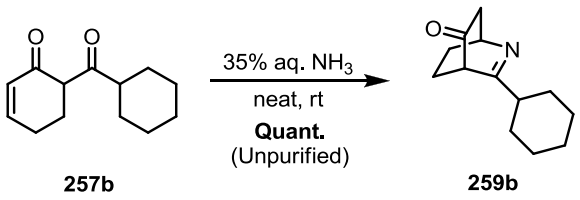
4.1.2 A Cyclohexyl-Substituted Model Substrate

Deprotonation of cyclohexenone **104** with LDA at −78 ºC and subsequent trapping with cyclohexane carboxaldehyde gave the aldol product **260b**, Scheme **4.6**. Oxidation with Dess-Martin periodinane,[95] gave diketone **257b** in 55% yield, which again was found to exist as a mixture of keto/enol tautomers.



Scheme 4.6 Synthesis of cyclohexyl-substituted 1,3-diketone **257b**.

In parallel with the previous results, an initial small-scale reaction yielded isoquinuclidinone **259b** as the predominant product on treatment with aqueous ammonia, Scheme **4.7**. The product was sufficiently pure to allow full characterisation and therefore conclusive evidence for the formation of bicyclic imine **259b** was obtained.



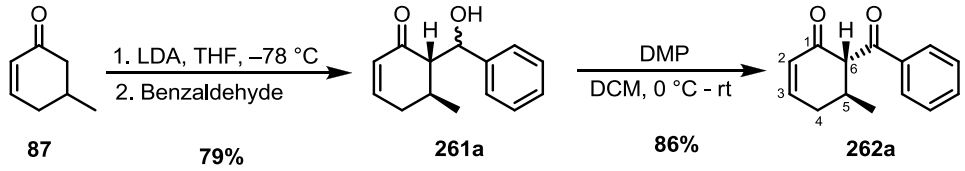
Scheme 4.7 Synthesis of isoquinuclidinone **259b** *via* amination/cyclisation sequence.

Bridgehead signals at 4.50 ppm and 3.34 ppm in the ^{1}H NMR spectrum were consistent with the bicyclic structure. The ^{13}C NMR spectrum showed two quaternary signals corresponding to the bridging ketone (209.6 ppm) and the cyclic imine (178.8 ppm). Disappointingly, repeating the reaction on a larger scale led to the formation of a number of products, evident in the ^{1}H NMR spectrum of the unpurified product. Attempts to separate/characterise the products in order to provide further insights into the reaction proved unsuccessful.

Although at this stage results were mixed, we felt it would be instructive to apply the methodology to a model system representative of that found in grandisine B **15**, in order to determine whether the route was viable for use in the proposed synthesis. Initial studies on model compounds **257a** and **257b** suggested that the exocyclic ketone substituent had little effect on the cyclisation, however, we proposed that the cyclohexenone methyl substituent may play a role in the cyclisation. In Chapter 3 it was noted that in the cyclisation of the unsubstituted bicyclic lactam **248e** the unpurified reaction mixture was more complex than substituted examples.

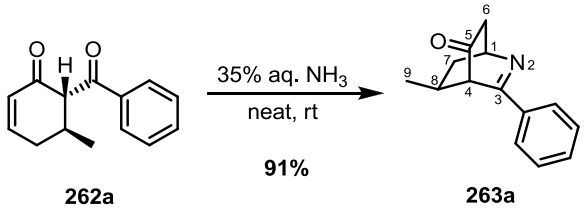
4.2 Synthesis of Substituted Isoquinuclidinones

The methyl substituted diketone **262a** was prepared using the two step aldol/oxidation sequence in 68% overall yield from 5-methylcyclohexenone **87**, Scheme **4.8**. The ^{1}H NMR spectroscopic data were consistent with the *trans*-stereochemistry depicted, evident from the large (10.7 Hz) coupling constant between protons H-5 and H-6.



Scheme 4.8 Synthesis of methyl-substituted diketone **262a**.

On treatment of diketone **262a** with 35% aqueous ammonia, the rapid consumption of starting material was observed, however, in contrast to previous reactions, TLC analysis showed the formation of only one product, Scheme **4.9**.



Scheme 4.9 Synthesis of isoquinuclidinone **263a** *via* amination/cyclisation sequence.

Pleasingly, analysis of the ^{1}H NMR spectrum of the unpurifed reaction mixture showed the predominant product was the desired bicyclic imine **263a**, which was isolated in 91% yield after purification by column chromatography. In subsequent studies it was found that methanol could be successfully employed as a co-solvent in the reaction, ensuring substrate solubility in the aqueous solvent system.

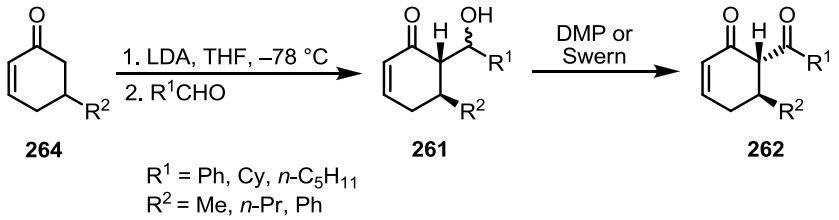
4.2.1 Structure Elucidation

The HRMS data were consistent with the expected product, supporting a molecular formula of $C_{14}H_{16}NO$. Analysis of the purified material by $^{1}H/^{13}C$ NMR spectroscopy provided further evidence to suggest the product was the desired isoquinuclidinone **263a**. Characteristic bridgehead signals were observed at 4.8 ppm and 3.9 ppm in the ^{1}H NMR spectrum and the ^{13}C NMR spectrum showed signals at 208.3 ppm and 171.6 ppm consistent with the bridging ketone and bicyclic imine respectively.

Unfortunately, attempts to confirm the relative stereochemistry of the product by coupling constant analysis, in analogy with the previously prepared bicyclic lactams, was not possible. An additional coupling (~3 Hz) to proton H-6a was consistent with a W-coupling, but, the signals for the C-7 protons were obscured, and so the corresponding coupling constant could not be picked out.

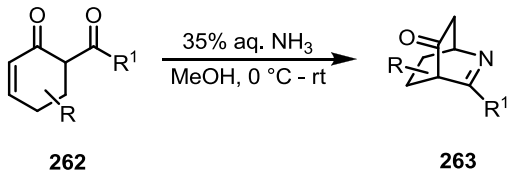
4.3 Scope of the Amination/Imination Sequence

Having demonstrated the viability of the amination/imination sequence we were keen to explore the scope of the transformation. A range of substrates **262** was prepared using the lithium aldol reaction to yield the β-hydroxy ketones **261** which were readily oxidised with Dess-Martin periodinane or modified Swern conditions using TFAA, Scheme **4.10**.



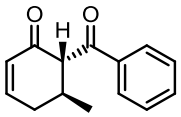
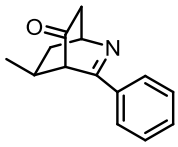
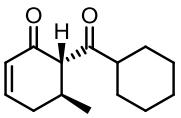
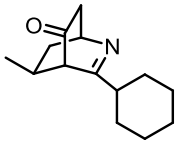
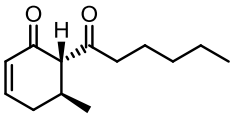
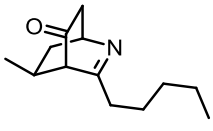
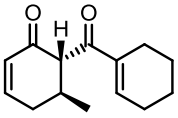
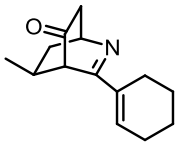
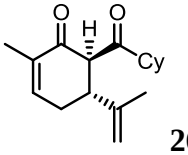
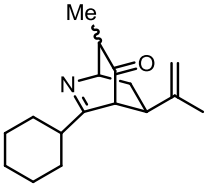
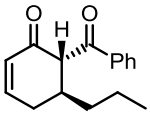
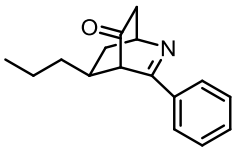
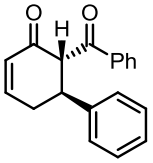
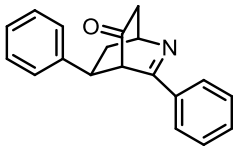
Scheme 4.10 Synthesis of 1,3-diketone substrates **262**.

Using the optimised reaction conditions, a range of substrates were found to cyclise in moderate to excellent yield, Scheme **4.11**, Table **4.1**.



Scheme 4.11 Scope of the amination/cyclisation sequence.

Table 4.1 Scope of amination/imination sequence.[a]

Entry	Substrate (262)	Product (263)	Time (h)	Yield[b] (%)
1	 **262a**	 **263a**	2	91
2	 **262b**	 **263b**	2	89
3	 **262c**	 **263c**	2	65
4	 **262d**	 **263d**	2	80
5	 **262e**	 **263e**	72	75[c]
6	 **262f**	 **263f**	4	80
7	 **262g**	 **263g**	8	~ 50%[d]

[a] All reaction were performed on 0.25 mmol scale using MeOH (1 mL), 35% aq. NH_3 (0.5 mL) at 0 ºC to rt.

[b] Isolated yields.

[c] dr = 3.4:1.

[d] An inseperable mixture of **263g** and side-products (yield estimated by ^{1}H NMR spectroscopy).

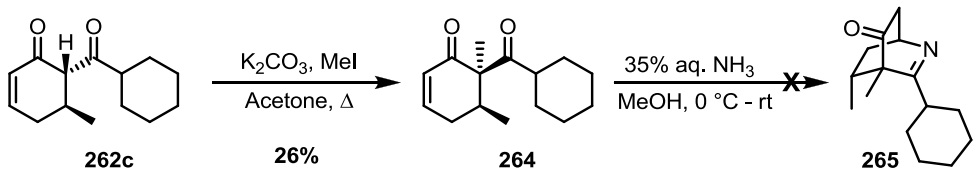
The phenyl substituted diketone **262a** used in initial studies gave isoquinuclidinone **263a** in 91% yield (entry 1). The reaction was also found to be applicable to aliphatic diketones. The cyclohexyl and hexyl substituted isoquinuclidinones were prepared in 89% and 65% yield respectively (entries 2 and 3). The bis-enone substrate **262d** readily cyclised to give the isoquinuclidinone **263d** in 80% yield, containing the α,β-unsaturated imine found in grandisine B **15** (entry 4). Whilst it was previously assumed

that the unsaturated imine moiety would be unstable, no evidence of degradation was noted with isoquinuclidinone **263d**. The reaction was not just applicable to the synthesis of methyl substituted isoquinuclidinones, although on increasing the steric bulk of the cyclohexenone ring substitutents an increase in the reaction time was observed. Initially, the cyclisation of the trisubstituted carvone derived diketone **262e** was investigated. Although the cyclisation proceeded using the optimised conditions, the reaction took three days to go to completion. ^{1}H NMR spectroscopic analysis of the purified product revealed a diastereomeric mixture (~3.4-1) corresponding to the two possible isomers at the C-6 stereocentre (entry 5). Attempts to determine the relative stereochemistry of the diastereoisomers by ^{1}H NMR spectroscopy were unsuccessful and we were unable to obtain a crystalline derivative for X-ray analysis. The relative stereochemistry of the major isomer **262e** remains to be assigned.

The propyl substituted cyclohexenone cyclised in good yield to afford the corresponding isoquinuclidinone **263f** (entry 6). However, in the case of the phenyl substituted diketone **262g**, whilst cyclisation was observed, the product **263g** was inseparable from a number of side-products formed during the reaction (entry 7).

4.4 Bridgehead Substituted Isoquinuclidinones

The synthesis of isoquinuclidinones with bridgehead substitution was also investigated. Alkylation of the 1,3-diketone **262b** with methyl iodide in the presence of K_2CO_3 gave the substituted derivative **264** in 26% yield, Scheme **4.12**. On subjecting diketone **264** to the optimised reaction conditions, the formation of a number of products was observed by TLC analysis.



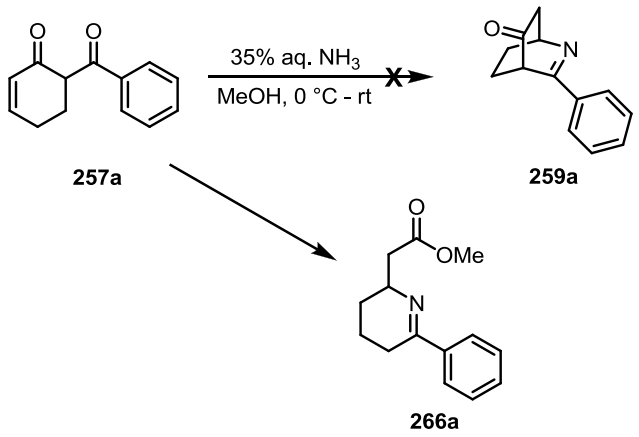
Scheme 4.12 Attempted synthesis of bridgehead substituted isoquinuclidinone **265**.

Disappointingly, ^{1}H NMR spectroscopic analysis revealed a complex mixture of compounds in the unpurified material, but, no evidence of the bicyclic imine **265** was

observed. In this instance, cyclisation on the sterically hindered face of the cyclohexenone ring was not possible, which we attributed the increased steric bulk of the cyclohexyl substituent on the ketone.

4.5 Attempted Synthesis of Unsubstituted Isoquinuclidinones

In the final part of this study we returned to investigate the cyclisation of unsubstituted cyclohexenone derivatives using the optimised reaction conditions. In contrast to the initial investigations, on addition of aqueous ammonia to a solution of diketone **257a** in methanol, rapid consumption of the starting material was observed with the formation of a single product apparent by TLC analysis, Scheme **4.13**.



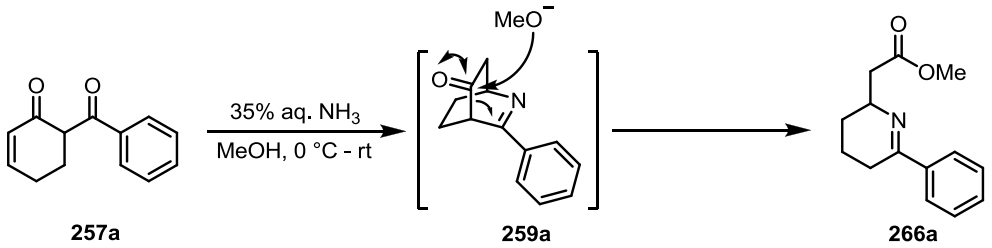
Scheme 4.13 Unexpected ring opening of isoquinuclidinones to form methyl esters **266**.

Upon inspection of the ^{1}H NMR spectrum of the unpurified product, signals corresponding to the expected isoquinuclidinone **259a** were absent and the presence of a 3 H singlet at 3.74 ppm was consistent with a methoxy group. The molecular formula was established as $C_{14}H_{18}NO_2$ based on HRMS data, which was also consistent with the addition of a methoxy group. ^{1}H/^{13}C NMR spectroscopy revealed a number of differences with the previously isolated isoquinuclidinones. The absence of bridgehead signals in the ^{1}H NMR spectrum was noted, however, a multiplet at 3.98 ppm was consistent with a proton adjacent to a heteroatom. In the ^{13}C NMR spectrum, the signal corresponding to the bridging ketone was also absent; however, a quaternary carbon signal at 165.4 ppm suggested an ester or related functional group. An IR stretch at

1735 cm^{-1} was also consistent with the proposed ester. The spectroscopic data were consistent with the monocyclic imine **266a**.

4.5.1 Proposed Mechanism of Ring Opening

Mechanistically, the formation of imine **266a** is proposed to proceed *via* the expected isoquinuclidinone **259a**, which underwent *in situ* methoxide induced ring opening to give the methyl ester **266a**, Scheme **4.14**. An analogous mechanism was proposed by Carroll and co-workers to account for the formation of grandisine G **20**.[10]

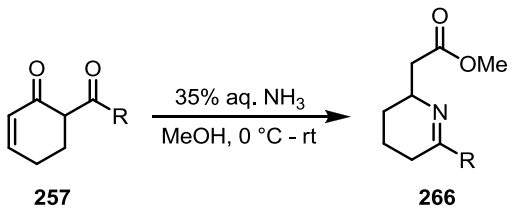


Scheme 4.14 Mechanism proposed for the formation of methyl ester **266a**.

It seems likely that the presence of the methyl susbtituent on previously prepared isoquinuclidinones increased the steric hindrance around the bridging ketone, preventing the attack of methoxide, however, more detailed studies would be required to prove this conclusively.

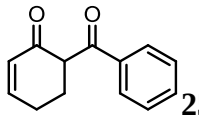
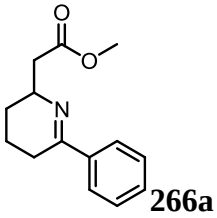
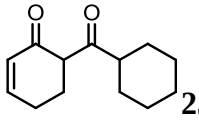
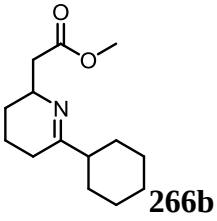
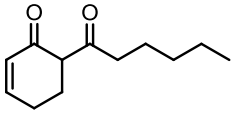
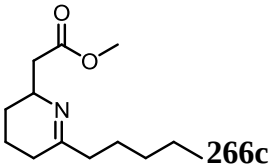
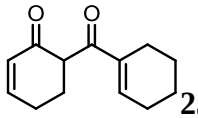
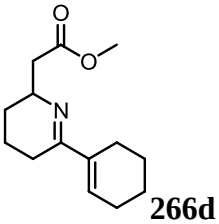
4.5.2 Scope of the Ring Opening

The *in situ* ring opening was found to be general for a range of unsubsituted enones **257**, Scheme **4.15**, Table **4.2**.



Scheme 4.15 Scope of methyl ester formation.

Table 4.2 Scope of methyl ester formation.

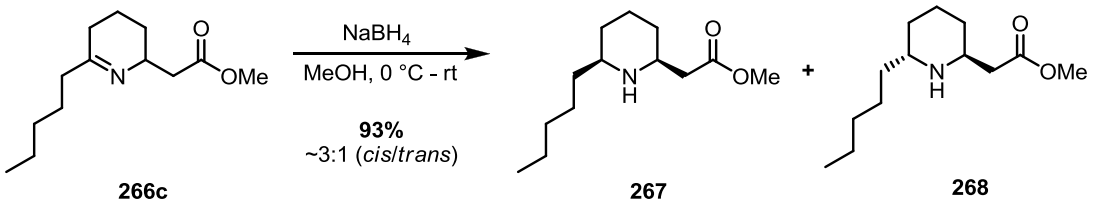
Entry	Substrate (257)	Product (266)	Time (h)	Yield[a] (%)
1	 **257a**	 **266a**	2	72%
2	 **257b**	 **266b**	2	Quant.
3	 **257c**	 **266c**	2	89%
4	 **257d**	 **266d**	2	96%

[a] Isolated yields.

The phenyl substituted monocyclic imine **266a** was prepared in 72% yield and the cyclohexyl derivative **266b** was prepared in an excellent 89% yield (entries 1 and 2). The pentyl and cyclohexenyl derivative also underwent the cyclisation/ring-opening to yield the methyl esters **266c** and **266d** in 89% and 96% yield, respectively (entries 3 and 4). In all instances, the crude material was found to be essentially homogeneous requiring no purification.

Further evidence for the proposed structure was obtained on reduction of imine **266c** with sodium borohydride in methanol, which gave the diastereomeric piperidine derivatives **267** and **268** in 93% yield, Scheme **4.16**. These known compounds were previously isolated from the ladybird species *Calvia* 14-guttata,[96] and recently used by Daloze as an intermediate in the synthesis of calvine **270**.[97] The reduction could potentially be used as a route into other 2,6-disubstituted piperidine derivatives,

however, the scope of the transformation was not investigated during the course of this work.

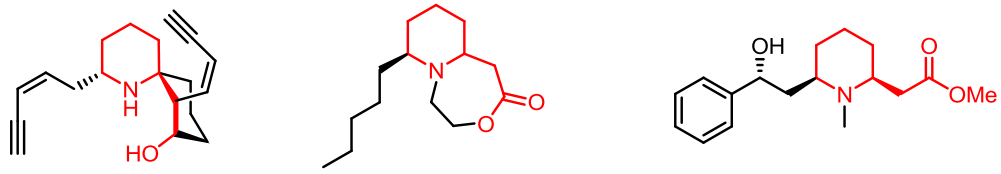


266c **267** **268**

Scheme 4.16 Reduction of imine **266c** with sodium borohydride.

4.6 Applications of β-Imino Esters (266)

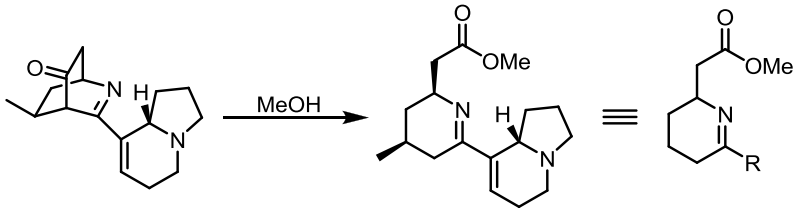
While the monocyclic imines **266** prepared were all novel, a structurally related piperidine was used by Corey *et al*. in the synthesis of analogues of the alkaloid histrionicotoxin **269**.[98] The partial structure is also common to a number of alkaloids, with representative examples including calvine **270** and sederine **271** (Figure **4.1**).[96,99]



269 **270** **271**

Figure 4.1 Structures of histrionicotoxin **269**, calvine **270** and sederine **271**.

More relevant to current research is the close resemblance of the monocyclic imines **266** to grandisine G **20**. The alkaloid, isolated by Carroll and co-workers,[10] was proposed to arise *via* methoxide promoted ring opening of grandisine B **15**, a transformation analogous to that observed for the unsubstituted isoquinuclidinones **259**, Scheme **4.17**.



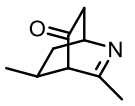
15 **20** **266**

Scheme 4.17 Proposed formation of grandisine G **20** from grandisine B **15**.[10]

It is interesting to note that grandisine G **20** possesses a methyl substituent, however in the current study, isoquinuclidinones bearing methyl substituents were found not to undergo the methanol promoted ring opening. The isolation of grandisine G **20** provides evidence to suggest that ring opening is possible when the methyl group is present, however, this may not occur *via* the mechanism proposed. Additional work would be required to determine whether the sequence could be used in the synthesis of grandisine G **20**.

4.7 The Total Synthesis of (−)-Mearsine (27)

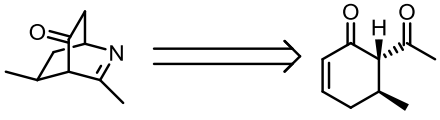
Mearsine **27**, was isolated by Robertson *et al*. in 1984 from the leaves of the species *Peripentadenia mearsii*.[14] To date, it remains the only alkaloid known to possess the same structure as the isoquinuclidinone core unit in grandisine B **15**. The compound has been the subject of one total synthesis reported by Pinder and Crouse in 1989, but this was of the unnatural (+)-mearsine **27** (Figure **4.2**).



27

Figure 4.2 Structure of the *Elaeocarpus* alkaloid mearsine **27**.[14]

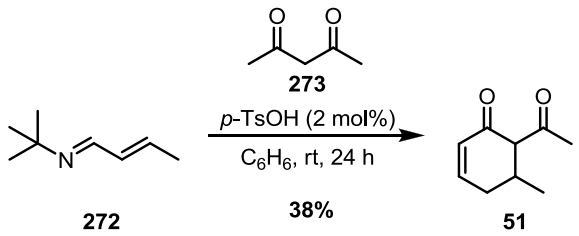
It was proposed that mearsine **27** is derived from diketone **51**, a biosynthetic pathway unusual in the fact that the carbon skeleton is comprised entirely of acetate units.[14] We envisaged that mearsine **27** would provide an ideal target to further test the utility of the amination/cyclisation methodology using the proposed biosynthetic intermediate **51** as a synthetic intermediate, Scheme **4.19**.



27 **51**

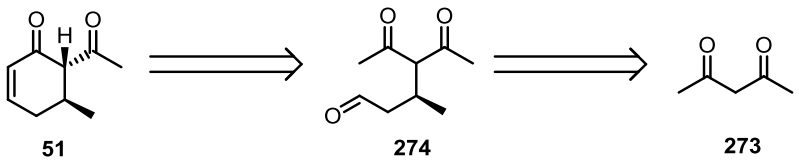
Scheme 4.19 Proposed synthesis of mearsine **27** from diketone **51**.

Although the racemic synthesis of diketone **51** had previously been reported by Geirsson, Scheme **4.20**,[100] there was no precedent for its enantioselective synthesis.



Scheme 4.20 Geirsson's synthesis of diketone **51**.[100]

We envisaged preparing diketone **51** from acetylacetone as depicted retrosynthetically in Scheme **4.21**.

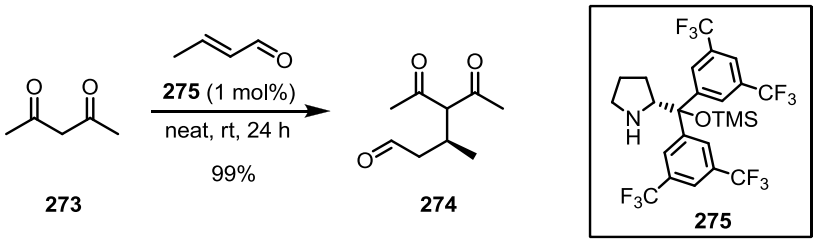


Scheme 4.21 Retrosynthetic analysis of diketone **51**.

4.7.1 Synthesis of Aldehyde (274)

It was proposed that an organocatalytic Michael addition of acetylacetone **273** to crotonaldehyde using the silyl prolinol catalyst **275** would afford the novel aldehyde **274**,[101] which would undergo an acid catalysed aldol condensation to afford the desired enone **51**. Thus, an initial reaction of acetylacetone **273** and crotonaldehyde in toluene mediated by Jørgensen‟s prolinol catalyst **275** (10 mol%) gave the desired aldehyde **274** in 91% yield after purification.

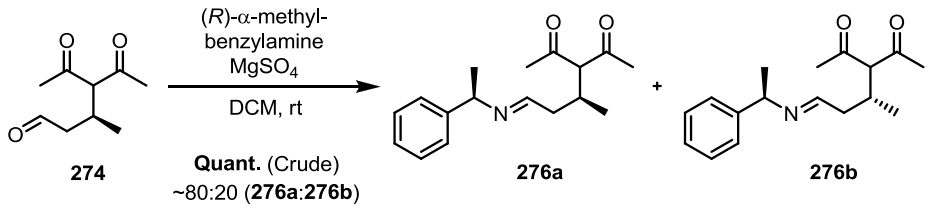
While no extensive optimisation studies were undertaken, it was subsequently found that the catalyst loading could be decreased to 1 mol% if the reaction was carried out neat, giving aldehyde **274** in essentially quantitative yield, which was of sufficient purity to use without purification, Scheme **4.22**.



Scheme 4.22 Synthesis of aldehyde **274**.

Although at the time unprecedented, a paper by Rovis and Lathrop recently reported the synthesis of aldehyde **274** using the described sequence.[102] Importantly, Rovis reported that a retro-Michael reaction was observed in the presence of catalyst **275**, which was enhanced in the presence of silica, highlighting the need to avoid purification of aldehyde **274** on silica.

Attempts to determine the enantiomeric excess of aldehyde **274** by chiral HPLC were unsuccessful, however, condensation of aldehyde **274** with enantiomerically pure α-methyl benzylamine yielded an ~80:20 diastereomeric mixture of imines **276** observable in the ^{1}H NMR spectrum of the unpurified product, Scheme **4.23**.

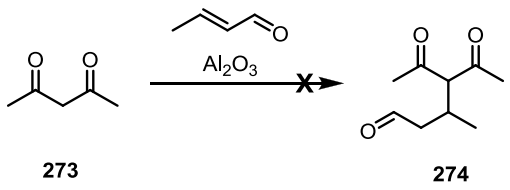


Scheme 4.23 Formation of the diastereomeric imines **276**.

Imine **276** could also potentially undergo a retro-Micheal reaction in the presence of α-methyl benzylamine and as such, the actual enantiomeric ratio could be greater than the NMR spectroscopic data would suggest.

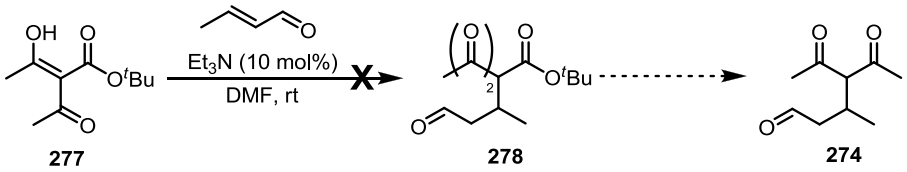
In order to prepare material for chiral HPLC studies and to optimise the concluding steps in the sequence, we felt it would be instructive to also consider the synthesis of racemic aldehyde **274**. Attempts to use pyrrolidine or Et_3N in place of organocatalyst **275** gave only traces of the desired aldehyde, along with numerous unidentified products. A modification of the procedure reported by Ranu,[103] using alumina to

catalyse the Michael addition of β-ketoesters to unsaturated aldehydes, also failed to yield aldehyde **274**, Scheme **4.24**.



Scheme 4.24 Attempted synthesis of aldehyde **274** using the procedure of Ranu.[103]

An alternative strategy for the racemic synthesis of aldehyde **274** was proposed, commencing from the known *tert*-butyl ester **277**,[104] readily prepared by treatment of *tert*-butyl acetoacetate with acetyl chloride in the presence of magnesium chloride. We envisaged that conjugate addition into crotonaldehyde would yield aldehyde **278**, which would undergo an acid-catalysed decarboxylation on treatment with acid. Disappointingly, all attempts to promote the conjugate addition proved unsuccessful, negating the possibly of using the sequence in the synthesis of mearsine **27**, Scheme **4.25**.



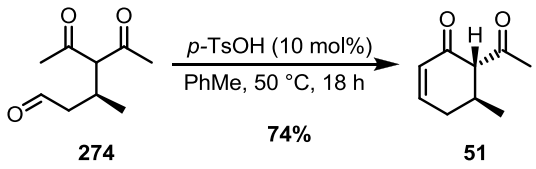
Scheme 4.25 Attempted synthesis of aldehyde **274** from *tert*-butyl ester **277**.

At this point in time we felt it would be counter-productive to spend further time attempting the racemic synthesis of aldehyde **274**; for the purpose of chiral HPLC studies a sample of racemic material was prepared using equimolar amounts of (*R*) and (*S*)-organocatalysts using the previously described procedure.

4.7.2 Synthesis of the Mearsine Biosynthetic Precursor (51)

With aldehyde **274** in hand, we were in a position to investigate the aldol condensation. On treatment of aldehyde **274** with *p*-TsOH in toluene at 80 ºC, following the procedure of Jørgensen,[105] enone **51** was isolated in a disappointing 22% yield. It was thought that

carrying out the reaction at a lower concentration would favour the intramolecular ring closure. Pleasingly, treatment of aldehyde **274** with *p*-TsOH (10 mol%) in toluene (0.15 M) at 50 ºC furnished enone **51** in a respectable 74% yield, Scheme **4.26**.



Scheme 4.26 Synthesis of diketone **51** *via* an acid-catalysed aldol condensation.

Alternative procedures using Amberlyst H-15 acidic resin failed to offer any improvement over the initial yield. A base induced ring closure using NaOH in ethanol also failed to yield the desired enone **51**.

The isolation of a minor impurity observed in the ^{1}H NMR spectrum of the unpurified reaction mixture revealed a structurally intriguing side-product formed during the reaction. The molecular formula was established as $C_9H_{14}O_3$ through HRMS analysis, suggesting a rearrangement product of aldehyde **274**. 1D and 2D NMR spectroscopic data were consistent with the loss of both ketones, however, a signal at 168.5 ppm in the ^{13}C NMR spectrum suggested the presence of an ester functionality (an IR stretch at 1736 cm^{-1} was also observed). A quaternary carbon at 104.4 ppm was consistent with a carbon bonded to two heteroatoms. The spectroscopic data were consistent with a structure such as lactone **279** (Figure **4.3**), however, the relative stereochemistry remains to be established.

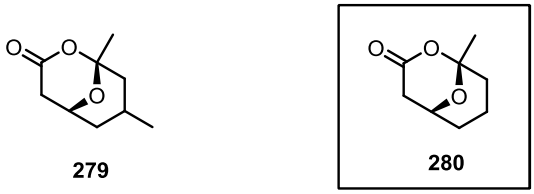
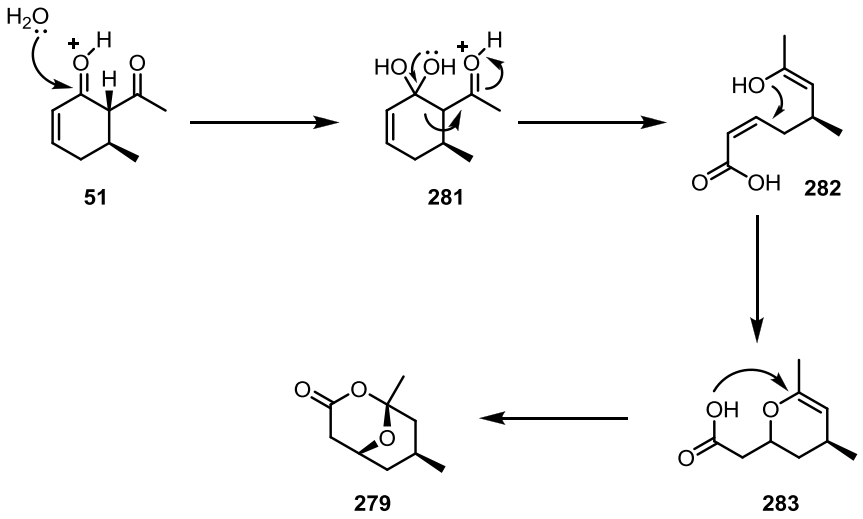


Figure 4.3 Structure proposed for side-product **279**.

Although no conclusive evidence for the mechanism of formation of lactone **279** has been obtained, it was proposed that enone **51** could undergo a retro-Claisen reaction in the presence of *p*-TsOH to give the unsaturated carboxylic acid derivative **282**, Scheme

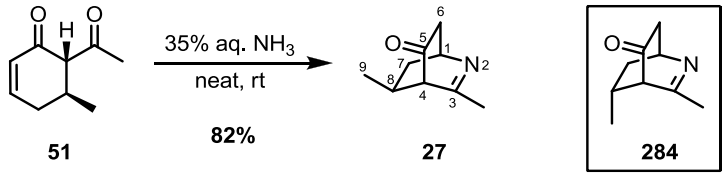
4.27. The enol tautomer **282** of the methyl ketone could add into the enone to form the pyran derivative **283**. Under acidic conditions an intramolecular cyclisation would occur to give the lactone **279**. A structurally similar compound **280** was previously prepared by Adams and Frenette, however, in this instance, the lactone was installed *via* Baeyer-Villiger oxidation of the corresponding ketone.[106]



Scheme 4.27 Proposed mechanism for the formation of side-product **279**.

4.7.3 Application of the Amination/Cyclisation Sequence to the Synthesis of (−)-Mearsine (27)

With enone **51** in hand we were in a position to investigate the one-pot amination/ cyclisation sequence. On treatment of enone **51** with 35% aqueous ammonia, consumption of the starting material was observed with the concomitant formation of a more polar species apparent by TLC analysis, Scheme **4.28**.



Scheme 4.28 An amination/cyclisation approach to mearsine **27**.

On inspection of the ^{1}H NMR spectrum of the unpurified product, we were pleased to observe signals corresponding to those reported for mearsine **27**, although slight

discrepancies were noted. Whilst the ^{13}C NMR spectroscopic data were consistent with those reported, the signals in the ^{1}H NMR spectrum corresponding to the C-4 bridgehead proton was shifted by ~0.15 ppm (3.13 ppm, Lit.[42] 3.27 ppm). The $[\alpha]_D$ also differed significantly from that reported in the literature, the optical rotation for the synthetic material was found to be −252.6 (*c* 0.51, DCM), while the optical rotation for the natural product was reported to be −34.5 (*c* 0.495, DCM).[42] These inconsistencies raised concerns about the structure of the isolated material. We initially proposed that conjugate addition of ammonia occurred *anti* to the methyl substituent, in order to minimise steric interactions, however, the epimeric compound **284** could potentially form if the addition of ammonia occurs *syn* to the methyl substituent. A sample of the synthetic material was therefore converted into the crystalline picrate salt for X-ray diffraction analysis, which provided conclusive evidence for the structure of the synthetic mearsine **27** (Figure **4.4**).

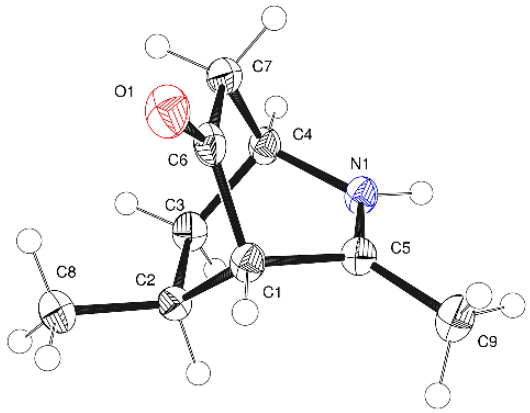


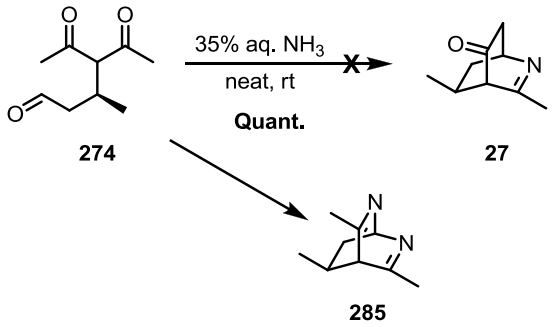
Figure 4.4 Crystal structure of mearsine **27** depicted using ORTEP-3 (picrate counter anion omitted for clarity) (CCDC 825975).

Due to the inconsistency noted with the optical rotation value, the enantiomeric ratio was determined through chiral HPLC analysis (Phenomenex Lux Cellulose-2 column, 95:5 *iso*-hexane/EtOH, flow rate 1.0 mL/min) which showed the enantiomeric ratio to be 90.5:9.5 (peak identity was confirmed using racemic material).[*] Whilst the inconsistencies in the NMR spectroscopic data could possibly be attributed to solvent/concentration effects, no satisfactory explanation for the significant difference in the optical rotation has been found.

[*] We thank Dr. A. Hard (AZ Macclesfield) for assistance with chiral HPLC analysis.

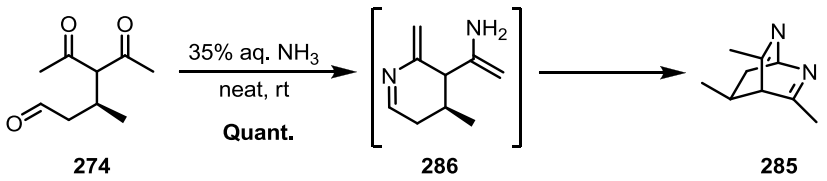
4.7.4 A One-pot Aldol Condensation/Cyclisation Strategy

A speculative one pot base-catalysed aldol condensation and subsequent amination/cyclisation was also considered for the synthesis of mearsine **27**. It was proposed that aldehyde **274** would undergo a base-catalysed aldol condensation to yield the intermediate enone **51**, which would cyclise *in situ*. On treatment of aldehyde **274** with 35% aqueous ammonia, complete consumption of the starting material was observed, to give a single product apparent by TLC analysis, which had an R_f value similar to that observed for mearsine **27**, Scheme **4.29**.



Scheme 4.29 Formation of novel bis-imine **285**.

^{1}H NMR spectroscopic analysis of the unpurified reaction mixture showed peaks corresponding to a bicyclic species, including bridgehead signals at 6.24 ppm and 3.71 ppm, however, these were not consistent with mearsine **27**. The molecular formula was determined to be $C_9H_{14}N_2$ through HRMS analysis. The absence of the bridging ketone was apparent in the ^{13}C NMR spectrum, but an additional quaternary carbon was present at ~170 ppm, consistent with a second imine. The structure of the isolated material was eventually established through a combination of 2D NMR spectroscopy techniques which showed the compound to be the novel *bis*-imine **285**. The compound was proposed to form *via* the intermediate monocyclic imine/enamine **286**. Subsequent cyclisation of the *exo*-cyclic enamine, yields the novel bis-imine **285**, after tautomerisation, Scheme **4.30**.



Scheme 4.30 Mechanism proposed for the formation of bis-imine **285**.

It was subsequently found that bis-imine **285** could also be prepared by treatment of acetylacetone and crotonaldehyde with aqueous ammonia. Whilst the unpurified reaction mixture was more complex than that from the reaction using the preformed aldehyde **274**, the bis-imine **285** was the predominant product evident in the ^{1}H NMR spectrum. Disappointingly, attempts to isolate the product from the mixture were unsuccessful, which we attributed to the low stability of bis-imine **285**.

4.8 Summary

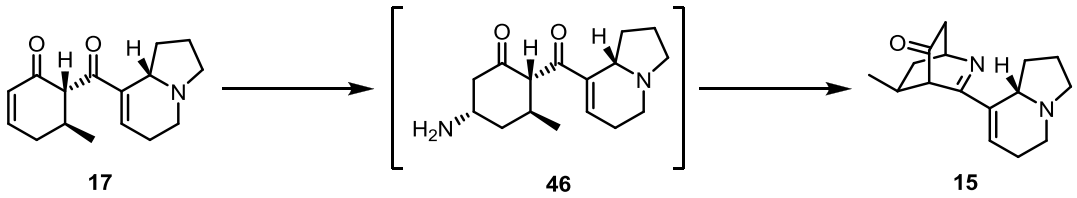
An expedient synthesis of isoquinuclidinones has been developed using aqueous ammonia in a one-pot amination/imination sequence. Using the optimised methodology, we have completed the total synthesis of enantioenriched (−)-mearsine **27** in 3 steps (60% overall yield, 81% *ee*) from commercially available materials. Unsubstituted isoquinuclidinones have been shown to undergo *in situ* ring opening to afford monocyclic imines structurally similar to the alkaloid grandsine G **20**. This transformation provides a potential synthetic route to grandisine G **20** which will be discussed in Chapter 5.

The work described in this chapter was the subject of a recent publication.[107]

Chapter 5. A Biomimetic Synthesis of (±)-Grandisine B (15)

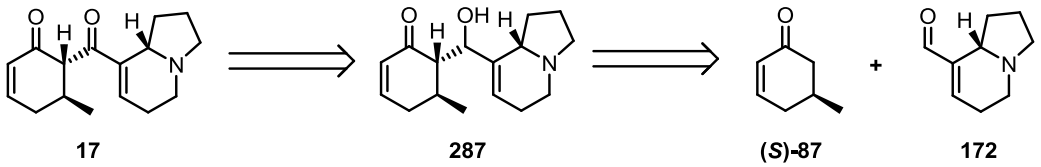
5.1 A Biomimetic Approach to Grandisine B (15)

Having developed a viable route to isoquinuclidinone frameworks using aqueous ammonia in a one-pot amination/cyclisation sequence, we set out to apply the methodology to the synthesis grandisine B **15**. The biomimetic strategy, based on Carroll's proposed biosynthesis,[9] would use the 1,3-diketone grandisine D **17** as a synthetic intermediate, Scheme **5.1**.



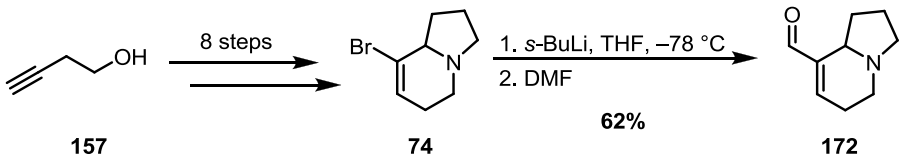
Scheme 5.1 Proposed synthesis of grandisine B **15** *via* a biomimetic amination/cyclisation sequen**ce**.[9]

As proposed retrosynthetically in Scheme **5.2**, we envisaged preparing grandisine D **17**, from indolizidine aldehyde **172** and (*S*)-methylcyclohexenone **87** *via* an aldol/oxidation sequence.



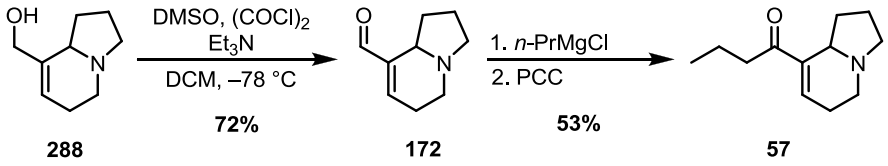
Scheme 5.2 Retrosynthetic analysis of grandisine D **17**.

Although we had previously shown that aldehyde **172** could be accessed from vinyl bromide **74** *via* halogen-lithium exchange and subsequent trapping with DMF, Scheme **5.3**, Overman's eight step synthesis of vinyl bromide **74** was unsuitable for bringing through large quantities of material.[57]



Scheme 5.3 Synthesis of indolizidine aldehyde **172** using Overman's route.[57]

To begin our racemic synthesis of grandisine B **15**, we chose to prepare allylic alcohol **288**, an intermediate previously reported by Taber *et al*. in their synthesis of the *Elaeocarpus* alkaloid (±)-elaeokanine A **57**, Scheme **5.4**.[35] The brevity of the route (six steps) appeared to be ideal for accessing quantities of alcohol **288** for use in coupling studies.



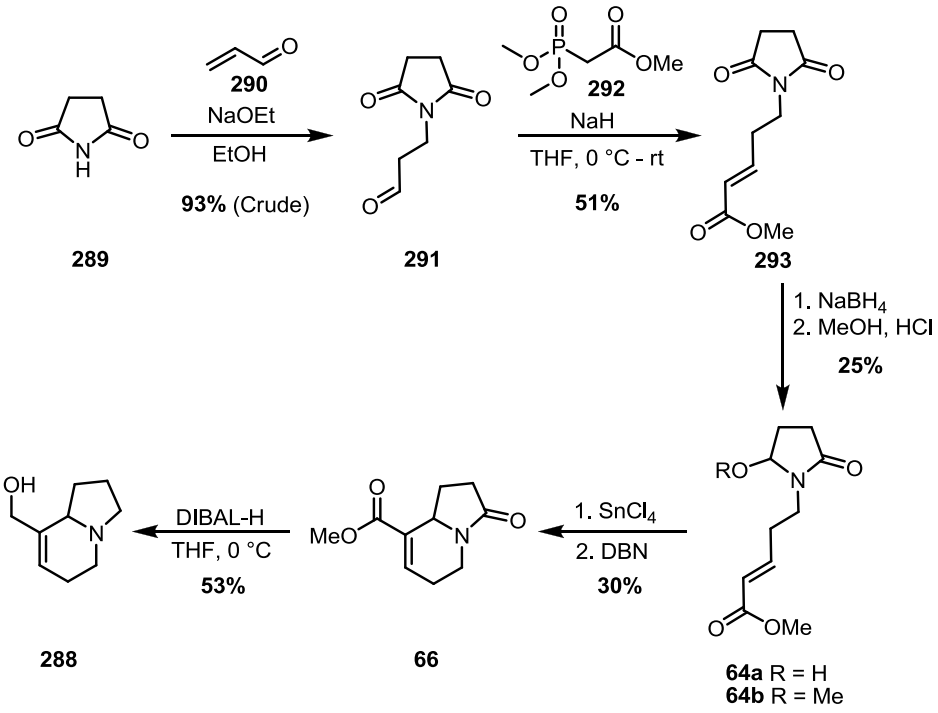
Scheme 5.4 Concluding steps in Taber's synthesis of elaeokanine A **57**.[35]

5.2 Synthesis (1,2,3,5,6,8a-Hexahydroindolizin-8-yl)methanol (288)

Following the reported procedure,[35] the synthesis of alcohol **288** commenced with the conjugate addition of succinimide **289** to acrolein **290** in the presence of catalytic sodium ethoxide. Olefination of aldehyde **291** with trimethylphosphonoacetate **292** and sodium hydride in THF gave the unsaturated ester **293** in 51% yield after distillation. In our hands, the reduction of imide **293** with sodium borohydride was capricious, generally requiring additional reductant to ensure complete consumption of the starting material. Attempts to optimise the reaction by changing the solvent, concentration and reaction temperature failed to offer a reproducible method for the reduction. Subsequent treatment of hydroxylactam **64a** with catalytic HCl gave the methoxy-lactam **64b** in 25% yield over 2 steps, Scheme **5.5**.

The tin(IV) chloride promoted cyclisation of methoxy-lactam **64b** proceeded in 1,2-dichloroethane at 70 ºC to give the chloroester **65** isolated as a complex mixture of diastereoisomers. Dehydrochlorination with DBN in toluene furnished the indolizidine

ester **66** in 29% over 2 steps (Lit.[35] 27%). Reduction of both the amide and ester functionalities with excess DIBAL-H gave allylic alcohol **288** in a moderate 53% yield (Lit.[35] 44%), Scheme **5.5**. Alternative conditions for the reduction using $LiAlH_4$ offered no improvement over the published conditions. The low yield was partially attributed to losses during work-up and purification, due to the polarity of alcohol **288**.



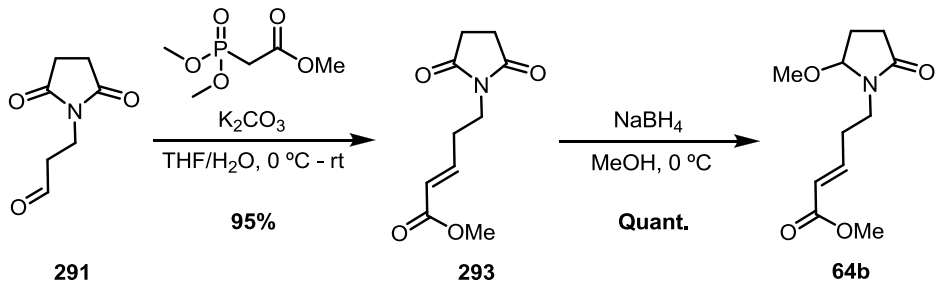
Scheme 5.5 Taber's synthesis of alcohol **288**.[35]

Although the yields for the sequence were generally modest, the expedient nature of the route enabled allylic alcohol **288** to be prepared in gram-scale quantities.

5.2.1 Challenges of Taber's Synthesis

A number of difficulties were encountered with Taber's route to alcohol **288**. The conjugate addition of succinimide to acrolein generally proceeded cleanly, but the viscous nature of the unpurified aldehyde **291** made it difficult to remove residual ethanol. It was proposed that running the reaction in methanol using catalytic sodium methoxide would enable easier removal of the residual solvent. However, on repeating the reaction in methanol, ^{1}H NMR spectroscopic analysis of the isolated material showed a number of impurities along with residual solvent.

The HWE olefination using trimethylphosphonoacetate and sodium hydride required large volumes of solvent to mobilise the thick slurries caused by sodium salts. Although distillation of the product was precedented, in our hands this generally led to poor yields and partial decomposition of the material. An alternative HWE procedure reported by Cordero came to our attention utilising potassium carbonate in aqueous ether to give unsaturated esters in near-quantitative yield.[108] Addition of a solution of aldehyde **291** in THF to an aqueous solution of potassium carbonate and trimethylphosphonoacetate gave after work-up the unsaturated ester **293** in 95% yield, Scheme **5.6**; the unpurified material was found to be homogeneous by ^{1}H NMR spectroscopic analysis, requiring no purification.



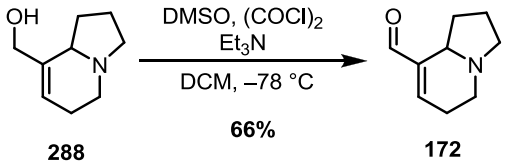
Scheme 5.6 Olefination of aldehyde **291** using the procedure of Cordero.[108]

Furthermore, subjecting imide **293** to the sodium borohydride reduction conditions, which had previously proved capricious, proceeded cleanly to give methoxy-lactam **64b** in quantitative yield. The problems observed previously with the reduction were attributed to minor impurities present in the unsaturated ester **293**. Having optimised a number of steps in the reaction sequence, we were in a position to investigate the concluding steps in the racemic synthesis of grandisine B **15**.

5.3 Oxidation of Allylic Alcohol (288)

Although the oxidation of allylic alcohol **288** is precedented in the literature using Swern conditions,[35] in our hands, the yields for the reaction were inconsistent. Alternative reaction conditions were briefly investigated. Oxidation using manganese dioxide gave traces amounts of the desired aldehyde **172**, but attempts to force the reaction to completion were unsuccessful. Oxidation of allylic alcohol **288** with Dess-

Martin periodinane furnished aldehyde **172** in a disappointing 32% yield after purification. When repeated using sodium bicarbonate as a buffer, following the procedure of De Brabander and Liu,[109] fewer impurities were observed in the ^{1}H NMR spectrum of the unpurifed material, however, no improvement in the isolated yield was observed.



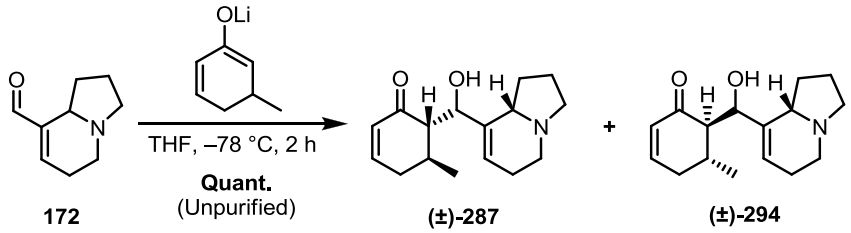
Scheme 5.7 Oxidation of allylic alcohol **288** using Swern Conditions.

It was subsequently found that more consistent yields could be obtained using Swern conditions if the reaction was quenched with saturated aqueous sodium bicarbonate. Using the optimised reaction conditions, aldehyde **172** was isolated in 66% yield, Scheme **5.7**. Furthermore, ^{1}H NMR spectroscopic analysis showed the material to be of sufficient purity to use without purification. The problems encountered with the oxidation were partially attributed to instability of aldehyde **172**.

5.4 Synthesis of the Grandisine B Carbon Skeleton

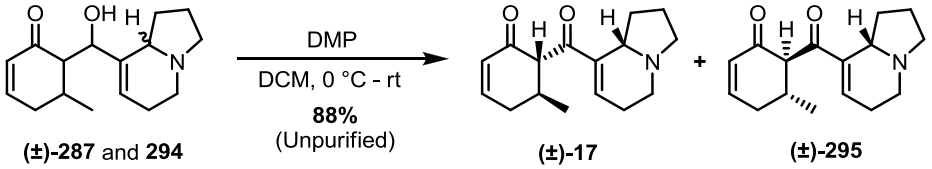
With indolizidine aldehyde **172** in hand, we were in a position to investigate the aldol coupling with methylcyclohexenone **87**. For the purposes of initial studies we chose to couple racemic methylcyclohexenone **87** with aldehyde **172**. When work initially commenced on the project, the relative stereochemistry of grandisine B **15** was unknown, the route would therefore provide access to both possible diastereoisomers of grandisine B **15**.

Treatment of methylcyclohexenone **87** with LDA in THF at −78 ºC and subsequent trapping with aldehyde **172** furnished a diastereomeric mixture of hydroxy-ketones **287** and **294**, contaminated with minor amounts of unreacted aldehyde **172**, Scheme **5.8**. Initial attempts to separate the products from unreacted starting material were unsuccessful, with no product recovered after attempted purification on silica.



Scheme 5.8 Synthesis of hydroxy-ketones **287** and **294** *via* aldol coupling with cyclohexenone **87**.

Before further investigating the aldol reaction, we were keen to determine whether the developed cyclisation sequence would work. The diastereomeric mixture was therefore oxidised using DMP to give the diastereomeric diketones **17** and **295** in 88% unpurified yield, Scheme **5.9**.

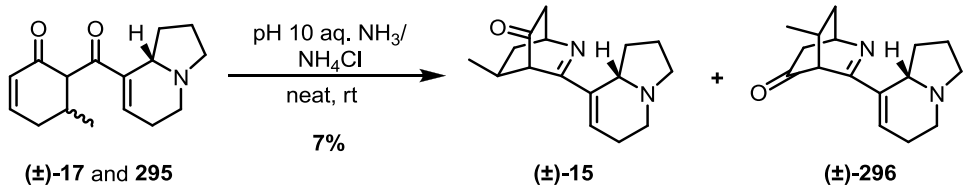


Scheme 5.9 Oxidation of hydroxy-ketones **287** and **294** using Dess-Martin Periodinane.

With diketones **17** and **295** in hand, we were in a position to investigate the cyclisation reaction using aqueous ammonia, a transformation also used by Tamura and co-workers in their synthesis of grandisine B **15**.[55] On treatment of the mixture of diketones **17** and **295** with 35% aqueous ammonia, complete consumption of starting material was observed, with the formation of a number of products apparent by TLC analysis. HRMS analysis of the unpurified reaction mixture revealed a molecular ion peak consistent with grandisine B **15** but on inspection of the ^{1}H NMR spectrum of the unpurified product, signals corresponding to grandisine B **15** were absent. More striking differences were apparent with the ^{13}C NMR spectroscopic data, notably, the absence of peaks corresponding to the ketone and imine functionality.

Whilst the identity of the isolated compound remained to be established, we were keen to continue efforts to prepare grandisine B **15**. Despite initial disappointment with the amination/cyclisation result, we felt that the synthesis of grandisine B **15** using the proposed sequence was still possible. The use of aqueous ammonia buffered with ammonium chloride had been shown by Korshevets to alter the selectivity of amination

reactions,[110] an effect employed by Snider in the synthesis of the cyclindricines.[89] Repeating the amination/cyclisation sequence using aqueous ammonia buffered to pH ~10 with ammonium chloride again resulted in complete consumption of starting material to give a single product apparent by TLC analysis.



Scheme 5.10 Cyclisation of diketones **17** and **295** using buffered aqueous ammonia.

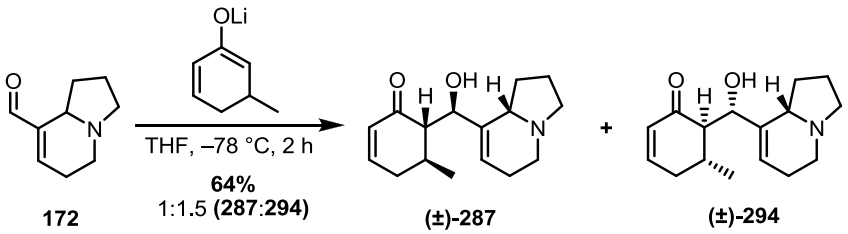
Spectroscopic analysis of the isolated product revealed signals corresponding to grandisine B **15** and the diastereomeric product **296**, arising from the coupling of the racemic cores, Scheme **5.10**. Although the isolated yield was low, we felt the sequence provided a viable route to grandisine B **15** and as such, attempts were made to optimise the concluding steps in the synthesis.

5.5 Optimisation of the Aldol Reaction

Whilst the lithium aldol reaction had provided an intial route to the hydroxy-ketones **287** and **294**, the yields for the reaction were unreliable. Difficulties in forcing the reaction to completion led us to search for alternative conditions. A similar procedure reported by Kita using LHMDS,[111] also failed to deliver the required hydroxy-ketone**s**. A recent publication by Tamura and co-workers *et al*. utilised a diastereoselective boron-aldol coupling (on different substrates) in their total synthesis of grandisine D **17**.[25] Following the reported procedure, treatment of methylcyclohexenone **87** with triethylamine and dibutylboron triflate followed by addition of indolizidine aldehyde **172** gave only traces of the aldol products **287** and **294**.

Returning to the lithium aldol reaction, it was found that yields for the reaction were generally improved using freshly prepared aldehyde **172**. Quenching the reaction with acetic acid was also found to give more consistent results. The reaction was also repeated in the presence of HMPA, however, this offered no improvement over previous

reactions, with hydroxy-ketones **287** and **294** obtained in 47% yield. Using the optimised procedure, formation of the lithium enolate of cyclohexenone **87** with LDA and trapping with aldehyde **172**, gave hydroxy-ketones **287** and **294** in 64% yield (73% BRSM) as a mixture of diastereoisomers (~1:1.5), which were separable by column chromatography, Scheme **5.11**.



Scheme 5.11 Optimised formation of hydroxy-ketones **287** and **294**.

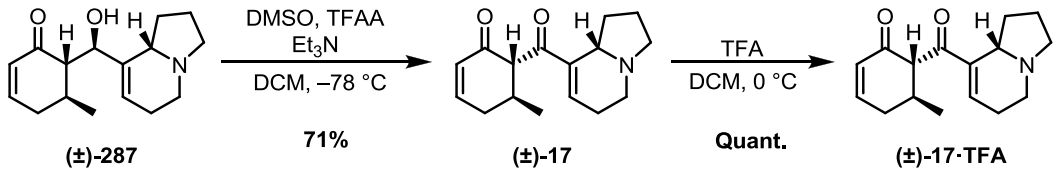
In an attempt to ensure complete consumption of aldehyde **172**, an excess of cyclohexenone **87** had been used in the reaction. It was noted that the ratio of products obtained was not 50:50 as expected, but favoured the formation of one isomer preferentially. The result suggests a matched/mismatched reaction in which one isomer of methylcyclohexenone **87** reacts more favourably with aldehyde **172**, to give an excess of the matched (kinetic) product. A similar observation was made by Danishefsky and co-workers in studies towards the epothilones, who reported long-range stereochemical induction in aldol reactions,[112] giving, in some instances, the matched product exclusively.

Although the relative stereochemistry of grandisine B **15** has recently been confirmed by Tamura,[55] we were unable to determine the relative stereochemistry of the hydroxy-ketones **287** and **294**, which were tentatively assigined as the *anti*-aldol products. The initial cyclisation reaction suggested the minor product **287** corresponded to the grandisine stereochemical series; however, subsequent chemistry was carried out on both diastereoisomers in order to confirm which compound had the same relative stereochemistry as grandisine B **15**.

5.6 Synthesis of rac-Grandisine D (17)

Previous work by Geyelin had shown that oxidation of a diastereomeric mixture of aldol products **287** and **294** to the corresponding diketones **17** and **295** could be achieved using modified Swern oxidation conditions.[56] Initial attempts to repeat the reaction gave diketones **17** and **295** in 71% yield. The stereochemistry around the cyclohexenone ring was determined to be that depicted in Scheme **5.12**, evident from the large (11.5 Hz) coupling constant between the protons adjacent to the methyl substitutent and *exo*-cyclic ketone. In contrast to 1,3-diketone substrates used in previous studies, only traces of the *cis*-isomer/enol tautomer were apparent in the ^{1}H NMR spectrum.

Alternative oxidation conditions were briefly investigated to determine whether the yield for the oxidation could be improved further. On treatment of alcohol **287** with MnO_2, no reaction was observed by TLC analysis after 24 h, and furthermore, attempts to recover the polar starting material from the reaction mixture were unsuccessful. Conditions reported by Taber,[35] using PCC buffered with NaOAc resulted in complete conversion to diketone **17** as determined by ^{1}H NMR spectroscopy, but the product could not be recovered from the chromium residues. Dess-Martin periodinane oxidation of alcohol **287** proceeded cleanly to furnish diketone **17** in 67% isolated yield. Oxidations using DMP and the TFAA Swern conditions both gave similar yields, however, the modified Swern reaction conditions were generally cleaner and we therefore chose to use these conditions in subsequent chemistry.

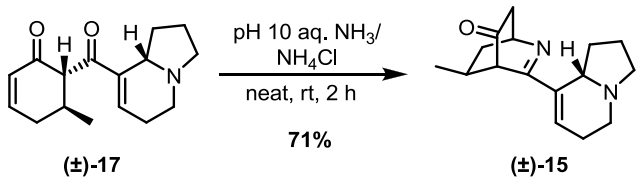


Scheme 5.12 Oxidation of hydroxy-ketone **287** using Swern conditions.

Treatment of grandisine D **17** with TFA in DCM gave the grandisine D **17**.TFA salt, the ^{1}H/^{13}C NMR spectroscopic data for which were consistent with those reported by Tamura and Carroll,[10, 55] Appendix **I**.

5.7 Synthesis of Grandisine B (15) via an Amination/Cyclisation Strategy

On treatment of *rac*-grandisine D **17** with a pH 10 aqueous ammonia/ammonium chloride solution, using the conditions developed previously, grandisine B **15** was isolated in 71% yield after purification, Scheme **5.13**. The NMR spectroscopic data for the compound were consistent with those reported by Carroll and Tamura, Appendix **II**.[9,55]



Scheme 5.13 Synthesis of grandisine B **15** *via* the developed amination/cyclisation sequence.

Conversion of a small sample of grandisine B **15** into the dipicrate salt provided conclusive evidence for the structure *via* single crystal X-ray diffraction analysis (Figure **5.1**).

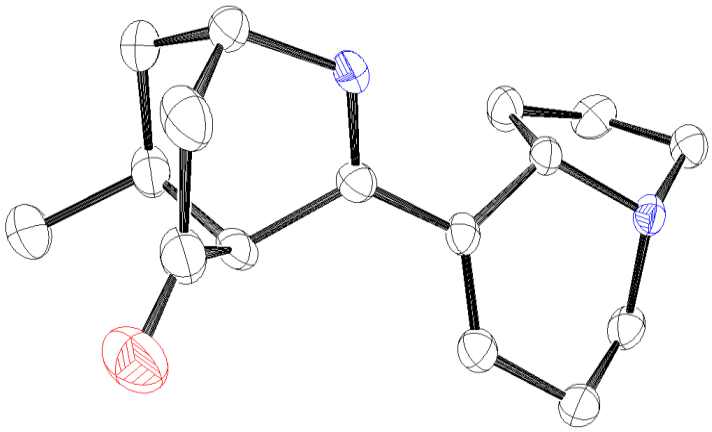
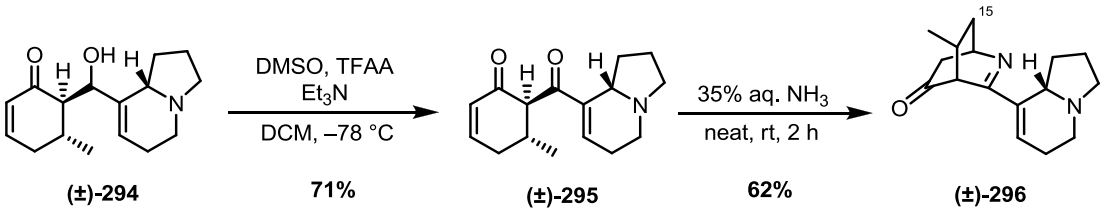


Figure 5.1 X-ray structure of grandisine B **15**.dipicrate (picrate counter anions omitted for clarity) depicted using ORTEP-3 (CCDC 815228).

The sequence of reactions was also applied to the opposite diastereomeric series to give *epi*-grandisine B **296** in 44% yield over 2 steps, Scheme **5.14**. The ^{1}H NMR spectroscopic data for the compound were similar to those observed for grandisine B, however, a notable difference in the signals for the C-15 protons was observed. In

grandisine B **15**, two signals for the diastereomeric protons were observed in the ^{1}H NMR spectrum, however, in *epi*-grandisine B **296**, these signals coalesced to give a single (broad) peak at 2.1 ppm.



(±)-294 **71%** **(±)-295** **62%** **(±)-296**

Scheme 5.14 Synthesis of *epi*-grandisine B **296** using the optimised sequence.

5.8 The Origin of Grandisine B (15)

We were intrigued by the apparent simplicity with which grandisine D **17** was converted into grandisine B **15**; the nature of the transformation raised questions about the origins of the natural product. On close inspection of the isolation paper, it became apparent that aqueous ammonia was used during the extraction process for the neutralisation of acidic extracts.[9] We conjectured that grandisine B **15** was actually an artefact of the isolation process formed from grandisine D **17** on treatment with aqueous ammonia.

To provide evidence to support this theory, a sample of grandisine D **17** was taken up in dichloromethane and extracted with aqueous HCl. On neutralisation of the acidic extracts with 35% aqueous ammonia and extraction into dichloromethane, two species were apparent in the ^{1}H NMR spectrum of the unpurified material, consistent with grandisine B **15** and grandisine D **17**. Although complete consumption of grandisine D **15** did not occur, it was shown that on brief exposure to aqueous ammonia, the formation of grandisine B **15** readily occurs.

To gain further insights/understanding of this transformation, we contacted Carroll who replied stating "Yes, we have certainly speculated about whether some of the compounds might be artefacts of the extraction and purification process. Grandisines B, F and G in particular are not observed by (+) ESI MS in crude methanol extracts of the leaves suggesting that these compounds at least are artefacts formed on treatment with

ammonia."* Based on this evidence it would suggest that grandisine B does not occur naturally in the plant material, but is formed during the isolation process on extraction with aqueous ammonia.

5.9 Artefact Alkaloids

When considering the variety of molecular architectures found in nature, it is unsurprising that on subjecting compounds to ammonia-based isolation procedures, the formation of artefacts can occur. Such artefacts are generally indistinguishable from true natural products, exhibiting plausible structures found in nature. A brief overview of artefact alkaloids formed on treatment with aqueous ammonia follows.

5.9.1 Rosmaricine (297)

Although the isolation of betaine natural products from the family *Labiatae* was precedented, no alkaloids had been isolated from the family until the anomalous discovery of the alkaloid rosmaricine **297** in 1962 (Figure **5.2**).[113]

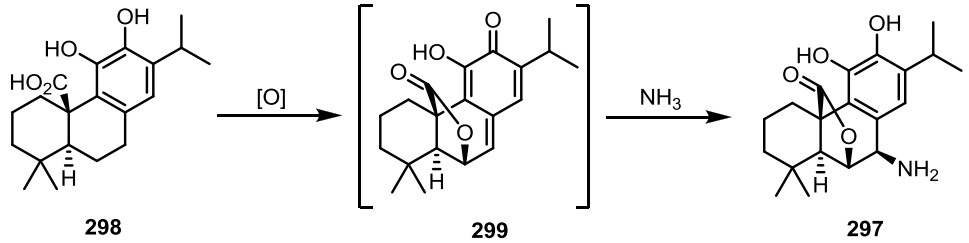
297

Figure 5.2 Structure of rosmaricine **297** as determined by Wenkert.[113]

A comprehensive investigation by Wenkert in 1965 revealed the true origin of the species. Using a combination of synthesis and spectroscopy, the structure of rosmaricine **297** was determined to be that depicted in Figure **5.2**, containing a bridging lactone and primary amine functionality. The presence of the primary amine group raised questions about the true origin of the compound which was proposed to arise as a result of the use of aqueous ammonia during the isolation process. Further confirmation of this

* *Private email communication with Prof. A.R. Carroll, Eskitis Institute, Griffith University, Brisbane, Queensland, Australia (23rd May 2009).*

hypothesis was obtained when the isolation was carried out in the absence of ammonia and no rosmaricine **297** was obtained. Subsequent exposure of the isolated material to ammonia led to the formation of rosmaricine **297**. The transformation was proposed to occur *via* oxidation and intramolecular cyclisation of carnosic acid **298** to give the quinone derivative **299**, which yields rosmaricine **297** *via* a 1,6-conjugate addition of ammonia, Scheme **5.15**.

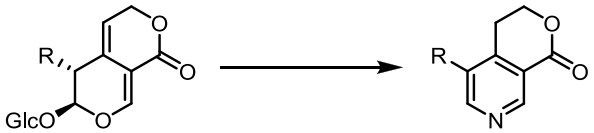


298 **299** **297**

Scheme 5.15 Conversion of carnosic acid **298** into rosmaricine **297**.[113]

5.9.2 Pyridine Monoterpene Alkaloids

The pyridine monoterpenoid alkaloids **301** constitute a second class of commonly encountered artefact alkaloids, which are derived from the parent iridoid glycosides **300**, Scheme **5.16**.[114]



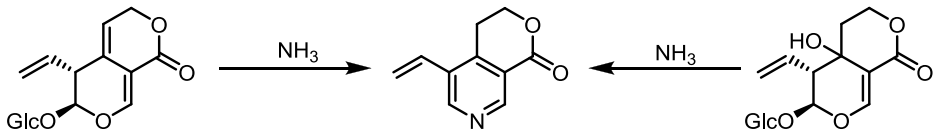
300 **301**

Scheme 5.16 General synthesis of the pyridine monoterpene alkaloids **301**.

Although Scheme **5.16** could also represent a plausible biosynthesis of these compounds, studies have shown that the use of extraction methods avoiding aqueous ammonia generally produced no detectable levels of the alkaloid components.[115]

The base gentianine **303** has been isolated from a number of species of the families *Gentianaceae* and *Loganiaceae*. The structurally related compounds gentiopicrin **302** and swertiarmarin **304** containing a labile acetal functionality have also been isolated

from the same family. Studies have shown that on treatment with aqueous ammonia under mild conditions both compounds **302** and **304** can be converted into gentianine **303**, Scheme **5.17**.[116, 117]

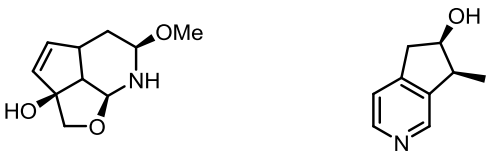


302 **303** **304**

Scheme 5.17 Synthesis of gentianine **303** from gentiopicrin **302** and swertiarmarin **304**.[116, 117]

Subjecting plants of the family *Gentainaceae*, from which gentianine had been isolated, to ammonia-free extractions showed that only *gentiana fetisowii* contained gentianine in detectable amounts.

Other monoterpene alkaloids also thought to be artefacts of the isolation process, include both buddamin **305** and cantleyine **306** (Scheme **5.18**), neither of which are commonly found in plant materials when ammonia-free extractions are used.[118]

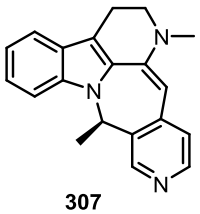


305 **306**

Scheme 5.18 Structures of the pyridine monoterpene alkaloids buddamin **305** and cantleyine **306**.[118]

5.9.3 Decussine (307)

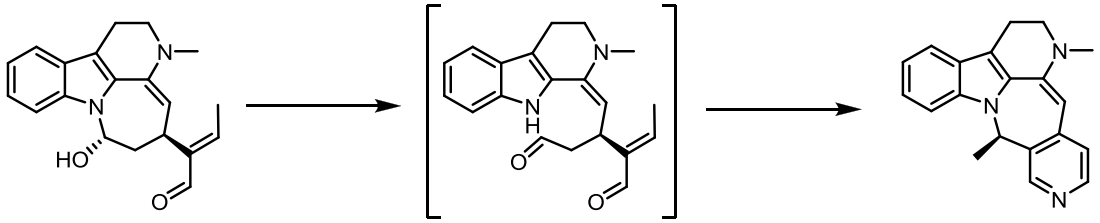
Work by Rolfsen *et al.* identified biologically active compounds in extracts of the species *Styrchnos decussate*.[119] Characterisation of the alkaloid components revealed a number of indole-type structures including decussine **307**, a pentacyclic indole alkaloid, containing a novel azepine/pyridine fused ring system (Figure **5.3**).



307

Figure 5.3 Decussine **307**, an artefact alkaloid identifed by Rolfsen.[119]

Subsequent investigations suggested that the formation of the pyridine ring occurred during the acid/base extraction process, with ammonia acting as the source of nitrogen. Rolfsen proposed that decussine **307** is formed from an indole derivative such aldehyde **308**, Scheme **5.19**.

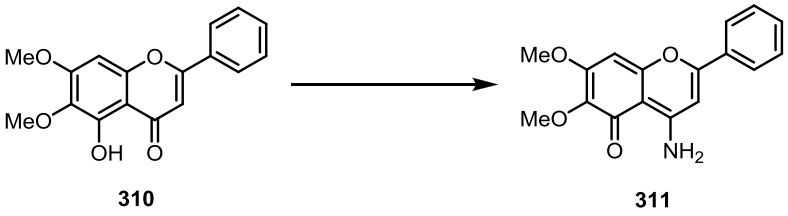


308 309 307

Scheme 5.19 Proposed synthesis of the artefact alkaloid decussine **307**.[119]

5.9.4 Desmosine (311)

The alkaloid desmosine **311** was isolated in 1998 by Pas and co-workers from *Desmos dumosus*.[120] The unusual structure exhibited by the compound suggested the species could be an artefact formed from phenol **310** during the isolation process, Scheme **5.20**. The absence of the alkaloid component in extraction procedures avoiding the use of aqueous ammonia provided further evidence to support this hypothesis.

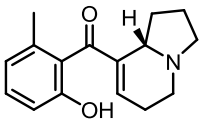


310 311

Scheme 5.20 Proposed synthesis of desmosine **311** from biological precursor **310**.[120]

5.10 Synthesis of Elaeocarpus Alkaloids

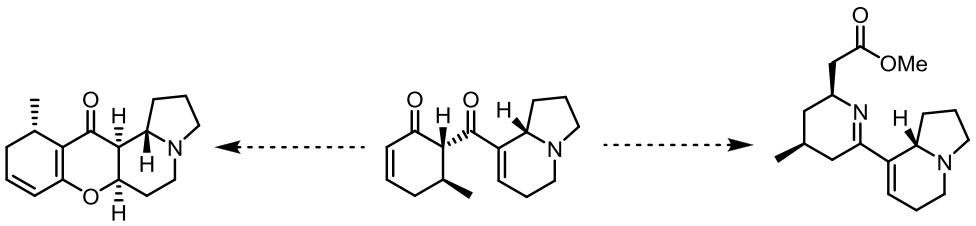
Having established a route to grandisine B **15**, the synthesis of structurally related alkaloids isolated from the family *Elaeocarpaceae* were considered. Such studies would provide further insights into the origins of the *Elaeocarpus* alkaloids, which are potentially artefacts formed during the isolation process. Evidence for the formation of artefacts from *Elaeocarpus sp.* was recently provided by Carroll an co-workers,[13] who reported that the alkaloid elaeocarpenine **24** (Figure **5.4**) was only isolated when acid/base extraction protocols were avoided, suggesting the compound is susceptible to artefact formation under conditions encountered during the isolation process.



24

Figure 5.4 Structure of elaeocarpenine **24** isolated by Carroll and co-workers.[13]

The focus of initial studies were the syntheses of isoelaeocarpiline **5** and grandisine G **20**, the two alkaloids most closely related to grandisine D **17**, Scheme **5.21**.[9,10]



5 **17** **20**

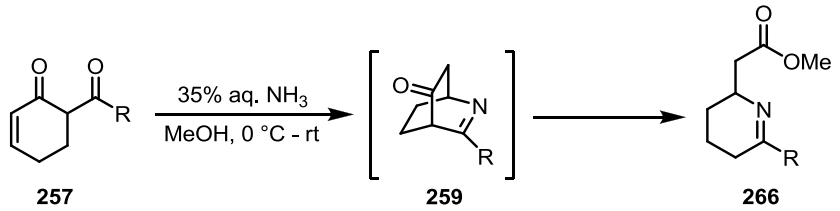
Scheme 5.21 Potential applications of grandisine D **17** in the synthesis of other *Elaeocarpus* alkaloids.

5.10.1 Grandisine G (20)

Grandisine G **20**, isolated in 2006 from *Elaeocarpus grandis* by Carroll and co-workers was proposed to be derived from grandisine B **15** *via* methoxide-promoted opening of the isoquinuclidinone ring.[10] Grandisine G **20** was the least abundant of the grandisine

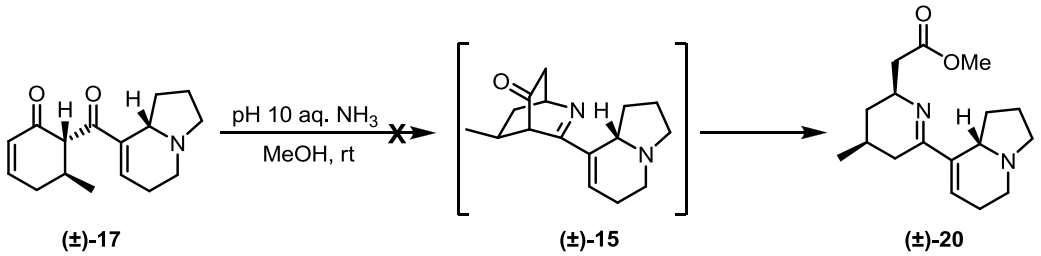
alkaloids isolated to date, with 3.8 mg isolated from 1.73 Kg of plant material, representing an isolated yield of 0.00021%.

Previous work on model systems had shown that the unsubstituted isoquinuclidinone core unit was susceptible to ring opening on treatment with aqueous ammonia in methanol, to give structures analogous to grandisine G **15**, Scheme **5.22**. However, in previous studies this transformation was not observed with substituted isoquinuclidinone derivatives.



Scheme 5.22 Ring opening of unsubstituted isoquinuclidinones **259**.

We initially proposed a synthesis of grandisine G **20** using the amination/cyclisation conditions shown in Scheme **5.23**, in which methanol was employed as the solvent. Treatment of diketone **17** with buffered aqueous ammonia in methanol gave rise to a number of species including grandisine B **15** and other unidentified cyclisation products, however, no evidence of methyl ester **20** was observed.

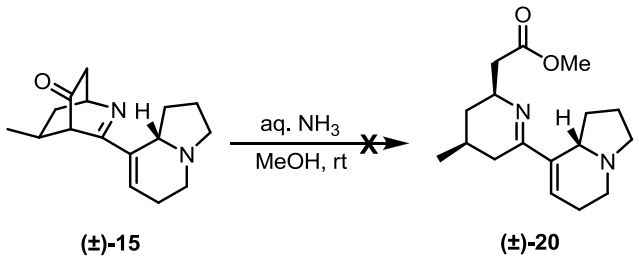


Scheme 5.23 Attempted synthesis of grandisine G **20** from grandisine D **17**.

Upon repeating the reaction in methanol at reflux, minor peaks were observed in the ^{1}H NMR spectrum of the unpurified product, which were consistent with the ring-opened methyl ester **20**, in particular a sharp signal at 3.6 ppm was consistent with the expected methoxy group. Attempts to achieve complete conversion of grandisine D **17** into grandisine G **20** by holding for extended periods at reflux were unsuccessful, resulting

in decomposition. Cyclisation of grandisine D **17** with 35% aqueous ammonia in place of the ammonium chloride buffered solution also failed to yield the desired methyl ester **20**.

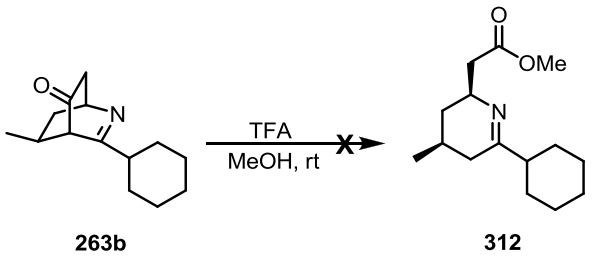
A stepwise approach was also investigated in which grandisine B **15** was initially prepared, then treated with ammonia in methanol, Scheme **5.24**. In this instance, only unreacted starting material was recovered on work-up.



Scheme 5.24 Attempted methoxide promoted ring opening of grandisine B **15**.

On closer inspection of the extraction procedure,[10] it was noted that whilst an acid/base isolation procedure was used, the crude alkaloid extracts were not exposed to methanol until HPLC separation using a gradient of 1% TFA in H_2O to 1% TFA in MeOH. We therefore proposed that grandisine G **20** was actually formed under acidic conditions *via* an acid-promoted ring opening of the isoquinuclidinone core in the presence of methanol.

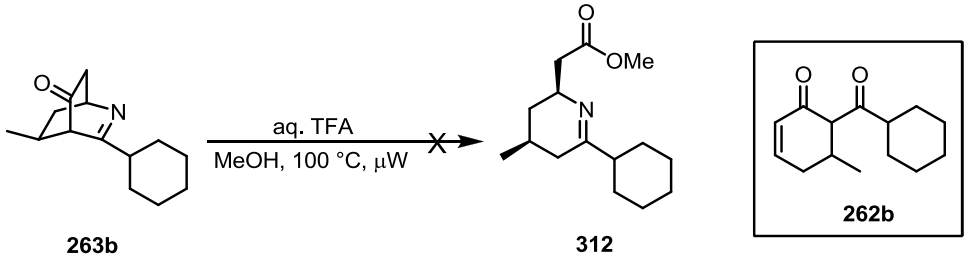
Due to limited supplies of grandisine B **15**, initial investigations were carried out using the model isoquinuclidinone **263b**. Treatment of the cyclohexyl substituted isoquinuclidinone **263b** with TFA in methanol at room temperature failed to give any of the expected methyl ester **312**, Scheme **5.25**; analysis of the ^{1}H NMR spectroscopic data showed only unreacted starting material. Repeating the reaction in the presence of water also failed to show any of the ring opened product **312**.



263b 312

Scheme 5.25 Attempted acid promoted ring-opening of model isoquinuclidinone **263b**.

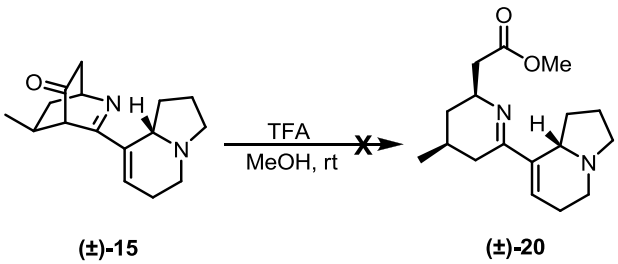
When repeated using microwave heating, TLC analysis of the unpurified reaction mixture showed the presence of two compounds. On inspection of the ^{1}H NMR spectrum for the unpurified material, no evidence of the methyl ester **312** was found, but, peaks corresponding to the starting material **263b** and the hydrolysis product, diketone **262b** were observed, Scheme **5.26**.



263b 312

Scheme 5.26 Attempted ring opening of isoquinuclidinone **263b** using microwave heating.

Despite unsuccessful attempts to promote the ring opening on the model system, the acid promoted ring opening of grandisine B **15**, was briefly investigated. Disappointingly, attempts to promote the ring opening of grandisine B **15** using the conditions investigated on the model system proved unsuccessful. On treatment with TFA in methanol or aqueous TFA in methanol, no evidence of grandisine G **20** was observed, Scheme **5.27**.



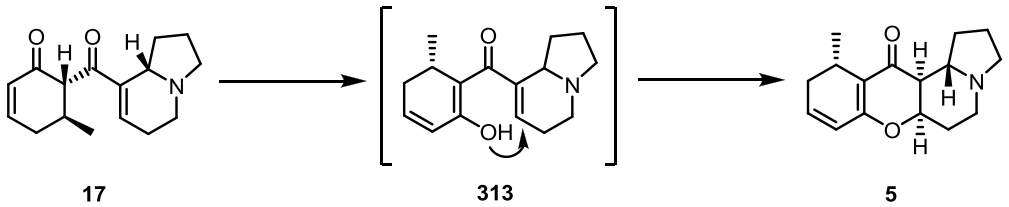
(±)-15 (±)-20

Scheme 5.27 Attempted conversion of grandisine B **15** into grandisine G **20**.

Due to time constraints, we felt it would be counter-productive to spend further time investigating the synthesis of grandisine G **20**.

5.11 Synthesis of Elaeocarpiline (4) / Isoelaeocarpiline (5)

The applications of grandisine D **17** in the synthesis of other *Elaeocarpus* alkaloids were briefly investigated. Of particular interest was isoelaeocarpiline **5**, isolated previously from *Elaeocarpus dolichostylis* and *Elaeocarpus grandis*.[5, 9] Carroll proposed isoelaeocarpiline **5** formed *via* cyclisation of the enolate of grandisine D **17** as shown in Scheme **5.28**.

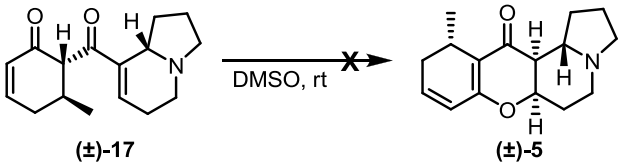


17 **313** **5**

Scheme 5.28 Proposed synthesis of isoelaeocarpiline **5** from grandisine D **17**.

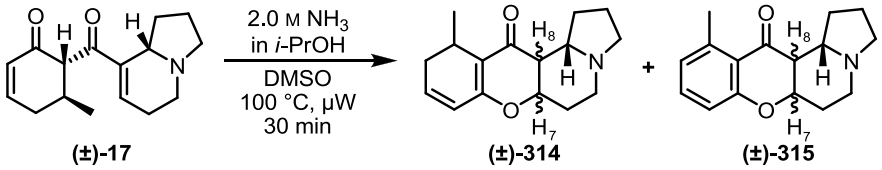
Previous work in the group had shown that treatment of a diastereomeric mixture of diketones **17** and **295** with 2.0 M NH_3 in isopropanol resulted in conversion into a mixture of cyclised products on microwave heating.[56] We were keen to look for milder reaction conditions which could provide evidence to suggest that cyclisation occurs during the extraction process.

Carroll previously reported the conversion of grandisine D **17** into isoelaeocarpiline **5** on standing in DMSO.[9] Attempts to replicate this transformation were unsuccessful, Scheme **5.29**; in our hands, samples of grandisine D **17** in DMSO held at room temperature were found to be stable for prolonged periods. Heating the samples to 50 ºC and 100 ºC showed no evidence of the cyclisation product **5**, however, signs of decomposition were observed in the latter.



