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

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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).

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.

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 *Elaocarpus* alkaloids are described (Chapter 6).
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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
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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 isoelaeocarpicine 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 (+)-elaeocarpine 4 and (−)-isoelaeocarpine 5 in which the C-15, C-16 bond is saturated.⁴,⁵

![Figure 1.2 Structures of (+)-elaeocarpine 4 and (−)-isoelaeocarpine 5.](image)

The relative stereochemistry of isoelaeocarpine 5 at C-16 was determined by sodium borohydride reduction studies. On reduction, the carbonyl group of isoelaeocarpine 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 isoelaeocarpine 5, the relative configuration of elaeocarpine 4 could not be determined.

Subsequent studies determined the absolute configuration of (−)-isoelaeocarpine 5 *via* oxidative degradation with KMnO₄ to yield the known compound (S)-methylsuccinic acid 6, the absolute configuration of which corresponds to the C-16 stereocentre.⁶

Dehydrogenation of elaeocarpine 4 and isoelaeocarpine 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 °C was reported to occur over a period of days.⁵
1.1.3 *E. sphaericus*

![Figure 1.3 Alkaloids isolated from Elaeocarpus sphaericus.](image)

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. The absolute configurations of the alkaloids were determined by dehydrogenation studies to yield the known compounds elaeocarpine 1 and isoeleocarpine 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 *Elaeocarpaceae* continues to reveal novel indolizidine alkaloids. Recent studies by Gan *et al.* described the isolation and structural elucidation of (±)-oxoisoeleocarpine 12 and (±)-eleocarpine *N*-oxide 13 from *Elaeocarpus sphaericus*. 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 (±)-oxoisoeleocarpine 12 and (±)-eleocarpine *N*-oxide 13.](image)
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*. 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 receptors. Isolation of the bioactive components revealed the known alkaloid (−)-isoeleaeocarpiline 5 along with the novel indolizidine alkaloids grandisine A 14 and grandisine B 15.

![Figure 1.5](image)

*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

![Figure 1.6](image)

*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*.](image)

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.](image)

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 elaeocarpene 24, along with three previously isolated alkaloids. The analytical data for elaeocarpene 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.

![Figure 1.8 Elaeocarpene 24 isolated from *E. fuscoides* by Carroll *et al.*](image)

Carroll reported that on treatment of elaeocarpene 24 with aqueous ammonia in methanol conversion to the known alkaloids elaeocarpine 1 and isoelaeocarpine 2 was observed, 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 peripentadene 25. The molecular formula was assigned as C_{22}H_{34}N_{2}O_{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.
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.\(^4\) 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.\(^5\) 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.

Recently, studies by Carroll and co-workers reported the isolation and characterisation of four additional alkaloids from the leaves of *P. mearsii*.\(^6\) 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.*

The third compound, peripontonine 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. 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.
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.\(^\text{18, 19}\)

Non-peptidic δ-opioid selective agonists, such as SNC80 \(^\text{34}\) and KNT-127 \(^\text{35}\) have also demonstrated antidepressant-like activity in animal studies.\(^\text{21}\) 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 elaeocarpene 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.\(^23\)
Figure 1.14 Elaeocarpene 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 9R-23 found to be more active than the 9S-23 enantiomer although a decreased selectivity for receptor subtypes was observed.23

1.4 Grandisine B (15) – Structure Elucidation

Figure 1.15 Grandisine B 15.9

Grandisine B 15 was assigned the molecular formula C_{16}H_{22}N_{2}O 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.\cite{9}

### 1.5 Elaeocarpus Alkaloid Biosynthesis

In early studies on the family *Elaeocarpaceae*, Johns \textit{et al.} proposed that the *Elaeocarpus* alkaloids are biosynthesised from a polyketomethylene chain derived from 6 acetate units 40 and \textit{l}-ornithine 41, Scheme 1.2.\cite{5}

\begin{equation}
\text{6} \times \text{OH} + \text{H}_2\text{N} - \text{CO}_2\text{H} \rightarrow \text{42}
\end{equation}

**Scheme 1.2** Johns’ proposed biosynthesis of *Elaeocarpus* alkaloids.\cite{5}

On the basis of Johns’ biosynthetic proposal,\cite{5} Carroll \textit{et al.} later hypothesised that the grandisine alkaloids could be derived from a common precursor 42, Scheme 1.3.\cite{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 $5^5$, a proposal that was later confirmed by Danishefsky and Tamura.\(^\text{24,25}\)

Alternatively, Onaka proposed that the \textit{Elaeocarpus} alkaloids are derived from the common intermediate $\text{48}^\text{26}$, which could be obtained \textit{via} the enzymatic oxidation of spermidine $\text{47}$, Scheme 1.4. Gribble proposed that the alkaloid peripentadenine $\text{25}$ isolated from \textit{P. mearsii} could also be derived from spermidine $\text{47}^\text{27}$, providing evidence to support Onaka’s biosynthetic proposal.

Scheme 1.3 Carroll's proposed biosynthesis of the elaeocarpus alkaloids $5$, $14$, $15$ and $17$.\(^9\)

Scheme 1.4 Onaka’s proposed biosynthetic intermediate $\text{48}$.\(^\text{26}\)
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](image)

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](image)

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. 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. Other members include the Lycopodium alkaloid serratinine 55, and the pumiliotoxins 56 isolated from the poison dart frog family Dendrobatidae.

![Figure 1.16 A selection of indolizidine alkaloids.](image)

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 indolizidine alkaloids was recently reported by Michael.

#### 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. 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.

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 SnCl₄ mediated cyclisation in Taber's synthesis of (±)-57.⁵⁵

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 69.⁶⁶ 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 69.⁶⁶

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.
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, 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 1.10** Gribble's synthesis of (±)-57.\(^\text{27}\)

**Scheme 1.11** Dieter's synthesis of (+)-57 via the asymmetric deprotonation of Boc-pyrrolidine 72.\(^\text{37}\)
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. 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. 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.](image)

1.7 Isoquinuclidinones

Whilst the saturated isoquinuclidine nucleus is incorporated into alkaloids from the species *Daphniphyllum*, such as methyl homosecodaphniphyllate 85 and Iboga alkaloids such as ibogaine 86, it is only mearsine 27, 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.](image)
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.\textsuperscript{12} Subsequent debenzylation and chlorination/elimination furnished (+)-mearsine 27 in 30% overall yield.

![Scheme 1.14](image)

Scheme 1.14  Pinder's synthesis of (+)-27 via an intramolecular conjugate addition.\textsuperscript{12}

An alternative synthesis of isoquinuclidinones reported by Bonjoch et al. utilised a trimethylaluminium-promoted lactamisation of the substituted cyclohexane derivative 91,\textsuperscript{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](image)

Scheme 1.15  Synthesis of isoquinuclidinone 93 via a trimethylaluminium-promoted epimerisation-lactamisation sequence.\textsuperscript{43}

An early synthesis of simple isoquinuclidinone structures was reported by Rassat, using a double conjugate addition of ammonia to construct the bicyclic framework.\textsuperscript{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
Alternative approaches to isoquinuclidinone frameworks include the azadiels-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. 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.

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.

A similar approach to isoquinuclidinones was reported by Peirmatti et al., using an azadiels-Alder reaction in aqueous media. 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 cyclohexeneone derived diene, to give
isoquinuclidinone products in moderate to high yield and excellent enantioselectivity, Scheme 1.23.\textsuperscript{50}

![Scheme 1.23](image)

Scheme 1.23 Proline catalysed enantioselective \textit{aza}-Diels-Alder reaction.\textsuperscript{50}

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

![Scheme 1.24](image)

Scheme 1.24 Application of Cordova’s proline catalysed \textit{aza}-Diels-Alder reaction in studies towards the synthesis of xestocyclamine A \textit{117}.\textsuperscript{51}

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

![Scheme 1.25](image)

Scheme 1.25 Carter’s organocatalytic \textit{aza}-Diels-Alder approach to isoquinuclidinones \textit{110}.\textsuperscript{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 $\text{119}$ were used in the reaction, bicyclo[2.2.2]octane $\text{120}$ products were obtained, Scheme 1.26.⁵²

![Scheme 1.26](image)

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 $\text{121}$ into the activated enone $\text{122}$. Enamine isomerisation and intramolecular Mannich reaction gave the bicyclo[2.2.2] framework $\text{125}$, which was readily converted into isoquinuclidinone $\text{120}$ upon hydrolysis.⁵²

![Scheme 1.27](image)

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.

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 \(\alpha,\beta\)-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\(^{\circledast}\) nickel furnished grandisine A \(^{14}\) in 92% yield, Scheme 1.29.
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. Tamura's approach utilised Aggarwal's Brønsted acid mediated Morita-Baylis-Hillman (MBH) ring closure to construct the indolizidine ring. Imide 134, prepared from (S)-malic acid using Lee's method, was subjected to regioselective reduction with NaBH₄, 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.

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.

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.

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.
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. 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](image)

Scheme 1.34 Conversion of grandisine D 17 into grandisine B 15.

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](image)

Scheme 1.35 Conversion of diketone 143 into grandisine F 19.

1.9 Aims and Objectives: Retrosynthetic Analysis

Following on from worked carried out by Geyelin, our initial aim was to complete the total synthesis of grandisine B 15. Despite grandisine B 15 exhibiting one of the highest IC\textsubscript{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](image)

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.\textsuperscript{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](image)

Scheme 1.37 Retrosynthetic analysis of indolizidine coupling partners.

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

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), 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.

Scheme 1.39 Synthesis of a model isoquinuclidinone core 154.

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.
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](image)

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-butyln-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.\textsuperscript{57} 67%), the data for which were consistent with those reported by Overman.\textsuperscript{57}

Scheme 2.2 Overman's synthesis of vinyl bromide 74.\textsuperscript{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 \textit{et al.} proposed two viable pathways,\textsuperscript{57} Scheme 2.3. Mechanism A involved direct cyclisation onto iminium ion 165 to give the intermediate \( \beta \)-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.\textsuperscript{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 vinilsilane 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.
Treatment 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 1H NMR spectroscopic analysis and could be used in subsequent chemistry without purification.

**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.

**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. Following the procedure of Marsden, 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.

**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.\textsuperscript{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,\textsuperscript{56} treatment of vinyl bromide 74 with $t$-butyllithium in THF at $-78 \, ^\circ C$ 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.

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.
Previous work in the Taylor group had shown that the corresponding vinyl stannane \textbf{173} could be accessed via trapping with tributyltin chloride.\textsuperscript{56} We also envisaged that trapping with triisopropyl 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 \textbf{154} was required. Following the procedure reported by Werner,\textsuperscript{58} bicyclic lactam \textbf{154} was prepared in 84\% yield via a thermally induced cyclisation of commercially available \textit{cis}-aminocyclohexane carboxylic acid \textbf{153}, Scheme 2.10.

Due to the high cost of \textit{cis}-aminocyclohexane carboxylic acid, we felt it would be instructive to attempt the reaction using the cheaper \textit{cis}/\textit{trans}-mixture. On subjecting the \textit{cis}/\textit{trans}-mixture to the thermal cyclisation conditions, bicyclic lactam \textbf{154} was isolated in 80\% yield; the \textit{trans}-isomer clearly epimerises when subjected to the high temperatures. Although lacking the ketone functionality present in the isoquinuclidinone core unit of grandisine B \textbf{15}, we felt the bicyclic lactam \textbf{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, attempt was 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, in which lactam 154 was treated with PCl$_5$ in toluene at reflux, was also unsuccessful.

![Scheme 2.11](image)

**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$_2$O and DIPEA in DCM at $-78^\circ$C, failed to give any of the desired imidoyl triflate 175, Scheme 2.12.

![Scheme 2.12](image)

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

Alternative conditions reported by Donohoe were also investigated. 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.

\[
\text{Scheme 2.13} \quad \text{Retrosynthetic analysis of the grandisine B model 155.}
\]

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.

\[
\text{Scheme 2.14} \quad \text{Synthesis of nitrone 180 using the procedure of Murahashi.}^{65,66}
\]

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 \( \sim 90\% \) 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.

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$_2$O, 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.

Scheme 2.16 Trapping of amine 181 with Boc$_2$O.

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](image)

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 ¹H NMR spectrum of the unpurified reaction mixture, or peaks corresponding to an indolizidine species. It was therefore proposed that vinylolithium 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](image)

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. Following Hua's procedure, treatment of 2-pyrolidinone 187 with trimethylsilyl chloride and triethylamine gave the known silylated lactam 188 in 73% yield.
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. 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.

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 \textit{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.

Using a similar procedure reported by Romo \textit{et al.}, 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

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**Scheme 2.19** Hua's procedure for the synthesis of cyclic ketimine 189.\(^{67}\)

**Scheme 2.20** Attempted synthesis of TMS-Lactam 190 using Hua's procedure.\(^{67}\)

**Scheme 2.21** Attempted \textit{in situ} trapping on TMS-lactam 190.
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, 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](image)

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

Whilst not providing direct access to the required imine, there is literature precedent for the conversion of secondary amines into imines. 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](image)

**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 °C 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. In order to investigate this approach, the model Boc-protected lactam 197 was prepared via treatment of lactam 154 with $n$-butyllithium and Boc$_2$O, 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, 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. 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.

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. 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.

\[ \text{Scheme 2.29} \quad \text{Synthesis of thiolactam 204 from bicyclic lactam 154.} \]

The publication by Kappe focused on the coupling of aromatic boronic acids, 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.

![Figure 3.1 Bicyclic lactam 154 and functionalised bicyclic lactam 209.](image)

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.\(^{45}\)

![Scheme 3.1 Attempted synthesis of bicyclic lactam 98 using the procedure of McClure.](image)

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 °C 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. 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. Although lacking the amide functionality required, it was envisaged that this could be subsequently installed by oxidation of isoquinuclidinone 212.

![Scheme 3.2 Cordova's enantioselective synthesis of isoquinuclidinones 212.](image)

Following the reported procedure, isoquinuclidinone 213 was prepared in a moderate 34% yield (Lit. 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.\textsuperscript{50}

*In situ* reduction of isoquinuclidinone 213 using NaBH\textsubscript{4} and subsequent isolation of the diastereomeric alcohols 214 was also attempted. Addition of excess NaBH\textsubscript{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.\textsuperscript{50} 70\%), Scheme 3.4.

Scheme 3.4 Synthesis of isoquinuclidinone 114 using the procedure of Cordova.\textsuperscript{50}

Analysis of the unpurified reaction mixture by \textsuperscript{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.
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 preceded 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. After 1 h at 0 °C, 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.
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.

A one-pot deprotection/acetate protection procedure reported by Tomioka caught our attention as it would negate the need to isolate amine 222. 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.
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. Treatment of isoquinuclidinone 114 with CAN in acetonitrile and subsequent protection with Boc$_2$O in aqueous toluene, gave after purification, the novel Boc-protected isoquinuclidinone 225 in an unoptimised 39% yield, Scheme 3.10.

![Scheme 3.10](image)

Scheme 3.10 Synthesis of isoquinuclidinone 225 via a deprotection/Boc-protection strategy.

### 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](image)

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 precedent in the literature,\textsuperscript{78} to our knowledge, there are only limited reported oxidations of tertiary amines bearing aromatic substituents.\textsuperscript{79} Initial studies were undertaken using conditions reported by Arakawa.\textsuperscript{80} Disappointingly, treatment of isoquinuclidinone \textbf{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.](image)

A particularly relevant paper by Benn \textit{et al.}, reported the oxidation of the alkaloid lycoctonine using potassium permanganate in aqueous solvent systems to yield the corresponding tertiary amide.\textsuperscript{81} Following the reported procedure, on addition of a slight excess of aqueous potassium permanganate to a solution of amine \textbf{114} in DCM, the appearance of a more polar species was observed by TLC analysis, Scheme 3.13. Pleasingly, \textsuperscript{1}H NMR spectroscopic analysis of the unpurified product, revealed signals corresponding to residual starting material \textbf{114} and the desired bicyclic lactam \textbf{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.](image)

A paper published by Suginome, reported the oxidation of tertiary amines with KMnO$_4$ in aqueous acetone.\textsuperscript{82} The reaction of amine \textbf{114} with KMnO$_4$ was therefore repeated in both aqueous acetone and acetonitrile, to establish whether complete oxidation of amine \textbf{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 KMnO₄ 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 KMnO₄, to give bicyclic lactam 227 in 47% yield, Scheme 3.14.

![Scheme 3.14](image)

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](image)

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.
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., 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.

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 CO₂ 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.
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 1H 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 ¹H 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 precedednted 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. Recent reports on the asymmetric addition of carbamates to unsaturated carbonyl compounds using chiral Lewis acid catalysts, could provide an enantioselective route to the isoquinuclidinone core.

$$\begin{array}{c}
\text{O} \\
\text{104} \\
\text{CBzNH}_2 \\
\text{Cu(OTf)}_2 \\
\text{(10 mol%)} \\
\text{MeCN, rt} \\
\text{87\%} \\
\text{O} \\
\text{241} \\
\end{array}$$

**Scheme 3.22** Spencer's copper-catalysed conjugate addition of benzyl carbamate. 

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

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.

$$\begin{array}{c}
\text{O} \\
\text{232} \\
\text{NH}_3 \\
\text{240} \\
\text{H}_2\text{N} \\
\text{O} \\
\text{208} \\
\text{O} \\
\text{242} \\
\end{array}$$

**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. 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.\textsuperscript{90}

The relative stereochemistry was determined by \(^1\text{H}\) 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.

Table 3.1  Conditions screened for the amination of enone 232.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>NH\textsubscript{3} Source</th>
<th>Co-solvent</th>
<th>Time (h)</th>
<th>Conversion\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0 M in IPA</td>
<td>-</td>
<td>24</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2</td>
<td>35% aq. DCM</td>
<td>24</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>35% aq. THF</td>
<td>24</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>35% aq. MeCN</td>
<td>6</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>35% aq. MeOH</td>
<td>2</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>35% aq.</td>
<td>1</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} All reactions were performed on a 0.1 mmol scale; entries 2-6 were carried out using 35\% aq. NH\textsubscript{3} (0.25 mL) and solvent (0.5 mL).

\textsuperscript{b} Conversion estimated by \(^1\text{H}\) NMR spectroscopic analysis of the unpurified reaction mixture.
An initial amination attempt using ammonia in isopropanol 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.

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

#### 3.6.2 Structure Elucidation

The isolated product was assigned the molecular formula $\text{C}_8\text{H}_{12}\text{NO}_2$ based on HRMS and elemental analysis. Analysis of the material by $^1$H/$^13$C NMR spectroscopy revealed characteristic bridgehead signals at $\delta$ 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 conclusive, 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. 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).

![Figure 3.2 Evidence for the stereochemistry of bicyclic lactam 209.](image)

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.](image)
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.

\[
\begin{array}{c}
\text{232} \\
\text{245}
\end{array}
\]

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 isoquiniuculinones via a one-pot amination/lactamisation sequence, the scope of the transformation was investigated. Following the procedure of Shing, 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.
Scheme 3.29 Synthesis of β-ketoester substrates 246 from cyclohexenones 211.\textsuperscript{91}

The phenyl substituted derivative 246b was prepared in 61% yield using the procedure reported by Pietrusiewicz,\textsuperscript{92} Scheme 3.30.

Scheme 3.30 Synthesis of substrate 246b using the procedure of Pietrusiewicz.\textsuperscript{92}

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

Scheme 3.31 Scope of the amination/cyclisation sequence.
### Table 3.2 Scope of amination/cyclisation sequence for the synthesis of bicyclic lactams 248

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (246)</th>
<th>Product (248)</th>
<th>Time (h)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>246a</td>
<td>248a</td>
<td>2</td>
<td>93%</td>
</tr>
<tr>
<td>2</td>
<td>246b</td>
<td>248b</td>
<td>2</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td>246c</td>
<td>248c</td>
<td>2</td>
<td>83%</td>
</tr>
<tr>
<td>4</td>
<td>246d</td>
<td>248d</td>
<td>24</td>
<td>98%$^c$</td>
</tr>
<tr>
<td>5</td>
<td>246e</td>
<td>248e</td>
<td>4</td>
<td>60%</td>
</tr>
</tbody>
</table>

$^a$ 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.

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, but, a significant difference in the melting point was noted; 207-209 °C (Lit. 143-144 °C).

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.

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.](image)

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.](image)

1H 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-7\(a\) 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.

![Diagram of compound 252](image)

**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).

![X-ray structure of compound 252](image)

**Figure 3.4** X-ray structure 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.

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 structre 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.

![Scheme 3.37](image)

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methylamine</td>
<td>24 h</td>
<td>62%</td>
</tr>
<tr>
<td>2</td>
<td>n-Propylamine</td>
<td>48 h</td>
<td>49% (49%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Allylamine</td>
<td>48 h</td>
<td>43%</td>
</tr>
<tr>
<td>4</td>
<td>Hexylamine</td>
<td>48 h</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Benzylamine</td>
<td>48 h</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>Tryptamine</td>
<td>48 h</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>tert-Butylamine</td>
<td>48 h</td>
<td>0%</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions performed on 0.25 mmol scale using amine (0.25 mmol) in H<sub>2</sub>O (1 mL).
<sup>b</sup> Isolated yields after purification by column chromatography.
<sup>c</sup> Reaction complete in 18 h at 80 °C.

As seen in Table 3.3, propyl and allylamine 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 hexyamine, 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.

![Scheme 3.38](image)

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](image)

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, Scheme 4.2.

![Scheme 4.2](image)

Scheme 4.2 Selected steps in the synthesis of grandisine B 15 and mearsine 27.
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.](image)

### 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 diisopropylamide at −78 °C 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 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.](image)

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.
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$_4$Cl 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 °C and subsequent trapping with cyclohexane carboxaldehyde gave the aldol product 260b, Scheme 4.6. Oxidation with Dess-Martin periodinane 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 1H NMR spectrum were consistent with the bicyclic structure. The 13C 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 1H 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](image)

**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](image)

**Scheme 4.9** Synthesis of isoquinuclidinone 263a via amination/cyclisation sequence.
Pleasingly, analysis of the $^1$H NMR spectrum of the unpurified 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.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (262)</th>
<th>Product (263)</th>
<th>Time (h)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="262a" /></td>
<td><img src="image" alt="263a" /></td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="262b" /></td>
<td><img src="image" alt="263b" /></td>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="262c" /></td>
<td><img src="image" alt="263c" /></td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="262d" /></td>
<td><img src="image" alt="263d" /></td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="262e" /></td>
<td><img src="image" alt="263e" /></td>
<td>72</td>
<td>75(^c)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="262f" /></td>
<td><img src="image" alt="263f" /></td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="262g" /></td>
<td><img src="image" alt="263g" /></td>
<td>8</td>
<td>(~50%)^(^d)</td>
</tr>
</tbody>
</table>

\(^a\) 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.

\(^c\) dr = 3.4:1.

\(^d\) An inseparable 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 \(\alpha,\beta\)-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 substituents 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$_2$CO$_3$ 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](image_url)

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.

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 \textit{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](image)

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

It seems likely that the presence of the methyl substituent 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 \textit{in situ} ring opening was found to be general for a range of unsubstituted enones 257, Scheme 4.15, Table 4.2.

![Scheme 4.15](image)

**Scheme 4.15** Scope of methyl ester formation.
Table 4.2 Scope of methyl ester formation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (257)</th>
<th>Product (266)</th>
<th>Time (h)</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="257a" /></td>
<td><img src="image" alt="266a" /></td>
<td>2</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="257b" /></td>
<td><img src="image" alt="266b" /></td>
<td>2</td>
<td>Quant.</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="257c" /></td>
<td><img src="image" alt="266c" /></td>
<td>2</td>
<td>89%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="257d" /></td>
<td><img src="image" alt="266d" /></td>
<td>2</td>
<td>96%</td>
</tr>
</tbody>
</table>

\(^a\) 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,\(^6\) and recently used by Daloze as an intermediate in the synthesis of calvine 270.\(^7\) 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.

\[ 
\text{Scheme 4.16 Reduction of imine 266c with sodium borohydride.} 
\]

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. The partial structure is also common to a number of alkaloids, with representative examples including calvine 270 and sederine 271 (Figure 4.1).

\[ 
\text{Figure 4.1 Structures of histrionicotoxin 269, calvine 270 and sederine 271.} 
\]

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, 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.

\[ 
\text{Scheme 4.17 Proposed formation of grandisine G 20 from grandisine B 15.} 
\]
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*. 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).

![Figure 4.2 Structure of the *Elaeocarpus* alkaloid mearsine 27.](image)

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. 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.

![Scheme 4.19 Proposed synthesis of mearsine 27 from diketone 51.](image)
Although the racemic synthesis of diketone 51 had previously been reported by Geirsson, Scheme 4.20, there was no precedent for its enantioselective synthesis.

![Scheme 4.20](image)

**Scheme 4.20** Geirsson’s synthesis of diketone 51.

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

![Scheme 4.21](image)

**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, 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.
Although at the time unprecedented, a paper by Rovis and Lathrop recently reported the synthesis of aldehyde 274 using the described sequence.\textsuperscript{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 \(\alpha\)-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.

Imine 276 could also potentially undergo a retro-Michael reaction in the presence of \(\alpha\)-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\(_3\)N 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,\textsuperscript{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 °C, 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 °C furnished enone 51 in a respectable 74% yield, Scheme 4.26.

![Scheme 4.26](image)

**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 \( \text{C}_9\text{H}_{14}\text{O}_3 \) 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](image)

**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.](image)

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.](image)

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 $\sim$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$_9$H$_{14}$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.
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, would use the 1,3-diketone grandisine D 17 as a synthetic intermediate, Scheme 5.1.

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.

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.
Scheme 5.3 Synthesis of indolizidine aldehyde 172 using Overman's route.\(^5\)

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.\(^3\) 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.\(^3\)

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

Following the reported procedure,\(^3\) 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 °C 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.\textsuperscript{35} 27%). Reduction of both the amide and ester functionalities with excess DIBAL-H gave allylic alcohol 288 in a moderate 53% yield (Lit.\textsuperscript{35} 44%), Scheme 5.5. Alternative conditions for the reduction using LiAlH\textsubscript{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.

\begin{center}
\begin{tikzpicture}
\node[rotate=90] at (0,0) {Scheme 5.5 Taber's synthesis of alcohol 288.\textsuperscript{35}};
\end{tikzpicture}
\end{center}

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, \textsuperscript{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 preceded, 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. 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.](image)

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 preceded in the literature using Swern conditions, 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, fewer impurities were observed in the $^1$H NMR spectrum of the unpurified material, however, no improvement in the isolated yield was observed.

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 $-78 \, ^\circ \text{C}$ 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.
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.

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. 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, an effect employed by Snider in the synthesis of the cyclindricines. 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 initial 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, also failed to deliver the required hydroxy-ketones. 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. 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.](image)

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, giving, in some instances, the matched product exclusively.

Although the relative stereochemistry of grandisine B 15 has recently been confirmed by Tamura, we were unable to determine the relative stereochemistry of the hydroxy-ketones 287 and 294, which were tentatively assigned 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.\textsuperscript{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 substituent and exo-cyclic ketone. In contrast to 1,3-diketone substrates used in previous studies, only traces of the \textit{cis}-isomer/enol tautomer were apparent in the \textsuperscript{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\textsubscript{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,\textsuperscript{35} using PCC buffered with NaOAc resulted in complete conversion to diketone 17 as determined by \textsuperscript{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](image)

\textbf{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 \textsuperscript{1}H/\textsuperscript{13}C NMR spectroscopic data for which were consistent with those reported by Tamura and Carroll,\textsuperscript{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](image)

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](image)

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 1H 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.

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. 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 preceded, no alkaloids had been isolated from the family until the anomalous discovery of the alkaloid rosmaricine 297 in 1962 (Figure 5.2).113

![Figure 5.2 Structure of rosmaricine 297 as determined by Wenkert.](image)

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

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1 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.

![Scheme 5.15 Conversion of carnosic acid 298 into rosmaricine 297.](image)

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

![Scheme 5.16 General synthesis of the pyridine monoterpene alkaloids 301.](image)

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.\textsuperscript{116, 117}

\begin{center}
\begin{tikzpicture}
\t\node (a) at (0,0) {\textbf{302}}; \node (b) at (1,0) {\textbf{303}}; \node (c) at (2,0) {\textbf{304}};
\t\draw[->] (a) to node[above]{$\text{NH}_3$} (b);
\t\draw[->] (b) to node[above]{$\text{NH}_3$} (c);
\t\node (d) at (0,-1) {GlC O}; \node (e) at (1,-1) {GlC O}; \node (f) at (2,-1) {GlC O};
\end{tikzpicture}
\end{center}

\textbf{Scheme 5.17} Synthesis of gentianine 303 from gentiopicrin 302 and swertiarmarin 304.\textsuperscript{116, 117}

Subjecting plants of the family \textit{Gentainaceae}, from which gentianine had been isolated, to ammonia-free extractions showed that only \textit{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.\textsuperscript{118}

\begin{center}
\begin{tikzpicture}
\t\node (a) at (0,0) {\textbf{305}}; \node (b) at (1,0) {\textbf{306}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 5.18} Structures of the pyridine monoterpene alkaloids buddamin 305 and cantleyine 306.\textsuperscript{118}

\subsection*{5.9.3 Decussine (307)}

Work by Rolfsen \textit{et al.} identified biologically active compounds in extracts of the species \textit{Styrchnos decussate}.\textsuperscript{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).
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. Rolfson proposed that decussine 307 is formed from an indole derivative such aldehyde 308, Scheme 5.19.

Scheme 5.19 Proposed synthesis of the artefact alkaloid decussine 307.\textsuperscript{119}

5.9.4 Desmosine (311)

The alkaloid desmosine 311 was isolated in 1998 by Pas and co-workers from Desmos dumosus.\textsuperscript{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.

Scheme 5.20 Proposed synthesis of desmosine 311 from biological precursor 310.\textsuperscript{120}
5.10 Synthesis of Elaeocarpus Alkaloids

Having established a route to grandisine B, 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 and co-workers, who reported that the alkaloid elaeocarpenine 24 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.

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

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.

**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 via methoxide-promoted opening of the isoquinuclidinone ring. 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](image)

**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](image)

**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.

$$\text{Scheme 5.24 Attempted methoxide promoted ring opening of grandisine B 15.}$$

On closer inspection of the extraction procedure, 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$_2$O 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.
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.

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.

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 Elaeocarpine (4) / Isoelaeocarpine (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.

\[ \text{Scheme 5.28 Proposed synthesis of isoelaeocarpiline 5 from grandisine D 17.} \]

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 °C and 100 °C 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 isoeleacarpiline 5.

Repeating the microwave conditions reported by Geyelin gave a complex mixture of products, Scheme 5.30. 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 BCl3 in DCM to afford phenol 317 in 24% over two steps, Scheme 5.34.

Scheme 5.34 Synthesis of the elaecarpine 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 1H 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 1H NMR spectrum of the unpurified reaction mixture could represent the thermodynamic 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 elaecarpiline 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.

![Scheme 5.37 Proposed synthesis of grandisine C 16](image)

5.12 Selectivity of the Cyclisation Reaction

Carroll and co-workers only reported the isolation of isoelaeocarpiline 5, 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).

![Figure 5.5 Cyclisation intermediate 328.](image)

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](image)

**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\(_2\)SO\(_4\) also failed to show any evidence of the cyclisation product 5, Scheme 5.40.

![Scheme 5.39](image)

**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.

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.](image)

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

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. 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.
Whilst the anti-Markovnikov hydration of alkynes is preceded using transition metal catalysts on simple systems,\textsuperscript{123-127} classical methods for alkyne hydration are known to give the Markovnikov product.\textsuperscript{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.

\[ \text{Scheme 6.5} \text{ Retrosynthesis of carbonyl compound 333.} \]

### 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 \textit{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

\[ \text{Figure 6.1} \text{ Structures of elaeokanine 57 and elaeocarpenine 24.} \]

### 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,\textsuperscript{131} an intermediate previously used by Gmeiner, in the synthesis of triazolopeptide derivatives 337, Scheme 6.6.
Following a literature procedure,\textsuperscript{131} commercially available (S)-proline 338 was Boc-protected \textit{via} treatment with di-\textit{tert}-butyl carbonate in DCM, Scheme 6.7. Reduction of the carboxylic acid 339 with BH\textsubscript{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 preceded using the Corey-Fuchs protocol,\textsuperscript{131} or the Ohira-Bestmann reagent,\textsuperscript{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\textsubscript{4} and PPh\textsubscript{3} in DCM gave the dibromide 342 in 73% yield. Subsequent treatment with \textit{n}-BuLi in THF at \(-78 \, ^\circ\text{C}\) 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,\textsuperscript{133} also gave alkyne 336 in 74% yield.

**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,\textsuperscript{134} however, a number of impurities were also evident in the \textsuperscript{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.](image)

In order to test the viability of the route, we initially chose to investigate the synthesis of the *Elaeocarpus* alkaloid 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 elaokanine 57.](image)

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.
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.

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 $\alpha,\beta$-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. 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.

Scheme 6.12 Attempted elimination of hydroxy-ketone 59 using conditions reported by Koizumi.\textsuperscript{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.\textsuperscript{136}

Scheme 6.13 Attempted deprotection of cyclic acetal 346.

Heating acetal 346 in TFA led to complete consumption of the starting material, however, the \(^1\text{H} \) 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,\textsuperscript{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.\textsuperscript{138-145}

A particularly relevant paper by Saá, reported the Brønsted acid promoted intramolecular cyclisation of alkyne/aldehydes.\textsuperscript{146} Disappointingly, when alkyne \textbf{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 \textit{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) chloride to catalyse the cyclisation of alkyne/acetals to prepare a range of heterocycles.\textsuperscript{139} Due to unsuccessful cyclisation reactions using the proline-derived alkyne \textbf{346}, a literature example from the Yu's paper was initially repeated. The model substrate \textbf{351a} was prepared using a modification of the procedure reported by Yu;\textsuperscript{147} deprotonation of 3-phenyl-2-propyn-1-ol \textbf{349} with NaH in THF and trapping with bromo-acetaldehyde diethyl acetal \textbf{350} gave alkyne \textbf{351a} in 32\% yield, Scheme 6.14.

![Scheme 6.14 Synthesis of the model cyclisation substrate 351a.\textsuperscript{147}](image)

On subjecting alkyne \textbf{351a} to the reported conditions,\textsuperscript{139} TLC analysis showed a number of products to be present after 18 h at room temperature (Lit.\textsuperscript{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 \textbf{352a}, unreacted starting material \textbf{351a} and aldehyde \textbf{353} resulting from acetal hydrolysis, Scheme 6.15.
Based on previous work in the Taylor group, the reaction was also repeated using catalytic (10 mol%) tin(II) chloride dihydrate,\textsuperscript{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 \textsuperscript{15}. Aromatic-substituted alkynes are commonly used in literature studies; we therefore chose to prepare phenyl alkyne \textsuperscript{354} (Figure \textit{6.2}). The cyclic acetal was also replaced with the corresponding diethyl acetal, which we envisaged would be more susceptible to \textit{in situ} hydrolysis.

![Figure 6.2](image_url) Alternative cyclisation substrate \textsuperscript{354}.

The required alkylating agent was prepared using the procedure reported by Abad.\textsuperscript{149} Treatment of acrolein and sodium iodide in the presence of trimethylsilyl chloride and subsequent addition of ethanol gave the iodo-acetal \textsuperscript{355} in 81% yield, Scheme \textit{6.16}.\textsuperscript{150}
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.\textsuperscript{150, 151} Whilst the hydration of alkynes in the presence of metal catalysts is preceded, the reaction was unusual in the fact that the hydration of alkynes was achieved by simply heating in formic acid, Scheme 6.19.

\begin{center}
\textbf{Scheme 6.19} Formic acid mediated hydration of alkynes reported by Shvo.\textsuperscript{151}
\end{center}

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.\textsuperscript{151}

\begin{center}
\textbf{Scheme 6.20} Shvo's proposed mechanism for the formic acid mediated hydration of alkynes.\textsuperscript{151}
\end{center}

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.\textsuperscript{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 °C 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.](image)

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 initial alkyne hydration (Mechanism A).

Alternatively, the reaction could proceed via an oxete intermediate 374 (Mechanism B) as proposed by Harding,\textsuperscript{152} and more recently Krische and Li,\textsuperscript{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.\textsuperscript{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.

![Scheme 6.26](image)

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

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

![Scheme 6.27](image)

**Scheme 6.27** Scope of the formic acid mediated cyclisation.
Table 6.1 Scope of the formic acid mediated alkyne/acetal cyclisation.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (351)</th>
<th>Product (352)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Structure]</td>
<td>352a</td>
<td>98% (98%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>[Structure]</td>
<td>352b</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>[Structure]</td>
<td>352c</td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td>[Structure]</td>
<td>352d</td>
<td>64%</td>
</tr>
<tr>
<td>5</td>
<td>[Structure]</td>
<td>352e</td>
<td>77%</td>
</tr>
<tr>
<td>6</td>
<td>[Structure]</td>
<td>352f</td>
<td>69%</td>
</tr>
</tbody>
</table>

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

<sup>b</sup> Isolated yields after column chromatography.

<sup>c</sup> 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.](image)

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.](image)

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; reduction with DIBAL-H gave the corresponding alcohol 380, the data for
which were consistent with the \textit{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.

\begin{center}
\begin{tikzpicture}
\node[draw] (a) at (0,0) {378};
\node[draw] (b) at (2,0) {380};
\node[draw] (c) at (2,1) {381};
\node[draw] (d) at (0,1) {382};
\draw[->] (a) -- (b) node[midway,above] {\text{DIBAL-H}};
\draw[->] (b) -- (c) node[midway,above] {\text{DCM, -78 °C}};
\draw[->] (d) -- (b) node[pos=0.5,above] {65\%};
\end{tikzpicture}
\end{center}

\textbf{Scheme 6.30} Reduction of \textit{exo}-cyclic ketone 378.\textsuperscript{154}

The same reaction conditions were also applied to the analogous \textit{N}-tosyl substrate 384, prepared in 2 steps from 2-pentynyl aniline 382. Treatment with tosyl chloride and pyridine gave the corresponding \textit{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.

\begin{center}
\begin{tikzpicture}
\node[draw] (a) at (0,0) {382};
\node[draw] (b) at (2,0) {383};
\node[draw] (c) at (4,0) {384};
\node[draw] (d) at (0,1) {1. \text{TsCl, Py}};
\node[draw] (e) at (2,1) {2. \text{PPh\textsubscript{3}, DIAD}};
\node[draw] (f) at (0,2) {100 °C, 30 min};
\node[draw] (g) at (2,2) {HCO\textsubscript{2}H};
\draw[->] (a) -- (b) node[pos=0.5,above] {87\%};
\draw[->] (b) -- (c) node[pos=0.5,above] {60\%};
\end{tikzpicture}
\end{center}

\textbf{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](image)

**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](image)

**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 multiplet at 6.55 ppm was consistent with the unsaturated ketone. On scale-up the phenyl-substituted 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 substituents, which could be used as a handle to further elaborate the indolizidine core unit, were therefore considered, Scheme 6.36.

\[ \text{Scheme 6.36 Proposed synthesis of grandisine D 17.} \]

### 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.\(^{155}\)

\[ \text{Scheme 6.37 Gesson's } N\text{-acyliminium ion cyclisation using bromo-alkyne 391.}^{155} \]

Disappointingly, attempts to prepare the bromo-alkyne 394 using a range of reported conditions proved unsuccessful,\(^{156-158}\) Scheme 6.38, Table 6.2.

\[ \text{Scheme 6.38 Attempted synthesis of bromo-alkyne 394.} \]
Table 6.2 Attempted synthesis of bromo alkyne 394.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CBr₄, PPh₃, DCM, rt</td>
<td>Complex mixture</td>
<td>156</td>
</tr>
<tr>
<td>2</td>
<td>NBS, AgNO₃, Acetone, rt</td>
<td>Complex mixture</td>
<td>157</td>
</tr>
<tr>
<td>3</td>
<td>Br₂, KOH, H₂O, 0 ºC</td>
<td>Complex mixture</td>
<td>158</td>
</tr>
</tbody>
</table>

6.10.2 Thioalkynes

Publications as early as 1959 reported the conversion of thioalkynes into the corresponding thioesters on treatment with acid. 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, and also by Maruyama and co-workers in synthetic studies towards carbapenem derivatives.


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, 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$_2$S$_2$, 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.

![Scheme 6.41](image1)

**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.

![Scheme 6.42](image2)

**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. 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.
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 preceded Fukuyama reduction, Scheme 6.46.164

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(PPh₃)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, H₂) 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 NaBH₄ 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 ¹H 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 ¹H NMR spectroscopic data for which corresponded to the natural products tashiromine 407 and *epi*-tashiromine 408.⁶⁶ 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.

![Scheme 6.47 Attempted reduction of thioester 400 with LiAlH₄.](image)

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.⁶⁶ +44.7 (c 1.1, EtOH)] suggesting no loss of enantiomeric purity throughout the synthesis.
Conditions reported by Wang,\textsuperscript{168} for the selective reduction of unsaturated esters, using lithium aluminium hydride and benzyl chloride to generate AlH\textsubscript{3} \textit{in situ}, also failed to yield alcohol 288. Difficulties were also encountered when DIBAL-H was used as the reductant, which gave inseparable 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.

![Scheme 6.48](image)

\textbf{Scheme 6.48} Attempted reduction of ethyl thioester 402.

\textbf{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.\textsuperscript{169}
On treating ethyl thioester 288 with sodium methoxide in methanol, following the procedure of Krische,\textsuperscript{170} the formation of a second species was noted on TLC analysis. \textsuperscript{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.

Scheme 6.49  Attempted synthesis of methyl ester 409 using conditions reported by Krische.\textsuperscript{170}

A reaction using silver(I) trifluoromethanesulfonate in DCM/methanol following the procedure of Hanessian,\textsuperscript{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 °C 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.

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.\textsuperscript{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.

The optical rotation for the synthetic material [(+70.0 (c 0.52, CHCl₃))] was similar to that reported by Jørgensen [(Lit. [105] −74.6 (c 0.5, CHCl₃))], 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.
A similar strategy was used by Danheiser et al. in their synthesis of the natural product ascochlorin. Alkylation of the menthol-derived alkoxy ketone 414 via treatment with lithium diisopropyl 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.

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

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 1H 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.](image)

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.
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,\textsuperscript{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.

Although low yielding, we were encouraged by this initial result. The more complex target, elaeokanidine A 419, isolated from the \textit{Elaeocarpus kaniensis} by Lamberton and co-workers in 1972,\textsuperscript{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 \textit{via} addition of propenyl magnesium bromide to thioester 400, Scheme 6.59.
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. 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 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.
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.

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 quantities 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.
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). 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, 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. 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).

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\textsuperscript{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\textsubscript{3} (2 × 100 mL) and brine (100 mL). The organic phase was dried (Na\textsubscript{2}SO\textsubscript{4}), then concentrated \textit{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 °C (0.5 mmHg); \( R_f \) 0.25 (DCM); \( \delta \textsubscript{H} \) (400 MHz, CDCl\textsubscript{3}) 4.64 (1 H, dd, \( J = 4.0, 3.0, \) H-5), 3.90-3.82 (1 H, m, H-9\textsubscript{a}), 3.82 (1 H, dt, \( J = 9.7, 7.0, \) H-4\textsubscript{a}), 3.55 (1 H, dt, \( J = 9.7, 7.0, \) H-4\textsubscript{b}), 3.53-3.46 (1 H, m, H-9\textsubscript{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).

\textbf{Lab Book Ref.} = JDC/1/1

Data were consistent with those published.\textsuperscript{57}

\[
\begin{align*}
\text{Trimethyl(4-(tetrahydro-2H-pyran-2-yl oxy)but-1-ynyl)silane}\textsuperscript{57} 159: & \quad \text{To a stirred solution of alkyne 158 (50.0 g, 324.5 mmol, 1.0 equiv.) in diethyl ether (180 mL) at −78 °C was added } n\text{-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 °C then chlorotrimethylsilane (43.2 mL, 340.7 mmol, 1.05 equiv.) was added dropwise over 1 h. After stirring at −78 °C 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\textsubscript{4}), then concentrated \textit{in vacuo} to give the title compound 159 (69.6 g, 95%) as an orange oil; \( R_f \) 0.56 (DCM); \( \delta \textsubscript{H} \) (400 MHz, CDCl\textsubscript{3}) 4.65 (1 H, dd, \( J = 3.5, 3.5, \) H-5), 3.92-3.85 (1 H, m, H-9\textsubscript{a}), 3.80 (1 H, dt, \( J = 9.6, 7.2, \) H-4\textsubscript{a}), 3.53 (1 H, dt, \( J = 9.6, 7.2, \) H-4\textsubscript{b}), 3.53-3.46 (1 H, m, H-9\textsubscript{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).
\end{align*}
\]

\textbf{Lab Book Ref.} = JDC/1/16

Data were consistent with those published.\textsuperscript{57}
(E)-(1-Bromo-4-(tetrahydro-2H-pyran-2-yl oxy)but-1-enyl)trimethylsilane\textsuperscript{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 °C was added dropwise diisobutylaluminium 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 °C and held for 2 h. The colourless solution was cooled to 0 °C, then pyridine (4.56 mL, 56.4 mmol, 1.7 equiv.) was added. The yellow solution was cooled to −78 °C 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 °C, 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), H₂O (2 × 20 mL) and brine (20 mL), then dried (Na₂SO₄). 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 °C (0.25 mmHg); R\textsubscript{f} 0.32 (DCM); δ\textsubscript{H} (400 MHz, CDCl₃) 6.78 (1 H, t, \(J = 8.0\), H₂), 4.58 (1 H, dd, \(J = 3.9, 2.9\), H-5), 3.90-3.79 (1 H, m, H-9\textsubscript{a}), 3.75 (1 H, dt, \(J = 9.6, 6.7\), H-4\textsubscript{a}), 3.55-3.45 (1 H, m, H-9\textsubscript{b}), 3.41 (1 H, dt, \(J = 9.6, 6.7\), H-4\textsubscript{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.\textsuperscript{57}

(E)-4-Bromo-4-(trimethylsilyl)but-3-en-1-ol\textsuperscript{57} 161: A stirred solution of alkene 160 (4.50 g, 14.6 mmol, 1.0 equiv.) and pyridinium p-toluenesulphonate (0.28 g, 1.10 mmol, 0.08 equiv.) in methanol (170 mL) was heated at 40 °C 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); \( \delta_H \) (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.\(^{57}\)

\( (E)\)-(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 °C 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\(_2\)SO\(_4\)). 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); \( \delta_H \) (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.\(^{57}\)

\( (E)\)-(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 °C was added sodium borohydride (0.95 g, 25.4 mmol, 4.0 equiv.). The reaction was stirred at 0 °C 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 (Na₂SO₄), then concentrated in vacuo to give the title compound 163 (1.80 g, 93%) as a pale yellow oil; Rf 0.38 (DCM/methanol, 9:1); δH (400 MHz, CDCl₃) 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-4a), 3.30-3.20 (1 H, m, H-4b), 2.57-2.49 (1 H, m, H-3a), 2.48-2.24 (4 H, m, H-6, 7), 1.93-1.86 (1 H, m, H-3b), 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(8H)-one⁵⁷ 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 (SiO₂, DCM/MeOH, 98:2) to give the title compound 164 (1.05 g, 83%) as a pale yellow oil; Rf 0.19 (EtOAc/PE, 7:3); δH (400 MHz, CDCl₃) 6.12 (1 H, ddd, J = 6.1, 2.3, 2.0, H-7), 4.27-4.19 (2 H, m, H-5a, 9), 2.85 (1 H, ddd, J = 13.4, 11.5, 4.7, H-5b), 2.49-2.27 (4 H, m, H-1a, 2, 6a), 2.21-2.09 (1 H, m, H-6b), 1.81-1.69 (1 H, m, H-1b).

Lab Book Ref. = JDC/3/88
Data were consistent with those published.⁵⁷

8-Bromo-1,2,3,5,6,8a-hexahydroindolizine⁵⁷ 74: To a stirred solution of lithium aluminium hydride (4.0 M in Et₂O, 1.70 mL, 6.80 mmol, 2.7 equiv.) in diethyl ether (60 mL) at 0 °C 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 °C before quenching with excess sodium sulfate decahydrate. The slurry was stirred at 0 °C for 45 min., then filtered through celite and the residual solid washed with diethyl ether (2 × 25 mL). The combined organic extracts were dried (Na₂SO₄), then concentrated in vacuo to give the title compound 74 (148 mg, 85%) as a pale yellow oil; Rᵥ 0.31 (DCM/MeOH, 9:1); δH (400 MHz, CDCl₃) 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-5a), 2.93-2.84 (2 H, m, H-3a, 5b), 2.83-2.77 (1 H, m, H-3b), 2.40 (1 H, ddddd, J = 17.4, 10.0, 5.9, 3.1, 3.1, H-6a), 2.16-2.06 (1 H, m, H-1a), 2.06-1.97 (1 H, m, H-6b), 1.88-1.73 (3 H, m, H-1b, 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 °C 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. NaHCO₃ (5 mL). The organic phase was separated and the aqueous phase extracted with DCM (4 × 5 mL). The combined organics were dried (Na₂SO₄) then concentrated in vacuo to give the title compound 168 (128 mg, 94%) as a colourless oil; Rᵥ 0.86 (DCM); νₓₒₓₓ/cm⁻¹ (neat) 2958, 2901, 1607, 1356, 1251, 1174, 968; δH (400 MHz, CDCl₃) 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); δC (125 MHz, CDCl₃) 141.0 (CH, C-2), 132.2 (C, C-1), 67.9 (CH₂, C-4), 37.7 (CH₃, C-6), 32.1 (CH₂, C-3), 0.2 (CH₃, C-5); m/z (ESI) 323 [MNa]+; [HRMS (ESI): calcd. for C₈H₁₇⁷⁹BrNaO₃SiS, 322.9743. Found: [MNa]+, 322.9748 (1.5 ppm error)].