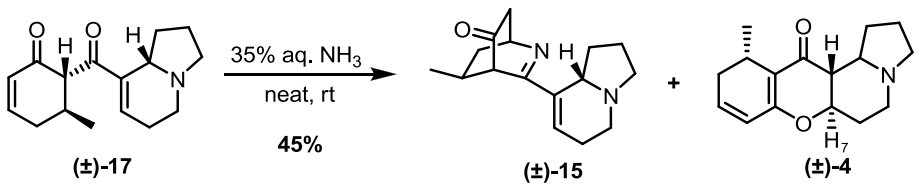
Scheme 5.29 Attempted cyclisation of grandisine D **17** to give isoelaeocarpiline **5**.

Repeating the microwave conditions reported by Geyelin gave a complex mixture of products, Scheme **5.30**.[56] Spectroscopic analysis of the unpurified material showed peaks corresponding to starting material **17** and minor peaks consistent with cyclised products **314**. Signals in the aromatic region were also observed suggesting aromatization of the cyclohexenone moiety had occurred under the reaction conditions to give aromatic derivatives **315**.



Scheme 5.30 Attempted cyclisation of grandisine D **17** under microwave heating.

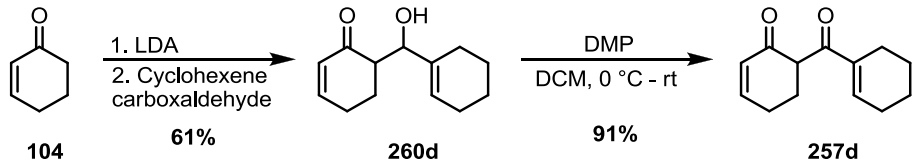
During previous investigations into the synthesis of grandisine B **15** *via* the amination/ cyclisation sequence, trace amounts of elaeocarpiline **4** were observed during a number of cyclisation reactions, evident from a distinct signal at 4.0 ppm in the ^{1}H NMR spectrum of the unpurified product, consistent with the H-7 proton in elaeocarpiline **4**, Scheme **5.31**. It was therefore proposed that replacing aqueous ammonia with aqueous sodium hydroxide would yield the cyclised product **4**, without the possibility of forming the amination/cyclisation product grandisine B **15**.



Scheme 5.31 Formation of elaeocarpiline **4** during the amination/cyclisation reaction.

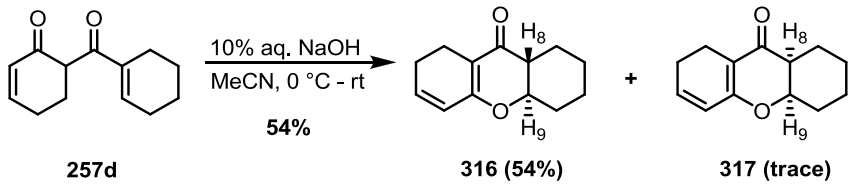
5.11.1 Model Studies

Due to limited quantities of grandisine D **17** with which to investigate the cyclisation, the simple *bis*-enone **257d** prepared previously, Scheme **5.32**, was used in initial investigations.



Scheme 5.32 Synthesis of model *bis*-enone **257d** *via* an aldol/oxidation sequence.

In an initial small-scale reaction, treatment of enone **257d** with aqueous sodium hydroxide in acetonitrile, resulted in complete conversion into the cyclised products **316** and **317** after 48 h at rt, Scheme **5.33**.



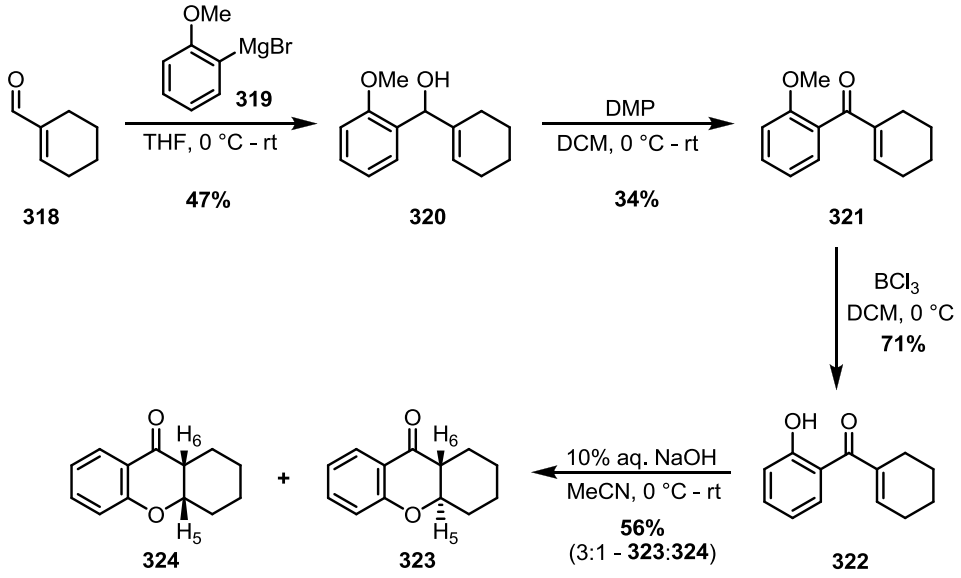
Scheme 5.33 Cyclisation of the model *bis*-enone **257d**.

Inspection of the ^{1}H NMR spectrum suggested the compound was the thermodynamic *trans*-product **316**. The large (11 Hz) coupling between the C-8 and C-9 protons was consistent with the depicted stereochemistry. Minor traces of the *cis*-isomer were also observed, evident from a signal at 4.5 ppm in the ^{1}H NMR spectrum. Repeating the reaction on a larger scale gave the *trans*-cyclised product **316** in 54% yield after 18 h at room temperature, containing minor traces of the *cis*-product.

5.11.2 Aromatic Model Cyclisation Precursor

In order to further investigate the scope of the cyclisation reaction, an aromatic model system representative of the core structure in elaeocarpine **1** and isoelaeocarpine **2**, was prepared. Generation of Grignard reagent **319** from bromoanisole and subsequent

trapping with cyclohexane carboxaldehyde **318** gave the benzylic alcohol **320** in 47% yield. Oxidation with Dess-Martin periodinone proceeded to afford the benzyl ketone **316**, which underwent demethylation on treatment with BCl_3 in DCM to afford phenol **317** in 24% over two steps, Scheme **5.34**.



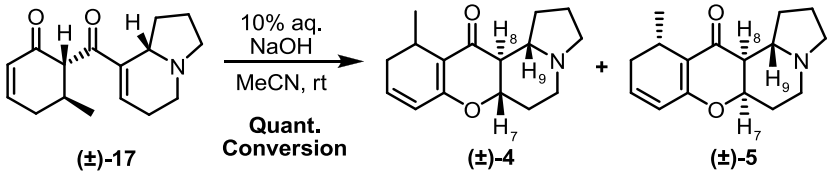
Scheme 5.34 Synthesis of the elaeocarpine model **323**.

On treatment with aqueous sodium hydroxide in acetonitrile, rapid consumption of the starting material was observed, with the formation of a two species evident by TLC analysis. The ^{1}H NMR spectroscopic data for the major product were consistent with the depicted *trans*-isomer **323**, evident from the large coupling (11.0 Hz) between the H-5 and H-6 protons at the ring junction. The ~3:1 ratio of *trans*/*cis*-products observed in the ^{1}H NMR spectrum of the unpurified reaction mixture could represent the thermodyanmic equilibrium. In order to confirm this, it would be necessary to re-subject a pure sample of one isomer to the cyclisation conditions to determine whether the equilibrium is re-established.

5.11.3 Attempted Synthesis of Elaeocarpiline (4)

Having demonstrated the cyclisation conditions were general to both aromatic and aliphatic model substrates, we were keen to apply the transformation to the synthesis of elaeocarpiline **4** and isoelaeocarpiline **5**, Scheme **5.35**. In an initial small scale reaction, treatment of grandisine D **17** with aqueous sodium hydroxide in acetonitrile resulted in

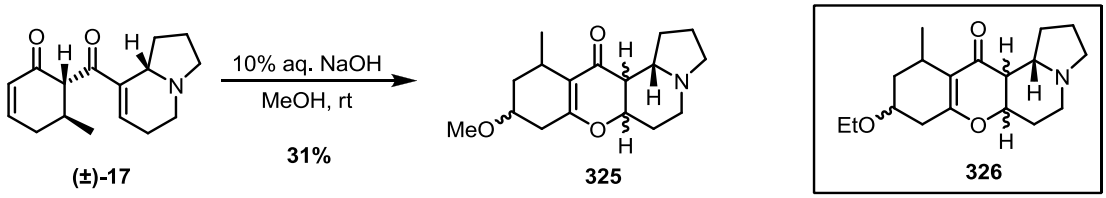
complete consumption of the starting material, with the formation of a more lipophilic species apparent on TLC analysis.



Scheme 5.35 Cyclisation of grandisine D **17** on treatment with aqueous sodium hydroxide.

The ^{1}H NMR spectroscopic data were consistent with the *trans*-product **4**, evident from two alkene signals at 6.25 and 5.84 ppm and a distinctive signal at 4.0 ppm consistent with the C-7 proton. Traces of second product were also observed, which we proposed to be isoelaeocarpiline **5**, based on a minor signal at 4.5 ppm corresponding to the C-7 proton. Although the reaction proceeded cleanly on a small scale, attempts to scale up the transformation to enable full characterisation of the products proved unsuccessful; therefore, the structures of the cyclised products were not conclusively established.

The reaction was also repeated using alcohol co-solvents. On treatment of grandisine D **17** with aqueous sodium hydroxide in methanol, complete consumption of starting material was observed to give a single product. The ^{1}H NMR spectroscopic data for the product were not consistent with isoelaeocarpiline **4** or elaeocarpiline **5**, and furthermore, HRMS analysis failed to show a mass ion corresponding to the cyclised product **4**. Whilst insufficient material was obtained to fully characterise the product, a signal at 3.30 ppm in the ^{1}H NMR spectrum was consistent with a methoxy group. Based on the ^{1}H NMR spectral data and HRMS analysis the structure was speculatively proposed to be tetracycle **325**, Scheme **5.36**.

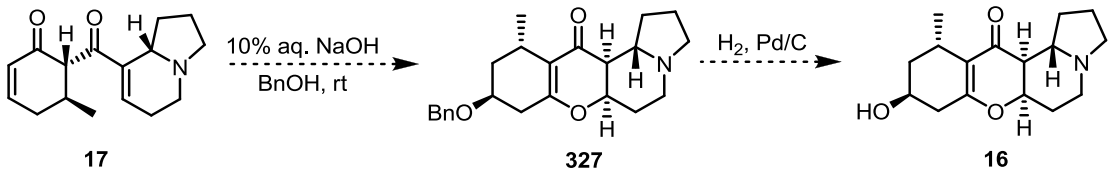


Scheme 5.36 Attempted cyclisation of grandisine D **17** with sodium hydroxide.

Repeating the reaction in EtOH resulted in the formation of a structurally similar product **326**. Signals corresponding to an ethoxy group were observed in the ^{1}H NMR spectrum, but, in this instance, HRMS analysis failed to show the mass ion corresponding to ethoxy derivative **326**.

5.11.4 Potential Strategy for the Synthesis of Grandisine C (16)

Although not investigated during the course of these studies, the cyclisation approach could potentially provide a synthetic route to grandisine C **16**. We envisaged that the use of benzyl alcohol in the cyclisation reaction would yield the corresponding benzyl derivative **327** which would give grandisine C **16** on debenzylation under hydrogenation conditions, Scheme **5.37**.

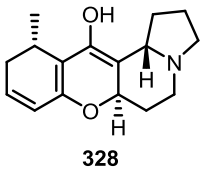


17 **327** **16**

Scheme 5.37 Proposed synthesis of grandisine C **16**

5.12 Selectivity of the Cyclisation Reaction

Carroll and co-workers only reported the isolation of isoelaeocarpiline **5**,[9] which features a *cis*-stereochemistry at the C-7/C-8 ring junction. This corresponds to the kinetic cyclisation product, in which protonation of the enolate intermediate **328** occurs on the least hindered face of the molecule (Figure **5.5**).[121]

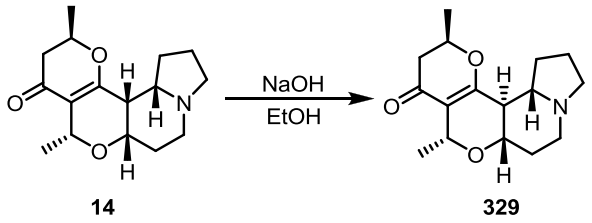


328

Figure 5.5 Cyclisation intermediate **328**.

Preliminary results on model systems have shown the thermodynamic *trans*-diastereoisomer to be the major product formed under the conditions investigated, with

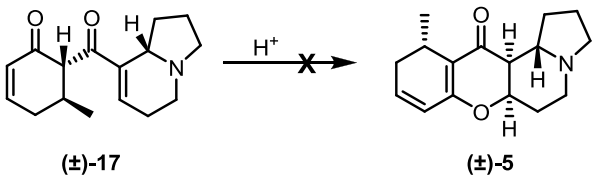
only traces of the *cis*-diastereoisomer observed. These results are also consistent with studies by Danishefsky and Maloney who showed that on treatment with sodium hydroxide in ethanol, the kinetic *cis*-isomer of grandisine A **14** was readily converted into the more stable thermodynamic *trans*-diastereoisomer **329**, Scheme **5.38**.[24]



Scheme 5.38 Epimerisation of grandisine A **14** reported by Danishefsky.[24]

5.13 Attempted Cyclisation Under Acidic Conditions

It was proposed that the cyclisation of grandisine D **17** could potentially occur on exposure to acid during the extraction process. Thus, diketone **17** was subjected to conditions encountered during the isolation procedure. On treatment with TFA in MeOH or aqueous TFA in MeOH no reaction was observed by TLC analysis, and the ^{1}H NMR spectra for the isolated material were consistent with the starting material **17**. Exposure to aqueous H_2SO_4 also failed to show any evidence of the cyclisation product **5**, Scheme **5.40**.



Scheme 5.39 Attempted cyclisation of grandisine D **17** under acidic conditions.

Repeating the reaction using Amberlyst H-15 acidic resin, MSA and *p*-TsOH in non-protic solvents, lead to the recovery of starting material in all instances, suggesting that cyclisation only occurs under basic conditions. Additional work is required to gain a more comprehensive understanding of the cyclisation reaction.

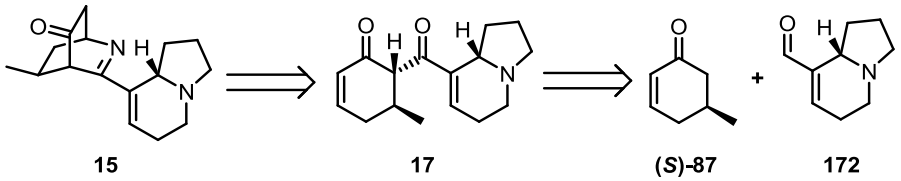
5.14 Summary

The racemic synthesis of grandisine B **15** has been completed using a biomimetic amination/cyclisation sequence to construct the isoquinuclidinone core. Initial attempts to use grandisine D **17** as a precursor to other *Elaeocarpus* alkaloids have so far proved inconclusive or unsuccessful. Further work towards the synthesis of these compounds should be undertaken in the future. Studies towards the asymmetric synthesis of (−)-grandisine B **15** are detailed in Chapter 6.

Chapter 6. Alkyne/Acetal Cyclisation Reactions in the Synthesis of Indolizidine Alkaloids: The Total Synthesis of (–)-Grandisine B (15)

6.1 Retrosynthesis of (–)-Grandisine B (15)

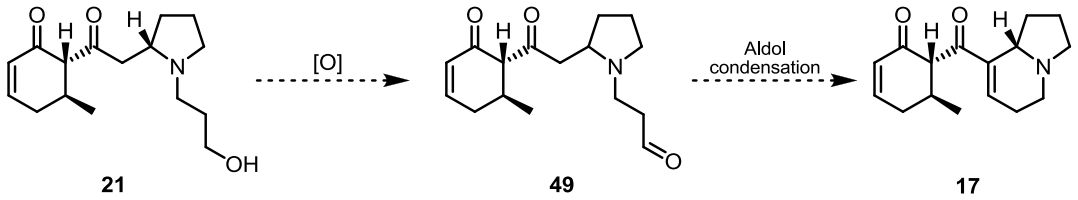
Having established a racemic route to grandisine B **15** using a biomimetic amination/cyclisation sequence, we were keen to develop an asymmetric synthesis of grandisine B **15**. Using the previously described retrosynthesis, Scheme **6.1**, enantioselective routes to both the indolizidine aldehyde **172** and (*S*)-5-methylcyclohexenone **87**, would be required



Scheme 6.1 Retrosynthesis of grandisine B **15**.

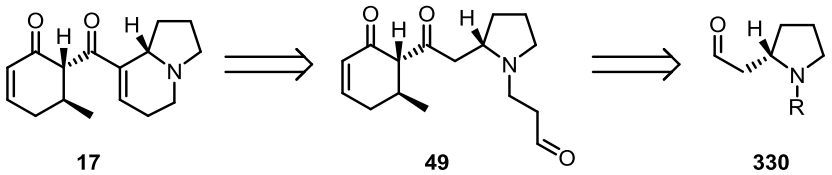
Whilst we envisaged the synthesis of enantio-enriched (*S*)-methyl-cyclohexenone **87** would be achieved using the organocatalytic procedure recently reported by Jorgensen,[105] the precedented routes to the indolizidine core unit suffered from a number of problems (long, low yields etc). Alternative strategies for the synthesis of the indolizidine ring system were therefore considered.

Although a number of disconnections could be envisaged, we were keen to investigate potential biomimetic strategies for the synthesis of the indolizidine core unit. A recent publication by Carroll and co-workers detailed the isolation of the pyrrolidine alkaloids habbemines A **21** and B **22**, which were proposed to be biosynthetic precursors to the grandisine alkaloids, Scheme **6.2**.[11]



Scheme 6.2 Carroll's proposed formation of grandisine D **17** from habbemine A **21**.[11]

Intrigued by this disconnection, we proposed a route to grandisne D **17**, shown retrosynthetically in Scheme **6.3**.

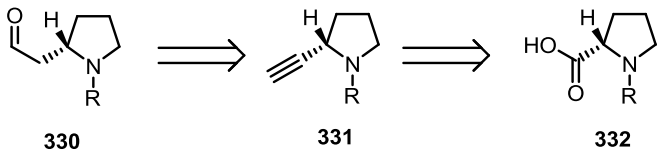


Scheme 6.3 Biomimetic retrosynthesis of grandisine D **17**.

Disconnection of the indolizidine core unit *via* an aldol condensation sequence, reveals the β-amino carbonyl compound **49**. A similar strategy was previously used by Koizumi in the synthesis of the *Elaeocarpus* alkaloid elaeokanine A **57**.[122] Using an aldol/oxidation sequence, the 1,3-diketone substrate **49**, could be prepared from aldehyde **330**.

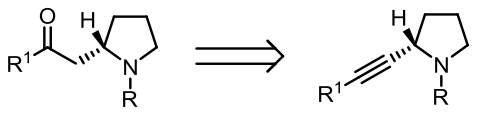
Due to concerns regarding the stability of β-amino carbonyl compound **49** and aldehyde **330**, classes of compounds known to readily racemise, the carbonyl compound would ideally be masked/protected, the deprotection of which would constitute one of the concluding steps in the synthesis.

It was proposed that the carbonyl function could be accessed *via* hydration of an alkyne, which would provide a stable precursor to the required carbonyl function, Scheme **6.4**.



Scheme 6.4 Retrosynthesis of aldehyde **330** *via* alkyne **331**.

Whilst the anti-Markovnikov hydration of alkynes is precedented using transition metal catalysts on simple systems,[123-127] classical methods for alkyne hydration are known to give the Markovnikov product.[128-130] To overcome this problem, we proposed the introduction of a substituent onto the alkyne which would direct the hydration and could provide a handle to further functionalise the indolizidine core unit, Scheme **6.5**.

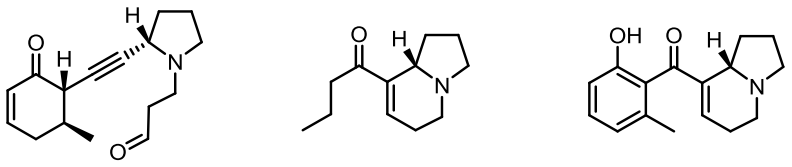


333 **334**

Scheme 6.5 Retrosynthesis of carbonyl compound **333**.

6.2 A Mercury-Mediated Alkyne Hydration Approach

Although there is no literature precedent for the synthesis of compounds such as alkynyl cyclohexenone **335**, we felt the viability of the approach could be initially confirmed by investigating the synthesis of simple *Elaeocarpus* alkaloids such as elaeokanine A **57** and elaeocarpenine **24** (Figure **6.1**). These could be potentially accessed from readily accessible alkyl or aryl-substituted alkynes

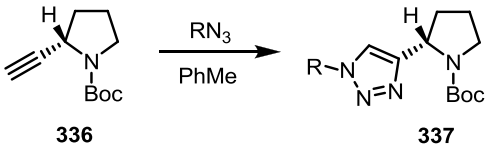


335 **57** **24**

Figure 6.1 Structures of elaeokanine **57** and elaeocarpenine **24**.

6.2.1 Synthesis of Proline Alkyne (336)

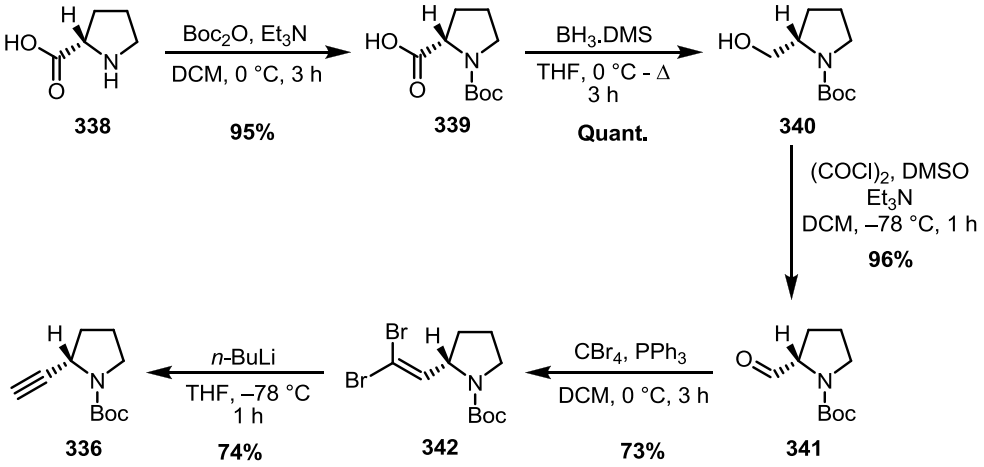
To commence the asymmetric synthesis of the indolizidine core unit of grandisine B **15**, we chose to prepare the known alkyne **336**,[131] an intermediate previously used by Gmeiner, in the synthesis of triazolopeptide derivatives **337**, Scheme **6.6**.



336 **337**

Scheme 6.6 Applications of alkyne **336** in the synthesis of triazolopeptide derivatives **337**.[131]

Following a literature procedure,[131] commercially available (*S*)-proline **338** was Boc-protected *via* treatment with di-*tert*-butyl carbonate in DCM, Scheme **6.7**. Reduction of the carboxylic acid **339** with BH_3.DMS gave alcohol **340**, which was oxidised using Swern conditions to afford aldehyde **341** in 96% yield over 2 steps. Installation of the alkyne is precedented using the Corey-Fuchs protocol,[131] or the Ohira-Bestmann reagent,[132] however, the need to prepare the Ohira-Bestmann reagent led us to initially investigate the Corey-Fuchs route. Treatment of aldehyde **341** with CBr_4 and PPh_3 in DCM gave the dibromide **342** in 73% yield. Subsequent treatment with *n*-BuLi in THF at −78 ºC gave proline alkyne **336** in 74% yield after purification. Alternatively, treatment of dibromide **342** with caesium carbonate in DMSO, following the procedure recently reported by Yang,[133] also gave alkyne **336** in 74% yield.



338 **95%** **339** **Quant.** **340** **96%** **341** **73%** **342** **74%** **336**

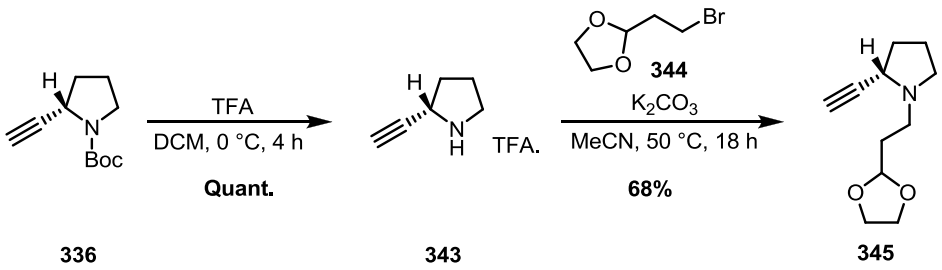
Scheme 6.7 Synthesis of proline alkyne **336**.

6.3 Initial Cyclisation Studies

Deprotection of Boc-amine **336** with conc. aqueous HCl in diethyl ether following the procedure of Maarseveen resulted in the removal of the Boc-group,[134] however, a number of impurities were also evident in the ^{1}H NMR spectrum of the product.

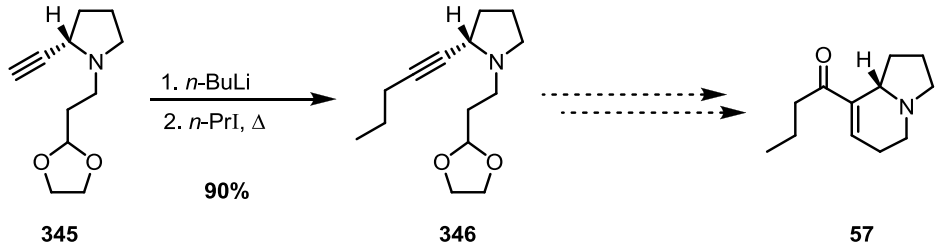
Conditions using trifluoroacetic acid in dichloromethane were superior, giving the amine·TFA salt **343** in quantitative yield.

Acetal **345** was initially prepared *via* alkylation of amine **343** with the commercially available bromide **344**. On treatment with acetal **344** and potassium carbonate in acetonitrile, amine **343** was converted into the corresponding *N*-alkylated derivative **345**, which was obtained in 68% yield, Scheme **6.8**.



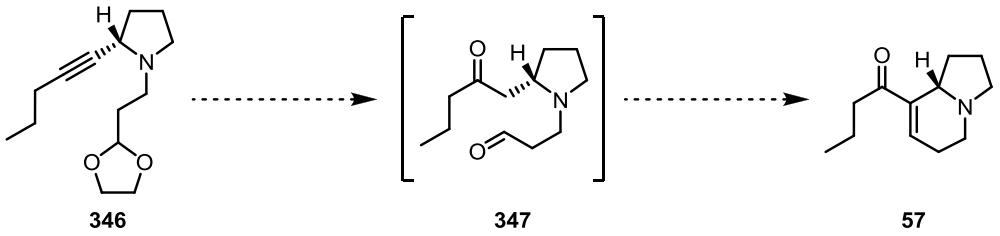
Scheme 6.8 Synthesis of acetal **345**.

In order to test the viability of the route, we initially chose to investigate the synthesis of the *Elaeocarpus* alklaloid elaokanine A **57**, isolated from *Elaeocarpus kaniensis* by Lamberton and co-workers.[33] Alkylation of alkyne **345** with *n*-propyl iodide in THF at reflux, following the procedure of Chong,[135] gave the cyclisation precursor **346** in 90% yield, Scheme **6.9**.



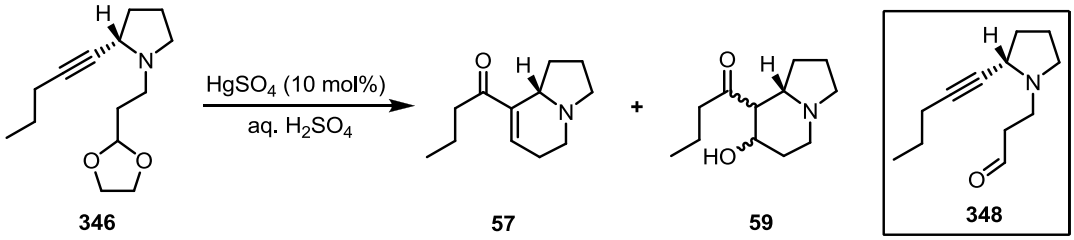
Scheme 6.9 Alkylation of alkyne **345** and proposed conversion to elaeokanine **57**.

We envisaged that hydration of alkyne **346** would yield the intermediate ketone **347**, which would undergo an acid-catalysed aldol condensation with the aldehyde formed on acetal hydrolysis, Scheme **6.10**. Initially classical alkyne hydration conditions using mercury salts in aqueous acid were investigated.



Scheme 6.10 Proposed alkyne hydration/aldol condensation sequence for the synthesis of elaeokanine **57**.

Treatment of alkyne **346** with mercuric sulfate in aqueous sulfuric acid resulted in consumption of starting material, with the concomitant formation of a number of products, apparent by TLC analysis, Scheme **6.11**.

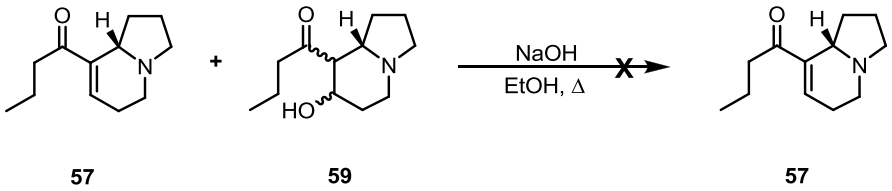


Scheme 6.11 Attempted mercury-mediated hydration of alkyne **346**.

Upon inspection of the ^{1}H NMR spectrum of the unpurified material, peaks corresponding to the cyclic acetal were absent and no evidence of the deprotected aldehyde **348** was observed. Furthermore, a minor peak at 6.81 ppm was consistent with an α,β-unsaturated carbonyl compound. Disappointingly, attempts to separate the individual products were unsuccessful and we were unable to conclusively establish the identity of the products. HRMS analysis showed molecular ions corresponding to compounds of formula $C_{12}H_{19}NO$ and $C_{12}H_{21}NO_2$ suggesting that cyclisation had occurred to give a mixture of the aldol **59** and eliminated aldol products **57**. Holding the reaction for prolonged periods at reflux failed to give the unsaturated ketone **57** as the predominant product. Reducing the temperature also proved unsuccessful, with no reaction observed at room temperature.

In an attempt to convert the aldol product **59** into the desired unsaturated ketone **57**, the reaction was repeated and the unpurified material was subjected to the elimination conditions reported by Koizumi, Scheme **6.12**.[122] Treatment with sodium hydroxide in ethanol gave a complex mixture of products, from which we were unable to isolate

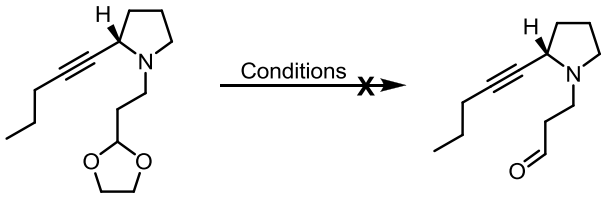
elaeokanine A **57**. Alternative conditions using mesyl chloride and triethylamine in dichloromethane also failed to give elaeokanine A **57**.



57 **59** **57**

Scheme 6.12 Attempted elimination of hydroxy-ketone **59** using conditions reported by Koizumi.[122]

Following our unsuccessful cyclisation reactions using acetal **346**, attempts were also made to deprotect acetal **346** in order to access aldehyde **348** for direct use in the proposed aldol condensation. Treatment with *p*-TsOH in aqueous acetone at reflux gave only recovered starting material after work-up, and similarly, treatment with 1 M aqueous HCl following the procedure of Dixon also failed to give aldehyde **348**, Scheme **6.13**.[136]



346 **348**

Scheme 6.13 Attempted deprotection of cyclic acetal **346**.

Heating acetal **346** in TFA led to complete consumption of the starting material, however, the ^{1}H NMR spectrum of the unpurified material showed multiple unidentified products. Conditions previously used in the Taylor group for the deprotection of cyclic acetals using tin(II) chloride dihydrate,[137] also failed to give the deprotected aldehyde **348**, giving only recovered starting material on work-up.

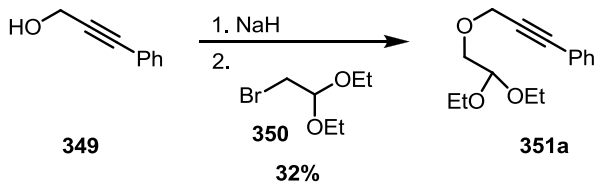
6.4 Alkyne/Acetal Cyclisation Reactions

Due to disappointing initial results with the mercury-mediated alkyne hydration/ cyclisation reactions, we were keen to look for alternative conditions. The cyclisation

reactions of alkyne/acetals or alkyne/aldehydes have received considerable interest in recent years, with a range of transformations reported using transition metal, Lewis acid and Brønsted acid catalysts.[138-145]

A particularly relavent paper by Saá, reported the Brønsted acid promoted intramolecular cyclisation of alkyne/aldehydes.[146] Disappointingly, when alkyne **346** was subjected to the reported conditions, a complex mixture of unidentified products was observed in the ^{1}H NMR spectrum of the unpurified reaction mixture. Although one example of an alkyne/acetal cyclisation was reported by Saá, in general, the cyclisations were carried out with the corresponding aldehydes. We proposed that in this instance, the *in situ* deprotection of the cyclic acetal was not compatible with the cyclisation conditions.

A mild Lewis acid catalysed cyclisation procedure was recently reported by Yu and co-workers using iron(III) choride to catalyse the cyclisation of alkyne/acetals to prepare a range of heterocycles.[139] Due to unsuccessful cyclisation reactions using the proline-derived alkyne **346**, a literature example from the Yu's paper was initially repeated. The model susbtrate **351a** was prepared using a modification of the procedure reported by Yu;[147] deprotonation of 3-phenyl-2-propyn-1-ol **349** with NaH in THF and trapping with bromo-acetaldehyde diethyl acetal **350** gave alkyne **351a** in 32% yield, Scheme **6.14**.

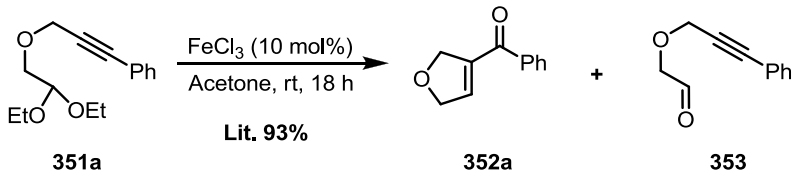


349 **350** **351a**

32%

Scheme 6.14 Synthesis of the model cyclisation substrate **351a**.[147]

On subjecting alkyne **351a** to the reported conditions,[139] TLC analysis showed a number of products to be present after 18 h at room temperature (Lit.[139] 93%, 2 h). Analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy confirmed the presence of a number of species, identified as the desired cyclisation product **352a**, unreacted starting material **351a** and aldehyde **353** resulting from acetal hydrolysis, Scheme **6.15**.

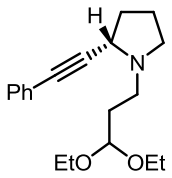


Scheme 6.15 Attempted cyclisation of alkyne-acetal **351** using the procedure of Yu.[139]

Based on previous work in the Taylor group, the reaction was also repeated using catalytic (10 mol%) tin(II) chloride dihydrate,[148] which gave a product distribution similar to the analogous reaction using iron(III) chloride.

6.5 Attempted Synthesis of Indolizidines via A Lewis Acid Mediated Cyclisation

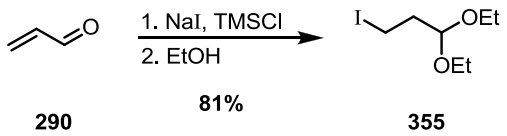
Having shown the cyclisation proceeded, albeit not as well as reported, we felt it would be instructive to apply the conditions to a model system more representative of the indolizidine core unit in grandisine B **15**. Aromatic-substituted alkynes are commonly used in literature studies; we therefore chose to prepare phenyl alkyne **354** (Figure **6.2**). The cyclic acetal was also replaced with the corresponding diethyl acetal, which we envisaged would be more susceptible to *in situ* hydrolysis.



354

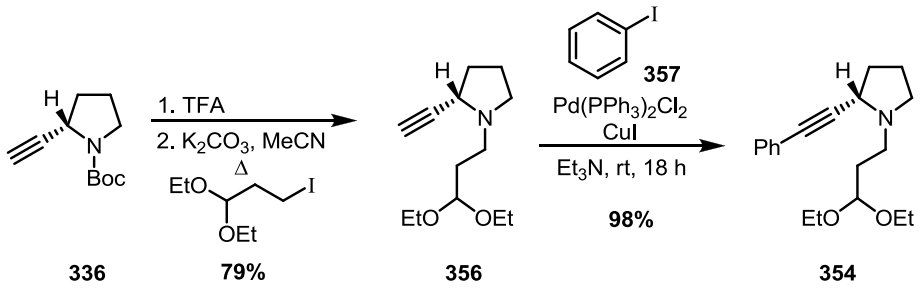
Figure 6.2 Alternative cyclisation substrate **354**.

The required alkylating agent was prepared using the procedure reported by Abad.[149] Treatment of acrolein and sodium iodide in the presence of trimethylsilyl chloride and subsequent addition of ethanol gave the iodo-acetal **355** in 81% yield, Scheme **6.16**.



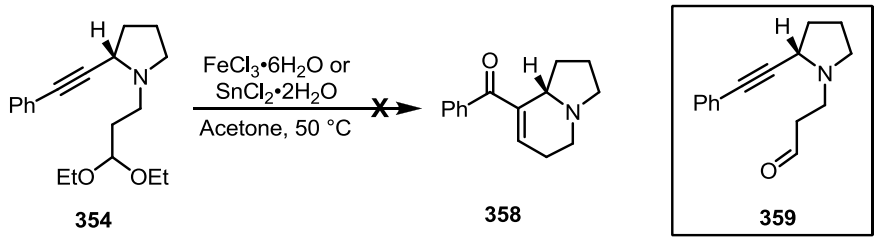
Scheme 6.16 Synthesis of iodo-acetal **355**.

Deprotection of Boc-alkyne **336** with TFA gave amine **343** which was alkylated with iodide **355**, to give diethyl acetal **356** in 79% yield over two steps. Sonogashira coupling of alkyne **356** with iodobenzene **357** gave the phenyl acetylene derivative **354** in 98% yield, Scheme **6.17**.



Scheme 6.17 Synthesis of diethyl acetal **354**.

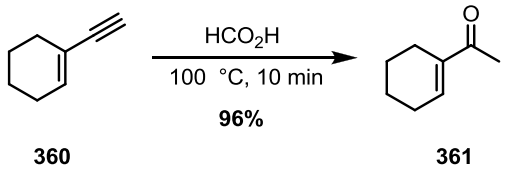
Treatment of the acetal **354** with iron(III) chloride hexahydrate and tin(II) chloride dihydrate in acetone at 50 ºC, following the reported procedures, showed only the acetal hydrolysis product **359** on inspection of the ^{1}H NMR spectra. Repeating the reaction with a large excess (5 equiv.) of tin(II) chloride dihydrate also failed to give the cyclised product **358**, Scheme **6.18**.



Scheme 6.18 Attempted cyclisation of alkyne/acetal **354** using Lewis acid catalysts.

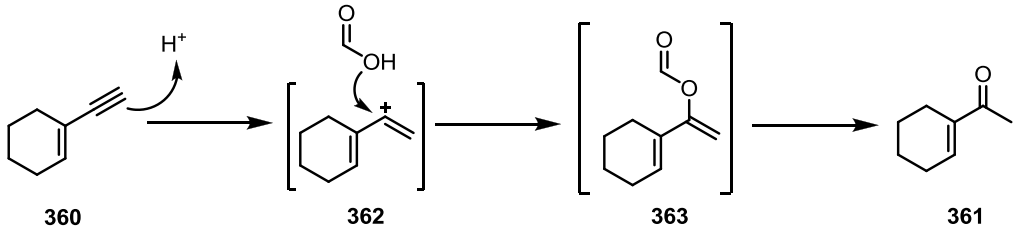
6.6 A Formic Acid Mediated Alkyne Hydration Strategy

A series of papers by Shvo and Menashe came to our attention reporting the hydration of alkynes with formic acid.[150, 151] Whilst the hydration of alkynes in the presence of metal catalysts is precedented, the reaction was unusual in the fact that the hydration of alkynes was achieved by simply heating in formic acid, Scheme **6.19**.



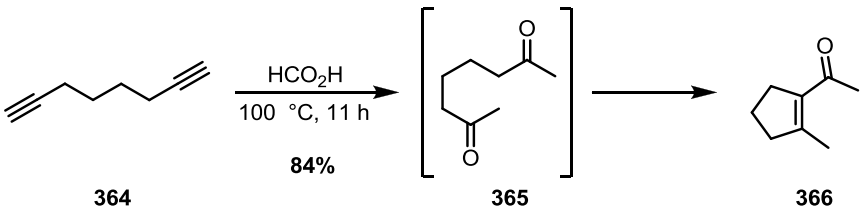
Scheme 6.19 Formic acid mediated hydration of alkynes reported by Shvo.[151]

The reaction was applicable to a range of simple hydrocarbon alkynes, giving the corresponding ketones in excellent yield. Mechanistically, Shvo proposed that the reaction proceeded *via* an initial protonation of the alkyne **360** to give the intermediate enol formate **363** on trapping of carbocation **362** with formic acid. Subsequent hydrolysis of the enol formate **363** yielded ketone **361**, the formal alkyne hydration product, Scheme **6.20**.[151]



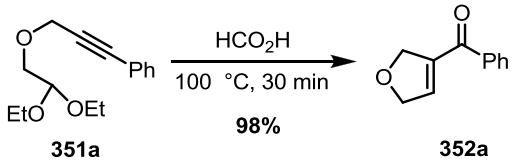
Scheme 6.20 Shvo's proposed mechanism for the formic acid mediated hydration of alkynes.[151]

An intriguing result in the paper revealed that hydration of 1,7-octadiyne **364**, did not give the expected diketone **365**, but proceeded to give 1-acetyl-2-methylcyclopentene **366** in 84% yield. The transformation was proposed to proceed *via* the intermediacy of diketone **365** which underwent an intramolecular aldol condensation/dehydration sequence in the acidic media, Scheme **6.21**.[151]



Scheme 6.21 Intramolecular cyclisation of 1,7-octadiyne **364** in formic acid.[151]

It was proposed that formic acid could potentially be used in the synthesis of the indolizidine core unit. In order to test the viability of the route, we initially investigated the cyclisation of model substrate **351a**. After heating a sample of alkyne **351a** in formic acid at 100 ºC for 2 h, the cyclisation product **352a** was isolated as a crystalline solid in essentially quantitative yield on removal of the formic acid.



Scheme 6.22 Cyclisation of alkyne **351a** in formic acid.

Analysis of the material by ^{1}H NMR spectroscopy showed the product to be homogeneous, requiring no additional purification. Subsequently, it was found that quantitative conversion was observed in 30 min at reflux giving the cyclised product **352a** in 98% yield, Scheme **6.22**. On repeating the reaction at room temperature, the cyclisation product **352a** was again isolated in 98% yield, however, the reaction time was significantly increased (~24 h).

6.7 Mechanism of the Formic Acid Mediated Cyclisation Reaction

Interestingly, it was found that if the reaction was stopped after 15 min at room temperature, 4 species were apparent by in the ^{1}H NMR spectrum of the unpurified reaction mixture. Two sets of signals were attributed to unreacted starting material **351a** and the cyclised product **352a**. The other two sets of signals were attributed to intermediates in the cyclisation reaction.

Although both compounds were found to be unstable, attempts to separate the products by column chromatography provided samples of each product of sufficient purity to fully characterise them. The ^{1}H NMR spectrum of the first compound showed two sets of diastereomeric protons, as well as two CH_2 carbons apparent in the ^{13}C DEPT spectrum. A signal at 8.14 ppm in the ^{1}H NMR spectrum suggested the presence of a formyl group. A broad peak at 3396 cm^{-1} in the IR spectrum was consistent with a hydroxyl group. Based on the spectroscopic data, the structure was proposed as enol formate **367** (Figure **6.3**).

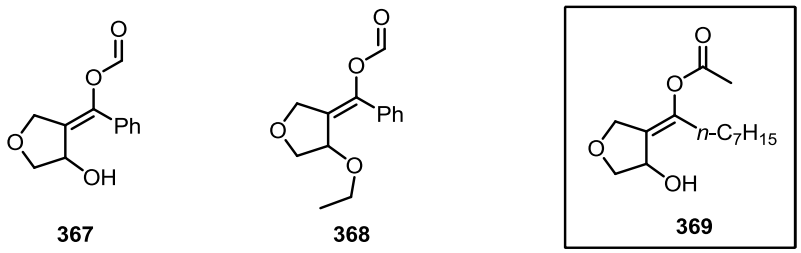
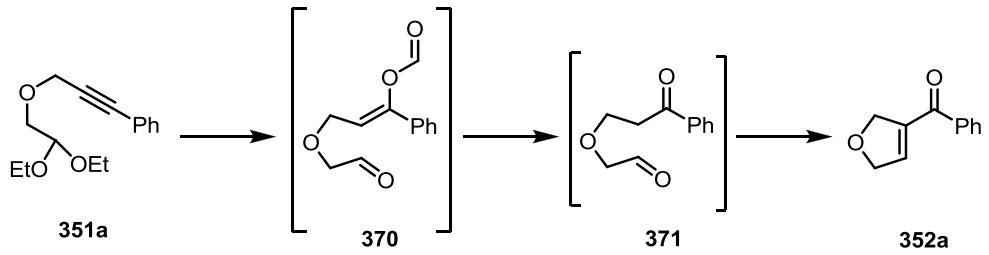


Figure 6.3 Intermediates **367** and **368** isolated in the formic acid cyclisation reaction.

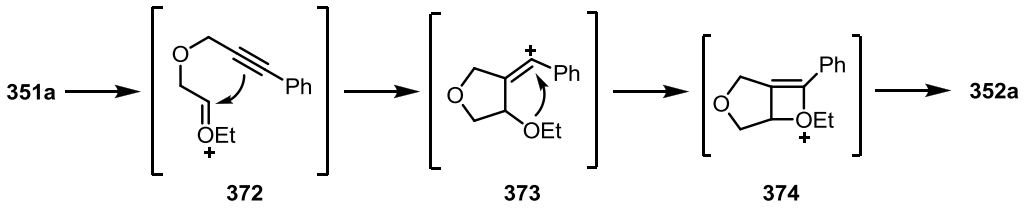
Similarities between the two products suggested the second compound was the analogous ethoxy-derivative **368** with additional signals corresponding to the ethyl group observed in the ^{1}H and ^{13}C NMR spectra. HRMS analysis showed molecular ions corresponding to the two products, however, other species were also observed suggesting the compounds were unstable under HRMS conditions. Although, both the isolated intermediates were novel, a structurally similar compound **369** was previously isolated by Lu *et al.* during studies on the palladium-catalysed cyclisation reactions of alkyne/aldehydes.[140]

When considering the cyclisation reaction, a number of plausible mechanisms could be proposed, Scheme **6.23-6.25**. Mechanism A proceeds according to the sequence proposed by Shvo.[151] An initial formic acid mediated alkyne hydration gives the intermediate formate ester **370**, which upon hydrolysis, undergoes an acid-mediated aldol condensation/dehyderation sequence to yield the cyclised product **352a**, Scheme **6.23**.



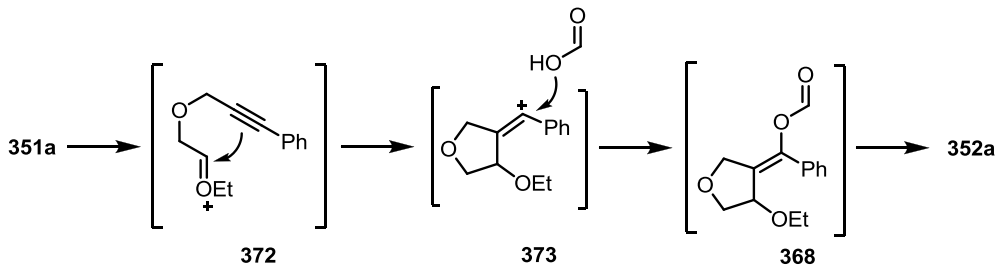
Scheme 6.23 Cyclisation of alkyne/acetal **351a** *via* an intial alkyne hydration (Mechanism A).

Alternatively, the reaction could proceed *via* an oxete intermediate **374** (Mechanism B) as proposed by Harding,[152] and more recently Krische and Li,[139, 153] Scheme **6.24**. Alkyne addition to oxonium ion **372** and subsequent intramolecular cyclisation would give oxete **374** which can rearrange to yield the unsaturated ketone **352a**.



Scheme 6.24 Cyclisation of alkyne/acetal **351a** *via* oxete intermediate **374** (Mechanism B).

Finally, the reaction could proceed *via* addition of the alkyne to the oxonium ion **372** consistent with the Prins-type process proposed in Mechanism B. However, in this instance, the resulting carbocation **373** is trapped with formic acid to yield the formate ester **368**, which hydrolyses to give the unsaturated product **352a**, Scheme **6.25**.[141, 147]



Scheme 6.25 Prins-type cyclisation of alkyne/acetal **351a** *via* enol formate intermediate **368** (Mechanism C).

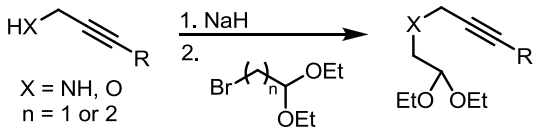
The isolation of intermediates **367** and **368** in reactions carried out at room temperature would suggest that under these conditions, Mechanism C is operative, proceeding *via*

oxonium ion **372** or the corresponding aldehyde formed on *in situ* acetal hydrolysis. ReactIR studies could provide further insights into the mechanism of the reaction, however, due to time constraints we did not carry out this investigation.

The selectivity for the 5-membered *exo*-cyclic ketone **352a** can be accounted for by the kinetic preference for the formation of a 5-membered ring, rather than the 6-membered *endo*-cyclic ketone. The carbocation formed could also be stabilised by the aromatic π-system, providing additional benefit for the formation of the 5-membered product.

6.8 Scope of the Formic Acid Mediated Cyclisation

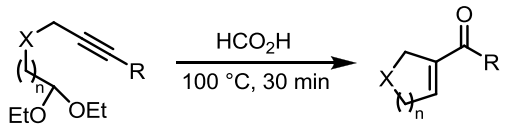
Having developed a procedure for the synthesis of α,β-unsaturated carbonyl compounds using a formic acid mediated alkyne-acetal cyclisation we were keen to explore the scope of the reaction. A range of substrates were prepared *via* alkylation of the corresponding propargylic alcohols or amines, Scheme **6.26**.



349 **351**

Scheme 6.26 Synthesis of alkyne/acetal cyclisation substrates **351**.

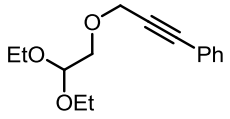
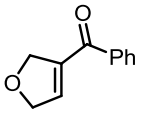
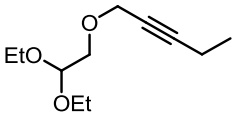
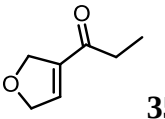
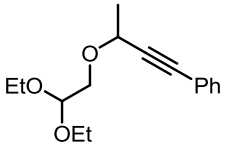
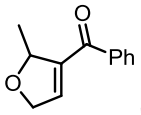
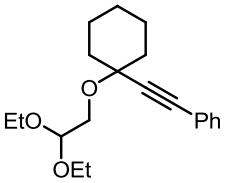
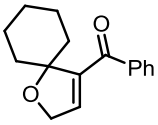
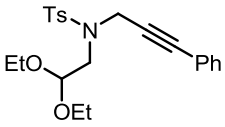
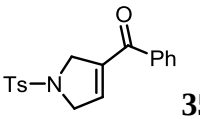
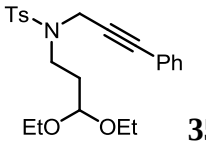
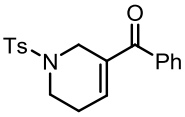
Each substrate was heated in formic acid at 100 ºC for 30 min. (Scheme **6.27**), with results shown in Table **6.1**.



351 **352**

Scheme 6.27 Scope of the formic acid mediated cyclisation.

Table 6.1 Scope of the formic acid mediated alkyne/acetal cyclisation.[a]

Entry	Substrate (351)	Product (352)	Yield[b]
1	 **351a**	 **352a**	98% (98%)[c]
2	 **351b**	 **352b**	70%
3	 **351c**	 **352c**	80%
4	 **351d**	 **352d**	64%
5	 **351e**	 **352e**	77%
6	 **351f**	 **352f**	69%

[a] All reactions were performed on 0.25 mmol scale in formic acid (1 mL).

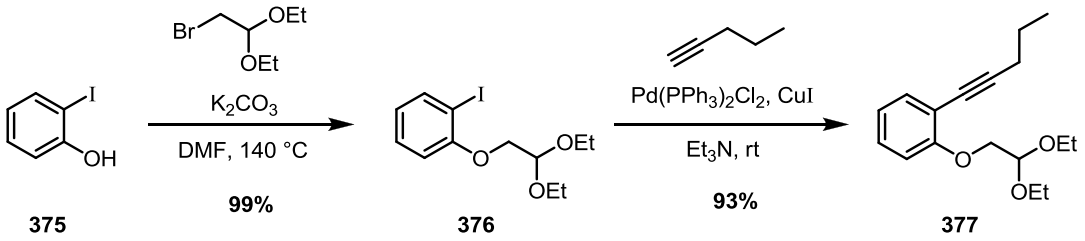
[b] Isolated yields after column chromatography.

[c] Reaction carried out at room temperature.

The phenyl-substituted alkyne **351a** used in preliminary studies cyclised to give the corresponding unsaturated ketone **352a** in 98% yield (entry 1). The cyclisation was not just applicable to phenyl-substituted alkynes, the ethyl ketone **352b** was also prepared in a reasonable 70% yield (entry 2). Substituted alkynes were also tolerated in the cyclisation reaction; the methyl-substituted dihydrofuran **352c** was prepared in 80% yield and the spirocyclic derivative **352d** was prepared in 64% yield (entries 3 and 4). The reaction conditions were not just amenable to the synthesis of oxygen heterocycles, the 5 and 6-membered *N*-tosyl analogues **352e** and **352f** were also prepared in 77% and 69% yield respectively (entries 5 and 6).

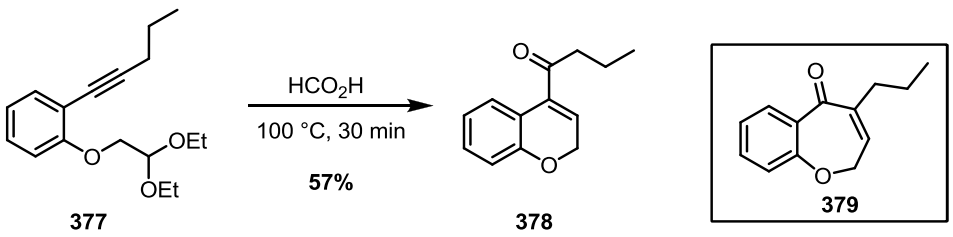
6.8.1 Aromatic-Substituted Heterocycles

In the final part of this study, we investigated the synthesis of aromatic-substituted heterocycles. Alkylation of 2-iodophenol **375** with bromo acetaldehyde diethyl acetal gave acetal **376** in 99% yield. Sonogashira coupling of acetal **376** with 1-pentyne gave the cyclisation precursor **377** in 93% yield, Scheme **6.28**.



Scheme 6.28 Synthesis of phenol derived alkyne **377**.

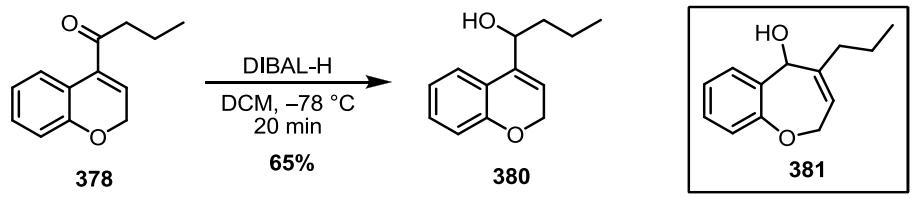
On subjecting acetal **377** to the cyclisation conditions the formation of a single product was apparent on TLC analysis, which was isolated in 57% yield after purification, Scheme **6.29**.



Scheme 6.29 Cyclisation of phenol derived alkyne/acetal **377**.

The HRMS data were consistent with the expected product **378**, however, the ^{1}H NMR spectroscopic data were inconclusive regarding the structure of the product. Although previous examples had cyclised to give the corresponding *exo*-cyclic ketones, it was also conceivable that the reaction had proceeded to give the *endo*-cyclic ketone **379**. Inspection of the 2D NMR spectroscopic data suggested the product was the 6-membered *exo*-cyclic ketone **378**. HMBC correlations between the carbonyl and propyl side chain were observed, however, no correlations with the aromatic ring were seen. Subsequent work by Unsworth confirmed the structure as the 6-membered product **378**;[154] reduction with DIBAL-H gave the corresponding alcohol **380**, the data for

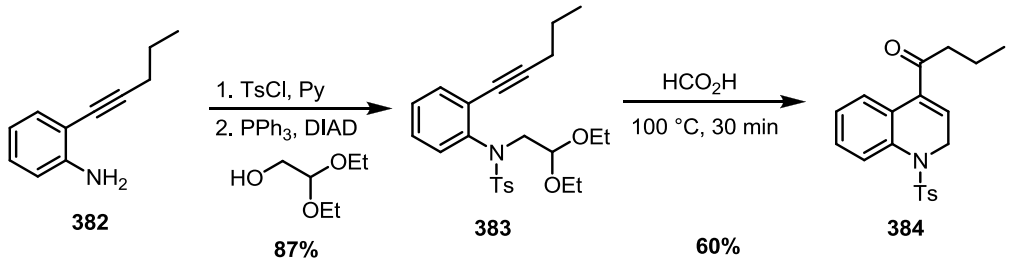
which were consistent with the *exo*-cyclic product **380**, Scheme **6.30**. A correlation between the proton adjacent to the hydroxy group and the propyl side chain was also evident in the COSY spectrum.



378 **380** **381**

Scheme 6.30 Reduction of *exo*-cyclic ketone **378**.[154]

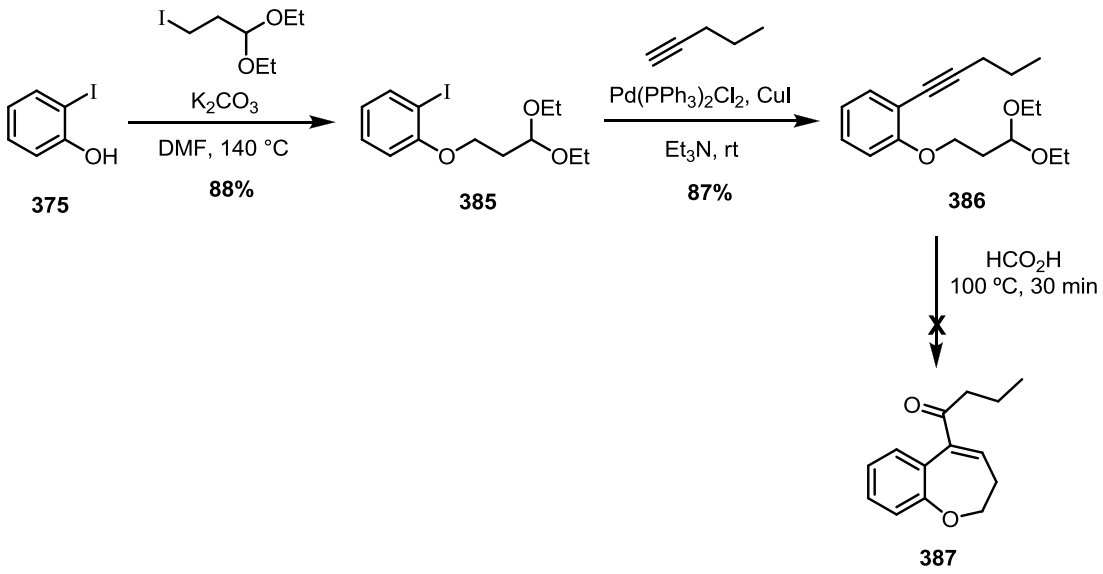
The same reaction conditions were also applied to the analogous *N*-tosyl substrate **384**, prepared in 2 steps from 2-pentynyl aniline **382**. Treatment with tosyl chloride and pyridine gave the corresponding *N*-tosyl aniline, which was coupled with glycol aldehyde diethyl acetal under Mitsunobu conditions to give the cyclisation precursor **383** in 87% over 2 steps. Treatment with formic acid gave the 1,2-dihydroquinoline **384** in 60% yield, Scheme **6.31**.



382 **87%** **383** **60%** **384**

Scheme 6.31 Cyclisation of the aniline derived alkyne/acetal **383**.

Unfortunately, attempts to extend the methodology to enable the synthesis of 7-membered oxepine analogues were unsuccessful. Whilst a model substrate **386** could be readily accessed using the previously developed sequence, Scheme **6.32**, heating alkyne **386** in formic acid gave a complex mixture of unidentifiable products.

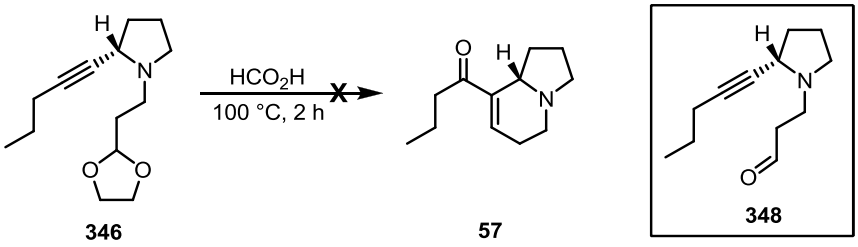


Scheme 6.32 Synthesis of oxepine cyclisation precursor **386** and attempted cyclisation.

6.9 Applications of Alkyne/Acetal Cyclisation Reactions in the Synthesis of Indolizidine Alkaloids

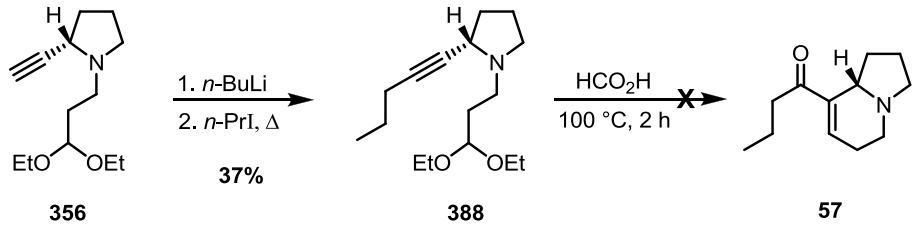
Having demonstrated the utility of the formic acid alkyne/acetal cyclisation in the synthesis of a range of oxygen and nitrogen heterocycles, we were keen to apply the methodology to the synthesis of the indolizidine core unit in grandisine B **15**.

Initially, the transformation was applied to the synthesis of elaeokanine A **57** using the previously prepared cyclic acetal **346**. When subjected to the cyclisation conditions the formation of predominantly one product was apparent by TLC analysis. Disappointingly, the ^{1}H NMR spectroscopic data suggested the major product was aldehyde **348**, formed by hydrolysis of the cyclic acetal, Scheme **6.33**.



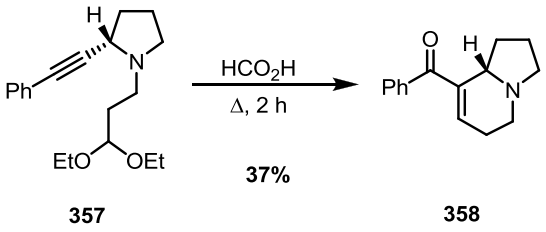
Scheme 6.33 Attempted synthesis of elaeokanine A **57** *via* an alkyne/acetal cyclisation.

The corresponding diethyl acetal **388** was prepared from alkyne **356**, Scheme **6.34**. Deprotonation of alkyne **356** with *n*-BuLi and trapping with *n*-propyl iodide gave the cyclisation precursor **388** in 37% yield. Disappointingly, when diethyl acetal **388** was subjected to the cyclisation conditions the formation of a number of products was apparent by TLC analysis, however, no evidence of the cyclisation product **57** was observed in the ^{1}H NMR spectrum of the unpurified reaction mixture.



Scheme 6.34 Attempted synthesis of elaeokanine A **57** *via* diethyl acetal **388**.

The reaction was also repeated with the phenyl substituted alkyne **357**. In an initial small-scale reaction, heating alkyne **357** in formic acid led to the formation of predominantly one product, observed by TLC analysis, Scheme **6.35**.



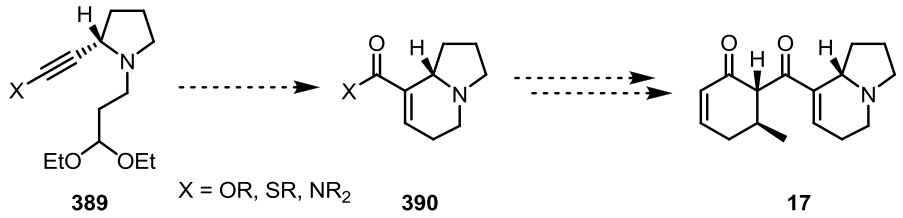
Scheme 6.35 Cyclisation of phenyl substituted alkyne **357**.

On inspection of the ^{1}H NMR spectroscopic data for the unpurified product, signals corresponding to indolizidine **358** were apparent, in particular, a mutliplet at 6.55 ppm was consistent with the unsaturated ketone. On scale-up the phenyl-susbstituted indolizidine derivative **358** was isolated in an unoptimised 37% yield.

6.10 Cyclisations of Heteroatom Substituted Alkynes

Although the cyclisation reaction had shown promise on the phenyl substituted alkyne **357**, attempts to cyclise aliphatic substituted alkynes had proved unsuccessful.

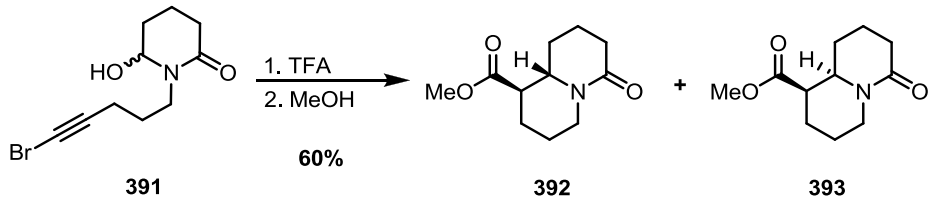
Alternative alkyne substitutuents, which could be used as a handle to further elaborate the indolizidine core unit, were therefore considered, Scheme **6.36**.



Scheme 6.36 Proposed synthesis of grandisine D **17**.

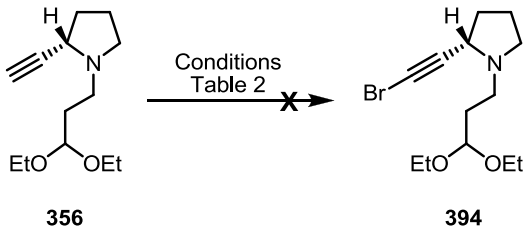
6.10.1 Bromo-Alkynes

A paper by Gesson and co-workers reported the use of bromo alkynes in *N*-acyliminium ion cyclisations to give methyl esters **392** and **393** on methanolysis, Scheme **6.37**.[155]



Scheme 6.37 Gesson's *N*-acyliminium ion cyclisation using bromo-alkyne **391**.[155]

Disappointingly, attempts to prepare the bromo-alkyne **394** using a range of reported conditions proved unsuccessful,[156-158] Scheme **6.38**, Table **6.2**.



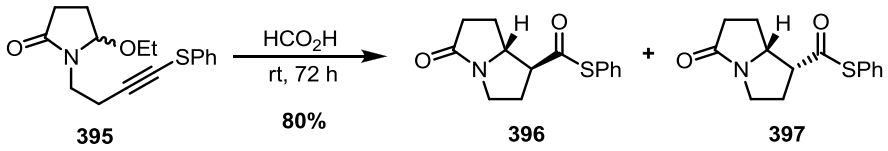
Scheme 6.38 Attempted synthesis of bromo-alkyne **394**.

Table 6.2 Attempted synthesis of bromo alkyne **394**.

Entry	Conditions	Result	Ref.
1	CBr_4, PPh_3, DCM, rt	Complex mixture	156
2	NBS, $AgNO_3$, Acetone, rt	Complex mixture	157
3	Br_2, KOH, H_2O, 0 ºC	Complex mixture	158

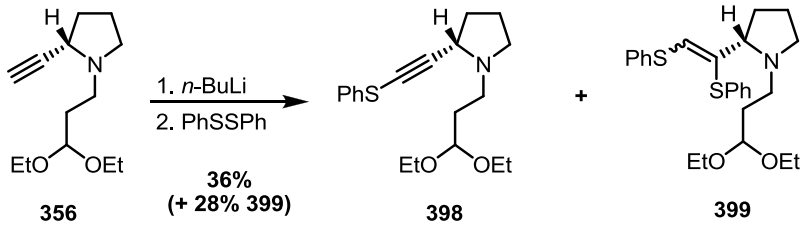
6.10.2 Thioalkynes

Publications as early as 1959 reported the conversion of thioalkynes into the corresponding thioesters on treatment with acid.[159] More recently, the transformation was used by Speckamp and co-workers in the synthesis of pyrrolizidine alkaloid derivatives **396** and **397** *via* an *N*-acyliminium cyclisation, Scheme **6.39**,[160] and also by Maruyama and co-workers in synthetic studies towards carbapenem derivatives.[161]



Scheme 6.39 Speckamp's *N*-acyliminium cyclisation using thioalkyne **395**.[160]

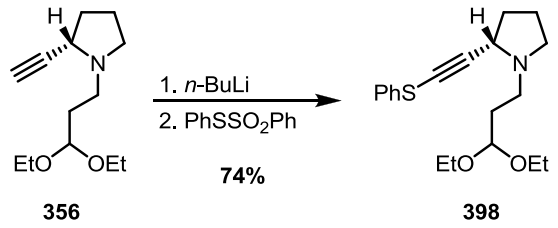
We therefore set out to prepare thioalkyne **398** in order to investigate its potential applications in the formic acid mediated cyclisation reaction. Following the procedure of Glass,[162] deprotonation of alkyne **356** with *n*-BuLi and trapping with phenyl disulfide gave the thioalkyne **398** in 57% yield. Attempts to scale up the reaction gave thioalkyne **398** in a disappointing 36% yield, along with side-product **399** formed in 28% yield, Scheme **6.40**.



Scheme 6.40 Attempted synthesis of *S*-phenyl thioalkyne **398**.

Although the structurally-related side-product still contained the pyrrolidine ring and ethyl acetal, a signal at 7.14 ppm in the ^{1}H NMR spectrum was consistent with an alkene. The aromatic region integrated to double the expected value, which was consistent with the HRMS data, which showed the molecular formula to be $C_{24}H_{33}NO_2S_2$, suggesting the incorporation of a second thiophenyl group. The structure for the side product was tentatively assigned as the dithioalkene **399** based on the molecular formula and NMR spectroscopic data, however, the mechanism by which it forms remains to be established.

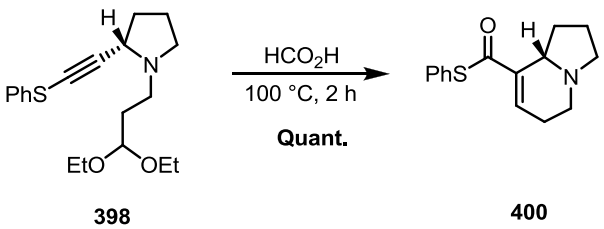
In an attempt to overcome the formation of thioalkene **399**, the reaction was repeated using *S*-phenyl benzene thiosulfonate. In this instance the desired thioalkyne was isolated in 74% yield, with no evidence of the previously observed side-product **399**, Scheme **6.41**.



356 **398**

Scheme 6.41 Synthesis of thioalkyne **398** from alkyne **356**.

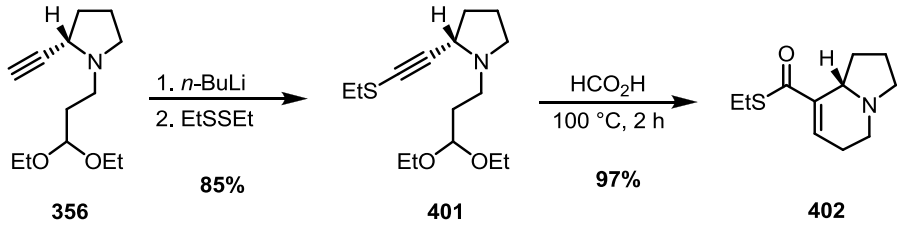
On treatment of alkyne **398** with formic acid at reflux, consumption of the starting material was observed, with the concomitant formation of a single product apparent by TLC analysis. Pleasingly, ^{1}H NMR spectroscopic analysis of the unpurified material showed the product to be the unsaturated thioester **400**, furthermore, the material was homogeneous, requiring no purification. When repeated on a larger scale the phenyl thioester **400** was isolated in quantitative yield, Scheme **6.42**.



398 **400**

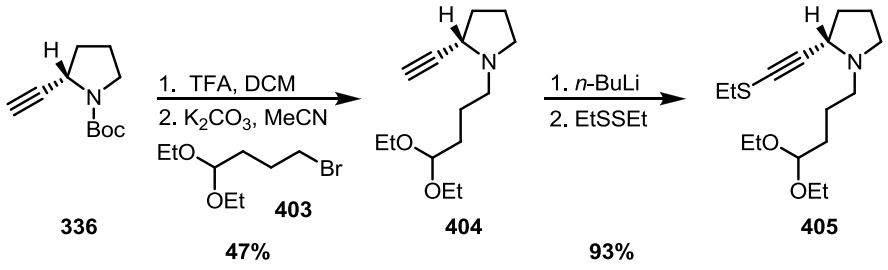
Scheme 6.42 Formic acid mediated cyclisation of *S*-phenyl thioalkyne **398**.

The reaction sequence could also be used to prepare the analogous ethyl thioester **402**, which was isolated in 82% yield over 2 steps, Scheme **6.43**.



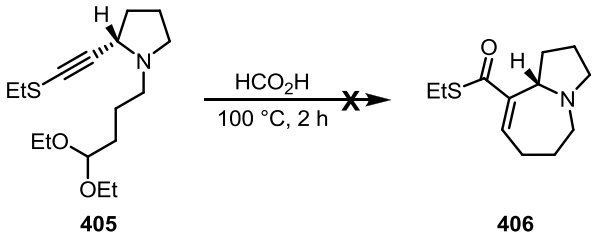
Scheme 6.43 Synthesis of indolizidine thioester **402**.

Attempts were briefly made to extend the methodology to enable the synthesis of 5,7-ring systems, a structural motif commonly encountered in alkaloids isolated from plants of the *Stemonaceae* family.[163] The required cyclisation precursor **405** could be readily accessed using the sequence described previously. Deprotection of proline alkyne **336** and subsequent alkylation with bromide **403**, prepared in 2 steps from ethyl-4-bromobutyrate, gave acetal **404** in 47% yield. Deprotonation with *n*-BuLi and trapping with diethyl disulfide gave the cyclisation precursor **405**, Scheme **6.44**.



Scheme 6.44 Synthesis of stemona alkaloid precursor **405**.

Disappointingly, on treatment with formic acid, consumption of the starting material **405** was observed, however, a complex mixture of products was apparent in the ^{1}H NMR spectrum of the unpurified material, with no evidence of the cyclisation product **400**, Scheme **6.45**.



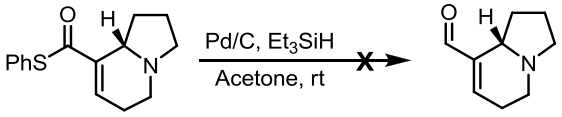
405 **406**

Scheme 6.45 Attempted synthesis of the stemona alkaloid skeleton **406** *via* an alkyne/acetal cyclisation.

Despite the initial failure to prepare the stemona alkaloid skeleton **406**, the transformation could significantly expand the utility of the cyclisation methodology and as such will be investigated further in due course.

6.11 Fukuyama Reduction of (S)-Phenyl Thioester

With thioester **400** in hand, the concluding steps in the synthesis of grandisine B **15** were investigated. We envisaged that reduction of the thioester would give the indolizidine aldehyde **172** an intermediate used previously in the racemic synthesis of grandisine B **15**. Initial attempts to reduce the thioester **400** focussed on the well precedented Fukuyama reduction, Scheme **6.46**.[164]



400 **172**

Scheme 6.46 Attempted reduction of thioester **400** under Fukuyama conditions.[164]

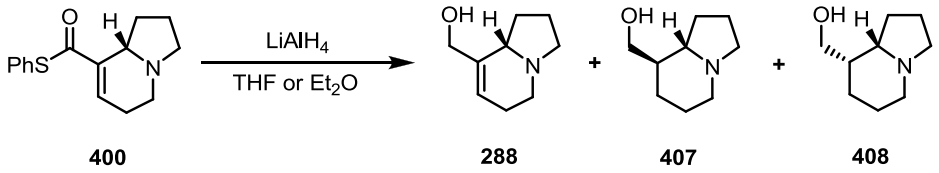
Treatment of thioester **400** with Pd/C and triethylsilane in acetone gave no evidence of the desired aldehyde **172** after holding overnight at room temperature. Repeating the reaction in DCM, using conditions reported by Winssinger,[165] also proved unsuccessful. Conditions for the reduction using other palladium sources such as $Pd(PPh_3)_4$ also failed to give the desired aldehyde **172**. It was proposed that traces of thiophenol in the starting material may be poisoning the catalyst, however, a procedure using a high catalyst loading of $Pd(OAc)_2$ (50 mol%) reported by Eberle also proved unsuccessful, giving only a trace of aldehyde **172** after prolonged reaction at room temperature.[166] Subjecting thioester **400** to standard hydrogenation conditions (Pd/C, H_2) showed

neither reduction of the thioester or the double bond, providing further evidence that catalyst poisoning could be the problem.

6.12 Alternative Methods for the Reduction of Thioester (400)

Due to unsuccessful attempts to reduce the phenyl thioester **400** to aldehyde **172** using Fukuyama reduction conditions, methods for reducing thioester **400** directly to the allylic alcohol **288** were considered. Treatment of thioester **400** with $NaBH_4$ in methanol or ethanol resulted in the formation of a number of products apparent by TLC analysis. Although attempts to separate the products proved unsuccessful, the ^{1}H NMR spectroscopic data suggested the products were 1,4-reduction products, with no evidence of allylic alcohol **288**. Interestingly, when the reduction was carried out in the presence of cerium(III) chloride heptahydrate using Luche conditions, no reaction was observed, with starting material recovered on work-up.

More promising results were observed when lithium aluminium hydride was used as the reductant. In an initial small-scale reaction, treatment of thioester **400** with lithium aluminium hydride gave a mixture of indolizidine alcohol **288**, along with the two 1,4-reduction products **407** and **408**, the ^{1}H NMR spectroscopic data for which corresponded to the natural products tashiromine **407** and *epi*-tashiromine **408**.[167] On scale-up, a similar product ratio was observed, but we were unable to separate indolizidine alcohol **288** from the 1,4-reduction products **407** and **408**, Scheme **6.47**.



400 **288** **407** **408**

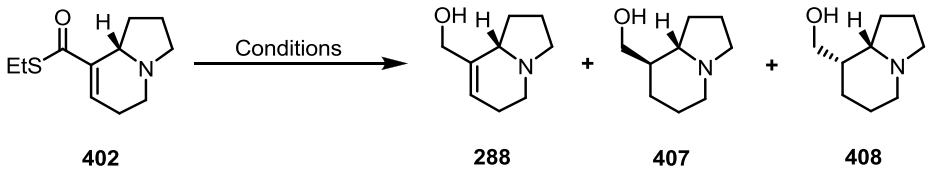
Scheme 6.47 Attempted reduction of thioester **400** with $LiAlH_4$.

Although alcohol **288** could not be isolated cleanly, a sample of tashiromine **407** was isolated. The optical rotation of synthetic tashiromine **407** was consistent with that reported in the literature for the natural product [−42.6 (*c* 1.08, EtOH); Lit.[167] +44.7 (*c* 1.1, EtOH)] suggesting no loss of enantiomeric purity throughout the synthesis.

Conditions reported by Wang,[168] for the selective reduction of unsaturated esters, using lithium aluminium hydride and benzyl chloride to generate AlH_3 *in situ*, also failed to yield alcohol **288**. Difficulties were also encountered when DIBAL-H was used as the reductant, which gave inseperable mixtures of 1,4 and 1,2-reduction products under a range of conditions.

Treatment of thioester **400** with Raney Nickel in ethanol/ether resulted in complete reduction of the unsaturated indolizidine core unit to give a complex mixture of 1,4 and 1,2-reduction products, including tashiromine **407**. Repeating the reaction in refluxing acetone also resulted in complete consumption of the starting material, to give a complex mixture of unidentified products. In an alternative procedure, Raney Nickel was first deactivated by heating at reflux in acetone. Disappointingly, no reduction of the thioester **400** was observed under these conditions, giving only starting material on work-up.

Due to unsuccessful attempts to reduce the phenyl thioester **400**, attempts were made to reduce the analogous ethyl thioester **402**. When subjected to the conditions previously investigated for the reduction of the phenyl thioester **400**, the same difficulties were encountered. In most instances, the desired 1,2-reduction product was isolated as a mixture with conjugate reduction products and unreacted starting material, Scheme **6.48**.



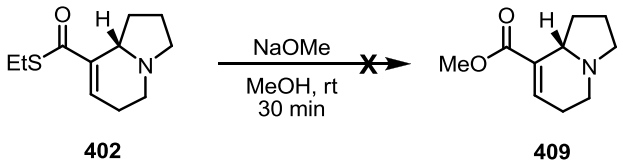
402 **288** **407** **408**

Scheme 6.48 Attempted reduction of ethyl thioester **402**.

6.13 Conversion of Ethyl Thioester (402) into Methyl Ester (409)

In order to overcome the problems encountered with the reduction of the thioester, we proposed that conversion into the known methyl ester **409** and subsequent reduction would provide access to the indolizidine alcohol **288**.[169]

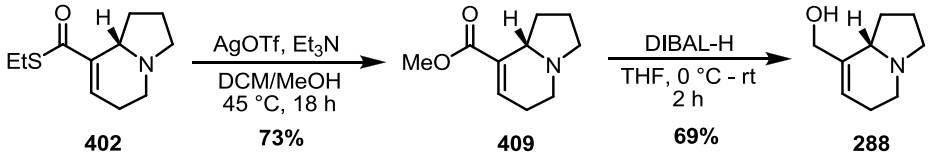
On treating ethyl thioester **288** with sodium methoxide in methanol, following the procedure of Krische,[170] the formation of a second species was noted on TLC analysis. ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture showed the presence of the desired methyl ester **409** and unreacted starting material, along with minor impurities. Attempts to push the reaction to completion using excess sodium methoxide were unsuccessful, generally resulting in the formation of a number of impurities, Scheme **6.49**.



402 **409**

Scheme 6.49 Attempted synthesis of methyl ester **409** using conditions reported by Krische.[170]

A reaction using silver(I) trifluoromethanesulfonate in DCM/methanol following the procedure of Hanessian,[171] gave more promising results. In an initial reaction, whilst complete consumption of the starting material **402** was not observed, the unpurified mixture contained only the desired product **409** and unreacted starting material **402** in a 4:1 ratio. It was subsequently found that if the reaction was carried out at 45 ºC in the presence of triethylamine, complete consumption of the starting material was observed, giving methyl ester **409** in 73% yield after purification, Scheme **6.50**.



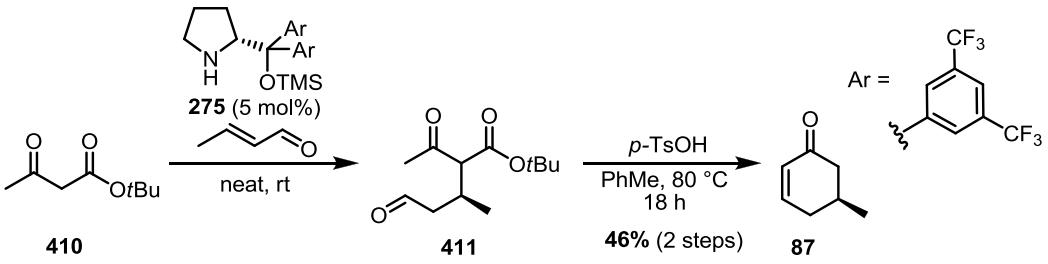
402 **73%** **409** **69%** **288**

Scheme 6.50 Synthesis of indolizidine alcohol **288** from ethyl thioester **402**.

Reduction of methyl ester **409** following the procedure of Brandi, proceeded as reported to give indolizidine alcohol **288** in 69% yield (Lit.[169] 65%).

6.14 Synthesis of (S)-5-methylcyclohexenone (87)

With indolizidine alcohol **288** in hand, (*S*)-5-methylcyclohexenone **87** was prepared using the procedure of Jørgensen,[105] *via* the organocatalysed conjugate addition of *tert*-butyl acetoacetate into crotonaldehyde and subsequent *p*-TsOH-catalysed ring-closure/decarboxylation, Scheme **6.51**.

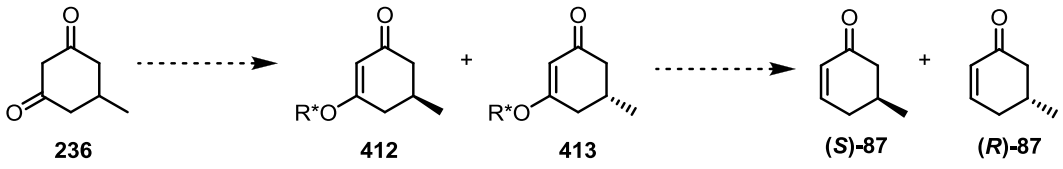


Scheme 6.51 Jørgensen's synthesis of (*S*)-methyl cyclohexenone **87**.[105]

The optical rotation for the synthetic material [(+70.0 (*c* 0.52, $CHCl_3$))] was similar to that reported by Jørgensen [(Lit.[105] −74.6 (*c* 0.5, $CHCl_3$))], suggesting the enantiomeric excess was approximately 80%, however, yields for the procedure were significantly lower than those published (Lit.[105] 93%).

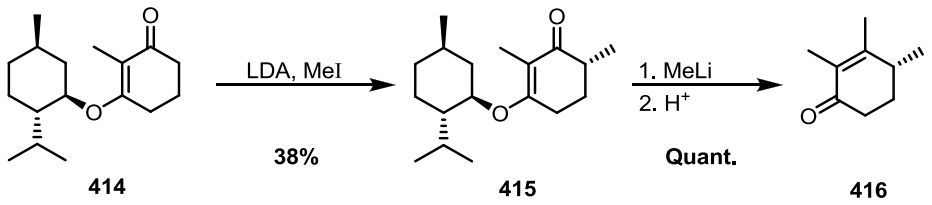
6.14.1 Resolution Approach to (S)-Methylcyclohexenone (87)

An alternative resolution-based approach to methylcyclohexenone **87** was also briefly considered. We envisaged that condensation of 5-methyl-1,3-cyclohexanedione **236** with an enantiomerically pure alcohol would afford a diastereomeric mixture of enones **412** and **413**. Separation of the diastereoisomers and subsequent treatment with lithium aluminium hydride would enable rapid access to both enantiomers of methylcyclohexenone **87**, Scheme **6.52**.



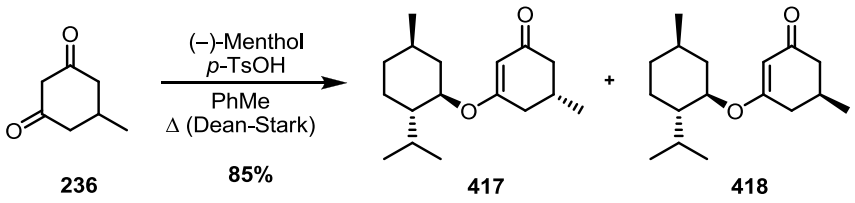
Scheme 6.52 Proposed synthesis of 5-methylcyclohexenone **87**.

A similar strategy was used by Danheiser *et al*. in their synthesis of the natural product ascochlorin.[172] Alkylation of the menthol-derived alkoxy ketone **414** *via* treatment with lithium di*iso*propyl amide and methyl iodide, gave a diastereomeric mixture of enones **415** which were separable by fractional crystallisation. Treatment with MeLi and subsequent acidic hydrolysis gave the enantiomerically pure ketone **416**, Scheme **6.53**.[172]



Scheme 6.53 Selected steps in Danheiser's synthesis of ascochlorin.[172]

On treatment of 1,3-diketone **236** with (−)-menthol and catalytic *p*-TsOH in toluene, the diastereomeric alkoxy enones **417** and **418** were obtained as a 1:1 mixture, Scheme **6.54**. Unfortunately, all efforts to separate the diastereoisomers *via* chromatography or crystallisation were unsuccessful, negating the possibility of using the sequence in the synthesis of enantiomerically pure (*S*)-5-methylcyclohexenone **87**.