Lab Book Ref. = JDC/1/57

165
(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 °C was added triphenylphosphine (131 mg, 0.50 mmol, 1.1 equiv.). The reaction was stirred at 0 °C 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); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3019, 2977, 2873, 1253, 1217, 844, 759; \(\delta_H\) (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); \(\delta_C\) (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\(_7\)H\(_{14}\)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 °C was added dropwise tert-BuLi (1.6 M in pentane, 155 \(\mu\)L, 0.25 mmol, 2.1 equiv.). The reaction was stirred at −78 °C for 30 min. then benzaldehyde (30 \(\mu\)L, 0.27 mmol, 2.3 equiv.) was added dropwise. The reaction was stirred at −78 °C 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\(_2\)CO\(_3\) then extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na\(_2\)SO\(_4\)), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (Al\(_2\)O\(_3\), DCM/methanol, 95:5) to give the title compounds 170 and 171 (16 mg, 56%, 1:1

166
mixture of diastereoisomers) as a yellow oil; $R_f$ 0.10 (DCM/MeOH, 4:1); $\delta_H$ (400 MHz, CDCl$_3$) 7.39-7.28 (10 H, 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-3a, 5a, 9'), 2.61-2.44 (4 H, m, H-3b, 5b), 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-1a, 1b, 1a', 2), 1.41-1.30 (1 H, m, H-1b').

**Lab Book Ref. = JDC/1/31**

Data were consistent with those published.$^56$

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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 °C 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 °C (Lit. 197-198 °C); $R_f$ 0.36 (DCM/MeOH, 9:1); $\delta_H$ (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.$^{179}$

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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 °C was added dropwise hydrogen peroxide (30 wt% aq., 1.5 mL, 13.0 mmol, 2.2 equiv). The solution was stirred at 0 °C 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$_2$SO$_4$), 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); $\delta_H$ (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

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**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 Boc₂O (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 (Na₂SO₄), then concentrated *in vacuo* to give the title compound 182 (127 mg, 75%) as a colourless oil; *Rf* 0.33 (SiO₂, PE/EtOAc, 2:1); δ₉ (400 MHz, C₆D₆, 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

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**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. NH₄Cl (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 (MgSO₄), then concentrated in vacuo to give a yellow oil which was purified by column chromatography (SiO₂, PE/EtOAc, 2:1) to give the title compound 195 (83 mg, 97%) as a colourless crystalline solid; mp. 90–91 °C (Lit. 95–97 °C); Rₚ 0.39 (SiO₂, DCM/MeOH, 19:1); δₓ (400 MHz, CDCl₃) 7.33–7.22 (5 H, m, ArH), 4.55 (2 H, s, Hₗ7), 3.49–3.44 (1 H, m, H₁), 2.67-2.62 (1 H, m, H₄), 1.75-1.65 (2 H, m, H₅a), 1.75-1.65 (2 H, m, H₅b), 1.59-1.47 (4 H, m, H₆); δₓ (100 MHz, CDCl₃) 175.5 (CO, C₃), 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 (CH₂, C-7), 38.4 (CH, C-4), 27.0 (2 × CH₂, C-6), 24.4 (2 × CH₂, C-5).

**Lab Book Ref. = JDC/2/77**

Data were consistent with those published.

**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 °C 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 °C for 1 h, then Boc₂O (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. NH₄Cl (5 mL). The organic phase was extracted with diethyl ether (3 × 20 mL), dried (MgSO₄), then concentrated in vacuo to afford a white residue which was purified by column chromatography (SiO₂, PE/Et₂O, 1:1) to give the title compound 197 (72 mg, 80%) as a colourless crystalline solid; mp. 120-121 °C; Rₚ 0.79 (DCM/MeOH, 9:1); νₚₓ/cm⁻¹ (thin film) 2966, 1729, 1706, 1302, 1157; δₓ (400 MHz, CDCl₃) 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); δₓ (100 MHz, CDCl₃) 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 × CH₃, C-9), 26.0 (2 × CH₂, C-6), 23.1 (2 × CH₂, C-5); m/z (ESI) 248 [MNa]⁺; [HRMS (ESI): calcd. for C₁₂H₁₉NNaO₃, 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 (SiO₂, PE/DCM, 1:1) to give the title compound 200 (304 mg, 94%) as a colourless crystalline solid; mp. 96-98 °C (Hexane); \( R_f \) 0.06 (SiO₂, PE/EtOAc, 1:1); \( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 3019, 2964, 1499, 1357, 1215, 755, 668; \( \delta_H \) (400 MHz, CDCl₃) 7.38-7.28 (5 H, m, ArH), 5.17 (2 H, s, H-7), 3.74 (1 H, tt, \( J = 3.8, 2.0, \text{ H-1} \)), 1.85-1.66 (4 H, m, H-5), 1.63-1.48 (4 H, m, H-6); \( \delta_C \) (100 MHz, CDCl₃) 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 (CH₂, C-7), 48.4 (CH, C-4), 27.0 (2 × CH₂, C-6), 24.5 (2 × CH₂, C-5); \( m/z \) (ESI) 254 [MNa]⁺; [HRMS (ESI): calcd. for C₁₄H_{17}NNaS, 254.0974. Found: [MNa]⁺, 254.0970 (1.7 ppm error)]; Anal. Calcd. for C₁₄H_{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 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 2942, 1571, 1452, 1354, 746; \( \delta_H \) (400 MHz, CDCl₃) 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-5a), 1.93-1.67 (6 H, m, H-5b, 6); \( \delta_C \) (100 MHz, CDCl₃)
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 (CH₂, C-7), 37.0 (CH, C-4), 25.7 (2 × CH₂, C-6), 24.1 (2 × CH₂, C-5), 17.2 (CH₃, C-8); m/z (ESI) 246 M⁺; [HRMS (ESI): calcd. for C₁₅H₂₀NS, 246.1311. Found: M⁺, 246.1319 (3.4 ppm error)].

**Lab Book Ref. = JDC/3/10**

![Chemical Structure](image)

**2-Azabicyclo[2.2.2]octane-3-thione**<sup>56</sup> 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 (SiO₂, PE/DCM, 1:1) to give the title compound 205 (92 mg, 79%) as a colourless crystalline solid; mp. 155-157 °C (Lit. 152-154 °C); R<sub>f</sub> 0.25 (PE/EtOAc, 2:1); δ<sub>H</sub> (400 MHz, CDCl₃) 8.73 (1 H, br s, H₅), 3.77-3.71 (1 H, m, H₄), 3.23-3.19 (1 H, m, H-1), 3.23-3.19 (1 H, m, H-1), 1.80-1.66 (8 H, m, H-5, 6).

**Lab Book Ref. = JDC/3/32**

Data were consistent with those published.<sup>56</sup>

![Chemical Structure](image)

**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 °C 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 °C 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 CHCl₃ (50 mL). The organic phase was washed with 25% aq. NH₃ (3 × 20 mL), then the combined aqueous washes were back extracted with CHCl₃ (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄), the concentrated in vacuo to afford a brown film which was purified by column chromatography (SiO₂, PE/EtOAc, 2:1) to give the title compound 205 (9 mg, 27%) as a yellow film; \( R_f \) 0.38 (SiO₂, PE/EtOAc, 2:1); δH (400 MHz, CDCl₃) 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.

(Cyclohexa-1,5-dienyloxy)trimethylsilane⁷⁴ 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 °C was added cyclohexenone (1.01 mL, 10.4 mmol, 1.0 equiv.). The solution was held at 0 °C for 30 min., then trimethylsilyl chloride (2.60 mL, 20.8 mmol, 2.0 equiv.) was added and the solution was held at 0 °C for a further 2 h. The reaction was quenched with triethylamine (0.2 mL) and saturated aqueous NaHCO₃ (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. NaHCO₃ (30 mL) and brine (30 mL), dried (Na₂SO₄), 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 °C (9 mmHg), (Lit.⁷⁴ 60 °C (9 mmHg)); δH (400 MHz, CDCl₃) 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 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 (MgSO₄), then concentrated in vacuo to afford a dark brown oil which was purified by column chromatography (SiO₂, PE/EtOAc, 1:2) to give the title compound 213 (429 mg, 34%) as an off-white solid; mp. 129-131 ºC (n-hexane); R₅ 0.53 (SiO₂, PE/EtOAc, 2:1); υmax/cm⁻¹ (thin film) 2949, 1726, 1513, 1248, 1212, 1040, 754; δH (400 MHz, CDCl₃) 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, H₁), 3.76 (3 H, s, H₁₃), 3.64 (1 H, ddd, J = 9.9, 2.4, 2.4, H₃ₐ), 3.47 (1 H, br d, J = 9.9, H₃ₐ), 2.67 (1 H, ddd, J = 18.5, 2.9, 2.9, H₆ₐ), 2.64-2.60 (1 H, m, H₄), 2.42 (1 H, dd, J = 18.5, 1.9, H₆ₐ), 2.22-2.12 (1 H, m, H₇ₐ), 2.06-1.91 (2 H, m, H₈), 1.85-1.75 (1 H, m, H₇ₐ); δC (100 MHz, CDCl₃) 213.9 (CO, C₅), 151.5 (C, ArC), 142.9 (C, ArC), 115.0 (2 × CH, ArCH), 112.9 (2 × CH, ArCH), 55.8 (CH₃, C-13), 50.7 (CH₂, C-3), 48.2 (CH, C-1), 45.0 (CH₂, C-6), 44.3 (CH, C-4), 25.0 (CH₂, C-7), 22.2 (CH₂, C-8); m/z (ESI) 254 [M+Na]⁺; [HRMS (ESI): calcd. for C₁₄H₁₇NNaO₂, 254.1151. Found: [M+Na]⁺, 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 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,
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$_2$SO$_4$), 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 °C (diisopropyl ether); $R_f$ 0.66 (PE/EtOAc, 1:1); [α]$^D_{24}$ −85.6 ($c$ 0.85, CHCl$_3$), (Lit.$^{50}$ −71.8 ($c$ 1.7, CHCl$_3$); $v_{	ext{max}}$/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$_3$), 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$_2$, 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.$^{50}$

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**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$_2$O (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$_2$SO$_4$), then concentrated in vacuo to afford a brown film which was purified by
flash chromatography (SiO\textsubscript{2}, PE/EtOAc, 2:1) to give the title compound \textit{225} (11 mg, 39\%) as a colourless oil; \(R_f\) 0.49 (PE/EtOAc, 2:1); \(v_{\text{max}}/\text{cm}^{-1}\) (thin film) 2967, 2929, 1737, 1695, 1401, 1172, 1108; \(\delta_H\) (400 MHz, CDCl\textsubscript{3}, Rotamers observed) 4.08 (1 H, dd, \(J = 3.4, 3.4, \text{H-1}\)), 3.91 (1 H, dd, \(J = 3.3, 2.4, \text{H-1}\)), 3.59-3.52 (2 H, m, H-2), 3.50-3.40 (2 H, m, H-2), 2.64 (1 H, dd, \(J = 19.1, 3.4, \text{H-6}\_a\)), 2.62 (1 H, dd, \(J = 19.1, 2.5, \text{H-6}\_a\)), 2.5-2.51 (1 H, m, H-3), 2.43 (1 H, \(J = 19.1, 3.4, \text{H-6}\_b\)), 2.41 (1 H, dd, \(J = 19.1, 3.3, \text{H-6}\_b\)), 1.69-1.66 (4 H, m, H-8), 1.48-1.44 (18 H, s, H-11), 1.10 (3 H, s, CH\textsubscript{3}), 1.09 (3 H, s, CH\textsubscript{3}), 1.03 (3 H, s, CH\textsubscript{3}), 1.02 (3 H, s, CH\textsubscript{3}); \(\delta_C\) (100 MHz, CDCl\textsubscript{3}) 213.0 (CO, C\textsubscript{5}), 212.5 (CO, C\textsubscript{5}'), 154.9 (CO, C\textsubscript{9}), 154.8 (CO, C\textsubscript{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\textsubscript{2}, C-3), 44.9 (CH, C-4'), 44.4 (CH\textsubscript{2}, C-3'), 41.6 (CH\textsubscript{2}, C-6), 41.5 (CH\textsubscript{2}, C-6'), 38.3 (CH\textsubscript{2}, C-8), 38.2 (CH\textsubscript{2}, C-8'), 34.6 (C, C-7), 34.5 (C, C-7), 29.5 (CH\textsubscript{3}), 29.4 (CH\textsubscript{3}), 28.4 (CH\textsubscript{3}, C-11, 11'); \(m/z\) (ESI) 276 [MNa]\textsuperscript{+}; [HRMS (ESI): calcd. for C\textsubscript{14}H\textsubscript{23}NNaO\textsubscript{3}, 276.1570. Found: [MNa]\textsuperscript{+}, 276.1577 (2.3 ppm error)].

\textbf{Lab Book Ref.} = JDC/3/3

\begin{align*}
\text{2-(4-Methoxyphenyl)-7,7-dimethyl-2-azabicyclo[2.2.2]octane-3,5-dione 227:} & \quad \text{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}_2\text{O (1 mL). The reaction was held at rt for 3 h, then excess sodium metabisulfite was added until a colourless solution remained. The organic} \quad \text{compounds were extracted with DCM (3 \times 10 mL), dried (Na}_2\text{SO}_4), \text{then concentrated in vacuo to give the title compound 227 (46 mg, 48\%) as a white solid; mp. 136-139 °C; } R_t 0.41 (PE/EtOAc, 1:1); [\alpha]^{24}_D + 4.3 (c 1.01, CHCl\textsubscript{3}); v_{\text{max}}/\text{cm}^{-1}\text{ (thin film) 3019, 1739, 1680, 1513, 1214, 754; } \delta_H\text{ (400 MHz, CDCl}_3) 7.28 (2 H, d, } J = 9.0, \text{ArCH}), 6.91 (2 H, d, } J = 9.0, \text{ArCH}), 3.84 (1 H, dd, } J = 3.2, 2.1, \text{H-1}), 3.80 (3 H, s, H-13), 3.37 (1 H, dd, } J = 3.4, 2.4, \text{H-4}), 2.79 (1 H, dd, } J = 18.9, 2.1, \text{H-6}_a), 2.60 (1 H, dd, } J = 18.9, 3.2, \text{H-6}_b), 2.06 (1 H, dd, } J = 13.8, 3.4, \text{H-8}_a), 1.89 (1 H, dd, } J = 13.8, 2.4, \text{H-8}_b), 1.25 (3 H, s, CH\textsubscript{3}), 1.17 (3 H, s, CH\textsubscript{3}); \delta_C\text{ (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 \times CH,} \end{align*}
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 °C was added ceric ammonium nitrate (44 mg, 0.08 mmol, 4.4 equiv.) as a solution in H₂O (0.25 mL). The solution was held at 0 °C 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 (Na₂SO₄), then concentrated in vacuo to give the title compound 228 (3 mg, Quant.) as an off-white film contaminated with p-benzoquinone; Rₖ 0.41 (DCM/MeOH, 9:1); νmax/cm⁻¹ (thin film) 3249, 2964, 1734, 1688; δ₁H (400 MHz, CDCl₃) 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-6ₐ), 2.38 (1 H, dd, J = 18.9, 3.2, H-6ₐ), 1.90 (1 H, dd, J = 13.8, 2.5, H-8ₐ), 1.81 (1 H, dd, J = 13.8, 2.5, H-8ₐ), 1.18 (3 H, s, CH₃), 1.13 (3 H, s, CH₃); δ₁C (100 MHz, CDCl₃) 205.8 (CO, C-5), 170.8 (CO, C-3), 58.6 (CH, C-4), 57.7 (CH, C-1), 39.8 (CH₂, C-6), 37.4 (CH₂, C-8), 35.7 (C, C-7), 29.2 (CH₃), 27.6 (CH₃); m/z (ESI) 190 [MNa]⁺; [HRMS (ESI): calcd. for C₉H₁₃NNaO₂, 190.0838. Found: [MNa]⁺, 190.0846 (3.8 ppm error)].

Lab Book Ref. = JDC/2/100

3-Ethoxy-5-methylcyclohex-2-enone 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. NaHCO₃ (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 (MgSO₄), then concentrated in vacuo to give the title compound 237 (5.74 g, 94%) as a pale yellow oil; Rₛ 0.53 (EtOAc); δ_H (400 MHz, CDCl₃) 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-4ₐ), 2.02 (1 H, dd, J = 16.8, 11.7, H-4ₐ), 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

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### 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 H₂O (0.35 mL), 10% aq. NaOH (1.05 mL) then H₂O (0.35 mL). The resulting slurry was stirred at rt for 2 h, then filtered. To the colourless filtrate was added 10% aq. H₂SO₄ (10 mL), then the biphasic solution was stirred overnight. The organic phase was separated and washed with sat. aq. NaHCO₃ (25 mL), dried (Na₂SO₄), 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 °C (8 mmHg), (Lit.⁸⁴ 38-41 °C (1 mmHg)); Rₛ 0.58 (PE/EtOAc, 2:1); δ_H (400 MHz, CDCl₃) 6.95 (1 H, ddd, J = 10.1, 2.5, 1.0, 1.0, H-2), 2.50-2.45 (1 H, m, H-6ₐ), 2.45-2.37 (1 H, m, H-4ₐ), 2.29-2.15 (1 H, m, H-5), 2.11 (1 H, dd, J = 15.9, 12.3, H-6ₐ), 2.03 (1 H, dddd, J = 18.5, 9.8, 2.6, 2.5, H-4ₐ), 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-(1R*,6S*)-6-methyl-2-oxocyclohex-3-enecarboxylate 246a:**

![Chemical Structure](image)

Ethyl (1R*,2S*)-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. NH₄Cl (20 mL). The ethanol was removed under reduced pressure and the oil was taken up in Et₂O (100 mL). The aqueous phase was separated and extracted with Et₂O (100 mL), then the combined organic extracts were washed with brine (100 mL), dried (MgSO₄), 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-(1R*,6S*)-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. NaHCO₃ (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL), then the combined organics were washed with brine (50 mL), dried (MgSO₄), then concentrated in vacuo to afford a brown oil which was purified by column chromatography (SiO₂, PE/EtOAc, 4:1) to give the title compound 246a (1.39 g, 30%) as a pale yellow oil; Rₖ 0.38 (PE/Et₂O, 2:1); νₘₐₓ/cm⁻¹ (neat) = 2964, 2932, 1738, 1678, 1261, 1148; δ (400 MHz, CDCl₃) 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-8a), 4.25 (1 H, dq, J = 10.8, 7.1, H-8b), 3.10 (1 H, d, J = 11.7, H-1), 2.65-2.44 (2 H, m,
H-5<sub>a</sub>, 6), 2.12 (1 H, dddd, J = 18.9, 10.0, 2.8, 2.6, H-5<sub>b</sub>), 1.29 (3 H, t, J = 7.1, H-9), 1.08 (3 H, d, J = 6.5, H-10); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 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<sub>2</sub>, C-8), 33.0 (CH<sub>2</sub>, C-5), 32.7 (CH, C-6), 19.7 (CH<sub>3</sub>, C-10), 14.1 (CH<sub>3</sub>, C-9); m/z (ESI) 205 [MNa]<sup>+</sup>; [HRMS (ESI): calcd. for C<sub>10</sub>H<sub>14</sub>NaO<sub>3</sub>, 205.0835. Found: [MNa]<sup>+</sup>, 205.0832 (1.6 ppm error)]

**Lab Book Ref. = JDC/4/29**

Data were consistent with those published.<sup>90</sup>

![Ethyl-(1R*,6S*)-2-oxo-6-phenylcyclohex-3-enecarboxylate](image)

**Ethyl-(1R*,6S*)-2-oxo-6-phenylcyclohex-3-enecarboxylate**<sup>92</sup> **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 °C. 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 °C for 1 h, then quenched with 10% aq. HCl (10 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 × 10 mL), then the combined organics were washed with brine (10 mL), dried (MgSO<sub>4</sub>), then concentrated <i>in vacuo</i> to afford a yellow oil which was purified by column chromatography (SiO<sub>2</sub>, PE/EtOAc, 9:1) to give the title compound **246b** (297 mg, 61%) as a colourless crystalline solid; mp. 53-55 °C; R<sub>f</sub> 0.69 (PE/EtOAc, 2:1); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 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<sub>b</sub>), 2.62 (1 H, dddd, J =18.8, 9.9, 2.7, 2.5, H-5<sub>a</sub>), 1.01 (3 H, t, J = 7.1, H-9).

**Lab Book Ref. = JDC/11/3**

Data were consistent with those published.<sup>92</sup>
Representative Procedure for the Synthesis of $\beta$-Ketoester Substrates 246:

**Ethyl 5,5-dimethyl-2-oxocyclohex-3-enecarboxylate** 246c: To a stirred solution of diisopropylamine (0.70 mL, 4.95 mmol, 1.5 equiv.) in THF (10 mL) at 0 °C 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 °C for 30 min. then cooled to −78 °C, 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 °C for 1 h, then ethyl cyanoformate (0.49 mL, 4.95 mmol, 1.5 equiv.) was added. The solution was stirred at −78 °C for a further 1 h, then quenched with sat. aq. NH$_4$Cl (5 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), then the combined organic extracts were washed with H$_2$O (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/EtOAc, 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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2962, 1740, 1683, 1302, 1238; $\delta_H$ (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-8a), 4.22 (1 H, dq, $J = 10.8$, 7.1, H-8b), 3.52 (1 H, dd, $J = 13.7$, 4.8, H-1), 2.29 (1 H, dd, $J = 13.7$, 13.5, H-6a), 1.97 (1 H, ddd, $J = 13.5$, 4.8, 2.0, H-6b), 1.29 (3 H, t, $J = 7.1$, H-9), 1.19 (3 H, s, CH$_3$), 1.04 (3 H, s, CH$_3$); $\delta_C$ (100 MHz, CDCl$_3$, **Keto**) 194.0 (CO, C2), 170.4 (CO, C7), 159.5 (CH, C4), 126.0 (CH, C3), 61.2 (CH$_2$, C8), 50.8 (CH, C1), 38.8 (CH$_2$, C6), 33.0 (C, C5), 30.0 (CH$_3$), 25.7 (CH$_3$), 14.1 (CH$_3$, C9); $\delta_H$ (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$_3$); $\delta_C$ (100 MHz, CDCl$_3$, **Enol**) 170.4 (CO, C7), 165.0 (C, C2), 149.6 (CH, C4), 121.2 (CH, C3), 93.2 (C, C1), 60.2 (CH$_2$, C8), 34.3 (CH$_2$, C6), 32.4 (C, C5), 27.7 (2 × CH$_3$), 14.3 (CH$_3$, C9); $m/z$ (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-(1S,6R)-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); $[\alpha]_{D}^{21} = -46.4$ (c 1.00, CHCl$_3$); $\nu_{max}$/cm$^{-1}$ (neat) 2983, 2939, 1736, 1679, 1307, 1226, 1166; $\delta_H$ (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); $\delta_C$ (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); $\nu_{max}$/cm$^{-1}$ (neat) 2979, 2924, 1740, 1674, 1370, 1257, 1182, 1152; $\delta_H$ (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$_b$), 2.22-2.16 (1 H, m, H-6$_b$), 1.26 (3 H, t, $J = 7.1$, H-9); $\delta_C$ (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);
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. NH₃ (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 (SiO₂, DCM/MeOH, 98:2) to give the title compound 248a (36 mg, 93%) as a colourless crystalline solid; mp. 135-137 °C; Rₖ 0.40 (DCM/MeOH, 9:1); νmax/cm⁻¹ (thin film) 3244, 2961, 1730, 1335, 1105; δH (400 MHz, CDCl₃) 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-6a, 8), 2.32 (1 H, dddd, J = 13.0, 10.8, 3.9, 2.8, H-7a), 2.20 (1 H, dd, J = 18.5, 1.9, H-6b), 1.31 (1 H, ddd, J = 13.0, 4.6, 1.0, H-7b), 1.06 (3 H, d, J = 7.1, H-9); δC (100 MHz, CDCl₃) 205.1 (CO, C-5), 171.8 (CO, C-3), 64.4 (CH, C-4), 47.0 (CH, C-1), 43.8 (CH₂, C-6), 35.4 (CH₂, C-7), 29.4 (CH, C-8), 20.8 (CH₃, C-9); m/z (ESI) 154 [MH]+; [HRMS (ESI): calcd. for C₈H₁₂NO₂, 154.0863. Found: [MH]+, 154.0864 (0.6 ppm error)]; Anal. Calcd. for C₈H₁₁NO₂: 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); \( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 3413, 1727, 1678, 1025; \( \delta_H \) (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, \( J = 11.2, 6.0, 2.3, \text{H-8} \)), 3.30 (1 H, dd, \( J = 2.3, 2.3 \text{ H-4} \)), 2.62-2.53 (1 H, m, H-7\(_a\)), 2.52 (1 H, ddd, \( J = 18.1, 3.1, 3.1 \text{ H-6}\_a \)), 2.35 (1 H, dd, \( J = 18.1, 2.0, \text{H-6}\_b \)), 1.93 (1 H, ddd, \( J = 13.3, 6.0, 1.1, \text{H-7}\_b \)); \( \delta_C \) (100 MHz, CDCl\(_3\)) 204.4 (C, C-5), 170.6 (C, C-3), 140.5 (C, ArC), 128.7 (2 \times \text{CH, ArCH} \)), 127.1 (CH, ArCH), 126.8 (2 \times \text{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)].

\textbf{Lab Book Ref.} = JDC/11/7

\[
\begin{align*}
\text{7,7-Dimethyl-2-azabicyclo[2.2.2]octane-3,5-dione 248c:} & \quad \text{Using the procedure described for the preparation of compound 248a, the title compound 248c (35 mg, 80%) was isolated as a colourless crystalline solid; mp. 182-185 ºC; } R_f \ 0.41 \ (\text{DCM/MeOH, 9:1}); \nu_{\text{max}}/\text{cm}^{-1} \ (\text{thin film}) 3249, 2964, 1734, 1688; \delta_H \ (400 \text{MHz, CDCl}_3) 7.81 (1 \text{H, br s, NH}), 3.43-3.39 (1 \text{H, m, H-1}), 3.16-3.13 (1 \text{H, m, H-4}), 2.66 (1 \text{H, dd, } J = 18.9, 2.0, \text{H-6}\_a), 2.38 (1 \text{H, dd, } J = 18.9, 3.3, \text{H-6}\_b), 1.90 (1 \text{H, dd, } J = 13.8, 3.3, \text{H-8}\_a), 1.81 (1 \text{H, dd, } J = 13.8, 2.5, \text{H-8}\_b), 1.18 (3 \text{H, s, CH}_3), 1.13 (3 \text{H, s, CH}_3); \delta_C \ (100 \text{MHz, CDCl}_3) 205.8 \text{(C, C-5), 170.8 \text{(C, C-3), 58.6 \text{(CH, C-4), 57.7 \text{(CH, C-1), 39.8 \text{(CH}_2, C-6), 37.4 \text{(CH}_2, C-8), 35.7 \text{(C, C-7), 29.2 \text{(CH}_3), 27.6 \text{(CH}_3); m/z (ESI) 168 [MH]^+; [HRMS (ESI): calcd. for C}_{9}\text{H}_{14}\text{NO}_2, 168.1019. Found: [MH]^+, 168.1022 (1.6 ppm error)]; Anal. Calcd. for C}_{9}\text{H}_{13}\text{NO}_2: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.67; H, 7.81; N, 8.42.} \end{align*}
\]

\textbf{Lab Book Ref.} = JDC/10/84
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 °C; Rf 0.51 (Major), 0.47 (Minor) (DCM/MeOH, 9:1); v_max/cm⁻¹ (thin film) 3273, 2939, 1729, 1679, 1073; δ_H (400 MHz, CDCl₃, Major) 7.81 (1 H, br s, NH), 4.83 (1 H, br s, H-10a), 4.76 (1 H, br s, H-10b), 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-7a), 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-7b), 1.73 (3 H, s, H-11), 1.15 (3 H, d, J = 7.2, H-12); δ_C (100 MHz, CDCl₃, Major) 207.7 (CO, C-5), 171.0 (CO, C-3), 144.3 (C, C-9), 111.6 (CH₂, C-10), 61.7 (CH, C-4), 52.6 (CH, C-1), 46.7 (CH, C-6), 40.4 (CH, C-8), 32.8 (CH₂, C-7), 22.0 (CH₃, C-11), 14.4 (CH₃, C-12); δ_H (400 MHz, CDCl₃, Minor) 8.07 (1 H, br s, NH), 4.85 (1 H, br s, H-10a), 4.77 (1 H, br s, H-10b), 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-7a), 1.89 (1 H, ddd, J = 13.7, 6.7, 1.1, H-7b), 1.73 (3 H, s, H-11), 1.09 (3 H, d, J = 7.4, H-12); δ_C (100 MHz, CDCl₃, Minor) 207.6 (CO, C-5), 172.1 (CO, C-3), 143.6 (C, C-9), 111.9 (CH₂, C-10), 61.2 (CH, C-4), 52.0 (CH₂, C-1), 48.0 (CH, C-6), 41.9 (CH, C-8), 26.7 (CH₂, C-7), 22.3 (CH₃, C-11), 12.1 (CH₃, C-12); m/z (ESI) 194 [MH]+; [HRMS (ESI): calcd. for C₁₁H₁₅NO₂, 194.1176. Found: [MH]+, 194.1181 (2.6 ppm error)]; Anal. Calcd. for C₁₁H₁₅NO₂: 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 °C (Lit. 143-144 °C); $R_t$ 0.39 (DCM/MeOH, 9:1); $\nu_{\text{max}}$/cm$^{-1}$ (thin film) 3189, 1733, 1697, 1096; $\delta_{\text{H}}$ (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$_b$); $\delta_{\text{C}}$ (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$_7$H$_{10}$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.$^{45}$

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**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; $R_t$ 0.39 (PE/EtOAc, 2:1); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2982, 1734, 1675, 1258, 1183; $\delta_{\text{H}}$ (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); $\delta_{\text{C}}$ (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**

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**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 °C 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. NH₄Cl (5 mL), then the aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, PE/Et₂O, 9:1) to give the title compound 251 (103 mg, 38%) as a colourless oil; Rₚ 0.54 (PE/EtOAc, 2:1); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2982, 1734, 1674, 1191, 1113; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 6.95 (1 H, ddd, \( J = 10.1, 5.7, 2.4, \text{-H-4} \)), 6.07 (1 H, ddd, \( J = 10.1, 2.7, 1.1, \text{-H-3} \)), 4.14 (1 H, dq, 10.8, 7.1, H-8ₐ), 4.08 (1 H, dq, \( J = 10.8, 7.1, \text{-H-8ₐ} \)), 2.40 (1 H, dddd, \( J = 19.2, 10.8, 2.7, 2.4, \text{-H-5ₐ} \)), 3.24-3.25 (1 H, dddd, \( J = 19.2, 5.7, 4.9, 1.1, \text{-H-5ₐ} \)), 2.14-2.03 (1 H, dqd, \( J = 10.8, 6.9, 4.9, \text{-H-6} \)), 1.40 (3 H, s, H-11), 1.20 (3 H, t, \( J = 7.1, \text{-H-9} \)), 1.12 (3 H, d, \( J = 6.9, \text{-H-10} \)); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 197.0 (CO, C₄), 170.7 (CO, C-7), 149.5 (CH, C-4), 128.8 (CH, C-3), 60.9 (CH₂, C-8), 57.1 (C, C-1), 38.7 (CH, C-6), 32.4 (CH₂, C-5), 18.4 (CH₃, C-11), 16.4 (CH₃, C-10), 14.1 (CH₃, C-9); \( m/z \) (ESI) 219 [MNa]⁺; [HRMS (ESI): calcd. for C₁₁H₁₆NaO₃, 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); \( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 3239, 1731, 1686, 1443, 1056; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 8.05 (1 H, br s, NH), 3.98-3.93 (1 H, m, H-1), 2.44 (1 H, ddd, \( J = 18.5, 3.4, 3.3, \text{-H-6ₐ} \)), 2.31 (1 H, dd, \( J = 18.5, 1.9, \text{-H-6ₐ} \)), 2.16 (1 H, ddd, \( J = 13.0, 9.8, 1.9, \text{-H-7ₐ} \)), 2.07-1.97 (1 H, m, H-8), 1.58 (1 H, dddd, \( J = 13.0, 4.6, 3.4, 3.3, \text{-H-7ₐ} \)), 1.21 (3 H, s, H-10), 1.02 (3 H, d, \( J = 6.9, \text{-H-9} \)); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 207.7 (CO, C-5), 171.7 (CO, C-3), 61.0 (C, C-4), 45.9 (CH, C-1), 42.4 (CH₂, C-6), 36.8 (CH₂, C-7), 33.4 (CH, C-8) 18.9 (CH₃, C-9), 10.4 (CH₃, C-11).
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. MeNH₂ (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; Rf 0.55 (DCM/MeOH, 9:1); νmax/cm⁻¹ (neat) 2958, 1729, 1679, 1398, 1249; δH (400 MHz, CDCl₃, Major) 3.69-3.64 (1 H, m, H₁), 3.08 (1 H, d, J = 2.5, H₄), 3.06-3.02 (3 H, s, H₁₁), 2.92 (3 H, s, H₁₀), 2.44-2.37 (1 H, m, H₆ₐ), 2.30-2.31 (3 H, m, H₆₈, 7ₐ, 8), 1.12-0.99 (1 H, m, H₇ᵦ), 0.97 (3 H, d, J = 6.7, H₉); δC (100 MHz, CDCl₃, Major) 171.5 (CN, C₅), 167.6 (CO, C₃), 59.1 (CH, C₄), 54.7 (CH, C₁), 39.0 (CH₃, C₁₁), 34.5 (CH₂, C₇), 34.1 (CH₂, C₆), 31.4 (CH₃, C₁₀), 29.5 (CH, C₈), 20.5 (CH₃, C₉); δH (400 MHz, CDCl₃, Minor) 3.69-3.65 (1 H, m, H₄), 3.61-3.57 (1 H, m, H₁), 3.15 (3 H, dd, J = 1.8, 1.8, H₁₁), 2.92 (3 H, s, H₁₀), 2.53-2.38 (2 H, m, H₆ₐ, 7ₐ), 2.30-2.14 (2 H, m, H₆₈, 8), 1.14-1.02 (1 H, m, H₇ᵦ), 0.97 (3 H, d, J = 6.7, H₉); δC (100 MHz, CDCl₃, Minor) 170.4 (CN, C₅), 166.7 (CO, C₃), 55.2 (CH, C₁), 50.5 (CH, C₄), 40.1 (CH₂, C₆), 38.5 (CH₃, C₁₁), 34.1 (CH₂, C₇), 31.5 (CH₃, C₁₀), 30.2 (CH, C₈), 20.2 (CH₃, C₉); m/z (ESI) 181 [MH⁺]; [HRMS (ESI): calcd. for C₁₀H₁₇N₂O, 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 H₂O (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 (SiO₂, DCM/MeOH, 98:2) to give the title compound 255a (26 mg, 62%) as a colourless crystalline solid; mp. 131-133 ºC; Rₚ 0.54 (DCM/MeOH, 9:1); vₘₐₓ/cm⁻¹ (thin film) 2970, 2932, 1728, 1668, 1396; δ_H (400 MHz, CDCl₃) 3.81-3.77 (1 H, m, H₁), 3.15 (1 H, d, J = 2.8, H-4), 3.00 (3 H, s, H₁₀), 2.49 (1 H, ddd, J = 18.5, 3.2, 3.2, H-6ₐ), 2.45-2.30 (2 H, m, H-7ₐ, 8), 2.21 (1 H, dd, J = 18.5, 2.0, H-6ₐ), 1.31 (1 H, ddd, J = 13.2, 4.4, 1.6, H-7ₐ), 1.06 (3 H, d, J = 7.0, H-9); δ_C (100 MHz, CDCl₃) 204.9 (CO, C₅), 168.6 (CO, C-3), 64.3 (CH, C-4), 54.8 (CH, C-1), 42.9 (CH₂, C-6), 34.2 (CH₂, C-7), 31.8 (CH₃, C-10), 29.8 (CH, C-8), 20.9 (CH₃, C-9); m/z (ESI) 168 [MH⁺]; [HRMS (ESI): calcd. for C₉H₁₄NO₂, 168.1019. Found: [MH⁺], 168.1017 (1.1 ppm error)]; Anal. Calcd. for C₉H₁₃NO₂: 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; Rₚ 0.60 (DCM/MeOH, 9:1); vₘₐₓ/cm⁻¹ (thin film) 2962, 1730, 1672, 1463; δ_H (400 MHz, CDCl₃) 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, 1.6, H-6ₐ), 2.30 (1 H, dddd, J = 13.5, 10.8, 3.7, 3.1, H-7ₐ), 2.22 (1 H, dd, J = 18.5, 2.0,
H-6b), 1.60-1.49 (2 H, m, H-11), 1.32 (1 H, ddd, J = 13.5, 4.7, 1.4, H-7b), 1.05 (3 H, d, J = 7.1, H-9), 0.90 (3 H, t, J = 7.4, H-12); δC (100 MHz, CDCl₃) 205.2 (CO, C-5), 168.2 (CO, C-3), 64.7 (CH, C-4), 52.8 (CH, C-1), 46.3 (CH₂, C-10), 43.6 (CH₂, C-6), 34.9 (CH₂, C-7), 29.7 (CH, C-8), 21.5 (CH₂, C-11), 20.8 (CH₃, C-9), 11.2 (CH₃, C-12); m/z (ESI) 196 [MH⁺]; [HRMS (ESI): calcd. for C₁₁H₁₈NO₂, 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; Rf 0.59 (DCM/MeOH, 9:1); v_max/cm⁻¹ (thin film) 2961, 1728, 1668, 1461; δH (400 MHz, CDCl₃) 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-10a), 3.95 (1 H, dd, J = 14.9, 6.5, H-10b), 3.85-3.81 (1 H, m, H-6a), 3.29 (1 H, dddd, J = 13.5, 10.7, 3.8, 2.2, H-7a), 2.21 (1 H, dd, J = 18.5, 1.9, H-6b), 1.30 (1 H, ddd, J = 13.5, 4.8, 1.9, H-7b), 1.06 (3 H, d, J = 7.1, H-9); δC (100 MHz, CDCl₃) 205.1 (CO, C-5), 168.1 (CO, C-3), 132.4 (CH, C-11), 119.2 (CH₂, C-12), 64.8 (CH, C-4), 51.8 (CH, C-1), 47.0 (CH₂, C-10), 43.5 (CH₂, C-6), 34.8 (CH₂, C-7), 29.9 (CH, C-8), 20.9 (CH₃, C-9); m/z (ESI) 194 [MH⁺]; [HRMS (ESI): calcd. for C₁₁H₁₆NO₂, 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 (SiO₂, PE/EtOAc, 2:1) to give the title compound 208 (21 mg, 38%) as a yellow film; Rf 0.51 (DCM/MeOH, 9:1); v_max/cm⁻¹ (thin film) 3203, 2959, 2925, 1729, 1509, 1330, 1096; δ_H (400 MHz, CDCl₃) 9.36 (1 H, s, NH), 4.11 (1 H, br s, Hₖ₁), 3.74-3.72 (1 H, m, Hₖ₄), 2.49-2.32 (3 H, m, Hₖ₆ₐ, 7ₐ, 8), 2.24 (1 H, dd, J = 18.6, 1.6, H-₆ₐ), 1.42-1.33 (1 H, m, H-₇ₖₐ), 1.09 (3 H, d, J = 6.8, H-₉); δ_C (100 MHz, CDCl₃) 203.4 (C), 199.8 (C), 72.0 (CH, C-₄), 50.6 (CH, C-1), 41.8 (CH₂, C-₆), 35.0 (CH₂, C-₇), 30.7 (CH, C-₈), 20.6 (CH₃, C-₉); m/z (ESI) 170 [MH]⁺; [HRMS (ESI): calcd. for C₈H₁₂NOS, 170.0634. Found: [MH]⁺, 170.0632 (1.0 ppm error)].

Lab Book Ref. = JDC/8/6

(6S*)-6-[(R*)-Hydroxy(phenyl)methyl]cyclohex-2-en-1-one 260a: To a stirred solution of diisopropylamine (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. NaHCO₃ (50 mL) and brine (50 mL), dried (MgSO₄), then concentrated in vacuo to give a yellow oil which was purified by column chromatography (SiO₂, PE/EtOAc, 9:1) to give the title compound 260a (1.49 g, 71%) as a colourless oil; Rf 0.34 (PE/EtOAc, 4:1); v_max/cm⁻¹ (neat) 3443 (br), 2925, 2869, 1666, 1423, 1223, 1045; δ_H (400 MHz, CDCl₃) 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, CDCl₃) 203.6 (CO,
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 Et3N (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 H2O (20 mL), then the aqueous phase was separated and extracted with Et2O (3 × 20 mL). The combined organic extracts were washed with 1 M aq. HCl (20 mL), sat. aq. NaHCO3 (20 mL) and brine (20 mL), dried (MgSO4), then concentrated in vacuo to afford a brown oil which was purified by column chromatography (SiO2, PE/Et2O, 4:1) to give the title compound 257a (0.41 g, 81%) as a pale yellow oil; Rf 0.33 (PE/EtOAc, 2:1); νmax/cm⁻¹ (neat) 2935, 1686, 1667, 1448, 1290; δH (400 MHz, CDCl3, ~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-3keto), 6.82 (1 H, ddd, J = 10.0, 4.3, 4.3, H-3enol), 6.19 (1 H, ddd, J = 10.0, 1.9, 1.9, H-2enol), 6.10 (1 H, ddd, J = 10.1, 2.0, 2.0, H-2keto), 4.42 (1 H, dd, J = 8.9, 5.0, H-6keto), 2.67 (2 H, t, J = 7.3, H-5enol), 2.65-2.37 (3 H, m, H-4keto, 5a keto), 2.32-2.20 (3 H, m, H-4enol, 5b keto); δC (100 MHz, CDCl3, 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 (CH2), 24.4 (CH2); δC (100 MHz, CDCl3, 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 (CH2), 23.7 (CH2);
m/z (ESI) 223 [MNa]⁺; [HRMS (ESI): calcd. for C₁₃H₁₂NaO₂, 223.0730. Found: [MNa]⁺, 223.0736 (2.9 ppm error)].

Lab Book Ref. = JDC/2/60

(6S*)-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; Rf 0.40 (PE/EtOAc, 2:1); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3486 (br), 2926, 2852, 1661, 1449, 1390, 1223; \( \delta_H \) (400 MHz, CDCl₃) 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, \( J = 7.8, 2.2, \text{H-7} \)), 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); \( \delta_C \) (100 MHz, CDCl₃) 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 (CH₂), 26.7 (CH₂), 26.4 (CH₂), 26.3 (CH₂), 25.8 (CH₂), 25.2 (CH₂), 25.1 (CH₂); m/z (ESI) 209 [MH⁺]; [HRMS (ESI): calcd. for C₁₃H₂₁O₂, 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. NaHCO₃/Na₂S₂O₄ (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 (MgSO₄), then concentrated in vacuo to give a pale yellow oil which was purified by column chromatography (SiO₂, 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); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 2929, 2854, 1713, 1672, 1449; \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.00 (1 H, ddd, \(J = 10.1, 3.7, 3.7\), H-3\(_{\text{keto}}\)), 6.67 (1 H, dd, \(J = 9.9, 4.3, 4.3\), H-3\(_{\text{enol}}\)), 6.07 (1 H, ddd, \(J = 9.9, 1.9, 1.9\), H-2\(_{\text{enol}}\)), 6.02 (1 H, ddd, \(J = 10.1, 2.0, 2.0\), H-2\(_{\text{keto}}\)), 3.66 (1 H, dd, \(J = 8.4, 4.9\), H-6\(_{\text{keto}}\)), 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); \(\delta_C\) (100 MHz, CDCl\(_3\), Keto) 210.5 (CO, C7), 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 (CH2), 27.5 (CH2), 25.7 (CH2), 25.2 (CH2), 24.2 (CH2); \(\delta_C\) (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 (CH2), 25.8 (CH2), 24.5 (CH2), 21.3 (CH2), 25.9 (CH2); \(m/z\) (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); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 2927, 2852, 1728, 1623; \(\delta_H\) (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); \(\delta_C\) (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 (CH2), 29.3 (CH2), 29.3 (CH2), 25.9 (CH2), 25.7 (CH2), 25.7 (CH2), 23.3 (CH2), 21.1 (CH2); \(m/z\) (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:

(55*,65*)-6-[(R*)-Hydroxy(phenyl)methyl]-5-methycyclohex-2-en-1-one anti-261a:

To a stirred solution of diisopropylamine (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 (MgSO₄), then concentrated in vacuo to afford the crude product which was purified by column chromatography (SiO₂, 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; Rᵣ 0.24 (PE/EtOAc, 2:1); v<sub>max</sub>/cm<sup>⁻¹</sup> (thin film) 3430 (br), 2918, 1666, 1454, 1391, 1049; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 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<sub>a</sub>), 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<sub>b</sub>), 1.99-1.98 (1 H, m, H-5), 1.01 (3 H, d, J = 7.1, H-7); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 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<sub>2</sub>, C-4), 30.0 (CH, C-5), 19.9 (CH<sub>3</sub>, C-7); m/z (ESI) 239 [MNa]<sup>+</sup>; [HRMS (ESI): calcd. for C₁₄H₁₀NaO₂, 239.1043. Found: [MNa]<sup>+</sup>, 239.1044 (0.6 ppm error)].
(55',65')-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); $\nu_{\max}$/cm$^{-1}$ (neat) 3410 (br), 2959, 2920, 1665, 1390, 1050; $\delta_{\text{H}}$ (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, ddd, $J = 18.7, 4.8, 4.7, 1.7$, H-4a), 2.23-2.12 (1 H, m, H-5), 2.10 (1 H, ddd, $J = 18.7, 7.4, 3.5, 2.3$, H-4b), 1.04 (3 H, d, $J = 6.6$, H-7); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 202.1 (CO, C1), 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**

(55',65')-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); $\nu_{\max}$/cm$^{-1}$ (neat) 3469 (br), 2926, 1666, 1450, 1391, 1258, 1096; $\delta_{\text{H}}$ (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, ddd, $J = 19.2, 4.6, 4.0, 2.0$, H-4a), 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-4b), 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); $\delta_{\text{C}}$ (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); \nu_{\text{max}}/cm^{-1} (neat) 3442 (br), 2956, 2929, 1665, 1390; \delta_{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, ddd, 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,syn}, 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}; \delta_{C} (400 MHz, CDCl_{3}, \textit{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); \delta_{C} (400 MHz, CDCl_{3}, \textit{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
\[(5S^*,6S^*)-6-[(R^*)-\text{Cyclohexenyl(hydroxy)methyl}]\text{-5-methylcyclohex-2-en-1-one} \]

**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); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3438 (br), 2926, 1666; \(\delta_H\) (400 MHz, CDCl3) 6.82 (1 H, dddd, \(J = 10.0, 5.5, 2.6, 1.2, \text{H-3}\)), 5.97 (1 H, dddd, \(J = 10.0, 2.8, 1.2, 0.7, \text{H-2}\)), 5.72-5.68 (1 H, m, H-9), 4.08 (1 H, d, \(J = 9.7, \text{H-7}\)), 2.52 (1 H, dddd, \(J = 19.7, 5.5, 2.8, 2.6, \text{H-4}_a\)), 2.26 (1 H, dd, \(J = 9.7, 2.8, \text{H-6}\)), 2.20-2.06 (2 H, m H-5, 13\(\text{a}\)), 1.02 (3 H, d, \(J = 7.2, \text{H-14}\)); \(\delta_C\) (100 MHz, CDCl3) 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 (CH2, C-4), 24.9 (CH2, C-10), 22.3 (CH2), 22.3 (CH2), 22.0 (CH2, C-13), 19.8 (CH3, 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)].

\[(5S^*,6S^*)-6-[(S^*)-\text{Cyclohexenyl(hydroxy)methyl}]\text{-5-methylcyclohex-2-en-1-one} \]

**syn-261d:** A colourless oil; 25 mg (2%); 0.41 (PE/EtOAc, 2:1); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3438 (br), 2926, 1666; \(\delta_H\) (400 MHz, CDCl3) 6.91 (1 H, ddd, \(J = 10.1, 4.7, 3.8, \text{H-3}\)), 5.99 (1 H, ddd, \(J = 10.1, 2.0, 2.0, \text{H-2}\)), 5.64-5.61 (1 H, m, H-9), 4.28 (1 H, d, \(J = 6.6, \text{H-7}\)), 2.58 (1 H, dddd, \(J = 19.1, 4.8, 4.7, 2.0, \text{H-4}_a\)), 2.41 (1 H, dd, \(J = 7.6, 6.6, \text{H-6}\)), 2.27 (1 H, ddqd, \(J = 7.6, 6.8, 6.8, 4.8, \text{H-5}\)), 2.09 (1 H, dddd, \(J = 19.1, 6.8, 3.8, 2.0, \text{H-4}_b\)), 2.05-1.96 (3 H, m, H-10, 13\(\text{a}\)), 1.88-1.78 (1 H, m, H-13\(\text{b}\)), 1.70-1.40 (4 H, m, H-11, 12), 1.05 (3 H, d, \(J = 6.8, \text{H-14}\)); \(\delta_C\) (100 MHz, CDCl3) 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 (CH2, C-4), 29.8 (CH, C-5), 25.0 (CH2, C-10), 24.4 (CH2, C-13), 22.5 (CH2), 22.3 (CH2), 19.7
(CH₃, C-14); m/z (ESI) 243 [MNa]⁺; [HRMS (ESI): calcd. for C₁₄H₂₀NaO₂, 243.1356. Found: [MNa]⁺, 243.1348 (3.0 ppm error)].