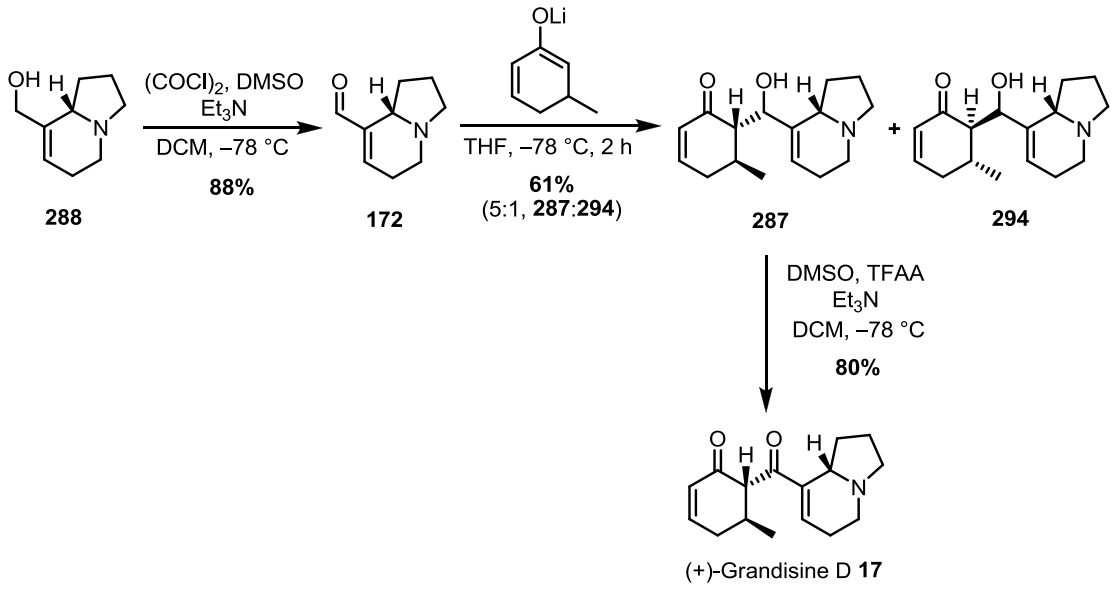


Scheme 6.54 Synthesis of diastereomeric alkoxy enones **417** and **418**.

It was subsequently found that samples of the diastereomeric enones **417** and **418** partially crystallised on standing for prolonged periods. Analysis of the crystalline material by ^{1}H NMR spectroscopy showed the sample to be enriched in one diastereoisomer, however, due to the high solubility of the compounds in most solvents, attempts to exploit the difference in crystallinity for the separation of the two diastereoisomers proved unsuccessful. Although not applicable to the synthesis of 5-methyl-cyclohexenone **87**, the route could provide a useful method for the separation of other cyclohexenone derivatives.

6.15 The Synthesis of (+)-Grandisine D (17)

Following the sequence developed for the racemic synthesis of grandisine B **15**, oxidation of indolizidine alcohol **288** under Swern conditions gave the unstable aldehyde **172** in 88% yield, which was used immediately without purification (decomposition of aldehyde **172** was observed on storage). The aldol reaction of aldehyde **172** with the lithium enolate of (*S*)-5-methylcyclohexenone **87**, formed on treatment with LDA, proceeded to give the alcohol **287** along with small amounts of the diasteromeric alcohol **294** derived from (*R*)-5-methylcyclohexenone. We were unable to determine the stereochemistry of the aldol products **287** and **294** from the NMR spectroscopic data, however this was unimportant as the stereochemistry was lost in the proceeding step. Oxidation of hydroxyl-ketone **287** using modified Swern conditions gave grandisine D **17** in 80% yield, Scheme **6.55**.

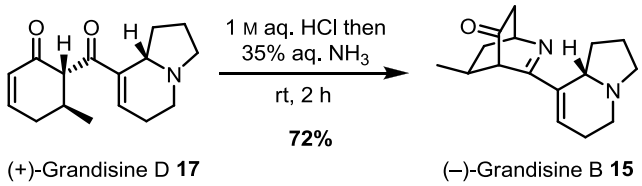


Scheme 6.55 Concluding steps in the synthesis of grandisine D **17**.

Conversion of grandisine D **17** into its TFA salt allowed comparison with the literature data which were identical to those reported in all aspects but optical rotation. Although our value [(+73.7 (*c* 0.1, MeOH))] was consistent with that reported by Tamura [(+65.7 (*c* 0.09, MeOH))],[25] the value reported for the natural product was considerably lower [(+34.6 (*c* 0.09, MeOH))],[10] which we attributed to the natural product being of a lower degree of purity.

6.16 The Synthesis of (−)-Grandisine B (15)

In the racemic series, we reported that the cyclisation of grandisine D **17** to give grandisine B **15** did not proceed with 35% aqueous ammonia. It was subsequently found that on treatment with 35% aqueous ammonia, a solution of grandisine D **17** in 1 M aqueous hydrochloric acid was readily converted into (−)-grandisine B **15**, which was isolated in 72% yield after purification, Scheme **6.56**. The optimised reaction procedure was similar to conditions used during the isolation process providing evidence to support the theory that grandisine B **15** is an artefact of the isolation process as discussed previously in Chapter 5.

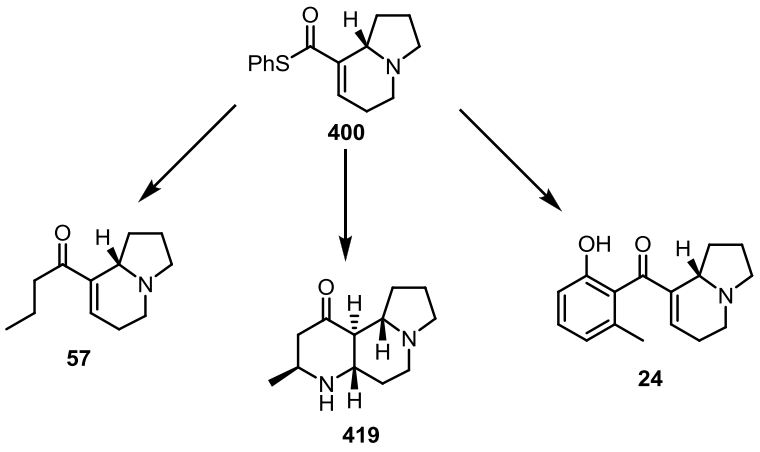


Scheme 6.56 Conversion of grandisine D **17** into grandisine B **15**.

The NMR spectroscopic data were consistent with those published in the isolation paper and the recent publication by Tamura and co-workers,[9, 55] however, discrepancies were again noted between Carroll and Tamura regarding the optical rotation of grandisine B **15** [(Lit.[9] +11 (*c* 0.1, DCM)); (Lit.[55] −159 (*c* 0.08, DCM))]. The optical rotation of our synthetic material [(−177.5 (*c* 0.08, DCM))] was consistent with that reported by Tamura, suggesting an error in the value reported in the original isolation paper.

6.17 Applications of Thioester (400) in the Synthesis of Other Elaeocarpus Alkaloids

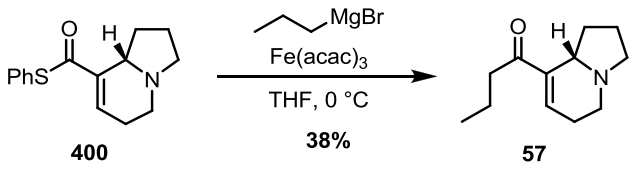
With the synthesis of (−)-grandisine B **15** complete, we were in a position to investigate the synthesis of other *Elaeocarpus* alkaloids using methodology developed over the course of this project. We envisaged that the indolizidine thioester **400** could function as a general precursor to other indolizidine alkaloids as shown in Scheme **6.57**.



Scheme 6.57 Potential applications of thioester **400** in the synthesis of other *elaeocarpus* alkaloids.

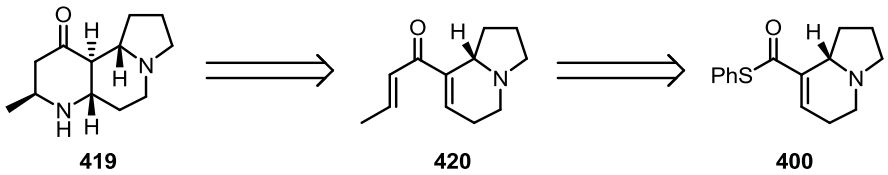
6.18 Addition of Grignard Reagents to Thioester (400)

We initially chose to investigate the coupling of thioesters with Grignard reagents in the presence of iron catalysts as reported by Marchese,[173, 174] which we envisaged would provide access to ketones such as elaeokanine A **57**. Pleasingly, in an initial experiment, treatment of thioester **400** with propyl magnesium chloride in the presence of iron(III) acetylacetonate, the desired product elaeokanine A **57** was isolated in an unoptimised 38% yield, Scheme **6.58**.



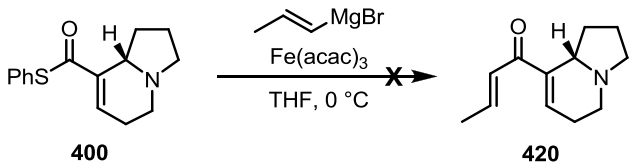
Scheme 6.58 Synthesis of elaeokanine A **57** *via* Grignard addition to thioester **400**.

Although low yielding, we were encouraged by this initial result. The more complex target, elaeokanidine A **419**, isolated from the *Elaeocarpus kaniensis* by Lamberton and co-workers in 1972,[33] was selected to further test the utility of thioester **400**. Retrosynthetically, we proposed that elaeokanidine A **57** could be obtained from enone **420**, which could be accessed *via* addition of propenyl magnesium bromide to thioester **400**, Scheme **6.59**.



Scheme 6.59 Retrosynthesis of elaeokanidine A **419**.

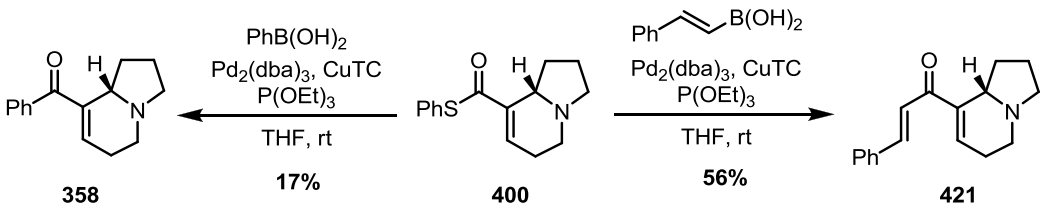
Attempts to add propenyl magnesium bromide into thioester **400** following the reported conditions failed to give the expected enone **420**, yielding only unreacted starting material on work-up, Scheme **6.60**. The reaction was also repeated with allyl magnesium bromide, which we proposed could be isomerised to give enone **420**. Disappointingly, only recovered starting material was observed in the ^{1}H NMR spectrum of the unpurified reaction mixture.



Scheme 6.60 Attempted addition of propenyl magnesium bromide into thioester **400**.

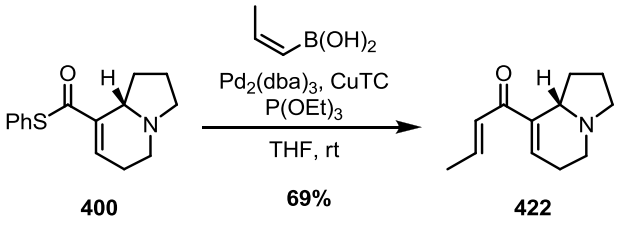
6.19 A Liebeskind-Srogl Approach to Elaeokanidine A (419)

An alternative route to enone **420** was proposed using the Liebeskind-Srogl coupling reaction.[175] We envisaged that coupling of thioester **400** with propenyl boronic acid would provide access to the enone **420**. Initially the reaction was attempted with phenyl boronic acid in order to test the viability of the route. Coupling of thioester **400** using conditions reported by Liebeskind[176] gave phenyl indolizidine **358** in an unoptimised 17% yield. The transformation was also applicable to the synthesis of the styrenyl analogue **421** which was isolated in 56% yield, Scheme **6.61**.



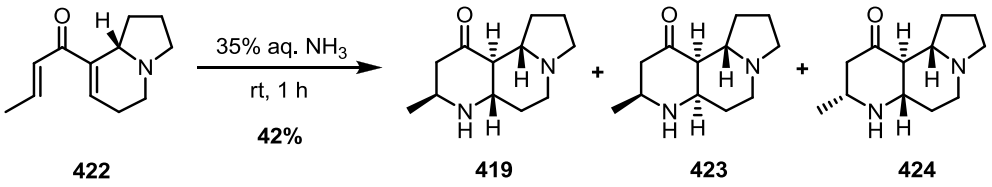
Scheme 6.61 Liebeskind-Srogl coupling of thioester **400** with phenyl and styrenyl boronic acid.

On subjecting thioester **400** to the cross-coupling conditions with *cis*-propenyl boronic acid, we were pleased to observe the formation of a new product on TLC analysis. Analysis of the unpurified reaction mixture using ^{1}H NMR spectroscopy, revealed the desired product **422** as a mixture of *cis* and *trans*-isomers. However, after purification on silica, only *trans*-**422** was isolated, which was attributed to isomerisation on the acidic media, Scheme **6.62**.



Scheme 6.62 Liebeskind-Srogl coupling of thioester **400** with *cis*-propenyl boronic acid.

On scale-up the enone **422** was isolated in 69% yield, containing a small amount of an inseparable impurity. Due to time constraints we felt it would be instructive to investigate the final step using the impure material. We envisaged that on treatment with aqueous ammonia, a double conjugate addition of ammonia would occur to give the piperidone skeleton. With limited quantitites of the enone **422** available, the conditions developed for the synthesis of grandisine B **15** were initially investigated. Dissolving the precursor enone **422** in 1 M aqueous HCl and subsequent treatment with aqueous ammonia, led to the rapid consumption of starting material, with formation of a number of products apparent by TLC analysis, Scheme **6.63**.



Scheme 6.63 Synthesis of elaeokanidine A **419** *via* a double conjugate addition of ammonia.

The ^{1}H NMR spectrum of the unpurified reaction mixture showed peaks consistent with the expected product **419**, isolated as a complex mixture of diastereoisomers. Although the ^{1}H NMR spectra for all diastereoisomers of elaeokanidine show similarities, the C-12 proton in elaeokanidine A **419** is shifted downfield to ~3.8 ppm, relative to elaeokanidines B **423** and C **424** (~3.0 ppm).[33] Integration of this signal in the unpurified mixture suggested elaeokanidine A **419** was a minor component formed in the cyclisation reaction. In the isolation paper, Lamberton *et al*. reported the isolation of two other diastereoisomers, proposed to be the *cis*-isomer **423** and the C-12 epimer **424**,[33] which could account for the other products formed during the reaction.

Although attempts to completely separate the diastereoisomers by column chromatography were unsuccessful, we were able to obtain an enriched sample of elaeokanidine A **419** of sufficient purity for characterisation purposes. The ^{1}H NMR spectroscopic data were consistent with those reported by Lamberton.[33] Large couplings between the C-7 and C-8 protons (~10 Hz) and C-8 and C-9 protons (~10 Hz) confirmed the *trans*-stereochemistry at the ring junctions (Figure **6.4**).

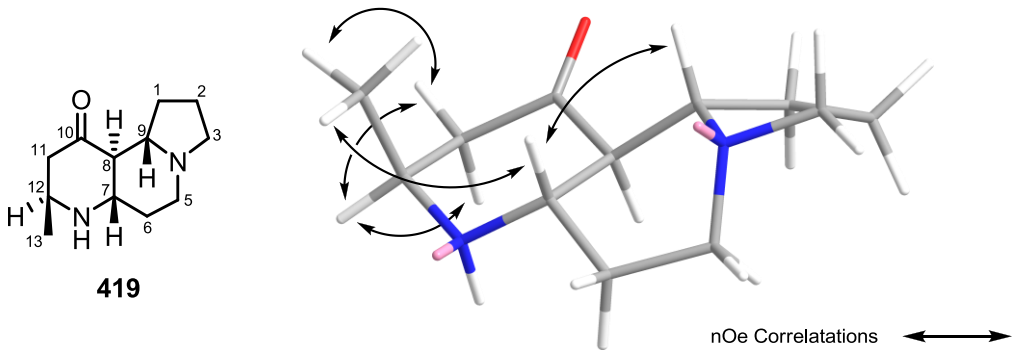


Figure 6.4 Structure of elaeokanidine A **419**.

Further evidence for the relative stereochemistry of elaeokanidine A **419** was obtained from nOe studies. Irradiation of the C-12 proton signal showed correlations to both C-

11 protons as well as the C-13 methyl group, suggesting the proton was in an equatorial conformation. On irradiation of the C-7 proton signal, correlations to the C-5, C-9 and C-13 protons were observed. Finally, irradiation of the C-13 methyl signal, showed correlations to the C-7 and C-12 protons, however, a correlation to only one of the C-11 protons was apparent, suggesting the methyl group adopted an axial conformation. Additional work is required to confirm the structures of the other diastereoisomers **423** and **424** formed during the reaction, the results of the studies will be reported in due course.

Based on previous observations regarding the formation of artefact alkaloids during isolation from *Elaeocarpus sp*., the natural origins of the elaeokanidines are also questionable. Inspection of the isolation paper revealed that aqueous ammonia was used during the extraction process, in a procedure similar to that employed in the isolation of grandisine B **15**, suggesting that elaeokanidines A, B and C could also be artefacts.

6.20 Summary

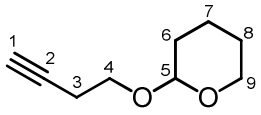
In summary, the total synthesis of (−)-grandisine B **15** has been achieved using an alkyne/acetal cyclisation to efficiently construct the indolizidine core unit. A "biomimetic" amination/cyclisation sequence was used to assemble the isoquinuclidinone core unit, using the known alkaloid grandisine D **17** as a precursor. Results of these studies provide evidence to suggest that grandisine B **15** is an artefact of the isolation process formed as a consequence of using aqueous ammonia in the extraction procedure.

Initial studies have shown that the indolizidine thioester **400** is a valuable building block in the synthesis of *elaeocarpus* alkaloids. Preliminary results have shown that the thioester group can be elaborated *via* Grignard addition or Liebeskind-Srogl coupling, a strategy applied to the synthesis of elaeokanidine A **419**. The utility of thioester **400** in the synthesis of other *elaeocarpus* alkaloids is the subject of current investigations.

The work described in this Chapter was recently the subject of two publications.[177, 178]

Chapter 7. Experimental

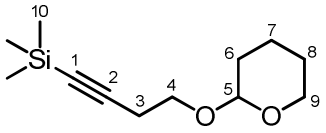
NMR spectra were recorded on a Jeol ECX-400 instrument at 400 MHz (^{1}H) and 100 MHz (^{13}C); chemical shifts (δ) are quoted in parts per million (ppm) calibrated to residual non-deuterated solvent (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). Coupling constants (*J*) are quoted in Hertz and are to the nearest 0.1 Hz. Multiplicities are given as: singlet (s), doublet (d), triplet (t), quartet (q), pentet (pent) or broad (br). Infrared spectra were recorded on a ThermoNicolet IR100 spectrometer with NaCl plates. Low resolution electrospray ionisation (ESI) mass spectra were recorded on a Kratos MS 25 spectrometer. High resolution mass spectra were recorded on a Bruker MicrOTOF spectrometer. Melting points were recorded on Gallenkamp apparatus and are uncorrected. Thin layer chromatography was performed on aluminium plates coated with Merck Silica gel 60 F254 and flash column chromatography was carried out using Fluka flash silica gel 60 and the specified eluent. Petrol refers to the fraction of petroleum ether that boils in the range 40-60 °C. Where necessary, solvents were dried on an Innovative Technology Inc. PureSolv® Purification System, and THF was distilled from sodium benzophenone ketyl immediately before use. Except where specified, all reagents were purchased from commercial sources and used without further purification. Alkyllithium reagents were titrated against *N*-benzylbenzamide before use. Unless otherwise stated all reactions were carried out in oven-dried glassware under an atmosphere of argon with magnetic stirring. Reaction temperatures of −78 °C were achieved using dry ice/acetone mixtures. Structural assignment was aided by the use of DEPT, COSY, HSQC and HMBC spectroscopy. All numbering on the structures below is for the benefit of structure characterisation and does not conform to IUPAC rules.



2-(But-3-ynyloxy)tetrahydro-*2H*-pyran[57] **158:** To a stirred solution of 3-butynol (5.40 mL, 71.3 mmol, 1.0 equiv.) and 3,4-dihydro-*2H*-pyran (8.46 mL, 92.7 mmol, 1.3 equiv.) in DCM (175 mL) at rt was added *p*-TsOH (0.14 g, 0.71 mmol, 0.01 equiv.). The dark blue solution was held at rt for 7 h then washed with sat. aq. $NaHCO_3$ (2 × 100 mL) and brine (100 mL). The organic phase was dried (Na_2SO_4), then concentrated *in vacuo* to afford an orange oil which was distilled to give the title compound **158** (10.4 g, 95%) as a colourless oil; bp. 38-41 ºC (0.5 mmHg); R_f 0.25 (DCM); δ_H (400 MHz, $CDCl_3$) 4.64 (1 H, dd, J = 4.0, 3.0, H-5), 3.90-3.82 (1 H, m, H-9_a), 3.82 (1 H, dt, J = 9.7, 7.0, H-4_a), 3.55 (1 H, dt, J = 9.7, 7.0, H-4_b), 3.53-3.46 (1 H, m, H-9_b), 2.49 (2 H, td, J = 7.0, 2.7, H-3), 1.97 (1 H, t, J = 2.7, H-1), 1.87-1.47 (6 H, m, H-6, 7, 8).

Lab Book Ref. = JDC/1/1

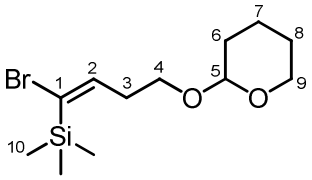
Data were consistent with those published.[57]



Trimethyl(4-(tetrahydro-*2H*-pyran-2-yloxy)but-1-ynyl)silane[57] **159:** To a stirred solution of alkyne **158** (50.0 g, 324.5 mmol, 1.0 equiv.) in diethyl ether (180 mL) at −78 ºC was added *n*-BuLi (1.3 M in hexanes, 262 mL, 340.7 mmol, 1.05 equiv.) dropwise over 3 h. The resulting suspension was stirred for a further 1 h at −78 ºC then chlorotrimethylsilane (43.2 mL, 340.7 mmol, 1.05 equiv.) was added dropwise over 1 h. After stirring at −78 ºC for 1 h, the reaction was warmed to rt and held overnight. The reaction was quenched with water (40 mL) and the aqueous layer extracted with pentane (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$), then concentrated *in vacuo* to give the title compound **159** (69.6 g, 95%) as an orange oil; R_f 0.56 (DCM); δ_H (400 MHz, $CDCl_3$) 4.65 (1 H, dd, J = 3.5, 3.5, H-5), 3.92-3.85 (1 H, m, H-9_a), 3.80 (1 H, dt, J = 9.6, 7.2, H-4_a), 3.53 (1 H, dt, J = 9.6, 7.2, H-4_b), 3.53-3.46 (1 H, m, H-9_b), 2.52 (2 H, t, J = 7.2, H-3), 1.88-1.46 (6 H, m, H-6, 7, 8), 0.13 (9 H, s, H-10).

Lab Book Ref. = JDC/1/16

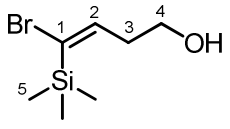
Data were consistent with those published.[57]



(*E*)-(1-Bromo-4-(tetrahydro-*2H*-pyran-2-yloxy)but-1-enyl)trimethylsilane[57] **160:** To a stirred solution of alkyne **159** (7.50 g, 33.2 mmol, 1.0 equiv.) in diethyl ether (25 mL) at 0 ºC was added dropwise di*iso*butylaluminium hydride (1.0 M in toluene, 33.2 mL, 33.2 mmol, 1.0 equiv.). The reaction was warmed to rt and held for 30 min., then heated to 40 ºC and held for 2 h. The colourless solution was cooled to 0 ºC, then pyridine (4.56 mL, 56.4 mmol, 1.7 equiv.) was added. The yellow solution was cooled to −78 ºC then a solution of bromine (2.10 mL, 41.5 mmol, 1.25 equiv.) in DCM (6 mL) was added dropwise over 1 h. The resulting yellow slurry was held for a further 20 min. at −78 ºC, then poured onto a mixture of 1 M aq. NaOH (33 mL), ice (33 g) and hexane (50 mL) and stirred for 45 min. The organic phase was separated, washed with 10% aq. HCl (2 × 20 mL), H_2O (2 × 20 mL) and brine (20 mL), then dried (Na_2SO_4). The combined organic extracts were concentrated *in vacuo* to afford an orange oil, which was distilled to give the title compound **160** (5.60 g, 55%) as a colourless oil; bp. 93-96 ºC (0.25 mmHg); R_f 0.32 (DCM); δ_H (400 MHz, $CDCl_3$) 6.78 (1 H, t, J = 8.0, H-2), 4.58 (1 H, dd, J = 3.9, 2.9, H-5), 3.90-3.79 (1 H, m, H-9_a), 3.75 (1 H, dt, J = 9.6, 6.7, H-4_a), 3.55-3.45 (1 H, m, H-9_b), 3.41 (1 H, dt, J = 9.6, 6.7, H-4_b), 2.39 (2 H, dt, J = 8.0, 6.7, H-3), 1.88-1.43 (6 H, m, H-6, 7, 8), 0.27 (9 H, s, H-10).

Lab Book Ref. = JDC/1/6

Data were consistent with those published.[57]

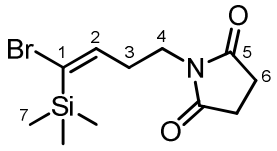


(*E*)-4-Bromo-4-(trimethylsilyl)but-3-en-1-ol[57] **161:** A stirred solution of alkene **160** (4.50 g, 14.6 mmol, 1.0 equiv.) and pyridinium *p*-toluenesulfonate (0.28 g, 1.10 mmol, 0.08 equiv.) in methanol (170 mL) was heated at 40 ºC for 20 h. After cooling to rt the solvent was evaporated under reduced pressure and the residue taken up in diethyl ether (100 mL). The resulting precipitate was filtered and washed with diethyl ether (2 × 20

mL). The filtrate was concentrated *in vacuo* to give the title compound **161** (3.30 g, Quant.) as a pale yellow oil; R_f 0.29 (DCM); δ_H (400 MHz, $CDCl_3$) 6.76 (1 H, t, J = 8.1, H-2), 3.67 (2 H, t, J = 6.4, H-4), 2.37 (2 H, dt, J = 8.1, 6.4, H-3), 0.28 (9 H, s, H-5).

Lab Book Ref. = JDC/1/7

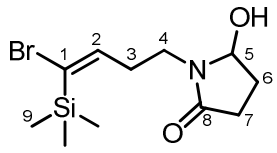
Data were consistent with those published.[57]



(*E*)-1-(4-Bromo-4-(trimethylsilyl)but-3-enyl)pyrrolidine-2,5-dione[57] **162:** To a stirred solution of alcohol **161** (2.01 g, 9.00 mmol, 1.2 equiv.), succinimide (0.74 g, 7.50 mmol, 1.0 equiv.) and triphenylphosphine (2.56 g, 9.75 mmol, 1.3 equiv.) in THF (40 mL) at 0 ºC was added diethyl azodicarboxylate (1.54 mL, 9.75 mmol, 1.3 equiv.) dropwise. The yellow solution was allowed to warm to rt and held for 48 h. The solvent was evaporated under reduced pressure and the residue taken up in DCM (40 mL). The organics phase was washed with 5 M aq. KOH (2 × 20 mL), 10% aq. HCl (2 × 20 mL) and brine (20 mL) then dried (Na_2SO_4). The organic phase was concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM) to give the title compound **162** (1.95 g, 85%) as a colourless oil; R_f 0.29 (DCM); δ_H (400 MHz, $CDCl_3$) 6.67 (1 H, t, J = 8.1, H-2), 3.54 (2 H, t, J = 7.3, H-4), 2.70 (4 H, s, H-6), 2.38 (2 H, dt, J = 8.1, 7.3, H-3), 0.26 (9 H, s, H-7).

Lab Book Ref. = JDC/3/71

Data were consistent with those published.[57]

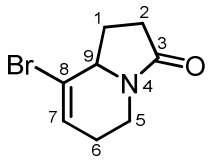


(*E*)-1-(4-Bromo-4-(trimethylsilyl)but-3-enyl)-5-hydroxypyrrolidin-2-one[57] **163:** To a stirred solution of alkene **162** (1.93 g, 6.34 mmol, 1.0 equiv.) in methanol (25 mL) at 0 ºC was added sodium borohydride (0.95 g, 25.4 mmol, 4.0 equiv.). The reaction was stirred at 0 ºC for 4 h then poured into a mixture of DCM (10 mL) and sat. aq. $NaHCO_3$

(5 mL). The mixture was stirred for 20 min. then the organic phase was separated and the aqueous phase extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), then concentrated *in vacuo* to give the title compound **163** (1.80 g, 93%) as a pale yellow oil; R_f 0.38 (DCM/methanol, 9:1); δ_H (400 MHz, $CDCl_3$) 6.70 (1 H, t, J = 8.0, H-2), 5.18 (1 H, br s, H-5), 3.46 (1 H, ddd, J = 14.1, 8.0, 6.4, H-4_a), 3.30-3.20 (1 H, m, H-4_b), 2.57-2.49 (1 H, m, H-3_a), 2.48-2.24 (4 H, m, H-6, 7), 1.93-1.86 (1 H, m, H-3_b), 0.26 (9 H, s, H-9).

Lab Book Ref. = JDC/3/85

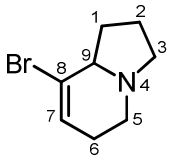
Data were consistent with those published.[57]



8-Bromo-1,2,5,6-tetrahydroindolizin-3(*8aH*)-one[57] **164:** A solution of vinyl silane **163** (1.80 g, 5.88 mmol, 1.0 equiv.) in trifluoroacetic acid (25 mL) was heated at reflux for 5 h. The reaction mixture was cooled to rt and concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, DCM/MeOH, 98:2) to give the title compound **164** (1.05 g, 83%) as a pale yellow oil; R_f 0.19 (EtOAc/PE, 7:3); δ_H (400 MHz, $CDCl_3$) 6.12 (1 H, ddd, J = 6.1, 2.3, 2.0, H-7), 4.27-4.19 (2 H, m, H-5_a, 9), 2.85 (1 H, ddd, J = 13.4, 11.5, 4.7, H-5_b), 2.49-2.27 (4 H, m, H-1_a, 2, 6_a), 2.21-2.09 (1 H, m, H-6_b), 1.81-1.69 (1 H, m, H-1_b).

Lab Book Ref. = JDC/3/88

Data were consistent with those published.[57]

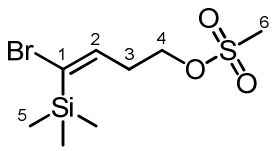


8-Bromo-1,2,3,5,6,8a-hexahydroindolizine[57] **74:** To a stirred solution of lithium aluminium hydride (4.0 M in Et_2O, 1.70 mL, 6.80 mmol, 2.7 equiv.) in diethyl ether (60 mL) at 0 ºC was added dropwise lactam **164** (537 mg, 2.48 mmol, 1.0 equiv.) as a solution in diethyl ether (15 mL). The solution was heated to reflux and held for 4 h

then cooled to 0 ºC before quenching with excess sodium sulfate decahydrate. The slurry was stirred at 0 ºC for 45 min., then filtered through celite and the residual solid washed with diethyl ether (2 × 25 mL). The combined organic extracts were dried (Na_2SO_4), then concentrated *in vacuo* to give the title compound **74** (148 mg, 85%) as a pale yellow oil; R_f 0.31 (DCM/MeOH, 9:1); δ_H (400 MHz, $CDCl_3$) 6.07-6.03 (1 H, m, H-7), 3.65-3.57 (1 H, m, H-9), 2.98 (1 H, ddd, J = 13.0, 5.7, 2.5, H-5_a), 2.93-2.84 (2 H, m, H-3_a, 5_b), 2.83-2.77 (1 H, m, H-3_b), 2.40 (1 H, ddddd, J = 17.4, 10.0, 5.9, 3.1, 3.1, H-6_a), 2.16-2.06 (1 H, m, H-1_a), 2.06-1.97 (1 H, m, H-6_b), 1.88-1.73 (3 H, m, H-1_b, 2).

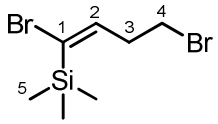
Lab Book Ref. = JDC/3/70

Data were consistent with those published.[57]

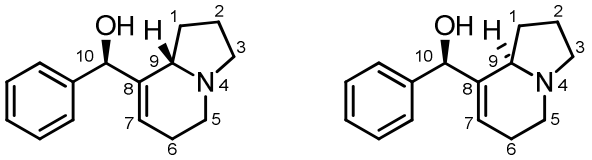


(*E*)-4-Bromo-4-(trimethylsilyl)but-3-enyl methanesulfonate 168: To a stirred solution of alcohol **161** (100 mg, 0.45 mmol, 1.0 equiv.) and triethylamine (70 µL, 0.50 mmol, 1.1 equiv.) in DCM (3 mL) at 0 ºC was added methanesulfonyl chloride (40 µL, 0.50 mmol, 1.1 equiv.). The reaction was warmed to rt and stirred for 1 h then quenched with sat. aq. $NaHCO_3$ (5 mL). The organic phase was separated and the aqueous phase extracted with DCM (4 × 5 mL). The combined organics were dried (Na_2SO_4) then concentrated *in vacuo* to give the title compound **168** (128 mg, 94%) as a colourless oil; R_f 0.86 (DCM); υ_{max}/cm^{-1} (neat) 2958, 2901, 1607, 1356, 1251, 1174, 968; δ_H (400 MHz, $CDCl_3$) 6.70 (1 H, t, J = 8.0, H-2), 4.22 (2 H, t, J = 6.5, H-4), 3.01 (3 H, s, H-6), 2.66 (2 H, dt, J = 8.0, 6.5, H-3), 0.28 (9 H, s, H-5); δ_C (125 MHz, $CDCl_3$) 141.0 (CH, C-2), 132.2 (C, C-1), 67.9 (CH_2, C-4), 37.7 (CH_3, C-6), 32.1 (CH_2, C-3), 0.2 (CH_3, C-5); *m/z* (ESI) 323 $[MNa]^+$; [HRMS (ESI): calcd. for $C_8H_{17}{}^{79}BrNaO_3SSi$, 322.9743. Found: $[MNa]^+$, 322.9748 (1.5 ppm error)].

Lab Book Ref. = JDC/1/57



(*E*)-(1,4-Dibromobut-1-enyl)trimethylsilane 169: To a stirred solution of alcohol **161** (100 mg, 0.45 mmol, 1.0 equiv.) and carbon tetrabromide (166 mg, 0.50 mmol, 1.1 equiv.) in DCM (1 mL) at 0 ºC was added triphenylphosphine (131 mg, 0.50 mmol, 1.1 equiv.). The reaction was stirred at 0 ºC for 30 min., then warmed to rt and held for 2 h. The solvent was evaporated under reduced pressure and the residue taken up in hexane (2 mL). The resulting precipitate was filtered and the filtrate concentrated *in vacuo* to give a colourless oil which was purified by flash chromatography (SiO_2, PE/ether, 49:1) to give the title compound **169** (81 mg, 63%) as a colourless oil; R_f 0.70 (PE/ether, 4:1); υ_{max}/cm^{-1} (neat) 3019, 2977, 2873, 1253, 1217, 1110, 844, 759; δ_H (400 MHz, $CDCl_3$) 6.72 (1 H, t, *J* = 8.0, H-2), 3.36 (2 H, t, *J* = 7.0, H-4), 2.66 (2 H, dt, *J* = 8.0, 7.0, H-3), 0.28 (9 H, s, H-5); δ_C (125 MHz, $CDCl_3$) 143.8 (CH, C-2), 131.3 (C, C-1), 35.2 (CH_2, C-4), 31.0 (CH_2, C-3), 0.3 (CH_3, C-5); *m/z* (EI) 271 (17), 205 (7), 137 (100); [HRMS (EI): calcd. for $C_7H_{14}Si^{79}Br_2$, 283.9232. Found: $[MH]^+$, 283.9241 (3.2 ppm error)].
Lab Book Ref. = JDC/2/80

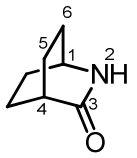


(1,2,3,5,6,8a-Hexahydroindolizin-8-yl)(phenyl)methanol[56] **170** and **171:** To a stirred solution of vinyl bromide **74** (25 mg, 0.12 mmol, 1.0 equiv.) in THF (1 mL) at −78 ºC was added dropwise *tert*-BuLi (1.6 M in pentane, 155 μL, 0.25 mmol, 2.1 equiv.). The reaction was stirred at −78 ºC for 30 min. then benzaldehyde (30 μL, 0.27 mmol, 2.3 equiv.) was added dropwise. The reaction was stirred at −78 ºC for a further 30 min., then warmed to rt and held overnight. The reaction was quenched with 2 M aq. HCl (5 mL), then the aqueous phase was washed with diethyl ether (2 × 5 mL). The aqueous phase was basified with K_2CO_3 then extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (Al_2O_3, DCM/methanol, 95:5) to give the title compounds **170** and **171** (16 mg, 56%, 1:1

mixture of diastereoisomers) as a yellow oil; R_f 0.10 (DCM/MeOH, 4:1); δ_H (400 MHz, $CDCl_3$) 7.39-7.28 (10 H, m, ArH), 5.99-5.94 (1 H, m, H-7), 5.62-5.58 (1 H, m, H-7'), 5.18 (1 H, s, H-10'), 5.15 (1 H, s, H-10), 3.07-2.98 (1 H, m, H-9), 2.94-2.75 (5 H, m, H-3_a, 5_a, 9'), 2.61-2.44 (4 H, m, H-3_b, 5_b), 2.36-2.29 (2 H, m, H-6), 2.29-2.20 (2 H, m, H-6'), 1.96-1.44 (7 H, m, H-1_a, 1_b, 1_a', 2), 1.41-1.30 (1 H, m, H-1_b').

Lab Book Ref. = JDC/1/31

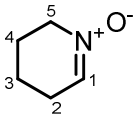
Data were consistent with those published.[56]



2-Azabicyclo[2.2.2]octan-3-one[179] **154:** 4-Aminocyclohexane carboxylic acid (0.50 g, 3.34 mmol, 1.0 equiv.) was heated at 250 ºC for 30 min. then cooled to rt. The brown residue was taken up in hot toluene (50 mL), then the solution was filtered. The filtrate was concentrated *in vacuo* to give the title compound **154** an off-white solid (0.37 g, 84%); mp. 196-197 ºC (Lit. 197-198 ºC); R_f 0.36 (DCM/MeOH, 9:1); δ_H (400 MHz, $CDCl_3$) 7.05 (1 H, br s, H-2), 3.63-3.57 (1 H, m, H-1), 2.52-2.47 (1 H, m, H-4), 1.85-1.55 (8 H, m, H-5, 6).

Lab Book Ref. = JDC/1/35

Data were consistent with those published.[179]

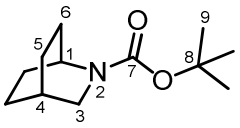


2,3,4,5-Tetrahydropyridine 1-oxide[65] **180:** To a stirred solution of piperidine (0.58 mL, 5.87 mmol, 1.0 equiv.) and selenium dioxide (33 mg, 0.3 mmol, 0.05 equiv.) in acetone (15 mL) at 0 ºC was added dropwise hydrogen peroxide (30 wt% aq., 1.5 mL, 13.0 mmol, 2.2 equiv). The solution was stirred at 0 ºC for 30 min., then warmed to rt and held for a further 3 h. The acetone was evaporated under reduced pressure and the organics were extracted with DCM (4 × 50 mL). The combined organic extracts were dried (Na_2SO_4), then concentrated *in vacuo* to give the title compound **180** (~90% Yield by NMR) as an unstable yellow oil; R_f 0.10 (DCM/MeOH, 9:1); δ_H (400 MHz, $CDCl_3$)

7.22-7.19 (1 H, m, H-1), 3.81-3.76 (2 H, m, H-5), 2.46-2.39 (2 H, m, H-2), 1.99-1.91 (2 H, m, H-4), 1.75-1.66 (2 H, m, H-3).

Lab Book Ref. = JDC/1/33

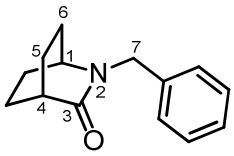
Data were consistent with those published.[65]



***tert*-butyl 2-azabicyclo[2.2.2]octane-2-carboxylate**[180] **182:** To a stirred solution of lactam **154** (100 mg, 0.80 mmol, 1.0 equiv.) in THF (5 mL) was added lithium aluminium hydride (1.0 M in THF, 2.80 mL, 2.80 mmol, 3.5 equiv.). The solution was heated to reflux and held for 2 h, then cooled to 0 ºC. Sodium sulfate decahydrate was added slowly until effervescence ceased, then the resulting slurry was filtered through celite into a 25 mL round bottom flask. To the filtrate was added Boc_2O (153 mg, 0.70 mmol, 1.0 equiv.), then the solution was stirred at rt overnight. The reaction was diluted with ethyl acetate (10 mL), washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to give the title compound **182** (127 mg, 75%) as a colourless oil; R_f 0.33 (SiO_2, PE/EtOAc, 2:1); δ_H (400 MHz, C_6D_6, Rotamers observed) 4.25-4.21 (1 H, m, H-1), 3.89-3.84 (1 H, m, H-1'), 3.39-3.35 (2 H, m, H-3), 3.23-3.29 (2 H, m, H-3'), 1.70-1.57 (4 H, m), 1.48 (9 H, s, H-9), 1.45 (9 H, s, H-9'), 1.30-1.07 (14 H, m).

Lab Book Ref. = JDC/2/21

Data were consistent with those published.[180]

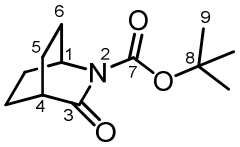


2-Benzyl-2-azabicyclo[2.2.2]octan-3-one[181] **195:** To a stirred suspension of NaH (60 wt%, 32 mg, 0.80 mmol, 2.0 equiv.) in THF (1 mL) at 0 ºC was added lactam **154** (50 mg, 0.40 mmol, 1.0 equiv.). The slurry was stirred at 0 ºC for 30 min., then warmed to rt and held for a further 30 min. The slurry was re-cooled to 0 ºC, then benzyl bromide (92 µL, 0.80 mmol, 2.0 equiv.) was added dropwise. The slurry was warmed to rt and held overnight then quenched with sat. aq. NH_4Cl (5 mL). The aqueous phase was

separated and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to give a yellow oil which was purified by column chromatography (SiO_2, PE/EtOAc, 2:1) to give the title compound **195** (83 mg, 97%) as a colourless crystalline solid; mp. 90-91 ºC (Lit. 95-97 ºC); R_f 0.39 (SiO_2, DCM/MeOH, 19:1); δ_H (400 MHz, $CDCl_3$) 7.33-7.22 (5 H, m, ArH), 4.55 (2 H, s, H-7), 3.49-3.44 (1 H, m, H-1), 2.67-2.62 (1 H, m, H-4), 1.75-1.65 (2 H, m, H-5a), 1.75-1.65 (2 H, m, H-5b), 1.59-1.47 (4 H, m, H-6); δ_C (100 MHz, $CDCl_3$) 175.5 (CO, C-3), 137.8 (C, ArC), 128.5 (2 × CH, ArCH), 128.2 (2 × CH, ArCH), 127.4 (CH, ArCH), 52.4 (CH, C-1), 47.6 (CH_2, C-7), 38.4 (CH, C-4), 27.0 (2 × CH_2, C-6), 24.4 (2 × CH_2, C-5).

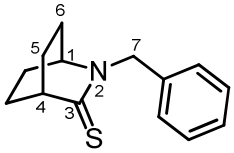
Lab Book Ref. = JDC/2/77

Data were consistent with those published.[181]



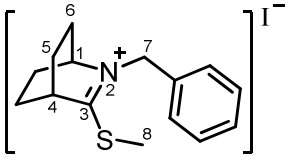
***tert*-Butyl 3-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate 197:** To a stirred solution of lactam **154** (50 mg, 0.40 mmol, 1.0 equiv.) in THF (3 mL) at −78 ºC was added dropwise *n*-BuLi (2.36 M in hexanes, 0.25 mL, 0.60 mmol, 1.5 equiv.). The solution was held at −78 ºC for 1 h, then Boc_2O (153 mg, 0.70 mmol, 1.8 equiv.) was added as a solution in THF (1 mL). The reaction was warmed to rt over 3 h then quenched with sat. aq. NH_4Cl (5 mL). The organic phase was extracted with diethyl ether (3 × 20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a white residue which was purified by column chromatography (SiO_2, PE/Et_2O, 1:1) to give the title compound **197** (72 mg, 80%) as a colourless crystalline solid; mp. 120-121 ºC; R_f 0.79 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 2966, 1729, 1706, 1302, 1157; δ_H (400 MHz, $CDCl_3$) 4.66-4.62 (1 H, m, H-1), 2.63-2.59 (1 H, m, H-4), 1.94-1.64 (8 H, m, H-5, 6), 1.54 (9 H, s, H-9); δ_C (100 MHz, $CDCl_3$) 174.8 (C, C-3), 150.5 (C, C-7), 82.8 (C, C-8), 50.1 (CH, C-1), 39.9 (CH, C-4), 28.1 (3 × CH_3, C-9), 26.0 (2 × CH_2, C-6), 23.1 (2 × CH_2, C-5); *m/z* (ESI) 248 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{12}H_{19}NNaO_3$, 248.1257. Found: $[MNa]^+$, 248.1260 (1.2 ppm error)]

Lab Book Ref. = JDC/3/27



2-Benzyl-2-azabicyclo[2.2.2]octane-3-thione 200: A stirred solution of lactam **195** (300 mg, 1.40 mmol, 1.0 equiv.) and Lawesson's reagent (340 mg, 0.84 mmol, 0.6 equiv.) in PhMe (15 mL) was heated at reflux for 5 h. The solution was cooled to rt then concentrated *in vacuo* to afford an oily residue which was purified by column chromatography (SiO_2, PE/DCM, 1:1) to give the title compound **200** (304 mg, 94%) as a colourless crystalline solid; mp. 96-98 ºC (Hexane); R_f 0.06 (SiO_2, PE/EtOAc, 1:1); υ_{max}/cm^{-1} (thin film) 3019, 2964, 1499, 1357, 1215, 1157, 755, 668; δ_H (400 MHz, $CDCl_3$) 7.38-7.28 (5 H, m, ArH), 5.17 (2 H, s, H-7), 3.74 (1 H, tt, *J* = 3.8, 2.0, H-1), 3.41-3.37 (1 H, m, H-4), 1.85-1.66 (4 H, m, H-5), 1.63-1.48 (4 H, m, H-6); δ_C (100 MHz, $CDCl_3$) 205.1 (CS, C-3), 136.0 (C, ArC), 128.7 (2 × CH, ArCH), 128.3 (2 × CH, ArCH), 127.9 (CH, ArCH), 55.3 (CH, C-1), 54.3 (CH_2, C-7), 48.4 (CH, C-4), 27.0 (2 × CH_2, C-6), 24.5 (2 × CH_2, C-5); *m/z* (ESI) 254 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{17}NNaS$, 254.0974. Found: $[MNa]^+$, 254.0970 (1.7 ppm error)]; Anal. Calcd. for $C_{14}H_{17}NS$: C, 72.68; H, 7.42; N, 6.06. Found C, 72.75; H, 7.42; N, 6.03.

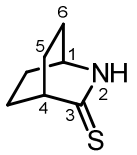
Lab Book Ref. = JDC/2/99



2-Benzyl-3-(methylthio)-2-azoniabicyclo[2.2.2]oct-2-ene iodide 201: To a stirred solution of thiolactam **200** (150 mg, 0.65 mmol, 1.0 equiv.) in diethyl ether (3 mL) was added dropwise methyl iodide (0.69 mL, 11.1 mmol, 17 equiv.). The colourless solution was stirred at rt for 18 h, after which time the suspension was filtered and the filter cake washed with diethyl ether (2 × 2 mL) to give the title compound **201** (221 mg, 91%) as a colourless crystalline solid; mp. 154-157 ºC; υ_{max}/cm^{-1} (thin film) 2942, 1571, 1452, 1354, 1158, 746; δ_H (400 MHz, $CDCl_3$) 7.49-7.44 (2 H, m, ArH), 7.40-7.36 (3 H, m, ArH), 5.28 (2 H, s, H-7), 4.52-4.48 (1 H, m, H-1), 3.88-3.85 (1 H, m, H-4), 3.05 (3 H, s, H-8), 2.08-1.97 (2 H, m, H-5_a), 1.93-1.67 (6 H, m, H-5_b, 6); δ_C (100 MHz, $CDCl_3$)

194.0 (C, C-3), 131.1 (C, ArC), 129.6 (CH, ArCH), 129.5 (2 × CH, ArCH), 129.1 (2 × CH, ArCH), 60.3 (CH, C-1), 58.6 (CH_2, C-7), 37.0 (CH, C-4), 25.7 (2 × CH_2, C-6), 24.1 (2 × CH_2, C-5), 17.2 (CH_3, C-8); *m/z* (ESI) 246 M^+; [HRMS (ESI): calcd. for $C_{15}H_{20}NS$, 246.1311. Found: M^+, 246.1319 (3.4 ppm error)].

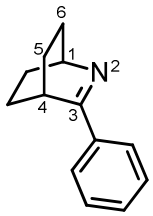
Lab Book Ref. = JDC/3/10



2-Azabicyclo[2.2.2]octane-3-thione[56] **204:** A stirred solution of lactam **154** (100 mg, 0.80 mmol, 1.0 equiv.) and Lawesson's reagent (194 mg, 0.48 mmol, 0.6 equiv.) in PhMe (10 mL) was heated at reflux for 5 h. The solution was cooled to rt, then concentrated *in vacuo* to give an oily residue which was purified by column chromatography (SiO_2, PE/DCM, 1:1) to give the title compound **205** (92 mg, 79%) as a colourless crystalline solid; mp. 155-157 ºC (Lit. 152-154 ºC); R_f 0.25 (PE/EtOAc, 2:1); δ_H (400 MHz, $CDCl_3$) 8.73 (1 H, br s, H-2), 3.77-3.71 (1 H, m, H-1), 3.23-3.19 (1 H, m, H-4), 1.80-1.66 (8 H, m, H-5, 6).

Lab Book Ref. = JDC/3/32

Data were consistent with those published.[56]

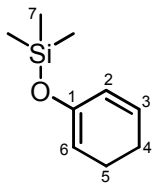


3-Phenyl-2-azabicyclo[2.2.2]oct-2-ene 205: A stirred suspension of thioamide **205** (26 mg, 0.18 mmol, 1.0 equiv.), tetrakis(triphenylphosphine)palladium (8 mg, 0.007 mmol, 0.04 equiv.), copper thiophene carboxylate (103 mg, 0.54 mmol, 3.0 equiv.) and phenylboronic acid (26 mg, 0.22 mmol, 1.2 equiv.) in THF (1.8 mL) was heated in a microwave reactor at 100 ºC for 1 h. The brown solution was cooled to rt, then an additional quantity of tetrakis(triphenylphosphine)palladium (8 mg, 0.007 mmol, 0.04

equiv.) was added. The reaction mixture was heated to 100 ºC and held for a further 1 h. The reaction was cooled to rt and the solvent was evaporated under reduced pressure, then the residue was taken up in $CHCl_3$ (50 mL). The organic phase was washed with 25% aq. NH_3 (3 × 20 mL), then the combined aqueous washes were back extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), the concentrated *in vacuo* to afford a brown film which was purified by column chromatography (SiO_2, PE/EtOAc, 2:1) to give the title compound **205** (9 mg, 27%) as a yellow film; R_f 0.38 (SiO_2, PE/EtOAc, 2:1); δ_H (400 MHz, $CDCl_3$) 7.85-7.80 (2 H, m, ArH), 7.43-7.38 (3 H, m, ArH), 4.40-4.36 (1 H, m, H-1), 3.35-3.31 (1 H, m, H-4), 1.73-1.65 (4 H, m, H-5), 1.50-1.37 (4 H, m, H-6).

Lab Book Ref. = JDC/3/37

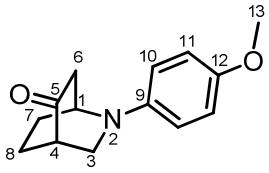
Data were consistent with those published.[56]



(Cyclohexa-1,5-dienyloxy)trimethylsilane[74] **96:** To a stirred solution of lithium hexamethyldisilazide (1.0 M in THF, 12.5 mL, 12.5 mmol, 1.2 equiv.) in THF (20 mL) at 0 ºC was added cyclohexenone (1.01 mL, 10.4 mmol, 1.0 equiv.). The solution was held at 0 ºC for 30 min., then trimethylsilyl chloride (2.60 mL, 20.8 mmol, 2.0 equiv.) was added and the solution was held at 0 ºC for a further 2 h. The reaction was quenched with triethylamine (0.2 mL) and saturated aqueous $NaHCO_3$ (6 mL). The organic layer was separated, then the aqueous phase was extracted with hexane (2 × 30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford an orange oil. Distillation gave the title compound **96** (1.53 g, 88%) as a colourless oil; bp. 60 ºC (9 mmHg), (Lit.[74] 60 ºC (9 mmHg)); δ_H (400 MHz, $CDCl_3$) 5.86 (1 H, ddd, J = 9.9, 4.0, 0.8, H-3), 5.69 (1 H, ddd, J = 9.9, 3.9, 1.9, H-2), 4.88 (1 H, ddt, J = 4.5, 2.1, 0.8, H-6), 2.20-2.04 (4 H, m, H-4, 5), 0.19 (9 H, s, H-7).

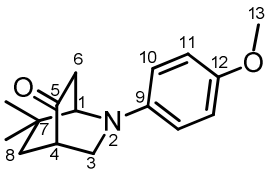
Lab Book Ref. JDC/1/59

Data were consistent with those published.[74]



2-(4-Methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-one[50] **213:** To a stirred solution of *p*-methoxyaniline (0.70 g, 5.70 mmol, 1.1 equiv.), (*S*)-proline (0.18 g, 1.60 mmol, 0.3 equiv.) and formaldehyde (37 wt% aq., 0.45 mL, 5.20 mmol, 1.0 equiv.) in DMSO (20 mL) at rt was added 2-cyclohexen-1-one (1.01 mL, 10.4 mmol, 2.0 equiv.). The orange solution was heated to 50 ºC and held for 24 h before cooling to rt and diluting with water (200 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a dark brown oil which was purified by column chromatography (SiO_2, PE/EtOAc, 1:2) to give the title compound **213** (429 mg, 34%) as an off-white solid; mp. 129-131 ºC (*n*-hexane); R_f 0.53 (SiO_2, PE/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 2949, 1726, 1513, 1248, 1212, 1040, 754; δ_H (400 MHz, $CDCl_3$) 6.85 (2 H, d, *J* = 9.1, ArCH), 6.64 (2 H, d, *J* = 9.1, ArCH), 4.23-4.18 (1 H, m, H-1), 3.76 (3 H, s, H-13), 3.64 (1 H, ddd, *J* = 9.9, 2.4, 2.4, H-3_a), 3.47 (1 H, br d, *J* = 9.9, H-3_b), 2.67 (1 H, ddd, *J* = 18.5, 2.9, 2.9, H-6_a), 2.64-2.60 (1 H, m, H-4), 2.42 (1 H, dd, *J* = 18.5, 1.9, H-6_b), 2.22-2.12 (1 H, m, H-7_a), 2.06-1.91 (2 H, m, H-8), 1.85-1.75 (1 H, m, H-7_b); δ_C (100 MHz, $CDCl_3$) 213.9 (CO, C-5), 151.5 (C, ArC), 142.9 (C, ArC), 115.0 (2 × CH, ArCH), 112.9 (2 × CH, ArCH), 55.8 (CH_3, C-13), 50.7 (CH_2, C-3), 48.2 (CH, C-1), 45.0 (CH_2, C-6), 44.3 (CH, C-4), 25.0 (CH_2, C-7), 22.2 (CH_2, C-8); *m/z* (ESI) 254 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{17}NNaO_2$, 254.1151. Found: $[MNa]^+$, 254.1148 (1.4 ppm error)].

Lab Book Ref. = JDC/1/20

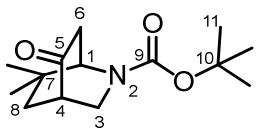


2-(4-Methoxyphenyl)-7,7-dimethyl-2-azabicyclo[2.2.2]octan-5-one[50] **114:** To a stirred solution of *p*-methoxyaniline (1.40 g, 11.4 mmol, 1.1 equiv.), (*S*)-proline (0.36 g, 3.20 mmol, 0.3 equiv.) and formaldehyde (37 wt% aq., 0.90 mL, 10.4 mmol, 1.0 equiv.) in DMSO (40 mL) at rt was added 4,4-dimethylcyclohexen-2-one (2.74 mL, 20.8 mmol,

2.0 equiv.). The orange solution was held at rt for 48 h then diluted with water (150 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a dark brown oil which was purified by column chromatography (SiO_2, DCM) to give the title compound **114** (1.82 g, 67%) as an off-white solid; mp. 92-94 ºC (di*iso*propyl ether); R_f 0.66 (PE/EtOAc, 1:1); $[\alpha]^{24}_D$ −85.6 (*c* 0.85, $CHCl_3$), (Lit.[50] −71.8 (*c* 1.7, $CHCl_3$); υ_{max}/cm^{-1} (thin film) 2956, 1730, 1514, 1244, 1039, 811; δ_H (400 MHz, $CDCl_3$) 6.85 (2 H, d, *J* = 9.1, ArCH), 6.61 (2 H, d, *J* = 9.1, ArCH), 3.78-3.74 (4 H, m, H-1, 13), 3.52-3.44 (2 H, m, H-3), 2.68 (1 H, dd, *J* = 18.9, 2.2, H-6_a), 2.63-2.60 (1 H, m, H-4), 2.46 (1 H, dd, *J* = 18.9, 3.2, H-6_b), 1.81-1.72 (2 H, m, H-8), 1.08 (3 H, s, CH_3), 1.07 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 214.0 (CO, C-5), 151.0 (C, ArC), 142.9 (C, ArC), 115.1 (2 × CH, ArCH), 111.7 (2 × CH, ArCH), 58.0 (CH, C-1), 55.8 (CH_3, C-13), 47.6 (CH_2, C-3), 45.7 (CH, C-4), 41.0 (CH_2, C-6), 38.6 (CH_2, C-8), 35.8 (C, C-7), 29.9 (CH_3), 28.6 (CH_3); *m/z* (ESI) 282 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{16}H_{21}NNaO_2$, 282.1465. Found: $[MNa]^+$, 282.1465 (0.2 ppm error)].

Lab Book Ref. = JDC/3/3

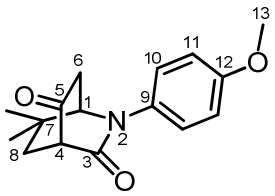
Data were consistent with those published.[50]



***tert*-Butyl 7,7-dimethyl-5-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate 225:** To a stirred solution of isoquinuclidinone **114** (29 mg, 0.11 mmol, 1.0 equiv.) in acetonitrile/water (3:1, 2.8 mL) at rt was added ceric ammonium nitrate (241 mg, 0.44 mmol, 4.0 equiv.). After stirring at rt for 30 min., the reaction was quenched with 1 M NaOH (5 mL), then extracted with DCM (4 × 20 mL). The combined extracts were washed with brine (20 mL), then the solvent evaporated under reduced pressure to give a red oil. The oil was taken up in toluene/water (2:1, 1 mL), then Boc_2O (48 mg, 0.22 mmol, 2.0 equiv.) and 25 wt% NaOH (27 μL, 0.17 mmol, 0.15 equiv.) were added sequentially. The biphasic solution was stirred at rt for 4 h, then diluted with water (2 mL). The organic phase was separated, then the aqueous phase extracted with ethyl acetate (2 × 10 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a brown film which was purified by

flash chromatography (SiO_2, PE/EtOAc, 2:1) to give the title compound **225** (11 mg, 39%) as a colourless oil; R_f 0.49 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 2967, 2929, 1737, 1695, 1401, 1172, 1108; δ_H (400 MHz, $CDCl_3$, Rotamers observed) 4.08 (1 H, dd, J = 3.4, 3.4, H-1), 3.91 (1 H, dd, J = 3.3, 2.4, H-1), 3.59-3.52 (2 H, m, H-2), 3.50-3.40 (2 H, m, H-2), 2.64 (1 H, dd, J = 19.1, 3.4, H-6_a), 2.62 (1 H, dd, J = 19.1, 2.5, H-6_a), 2.55-2.51 (1 H, m, H-3), 2.43 (1 H, J = 19.1, 3.4, H-6_b), 2.41 (1 H, dd, J = 19.1, 3.3, H-6_b), 1.69-1.66 (4 H, m, H-8), 1.48-1.44 (18 H, s, H-11), 1.10 (3 H, s, CH_3), 1.09 (3 H, s, CH_3), 1.03 (3 H, s, CH_3), 1.02 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 213.0 (CO, C-5), 212.5 (CO, C-5'), 154.9 (CO, C-9), 154.8 (CO, C-9'), 79.9 (C, C-10), 79.8 (C, C-10'), 57.2 (CH, C-1), 55.7 (CH, C-1'), 45.2 (CH, C-4), 45.0 (CH_2, C-3), 44.9 (CH, C-4'), 44.4 (CH_2, C-3'), 41.6 (CH_2, C-6), 41.5 (CH_2, C-6'), 38.3 (CH_2, C-8), 38.2 (CH_2, C-8'), 34.6 (C, C-7), 34.5 (C, C-7), 29.5 (CH_3), 29.4 (CH_3), 28.4 (CH_3, C-11, 11'); *m/z* (ESI) 276 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{23}NNaO_3$, 276.1570. Found: $[MNa]^+$, 276.1577 (2.3 ppm error)].

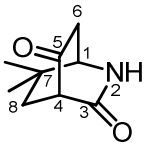
Lab Book Ref. = JDC/3/3



2-(4-Methoxyphenyl)-7,7-dimethyl-2-azabicyclo[2.2.2]octane-3,5-dione 227: To a stirred solution of amine **114** (90 mg, 0.35 mmol, 1.0 equiv.) in MeCN (3 mL) at rt was added potassium permanganate (166 mg, 1.05 mmol, 3.0 equiv.) as a solution in H_2O (1 mL). The reaction was held at rt for 3 h, then excess sodium metabisulfite was added until a colourless solution remained. The organics were extracted with DCM (3 × 10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to give the title compound **227** (46 mg, 48%) as a white solid; mp. 136-139 ºC; R_f 0.41 (PE/EtOAc, 1:1); $[\alpha]^{24}_D$ + 4.3 (*c* 1.01, $CHCl_3$); υ_{max}/cm^{-1} (thin film) 3019, 1739, 1680, 1513, 1214, 754; δ_H (400 MHz, $CDCl_3$) 7.28 (2 H, d, J = 9.0, ArCH), 6.91 (2 H, d, J = 9.0, ArCH), 3.84 (1 H, dd, J = 3.2, 2.1, H-1), 3.80 (3 H, s, H-13), 3.37 (1 H, dd, J = 3.4, 2.4, H-4), 2.79 (1 H, dd, J = 18.9, 2.1, H-6_a), 2.60 (1 H, dd, J = 18.9, 3.2, H-6_b), 2.06 (1 H, dd, J = 13.8, 3.4, H-8_a), 1.89 (1 H, dd, J = 13.8, 2.4, H-8_b), 1.25 (3 H, s, CH_3), 1.17 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 205.7 (CO, C-5), 166.6 (CO, C-3), 157.8 (C, ArC), 133.7 (C, ArC), 125.1 (2 × CH,

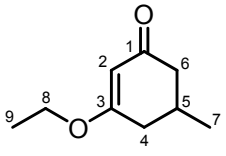
ArCH), 114.4 (2 × CH, ArCH), 66.8 (CH, C-1), 59.4 (CH, C-4), 55.5 (CH_3, C-13), 39.8 (CH_2, C-6), 37.3 (CH_2, C-8), 36.1 (C, C-7), 29.8 (CH_3), 27.8 (CH_3); *m/z* (ESI) 296 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{16}H_{19}NNaO_3$, 296.1257. Found: $[MNa]^+$, 296.1265 (2.6 ppm error)].

Lab Book Ref. = JDC/2/98



7,7-Dimethyl-2-azabicyclo[2.2.2]octane-3,5-dione 228: To a stirred solution of lactam **227** (5 mg, 0.018 mmol, 1.0 equiv.) in MeCN (0.75 mL) at 0 ºC was added ceric ammonium nitrate (44 mg, 0.08 mmol, 4.4 equiv.) as a solution in H_2O (0.25 mL). The solution was held at 0 ºC for 30 min. then quenched with 1 M aq. NaOH (2 mL) before extracting with DCM (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to give the title compound **228** (3 mg, Quant.) as an off-white film contaminated with *p*-benzoquinone; R_f 0.41 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 3249, 2964, 1734, 1688; δ_H (400 MHz, $CDCl_3$) 7.81 (1 H, br s, H-2), 3.41 (1 H, ddd, *J* = 5.4, 3.2, 2.1, H-1), 3.16-3.13 (1 H, m, H-4), 2.66 (1 H, dd, *J* = 18.9, 2.1, H-6_a), 2.38 (1 H, dd, *J* = 18.9, 3.2, H-6_b), 1.90 (1 H, dd, *J* = 13.8, 3.3, H-8_a), 1.81 (1 H, dd, *J* = 13.8, 2.5, H-8_b), 1.18 (3 H, s, CH_3), 1.13 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 205.8 (CO, C-5), 170.8 (CO, C-3), 58.6 (CH, C-4), 57.7 (CH, C-1), 39.8 (CH_2, C-6), 37.4 (CH_2, C-8), 35.7 (C, C-7), 29.2 (CH_3), 27.6 (CH_3); *m/z* (ESI) 190 $[MNa]^+$; [HRMS (ESI): calcd. for $C_9H_{13}NNaO_2$, 190.0838. Found: $[MNa]^+$, 190.0846 (3.8 ppm error)].

Lab Book Ref. = JDC/2/100

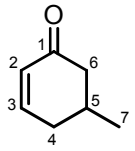


3-Ethoxy-5-methylcyclohex-2-enone[85] **237:** A stirred solution of 5-methylcyclohexane-1,3-dione (5.00 g, 39.6 mmol, 1.0 equiv.) and *p*-TsOH (0.23 g, 1.2

mmol, 0.03 equiv.) in benzene (90 mL) and ethanol (25 mL) was heated at reflux (Dean-Stark) for 8 h. The reaction was cooled to rt, then the solvent was evaporated under reduced pressure to afford a yellow oil which was partitioned between ether (60 mL) and sat. aq. $NaHCO_3$ (30 mL). The organic phase was separated and the aqueous phase was extracted with ether (30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), then concentrated *in vacuo* to give the title compound **237** (5.74 g, 94%) as a pale yellow oil; R_f 0.53 (EtOAc); δ_H (400 MHz, $CDCl_3$) 5.32 (1 H, d, J = 1.5, H-2), 3.94-3.82 (2 H, m, H-8), 2.44-2.36 (2 H, m, H-6), 2.26-2.09 (1 H, m, H-5), 2.13 (1 H, ddd, J = 16.8, 10.2, 1.5, H-4_a), 2.02 (1 H, dd, J = 16.8, 11.7, H-4_b), 1.35 (3 H, t, J = 7.1, H-9), 1.06 (3 H, d, J = 7.1, H-7).

Lab Book Ref. = JDC/7/87

Data were consistent with those published.[85]

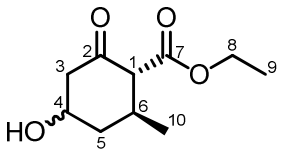


5-Methylcyclohex-2-enone[84] **87:** To a stirred solution of lithium aluminium hydride (4.0 M in diethyl ether, 2.03 mL, 8.11 mmol, 1.0 equiv.) in diethyl ether (20 mL) was added ethoxy enone **237** (4.63 g, 30.0 mmol, 3.7 equiv.) as a solution in diethyl ether (15 mL) over 30 min. The solution was held overnight at rt, then carefully quenched with H_2O (0.35 mL), 10% aq. NaOH (1.05 mL) then H_2O (0.35 mL). The resulting slurry was stirred at rt for 2 h, then filtered. To the colourless filtrate was added 10% aq. H_2SO_4 (10 mL), then the biphasic solution was stirred overnight. The organic phase was separated and washed with sat. aq. $NaHCO_3$ (25 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a pale yellow oil. Distillation gave the title compound **87** (2.00 g, 59%) as a colourless oil; bp. 63-64 ºC (8 mmHg), (Lit.[84] 38-41 ºC (1 mmHg)); R_f 0.58 (PE/EtOAc, 2:1); δ_H (400 MHz, $CDCl_3$) 6.95 (1 H, ddd, J = 10.1, 5.6, 2.6, H-3), 6.00 (1 H, dddd, J = 10.1, 2.5, 1.0, 1.0, H-2), 2.50-2.45 (1 H, m, H-6_a), 2.45-2.37 (1 H, m, H-4_a), 2.29-2.15 (1 H, m, H-5), 2.11 (1 H, dd, J = 15.9, 12.3, H-6_b), 2.03 (1 H, dddd, J = 18.5, 9.8, 2.6, 2.5, H-4_b), 1.06 (3 H, d, J = 6.5, H-7).

Lab Book Ref. = JDC/3/14

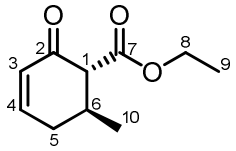
Data were consistent with those published.[84]

Synthesis of Ethyl-(1*R,6*S**)-6-methyl-2-oxocyclohex-3-enecarboxylate 246a:**



Ethyl (1*R,2*S**)-4-hydroxy-2-methyl-6-oxocyclohexanecarboxylate 235:** To a stirred solution of sodium (173 mg, 7.52 mmol, 0.03 equiv.) in EtOH (65 mL) was added ethyl acetoacetate (31.6 mL, 250 mmol, 1.01 equiv.). The solution was cooled to 0 ºC, the crotonaldehyde (20.5 mL, 0.25 mmol, 1.0 equiv.) was added dropwise over 30 min. The reaction was warmed to rt and stirred for 48 h, then quenched with sat. aq. NH_4Cl (20 mL). The ethanol was removed under reduced pressure and the oil was taken up in Et_2O (100 mL). The aqueous phase was separated and extracted with Et_2O (100 mL), then the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), then concentrated *in vacuo* to give the crude title compound **235** (Quant.) as yellow oil, which was used without purification.

Lab Book Ref. = JDC/3/14

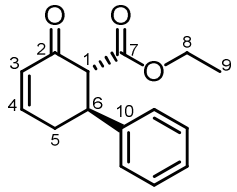


Ethyl-(1*R,6*S**)-6-methyl-2-oxocyclohex-3-enecarboxylate 246a:** To a stirred solution of ester **235** (5.00 g, 25.0 mmol, 1.0 equiv.) in PhMe (100 mL) at rt was added *p*-TsOH (0.95 g, 5.0 mmol, 0.2 equiv.). The solution was heated to 50 ºC and held for 18 h, then cooled to rt and quenched with sat. aq. $NaHCO_3$ (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL), then the combined organics were washed with brine (50 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, PE/EtOAc, 4:1) to give the title compound **246a** (1.39 g, 30%) as a pale yellow oil; R_f 0.38 (PE/Et_2O, 2:1); υ_{max}/cm^{-1} (neat) = 2964, 2932, 1738, 1678, 1261, 1148; δ_H (400 MHz, $CDCl_3$) 6.98 (1 H, ddd, *J* = 10.1, 5.6, 2.6, H-4), 6.07 (1 H, ddd, *J* = 10.1, 2.8, 1.3, H-3), 4.25 (1 H, dq, *J* = 10.8, 7.1, H-8_a), 4.25 (1 H, dq, *J* = 10.8, 7.1, H-8_b), 3.10 (1 H, d, *J* = 11.7, H-1), 2.65-2.44 (2 H, m,

H-5_a, 6), 2.12 (1 H, dddd, J = 18.9, 10.0, 2.8, 2.6, H-5_b), 1.29 (3 H, t, J = 7.1, H-9), 1.08 (3 H, d, J = 6.5, H-10); δ_C (100 MHz, $CDCl_3$) 194.5 (CO, C-2), 169.9 (CO, C-7), 149.7 (CH, C-4), 128.7 (CH, C-3), 61.6 (CH, C-1), 61.0 (CH_2, C-8), 33.0 (CH_2, C-5), 32.7 (CH, C-6), 19.7 (CH_3, C-10), 14.1 (CH_3, C-9); *m/z* (ESI) 205 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{10}H_{14}NaO_3$, 205.0835. Found: $[MNa]^+$, 205.0832 (1.6 ppm error)]

Lab Book Ref. = JDC/4/29

Data were consistent with those published.[90]

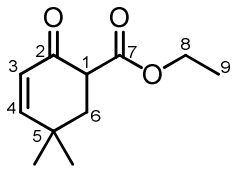


Ethyl-(1*R,6*S**)-2-oxo-6-phenylcyclohex-3-enecarboxylate**[92] **246b:** To a stirred solution of ethyl 3-oxo-4-(triphenylphosphoranylidene)butanoate (781 mg, 2.00 mmol, 1.0 equiv.) in THF (17.5 mL) at rt was added cinnamaldehyde (251 µL, 2.00 mmol, 1.0 equiv.), then the solution was warmed to 35 ºC. To the yellow solution was added NaH (60 wt%, 160 mg, 4.00 mmol, 2.0 equiv.), then water (1 drop) was cautiously added. The reaction was stirred at 35 ºC for 1 h, then quenched with 10% aq. HCl (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), then the combined organics were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give the title compound **246b** (297 mg, 61%) as a colourless crystalline solid; mp. 53-55 ºC; R_f 0.69 (PE/EtOAc, 2:1); δ_H (400 MHz, $CDCl_3$) 7.35-7.29 (2 H, m, ArH), 7.28-7.24 (3 H, m, ArH), 7.06 (1 H, ddd, J = 10.1, 5.7, 2.5, H-4), 6.18 (1 H, ddd, J = 10.1, 2.7, 1.2, H-3), 4.02 (2 H, q, J = 7.1, H-8), 3.75 (1 H, d, J = 13.1, H-1), 3.69 (1 H, ddd, J = 13.1, 9.9, 4.8, H-6), 2.69 (1 H, dddd, J = 18.8, 5.7, 4.8, 1.2, H-5_a), 2.62 (1 H, dddd, J =18.8, 9.9, 2.7, 2.5, H-5_b), 1.01 (3 H, t, J = 7.1, H-9).

Lab Book Ref. = JDC/11/3

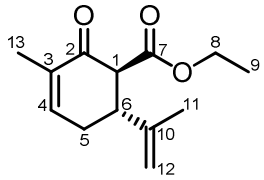
Data were consistent with those published.[92]

Representative Procedure for the Synthesis of β-Ketoester Substrates 246:



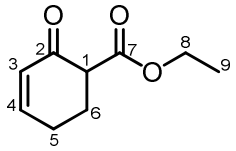
Ethyl 5,5-dimethyl-2-oxocyclohex-3-enecarboxylate 246c: To a stirred solution of di*iso*propylamine (0.70 mL, 4.95 mmol, 1.5 equiv.) in THF (10 mL) at 0 ºC was added dropwise *n*-BuLi (1.6 M in hexanes, 2.89 mL, 4.62 mmol, 1.4 equiv.). The colourless solution was stirred at 0 ºC for 30 min. then cooled to −78 ºC, before adding 4,4-dimethyl-2-cyclohexenone (0.43 mL, 3.3 mmol, 1.0 equiv.) as a pre-cooled in THF/DMPU (5:1, 6 mL) *via* cannula. The resulting yellow solution was stirred at −78 ºC for 1 h, then ethyl cyanoformate (0.49 mL, 4.95 mmol, 1.5 equiv.) was added. The solution was stirred at −78 ºC for a further 1 h, then quenched with sat. aq. NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), then the combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/Et_2O, 6:1) to give the title compound **246c** (481 mg, 74%) as a pale yellow oil as a mixture of keto and enol tautomers; R_f 0.54 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2962, 1740, 1683, 1302, 1238; δ_H (400 MHz, $CDCl_3$, **Keto**) 6.66 (1 H, dd, *J* = 10.1, 2.0, H-4), 5.87 (1 H, d, *J* = 10.1, H-3), 4.23 (1 H, dq, *J* = 10.8, 7.1, H-8_a), 4.22 (1 H, dq, *J* = 10.8, 7.1, H-8_b), 3.52 (1 H, dd, *J* = 13.7, 4.8, H-1), 2.29 (1 H, dd, *J* = 13.7, 13.5, H-6_a), 1.97 (1 H, ddd, *J* = 13.5, 4.8, 2.0, H-6_b), 1.29 (3 H, t, *J* = 7.1, H-9), 1.19 (3 H, s, CH_3), 1.04 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$, **Keto**) 194.0 (CO, C-2), 170.4 (CO, C-7), 159.5 (CH, C-4), 126.0 (CH, C-3), 61.2 (CH_2, C-8), 50.8 (CH, C-1), 38.8 (CH_2, C-6), 33.0 (C, C-5), 30.0 (CH_3), 25.7 (CH_3), 14.1 (CH_3, C-9); δ_H (400 MHz, $CDCl_3$, **Enol**) 6.03 (1 H, d, *J* = 9.8, H-4), 5.82 (1 H, d, *J* = 9.8, H-3), 4.29-4.16 (2 H, m, H-8), 2.33 (2 H, s, H-6), 1.31 (3 H, t, *J* = 7.1, H-9), 1.19 (6 H, s, CH_3); δ_C (100 MHz, $CDCl_3$, **Enol**) 170.4 (CO, C-7), 165.0 (C, C-2), 149.6 (CH, C-4), 121.2 (CH, C-3), 93.2 (C, C-1), 60.2 (CH_2, C-8), 34.3 (CH_2, C-6), 32.4 (C, C-5), 27.7 (2 × CH_3), 14.3 (CH_3, C-9); *m/z* (ESI) 197 $[MH]^+$; [HRMS (ESI): calcd. for $C_{11}H_{17}O_3$, 197.1172. Found: $[MH]^+$, 197.1167 (2.5 ppm error)].

Lab Book Ref. = JDC/10/25



Ethyl-(1*S*,6*R*)-3-methyl-2-oxo-6-(prop-1-en-2-yl)cyclohex-3-enecarboxylate 246d: Using the procedure described for the preparation of compound **246c**, the title compound **246d** (209 mg, 28%) was isolated as a colourless oil; R_f 0.39 (PE/EtOAc, 2:1); $[\alpha]^{21}_D$ = −46.4 (*c* 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2983, 2939, 1736, 1679, 1307, 1226, 1166; δ_H (400 MHz, $CDCl_3$) 6.77-6.73 (1 H, m, H-4), 4.83-4.81 (2 H, m, H-12), 4.19 (1 H, dq, *J* = 13.8, 6.9, H-8_a), 4.18 (1 H, dq, *J* = 13.8, 6.9, H-8_b), 3.46 (1 H, d, *J* = 13.0, H-1), 3.11 (1 H, ddd, *J* = 13.0, 11.0, 4.9, H-6), 2.46 (1 H, dddd, *J* = 18.7, 6.1, 4.9, 1.4, H-5_a), 2.38-2.27 (1 H, m, H-5_b), 1.78 (3 H, ddd, *J* = 2.6, 1.4, 1.4, H-13), 1.74 (3 H, m, H-11), 1.24 (3 H, t, *J* = 6.9, H-9); δ_C (100 MHz, $CDCl_3$) 194.7 (CO, C-2), 169.7 (CO, C-7), 144.5 (C, C-10), 144.3 (CH, C-4), 134.7 (C, C-3), 112.8 (CH_2, C-12), 60.8 (CH_2, C-8), 58.4 (CH, C-1), 45.6 (CH, C-6), 30.7 (CH_2, C-5), 19.6 (CH_3, C-11), 15.7 (CH_3, C-13), 14.1 (CH_3, C-9); *m/z* (ESI) 223 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{19}O_3$, 223.1329. Found: MH^+, 223.1321 (3.4 ppm error)].

Lab Book Ref. = JDC/10/24



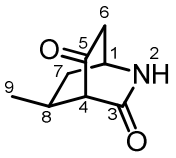
Ethyl 2-oxocyclohex-3-enecarboxylate 246e: Using the procedure described for the preparation of compound **246c**, the title compound **246e** (239 mg, 43%) was isolated as a pale yellow oil; R_f 0.38 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2979, 2924, 1740, 1674, 1370, 1257, 1182, 1152; δ_H (400 MHz, $CDCl_3$) 6.99 (1 H, ddd, *J* = 10.2, 3.6, 3.6, H-4), 6.05 (1 H, ddd, *J* = 10.2, 2.0, 2.0, H-3), 4.20 (1 H, dq, *J* = 10.8, 7.1, H-8_a), 4.20 (1 H, dq, *J* = 10.8, 7.1, H-8_b), 3.38 (1 H, dd, *J* = 10.0, 4.9, H-1), 2.54-2.43 (1 H, m, H-5_a), 2.43-2.32 (2 H, m, H-5_b, 6_a), 2.24-2.16 (1 H, m, H-6_b), 1.26 (3 H, t, *J* = 7.1, H-9); δ_C (100 MHz, $CDCl_3$) 193.9 (CO, C-2), 169.9 (CO, C-7), 150.5 (CH, C-4), 129.0 (CH, C-3), 61.1 (CH_2, C-8), 53.3 (CH, C-1), 25.5 (CH_2, C-6), 24.2 (CH_2, C-5), 14.0 (CH_3, C-9);

m/z (ESI) 169 $[MH]^+$; [HRMS (ESI): calcd. for $C_9H_{13}O_3$, 169.0859. Found: $[MH]^+$, 169.0862 (1.6 ppm error)].

Lab Book Ref. = JDC/10/28

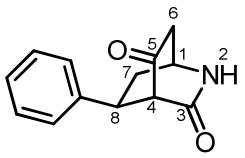
Data were consistent with those published.[92]

Representative Procedure for the Synthesis of Bicyclic Lactams:



8-Methyl-2-azabicyclo[2.2.2]octane-3,5-dione 248a: A stirred solution of β-ketoester **246a** (46 mg, 0.25 mmol, 1.0 equiv.) in 35% aq. NH_3 (1 mL) was held at rt until consumption of the starting material was observed by TLC (DCM/MeOH, 9:1). The solution was concentrated *in vacuo* to afford a pale yellow solid was purified by column chromatography (SiO_2, DCM/MeOH, 98:2) to give the title compound **248a** (36 mg, 93%) as a colourless crystalline solid; mp. 135-137 ºC; R_f 0.40 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 3244, 2961, 1730, 1681, 1335, 1105; δ_H (400 MHz, $CDCl_3$) 7.92 (1 H, br s, NH), 3.98-3.93 (1 H, m, H-1), 3.08-3.05 (1 H, m, H-4), 2.49-2.40 (2 H, m, H-6_a, 8), 2.32 (1 H, dddd, *J* = 13.0, 10.8, 3.9, 2.8, H-7_a), 2.20 (1 H, dd, *J* = 18.5, 1.9, H-6_b), 1.31 (1 H, ddd, *J* = 13.0, 4.6, 1.0, H-7_b), 1.06 (3 H, d, *J* = 7.1, H-9); δ_C (100 MHz, $CDCl_3$) 205.1 (CO, C-5), 171.8 (CO, C-3), 64.4 (CH, C-4), 47.0 (CH, C-1), 43.8 (CH_2, C-6), 35.4 (CH_2, C-7), 29.4 (CH, C-8), 20.8 (CH_3, C-9); *m/z* (ESI) 154 $[MH]^+$; [HRMS (ESI): calcd. for $C_8H_{12}NO_2$, 154.0863. Found: $[MH]^+$, 154.0864 (0.6 ppm error)]; Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.50; H, 7.18; N, 9.11.

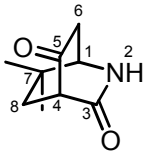
Lab Book Ref. = JDC/11/15



8-Phenyl-2-azabicyclo[2.2.2]octane-3,5-dione 248b: Using the procedure described for the preparation of compound **248a**, the title compound **248b** (41 mg, 76%) was

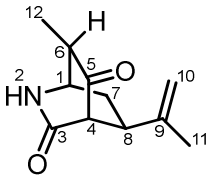
isolated as a colourless crystalline solid; mp. 188-191 ºC; R_f 0.44 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 3413, 1727, 1678, 1025; δ_H (400 MHz, $CDCl_3$) 7.26-7.21 (2 H, m, ArH), 7.18-7.13 (1 H, m, ArH), 7.08-7.02 (2 H, m, ArH), 4.06-4.01 (1 H, m, H-1), 3.57 (1 H, ddd, *J* = 11.2, 6.0, 2.3, H-8), 3.30 (1 H, dd, *J* = 2.3, 2.3 H-4), 2.62-2.53 (1 H, m, H-7_a), 2.52 (1 H, ddd, *J* = 18.1, 3.1, 3.1 H-6_a), 2.35 (1 H, dd, *J* = 18.1, 2.0, H-6_b), 1.93 (1 H, ddd, *J* = 13.3, 6.0, 1.1, H-7_b); δ_C (100 MHz, $CDCl_3$) 204.4 (CO, C-5), 170.6 (CO, C-3), 140.5 (C, ArC), 128.7 (2 × CH, ArCH), 127.1 (CH, ArCH), 126.8 (2 × CH, ArCH), 64.9 (CH, C-4), 46.6 (CH, C-1), 44.6 (CH_2, C-6), 40.2 (CH, C-8), 34.4 (CH_2, C-7); *m/z* (ESI) 216 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{14}NO_2$, 216.1019. Found: $[MH]^+$, 216.1017 (1.0 ppm error)].

Lab Book Ref. = JDC/11/7

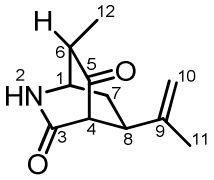


7,7-Dimethyl-2-azabicyclo[2.2.2]octane-3,5-dione 248c: Using the procedure described for the preparation of compound **248a**, the title compound **248c** (35 mg, 80%) was isolated as a colourless crystalline solid; mp. 182-185 ºC; R_f 0.41 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 3249, 2964, 1734, 1688; δ_H (400 MHz, $CDCl_3$) 7.81 (1 H, br s, NH), 3.43-3.39 (1 H, m, H-1), 3.16-3.13 (1 H, m, H-4), 2.66 (1 H, dd, *J* = 18.9, 2.0, H-6_a), 2.38 (1 H, dd, *J* = 18.9, 3.3, H-6_b), 1.90 (1 H, dd, *J* = 13.8, 3.3, H-8_a), 1.81 (1 H, dd, *J* = 13.8, 2.5, H-8_b), 1.18 (3 H, s, CH_3), 1.13 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 205.8 (CO, C-5), 170.8 (CO, C-3), 58.6 (CH, C-4), 57.7 (CH, C-1), 39.8 (CH_2, C-6), 37.4 (CH_2, C-8), 35.7 (C, C-7), 29.2 (CH_3), 27.6 (CH_3); *m/z* (ESI) 168 $[MH]^+$; [HRMS (ESI): calcd. for $C_9H_{14}NO_2$, 168.1019. Found: $[MH]^+$, 168.1022 (1.6 ppm error)]; Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.67; H, 7.81; N, 8.42.

Lab Book Ref. = JDC/10/84



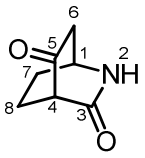
Major



Minor

6-Methyl-8-(prop-1-en-2-yl)-2-azabicyclo[2.2.2]octane-3,5-dione 248d: Using the procedure described for the preparation of compound **248a**, the title compound **248d** (47 mg, 98%, ~4:1) was isolated as a colourless crystalline solid; mp. 112-115 ºC; R_f 0.51 (Major), 0.47 (Minor) (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 3273, 2939, 1729, 1679, 1073; δ_H (400 MHz, $CDCl_3$, **Major**) 7.81 (1 H, br s, NH), 4.83 (1 H, br s, H-10_a), 4.76 (1 H, br s, H-10_b), 3.68 (1 H, dddd, *J* = 5.6, 4.0, 1.7, 1.5, H-1), 3.36-3.31 (1 H, dd, *J* = 2.4, 1.6, H-4), 2.89-2.81 (1 H, m, H-8), 2.35 (1 H, ddd, *J* = 13.5, 11.3, 4.0, H-7_a), 2.17 (1 H, qd, *J* = 7.2, 1.5, H-6), 1.79 (1 H, ddd, *J* = 13.5, 5.6, 1.7, H-7_b), 1.73 (3 H, s, H-11), 1.15 (3 H, d, *J* = 7.2, H-12); δ_C (100 MHz, $CDCl_3$, **Major**) 207.7 (CO, C-5), 171.0 (CO, C-3), 144.3 (C, C-9), 111.6 (CH_2, C-10), 61.7 (CH, C-4), 52.6 (CH, C-1), 46.7 (CH, C-6), 40.4 (CH, C-8), 32.8 (CH_2, C-7), 22.0 (CH_3, C-11), 14.4 (CH_3, C-12); δ_H (400 MHz, $CDCl_3$, **Minor**) 8.07 (1 H, br s, NH), 4.85 (1 H, br s, H-10_a), 4.77 (1 H, br s, H-10_b), 3.79-3.74 (1 H, m, H-1), 3.38 (1 H, dd, *J* = 1.9, 1.9, H-4), 2.90-2.81 (1 H, m, H-8), 2.44 (1 H, qdd, *J* = 7.4, 2.7, 1.8, H-6), 2.25-2.15 (1 H, m, H-7_a), 1.89 (1 H, ddd, *J* = 13.7, 6.7, 1.1, H-7_b), 1.73 (3 H, s, H-11), 1.09 (3 H, d, *J* = 7.4, H-12); δ_C (100 MHz, $CDCl_3$, **Minor**) 207.6 (CO, C-5), 172.1 (CO, C-3), 143.6 (C, C-9), 111.9 (CH_2, C-10), 61.2 (CH, C-4), 52.0 (CH_2, C-1), 48.0 (CH, C-6), 41.9 (CH, C-8), 26.7 (CH_2, C-7), 22.3 (CH_3, C-11), 12.1 (CH_3, C-12); *m/z* (ESI) 194 $[MH]^+$; [HRMS (ESI): calcd. for $C_{11}H_{16}NO_2$, 194.1176. Found: $[MH]^+$, 194.1181 (2.6 ppm error)]; Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.37; H, 7.81; N, 7.25.

Lab Book Ref. = JDC/11/12

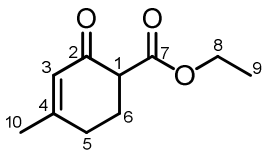


2-Azabicyclo[2.2.2]octane-3,5-dione 248e: Using the procedure described for the preparation of compound **248a**, the title compound **248e** (21 mg, 60%) was isolated as a

colourless crystalline solid; mp. 207-209 ºC (Lit.[45] 143-144 ºC); R_f 0.39 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 3189, 1733, 1697, 1096; δ_H (400 MHz, $CDCl_3$) 7.81 (1 H, br s, NH), 4.04-3.99 (1 H, m, H-1), 3.26 (1 H, dd, *J* = 4.8, 2.7, H-4), 2.47 (1 H, ddd, *J* = 18.6, 3.1, 3.1, H-6_a), 2.29 (1 H, dd, *J* = 18.6, 2.0, H-6_b), 2.18-1.97 (3 H, m, H-7_a, 8), 1.88-1.79 (1 H, m, H-7_b); δ_C (100 MHz, $CDCl_3$) 205.7 (CO, C-5), 171.2 (CO, C-3), 57.3 (CH, C-4), 47.3 (CH, C-1), 43.3 (CH_2, C-6), 26.6 (CH_2, C-7), 21.0 (CH_2, C-8); *m/z* (ESI) 140 $[MH]^+$; [HRMS (ESI): calcd. for $C_7H_{10}NO_2$, 140.0706. Found: $[MH]^+$, 140.0704 (1.2 ppm error)].

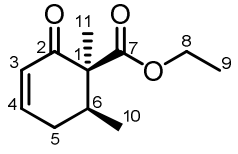
Lab Book Ref. = JDC/11/25

All data, except melting point, were consistent with those published.[45]



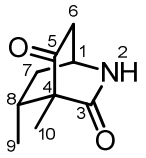
Ethyl 4-methyl-2-oxocyclohex-3-enecarboxylate 249: Using the procedure described for the preparation of compound **246c**, the title compound **249** (376 mg, 62%) was isolated as a pale yellow oil; R_f 0.39 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2982, 1734, 1675, 1258, 1183; δ_H (400 MHz, $CDCl_3$) 5.91-5.89 (1 H, m, H-3), 4.19 (1 H, dq, *J* = 10.8, 7.1, H-8_a), 4.19 (1 H, dq, *J* = 10.8, 7.1, H-8_b), 3.29 (1 H, dd, *J* = 9.8, 5.1, H-1), 2.44-2.24 (3 H, m, H-5, 6_a), 2.22-2.13 (1 H, m, H-6_b), 1.95 (3 H, s, H-10), 1.26 (3 H, t, *J* = 7.1, H-9); δ_C (100 MHz, $CDCl_3$) 193.7 (CO, C-2), 170.2 (CO, C-7), 162.8 (C, C-4), 125.7 (CH, C-3), 61.1 (CH_2, C-8), 52.4 (CH, C-1), 29.3 (CH_2, C-5), 25.4 (CH_2, C-6), 24.3 (CH_3, C-10), 14.0 (CH_3, C-9); *m/z* (ESI) 183 $[MH]^+$; [HRMS (ESI): calcd. for $C_{10}H_{15}O_3$, 183.1016. Found: $[MH]^+$, 183.1011 (2.5 ppm error)].

Lab Book Ref. = JDC/10/33



Ethyl-(1*R,6*R**)-1,6-dimethyl-2-oxocyclohex-3-enecarboxylate 251:** To a stirred suspension of NaH (60 wt%, 60 mg, 1.51 mmol, 1.1 equiv.) in THF (5 mL) at 0 ºC was

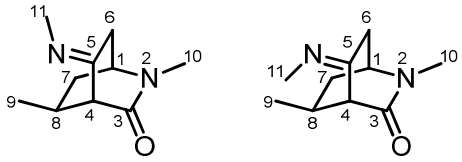
added ester **246a** (250 mg, 1.37 mmol, 1.0 equiv.) as a solution in THF (1 mL). The suspension was stirred at 0 ºC for 30 min, then methyl iodide (102 µL, 1.64 mmol, 1.2 equiv.) was added dropwise. The suspension was held at 0 ºC for a further 30 min., then warmed to rt and held for 8 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL), then the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/Et_2O, 9:1) to give the title compound **251** (103 mg, 38%) as a colourless oil; R_f 0.54 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2982, 1734, 1674, 1191, 1113; δ_H (400 MHz, $CDCl_3$) 6.95 (1 H, ddd, *J* = 10.1, 5.7, 2.4, H-4), 6.07 (1 H, ddd, *J* = 10.1, 2.7, 1.1, H-3), 4.14 (1 H, dq, 10.8, 7.1, H-8_a), 4.08 (1 H, dq, *J* = 10.8, 7.1, H-8_b), 2.40 (1 H, dddd, *J* = 19.2, 10.8, 2.7, 2.4, H-5_a), 3.24-3.25 (1 H, dddd, *J* = 19.2, 5.7, 4.9, 1.1, H-5_b), 2.14-2.03 (1 H, dqd, *J* = 10.8, 6.9, 4.9, H-6), 1.40 (3 H, s, H-11), 1.20 (3 H, t, *J* = 7.1, H-9), 1.12 (3 H, d, *J* = 6.9, H-10); δ_C (100 MHz, $CDCl_3$) 197.0 (CO, C-2), 170.7 (CO, C-7), 149.5 (CH, C-4), 128.8 (CH, C-3), 60.9 (CH_2, C-8), 57.1 (C, C-1), 38.7 (CH, C-6), 32.4 (CH_2, C-5), 18.4 (CH_3, C-11), 16.4 (CH_3, C-10), 14.1 (CH_3, C-9); *m/z* (ESI) 219 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{11}H_{16}NaO_3$, 219.0992. Found: $[MNa]^+$, 219.0999 (3.5 ppm error)].
Lab Book Ref. = JDC/10/4



4,8-Dimethyl-2-azabicyclo[2.2.2]octane-3,5-dione 252: Using the procedure described for the preparation of compound **248a**, the title compound **252** (35 mg, 83%) was isolated as a colourless crystalline solid; mp. 97-99 ºC; R_f 0.42 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 3239, 1731, 1686, 1443, 1056; δ_H (400 MHz, $CDCl_3$) 8.05 (1 H, br s, NH), 3.98-3.93 (1 H, m, H-1), 2.44 (1 H, ddd, *J* = 18.5, 3.4, 3.3, H-6_a), 2.31 (1 H, dd, *J* = 18.5, 1.9, H-6_b), 2.16 (1 H, ddd, *J* = 13.0, 9.8, 1.9, H-7_a), 2.07-1.97 (1 H, m, H-8), 1.58 (1 H, dddd, *J* = 13.0, 4.6, 3.4, 3.3, H-7_b), 1.21 (3 H, s, H-10), 1.02 (3 H, d, *J* = 6.9, H-9); δ_C (100 MHz, $CDCl_3$) 207.7 (CO, C-5), 171.7 (CO, C-3), 61.0 (C, C-4), 45.9 (CH, C-1), 42.4 (CH_2, C-6), 36.8 (CH_2, C-7), 33.4 (CH, C-8) 18.9 (CH_3, C-9), 10.4 (CH_3, C-

10); *m/z* (ESI) 168 $[MH]^+$; [HRMS (ESI): calcd. for $C_9H_{14}NO_2$, 168.1019. Found: $[MH]^+$, 168.1023 (2.2 ppm error)].

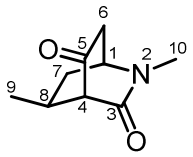
Lab Book Ref. = JDC/11/49



2,5-Dimethyl-8-(methylimino)-2-azabicyclo[2.2.2]octan-3-one 253 and **254:** A stirred solution of β-ketoester **247a** (46 mg, 0.25 mmol, 1.0 equiv.) in aq. $MeNH_2$ (40 wt%, 1 mL) was held at rt for 24 h, then concentrated *in vacuo* to afford the title compound **253**/**254** (44 mg, 98%, 4:1 ratio of diastereoisomers) as a yellow oil; R_f 0.55 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (neat) 2958, 1729, 1679, 1398, 1249; δ_H (400 MHz, $CDCl_3$, **Major**) 3.69-3.64 (1 H, m, H-1), 3.08 (1 H, d, *J* = 2.5, H-4), 3.06-3.02 (3 H, s, H-11), 2.92 (3 H, s, H-10), 2.44-2.37 (1 H, m, H-6_a), 2.30-2.31 (3 H, m, H-6_b, 7_a, 8), 1.12-0.99 (1 H, m, H-7_b), 0.97 (3 H, d, *J* = 6.7, H-9); δ_C (100 MHz, $CDCl_3$, **Major**) 171.5 (CN, C-5), 167.6 (CO, C-3), 59.1 (CH, C-4), 54.7 (CH, C-1), 39.0 (CH_3, C-11), 34.5 (CH_2, C-7), 34.1 (CH_2, C-6), 31.4 (CH_3, C-10), 29.5 (CH, C-8), 20.5 (CH_3, C-9); δ_H (400 MHz, $CDCl_3$, **Minor**) 3.69-3.65 (1 H, m, H-4), 3.61-3.57 (1 H, m, H-1), 3.15 (3 H, dd, *J* = 1.8, 1.8, H-11), 2.92 (3 H, s, H-10), 2.53-2.38 (2 H, m, H-6_a, 7_a), 2.30-2.14 (2 H, m, H-6_b, 8), 1.14-1.02 (1 H, m, H-7_b), 0.97 (3 H, d, *J* = 6.7, H-9); δ_C (100 MHz, $CDCl_3$, **Minor**) 170.4 (CN, C-5), 166.7 (CO, C-3), 55.2 (CH, C-1), 50.5 (CH, C-4), 40.1 (CH_2, C-6), 38.5 (CH_3, C-11), 34.1 (CH_2, C-7), 31.5 (CH_3, C-10), 30.2 (CH, C-8), 20.2 (CH_3, C-9); *m/z* (ESI) 181 $[MH]^+$; [HRMS (ESI): calcd. for $C_{10}H_{17}N_2O$, 181.1335. Found: $[MH]^+$, 181.1335 (0.2 ppm error)].

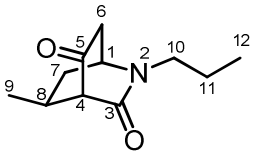
Lab Book Ref. = JDC/11/48

Representative Procedure for the Synthesis of *N*-Substituted Lactams 255:



2,8-Dimethyl-2-azabicyclo[2.2.2]octane-3,5-dione 255a: To a stirred solution of β-ketoester **246a** (46 mg, 0.25 mmol, 1.0 equiv.) in H_2O (1 mL) at rt was added amine (22 μL, 0.25 mmol, 1.0 equiv.). The solution was stirred at rt until consumption of the starting material was observed by TLC (DCM/MeOH, 9:1), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM/MeOH, 98:2) to give the title compound **255a** (26 mg, 62%) as a colourless crystalline solid; mp. 131-133 ºC; R_f 0.54 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 2970, 2932, 1728, 1668, 1396; δ_H (400 MHz, $CDCl_3$) 3.81-3.77 (1 H, m, H-1), 3.15 (1 H, d, J = 2.8, H-4), 3.00 (3 H, s, H-10), 2.49 (1 H, ddd, J = 18.5, 3.2, 3.2, H-6_a), 2.45-2.30 (2 H, m, H-7_a, 8), 2.21 (1 H, dd, J = 18.5, 2.0, H-6_b), 1.31 (1 H, ddd, J = 13.2, 4.4, 1.6, H-7_b), 1.06 (3 H, d, J = 7.0, H-9); δ_C (100 MHz, $CDCl_3$) 204.9 (CO, C-5), 168.6 (CO, C-3), 64.3 (CH, C-4), 54.8 (CH, C-1), 42.9 (CH_2, C-6), 34.2 (CH_2, C-7), 31.8 (CH_3, C-10), 29.8 (CH, C-8), 20.9 (CH_3, C-9); *m/z* (ESI) 168 $[MH]^+$; [HRMS (ESI): calcd. for $C_9H_{14}NO_2$, 168.1019. Found: $[MH]^+$, 168.1017 (1.1 ppm error)]; Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.58; H, 7.90; N, 8.33.

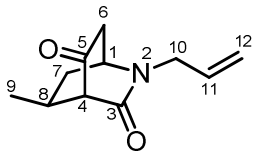
Lab Book Ref. = JDC/11/32



8-Methyl-2-propyl-2-azabicyclo[2.2.2]octane-3,5-dione 255b: Using the procedure described for the preparation of compound **255a**, the title compound **255b** (24 mg, 49%) was isolated as a yellow film; R_f 0.60 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 2962, 1730, 1672, 1463; δ_H (400 MHz, $CDCl_3$) 3.85-3.81 (1 H, m, H-1), 3.42-3.26 (2 H, m, H-10), 3.15 (1 H, d, J = 2.8, H-4), 2.47-2.38 (1 H, m, H-8), 2.42 (1 H, ddd, J = 18.5, 3.1, 3.1, H-6_a), 2.30 (1 H, dddd, J = 13.5, 10.8, 3.7, 3.1, H-7_a), 2.22 (1 H, dd, J = 18.5, 2.0,

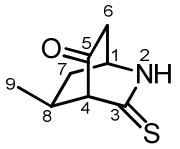
H-6_b), 1.60-1.49 (2 H, m, H-11), 1.32 (1 H, ddd, *J* = 13.5, 4.7, 1.4, H-7_b), 1.05 (3 H, d, *J* = 7.1, H-9), 0.90 (3 H, t, *J* = 7.4, H-12); δ_C (100 MHz, $CDCl_3$) 205.2 (CO, C-5), 168.2 (CO, C-3), 64.7 (CH, C-4), 52.8 (CH, C-1), 46.3 (CH_2, C-10), 43.6 (CH_2, C-6), 34.9 (CH_2, C-7), 29.7 (CH, C-8), 21.5 (CH_2, C-11), 20.8 (CH_3, C-9), 11.2 (CH_3, C-12); *m/z* (ESI) 196 $[MH]^+$; [HRMS (ESI): calcd. for $C_{11}H_{18}NO_2$, 196.1332. Found: $[MH]^+$, 196.1329 (1.6 ppm error)].

Lab Book Ref. = JDC/11/22



2-Allyl-8-methyl-2-azabicyclo[2.2.2]octane-3,5-dione 255c: Using the procedure described for the preparation of compound **255a**, the title compound **255c** (21 mg, 43%) was isolated as a yellow film; R_f 0.59 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 2961, 1729, 1668, 1461; δ_H (400 MHz, $CDCl_3$) 5.74 (1 H, ddt, *J* = 17.0, 10.0, 6.5, H-11), 5.25 (1 H, dd, *J* = 17.0, 1.5, H-12), 5.23 (1 H, dd, *J* = 10.0, 1.5, H-12), 4.07 (1 H, dd, *J* = 14.9, 6.5, H-10_a), 3.95 (1 H, dd, *J* = 14.9, 6.5, H-10_b), 3.85-3.81 (1 H, m, H-1), 3.18 (1 H, d, *J* = 2.8, H-4), 2.50-2.41 (1 H, m, H-8), 2.41 (1 H, ddd, *J* = 18.5, 3.2, 3.2, H-6_a), 2.29 (1 H, dddd, *J* = 13.5, 10.7, 3.8, 3.2, H-7_a), 2.21 (1 H, dd, *J* = 18.5, 1.9, H-6_b), 1.30 (1 H, ddd, *J* = 13.5, 4.8, 1.9, H-7_b), 1.06 (3 H, d, *J* = 7.1, H-9); δ_C (100 MHz, $CDCl_3$) 205.1 (CO, C-5), 168.1 (CO, C-3), 132.4 (CH, C-11), 119.2 (CH_2, C-12), 64.8 (CH, C-4), 51.8 (CH, C-1), 47.0 (CH_2, C-10), 43.5 (CH_2, C-6), 34.8 (CH_2, C-7), 29.9 (CH, C-8), 20.9 (CH_3, C-9); *m/z* (ESI) 194 $[MH]^+$; [HRMS (ESI): calcd. for $C_{11}H_{16}NO_2$, 194.1176. Found: $[MH]^+$, 194.1168 (3.8 ppm error)].

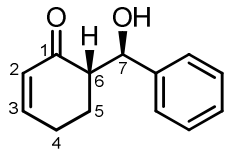
Lab Book Ref. = JDC/11/6



8-Methyl-3-thioxo-2-azabicyclo[2.2.2]octan-5-one 208: To a stirred solution of lactam **248a** (50 mg, 0.33 mmol, 1.0 equiv.) in PhMe (2 mL) at rt was added

Lawesson's reagent (73 mg, 0.18 mmol, 0.55 equiv.). The solution was heated to 60 ºC and held for 30 min., then cooled to rt. The solution was concentrated *in vacuo* to afford an orange residue which was purified by column chromatography (SiO_2, PE/EtOAc, 2:1) to give the title compound **208** (21 mg, 38%) as a yellow film; R_f 0.51 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 3203, 2959, 2925, 1729, 1509, 1330, 1096; δ_H (400 MHz, $CDCl_3$) 9.36 (1 H, s, NH), 4.11 (1 H, br s, H-1), 3.74-3.72 (1 H, m, H-4), 2.49-2.32 (3 H, m, H-6_a, 7_a, 8), 2.24 (1 H, dd, J = 18.6, 1.6, H-6_b), 1.42-1.33 (1 H, m, H-7_b), 1.09 (3 H, d, J = 6.8, H-9); δ_C (100 MHz, $CDCl_3$) 203.4 (C), 199.8 (C), 72.0 (CH, C-4), 50.6 (CH, C-1), 41.8 (CH_2, C-6), 35.0 (CH_2, C-7), 30.7 (CH, C-8), 20.6 (CH_3, C-9); *m/z* (ESI) 170 $[MH]^+$; [HRMS (ESI): calcd. for $C_8H_{12}NOS$, 170.0634. Found: $[MH]^+$, 170.0632 (1.0 ppm error)].

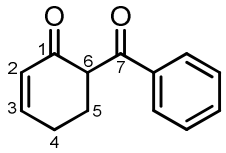
Lab Book Ref. = JDC/8/6



(6*S)-6-[(*R**)-Hydroxy(phenyl)methyl]cyclohex-2-en-1-one 260a:** To a stirred solution of di*iso*propylamine (1.76 mL, 12.5 mmol, 1.2 equiv.) in THF (50 mL) at 0 ºC was added *n*-BuLi (1.38 M in hexane, 9.00 mL, 12.5 mmol, 1.2 equiv.). The solution was stirred at 0 ºC for 30 min., then cooled to −78 ºC before adding cyclohexenone (1.00 mL, 10.4 mmol, 1.0 equiv.). The solution was held at −78 ºC for 1 h, then benzaldehyde (1.10 mL, 10.9 mmol, 1.05 equiv.) was added dropwise. The solution was held at −78 ºC for a further 2 h, then quenched with 10% aq. HCl (10 mL). After warming to rt, the organic phase was separated, then the aqueous phase was extracted with DCM (3 × 50 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), then concentrated *in vacuo* to give a yellow oil which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give the title compound **260a** (1.49 g, 71%) as a colourless oil; R_f 0.34 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3443 (br), 2925, 2869, 1666, 1423, 1223, 1045; δ_H (400 MHz, $CDCl_3$) 7.37-7.29 (5 H, m, ArH), 7.02 (1 H, dddd, J = 10.0, 5.2, 3.1, 1.0, H-3), 6.08 (1 H, ddd, J = 10.0, 2.6, 1.5, H-2), 4.82, (1 H, dd, J = 9.6, 1.6, H-7), 2.61-2.53 (1 H, m, H-6), 2.33-2.26 (2 H, m, H-4), 1.57-1.48 (2 H, m, H-5); δ_C (100 MHz, $CDCl_3$) 203.6 (CO,

C-1), 151.6 (CH, C-3), 140.9 (C, ArC), 129.5 (CH, C-2), 128.3 (2 × CH, ArCH), 127.9 (CH, ArCH), 127.1 (2 × CH, ArCH), 75.4 (CH, C-7), 52.6 (CH, C-6), 25.6 (CH_2), 25.3 (CH_2); *m/z* (ESI) 225 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{13}H_{14}NaO_2$, 225.0886. Found: $[MNa]^+$, 225.0894 (3.7 ppm error)].

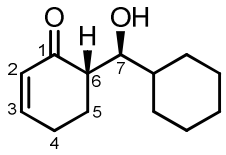
Lab Book Ref. = JDC/2/53



6-Benzoylcyclohex-2-en-1-one 257a: To a stirred solution of DMSO (0.35 mL, 5.00 mmol, 2.0 equiv.) in DCM (5 mL) at −78 ºC was added dropwise trifluoroacetic anhydride (0.53 mL, 3.75 mmol, 1.5 equiv.). The solution was held at −78 ºC for 30 min. before adding alcohol **260a** (0.51 g, 2.50 mmol, 1.0 equiv.) as a pre-cooled solution in DCM (1.5 mL) *via* cannula. The yellow solution was held at −78 ºC for 1 h, then Et_3N (1.74 mL, 12.5 mmol, 5.0 equiv.) was added dropwise. The solution was held at −78 ºC for a further 15 min., then warmed to rt and held for 1 h. The reaction was quenched with H_2O (20 mL), then the aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with 1 M aq. HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, PE/Et_2O, 4:1) to give the title compound **257a** (0.41 g, 81%) as a pale yellow oil; R_f 0.33 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2935, 1686, 1667, 1448, 1290; δ_H (400 MHz, $CDCl_3$, ~1:1(keto/enol)) 16.15 (1 H, s, OH), 7.98-7.93 (2 H, m, ArH), 7.61-7.50 (3 H, m, ArH), 7.50-7.39 (5 H, m, ArH), 7.06 (1 H, ddd, J = 10.1, 4.0, 4.0, H-3_{keto}), 6.82 (1 H, ddd, J = 10.0, 4.3, 4.3, H-3_{enol}), 6.19 (1 H, ddd, J = 10.0, 1.9, 1.9, H-2_{enol}), 6.10 (1 H, ddd, J = 10.1, 2.0, 2.0, H-2_{keto}), 4.42 (1 H, dd, J = 8.9, 5.0, H-6_{keto}), 2.67 (2 H, t, J = 7.3, H-5_{enol}), 2.65-2.37 (3 H, m, H-4_{keto}, $5_{a\ keto}$), 2.32-2.20 (3 H, m, H-4_{enol}, $5_{b\ keto}$); δ_C (100 MHz, $CDCl_3$, **Keto**) 198.0 (CO), 195.9 (CO), 150.8 (CH, C-3), 136.6 (C, ArC), 133.3 (CH, C-2), 129.5 (CH, ArCH), 128.8 (2 × CH, ArCH), 128.5 (2 × CH, ArCH), 54.6 (CH, C-6), 25.5 (CH_2), 24.4 (CH_2); δ_C (100 MHz, $CDCl_3$, **Enol**) 188.7 (C), 177.9 (C), 146.7 (CH, C-3), 135.3 (C, ArC), 130.1 (CH, C-2), 129.0 (CH, ArCH), 128.1 (2 × CH, ArCH), 128.0 (2 × CH, ArCH), 104.7 (C, C-6), 24.8 (CH_2), 23.7 (CH_2);

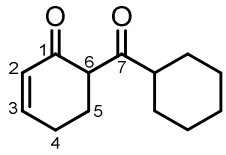
m/z (ESI) 223 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{13}H_{12}NaO_2$, 223.0730. Found: $[MNa]^+$, 223.0736 (2.9 ppm error)].

Lab Book Ref. = JDC/2/60



(6*S)-6-[(*S**)-Cyclohexyl(hydroxy)methyl]cyclohex-2-en-1-one 260b:** Using the procedure described for the preparation of compound **260a**, the title compound **260b** (1.67 g, 76%) was isolated as a pale yellow oil; R_f 0.40 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 3486 (br), 2926, 2852, 1661, 1449, 1390, 1223; δ_H (400 MHz, $CDCl_3$) 7.01-6.95 (1 H, m, H-3), 6.01-5.97 (1 H, m, H-2), 3.90 (1 H, br s, OH), 3.61 (1 H, dd, *J* = 7.8, 2.2, H-7), 2.48-2.38 (3 H, m, H-4, 6), 2.05-1.97 (1 H, m), 1.80-1.57 (5 H, m), 1.54-1.40 (3 H, m), 1.29-1.12 (4 H, m); δ_C (100 MHz, $CDCl_3$) 204.5 (CO, C-1), 150.8 (CH, C-3), 129.9 (CH, C-2), 75.6 (CH, C-7), 48.9 (CH, C-6), 39.5 (CH, CyCH), 30.2 (CH_2), 26.7 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 25.2 (CH_2), 25.1 (CH_2); *m/z* (ESI) 209 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{21}O_2$, 209.1536. Found: $[MH]^+$, 209.1535 (0.4 ppm error)].

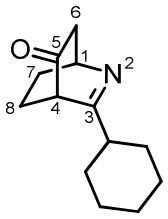
Lab Book Ref. = JDC/3/100



6-(Cyclohexanecarbonyl)cyclohex-2-en-1-one 257b: To a stirred solution of alcohol **260b** (100 mg, 0.48 mmol, 1.0 equiv.) in DCM (5 mL) at rt, was added in one portion DMP (246 mg, 0.58 mmol, 1.2 equiv.). The reaction mixture was stirred at rt for 2 h, then additional DMP (102 mg, 0.24 mmol, 1.0 equiv.) was added. The reaction mixture was held for 18 h, then diluted with diethyl ether (5 mL) before quenching with sat. aq. $NaHCO_3/Na_2S_2O_4$ (1:1, 5 mL). The organic phase was separated, then the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to give a pale yellow oil which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to

give the title compound **257b** (54 mg, 55%, keto/enol, ~1:2) as a yellow oil; R_f 0.65 (keto) and 0.50 (enol) (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2929, 2854, 1713, 1672, 1449; δ_H (400 MHz, $CDCl_3$) 7.00 (1 H, ddd, J = 10.1, 3.7, 3.7, H-3_{keto}), 6.67 (1 H, dd, J = 9.9, 4.3, 4.3, H-3_{enol}), 6.07 (1 H, ddd, J = 9.9, 1.9, 1.9, H-2_{enol}), 6.02 (1 H, ddd, J = 10.1, 2.0, 2.0, H-2_{keto}), 3.66 (1 H, dd, J = 8.4, 4.9, H-6_{keto}), 2.69-2.47 (4 H, m), 2.40-2.27 (4 H, m), 2.10-2.02 (1 H, m), 1.94-1.61 (10 H, m), 1.53-1.41 (2 H, m), 1.37-1.18 (10 H, m); δ_C (100 MHz, $CDCl_3$, **Keto**) 210.5 (CO, C-7), 195.9 (CO, C-1), 151.1 (CH, C-3), 129.2 (CH, C-2), 57.6 (CH, C-6), 50.4 (CH, CyCH), 28.7 (CH_2), 27.5 (CH_2), 25.7 (CH_2), 25.2 (CH_2), 24.2 (CH_2); δ_C (100 MHz, $CDCl_3$, **Enol**) 192.5 (C), 183.4 (C), 144.8 (CH, C-3), 127.9 (CH, C-2), 102.8 (C, C-6), 41.8 (CH, CyCH), 28.9 (CH_2), 25.8 (CH_2), 24.5 (CH_2), 21.3 (CH_2), 25.9 (CH_2); *m/z* (ESI) 207 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{19}O_2$, 207.1380. Found: $[MH]^+$, 207.1379 (0.5 ppm error)].

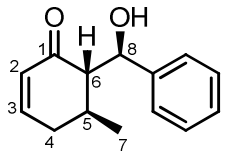
Lab Book Ref. = JDC/4/1



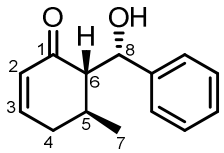
3-Cyclohexyl-2-azabicyclo[2.2.2]oct-2-en-5-one 259b: A stirred solution of enone **257b** (5 mg, 0.03 mmol, 1.0 equiv.) in 35 % aq. NH_3 (1 mL) was held at rt, then concentrated *in vacuo* to afford the title compound **259b** (5 mg, Quant.) as a yellow film; R_f 0.45 (DCM/MeOH/NH_3, 190:9:1); υ_{max}/cm^{-1} (neat) 2927, 2852, 1728, 1623; δ_H (400 MHz, $CDCl_3$) 4.58-4.54 (1 H, m, H-1), 3.41-3.39 (1 H, dd, J = 3.0, 1.9, H-4), 2.12-2.08 (2 H, m, H-6), 1.96-1.06 (15 H, m); δ_C (100 MHz, $CDCl_3$) 209.6 (CO, C-5), 178.8 (CN, C-4), 55.2 (CH, C-4), 52.2 (CH, C-1), 46.7 (CH, CyCH), 39.1 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 25.7 (CH_2), 23.3 (CH_2), 21.1 (CH_2); *m/z* (ESI) 206 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{20}NO$, 206.1539. Found: $[MH]^+$, 206.1544 (2.3 ppm error)].

Lab Book Ref. = JDC/4/3

Representative Procedure for Aldol Reactions:

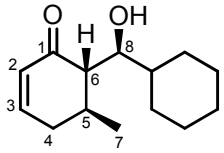


(5*S,6*S**)-6-[(*R**)-Hydroxy(phenyl)methyl]-5-methylcyclohex-2-en-1-one *anti*-261a:** To a stirred solution of di*iso*propylamine (364 μL, 2.60 mmol, 1.3 equiv.) in THF (10 mL) at 0 ºC was added dropwise *n*-BuLi (1.53 M in hexane, 1.57 mL, 2.40 mmol, 1.2 equiv.). The colourless solution was stirred at 0 ºC for 30 min., then cooled to −78 ºC before adding cyclohexenone **87** (220 mg, 2.00 mmol, 1.0 equiv.) dropwise. The solution was held at −78 ºC for 1 h, then benzaldehyde (304 μL, 3.00 mmol, 1.5 equiv.) was added dropwise. The solution was held at −78 ºC for 2 h before quenching with AcOH (0.5 mL). The reaction was diluted with water (10 mL), then the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the crude product which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give the *syn*-isomer ***syn*-261a** (50 mg, 12%) as a colourless oil and the title compound ***anti*-261a** (289 mg, 67%) as a colourless crystalline solid; mp. 115-117 ºC; R_f 0.24 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 3430 (br), 2918, 1666, 1454, 1391, 1049; δ_H (400 MHz, $CDCl_3$) 7.40-7.28 (5 H, m, ArH), 6.90 (1 H, dddd. *J* = 10.1, 4.8, 3.1, 1.0, H-3), 6.07 (1 H, dddd, *J* = 10.1, 2.3, 1.6, 0.5, H-2), 4.83 (1 H, dd, *J* = 8.4, 4.3, H-8), 2.94 (1 H, d, *J* = 4.3, OH), 2.59 (1 H, dddd, *J* = 19.7, 5.6, 3.1, 2.3, H-4_a), 2.52 (1 H, dd, *J* = 8.4, 4.3, H-6), 2.08 (1 H, dddd, *J* = 19.7, 4.8, 3.7, 1.6, H-4_b), 1.99-1.98 (1 H, m, H-5), 1.01 (3 H, d, *J* = 7.1, H-7); δ_C (100 MHz, $CDCl_3$) 201.2 (CO, C-1), 148.1 (CH, C-3), 142.1 (C, ArC), 128.5 (2 × CH, ArH), 128.5 (CH, C-2), 128.0 (CH, ArH), 126.3 (2 × CH, ArCH), 73.3 (CH, C-8), 60.5 (CH, C-6), 30.8 (CH_2, C-4), 30.0 (CH, C-5), 19.9 (CH_3, C-7); *m/z* (ESI) 239 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{16}NaO_2$, 239.1043. Found: $[MNa]^+$, 239.1044 (0.6 ppm error)].



(5*S,6*S**)-6-[(*S**)-Hydroxy(phenyl)methyl]-5-methylcyclohex-2-en-1-one *syn*-261a:** A colourless oil; 50 mg (12%); R_f 0.30 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 3410 (br), 2959, 2920, 1665, 1390, 1050; δ_H (400 MHz, $CDCl_3$) 7.32-7.21 (5 H, m, ArH), 6.91 (1 H, ddd, *J* = 10.0, 4.7, 3.5, H-3), 5.99 (1 H, ddd, *J* = 10.0, 2.3, 1.7, H-2), 5.06 (1 H, d, *J* = 5.3, H-8), 2.62 (1 H, dd, *J* = 8.3, 5.3, H-6), 2.51 (1 H, dddd, *J* = 18.7, 4.8, 4.7, 1.7, H-4_a), 2.23-2.12 (1 H, m, H-5), 2.10 (1 H, dddd, *J* = 18.7, 7.4, 3.5, 2.3, H-4_b), 1.04 (3 H, d, *J* = 6.6, H-7); δ_C (100 MHz, $CDCl_3$) 202.1 (CO, C-1), 150.2 (CH, C-3), 141.8 (C, ArC), 129.7 (CH, C-2), 128.2 (2 × CH, ArH), 127.4 (CH, ArH), 126.7 (2 × CH, ArH), 73.9 (CH, C-8), 58.7 (CH, C-6), 32.9 (CH_2, C-4), 29.9 (CH, C-5), 19.9 (CH_3, C-7); *m/z* (ESI) 239 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{16}NaO_2$, 239.1043. Found: $[MNa]^+$, 239.1045 (1.1 ppm error)].

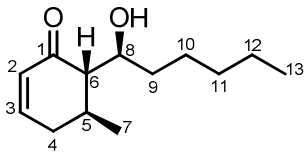
Lab Book Ref. = JDC/9/27

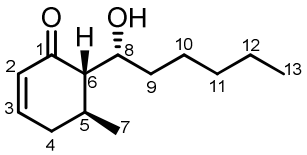


(5*S,6*S**)-6-[(*S**)-Cyclohexyl(hydroxy)methyl]-5-methylcyclohex-2-en-1-one *anti*-261b:** Using the procedure described for the preparation of compound **261a**, the title compound ***anti*-261b** (444 mg, 67%) was isolated as a colourless oil; R_f 0.32 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 3469 (br), 2926, 1666, 1450, 1391, 1258, 1096; δ_H (400 MHz, $CDCl_3$) 6.84 (1 H, ddd, *J* = 10.1, 4.0, 4.0, H-3), 5.95 (1 H, ddd, *J* = 10.1, 2.0, 2.0, H-2), 3.51-3.44 (1 H, m, H-8), 2.50 (1 H, dddd, *J* = 19.2, 4.6, 4.0, 2.0, H-4_a), 2.41-2.30 (1 H, m, H-5), 2.29 (1 H, dd, *J* = 8.1, 4.5, H-6), 2.16 (1 H, d, *J* = 7.8, OH), 2.16-2.06 (1 H, m, H-4_b), 1.94-1.87 (1 H, m, CyH), 1.80-1.68 (3 H, m, CyH), 1.67-1.53 (2 H, m, CyH), 1.29-0.96 (5 H, m, CyH), 1.08 (3 H, d, *J* = 6.6, H-7); δ_C (100 MHz, $CDCl_3$) 202.3 (CO, C-1), 148.3 (CH, C-3), 129.5 (CH, C-2), 74.4 (CH, C-8), 55.3 (CH, C-6), 41.7 (CH, CyCH), 33.0 (CH_2, C-4), 31.3 (CH, C-5), 30.2 (CH_2, $CyCH_2$), 27.9 (CH_2, $CyCH_2$), 26.3 (CH_2, $CyCH_2$), 26.2 (CH_2, $CyCH_2$), 25.9 (CH_2, $CyCH_2$), 19.8 (CH_3, C-7);

m/z (ESI) 245 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{22}NaO_2$, 245.1512. Found: $[MNa]^+$, 245.1512 (0.1 ppm error)].

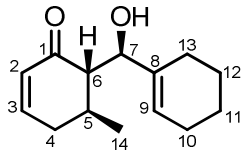
Lab Book Ref. = JDC/9/27



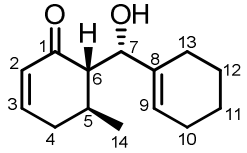


6-(1-Hydroxyhexyl)-5-methylcyclohex-2-en-1-one 261c: Using the procedure described for the preparation of compound **261a**, the title compound **261c** (287 mg, 45%, ~2.5:1(*anti/syn*)) was isolated as a yellow oil; R_f 0.44 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 3442 (br), 2956, 2929, 1665, 1390; δ_H (400 MHz, $CDCl_3$, ~2.5:1(*anti/syn*)) 6.95 (1 H, ddd, *J* = 10.1, 5.6, 2.4, H-3_{syn}), 6.85 (1 H, ddd, *J* = 10.1, 4.7, 4.0, H-3_{anti}), 6.00-5.95 (2 H, m, H-2), 3.88-3.73 (2 H, m, H-8), 2.51 (1 H, dddd, *J* = 19.2, 4.8, 4.7, 1.8, H-$4_{a\ anti}$), 2.47-2.31 (3 H, m, H-$4_{a\ syn}$, 5_{anti}, 6_{syn}), 2.21-2.08 (3 H, m, H-4_b, 5_{syn}), 2.14 (1 H, dd, *J* = 8.2, 4.5, H-6_{anti}), 1.79-1.68 (2 H, m, H-9_a), 1.66-1.55 (2 H, m, H-9_b), 1.54-1.40 (2 H, m, H-11_a), 1.40-1.19 (10 H, m, H-10, 11_b, 12), 1.12 (3 H, d, *J* = 6.8, H-7_{anti}), 1.05 (3 H, d, *J* = 6.2, H-7_{syn}), 0.88 (3 H, t, *J* = 6.8, H-13_{anti}), 0.87 (3 H, t, *J* = 6.9, H-13_{syn}); δ_C (400 MHz, $CDCl_3$, ***Anti***) 201.9 (CO, C-1), 148.5 (CH, C-3), 129.6 (CH, C-2), 70.5 (CH, C-8), 58.4 (CH, C-6), 36.4 (CH_2, C-9), 33.1 (CH_2, C-4), 31.7 (CH_2, C-11), 31.6 (CH, C-5), 25.7 (CH_2, C-10), 22.6 (CH_2, C-12), 20.0 (CH_3, C-7), 14.0 (CH_3, C-13); δ_C (400 MHz, $CDCl_3$, ***Syn***) 203.5 (CO, C-1), 150.1 (CH, C-3), 130.1 (CH, C-2), 71.1 (CH, C-8), 57.8 (CH, C-6), 36.4 (CH_2, C-9), 34.2 (CH_2, C-4), 31.9 (CH_2, C-11), 31.7 (CH, C-5), 25.9 (CH_2, C-10), 22.6 (CH_2, C-12), 19.0 (CH_3, C-7), 14.0 (CH_3, C-13); *m/z* (ESI) 233 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{13}H_{22}NaO_2$, 233.1512. Found: $[MNa]^+$, 233.1503 (4.0 ppm error)].

Lab Book Ref. = JDC/9/27



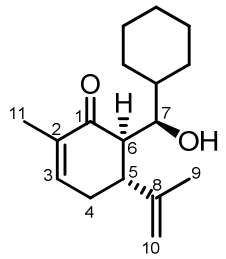
(5*S,6*S**)-6-[(*R**)-Cyclohexenyl(hydroxy)methyl]-5-methylcyclohex-2-en-1-one *anti*-261d:** Using the procedure described for the preparation of compound **261a**, the *syn*-isomer ***syn*-261d** (25 mg, 2%) was isolated as a colourless oil and the title compound ***anti*-261d** (491 mg, 50%) was isolated as a colourless oil; 0.31 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 3438 (br), 2926, 1666; δ_H (400 MHz, $CDCl_3$) 6.82 (1 H, dddd, *J* = 10.0, 5.5, 2.6, 1.2, H-3), 5.97 (1 H, dddd, *J* = 10.0, 2.8, 1.2, 0.7, H-2), 5.72-5.68 (1 H, m, H-9), 4.08 (1 H, d, *J* = 9.7, H-7), 2.52 (1 H, dddd, *J* = 19.7, 5.5, 2.8, 2.6, H-4_a), 2.26 (1 H, dd, *J* = 9.7, 2.8, H-6), 2.20-2.06 (2 H, m H-5, 13_a), 2.06-1.97 (3 H, m, H-4_b, 10), 1.79-1.69 (1 H, m, H-13_b), 1.67-1.54 (3 H, m, H-11_a, 12), 1.54-1.43 (1 H, m, H-11_b), 1.02 (3 H, d, *J* = 7.2, H-14); δ_C (100 MHz, $CDCl_3$) 201.7 (CO, C-1), 147.9 (CH, C-3), 137.6 (C, C-8), 128.0 (CH, C-2), 126.2 (CH, C-9), 75.9 (CH, C-7), 56.2 (CH, C-6), 29.7 (CH, C-5), 29.6 (CH_2, C-4), 24.9 (CH_2, C-10), 22.3 (CH_2), 22.3 (CH_2), 22.0 (CH_2, C-13), 19.8 (CH_3, C-14); *m/z* (ESI) 243 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{20}NaO_2$, 243.1356. Found: $[MNa]^+$, 243.1348 (3.0 ppm error)].



(5*S,6*S**)-6-[(*S**)-Cyclohexenyl(hydroxy)methyl]-5-methylcyclohex-2-en-1-one *syn*-261d:** A colourless oil; 25 mg (2%); 0.41 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 3438 (br), 2926, 1666; δ_H (400 MHz, $CDCl_3$) 6.91 (1 H, ddd, *J* = 10.1, 4.7, 3.8, H-3), 5.99 (1 H, ddd, *J* = 10.1, 2.0, 2.0, H-2), 5.64-5.61 (1 H, m, H-9), 4.28 (1 H, d, *J* = 6.6, H-7), 2.58 (1 H, dddd, *J* = 19.1, 4.8, 4.7, 2.0, H-4_a), 2.41 (1 H, dd, *J* = 7.6, 6.6, H-6), 2.27 (1 H, ddqd, *J* = 7.6, 6.8, 6.8, 4.8, H-5), 2.09 (1 H, dddd, *J* = 19.1, 6.8, 3.8, 2.0, H-4_b), 2.05-1.96 (3 H, m, H-10, 13_a), 1.88-1.78 (1 H, m, H-13_b), 1.70-1.40 (4 H, m, H-11, 12), 1.05 (3 H, d, *J* = 6.8, H-14); δ_C (100 MHz, $CDCl_3$) 202.2 (CO, C-1), 149.4 (CH, C-3), 137.7 (C, C-8), 129.5 (CH, C-2), 125.6 (CH, C-9), 76.7 (CH, C-7), 55.6 (CH, C-6), 32.2 (CH_2, C-4), 29.8 (CH, C-5), 25.0 (CH_2, C-10), 24.4 (CH_2, C-13), 22.5 (CH_2), 22.3 (CH_2), 19.7

(CH_3, C-14); *m/z* (ESI) 243 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{20}NaO_2$, 243.1356. Found: $[MNa]^+$, 243.1348 (3.0 ppm error)].

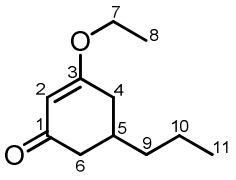
Lab Book Ref. = JDC/9/52



(5*R*,6*R*)-6-[(*R*)-Cyclohexyl(hydroxy)methyl]-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one *anti*-261e: Using the procedure described for the preparation of compound **261a**, the title compound ***anti*-261e** (1.97 g, Quant.) was isolated as a colourless crystalline solid; mp. 87-89 ºC R_f 0.44 (PE/EtOAc, 4:1); $[\alpha]^{21}_D$ +75.1 (*c* 1.02, $CHCl_3$); υ_{max}/cm^{-1} (thin film) 3501, 2923, 1656, 1448, 1370; δ_H (400 MHz, $CDCl_3$) 6.61 (1 H, ddd, *J* = 5.5, 2.8, 1.4, H-3), 4.85-4.82 (1 H, m, H-10_a), 4.82-4.80 (1 H, m, H-10_b), 3.16 (1 H, ddd, *J* = 10.0, 8.6, 2.0, H-7), 2.96 (1 H, ddd, *J* = 11.8, 10.2, 5.1, H-5), 2.56 (1 H, dd, *J* = 11.8, 2.0, H-6), 2.46-2.35 (1 H, m, H-4_a), 2.33-2.22 (1 H, m, H-4_b), 2.27-2.19 (1 H, d, *J* = 10.0, OH), 2.08-2.00 (1 H, m, CyH), 1.93-1.82 (1 H, m, CyH), 1.72-1.54 (4 H, m, CyH), 1.70-1.67 (3 H, m, H-11), 1.63 (3 H, br s, H-9), 1.25-1.11 (3 H, m, CyH), 1.05 (2 H, m, CyH); δ_C (100 MHz, $CDCl_3$) 202.0 (CO, C-1), 144.8 (C, C-8), 143.5 (CH, C-3), 135.6 (C, C-2), 114.0 (CH_2, C-10), 75.2 (CH, C-7), 50.0 (CH, C-6), 46.2 (CH, C-7), 42.0 (CH, CyCH), 30.8 (CH_2, C-4), 30.2 (CH_2, $CyCH_2$), 29.5 (CH_2, $CyCH_2$), 26.2 (CH_2, $CyCH_2$), 26.0 (CH_2, $CyCH_2$), 25.7 (CH_2, $CyCH_2$), 18.6 (CH_3, C-9), 15.5 (CH_3, C-11); *m/z* (ESI) 263 $[MH]^+$; [HRMS (ESI): calcd. for $C_{17}H_{27}O_2$, 263.2006. Found: $[MH]^+$, 263.2006 (0.2 ppm error)]; Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.98; H, 9.96.

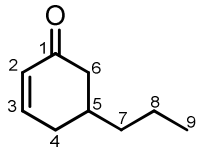
Lab Book Ref. = JDC/9/61

Synthesis of (5*S,6*S**)-6-Hydroxy(phenyl)methyl]-5-propylcyclohex-2-en-1-one 261f:**



3-Ethoxy-5-propylcyclohex-2-en-1-one: To a stirred solution of 5-propylcyclohexane-1,3-dione (1.75 g, 11.3 mmol, 1.0 equiv.) in PhMe (40 mL) and EtOH (10 mL) at rt was added *p*-TsOH (65 mg, 0.34 mmol, 0.03 equiv). The yellow solution was heated to reflux (Dean-Stark) and held for 48 h before cooling to rt and quenching with sat. aq. $NaHCO_3$ (20 mL). The aqueous phase was separated and extracted with EtOAc (2 × 20 mL), then the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound 3-ethoxy-5-propylcyclohex-2-enone (1.60 g, 78%) as a pale yellow oil; R_f 0.53 (EtOAc); υ_{max}/cm^{-1} (neat) 2958, 2873, 1655, 1605, 1380, 1212, 1140; δ_H (400 MHz, $CDCl_3$) 5.29 (1 H, s, H-2), 3.88 (1 H, dq, J = 9.7, 7.1, H-7_a), 3.84 (1 H, dq, J = 9.7, 7.1, H-7_b), 2.44-2.35 (2 H, m, H-4_a, 6_a), 2.16-1.94 (3 H, m, H-4_b, 5, 6_b), 1.35-1.29 (7 H, m, H-8, 9, 10), 0.87 (3 H, t, J = 7.0, H-11); δ_C (100 MHz, $CDCl_3$) 200.3 (CO, C-1), 178.0 (C, C-3), 102.2 (CH, C-2), 64.3 (CH_2, C-7), 43.1 (CH_2, C-6), 37.6 (CH_2, C-9), 35.4 (CH_2, C-4), 33.3 (CH, C-5), 19.5 (CH_2, C-10), 14.0 (CH_3), 13.9 (CH_3); *m/z* (ESI) 205 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{11}H_{18}NaO_2$, 205.1199. Found: $[MNa]^+$, 205.1190 (4.2 ppm error)].

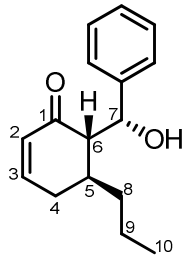
Lab Book Ref. = JDC/12/94



5-Propylcyclohex-2-en-1-one: To a stirred solution of $LiAlH_4$ (4.0 M in Et_2O, 0.58 mL, 2.30 mmol, 1.0 equiv.) in Et_2O (6 mL) at 0 ºC was added dropwise enone 3-ethoxy-5-propylcyclohex-2-enone (1.56 g, 8.60 mmol, 3.7 equiv.) as a solution in Et_2O (4 mL). The resulting white slurry was held at 0 ºC for 30 min. before warming to rt and holding for 18 h. The reaction was cooled to 0 ºC, then sodium sulfate decahydrate was

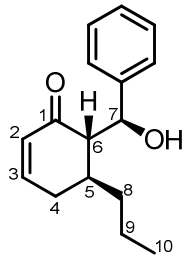
carefully added until effervescence ceased. The slurry was filtered, then to the filtrate was added 10% aq. H_2SO_4 (5 mL). The biphasic solution was stirred at rt for 18 h, then the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/Et_2O, 9:1) to give the title compound 5-propylcyclohex-2-enone (421 mg, 36%) as a colourless oil; R_f 0.58 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2958, 2926, 2873, 1681, 1388, 1247; δ_H (400 MHz, $CDCl_3$) 6.92 (1 H, ddd, J = 10.0, 5.7, 2.4, H-3), 5.95 (1 H, dddd, J = 10.0, 2.7, 1.0, 1.0, H-2), 2.52-2.34 (2 H, m, H-4_a, 6_a), 2.11-1.93 (3 H, m, H-4_b, 5, 6_b), 1.36-1.25 (4 H, m, H-7, 8), 0.85 (3 H, t, J = 7.1, H-9); δ_C (100 MHz, $CDCl_3$) 200.0 (CO, C-1), 149.9 (CH, C-3), 129.5 (CH, C-2), 44.3 (CH_2, C-6), 37.8 (CH_2, C-7), 34.8 (CH, C-5), 32.1 (CH_2, C-4), 19.5 (CH_2, C-8), 13.9 (CH_3, C-9); *m/z* (ESI) 161 $[MNa]^+$; [HRMS (ESI): calcd. for $C_9H_{14}NaO$, 161.0937. Found: $[MNa]^+$, 161.0937 (0.2 ppm error)].

Lab Book Ref. = JDC/13/3



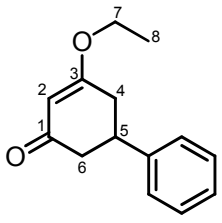
(5*S,6*S**)-6-[(*R**)-Hydroxy(phenyl)methyl]-5-propylcyclohex-2-en-1-one *anti*-261f:** Using the procedure described for the preparation of compound **261a**, the *syn*-isomer ***syn*-261f** (61 mg, 13%) was isolated as a colourless oil and the title compound ***anti*-261f** (356 mg, 73%) was isolated as an amorphous yellow solid; R_f 0.29 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 3415 (br), 2957, 2927, 1661, 1392; δ_H (400 MHz, $CDCl_3$) 7.42-7.27 (5 H, m, ArH), 6.88 (1 H, dddd, J = 9.9, 5.3, 2.6, 1.1, H-3), 6.08-6.02 (1 H, m, H-2), 4.79 (1 H, d, J = 9.3, H-7), 3.02 (1 H, br s, OH), 2.60 (1 H, dd, J = 9.3, 2.8, H-6), 2.55 (1 H, dddd, J = 19.8, 5.6, 2.8, 2.6, H-4_a), 2.14-2.06 (1 H, m, H-4_b), 1.70-1.62 (1 H, m, H-5), 1.38-1.06 (4 H, m, H-8, 9), 0.71 (3 H, t, J = 7.2, H-10); δ_C (400 MHz, $CDCl_3$) 201.3 (CO, C-1), 148.3 (CH, C-3, 141.9 (C, ArC), 128.6 (2 × CH, ArCH), 128.3 (CH, C-2), 128.1 (CH, ArCH), 126.4 (2 × CH, ArCH), 73.6 (CH, C-7), 58.7 (CH, C-6), 35.3

(CH_2, C-8), 34.4 (CH, C-5), 28.3 (CH_2, C-4), 19.9 (CH_2, C-9), 13.6 (CH_3, C-10); *m/z* (ESI) 267 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{16}H_{20}NaO_2$, 267.1356. Found: $[MNa]^+$, 267.1359 (1.5 ppm error)].



(5*S,6*S**)-6-[(*S**)-Hydroxy(phenyl)methyl]-5-propylcyclohex-2-en-1-one *syn*-261f:** A colourless oil; 61 mg (13%); R_f 0.45 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 3431 (br), 2957, 2926, 1668, 1391, 1029; δ_H (400 MHz, $CDCl_3$) 7.38-7.23 (5 H, m, ArH), 6.94-6.88 (1 H, m, H-3), 5.99 (1 H, ddd, *J* = 10.1, 1.9, 1.9, H-2), 5.06 (1 H, dd, *J* = 6.1, 5.7, H-7), 3.54 (1 H, d, *J* = 6.1, OH), 2.70-2.59 (1 H, m, H-4_a), 2.68 (1 H, dd, *J* = 6.0, 5.7, H-6), 2.23-2.09 (2 H, m, H-4_b, 5), 1.49-1.39 (1 H, m, H-8_a) 1.37-1.15 (3 H, m, H-8_b, 9). 0.81 (3 H, t, *J* = 7.2, H-10); δ_C (400 MHz, $CDCl_3$) 201.5 (CO, C-1), 149.9 (CH, C-3), 141.9 (C, ArC), 129.6 (CH, C-2), 128.3 (2 × CH, ArCH), 127.7 (CH, ArCH), 126.5 (2 × CH, ArCH), 74.5 (CH, C-7), 57.6 (CH, C-6), 35.6 (CH_2, C-8), 33.9 (CH, C-5), 29.5 (CH_2, C-4), 19.7 (CH_2, C-9), 13.9 (CH_3, C-10); *m/z* (ESI) 267 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{16}H_{20}NaO_2$, 267.1356. Found: $[MNa]^+$, 267.1350 (1.9 ppm error)].
Lab Book Ref. = JDC/13/27/B

Synthesis of (5*S,6*S**)-6-(Hydroxy(phenyl)methyl)-5-phenylcyclohex-2-en-1-one 261g:**

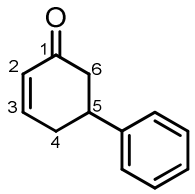


3-Ethoxy-5-phenylcyclohex-2-en-1-one: To a stirred solution of 5-phenylcyclohexane-1,3-dione (5.00 g, 26.6 mmol, 1.0 equiv.) in PhMe (90 mL) and EtOH (25 mL) at rt was added *p*-TsOH (152 mg, 0.80 mmol, 0.03 equiv). The yellow

solution was heated to reflux (Dean-Stark) and held for 18 h before cooling to rt and quenching with sat. aq. $NaHCO_3$ (25 mL). The aqueous phase was separated and extracted with EtOAc (2 × 25 mL), then the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound 3-ethoxy-5-phenylcyclohex-2-enone (3.86 g, 67%) as a pale yellow oil; R_f 0.58 (EtOAc); υ_{max}/cm^{-1} (neat) 2982, 2941, 1655, 1603, 1379, 1350, 1210; δ_H (400 MHz, $CDCl_3$) 7.36-7.30 (2 H, m, ArH), 7.27-7.21 (3 H, m, ArH), 5.42 (1 H, s, H-2), 3.94 (1 H, dq, J = 9.8, 7.0, H-7_a), 3.90 (1 H, dq, J = 9.8, 7.0, H-7_b), 3.34 (1 H, dddd, J = 12.4, 10.4, 5.0, 5.0, H-5), 2.71-2.56 (3 H, m, H-4, 6_a), 2.54 (1 H, dd, J = 16.4, 12.4, H-6_b), 1.36 (3 H, t, J = 7.0, H-8); δ_C (100 MHz, $CDCl_3$) 198.6 (CO, C-1), 176.8 (C, C-3), 142.6 (C, ArC), 128.6 (2 × CH, ArCH), 126.9 (CH, ArCH), 126.5 (2 × CH, ArCH), 102.3 (CH, C-2), 64.4 (CH_2, C-7), 43.7 (CH_2, C-6), 39.2 (CH, C-5), 36.5 (CH_2, C-4), 14.0 (CH_3, C-8). *m/z* (ESI) 239 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{16}NaO_2$, 239.1043. Found: $[MNa]^+$, 239.1042 (0.2 ppm error)].

Lab Book Ref. = JDC/12/87

Data were consistent with those published.[182]

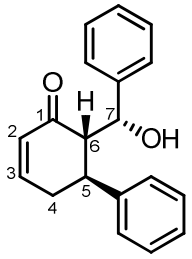


5-Phenylcyclohex-2-en-1-one: To a stirred solution of $LiAlH_4$ (4.0 M in Et_2O, 1.18 mL, 4.70 mmol, 1.0 equiv.) in Et_2O (11 mL) at 0 ºC was added dropwise enone 3-ethoxy-5-phenylcyclohex-2-enone (3.77 g, 17.4 mmol, 3.70 equiv.) as a solution in Et_2O (9 mL). The resulting white slurry was held at 0 ºC for 30 min. before warming to rt and holding for 18 h. The reaction was cooled to 0 ºC, then sodium sulfate decahydrate was carefully added until effervescence ceased. The slurry was filtered, then to the filtrate was added 10% aq. H_2SO_4 (5 mL). The biphasic solution was stirred at rt for 18 h, then the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/Et_2O, 9:1) to give the title compound 5-phenylcyclohex-2-enone (1.95 g, 65%) as a colourless oil; R_f 0.47 (PE/EtOAc, 2:1); δ_H

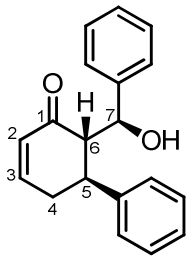
(400 MHz, $CDCl_3$) 7.38-7.33 (2 H, m, ArH), 7.29-7.23 (3 H, m, ArH), 7.06 (1 H, ddd, *J* = 10.1, 5.7, 2.5, H-3), 6.13 (1 H, dd, *J* = 10.1, 2.8, H-2), 3.36 (1 H, dddd, *J* = 12.5, 10.8, 4.9, 4.9, H-5), 2.76-2.60 (3 H, m, H-4_a, 6), 2.54 (1 H, dddd, *J* = 18.7, 10.8, 2.8, 2.5, H-4_b).

Lab Book Ref. = JDC/13/2

Date were consistent with those published.[183]



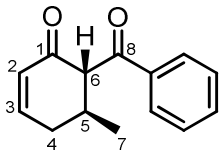
(5*S,6*S**)-6-[(*R**)-Hydroxy(phenyl)methyl]-5-phenylcyclohex-2-en-1-one *anti*-261g:** Using the procedure described for the preparation of compound **261a**, the *syn*-isomer ***syn*-261g** (129 mg, 15%) was isolated as a colourless crystalline solid and the title compound ***anti*-261g** (558 mg, 67%) was isolated as a colourless crystalline solid; mp. 140-143 ºC; R_f 0.21 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 3433 (br), 3029, 1657, 1452, 1392; δ_H (400 MHz, $CDCl_3$) 7.36-7.28 (6 H, m, ArH), 7.28-7.21 (4 H, m, ArH), 6.97 (1 H, ddd, *J* = 10.1, 4.6, 3.5, H-3), 6.10 (1 H, ddd, *J* = 10.1, 2.0, 1.7, H-2), 4.69 (1 H, dd, *J* = 8.5, 4.2, H-7), 3.42 (1 H, ddd, *J* = 9.6, 8.0, 5.7, H-5), 3.24 (1 H, d, *J* = 8.5, OH), 3.22 (1 H, dd, *J* = 9.6, 4.2, H-6), 2.76 (1 H, dddd, *J* = 19.5, 5.7, 4.6, 1.7, H-4_a), 2.67 (1 H, dddd, *J* = 19.5, 8.0, 3.5, 2.0, H-4_b); δ_C (400 MHz, $CDCl_3$) 200.7 (CO, C-1), 148.5 (CH, C-3), 143.1 (C, ArC), 142.4 (C, ArC), 130.0 (CH, C-2), 128.9 (CH, ArCH), 128.2 (2 × CH, ArCH), 127.5 (2 × CH, ArCH), 127.2 (2 × CH, ArCH), 127.1 (CH, ArCH), 125.7 (2 × CH, ArCH), 72.4 (CH, C-7), 58.3 (CH, C-6), 43.3 (CH, C-5), 33.1 (CH_2, C-4); *m/z* (ESI) 301 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{19}H_{18}NaO_2$, 301.1199. Found: $[MNa]^+$, 301.1203 (1.4 ppm error)]; Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.87; H, 6.54.



(5*S,6*S**)-6-[(*S**)-Hydroxy(phenyl)methyl]-5-phenylcyclohex-2-en-1-one *syn*-261g:** A colourless crystalline solid; 129 mg (15%); mp. 79-82 ºC; R_f 0.36 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 3475 (br), 1664, 1389, 908; δ_H (400 MHz, $CDCl_3$) 7.35-7.30 (2 H, m, ArH), 7.29-7.21 (4 H, m, ArH), 7.19-7.15 (2 H, m, ArH), 7.12-7.07 (2 H, m, ArH), 6.98 (1 H, ddd, *J* = 10.0, 5.5, 2.9, H-3), 6.12 (1 H, ddd, *J* = 10.0, 2.4, 1.2, H-2), 5.05 (1 H, d, *J* = 9.5, OH), 4.74 (1 H, dd, *J* = 9.5, 4.6, H-7), 3.39 (1 H, dd, *J* = 11.8, 4.6, H-6), 3.06 (1 H, ddd, *J* = 11.8, 9.9, 5.4, H-5), 2.58 (1 H, dddd, *J* = 19.1, 5.5, 5.4, 1.2, H-4_a), 2.50 (1 H, dddd, *J* = 19.1, 9.9, 2.9, 2.4, H-4_b); δ_C (400 MHz, $CDCl_3$) 202.5 (CO, C-1), 150.2 (CH, C-3), 141.9 (C, ArC), 141.2 (C, ArC), 130.3 (CH, C-2), 128.8 (2 × CH, ArCH), 128.0 (2 × CH, ArCH), 127.6 (2 × CH, ArCH), 127.4 (CH, ArCH), 127.4 (2 × CH, ArCH), 127.1 (CH, ArCH), 74.3 (CH, C-7), 55.5 (CH, C-6), 42.4 (CH, C-5), 35.0 (CH_2, C-4); *m/z* (ESI) 301 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{19}H_{18}NaO_2$, 301.1199. Found: $[MNa]^+$, 301.1194 (1.6 ppm error)].

Lab Book Ref. = JDC/13/28/B

Representative Procedures for the Swern Oxidation of β-Hydroxy Ketones:

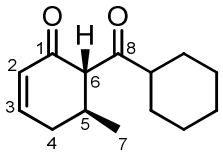


(5*S,6*R**)-6-Benzoyl-5-methylcyclohex-2-en-1-one 262a:** To a stirred solution of DMSO (0.20 mL, 2.80 mmol, 2.0 equiv.) in DCM (10 mL) at −78 ºC was added dropwise trifluoroacetic anhydride (294 μL, 2.10 mmol, 1.5 equiv.). The solution was held at −78 ºC for 30 min. before adding alcohol **261a** (300 mg, 1.40 mmol, 1.0 equiv.) as a pre-cooled solution in DCM (5 mL) *via* cannula. The yellow solution was held at −78 ºC for 1 h, then Et_3N (0.98 mL, 7.00 mmol, 5.0 equiv.) was added dropwise. The

solution was held at −78 ºC for a further 15 min., then warmed to rt and held for 1 h. The reaction was quenched with H_2O (20 mL), then the aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with 1 M aq. HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, PE/Et_2O, 4:1) to give the title compound **262a** (258 mg, 86%) as a colourless oil; R_f 0.44 (PE/EtOAc, 2:1), υ_{max}/cm^{-1} (neat) 2961, 1685, 1663, 1448, 1388, 1298; δ_H (400 MHz, $CDCl_3$) 7.95-7.89 (2 H, m, ArH), 7.57-7.52 (1 H, m, ArH), 7.47-7.42 (2 H, m, ArH), 7.01 (1 H, ddd, J = 10.1, 5.5, 2.8, H-3), 6.07 (1 H, ddd, J = 10.1, 2.6, 1.4, H-2), 4.14 (1 H, d, J = 10.7, H-6), 2.87-2.74 (1 H, m, H-5), 2.59 (1 H, dddd, J = 19.1, 5.5, 5.2, 1.4, H-4_a), 2.19 (1 H, dddd, J = 19.1, 9.6, 2.8, 2.6, H-4_b), 1.00 (3 H, d, J = 6.6, H-7); δ_C (100 MHz, $CDCl_3$) 198.7 (CO), 196.5 (CO), 149.9 (CH, C-3), 137.7 (C, ArC), 133.1 (CH, ArCH), 129.1 (CH, C-2), 128.6 (2 × CH, ArCH), 128.5 (2 × CH, ArCH), 61.8 (CH, C-6), 32.9 (CH_2, C-4), 32.6 (CH, C-5), 19.8 (CH_3, C-7); *m/z* (ESI) 215 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{15}O_2$, 215.1067. Found: $[MH]^+$, 215.1064 (1.2 ppm error)].

Lab Book Ref. = JDC/9/91

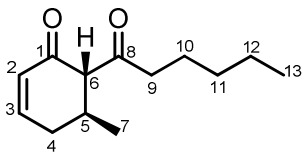
Representative Procedures for the Oxidation of β-Hydroxy Ketones using Dess-Martin Periodinane:



(5*S,6*S**)-6-(Cyclohexanecarbonyl)-5-methylcyclohex-2-en-1-one 262b:** To a stirred solution of alcohol **261b** (444 mg, 2.00 mmol, 1.0 equiv.) in DCM (20 mL) at 0 ºC was added DMP (1.02 g, 2.40 mmol, 1.2 equiv.). The solution was held at 0 ºC for 30 min., then warmed to rt and held for 2 h. The reaction was diluted with Et_2O (20 mL) before quenching with sat. aq. $NaHCO_3$/sat. aq. $Na_2S_2O_3$ (1:1, 20 mL). The biphasic solution was stirred vigourously for 30 min., then the aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **262b** (433 mg, 99%) as a colourless oil; R_f 0.56 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2929,

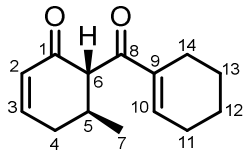
2855, 1713, 1668, 1449, 1386, 1255; δ_H (400 MHz, $CDCl_3$) 6.95 (1 H, ddd, *J* = 10.1, 5.3, 2.9, H-3), 6.00 (1 H, ddd, *J* = 10.1, 2.6, 1.4, H-2), 3.45 (1 H, d, *J* = 10.5, H-6), 2.68-2.47 (3 H, m, H-4_a, 5, CyH), 2.10 (1 H, dddd, *J* = 19.0, 9.3, 2.9, 2.6, H-4_b), 1.95-1.73 (4 H, m, CyH), 1.73-1.62 (1 H, m, CyH), 1.33-1.13 (5 H, m, CyH), 0.97 (3 H, d, *J* = 6.5, H-7); δ_C (100 MHz, $CDCl_3$) 211.3 (CO, C-8), 193.5 (CO, C-1), 149.9 (CH, C-3), 129.1 (CH, C-2), 64.6 (CH, C-6), 52.2 (CH, CyCH), 32.8 (CH_2, C-4), 31.4 (CH, C-5), 28.1 (CH_2, $CyCH_2$), 27.2 (CH_2, $CyCH_2$), 25.8 (2 × CH_2, $CyCH_2$), 25.3 (CH_2, $CyCH_2$) 19.9 (CH_3, C-7); *m/z* (ESI) 221 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{21}O_2$, 221.1536. Found: $[MH]^+$, 221.1533 (1.3 ppm error)].

Lab Book Ref. = JDC/9/43



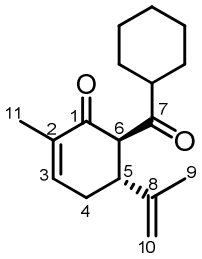
(5*S,6*S**)-6-(Cyclohexanecarbonyl)-5-methylcyclohex-2-en-1-one 262c:** Using the procedure described for the preparation of compound **262b**, the title compound **262c** (276 mg, 98%) was isolated as a pale yellow oil; R_f 0.59 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2959, 1717, 1672; δ_H (400 MHz, $CDCl_3$) 6.93 (1 H, ddd, *J* = 10.1, 5.3, 2.9, H-3), 5.98 (1 H, ddd, *J* = 10.1, 2.6, 1.5, H-2), 3.20 (1 H, d, *J* = 10.3, H-6), 2.64-2.48 (3 H, m, H-4_a, 5, 9_a), 2.47-2.36 (1 H, m, H-9_b), 2.07 (1 H, dddd, *J* = 18.9, 9.0, 2.9, 2.6, H-4_b), 1.66-1.51 (2 H, m, H-10), 1.33-1.20 (4 H, m, H-11, 12), 0.97 (3 H, d, *J* = 6.6, H-7), 0.84 (3 H, t, *J* = 7.0, H-13); δ_C (100 MHz, $CDCl_3$) 207.9 (CO, C-8), 196.2 (CO, C-1), 149.9 (CH, C-3), 128.8 (CH, C-2), 66.6 (CH, C-6), 43.9 (CH_2, C-9), 32.7 (CH_2, C-4), 31.6 (CH, C-5), 25.5 (CH_2, C-11), 22.7 (CH_2, C-10), 22.4 (CH_2, C-12), 19.6 (CH_3, C-7), 13.8 (CH_3, C-13); *m/z* (ESI) 209 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{21}O_2$, 209.1536. Found: $[MH]^+$, 209.1536 (0.2 ppm error)].

Lab Book Ref. = JDC/9/45



(5*S,6*R**)-6-(Cyclohex-1-enecarbonyl)-5-methylcyclohex-2-en-1-one 262d:** Using the procedure described for the preparation of compound **262b**, the title compound **262d** (98 mg, Quant.) was isolated as a colourless oil; R_f 0.29 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2930, 1675, 1655, 1387, 1290, 1176; δ_H (400 MHz, $CDCl_3$) 6.94 (1 H, ddd, *J* = 10.1, 5.5, 2.8, H-3), 6.85-6.81 (1 H, m, H-10), 6.00 (1 H, ddd, *J* = 10.1, 2.7, 1.4, H-2), 3.84 (1 H, d, *J* = 10.7, H-6), 2.71-2.58 (1 H, m, H-5), 2.53 (1 H, dddd, *J* = 19.0, 5.5, 5.2, 1.4, H-4_a), 2.36-2.16 (4 H, m, H-11, 14), 2.11 (1 H, dddd, 19.0, 9.7, 2.8, 2.7, H-4_b), 1.68-1.54 (4 H, m, H-12, 13), 0.94 (1 H, d, *J* = 6.6, H-7); δ_C (100 MHz, $CDCl_3$) 199.2 (CO), 196.9 (CO), 149.5 (CH, C-3), 141.9 (CH, C-10), 140.7 (C, C-9), 129.2 (CH, C-2), 60.1 (CH, C-6), 33.0 (CH_2, C-4), 32.7 (CH, C-5), 26.1 (CH_2, $CyCH_2$), 22.9 (CH_2, $CyCH_2$), 21.7 (CH_2, $CyCH_2$), 21.3 (CH_2, $CyCH_2$), 19.8 (CH_3, C-7); *m/z* (ESI) 219 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{19}O_2$, 219.1380. Found: $[MH]^+$, 219.1381 (0.8 ppm error)].

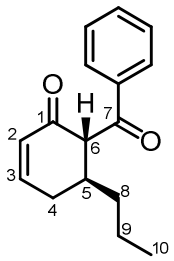
Lab Book Ref. = JDC/11/62



(5*R*,6*R*)-6-(Cyclohexanecarbonyl)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one 262e: Using the procedure described for the preparation of compound **262a**, the title compound **262e** (0.92 g, 93%) was isolated as a colourless oil; $[\alpha]^{24}_D$ −103.2 (*c* 1.25, $CHCl_3$); R_f 0.79 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2923, 1712, 1661, 1449, 1366; δ_H (400 MHz, $CDCl_3$, ~1.6:1 (keto/enol)) 6.71 (1 H, ddq, *J* = 5.6, 2.7, 1.3, H-3_{keto}), 6.21-6.17 (1 H, m, H-3_{enol}), 4.81-4.78 (1 H, m, H-$10_{a\ keto}$), 4.76-4.74 (1 H, m, H-$10_{a\ enol}$), 4.74 (1 H, br s, H-$10_{b\ keto}$), 4.63 (1 H, br s, H-$10_{b\ enol}$), 3.78 (1 H, d, *J* = 11.3, H-6_{keto}), 3.29 (1 H, br d, *J* = 8.1, H-5_{enol}), 3.14 (1 H, ddd, *J* = 11.3, 10.1, 5.1, H-5_{keto}), 2.60-2.40 (3 H, m),

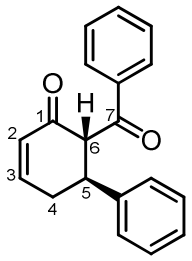
2.39-2.27 (2 H, m), 1.91-1.42 (24 H, m), 1.41-1.09 (9 H, m); δ_C (100 MHz, $CDCl_3$, **Keto**) 210.9 (CO, C-7), 196.9 (CO, C-1), 145.2 (C, C-8), 144.6 (CH, C-3), 135.0 (C, C-2), 112.7 (CH_2, C-10), 61.7 (CH, C-6), 51.8 (CH, CyCH), 44.0 (CH, C-5), 30.1 (CH_2), 28.5 (CH_2), 28.1 (CH_2), 27.4 (CH_2), 25.7 (CH_2), 25.4 (CH_2), 20.6 (CH_3, C-9), 15.6 (CH_3, C-11); δ_C (100 MHz, $CDCl_3$, **Enol**) 193.6 (CO, C-1), 185.0 (C, C-7), 147.0 (C, C-8), 137.1 (CH, C-3), 133.9 (C, C-2), 112.0 (CH_2, C-10), 105.1 (C, C-6), 41.6 (CH, CyCH), 39.0 (CH, C-5), 30.3 (CH_2), 28.5 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 21.0 (CH_3, C-9), 15.6 (CH_3, C-11); *m/z* (ESI) 261 $[MH]^+$; [HRMS (ESI): calcd. for $C_{17}H_{25}O_2$, 261.1849. Found: $[MH]^+$, 261.1856 (2.5 ppm error)].

Lab Book Ref. = JDC/9/90



(5*S,6*R**)-6-Benzoyl-5-propylcyclohex-2-en-1-one 262f:** Using the procedure described for the preparation of compound **262b**, the title compound **262f** (201 mg, 83%) was isolated as a colourless crystalline solid; mp. 61-63 ºC; R_f 0.48 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 2959, 2929, 1687, 1664, 1388, 1298, 1190; δ_H (400 MHz, $CDCl_3$) 7.96-7.88 (2 H, m, ArH), 7.56-7.50 (1 H, m, ArH), 7.49-7.39 (2 H, m, ArH), 7.00 (1 H, ddd, *J* = 10.0, 5.1, 3.1, H-3), 6.07 (1 H, ddd, *J* = 10.0, 2.3, 1.6, H-2), 4.23 (1 H, d, *J* = 9.6, H-6), 2.75-2.65 (1 H, m, H-5), 2.65 (1 H, dddd, *J* = 18.9, 5.1, 5.1, 1.6, H-4_a), 2.16 (1 H, dddd, *J* = 18.9, 8.3, 3.1, 2.3 H-4_b), 1.41-1.18 (4 H, m, H-8, 9), 0.81 (3 H, t, *J* = 5.6, H-10); δ_C (400 MHz, $CDCl_3$) 198.8 (CO, C-1), 196.6 (CO, C-7), 149.8 (CH, C-3), 137.5 (C, ArC), 133.1 (CH, ArCH), 129.1 (CH, C-2), 128.5 (4 × CH, ArCH), 60.4 (CH, C-6), 37.0 (CH, C-5), 36.1 (CH_2, C-8), 29.9 (CH_2, C-4), 19.5 (CH_2, C-9), 13.8 (CH_3, C-10); *m/z* (ESI) 243 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{19}O_2$, 243.1380. Found: $[MH]^+$, 243.1381 (0.6 ppm error)].

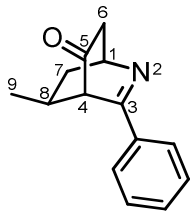
Lab Book Ref. = JDC/13/32



(5*S,6*R**)-6-Benzoyl-5-phenylcyclohex-2-en-1-one 262g:** Using the procedure described for the preparation of compound **262b**, the title compound **262g** (401 mg, 93%) was isolated as a colourless crystalline solid; mp. 148-151 ºC; R_f 0.32 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (thin film) 3030, 1687, 1666, 1449, 1294; δ_H (400 MHz, $CDCl_3$) 7.82-7.75 (2 H, m, ArH), 7.53-7.46 (1 H, m, ArH), 7.41-7.35 (2 H, m, ArH), 7.24-7.19 (4 H, m, ArH), 7.18-7.13 (1 H, m, ArH), 7.11 (1 H, ddd, *J* = 10.1, 5.0, 2.3, H-3), 6.20 (1 H, ddd, *J* = 10.1, 2.6, 1.3, H-2), 4.81 (1 H, d, *J* = 11.8, H-6), 3.99 (1 H, ddd, *J* = 11.8, 10.4, 5.2, H-5), 2.81 (1 H, dddd, *J* = 19.2, 5.2, 5.0, 1.3, H-4_a), 2.69 (1 H, dddd, *J* = 19.2, 10.4, 2.6, 2.3, H-4_b); δ_C (100 MHz, $CDCl_3$) 198.0 (CO), 196.1 (CO), 149.5 (CH, C-3), 141.6 (C, ArC), 137.9 (C, ArC), 133.0 (CH, ArCH), 129.5 (CH, C-2), 128.7 (2 × CH, ArCH), 128.4 (4 × CH, ArCH), 127.2 (2 × CH, ArCH), 127.1 (CH, ArCH), 60.1 (CH, C-6), 43.5 (CH, C-5), 33.6 (CH_2, C-4); *m/z* (ESI) 299 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{19}H_{16}NaO_2$, 299.1043. Found: $[MNa]^+$, 299.1040 (0.7 ppm error)]; Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.08; H, 5.84.

Lab Book Ref. = JDC/11/33

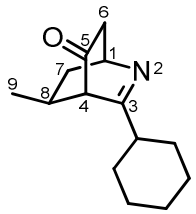
Representative Procedure for the Synthesis of Isoquinuclidinones 263:



8-Methyl-3-phenyl-2-azabicyclo[2.2.2]oct-2-en-5-one 263a: To a stirred solution of diketone (54 mg, 0.25 mmol, 1.0 equiv.) in MeOH (1 mL) at 0 ºC was added dropwise 35% aqueous NH_3 (0.5 mL). The resulting yellow solution was held at 0 ºC for 30 min. then warmed to rt and held until consumption of starting material was observed by TLC

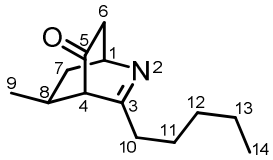
(DCM/MeOH, 95:5). The reaction mixture was diluted with water (5 mL), then extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM/MeOH, 98:2) to give the title compound **263a (**49 mg, 91%) as a yellow oil; R_f 0.53 (DCM/MeOH, 95:5); υ_{max}/cm^{-1} (neat) 2957, 2871, 1730, 1600, 1572, 1447, 1346; δ_H (400 MHz, $CDCl_3$) 7.81-7.77 (2 H, m, ArH), 7.45-7.38 (3 H, m, ArH), 4.79-4.76 (1 H, m, H-1), 3.87 (1 H, d, J = 2.8, H-4), 2.22 (1 H, ddd, J = 19.0, 3.0, 3.0, H-6_a), 2.13 (1 H, dd, J = 19.0, 1.9, H-6_b), 2.11-1.98 (2 H, m, H-7_a, 8), 1.37-1.32 (1 H, m, H-7_b), 1.12 (3 H, d, J = 6.8, H-9); δ_C (100 MHz, $CDCl_3$) 208.3 (CO, C-5), 171.6 (CN, C-3), 135.7 (C, ArC), 130.8 (CH, ArCH), 128.6 (2 × CH, ArCH), 126.2 (2 × CH, ArCH), 57.7 (CH, C-4), 56.1 (CH, C-1), 39.5 (CH_2, C-6), 32.3 (CH_2, C-7), 29.4 (CH, C-8), 21.2 (CH_3, C-9); *m/z* (ESI) 214 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{16}NO$, 214.1226. Found: $[MH]^+$, 214.1231 (2.1 ppm error)].

Lab Book Ref. = JDC/9/98



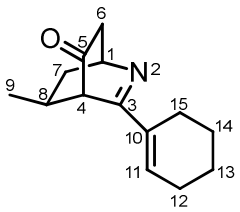
3-Cyclohexyl-8-methyl-2-azabicyclo[2.2.2]oct-2-en-5-one 263b: Using the procedure described for the preparation of compound **263a**, the title compound **263b** (49 mg, 89%) was isolated as a yellow oil; R_f 0.56 (DCM/MeOH, 95:5); υ_{max}/cm^{-1} (neat) 2928, 2853, 1730, 1624, 1450; δ_H (400 MHz, $CDCl_3$) 4.51 (1 H, br s, H-1), 3.23 (1 H, d, J = 3.1, H-4), 2.30-2.22 (1 H, m, CyH), 2.09 (1 H, ddd, J = 19.0, 3.0, 3.0, H-6_a), 2.00 (1 H, dd, J = 19.0, 1.8, H-6_b), 1.99-1.90 (1 H, m, H-7_a), 1.91-1.83 (1 H, m, H-8), 1.82-1.73 (4 H, m, CyH), 1.71-1.64 (1 H, m, CyH), 1.34-1.15 (6 H, m, H-7_b, CyH), 1.02 (3 H, d, J = 7.0, H-9); δ_C (100 MHz, $CDCl_3$) 209.0 (CO, C-5), 179.7 (CN, C-3), 59.3 (CH, C-4), 55.3 (CH, C-1), 46.6 (CH, CyCH), 39.7 (CH_2, C-6), 32.4 (CH_2, C-7), 29.3 (2 × CH_2, $CyCH_2$), 29.1 (CH, C-8), 25.9 (CH_2, $CyCH_2$), 25.7 (2 × CH_2, $CyCH_2$), 21.3 (CH_3, C-9); *m/z* (ESI) 220 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{22}NO$, 220.1696. Found: $[MH]^+$, 220.1702 (2.6 ppm error)].

Lab Book Ref. = JDC/9/84



8-Methyl-3-pentyl-2-azabicyclo[2.2.2]oct-2-en-5-one 263c: Using the procedure described for the preparation of compound **263a**, the title compound **263c** (34 mg, 65%) was isolated as a yellow oil; R_f 0.60 (DCM/MeOH, 95:5); υ_{max}/cm^{-1} (neat) 2956, 2930, 2871, 1731, 1628; δ_H (400 MHz, $CDCl_3$) 4.51-4.47 (1 H, m, H-1), 3.13 (1 H, d, J = 3.0, H-4), 2.35-2.30 (2 H, m, H-10), 2.13-2.06 (1 H, ddd, J = 19.0, 3.4, 2.4, H-6_a), 1.99 (1 H, dd, J = 19.0, 1.8, H-6_b), 1.99-1.84 (2 H, m, H-7_a, 8), 1.57-1.47 (2 H, m, H-11), 1.33-1.18 (5 H, m, H-7_b, 12, 13), 1.01 (3 H, d, J = 6.7, H-9), 0.85 (3 H, t, J = 7.0, H-14); δ_C (100 MHz, $CDCl_3$) 208.6 (CO, C-5), 176.7 (CN, C-3), 60.6 (CH, C-4), 55.5 (CH, C-1), 39.6 (CH_2, C-6), 38.3 (CH_2, C-10), 32.5 (CH_2, C-7), 31.4 (CH_2, C-13), 28.9 (CH, C-8), 25.3 (CH_2, C-11), 22.3 (CH_2, C-12), 21.2 (CH_3, C-9), 13.9 (CH_3, C-14); *m/z* (ESI) 208 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{22}NO$, 208.1696. Found: $[MH]^+$, 208.1697 (0.6 ppm error)].

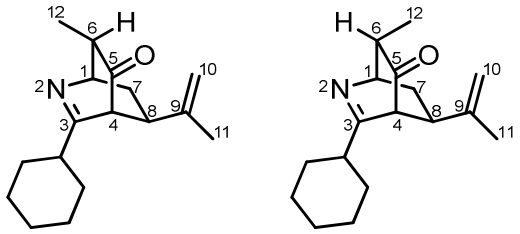
Lab Book Ref. = JDC/9/83



3-Cyclohexenyl-8-methyl-2-azabicyclo[2.2.2]oct-2-en-5-one 263d: Using the procedure described for the preparation of compound **263a**, the title compound **263d** (44 mg, 80%) was isolated as a yellow oil; R_f 0.49 (DCM/MeOH, 95:5); υ_{max}/cm^{-1} (neat) 2930, 2868, 1731, 1576, 1340; δ_H (400 MHz, $CDCl_3$) 6.41 (1 H, m, H-11), 4.60 (1 H, dddd, J = 3.6, 3.6, 1.8, 1.8, H-1), 3.62 (1 H, d, J = 3.1, H-4), 2.30-2.25 (2 H, m, H-15), 2.21-2.15 (2 H, m, H-12), 2.12 (1 H, ddd, J = 19.0, 3.6, 3.0, H-6_a), 2.02 (1 H, dd, J = 19.0, 1.8, H-6_b), 2.01-1.93 (1 H, m, H-7_a), 1.91-1.81 (1 H, m, H-8), 1.67-1.54 (4 H, m, H-13, 14), 1.24 (1 H, ddd, J = 12.8, 4.4, 1.8, H-7_b), 1.03 (3 H, d, J = 7.0, H-9); δ_C (100 MHz, $CDCl_3$) 209.2 (CO, C-5), 172.2 (CN, C-4), 135.3 (C, C-10), 133.0 (CH, C-11), 55.8 (CH, C-4), 55.6 (CH, C-1), 39.8 (CH_2, C-6), 32.7 (CH_2, C-7), 29.2 (CH, C-8), 26.0

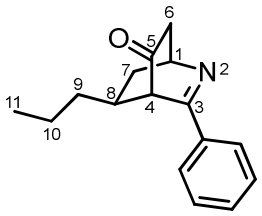
(CH_2, C-12), 24.0 (CH_2, C-15), 22.1 (CH_2, $CyCH_2$), 21.8 (CH_2, $CyCH_2$), 21.3 (CH_3, C-9); *m/z* (ESI) 218 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{20}NO$, 218.1539. Found: $[MH]^+$, 218.1540 (0.4 ppm error)].