**Lab Book Ref. = JDC/9/52**

![Chemical Structure](image)

**5R,6R)-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 °C Rf 0.44 (PE/EtOAc, 4:1); [α]²⁰ D +75.1 (c 1.02, CHCl₃); υmax/cm⁻¹ (thin film) 3501, 2923, 1484, 1370; δH (400 MHz, CDCl₃) 6.61 (1 H, ddd, J = 5.5, 2.8, 1.4, H-3), 4.85-4.82 (1 H, m, H-10a), 4.82-4.80 (1 H, m, H-10b), 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-4a), 2.33-2.22 (1 H, m, H-4b), 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); δC (100 MHz, CDCl₃) 202.0 (CO, C-1), 144.8 (C, C-8), 143.5 (CH, C-3), 135.6 (C, C-2), 114.0 (CH₂, C-10), 75.2 (CH, C-7), 50.0 (CH, C-6), 46.2 (CH, C-7), 42.0 (CH, CyCH), 30.8 (CH₂, C-4), 30.2 (CH₂, CyCH₂), 29.5 (CH₂, CyCH₂), 26.2 (CH₂, CyCH₂), 26.0 (CH₂, CyCH₂), 25.7 (CH₂, CyCH₂), 18.6 (CH₃, C-9), 15.5 (CH₃, C-11); m/z (ESI) 263 [MH]⁺; [HRMS (ESI): calcd. for C₁₇H₂₇O₂, 263.2006. Found: [MH]⁺, 263.2006 (0.2 ppm error)]; Anal. Calcd. for C₁₇H₂₇O₂: C, 77.82; H, 9.99. Found: C, 77.98; H, 9.96.

**Lab Book Ref. = JDC/9/61**
Synthesis of \((5S^*,6S^*)\)-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-propylcyclohexan-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 \textit{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); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 2958, 2873, 1655, 1605, 1380, 1212, 1140; \(\delta_H\) (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, \(J = 7.0, H-11\)); \(\delta_C\) (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\(_3\)); \textit{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)].

\textbf{Lab Book Ref.} = JDC/12/94

5-Propylcyclohex-2-en-1-one: To a stirred solution of LiAlH\(_4\) (4.0 M in Et\(_2\)O, 0.58 mL, 2.30 mmol, 1.0 equiv.) in Et\(_2\)O (6 mL) at 0 °C was added dropwise enone 3-ethoxy-5-propylcyclohex-2-enone (1.56 g, 8.60 mmol, 3.7 equiv.) as a solution in Et\(_2\)O (4 mL). The resulting white slurry was held at 0 °C for 30 min. before warming to rt and holding for 18 h. The reaction was cooled to 0 °C, then sodium sulfate decahydrate was
carefully added until effervescence ceased. The slurry was filtered, then to the filtrate was added 10% aq. H$_2$SO$_4$ (5 mL). The biphasic solution was stirred at rt for 18 h, then the aqueous phase was separated and extracted with Et$_2$O (3 x 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$_2$O, 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); $\nu$$_{max}$/cm$^{-1}$ (neat) 2958, 2926, 2873, 1681, 1388, 1247; $\delta$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-4a, 6a), 2.11-1.93 (3 H, m, H-4b, 5, 6b), 1.36-1.25 (4 H, m, H-7, 8), 0.85 (3 H, t, $J$ = 7.1, H-9); $\delta$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$_9$H$_{14}$NaO, 161.0937. Found: [MNa]$^+$, 161.0937 (0.2 ppm error)].

**Lab Book Ref. = JDC/13/3**

(5S*,6S*)-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); $\nu$$_{max}$/cm$^{-1}$ (thin film) 3415 (br), 2957, 2927, 1661, 1392; $\delta$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-4a), 2.14-2.06 (1 H, m, H-4b), 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); $\delta$C (400 MHz, CDCl$_3$) 201.3 (CO, C-1), 148.3 (CH, C-3, 141.9 (C, ArC), 128.6 (2 x CH, ArCH), 128.3 (CH, C-2), 128.1 (CH, ArCH), 126.4 (2 x CH, ArCH), 73.6 (CH, C-7), 58.7 (CH, C-6), 35.3
(CH₂, C-8), 34.4 (CH, C-5), 28.3 (CH₂, C-4), 19.9 (CH₂, C-9), 13.6 (CH₃, C-10); m/z (ESI) 267 [MNa]+; [HRMS (ESI): calcd. for C₁₆H₂₀NaO₂, 267.1356. Found: [MNa]+, 267.1359 (1.5 ppm error)].

(5S*,6S*)-6-[(S*)-Hydroxy(phenyl)methyl]-5-propylcyclohex-2-en-1-one  syn-261f: A colourless oil; 61 mg (13%); Rₜ 0.45 (PE/EtOAc, 2:1); v_max/cm⁻¹ (neat) 3431 (br), 2957, 2926, 1668, 1391, 1029; δ_H (400 MHz, CDCl₃) 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-4a), 2.68 (1 H, dd, J = 6.0, 5.7, H-6), 2.23-2.09 (2 H, m, H-4b, 5), 1.49-1.39 (1 H, m, H-8a) 1.37-1.15 (3 H, m, H-8b, 9), 0.81 (3 H, t, J = 7.2, H-10); δ_C (400 MHz, CDCl₃) 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 (CH₂, C-8), 33.9 (CH, C-5), 29.5 (CH₂, C-4), 19.7 (CH₂, C-9), 13.9 (CH₃, C-10); m/z (ESI) 267 [MNa]+; [HRMS (ESI): calcd. for C₁₆H₂₀NaO₂, 267.1356. Found: [MNa]+, 267.1350 (1.9 ppm error)].

Lab Book Ref. = JDC/13/27/B

Synthesis of (5S*,6S*)-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. NaHCO₃ (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 (MgSO₄), then concentrated in vacuo to afford the title compound 3-ethoxy-5-phenylcyclohex-2-enone (3.86 g, 67%) as a pale yellow oil; Rf 0.58 (EtOAc); ʋmax/cm⁻¹ (neat) 2982, 2941, 1655, 1603, 1379, 1350, 1210; δH (400 MHz, CDCl₃) 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-7a), 3.90 (1 H, dq, J = 9.8, 7.0, H-7b), 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, 6a), 2.54 (1 H, dd, J = 16.4, 12.4, H-6b), 1.36 (3 H, t, J = 7.0, H-8); δC (100 MHz, CDCl₃) 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 (CH₂, C-7), 43.7 (CH₂, C-6), 39.2 (CH, C-5), 36.5 (CH₂, C-4), 14.0 (CH₃, C-8). m/z (ESI) 239 [MNa]⁺; [HRMS (ESI): calcd. for C₁₄H₁₆NaO₂, 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 LiAlH₄ (4.0 M in Et₂O, 1.18 mL, 4.70 mmol, 1.0 equiv.) in Et₂O (11 mL) at 0 °C was added dropwise enone 3-ethoxy-5-phenylcyclohex-2-enone (3.77 g, 17.4 mmol, 3.70 equiv.) as a solution in Et₂O (9 mL). The resulting white slurry was held at 0 °C for 30 min. before warming to rt and holding for 18 h. The reaction was cooled to 0 °C, then sodium sulfate decahydrate was carefully added until effervescence ceased. The slurry was filtered, then to the filtrate was added 10% aq. H₂SO₄ (5 mL). The biphasic solution was stirred at rt for 18 h, then the aqueous phase was separated and extracted with Et₂O (3 × 10 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (10 mL) and brine (10 mL), dried (MgSO₄), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, PE/Et₂O, 9:1) to give the title compound 5-phenylcyclohex-2-enone (1.95 g, 65%) as a colourless oil; Rf 0.47 (PE/EtOAc, 2:1); δH
Using the procedure described for the preparation of compound 261a, the syn-isomer \textit{syn-261g} (129 mg, 15\%) was isolated as a colourless crystalline solid and the title compound \textit{anti-261g} (558 mg, 67\%) was isolated as a colourless crystalline solid; mp. 140-143 °C; \textit{R}_{f} 0.21 (PE/EtOAc, 2:1); \nu_{\text{max/cm}^{-1}} (thin film) 3433 (br), 3029, 1657, 1452, 1392; \delta_{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, \textit{J} = 10.1, 4.6, 3.5, H-3), 6.10 (1 H, ddd, \textit{J} = 10.1, 2.0, 1.7, H-2), 4.69 (1 H, dd, \textit{J} = 8.5, 4.2, H-7), 3.42 (1 H, ddd, \textit{J} = 9.6, 8.0, 5.7, H-5), 3.24 (1 H, d, \textit{J} = 8.5, OH), 3.22 (1 H, dd, \textit{J} = 9.6, 4.2, H-6), 2.76 (1 H, dddd, \textit{J} = 19.5, 5.7, 4.6, 1.7, H-4$_{a}$), 2.67 (1 H, dddd, \textit{J} = 19.5, 8.0, 3.5, 2.0, H-4$_{b}$); \delta_{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 \times CH, ArCH), 127.5 (2 \times CH, ArCH), 127.2 (2 \times CH, ArCH), 127.1 (CH, ArCH), 125.7 (2 \times CH, ArCH), 72.4 (CH, C-7), 58.3 (CH, C-6), 43.3 (CH, C-5), 33.1 (CH$_{2}$, C-4); \textit{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.
(5S*,6S*)-6-[(5S*)-Hydroxy(phenyl)methyl]-5-phenylcyclohex-2-en-1-one syn-261g:
A colourless crystalline solid; 129 mg (15%); mp. 79-82 °C; Rf 0.36 (PE/EtOAc, 2:1);
υmax/cm⁻¹ (thin film) 3475 (br), 1664, 1389, 908; δH (400 MHz, CDCl₃) 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, ddd, J = 19.1, 5.5, 5.4, 1.2, H-4a), 2.50 (1 H, ddd, J = 19.1, 9.9, 2.9, 2.4, H-4b); δC (400 MHz, CDCl₃) 202.5 (CO, Ck1), 150.2 (CH, Ck3), 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 (CH₂, C-4); m/z (ESI) 301 [MNa]+; [HRMS (ESI): calcd. for C₁₉H₁₈NaO₂, 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:

(5S*,6R*)-6-Benzoyl-5-methylecyclohex-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 °C was added dropwise trifluoroacetic anhydride (294 µL, 2.10 mmol, 1.5 equiv.). The solution was held at −78 °C 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 °C for 1 h, then Et₃N (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$_2$O (20 mL), then the aqueous phase was separated and extracted with Et$_2$O (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$_2$O, 4:1) to give the title compound 262a (258 mg, 86%) as a colourless oil; $R_f$ 0.44 (PE/EtOAc, 2:1), $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2961, 1685, 1663, 1448, 1388, 1298; $\delta$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-4a), 2.19 (1 H, dddd, $J = 19.1, 9.6, 2.8, 2.6$, H-4b), 1.00 (3 H, d, $J = 6.6$, H-7); $\delta$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:**

(5S*,6S*)-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$_2$O (20 mL) before quenching with sat. aq. NaHCO$_3$/sat. aq. Na$_2$S$_2$O$_3$ (1:1, 20 mL). The biphasic solution was stirred vigourously for 30 min., then the aqueous phase was separated and extracted with Et$_2$O (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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2929,
2855, 1713, 1668, 1449, 1386, 1255; δH (400 MHz, CDCl₃) 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-4b, 5, CyH), 2.10 (1 H, dddd, J = 19.0, 9.3, 2.9, 2.6, H-4b), 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); δC (100 MHz, CDCl₃) 211.3 (CO, C₈), 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 (CH₂, C-4), 31.4 (CH, C-5), 28.1 (CH₂, CyCH₂), 27.2 (CH₂, CyCH₂), 25.8 (2 × CH₂, CyCH₂), 25.3 (CH₂, CyCH₂) 19.9 (CH₃, C-7); m/z (ESI) 221 [MH]+; [HRMS (ESI): calcd. for C₁₄H₂₁O₂, 221.1536. Found: [MH]+, 221.1533 (1.3 ppm error)].

Lab Book Ref. = JDC/9/43

(55*,65*)-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; Rf 0.59 (PE/EtOAc, 2:1); νmax/cm⁻¹ (neat) 2959, 1717, 1672; δH (400 MHz, CDCl₃) 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-4a, 5, 9a), 2.47-2.36 (1 H, m, H-9b), 2.07 (1 H, dddd, J = 18.9, 9.0, 2.9, 2.6, H-4b), 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); δC (100 MHz, CDCl₃) 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 (CH₂, C-9), 32.7 (CH₂, C-4), 31.6 (CH, C-5), 25.5 (CH₂, C-11), 22.7 (CH₂, C-10), 22.4 (CH₂, C-12), 19.6 (CH₃, C-7), 13.8 (CH₃, C-13); m/z (ESI) 209 [MH]+; [HRMS (ESI): calcd. for C₁₃H₂₁O₂, 209.1536. Found: [MH]+, 209.1536 (0.2 ppm error)].

Lab Book Ref. = JDC/9/45
(5S*,6R*)-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); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2930, 1675, 1655, 1387, 1290, 1176; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 6.94 (1 H, ddd, \( J = 10.1, 5.5, 2.8, \text{H-3} \)), 6.85-6.81 (1 H, m, H-10), 6.00 (1 H, ddd, \( J = 10.1, 2.7, 1.4, \text{H-2} \)), 3.84 (1 H, d, \( J = 10.7, \text{H-6} \)), 2.71-2.58 (1 H, m, H-5), 2.53 (1 H, dddd, \( J = 19.0, 5.5, 5.2, 1.4, \text{H-4}_a \)), 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, \( J = 6.6, \text{H-7} \)); \( \delta_{\text{C}} \) (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); \( \text{m/z} \) (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

(5R,6R)-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); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2923, 1712, 1661, 1449, 1366; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)), \( ~1.6:1 \) (keto/enol)) 6.71 (1 H, ddq, \( J = 5.6, 2.7, 1.3, \text{H-3}_\text{keto} \)), 6.21-6.17 (1 H, m, H-3\(_\text{enol} \)), 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, \( J = 11.3, \text{H-6}_\text{keto} \)), 3.29 (1 H, br d, \( J = 8.1, \text{H-5}_\text{enol} \)), 3.14 (1 H, ddd, \( J = 11.3, 10.1, 5.1, \text{H-5}_\text{keto} \)), 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); δC (100 MHz, CDCl₃, **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 (CH₂, C-10), 61.7 (CH, C-6), 51.8 (CH, CyCH), 44.0 (CH, C-5), 30.1 (CH₂), 28.5 (CH₂), 28.1 (CH₂), 27.4 (CH₂), 25.7 (CH₂), 25.4 (CH₂), 20.6 (CH₃, C-9), 15.6 (CH₃, C-11); δC (100 MHz, CDCl₃, **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 (CH₂, C-10), 105.1 (C, C-6), 41.6 (CH, CyCH), 39.0 (CH, C-5), 30.3 (CH₂), 28.5 (CH₂), 26.0 (CH₂), 25.7 (CH₂), 25.6 (CH₂), 21.0 (CH₃, C-9), 15.6 (CH₃, C-11); m/z (ESI) 261 [MH]+; [HRMS (ESI): calcd. for C₁₇H₂₅O₂, 261.1849. Found: [MH]+, 261.1856 (2.5 ppm error)].

**Lab Book Ref.** = JDC/9/90

(5S*,6R*)-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; Rf 0.48 (PE/EtOAc, 2:1); υmax/cm⁻¹ (thin film) 2959, 2929, 1687, 1664, 1388, 1298, 1190; δH (400 MHz, CDCl₃) 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-4a), 2.16 (1 H, dddd, J = 18.9, 8.3, 3.1, 2.3 H-4b), 1.41-1.18 (4 H, m, H-8, 9), 0.81 (3 H, t, J = 5.6, H-10); δC (400 MHz, CDCl₃) 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 (CH₂, C-8), 29.9 (CH₂, C-4), 19.5 (CH₂, C-9), 13.8 (CH₃, C-10); m/z (ESI) 243 [MH]+; [HRMS (ESI): calcd. for C₁₆H₁₉O₂, 243.1380. Found: [MH]+, 243.1381 (0.6 ppm error)].

**Lab Book Ref.** = JDC/13/32
(5S*,6R*)-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 °C; Rf 0.32 (PE/EtOAc, 2:1); \( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 3030, 1687, 1666, 1449, 1294; \( \delta_{\text{H}} \) (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\(_b\)); \( \delta_{\text{C}} \) (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); \textit{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 °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 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 (MgSO₄), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, 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); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2957, 2871, 1730, 1572, 1447, 1346; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 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-6a), 2.13 (1 H, dd, \( J = 19.0, 1.9 \), H-6b), 2.11-1.98 (2 H, m, H-7a, 8), 1.37-1.32 (1 H, m, H-7b), 1.12 (3 H, d, \( J = 6.8 \), H-9); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 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 (CH₂, C-6), 32.3 (CH₂, C-7), 29.4 (CH, C-8), 21.2 (CH₃, C-9); \( m/z \) (ESI) 214 [MH⁺]; [HRMS (ESI): calcd. for C₁₄H₁₆NO, 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); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2928, 2853, 1730, 1624, 1450; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 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-6a), 2.00 (1 H, dd, \( J = 19.0, 1.8 \), H-6b), 1.99-1.90 (1 H, m, H-7a), 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-7b, CyH), 1.02 (3 H, d, \( J = 7.0 \), H-9); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 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 (CH₂, C-6), 32.4 (CH₂, C-7), 29.3 (2 × CH₂, CyCH₂), 29.1 (CH, C-8), 25.9 (CH₂, CyCH₂), 25.7 (2 × CH₂, CyCH₂), 21.3 (CH₃, C-9); \( m/z \) (ESI) 220 [MH⁺]; [HRMS (ESI): calcd. for C₁₄H₂₂NO, 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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2956, 2930, 2871, 1731, 1628; $\delta_H$ (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-6a), 1.99 (1 H, ddd, $J = 19.0$, 1.8, H-6b), 1.99-1.84 (2 H, m, H-7a, 8), 1.57-1.47 (2 H, m, H-11), 1.33-1.18 (5 H, m, H-7b, 12, 13), 1.01 (3 H, d, $J = 6.7$, H-9), 0.85 (3 H, t, $J = 7.0$, H-14); $\delta_C$ (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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2930, 2868, 1731, 1576, 1340; $\delta_H$ (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-6a), 2.02 (1 H, dd, $J = 19.0$, 1.8, H-6b), 2.01-1.93 (1 H, m, H-7a), 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-7b), 1.03 (3 H, d, $J = 7.0$, H-9); $\delta_C$ (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
(CH₂, C-12), 24.0 (CH₂, C-15), 22.1 (CH₂, CyCH₂), 21.8 (CH₂, CyCH₂), 21.3 (CH₃, C-9); m/z (ESI) 218 [MH⁺]; [HRMS (ESI): calcd. for C₁₄H₂₀NO, 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; Rf 0.63 (DCM/MeOH, 95:5); νmax/cm⁻¹ (neat) 2929, 2853, 1725, 1450; δH (400 MHz, CDCl₃) 4.82 (1 H, d, J = 1.0, H-10₁₉ minor), 4.79 (1 H, d, J = 1.0, H-10₁₉ major), 4.78 (1 H, d, J = 1.0, H-10₂₉ minor), 4.76 (1 H, d, J = 1.0, H-10₂₉ 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_major, 7_minor), 1.91-1.61 (14 H, m, H-7_major, 7_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); δC (100 MHz, CDCl₃, Major) 211.4 (CO, C-5), 178.5 (CN, C-3), 145.4 (C, C-9), 111.0 (CH₂, 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 (CH₂, C-7), 29.5 (CH₂, CyCH₂), 29.4 (CH₂, CyCH₂), 25.8 (CH₂, CyCH₂), 25.7 (2 × CH₂, CyCH₂), 22.1 (CH₃, C-11), 15.7 (CH₃, C-12); δC (100 MHz, CDCl₃, Minor) 211.4 (CO, C-5), 180.2 (CN, C-3), 144.5 (C, C-9), 111.5 (CH₂, 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 (CH₂, CyCH₂), 25.8 (CH₂, CyCH₂), 25.7 (2 × CH₂, CyCH₂), 23.7 (CH₂, CyCH₂), 22.5 (CH₃, C-11), 11.7 (CH₃, C-12); m/z (ESI) 260 [MH⁺]; [HRMS (ESI): calcd. for C₁₇H₂₆NO, 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); $\nu_{\text{max}}$ (neat) 2956, 2929, 2871, 1731, 1601, 1446, 1346; $\delta_H$ (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-6a), 2.14 (1 H, dd, $J = 19.0, 1.9$, H-6b), 2.02 (1 H, dddd, $J = 13.2, 10.9, 3.7, 2.5$, H-7a), 1.93-1.84 (1 H, m, H-8), 1.46-1.28 (5 H m, H-7b, 9, 10), 0.90 (3 H, t, $J = 7.1$, H-11); $\delta_C$ (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 $^1$H NMR Spectroscopy) was isolated as a yellow oil; $R_f$ 0.64 (DCM/MeOH, 95:5); $\delta_H$ (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-7a), 2.41-2.38 (2 H, m, H-6), 2.06 (1 H, ddd, $J = 13.1, 5.9, 1.2$, H-7b); $\delta_C$ (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,
(55*,6R*)-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 K₂CO₃ (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 H₂O (5 mL). The aqueous solution was extracted with Et₂O (3 × 10 mL), then the combined organic extracts were washed with brine (10 mL), dried (MgSO₄), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, PE/Et₂O, 9:1) to give the title compound 264 (53 mg, 26%) as a colourless oil; Rᵣ 0.64 (PE/EtOAc, 2:1); νₛₔcm⁻¹ (neat) 2930, 2855, 1674, 1450, 1386, 987; δₛH (400 MHz, CDCl₃) 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-4ₐ), 2.63-2.55 (1 H, m, CyH), 2.27 (1 H, dddd, J = 19.9, 5.5, 5.4, 1.2, H-4ₐ), 2.01 (1 H, dqqd, 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); δₛC (100 MHz, CDCl₃) 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 (CH₂, C-4), 29.8 (CH₂, CyCH₂), 29.5 (CH₂, CyCH₂), 25.5 (CH₂, CyCH₂), 25.3 (2 × CH₂, CyCH₂), 17.9 (CH₃, C-9), 16.0 (CH₃, C-8); m/z (ESI) 235 [MH⁺]; [HRMS (ESI): calcd. for C₁₅H₂₃O₂, 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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3455 (br), 2929, 2860, 1667, 1389; $\delta_{\text{H}}$ (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, H-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); $\delta_{\text{C}}$ (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); $\delta_{\text{C}}$ (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): calcld. 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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2956, 2931, 1716, 1674, 1634, 1582; $\delta_{\text{H}}$ (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$_b$$_{enol}$, 8$_{enol}$), 2.39-2.27 (5 H, m, H-4$_b$, 5$_a$$_{keto}$, 8$_{keto}$), 2.11-2.01 (1 H, m, 5$_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); δC (100 MHz, CDCl3) 207.3 (CO, C-7keto), 195.6 (C, C-1keto), 188.7 (C, C-1enol), 183.3 (C, C-7enol), 151.3 (CH, C-3keto), 145.1 (CH, C-3enol), 129.1 (CH, C-2keto), 127.9 (CH, C-2enol), 103.8 (C, C-6enol), 59.4 (CH, C-6keto), 42.7 (CH2, C-8keto), 34.2 (CH2, C-8enol), 31.5 (CH2), 31.2 (CH2), 25.4 (CH2, C-9enol), 24.5 (CH2), 24.3 (CH2), 24.2 (CH2), 23.0 (CH2), 22.4 (2 × CH2), 21.6 (CH2, C-5enol), 13.9 (CH3), 13.8 (CH3); m/z (ESI) 217 [MNa]+; [HRMS (ESI): calcd. for C12H18NaO2, 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; Rf 0.38 (PE/EtOAc, 2:1); v_max/cm⁻¹ (neat) 3469 (br), 2926, 2858, 1658, 1390, 1222, 1017; δH (400 MHz, CDCl3) 7.03-6.98 (1 H, m, Hk3), 6.00 (1 H, ddd, J = 10.0, 2.4, 1.6, H-2), 5.67-5.64 (1 H, m, Hk9), 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-13a), 2.08-1.94 (2 H, m, H-10), 1.85-1.72 (2 H, m, H-5, 13b), 1.67-1.58 (3 H, m, H-11a, 12), 1.57-1.44 (2 H, m, H-5, 11b); δC (100 MHz, CDCl3) 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 (CH2, C-4), 25.2 (CH2, C-5), 24.9 (CH2, C-10), 22.4 (2 × CH2), 22.4 (CH2); m/z (ESI) 229 [MNa]+; [HRMS (ESI): calcd. for C13H18NaO2, 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 °C; Rf 0.46 (PE/EtOAc, 2:1);
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 NH₃ (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 (MgSO₄), then concentrated in vacuo to afford the title compound 266a (42 mg, 72%) as a yellow; Rₜ 0.54 (DCM/MeOH, 9:1); υ_{max}/cm⁻¹ (neat) 2931, 2858, 1735, 1604, 1279, 1173; δ_H (400 MHz, CDCl₃) 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-6a), 2.74-2.65 (1 H, m, H-2a), 2.55-2.46 (1 H, m, H-2b), 2.52 (1 H, dd, J = 14.9, 7.8, H-6b), 2.00-1.89 (2 H, m, H-3a, 4a), 1.82-1.68 (1 H, m, H-3b), 1.35-1.24 (1 H, m, H-4b); δ_C (400 MHz, CDCl₃) 172.8 (CO, C-7), 165.4 (CN, C-1), 139.7 (C, ArC), 129.6 (CH, ArCH), 128.1 (2 × CH₂, ArCH), 126.1 (2 × CH₂, ArCH), 55.7 (CH, C-5), 51.5 (CH₃, C-8), 42.5 (CH₂, C-6), 27.0 (CH₂, C-4), 26.5 (CH₂, C-2), 18.9 (CH₂,
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](image)

**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); ν_{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}), 26.1 (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](image)

**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); ν_{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,
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); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2931, 2858, 1738, 1617, 1435, 1172; \( \delta_{\text{H}} \) (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, \( J = 14.7, 7.0, \text{H-6}_a \)), 2.43 (1 H, dd, \( J = 14.7, 7.8, \text{H-6}_b \)), 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\(_b\)); \( \delta_{\text{C}} \) (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-[(2S*,6S*)-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 °C was added NaBH₄ (28 mg, 0.74 mmol, 1.6 equiv.). The colourless solution was held at 0 °C 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 (Na₂SO₄), 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; Rₘ 0.50 (DCM/MeOH, 9:1); δH (400 MHz, CDCl₃, cis-isomer) 3.68 (3 H, s, H₈), 2.93 (1 H, dddd, J = 10.5, 7.7, 5.5, 2.6, H₅), 2.55-2.46 (1 H, m, H₁), 2.42 (1 H, dd, J = 16.2, 5.5, H₆a), 2.37 (1 H, dd, J = 16.2, 7.7, H₆b), 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, H₁₃).