Lab Book Ref. = JDC/9/81



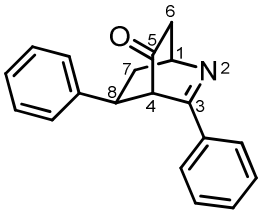
3-Cyclohexyl-6-methyl-8-(prop-1-en-2-yl)-2-azabicyclo[2.2.2]oct-2-en-5-one 263e: Using the procedure described for the preparation of compound **263a**, the title compound **263e** (49 mg, 75%, 3:1) was isolated as a yellow oil; R_f 0.63 (DCM/MeOH, 95:5); υ_{max}/cm^{-1} (neat) 2929, 2853, 1725, 1623, 1450; δ_H (400 MHz, $CDCl_3$) 4.82 (1 H, d, *J* = 1.0, H-$10_{a\ minor}$), 4.79 (1 H, d, *J* = 1.0, H-$10_{a\ major}$), 4.78 (1 H, d, *J* = 1.0, H-$10_{b\ minor}$), 4.76 (1 H, d, *J* = 1.0, H-$10_{b\ major}$), 4.41-4.38 (1 H, m, H-1_{major}), 4.33-4.30 (1 H, m, H-1_{minor}), 3.52 (1 H, d, *J* = 2.7, H-4_{major}), 3.51 (1 H, d, *J* = 2.5, H-4_{minor}), 2.34-2.23 (4 H, m, H-8_{major}, 8_{minor}, CyH_{major}, CyH_{minor}), 2.05-1.91 (4 H, m, H-6_{major}, 6_{minor}, $7_{a\ major}$, $7_{a\ minor}$), 1.91-1.61 (14 H, m, H- $7_{b\ major}$, $7_{b\ minor}$, CyH), 1.73 (3 H, s, H-11_{minor}), 1.72 (3 H, s, H-11_{major}), 1.40-1.14 (8 H, m, CyH), 1.05 (3 H, d, *J* = 7.3, H-12_{major}), 1.04 (3 H, d, *J* = 7.4, H-12_{minor}); δ_C (100 MHz, $CDCl_3$, **Major**) 211.4 (CO, C-5), 178.5 (CN, C-3), 145.4 (C, C-9), 111.0 (CH_2, C-10), 61.2 (CH, C-1), 57.3 (CH, C-4), 46.5 (CH, CyCH), 44.7 (CH, C-6), 40.5 (CH, C-8), 29.8 (CH_2, C-7), 29.5 (CH_2, $CyCH_2$), 29.4 (CH_2, $CyCH_2$), 25.8 (CH_2, $CyCH_2$), 25.7 (2 × CH_2, $CyCH_2$), 22.1 (CH_3, C-11), 15.7 (CH_3, C-12); δ_C (100 MHz, $CDCl_3$, **Minor**) 211.4 (CO, C-5), 180.2 (CN, C-3), 144.5 (C, C-9), 111.5 (CH_2, C-10), 61.0 (CH, C-1), 55.9 (CH, C-4), 46.6 (CH, CyCH), 43.1 (CH, C-6), 42.4 (CH, C-8), 29.4 (CH_2, $CyCH_2$), 25.8 (CH_2, $CyCH_2$), 25.7 (2 × CH_2, $CyCH_2$), 23.7 (CH_2, $CyCH_2$), 22.5 (CH_3, C-11), 11.7 (CH_3, C-12); *m/z* (ESI) 260 $[MH]^+$; [HRMS (ESI): calcd. for $C_{17}H_{26}NO$, 260.2009. Found: $[MH]^+$, 260.2007 (0.9 ppm error)].

Lab Book Ref. = JDC/9/97



3-Phenyl-8-propyl-2-azabicyclo[2.2.2]oct-2-en-5-one 263f: Using the procedure described for the preparation of compound **263a**, the title compound **263f** (48 mg, 80%) was isolated as a yellow oil; R_f 0.54 (DCM/MeOH, 95:5); υ_{max}/cm^{-1} (neat) 2956, 2929, 2871, 1731, 1601, 1446, 1346; δ_H (400 MHz, $CDCl_3$) 7.81-7.77 (2 H, m, ArH), 7.46-7.38 (3 H, m, ArH), 4.86-4.77 (1 H, m, H-1), 3.96 (1 H, d, J = 3.1, H-4), 2.25-2.18 (1 H, ddd, J = 19.0, 3.0, 2.5 H-6_a), 2.14 (1 H, dd, J = 19.0, 1.9, H-6_b), 2.02 (1 H, dddd, J = 13.2, 10.9, 3.7, 2.5, H-7_a), 1.93-1.84 (1 H, m, H-8), 1.46-1.28 (5 H m, H-7_b, 9, 10), 0.90 (3 H, t, J = 7.1, H-11); δ_C (100 MHz, $CDCl_3$) 208.3 (CO, C-5), 171.4 (CN, C-3), 135.8 (C, ArC), 130.8 (CH, ArCH), 128.6 (2 × CH, ArCH), 126.2 (2 × CH, ArCH), 56.2 (2 × CH, C-1, 4), 39.5 (CH_2, C-6), 38.3 (CH_2, C-9), 34.6 (CH, C-8), 31.1 (CH_2, C-7), 20.5 (CH_2, C-10), 13.8 (CH_3, C-11); *m/z* (ESI) 242 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{20}NO$, 242.1539. Found: $[MH]^+$, 242.1543 (1.6 ppm error)].

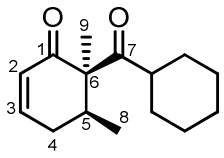
Lab Book Ref. = JDC/10/15



3,8-Diphenyl-2-azabicyclo[2.2.2]oct-2-en-5-one 263g: Using the procedure described for the preparation of compound **263a**, the title compound **263g** (~50% by ^1H NMR Spectroscopy) was isolated as a yellow oil; R_f 0.64 (DCM/MeOH, 95:5); δ_H (400 MHz, $CDCl_3$) 7.87-7.83 (2 H, m, ArH), 7.53-7.42 (3 H, m, ArH), 7.38-7.31 (2 H, m, ArH), 7.29-7.21 (1 H, m, ArH), 7.21-7.17 (2 H, m, ArH), 4.98-4.95 (1 H, m, H-1), 4.17 (1 H, d, J = 2.8, H-4), 3.24 (1 H, ddd, J = 11.6, 5.9, 2.8, H-8), 2.47-2.42 (1 H, m, H-7_a), 2.41-2.38 (2 H, m, H-6), 2.06 (1 H, ddd, J = 13.1, 5.9, 1.2, H-7_b); δ_C (100 MHz, $CDCl_3$) 207.5 (CO, C-5), 171.7 (CN, C-3), 141.1 (C, ArC), 135.4 (C, ArC), 131.0 (CH, ArCH), 128.9 (2 × CH, ArCH), 128.7 (2 × CH, ArCH), 127.3 (2 × CH, ArCH), 127.2 (CH,

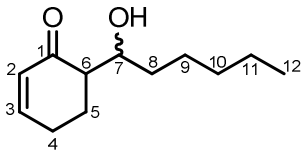
ArCH), 126.3 (2 × CH, ArCH), 57.8 (CH, C-4), 56.1 (CH, C-1), 41.0 (CH, C-8), 40.6 (CH_2, C-6), 31.3 (CH_2, C-7); *m/z* (ESI) 276 $[MH]^+$; [HRMS (ESI): calcd. for $C_{19}H_{18}NO$, 276.1383. Found: $[MH]^+$, 276.1382 (0.5 ppm error)].

Lab Book Ref. = JDC/10/69



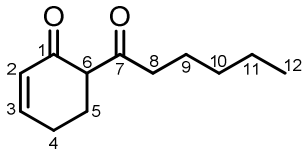
(5*S,6*R**)-6-(Cyclohexanecarbonyl)-5,6-dimethylcyclohex-2-en-1-one 264:** To a stirred solution of diketone **262b** (189 mg, 0.86 mmol, 1.0 equiv.) in acetone (2 mL) at rt were added K_2CO_3 (178 mg, 1.29 mmol, 1.5 equiv.) and MeI (67 μL, 1.08 mmol, 1.25 equiv.). The suspension was heated to reflux and held for 24 h, then cooled to rt and diluted with H_2O (5 mL). The aqueous solution was extracted with Et_2O (3 × 10 mL), then the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/Et_2O, 9:1) to give the title compound **264** (53 mg, 26%) as a colourless oil; R_f 0.64 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2930, 2855, 1674, 1450, 1386, 987; δ_H (400 MHz, $CDCl_3$) 6.94 (1 H, ddd, *J* = 10.1, 5.5, 2.4, H-3), 6.01 (1 H, ddd, *J* = 10.1, 2.9, 1.2, H-2), 2.68 (1 H, dddd, *J* = 19.9, 10.7, 2.9, 2.4, H-4_a), 2.63-2.55 (1 H, m, CyH), 2.27 (1 H, dddd, *J* = 19.9, 5.5, 5.4, 1.2, H-4_b), 2.01 (1 H, dqd, *J* = 10.7, 7.0, 5.4, H-5), 1.73-1.55 (4 H, m, CyH), 1.47-1.41 (1 H, m, CyH), 1.41 (3 H, s, H-9), 1.35-1.10 (5 H, m, CyH), 1.18 (3 H, d, *J* = 7.0, H-8); δ_C (100 MHz, $CDCl_3$) 212.0 (CO, C-7), 198.5 (CO, C-1), 150.9 (CH, C-3), 128.5 (CH, C-2), 63.3 (C, C-6), 47.0 (CH, CyCH), 38.9 (CH, C-5), 32.8 (CH_2, C-4), 29.8 (CH_2, $CyCH_2$), 29.5 (CH_2, $CyCH_2$), 25.5 (CH_2, $CyCH_2$), 25.3 (2 × CH_2, $CyCH_2$), 17.9 (CH_3, C-9), 16.0 (CH_3, C-8); *m/z* (ESI) 235 $[MH]^+$; [HRMS (ESI): calcd. for $C_{15}H_{23}O_2$, 235.1693. Found: $[MH]^+$, 235.1694 (0.6 ppm error)].

Lab Book Ref. = JDC/10/67



6-(1-Hydroxyhexyl)cyclohex-2-en-1-one 260c: Using the procedure described for the preparation of compound **260a**, the title compound **260c** (1.06 g, 72%, ~3.5:1 (*anti*:*syn*)) was isolated as a yellow oil; R_f 0.54$_{anti}$ and 0.26$_{syn}$ (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 3455 (br), 2929, 2860, 1667, 1389; δ_H (400 MHz, $CDCl_3$) 7.02-6.94 (2 H, m, H-3), 6.03-5.97 (2 H, m, H-2), 4.20-4.13 (1 H, m, H-7$_{syn}$), 3.85 (1 H, ddd, J = 7.7, 7.6, 2.9, H-7$_{anti}$), 2.47-2.38 (5 H, m, H-4, 6 $_{syn}$), 2.32 (1 H, ddd, J = 13.5, 7.6, 4.7, H-6$_{anti}$), 2.12-1.94 (3 H, m, H-5$_a$, 5$_{b\ syn}$), 1.76-1.65 (1 H, ddd, J = 13.5, 13.4, 9.2, 7.1, H-5$_{b\ anti}$), 1.59-1.19 (16 H, m, H-8, 9, 10, 11), 0.87 (6 H, t, J = 6.9, H-12); δ_C (400 MHz, $CDCl_3$, ***Anti***) 203.8 (CO, C-1), 150.9 (CH, C-3), 129.8 (CH, C-2), 71.7 (CH, C-7), 51.5 (CH, C-6), 33.6 (CH_2, C-8), 31.9 (CH_2, C-10), 25.8 (CH_2, C-4), 25.0 (CH_2, C-5), 24.5 (CH_2, C-9), 22.6 (CH_2, C-11), 14.0 (CH_3, C-12); δ_C (400 MHz, $CDCl_3$, ***Syn***) 202.1 (CO, C-1), 150.7 (CH, C-3), 130.1 (CH, C-2), 69.8 (CH, C-7), 51.5 (CH, C-6), 32.8 (CH_2, C-8), 31.7 (CH_2, C-10), 25.9 (CH_2, C-4), 22.6 (CH_2, C-9), 22.6 (CH_2, C-11), 22.3 (CH_2, C-5), 14.0 (CH_3, C-12); *m/z* (ESI) 219 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{12}H_{20}NaO_2$, 219.1361. Found: $[MNa]^+$, 219.1359 (1.0 ppm error)].

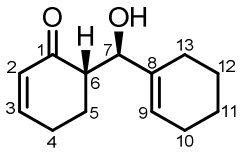
Lab Book Ref. = JDC/9/56



6-Hexanoylcyclohex-2-en-1-one 257c: Using the procedure described for the preparation of compound **262a**, the title compound **257c** (0.88 g, 88%, 1:1 (keto:enol)) was isolated as an orange oil; R_f 0.55 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2956, 2931, 1716, 1674, 1634, 1582; δ_H (400 MHz, $CDCl_3$) 6.99 (1 H, ddd, J = 10.0, 3.9, 3.9, H-3$_{keto}$), 6.66 (1 H, ddd, J = 9.9, 4.3, 4.3, H-3$_{enol}$), 6.04 (1 H, ddd, J = 9.9, 1.9, 1.9, H-2$_{enol}$), 6.00 (1 H, ddd, J = 10.0, 2.0, 2.0, H-2$_{keto}$), 3.46 (1 H, dd, J = 8.3, 5.0, H-6$_{keto}$), 2.65-2.44 (6 H, m, H-4$_a$, 5$_{enol}$, 8$_{keto}$), 2.39-2.27 (5 H, m, H-4$_b$, 5$_{a\ keto}$, 8$_{enol}$), 2.11-2.01 (1 H, m, 5$_{b\ keto}$), 1.64-1.51 (4 H, m, H-9), 1.38-1.18 (8 H, m, H-10, 11), 0.88 (3 H, t, J = 7.0, H-12),

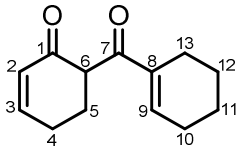
0.86 (3 H, t, J = 7.0, H-12); δ_C (100 MHz, $CDCl_3$) 207.3 (CO, C-7_{keto}), 195.6 (C, C-1_{keto}), 188.7 (C, C-1_{enol}), 183.3 (C, C-7_{enol}), 151.3 (CH, C-3_{keto}), 145.1 (CH, C-3_{enol}), 129.1 (CH, C-2_{keto}), 127.9 (CH, C-2_{enol}), 103.8 (C, C-6_{enol}), 59.4 (CH, C-6_{keto}), 42.7 (CH_2, C-8_{keto}), 34.2 (CH_2, C-8_{enol}), 31.5 (CH_2), 31.2 (CH_2), 25.4 (CH_2, C-9_{enol}), 24.5 (CH_2), 24.3 (CH_2), 24.2 (CH_2), 23.0 (CH_2), 22.4 (2 × CH_2), 21.6 (CH_2, C-5_{enol}), 13.9 (CH_3), 13.8 (CH_3); *m/z* (ESI) 217 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{12}H_{18}NaO_2$, 217.1204. Found: $[MNa]^+$, 217.1197 (3.6 ppm error)].

Lab Book Ref. = JDC/9/65



(*6S)-6-[(*R**)-Cyclohexenyl(hydroxy)methyl]cyclohex-2-en-1-one 260d:** Using the procedure described for the preparation of compound **260a**, the title compound **260d** (190 mg, 61%) was isolated as a colourless oil; R_f 0.38 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 3469 (br), 2926, 2858, 1658, 1390, 1222, 1017; δ_H (400 MHz, $CDCl_3$) 7.03-6.98 (1 H, m, H-3), 6.00 (1 H, ddd, J = 10.0, 2.4, 1.6, H-2), 5.67-5.64 (1 H, m, H-9), 4.40 (1 H, d, J = 1.4, OH), 4.13 (1 H, d, J = 9.2, H-7), 2.45-2.33 (3 H, m, H-4, 6), 2.25-2.15 (1 H, m, H-13_a), 2.08-1.94 (2 H, m, H-10), 1.85-1.72 (2 H, m, H-5, 13_b), 1.67-1.58 (3 H, m, H-11_a, 12), 1.57-1.44 (2 H, m, H-5, 11_b); δ_C (100 MHz, $CDCl_3$) 204.5 (CO, C-1), 151.5 (CH, C-3), 136.1 (C, C-8), 129.6 (CH, C-2), 126.9 (CH, C-9), 77.9 (CH, C-7), 48.6 (CH, C-6), 25.8 (CH_2, C-4), 25.2 (CH_2, C-5), 24.9 (CH_2, C-10), 22.4 (2 × CH_2), 22.4 (CH_2); *m/z* (ESI) 229 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{13}H_{18}NaO_2$, 229.1199. Found: $[MNa]^+$, 229.1195 (1.9 ppm error)].

Lab Book Ref. = JDC/8/44

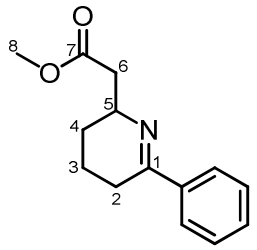


6-(Cyclohexanecarbonyl)cyclohex-2-en-1-one 257d: Using the procedure described for the preparation of compound **262a**, the title compound **257d** (171 mg, 91%) was isolated as a colourless crystalline solid; mp. 77-79 ºC; R_f 0.46 (PE/EtOAc, 2:1);

υ_{max}/cm^{-1} (thin film) 2937, 2867, 1672, 1650, 1127; δ_H (400 MHz, $CDCl_3$) 6.97 (1 H, ddd, *J* = 10.1, 4.4, 3.4, H-3), 6.90-6.86 (1 H, m, H-2), 5.98 (1 H, ddd, *J* = 10.1, 1.9, 1.9, H-2), 4.09 (1 H, dd, *J* = 8.9, 5.1, H-6), 2.57-2.45 (1 H, m, H-4$_a$), 2.38-2.10 (6 H, m, H-4$_b$, 5$_a$, 10, 13), 2.10-2.01 (1 H, m, H-5$_b$), 1.66-1.51 (4 H, m, H-11, 12); δ_C (100 MHz, $CDCl_3$) 198.5 (CO), 196.4 (CO), 150.6 (CH, C-3), 142.3 (CH, C-9), 139.1 (C, C-8), 129.4 (CH, C-2), 52.8 (CH, C-6), 26.1 (CH_2, C-10), 25.7 (CH_2, C-5), 24.4 (CH_2, C-4), 22.9 (CH_2, C-13), 21.7 (CH_2), 21.3 (CH_2); *m/z* (ESI) 205 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{17}O_2$, 205.1223. Found: $[MH]^+$, 205.1230 (3.5 ppm error)].

Lab Book Ref. = JDC/8/69

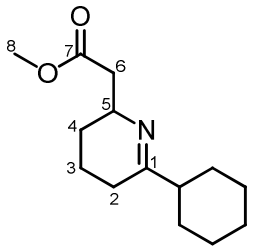
Representative Procedure for the Synthesis of Methyl Esters 266:



Methyl 2-(6-phenyl-2,3,4,5-tetrahydropyridin-2-yl)acetate 266a: To a stirred solution of diketone **257a** (50 mg, 0.25 mmol, 1.0 equiv.) in MeOH (1 mL) at 0 ºC was added dropwise 35% aqueous NH_3 (0.5 mL). The resulting yellow solution was held at 0 ºC for 30 min., then warmed to rt and held until consumption of starting material was observed by TLC (DCM/MeOH, 95:5). The reaction mixture was diluted with water (5 mL), then extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **266a** (42 mg, 72%) as a yellow; R_f 0.54 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (neat) 2931, 2858, 1735, 1604, 1279, 1173; δ_H (400 MHz, $CDCl_3$) 7.80-7.75 (2 H, m, ArH), 7.39-7.32 (3 H, m, ArH), 4.09-3.98 (1 H, m, H-5), 3.74 (3 H, s, H-8) 2.79 (1 H, dd, *J* = 14.9, 6.9, H-6$_a$), 2.74-2.65 (1 H, m, H-2$_a$), 2.55-2.46 (1 H, m, H-2$_b$), 2.52 (1 H, dd, *J* = 14.9, 7.8, H-6$_b$), 2.00-1.89 (2 H, m, H-3$_a$, 4$_a$), 1.82-1.68 (1 H, m, H-3$_b$), 1.35-1.24 (1 H, m, H-4$_b$); δ_C (400 MHz, $CDCl_3$) 172.8 (CO, C-7), 165.4 (CN, C-1), 139.7 (C, ArC), 129.6 (CH, ArCH), 128.1 (2 × CH_2, ArCH), 126.1 (2 × CH_2, ArCH), 55.7 (CH, C-5), 51.5 (CH_3, C-8), 42.5 (CH_2, C-6), 27.0 (CH_2, C-4), 26.5 (CH_2, C-2), 18.9 (CH_2,

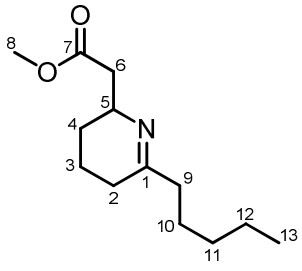
C-3); *m/z* (ESI) 232 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{18}NO_2$, 232.1332. Found: $[MH]^+$, 232.1336 (1.6 ppm error)].

Lab Book Ref. = JDC/10/86



Methyl 2-(6-cyclohexyl-2,3,4,5-tetrahydropyridin-2-yl)acetate 266b: Using the procedure described for the preparation of compound **266a**, the title compound **266b** (6 mg, Quant. (0.03 mmol scale)) was isolated as a yellow oil; R_f 0.48 (DCM/MeOH/NH_3, 190:9:1); υ_{max}/cm^{-1} (neat) 2927, 2852, 1739, 1657, 1170; δ_H (400 MHz, $CDCl_3$) 3.79-3.70 (1 H, m, H-5), 3.68 (3 H, s, H-8), 2.70 (1 H, dd, J = 15.0, 5.9, H-6_a), 2.37 (1 H, dd, J = 15.0, 8.5, H-6_b), 2.11-1.97 (2 H, m), 1.87-1.48 (8 H, m), 1.35-1.07 (7 H, m); δ_C (100 MHz, $CDCl_3$) 175.3 (CO, C-7), 172.8 (CN, C-1), 54.6 (CH, C-5), 51.4 (CH_3, C-8), 49.0 (CH, CyCH), 42.3 (CH_2, C-6), 30.3 (CH_2), 30.2 (CH_2), 27.1 (CH_2), 26.2 (CH_2), 26.2 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 18.5 (CH_2); *m/z* (ESI) 238 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{24}NO_2$, 238.1802. Found: $[MH]^+$, 238.1804 (1.2 ppm error)].

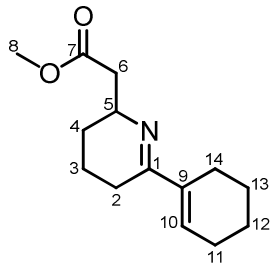
Lab Book Ref. = JDC/4/3



Methyl 2-(6-pentyl-2,3,4,5-tetrahydropyridin-2-yl)acetate 266c: Using the procedure described for the preparation of compound **266a**, the title compound **266c** (50 mg, 89%) as a yellow oil; R_f 0.38 (DCM/MeOH, 95:5); υ_{max}/cm^{-1} (neat) 2931, 2869, 1740, 1660, 1437, 1280, 1172; δ_H (400 MHz, $CDCl_3$) 3.83-3.71 (1 H, m, H-5), 3.69 (3 H, s, H-8), 2.73 (1 H, dd, J = 15.1, 5.9, H-6_a), 2.38 (1 H, dd, J = 15.1, 8.6, H-6_b), 2.19-2.01 (4 H m,

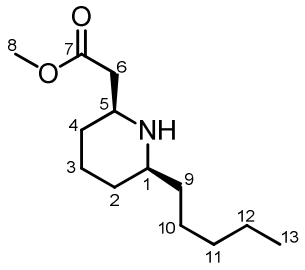
H-2, 9), 1.86-1.70 (2 H, m, H-3_a, 4_a), 1.65-1.45 (3 H, m, H-3_b, 10), 1.37-1.14 (5 H, m, H-4_b, 11, 12), 0.88 (3 H, t, J = 7.0, H-13); δ_C (400 MHz, $CDCl_3$) 172.7 (CO, C-7), 172.0 (CN, C-1), 54.7 (CH, C-5), 51.5 (CH_3, C-8), 42.2 (CH_2, C-6), 40.9 (CH_2, C-9), 31.6 (CH_2, C-11), 28.5 (CH_2, C-2), 26.9 (CH_2, C-4), 26.4 (CH_2, C-10), 22.5 (CH_2, C-12), 18.5 (CH_2, C-3), 14.0 (CH_3, C-13); *m/z* (ESI) 226 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{24}NO_2$, 226.1802. Found: $[MH]^+$, 226.1803 (0.7 ppm error)].

Lab Book Ref. = JDC/10/82



Methyl 2-(6-cyclohexenyl-2,3,4,5-tetrahydropyridin-2-yl)acetate 266d: Using the procedure described for the preparation of compound **266a**, the title compound **266d** (11 mg, 96% (0.05 mmol scale)) was isolated as a yellow oil; R_f 0.52 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (neat) 2931, 2858, 1738, 1617, 1435, 1172; δ_H (400 MHz, $CDCl_3$) 6.29-6.24 (1 H, m, H-10), 3.95-3.84 (1 H, m, H-5), 3.69 (3 H, s, H-8), 2.64 (1 H, dd, J = 14.7, 7.0, H-6_a), 2.43 (1 H, dd, J = 14.7, 7.8, H-6_b), 2.43-2.34 (1 H, m, H-2_a), 2.32-2.06 (5 H, m, H-2_b, 11, 14), 1.86-1.75 (2 H, m, H-3_a, 4_a), 1.70-1.52 (5 H, m, H-3_b, 12, 13), 1.22-1.11 (1 H, m, H-4_b); δ_C (400 MHz, $CDCl_3$) 173.0 (CO, C-7), 166.4 (CN, C-1), 139.0 (C, C-9), 129.7 (CH, C-10), 55.3 (CH, C-5), 51.4 (CH_3, C-8), 42.6 (CH_2, C-6), 27.2 (CH_2, C-4), 25.9 (CH_2, C-11), 24.9 (CH_2, C-2), 24.5 (CH_2, C-14), 22.6 (CH_2, C-12), 22.2 (CH_2, C-13), 18.9 (CH_2, C-3); *m/z* (ESI) 235 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{22}NO_2$, 236.1645. Found: $[MH]^+$, 236.1641 (1.8 ppm error)].

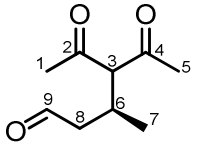
Lab Book Ref. = JDC/9/7



Methyl 2-[(2*S,6*S**)-6-pentylpiperidin-2-yl)acetate 267:** To a stirred solution of imine **266c** (104 mg, 0.46 mmol, 1.0 equiv.) in MeOH (3 mL) at 0 ºC was added $NaBH_4$ (28 mg, 0.74 mmol, 1.6 equiv.). The colourless solution was held at 0 ºC for 30 min. before warming to rt and holding for 1 h. The reaction was quenched with 1 M aq. NaOH (1 mL), then the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound **267** (98 mg, 93%, Inseparable mixture of diastereoisomers (~3:1 – *cis*/*trans*)) as a yellow oil; R_f 0.50 (DCM/MeOH, 9:1); δ_H (400 MHz, $CDCl_3$, *cis*-isomer) 3.68 (3 H, s, H-8), 2.93 (1 H, dddd, J = 10.5, 7.7, 5.5, 2.6, H-5), 2.55-2.46 (1 H, m, H-1), 2.42 (1 H, dd, J = 16.2, 5.5, H-6_a), 2.37 (1 H, dd, J = 16.2, 7.7, H-6_b), 1.82-1.72 (1 H, m), 1.69-1.55 (3 H, m), 1.38-1.23 (8 H, m), 1.16-0.94 (2 H, m), 0.88 (3 H, t, J = 6.6, H-13).

Lab Book Ref. = JDC/10/19

Data were consistent with those published.[97]

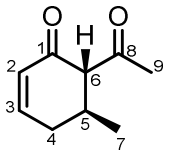


(3*S*)-4-Acetyl-3-methyl-5-oxohexanal 274: To a stirred solution of acetylacetone (0.82 mL, 8.00 mmol, 1 equiv.) and catalyst **275** (50 mg 0.08 mmol, 0.01 equiv.) at r.t was added crotonaldehyde (0.98 mL, 12.0 mmol, 1.5 equiv.). The solution was stirred at rt for 24 h, then concentrated *in vacuo* to give the title compound **274** (1.35 g, 99 %) as a pale yellow oil which was used without further purification; R_f 0.13 (PE/Et_2O, 1:1); υ_{max}/cm^{-1} (neat) 2969, 1723, 1698, 1359, 1159; δ_H (400 MHz, $CDCl_3$) 9.71 (1 H, dd, J = 2.0, 1.1, H-9), 3.69 (1 H, d, J = 9.4, H-3), 2.90 (1 H, ddqd, J = 9.4, 8.4, 6.8, 4.1, H-6), 2.48 (1 H, ddd, J = 17.3, 4.1, 1.1, H-8_a), 2.33 (1 H, ddd, J = 17.3, 8.4, 2.0, H-8_b), 2.18 (6

H, s, H-1, 5), 0.97 (3 H, d, J = 6.8, H-7); δ_C (100 MHz, $CDCl_3$) 203.8 (CO), 203.5 (CO), 200.8 (CO, C-9), 73.8 (CH, C-3), 48.0 (CH_2, C-8), 30.2 (CH_3), 29.6 (CH_3), 28.1 (CH, C-6), 17.9 (CH_3, C-7); *m/z* (ESI) 171 $[MH]^+$; [HRMS (ESI): calcd. for $C_9H_{15}O_3$, 171.1016. Found: $[MH]^+$, 171.1020 (2.7 ppm error)].

Lab Book Ref. = JDC/6/46

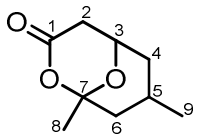
Data were consistent with those published.[102]



(5*S*,6*S*)-6-Acetyl-5-methylcyclohex-2-enone 51: To a stirred solution of aldehyde **272** (125 mg, 0.73 mmol, 1.0 equiv.) in PhMe (5 mL) at rt was added *p*-TsOH (15 mg, 0.07 mmol, 0.1 equiv.). The solution was heated to 50 ºC and held for 18 h, before cooling to rt and diluting with ether (5 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$) then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, PE/Et_2O, 4:1) to give the title compound **51** (82 mg, 74%) as a pale yellow oil; R_f 0.71 (PE/EtOAc, 1:1); υ_{max}/cm^{-1} (neat) 2961, 1716, 1672, 1425, 1280; δ_H (400 MHz, $CDCl_3$) 6.96 (1 H, ddd, J = 10.2, 5.3, 2.9, H-3_{keto}), 6.52 (1 H, dddd, J = 9.9, 6.3, 2.3, 1.2, H-3_{enol}), 6.01 (1 H, ddd, J = 9.9, 3.1, 0.7, H-2_{enol}), 6.00 (1 H, ddd, J = 10.2, 2.6, 1.4, H-2_{keto}), 3.18 (1 H, d, J = 10.6, H-6_{keto}), 2.81 (1 H, dqdd, J = 7.0, 7.0, 1.3, 1.3, H-5_{enol}), 2.62-2.49 (3 H, m, H-$4_{a\ keto}$, $4_{a\ enol}$, 5_{keto}), 2.22 (1 H, dddd, J = 18.2, 6.3, 1.3, 0.7, H-$4_{b\ enol}$), 2.20 (3 H, s, H-9_{enol}), 2.14-2.11 (1 H, m, H-4_{keto}), 2.09 (3 H, s, H-9_{keto}), 1.08 (3 H, d, J = 7.0, H-7_{enol}), 1.03 (3 H, d, J = 6.5, H-7_{keto}); δ_C (100 MHz, $CDCl_3$, **Keto**) 205.8 (CO, C-8), 196.0 (CO, C-1), 150.1 (CH, C-3), 128.8 (CH, C-2), 67.6 (CH, C-6), 32.8 (CH_2, C-4), 31.9 (CH, C-5), 30.5 (CH_3, C-9), 19.6 (CH_3, C-7); δ_C (100 MHz, $CDCl_3$, **Enol**) 187.2 (CO, C-8), 181.6 (C, C-2), 142.9 (CH, C-3), 126.7 (CH, C-2), 109.9 (C, C-6), 31.8 (CH_2, C-4), 27.1 (CH, C-5), 21.1 (CH_3, C-9), 20.5 (CH_3, C-7); *m/z* (ESI) 175 $[MNa]^+$; [HRMS (ESI): calcd. for $C_9H_{12}NaO_2$, 175.0730. Found: $[MNa]^+$, 175.0727 (1.4 ppm error)].

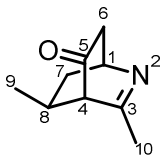
Lab Book Ref. = JDC/5/2

Data were consistent with those published.[100]



1,7-Dimethyl-2,9-dioxabicyclo[3.3.1]nonan-3-one 279: To a stirred solution of aldehyde **272** (125 mg, 0.73 mmol, 1.0 equiv.) in PhMe (5 mL) at rt was added *p*-TsOH (15 mg, 0.07 mmol, 0.1 equiv.). The solution was heated to 50 ºC and held for 18 h, before cooling to rt and diluting with ether (5 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$) then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, PE/Et_2O, 4:1) to give enone **51** (68 mg, 61%) as a pale yellow oil and the title compound **279** (10 mg, 8%) as a colourless oil; R_f 0.60 (PE/Et_2O, 1:1); υ_{max}/cm^{-1} (neat) 2921, 1736, 1290, 1253, 1124, 1037; δ_H (400 MHz, $CDCl_3$) 4.47 (1 H, ddd, *J* = 8.0, 4.6, 1.8, H-3), 2.92 (1 H, ddd, *J* = 18.1, 8.0, 0.9, H-2_a), 2.37 (1 H, d, *J* = 18.1, H-2_b), 2.01 (1 H, ddd, *J* = 13.5, 4.2, 1.9, H-6_a), 1.98-1.84 (1 H, m, H-5), 1.66 (1 H, dddd , *J* = 13.7, 4.0, 1.9, 1.8, H-4_a), 1.62-1.55 (1 H, m, H-4_b), 1.53 (3 H, s, H-8), 1.30 (1 H, dd, *J* = 13.5, 11.9, H-6_b), 0.95 (3 H, d, *J* = 6.4, H-9); δ_C (100 MHz, $CDCl_3$) 168.5 (CO, C-1), 104.4 (C, C-7), 68.1 (CH, C-3), 43.1 (CH_2, C-6), 37.5 (CH_2, C-4), 33.8 (CH_2, C-2), 27.6 (CH_3, C-8), 21.2 (CH/CH_3, C-5/9); *m/z* (ESI) 171 $[MH]^+$; [HRMS (ESI): calcd. for $C_9H_{15}O_3$, 171.1016. Found: $[MH]^+$, 171.1015 (0.5 ppm error)].

Lab Book Ref. = JDC/5/30

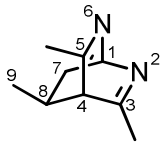


3,8-Dimethyl-2-azabicyclo[2.2.2]oct-2-en-5-one 27: To a stirred solution of enone **51** (76 mg, 0.50 mmol, 1.0 equiv.) in MeOH (1 mL) at 0 ºC was added 35% aq. NH_3 (0.5 mL). The resulting yellow solution was held at 0 ºC for 30 min., then warmed to rt and held for 2 h. The reaction was diluted with water (5 mL) then extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound **27** (64 mg, 84%) as yellow oil which partially solidified on storage at −20 ºC; Picrate mp. 208-210 ºC (Lit.[42] 212-213 ºC); R_f 0.33 (DCM/MeOH, 95:5); $[\alpha]^{24}_D$ −252.7 (c 0.51, DCM), [Lit.[42] −34.5 (*c*

0.50, DCM)]; υ_{max}/cm^{-1} (neat) 2957, 1729, 1633, 1379; δ_H (400 MHz, $CDCl_3$) 4.50 (1 H, dddd, *J* = 3.5, 3.5, 1.9, 1.9, H-1), 3.13 (1 H, d, *J* = 2.9, H-4), 2.17-2.08 (1 H, m, H-6_a), 2.12 (3 H, s, H-10), 2.01 (1 H, dd, *J* = 19.0, 1.9, H-6_b), 1.99-1.91 (2 H, m, H-7_a, 8), 1.27-1.19 (1 H, m, H-7_b), 1.04 (3 H, d, *J* = 6.9, H-9); δ_C (100 MHz, $CDCl_3$) 208.4 (CO, C-5), 173.7 (CN, C-3), 61.4 (CH, C-4), 55.5 (CH, C-1), 39.5 (CH_2, C-6), 32.4 (CH_2, C-7), 28.8 (CH, C-8), 24.5 (CH_3, C-10), 21.0 (CH_3, C-9); *m/z* (ESI) 152 $[MH]^+$; [HRMS (ESI): calcd. for $C_9H_{14}NO$, 152.1070. Found: $[MH]^+$, 152.1070 (0.1 ppm error)]; HPLC Analysis (Phenomenex Lux Cellulose-2 column, 95:5 *iso*-hexane/EtOH, flow rate 1.0 mL/min,; R_T = 9.51 (minor, 9.5%) and 10.62 (major, 90.5%)).

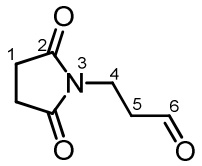
Lab Book Ref. = JDC/9/32

Data were consistent with those published.[42]



3,5,8-Trimethyl-2,6-diazabicyclo[2.2.2]octa-2,5-diene 285: A stirred solution of aldehyde **274** (10 mg, 0.06 mmol, 1.0 equiv.) in 35% aq. NH_3 (1 mL) was held at rt for 2 h, then diluted with water (5 mL). The organic phase was separated and the aqueous phase extracted with DCM (4 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound **285** (9 mg, Quant.) as yellow film; R_f 0.39 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 2958, 1658, 1433, 1380, 1280; δ_H (400 MHz, $CDCl_3$) 6.24 (1 H, dd, *J* = 2.4, 2.4, H-1), 3.71 (1 H, d, *J* = 2.3, H-4), 2.12 (3 H, s, CH_3), 2.11 (3 H, s, CH_3), 1.71 (1 H, ddd, *J* = 12.1, 9.3, 2.4, H-7_a), 1.48 (1 H, dqdd, *J* = 9.3, 6.9, 4.6, 2.3, H-8), 0.92 (1 H, ddd, *J* = 12.1, 4.6, 2.4, H-7_b), 0.87 (3 H, d, *J* = 6.9, H-9); δ_C (100 MHz, $CDCl_3$) 172.3 (CN), 170.3 (CN), 76.6 (CH, C-1), 55.5 (CH, C-4), 32.2 (CH_2, C-7), 27.2 (CH, C-8), 25.3 (CH_3), 22.7 (CH_3), 20.5 (CH_3, C-9); *m/z* (ESI) 151 $[MH]^+$; [HRMS (ESI): calcd. for $C_9H_{15}N_2$, 151.1230. Found: $[MH]^+$, 151.1232 (1.7 ppm error)].

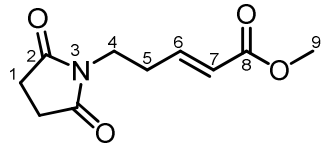
Lab Book Ref. = JDC/4/90



3-(2,5-Dioxopyrrolidin-1-yl)propanal[35] **291:** To a stirred solution of sodium (58 mg, 2.50 mmol, 0.01 equiv.) in absolute ethanol (50 mL) at rt, was added in one portion succinimide (24.8 g, 250 mmol, 1.0 equiv.). The suspension was stirred at rt for 5 min., then acrolein (16.7 mL, 250 mmol, 1.0 equiv.) was added dropwise over 2 h, ensuring the internal temperature remained below 30 ºC. The resulting yellow solution was stirred at rt for a further 2 h, then quenched with glacial acetic acid (1 mL). The solution was concentrated *in vacuo* to give a yellow oil, which was passed through a plug of silica (50 g, $CHCl_3$:Acetone, 95:5) to give the semi-pure aldehyde **291** (36.1 g, 93%) as a viscous yellow oil; R_f 0.25 (DCM/MeOH, 95:5); δ_H (400 MHz, $CDCl_3$) 9.76 (1 H, t, J = 1.4, H-6), 3.85 (2 H, t, J = 7.0, H-4), 2.77 (2 H, td, J = 7.0, 1.4, H-5), 2.71 (4 H, s, H-1).

Lab Book Ref. = JDC/5/75

Data were consistent with those published.[35]

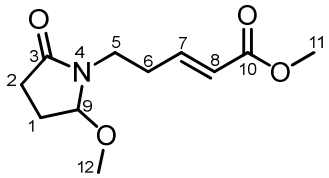


Methyl (*E*)-5-(2,5-dioxopyrrolidin-1-yl)pent-2-enoate 293: To a stirred solution of K_2CO_3 (10.4 g, 75.1 mmol, 1.05 equiv.) in H_2O (50 mL) at 0 ºC was added dropwise trimethyl phosphonoacetate (12.2 mL, 75.1 mmol, 1.05 equiv.). The solution was stirred at 0 ºC for 30 min., then aldehyde **291** (11.1 g, 71.5 mmol, 1.0 equiv.) was added as a solution in THF (50 mL). The solution was held at 0 ºC for 30 min., then warmed to rt and held for 18 h. The reaction was diluted with ether (50 mL) and H_2O (50 mL), then the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL) and brine (50 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **293** (14.3 g, 95%) as a yellow oil which partially solidified on standing; R_f 0.68 (DCM/MeOH, 95:5); δ_H (400 MHz,

$CDCl_3$) 6.85 (1 H, dt, *J* = 15.7, 7.1, H-6), 5.86 (1 H, dt *J* = 15.7, 1.6, H-7), 3.72 (3 H, s, H-9), 3.65 (2 H, t, *J* = 7.2, H-4), 2.71 (4 H, s, H-1), 2.50 (2 H, tdd, *J* = 7.2, 7.1, 1.6, H-5).

Lab Book Ref. = JDC/6/61

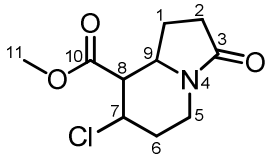
Data were consistent with those published.[35]



Methyl (*E*)-5-(2-methoxy-5-oxopyrrolidin-1-yl)pent-2-enoate[35] **64b:** To a stirred solution of imide **293** (16.6 g, 78.6 mmol, 1.0 equiv.), in MeOH (150 mL) at 0 ºC, was added $NaBH_4$ (5.94 g, 157.2 mmol, 2.0 equiv.) portionwise over 2 h. The colourless solution was stirred at 0 ºC for a further 2 h, then carefully quenched with conc. HCl (50 mL). The reaction mixture was diluted with water (100 mL), then extracted with DCM (3 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **64b** (17.9 g, Quant.) as a pale yellow oil; R_f 0.46 ($CHCl_3$/acetone, 4:1); δ_H (400 MHz, $CDCl_3$) 6.91 (1 H, dt, *J* = 15.7, 7.1, H-7), 5.88 (1 H, dt, *J* = 15.7, 1.6, H-8), 4.90 (1 H, dd, *J* = 6.3, 1.4, H-9), 3.73 (3 H, s, H-11), 3.58 (1 H, ddd, *J* = 13.8, 7.8, 6.3, H-5_a), 3.26 (3 H, s, H-12), 2.59-2.41 (3 H, m, H-2_a, 6), 2.37-2.27 (2 H, m, H-2_b, 5_b), 2.19-2.06 (1 H, m, H-1_a), 2.00 (1 H, dddd, *J* = 14.0, 9.6, 3.1, 1.4, H-1_b).

Lab Book Ref. = JDC/6/98

Data were consistent with those published.[35]

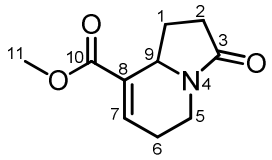


Methyl 7-chloro-3-oxooctahydroindolizine-8-carboxylate[35] **65:** To a stirred solution of ester **64b** (2.29 g, 10.1 mmol, 1.0 equiv.) in 1,2-dichloroethane (40 mL) at 0 ºC, was added $SnCl_4$ (2.96 mL, 25.3 mmol, 2.5 equiv.). The reaction was held at 0 ºC for 30 min., then warmed to 70 ºC and held for 18 h. The reaction mixture was cooled to 0 ºC, then quenched with 10% aq. NaOH (20 mL). The aqueous phase was extracted with

DCM (4 × 50 mL), then the combined extracts were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound **65** (1.75 g, 75%) as a complex mixture of diastereoisomers which was used directly without further purification; R_f 0.24 ($CHCl_3$/acetone, 4:1); δ_H (400 MHz, $CDCl_3$) 4.25-4.11 (2 H, m), 3.79 (3 H, s), 3.63-3.56 (1 H, m), 2.78-2.68 (1 H, m), 2.56-2.12 (4 H, m), 1.90-1.66 (3 H, m).

Lab Book Ref. = JDC/5/94

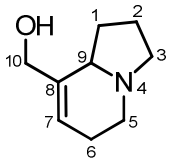
Data were consistent with those published.[35]



Methyl 3-oxo-1,2,3,5,6,8a-hexahydroindolizine-8-carboxylate[35] **66:** To a stirred solution of ester **65** (2.35 g, 10.0 mmol, 1.0 equiv.) in PhMe (35 mL) at rt, was added DBN (2.47 mL, 20.0 mmol, 2.0 equiv.). The solution was heated to reflux and held for 18 h, before cooling to rt and diluting with DCM (50 mL). The organic phase was washed with 10% aq. HCl (50 mL) and water (50 mL), then the combined aqueous washes were back extracted with DCM (50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), then concentrated *in vacuo* to give a brown oil which was purified by column chromatography (SiO_2, DCM/MeOH, 9:1) to give the title compound **66** (0.73 g, 37%) as a pale yellow oil; R_f 0.65 (DCM/MeOH, 9:1); δ_H (400 MHz, $CDCl_3$) 7.08-7.04 (1 H, m, H-7), 4.44-4.37 (1 H, m, H-9), 4.27 (1 H, dd, J = 13.1, 6.4, H-5_a), 3.77 (3 H, s, H-11), 2.79-2.69 (1 H, m, H-5_b), 2.64 (1 H, dddd, J = 12.5, 8.6, 6.8, 1.7, H-1_a), 2.56-2.45 (1 H, m, H-2_a), 2.44-2.23 (3 H, m, H-2_b, 6), 1.60 (1 H, ddd, J = 12.5, 12.5, 11.3, 9.5, H-1_b).

Lab Book Ref. = JDC/5/97

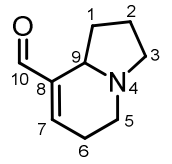
Data were consistent with those published.[35]



(1,2,3,5,6,8a-Hexahydroindolizin-8-yl)methanol[35] **288:** To a stirred solution of ester **66** (0.95 g, 4.90 mmol, 1.0 equiv.) in THF (16 mL) at 0 ºC was added dropwise DIBAL-H (1.2 M in toluene, 22.5 mL, 27.0 mmol, 5.5 equiv.) over 30 min. The resulting white suspension was held at 0 ºC for 30 min., then warmed to rt and held for 4 h. The reaction was cooled to 0 ºC and quenched with MeOH (5 mL), then sat. aq. Rochelle's salt (20 mL) was added. The viscous solution was stirred vigourously for 2 h, then extracted with DCM (4 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 40:9:1) to give the title compound **288** (399 mg, 53%) as an orange oil; R_f 0.10 (DCM/MeOH, 4:1); δ_H (400 MHz, $CDCl_3$) 5.68-5.64 (1 H, m, H-7), 4.05-4.03 (2 H, m, H-10), 3.35 (1 H, br s, OH), 3.19-3.12 (1 H, m, H-9), 2.91 (1 H, ddd, J = 10.5, 8.1, 3.8, H-3_a), 2.80 (1 H, ddd, J = 11.3, 5.7, 5.7, H-5_a), 2.67 (1 H, ddd, J = 10.5, 8.9, 7.9, H-3_b), 2.53 (1 H, ddd, J = 11.3, 6.0, 6.0, H-5_b), 2.27-2.13 (2 H, m, H-6), 2.03 (1 H, dddd, J = 12.1, 9.5, 6.9, 3.6, H-1_a), 1.89 (1 H, ddddd, J = 12.8, 10.5, 8.1, 7.9, 3.6, H-2_a), 1.75 (1 H, ddddd, J = 12.8, 9.5, 8.9, 7.3, 3.8, H-2_b), 1.54 (1 H, dddd, J = 12.1, 10.5, 10.5, 7.3, H-1_b).

Lab Book Ref. = JDC/6/70

Data were consistent with those published.[35]

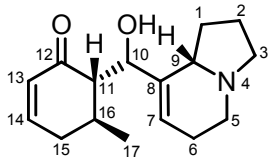


1,2,3,5,6,8a-Hexahydroindolizine-8-carbaldehyde[35] **172:** To a stirred solution of oxalyl chloride (201 µL, 2.38 mmol, 1.2 equiv.) in DCM (10 mL) at −78 ºC was added dropwise DMSO (337 µL, 4.76 mmol, 2.4 equiv.). The colourless solution was held at −78 ºC for 30 min., then alcohol **288** (304 mg, 1.98 mmol, 1.0 equiv.) was added *via* cannula as a pre-cooled solution in DCM (5 mL). The reaction was held at −78 ºC for 1 h, then Et_3N (1.38 mL, 9.90 mmol, 5.0 equiv.) was added dropwise. The yellow

solution was held at −78 ºC for a further 30 min. then warmed to rt and held for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) then the aqueous phase was extracted with DCM (4 × 20 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound **172** (198 mg, 66%) as a yellow oil which was used immediately without further purification; R_f 0.28 (DCM/MeOH, 9:1); δ_H (400 MHz, $CDCl_3$) 9.41 (1 H, s, H-10), 6.84 (1 H, ddd, J = 4.0, 3.9, 1.7, H-7), 3.45-3.37 (1 H, m, H-9), 2.97-2.90 (1 H, m, H-5_a), 2.90 (1 H, ddd, J = 10.1, 7.9, 4.8, H-3_a), 2.74 (1 H, ddd, J = 10.1, 8.5, 7.3, H-3_b), 2.68-2.61 (1 H, m, H-5_b), 2.61-2.51 (1 H, m, H-6_a), 2.48-2.38 (1 H, m, H-6_b), 2.40-2.31 (1 H, m, H-1_a), 1.94-1.75 (2 H, m, H-2), 1.45 (1 H, dddd, J = 12.8, 10.2, 9.4, 7.6, H-1_b).

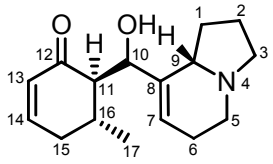
Lab Book Ref. = JDC/7/68

Data were consistent with those published.[35]



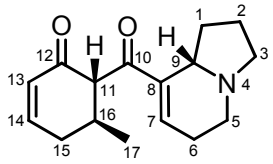
(5*S,6*S**)-6-[(8a*S**)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl(hydroxy)methyl]-5-methylcyclohex-2-en-1-one 287:** To a stirred solution of di*iso*propylamine (62 µL, 0.44 mmol, 1.3 equiv.) in THF (5 mL) at 0 ºC was added dropwise *n*-BuLi (1.53 M in hexanes, 0.27 mL, 0.41 mmol, 1.2 equiv.). The colourless solution was held at 0 ºC for 30 min., then cooled to −78 ºC before the addition of enone **87** (41 mg, 0.37 mmol, 1.1 equiv.) as a pre-cooled solution in THF (1 mL). The resulting pale yellow solution was held at −78 ºC for 1 h, before the addition of aldehyde **172** (51 mg, 0.34 mmol, 1.0 equiv.) as a pre-cooled solution in THF (1.5 mL). The reaction was held at −78 ºC for a further 30 min., then quenched with AcOH (0.25 mL). The organic phase was basified (sat. aq. $NaHCO_3$) then extracted with DCM (4 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 110:9:1) to give the title compound **287** and diastereoisomer **294** (57 mg, 73% BRSM, 1:1.5 – **287**:**294**) as a yellow oil and recovered aldehyde **172** (6 mg, 12%) as a yellow film; R_f 0.49 (DCM/MeOH/NH_3, 40:9:1); υ_{max}/cm^{-1} (neat) 3399 (br),

2957, 2918, 1676, 1389, 1026, 730; δ_H (400 MHz, $CDCl_3$) 6.86 (1 H, dddd, *J* = 10.1, 5.2, 2.8, 1.1, H-14), 6.03 (1 H, dddd, *J* = 10.1, 2.6, 1.5, 0.7, H-13), 5.77 (1 H, ddd, *J* = 3.8, 3.8, 1.3, H-7), 4.25 (1 H, d, *J* = 9.5, H-10), 3.06-2.99 (1 H, m, H-9), 2.95 (1 H, ddd, *J* = 10.5, 8.4, 3.4, H-3_a), 2.84 (1 H, ddd, *J* = 11.3, 5.7, 5.7, H-5_a), 2.72-2.63 (1 H, m, H-3_b), 2.56 (1 H, dddd, *J* = 19.7, 5.6, 2.8, 2.6, H-15_a), 2.50 (1 H, ddd, *J* = 11.3, 5.6, 5.3, H-5_b), 2.38 (1 H, dd, *J* = 9.5, 3.2, H-11), 2.44-2.11 (4 H, m, H-1_a, 6, 16), 2.07 (1 H, dddd, *J* = 19.7, 5.2, 2.3, 1.5, H-15_b), 2.00-1.86 (1 H, m, H-2_a), 1.82-1.67 (2 H, m, H-1_b, 2_b), 1.07 (3 H, d, *J* = 7.1, H-17); δ_C (100 MHz, $CDCl_3$) 201.4 (CO, C-12), 147.9 (CH, C-14), 139.1 (C, C-8), 128.3 (CH, C-13), 124.5 (CH, C-7), 74.7 (CH, C-10), 59.8 (CH, C-9), 56.6 (CH, C-11), 53.0 (CH_2, C-3), 46.3 (CH_2, C-5), 30.1 (CH, C-16), 30.0 (CH_2, C-15), 29.6 (CH_2, C-1), 25.5 (CH_2, C-6), 22.3 (CH_2, C-2), 19.9 (CH_3, C-17); *m/z* (ESI) 262 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{24}NO_2$, 262.1802. Found: $[MH]^+$, 262.1799 (1.1 ppm error)].



(5*R,6*R**)-6-[(8a*S**)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl(hydroxy)methyl]-5-methylcyclohex-2-en-1-one 294:** A yellow oil; R_f 0.35 (DCM/MeOH/NH_3, 40:9:1); υ_{max}/cm^{-1} (neat) 3340 (br), 2956, 2915, 1668, 730; δ_H (400 MHz, $CDCl_3$) 6.82-6.77 (1 H, m, H-14), 5.95 (1 H, ddd, *J* = 10.1, 2.4, 1.6, H-13), 5.74-5.71 (1 H, m, H-7), 4.26 (1 H, d, *J* = 7.9, H-10), 3.12-3.05 (1 H, m, H-9), 2.88 (1 H, ddd, *J* = 10.6, 8.5, 3.5, H-3_a), 2.76 (1 H, ddd, *J* = 11.3, 5.7, 5.7 H-5_a), 2.63-2.48 (2 H, m, H-3_b, 15_a), 2.47 (1 H, ddd, *J* = 11.3, 5.6, 5.6, H-5_b), 2.31 (1 H, dd, *J* = 7.9, 4.3, H-11), 2.28-2.19 (3 H, m, H-6, 16), 2.09-1.98 (2 H, m, H-1_a, 15_b), 1.93-1.80 (1 H, m, H-2_a), 1.78-1.66 (1 H, m, H-2_b), 1.53-1.42 (1 H, m, H-1_b), 1.02 (3 H, d, *J* = 7.0, H-17); δ_C (100 MHz, $CDCl_3$) 201.0 (CO, C-12), 147.6 (CH, C-14), 139.6 (C, C-8), 128.5 (CH, C-13), 122.1 (CH, C-7), 73.4 (CH, C-10), 60.1 (CH, C-9), 57.5 (CH, C-11), 52.7 (CH_2, C-3), 46.3 (CH_2, C-5), 30.8 (CH, C-16), 30.4 (CH_2, C-15), 28.2 (CH_2, C-1), 25.4 (CH_2, C-6), 22.0 (CH_2, C-2), 19.9 (CH_3, C-17); *m/z* (ESI) 262 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{24}NO_2$, 262.1802. Found: MH^+, 262.1803 (0.5 ppm error)].

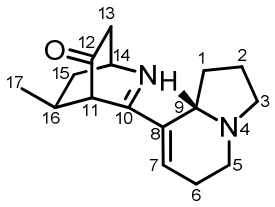
Lab Book Ref. = JDC/8/2



(5*S,6*R**)-6-[(8a*S**)-1,2,3,5,6,8a-Hexahydroindolizine-8-carbonyl]-5-methylcyclohex-2-en-1-one 17:** To a stirred solution of DMSO (10 μL, 0.14 mmol, 2.0 equiv.) in DCM (1 mL) at −78 ºC was added dropwise trifluoroacetic anhydride (15 μL, 0.11 mmol, 1.5 equiv.). The colourless solution was held at −78 ºC for 30 min., before adding alcohol **287** (17 mg, 0.07 mmol, 1.0 equiv.) as a pre-cooled solution in DCM (1 mL) *via* cannula. The reaction was held at −78 ºC for 1 h, then Et_3N (48 μL, 0.35 mmol, 5.0 equiv.) was added dropwise. The yellow solution was held at −78 ºC for a further 15 min., then warmed to rt and held for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), then the aqueous phase was extracted with DCM (4 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 190:9:1) to give the title compound **17** (12 mg, 71%) as a colourless oil. To a solution of the product **17** (11 mg, 0.05 mmol, 1.0 equiv.) in DCM (0.5 mL) at 0 ºC was added dropwise TFA (3 μL, 0.06 mmol, 1.2 equiv.). The colourless solution was held at 0 ºC for 30 min., then warmed to rt and held for 2 h. The pale yellow solution was concentrated *in vacuo* to afford the title compound **17**·TFA (16 mg, Quant.) as a pale yellow film; R_f 0.69 (DCM/MeOH/NH_3, 40:9:1); υ_{max}/cm^{-1} (neat) 2959, 1676, 1656, 1390, 1190; δ_H (400 MHz, DMSO-d_6) 10.37 (1 H, br s, NH^+), 7.35 (1 H, dd, *J* = 3.8, 3.8, H-7), 7.16 (1 H, ddd, *J* = 9.9, 5.5, 2.2, H-14), 5.97 (1 H, dd, *J* = 9.9, 2.1, H-13), 4.40 (1 H, dd, *J* = 8.7, 8.7, H-9), 4.33 (1 H, d, *J* = 11.5, H-11), 3.62-3.50 (1 H, m, H-3_a), 3.41-3.27 (2 H, m, H-3_b, 5_a), 3.18-3.05 (1 H, m, H-5_b), 2.66-2.59 (2 H, m, H-6), 2.53-2.37 (3 H, m, H-1_a, 15_a, 16), 2.27-2.15 (1 H, m, H-15_b), 2.08-1.98 (2 H, m, H-2), 1.71-1.58 (1 H, m, 1_b) 0.86 (3 H, d, *J* = 6.2, H-17); δ_C (100 MHz, DMSO-d_6) 198.3 (CO, C-10), 196.7 (CO, C-12), 151.6 (CH, C-14), 140.1 (CH, C-7), 137.2 (C, C-8), 128.3 (CH, C-13), 59.2 (CH, C-11), 57.9 (CH, C-9), 52.9 (CH_2, C-3), 43.1 (CH_2, C-5), 33.0 (CH, C-16), 32.6 (CH_2, C-15), 28.1 (CH_2, C-1), 22.9 (CH_2, C-6), 20.2 (CH_2, C-2), 19.1 (CH_3, C-17); *m/z* (ESI) 260 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{22}NO_2$, 260.1645. Found: $[MH]^+$, 260.1644 (0.4 ppm error)].

Lab Book Ref. = JDC/8/16 and JDC/8/18

Data were consistent with those published.[10, 25]



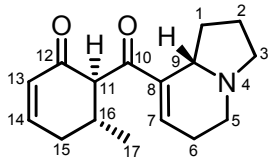
3-[(8a*S)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl]-8-methyl-2-azabicyclo[2.2.2]oct-2-en-5-one 15:** To a stirred solution of diketone **17** (7 mg, 0.03 mmol, 1.0 equiv.) in 1 M aq. HCl (1 mL) at 0 ºC was added dropwise pH 10 NH_3/NH_4Cl aq. solution (1 mL). The yellow solution was held at rt for 1 h, then extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow film which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 90:9:1) to give the title compound **17** (5 mg, 71%) as a yellow film; R_f 0.33 (DCM/MeOH/NH_3, 90:9:1); υ_{max}/cm^{-1} (neat) 2954, 2872, 1730, 1578, 1341, 1102; δ_H (400 MHz, $CDCl_3$) 6.41 (1 H, ddd, *J* = 4.2, 4.2, 1.5, H-7), 4.63 (1 H, dddd, *J* = 3.6, 3.3, 1.8, 1.8, H-14), 3.70-3.63 (1 H, m, H-9), 3.55 (1 H, d, *J* = 3.1, H-11), 2.92 (1 H, ddd, *J* =10.2, 7.7, 4.7, H-3_a), 2.87 (1 H, ddd, *J* = 11.0, 3.2, 3.2, H-5_a), 2.77 (1 H, ddd, *J* = 10.2, 8.2, 7.5, H-3_b), 2.64 (1 H, ddd, *J* = 11.0, 7.0, 5.1, H-5_b), 2.47-2.36 (1 H, m, H-6_a), 2.36-2.24 (2 H, m, H-1_a, 6_b), 2.16 (1 H, ddd, *J* = 18.8, 3.3, 2.7, H-13_a), 2.06 (1 H, dd, *J* = 18.8, 1.8, H-13_b), 2.00-1.92 (1 H, m, H-15_a), 1.91-1.72 (3 H, m, H-2, 16), 1.35 (1 H, dddd, *J* = 12.7, 10.3, 9.3, 7.6, H-1_b), 1.27 (1 H, ddd, *J* = 12.6, 4.5, 1.8, H-15_b), 1.06 (3 H, d, *J* = 7.0, H-17); δ_C (100 MHz, $CDCl_3$) 208.9 (CO, C-12), 171.1 (CN, C-10), 138.6 (C, C-8), 130.2 (CH, C-7), 58.9 (CH, C-9), 56.5 (CH, C-11), 55.6 (CH, C-14), 52.6 (CH_2, C-3), 45.2 (CH_2, C-5), 40.0 (CH_2, C-13), 32.2 (CH_2, C-15), 30.0 (CH_2, C-1), 29.2 (CH, C-16), 24.9 (CH_2, C-6), 22.4 (CH_2, C-2), 21.2 (CH_3, C-17); *m/z* (ESI) 259 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{23}N_2O$, 259.1805. Found: $[MH]^+$, 259.1810 (2.1 ppm error)].

Lab. Book Ref. = JDC/8/10

Data were consistent with those published.[9, 55]

Grandisine B Dipicrate: An aqueous solution of grandisine B **15** (*ca*. 10 mg in 1 mL) was treated with a slight excess of 1% aqueous picric acid solution (~1.25 equiv.) to

give grandisine B dipicrate as an orange crystalline solid. A crystal suitable for X-ray diffraction analysis was obtained using solvent diffusion techniques (DCM/Hexane).

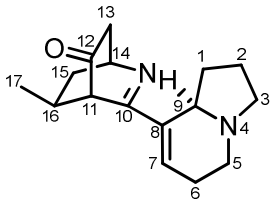


(5*R,6*S**)-6-[(8a*S**)-1,2,3,5,6,8a-Hexahydroindolizine-8-carbonyl]-5-methylcyclohex-2-en-1-one 295:** To a stirred solution of DMSO (21 μL, 0.30 mmol, 2.0 equiv.) in DCM (4 mL) at −78 ºC was added dropwise trifluoroacetic anhydride (32 μL, 0.23 mmol, 1.5 equiv.). The colourless solution was held at −78 ºC for 30 min., before adding alcohol **294** (40 mg, 0.15 mmol, 1.0 equiv.) as a pre-cooled solution in DCM (2 mL) *via* cannula. The reaction was held at −78 ºC for 1 h, then Et_3N (105 μL, 0.75 mmol, 5.0 equiv.) was added dropwise. The yellow solution was held at −78 ºC for a further 15 min., then warmed to rt and held for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL), then the aqueous phase was extracted with DCM (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 190:9:1) to give the title compound **295** (32 mg, 80%) as a colourless oil. To a stirred solution of the product **295** (30 mg, 0.12 mmol, 1.0 equiv.) in DCM (1 mL) at 0 ºC was added dropwise TFA (12 μL, 0.15 mmol, 1.3 equiv.). The solution was stirred at 0 ºC for 30 min., then warmed to rt and held for 2 h. The solution was concentrated *in vacuo* to afford the title compound **295** (45 mg, Quant.) as a yellow oil; R_f 0.34 (DCM/MeOH/NH_3, 190:9:1); υ_{max}/cm^{-1} (neat) = 2958, 2927, 2874, 1677, 1656, 1389; δ_H (400 MHz, DMSO-d_6) 10.60 (1 H, br s, NH^+), 7.33 (1 H, dd, *J* = 4.0, 4.0 H-7), 7.16 (1 H, ddd, *J* = 10.0, 5.7, 2.2, H-14), 5.94 (1 H, dd, *J* = 10.0, 2.0, H-13), 4.46-4.38 (1 H, m, H-9), 4.38 (1 H, d, *J* = 11.8, H-11), 3.60-3.48 (1 H, m, H-3_a), 3.39-3.28 (2 H, m, H-3_b, 5_a), 3.21-3.09 (1 H, m, H-5_b), 2.66-2.59 (2 H, m, H-6), 2.53-2.34 (3 H, m, H-1_a, 15_a, 16), 2.29-2.16 (1 H, m, H-15_b), 2.09-1.97 (2 H, m, H-2), 1.77 (1 H, dddd, *J* = 13.2, 9.6, 9.5, 7.3, H-1_b), 0.87 (3 H, d, *J* = 6.3, H-17); δ_C (100 MHz, DMSO-d_6) 198.4 (CO, C-10), 196.7 (CO, C-12), 151.9 (CH, C-14), 138.9 (CH, C-7), 137.3 (C, C-8), 128.3 (CH, C-13), 59.0 (CH, C-11), 57.9 (CH, C-9), 52.6 (CH_2, C-3), 42.9 (CH_2, C-5), 32.6 (CH_2, C-15), 32.3 (CH, C-16), 27.9 (CH_2, C-1) 22.3 (CH_2, C-6),

20.4 (CH_2, C-2), 19.0 (CH_3, C-17); *m/z* (ESI) 260 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{22}NO_2$, 260.1645. Found: $[MH]^+$, 260.1636 (3.5 ppm error)].

Lab Book Ref. = JDC/7/60

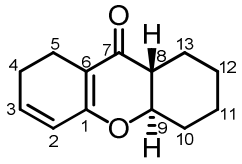
Data were consistent with those reported.[55]



3-[(8a*S)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl]-8-methyl-2-azabicyclo[2.2.2]oct-2-en-5-one 296:** A stirred solution of diketone **295** (13 mg, 0.05 mmol, 1.0 equiv.) in 1 M aq. HCl (0.5 mL) was basified with 35 % aq. NH_3 (1 mL) and the resulting yellow solution held at rt for 1 h. The reaction mixture was extracted with DCM (4 × 5 mL), then the combined organics were washed with brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow film which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 90:9:1) to give the title compound **296** (8 mg, 62%) as a yellow film; R_f 0.33 (DCM/MeOH/NH_3, 90:9:1); υ_{max}/cm^{-1} (thin film) 2954, 2872, 1730, 1577, 1399, 1101; δ_H (400 MHz, $CDCl_3$) 6.40 (1 H, dd, *J* = 4.2, 4.2, H-7), 4.66-4.62 (1 H, m, H-14), 3.75 (1 H, dd, *J* = 7.9, 7.9, H-9), 3.60 (1 H, d, *J* = 3.0, H-11), 2.93-2.83 (2 H, m, H-3), 2.79 (1 H, ddd, *J* = 11.6, 5.7, 5.7, H-5_a), 2.66 (1 H, ddd, *J* = 11.6, 5.6, 5.6, H-5_b), 2.39-2.33 (2 H, m, H-6), 2.32-2.23 (1 H, m, H-1_a), 2.11-2.08 (2 H, m, H-13), 2.07-1.72 (3 H, m, H-2, 15_a, 16), 1.39-1.32 (1 H, m, H-1_b), 1.28 (1 H, ddd, *J* = 12.3, 4.0, 1.7, H-15_b), 1.06 (3 H, d, *J* = 6.9, H-17); δ_C (100 MHz, $CDCl_3$) 209.0 (CO, C-12), 170.8 (CN, C-10), 138.1 (C, C-8), 130.0 (CH, C-7), 58.7 (CH, C-9), 56.4 (CH, C-11), 55.8 (CH, C-14), 52.9 (CH_2, C-3), 44.9 (CH_2, C-5), 39.5 (CH_2, C-13), 33.0 (CH_2, C-15), 29.8 (CH_2, C-1), 29.4 (CH, C-16), 25.2 (CH_2, C-6), 22.5 (CH_2, C-2), 21.3 (CH_3, C-17); *m/z* (ESI) 259 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{23}N_2O$, 259.1805. Found: $[MH]^+$, 259.1805 (0.1 ppm error)].

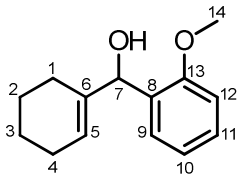
Lab Book Ref. = JDC/8/14

Data were consistent with those published.[55]



(4a*R,9a*R**)-1,2,3,4,4a,7,8,9a-octahydro-9*H*-xanthen-9-one 316:** To a stirred solution of diketone **257d** (50 mg, 0.24 mmol, 1.0 equiv.) in MeCN (5 mL) at rt was added 10% aq. NaOH (0.5 mL). The resulting yellow solution was held at rt for 18 h, then diluted with H_2O (10 mL) before extracting with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/Et_2O, 98:2) to give the title compound **316** (27 mg, 54%) as a colourless crystalline solid; mp. 75-78 ºC; R_f 0.54 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (thin film) 2928, 2859, 1634, 1566, 1428, 1185; δ_H (400 MHz, $CDCl_3$) 6.40 (1 H, ddd, J = 9.9, 4.3, 4.3, H-3), 5.91 (1 H, ddd, J = 9.9, 2.0, 2.0, H-2), 3.97 (1 H, ddd, J = 13.5, 11.3, 4.4, H-9), 2.53-2.32 (3 H, m, H-5, 13_a), 2.30-2.11 (4 H, m, H-4, 8, 10_a), 1.89-1.75 (2 H, m, H-11_a, 13_b), 1.67-1.56 (1 H, m, H-10_b), 1.37-1.15 (2 H, m, H-11_b, 12_a), 1.14-1.01 (1 H, m, H-12_b); δ_C (100 MHz, $CDCl_3$) 193.3 (CO, C-7), 164.6 (C, C-1), 140.2 (CH, C-3), 123.0 (CH, C-2), 107.6 (C, C-6), 81.3 (CH, C-9), 47.8 (CH, C-8), 31.8 (CH_2, C-10), 24.8 (CH_2), 24.1 (CH2), 24.0 (CH_2), 23.4 (CH_2), 17.6 (CH_2, C-5); *m/z* (ESI) 205 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{17}O_2$, 205.1223. Found: $[MH]^+$, 205.1222 (0.3 ppm error)].

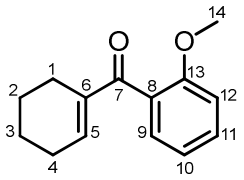
Lab Book Ref. = JDC/11/44



Cyclohexenyl(2-methoxyphenyl)methanol 320: To a stirred suspension of Mg turnings (78 mg, 3.20 mmol, 1.0 equiv.) in THF (5 mL) at rt was added dropwise 2-bromoanisole (333 μL, 3.20 mmol, 1.0 equiv.). The resulting orange solution was held at rt for 1 h then transferred *via* cannula into a cooled (−78 ºC) solution of cyclohexene carboxaldehyde (353 mg, 3.20 mmol, 1.0 equiv.) in THF (5 mL). The solution was held at −78 ºC for 30 min., then warmed to rt and held for 18 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL), then the aqueous phase was extracted with Et_2O (3 × 10

mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/Et_2O, 9:1) to give the title compound **320** (326 mg, 47%) as a colourless oil; R_f 0.40 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 3400 (br), 2926, 1489, 1241; δ_H (400 MHz, $CDCl_3$) 7.27 (1 H, dd, *J* = 7.5, 1.8, H-9), 7.23 (1 H, dd, *J* = 7.7, 1.8, H-11), 6.94 (1 H, ddd, *J* = 7.7, 7.5, 1.1, H-10), 6.89-6.86 (1 H, m, H-12), 5.78-5.75 (1 H, m, H-5), 5.31 (1 H, d, *J* = 5.1, H-7), 3.83 (3 H, s, H-14), 2.64 (1 H, d, *J* = 5.1, OH), 2.09-2.03 (2 H, m, H-4), 1.95-1.89 (2 H, m, H-1), 1.65-1.52 (4 H, m, H-2, 3); δ_C (100 MHz, $CDCl_3$) 157.1 (C, C-13), 138.6 (C, C-6), 130.8 (C, C-8), 128.4 (CH, ArCH), 127.8 (CH, ArCH), 122.5 (CH, C-1), 120.6 (CH, C-12), 110.7 (CH, C-12), 73.4 (CH, C-7), 55.5 (CH_3, C-14), 25.2 (CH_2, C-1), 25.0 (CH_2, C-4), 22.6 (CH_2), 22.5 (CH_2); *m/z* (ESI) 241 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{18}NaO_2$, 241.1199. Found: $[MNa]^+$, 241.1203 (1.5 ppm error)].

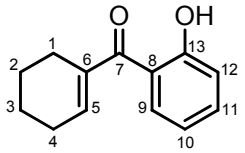
Lab Book Ref = JDC/11/1



Cyclohexenyl(2-methoxyphenyl)methanone 321: To a stirred solution of alcohol **320** (298 mg, 1.37 mmol, 1.0 equiv.) in DCM (15 mL) at 0 ºC was added in one portion DMP (721 mg, 1.70 mmol, 1.2 equiv.). The solution was stirred at 0 ºC for 30 min. before warming to rt and holding for 2 h. The reaction was diluted with Et_2O (20 mL), then quenched with sat. aq. $NaHCO_3$/sat. aq. thiosulfate (1:1, 20 mL). The biphasic solution was stirred for 30 min., then the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/Et_2O, 9:1) to give the title compound **321** (102 mg, 34%) as a colourless oil; R_f 0.44 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2934, 1653, 1388, 1435, 1243; δ_H (400 MHz, $CDCl_3$) 7.38-7.32 (1 H, m, H-11), 7.15 (1 H, dd, *J* = 7.4, 1.8, H-9), 6.97-6.91 (2 H, m, H-10, 12), 6.65-6.51 (1 H, m, H-5), 3.78 (3 H, s, H-14), 2.23-2.17 (2 H, m, H-1), 1.74-1.60 (2 H, m, H-4), 2.42-2.37 (4 H, m, H-2, 3); δ_C (100 MHz, $CDCl_3$) 197.8 (CO, C-7), 156.7 (C, C-13), 145.7 (CH, C-5), 140.0 (C, C-6), 130.5 (CH, C-11), 129.6 (C, C-8), 128.6 (CH, C-9), 120.0 (CH, C-10), 111.3 (CH, C-12), 55.7 (CH_3, C-14), 26.3

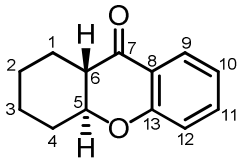
(CH_2, C-4), 22.9 (CH_2, C-1), 21.9 (CH_2), 21.6 (CH_2); *m/z* (ESI) 217 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{17}O_2$, 217.1223. Found: $[MH]^+$, 217.1214 (4.3 ppm error)].

Lab Book Ref. = JDC/11/5



Cyclohexenyl(2-hydroxyphenyl)methanone 322: To a stirred solution of ketone **321** (76 mg, 0.35 mmol, 1.0 equiv.) in DCM (2 mL) at 0 ºC was added dropwise BCl_3 (1.0 M in DCM, 0.70 mL, 2.0 equiv.). The solution was stirred at 0 ºC for 30 min. before warming to rt and holding for 4 h. The reaction was quenched by pouring onto ice, then the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give the title compound **322** (50 mg, 71%) as a colourless oil; R_f 0.89 (DCM/MeOH, 95:5); υ_{max}/cm^{-1} (neat) 2934, 1692, 1621, 1597, 1239; δ_H (400 MHz, $CDCl_3$) 7.67 (1 H, dd, *J* = 8.0, 1.7, H-9), 7.44 (1 H, ddd, *J* = 8.4, 7.3, 1.7, H-11), 6.99 (1 H, dd, *J* = 8.4, 1.2, H-12), 6.85 (1 H, ddd, *J* = 8.0, 7.3, 1.2, H-10), 6.38-6.35 (1 H, m, H-5), 2.43-2.37 (2 H, m, H-1), 2.31-2.25 (2 H, m, H-4), 1.80-1.67 (4 H, m, H-2, 3); δ_C (100 MHz, $CDCl_3$) 202.8 (CO, C-7), 162.6 (C, C-13), 139.5 (CH, C-5), 137.4 (C, C-6), 135.6 (CH, C-11), 132.5 (CH, C-9), 119.0 (C, C-8), 118.2 (CH, ArCH), 118.1 (CH, ArCH), 25.5 (CH_2, C-4), 24.6 (CH_2, C-1), 21.9 (CH_2), 21.5 (CH_2); *m/z* (ESI) 241 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{13}H_{14}NaO_2$, 225.0886. Found: $[MNa]^+$, 225.0885 (0.5 ppm error)].

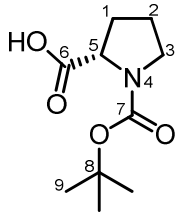
Lab Book Ref. = JDC/11/16



(4a*S,9a*S**)-1,2,3,4,4a,9a-Hexahydro-9*H*-xanthen-9-one 323:** To a stirred solution of phenol **322** (27 mg, 0.13 mmol, 1.0 equiv.) in MeCN (2 mL) at rt was added 10% aq.

NaOH (0.1 mL). The resulting yellow solution was held at rt for 1 h, then diluted with H_2O (5 mL) before extracting with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/EtOAc, 49:1) to give the title compound **323** (15 mg, 56%) as a colourless oil containing traces of the *cis*-diastereoisomer; R_f 0.37 (PE/EtOAc, 9:1); υ_{max}/cm^{-1} (neat) 2937, 2862, 1686, 1605, 1322, 766; δ_H (400 MHz, $CDCl_3$) 7.87 (1 H, dd, *J* = 7.9, 1.8, H-9), 7.45 (1 H, ddd, *J* = 8.5, 7.2, 1.8, H-11), 7.00 (1 H, ddd, *J* = 7.9, 7.2, 1.0, H-10), 6.95 (1 H, ddd, *J* = 8.5, 1.0, 0.5, H-12), 4.09 (1 H, ddd, *J* = 12.5, 11.0, 4.5, H-5), 2.48 (1 H, ddd, *J* = 12.2, 11.0, 4.0, H-6), 2.46-2.37 (1 H, m, H-1_a), 2.30-2.23 (1 H, m, H-4_a), 1.93-1.82 (2 H, m, H-2_a, 3_a), 1.72 (1 H, dddd, *J* = 12.5, 12.5, 11.2, 5.4, H-4_b), 1.40-1.17 (3 H, m, H-1_b, 2_b, 3_b); δ_C (100 MHz, $CDCl_3$) 194.2 (CO, C-7), 161.4 (C, C-13), 135.6 (CH, C-11), 127.1 (CH, C-9), 121.1 (CH, C-10), 120.9 (C, C-8), 117.6 (CH, C-12), 80.5 (CH, C-5), 49.6 (CH, C-6), 32.4 (CH_2, C-4), 24.7 (CH_2), 23.8 (CH_2), 23.6 (CH_2); *m/z* (ESI) 203 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{15}O_2$, 203.1067. Found: $[MH]^+$, 203.1061 (2.8 ppm error)].

Lab Book Ref. = JDC/11/34

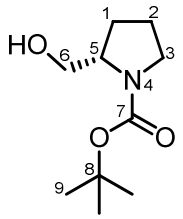


(*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxylic acid 339: To a stirred solution of (*S*)-proline (10.0 g, 86.7 mmol, 1.0 equiv.) and triethylamine (12.7 mL, 91.0 mmol, 1.05 equiv.) in DCM (200 mL) at 0 ºC was added dropwise di*tert*-butyl dicarbonate (20.8 g, 95.4 mmol, 1.1 equiv.) as a solution in DCM (20 mL). The colourless solution was held at 0 ºC for 3 h, then quenched with sat. aq. citric acid (100 mL). The aqueous phase was separated and extracted with DCM (2 × 100 mL), then the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a colourless oil. The oil was taken up in hot EtOAc (10 mL) and the product precipitated by slow addition of hexane (500mL). The resulting suspension was filtered and dried to afford the title compound **339** (17.7 g, 95%) as a colourless crystalline solid; mp. 134-136 ºC [(Lit.[184] 135-137 ºC)]; R_f 0.37 (DCM/MeOH, 9:1); $[\alpha]^{20}_D$ −102.5 (*c*

1.05, $CHCl_3$), (Lit.[184] −80.0 (*c* 1.375, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$, Rotamers observed) 4.39-4.21 (2 H, m, H-5, 5'), 3.61-3.29 (4 H, m, H-3, 3'), 2.45-2.22 (2 H, m, H-1), 2.12-1.84 (6 H, m, H-1', 2, 2'), 1.49 (9 H, s, H-9), 1.43 (9 H, s, H-9').

Lab Book Ref. = JDC/13/53

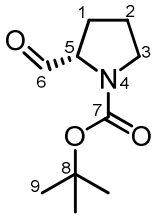
Melting Point and ^{1}H NMR Spectroscopic data were consistent with those published.[184]



***tert*-Butyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate 340:** To a stirred solution of acid **339** (17.50 g, 81.3 mmol, 1.0 equiv.) in THF (200 mL) at 0 ºC as added dropwise BH_3·DMS (8.48 mL, 89.4 mmol, 1.1 equiv.) over 1 h *via* syringe pump. The colourless solution was held at 0 ºC for 30 min., then heated to reflux and held for 3 h. The reaction was cooled to 0 ºC and carefully quenched with H_2O (100 mL). The aqueous phase was extracted with EtOAc (2 × 100 mL), then the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **340** (16.3 g, Quant.) as a colourless crystalline solid; mp. 56-59 ºC (Lit.[185] 58-59 ºC); R_f 0.37 (DCM/MeOH, 9:1); $[\alpha]^{24}_D$ −48.4 (*c* 1.01, $CHCl_3$), (Lit.[185] −47.0 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 3.95 (1 H, dddd, *J* = 7.9, 7.7, 5.6, 3.3, H-5), 3.64 (1 H, dd, *J* = 11.1, 3.3, H-6_a), 3.58 (1 H, dd, *J* = 11.1, 7.7, H-6_b), 3.46 (1 H, ddd, *J* = 10.9, 7.1, 6.6, H-3_a), 3.31 (1 H, ddd, *J* = 10.9, 7.1, 6.5, H-3_b), 2.06-1.96 (1 H, m, H-1_a), 1.90-1.71 (2 H, m, H-2), 1.63-1.54 (1 H m, H-1_b), 1.47 (9 H, s, H-9).

Lab Book Ref. = JDC/13/60

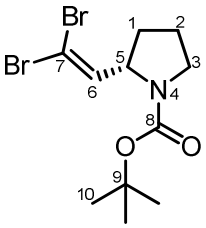
Data were consistent with those published.[185]



***tert*-Butyl (*S*)-2-formylpyrrolidine-1-carboxylate 341:** To a stirred solution of oxalyl chloride (7.76 mL, 91.7 mmol, 1.2 equiv.) in DCM (450 mL) at −78 ºC was added dropwise DMSO (13.0 mL, 183.4 mmol, 2.4 equiv.) over 45 min. *via* syringe pump. The colourless solution was held at −78 ºC for 30 min., then alcohol **340** (15.38 g, 76.4 mmol, 1.0 equiv.) was added as a pre-cooled solution in DCM (50 mL) *via* cannula. The reaction was held at −78 ºC for 1 h, then triethylamine (53.3 mL, 382.0 mmol, 5.0 equiv.) was added dropwise. The reaction was held at −78 ºC for a further 15 min., then warmed to rt and held for 1 h. The reaction was quenched with H_2O (50 mL), then the aqueous phase was extracted with DCM (2 × 150 mL). The combined organic extracts were washed with H_2O (150 mL) and brine (150 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound **341** (14.5 g, 96%) as a colourless oil that was used without further purification; R_f 0.19 (PE/EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$, Rotamers observed) 9.55 (1 H, d, *J* = 1.8, H-6), 9.46 (1 H, d, *J* = 3.0, H-6'), 4.25-4.16 (1 H, m, H-5), 4.04 (1 H, ddd, *J* = 8.9, 6.2, 3.0, H-5'), 3.60-3.35 (4 H, m, H-3, 3'), 2.18-1.77 (8 H, m, H-1, 1', 2, 2'), 1.47 (9 H, s, H-9), 1.42 (9 H, s, H-9').

Lab Book Ref. = JDC/13/71

Data were consistent with those published.[186]

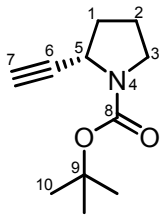


***tert*-Butyl (*S*)-2-(2,2-dibromovinyl)pyrrolidine-1-carboxylate 342:** To a stirred solution of triphenylphosphine (57.4 g, 219.0 mmol, 3.0 equiv.), in DCM (450 mL) at 0 ºC was added dropwise carbon tetrabromide (36.3 g, 109.5 mmol, 1.5 equiv.) as a solution in DCM (15 mL) *via* syringe pump over 45 min. The resulting orange solution was held at 0 ºC for 30 min., then aldehyde **341** (14.5 g, 73.0 mmol, 1.0 equiv.) was

added dropwise as a solution in DCM (40 mL) over 45 min. The solution was held at 0 ºC for 3 h, then quenched with sat. aq. $NaHCO_3$ (300 mL). The aqueous phase was extracted with DCM (2 × 150 mL), then the combined organic extracts were washed with brine (150 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow solid, which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give the title compound **342** (18.8 g, 73%) as a colourless crystalline solid; mp. 61-63 ºC (Lit.[187] 61-62 ºC); R_f 0.38 (PE/EtOAc, 4:1); $[\alpha]_D$ +26.4 (*c* 1.01, $CHCl_3$), (Lit.[188] +30.6 (*c* 1.04, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.47-6.30 (1 H, m, H-6), 4.50-4.28 (1 H, m, H-5), 3.51-3.34 (2 H, m, H-3), 2.23-2.11 (1 H, m, H-1_a), 1.90-1.79 (2 H, m, H-2), 1.78-1.68 (1 H, m, H-1_b), 1.46 (9 H, s, H-9).

Lab Book Ref. = JDC/13/76

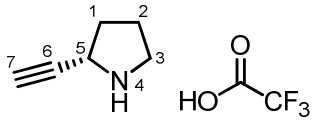
Data were consistent with those published.[187, 188]



***tert*-Butyl (*S*)-2-ethynylpyrrolidine-1-carboxylate 336:** To a stirred solution of bromide **342** (5.32 g, 15.0 mmol, 1.0 equiv.) in DMSO (180 mL) at rt was added Cs_2CO_3 (12.2 g, 37.5 mmol, 2.5 equiv.). The suspension was heated to 115 ºC and held for 18 h, then cooled to rt and poured into H_2O (500 mL). The aqueous phase was extracted with EtOAc (3 × 150 mL), then the combined organic extracts were washed with H_2O (150 mL) and brine (150 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give the title compound **336** (2.16 g, 74%) as a colourless oil; R_f 0.38 (PE/EtOAc, 4:1); $[\alpha]^{24}_D$ –102.1 (*c* 1.03, MeOH), (Lit.[187] –99.0 (*c* 1.0, MeOH)); δ_H (400 MHz, $CDCl_3$, Rotamers observed) 4.58-4.36 (1 H, m, H-5), 3.54-3.22 (2 H, m, H-3), 2.26-2.17 (1 H, m, H-1_a), 2.14-1.98 (3 H, m, H-2, 6), 1.96-183 (1 H, m, H-1_b), 1.48 (9 H, s, H-10).

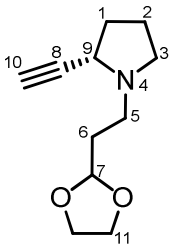
Lab Book Ref. = JDC/13/84

Data were consistent with those published.[187, 189]



(*S*)-2-Ethynylpyrrolidine 2,2,2-trifluoroacetate 343: To a stirred solution of alkyne **336** (2.00 g, 10.2 mmol, 1.0 equiv.) in DCM (50 mL) at 0 ºC was added dropwise TFA (5 mL). The resulting orange solution was held at 0 ºC for 30 min., then warmed to rt and held until consumption of the starting material was observed by TLC (~4 h). The orange solution was concentrated *in vacuo* to afford the crude product as an orange oil which was purified by column chromatography (SiO_2, DCM/MeOH, 9:1) to give the title compound **343** (2.13 g, Quant) as a colourless oil; R_f 0.18 (DCM/MeOH, 9:1); $[\alpha]^{24}_D$ –33.6 (*c* 0.88, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3307, 3250, 2968, 1674, 1201, 1134; δ_H (400 MHz, $CDCl_3$) 4.33 (1 H, ddd, *J* = 6.8, 6.5, 2.3, H-5), 3.45 (1 H, ddd, *J* = 11.5, 8.2, 6.9, H-3_a), 3.34 (1 H, ddd, *J* = 11.5, 8.2, 5.8, H-3_b), 2.58 (1 H, d, *J* = 2.3, H-7), 2.39-2.29 (1 H, m, H-1_a), 2.26-2.03 (3 H, m, H-1_b, 2); δ_C (100 MHz, $CDCl_3$) 77.2 (CH, C-7), 76.4 (C, C-6), 49.0 (CH, C-5), 44.5 (CH_2, C-3), 32.2 (CH_2, C-1), 23.5 (CH_2, C-2); *m/z* (ESI) 96 $[MH]^+$; [HRMS (ESI): calcd. for $C_6H_{10}N$, 96.0813. Found: $[MH]^+$, 96.0811 (2.8 ppm error)].

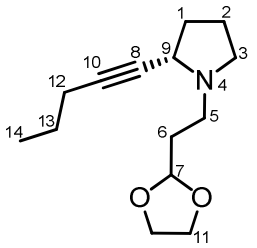
Lab Book Ref. = JDC/13/94



(*S*)-1-(2-(1,3-Dioxolan-2-yl)ethyl)-2-ethynylpyrrolidine 345: To a stirred solution of amine **343** (1.07 g, 5.10 mmol, 1.0 equiv.) in MeCN (25 mL) at rt were added successively K_2CO_3 (2.11 g, 15.3 mmol, 3.0 equiv.) and 2-(2-bromoethyl)-1,3-dioxolane (0.90 mL, 7.70 mmol, 1.5 equiv.). The suspension was heated to 50 ºC and held for 24 h, then cooled to rt and the solvent removed under reduced pressure. The residue was taken up in EtOAc (20 mL) and the organic phase was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, DCM/MeOH, 98:2) to

give the title compound **345** (677 mg, 68%) as an orange oil; R_f 0.51 (DCM/MeOH, 9:1); $[\alpha]^{20}_D$ –108.3 (*c* 0.99, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2957, 2881, 2813, 1140, 1033; δ_H (400 MHz, $CDCl_3$) 4.92 (1 H, t, *J* = 4.9, H-7), 3.98-3.92 (2 H, m, H-11_a, 11_a'), 3.86-3.81 (2 H, m, H-11_b, 11_b'), 3.42-3.38 (1 H, m, H-9), 2.91 (1 H, ddd, *J* = 11.9, 9.0, 7.1, H-5_a), 2.75 (1 H, ddd, *J* = 8.8, 8.1, 5.4, H-3_a), 2.55-2.46 (2 H, m, H-3_b, 5_b), 2.26 (1 H, d, *J* = 2.1, H-10), 2.14-2.03 (1 H, m, H-1_a), 1.96-1.71 (5 H, m, H-1_b, 2, 6); δ_C (100 MHz, $CDCl_3$) 103.3 (CH, C-7), 82.9 (C, C-8), 72.3 (CH, C-10), 64.8 (2 × CH_2, C-11, 11'), 54.1 (CH, C-9), 51.7 (CH_2, C-3), 48.1 (CH_2, C-5), 33.0 (CH_2, C-6), 31.6 (CH_2, C-1), 22.0 (CH_2, C-2); *m/z* (ESI) 196 $[MH]^+$; [HRMS (ESI): calcd. for $C_{11}H_{18}NO_2$, 196.1332. Found: $[MH]^+$, 196.1334 (1.2 ppm error)].

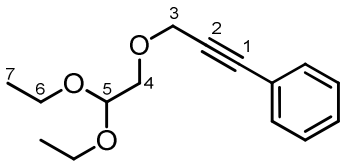
Lab Book Ref. = JDC/9/64



(*S*)-1-(2-(1,3-Dioxolan-2-yl)ethyl)-2-(pent-1-ynyl)pyrrolidine 346: To a stirred solution of alkyne **345** (195 mg, 1.00 mmol, 1.0 equiv.) in THF (5 mL) at −78 ºC was added dropwise *n*-BuLi (1.6 M, 0.69 mL, 1.10 mmol, 1.1 equiv.). The yellow solution was held at −78 ºC for 1 h, then warmed to rt before adding *n*-propyl iodide (117 µL, 1.20 mmol, 1.2 equiv.). The reaction was heated to reflux and held for 18 h, then cooled to rt and quenched with sat. aq. NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), then the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **346** (214 mg, 90%) as a pale yellow oil; R_f 0.49 (DCM/MeOH, 9:1); $[\alpha]^{24}_D$ – 93.3 (*c* 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2960, 2876, 1141, 1034; δ_H (400 MHz, $CDCl_3$) 4.94 (1 H, t, *J* = 4.9, H-7), 4.00-3.91 (2 H, m, H-11_a, 11_a'), 3.90-3.80 (2 H, m, H-11_b, 11_b'), 3.34-3.27 (1 H, m, H-9), 2.96 (1 H, ddd, *J* = 11.6, 9.7, 6.6, H-5_a), 2.81 (1 H, ddd, *J* = 8.8, 8.7, 4.8, H-3_a), 2.49-2.37 (2 H, m, H-3_b, 5_b), 2.16 (2 H, td, *J* = 7.0, 1.9, H-12), 2.12-2.01 (1 H, m, H-1_a), 1.98-1.68 (5 H, m, H-1_b, 2, 6), 1.57-1.45 (2 H, qt, *J* = 7.4, 7.0, H-13), 0.96 (3 H, t, *J* = 7.4, H-14); δ_C (100 MHz, $CDCl_3$) 103.4 (CH, C-7), 84.5 (C, C-10), 79.0 (C, C-8), 64.8 (2 × CH_2, C-11, 11'), 54.9 (CH, C-9), 51.9 (CH_2, C-3), 48.4

(CH_2, C-5), 33.1 (CH_2, C-6), 32.0 (CH_2, C-1), 22.3 (CH_2, C-13), 22.0 (CH_2, C-2), 20.7 (CH_2, C-12), 13.5 (CH_3, C-14); *m/z* (ESI) 238 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{24}NO_2$, 238.1802. Found: $[MH]^+$, 238.1803 (0.5 ppm error)].

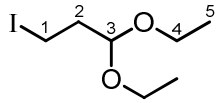
Lab Book Ref. = JDC/9/69



(3-(2,2-Diethoxyethoxy)prop-1-ynyl)benzene[147] **351a:** To a stirred suspension of sodium hydride (60 wt%, 600 mg, 15.0 mmol, 1.0 equiv.) in DMF (12 mL) at 0 ºC was added dropwise 3-phenyl-2-propyn-1-ol (1.87 mL, 15.0 mmol, 1.0 equiv.). The resulting yellow slurry was held at 0 ºC for 1 h, then bromo acetaldehyde diethyl acetal (2.26 ml, 15.0 mmol, 1.0 equiv.) was added dropwise. The solution was held at 0 ºC for 30 min., then heated to 100 ºC and held for 18 h. The brown solution was cooled to rt then quenched with H_2O (50 mL). The aqueous phase was extracted with Et_2O (3 × 25 mL), then the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, PE/Et_2O, 19:1) to give the title compound **351a** (1.21 g, 32%) as a pale yellow oil; R_f 0.45 (PE/EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$) 7.46-7.42 (2 H, m, ArH), 7.34-7.29 (3 H, m, ArH), 4.71 (1 H, t, *J* = 5.2, H-5), 4.45 (2 H, s, H-3), 3.73 (2 H, dq, *J* = 9.3, 7.1, H-6_a, 6_a'), 3.66 (2 H, d, *J* = 5.2, H-4), 3.60 (2 H, dq, *J* = 9.3, 7.1, H-6_b, 6_b'), 1.24 (6 H, t, *J* = 7.1, H-7, 7').

Lab Book Ref. = JDC/12/93

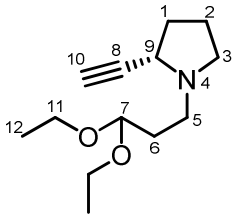
Data were consistent with those published.[147]



1,1-Diethoxy-3-iodopropane[149] **355:** To a stirred solution of acrolein (3.35 mL, 50.0 mmol, 1.0 equiv.) and NaI (8.99 g, 60.0 mmol, 1.2 equiv.) in MeCN (125 mL) at 0 ºC was added dropwise TMSCl (7.62 mL, 60.0 mmol, 1.2 equiv.). The resulting slurry was stirred at 0 ºC for 5 min., then EtOH (7.5 mL) was added. The yellow slurry was held at 0 ºC for a further 20 min., then quenched with sat. aq. $NaHCO_3$ (200 mL). The aqueous phase was diluted with water (100 mL), then extracted with hexane (3 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **355** (10.5 g, 81%) as a colourless oil; R_f 0.60 (PE/EtOAc, 9:1); δ_H (400 MHz, $CDCl_3$) 4.58 (1 H, t, J = 5.5, H-3), 3.68 (2 H, dq, J = 9.4, 7.1, H-4_a, 4_a'), 3.53 (2 H, dq, J = 9.4, 7.1, H-4_b, 4_b'), 3.19 (2 H, t, J = 7.0, H-1), 2.13 (2 H, td, J = 7.0, 5.5, H-2), 1.21 (6 H, t, J = 7.1, H-5, 5').

Lab Book Ref. = JDC/13/93

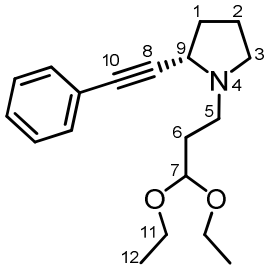
Data were consistent with those published.[149]



(*S*)-1-(3,3-Diethoxypropyl)-2-ethynylpyrrolidine 356: To a stirred solution of amine **343** (2.13 g, 10.2 mmol, 1.0 equiv.) in MeCN (130 mL) at rt were added successively K_2CO_3 (4.23 g, 30.6 mmol, 3.0 equiv.) and 1,1-diethoxy-3-iodopropane **355** (2.76 g, 10.7 mmol, 1.05 equiv.). The suspension was heated to reflux and held for 18 h, then cooled to rt and the solvent removed under reduced pressure. The residue was taken up in H_2O (100 mL) and the aqueous phase extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, DCM/MeOH, 99:1-98:2) to give the title compound **356** (1.81 g, 79%) as a pale yellow oil; R_f 0.56 (DCM/MeOH, 9:1); $[\alpha]^{24}_D$ –101.0 (*c* 0.70, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2973, 2879, 2877, 1126, 1062; δ_H (400 MHz, $CDCl_3$) 4.60 (1 H, t, J =

5.8, H-7), 3.66 (1 H, dq, J = 9.3, 7.0, H-11$_a$), 3.64 (1 H, dq, J = 9.3, 7.0, H-11$_a$'), 3.52 (1 H, dq, J = 9.3, 7.0, H-11$_b$), 3.49 (1 H, dq, J = 9.3, 7.0, H-11$_b$'), 3.38 (1 H, ddd, J = 7.9, 4.5, 2.1, H-9), 2.86 (1 H, ddd, J = 11.9, 8.7, 7.3, H-5$_a$), 2.77 (1 H, ddd, J = 9.3, 7.7, 5.1, H-3$_a$), 2.49 (1 H, ddd, J = 9.3, 8.0, 5.6, H-3$_b$), 2.44-2.39 (1 H, m, H-5$_b$), 2.25 (1 H, d, J = 2.1, H-10), 2.15-2.03 (1 H, m, H-1$_a$), 1.97-1.71 (5 H, m, H-1$_b$, 2, 6), 1.20 (6 H, t, J = 7.0, H-12, 12'); δ_C (100 MHz, $CDCl_3$) 101.5 (CH, C-7), 83.1 (C, C-8), 72.1 (CH, C-10), 61.1 (CH_2, C-11), 60.9 (CH_2, C-11'), 54.2 (CH, C-9), 51.8 (CH_2, C-3), 48.7 (CH_2, C-5), 32.7 (CH_2, C-6), 31.7 (CH_2, C-1), 22.0 (CH_2, C-2), 15.3 (2 × CH_3, C-12, 12'); *m/z* (ESI) 226 $[MH]^+$; [HRMS (ESI): calcd. for $C_{13}H_{24}NO_2$, 226.1802. Found: $[MH]^+$, 226.1805 (1.7 ppm error)].

Lab Book Ref. = JDC/13/99

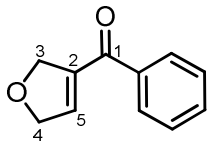


(*S*)-1-(3,3-Diethoxypropyl)-2-(phenylethynyl)pyrrolidine 354: To a stirred solution of alkyne **356** (140 mg, 0.62 mmol, 1.0 equiv.), CuI (11 mg, 0.06 mmol, 0.1 equiv.) and $Pd(PPh_3)_2Cl$ (21 mg, 0.03 mmol, 0.05 equiv.) in Et_3N (2 mL, degassed) at rt was added iodobenzene (139 μL, 1.24 mmol, 2.0 equiv.). The dark brown solution was held at rt for 18 h, then concentrated *in vacuo* to afford a dark brown residue which was purified by column chromatography (SiO_2, DCM/MeOH, 98:2) to give the title compound **354** (185 mg, 98%) as a yellow oil; R_f 0.66 (DCM/MeOH, 9:1); $[\alpha]^{24}_D$ –95.0 (*c* 1.05, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2973, 2895, 1444, 1126, 1061; δ_H (400 MHz, $CDCl_3$) 7.54-7.41 (2 H, m, ArH), 7.36-7.27 (3 H, m, ArH), 4.63 (1 H, t, J = 5.2, H-7), 4.22 (1 H, br s, H-9), 3.65 (2 H, dq, J = 9.4, 7.1, H-11$_a$, 11$_a$'), 3.52 (1 H, dq, J = 9.4, 7.1, H-11$_b$), 3.51 (1 H, dq, J = 9.4, 7.1, H-11$_b$'), 3.27-3.08 (2 H, m, H-3$_a$, 5$_a$), 3.06-2.90 (2 H, m, H-3$_b$, 5$_b$), 2.51-2.36 (1 H, m, 1$_a$), 2.24-2.00 (5 H, m, H-1$_b$, 2, 6), 1.17 (6 H, t, J = 7.1, H-12, 12'); δ_C (100 MHz, $CDCl_3$) 131.8 (2 × CH, ArCH), 128.8 (CH, ArCH), 128.3 (2 × CH, ArCH), 121.9 (C, ArC), 100.9 (CH, C-7), 87.5 (C), 84.2 (C), 61.9 (CH_2, C-11), 61.8 (CH_2, C-11'), 55.9 (CH, C-9), 52.1 (CH_2, C-3), 48.6 (CH_2, C-5), 31.6 (CH_2), 31.3 (CH_2), 21.8 (CH_2, C-2),

15.2 (2 × CH_3, C-12, 12'); *m/z* (ESI) 302 $[MH]^+$; [HRMS (ESI): calcd. for $C_{19}H_{28}NO_2$, 302.2115. Found: $[MH]^+$, 302.2116 (0.3 ppm error)].

Lab Book Ref. = JDC/14/80

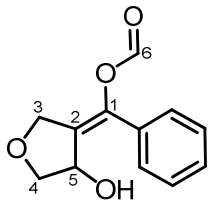
Representative Procedure for the Formic Acid Cyclisation Reaction:



(2,5-Dihydrofuran-3-yl)(phenyl)methanone 352a: A stirred solution of alkyne **351a** (62 mg, 0.25 mmol, 1.0 equiv.) in formic acid (1 mL) was heated at 100 ºC (oil-bath pre-heated) for 30 min. The brown solution was cooled to rt then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give the title compound **352a** (43 mg, 98%) as a colourless crystalline solid; mp. 67-69 ºC (Lit.[153] 48-50 ºC); R_f 0.23 (SiO_2, PE/EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$) 7.82-7.78 (2 H, m, ArH), 7.61-7.56 (1 H, m, ArH), 7.50-7.45 (2 H, m, ArH), 6.64-6.61 (1 H, m, H-5), 5.04-4.99 (2 H, m, H-3_a, 4_a), 4.95-4.91 (2 H, m, H-3_b, 4_b).

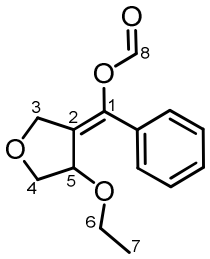
Lab Book Ref. = JDC/13/85

^{1}H NMR spectroscopic Data were consistent with those published.[153]



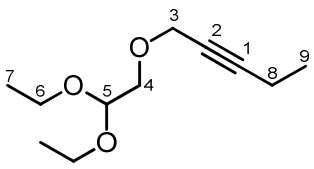
(4-Hydroxydihydrofuran-3(2*H*)-ylidene)(phenyl)methyl formate 367: A stirred solution of alkyne **351a** (248 mg, 1.00 mmol, 1.0 equiv.) in formic acid (5 mL) was held at rt for 30 min., then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1-2:1) to give formate **368** (15 mg, 6%) as an unstable colourless oil and the title compound **367** (45 mg, 20%) as an unstable yellow oil; R_f 0.07 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3396 (br), 1737, 1125, 1069; δ_H (400 MHz, $CDCl_3$) 8.14 (1 H, s, H-6), 7.70-7.65 (2 H, m, ArH), 7.45-7.37 (3 H, m,

ArH), 4.69 (1 H, d, J = 3.5, H-5), 4.63 (1 H, d, J = 14.5, H-3_a), 4.40 (1 H, d, J = 14.5, H-3_b), 4.07 (1 H, d, J = 10.1, H-4_a), 3.80 (1 H, dd, J = 10.1, 3.5, H-4_b); δ_C (100 MHz, $CDCl_3$) 158.4 (CH, C-6), 142.4 (C, C-1), 133.3 (C, ArC), 131.0 (C, C-2), 129.4 (CH, ArCH), 128.6 (2 × CH, ArCH), 127.0 (2 × CH, ArCH), 77.1 (CH_2, C-4), 71.4 (CH, C-5), 68.7 (CH_2, C-3); *m/z* (ESI) 243 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{12}H_{12}NaO_4$, 243.0628. Found: $[MNa]^+$, 243.0627 (0.1 ppm error)].



(4-Ethoxydihydrofuran-3(2*H*)-ylidene)(phenyl)methyl formate 368: A colourless oil; R_f 0.24 (PE/EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$) 8.14 (1 H, s, H-8), 7.62-7.58 (2 H, m, ArH), 7.43-7.36 (3 H, m, ArH), 4.63 (1 H, d, J = 14.3, H-3_a), 4.42 (1 H, d, J = 14.3, H-3_b), 4.41 (1 H, d, J = 3.6, H-5), 4.20 (1 H, d, J = 10.2, H-4_a), 3.75 (1 H, dd, J = 10.2, 3.6, H-4_b), 3.53 (1 H, dq, J = 9.0, 7.0, H-6_a), 3.45 (1 H, dq, J = 9.0, 7.0, H-6_b), 1.22 (3 H, t, J = 7.0, H-7); δ_C (100 MHz, $CDCl_3$) 158.3 (CH, C-8), 142.8 (C, C-1), 134.0 (C, ArC), 129.7 (C, C-2), 128.7 (CH, ArCH), 128.4 (2 × CH, ArCH), 127.3 (2 × CH, ArCH), 78.0 (CH, C-5), 73.5 (CH_2, C-4), 68.9 (CH_2, C-3), 63.6 (CH_2, C-6), 15.4 (CH_3, C-7); *m/z* (ESI) 271 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{14}H_{16}NaO_4$, 271.0941. Found: $[MNa]^+$, 271.0929 (4.2 ppm error)].

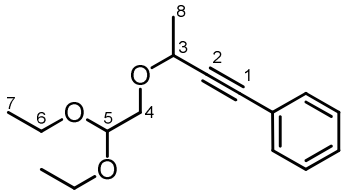
Lab Book Ref. = JDC/14/14



1-(2,2-Diethoxyethoxy)pent-2-yne 351b: To a stirred suspension of sodium hydride (60 wt%, 220 mg, 5.50 mmol, 1.1 equiv.) in DMF (5 mL) at 0 ºC was added dropwise 2-pentyn-1-ol (0.51 mL, 5.50 mmol, 1.1 equiv.). The resulting yellow slurry was held at 0 ºC for 30 min., then bromo acetaldehyde diethyl acetal (0.76 ml, 5.00 mmol, 1.0

equiv.) was added dropwise. The solution was held at 0 ºC for 30 min., then heated to reflux and held for 18 h. The brown solution was cooled to rt then quenched with H_2O (25 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), then the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, PE/Et_2O, 9:1) to give the title compound **351b** (495 mg, 49%) as a pale yellow oil; R_f 0.67 (PE/EtOAc, 2:1); υ_{max}/cm^{-1} (neat) 2977, 2935, 1135, 1102; δ_H (400 MHz, $CDCl_3$) 4.66 (1 H, t, *J* = 5.3, H-5), 4.19 (2 H, t, *J* = 2.2, H-3), 3.71 (2 H, dq, *J* = 9.4, 7.1, H-6_a. 6_a'), 3.58 (2 H, dq, *J* = 9.4, 7.1, H-6_b, 6_b'), 3.56 (2 H, d, *J* = 5.3, H-4), 2.22 (2 H, qt, *J* = 7.5, 2.2, H-8), 1.23 (6 H, t, *J* = 7.1, H-7, 7'), 1.13 (3 H, t, *J* = 7.5, H-9); δ_C (100 MHz, $CDCl_3$) 100.8 (CH, C-5), 88.5 (C, C-1), 74.9 (C, C-2), 69.7 (CH_2, C-4), 62.1 (2 × CH_2, C-6, 6'), 59.0 (CH_2, C-3), 15.2 (2 × CH_3, C-7, 7'), 13.7 (CH_3, C-9), 12.3 (CH_2, C-8); *m/z* (ESI) 223 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{11}H_{20}NaO_3$, 223.1305. Found: $[MNa]^+$, 223.1305 (0.3 ppm error)].

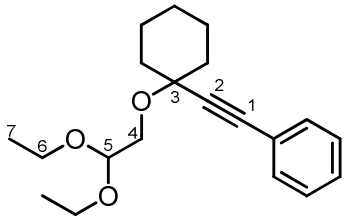
Lab Book Ref. = JDC/12/19



(3-(2,2-Diethoxyethoxy)but-1-ynyl)benzene 351c: To a stirred suspension of sodium hydride (60 wt%, 136 mg, 3.40 mmol, 1.0 equiv.) in DMF (4 mL) at 0 ºC was added dropwise 4-phenyl-3-butyn-2-ol (500 mg, 3.40 mmol, 1.0 equiv.). The resulting orange solution was held at 0 ºC for 1 h, then bromo acetaldehyde diethyl acetal (2.26 ml, 15.0 mmol, 1.0 equiv.) and TBAI (126 mg, 0.34 mmol, 0.1 equiv.) were added. The solution was held at 0 ºC for 30 min., then heated to 100 ºC and held for 18 h. The brown solution was cooled to rt then quenched with H_2O (50 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), then the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, PE/Et_2O, 19:1-9:1) to give the title compound **351c** (152 mg, 17%) as a pale yellow oil; R_f 0.53 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2977, 2876, 1328, 1110; δ_H (400 MHz, $CDCl_3$) 7.46-7.39 (2 H, m, ArH), 7.33-7.28 (3 H, m, ArH), 4.70 (1 H, dd, *J* = 5.7, 4.9, H-5), 4.49 (1 H, q, *J* = 6.6, H-3), 3.83 (1

H, dd, J = 10.4, 4.9, H-4_a), 3.74 (1 H, dq, J = 10.7, 7.1, H-6_a), 3.73 (1 H, dq, J = 10.7, 7.1, H-6_a'), 3.64-3.55 (2 H, m, H-6_b, 6_b'), 3.56 (1 H, dd, J = 10.4, 5.7, H-4_b), 1.53 (3 H, d, J = 6.6, H-8), 1.23 (3 H, t, J = 7.1, H-7), 1.22 (3 H, t, J = 7.1, H-7'); δ_C (100 MHz, $CDCl_3$) 131.7 (2 × ArCH), 128.3 (ArCH), 128.2 (2 × ArCH), 122.7 (ArC), 101.0 (CH, C-5), 88.8 (C, C-2), 85.0 (C, C-1), 68.9 (CH_2, C-4), 66.2 (CH, C-3), 62.4 (CH_2, C-6), 61.8 (CH_2, C-6'), 22.0 (CH_3, C-8), 15.3 (2 × CH_3, C-7, 7'); *m/z* (ESI) 285 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{16}H_{22}NaO_3$, 285.1461. Found: $[MNa]^+$, 285.1463 (0.5 ppm error)].

Lab Book Ref. = JDC/13/14

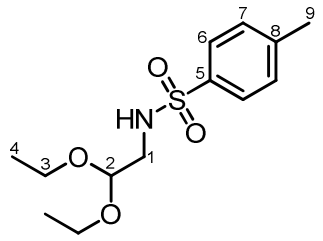


((1-(2,2-Diethoxyethoxy)cyclohexyl)ethynyl)benzene 351d: To a stirred suspension of sodium hydride (60 wt%, 100 mg, 2.50 mmol, 1.0 equiv.) in DMF (2 mL) at 0 ºC was added dropwise 1-(phenylethynyl)cyclohexanol (0.50 g, 2.50 mmol, 1.0 equiv.) as a solution in DMF (1 mL). The resulting yellow slurry was held at 0 ºC for 1 h, then bromo acetaldehyde diethyl acetal (0.37 ml, 2.50 mmol, 1.0 equiv.) was added dropwise. The solution was held at 0 ºC for 30 min., then heated to 100 ºC and held for 18 h. The brown solution was cooled to rt then quenched with H_2O (50 mL). The aqueous phase was extracted with Et_2O (3 × 25 mL), then the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, PE/Et_2O, 19:1) to give the title compound **351d** (303 mg, 38%) as a pale yellow oil; R_f 0.53 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2934, 1135, 1092, 756; δ_H (400 MHz, $CDCl_3$) 7.45-7.39 (2 H, m, ArH), 7.33-7.27 (3 H, m, ArH), 4.68 (1 H, t, J = 5.3, H-5), 3.74 (2 H, dq, J = 9.4, 7.1, H-6_a, 6_a'), 3.71 (2 H, d, J = 5.3, H-4), 3.60 (2 H, dq, J = 9.4, 7.1, H-6_b, 6_b'), 2.02-1.93 (2 H, m, CyH), 1.76-1.64 (4 H, m, CyH), 1.64-1.47 (3 H, m, CyH), 1.41-1.26 (1 H, m, CyH), 1.22 (6 H, t, J = 7.1, H-7, 7'); δ_C (100 MHz, $CDCl_3$) 131.6 (2 × CH, ArCH), 128.2 (2 × CH, ArCH), 128.1 (CH, ArCH), 123.0 (C, ArC), 101.4 (CH, C-5), 90.5 (C, C-2), 86.0 (C, C-1), 74.2 (C, C-3), 64.2 (CH_2, C-4), 61.9 (2 × CH_2, C-6, 6'), 37.1 (2 × CH_2, CyCH), 25.4

(CH_2, CyCH), 22.8 (2 × CH_2, CyCH), 15.3 (2 × CH_3, C-7, 7'); *m/z* (ESI) 339 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{20}H_{28}NaO_3$, 339.1931. Found: $[MNa]^+$, 339.1928 (0.8 ppm error)].

Lab Book Ref. = JDC/13/96

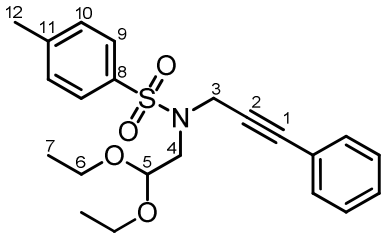
Synthesis of *N*-(2,2-Diethoxyethyl)-4-methyl-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide 351e:



***N*-(2,2-Diethoxyethyl)-4-methylbenzenesulfonamide**[190]**:** To a stirred solution of 2,2-diethoxyethanamine (3.64 mL, 25.0 mmol, 1.0 equiv.) and Et_3N (6.97 mL, 50.0 mmol, 2.0 equiv.) in DCM (50 mL) at 0 ºC was added dropwise *p*-toluenesulfonyl chloride (5.24 g, 27.5 mmol, 1.1 equiv.) as a solution in DCM (50 mL). The reaction was held at 0 ºC for 2 h, then diluted with H_2O (100 mL). The aqueous phase was extracted with DCM (50 mL), then the combined organic extracts were washed with 1 M aq. HCl (25 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound (7.20 g, Quant.) as a colourless crystalline solid; R_f 0.38 (PE/EtOAc, 2:1); mp. 65-67 ºC (Lit. 67-68 ºC) δ_H (400 MHz, $CDCl_3$) 7.74 (2 H, d, *J* = 8.3, H-6), 7.31 (2 H, d, *J* = 8.3, H-7), 4.59 (1 H, t, *J* = 6.2, NH), 4.47 (1 H, t, *J* = 5.7, H-2), 3.64 (2 H, dq, *J* = 9.4, 7.1, H-3_a, 3_a'), 3.47 (2 H, dq, *J* = 9.4, 7.1, H-3_b, 3_b'), 3.02 (2 H, dd, *J* = 6.2, 5.7, H-1), 2.43 (3 H, s, H-9), 1.17 (6 H, t, *J* = 7.1, H-4, 4').

Lab Book Ref. = JDC/13/24

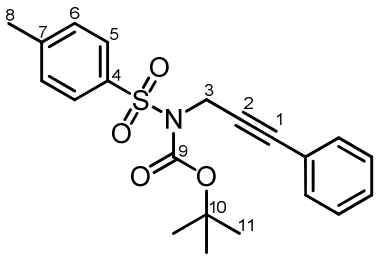
Data were consistent with those published.[190]



***N*-(2,2-Diethoxyethyl)-4-methyl-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide 351e:** To a stirred suspension of *N*-(2,2-Diethoxyethyl)-4-methylbenzenesulfonamide (431 mg, 1.50 mmol, 1.0 equiv.) and K_2CO_3 (442 mg, 3.20 mmol, 2.1 equiv.) in DMF (5 mL) at rt was added 3-phenyl-2-propynyl methanesulfonate (315 mg, 1.50 mmol, 1.0 equiv.). The viscous slurry was heated to 80 ºC and held for 24 h, then cooled to rt and diluted with water (50 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), then the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give the title compound **351e** (500 mg, 83%) as a pale yellow oil; R_f 0.18 (PE/EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$) 7.79 (2 H, d, J = 8.3, H-9), 7.27-7.21 (5 H, m ArH), 7.03 (2 H, d, J = 8.3, H-10), 4.74 (1 H, t, J = 5.6, H-5), 4.49 (2 H, s, H-3), 3.79 (2 H, dq, J = 9.3, 7.1, H-6_a, 6_a'), 3.60 (2 H, dq, J = 9.3, 7.1, H-6_b, 6_b'), 3.32 (2 H, d, J = 5.6, H-4), 2.32 (3 H, s, H-12), 1.24 (6 H, t, J = 7.1, H-7, 7'). **Lab Book Ref.** = JDC/13/31

Data were consistent with those published.[147]

Synthesis of *N*-(3,3-Diethoxypropyl)-4-methyl-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide 351f:

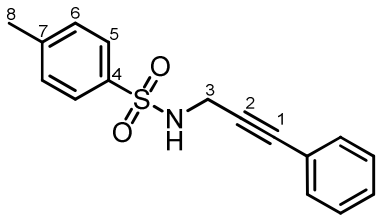


***tert*-Butyl 3-phenylprop-2-ynyl(tosyl)carbamate:** To a stirred suspension of NaH (60wt%, 336 mg, 8.40 mmol, 1.4 equiv.) in DMF (9 mL) at 0 ºC was added *tert* butyl tosylcarbamate (1.95 g, 7.20 mmol, 1.2 equiv.) as a solution in DMF (4 mL). The

suspension was held at 0 ºC for 30 min., then 3-phenyl-2-propynyl bromide (1.17 g, 6.00 mmol, 1.0 equiv.) was added as a solution in DMF (2 mL). The solution was allowed to warm to rt, then heated to 100 ºC and held for 4 h. The brown solution was cooled to rt and poured into H_2O (50 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), then the combined organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, PE/EtOAc, 19:1-9:1) to give the title compound (1.70 g, 61%) as a pale yellow oil; R_f 0.41 (PE/EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$) 7.98 (2 H, d, J = 8.4, H-5), 7.42-7.25 (7 H, m, ArH), 4.85 (2 H, s, H-3), 2.42 (3 H, s, H-8), 1.37 (9 H, s, H-11).

Lab Book Ref. = JDC/13/38

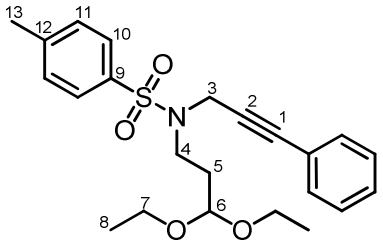
Data were consistent with those published.[191]



4-Methyl-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide[192] **:** To a stirred solution of *tert*-Butyl 3-phenylprop-2-ynyl(tosyl)carbamate (1.69 g, 4.40 mmol, 1.0 equiv.) in DCM (10 mL) at 0 ºC was added dropwise TFA (1.69 mL, 22.0 mmol, 5.0 equiv.). The brown solution was held at 0 ºC for 30 min., then warmed to rt and held for 4 h. The reaction was carefully quenched with sat. aq. $NaHCO_3$, then the aqueous phase was extracted with EtOAc (3 × 20 mL) The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/Et_2O, 9:1-4:1) to give the title compound (0.88 g, 70%) as an off-white amorphous solid; (Lit.[192] 121-123 ºC); R_f 0.24 (PE/EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$) 7.81 (2 H, d, J = 8.3, H-5), 7.35-7.22 (5 H, m, ArH), 7.13 (2 H, d, J = 8.3, H-6) 4.08 (2 H, d, J = 6.2, H-3), 2.36 (3 H, s, H-8).

Lab Book Ref. = JDC/13/43

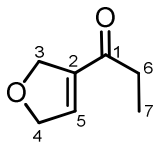
Data were consistent with those published.[192]



***N*-(3,3-Diethoxypropyl)-4-methyl-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide 351f:** To a stirred suspension of sodium hydride (60 wt%, 50 mg, 1.30 mmol, 1.05 equiv.) in DMF (2 mL) at 0 ºC was added dropwise 4-Methyl-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide (342 mg, 1.20 mmol, 1.0 equiv.). The resulting yellow slurry was held at 0 ºC for 30 min., then acetal **355** (248 mg, 1.30 mmol, 1.05 equiv.) was added dropwise. The solution was held at 0 ºC for 30 min., then warmed to rt and held for 4 h. The brown solution was quenched with sat. aq. NH_4Cl (5 mL), then diluted with H_2O (25 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), then the combined organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give the title compound **351f** (462 mg, 93%) as a colourless oil; R_f 0.32 (PE/EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$) 7.77 (2 H, d, J = 8.3, H-10), 7.31-7.20 (5 H, m, ArH), 7.06 (2 H, d, J = 8.3, H-11), 4.63 (1 H, t, J = 5.6, H-6), 4.35 (2 H, s, H-3), 3.67 (2 H, dq, J = 9.3, 7.1, H-7_a, 7_a'), 3.53 (2 H, dq, J = 9.3, 7.1, H-7_b, 7_b'), 3.36-3.32 (2 H, m, H-4), 2.34 (3 H, s, H-13), 1.98-1.92 (2 H, m, H-5), 1.20 (6 H, t, J = 7.1, H-8, 8').

Lab Book Ref. = JDC/13/50

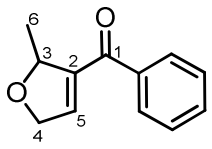
Data were consistent with those published.[139]



1-(2,5-Dihydrofuran-3-yl)propan-1-one 352b: Using the procedure described for the preparation of compound **352a**, the title compound **352b** (22 mg, 70%) was isolated as a pale yellow oil; R_f 0.21 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2855, 1641, 1124, 1074; δ_H (400 MHz, $CDCl_3$) 6.74-6.71 (1 H, m, H-5), 4.88-4.80 (4 H, m, H-3, 4), 2.72 (2 H, q, J = 7.3, H-6), 1.13 (3 H, t, J = 7.3, H-7); δ_C (100 MHz, $CDCl_3$) 197.0 (CO, C-1), 141.0 (C,

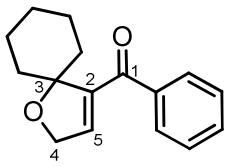
C-2), 136.3 (CH, C-5), 76.3 (CH_2), 74.4 (CH_2), 32.7 (CH_2, C-6), 7.9 (CH_3, C-7); *m/z* (ESI) 127 $[MH]^+$; [HRMS (ESI): calcd. for $C_7H_{11}O_2$, 127.0754. Found: $[MH]^+$, 127.0757 (2.7 ppm error)].

Lab Book Ref. = JDC/13/86



(2-Methyl-2,5-dihydrofuran-3-yl)(phenyl)methanone 352c: Using the procedure described for the preparation of compound **352a**, the title compound **352c** (38 mg, 80%) was isolated as a pale yellow oil; R_f 0.33 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2973, 2848, 1644, 1359, 1276, 1240, 1084; δ_H (400 MHz, $CDCl_3$) 7.81-7.77 (2 H, m, ArH), 7.60-7.54 (1 H, m, ArH), 7.49-7.44 (2 H, m, ArH), 6.56-6.54 (1 H, m, H-5), 5.38-5.30 (1 H, m, H-3), 4.93 (1 H, ddd, *J* = 16.1, 5.6, 1.9, H-4_a), 4.77 (1 H, ddd, *J* = 16.1, 4.9, 1.9, H-4_b), 1.45 (3 H, d, *J* = 6.3, H-6); δ_C (100 MHz, $CDCl_3$) 191.4 (CO, C-1), 143.5 (C, C-2), 139.5 (CH, C-5), 138.2 (C, ArC), 132.6 (CH, ArCH), 128.8 (2 × CH, ArCH), 128.4 (2 × CH, ArCH), 82.2 (CH, C-3), 74.5 (CH_2, C-4), 20.5 (CH_3, C-6); *m/z* (ESI) 189 $[MH]^+$; [HRMS (ESI): calcd. for $C_{12}H_{13}O_2$, 189.0910. Found: $[MH]^+$, 189.0912 (1.2 ppm error)].

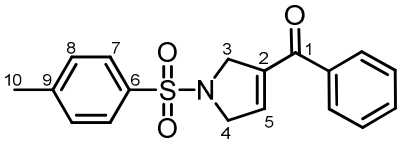
Lab Book Ref. = JDC/13/88



Phenyl(1-oxaspiro[4.5]dec-3-en-4-yl)methanone 352d: Using the procedure described for the preparation of compound **352a**, the title compound **352d** (39 mg, 64%) was isolated as a yellow oil; R_f 0.49 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2929, 1646, 1317, 1240, 1089; δ_H (400 MHz, $CDCl_3$) 7.77-7.73 (2 H, m, ArH), 7.58-7.53 (1 H, m, ArH), 7.47-7.42 (2 H, m, ArH), 6.45 (1 H, t, *J* = 1.9, H-5), 4.75 (2 H, d, *J* = 1.9, H-4), 2.11-2.00 (2 H, m, CyH), 1.76-1.61 (7 H, m, CyH), 1.36-1.23 (1 H, m, CyH); δ_C (100 MHz, $CDCl_3$) 192.4 (CO, C-1), 145.5 (C, C-2), 139.9 (CH, C-5), 139.1 (C, ArC), 132.4 (CH, ArCH), 128.9 (2 × CH_2, ArCH), 128.3 (2 × CH_2, ArCH), 90.4 (C, C-3), 71.9 (CH_2, C-4),

34.1 (2 × CH_2, CyCH), 25.0 (CH_2, CyCH), 22.3 (2 × CH_2, CyCH); *m/z* (ESI) 265 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{16}H_{18}NaO_2$, 265.1199. Found: $[MNa]^+$, 265.1192 (2.5 ppm error)].

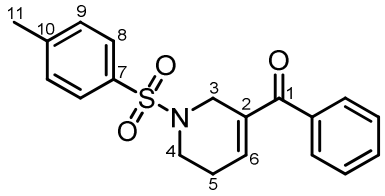
Lab Book Ref. = JDC/14/6



Phenyl(1-tosyl-2,5-dihydro-*1H*-pyrrol-3-yl)methanone 352e: Using the procedure described for the preparation of compound **352a**, the title compound **352e** (63 mg, 77%) was isolated as a colourless crystalline solid; mp. 147-149 ºC, (Lit.[153] 134-136 ºC); R_f 0.18 (PE/EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$) 7.77 (2 H, d, *J* = 8.3, H-7), 7.68-7.64 (2 H, m, ArH), 7.59-7.53 (1 H, m, ArH), 7.46-7.41 (2 H, m, ArH), 7.35 (2 H, d, *J* = 8.3, H-8), 6.35 (1 H, dddd, *J* = 1.9, 1.9, 1.8, 1.8, H-5), 4.48-4.39 (4 H, m, H-3, 4), 2.44 (3 H, s, H-10).

Lab Book Ref. = JDC/13/87

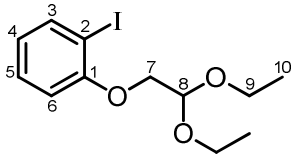
Data were consistent with those published.[153]



Phenyl(1-tosyl-1,2,5,6-tetrahydropyridin-3-yl)methanone 352f: Using the procedure described for the preparation of compound **352a**, the title compound **352f** (59 mg, 69%) was isolated as a yellow oil; R_f 0.16 (PE/EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$) 7.74 (2 H, d, *J* = 8.3, H-8), 7.63-7.46 (3 H, m, ArH), 7.45-7.40 (2 H, m, ArH), 7.35 (2 H, d, *J* = 8.3, H-9), 6.66-6.40 (1 H, m, H-6), 3.96 (2 H, dd, *J* = 4.5, 2.4, H-3), 3.24 (2 H, t, *J* = 5.8, H-4), 2.53-2.46 (2 H, m, H-5), 2.44 (3 H, s, H-11).

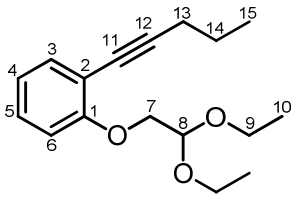
Lab Book Ref. = JDC/13/90

Data were consistent with those published.[139]



1-(2,2-Diethoxyethoxy)-2-iodobenzene 376: To a stirred solution of 2-iodophenol (660 mg, 3.00 mmol, 1.0 equiv.) in DMF (3 mL) at rt were added K_2CO_3 (1.66 g, 12.0 mmol, 4.0 equiv.) and bromo acetaldehyde diethyl acetal (0.50 mL, 3.30 mmol, 1.1 equiv.). The suspension was heated to 140 ºC and held for 5 h, then cooled to rt and poured into H_2O (50 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), then the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **376** (1.00 g, 99%) as a yellow oil; R_f 0.58 (PE/EtOAc); υ_{max}/cm^{-1} (neat) 2975, 1475, 1135, 1075, 749; δ_H (400 MHz, $CDCl_3$) 7.76 (1 H, dd, *J* = 7.8, 1.6, H-3), 7.30-7.25 (1 H, ddd, *J* = 8.4, 7.4, 1.6, H-5), 6.82 (1 H, dd, *J* = 8.4, 1.3, H-6), 6.74 (1 H, ddd, *J* = 7.8, 7.4, 1.3, H-4), 4.89 (1 H, t, *J* = 5.2, H-8), 4.04 (2 H, d, *J* = 5.2, H-7), 3.82 (2 H, dq, *J* = 9.3, 7.1, H-9_a, 9_a'), 3.72 (2 H, dq, *J* = 9.3, 7.1, H-9_b, 9_b'), 1.27 (6 H, t, *J* = 7.1, H-10, 10'); δ_C (100 MHz, $CDCl_3$) 157.2 (C, C-1), 139.4 (CH, C-3), 129.4 (CH, C-5), 122.8 (CH, C-4), 112.2 (CH, C-6), 100.7 (CH, C-8), 86.4 (C, C-2), 70.1 (CH_2, C-7), 63.4 (2 × CH_2, C-9, 9'), 15.4 (2 × CH_3, C-10, 10'); *m/z* (ESI) 359 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{12}H_{17}INaO_3$, 359.0115. Found: $[MNa]^+$, 359.0120 (1.9 ppm error)].

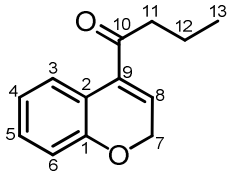
Lab Book Ref. = JDC/13/72



1-(2,2-Diethoxyethoxy)-2-(pent-1-ynyl)benzene 377: To a stirred suspension of iodide **376** (336 mg, 1.00 mmol, 1.0 equiv.), CuI (19 mg, 0.10 mmol, 0.1 equiv.) and $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol, 0.05 equiv.) in Et_3N (3 mL, degassed) at rt under argon (flask purged *via* 5 × vacuum/argon cycles) was added 1-pentyne (229 µL, 2.00 mmol, 2.0 equiv.). The dark brown solution was stirred at rt for 18 h, then concentrated *in vacuo* to afford a brown residue which was purified by column chromatography

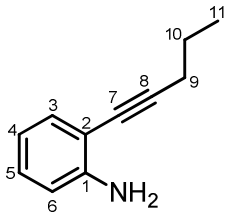
(SiO_2, PE/Et_2O, 19:1) to give the title compound **377** (258 mg, 93%) as a yellow oil; R_f 0.60 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2972, 2932, 2874, 1493, 1445, 1292, 1119, 1074; δ_H (400 MHz, $CDCl_3$) 7.36 (1 H, dd, *J* = 7.6, 1.7, H-3), 7.20 (1 H, ddd, *J* = 8.3, 7.5, 1.7, H-5), 6.87 (1 H, ddd, *J* = 7.6, 7.5, 1.0, H-4), 6.84 (1 H, dd, *J* = 8.3, 1.0, H-6), 4.87 (1 H, t, *J* = 5.2, H-8), 4.05 (2 H, d, *J* = 5.2, H-7), 3.81 (2 H, dq, *J* = 9.4, 7.1, H-9_a, 9_a'), 3.70 (2 H, dq, *J* = 9.4, 7.1, H-9_b, 9_b'), 2.41 (2 H, t, *J* = 7.0, H-13), 1.63 (2 H, qt, *J* = 7.4, 7.0, H-14), 1.25 (6 H, t, *J* = 7.1, H-10, 10'), 1.06 (3 H, t, *J* = 7.4, H-15); δ_C (100 MHz, $CDCl_3$) 159.0 (C, C-1), 133.4 (CH, C-3), 128.7 (CH, C-5), 120.7 (CH, C-4), 113.7 (C, C-2), 112.1 (CH, C-6), 100.9 (CH, C-8), 94.2 (C, C-12), 76.7 (C, C-11), 69.9 (CH_2, C-7), 63.3 (2 × CH_2, C-9, 9') 22.2 (CH_2, C-14), 21.6 (CH_2, C-13), 15.3 (2 × CH_3, C-10, 10'), 13.5 (CH_3, C-15); *m/z* (ESI) 299 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{17}H_{24}NaO_3$, 299.1618. Found: $[MNa]^+$, 299.1617 (0.4 ppm error)].

Lab Book Ref. = JDC/13/74



1-(2*H*-Chromen-4-yl)butan-1-one 378: Using the procedure described for the preparation of compound **352a**, the title compound **378** (29 mg, 57%) was isolated as a yellow oil; R_f 0.48 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2964, 1682, 1485, 1456, 1226; δ_H (400 MHz, $CDCl_3$) 7.25 (1 H, dd, *J* = 7.8, 1.6, H-3), 7.18 (1 H, ddd, *J* = 8.0, 7.6, 1.6, H-5), 6.95 (1 H, ddd, *J* = 7.8, 7.6, 1.3, H-4), 6.87 (1 H, dd, *J* = 8.0, 1.3, H-6), 6.56 (1 H, t, *J* = 4.1, H-8), 4.82 (2 H, d, *J* = 4.1, H-7), 2.75 (2 H, t, *J* = 7.3, H-11), 1.72 (2 H, qt, *J* = 7.4, 7.3, H-12), 0.98 (3 H, t, *J* = 7.4, H-13); δ_C (100 MHz, $CDCl_3$) 200.7 (CO, C-10), 154.3 (C, C-1), 135.1 (C, C-9), 129.8 (CH, C-5), 128.9 (CH, C-8), 126.6 (CH, C-3), 121.6 (CH, C-4), 119.7 (C, C-2), 116.3 (CH, C-6), 64.3 (CH_2, C-7), 41.6 (CH_2, C-11), 17.9 (CH_2, C-12), 13.8 (CH_3, C-13); *m/z* (ESI) 225 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{13}H_{14}NaO_2$, 225.0886. Found: $[MNa]^+$, 286.0890 (1.8 ppm error)].

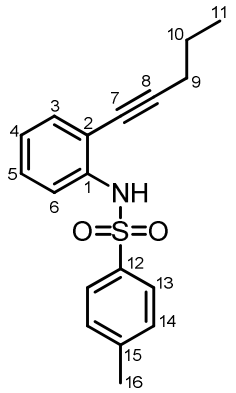
Lab Book Ref. = JDC/13/87



2-(Pent-1-ynyl)aniline[193] 382: To a stirred suspension of 2-iodoaniline (500 mg, 2.28 mmol, 1.0 equiv.), CuI (19 mg, 0.10 mmol, 0.05 equiv.) and $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol, 0.02 equiv.) in Et_3N (5 mL, degassed) at rt under argon (flask purged *via* 5 × vacuum/argon cycles) was added 1-pentyne (450 μL, 4.56 mmol, 2.0 equiv.). The dark brown solution was stirred at rt for 18 h, then concentrated *in vacuo* to afford a brown residue which was purified by column chromatography (SiO_2, PE/Et_2O, 19:1-9:1) to give the title compound **382** (335 mg, 92%) as a colourless oil; R_f 0.48 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3470, 3377, 2962, 1613, 1492, 1455, 1306; δ_H (400 MHz, $CDCl_3$) 7.25 (1 H, dd, *J* = 7.6, 1.5, H-3), 7.08 (1 H, ddd, *J* = 8.1, 7.5, 1.5, H-5), 6.70-6.67 (1 H, m, H-6), 6.66 (1 H, ddd, *J* = 7.6, 7.5, 1.1, H-4), 4.17 (2 H, br s, NH_2), 2.45 (2 H, t, *J* = 7.0, H-9), 1.65 (2 H, qt, *J* = 7.4, 7.0, H-10), 1.06 (3 H, t, *J* = 7.4, H-11); δ_C (100 MHz, $CDCl_3$) 147.6 (C, C-1), 132.0 (CH, C-3), 128.8 (CH, C-5), 117.8 (CH, C-4), 114.1 (CH, C-6), 108.9 (C, C-2), 95.6 (C, C-8), 77.1 (C, C-7), 22.4 (CH_2, C-10), 21.6 (CH_2, C-9), 13.6 (CH_3, C-11); *m/z* (ESI) 160 $[MH]^+$; [HRMS (ESI): calcd. for $C_{11}H_{14}N$, 160.1121. Found: $[MH]^+$, 160.1125 (2.9 ppm error)].

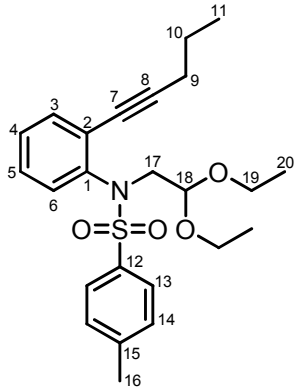
Lab Book Ref. = JDC/14/39

Data were consistent with those published.[193]



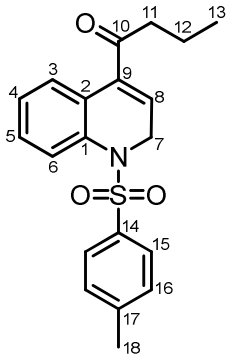
4-Methyl-*N*-(2-(pent-1-ynyl)phenyl)benzenesulfonamide 382a: To a stirred solution of aniline **382** (300 mg, 1.88 mmol, 1.0 equiv.), in pyridine (4 mL) at rt was added *p*-toluenesulfonyl chloride (395 mg, 2.07 mmol, 1.1 equiv.). The brown solution was stirred at rt for 5 h, then the solvent was removed under reduced pressure. The residue was taken up in EtOAc (30 mL), then washed with 1 M aq. HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **382a** (580 mg, 98%) as an off-white solid; mp. 84-86 ºC; R_f 0.38 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (thin film) 3255, 2961, 1487, 1397, 1330, 1167, 1092; δ_H (400 MHz, $CDCl_3$) 7.66 (2 H, d, *J* = 8.3, H-13), 7.56 (1 H, dd, *J* = 8.2, 1.2, H-6), 7.26-7.17 (4 H, m, H-3, 5, 14), 6.97 (1 H, ddd, *J* = 7.6, 7.6, 1.2, H-4), 2.39 (2 H, t, *J* = 7.1, H-9), 2.35 (3 H, s, H-16), 1.62 (2 H, qt, *J* = 7.4, 7.1, H-10), 1.04 (3 H, t, *J* = 7.4, H-11); δ_C (100 MHz, $CDCl_3$) 143.9 (C, C-15), 137.5 (C, C-1), 136.0 (C, C-12), 131.8 (CH, C-3), 129.5 (2 × CH, C-14), 128.7 (CH, C-5), 127.2 (2 × CH, C-13), 124.1 (CH, C-4), 119.3 (CH, C-6), 114.8 (C, C-2), 97.7 (C, C-7), 75.4 (C, C-8), 22.0 (CH_2, C-10), 21.5 (CH_3, C-16), 21.4 (CH_2, C-9), 13.6 (CH_3, C-11); *m/z* (ESI) 314 $[MH]^+$; [HRMS (ESI): calcd. for $C_{18}H_{20}NO_2S$, 314.1209. Found: $[MH]^+$, 314.1208 (0.4 ppm error)].

Lab Book Ref. = JDC/14/40



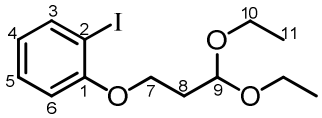
***N*-(2,2-Diethoxyethyl)-4-methyl-*N*-(2-(pent-1-ynyl)phenyl)benzenesulfonamide 383:** To a stirred solution of tosylate **382a** (500 mg, 1.60 mmol, 1.0 equiv.), glycoaldehyde diethyl acetal (215 mg, 1.60 mmol, 1.0 equiv.) and triphenylphosphine (462 mg, 1.76 mmol, 1.1 equiv.) in THF (4 mL) at 0 ºC was added dropwise DIAD (0.35 mL, 1.76 mmol, 1.1 equiv.). The orange solution was held at 0 ºC for 30 min., then warmed to rt and held for 18 h. The reaction mixture was concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, PE/EtOAc, 19:1) to give the title compound **383** (610 mg, 89%) as a colourless oil; R_f 0.40 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2974, 2932, 1485, 1350, 1162, 1095, 1067; δ_H (400 MHz, $CDCl_3$) 7.56 (2 H, d, *J* = 8.2, H-13), 7.39-7.34 (1 H, m, H-3), 7.30 (1 H, dd, *J* = 7.4, 1.8, H-5), 7.27-7.17 (4 H, m, H-4, 6, 14), 4.73 (1 H, t, *J* = 5.6, H-18), 3.93-3.63 (6 H, m, H-17, 19, 19'), 2.39 (3 H, s, H-16), 2.01 (2 H, t, *J* = 7.2, H-9), 1.40 (2 H, qt, *J* = 7.4, 7.2, H-10), 1.22-0.97 (6 H, m, H-20, 20'), 0.92 (3 H, t, *J* = 7.4, H-11); δ_C (100 MHz, $CDCl_3$) 142.9 (ArC), 140.5 (ArC), 137.1 (ArC), 133.4 (CH, C-5), 132.5 (CH, C-3), 129.2 (2 × CH, C-14), 127.7 (4 × CH, C-4, 6, 13), 123.5 (C, C-2), 101.8 (CH, C-18), 95.6 (C, C-8), 77.2 (C, C-7), 62.1 (2 × CH_2, C-19, 19'), 52.1 (CH_2, C-17), 21.9 (CH_2, C-10), 21.5 (CH_3, C-16), 21.4 (CH_2, C-9), 15.1 (2 × CH_3, C-20, 20'), 13.6 (CH_3, C-11); *m/z* (ESI) 452 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{24}H_{31}NNaO_4S$, 452.1866. Found: $[MNa]^+$, 452.1872 (1.3 ppm error)].

Lab Book Ref. = JDC/14/42



1-(1-Tosyl-1,2-dihydroquinolin-4-yl)butan-1-one 384: Using the procedure described for the preparation of compound **352a**, the title compound **384** (54 mg, 60%) was isolated as a yellow oil; R_f 0.33 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2964, 1683, 1354, 1165, 1089; δ_H (400 MHz, $CDCl_3$) 7.73 (1 H, dd, *J* = 8.1, 1.6, H-3), 7.61 (1 H, dd, *J* = 7.8, 1.4, H-6), 7.37 (1 H, ddd, *J* = 7.8, 7.7, 1.6, H-5), 7.30-7.25 (1 H, m, H-4), 7.27 (2 H, d, *J* = 8.3, H-15), 7.08 (2 H, d, *J* = 8.3, H-16), 6.24 (1 H, t, *J* = 4.6, H-8), 4.47 (2 H, d, *J* = 4.6, H-7), 2.30 (3 H, s, H-18), 2.24 (2 H, t, *J* = 7.3, H-11), 1.47 (2 H, qt, *J* = 7.4, 7.3, H-12), 0.85 (3 H, t, *J* = 7.4, H-13); δ_C (100 MHz, $CDCl_3$) 199.7 (CO, C-8), 143.7 (C, C-17), 136.5 (ArC), 136.1 (ArC), 135.6 (ArC), 130.7 (CH, C-8), 129.3 (2 × CH, C-16), 128.9 (CH, C-5), 127.7 (CH, C-3), 127.2 (2 × CH, C-15), 126.9 (CH, C-6), 126.8 (C, C-2), 126.7 (CH, C-4), 44.8 (CH_2, C-7), 41.2 (CH_2, C-11), 21.4 (CH_3, C-18) 17.5 (CH_2, C-12), 13.7 (CH_3, C-13); *m/z* (ESI) 356 $[MH]^+$; [HRMS (ESI): calcd. for $C_{20}H_{22}NO_3S$, 356.1315. Found: $[MH]^+$, 356.1313 (0.6 ppm error)].

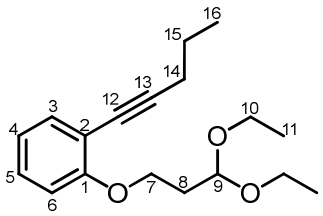
Lab Book Ref. = JDC/14/46



1-(3,3-Diethoxypropoxy)-2-iodobenzene 385: To a stirred suspension of iodide **355** (852 mg, 3.30 mmol, 1.1 equiv.) and K_2CO_3 (1.66 g, 12.0 mmol, 4.0 equiv.) in DMF (3 mL) at rt was added 2-iodophenol (660 mg, 3.00 mmol, 1.0 equiv.). The slurry was heated to 140 ºC and held for 18 h, then cooled to rt and poured into H_2O (50 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), then the combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **385** (929 mg, 88%) as an orange oil; R_f 0.47

(PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2973, 1464, 1123, 1057; δ_H (400 MHz, $CDCl_3$) 7.76 (1 H, dd, *J* = 7.8, 1.6, H-3), 7.28 (1 H, ddd, *J* = 8.3, 7.5, 1.6, H-5), 6.81 (1 H, dd, *J* = 8.3, 1.3, H-6), 6.70 (1 H, ddd, *J* = 7.8, 7.5, 1.3, H-4), 4.91 (1 H, t, *J* = 5.7, H-9), 4.10 (2 H, t, *J* = 5.9, H-7), 3.73 (2 H, dq, *J* = 9.4, 7.1, H-10_a, 10_a'), 3.57 (2 H, dq, *J* = 9.4, 7.1, H-10_b, 10_b'), 2.14 (2 H, td, *J* = 5.9, 5.7, H-8), 1.21 (6 H, t, *J* = 7.1, H-11, 11'); δ_C (100 MHz, $CDCl_3$) 157.3 (C, C-1), 139.3 (CH, C-3), 129.4 (CH, C-5), 122.4 (CH, C-4), 111.9 (CH, C-6), 100.5 (CH, C-9), 86.5 (C, C-2), 65.3 (CH_2, C-7), 62.2 (2 × CH_2, C-10, 10'), 33.8 (CH_2, C-8), 15.4 (2 × CH_3, C-11, 11'); *m/z* (ESI) 373 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{13}H_{19}INaO_3$, 373.0277. Found: $[MNa]^+$, 373.0261 (4.3 ppm error)].

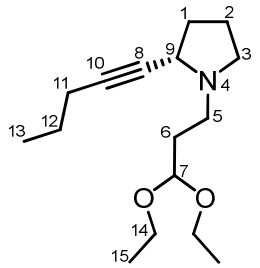
Lab Book Ref. = JDC/14/63



1-(3,3-Diethoxypropoxy)-2-(pent-1-ynyl)benzene 386: To a stirred suspension of iodide **385** (350 mg, 1.00 mmol, 1.0 equiv.), CuI (19 mg, 0.10 mmol, 0.1 equiv.) and $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol, 0.05 equiv.) in Et_3N (5 mL, degassed) at rt under argon (flask purged *via* 5 × vacuum/argon cycles) was added 1-pentyne (197 µL, 2.00 mmol, 2.0 equiv.). The dark brown solution was stirred at rt for 18 h, then concentrated *in vacuo* to afford a brown residue which was purified by column chromatography (SiO_2, PE/Et_2O, 19:1-9:1) to give the title compound **386** (252 mg, 87%) as a colourless oil; R_f 0.49 (PE/EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2971, 2933, 2876, 1492, 1447, 1261, 1120, 1060; δ_H (400 MHz, $CDCl_3$) 7.35 (1 H, dd, *J* = 7.6, 1.6, H-3), 7.21 (1 H, ddd, *J* = 8.0, 7.9, 1.6, H-5), 6.89-6.83 (2 H, m, H-4, 6), 4.84 (1 H, t, *J* = 5.8, H-9), 4.10 (2 H, t, *J* = 6.2, H-7), 3.71 (2 H, dq, *J* = 9.4, 7.1, H-10_a, 10_a'), 3.54 (2 H, dq, *J* = 9.4, 7.1, H-10_b 10_b'), 2.43 (2 H, t, *J* = 7.0, H-14), 2.13 (1 H, td, *J* = 6.2, 5.8, H-8), 1.64 (2 H, qt, *J* = 7.4, 7.0, H-15), 1.21 (6 H, t, *J* = 7.1, H-11, 11'), 1.07 (3 H, t, *J* = 7.4, H-16); δ_C (100 MHz, $CDCl_3$) 159.3 (C, C-1), 133.3 (CH, C-3), 128.7 (CH, C-5), 120.4 (CH, C-4), 113.5 (C, C-2), 111.8 (CH, C-6), 100.6 (CH, C-9), 94.2 (C, C-13), 76.8 (C, C-12), 64.7 (CH_2, C-7), 62.1 (2 × CH_2, C-10, 10'), 33.9 (CH_2, C-8), 22.3 (CH_2, C-15), 21.7 (CH_2, C-14),

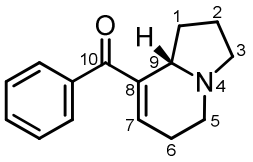
15.3 (2 × CH_3, C-11, 11'), 13.5 (CH_3, C-16); *m/z* (ESI) 313 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{18}H_{26}NaO_3$, 313.1774. Found: $[MNa]^+$, 313.1766 (2.5 ppm error)].

Lab Book Ref. = JDC/14/71



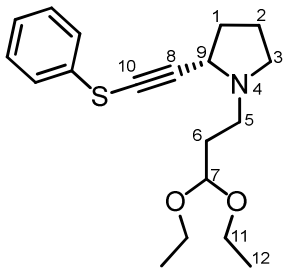
(*S*)-1-(3,3-diethoxypropyl)-2-(pent-1-ynyl)pyrrolidine 388: To a stirred solution of alkyne **356** (200 mg, 0.89 mmol, 1.0 equiv.) in THF (5 mL) at –78 ºC was added dropwise *n*-BuLi (1.6 M, 0.61 mL, 0.98 mmol, 1.1 equiv.). The yellow solution was held at –78 ºC for 1 h, then warmed to 0 ºC before adding *n*-propyl iodide (104 μL, 1.07 mmol, 1.2 equiv.). The reaction was allowed to warm to rt, the heated to reflux and held for 18 h. The reaction was cooled to rt, then quenched with sat. aq. NH_4Cl (5 mL). The aqueous phase was extracted with DCM (3 × 10 mL), then the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM/MeOH, 99:1-98:2) to give the title compound **388** (87 mg, 37%) as a colourless oil; R_f 0.50 (DCM/MeOH, 9:1); $[\alpha]^{20}_D$ –99.7 (*c* 1.15, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2966, 1457, 1375, 1127, 1063; δ_H (400 MHz, $CDCl_3$) 4.58 (1 H, t, *J* = 5.7, H-7), 3.65 (1 H, dq, *J* = 9.4, 7.1, H-14_a), 3.64 (1 H, dq, *J* = 9.4, 7.1, H-14_a'), 3.50 (1 H, qd, *J* = 9.4, 7.1, H-14_b), 3.49 (1 H, dq, *J* = 9.4, 7.1, H-14_b'), 3.35 (1 H, br s, H-9), 2.92 (1 H, ddd, *J* = 11.9, 8.7, 7.8, H-5_a), 2.82 (1 H, ddd, *J* = 8.8, 8.7, 5.2, H-3_a), 2.50-2.34 (2 H, m, H-3_b, 5_b), 2.15 (2 H, td, *J* =7.0, 2.0, H-11), 2.13-2.02 (1 H, m, H-1_a), 1.94-1.70 (4 H, m, H-1_b, 2_a, 6), 1.50 (2 H, qt, *J* = 7.4, 7.0, H-12), 1.19 (6 H, t, *J* = 7.1, H-15, 15'), 0.96 (3 H, t, *J* = 7.4, H-13); δ_C (100 MHz, $CDCl_3$) 101.6 (CH, C-7), 84.4 (C, C-10), 79.1 (C, C-8), 61.0 (CH_2, C-14), 60.7 (CH_2, C-14'), 54.9 (CH, C-9), 51.9 (CH_2, C-3), 48.9 (CH_2, C-5), 32.6 (CH_2, C-6), 32.0 (CH_2, C-1), 22.3 (CH_2, C-12), 21.9 (CH_2, C-2), 20.7 (CH_2, C-11), 15.3 (2 × CH_3, C-15, 15'), 13.5 (CH_3, C-13); *m/z* (ESI) 268 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{30}NO_2$, 268.2271. Found: $[MH]^+$, 268.2272 (0.3 ppm error)].

Lab Book Ref. = JDC/12/73



(*S*)-(1,2,3,5,6,8a-Hexahydroindolizin-8-yl)(phenyl)methanone 358: A solution of alkyne **357** (75 mg, 0.25 mmol, 1.0 equiv.) in formic acid (1 mL) was heated at 100 ºC (oil-bath pre-heated) for 2 h, then cooled to rt and the solution concentrated under reduced pressure. The residue was dissolved in DCM (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL), then the aqueous washes were back extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, DCM/MeOH, 95:5) to give the title compound **358** (21 mg, 37%) as a yellow film; R_f 0.28 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (neat) 2954, 1645, 1272, 710; δ_H (400 MHz, $CDCl_3$) 7.69-7.65 (2 H, m, ArH), 7.54-7.49 (1 H, m, ArH), 7.44-7.39 (2 H, m, ArH), 6.55 (1 H, ddd, J = 4.1, 4.1, 1.8, H-7), 3.77-3.71 (1 H, m, H-9), 3.08-2.99 (2 H, m, H-3_a, 5_a), 2.87 (1 H, ddd, J = 10.0, 8.7, 7.6, H-3_b), 2.74 (1 H, ddd, J = 11.9, 7.6, 5.1, H-5_b), 2.64-2.53 (1 H, m, H-6_a), 2.47-2.35 (2 H, m, H-1_a, 6_b), 2.01-1.83 (2 H, m, H-2), 1.58-1.47 (1 H, m, H-1_b); δ_C (100 MHz, $CDCl_3$) 196.4 (C, C-10), 140.3 (C, C-8), 140.0 (CH, C-7), 137.9 (C, ArC), 131.9 (CH, ArCH), 129.2 (2 × CH, ArCH), 128.2 (2 × CH, ArCH), 59.5 (CH, C-9), 52.5 (CH_2, C-3), 45.5 (CH_2, C-5), 28.9 (CH_2, C-1), 25.0 (CH_2, C-6), 22.1 (CH_2, C-2); *m/z* (ESI) 228 $[MH]^+$; [HRMS (ESI): calcd. for $C_{15}H_{18}NO$, 228.1383. Found: $[MH]^+$, 228.1380 (1.4 ppm error)].

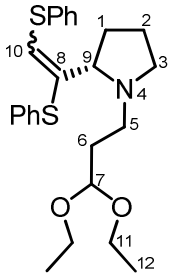
Lab Book Ref. = JDC/14/81



(*S*)-1-(3,3-Diethoxypropyl)-2-(phenylthioethynyl)pyrrolidine 398: To a stirred solution of alkyne **356** (750 mg, 3.30 mmol, 1.0 equiv.) in THF (12 mL) at −78 ºC was added dropwise *n*-BuLi (1.58 M, 2.30 mL, 3.63 mmol, 1.1 equiv.). The pale yellow

solution was held at −78 ºC for 30 min., then (*S*)-phenyl benzenethiosulfonate (909 mg, 3.63 mmol, 1.1 equiv.) was added dropwise as a solution in THF (3 mL). The solution was held at −78 ºC for a further 30 min., before warming to rt and holding for 2 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), then the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/EtOAc, 2:1-1:1) to give the title compound **398** (0.94 g, 85%) as a yellow oil; R_f 0.38 (DCM/MeOH, 95:5); $[\alpha]^{20}_D$ − 106.2 (*c* 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2973, 2877, 2808, 1478, 1126, 1062, 739; δ_H (400 MHz, $CDCl_3$) 7.42-7.37 (2 H, m, ArH), 7.35-7.29 (1 H, m, ArH), 7.22-7.17 (2 H, m, ArH), 4.60 (1 H, t, *J* = 5.8, H-7), 3.67-3.63 (1 H, m, H-9), 3.65 (1 H, dq, *J* = 9.4, 7.1, H-11_a), 3.64 (1 H, dq, *J* = 9.4, 7.1, H-11_a'), 3.50 (1 H, dq, *J* = 9.4, 7.1, H-11_b), 3.49 (1 H, dq, *J* = 9.4, 7.1, H-11_b'), 2.89 (1 H, ddd, *J* = 11.9, 8.7, 7.1, H-5_a), 2.80 (1 H, ddd, *J* = 8.8, 8.7, 5.5, H-3_a), 2.56 (1 H, ddd *J* = 8.8, 7.7, 5.3, H-3_b), 2.49 (1 H, ddd, *J* = 11.9, 8.5, 6.3, H-5_b), 2.22-2.12 (1 H, m, H-1_a), 2.05-1.76 (5 H, m, H-1_b, 2, 6), 1.19 (3 H, t, *J* = 7.1, H-12), 1.17 (3 H, t, *J* = 7.1, H-12'); δ_C (100 MHz, $CDCl_3$) 133.2 (C, ArC), 129.0 (2 × CH, ArCH), 126.2 (CH, ArCH), 125.9 (2 × CH, ArCH), 101.4 (CH, C-7), 98.5 (C, C-8), 69.8 (C, C-10), 61.2 (CH_2, C-11), 60.9 (CH_2, C-11'), 55.7 (CH, C-9), 51.8 (CH_2, C-3), 48.8 (CH_2, C-5), 32.8 (CH_2, C-6), 31.8 (CH_2, C-1), 22.1 (CH_2, C-2), 15.3 (2 × CH_3, C-12, 12'); *m/z* (ESI) 334 $[MH]^+$; [HRMS (ESI): calcd. for $C_{19}H_{28}NO_2S$, 334.1835. Found: $[MH]^+$, 334.1837 (0.4 ppm error)].

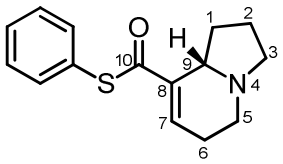
Lab Book Ref. = JDC/14/35



(*S*)-2-(1,2-bis(Phenylthio)vinyl)-1-(3,3-diethoxypropyl)pyrrolidine 399: To a stirred solution of alkyne **356** (1.17 g, 5.20 mmol, 1.0 equiv.) in THF (35 mL) at −78 ºC was added dropwise *n*-BuLi (1.6 M, 3.40 mL, 5.50 mmol, 1.05 equiv.). The pale yellow solution was held at −78 ºC for 30 min., then diphenyl disulfide (1.20 g, 5.50 mmol,

1.05 equiv.) was added dropwise as a pre-cooled solution in THF (5 mL). The solution was held at −78 ºC for a further 30 min., before warming to rt and holding for 2 h. The reaction was quenched with sat. aq. NH_4Cl (25 mL), then the aqueous phase was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, DCM/MeOH, 99:1-95:5) to give thioalkyne **398** (624 mg, 36%) as a yellow oil and the title compound **399** (653 mg, 28%) as a yellow oil; R_f 0.56 (DCM/MeOH, 9:1); $[\alpha]^{24}_D$ +85.9 (*c* 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2971, 2875, 2799, 1581, 1478, 1440, 1125, 1063, 742; δ_H (400 MHz, $CDCl_3$) 7.43-7.38 (2 H, m, ArH), 7.34-7.20 (7 H, m, ArH), 7.20-7.13 (1 H, m, ArH), 7.14 (1 H, s, H-10), 4.56 (1 H, t, *J* = 5.7, H-7), 3.61 (2 H, dq, *J* = 9.3, 7.1, H-11_a, 11_a'), 3.47 (1 H, dq, *J* = 9.3, 7.1, H-11_b), 3.45 (1 H, dq, *J* = 9.3, 7.1, H-11_b'), 3.23-3.15 (1 H, m, H-3_a), 3.01 (1 H, dd, *J* = 7.7, 6.2, H-9), 2.83 (1 H, ddd, *J* = 11.9, 8.5, 7.4, H-5_a), 2.19-2.10 (2 H m, H-3_b, 5_b), 1.98-1.87 (1 H, m, H-1_a), 1.85-1.62 (5 H, m, H-1_b, 2, 6), 1.19 (3 H, t, *J* = 7.1, H-12), 1.18 (3 H, t, *J* = 7.1, H-12'); δ_C (100 MHz, $CDCl_3$) 135.7 (C, ArC), 134.8 (C, ArC), 134.2 (CH, C-10), 132.8 (C, C-8), 129.9 (2 × CH, ArCH), 129.0 (2 × CH, ArCH), 128.8 (2 × CH, ArCH), 128.7 (2 × CH, ArCH), 126.9 (CH, ArCH), 125.9 (CH, ArCH), 101.4 (CH, C-7), 70.9 (CH, C-9), 61.0 (CH_2, C-11), 60.9 (CH_2, C-11'), 53.6 (CH_2, C-3), 49.9 (CH_2, C-5), 32.9 (CH_2, C-6), 31.8 (CH_2, C-1), 22.8 (CH_2, C-2), 15.4 (2 × CH_3, C-12, 12'); *m/z* (ESI) 444 $[MH]^+$; [HRMS (ESI): calcd. for $C_{25}H_{34}NO_2S_2$, 444.2025. Found: $[MH]^+$, 444.2033 (1.8 ppm error)].

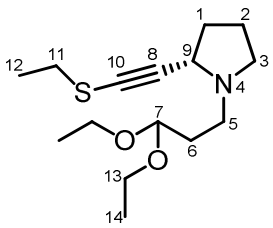
Lab Book Ref. = JDC/12/81



***S*-Phenyl (*S*)-1,2,3,5,6,8a-hexahydroindolizine-8-carbothioate 400:** A stirred solution of alkyne **398** (300 mg, 0.90 mmol, 1.0 equiv.) in formic acid (10 mL) was heated to 100 ºC (oil-bath pre-heated) and held for 2 h. The brown solution was cooled to rt then concentrated *in vacuo*. The residue was taken up in DCM (20 mL) and washed with sat. aq. $NaHCO_3$ (20 mL). The aqueous phase was back-extracted with DCM (3 × 10 mL), then the combined organic extracts were washed with brine (20 mL),

dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound **400** (232 mg, 99%) as an orange oil; R_f 0.34 (DCM/MeOH, 9:1); $[\alpha]^{24}_D$ −67.3 (*c* 1.30, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2956, 1670, 1163, 949, 746; δ_H (400 MHz, $CDCl_3$) 7.45-7.39 (5 H, m, ArH), 7.17 (1 H, ddd, *J* = 4.9, 3.8, 1.7, H-7), 3.60-3.54 (1 H, m, H-9), 2.97-2.88 (2 H, m, H-3_a, 5_a), 2.75 (1 H, ddd, *J* = 10.0, 8.3, 6.9, H-3_b), 2.70-2.63 (1 H, m, H-5_b), 2.56-2.45 (1 H, m, H-6_a), 2.37 (1 H, m, H-6_b), 2.27 (1 H, dddd, *J* = 13.0, 9.4, 7.4, 3.8, H-1_a), 1.98-1.71 (2 H, m, H-2), 1.52 (1 H, dddd, *J* = 13.0, 10.4, 8.8, 7.6, H-1_b); δ_C (100 MHz, $CDCl_3$) 189.8 (CO, C-10), 141.1 (C, C-8), 137.0 (CH, C-7), 135.0 (2 × CH, ArCH), 129.2 (CH, ArCH), 129.1 (2 × CH, ArCH), 127.5 (C, ArC), 58.9 (CH, C-9), 52.1 (CH_2, C-3), 45.0 (CH_2, C-5), 29.3 (CH_2, C-1), 24.6 (CH_2, C-6), 22.5 (CH_2, C-2); *m/z* (ESI) 260 $[MH]^+$; [HRMS (ESI): calcd. for $C_{15}H_{18}NOS$, 260.1104. Found: $[MH]^+$, 260.1109 (1.9 ppm error)].

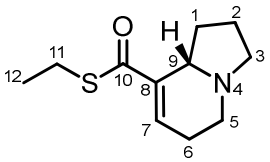
Lab Book Ref. = JDC/12/88



(*S*)-1-(3,3-Diethoxypropyl)-2-(ethylthioethynyl)pyrrolidine 401: To a stirred solution of alkyne **356** (1.50 g, 6.66 mmol, 1.0 equiv.) in THF (20 mL) at −78 ºC was added dropwise *n*-BuLi (1.58 M, 4.64 mL, 7.33 mmol, 1.1 equiv.). The pale yellow solution was held at −78 ºC for 30 min., then diethyl disulfide (902 µL, 7.33 mmol, 1.1 equiv.) was added dropwise. The solution was held at −78 ºC for a further 30 min., before warming to rt and holding for 2 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), then the aqueous phase was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM/MeOH, 98:2-97:3) to give the title compound **401** (1.61 g, 85%) as a colourless oil; R_f 0.38 (DCM/MeOH, 95:5); $[\alpha]^{20}_D$ −124.4 (*c* 1.07, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2973, 2929, 2877, 1126, 1062; δ_H (400 MHz, $CDCl_3$) 4.58 (1 H, t, *J* = 5.8, H-7), 3.65 (1 H, dq, *J* = 9.3, 7.0, H-13_a), 3.63 (1 H, dq, *J* = 9.3, 7.0, H-13_a'), 3.51 (1 H, dq, *J* = 9.3, 7.0, H-13_b), 3.50-3.45 (1 H, m, H-9), 3.48 (1 H, dq, *J* = 9.3, 7.0, H-13_b'),

2.84 (1 H, ddd, J = 11.9, 8.8, 7.1, H-5$_a$), 2.80-2.73 (1 H, m, H-3$_a$), 2.70 (1 H, dq, J = 12.4, 7.3, H-11$_a$), 2.66 (1 H, dq, J = 12.4, 7.3, H-11$_b$), 2.47 (1 H, ddd, J = 8.8, 8.7, 5.6, H-3$_b$), 2.44-2.35 (1 H, m, H-5$_b$), 2.14-2.02 (1 H, m, H-1$_a$), 1.94-1.70 (5 H, m, H-1$_b$, 2, 6), 1.37 (3 H, t, J = 7.3, H-12), 1.20 (3 H, t, J = 7.0, H-14), 1.19 (3 H, t, J = 7.0, H-14'); δ_C (100 MHz, $CDCl_3$) 101.5 (CH, C-7), 93.4 (C, C-8), 73.2 (C, C-10), 61.1 (CH_2, C-13), 60.9 (CH_2, C-13'), 55.6 (CH, C-9), 51.8 (CH_2, C-3), 48.8 (CH_2, C-5), 32.7 (CH_2, C-6), 31.7 (CH_2, C-1), 29.6 (CH_2, C-11), 22.0 (CH_2, C-2), 15.3 (2 × CH_3, C-14, 14'), 14.6 (CH_3, C-12); *m/z* (ESI) 286 $[MH]^+$; [HRMS (ESI): calcd. for $C_{15}H_{28}NO_2S$, 286.1835. Found: $[MH]^+$, 286.1836 (0.3 ppm error)]; Anal. Calcd. for $C_{15}H_{27}NO_2S$: C, 63.12; H, 9.53; N, 4.91. Found: C, 63.05; H, 9.08; N, 4.88.

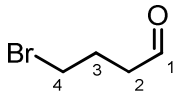
Lab Book Ref. = JDC/14/38



***S*-Ethyl (*S*)-1,2,3,5,6,8a-hexahydroindolizine-8-carbothioate 402:** A stirred solution of alkyne **401** (800 mg, 2.80 mmol, 1.0 equiv.) in formic acid (20 mL) was heated at 100 ºC (oil-bath pre-heated) for 2 h, then cooled to rt and the solution concentrated under reduced pressure. The residue was dissolved in DCM (20 mL) and washed with sat. aq. $NaHCO_3$ (20 mL), then the aqueous washes were back extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound **402** (575 mg, 97%) as a pale yellow oil; R_f 0.32 (DCM/MeOH, 9:1); $[\alpha]^{21}_D$ –86.9 (*c* 0.97, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2930, 1655, 1165, 954, 764; δ_H (400 MHz, $CDCl_3$) 6.95 (1 H, ddd, J = 5.1, 3.8, 1.7, H-7), 3.62-3.53 (1 H, m, H-9), 2.98-2.81 (4 H, m, H-3$_a$, 5$_a$, 11), 2.73 (1 H, ddd, J = 10.0, 8.3, 6.9, H-3$_b$), 2.62 (1 H, ddd, J = 11.5, 7.6, 5.0, H-5$_b$), 2.47-2.36 (1 H, m, H-6$_a$), 2.31-2.21 (2 H, m, H-1$_a$, 6$_b$), 1.90-1.71 (2 H, m, H-2), 1.47 (1 H, dddd, J = 12.7, 10.3, 8.7, 7.6, H-1$_b$), 1.25 (3 H, t, J = 7.4, H-12); δ_C (100 MHz, $CDCl_3$) 192.1 (CO, C-10), 141.6 (C, C-8), 135.5 (CH, C-7), 58.8 (CH, C-9), 52.1 (CH_2, C-3), 45.0 (CH_2, C-5), 29.3 (CH_2, C-1), 24.4 (CH_2, C-6), 22.8 (CH_2, C-11), 22.5 (CH_2, C-2), 14.8 (CH_3, C-12); *m/z* (ESI) 212 $[MH]^+$; [HRMS (ESI): calcd. for $C_{11}H_{18}NOS$, 212.1104. Found: $[MH]^+$, 212.1106 (1.2 ppm error)].

Lab Book Ref. = JDC/14/4

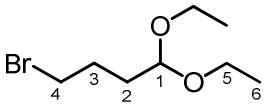
Synthesis of 4-Bromo-1,1-diethoxybutane 403:



4-Bromobutanal[194]**:** To a stirred solution of ethyl-4-bromobutyrate (0.73 mL, 5.10 mmol, 1.0 equiv.) in DCM (10 mL) at –78 ºC was added dropwise DIBAL-H (1.0 M in hexane, 5.36 mL, 5.36 mmol, 1.05 equiv.) over 30 min. *via* syringe pump. The solution was held at –78 ºC for 1 h, before quenching with MeOH (2 mL). The solution was warmed to rt and held for 30 min., then poured into sat. aq. Rochelle's salt (20 mL) and ether (20 mL). The biphasic solution was stirred vigourously for 2 h, then the aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound (0.77 g, Quant.) as a pale yellow oil which was sufficiently pure to use without further purification; R_f 0.19 (PE/EtOAc, 9:1); δ_H (400 MHz, $CDCl_3$) 9.82 (1 H, t, J = 0.9, H-1), 3.46 (2 H, t, J = 6.4, H-4), 2.68 (2 H, td, J = 7.0, 0.9, H-2), 2.19 (2 H, tt, J = 7.0, 6.4, H-3).

Lab Book Ref. = JDC/14/59

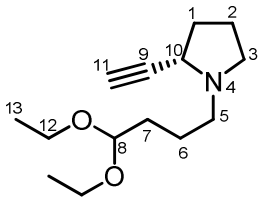
Data were consistent with those published.[194]



4-Bromo-1,1-diethoxybutane 403: To a stirred solution of 4-bromobutanal (770 mg, 5.10 mmol, 1.0 equiv.) in EtOH (7 mL) at rt was added NH_4Cl (20 mg). The solution was heated to reflux and held for 2 h, before cooling to rt and quenching with sat. aq. $NaHCO_3$ (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), then the combined organics were washed with brine (10 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a colourless oil which was purified by column chromatography (SiO_2, PE/Et_2O, 19:1) to give the title compound **403** (802 mg, 70%) as a colourless oil; R_f 0.49 (PE/EtOAc, 9:1); υ_{max}/cm^{-1} (neat) 2975, 2930, 2878, 1127, 1062; δ_H (400 MHz, $CDCl_3$) 4.49 (1 H, t, J = 5.6, H-1), 3.63 (2 H, dq, J = 9.4, 7.1, H-5_a, 5_a'), 3.47 (2 H, dq, J

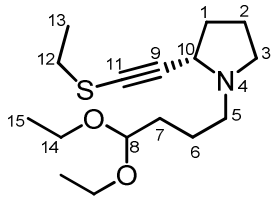
= 9.4, 7.1, H-5_b, 5_b'), 3.42 (2 H, t, *J* = 6.7, H-4), 1.96-1.88 (2 H, m, H-3), 1.78-1.71 (2 H, m, H-2), 1.18 (6 H, t, *J* = 7.1, H-6, 6'); δ_C (100 MHz, $CDCl_3$) 102.1 (CH, C-1), 61.2 (2 × CH_2, C-5, 5'), 33.6 (CH_2, C-4), 32.2 (CH_2, C-2), 28.0 (CH_2, C-3), 15.3 (2 × CH_3, C-6, 6'); *m/z* (ESI) 247 $[MNa]^+$; [HRMS (ESI): calcd. for $C_8H_{17}{}^{79}BrNaO_2$, 247.0304. Found: $[MNa]^+$, 247.0312 (3.2 ppm error)].

Lab Book Ref. = JDC/14/60



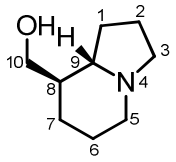
(*S*)-1-(4,4-Diethoxybutyl)-2-ethynylpyrrolidine 404: To a stirred solution of alkyne **356** (250 mg, 1.20 mmol, 1.0 equiv.) in MeCN (15 mL) at rt were added successively K_2CO_3 (498 mg, 3.60 mmol, 3.0 equiv.) and acetal **403** (297 mg, 1.32 mmol, 1.1 equiv.). The suspension was heated to reflux and held for 18 h, then cooled to rt and the solvent removed under reduced pressure. The residue was taken up in H_2O (20 mL) and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, DCM/MeOH, 99:1-98:2) to give the title compound **404** (133 mg, 47%) as a pale yellow oil; R_f 0.52 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (neat) 2974, 2877, 2808, 1376, 1128, 1065; δ_H (400 MHz, $CDCl_3$) 4.50 (1 H, t, *J* = 5.6, H-8), 3.63 (1 H, dq, *J* = 9.4, 7.1, H-12_a), 3.63 (1 H, dq, *J* = 9.4, 7.1, H-12_a'), 3.48 (2 H, dq, *J* = 9.4, 7.1, H-12_b, 12_b'), 3.41-3.34 (1 H, m, H-10), 2.82-2.73 (2 H, m, H-3_a, 5_a), 2.48 (1 H, ddd, *J* = 8.8, 8.8, 5.6, H-3_b), 2.40-2.32 (1 H, m, H-5_b), 2.24 (1 H, d, *J* = 2.1, H-11), 2.14-2.03 (1 H, m, H-1_a), 1.96-1.82 (2 H, m, H-1_b, 2_a), 1.82-1.69 (1 H, m, H-2_b), 1.69-1.52 (4 H, m, H-6, 7), 1.19 (6 H, t, *J* = 7.1, H-13, 13'); δ_C (100 MHz, $CDCl_3$) 102.7 (CH, C-8), 83.2 (C, C-9), 72.0 (CH, C-11), 60.9 (2 × CH_2, C-12, 12'), 54.2 (CH, C-10), 52.9 (CH_2, C-5), 51.6 (CH_2, C-3), 31.6 (2 × CH_2, C-1, 7), 23.9 (CH_2, C-6), 22.0 (CH_2, C-2), 15.3 (2 × CH_3, C-13, 13'); *m/z* (ESI) 240 $[MH]^+$; [HRMS (ESI): calcd. for $C_{14}H_{26}NO_2$, 240.1964. Found: $[MH]^+$, 240.1961 (1.2 ppm error)].