Lab Book Ref. = JDC/10/19
Data were consistent with those published.⁹⁷

(3S)-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; Rₘ 0.13 (PE/Et₂O, 1:1); νmax/cm⁻¹ (neat) 2969, 1723, 1698, 1359, 1159; δH (400 MHz, CDCl₃) 9.71 (1 H, dd, J = 2.0, 1.1, H₉), 3.69 (1 H, d, J = 9.4, H₃), 2.90 (1 H, ddqd, J = 9.4, 8.4, 6.8, 4.1, H₆), 2.48 (1 H, ddd, J = 17.3, 4.1, 1.1, H₈a), 2.33 (1 H, ddd, J = 17.3, 8.4, 2.0, H₈b), 2.18 (6
H, s, H-1, 5), 0.97 (3 H, d, J = 6.8, H-7); δC (100 MHz, CDCl3) 203.8 (CO), 203.5 (CO), 200.8 (CO, C-9), 73.8 (CH, C-3), 48.0 (CH2, C-8), 30.2 (CH3), 29.6 (CH3), 28.1 (CH, C-6), 17.9 (CH3, C-7); m/z (ESI) 171 [MH]+; [HRMS (ESI): calcd. for C9H15O3, 171.1016. Found: [MH]+, 171.1020 (2.7 ppm error)].

Lab Book Ref. = JDC/6/46
Data were consistent with those published.102

(5S,6S)-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 °C and held for 18 h, before cooling to rt and diluting with ether (5 mL). The organic phase was washed with sat. aq. NaHCO3 (2 × 5 mL) and brine (5 mL), dried (MgSO4) then concentrated in vacuo to afford a brown oil which was purified by column chromatography (SiO2, PE/EtOAc, 4:1) to give the title compound 51 (82 mg, 74%) as a pale yellow oil; Rf 0.71 (PE/EtOAc, 1:1); vmax/cm−1 (neat) 2961, 1716, 1425, 1280; δH (400 MHz, CDCl3) 6.96 (1 H, ddd, J = 10.2, 5.3, 2.9, H-3keto), 6.52 (1 H, dddd, J = 9.9, 6.3, 2.3, 1.2, H-3enol), 6.00 (1 H, ddd, J = 9.9, 3.1, 0.7, H-2enol), 3.18 (1 H, d, J = 10.6, H-6keto), 2.81 (1 H, dqdd, J = 7.0, 7.0, 1.3, 1.3, H-5enol), 2.62-2.49 (3 H, m, H-4keto, 4a enol, 5keto), 2.22 (1 H, dddd, J = 18.2, 6.3, 1.3, 0.7, H-4b enol), 2.20 (3 H, s, H-9 enol), 2.14-2.11 (1 H, m, H-4 enol), 2.09 (3 H, s, H-9keto), 1.08 (3 H, d, J = 7.0, H-7 enol), 1.03 (3 H, d, J = 6.5, H-7keto); δC (100 MHz, CDCl3, 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 (CH2, C-4), 31.9 (CH, C-5), 30.5 (CH3, C-9), 19.6 (CH3, C-7); δC (100 MHz, CDCl3, 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 (CH2, C-4), 27.1 (CH, C-5), 21.1 (CH3, C-9), 20.5 (CH3, C-7); m/z (ESI) 175 [MNa]+; [HRMS (ESI): calcd. for C9H12NaO2, 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 °C 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$_2$O, 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$_2$O, 1:1); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2921, 1736, 1290, 1253, 1124, 1037; $\delta_H$ (400 MHz, CDCl$_3$) 4.47 (1 H, ddd, $J$ = 8.0, 4.6, 1.8, H-$k_3$), 2.92 (1 H, ddd, $J$ = 18.1, 8.0, 0.9, H-$k_2^a$), 2.37 (1 H, d, $J$ = 18.1, H-$k_2^b$), 2.01 (1 H, ddd, $J$ = 13.5, 4.2, 1.9, H-$k_5$), 1.98-1.84 (1 H, m, H-$k_5$), 1.66 (1 H, dddd, $J$ = 13.7, 4.0, 1.9, 1.8, H-$k_4^a$), 1.62-1.55 (1 H, m, H-$k_4^b$), 1.53 (3 H, s, H-$k_8$), 1.30 (1 H, dd, $J$ = 13.5, 11.9, H-$k_6^b$), 0.95 (3 H, d, $J$ = 6.4, H-9); $\delta_C$ (100 MHz, CDCl$_3$) 168.5 (CO, C-$k_1$), 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$_9$H$_{15}$O$_3$, 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 °C was added 35% aq. NH$_3$ (0.5 mL). The resulting yellow solution was held at 0 °C 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$_2$SO$_4$), then concentrated in vacuo to afford the title compound 27 (64 mg, 84%) as yellow oil which partially solidified on storage at −20 °C; Picrate mp. 208-210 °C (Lit.$^{42}$ 212-213 °C); $R_f$ 0.33 (DCM/MeOH, 95:5); [\alpha]$^{24}$_D $-252.7$ (c 0.51, DCM), [Lit.$^{42}$ $-34.5$ (c
0.50, DCM); \nu_{\text{max}}/\text{cm}^{-1} \text{ (neat)} 2957, 1729, 1633, 1379; \delta_{\text{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-6a), 2.12 (3 H, s, H-10), 2.01 (1 H, dd, J = 19.0, 1.9, H-6b), 1.99-1.91 (2 H, m, H-7a, 8), 1.27-1.19 (1 H, m, H-7b), 1.04 (3 H, d, J = 6.9, H-9); \delta_{\text{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$_9$H$_{14}$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%)).

\textbf{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$_2$SO$_4$), then concentrated in vacuo to afford the title compound 285 (9 mg, Quant.) as yellow film; R$_f$ 0.39 (DCM/MeOH, 9:1); \nu_{\text{max}}/\text{cm}^{-1} \text{ (thin film)} 2958, 1658, 1433, 1380, 1280; \delta_{\text{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, dddd, J = 12.1, 9.3, 2.4, H-7a), 1.48 (1 H, dqd, J = 9.3, 6.9, 4.6, 2.3, H-8), 0.92 (1 H, dddd, J = 12.1, 4.6, 2.4, H-7b), 0.87 (3 H, d, J = 6.9, H-9); \delta_{\text{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$_9$H$_{15}$N$_2$, 151.1230. Found: [MH$^+$], 151.1232 (1.7 ppm error)].

\textbf{Lab Book Ref. = JDC/4/90}
3-(2,5-Dioxopyrrolidin-1-yl)propanal $^\text{35}$ 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); $\delta_H$ (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.$^\text{35}$

Methyl (E)-5-(2,5-dioxopyrrolidin-1-yl)pent-2-enoate 293: To a stirred solution of K$_2$CO$_3$ (10.4 g, 75.1 mmol, 1.05 equiv.) in H$_2$O (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$_2$O (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); $\delta_H$ (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 °C, was added NaBH$_4$ (5.94 g, 157.2 mmol, 2.0 equiv.) portionwise over 2 h. The colourless solution was stirred at 0 °C 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); $\delta_H$ (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 °C, was added SnCl$_4$ (2.96 mL, 25.3 mmol, 2.5 equiv.). The reaction was held at 0 °C for 30 min., then warmed to 70 °C and held for 18 h. The reaction mixture was cooled to 0 °C, 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 (Na₂SO₄), 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; Rₚ 0.24 (CHCl₃/acetone, 4:1); δ₁H (400 MHz, CDCl₃) 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](image)

Methyl 3-oxo-1,2,3,5,6,8a-hexahydroindolizine-8-carboxylate³⁵ 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 (Na₂SO₄), then concentrated in vacuo to give a brown oil which was purified by column chromatography (SiO₂, DCM/MeOH, 9:1) to give the title compound 66 (0.73 g, 37%) as a pale yellow oil; Rₚ 0.65 (DCM/MeOH, 9:1); δ₁H (400 MHz, CDCl₃) 7.08-7.04 (1 H, m, H₇), 4.44-4.37 (1 H, m, H₉), 4.27 (1 H, dd, J = 13.1, 6.4, H₅a), 3.77 (3 H, s, H-11), 2.79-2.69 (1 H, m, H-5b), 2.64 (1 H, dddd, J = 12.5, 8.6, 6.8, 1.7, H-1b), 2.56-2.45 (1 H, m, H-2a), 2.44-2.23 (3 H, m, H-2b, 6), 1.60 (1 H, ddd, J = 12.5, 12.5, 11.3, 9.5, H-1b).

**Lab Book Ref. = JDC/5/97**

Data were consistent with those published.³⁵
(1,2,3,5,6,8a-Hexahydroindolizin-8-yl)methanol\textsuperscript{35} 288: To a stirred solution of ester 66 (0.95 g, 4.90 mmol, 1.0 equiv.) in THF (16 mL) at 0 °C 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 °C for 30 min., then warmed to rt and held for 4 h. The reaction was cooled to 0 °C 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\textsubscript{2}SO\textsubscript{4}), then concentrated \textit{in vacuo} to afford an orange oil which was purified by column chromatography (SiO\textsubscript{2}, DCM/MeOH/NH\textsubscript{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); \(\delta_{H}\) (400 MHz, CDCl\textsubscript{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, \(J = 12.8, 10.5, 8.1, 7.9, H-2_a\)), 1.75 (1 H, ddddd, \(J = 12.8, 9.5, 8.9, 7.3, 3.8, H-2_b\)), 1.54 (1 H, dddd, \(J = 12.1, 10.5, 10.5, 7.3, H-1_b\)).

\textbf{Lab Book Ref.} = JDC/6/70

Data were consistent with those published.\textsuperscript{35}

\begin{center}
\includegraphics[width=0.5\textwidth]{image.png}
\end{center}

\textbf{1,2,3,5,6,8a-Hexahydroindolizine-8-carbaldehyde}\textsuperscript{35} 172: To a stirred solution of oxalyl chloride (201 µL, 2.38 mmol, 1.2 equiv.) in DCM (10 mL) at −78 °C was added dropwise DMSO (337 µL, 4.76 mmol, 2.4 equiv.). The colourless solution was held at −78 °C for 30 min., then alcohol 288 (304 mg, 1.98 mmol, 1.0 equiv.) was added \textit{via} cannula as a pre-cooled solution in DCM (5 mL). The reaction was held at −78 °C for 1 h, then Et\textsubscript{3}N (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$_2$SO$_4$), 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); $\delta_H$ (400 MHz, CDCl$_3$) 9.41 (1 H, s, H$_{k10}$), 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$_{5a}$), 2.90 (1 H, ddd, $J = 10.1$, 7.9, 4.8, H$_{3a}$), 2.74 (1 H, ddd, $J = 10.1$, 8.5, 7.3, H$_{3b}$), 2.68-2.61 (1 H, m, H$_{5b}$), 2.61-2.51 (1 H, m, H$_{6a}$), 2.48-2.38 (1 H, m, H$_{6b}$), 2.40-2.31 (1 H, m, H$_{1a}$), 1.94-1.75 (2 H, m, H-2), 1.45 (1 H, dddd, $J = 12.8$, 10.2, 9.4, 7.6, H$_{1b}$).

**Lab Book Ref. = JDC/7/68**

Data were consistent with those published.$^{35}$

(5S*,6S*)-6-[(8aS*)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl(hydroxy)methyl]-5-methylcyclohex-2-en-1-one 287: To a stirred solution of diisopropylamine (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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3399 (br),
(5R*,6R*)-6-[(8aS*)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl(hydroxy)methyl]-5-methylcyclohex-2-en-1-one 294: A yellow oil; Rf 0.35 (DCM/MeOH/NH₃, 40:9:1); νmax/cm⁻¹ (neat) 3340 (br), 2956, 2915, 1668, 730; δH (400 MHz, CDCl₃) 6.82-6.77 (1 H, m, H₁₄), 5.95 (1 H, d, J = 7.9, H-10), 3.12-3.05 (1 H, m, H₁₂), 2.88 (1 H, d, J = 8.5, 3.5, H-3a), 2.76 (1 H, d, J = 7.9, H-10), 3.12-3.05 (1 H, m, H-9), 2.88 (1 H, d, J = 10.6, 8.5, 3.5, H-3a), 2.76 (1 H, d, J = 11.3, 5.7, 5.7 H-5a), 2.63-2.48 (2 H, m, H-3b, 15a), 2.47 (1 H, d, J = 11.3, 5.6, 5.6, H-5b), 2.31 (1 H, d, 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-1a, 15b), 1.93-1.80 (1 H, m, H-2a), 1.78-1.66 (1 H, m, H-2b), 1.53-1.42 (1 H, m, H-1b), 1.02 (3 H, d, J = 7.0, H-17); δC (100 MHz, CDCl₃) 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 (CH₂, C-3), 46.3 (CH₂, C-5), 30.8 (CH, C-16), 30.4 (CH₂, C-15), 28.2 (CH₂, C-1), 25.4 (CH₂, C-6), 22.0 (CH₂, C-2), 19.9 (CH₃, C-17); m/z (ESI) 262 [MH⁺]; [HRMS (ESI): calcd. for C₁₆H₂₄NO₂, 262.1802. Found: [MH⁺], 262.1803 (0.5 ppm error)].

Lab Book Ref. = JDC/8/2
(5S*,6R*)-6-[(8aS*)-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 Et3N (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. NaHCO3 (10 mL), then the aqueous phase was extracted with DCM (4 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na2SO4), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO2, DCM/MeOH/NH3, 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 pale yellow 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; Rf 0.69 (DCM/MeOH/NH3, 40:9:1); vmax/cm−1 (neat) 2959, 1676, 1656, 1390, 1190; δH (400 MHz, DMSO-d6) 10.37 (1 H, br s, NH+), 7.35 (1 H, dd, J = 3.8, 3.8, H-77), 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-3a), 3.41-3.27 (2 H, m, H-3b, 5a), 3.18-3.05 (1 H, m, H-5b), 2.66-2.59 (2 H, m, H-6), 2.53-2.37 (3 H, m, H-1a, 15a, 16), 2.27-2.15 (1 H, m, H-15b), 2.08-1.98 (2 H, m, H-2), 1.71-1.58 (1 H, m, 1b) 0.86 (3 H, d, J = 6.2, H-17); δC (100 MHz, DMSO-d6) 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 (CH2, C-3), 43.1 (CH2, C-5), 33.0 (CH, C-16), 32.6 (CH2, C-15), 28.1 (CH2, C-1), 22.9 (CH2, C-6), 20.2 (CH2, C-2), 19.1 (CH3, C-17); m/z (ESI) 260 [MH]+; [HRMS (ESI): calcd. for C16H22NO2, 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.\textsuperscript{10, 25}

3-[(8aS\textsuperscript{*-})-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 °C was added dropwise pH 10 NH\textsubscript{3}/NH\textsubscript{4}Cl 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\textsubscript{2}SO\textsubscript{4}), then concentrated \textit{in vacuo} to afford a yellow film which was purified by column chromatography (SiO\textsubscript{2}, DCM/MeOH/NH\textsubscript{3}, 90:9:1) to give the title compound 17 (5 mg, 71\%) as a yellow film; \textit{R}\textsubscript{f} 0.33 (DCM/MeOH/NH\textsubscript{3}, 90:9:1); \textit{v}\textsubscript{max}/cm\textsuperscript{-1} (neat) 2954, 2872, 1730, 1578, 1341, 1102; \textit{δ\textsubscript{H}} (400 MHz, CDCl\textsubscript{3}) 6.41 (1 H, ddd, \textit{J} = 4.2, 4.2, 1.5, H\textsubscript{k7}), 4.63 (1 H, dddd, \textit{J} = 3.6, 3.3, 1.8, 1.8, H-14), 3.70-3.63 (1 H, m, H\textsubscript{k9}), 3.55 (1 H, d, \textit{J} = 3.1, H-11), 2.92 (1 H, ddd, \textit{J} =10.2, 7.7, 4.7, H-3\textsubscript{a}), 2.87 (1 H, ddd, \textit{J} = 11.0, 3.2, 3.2, H-5\textsubscript{a}), 2.77 (1 H, ddd, \textit{J} = 10.2, 8.2, 7.5, H-3\textsubscript{b}), 2.64 (1 H, ddd, \textit{J} = 11.0, 7.0, 5.1, H-5\textsubscript{b}), 2.47-2.36 (1 H, m, H-6\textsubscript{a}), 2.36-2.24 (2 H, m, H-1\textsubscript{a}, 6\textsubscript{b}), 2.16 (1 H, ddd, \textit{J} = 18.8, 3.3, 2.7, H-13\textsubscript{a}), 2.06 (1 H, dd, \textit{J} = 18.8, 1.8, H-13\textsubscript{b}), 2.00-1.92 (1 H, m, H-15\textsubscript{a}), 1.91-1.72 (3 H, m, H-2, 16), 1.35 (1 H, dddd, \textit{J} = 12.7, 10.3, 9.3, 7.6, H-1\textsubscript{b}), 1.27 (1 H, ddd, \textit{J} = 12.6, 4.5, 1.8, H-15\textsubscript{b}), 1.06 (3 H, d, \textit{J} = 7.0, H-17); \textit{δ\textsubscript{C}} (100 MHz, CDCl\textsubscript{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\textsubscript{2}, C-3), 45.2 (CH\textsubscript{2}, C-5), 40.0 (CH\textsubscript{2}, C-13), 32.2 (CH\textsubscript{2}, C-15), 30.0 (CH\textsubscript{2}, C-1), 29.2 (CH, C-16), 24.9 (CH\textsubscript{2}, C-6), 22.4 (CH\textsubscript{2}, C-2), 21.2 (CH\textsubscript{3}, C-17); \textit{m/z} (ESI) 259 [MH]\textsuperscript{+}; [HRMS (ESI): calcd. for C\textsubscript{16}H\textsubscript{23}N\textsubscript{2}O, 259.1805. Found: [MH]\textsuperscript{+}, 259.1810 (2.1 ppm error)].

\textbf{Lab. Book Ref.} = JDC/8/10

Data were consistent with those published.\textsuperscript{9, 55}

\textbf{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).

(5R*,6S*)-6-[(8aS*)-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 Et3N (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. NaHCO3 (20 mL), then the aqueous phase was extracted with DCM (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na2SO4), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO2, DCM/MeOH/NH3, 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; Rf 0.34 (DCM/MeOH/NH3, 190:9:1); vmax/cm−1 (neat) = 2958, 2927, 2874, 1677, 1656, 1389; δH (400 MHz, DMSO-d6) 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-3a), 3.39-3.28 (2 H, m, H-3b, 5a), 3.21-3.09 (1 H, m, H-5b), 2.66-2.59 (2 H, m, H-6), 2.53-2.34 (3 H, m, H-1a, 15a, 16), 2.29-2.16 (1 H, m, H-15b), 2.09-1.97 (2 H, m, H-2), 1.77 (1 H, dddd, J = 13.2, 9.6, 9.5, 7.3, H-1b), 0.87 (3 H, d, J = 6.3, H-17); δC (100 MHz, DMSO-d6) 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 (CH2, C-3), 42.9 (CH2, C-5), 32.6 (CH2, C-15), 32.3 (CH, C-16), 27.9 (CH2, C-1) 22.3 (CH2, C-6), 232
20.4 (CH₂, C-2), 19.0 (CH₃, C-17); m/z (ESI) 260 [MH⁺]; [HRMS (ESI): calcd. for C₁₆H₂₂NO₂, 260.1645. Found: [MH⁺], 260.1636 (3.5 ppm error)].

**Lab Book Ref. = JDC/7/60**

Data were consistent with those reported.⁵⁵

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3-[(8aS*)-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. NH₃ (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 (Na₂SO₄), then concentrated *in vacuo* to afford a yellow film which was purified by column chromatography (SiO₂, DCM/MeOH/NH₃, 90:9:1) to give the title compound 296 (8 mg, 62%) as a yellow film; Rₓ 0.33 (DCM/MeOH/NH₃, 90:9:1); v_{max}/cm⁻¹ (thin film) 2954, 2872, 1730, 1577, 1399, 1101; δ_H (400 MHz, CDCl₃) 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-5ₐ), 2.66 (1 H, ddd, J = 11.6, 5.6, 5.6, H-5ₐ), 2.39-2.33 (2 H, m, H-6), 2.32-2.23 (1 H, m, H-1ₐ), 2.11-2.08 (2 H, m, H-13), 2.07-1.72 (3 H, m, H-2, 1ₕ, 1ₕ), 1.39-1.32 (1 H, m, H-1ₕ), 1.28 (1 H, ddd, J = 12.3, 4.0, 1.7, H-1ₕ), 1.06 (3 H, d, J = 6.9, H-17); δ_C (100 MHz, CDCl₃) 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 (CH₂, C-3), 44.9 (CH₂, C-5), 39.5 (CH₂, C-13), 33.0 (CH₂, C-15), 29.8 (CH₂, C-1), 29.4 (CH, C-16), 25.2 (CH₂, C-6), 22.5 (CH₂, C-2), 21.3 (CH₃, C-17); m/z (ESI) 259 [MH⁺]; [HRMS (ESI): calcd. for C₁₆H₂₃N₂O, 259.1805. Found: [MH⁺], 259.1805 (0.1 ppm error)].

**Lab Book Ref. = JDC/8/14**

Data were consistent with those published.⁵⁵
(4aR*,9aR*)-1,2,3,4,4a,7,8,9α-octahydro-9H-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 H₂O (10 mL) before extracting with Et₂O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, PE/Et₂O, 98:2) to give the title compound 316 (27 mg, 54%) as a colourless crystalline solid; mp. 75-78 ºC; Rᶠ 0.54 (PE/EtOAc, 4:1); υ\text{max}/cm⁻¹ (thin film) 2928, 2859, 1634, 1566, 1428, 1185; δ\text{H} (400 MHz, CDCl₃) 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, 13α), 2.30-2.11 (4 H, m, H-4, 8, 10α), 1.89-1.75 (2 H, m, H-11\textsubscript{a}, 13\textsubscript{b}), 1.67-1.56 (1 H, m, H-10\textsubscript{b}), 1.37-1.15 (2 H, m, H-11\textsubscript{b}, 12\textsubscript{a}), 1.14-1.01 (1 H, m, H-12\textsubscript{b}); δ\text{C} (100 MHz, CDCl₃) 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 (CH₂, C-8), 31.8 (CH₂, C-10), 24.8 (CH₂), 24.1 (CH₂), 24.0 (CH₂), 23.4 (CH₂), 17.6 (CH₂, C-5); m/z (ESI) 205 [MH⁺]; [HRMS (ESI): calcd. for C₁₃H₁₇O₂, 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. NH₄Cl (5 mL), then the aqueous phase was extracted with Et₂O (3 × 10
mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄),
then concentrated in vacuo to afford a yellow oil which was purified by column
chromatography (SiO₂, PE/Et₂O, 9:1) to give the title compound **320** (326 mg, 47%) as
a colourless oil; Rf 0.40 (PE/EtOAc, 2:1); v_max/cm⁻¹ (neat) 3400 (br), 2926, 1489, 1241;
δ_H (400 MHz, CDCl₃) 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, CDCl₃) 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 (CH₃, C-14), 25.2 (CH₂, C-1), 25.0 (CH₂, C-4), 22.6 (CH₃), 22.5 (CH₂); m/z (ESI) 241 [MNa⁺]; [HRMS (ESI): calcd. for C₁₄H₁₈NaO₂, 241.1199. Found: [MNa⁺],
241.1203 (1.5 ppm error)].

**Lab Book Ref = JDC/11/1**

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**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 Et₂O (20 mL),
then quenched with sat. aq. NaHCO₃/sat. aq. thiosulfate (1:1, 20 mL). The biphasic
solution was stirred for 30 min., then the aqueous phase was extracted with Et₂O (2 × 20
mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄),
then concentrated in vacuo to afford a yellow oil which was purified by column
chromatography (SiO₂, PE/Et₂O, 9:1) to give the title compound **321** (102 mg, 34%) as
a colourless oil; Rf 0.44 (PE/EtOAc, 4:1); v_max/cm⁻¹ (neat) 2934, 1653, 1388, 1435, 1243;
δ_H (400 MHz, CDCl₃) 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, CDCl₃) 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 (CH₃, C-14), 26.3
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 BCl3 (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 (Na2SO4), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO2, PE/EtOAc, 9:1) to give the title compound 322 (50 mg, 71%) as a colourless oil; Rf 0.89 (DCM/MeOH, 95:5); ʋmax/cm-1 (neat) 2934, 1692, 1621, 1597, 1239; δH (400 MHz, CDCl3) 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); δC (100 MHz, CDCl3) 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 (CH2, C-4), 24.6 (CH2, C-1), 21.9 (CH2), 21.5 (CH2); m/z (ESI) 241 [MNa]+; [HRMS (ESI): calcd. for C13H14NaO2, 225.0886. Found: [MNa]+, 225.0885 (0.5 ppm error)].

Lab Book Ref. = JDC/11/16

(4aS*,9aS*)-1,2,3,4,4a,9a-Hexahydro-9H-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 H₂O (5 mL) before extracting with Et₂O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, PE/EtOAc, 49:1) to give the title compound 323 (15 mg, 56%) as a colourless oil containing traces of the cis-diastereoisomer; Rf 0.37 (PE/EtOAc, 9:1); vₘₐₓ/cm⁻¹ (neat) 2937, 2862, 1686, 1605, 1322, 766; δₜ (400 MHz, CDCl₃) 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-1ₐ), 2.30-2.23 (1 H, m, H-4ₐ), 1.93-1.82 (2 H, m, H-2ₐ, 3ₐ), 1.72 (1 H, dddd, J = 12.5, 12.5, 11.2, 5.4, H-4ₐ), 1.40-1.17 (3 H, m, H-1ₐ, 2ₐ, 3ₐ); δₜ (100 MHz, CDCl₃) 194.2 (CO, C₇), 161.4 (C, C₁₃), 135.6 (CH, C-11), 127.1 (CH, C₉), 121.1 (CH, C-10), 120.9 (C, C₈), 117.6 (CH, C-1₂), 80.5 (CH, C-₅), 49.6 (CH, C-₆), 32.4 (CH₂, C-₄), 24.7 (CH₂), 23.8 (CH₂), 23.6 (CH₂); m/z (ESI) 203 [MH]⁺; [HRMS (ESI): calcd. for C₁₃H₁₅O₂, 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 ditert-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 (Na₂SO₄), 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)]; Rf 0.37 (DCM/MeOH, 9:1); [α] D⁻¹⁰².5 (c
1.05, CHCl₃), (Lit.¹⁸⁴ −80.0 (c 1.375, CHCl₃)); δH (400 MHz, CDCl₃, 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 ¹H NMR Spectroscopic data were consistent with those published.¹⁸⁴

![Chemical Structure](image)

**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 °C as added dropwise BH₃·DMS (8.48 mL, 89.4 mmol, 1.1 equiv.) over 1 h via syringe pump. The colourless solution was held at 0 °C for 30 min., then heated to reflux and held for 3 h. The reaction was cooled to 0 °C and carefully quenched with H₂O (100 mL). The aqueous phase was extracted with EtOAc (2 × 100 mL), then the combined organic extracts were washed with brine (100 mL), then concentrated in vacuo to afford the title compound 340 (16.3 g, Quant.) as a colourless crystalline solid; mp. 56-59 °C (Lit.¹⁸⁵ 58-59 °C); Rf 0.37 (DCM/MeOH, 9:1); [α]²⁴D −48.4 (c 1.01, CHCl₃), (Lit.¹⁸⁵ −47.0 (c 1.0, CHCl₃)); δH (400 MHz, CDCl₃) 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-6a), 3.58 (1 H, dd, J = 11.1, 7.7, H-6b), 3.46 (1 H, ddd, J = 10.9, 7.1, 6.6, H-3a), 3.31 (1 H, ddd, J = 10.9, 7.1, 6.5, H-3b), 2.06-1.96 (1 H, m, H-1a), 1.90-1.71 (2 H, m, H-2), 1.63-1.54 (1 H m, H-1b), 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 H₂O (50 mL), then the aqueous phase was extracted with DCM (2 × 150 mL). The combined organic extracts were washed with H₂O (150 mL) and brine (150 mL), dried (Na₂SO₄), then concentrated in vacuo to afford the title compound 341 (14.5 g, 96%) as a colourless oil that was used without further purification; Rᵥ 0.19 (PE/EtOAc, 4:1); δH (400 MHz, CDCl₃, Rotamers observed) 9.55 (1 H, d, J = 1.8, Hk₆), 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.

**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 °C for 3 h, then quenched with sat. aq. NaHCO₃ (300 mL). The aqueous phase was extracted with DCM (2 × 150 mL), then the combined organic extracts were washed with brine (150 mL), dried (Na₂SO₄), then concentrated in vacuo to afford a yellow solid, which was purified by column chromatography (SiO₂, PE/EtOAc, 9:1) to give the title compound 342 (18.8 g, 73%) as a colourless crystalline solid; mp. 61-63 °C (Lit.¹⁸⁷ 61-62 °C); Rᵣ 0.38 (PE/EtOAc, 4:1); [α]D +26.4 (c 1.01, CHCl₃), (Lit.¹⁸⁸ +30.6 (c 1.04, CHCl₃); δH (400 MHz, CDCl₃) 6.47-6.30 (1 H, m, H₅), 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-1a), 1.90-1.79 (2 H, m, H-2), 1.78-1.68 (1 H, m, H-1b), 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 Cs₂CO₃ (12.2 g, 37.5 mmol, 2.5 equiv.). The suspension was heated to 115 °C and held for 18 h, then cooled to rt and poured into H₂O (500 mL). The aqueous phase was extracted with EtOAc (3 × 150 mL), then the combined organic extracts were washed with H₂O (150 mL) and brine (150 mL), dried (MgSO₄), then concentrated in vacuo to afford a brown oil which was purified by column chromatography (SiO₂, PE/EtOAc, 9:1) to give the title compound 336 (2.16 g, 74%) as a colourless oil; Rᵣ 0.38 (PE/EtOAc, 4:1); [α]D²⁴ –102.1 (c 1.03, MeOH), (Lit.¹⁸⁷ –99.0 (c 1.0, MeOH)); δH (400 MHz, CDCl₃, 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-1b), 2.14-1.98 (3 H, m, H-2, 6), 1.96-1.83 (1 H, m, H-1b), 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 (SiO₂, DCM/MeOH, 9:1) to give the title compound 343 (2.13 g, Quant) as a colourless oil; *Rf* 0.18 (DCM/MeOH, 9:1); [α]²⁴D −33.6 (c 0.88, CHCl₃); νmax/cm⁻¹ (neat) 3307, 3250, 2968, 1674, 1201, 1134; δH (400 MHz, CDCl₃) 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-3ₐ), 3.34 (1 H, ddd, *J* = 11.5, 8.2, 5.8, H-3ₚ), 2.58 (1 H, d, *J* = 2.3, H-7), 2.39-2.29 (1 H, m, H-1ₐ), 2.26-2.03 (3 H, m, H-1ₚ, 2); δC (100 MHz, CDCl₃) 77.2 (CH, C-7), 76.4 (C, C-6), 49.0 (CH, C-5), 44.5 (CH₂, C-3), 32.2 (CH₂, C-1), 23.5 (CH₂, C-2); m/z (ESI) 96 [MH]⁺; [HRMS (ESI): calcd. for C₆H₁₀N, 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 K₂CO₃ (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 H₂O (10 mL) and brine (10 mL), dried (MgSO₄), then concentrated in vacuo to afford a brown oil which was purified by column chromatography (SiO₂, 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); [\( \alpha \)]\(^D\) -108.3 (c 0.99, CHCl\(_3\)); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2957, 2881, 2813, 1140, 1033; \( \delta_H \) (400 MHz, CDCl\(_3\)) 4.92 (1 H, t, \( J = 4.9, \text{H-7} \)), 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, \( J = 11.9, 9.0, 7.1, \text{H-5}_a \)), 2.75 (1 H, ddd, \( J = 8.8, 8.1, 5.4, \text{H-3}_a \)), 2.55-2.46 (2 H, m, H-3\(_b\), 5\(_b\)), 2.26 (1 H, d, \( J = 2.1, \text{H-10} \)), 2.14-2.03 (1 H, m, H-1\(_a\)), 1.96-1.71 (5 H, m, H-1\(_b\), 2, 6); \( \delta_C \) (100 MHz, CDCl\(_3\)) 103.3 (CH, C-7), 82.9 (C, C-8), 72.3 (CH, C-10), 64.8 (2 \( \times \) 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 °C was added dropwise \( n \)-BuLi (1.6 M, 0.69 mL, 1.10 mmol, 1.1 equiv.). The yellow solution was held at −78 °C 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\(_4\)Cl (5 mL). The aqueous phase was extracted with EtOAc (3 \( \times \) 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); [\( \alpha \)]\(^D\) -93.3 (c 1.00, CHCl\(_3\)); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2960, 2876, 1141, 1034; \( \delta_H \) (400 MHz, CDCl\(_3\)) 4.94 (1 H, t, \( J = 4.9, \text{H-7} \)), 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, \( J = 11.6, 9.7, 6.6, \text{H-5}_a \)), 2.81 (1 H, ddd, \( J = 8.8, 8.7, 4.8, \text{H-3}_a \)), 2.49-2.37 (2 H, m, H-3\(_b\), 5\(_b\)), 2.16 (2 H, td, \( J = 7.0, 1.9, \text{H-12} \)), 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, \( J = 7.4, 7.0, \text{H-13} \)), 0.96 (3 H, t, \( J = 7.4, \text{H-14} \)); \( \delta_C \) (100 MHz, CDCl\(_3\)) 103.4 (CH, C-7), 84.5 (C, C-10), 79.0 (C, C-8), 64.8 (2 \( \times \) CH\(_2\), C-11, 11\(_'\)), 54.9 (CH, C-9), 51.9 (CH\(_2\), C-3), 48.4
(CH₂, C-5), 33.1 (CH₂, C-6), 32.0 (CH₂, C-1), 22.3 (CH₂, C-13), 22.0 (CH₂, C-2), 20.7 (CH₂, C-12), 13.5 (CH₃, C-14); m/z (ESI) 238 [MH]+; [HRMS (ESI): calcd. for C₁₄H₂₄NO₂, 238.1802. Found: [MH]+, 238.1803 (0.5 ppm error)].

**Lab Book Ref. = JDC/9/69**

(3-(2,2-Diethoxyethoxy)prop-1-ynyl)benzene<sup>147</sup> **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 H₂O (50 mL). The aqueous phase was extracted with Et₂O (3 × 25 mL), then the combined organic extracts were washed with brine (25 mL), dried (MgSO₄), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO₂, PE/Et₂O, 19:1) to give the title compound **351a** (1.21 g, 32%) as a pale yellow oil; Rₕ 0.45 (PE/EtOAc, 4:1); δ<sub>H</sub> (400 MHz, CDCl₃) 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<sub>a</sub>, 6<sub>a′</sub>), 3.66 (2 H, d, J = 5.2, H-4), 3.60 (2 H, dq, J = 9.3, 7.1, H-6<sub>b</sub>, 6<sub>b′</sub>), 1.24 (6 H, t, J = 7.1, H-7, 7′).

**Lab Book Ref. = JDC/12/93**

Data were consistent with those published.<sup>147</sup>
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 \textit{in vacuo} to afford the title compound 355 (10.5 g, 81%) as a colourless oil; \(R_f\) 0.60 (PE/EtOAc, 9:1); \(\delta_H\) (400 MHz, CDCl\(_3\)) 4.58 (1 H, t, \(J = 5.5\), H\(_{k3}\)), 3.68 (2 H, dq, \(J = 9.4, 7.1\), H\(_{k4a}, 4a'\)), 3.53 (2 H, dq, \(J = 9.4, 7.1\), H\(_{k4b}, 4b'\)), 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').

\textbf{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\(_2\)CO\(_3\) (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\(_2\)O (100 mL) and the aqueous phase extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na\(_2\)SO\(_4\)), then concentrated \textit{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\(_3\)); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 2973, 2879, 2877, 1126, 1062; \(\delta_H\) (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-11a), 3.64 (1 H, dq, J = 9.3, 7.0, H-11a'), 3.52 (1 H, dq, J = 9.3, 7.0, H-11b), 3.49 (1 H, dq, J = 9.3, 7.0, H-11b'), 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-5a), 2.77 (1 H, ddd, J = 9.3, 7.7, 5.1, H-3a), 2.49 (1 H, ddd, J = 9.3, 8.0, 5.6, H-3b), 2.44-2.39 (1 H, m, H-5b), 2.25 (1 H, d, J = 2.1, H-10), 2.15-2.03 (1 H, m, H-1a), 1.97-1.71 (5 H, m, H-1b, 2, 6), 1.20 (6 H, t, J = 7.0, H-12, 12'); δC (100 MHz, CDCl3) 101.5 (CH, Ck7), 83.1 (C), Ck8), 72.1 (CH, Ck10), 61.1 (CH2, C-11), 60.9 (CH2, C-11'), 54.1 (CH, C-9), 51.8 (CH2, C-3), 48.7 (CH2, C-5), 32.7 (CH2, C-6), 31.7 (CH2, C-1), 22.0 (CH2, C-2), 15.3 (2 × CH3, C-12, 12'); m/z (ESI) 226 [MH]+; [HRMS (ESI): calcd. for C13H24NO2, 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(PPh3)2Cl (21 mg, 0.03 mmol, 0.05 equiv.) in Et3N (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 (SiO2, DCM/MeOH, 98:2) to give the title compound 354 (185 mg, 98%) as a yellow oil; Rf 0.66 (DCM/MeOH, 9:1); [α]24D –95.0 (c 1.05, CHCl3); υmax/cm−1 (neat) 2973, 2895, 1444, 1126, 1061; δH (400 MHz, CDCl3) 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-11a, 11a'), 3.52 (1 H, dq, J = 9.4, 7.1, H-11a'), 3.51 (1 H, dq, J = 9.4, 7.1, H-11b, 11b'), 3.27-3.08 (2 H, m, H-3a, 5a), 3.06-2.90 (2 H, m, H-3b, 5b), 2.51-2.36 (1 H, m, 1a), 2.24-2.00 (5 H, m, H-1b, 2, 6), 1.17 (6 H, t, J = 7.1, H-12, 12'); δC (100 MHz, CDCl3) 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 (CH2, C-11), 61.8 (CH2, C-11'), 55.9 (CH, C-9), 52.1 (CH2, C-3), 48.6 (CH2, C-5), 31.6 (CH2), 31.3 (CH2), 21.8 (CH2, C-2),

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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 °C (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 °C (Lit.$^{153}$ 48-50 °C); $R_f$ 0.23 (SiO$_2$, PE/EtOAc, 4:1); $\delta_H$ (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$_b$).

$^1$H NMR spectroscopic Data were consistent with those published.$^{153}$

(4-Hydroxydihydrofuran-3(2H)-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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3396 (br), 1737, 1125, 1069; $\delta_H$ (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-3a), 4.40 (1 H, d, J = 14.5, H-3b), 4.07 (1 H, d, J = 10.1, H-4a), 3.80 (1 H, dd, J = 10.1, 3.5, H-4b); δC (100 MHz, CDCl₃) 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 (CH₂, C-4), 71.4 (CH, C-5), 68.7 (CH₂, C-3); m/z (ESI) 243 [MNa]+; [HRMS (ESI): calcd. for C₁₂H₁₂NaO₄, 243.0628. Found: [MNa]+, 243.0627 (0.1 ppm error)].

(4-Ethoxydihydrofuran-3(2H)-ylidene)(phenyl)methyl formate 368: A colourless oil; Rf 0.24 (PE/EtOAc, 4:1); δH (400 MHz, CDCl₃) 8.14 (1 H, s, H₈), 7.62-7.58 (2 H, m, ArH), 7.43-7.36 (3 H, m, ArH), 4.63 (1 H, d, J = 14.3, H₃a), 4.42 (1 H, d, J = 14.3, H₃b), 4.41 (1 H, d, J = 3.6, H-5), 4.20 (1 H, d, J = 10.2, H-4a), 3.75 (1 H, dd, J = 10.2, 3.6, H-4b), 3.53 (1 H, dq, J = 9.0, 7.0, H-6a), 3.45 (1 H, dq, J = 9.0, 7.0, H-6b), 1.22 (3 H, t, J = 7.0, H-7); δC (100 MHz, CDCl₃) 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 (CH₂, C-4), 68.9 (CH₂, C-3), 63.6 (CH₂, C-6), 15.4 (CH₃, C-7); m/z (ESI) 271 [MNa]+; [HRMS (ESI): calcd. for C₁₄H₁₆NaO₄, 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 H₂O (25 mL). The aqueous phase was extracted with Et₂O (3 × 10 mL), then the combined organic extracts were washed with brine (10 mL), dried (MgSO₄), and then concentrated in vacuo to afford an orange oil which was purified by column chromatography (SiO₂, PE/Et₂O, 9:1) to give the title compound 351b (495 mg, 49%) as a pale yellow oil; R₁ 0.67 (PE/EtOAc, 2:1); νmax/cm⁻¹ (neat) 2977, 2935, 1135, 1102; δH (400 MHz, CDCl₃) 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-6a, 6b), 3.58 (2 H, dq, J = 9.4, 7.1, H-6b, 6b'), 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); δC (100 MHz, CDCl₃) 100.8 (CH, C-5), 88.5 (C, C-1), 74.9 (C, C-2), 69.7 (CH₂, C-4), 62.1 (2 × CH₂, C-6, 6'), 59.0 (CH₂, C-3), 15.2 (2 × CH₃, C-7, 7'), 13.7 (CH₃, C-9), 12.3 (CH₂, C-8); m/z (ESI) 223 [MNa]+; [HRMS (ESI): calcd. for C₁₁H₂₀NaO₃, 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 H₂O (50 mL). The aqueous phase was extracted with Et₂O (3 × 20 mL), then the combined organic extracts were washed with brine (20 mL), dried (MgSO₄), and then concentrated in vacuo to afford an orange oil which was purified by column chromatography (SiO₂, PE/Et₂O, 19:1-9:1) to give the title compound 351c (152 mg, 17%) as a pale yellow oil; R₁ 0.53 (PE/EtOAc, 4:1); νmax/cm⁻¹ (neat) 2977, 2876, 1328, 1110; δH (400 MHz, CDCl₃) 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); ν_{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
(CH₂, CyCH), 22.8 (2 × CH₂, CyCH), 15.3 (2 × CH₃, C-7, 7’); m/z (ESI) 339 [MNa]⁺;
[HRMS (ESI): calcd. for C₂₀H₂₈NaO₃, 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-methylbenzenesulfonamide¹⁹⁰: To a stirred solution of 2,2-
diethoxyethanamine (3.64 mL, 25.0 mmol, 1.0 equiv.) and Et₃N (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 H₂O (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. NaHCO₃ (50 mL) and brine (50 mL), dried (Na₂SO₄), then concentrated in
vacuo to afford the title compound (7.20 g, Quant.) as a colourless crystalline solid; Rᵣ
0.38 (PE/EtOAc, 2:1); mp. 65-67 ºC (Lit. 67-68 ºC) δₓ (400 MHz, CDCl₃) 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-3a, 3’a), 3.47 (2 H, dq, J = 9.4, 7.1, H-3b, 3b’), 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$_2$CO$_3$ (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$_2$O (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); $\delta_H$ (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
The suspension was held at 0 °C 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 °C and held for 4 h. The brown solution was cooled to rt and poured into H2O (50 mL). The aqueous phase was extracted with Et2O (3 × 20 mL), then the combined organic extracts were washed with brine (2 × 20 mL), dried (MgSO4), then concentrated in vacuo to afford a brown oil which was purified by column chromatography (SiO2, PE/EtOAc, 19:1-9:1) to give the title compound (1.70 g, 61%) as a pale yellow oil; Rf 0.41 (PE/EtOAc, 4:1); δH (400 MHz, CDCl3) 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

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**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 °C was added dropwise TFA (1.69 mL, 22.0 mmol, 5.0 equiv.). The brown solution was held at 0 °C for 30 min., then warmed to rt and held for 4 h. The reaction was carefully quenched with sat. aq. NaHCO3, then the aqueous phase was extracted with EtOAc (3 × 20 mL) The combined organic extracts were washed with brine (20 mL), dried (MgSO4), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO2, PE/Et2O, 9:1-4:1) to give the title compound (0.88 g, 70%) as an off-white amorphous solid; (Lit.192 121-123 °C); Rf 0.24 (PE/EtOAc, 4:1); δH (400 MHz, CDCl3) 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 °C 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 °C for 30 min., then acetal 355 (248 mg, 1.30 mmol, 1.05 equiv.) was added dropwise. The solution was held at 0 °C for 30 min., then warmed to rt and held for 4 h. The brown solution was quenched with sat. aq. NH₄Cl (5 mL), then diluted with H₂O (25 mL). The aqueous phase was extracted with Et₂O (3 × 10 mL), then the combined organic extracts were washed with brine (2 × 20 mL), dried (MgSO₄), then concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (SiO₂, PE/EtOAc, 9:1) to give the title compound 351f (462 mg, 93%) as a colourless oil; Rf 0.32 (PE/EtOAc, 4:1); δH (400 MHz, CDCl₃) 7.77 (2 H, d, J = 8.3, H₃), 7.31-7.20 (5 H, m, ArH), 7.06 (2 H, d, J = 8.3, H₆), 4.63 (1 H, t, J = 5.6, H₆), 4.35 (2 H, s, H₃), 3.67 (2 H, dq, J = 9.3, 7.1, H₇), 3.53 (2 H, dq, J = 9.3, 7.1, H₇), 3.36-3.32 (2 H, m, H₄), 2.34 (3 H, s, H₁₃), 1.98-1.92 (2 H, m, H₅), 1.20 (6 H, t, J = 7.1, H₈).  
*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; Rf 0.21 (PE/EtOAc, 4:1); υmax/cm⁻¹ (neat) 2855, 1641, 1124, 1074; δH (400 MHz, CDCl₃) 6.74-6.71 (1 H, m, H₅), 4.88-4.80 (4 H, m, H-3, 4), 2.72 (2 H, q, J = 7.3, H₆), 1.13 (3 H, t, J = 7.3, H-7); δC (100 MHz, CDCl₃) 197.0 (CO, C-1), 141.0 (C,  

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¹³⁹ Lab Book Ref. = JDC/13/50

Data were consistent with those published.
C-2), 136.3 (CH, C-5), 76.3 (CH2), 74.4 (CH2), 32.7 (CH2, C-6), 7.9 (CH3, C-7); m/z (ESI) 127 [MH]+; [HRMS (ESI): calcd. for C7H11O2, 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; Rf 0.33 (PE/EtOAc, 4:1); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2973, 2848, 1644, 1359, 1276, 1240, 1084; \( \delta_{\text{H}} \) (400 MHz, CDCl3) 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-4a), 4.77 (1 H, ddd, \( J = 16.1, 4.9, 1.9, \) H-4b), 1.45 (3 H, d, \( J = 6.3, \) H-6); \( \delta_{\text{C}} \) (100 MHz, CDCl3) 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 (CH2, C-4), 20.5 (CH3, C-6); m/z (ESI) 189 [MH]+; [HRMS (ESI): calcd. for C12H13O2, 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; Rf 0.49 (PE/EtOAc, 4:1); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2929, 1646, 1317, 1240, 1089; \( \delta_{\text{H}} \) (400 MHz, CDCl3) 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); \( \delta_{\text{C}} \) (100 MHz, CDCl3) 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 × CH2, ArCH), 128.3 (2 × CH2, ArCH), 90.4 (C, C-3), 71.9 (CH2, C-4),
34.1 \(2 \times \text{CH}, \text{CyCH})\), 25.0 \(\text{CH}, \text{CyCH})\), 22.3 \(2 \times \text{CH}, \text{CyCH})\); \(m/z\) (ESI) 265 [MNa]⁺; [HRMS (ESI): calcd. for \(\text{C}_{16}\text{H}_{18}\text{NaO}_2\), 265.1199. Found: [MNa]⁺, 265.1192 (2.5 ppm error)].