Lab Book Ref. = JDC/14/67

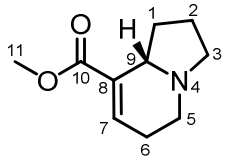


(*S*)-1-(4,4-diethoxybutyl)-2-(ethylthioethynyl)pyrrolidine 405: To a stirred solution of alkyne **404** (96 mg, 0.40 mmol, 1.0 equiv.) in THF (2.5 mL) at –78 ºC was added dropwise *n*-BuLi (1.58 M, 0.28 mL, 0.44 mmol, 1.1 equiv.). The pale yellow solution was held at –78 ºC for 30 min., then diethyl disulfide (54 μL, 0.44 mmol, 1.1 equiv.) was added dropwise. The solution was held at –78 ºC for a further 30 min., before warming to rt and holding for 2 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL), then the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM/MeOH, 98:2) to give the title compound **405** (112 mg, 93%) as a colourless oil; R_f 0.55 (DCM/MeOH, 9:1); $[\alpha]^{24}_D$ –107.1 (*c* 1.35, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2972, 2928, 2875, 1375, 1127, 1062; δ_H (400 MHz, $CDCl_3$) 4.49 (1 H, t, *J* = 5.4, H-8), 3.67-3.58 (2 H, m, H-14_a, 14_a'), 3.52-3.43 (3 H, m, H-10, 14_b, 14_b'), 2.80-2.72 (2 H, m, H-3_a, 5_a), 2.72-2.63 (2 H, m, H-12), 2.45 (1 H, ddd, *J* = 8.7, 8.5, 5.4, H-3_b), 2.33 (1 H, ddd, *J* = 11.7, 6.7, 6.7, H-5_b), 2.12-2.01 (1 H, m, H-1_a), 1.93-1.80 (2 H, m, 1_b, 2_a), 1.80-1.68 (1 H m, H-2_b), 1.68-1.50 (4 H, m, H-6, 7), 1.36 (3 H, t, *J* = 7.3, H-13), 1.18 (6 H, t, *J* = 7.1, H-15, 15'); δ_C (100 MHz, $CDCl_3$) 102.8 (CH, C-8), 93.5 (C, C-9), 73.1 (C, C-11), 61.0 (CH_2, C-14), 60.9 (CH_2, C-14'), 55.5 (CH, C-10), 53.0 (CH_2, C-5), 51.6 (CH_2, C-3), 31.7 (2 × CH_2, C-1, 7), 29.6 (CH_2, C-12), 23.9 (CH_2, C-6), 22.0 (CH_2, C-2), 15.3 (2 × CH_3, C-15, 15'), 14.6 (CH_3, C-13); *m/z* (ESI) 300 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{30}NO_2S$, 300.1992. Found: $[MH]^+$, 300.1993 (0.3 ppm error)].

Lab Book Ref. = JDC/14/69



(8*R*,8a*S*)-Octahydroindolizin-8-ylmethanol 407: To a stirred solution of $LiAlH_4$ (4.0 M in Et_2O, 0.19 mL, 0.76 mmol, 4.0 equiv.) in Et_2O (5 mL) at 0 ºC was added thioester **400** (50 mg, 0.19 mmol, 1.0 equiv.) as a solution in THF (1 mL). The solution was stirred at 0 ºC for 30 min., then warmed to rt and held for 2 h. The reaction was cooled to 0 ºC and quenched with excess sodium sulfate decahydrate. The slurry was filtered, then the filtrate was concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 90:9:1) to give allylic alcohol **288** (7 mg, 24%) as a yellow film and the title compound **407** (6 mg, 21%) as a yellow film; R_f 0.05 (DCM/MeOH, 9:1); $[\alpha]^{23}_D$ −42.6 (*c* 1.08, EtOH), (Lit.[167] +44.7 (*c* 1.1, EtOH)); υ_{max}/cm^{-1} (neat) 3365, 2930, 1444, 1164, 1042; δ_H (400 MHz, $CDCl_3$) 3.65 (1 H, dd, *J* = 10.8, 4.7, H-10_a), 3.50 (1 H, dd, *J* = 10.8, 6.3, H-10_b), 3.17-3.08 (2 H, m, H-3_a, 5_a), 2.12 (1 H, ddd, *J* = 9.1, 9.1, 9.1, H-3_b), 1.97-1.80 (3 H, m, H-1_a, 5_b, 7_a), 1.80-1.54 (5 H, m, H-2, 6, 9), 1.55-1.43 (2 H, m, H-1_b, 8), 1.05 (1 H, m, H-7_b); δ_C (100 MHz, $CDCl_3$) 66.4 (CH, C-9), 65.6 (CH_2, C-10), 54.0 (CH_2, C-3), 52.5 (CH_2, C-5), 44.2 (CH, C-8), 28.9 (CH_2, C-1), 27.3 (CH_2, C-7), 24.9 (CH_2, C-6), 20.6 (CH_2, C-2); *m/z* (ESI) 156 $[MH]^+$; [HRMS (ESI): calcd. for $C_9H_{18}NO$, 156.1383. Found: $[MH]^+$, 156.1386 (1.7 ppm error)].
Lab Book Ref. = JDC/12/7
Data were consistent with those published.[167]

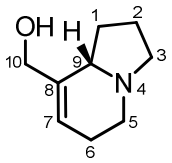


Methyl (*S*)-1,2,3,5,6,8a-hexahydroindolizine-8-carboxylate 409: To a stirred solution of thioester **402** (1.04 g, 4.92 mmol, 1.0 equiv.) and Et_3N (3.43 mL, 24.6 mmol, 5.0 equiv.) in DCM/MeOH (1:1, 40 mL) at rt was added in one portion AgOTf (3.80 g, 14.8 mmol, 3.0 equiv.). The brown solution was heated to 45 ºC and held for 18 h, then cooled to rt and filtered through a short plug of silica, washing with DCM/MeOH (100 mL, 9:1). The organic phase was washed with sat. aq. $NaHCO_3$ (100 mL), then the

aqueous washings were back-extracted with DCM (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, DCM/MeOH, 19:1-4:1) to give the title compound **409** (0.65 g, 73%) as a pale yellow oil; R_f 0.12 (DCM/MeOH, 9:1); $[\alpha]^{20}_D$ –55.6 (*c* 0.35, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2951, 1713, 1435, 1260, 1100, 1036; δ_H (400 MHz, $CDCl_3$) 6.98-6.94 (1 H, m, H-7), 3.69 (3 H, s, H-11), 3.61-3.53 (1 H, m, H-9), 2.93-2.80 (3 H, m, H-3, 5_a), 2.67 (1 H, ddd, *J* = 11.9, 6.0, 6.0, H-5_b), 2.38-2.26 (3 H, m, H-1_a, 6), 1.92-1.73 (2 H, m, H-2), 1.55-1.44 (1 H, m, H-1_b); δ_C (100 MHz, $CDCl_3$) 166.3 (CO, C-10), 137.4 (CH, C-7), 132.2 (C, C-8), 58.7 (CH, C-9), 52.5 (CH_2, C-3), 51.5 (CH_3, C-11), 44.9 (CH_2, C-5), 29.8 (CH_2, C-1), 24.4 (CH_2, C-6), 22.3 (CH_2, C-2); *m/z* (ESI) 182 $[MH]^+$; [HRMS (ESI): calcd. for $C_{10}H_{16}NO_2$, 182.1176. Found: $[MH]^+$, 182.1179 (1.8 ppm error)].

Lab Book Ref. = JDC/14/48

Data were consistent with those published.[169]

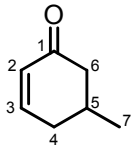


(*S*)-(1,2,3,5,6,8a-Hexahydroindolizin-8-yl)methanol[169] **288:** To a stirred solution of ester **409** (394 mg, 2.17 mmol, 1.0 equiv.) in THF (30 mL) at 0 ºC was added dropwise DIBAL-H (1.0 M in hexane, 8.68 mL, 8.68 mmol, 4.0 equiv.) over 20 min. *via* syringe pump. The solution was held at 0 ºC for 30 min., then warmed to rt and held for 2 h. The reaction was cooled to 0 ºC before quenching with MeOH (1 mL), then diluted with sat. aq. Rochelle's salt (25 mL) and EtOAc (25 mL). The biphasic solution was stirred vigourously for 2 h, then the aqueous phase was separated and extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound **288** (228 mg, 69%) as a pale orange oil; R_f 0.04 (DCM/MeOH, 9:1); $[\alpha]^{20}_D$ –54.6 (*c* 1.03, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3352 (br), 2909, 2875, 1458, 1062, 1018; δ_H (400 MHz, $CDCl_3$) 5.68-5.64 (1 H, m, H-7), 4.05-4.03 (2 H, m, H-10), 3.35 (1 H, br s, OH), 3.19-3.12 (1 H, m, H-9), 2.91 (1 H, ddd, *J* = 10.5, 8.1, 3.8, H-3_a), 2.80 (1 H, ddd, *J* = 11.3, 5.7, 5.7, H-5_a), 2.67 (1 H, ddd, *J* = 10.5, 8.9, 7.9, H-3_b), 2.53 (1 H, ddd, *J* = 11.3, 6.0, 6.0, H-5_b), 2.27-2.13 (2 H, m,

H-6), 2.03 (1 H, dddd, J = 12.1, 9.5, 6.9, 3.6, H-1_a), 1.89 (1 H, ddddd, J = 12.8, 10.5, 8.1, 7.9, 3.6, H-2_a), 1.75 (1 H, ddddd, J = 12.8, 9.5, 8.9, 7.3, 3.8, H-2_b), 1.54 (1 H, dddd, J = 12.1, 10.5, 10.5, 7.3, H-1_b); δ_C (100 MHz, $CDCl_3$) 139.4 (C, C-8), 120.5 (CH, C-7), 64.7 (CH_2, C-10), 60.4 (CH, C-9), 52.9 (CH_2, C-3), 46.6 (CH_2, C-5), 28.0 (CH_2, C-1), 25.0 (CH_2, C-6), 22.1 (CH_2, C-2); *m/z* (ESI) 154 $[MH]^+$; [HRMS (ESI): calcd. for $C_9H_{16}NO$, 154.1226. Found: $[MH]^+$, 154.1226 (0.3 ppm error)].

Lab Book Ref. = JDC/14/79

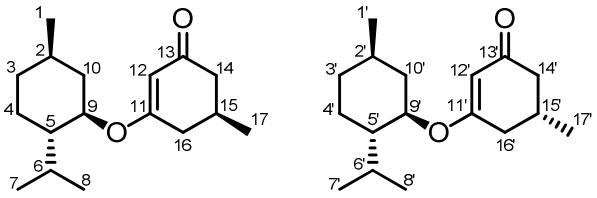
Data were consistent with those published.[35, 169]



(*S*)-5-Methylcyclohex-2-enone[105] **87:** To a stirred solution of organocatalyst **275** (299 mg, 0.50 mmol, 0.05 equiv.) in crotonaldehyde (1.24 mL, 15.0 mmol, 1.5 equiv.) at rt was added *tert*-butyl acetoacetate (1.66 mL, 10.0 mmol, 1.0 equiv.). The yellow solution was stirred at rt for 24 h, then excess crotonaldehyde was removed under reduced pressure. The yellow oil was taken up in PhMe (40 mL), then *p*-TsOH (380 mg, 2.00 mmol, 0.2 equiv.) was added. The solution was heated to 80 ºC and held for 18 h, then cooled to rt and quenched with sat. aq. $NaHCO_3$ (20 mL). The aqueous phase was separated, then extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, PE/Et_2O, 9:1) to give the title compound **87** (510 mg, 46%) as a pale yellow oil; R_f 0.32 (PE/EtOAc, 4:1); $[\alpha]^{21}_D$ +70.4 (*c* 0.52, $CHCl_3$), (Lit.[105] −74.6 (*c* 0.50, $CHCl_3$, 80% *ee*); δ_H (400 MHz, $CDCl_3$) 6.95 (1 H, ddd, J = 10.1, 5.6, 2.6, H-3), 6.00 (1 H, dddd, J = 10.1, 2.5, 1.0, 1.0, H-2), 2.50-2.45 (1 H, m, H-6_a), 2.45-2.37 (1 H, m, H-4_a), 2.29-2.15 (1 H, m, H-5), 2.11 (1 H, dd, J = 15.9, 12.3, H-6_b), 2.03 (1 H, dddd, J = 18.5, 9.8, 2.6, 2.5, H-4_b), 1.06 (3 H, d, J = 6.5, H-7).

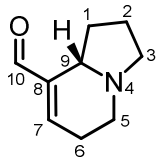
Lab Book Ref. = JDC/14/30

Data were consistent with those published.[105]



3-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-5-methylcyclohex-2-en-1-one 417 and 418: To a stirred suspension of 5-methyl-1,3-cyclohexanedione (0.92 g, 7.30 mmol, 1.0 equiv.) and (−)-menthol (1.14 g, 7.30 mmol, 1.0 equiv.) in PhMe (25 mL) at rt was added *p*-TsOH (70 mg, 0.37 mmol, 0.05 equiv.). The suspension was heated to reflux (Dean-Stark) and held for 24 h. The orange solution was cooled to rt, then quenched with sat. aq. $NaHCO_3$ (20 mL). The organic phase was separated, then the aqueous phase was extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, PE/EtOAc, 10:0-9:1) to give the title compounds **417** and **418** (1.64 g, 85%, 1:1 ratio of diastereoisomers) as a colourless oil; R_f 0.40 (PE/Et_2O, 1:1); υ_{max}/cm^{-1} (neat) 2954, 2871, 1655, 1600, 1377, 1208; δ_H (400 MHz, $CDCl_3$) 5.38 (2 H, s, H-12, 12'), 4.00-3.91 (2 H, m, H-9, 9'), 2.45-2.31 (4 H, m, H-14_a, 14_a', 16_a, 16_a'), 2.28-1.89 (10 H, m, H-6, 6', 10_a, 10_a', 14_b, 14_b', 15, 15', 16_b, 16_b'), 1.72-1.63 (4 H, m, H-3_a, 3_a', 4_a, 4_a'), 1.50-1.31 (4 H, m, H-2, 2', 5, 5'), 1.06 (3 H, d, J = 1.8, CH_3), 1.05 (3 H, d, J = 1.7, CH_3), 0.91-0.86 (12 H, m, CH_3), 0.73 (3 H, d, J = 4.4, CH_3), 0.72 (3 H, d, J = 4.4, CH_3); δ_C (100 MHz, $CDCl_3$) 200.0 (CO, C-13), 199.9 (CO, C-13), 176.8 (C, C-11), 176.5 (C, C-11), 102.2 (CH, C-12), 101.9 (CH, C-12), 78.4 (CH, C-9), 77.9 (CH, C-9), 47.4 (CH, C-5), 47.3 (CH, C-5), 45.0 (2 × CH_2, C-14), 39.4 (CH_2, C-10), 38.9 (CH_2, C-10), 37.7 (CH_2, C-16), 37.5 (CH_2, C-16), 34.2 (2 × CH_2, C-3), 31.2 (2 × CH, C-2), 28.8 (CH, C-15), 28.7 (CH, C-15), 26.4 (CH, C-6), 26.3 (CH, C-6), 23.8 (CH_2, C-4), 23.7 (C-4), 21.9 (2 × CH_3, C-1), 20.9 (CH_3), 20.8 (CH_3), 20.5 (CH_3), 20.4 (CH_3), 16.7 (CH_3), 16.6 (CH_3); *m/z* (ESI) 265 $[MH]^+$; [HRMS (ESI): calcd. for $C_{17}H_{29}O_2$, 265.2162. Found: $[MH]^+$, 265.2153 (3.4 ppm error)].

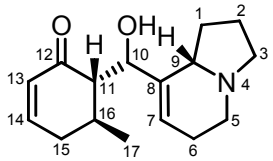
Lab Book Ref. = JDC/6/97



(*S*)-1,2,3,5,6,8a-Hexahydroindolizine-8-carbaldehyde 172: To a stirred solution of oxalyl chloride (105 μL, 1.24 mmol, 1.2 equiv.) in DCM (5 mL) at −78 ºC was added dropwise DMSO (176 μL, 2.48 mmol, 2.4 equiv.). The colourless solution was held at −78 ºC for 30 min., then alcohol **288** (158 mg, 1.03 mmol, 1.0 equiv.) was added *via* cannula as a pre-cooled solution in DCM (3 mL). The reaction was held at −78 ºC for 1 h, then Et_3N (718 μL, 5.15 mmol, 5.0 equiv.) was added dropwise. The yellow solution was held at −78 ºC for a further 30 min., then warmed to rt and held for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) then the aqueous phase was extracted with DCM (4 × 10 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford the title compound **172** (137 mg, 88%) as a yellow oil which was used immediately without further purification; R_f 0.28 (DCM/MeOH, 9:1); δ_H (400 MHz, $CDCl_3$) 9.41 (1 H, s, H-10), 6.84 (1 H, ddd, J = 4.0, 3.9, 1.7, H-7), 3.45-3.37 (1 H, m, H-9), 2.97-2.90 (1 H, m, H-5_a), 2.90 (1 H, ddd, J = 10.1, 7.9, 4.8, H-3_a), 2.74 (1 H, ddd, J = 10.1, 8.5, 7.3, H-3_b), 2.68-2.61 (1 H, m, H-5_b), 2.61-2.51 (1 H, m, H-6_a), 2.48-2.38 (1 H, m, H-6_b), 2.40-2.31 (1 H, m, H-1_a), 1.94-1.75 (2 H, m, H-2), 1.45 (1 H, dddd, J = 12.8, 10.2, 9.4, 7.6, H-1_b).

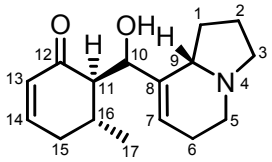
Lab Book Ref. = JDC/14/18

Data were consistent with those published.[35]



(5*S*,6*S*)-6-[(8a*S*)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl(hydroxy)methyl]-5-methylcyclohex-2-en-1-one 287: To a stirred solution of di*iso*propylamine (119 μL, 0.85 mmol, 1.3 equiv.) in THF (7 mL) at 0 ºC was added dropwise *n*-BuLi (1.58 M in hexanes, 0.49 mL, 0.77 mmol, 1.2 equiv.). The colourless solution was held at 0 ºC for 30 min., then cooled to −78 ºC before the addition of enone **87** (72 mg, 0.65 mmol, 1.0

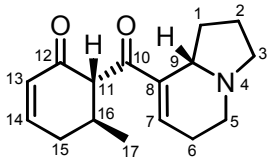
equiv.) as a pre-cooled solution in THF (1 mL). The resulting pale yellow solution was held at −78 ºC for 1 h, before the addition of aldehyde **172** (137 mg, 0.91 mmol, 1.4 equiv.) as a pre-cooled solution in THF (1 mL). The reaction was held at −78 ºC for a further 2 h, then quenched with AcOH (0.5 mL). The organic phase was diluted with water (20 mL) and basified (K_2CO_3) then extracted with DCM (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 120:9:1-90:9:1) to give the minor diastereoisomer **294** (18 mg, 10%) as an off-white solid and the title compound **287** (94 mg, 51%) as an off-white solid; mp. 113-116 ºC; R_f 0.49 (DCM/MeOH/NH_3, 40:9:1); $[\alpha]^{20}_D$ –20.4 (*c* 0.99, $CHCl_3$); υ_{max}/cm^{-1} (thin film) 3399 (br), 2957, 2918, 1676, 1389, 1026, 730; δ_H (400 MHz, $CDCl_3$) 6.86 (1 H, dddd, *J* = 10.1, 5.2, 2.8, 1.1, H-14), 6.03 (1 H, dddd, *J* = 10.1, 2.6, 1.5, 0.7, H-13), 5.77 (1 H, ddd, *J* = 3.8, 3.8, 1.3, H-7), 4.25 (1 H, d, *J* = 9.5, H-10), 3.06-2.99 (1 H, m, H-9), 2.95 (1 H, ddd, *J* = 10.5, 8.4, 3.4, H-3_a), 2.84 (1 H, ddd, *J* = 11.3, 5.7, 5.7, H-5_a), 2.72-2.63 (1 H, m, H-3_b), 2.56 (1 H, dddd, *J* = 19.7, 5.6, 2.8, 2.6, H-15_a), 2.50 (1 H, ddd, *J* = 11.3, 5.6, 5.3, H-5_b), 2.38 (1 H, dd, *J* = 9.5, 3.2, H-11), 2.44-2.11 (4 H, m, H-1_a, 6, 16), 2.07 (1 H, dddd, *J* = 19.7, 5.2, 2.3, 1.5, H-15_b), 2.00-1.86 (1 H, m, H-2_a), 1.82-1.67 (2 H, m, H-1_b, 2_b), 1.07 (3 H, d, *J* = 7.1, H-17); δ_C (100 MHz, $CDCl_3$) 201.4 (CO, C-12), 147.9 (CH, C-14), 139.1 (C, C-8), 128.3 (CH, C-13), 124.5 (CH, C-7), 74.7 (CH, C-10), 59.8 (CH, C-9), 56.6 (CH, C-11), 53.0 (CH_2, C-3), 46.3 (CH_2, C-5), 30.1 (CH, C-16), 30.0 (CH_2, C-15), 29.6 (CH_2, C-1), 25.5 (CH_2, C-6), 22.3 (CH_2, C-2), 19.9 (CH_3, C-17); *m/z* (ESI) 262 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{24}NO_2$, 262.1802. Found: $[MH]^+$, 262.1799 (1.1 ppm error)].



(5*R*,6*R*)-6-[(8a*S*)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl(hydroxy)methyl]-5-methylcyclohex-2-en-1-one 294: (18 mg, 10%) as an off-white solid; mp. 105-108 ºC; R_f 0.35 (DCM/MeOH/NH_3, 40:9:1); $[\alpha]^{24}_D$ –65.4 (*c* 0.55, $CHCl_3$); υ_{max}/cm^{-1} (thin film) 3340 (br), 2956, 2915, 1668, 730; δ_H (400 MHz, $CDCl_3$) 6.82-6.77 (1 H, m, H-14), 5.95 (1 H, ddd, *J* = 10.1, 2.4, 1.6, H-13), 5.74-5.71 (1 H, m, H-7), 4.26 (1 H, d, *J* = 7.9, H-

10), 3.12-3.05 (1 H, m, H-9), 2.88 (1 H, ddd, J = 10.6, 8.5, 3.5, H-3_a), 2.76 (1 H, ddd, J = 11.3, 5.7, 5.7 H-5_a), 2.63-2.48 (2 H, m, H-3_b, 15_a), 2.47 (1 H, ddd, J = 11.3, 5.6, 5.6, H-5_b), 2.31 (1 H, dd, J = 7.9, 4.3, H-11), 2.28-2.19 (3 H, m, H-6, 16), 2.09-1.98 (2 H, m, H-1_a, 15_b), 1.93-1.80 (1 H, m, H-2_a), 1.78-1.66 (1 H, m, H-2_b), 1.53-1.42 (1 H, m, H-1_b), 1.02 (3 H, d, J = 7.0, H-17); δ_C (100 MHz, $CDCl_3$) 201.0 (CO, C-12), 147.6 (CH, C-14), 139.6 (C, C-8), 128.5 (CH, C-13), 122.1 (CH, C-7), 73.4 (CH, C-10), 60.1 (CH, C-9), 57.5 (CH, C-11), 52.7 (CH_2, C-3), 46.3 (CH_2, C-5), 30.8 (CH, C-16), 30.4 (CH_2, C-15), 28.2 (CH_2, C-1), 25.4 (CH_2, C-6), 22.0 (CH_2, C-2), 19.9 (CH_3, C-17); *m/z* (ESI) 262 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{24}NO_2$, 262.1802. Found: $[MH]^+$, 262.1803 (0.5 ppm error)].

Lab Book Ref. = JDC/14/52

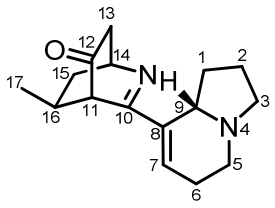


(5*S*,6*R*)-6-[(8a*S*)-1,2,3,5,6,8a-Hexahydroindolizine-8-carbonyl]-5-methylcyclohex-2-en-1-one 17: To a stirred solution of DMSO (21 μL, 0.30 mmol, 2.0 equiv.) in DCM (4 mL) at −78 ºC was added dropwise trifluoroacetic anhydride (32 μL, 0.23 mmol, 1.5 equiv.). The colourless solution was held at −78 ºC for 30 min., before adding alcohol **287** (40 mg, 0.15 mmol, 1.0 equiv.) as a pre-cooled solution in DCM (2 mL) *via* cannula. The reaction was held at −78 ºC for 1 h, then Et_3N (105 μL, 0.75 mmol, 5.0 equiv.) was added dropwise. The yellow solution was held at −78 ºC for a further 15 min., then warmed to rt and held for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL), then the aqueous phase was extracted with DCM (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 190:9:1) to give the title compound **17** (32 mg, 80%) as a colourless oil. To a solution of the product **17** (14 mg, 0.05 mmol, 1.0 equiv.) in DCM (1 mL) at 0 ºC was added dropwise TFA (5 μL, 0.07 mmol, 1.4 equiv). The colourless solution was held at 0 ºC for 15 min., then warmed to rt and held for 1 h. The pale yellow solution was concentrated *in vacuo* to afford the title compound **17**·TFA (19 mg, Quant.) as a pale yellow oil; R_f 0.69 (DCM/MeOH/NH_3, 40:9:1); $[\alpha]^{22}_D$

+73.7 (*c* 0.10, MeOH), (Lit.[25] +65.7 (*c* 0.09, MeOH)); υ_{max}/cm^{-1} (thin film) 2959, 1676, 1656, 1390, 1190; δ_H (400 MHz, DMSO-d_6) 10.37 (1 H, br s, NH^+), 7.35 (1 H, dd, *J* = 3.8, 3.8, H-7), 7.16 (1 H, ddd, *J* = 9.9, 5.5, 2.2, H-14), 5.97 (1 H, dd, *J* = 9.9, 2.1, H-13), 4.40 (1 H, dd, *J* = 8.7, 8.7, H-9), 4.33 (1 H, d, *J* = 11.5, H-11), 3.62-3.50 (1 H, m, H-3_a), 3.41-3.27 (2 H, m, H-3_b, 5_a), 3.18-3.05 (1 H, m, H-5_b), 2.66-2.59 (2 H, m, H-6), 2.53-2.37 (3 H, m, H-1_a, 15_a, 16), 2.27-2.15 (1 H, m, H-15_b), 2.08-1.98 (2 H, m, H-2), 1.71-1.58 (1 H, m, 1_b) 0.86 (3 H, d, *J* = 6.2, H-17); δ_C (100 MHz, DMSO-d_6) 198.3 (CO, C-10), 196.7 (CO, C-12), 151.6 (CH, C-14), 140.1 (CH, C-7), 137.2 (C, C-8), 128.3 (CH, C-13), 59.2 (CH, C-11), 57.9 (CH, C-9), 52.9 (CH_2, C-3), 43.1 (CH_2, C-5), 33.0 (CH, C-16), 32.6 (CH_2, C-15), 28.1 (CH_2, C-1), 22.9 (CH_2, C-6), 20.2 (CH_2, C-2), 19.1 (CH_3, C-17); *m/z* (ESI) 260 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{22}NO_2$, 260.1645. Found: $[MH]^+$, 260.1644 (0.4 ppm error)].

Lab Book Ref. = JDC/14/54

Data were consistent with those published.[10, 25]

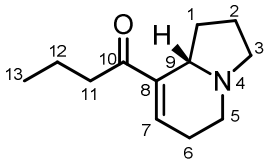


3-((*S*)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl)-8-methyl-2-azabicyclo[2.2.2]oct-2-en-5-one 15: To a stirred solution of diketone **17** (14 mg, 0.054 mmol, 1.0 equiv.) in 1 M aq. HCl (1 mL) at 0 ºC was added dropwise 35% aq. NH_3 (1 mL, *ca*. 18 mmol). The yellow solution was held at 0 ºC for 30 min., then warmed to rt and held for 2 h. The yellow solution was diluted with brine (10 mL), then extracted with DCM (4 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow film which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 90:9:1) to give the title compound **15** (10 mg, 72%) as a yellow film; R_f 0.33 (DCM/MeOH/NH_3, 90:9:1); $[\alpha]^{20}_D$ = −177.5 (*c* 0.08, DCM), (Lit.[55] −159.0 (*c* 0.08, DCM)); υ_{max}/cm^{-1} (neat) 2954, 2872, 1730, 1578, 1341, 1102; δ_H (400 MHz, $CDCl_3$) 6.41 (1 H, ddd, *J* = 4.2, 4.2, 1.5, H-7), 4.63 (1 H, dddd, *J* = 3.6, 3.3, 1.8, 1.8, H-14), 3.70-3.63 (1 H, m, H-9), 3.55 (1 H, d, *J* = 3.1, H-11), 2.92 (1 H, ddd, *J* = 10.2, 7.7, 4.7, H-3_a), 2.87 (1 H, ddd, *J* = 11.0, 3.2, 3.2, H-5_a), 2.77 (1 H, ddd, *J*

= 10.2, 8.2, 7.5, H-3_b), 2.64 (1 H, ddd, *J* = 11.0, 7.0, 5.1, H-5_b), 2.47-2.36 (1 H, m, H-6_a), 2.36-2.24 (2 H, m, H-1_a, 6_b), 2.16 (1 H, ddd, *J* = 18.8, 3.3, 2.7, H-13_a), 2.06 (1 H, dd, *J* = 18.8, 1.8, H-13_b), 2.00-1.92 (1 H, m, H-15_a), 1.91-1.72 (3 H, m, H-2, 16), 1.35 (1 H, dddd, *J* = 12.7, 10.3, 9.3, 7.6, H-1_b), 1.27 (1 H, ddd, *J* = 12.6, 4.5, 1.8, H-15_b), 1.06 (3 H, d, *J* = 7.0, H-17); δ_C (100 MHz, $CDCl_3$) 208.9 (CO, C-12), 171.1 (CN, C-10), 138.6 (C, C-8), 130.2 (CH, C-7), 58.9 (CH, C-9), 56.5 (CH, C-11), 55.6 (CH, C-14), 52.6 (CH_2, C-3), 45.2 (CH_2, C-5), 40.0 (CH_2, C-13), 32.2 (CH_2, C-15), 30.0 (CH_2, C-1), 29.2 (CH, C-16), 24.9 (CH_2, C-6), 22.4 (CH_2, C-2), 21.2 (CH_3, C-17); *m/z* (ESI) 259 $[MH]^+$; [HRMS (ESI): calcd. for $C_{16}H_{23}N_2O$, 259.1805. Found: $[MH]^+$, 259.1810 (2.1 ppm error)].

Lab Book Ref. = JDC/14/56

Data were consistent with those published.[9, 55]

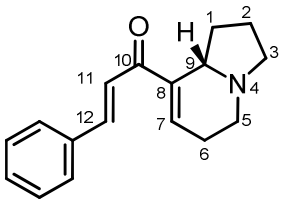


1-[(8a*S*)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl]butan-1-one 57: To a stirred solution of thioester **400** (54 mg, 0.21 mmol, 1.0 equiv.) in THF (1 mL) at 0 ºC was added $Fe(acac)_3$ (3 mg, 0.008 mmol, 0.04 equiv.). The orange solution was held at 0 ºC for 5 min., then propyl magnesium bromide (2.0 M in Et_2O, 145 μL, 0.29 mmol, 1.4 equiv.) was added dropwise. The resulting black solution was held at 0 ºC for 30 min., then quenched with sat. aq. NH_4Cl (1 mL). The aqueous phase was extracted with DCM (3 × 5 mL), then the combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO_2, DCM/MeOH, 98:2-9:1) to give the title compound **57** (16 mg, 39%) as a colourless oil; R_f 0.16 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (neat) = 2961, 2875, 1666, 1461, 1395, 1201; δ_H (400 MHz, $CDCl_3$) 6.92 (1 H, ddd, *J* = 4.3, 4.2, 1.4, H-7), 3.77 (1 H, dd, *J* = 8.6, 8.3, H-9), 3.09 (1 H, ddd, *J* = 11.1, 8.3, 8.3, H-3_a), 3.01-2.94 (1 H, m, H-3_b), 2.89-2.84 (2 H, m, H-5), 2.68-2.53 (1 H, m, H-6_a), 2.63 (1 H, dt, *J* = 16.4, 7.3, H-11_a), 2.58 (1 H, dt, *J* = 16.4, 7.3, H-11_b), 2.52-2.42 (2 H, m, H-1_a, 6_b), 1.96-1.87 (2 H, m, H-2), 1.62 (2 H, qt, *J* = 7.4, 7.3, H-12), 1.47 (1 H, dddd, *J* = 13.1, 9.8, 9.7, 8.3, H-1_b), 0.91 (3 H, t, *J* = 7.4, H-13); δ_C (100 MHz, $CDCl_3$) 199.8 (CO, C-10),

139.9 (C, C-8), 136.3 (CH, C-7), 58.6 (CH, C-9), 52.9 (CH_2, C-3), 44.8 (CH_2, C-5), 39.1 (CH_2, C-11), 29.4 (CH_2, C-1), 24.6 (CH_2, C-6), 21.9 (CH_2, C-2), 17.9 (CH_2, C-12), 13.7 (CH_3, C-13); *m/z* (ESI) 194 $[MH]^+$; [HRMS (ESI): calcd. for $C_{12}H_{20}NO$, 194.1539. Found: $[MH]^+$, 194.1541 (0.9 ppm error)].

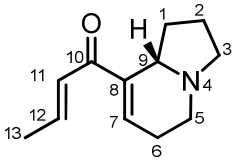
Lab Book Ref. = JDC/12/1

Data were consistent with those published.[37]



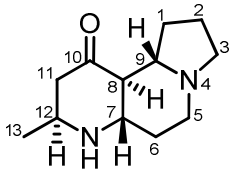
(2*E*)-1-[(8a*S*)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl]-3-phenylprop-2-en-1-one 421: To a stirred solution thioester **400** (20 mg, 0.08 mmol, 1.0 equiv.), styrenyl boronic acid (21 mg, 0.14 mmol, 1.7 equiv.), copper(I) thiophene carboxylate (27 mg, 0.14 mmol, 1.7 equiv.) and $Pd_2(dba)_3$ (2 mg, 0.002 mmol, 0.025 equiv.) in THF (1 mL, degassed) under argon (flask purged *via* 5 × vacuum/Ar cycles) at rt was added $P(OEt)_3$ (3 μL, 0.02 mmol, 0.2 equiv.). The dark brown solution was held at rt for 4 h, then quenched with sat. aq. $NaHCO_3$ (2 mL). The aqueous phase was extracted with DCM (3 × 5 mL), then the combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 95:5:0-190:9:1) to give the title compound **421** (11 mg, 56%) as a yellow film; R_f 0.11 (DCM/MeOH, 9:1); υ_{max}/cm^{-1} (thin film) 2923, 1654, 1597, 1202; δ_H (400 MHz, $CDCl_3$) 7.65 (1 H, d, *J* = 15.7, H-12), 7.61-7.54 (2 H, m, ArH), 7.41-7.37 (3 H, m, ArH), 7.23 (1 H, d, *J* = 15.7, H-11), 7.06 (1 H, ddd, *J* = 4.2, 4.2, 1.5, H-7), 4.02 (1 H, dd, *J* = 9.2, 8.6, H-9), 3.23 (1 H, ddd, *J* = 10.7, 8.3, 8.3, H-3_a), 3.05 (1 H, ddd, *J* = 10.7, 6.7, 6.7, H-3_b), 3.01-2.96 (2 H, m, H-5), 2.79-2.68 (1 H, m, H-6_a), 2.63-2.52 (2 H, m, H-1_a, 6_b), 2.04-1.95 (2 H, m, H-2), 1.58 (1 H, ddd, *J* = 13.1, 9.4, 9.2, H-1_b); δ_C (100 MHz, $CDCl_3$) 188.9 (CO, C-10), 143.9 (CH, C-12), 140.2 (C, C-8), 136.2 (CH, C-7), 134.7 (C, ArC), 130.5 (CH, ArCH), 128.9 (2 × CH, ArCH), 128.3 (2 × CH, ArCH), 120.6 (CH, C-11), 58.9 (CH, C-9), 53.0 (CH_2, C-3), 45.0 (CH_2, C-5), 29.3 (CH_2, C-1), 24.3 (CH_2, C-6), 21.8 (CH_2, C-2); *m/z* (ESI) 254 $[MH]^+$; [HRMS (ESI): calcd. for $C_{17}H_{20}NO$, 254.1539. Found: $[MH]^+$, 254.1536 (1.5 ppm error)].

Lab Book Ref. = JDC/12/44



(2*E*)-1-[(8a*S*)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl]but-2-en-1-one 422: To a stirred solution thioester **400** (200 mg, 0.77 mmol, 1.0 equiv.), *cis*-propenyl boronic acid (113 mg, 1.31 mmol, 1.7 equiv.), copper(I) thiophene carboxylate (250 mg, 1.31 mmol, 1.7 equiv.) and $Pd_2(dba)_3$ (18 mg, 0.02 mmol, 0.025 equiv.) in THF (10 mL, degassed) under argon (flask purged *via* 5 × vacuum/Ar cycles) at rt was added $P(OEt)_3$ (26 μL, 0.15 mmol, 0.2 equiv.). The dark brown solution was held at rt for 4 h, then quenched with sat. aq. $NaHCO_3$ (5 mL). The aqueous phase was extracted with DCM (3 × 10 mL), then the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (SiO_2, DCM/MeOH, 9:1-4:1) to give the title compound **422** (102 mg, 69%) as an orange oil containing minor aromatic impurities; R_f 0.16 (DCM/MeOH, 4:1); υ_{max}/cm^{-1} (neat) 2958, 1662, 1616, 1443, 1293, 1205; δ_H (400 MHz, $CDCl_3$) 6.87-6.83 (1 H, m, H-7), 6.85 (1 H, dq, *J* = 15.1, 6.9, H-12), 6.57 (1 H, dq, *J* = 15.1, 1.4, H-11), 3.71 (1 H, dd, *J* = 7.8, 7.5, H-9), 2.92 (2 H, dd, *J* = 7.2, 7.2, H-3), 2.91-2.82 (1 H, m, H-5_a), 2.75 (1 H, ddd, *J* = 11.2, 5.5, 5.5, H-5_b), 2.49-2.41 (2 H, m, H-6), 2.40-2.31 (1 H, m, 1_a), 1.91-1.79 (2 H, m, H-2), 1.87 (3 H, dd, *J* = 6.9, 1.4, H-13), 1.41 (1 H, dddd, *J* = 13.0, 9.8, 9.7, 7.8, H-1_b); δ_C (100 MHz, $CDCl_3$) 189.8 (C, C-10), 143.2 (CH, C-12), 140.9 (C, C-8), 136.5 (CH, C-7), 126.4 (CH, C-11), 58.5 (CH, C-9), 52.4 (CH_2, C-3), 44.7 (CH_2, C-5), 29.1 (CH_2, C-1), 24.6 (CH_2, C-6), 22.0 (CH_2, C-2), 18.3 (CH_3, C-13); *m/z* (ESI) 192 $[MH]^+$; [HRMS (ESI): calcd. for $C_{12}H_{18}NO$, 192.1383. Found: $[MH]^+$, 192.1382 (0.4 ppm error)].

Lab Book Ref. = JDC/14/47



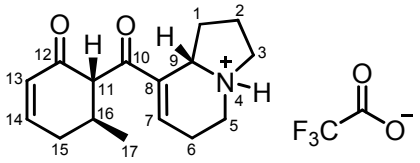
(3*S*,4a*S*,10a*S*,10b*R*)-3-Methyldecahydropyrrolo[2,1-*f*][1,6]naphthyridin-1(2*H*)-one 419: To a stirred solution of enone **422** (102 mg, 0.53 mmol, 1.0 equiv.) in 1 M. aq. HCl (2.5 mL) at 0 ºC was added 35 % aq. NH_3 (5 mL). The solution was held at 0 ºC for 30 min., then diluted with H_2O (10 mL). The aqueous phase was extracted with DCM (3 × 10 mL), then the combined organics were washed with brine (10 mL), dried (Na_2SO_4), then concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography (SiO_2, DCM/MeOH/NH_3, 190:9:1-90:9:1) to give the title compound **419** (28 mg, 25%) as a yellow oil containing minor diastereomeric impurities; R_f 0.16 (DCM/MeOH/NH_3, 90:9:1); υ_{max}/cm^{-1} (neat) 2960, 2928, 2799, 1705, 1330, 1168; δ_H (400 MHz, $CDCl_3$) 3.80 (1 H, dqd, *J* = 6.9, 6.8, 1.8, H-12), 3.13 (1 H, ddd, *J* = 11.4, 4.1, 2.5, H-5_a), 3.02 (1 H, ddd, *J* = 8.8, 8.6, 2.3, H-3_a), 2.87 (1 H, ddd, *J* = 10.7, 10.7, 4.2, H-7), 2.71 (1 H, dd, *J* = 12.8, 6.9, H-11_a), 2.31 (1 H, ddd, *J* = 12.8, 6.0, 3.6, H-1_a), 2.20 (1 H, dd, *J* = 12.8, 1.8, H-11_b), 2.12 (3 H, m, H-3_b, 5_b, 8), 2.04 (1 H, ddd, *J* = 9.7, 9.5, 6.0, H-9), 1.91-1.71 (4 H, m, H-2, 6), 1.37-1.26 (1 H, m, 1_b), 1.16 (3 H, t, *J* = 6.9, H-13); δ_C (100 MHz, $CDCl_3$) 208.9 (CO, C-10), 62.0 (CH, C-8), 61.8 (CH, C-9), 56.1 (CH, C-7), 53.1 (CH_2, C-3), 51.3 (CH, C-12), 50.4 (CH_2, C-5), 49.1 (CH_2, C-11), 33.1 (CH_2, C-6), 29.0 (CH_2, C-1), 21.7 (CH_2, C-2), 19.8 (CH_3, C-13); *m/z* (ESI) 209 $[MH]^+$; [HRMS (ESI): calcd. for $C_{12}H_{21}N_2O$, 209.1648. Found: $[MH]^+$, 209.1645 (1.8 ppm error)].

Lab Book Ref. = JDC/14/49

Data were consistent with those published.[33]

Appendices

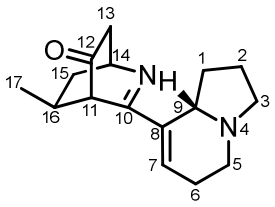
Appendix I. Comparison of $^{1}H/^{13}C$ Spectral Data for Grandisine D·TFA (17)



Atom	Synthetic (ppm) (d_6-DMSO, 400 MHz)	Tamura (ppm) (d_6-DMSO, 300 MHz)	Carroll (ppm) (d_6-DMSO, 600 MHz)
1	1.64 m / 2.45 m	1.64 m	1.62 dddd / 2.40 dddd
2	2.03 m / 2.03 m	2.01 m / 2.01 m	2.00 t / 2.00 t
3	3.35 m / 3.55 m	3.34 m / 3.55 m	3.28 m / 3.48 ddd
4	10.37 bs	10.15 bs	10.25 bs
5	3.35 m / 3.11 m	3.34 m / 3.11 m	3.28 m / 3.09 ddd
6	2.61 m	2.62 m	2.60 m
7	7.35 dd	7.34 dd	7.30 bdd
8	/	/	/
9	4.40 dd	4.39 bs	4.32 dd
10	/	/	/
11	4.33 d	4.32 d	4.29 d
12	/	/	/
13	5.97 dd	5.96 dd	5.94 d
14	7.16 ddd	7.15 m	7.13 ddd
15	2.21 m / 2.45 m	2.20 m / 2.44 m	2.20 dd / 2.45 m
16	2.45 m	2.44 m	2.45 m / 2.40 ddq
17	0.86 d	0.85 d	0.84 d

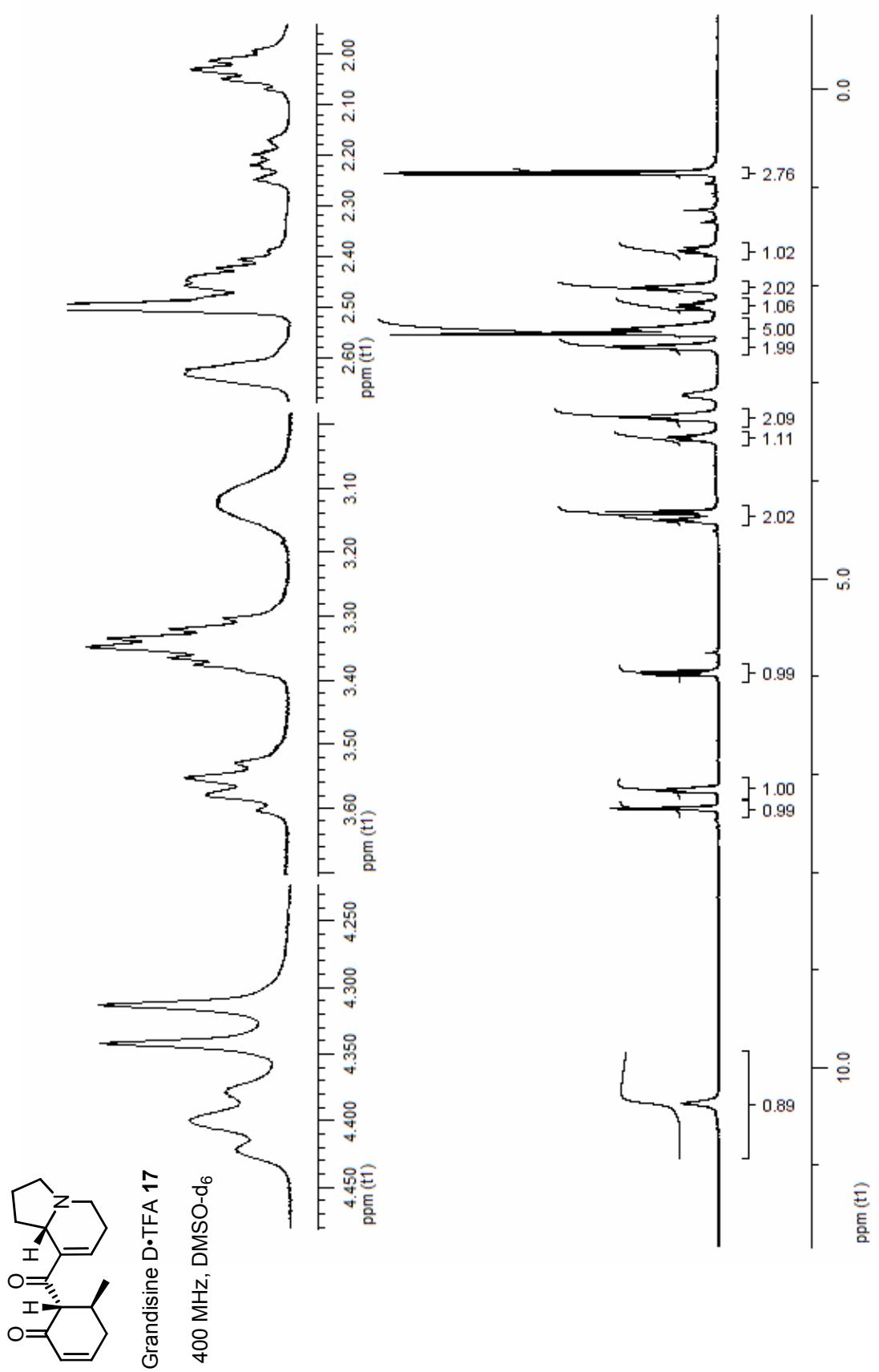
Atom	Synthetic (ppm) (d_6-DMSO, 100 MHz)	Tamura (ppm) (d_6-DMSO, 75 MHz)	Carroll (ppm) (d_6-DMSO, 100 MHz)
1	28.1	28.1	28.2
2	20.2	20.3	20.3
3	52.9	53.0	52.9
4	/	/	/
5	43.1	43.1	43.2
6	22.9	23.0	23.0
7	140.1	140.2	140.1
8	137.2	137.3	137.7
9	57.9	58.0	58.0
10	198.3	198.4	198.3
11	59.2	59.3	59.3
12	196.7	196.8	196.6
13	128.3	128.4	128.4
14	151.6	151.8	151.6
15	32.6	32.7	32.6
16	33.0	33.0	33.0
17	19.1	19.2	19.1

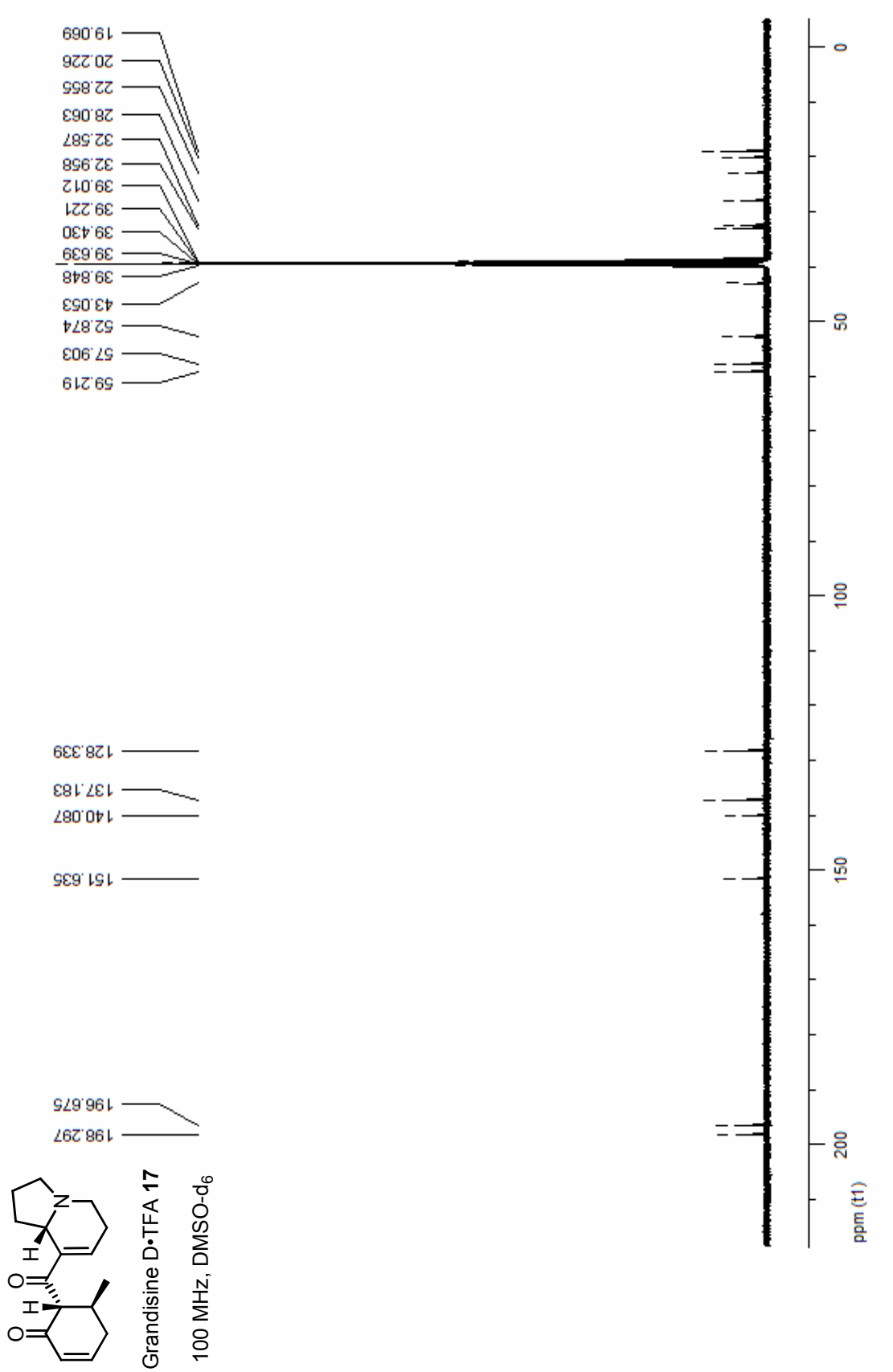
Appendix II. Comparison of $^{1}H/^{13}C$ Spectral Data for Grandisine B (15)

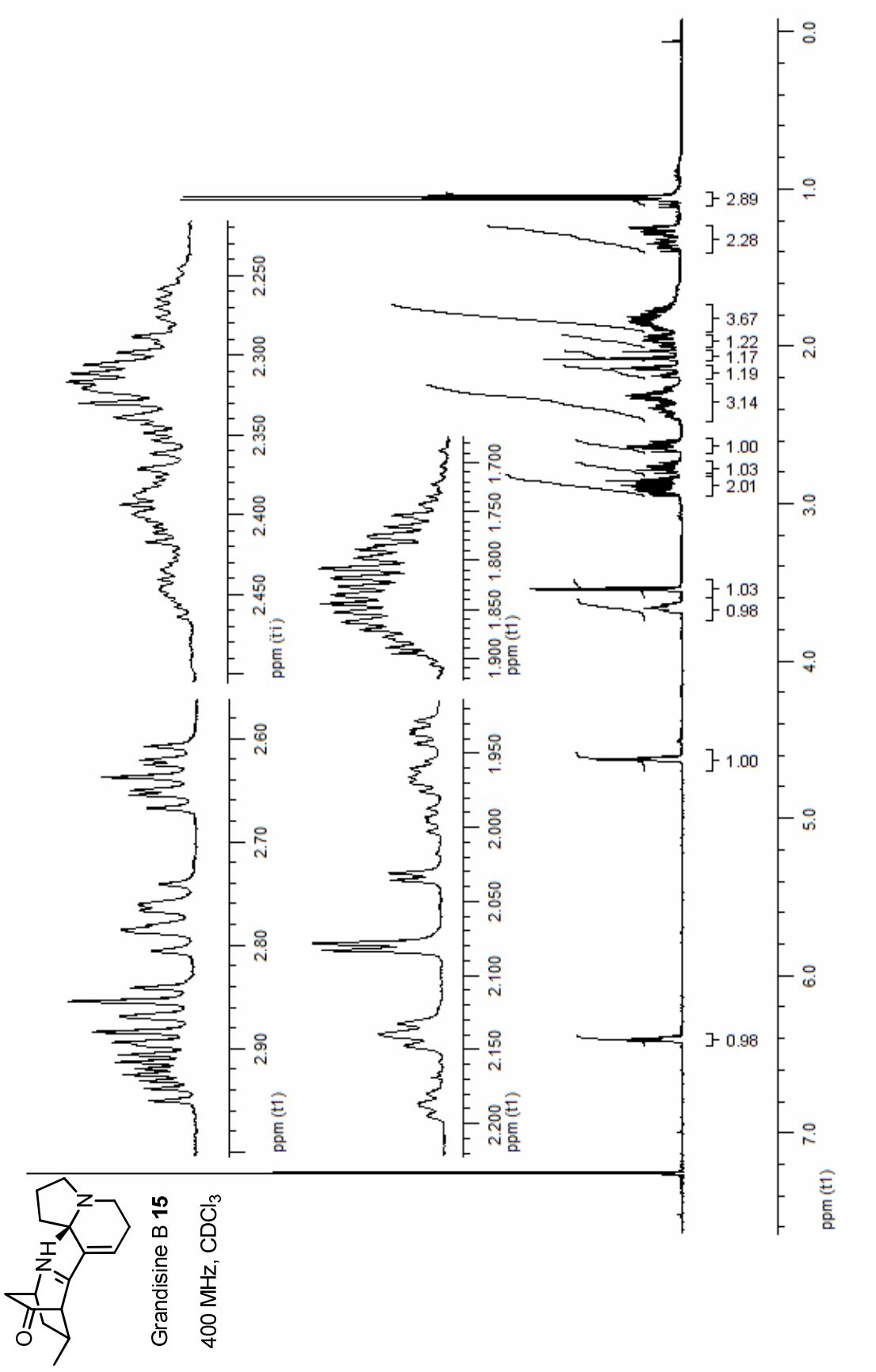


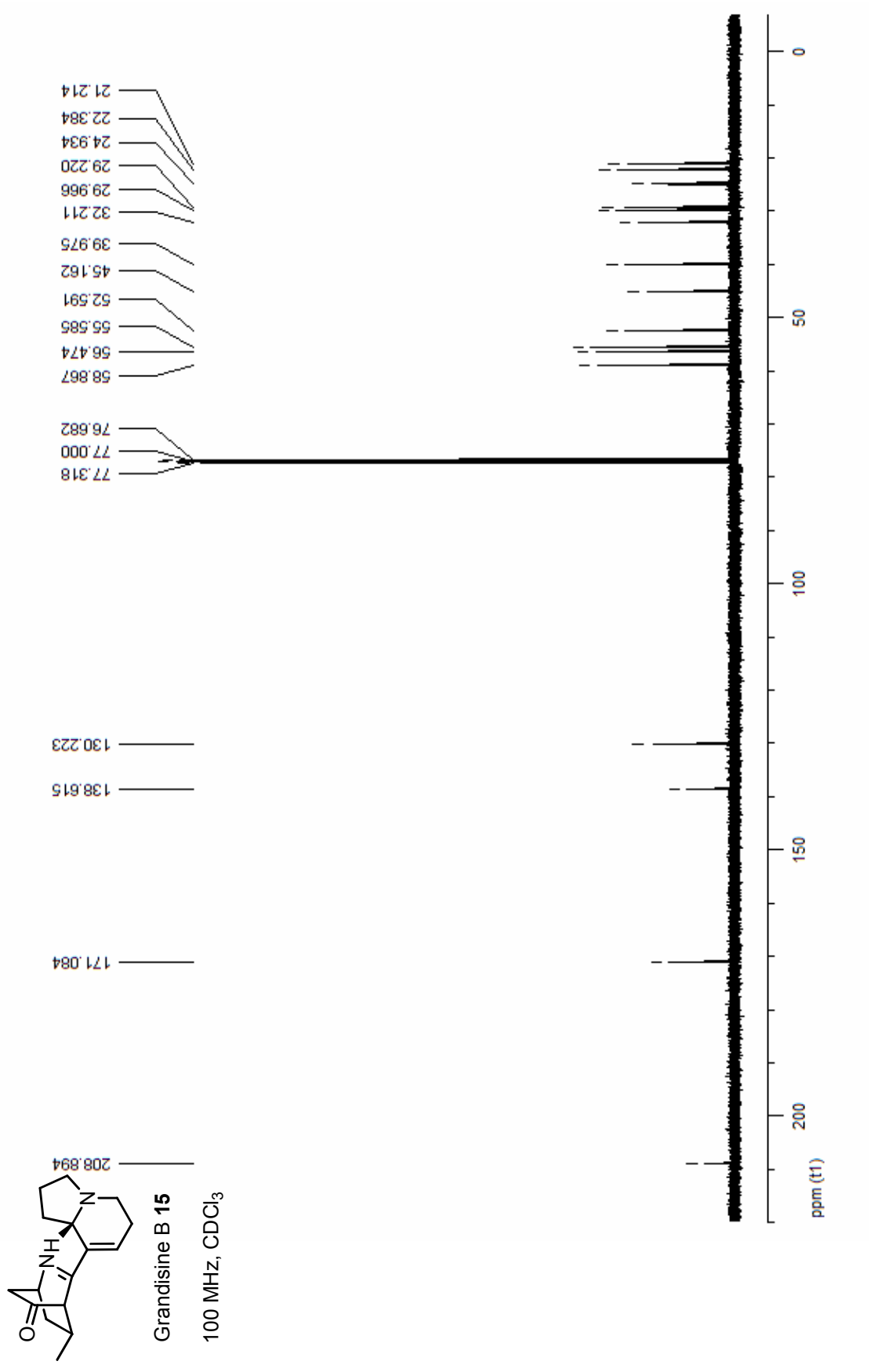
Atom	Synthetic (ppm) ($CDCl_3$, 400 MHz)	Tamura (ppm) ($CDCl_3$, 600 MHz)	Carroll (ppm) ($CDCl_3$, 600 MHz)
1	1.35 dddd / 2.30 m	1.34 m / 2.30 m	1.35 dddd / 2.30 m
2	1.80 m	1.80 m	1.76 m / 1.80 m
3	2.77 ddd / 2.92 ddd	2.8 m / 2.91 ddd	2.78 ddd / 2.92 ddd
4	/	/	/
5	2.64 ddd / 2.87 ddd	2.65 ddd / 2.86 ddd	2.64 ddd / 2.87 ddd
6	2.30 m / 2.41 m	2.30 m / 2.40 m	2.30 m / 2.40 m
7	6.41 ddd	6.40 ddd	6.40 s
8	/	/	/
9	3.66 m	3.69 m	3.67 dd
10	/	/	/
11	3.55 d	3.53 d	3.54 d
12	/	/	/
13	2.06 dd / 2.16 ddd	2.04 dd / 2.14 ddd	2.05 d / 2.16 bd
14	4.63 ddt	4.61 m	4.62 s
15	1.27 ddd / 1.96 m	1.25 ddd / 1.95 m	1.26 dd / 1.95 bdd
16	1.80 m	1.80 m	1.78 m
17	1.06 d	1.04 d	1.06 d

Atom	Synthetic (ppm) ($CDCl_3$, 100 MHz)	Tamura (ppm) ($CDCl_3$, 150 MHz)	Carroll (ppm) ($CDCl_3$, 150 MHz)
1	30.0	30.0	29.0
2	22.4	22.3	21.5
3	52.6	52.6	51.5
4	/	/	/
5	45.2	45.2	44.1
6	24.9	24.8	24.0
7	130.2	130.2	129.4
8	138.6	138.4	138.0
9	58.9	58.9	58.1
10	171.1	171.0	170.3
11	56.5	56.4	57.0
12	208.9	208.9	207.8
13	40.0	40.0	39.2
14	55.6	55.6	54.9
15	32.2	32.2	31.4
16	29.2	29.2	28.9
17	21.2	21.2	19.8

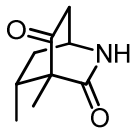

Grandisine D•TFA **17**
400 MHz, DMSO-d_6
4.450
4.400
4.350
4.300
4.250
3.60
3.50
3.40
3.30
3.20
3.10
2.60
2.50
2.40
2.30
2.20
2.10
2.00
ppm (t1)
2.76
1.02
2.02
1.06
5.00
1.99
2.09
1.11
2.02
0.99
1.00
0.99
0.89
10.0
5.0
0.0
ppm (t1)


19.069
20.226
22.855
28.063
32.587
32.958
39.012
39.221
39.430
39.639
39.848
43.053
52.874
57.903
59.219
128.339
137.183
140.087
151.635
196.675
198.297
0
50
100
150
200
ppm (t1)
Grandisine D•TFA 17
100 MHz, DMSO-d6


Grandisine B **15**
400 MHz, $CDCl_3$
ppm (t1)
2.89
2.28
3.67
1.22
1.17
1.19
3.14
1.00
1.03
2.01
1.03
0.98
1.00
0.98

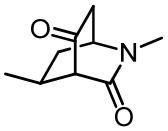

208.894
171.084
138.615
130.223
77.318
77.000
76.682
58.867
56.474
55.585
52.591
45.162
39.975
32.211
29.966
29.220
24.934
22.384
21.214
0
50
100
150
200
ppm (t1)
Grandisine B **15**
100 MHz, $CDCl_3$

Appendix VII. Crystallographic Data – Compound 252 (CCDC 789903)



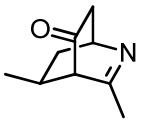
Identification code	2010src0766	
Empirical formula	$C_9H_{13}NO_2$	
Formula weight	167.20	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.60970(10) Å	α= 95.1970(10)°.
	b = 10.5480(3) Å	β= 91.371(2)°.
	c = 12.7041(3) Å	γ= 104.645(2)°.
Volume	852.41(3) $Å^3$	
Z	4	
Density (calculated)	1.303 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	360	
Crystal size	0.23 x 0.11 x 0.07 mm^3	
Theta range for data collection	3.19 to 27.67°.	
Index ranges	-8<=h<=8, -13<=k<=13, -16<=l<=16	
Reflections collected	14864	
Independent reflections	3919 [R(int) = 0.0378]	
Completeness to theta = 27.67°	98.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.994 and 0.910	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3919 / 0 / 229	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0451, wR2 = 0.1006	
R indices (all data)	R1 = 0.0526, wR2 = 0.1060	
Largest diff. peak and hole	0.340 and -0.213 $e.Å^{-3}$	

Appendix VIII. Crystallographic Data – Compound 255a (CCDC 789904)



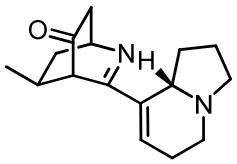
Identification code	rjt1007a	
Empirical formula	$C_9 H_{13} N O_2$	
Formula weight	167.20	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 6.9758(10) Å	α= 90°.
	b = 9.1944(13) Å	β= 90.960(3)°.
	c = 13.0978(19) Å	γ= 90°.
Volume	840.0(2) $Å^3$	
Z	4	
Density (calculated)	1.322 Mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	360	
Crystal size	0.39 x 0.14 x 0.11 mm^3	
Theta range for data collection	2.71 to 28.39°.	
Index ranges	-8<=h<=9, -12<=k<=12, -17<=l<=17	
Reflections collected	8378	
Independent reflections	2108 [R(int) = 0.0285]	
Completeness to theta = 28.39°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.990 and 0.792	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2108 / 0 / 111	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0414, wR2 = 0.1087	
R indices (all data)	R1 = 0.0462, wR2 = 0.1129	
Largest diff. peak and hole	0.394 and -0.157 e.$Å^{-3}$	

Appendix IX. Crystallographic Data – Compound 27·Picrate (CCDC 825975)



Identification code	rjt0906	
Empirical formula	$C_{15}H_{16}N_4O_8$	
Formula weight	380.32	
Temperature	120(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.50220(10) Å	α= 90°.
	b = 10.7807(2) Å	β= 90°.
	c = 23.3302(3) Å	γ= 90°.
Volume	1635.41(4) $Å^3$	
Z	4	
Density (calculated)	1.545 Mg/m^3	
Absorption coefficient	1.096 mm^{-1}	
F(000)	792	
Crystal size	0.30 x 0.12 x 0.07 mm^3	
Theta range for data collection	3.79 to 70.87°.	
Index ranges	-7<=h<=7, -12<=k<=12, -27<=l<=27	
Reflections collected	14408	
Independent reflections	3020 [R(int) = 0.0646]	
Completeness to theta = 70.87°	96.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.930 and 0.622	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3020 / 0 / 250	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0380, wR2 = 0.0943	
R indices (all data)	R1 = 0.0455, wR2 = 0.0987	
Absolute structure parameter	0.1(2)	
Largest diff. peak and hole	0.210 and -0.230 e.$Å^{-3}$	

Appendix X. Crystallographic Data for Compound 15·Dipicrate (CCDC 815228)



Identification code	rjt1010
Empirical formula	$C_{28}H_{28}N_8O_{15}$
Formula weight	716.58
Temperature / K	110.0
Crystal system	Monoclinic
Space group	$P2_1/n$
a / Å, b / Å, c / Å	7.0516(6), 17.5740(12), 24.3588(16)
α/°, β/°, γ/°	90.00, 95.553(7), 90.00
Volume / $Å^3$	3004.5(4)
Z	4
ρ_{calc} / mg mm^{-3}	1.584
μ / mm^{-1}	0.131
F(000)	1488
Crystal size / mm^3	0.2389 × 0.0855 × 0.0853
Theta range for data collection	2.86 to 25.05°
Index ranges	$-8 \le h \le 8$, $-20 \le k \le 20$, $-29 \le l \le 28$
Reflections collected	29380
Independent reflections	5329[R(int) = 0.0725]
Data/restraints/parameters	5329/6/485
Goodness-of-fit on F^2	0.960
Final R indexes [I>2σ (I)]	$R_1 = 0.0474$, $wR_2 = 0.1025$
Final R indexes [all data]	$R_1 = 0.0833$, $wR_2 = 0.1110$
Largest diff. peak/hole / e $Å^{-3}$	0.268/-0.189

A Tandem Amination/Lactamisation Route to 2-Azabicyclo[2.2.2]octanones

James D. Cuthbertson,[a] Andrew A. Godfrey,[b] Richard J. K. Taylor*[a]

[a] Department of Chemistry, University of York, Heslington, York YO10 5DD, UK
Fax +44(1904)434523; E-mail: rjkt1@york.ac.uk

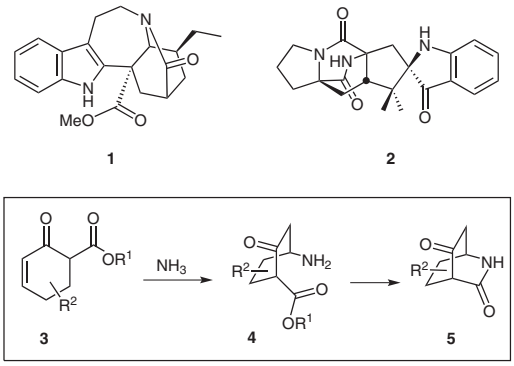
[b] AstraZeneca, Pharmaceutical Development, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NA, UK

Received 31 August 2010

Abstract: An efficient one-pot amination/lactamisation sequence for the preparation of 2-azabicyclo[2.2.2]octanones from 6-carboalkoxycyclohex-2-enones and aqueous ammonia is described. Scope and limitation studies are reported for this tandem procedure and a range of bicyclic compounds have been prepared, two of which were characterised by X-ray crystallography.

Key words: amination, lactamisation, azabicyclo[2.2.2]octanones, bicyclic compounds, 6-carboalkoxycyclohex-2-enones

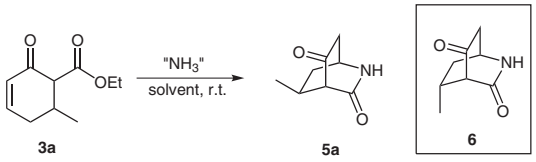
Functionalised 2-azabicyclo[2.2.2]octan-3-ones occur in a number of natural products such as 3-oxocoronaridine (**1**)[1] and brevianamide A (**2**; Scheme 1).[2] The best-described procedures for the preparation simple 2-azabicyclo[2.2.2]octan-3-ones involve the use of either Diels–Alder cycloaddition routes[3] or the thermal cyclisation of aminocyclohexane carboxylic acids.[4] We recently described an efficient method for preparing isoquinuclidinones from 6-acylcyclohex-2-enones using a tandem amination/imination sequence.[5] Herein we describe the application of a similar tandem procedure to prepare functionalised 2-azabicyclo[2.2.2]octane-3,5-diones **5** from 6-carboalkoxycyclohex-2-enones **3** as shown in Scheme 1. Thus, we envisaged that conjugate addition of ammonia into enones **3** would generate intermediate amino esters **4** which we expected to undergo intramolecular lactamisation to give the desired lactams **5**, possibly in a one-pot process.



Scheme 1

SYNLETT 2010, No. 18, pp 2805–2807
Advanced online publication: 12.10.2010
DOI: 10.1055/s-0030-1258811; Art ID: D23610ST

In order to establish the viability of this approach, we initially decided to examine the cyclisation of the known[6] methyl-substituted cyclohexenone **3a** (Scheme 2 and Table 1).



Scheme 2

Table 1 Conversion of Enone **3a** into 8β-Methyl-2-azabicyclo-[2.2.2]octane-3,5-dione (**5a**)[a]

Entry	NH_3 source	Co-solvent	Time (h)	Conv.[b]
1	2.0 M in IPA	–	24	<5%
2	35% aq	THF[c]	24	100%
3	35% aq	MeCN	6	100%
4	35% aq	MeOH	2	100%
5	35% aq	–	1	100%

[a] All reactions were performed on a 0.1 mmol scale; entries 2–5 were carried out using 35% aq NH_3 (0.25 mL) and solvent (0.5 mL).
[b] Conversion estimated by ^{1}H NMR spectroscopy.
[c] A similar result was observed using CH_2Cl_2 as solvent.

The first attempt was carried out using ammonia in isopropanol (IPA) but only a trace amount of 8β-methyl-2-azabicyclo[2.2.2]octane-3,5-dione (**5a**)[7] was observed, even after extended reaction times. On changing to 35% aqueous ammonia, success was achieved under a range of conditions (entries 2–5). When THF or dichloromethane were employed as co-solvents (entry 2), quantitative conversions were observed with a reaction time of 24 hours but the use of acetonitrile or methanol as co-solvent gave full conversion in just a few hours (entries 3 and 4). The optimum procedure, however, used 35% aqueous ammonia without a co-solvent and under these conditions the conversion was complete after one hour at room temperature (entry 5). All of the aqueous ammonia examples resulted in the formation of a single diastereomeric product which was confirmed as the desired methylated 2-azabicyclo[2.2.2]octane-3,5-dione **5a** by ^{1}H NMR/^{13}C NMR spectroscopy [characteristic bridgehead proton signals at

δ = 4.0 and 3.1 ppm; ^{13}C NMR signals at δ = 205.1 ppm (bridging ketone) and δ = 171.8 ppm (amide)]. This diastereomer was confirmed as the 8β-methyl isomer by NMR analysis and by X-ray crystallography of a crystalline derivative (see later), and the isomeric 8α-methyl isomer **6** was not observed; we assume that the 1,4-addition of ammonia occurs preferentially *anti* to the methyl substituent and that this is followed by in situ lactamisation.

Having confirmed the viability of the one-pot amination/lactamisation sequence, the scope of the transformation was investigated using a range of substrates (Table 2). First the required β-ketoesters **3** were prepared; substrate **3b** was prepared using a literature[8] procedure and the remaining substrates were obtained from cyclohexenones **7** by treatment with LDA in THF–DMPU followed by trapping with ethyl cyanoformate.

As can be seen, the tandem amination/lactamisation sequence was applicable to a range of substituted β-keto esters. The reactions generally proceeded rapidly to give the expected 2-azabicyclo[2.2.2]octane-3,5-diones **5** in good to excellent yields. The initial example giving the 8β-methyl product **5a** proceeded in 93% isolated yield (entry 1) and the corresponding process with a phenyl substituent (**3b** → **5b**) also proceeded smoothly and stereoselectively (entry 2). However, cyclisation was not observed when 3-methyl-6-carboethoxycyclohexenone (**3c**) was employed as starting material (entry 3), presumably substitution at the β-position of the enone disfavours the initial 1,4-addition of ammonia. Moving on to disubstituted enones (entries 4–6), 2-azabicyclo[2.2.2]octane-3,5-diones **5d**–**5f** were obtained bearing 7,7-, 6,8- and 4,8- substitution patterns in good to excellent yields. The successful cyclisation of the carvone-derived cyclohexenone (**3e** → **5e**; entry 5) indicated that the tandem amination/lactamisation sequence is compatible with substitution at the α-position of the cyclohexenone. Similarly, the successful formation of azabicyclo[2.2.2]octane **5f** (entry 6; structure confirmed by X-ray crystallography, Figure 1) illustrates that ammonia addition/cyclisation can occur on same face as methyl substituent (cyclisation is not possible from the *anti*-addition product due to the presence of the α-methyl substituent preventing ester epimerisation). In both of the latter examples (entries 5 and 6) longer reaction times were required for cyclisation to go to completion. Finally, in this part of the study, we investigated cyclisation of the parent unsubstituted cyclohexenone **3g** (entry 7); in this case the unpurified reaction mixture was slightly more complex but the required 2-azabicyclo-[2.2.2]octane-3,5-dione **5g** was isolated by column chromatography in 60% yield.

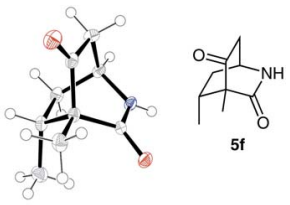
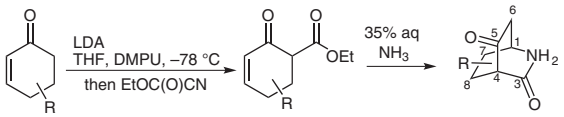
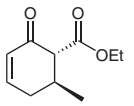
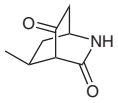
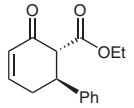
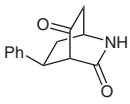
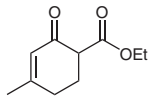
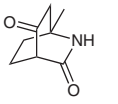
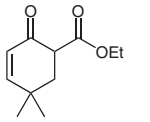
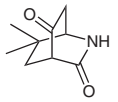
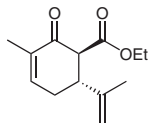
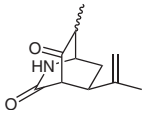
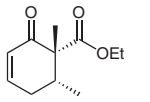
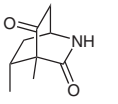
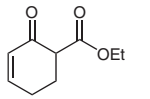
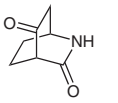


Figure 1 X-ray structure of compound **5f** depicted using ORTEP-3 (CCDC 789903)

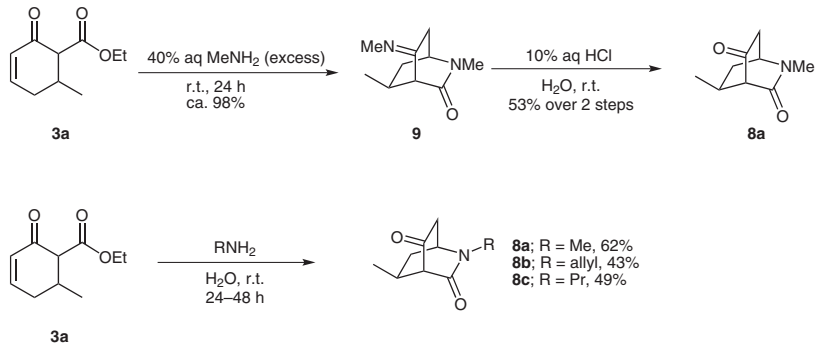
Table 2 Scope of Amination/Cyclisation Sequence[a]



Entry	Substrate **3**	Product **5**	Time (h)	Yield[b] (%)
1	 **3a**	 **5a**	2	93%[9]
2	 **3b**	 **5b**	2	76
3	 **3c**	 **5c**	24	0
4	 **3d**	 **5d**	2	83
5	 **3e**	 **5e**	24	98[c]
6	 **3f**	 **5f**	6	83
7	 **3g**	 **5g**	4	60

[a] All reactions were performed on a 0.25 mmol scale using 35% aq NH_3 (1.0 mL) at r.t.
[b] Isolated yields.
[c] Diastereomeric ratio ca. 4:1

Finally, we briefly explored the use of substituted amines in this process in order to directly prepare *N*-substituted 2-azabicyclo[2.2.2]octane-3,5-diones **8** (Scheme 3). First, the readily available enone **3a** was treated with excess aqueous methylamine. This procedure generated the ex-



Scheme 3

pected bicyclic product but, somewhat surprisingly in view of the ammonia reactions, led to the formation of the unstable imine **9** (characterised by NMR spectroscopy only). However, imine **9** could be readily hydrolysed with 10% aqueous HCl to afford the desired 2-azabicyclo-[2.2.2]octane **8a** in 53% overall yield.

Subsequently, it was found that the unwanted imine formation could be precluded by the use of a stoichiometric amount of methylamine giving adduct **8a** directly in 62% yield (Scheme 3). Similar reactions using allylamine and propylamine gave the corresponding *N*-alkyl-2-azabicyclo-[2.2.2]octane-3,5-diones **8b** and **8c** in fair yields. This process is susceptible to steric effects, however, and no cyclisation was observed when cyclohexenone **3a** was treated with *tert*-butylamine, anisidine or benzylamine. The structure of *N*-methyl 8β-methyl-2-azabicyclo-[2.2.2]octane-3,5-dione (**8a**) was confirmed by X-ray crystallography (Figure 2).

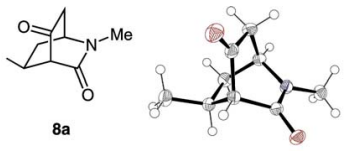


Figure 2 X-ray structure of compound **8a** depicted using ORTEP-3 (CCDC 789904)

In summary, an efficient tandem amination/lactamisation sequence has been developed for the preparation of 2-azabicyclo[2.2.2]octane-3,5-diones from 6-carboalkoxy-cyclohex-2-enones and aqueous ammonia. The scope and limitations of this methodology have been investigated and it has been extended to the direct preparation of some *N*-substituted 2-azabicyclo[2.2.2]octane-3,5-diones. Applications of the amination/lactamisation sequence in the synthesis of polycyclic alkaloids are currently under investigation.

Acknowledgment

We are grateful to the EPSRC and AstraZeneca for studentship support (J.D.C.).

References and Notes

(1) Perera, P.; Sandberg, F.; van Beek, T. A.; Verpoorte, R. *Phytochemistry* **1985**, *24*, 2097.
(2) Bringmann, G.; Lang, G.; Steffens, S.; Schaumann, K. *J. Nat. Prod.* **2004**, *67*, 311.
(3) (a) Brooke, G. M.; Matthews, R. S.; Robson, N. S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 102. (b) McClure, C. K.; Link, J. S. *J. Org. Chem.* **2003**, *68*, 8256.
(4) (a) Quirante, J.; Diaba, F.; Vila, X.; Bonjoch, J. *Magn. Reson. Chem.* **2005**, *43*, 599. (b) Gong, L.; Hogg, J. H.; Collier, J.; Wilhelm, R. S.; Soderberg, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3597.
(5) Cuthbertson, J. D.; Godfrey, A. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2010**, in press (http://dx.doi.org/10.1016/j.tetlet.2010.08.052).
(6) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635.
(7) All novel compounds were fully characterised by ^{1}H NMR, ^{13}C NMR, IR spectroscopies and by HRMS.
(8) Pietrusiewicz, K. M.; Monkiewicz, J. *J. Org. Chem.* **1983**, *48*, 788.
(9) **Typical Procedure for the Synthesis of 8β-Methyl-2-azabicyclo[2.2.2]octane-3,5-dione (5a)**: A solution of β-keto ester **3a** (46 mg, 0.25 mmol) in 35% aq NH_3 (1 mL) was stirred at r.t. until consumption of starting material was observed by TLC analysis (CH_2Cl_2–MeOH, 9:1), ca. 2 h. The reaction mixture was then concentrated in vacuo and purified by column chromatography (SiO_2, CH_2Cl_2–MeOH, 98:2) to give the title compound **5a** as a colourless crystalline sold (36 mg, 93%); mp 135–137 °C; R_f 0.40 (CH_2Cl_2–MeOH, 9:1). IR (thin film): 3244, 2961, 1730, 1681, 1335, 1105 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (br s, 1 H, NH), 3.93–3.98 (m, 1 H), 3.03–3.11 (m, 1 H), 2.40–2.49 (m, 2 H), 2.28–2.37 (m, 1 H), 2.20 (dd, *J* = 18.5, 1.9 Hz, 1 H), 1.31 (ddd, *J* = 13.0, 4.6, 1.0 Hz, 1 H), 1.06 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1 (CO), 171.8 (CO), 64.4 (CH), 47.0 (CH), 43.8 (CH_2), 35.4 (CH_2), 29.4 (CH), 20.8 (Me). MS: *m*/*z* (ESI) = 154 [MH]$^+$. HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_8H_{12}NO_2$: 154.0863; found: 154.0864 (0.6 ppm error).

Tetrahedron Letters 52 (2011) 2024–2027

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of isoquinuclidinones via a tandem amination/imination sequence: application to the synthesis of (−)-mearsine

James D. Cuthbertson [a], Andrew A. Godfrey [b], Richard J. K. Taylor [a,*]

[a] Department of Chemistry, University of York, Heslington, York YO10 5DD, UK
[b] AstraZeneca, Pharmaceutical Development, Silk Road Business Park, Macclesfield, Cheshire, SK10 2 NA, UK

ARTICLE INFO

Article history:
Available online 22 August 2010

Dedicated to Prof. Harry Wasserman in recognition of his many seminal achievements in organic chemistry and his friendship over numerous years of Tetrahedron Board Meetings.

Keywords:
Isoquinuclidinones
Mearsine
Tandem
Organocatalytic
2-Azabicyclo[2.2.2]octanes

ABSTRACT

The facile synthesis of a range of novel isoquinuclidinones from 6-acyl-cyclohex-2-enones is described, employing aqueous ammonia in a one-pot procedure involving initial conjugate addition of ammonia followed by cyclisation via intramolecular imine formation. The scope and limitations of the methodology are described as is an efficient synthesis of the *Elaeocarpus* alkaloid (−)-mearsine.

The development of new and improved routes to nitrogen-containing heterocycles represents an important and continuing challenge in organic chemistry,[1] due to the prevalence of such systems in natural products and pharmaceuticals/agrochemicals. Recently,[1b] we have become interested in naturally occurring isoquinuclidine alkaloids such as compounds **1–3** isolated from *Daphniphyllum*,[2] *Securinega*[3] and *Tabernaemontana*[4] species, respectively (Fig. 1). In turn, we were attracted to the rare isoquinuclidinone alkaloids mearsine **4**[5] and grandisine B **5**[6] which contain the unusual 2-azabicyclo[2.2.2]oct-2-en-5-one nucleus.

Functionalised 2-azabicyclo[2.2.2]octanes have previously been prepared via Diels–Alder cyclisations,[7] thermal cyclisations of 4-amino-cyclohexane carboxaldehyde derivatives,[8] double conjugate addition of aqueous ammonia into bifunctional Michael acceptors[9] and recently via cyclisation of silyl enol ethers onto iminium ions.[10] However, to our knowledge, there are no established methods for the direct preparation of 2-azabicyclo[2.2.2]oct-2-en-5-ones (i.e., containing both the ketone and imine functionalities). Retrosynthetic analysis as shown in Scheme 1, based on the biosynthetic proposal for mearsine put forward by Bick and co-workers,[5] suggested that the target compounds **6** might be accessed from 6-acyl-cyclohex-2-enones **8** by initial conjugate addition of ammonia to give the intermediate amine **7** which might then be expected to give the bicyclic system by intramolecular imine formation.

In this Letter, we describe the successful implementation of the tandem amination/imination route to isoquinuclidinones **6** as a one-pot process, and its application in natural product synthesis. Similar chemistry was utilised by Tamura and co-workers as part of their recent total synthesis of grandisine B **5**.[11]

Initial studies concentrated on the cyclisation of diketone **8a**, which bears the 5-methyl substituent found in mearsine **4** and grandisine B **5**. This was prepared (Scheme 2) by treatment of 5-methylcyclohexenone **9**[12] with LDA in THF at −78 °C and subsequent trapping with cyclohexane carboxaldehyde, followed by oxidation of the resulting β-hydroxy ketone **10**[13] using Dess–Martin periodinane. The novel 1,3-diketone **8a** exists as a mixture of diasteroisomers/tautomers, with the *trans*-diastereoisomer predominating.

With the desired 1,3-diketone **8a** in hand, we were in a position to investigate the proposed cyclisation sequence (Scheme 3). Upon treatment of diketone **8a** with 35% aqueous ammonia in methanol, rapid consumption of starting material was observed, with the formation of a single product. Isolation and analysis by $^{1}H/^{13}C$ NMR spectroscopy revealed the product to be the desired isoquinuclidinone **6a** [characteristic bridgehead proton signals at 4.5 and 3.2 ppm; ^{13}C NMR signals at 209.0 ppm (bridging ketone) and 179.7 ppm (imine)]. Compound **6a** was obtained in excellent yield

* Corresponding author. Tel.: +44 (0)1904 432606; fax: +44 (0)1904 434523.
E-mail address: rjkt1@york.ac.uk (R.J.K. Taylor).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.08.052

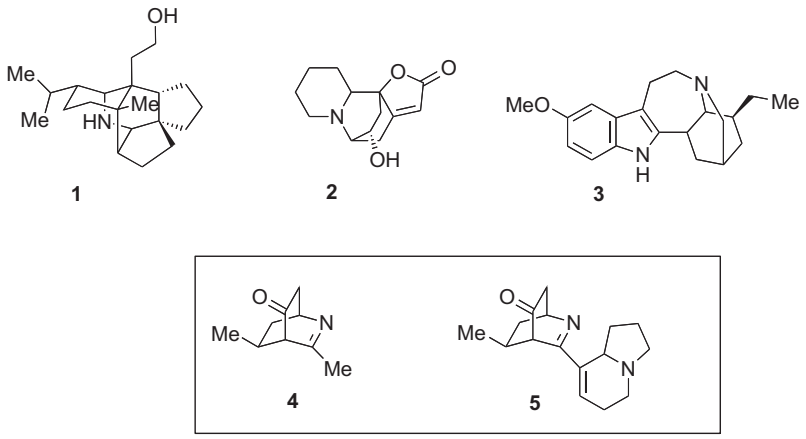
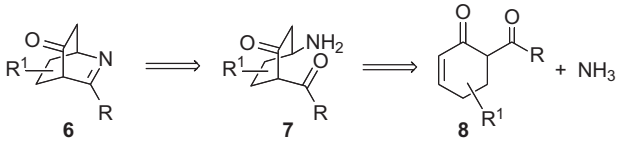


Figure 1. Isoquinuclidine and isoquinuclidinone alkaloids.



Scheme 1. Retrosynthetic analysis of isoquinuclidinone **6**.

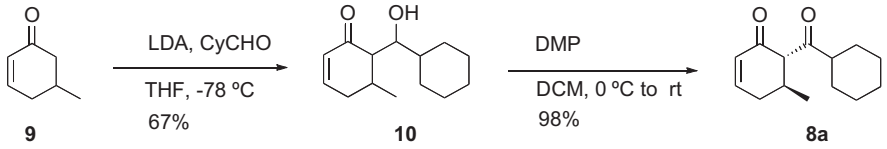
as a single diastereoisomer (8β-Me) and the isomeric compound **11** (8α-Me) was not observed. We assume that initial, reversible 1,4-addition of ammonia occurs followed by imine formation; presumably, some addition of ammonia *syn*-to the methyl group takes place but cyclisation to give **11** is unfavourable for steric reasons.

Having confirmed the viability of the proposed sequence, the scope of the reaction was investigated next utilising a range of substituted diketone substrates **8** (Table 1). The starting 1,3-diketones **8** were prepared from the corresponding cyclohexenones using the procedure outlined in Scheme 2.

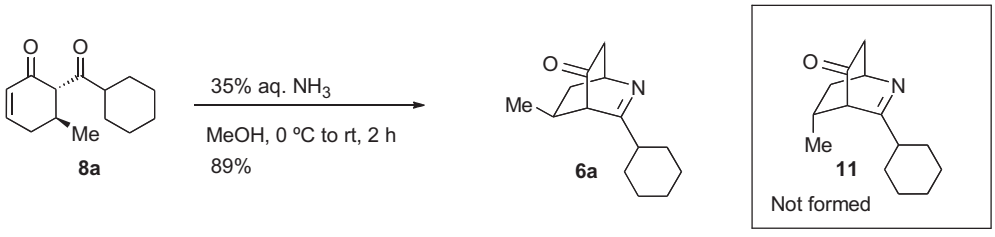
As can be seen, this tandem process was compatible with a range of aliphatic, aromatic and alkenyl substituents on the ketone (entries i–iv). However, on increasing the steric bulk of the substituents on the cyclohexenone ring, longer reaction times were required although the expected isoquinuclidinones **6e–g** were obtained in fair to excellent yield (entries v–vii). In the case of the 5-phenyl-cyclohexenone **8f**, a number of by-products were formed in addition to isoquinuclidinone **6f** (entry vi), and with the trisubstituted carvone-derived cyclohexenone **8g** the expected isoquinuclidinone **6g** was formed but a three-day reaction time was required (entry vii). In all cases, the reactions proceeded stereoselectively to give the 8β-substituted products exclusively.

Attempts were also made to prepare the 'unsubstituted' isoquinuclidinones **6h** and **6i** (Scheme 4). However, treatment of precursors **8h** and **8i** using the optimised reaction conditions did not produce the expected isoquinuclidinones **6h** and **6i** but instead gave clean conversion to the monocyclic methyl esters **12a** and **12b**. It seems likely that isoquinuclidinones **6h** and **6i** were formed but then underwent methoxide-induced ring-opening as illustrated in Scheme 4 to give compounds **13**.[15] We assume that the additional substitution around the isoquinuclidinone ring in compounds **6a–g** slows down this ring-opening process. The structural resemblance between esters **12** and the *Elaeocarpus* alkaloid grandisine G **13**, recently isolated by Carroll and co-workers,[16] should also be noted; it was proposed that grandisine G **13** results from the corresponding methanol-induced ring-opening of grandisine B **5**.[16]

In order to demonstrate the utility of this tandem amination/imination sequence, we utilised the procedure in a short total synthesis of (−)-mearsine **4** (Scheme 5). Mearsine was isolated in 1984 by Bick and co-workers from the Australian rainforest species *Peripentadenia mearsii*,[5] and subsequently the (+)-enantiomer of mearsine was synthesised from (+)-pulegone by Crouse and Pinder.[17] The first requirement was to prepare the requisite cyclohexenone **8j** and this was achieved prepared from 2,4-pentanedione and crotonaldehyde via an enantioselective, organocatalytic Michael addi-

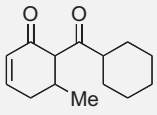
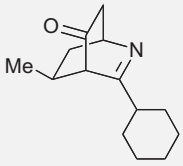
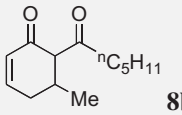
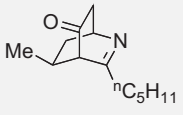
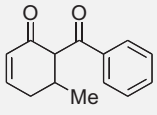
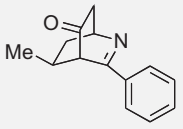
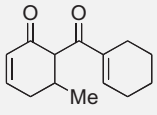
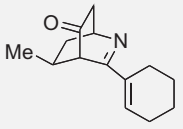
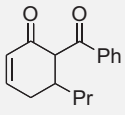
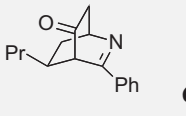
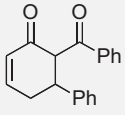
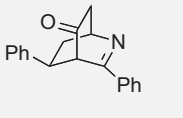
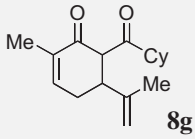
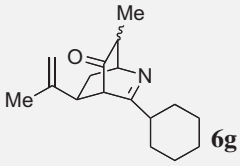


Scheme 2. Synthesis of cyclisation precursor 1,3-diketone **8a**.

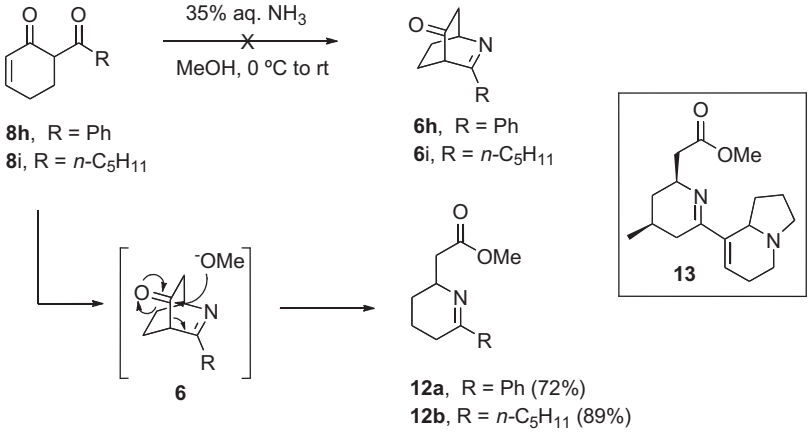


Scheme 3. Synthesis of isoquinuclidinone **6a** via amination/imination sequence.

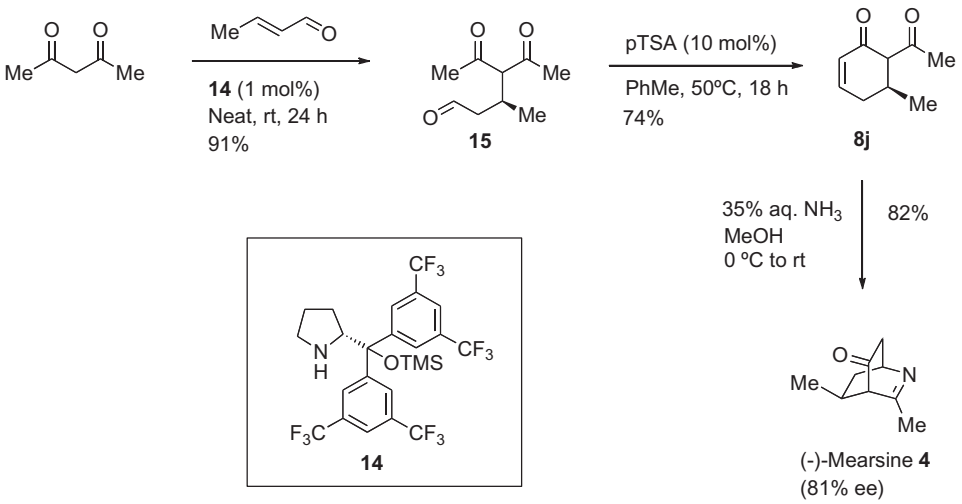
Table 1
Scope of amination/cyclisation sequence[a]

Entry	Substrate **8**	Product **6**	Time (h)	Yield[b] (%)
i	 **8a**	 **6a**	2	89
ii	 **8b**	 **6b**	2	65
iii	 **8c**	 **6c**	2	91
iv	 **8d**	 **6d**	2	80[c]
v	 **8e**	 **6e**	4	80
vi	 **8f**	 **6f**	8	~50%[d]
vii	 **8g**	 **6g**	72	75[e]

[a] All reactions were performed on 0.25 mmol scale using MeOH (1 mL), 35% aq NH_3 (0.5 mL) at 0 °C to rt.
[b] Isolated yields.
[c] Representative experimental procedure.[14]
[d] An inseparable mixture of **6f** (confirmed by ^{1}H NMR/HRMS) and by-products obtained; yield estimated using NMR spectroscopy.
[e] Dr = 3.4:1.



Scheme 4. Methoxide promoted ring-opening of isoquinuclidinone **6**.



Scheme 5. Synthesis of (−)-mearsine **4**.

tion[18] and subsequent aldol condensation. Thus, addition of 2,4-pentanedione to crotonaldehyde mediated by Jorgensen's catalyst **14** (1 mol %)[19] gave aldehyde **15** in 91% unpurified yield. Immediate treatment of the aldehyde **15** with pTSA (10 mol %) furnished the desired cyclohexenone **8j**, which was isolated as a complex mixture of diastereoisomers/tautomers. Treatment of diketone **8j** with 35% aqueous ammonia in methanol initiated the required tandem amination/imination sequence to produce (−)-mearsine **4** in 82% yield;[20] the melting point (mp 38–40 °C; lit.[5] 43–44 °C) and spectral data for the isolated product corresponded closely to those reported,[5,17] although there was a discrepancy in the optical rotation data {lit. $[\alpha]_D$ −34.5 (*c* 0.495, CH_2Cl_2);[5] synthetic **4**, $[\alpha]_D$ −252.6 (*c* 0.51, CH_2Cl_2)}. For this reason, chiral HPLC analysis (Phenomenex Lux Cellulose-2 column, 95:5 *iso*-hexane/EtOH, flow rate 1.0 mL/min) was performed which confirmed that the enantiomeric ratio was 90.5:9.5, and conclusive evidence for the structure and relative stereochemistry of synthetic **4** was provided by single crystal X-ray analysis of the picrate salt (mp 208–210 °C dec; lit.[5] mp 212–213 °C).

In summary, a tandem amination/imination route has been developed to convert 6-acyl-cyclohex-2-enones **8** into isoquinuclidinones **6** in a one-pot process.

The scope and limitations of the methodology have been investigated, and the utility of the sequence has been demonstrated with an efficient synthesis of the alkaloid (−)-mearsine (the first synthesis of the (−)-enantiomer). Applications of this new tandem methodology in the preparation of more complex natural product targets are currently underway.

Acknowledgements

We are grateful to the EPSRC and AstraZeneca for studentship support (JDC).

References and notes

1. (a)*Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ed.; Elsevier, 2008; Vols. 1–15, For recent publications in this area from our group see: (b) Pugh, D. S.; Klein, J. E. M. N.; Perry, A.; Taylor, R. J. K. *Synlett* **2010**, 934–938; Catozzi, N.; Edwards, M. G.; Raw, S. A.; Wasnaire, P.; Taylor, R. J. K. *J. Org. Chem.* **2009**, *74*, 8343–8354; Millemaggi, A.; Perry, A.; Whitwood, A. C.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2009**, 2947–2952; Donald, J. R.; Taylor, R. J. K. *Synlett* **2009**, 59–62; Bromley, W. J.; Gibson, M.; Lang, S.; Raw, S. A.; Whitwood, A. C.; Taylor, R. J. K. *Tetrahedron* **2007**, *63*, 6004–6014.
2. Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936–962.
3. Weinreb, S. *Nat. Prod. Rep.* **2009**, *26*, 758–775.
4. de Souza, J. J.; Mathias, L.; Braz-Filho, R.; Vieira, I. J. C. *Helv. Chim. Acta* **2010**, *93*, 422–429.
5. Robertson, G. B.; Tooptakong, U.; Lamberton, J. A.; Geewananda, Y. A.; Gunawardana, P.; Bick, I. R. C. *Tetrahedron Lett.* **1984**, *25*, 2695–2696; Lamberton, J. A.; Geewananda, Y. A.; Gunawardana, P.; Bick, I. R. C. *J. Nat. Prod.* **1983**, *46*, 235–247.
6. Carroll, A. R.; Arumugan, G.; Quinn, R. J.; Redburn, J.; Guymer, G.; Grimshaw, P. *J. Org. Chem.* **2005**, *70*, 1889–1892.
7. Brooke, G. M.; Matthews, R. S.; Robson, N. S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 102–106; Babu, G.; Perumal, P. T. *Tetrahedron* **1998**, *54*, 1627–1638; McClure, C. K.; Link, J. S. *J. Org. Chem.* **2003**, *68*, 8256–8257; Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877–4880; Yang, H.; Carter, R. G. *J. Org. Chem.* **2009**, *74*, 5151–5156.
8. Quirante, J.; Diaba, F.; Vila, X.; Bonjoch, J. *Magn. Reson. Chem.* **2005**, *43*, 599–601.
9. Rassat, A.; Rey, P. *Tetrahedron* **1972**, *28*, 741–750.
10. Larouche-Gauthier, R.; Bélanger, G. *Org. Lett.* **2008**, *10*, 4501–4504.
11. Kurasaki, H.; Okamoto, I.; Morita, N.; Tamura, O. *Chem. Eur. J.* **2009**, *15*, 12754–12763.
12. Fuchs, P. L.; Musser, A. K. *J. Org. Chem.* **1982**, *47*, 3121–3131.
13. All novel compounds were fully characterised by $^1H/^{13}C$ NMR spectroscopy, IR spectroscopy and HRMS.
14. *Representative experimental procedure*: To a stirred solution of diketone **8d** (55 mg, 0.25 mmol) in MeOH (1 mL) at 0 °C was added dropwise 35% aqueous NH_3 (0.5 mL). The resulting yellow solution was held at 0 °C for 30 min, then warmed to rt with stirring until consumption of starting material was observed by TLC analysis (DCM/MeOH, 95:5). The reaction mixture was then diluted with water (5 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and then concentrated in vacuo to afford a colourless oil which was purified by column chromatography (SiO_2, DCM/MeOH, 98:2) to give isoquinuclidinone **6d** (44 mg, 80%) as a colourless oil R_f 0.49 (DCM/MeOH, 95:5); ν_{max}/cm^{-1} (neat) 2930, 2868, 1731, 1576, 1340; δ_H (400 MHz, $CDCl_3$) 6.41 (1H, m), 4.60 (1H, dddd, *J* = 3.6, 3.6, 1.8, 1.8), 3.62 (1H, d, *J* = 3.1), 2.30–2.25 (2H, m), 2.21–2.15 (2H, m), 2.12 (1H, dm, *J* = 19.0), 2.02 (1H, dd, *J* = 19.0, 1.8), 2.01–1.93 (1H, m), 1.91–1.81 (1H, m), 1.67–1.54 (4H, m), 1.24 (1H, ddd, *J* = 12.8, 4.4, 1.8), 1.03 (3H, d, *J* = 7.0); δ_C (100 MHz, $CDCl_3$) 209.2 (CO), 172.2 (CN), 135.3 (C), 133.0 (CH), 55.8 (CH), 55.6 (CH), 39.8 (CH_2), 32.7 (CH_2), 29.2 (CH), 26.0 (CH_2), 24.0 (CH_2), 22.1 (CH_2), 21.8 (CH_2), 21.3 (CH_3); *m/z* (ESI) 218 $[MH]^+$; [HRMS (ESI): calcd for $C_{14}H_{20}NO$, 218.1539; found: MH^+, 218.1540 (0.4 ppm error)].
15. Lowering the reaction temperature or reducing the reaction time failed to prevent the undesired ring opening but instead gave incomplete conversion of the starting material.
16. Katavic, P. L.; Venables, D. A.; Forster, P. I.; Guymer, G.; Carroll, A. R. *J. Nat. Prod.* **2006**, *69*, 1295–1299.
17. Crouse, J. R.; Pinder, A. R. *J. Nat. Prod.* **1989**, *52*, 1227–1230.
18. Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628–13630.
19. Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797.
20. (−)-*Mearsine* **4**: R_f 0.45 (DCM/MeOH, 9:1); ν_{max}/cm^{-1} (neat) 2957, 1729, 1633, 1379; δ_H (400 MHz, $CDCl_3$) 4.50 (1H, dddd, *J* = 3.5, 3.5, 1.9, 1.9), 3.13 (1H, d, *J* = 2.9), 2.17–2.08 (1H, m), 2.12 (3H, s), 2.01 (1H, dd, *J* = 19.0, 1.8), 1.97 (2H, m), 1.22 (1H, m), 1.04 (3H, d, *J* = 6.9); δ_C (100 MHz, $CDCl_3$) 208.4 (CO), 173.7 (CN), 61.4 (CH), 55.5 (CH), 39.5 (CH_2), 32.4 (CH_2), 28.8 (CH), 24.5 (CH_3), 21.0 (CH_3); *m/z* (ESI) 152 $[MH]^+$; [HRMS (ESI): calcd for $C_9H_{14}NO$, 152.1070; found: MH^+, 152.1070 (0.1 ppm error)]; HPLC Analysis [Phenomenex Lux Cellulose-2 column, 95:5 *iso*-hexane/EtOH, flow rate 1.0 mL/min; R_T = 9.51 (minor, 9.5%) and 10.62 (major, 90.5%)]. Picrate salt mp 208–210 °C dec (lit.[5] mp 212–213 °C).

ORGANIC LETTERS

2011
Vol. 13, No. 15
3976–3979

The Preparation of (−)-Grandisine B from (+)-Grandisine D; A Biomimetic Total Synthesis or Formation of an Isolation Artefact?

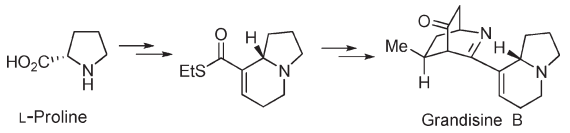
James D. Cuthbertson,[†] Andrew A. Godfrey,[‡] and Richard J. K. Taylor*[,†]

Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K., and AstraZeneca, Chemical Sciences, Pharmaceutical Development, Silk Road Business Park, Charter Way, Macclesfield, Cheshire SK10 2NA, U.K.

rjkt1@york.ac.uk

Received June 2, 2011

ABSTRACT



An efficient new alkyne-acetal cyclization procedure has been developed to prepare enantiopure indolizidine building blocks from L-proline and then applied to prepare the *Elaeocarpus*-derived alkaloids grandisine B and grandisine D in an efficient manner. However, evidence is presented which indicates that grandisine B does not occur naturally but is formed by reaction of grandisine D with ammonia during the extraction/purification process.

The *Elaeocarpaceae* plant family has been the source of numerous, structurally diverse alkaloids over the years.[1] Carroll and co-workers recently reported the isolation of the *Elaeocarpus*-derived indolizine alkaloids grandisines A **1** and B **2** (Figure 1) from the Australian rainforest tree *Elaeocarpus grandis* as part of a high throughput drug discovery program.[2a] Subsequently, further studies revealed the presence of five additional members of this family, grandisines C−G (**3**−**7**).[2b] These indolizidine alkaloids have attracted considerable attention as they display human δ-opioid receptor affinity.[2] First, Danishefsky and Maloney reported a total synthesis of (+)-grandisine A **1**,[3] and then Tamura's group published a total synthesis of (+)-grandisine D **4** (as its TFA salt).[4] Most recently, the latter group reported the conversion of grandisine B **2** into grandisine D **4** by the double addition of ammonia[5] (following the biosynthetic proposal by Carroll[2]).

Our interest also focused on grandisine B **2**, particularly in view of its structural novelty; it contains an unprecedented combination of both indolizidine and isoquinuclidinone units linked by a C_{sp^2}−C_{sp^2} bond. Although many indolizidine alkaloids have been isolated,[6] isoquinuclidinone alkaloids are very rare indeed. In fact, mearsine **8**,[7,8] isolated from another member of the *Elaeocarpaceae* family, *Peripentadenia mearsii*, appears to be the only other published example. We recently reported a facile route to a range of isoquinuclidinones from 6-acyl-cyclohex-2-enones, employing aqueous ammonia in a one-pot tandem amination/imination procedure, and applied this

[†] University of York.
[‡] AstraZeneca.

(1) Johns, S. R.; Lamberton, J. A. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1993; Vol. 14, p 324.
(2) (a) Carroll, A. R.; Arumugan, G.; Quinn, R. J.; Redburn, J.; Guymer, G.; Grimshaw, P. *J. Org. Chem.* **2005**, *70*, 1889. (b) Katavic, P. L.; Venables, D. A.; Forster, P. I.; Guymer, G.; Carroll, A. R. *J. Nat. Prod.* **2006**, *69*, 1295.
(3) Maloney, D. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7789.
(4) Kurasaki, H.; Okamoto, I.; Morita, N.; Tamura, O. *Org. Lett.* **2009**, *11*, 1179.
(5) Kurasaki, H.; Okamoto, I.; Morita, N.; Tamura, O. *Chem.—Eur. J.* **2009**, *15*, 12754.
(6) For a recent review, see: Michael, J. P. *Beilstein J. Org. Chem.* **2007**, *3*, 27.
(7) Robertson, G. B.; Tooptakong, U.; Lamberton, J. A.; Geewananda, Y. A.; Gunawardana, P.; Bick, I. R. C. *Tetrahedron Lett.* **1984**, *25*, 2695.
(8) Crouse, J. R.; Pinder, A. R. *J. Nat. Prod.* **1989**, *52*, 1227.

10.1021/ol2014939
Published on Web 06/30/2011

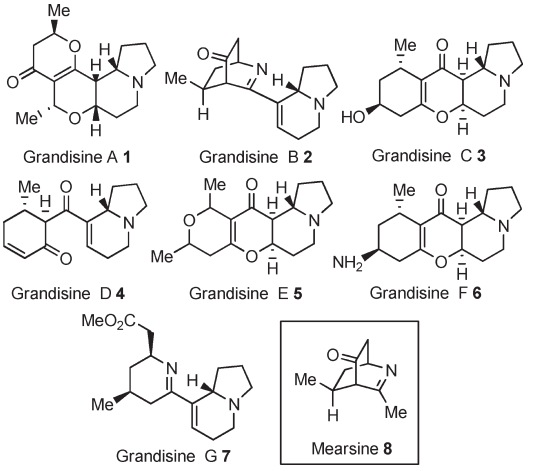


Figure 1. Structure of grandisines and mearsine.

methodology as part of an efficient synthesis of (−)-mearsine **8**.[9] Herein, we report an efficient new route to grandisine D **4** and its conversion into grandisine B **2** (with confirmation by X-ray crystallography); we also discuss the likely nonbiological origin of grandisine B **2**.

Our retrosynthetic approach is illustrated in Figure 2. Disconnection of the isoquinuclidinone moiety of grandisine B **2** by an imination/amination sequence *via* amine **9** leads back to grandisine D **4**. The use of an aldol/oxidation sequence involving enolate **10** derived from (*S*)-5-methylcyclohexenone[10] then leads to the requirement for indolizidine **11**.

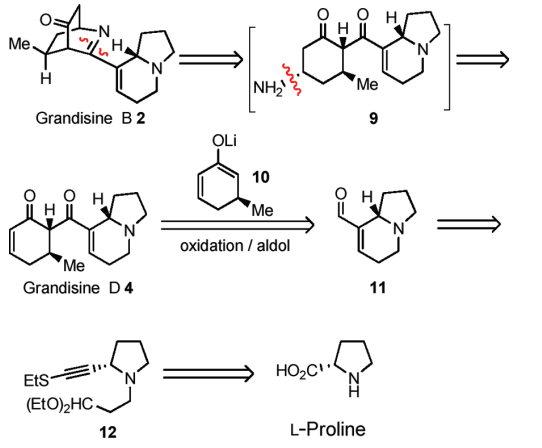
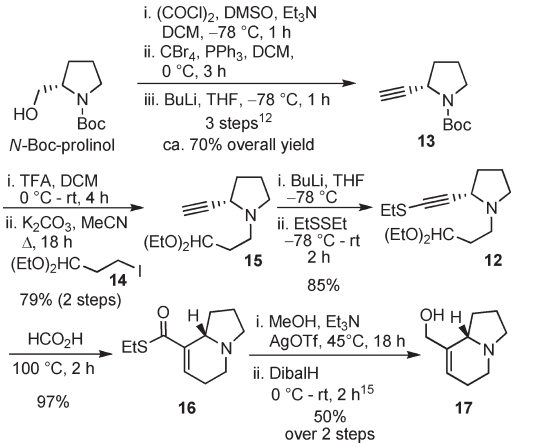


Figure 2. Retrosynthetic analysis of grandisine B **2**.

Given the recent interest in the cyclization reactions of alkynyl aldehydes/acetals,[11] we envisaged preparing **11** utimately from alkyne **12** which we felt would be readily accessible from L-proline.

Scheme 1. Synthesis of Indolizidine Alcohol **17**



The preparation of the key indolizidine building block is shown in Scheme 1. Thus, alkyne **13** was readily accessed on a multigram scale from commercially available *N*-Boc-prolinol in *ca.* 70% overall yield (3 steps) using known procedures.[12] Boc deprotection followed by *N*-alkylation with iodo-acetal **14** proceeded readily to afford acetal **15** in 79% yield over the two steps. Thioalkynes are known to undergo hydration in acidic media to afford the corresponding thioester,[13] and therefore, deprotonation of alkyne **15** with *n*-butyllithium and trapping with ethyl disulfide afforded the cyclization precursor **12** in 85% yield. Pleasingly, on heating a solution of thioalkyne **12** in formic acid,[14] clean cyclization was observed giving thioester **16** as the sole product and as a single enantiomer {$[\alpha]_D$ −87 (*c* 0.97, $CHCl_3$)}. This is an extremely efficient route (7 steps from *N*-Boc-prolinol, *ca.* 50% overall, unoptimised yield) which appears to be simple, robust, and scaleable. In order to prepare the desired allylic alcohol **17**, thioester **16** was converted into the corresponding methyl ester and then reduced using DibalH[15] (direct reduction of the thioester proved problematic).

(9) Cuthbertson, J. D.; Godfrey, A. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2011**, *52*, 2024. See also: Cuthbertson, J. D.; Godfrey, A. A.; Taylor, R. J. K. *Synlett* **2010**, 2805.

(10) (a) (*S*)-5-Methylcyclohexenone is available via a number of procedures; see: Carpenter, R. D.; Fettinger, J. C.; Lam, K. S.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6407 and ref 10b for lead references. (b) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jorgensen, K. A. *Chem. Commun.* **2006**, 4928.

(11) (a) Gonzalez-Rodriguez, C.; Escalante, L.; Varela, J. A.; Castedo, L.; Saa, C. *Org. Lett.* **2009**, *11*, 1531. (b) Xu, T.; Yang, Q.; Yu, Z.; Li, D.; Dong, J.; Li, Y. *Chem.—Eur. J.* **2010**, *16*, 9264 and references therein.

(12) Paul, A.; Bitterman, H.; Gmeiner, P. *Tetrahedron* **2006**, *62*, 8919 and references therein.

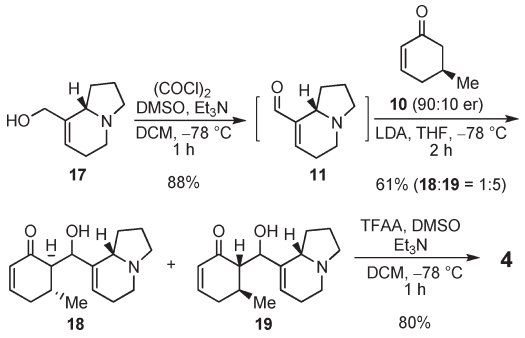
(13) Maruyama, H.; Shiozaki, M.; Oida, S. *Tetrahedron Lett.* **1985**, *26*, 4521.

(14) Menashe, N.; Shvo, Y. *J. Org. Chem.* **1993**, *58*, 7434.

(15) Cordero, F. M.; Anichini, B.; Goti, A.; Brandi, A. *Tetrahedron* **1993**, *49*, 9867.

We were now in a position to explore the final steps of the grandisine synthesis (Scheme 2). Swern oxidation of alcohol **17** gave aldehyde **11** which was reacted with the lithium enolate derived from (*S*)-5-methyl-cyclohexenone **10** (90:10 er; obtained from *tert*-butyl acetoacetate and crotonaldehyde by an organocatalytic procedure).[10b] This aldol reaction produced allylic alcohol **19** along with the diastereoisomer **18** derived from (*R*)-5-methyl-cyclohexenone, which was readily removed by chromatography. Alcohol **19** was obtained as a single diastereomer, tentatively assigned as the *trans*-isomer about the ring. Oxidation using Swern conditions gave grandisine D **4** in 80% yield {$[\alpha]_D$ +73.7 (*c* 0.1, MeOH); published values: $[\alpha]_D$[2] +34.6 (*c* 0.09, MeOH); $[\alpha]_D$[4,5] +65.7 (*c* 0.09, MeOH)}. Compound **4** was assigned as the *trans*-isomer, as evidenced by the large coupling constant (11.5 Hz) although minor traces of the enol tautomer/*cis*-isomer were also observed in the ^{1}H NMR spectrum.

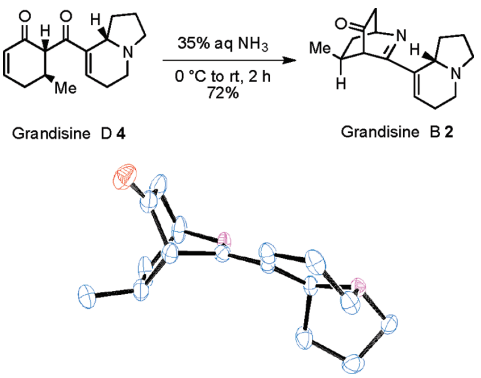
Scheme 2. Synthesis of Grandisine D **4**



With grandisine D **4** in hand, we were in a position to investigate the one-pot tandem amination/imination sequence to generate grandisine B **2** (Scheme 3). This reaction had also been utilized by Tamura's group in their studies.[5] Upon treatment of diketone **4** with 35% aq ammonia, the target compound **2** was obtained stereoselectively in 72% yield; key spectroscopic data were consistent with those published (see Supporting Information). The isolation paper[2] and the publication by Tamura et al.[5] were inconsistent concerning the optical rotation data {$[\alpha]_D$ +11 (*c* 0.1, CH_2Cl_2)[2]; $[\alpha]_D$ −159 (*c* 0.08, CH_2Cl_2)[5]}. Our sample had $[\alpha]_D$ −177.5 (*c* 0.08, CH_2Cl_2), which agreed well with Tamura's value. A further indication of the purity was that compound **2**, as its dipicrate salt, was readily crystallized and, for the first time, an X-ray crystal structure was obtained which fully confirmed the published structure (Scheme 3).

On close reading of the original publications describing the isolation of grandisine B, our attention was drawn to the extraction conditions: "The aqueous layer (400 mL) was basified with 27% NH_4OH (2 × 200 mL) and

Scheme 3. Synthesis of Grandisine B **2**[a]



[a] X-ray structure of compound **2**·(picric acid)$_2$ depicted using ORTPE-3 (CCDC 815228); picrate anions omitted for clarity.

partitioned with CH_2Cl_2."[2] These conditions were extremely close to the ones we had employed for the conversion of grandisine D **4** into grandisine B **2**; we therefore conjectured about the origin of grandisine B **2**. One distinct possibility appeared to be that grandisine D **4** is a true natural product but that on extraction using ammonia it is converted into grandisine B **2**. If true, then grandisine B **2** is not a natural product and is actually an artefact of the extraction procedure.[16] To gain greater understanding, we contacted Professor Carroll who replied stating "Yes, we have certainly speculated about whether some of these compounds might be artefacts of the extraction and purification process. Grandisines B, F, and G in particular are not observed by (+) ESI MS in crude methanol extracts of the leaves suggesting that these compounds at least are artefacts formed on treatment with ammonia." It would therefore appear that grandisine B **2** is not naturally occurring but is formed by reaction of grandisine D **4** with ammonia during the extraction/purification process.

In summary, an efficient new alkyne cyclization procedure has been developed to prepare enantiopure indolizidine building blocks from L-proline. Using this methodology, the natural product grandisine D **4** has been prepared in an efficient manner (9 steps, 14% overall yield from the known alkynyl-pyrrolidine **13**; 13 steps, 10% overall yield from prolinol); this route compares well with the procedure recently published by Tamura et al. (15 steps, 12% overall yield from (*S*)-malic acid).[4]

In addition, a tandem imination/amination sequence has been employed for the assembly of the isoquinuclidinone moiety in the conversion of grandisine D **4** into grandisine B **2** (and the first X-ray of grandisine B as its dipicrate salt has been obtained). Perhaps most

(16) For other examples of ammonia-induced artefact formation during the isolation of natural products, see: (a) Wenkert, E.; Fuchs, A.; McChesney, J. D *J. Org. Chem.* **1965**, *30*, 2931 (rosmaricine). (b) Suliman, M.; Martin, M. -T.; Pais, M.; Hadi, H. A.; Awang, K. *Phytochem.* **1998**, *49*, 2192 (desmosine).

significantly, evidence is presented which indicates that grandisine B **2** does not occur naturally but is formed by reaction of grandisine D **4** with ammonia during the extraction/purification process.

Acknowledgment. We are grateful to the EPSRC and AstraZeneca for studentship support (J.D.C.) and to Professor Tony Carroll (Griffith University, Brisbane, Australia) for valuable discussions.

Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all novel compounds. Crystallographic data for **2** (CCDC815228). This material is available free of charge via the Internet at http://pubs.acs.org.

HETEROCYCLES, Vol. 84, 2012, pp. -. © The Japan Institute of Heterocyclic Chemistry
Received, 8th July, 2011, Accepted, 1st August, 2011, Published online,
DOI: 10.3987/COM-11-S(P)79

ALKYNE-ACETAL CYCLISATION REACTIONS MEDIATED BY FORMIC ACID; 3-ACYLATED-2,5-DIHYDROFURANS AND RELATED OXYGEN AND NITROGEN HETEROCYCLES

James D. Cuthbertson,[a] Andrew A. Godfrey,[b] William P. Unsworth,[a] and Richard J. K. Taylor[a*]

[a]Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K. Tel: +44-(0)1904-322606; Fax: +44-(0)1904-324523; E-mail: richard.taylor@york.ac.uk

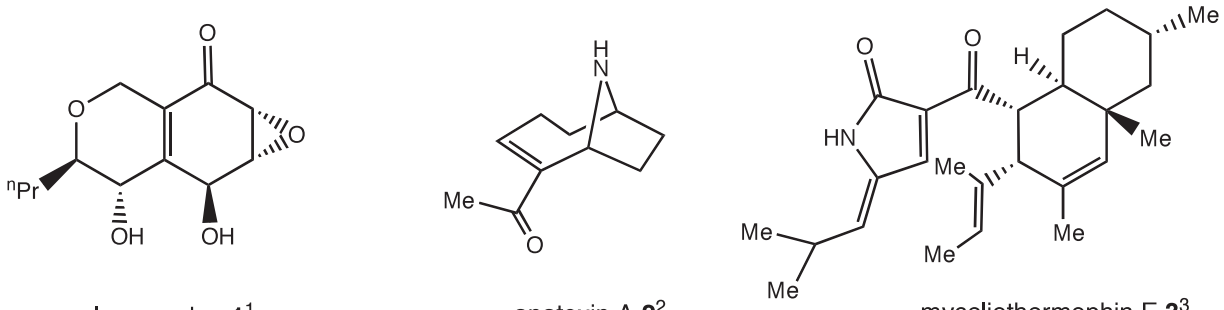
[b]AstraZeneca, Chemical Sciences, Pharmaceutical Development, Silk Road Business Park, Macclesfield, Cheshire, SK10 2 NA, U.K.

Abstract – The utility of formic acid for the cyclisation of alkyne ω-acetals is described; the scope and limitations of this process are outlined and a range of acylated heterocyclic building blocks (2,5-dihydrofurans, 2,5-dihydro-1*H*-pyrroles, tetrahydropyridines, 2*H*-chromenes, 1,2-dihydroquinolines and benzoxepin-5(2*H*)-ones are reported.

Dedicated to Professor Al Padwa to acknowledge his outstanding contributions to heterocyclic chemistry – and his friendship in the Lake District, in Istanbul, and in many other exotic locations!

INTRODUCTION

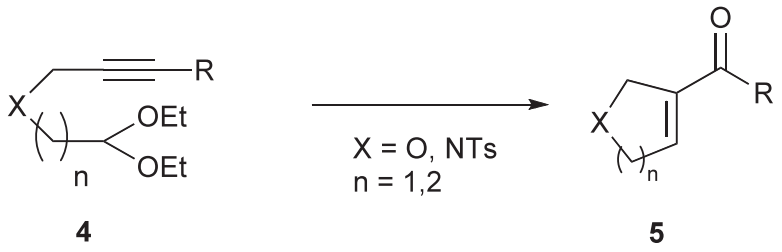
Partially reduced heterocycles bearing acyl substituents are valuable synthetic building blocks and are also found in biologically active natural products including cycloepoxydon (**1**), anatoxin A (**2**) and myceliothermophin E (**3**) (Figure 1).[1-3]



cycloepoxydon **1**[1] anatoxin A **2**[2] myceliothermophin E **3**[3]

Figure 1

As part of a natural product synthesis programme,[4] we required ready access to a range of acylated dihydrofurans, dihydropyrroles, and higher homologues **5** of this type. Given our interest in tandem reactions,[4,5] we became attracted to approaches based on the cyclisation of ω-formyl alkynes which can be mediated by both Lewis and Brønsted acids.[6,7] Given that aliphatic aldehydes can be difficult to purify and prone to decomposition on storage, we explored the direct use of the corresponding alkyne ω-acetals **4** as cyclisation precursors (Scheme 1).[8]



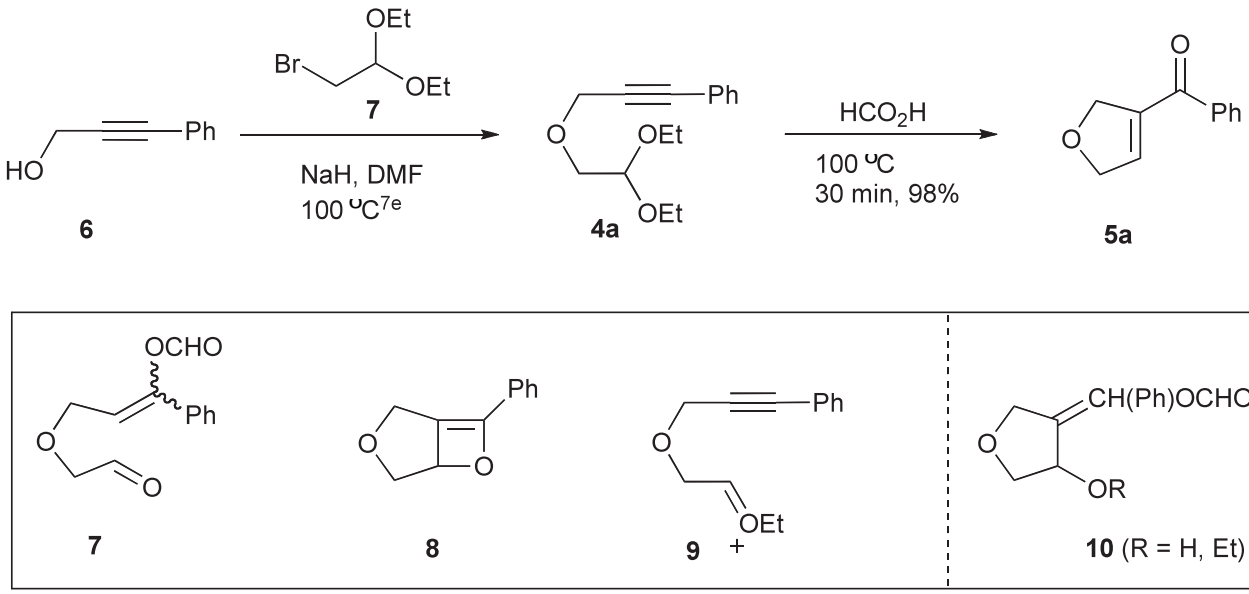
4 **5**

Scheme 1

RESULTS AND DISCUSSION

Initial studies were carried out using the known alkynyl acetal **4a**,[7e] which was readily prepared from alcohol **6** and commercially available acetal **7** using a modification of the published procedure (HMPA was omitted).[7e] When the acetal is prepared using this method, its direct use in the subsequent cyclisation reaction, removing the need to hydrolyse to the aldehyde, is obviously beneficial. A range of Lewis and Brønsted acids have been employed for alkyne cyclisations,[6,7] but our attention was taken by a report from Menashe and Shvo on the use of formic acid as an economical, metal-free method for the conversion of alkynes into carbonyl compounds.[9] We therefore explored the use of these formic acid conditions for the conversion of acetal **4a** into dihydrofuran **5a** (Scheme 2). We were delighted to

observe that, on heating acetal **4a** in neat formic acid at 100 ºC, rapid conversion into dihydrofuran **5a** took place and, after purification, compound **5a** was isolated in 98% yield. The reaction was also found to proceed at lower temperatures, with a resulting increase in reaction time (*e.g.* rt, 24 h, 98%). The practicality of this procedure should be emphasised – on completion of the reaction, the formic acid can be simply removed *in vacuo* to give the product which can be used directly or further purified by chromatography.

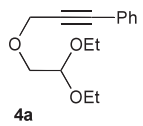
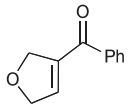
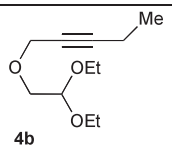
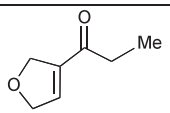
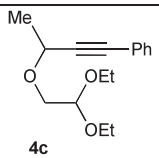
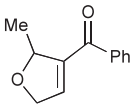
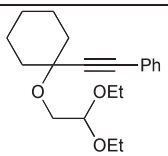
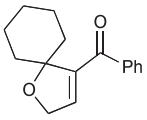
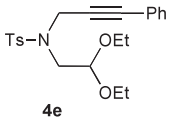
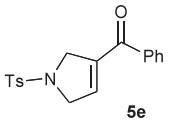
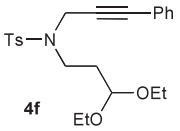
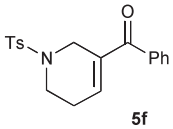
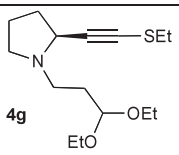
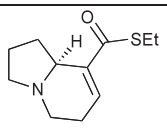


Scheme 2

Based on related studies, a number of mechanistic proposals could be considered, including: (i) initial addition of formic acid to the alkyne giving an intermediate **7** followed by an aldol-type condensation;[7d] (ii) proceeding by the intermediacy of an oxete **8**;[7a,7f,7g,10] (iii) a Prins-type cyclisation initiated by formation of oxonium ion **9**.[7e,g,h] We have not carried out a detailed mechanistic study on this process but when the reaction was carried at r.t. and stopped after ~30 min, potential intermediates tentatively assigned as enol formates **10** {*e.g.* for **10a**, HRMS (ESI): calcd. for $C_{12}H_{12}NaO_4$, 243.0628. Found: $[MNa]^+$, 243.0627 (0.1 ppm error); ^1H NMR, 8.14 ppm, OCHO} were isolated in addition to the expected product **5a**; this observation is in accord with the operation of a Prins-type process.

Having established conditions for the efficient cyclisation of acetal **4a**, we were in a position to investigate the scope of the transformation. Thus, a range of substrates **4b-4g** were prepared *via* alkylation of the corresponding propargylic alcohols or *N*-tosyl amines and subjected to the formic acid conditions (Table 1).

Table 1. Scope of formic acid-mediated cyclisation sequence[a]

Entry	Substrate	Product	Yield[b]
i	 **4a**	 **5a**	98%
ii	 **4b**	 **5b**	70%[c]
iii	 **4c**	 **5c**	80%[c]
iv	 **4d**	 **5d**	64%[c]
v	 **4e**	 **5e**	77%
vi	 **4f**	 **5f**	69%
vii	 **4g**	 **5g**	97%[d]

[a]All reactions were performed on a 0.25 mmol scale using formic acid (1 mL) at 100 ºC for 30 min.

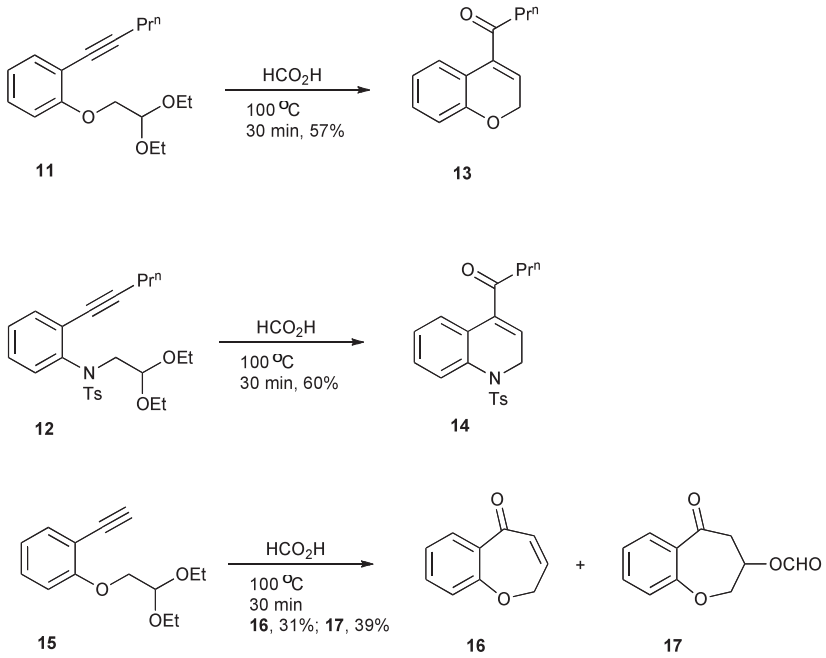
[b]Isolated yields after purification by column chromatography.

[c]Novel products.

[d]A reaction time of 2 h was employed.

As can be seen from Table 1, all of the substrates **4a-4g** were found to cyclise in moderate to excellent yield. In terms of dihydrofuran preparation, both aromatic and aliphatic alkyne substituents were tolerated (entries i-iv). The reaction was also found to be applicable to secondary and tertiary propargylic alcohols, which gave the methyl substituted dihydrofuran **5c** and the spirocyclic example **5d**, respectively. This methodology was equally applicable to the production of nitrogen heterocycles

(entries v-vi); thus, *N*-Ts amine **4e** gave 2,5-dihydro-1*H*-pyrrole **5e**, and the higher homologue **4f** gave tetrahydropyridine **5f**. Finally (entry vii), an example is shown to illustrate that heteroatom-substituted alkynes are also compatible with this methodology.[4c] Alkyne **4g**, easily available from L-proline, was treated with formic acid under the standard conditions giving almost quantitative cyclisation to the bicyclic thioester **5g** {$[\alpha]_D$ –87 (c 0.97, $CHCl_3$)}. Such thioesters appear to be valuable synthetic building blocks and, indeed, thioester **5g** has recently been employed by our group to prepare (–)-grandisine B and (+)-grandisine D *via* a novel synthetic route.[4c] In the final part of this study, we examined the cyclisation reactions of phenol- and aniline-derived substrates **11**, **12** and **15**. On subjection to the standard reaction conditions, the aromatic precursors **11** and **12** were converted into the novel chromene and 1,2-dihydroquinoline derivatives **13** and **14**, respectively, in reasonable yield. In all of the previous examples, cyclisation was observed at the proximal alkyne carbon atom but *endo*-cyclisation was seen when unsubstituted alkyne **15** was subjected to the reaction conditions. In this instance the known benzoxepinone derivative **16**[11] was isolated in 31% yield along with the formyl analogue **17** (39%; when re-subjected to the reaction conditions slow conversion to oxepine **16** was observed).



Scheme 3

In summary, a simple formic acid procedure has been developed for the conversion of alkyne ω-acetals directly into acyl heterocyclic building blocks. Preliminary studies into the scope and limitations of the methodology have been investigated and the sequence has been utilised to prepare 2,5-dihydrofurans, 3,6-dihydro-2*H*-pyrans, 2,5-dihydro-1*H*-pyrroles, tetrahydropyridines, 2*H*-chromenes,

1,2-dihydroquinolines and benzoxepin-5(2*H*)-ones. We are currently exploring the use of several of these compounds in natural product synthesis.

EXPERIMENTAL

NMR spectra were recorded on a Jeol ECX-400 instrument at 400 MHz (^{1}H) and 100 MHz (^{13}C); chemical shifts (δ) are quoted in parts per million (ppm) calibrated to residual non-deuterated solvent (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). Coupling constants (*J*) are quoted in Hertz and are to the nearest 0.1 Hz. Infrared spectra were recorded on a ThermoNicolet IR100 spectrometer with NaCl plates. Low resolution electrospray ionisation (ESI) mass spectra were recorded on a Kratos MS 25 spectrometer. High resolution mass spectra were recorded on a Bruker MicrOTOF spectrometer. Melting points were recorded on Gallenkamp apparatus and are uncorrected. Thin layer chromatography was performed on aluminium plates coated with Merck Silica gel 60 F254 and flash column chromatography was carried out using Fluka flash silica gel 60 and the specified eluent. PE refers to the fraction of petroleum ether that boils in the range 40-60 °C. Cyclisation substrates **4a**,[7e] **4e**,[7e] **4f**,[7f] **4g**[4c] and 2-(pent-1-ynyl)aniline[12] were prepared using previously reported methods and other starting materials were prepared using related procedures. All other chemicals used in this study were commercially available and used as received.

Typical Alkyne-Acetal Cyclisation Procedure:

(2,5-Dihydrofuran-3-yl)(phenyl)methanone 5a: A stirred solution of alkyne **4a** (62 mg, 0.25 mmol) in formic acid (1 mL) was heated at 100 ºC (oil-bath pre-heated) for 30 min. The solution was cooled to rt and then concentrated *in vacuo* to afford the crude product which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give compound **5a** (43 mg, 98%) as a crystalline solid; mp. 67-69 ºC; R_f 0.23 (PE/EtOAc, 4:1) (other data fully consistent to published values[7a]).

All other products were prepared using the above procedure. Products **5e**,[7a] **5f**,[7f] **5g**[4c] and **16**[11] gave data fully consistent to published values. Data for novel products follow:

1-(2,5-Dihydrofuran-3-yl)propan-1-one 5b (22 mg, 70%); pale yellow oil; R_f 0.21 (PE/EtOAc, 4:1); IR (neat) 2855, 1738, 1124, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.3 Hz, 3H), 2.72 (q, *J* = 7.3 Hz, 2H), 4.80-4.88 (m, 4H), 6.71-6.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9 (CH_3), 32.7 (CH_2), 74.4 (CH_2), 76.3 (CH_2), 136.3 (CH), 141.0 (C), 197.0 (C); *m/z* (ESI) 127 $[MH]^+$; [HRMS (ESI): calcd. for $C_7H_{11}O_2$, 127.0754. Found: $[MH]^+$, 127.0757 (2.7 ppm error)].

(2-Methyl-2,5-dihydrofuran-3-yl)(phenyl)methanone 5c: purified by column chromatography (SiO_2, PE/EtOAc, 9:1) as a pale yellow oil (38 mg, 80%); R_f 0.33 (PE/EtOAc, 4:1); IR (neat) 2973, 2848, 1644, 1359, 1276, 1240, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (d, J = 6.3 Hz, 3H), 4.77 (ddd, J = 16.1, 4.9, 1.9 Hz, 1H), 4.93 (ddd, J = 16.1, 5.6, 1.9 Hz, 1H), 5.30-5.38 (m, 1H), 6.54-6.56 (m, 1H), 7.44-7.49 (m, 2H), 7.54-7.60 (m, 1H), 7.77-7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (CH_3), 74.5 (CH_2), 82.2 (CH), 128.4 (2 × CH), 128.8 (2 × CH), 132.6 (CH), 138.2 (C), 139.5 (CH), 143.5 (C), 191.4 (C); *m/z* (ESI) 189 $[MH]^+$; [HRMS (ESI): calcd. for $C_{12}H_{13}O_2$, 189.0910. Found: $[MH]^+$, 189.0912 (1.2 ppm error)].

1-Oxaspiro[4.5]dec-3-en-4-yl(phenyl)methanone 5d: purified by column chromatography (SiO_2, PE/EtOAc, 19:1 to 9:1) as a yellow oil (39 mg, 64%); R_f 0.49 (PE/EtOAc, 4:1); IR (neat) 2929, 1646, 1317, 1240, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23-1.36 (m, 1H), 1.61-1.76 (m, 7H), 2.00-2.11 (m, 2H), 4.75 (d, J = 1.9 Hz, 2H), 6.45 (t, J = 1.9 Hz, 1H), 7.42-7.47 (m, 2H), 7.53-7.58 (m, 1H), 7.73-7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3 (2 × CH_2), 25.0 (CH_2), 34.1 (2 × CH_2), 71.9 (CH_2), 90.4 (C), 128.3 (2 × CH), 128.9 (2 × CH_2), 132.4 (CH), 139.1 (C), 139.9 (CH), 145.5 (C), 192.4 (C); *m/z* (ESI) 265 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{16}H_{18}NaO_2$, 265.1199. Found: $[MNa]^+$, 265.1192 (2.5 ppm error)].

1-(2*H*-Chromen-4-yl)butan-1-one 13: purified by column chromatography (SiO_2, PE/EtOAc, 9:1) as a yellow oil (29 mg, 57%); R_f 0.48 (PE/EtOAc, 4:1); IR (neat) 2964, 1682, 1485, 1456, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3H), 1.72 (qt, J = 7.4, 7.3 Hz, 2H), 2.75 (t, J = 7.3 Hz, 2H), 4.82 (d, J = 4.1 Hz, 2H), 6.56 (t, J = 4.1 Hz, 1H), 6.87 (dd, J = 8.0, 1.3 Hz, 1H), 6.95 (ddd, J = 7.8, 7.6, 1.3 Hz, 1H), 7.18 (ddd, J = 8.0, 7.6, 1.6 Hz, 1H), 7.75 (dd, J = 7.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 17.9 (CH_2), 41.6 (CH_2), 64.3 (CH_2), 116.3 (CH), 119.7 (C), 121.6 (CH), 126.6 (CH), 128.9 (CH), 129.8 (CH), 135.1 (C), 154.3 (C), 200.7 (C); *m/z* (ESI) 225 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{13}H_{14}NaO_2$, 225.0886. Found: $[MNa]^+$, 225.0890 (1.8 ppm error)].

1-{1-[(4-Methylphenyl)sulfonyl]-1,2-dihydroquinolin-4-yl}butan-1-one 14: purified by column chromatography (SiO_2, PE/EtOAc, 9:1) as a yellow oil (54 mg, 60%); R_f 0.33 (PE/EtOAc, 4:1); IR (neat) 2964, 1683, 1354, 1165, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7.4 Hz, 3H), 1.47 (qt, J = 7.4, 7.3 Hz, 2H), 2.24 (t, J = 7.3 Hz, 2H), 2.30 (s, 3H), 4.47 (d, J = 4.6 Hz, 2H), 6.24 (t, J = 4.6 Hz, 1H), 7.08 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.25-7.30 (m, 1H), 7.37 (ddd, J = 7.8, 7.7, 1.6 Hz, 1H), 7.61 (d, J = 7.8, 1.4, 1H), 7.73 (dd, J = 8.1, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 17.5 (CH_2), 21.4 (CH_3), 41.2 (CH_2), 44.8 (CH_2), 126.7 (CH), 126.8 (C), 126.9 (CH), 127.2 (2 × CH), 127.7

(CH), 128.9 (CH), 129.3 (2 × CH), 130.7 (CH), 135.6 (C), 136.1 (C), 136.5 (C), 143.7 (C), 199.7 (C); *m/z* (ESI) 356 $[MH]^+$; [HRMS (ESI): calcd. for $C_{20}H_{22}NO_3S$, 356.1315. Found: $[MH]^+$, 356.1313 (0.6 ppm error)].

5-Oxo-2,3,4,5-tetrahydrobenzo[b]oxepin-3-yl formate 17: purified by column chromatography (SiO_2, PE/Et_2O, 20:1 to 10:1) as a colourless crystalline solid (15 mg 39%); mp 60-62 °C; R_f 0.19 (PE/Et_2O, 4:1); IR (thin film) 3429, 1718, 1653, 1475, 1302, 1165, 1108, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.21 (dd, *J* = 12.3, 7.5 Hz, 1H), 3.28 (dd, *J* = 12.3, 6.0 Hz, 1H), 4.28-4.37 (m, 2H), 5.52-5.58 (m, 1H), 7.11-7.16 (m, 2H), 7.44-7.48 (m, 1H), 7.84 (dd, *J* = 7.9, 1.8, 1H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.2 (CH_2), 76.1 (CH), 76.7 (CH_2), 120.7 (CH), 123.4 (CH), 127.8 (C), 129.8 (CH), 134.4 (CH), 159.9 (CH), 162.8 (C), 194.7 (C);); *m/z* (ESI) 229 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{11}H_{10}NaO_4$, 229.0471. Found: $[MNa]^+$, 229.0470 (1.8 ppm error)].

ACKNOWLEDGEMENTS

The authors would like to thank the EPSRC and AstraZeneca for studentship support (J.D.C) and the EPSRC for postdoctoral support (W.P.U., EP/G068313/1).

REFERENCES AND NOTES

1. A. Gehrt, G. Erkel, T. Anke, and O. Sterner, *J. Antibiot.,* 1998, **51**, 455.
2. J. P. Devlin, O. E. Edwards, P. R. Gorham, N. R. Hunter, R. K. Pike, and B. Stavric, *Can. J. Chem.,* 1977, **55**, 1367.
3. Y.-L. Yang, C.-P. Lu, M.-Y. Chen, K.-Y. Chen, Y.-C. Wu, and S.-H. Wu, *Chem. Eur. J.*, 2007, **13**, 6985.
4. (a) J. D. Cuthbertson, A. A. Godfrey, and R. J. K. Taylor, *Synlett,* 2010, 2805; (b) J. D. Cuthbertson, A. A. Godfrey and R. J. K. Taylor, *Tetrahedron Lett.*, 2011, **52**, 2024; (c) J. D. Cuthbertson, A. A. Godfrey, and R. J. K. Taylor, *Org. Lett.*, 2011, *In press*.
5. R. J. K. Taylor, M. Reid, J. Foot, and S. A. Raw, *Acc. Chem. Res.,* 2005, **38***,* 851; A. R. Burns, G. D. McAllister, S. E. Shanahan, and R. J. K. Taylor, *Angew. Chem. Int. Ed.,* 2010, **49**, 5574 and references therein.
6. For the pioneering research on ω-carbonyl alkyne cyclisations see: (a) C. E. Harding and M. Hanack, *Tetrahedron Lett.,* 1971, **12**, 1253; (b) R. J. Balf, B. Rao, and L. Weiler, *Can. J. Chem.,* 1971, **49**, 3135.
7. For recent research on ω-carbonyl alkyne cyclisations see: (a) J. U. Rhee and M. J. Krische, *Org.*

Lett., 2005, **7**, 2493; (b) T. Jin and Y. Yamamoto, *Org*. *Lett*., 2007, **9**, 5259; (c) A. Saito, M. Umakoshi, N. Yagyu, and Y. Hanzawa, *Org*. *Lett*., 2008, **10**, 1783; (d) C. González-Rodríguez, L. Escalante, J. A. Varela, L. Castedo, and C. Saá, *Org*. *Lett*., 2009, **11**, 1531; (e) T. Xu, Z. Yu, and L. Wang, *Org*. *Lett*., 2009, **11**, 2113; (f) T. Jin, F. Yang, C. Liu, and Y. Yamamoto, *Chem*. *Commun*., 2009, 3533; (g) T. Xu, Q. Yang, Z. Yu, D. Li, J. Dong, and Y. Li, *Chem*. *Eur*. *J*., 2010, **16**, 9264; (h) D. Zheng, W. Gong, Z. Ma, B. Ma, X. Zhao, Z. Xie, and Y. Li, *Tetrahedron Lett*., 2011, **52**, 314 and references therein.

8. To the best of our knowledge, there are only two reports of the use of alkyne-acetals in a Brønsted acid mediated cyclisation (reference 7d, footnote 8 and reference 7f).
9. N. Menashe and Y. Shvo, *J*. *Org*. *Chem*., 1993, **58**, 7434.
10. C. E. Harding and S. L. King, *J*. *Org*. *Chem*., 1992, **57**, 883.
11. S.-R. Li, H.-M. Chen, L.-Y. Chen, J.-C. Tsai, P.-Y. Chen, S. C.-N. Hsu, and E.-C. Wang, *ARKIVOC*, **2008**, (ii), 172.
12. L. F. Kuyper, D. P. Baccanari, M. L. Jones, R. N. Hunter, R. L. Tansik, S. S. Joyner, C. M. Boytos, S. K. Rudolph, V. Knick, H. R. Wilson, J. M. Caddell, H. S. Friedman, J. C. W. Comley, and J. N. Stables, *J*. *Med*. *Chem*., 1996, **392**, 892.

Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
acac	Acetylacetone
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
Boc_2O	*tert*-Butyl dicarbonate
br	Broad
CAN	Ceric(IV) ammonium nitrate
Cbz	Carbobenzyloxy
COSY	Correlation spectroscopy
$Cu(OTf)_2$	Copper(II) trifluoromethanesulfonate
CuTC	Copper(I) thiophene carboxylate
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIBAL-H	Di*iso*butylaluminium hydride
DIPEA	Di*iso*propylethylamine
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide

DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
DMSO	Dimethyl sulfoxide
equiv.	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
Ether	Diethyl ether
EtOAc	Ethyl acetate
g	Gram(s)
h	Hour(s)
HEK	Human embryonic kidney
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
i	*Iso*
IR	Infra-red
J	Coupling constant in Hz
KO*t*-Bu	Potassium tert-Butoxide
LDA	Lithium di*iso*propylamine
LHMDS	Lithium hexamethyldisilazane
m	Multiplet
M	Molar

m/z	Mass to charge ratio
M^+	Molecular ion
Me	Methyl
MeCN	Acetonitrile
min.	Minute(s)
mL	Millilitre
mmol	Millimole
mp.	Melting point
Ms	Methanesulfonyl
MS	Mass spectrometry
Nap	Naphthyl
NBS	N-Bromosuccinimide
n-Bu_2OTf	Dibutylboron trifluoromethanesulfonate
n-BuLi	*n*-Butyllithium
NCS	*N*-chlorosuccinimide
n-Hex	*n*-Hexyl
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
n-Pr	*n*-Propyl
p	*para*
PE	Petroleum ether (Fraction which boils at 40-60 °C)
Ph	Phenyl
PhMe	Toluene
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl

ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
p-TsOH	*para*-Toluenesulfonic acid
Py	Pyridine
q	Quartet
Quant.	Quantitative
R	Alkyl group (undefined)
R_f	Retention factor
RSM	Recovered starting material
rt	Room temperature
s	Singlet
SAR	Structure-activity relationship
s-BuLi	*sec*-Butyllithium
SDS	Sodium dodecyl sulfate
SM	Starting material
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDMSCl	*tert*-Butyldimethylsilyl chloride
t-Bu	*tert*-Butyl
t-BuLi	*tert*-Butyllithium
Tf	Trifluoromethanesulfonyl
Tf_2O	Trifluormethanesulfonic anhydride
TFA	Trifluoroacetic acid

TFAA	Trifluoroacetic anhydride
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPSCl	Tri*iso*propylsilyl chloride
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Ts	*p*-Toluenesulfonyl
TsCN	*p*-Toluenesulfonyl cyanide
δ	Chemical shift
Δ	Heat
µL	Microlitre
µW	Microwave

References

1. S. R. Johns and J. A. Lamberton, *The Alkaloids*, Academic Press, New York, 1993.
2. S. R. Johns, J. A. Lamberton, A. A. Sioumis and J. A. Wunderlich, *Chem. Commun.*, 1968, 290-291.
3. S. R. Johns, J. A. Lamberton, A. A. Sioumis and R. I. Willing, *Aust. J. Chem.*, 1969, **22**, 775-792.
4. S. R. Johns, J. A. Lamberton and A. A. Sioumis, *Chem. Commun.*, 1968, 1324-1325.
5. S. R. Johns, J. A. Lamberton and A. A. Sioumis, *Aust. J. Chem.*, 1969, **22**, 793-800.
6. S. R. Johns, J. A. Lamberton, A. A. Sioumis, H. Suares and R. I. Willing, *Aust. J. Chem.*, 1971, **24**, 1679-1694.
7. S. R. Johns, J. A. Lamberton, A. A. Sioumis, H. Suares and R. I. Willing, *Chem. Commun.*, 1970, 804-805.
8. H. C. Acta, C.-X. Zhou, X.-Y. Wang, J.-X. Mo, J. Zhang and L.-S. Gan, *Helv. Chim. Acta.*, 2011, **94**, 347-354.
9. A. R. Carroll, G. Arumugan, R. J. Quinn, J. Redburn, G. Guymer and P. Grimshaw, *J. Org. Chem.*, 2005, **70**, 1889-1892.
10. P. L. Katavic, D. A. Venables, P. I. Forster, G. Guymer and A. R. Carroll, *J. Nat. Prod.*, 2006, **69**, 1295-1299.
11. P. L. Katavic, D. A. Venables, T. Rali and A. R. Carroll, *J. Nat. Prod.*, 2007, **70**, 866-868.
12. J. A. Lamberton, Y. A. Geewananda, P. Gunawardana and I. R. C. Bick, *J. Nat. Prod.*, 1983, **46**, 235-247.
13. P. L. Katavic, D. A. Venables, T. Rali and A. R. Carroll, *J. Nat. Prod.*, 2007, **70**, 872-875.
14. G. B. Robertson, U. Tooptakong, J. A. Lamberton, Y. A. G. P. Gunawardana and I. R. C. Bick, *Tetrahedron Lett.*, 1984, **25**, 2695-2696.
15. G. B. Robertson and U. Tooptakong, *Acta Crystallogr., Sect. C*, 1985, **C41**, 1332-1335.

16. P. L. Katavic, D. A. Venables, G. P. Guymer, P. I. Forster and A. R. Carroll, *J. Nat. Prod.*, 2007, **70**, 1946-1950.
17. R. M. Quock, T. H. Burkey, E. Varga, Y. Hosohata, K. Hosohata, S. M. Cowell, C. A. Slate, F. J. Ehlert, W. R. Roeske and H. I. Yamamura, *Pharmacol. Rev.*, 1999, **51**, 503-532.
18. M. Williams, E. A. Kowaluk and S. P. Arneric, *J. Med. Chem.*, 1999, **42**, 1481-1500.
19. G. Dondio, *Il Farmaco*, 2000, **55**, 178-180.
20. D. C. Broom, E. M. Jutkiewicz, K. C. Rice, J. R. Traynor and J. H. Woods, *Jpn. J. Pharmacol.*, 2002, **90**, 1-6.
21. A. Saitoh, A. Sugiyama, T. Nemoto, H. Fujii, K. Wada, J.-I. Oka, H. Nagase and M. Yamada, *Behav. Brain. Res.*, 2011, **223**, 271-279.
22. J. B. Thomas, X. M. Herault, R. B. Rothman, R. N. Atkinson, J. P. Burgess, S. W. Mascarella, C. M. Dersch, H. Xu, J. L. Flippen-Anderson, C. F. George and F. I. Carroll, *J. Med. Chem.*, 2001, **44**, 972-987.
23. H. Kurasaki, I. Okamoto, N. Morita and O. Tamura, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1601-1603.
24. D. J. Maloney and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2007, **46**, 7789-7792.
25. H. Kurasaki, I. Okamoto, N. Morita and O. Tamura, *Org. Lett.*, 2009, **11**, 1179-1181.
26. T. Onaka, *Tetrahedron Lett.*, 1971, **12**, 4395-4398.
27. G. W. Gribble, F. L. Switzer and R. M. Soll, *J. Org. Chem.*, 1988, **53**, 3164-3170.
28. E. Gellert, *J. Nat. Prod.*, 1982, **45**, 50-73.
29. J. F. Biard, S. Guyot, C. Roussakis, J. F. Verbist, J. Vercauteren, J. F. Weber and K. Boukef, *Tetrahedron Lett.*, 1994, **35**, 2691-2694.
30. K. Nishio, T. Fujiwara, K. Tomita, H. Ishii, Y. Inubushi and T. Harayama, *Tetrahedron Lett.*, 1969, **10**, 861-864.
31. J. W. Daly, T. Tokuyama, T. Fujiwara, R. J. Highet and I. L. Karle, *J. Am. Chem. Soc.*, 1980, **102**, 830-836.
32. J. P. Michael, *Nat. Prod. Rep.*, 2007, **24**, 191-222.
33. N. K. Hart, S. R. Johns and J. A. Lamberton, *Aust. J. Chem.*, 1972, **25**, 817-835.
34. D. L. Comins and Y. C. Myoung, *J. Org. Chem.*, 1990, **55**, 292-298.

35. D. F. Taber, R. S. Hoerrner and M. D. Hagen, *J. Org. Chem.*, 1991, **56**, 1287-1289.
36. E. Myers, J. G. Vries and V. K. Aggarwal, *Angew. Chem. Int. Ed.*, 2007, **46**, 1893-1896.
37. R. K. Dieter and N. Chen, *J. Org. Chem.*, 2006, **71**, 5674-5678.
38. D. H. Hua, S. N. Bharathi, P. D. Robinson and A. Tsujimoto, *J. Org. Chem.*, 1990, **55**, 2128-2132.
39. R. T. Yu, E. E. Lee, G. Malik and T. Rovis, *Angew. Chem. Int. Ed.*, 2009, **48**, 2379-2382.
40. C. H. Heathcock, *Angew. Chem. Int. Ed.*, 1992, **31**, 665-681.
41. W. I. Taylor, *J. Am. Chem. Soc.*, 1957, **79**, 3298-3299.
42. J. R. Crouse and A. R. Pinder, *J. Nat. Prod.*, 1989, **52**, 1227-1230.
43. J. Quirante, F. Diaba, X. Vila and J. Bonjoch, *Magn. Reson. Chem.*, 2005, **43**, 599-601.
44. A. Rassat and P. Rey, *Tetrahedron*, 1972, **28**, 741-750.
45. C. K. McClure and J. S. Link, *J. Org. Chem.*, 2003, **68**, 8256-8257.
46. R. J. Sundberg, M. Amat and A. M. Fernando, *J. Org. Chem.*, 1987, **52**, 3151-3159.
47. G. Babu and P. T. Perumal, *Tetrahedron*, 1998, **54**, 1627-1638.
48. C. Umberto, F. Francesco, O. Mara, N. Morena, P. Oriana and P. Ferdinando, *Eur. J. Org. Chem*, 2009, 1214-1220.
49. M. C. A. Rueping, *Angew. Chem. Int. Ed.*, 2006, **45**, 7832-7835.
50. H. Sundén, I. Ibrahem, L. Eriksson and A. Córdova, *Angew. Chem. Int. Ed.*, 2005, **44**, 4877-4880.
51. H. Yun, A. Gagnon and S. J. Danishefsky, *Tetrahedron Lett.*, 2006, **47**, 5311-5315.
52. H. Yang and R. G. Carter, *J. Org. Chem.*, 2009, **74**, 5151-5156.
53. D. J. Maloney and S. J. Danishefsky, *Heterocycles*, 2007, **72**, 167-174.
54. Y. S. Lee, J. Y. Lee, D. W. Kim and H. Park, *Tetrahedron*, 1999, **55**, 4631-4636.
55. H. Kurasaki, I. Okamoto, N. Morita and O. Tamura, *Chem. Eur. J.*, 2009, **15**, 12754-12763.
56. P. Geyelin, *The University of York, Thesis*, 2007.
57. C. Flann, T. C. Malone and L. E. Overman, *J. Am. Chem. Soc.*, 1987, **109**, 6097-6107.

58. L. H. Werner and S. Ricca, *J. Am. Chem. Soc.*, 1958, **80**, 2733-2736.
59. G. Zweifel and W. Lewis, *J. Org. Chem.*, 1978, **43**, 2739-2744.
60. T. W. Baughman, J. C. Sworen and K. B. Wagener, *Tetrahedron*, 2004, **60**, 10943-10948.
61. S. P. Marsden and A. D. McElhinney, *Synlett*, 2005, 2528-2530.
62. L. K. Ottesen, F. Ek and R. Olsson, *Org. Lett.*, 2006, **8**, 1771-1773.
63. T. J. Donohoe, L. P. Fishlock and P. A. Procopiou, *Org. Lett.*, 2008, **10**, 285-288.
64. S.-I. Murahashi and Y. Kodera, *Tetrahedron Lett.*, 1985, **26**, 4633-4636.
65. S. Murahashi, H. Mitsui, T. Shiota, T. Tsuda and S. Watanabe, *J. Org. Chem.*, 1990, **55**, 1736-1744.
66. S.-I. Murahashi and T. Shiota, *Tetrahedron Lett.*, 1987, **28**, 2383-2386.
67. D. H. Hua, S. W. Miao, S. N. Bharathi, T. Katsuhira and A. A. Bravo, *J. Org. Chem.*, 1990, **55**, 3682-3684.
68. R. Menezes and M. B. Smith, *Synth. Commun.*, 1988, **18**, 1625-1636.
69. Y. Ahn, G. I. Cardenas, J. Yang and D. Romo, *Org. Lett.*, 2001, **3**, 751-754.
70. W. J. Klaver, H. Hiemstra and W. N. Speckamp, *J. Am. Chem. Soc.*, 1989, **111**, 2588-2595.
71. S. T. M. Simila and S. F. Martin, *J. Org. Chem.*, 2007, **72**, 5342-5349.
72. J. E. Kropf, I. C. Meigh, M. W. P. Bebbington and S. M. Weinreb, *J. Org. Chem.*, 2006, **71**, 2046-2055.
73. H. Prokopcova and C. O. Kappe, *J. Org. Chem.*, 2007, **72**, 4440-4448.
74. A. Kuramochi, H. Usuda, K. Yamatsugu, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 14200-14201.
75. B. List, *J. Am. Chem. Soc.*, 2000, **122**, 9336-9337.
76. M. Hasegawa, D. Taniyama and K. Tomioka, *Tetrahedron*, 2000, **56**, 10153-10158.
77. G. Hughes, M. Kimura and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11253-11258.
78. J. C. Sheehan and R. W. Tulis, *J. Org. Chem.*, 1974, **39**, 2264-2267.
79. G. Bettoni, G. Carbonara, C. Franchini and V. Tortorella, *Tetrahedron*, 1981, **37**, 4159-4164.
80. Y. Arakawa, M. Tajima, Y. Arakawa and S. Yoshifuji, *Chem. Pharm. Bull.*, 2005, **53**, 81-85.

81. D. Abdelrahman, M. Benn, R. Hellyer and M. Parvez, *Can. J. Chem.*, 2006, **84**, 1167-1173.
82. H. Suginome, S. Imato, S. Yamada and N. Katsui, *Bull. Chem. Soc. Jpn.*, 1959, **32**, 819-824.
83. B.-D. Chong, Y.-I. Ji, S.-S. Oh, J.-D. Yang, W. Baik and S. Koo, *J. Org. Chem.*, 1997, **62**, 9323-9325.
84. A. K. Musser and P. L. Fuchs, *J. Org. Chem.*, 1982, **47**, 3121-3131.
85. K. M. Foote, C. J. Hayes, M. P. John and G. Pattenden, *Org. Biomol. Chem.*, 2003, **1**, 3917-3948.
86. M. J. Gaunt and J. B. Spencer, *Org. Lett.*, 2001, **3**, 25-28.
87. T. C. Wabnitz and J. B. Spencer, *Tetrahedron Lett.*, 2002, **43**, 3891-3894.
88. C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengoa and J. M. García, *J. Am. Chem. Soc.*, 2004, **126**, 9188-9189.
89. B. B. Snider and T. Liu, *J. Org. Chem.*, 1997, **62**, 5630-5633.
90. Y. Hamada, O. Hara, A. Kawai, Y. Kohno and T. Shioiri, *Tetrahedron*, 1991, **47**, 8635-8652.
91. T. K. M. Shing, X. Y. Zhu and Y. Y. Yeung, *Chem. Eur. J.*, 2003, **9**, 5489-5500.
92. K. M. Pietrusiewicz, J. Monkiewicz and R. Bodalski, *J. Org. Chem.*, 1983, **48**, 788-790.
93. J. D. Cuthbertson, A. A. Godfrey and R. J. K. Taylor, *Synlett*, 2010, 2805-2807.
94. K. Omura, A. K. Sharma and D. Swern, *J. Org. Chem.*, 1976, **41**, 957-962.
95. D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155-4156.
96. J.-C. Braekman, A. Charlier, D. Daloze, S. Heilporn, J. M. Pasteels, V. Plasman and S. F. Wang, *Eur. J. Org. Chem.*, 1999, 1749-1755.
97. P. Laurent, J.-C. Braekman and D. Daloze, *Eur. J. Org. Chem.*, 2000, 2057-2062.
98. E. J. Corey, Y. Ueda and R. A. Ruden, *Tetrahedron Lett.*, 1975, **16**, 4347-4350.
99. C. Hootelé, J. P. Etienne and B. Colau, *B. Soc. Chim. Belg.*, 1979, **88**, 111-112.
100. J. K. F. Geirsson and A. D. Gudmundsdottir, *Synthesis*, 1990, 993-994.
101. M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2005, **44**, 794-797.
102. S. P. Lathrop and T. Rovis, *J. Am. Chem. Soc.*, 2009, **131**, 13628-13630.
103. B. C. Ranu and S. Bhar, *Tetrahedron*, 1992, **48**, 1327-1332.
104. S. Neufeind, N. Hülsken, J.-M. Neudörfl, N. Schlörer and H.-G. Schmalz, *Chem. Eur. J.*, 2011, **17**, 2633-2641.

105. A. Carlone, M. Marigo, C. North, A. Landa and K. A. Jørgensen, *Chem. Commun.*, 2006, 4928-4930.
106. J. Adams and R. Frenette, *Tetrahedron Lett.*, 1987, **28**, 4773-4774.
107. J. D. Cuthbertson, A. A. Godfrey and R. J. K. Taylor, *Tetrahedron Lett.*, 2011, **52**, 2024-2027.
108. M. C. Franca , P. Federica, G. Martina, G. Andrea and B. Alberto, *Eur. J. Org. Chem.*, 2002, 1941-1951.
109. J. Liu and J. K. De Brabander, *J. Am. Chem. Soc.*, 2009, **131**, 12562-12563.
110. I. K. Korshevets and É. A. Mistryukov, *Russ. Chem. B+*, 1987, **36**, 1420-1425.
111. H. Fujioka, Y. Ohba, K. Nakahara, M. Takatsuji, K. Murai, M. Ito and Y. Kita, *Org. Lett.*, 2007, **9**, 5605-5608.
112. Z. Wu, F. Zhang and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2000, **39**, 4505-4508.
113. E. Wenkert, A. Fuchs and J. D. McChesney, *J. Org. Chem.*, 1965, **30**, 2931-2934.
114. C. A. Boros, F. R. Stermitz and G. H. Harris, *J. Nat. Prod.*, 1990, **53**, 72-80.
115. S. M. Frederiksen and F. R. Stermitz, *J. Nat. Prod.*, 1996, **59**, 41-46.
116. K. Takashi and K. Tadao, *Bull. Chem. Soc. Jpn.*, 1962, **35**, 1046-1046.
117. T. Kubota and Y. Tomita, *Tetrahedron Lett.*, 1961, **2**, 453-454.
118. F. R. Stermitz and G. H. Harris, *Tetrahedron Lett.*, 1985, **26**, 5251-5252.
119. W. N. A. Rolfsen, A. A. Olaniyi, R. Verpoorte and L. Bohlin, *J. Nat. Prod.*, 2004, **44**, 415-421.
120. M. Sulaiman, M.-T. Martin, M. Pas, A. H. A. Hadi and K. Awang, *Phytochem.*, 1998, **49**, 2191-2192.
121. H. E. Zimmerman, *Acc. Chem. Res.*, 1987, **20**, 263-268.
122. Y. Arai, T. Kontani and T. Koizumi, *J. Chem. Soc., Perkin Trans. 1*, 1994, 15-23.
123. M. Tokunaga and Y. Wakatsuki, *Angew. Chem. Int. Ed.*, 1998, **37**, 2867-2869.
124. M. Tokunaga, T. Suzuki, N. Koga, T. Fukushima, A. Horiuchi and Y. Wakatsuki, *J. Am. Chem. Soc.*, 2001, **123**, 11917-11924.
125. P. Alvarez, M. Bassetti, J. Gimeno and G. Mancini, *Tetrahedron Lett.*, 2001, **42**, 8467-8470.
126. F. Chevallier and B. Breit, *Angew. Chem. Int. Ed.*, 2006, **45**, 1599-1602.

127. F. Boeck, T. Kribber, L. Xiao and L. Hintermann, *J. Am. Chem. Soc.*, **133**, 8138-8141.
128. E. M. McMahon, J. N. Roper, W. P. Utermohlen, R. H. Hasek, R. C. Harris and J. H. Brant, *J. Am. Chem. Soc.*, 1948, **70**, 2971-2977.
129. H. Schick, B. Roatsch, S. Schramm, H.-D. Gilsing, M. Ramm and E. Gründemann, *J. Org. Chem.*, 1996, **61**, 5788-5792.
130. I. Paterson and M. Tudge, *Angew. Chem. Int. Ed.*, 2003, **42**, 343-347.
131. A. Paul, H. Bittermann and P. Gmeiner, *Tetrahedron*, 2006, **62**, 8919-8927.
132. H. D. Dickson, S. C. Smith and K. W. Hinkle, *Tetrahedron Lett.*, 2004, **45**, 5597-5599.
133. M. Zhao, C. Kuang, Q. Yang and X. Cheng, *Tetrahedron Lett.*, 2011, **52**, 992-994.
134. V. D. Bock, R. Perciaccante, T. P. Jansen, H. Hiemstra and J. H. van Maarseveen, *Org. Lett.*, 2006, **8**, 919-922.
135. M. Buck and J. M. Chong, *Tetrahedron Lett.*, 2001, **42**, 5825-5827.
136. P. Jakubec, D. M. Cockfield and D. J. Dixon, *J. Am. Chem. Soc.*, 2009, **131**, 16632-16633.
137. M. Reid and R. J. K. Taylor, *Tetrahedron Lett.*, 2004, **45**, 4181-4183.
138. C. E. Harding and M. Hanack, *Tetrahedron Lett.*, 1971, **12**, 1253-1256.
139. T. Xu, Q. Yang, D. Li, J. Dong, Z. Yu and Y. Li, *Chem. Eur. J.*, 2010, **16**, 9264-9272.
140. L. Zhao and X. Lu, *Angew. Chem. Int. Ed.*, 2002, **41**, 4343-4345.
141. D. Zheng, W. Gong, Z. Ma, B. Ma, X. Zhao, Z. Xie and Y. Li, *Tetrahedron Lett.*, 2011, **52**, 314-317.
142. J. J. Jaber, K. Mitsui and S. D. Rychnovsky, *J. Org. Chem.*, 2001, **66**, 4679-4686.
143. W. H. Bunnelle, D. W. Seamon, D. L. Mohler, T. F. Ball and D. W. Thompson, *Tetrahedron Lett.*, 1984, **25**, 2653-2654.
144. C. Kim, H. J. Bae, J. H. Lee, W. Jeong, H. Kim, V. Sampath and Y. H. Rhee, *J. Am. Chem. Soc.*, 2009, **131**, 14660-14661.
145. T. Jin and Y. Yamamoto, *Org. Lett.*, 2007, **9**, 5259-5262.
146. C. González-Rodríguez, L. Escalante, J. A. Varela, L. Castedo and C. Saá, *Org. Lett.*, 2009, **11**, 1531-1533.
147. T. Xu, Z. Yu and L. Wang, *Org. Lett.*, 2009, **11**, 2113-2116.

148. A. N. Cayley, K. A. Gallagher, C. Ménard-Moyon, J. P. Schmidt, L. J. Diorazio and R. J. K. Taylor, *Synthesis*, 2008, 3846-3856.
149. A. Abad, C. Agulló, M. Arnó, A. Cantín, A. C. Cuñat, B. Meseguer and R. J. Zaragozá, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1837-1844.
150. N. Menashe, D. Reshef and Y. Shvo, *J. Org. Chem.*, 1991, **56**, 2912-2914.
151. N. Menashe and Y. Shvo, *J. Org. Chem.*, 1993, **58**, 7434-7439.
152. C. E. Harding and S. L. King, *J. Org. Chem.*, 1992, **57**, 883-886.
153. J. U. Rhee and M. J. Krische, *Org. Lett.*, 2005, **7**, 2493-2495.
154. W. P. Unsworth, University of York, 2011, Unpublished results.
155. J. P. Gesson, J. C. Jacquesy and D. Rambaud, *Tetrahedron Lett.*, 1992, **33**, 3633-3636.
156. A. Wagner, M. P. Heitz and C. Mioskowski, *Tetrahedron Lett.*, 1990, **31**, 3141-3144.
157. R. E. Maleczka, L. R. Terrell, D. H. Clark, S. L. Whitehead, W. P. Gallagher and I. Terstiege, *J. Org. Chem.*, 1999, **64**, 5958-5965.
158. J. M. Montierth, D. R. DeMario, M. J. Kurth and N. E. Schore, *Tetrahedron*, 1998, **54**, 11741-11748.
159. H. J. Boonstra, L. Brandsma, A. M. Wiegman and J. F. Arens, *Recl. Trav. Chim. Pay-B*, 1959, **78**, 252-264.
160. P. M. M. Nossin and W. N. Speckamp, *Tetrahedron Lett.*, 1979, **20**, 4411-4414.
161. H. Maruyama, M. Shiozaki, S. Oida and T. Hiraoka, *Tetrahedron Lett.*, 1985, **26**, 4521-4522.
162. R. S. Glass, Q. Guo and Y. Liu, *Tetrahedron*, 1997, **53**, 12273-12286.
163. R. A. Pilli, G. B. Rosso and M. C. F. de Oliveira, *Nat. Prod. Rep.*, 2010, **27**, 1908-1937.
164. T. Fukuyama, S.-C. Lin and L. Li, *J. Am. Chem. Soc.*, 1990, **112**, 7050-7051.
165. F. Debaene, J. A. Da Silva, Z. Pianowski, F. J. Duran and N. Winssinger, *Tetrahedron*, 2007, **63**, 6577-6586.
166. M. K. Eberle, A.-M. Jutzi-Eme and F. Nuninger, *J. Org. Chem.*, 1994, **59**, 7249-7258.
167. O. David, J. Blot, C. Bellec, M.-C. Fargeau-Bellassoued, G. Haviari, J.-P. Célérier, G. Lhommet, J.-C. Gramain and D. Gardette, *J. Org. Chem.*, 1999, **64**, 3122-3131.

168. X. Wang, X. Li, J. Xue, Y. Zhao and Y. Zhang, *Tetrahedron Lett.*, 2009, **50**, 413-415.
169. F. M. Cordero, B. Anichini, A. Goti and A. Brandi, *Tetrahedron*, 1993, **49**, 9867-9876.
170. K. Agapiou and M. J. Krische, *Org. Lett.*, 2003, **5**, 1737-1740.
171. S. Hanessian, A. Tehim and P. Chen, *J. Org. Chem.*, 1993, **58**, 7768-7781.
172. G. B. Dudley, K. S. Takaki, D. D. Cha and R. L. Danheiser, *Org. Lett.*, 2000, **2**, 3407-3410.
173. C. Cardellicchio, V. Fiandanese, G. Marchese and L. Ronzini, *Tetrahedron Lett.*, 1985, **26**, 3595-3598.
174. V. Fiandanese, G. Marchese and F. Naso, *Tetrahedron Lett.*, 1988, **29**, 3587-3590.
175. L. S. Liebeskind and J. Srogl, *J. Am. Chem. Soc.*, 2000, **122**, 11260-11261.
176. H. Yang, H. Li, R. d. Wittenberg, M. Egi, W. Huang and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2007, **129**, 1132-1140.
177. J. D. Cuthbertson, A. A. Godfrey, W. P. Unsworth and R. J. K. Taylor, *Heterocycles*, 2011, **In Press**.
178. J. D. Cuthbertson, A. A. Godfrey and R. J. K. Taylor, *Org. Lett.*, 2011, **13**, 3976-3979.
179. C. F. Hammer and S. Chandrasegaran, *J. Am. Chem. Soc.*, 1984, **106**, 1543-1552.
180. M. Santiago, E. Low, G. Chambournier and R. E. Gawley, *J. Org. Chem.*, 2003, **68**, 8480-8484.
181. A. Archelas, R. Furstoss, B. Waegell, J. Le Petit and L. Deveze, *Tetrahedron*, 1984, **40**, 355-367.
182. M. G. Constantino, V. L. Júnior and G. V. J. da Silva, *Magn. Reson. Chem.*, 2005, **43**, 346-347.
183. M. S. Taylor, D. N. Zalatan, A. M. Lerchner and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2005, **127**, 1313-1317.
184. P. Huy, J.-M. Neudörfl and H.-G. Schmalz, *Org. Lett.*, 2011, **13**, 216-219.
185. K. S. Ravikumar and S. Chandrasekaran, *J. Org. Chem.*, 1996, **61**, 826-830.
186. K. Thai, L. Wang, T. Dudding, F. Bilodeau and M. Gravel, *Org. Lett.*, 2010, **12**, 5708-5711.
187. J. Cossy, M. Cases and D. G. Pardo, *Bull. Chem. Soc. Fr.*, 1997, **134**, 141-144.

188. G. Reginato, A. Mordini, F. Messina, A. Degl'Innocenti and G. Poli, *Tetrahedron*, 1996, **52**, 10985-10996.

189. A. G. M. Barrett, B. T. Hopkins, A. C. Love and L. Tedeschi, *Org. Lett.*, 2004, **6**, 835-837.

190. T. J. Donohoe, L. P. Fishlock, J. A. Basutto, J. F. Bower, P. A. Procopiou and A. L. Thompson, *Chem. Commun.*, 2009, 3008-3010.

191. W. Oppolzer and B. Stammen, *Tetrahedron*, 1997, **53**, 3577-3586.

192. C. Nieto-Oberhuber, P. Pérez-Galán, E. Herrero-Gómez, T. Lauterbach, C. Rodríguez, S. López, C. Bour, A. Rosellón, D. J. Cárdenas and A. M. Echavarren, *J. Am. Chem. Soc.*, 2008, **130**, 269-279.

193. L. F. Kuyper, D. P. Baccanari, M. L. Jones, R. N. Hunter, R. L. Tansik, S. S. Joyner, C. M. Boytos, S. K. Rudolph, V. Knick, H. R. Wilson, J. M. Caddell, H. S. Friedman, J. C. W. Comley and J. N. Stables, *J. Med. Chem.*, 1996, **39**, 892-903.

194. S. S. C. Koch and A. R. Chamberlin, *J. Org. Chem.*, 1993, **58**, 2725-2737.