**Lab Book Ref. = JDC/14/6**

![Phenyl(1AtosylA2,5AdihydroA1H ApyrrolA3Ayl)methanone 352e:](image)

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 °C, (Lit. 153 134-136 °C); \(R_f\) 0.18 (PE/EtOAc, 4:1); \(\delta_H\) (400 MHz, CDCl₃) 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:](image)

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); \(\delta_H\) (400 MHz, CDCl₃) 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 K₂CO₃ (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 °C and held for 5 h, then cooled to rt and poured into H₂O (50 mL). The aqueous phase was extracted with Et₂O (3 × 20 mL), then the combined organic extracts were washed with brine (20 mL), dried (MgSO₄), then concentrated in vacuo to afford the title compound 376 (1.00 g, 99%) as a yellow oil; Rᵣ 0.58 (PE/EtOAc); υₓₓₓₓ/cm⁻¹ (neat) 2975, 1475, 1135, 1075, 749; δₓₓ (400 MHz, CDCl₃) 7.76 (1 H, dd, J = 7.8, 1.6, H-3), 7.30-7.25 (1 H, ddd, J = 8.4, 1.6, H-5), 6.82 (1 H, dd, J = 8.4, 1.3, H-6), 6.74 (1 H, ddd, J = 7.8, 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-9a, 9a'), 3.72 (2 H, dq, J = 9.3, 7.1, H-9b, 9b'), 1.27 (6 H, t, J = 7.1, H-10, 10'); δₓ (100 MHz, CDCl₃) 157.2 (C, C₁), 139.4 (CH, C₃), 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 (CH₂, C-7), 63.4 (2 × CH₂, C-9, 9'), 15.4 (2 × CH₃, C-10, 10'); m/z (ESI) 359 [MNa⁺]; [HRMS (ESI): calcd. for C₁₂H₁₇INO₃, 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(PPh₃)₂Cl₂ (35 mg, 0.05 mmol, 0.05 equiv.) in Et₃N (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
(SiO₂, PE/Et₂O, 19:1) to give the title compound 377 (258 mg, 93%) as a yellow oil; \( R_f 0.60 \) (PE/EtOAc, 4:1); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2972, 2932, 2874, 1493, 1445, 1292, 1119, 1074; \( \delta_H \) (400 MHz, CDCl₃) 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\(_{a}, 9\)\(_{b}\) ), 3.70 (2 H, dq, \( J = 9.4, 7.1, \) H-9\(_{a}, 9\)\(_{b}\) ), 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\(_{a}\)), 1.06 (3 H, t, \( J = 7.4, \) H-15); \( \delta_C \) (100 MHz, CDCl₃) 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 (CH₂, C-7), 63.3 (2 × CH₂, C-9, 9\(_{a}\)), 22.2 (CH₂, C-14), 21.6 (CH₂, C-13), 15.3 (2 × CH₃, C-10, 10\(_{a}\)), 13.5 (CH₃, C-15); \( m/z \) (ESI) 299 [MNa⁺]; [HRMS (ESI): calcd. for C\(_{17}\)H\(_{24}\)NaO₃, 299.1618. Found: [MNa⁺], 299.1617 (0.4 ppm error)].

**Lab Book Ref. = JDC/13/74**

![Chemical Structure](image)

1-(2H-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); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2964, 1682, 1485, 1456, 1226; \( \delta_H \) (400 MHz, CDCl₃) 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); \( \delta_C \) (100 MHz, CDCl₃) 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 (CH₂, C-7), 41.6 (CH₂, C-11), 17.9 (CH₂, C-12), 13.8 (CH₃, C-13); \( m/z \) (ESI) 225 [MNa⁺]; [HRMS (ESI): calcd. for C\(_{13}\)H\(_{24}\)NaO₂, 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$_3$)$_2$Cl$_2$ (35 mg, 0.05 mmol, 0.02 equiv.) in Et$_3$N (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$_2$O, 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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3470, 3377, 2962, 1613, 1492, 1455, 1306; $\delta_H$ (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); $\delta_C$ (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. NaHCO₃ (20 mL) and brine (20 mL), dried (MgSO₄), then concentrated in vacuo to afford the title compound 382a (580 mg, 98%) as an off-white solid; mp. 84-86 ºC; Rₜ 0.38 (PE/EtOAc, 4:1); vₓmax/cm⁻¹ (thin film) 3255, 2961, 1487, 1397, 1330, 1167, 1092; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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 (CH₂, C-10), 21.5 (CH₃, C-16), 21.4 (CH₂, C-9), 13.6 (CH₃, C-11); m/z (ESI) 314 [MH⁺]; [HRMS (ESI): calcd. for C₁₈H₂₀NO₂S, 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 (SiO₂, PE/EtOAc, 19:1) to give the title compound 383 (610 mg, 89%) as a colourless oil; *R*ᵥ 0.40 (PE/EtOAc, 4:1); *ν*ₘₐₓ/cm⁻¹ (neat) 2974, 2932, 1485, 1350, 1162, 1095, 1067; *δ*<sub>H</sub> (400 MHz, CDCl₃) 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), 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*<sub>C</sub> (100 MHz, CDCl₃) 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 × CH₂, C-19, 19’), 52.1 (CH₂, C-17), 21.9 (CH₂, C-10), 21.5 (CH₃, C-16), 21.4 (CH₂, C-9), 15.1 (2 × CH₃, C-20, 20’), 13.6 (CH₃, C-11); *m/z* (ESI) 452 [MNa]<sup>+</sup>; [HRMS (ESI): calcd. for C₂₄H₃₁NNaO₄S, 452.1866. Found: [MNa]<sup>+</sup>, 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); $\nu_{max}/\text{cm}^{-1}$ (neat) 2964, 1683, 1354, 1165, 1089; $\delta_H$ (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); $\delta_C$ (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$_3$S, 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$_2$CO$_3$ (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$_2$O (50 mL). The aqueous phase was extracted with Et$_2$O (3 × 20 mL), then the combined organic extracts were washed with H$_2$O (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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2973, 1464, 1123, 1057; $\delta_{\text{H}}$(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'); $\delta_{\text{C}}$(100 MHz, CDCl$_3$) 157.3 (C, Ck1), 139.3 (CH, Ck3), 129.4 (CH, Ck5), 122.4 (CH, Ck4), 111.9 (CH, Ck6), 100.5 (CH, Ck9), 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$_3$)$_2$Cl$_2$ (35 mg, 0.05 mmol, 0.05 equiv.) in Et$_3$N (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$_2$O, 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); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2971, 2933, 2876, 1492, 1447, 1261, 1120, 1060; $\delta_{\text{H}}$(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); $\delta_{\text{C}}$(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), 262
(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 °C was added dropwise n-BuLi (1.6 M, 0.61 mL, 0.98 mmol, 1.1 equiv.). The yellow solution was held at –78 °C for 1 h, then warmed to 0 °C 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. NH₄Cl (5 mL). The aqueous phase was extracted with DCM (3 × 10 mL), then the combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), and concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, DCM/MeOH, 99:1-98:2) to give the title compound 388 (87 mg, 37%) as a colourless oil; Rₜ 0.50 (DCM/MeOH, 9:1); [α]²⁰°D –99.7 (c 1.15, CHCl₃); νmax/cm⁻¹ (neat) 2966, 1457, 1375, 1127, 1063; δH (400 MHz, CDCl₃) 4.58 (1 H, t, J = 5.7, Hk7), 3.65 (1 H, dq, J = 9.4, 7.1, Hk14a), 3.64 (1 H, dq, J = 9.4, 7.1, H-14a’), 3.50 (1 H, dq, J = 9.4, 7.1, H-14b), 3.49 (1 H, dq, J = 9.4, 7.1, H-14b’), 3.35 (1 H, br s, H-9), 2.92 (1 H, ddd, J = 11.9, 8.7, 7.8, H-5a), 2.82 (1 H, ddd, J = 8.8, 8.7, 5.2, H-3a), 2.50-2.34 (2 H, m, H-3b, 5b), 2.15 (2 H, td, J = 7.0, 2.0, H-11), 2.13-2.02 (1 H, m, H-1a), 1.94-1.70 (4 H, m, H-1b, 2a, 6), 1.50 (2 H, q, 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); δC (100 MHz, CDCl₃) 101.6 (CH, C-7), 84.4 (C, C-10), 79.1 (C, C-8), 61.0 (CH₂, C-14), 60.7 (CH₂, C-14’), 54.9 (CH, C-9), 51.9 (CH₂, C-3), 48.9 (CH₂, C-5), 32.6 (CH₂, C-6), 32.0 (CH₂, C-1), 22.3 (CH₂, C-12), 21.9 (CH₂, C-2), 20.7 (CH₂, C-11), 15.3 (2 × CH₃, C-15, 15’), 13.5 (CH₃, C-13); m/z (ESI) 268 [MH⁺]; [HRMS (ESI): calcd. for C₁₆H₃₀NO₂, 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 °C (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. NaHCO₃ (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 (Na₂SO₄), then concentrated in vacuo to afford an orange oil which was purified by column chromatography (SiO₂, DCM/MeOH, 95:5) to give the title compound 358 (21 mg, 37%) as a yellow film; Rf 0.28 (DCM/MeOH, 9:1); υ(max/cm⁻¹ (neat) 2954, 1645, 1272, 710; δH (400 MHz, CDCl₃) 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-3a, 5a), 2.87 (1 H, ddd, J = 10.0, 8.7, 7.6, H-3b), 2.74 (1 H, ddd, J = 11.9, 7.6, 5.1, H-5b), 2.64-2.53 (1 H, m, H-6a), 2.47-2.35 (2 H, m, H-1a, 6b), 2.01-1.83 (2 H, m, H-2), 1.58-1.47 (1 H, m, H-1b); δC (100 MHz, CDCl₃) 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 (CH₂, C-3), 45.5 (CH₂, C-5), 28.9 (CH₂, C-1), 25.0 (CH₂, C-6), 22.1 (CH₂, C-2); m/z (ESI) 228 [MH]+; [HRMS (ESI): calcd. for C₁₅H₁₈NO, 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 °C 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. NH₄Cl (10 mL), then the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, PE/EtOAc, 2:1-1:1) to give the title compound 398 (0.94 g, 85%) as a yellow oil; Rf 0.38 (DCM/MeOH, 95:5); [α]²⁰D – 106.2 (c 1.00, CHCl₃); νmax/cm⁻¹ (neat) 2973, 2877, 2808, 1478, 1126, 1062, 739; δH (400 MHz, CDCl₃) 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-11a), 3.64 (1 H, dq, J = 9.4, 7.1, H-11a’), 3.50 (1 H, dq, J = 9.4, 7.1, H-11b), 3.49 (1 H, dq, J = 9.4, 7.1, H-11b’), 2.89 (1 H, ddd, J = 11.9, 8.7, 7.1, H-5a), 2.80 (1 H, ddd, J = 8.8, 8.7, 5.5, H-3a); 2.56 (1 H, ddd, J = 8.8, 7.7, 5.3, H-3b); 2.49 (1 H, ddd, J = 11.9, 8.5, 6.3, H-5b), 2.22-2.12 (1 H, m, H-1a), 2.05-1.76 (5 H, m, H-1b, 2, 6), 1.19 (3 H, t, J = 7.1, H-12), 1.17 (3 H, t, J = 7.1, H-12’); δC (100 MHz, CDCl₃) 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 (CH₂, C-11), 60.9 (CH₂, C-11’), 55.7 (CH, C-9), 51.8 (CH₂, C-3), 48.8 (CH₂, C-5), 32.8 (CH₂, C-6), 31.8 (CH₂, C-1), 22.1 (CH₂, C-2), 15.3 (2 × CH₃, C-12, 12’); m/z (ESI) 334 [MH]+ ; [HRMS (ESI): calcd. for C₁₉H₂₈NO₂S, 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. NH₄Cl (25 mL), then the aqueous phase was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄), then concentrated in vacuo to afford an orange oil which was purified by column chromatography (SiO₂, 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; Rf 0.56 (DCM/MeOH, 9:1); [α]²⁴D +85.9 (c 1.00, CHCl₃); υmax/cm⁻¹ (neat) 2971, 2875, 2799, 1581, 1478, 1440, 1125, 1063, 742; δH (400 MHz, CDCl₃) 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-1₁a, 1₁a’), 3.47 (1 H, dq, J = 9.3, 7.1, H-1₁b), 3.45 (1 H, dq, J = 9.3, 7.1, H-1₁b’), 3.23-3.15 (1 H, m, H-3ₐ), 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-5ₐ), 2.19-2.10 (2 H m, H-3ₐ, 5ₐ), 1.98-1.87 (1 H, m, H-1ₐ), 1.85-1.62 (5 H, m, H-1₁b, 2, 6), 1.19 (3 H, t, J = 7.1, H-1₂), 1.18 (3 H, t, J = 7.1, H-1₂’); δC (100 MHz, CDCl₃) 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 (CH₂, C-11), 60.9 (CH₂, C-11’), 53.6 (CH₂, C-3), 49.9 (CH₂, C-5), 32.9 (CH₂, C-6), 31.8 (CH₂, C-1), 22.8 (CH₂, C-2), 15.4 (2 × CH₃, C-12’, 12’); m/z (ESI) 444 [MH]⁺; [HRMS (ESI): calcd. for C₂₅H₃₄NO₂S₂, 444.2025. Found: [MH]⁺, 444.2033 (1.8 ppm error)].

**Lab Book Ref.** = JDC/12/81

![Image of S-Phenyl (S)-1,2,3,5,6,8a-hexahydroindolizine-8-carbothioate 400](image)

**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. NaHCO₃ (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 (Na₂SO₄), 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, CHCl₃); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2956, 1670, 1163, 949, 746; \( \delta_H \) (400 MHz, CDCl₃) 7.45-7.39 (5 H, m, ArH), 7.19 (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-3ₐ, ₃ₐ), 2.75 (1 H, ddd, \( J = 10.0, 8.3, 6.9, \) H-3ₖ), 2.70-2.63 (1 H, m, H-5ₖ), 2.56-2.45 (1 H, m, H-6ₖ), 2.27 (1 H, dddd, \( J = 13.0, 9.4, 7.4, 3.8, \) H-1ₐ), 1.98-1.71 (2 H, m, H-2), 1.52 (1 H, dddd, \( J = 13.0, 10.4, 8.8, 7.6, \) H-1ₖ); \( \delta_C \) (100 MHz, CDCl₃) 189.8 (CO, C-10), 141.1 (C, C-8), 137.0 (CH, C-7), 135.0 (2 × CH, ArCH), 129.2 (CH, ArCH), 125.5 (2 × CH, ArCH), 127.5 (C, ArC), 58.9 (CH, C-9), 52.1 (CH₂, C-3), 45.0 (CH₂, C-5), 29.3 (CH₂, C-1), 24.6 (CH₂, C-6), 22.5 (CH₂, C-2); \( m/z \) (ESI) 260 [MH⁺]; [HRMS (ESI): calcd. for C₁₅H₁₈NOS, 260.1104. Found: [MH⁺], 260.1109 (1.9 ppm error)].

**Lab Book Ref.** = JDC/12/88

(S)-1-(3,3-Diethoxypropyl)-2-(ethylthioethyl)pyrroloidine 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. NH₄Cl (10 mL), then the aqueous phase was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, 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, CHCl₃); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2973, 2929, 2877, 1126, 1062; \( \delta_H \) (400 MHz, CDCl₃) 4.58 (1 H, t, \( J = 5.8, \) H-7), 3.65 (1 H, dq, \( J = 9.3, 7.0, \) H-1₃ₐ), 3.63 (1 H, dq, \( J = 9.3, 7.0, \) H-1₃ₖ), 3.51 (1 H, dq, \( J = 9.3, 7.0, \) H-1₃ₖ), 3.50-3.45 (1 H, m, H-9), 3.48 (1 H, dq, \( J = 9.3, 7.0, \) H-1₃ₖ),...
2.84 (1 H, ddd, J = 11.9, 8.8, 7.1, H-5a), 2.80-2.73 (1 H, m, H-3a), 2.70 (1 H, dq, J = 12.4, 7.3, H-11a), 2.66 (1 H, dq, J = 12.4, 7.3, H-11b), 2.47 (1 H, ddd, J = 8.8, 8.7, 5.6, H-3b), 2.44-2.35 (1 H, m, H-5b), 2.14-2.02 (1 H, m, H-1b), 1.94-1.70 (5 H, m, H-1b, 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'); δC (100 MHz, CDCl₃) 101.5 (CH, C₇), 93.4 (CH, C₈), 73.2 (CH₂, C₁₀), 61.1 (CH₂, C₁₃), 60.9 (CH₂, C₁₃'), 55.6 (CH, C₉), 51.8 (CH₂, C₃), 48.8 (CH₂, C₅), 32.7 (CH₂, C₆), 31.7 (CH₂, C₁), 29.6 (CH₂, C₁₁), 22.0 (CH₂, C₂), 15.3 (2 × CH₃, C₁₄, 14'), 14.6 (CH₃, C₁₂); m/z (ESI) 286 [MH]+; [HRMS (ESI): calcd. for C₁₅H₂₈NO₂S, 286.1835. Found: [MH]+, 286.1836 (0.3 ppm error)]; Anal. Calcd. for C₁₅H₂₇NO₂S: 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 °C (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. NaHCO₃ (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 (Na₂SO₄), then concentrated in vacuo to afford the title compound 402 (575 mg, 97%) as a pale yellow oil; Rf 0.32 (DCM/MeOH, 9:1); [α]²¹D −86.9 (c 0.97, CHCl₃); νmax/cm⁻¹ (neat) 2930, 1655, 1165, 954, 764; δH (400 MHz, CDCl₃) 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-3a, 5a, 11), 2.73 (1 H, ddd, J = 10.0, 8.3, 6.9, H-3b), 2.62 (1 H, ddd, J = 11.5, 7.6, 5.0, H-5b), 2.47-2.36 (1 H, m, H-6a), 2.31-2.21 (2 H, m, H-1a, 6b), 1.90-1.71 (2 H, m, H-2), 1.47 (1 H, ddd, J = 12.7, 10.3, 8.7, 7.6, H-1b), 1.25 (3 H, t, J = 7.4, H-12); δC (100 MHz, CDCl₃) 192.1 (CO, C₁₀), 141.6 (C, C₈), 135.5 (CH, C₇), 58.8 (CH, C₉), 52.1 (CH₂, C₃), 45.0 (CH₂, C₅), 29.3 (CH₂, C₁), 24.4 (CH₂, C₆), 22.8 (CH₂, C₁), 22.5 (CH₂, C₂), 14.8 (CH₃, C₁₂); m/z (ESI) 212 [MH]+; [HRMS (ESI): calcd. for C₁₁H₁₇NO₂S, 212.1104. Found: [MH]+, 212.1106 (1.2 ppm error)].
Synthesis of 4-Bromo-1,1-diethoxybutane 403:

4-Bromobutanal: To a stirred solution of ethyl-4-bromobutyrate (0.73 mL, 5.10 mmol, 1.0 equiv.) in DCM (10 mL) at −78 °C 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 °C 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<sub>2</sub>O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO<sub>4</sub>), 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; <i>R</i><sub>f</sub> 0.19 (PE/EtOAc, 9:1); <i>δ</i><sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 9.82 (1 H, t, <i>J</i> = 0.9, H<sub>1</sub>), 3.46 (2 H, t, <i>J</i> = 6.4, H-4), 2.68 (2 H, td, <i>J</i> = 7.0, 0.9, H-2), 2.19 (2 H, tt, <i>J</i> = 7.0, 6.4, H-3).

4-Bromo-1,1-diethoxybutane 403: To a stirred solution of 4-kbromobutanal (770 mg, 5.10 mmol, 1.0 equiv.) in EtOH (7 mL) at rt was added NH<sub>4</sub>Cl (20 mg). The solution was heated to reflux and held for 2 h, before cooling to rt and quenching with sat. aq. NaHCO<sub>3</sub> (10 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 × 10 mL), then the combined organics were washed with brine (10 mL), dried (MgSO<sub>4</sub>), then concentrated in vacuo to afford a colourless oil which was purified by column chromatography (SiO<sub>2</sub>, PE/Et<sub>2</sub>O, 19:1) to give the title compound 403 (802 mg, 70%) as a colourless oil; <i>R</i><sub>f</sub> 0.49 (PE/EtOAc, 9:1); <i>υ</i><sub>max</sub>/cm<sup>−1</sup> (neat) 2975, 2930, 2878, 1127, 1062; <i>δ</i><sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 4.49 (1 H, t, <i>J</i> = 5.6, H-1), 3.63 (2 H, dq, <i>J</i> = 9.4, 7.1, H-5<sub>a</sub>, 5<sub>a</sub>'), 3.47 (2 H, dq, <i>J</i>
= 9.4, 7.1, H-5b, 5’); 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’); δc (100 MHz, CDCl3) 102.1 (CH, C-1), 61.2 (2 × CH2, C-5, 5’), 33.6 (CH2, C-4), 32.2 (CH2, C-2), 28.0 (CH2, C-3), 15.3 (2 × CH3, C-6, 6’); m/z (ESI) 247 [MNa]+; [HRMS (ESI): calcd. for C8H1779BrNaO2, 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 K2CO3 (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 H2O (20 mL) and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na2SO4), then concentrated in vacuo to afford an orange oil which was purified by column chromatography (SiO2, DCM/MeOH, 99:1-98:2) to give the title compound 404 (133 mg, 47%) as a pale yellow oil; Rf 0.52 (DCM/MeOH, 9:1); υmax/cm−1 (neat) 2974, 2877, 2808, 1376, 1128, 1065; δH (400 MHz, CDCl3) 4.50 (1 H, t, J = 5.6, H-8), 3.63 (1 H, dq, J = 9.4, 7.1, H-12a), 3.63 (1 H, dq, J = 9.4, 7.1, H-12b), 3.48 (2 H, dq, J = 9.4, 7.1, H-12b, 12b’), 3.41-3.34 (1 H, m, H-10), 2.82-2.73 (2 H, m, H-3a, 5a), 2.48 (1 H, ddd, J = 8.8, 8.8, 5.6, H-3b), 2.40-2.32 (1 H, m, H-5b), 2.24 (1 H, d, J = 2.1, H-11), 2.14-2.03 (1 H, m, H-1a), 1.96-1.82 (2 H, m, H-1b, 2a), 1.82-1.69 (1 H, m, H-2b), 1.69-1.52 (4 H, m, H-6, 7), 1.19 (6 H, t, J = 7.1, H-13, 13’); δc (100 MHz, CDCl3) 102.7 (CH, C-8), 83.2 (C, C-9), 72.0 (CH, C-11), 60.9 (2 × CH2, C-12, 12’), 54.2 (CH, C-10), 52.9 (CH2, C-5), 51.6 (CH2, C-3), 31.6 (2 × CH2, C-1, 7), 23.9 (CH2, C-6), 22.0 (CH2, C-2), 15.3 (2 × CH3, C-13, 13’); m/z (ESI) 240 [MH]+; [HRMS (ESI): calcd. for C14H26NO2, 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. NH₄Cl (5 mL), then the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, 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, CHCl₃); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2972, 2928, 2875, 1375, 1127, 1062; \( \delta_H \) (400 MHz, CDCl₃) 4.49 (1 H, t, J = 5.4, H₈), 3.67-3.58 (2 H, m, H₁₄, H₁₄'), 3.52-3.43 (3 H, m, H₁₀, H₁₄b, H₁₄b'), 2.80-2.72 (2 H, m, H₃a, H₅a), 2.72-2.63 (2 H, m, H₁₂), 2.45 (1 H, ddd, J = 8.7, 8.5, 5.4, H₃b), 2.33 (1 H, ddd, J = 11.7, 6.7, 6.7, H₅b), 2.12-2.01 (1 H, m, H₁₃), 1.93-1.80 (2 H, m, H₁b, H₂a), 1.80-1.68 (1 H m, H₂b), 1.68-1.50 (4 H, m, H₆-7), 1.36 (3 H, t, J = 7.3, H₁₃), 1.18 (6 H, t, J = 7.1, H₁₅, H₁₅'); \( \delta_C \) (100 MHz, CDCl₃) 102.8 (CH, C₈), 93.5 (C, C₉), 73.1 (C, C₁₁), 61.0 (CH₂, C₁₄), 60.9 (CH₂, C₁₄'), 55.5 (CH, C₁₀), 53.0 (CH₂, C₅), 51.6 (CH₂, C₃), 31.7 (2 × CH₂, C₁, C₇), 29.6 (CH₂, C₁₂), 23.9 (CH₂, C₆), 22.0 (CH₂, C₂), 15.3 (2 × CH₃, C₁₅, C₁₅'), 14.6 (CH₃, C₁₃); \( m/z \) (ESI) 300 [MH]⁺; [HRMS (ESI): calcd. for C₁₆H₃₀NO₂S, 300.1992. Found: [MH]⁺, 300.1993 (0.3 ppm error)].

Lab Book Ref. = JDC/14/69
(8R,8aS)-Octahydroindolizin-8-ylmethanol 407: To a stirred solution of LiAlH₄ (4.0 M in Et₂O, 0.19 mL, 0.76 mmol, 4.0 equiv.) in Et₂O (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 (SiO₂, DCM/MeOH/NH₃, 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; Rᵣ 0.05 (DCM/MeOH, 9:1); [α]²³D −42.6 (c 1.08, EtOH), (Lit.¹⁶⁷ +44.7 (c 1.1, EtOH)); υmax/cm⁻¹ (neat) 3365, 2930, 1444, 1042; δH (400 MHz, CDCl₃) 3.65 (1 H, dd, J = 10.8, 4.7, H-10a), 3.50 (1 H, dd, J = 10.8, 6.3, H-10b), 3.17-3.08 (2 H, m, H-3a, 5a), 2.12 (1 H, ddd, J = 9.1, 9.1, 9.1, H-3b), 1.97-1.80 (3 H, m, H-1a, 5b, 7a), 1.80-1.54 (5 H, m, H-2, 6, 9), 1.55-1.43 (2 H, m, H-1b, 8), 1.05 (1 H, m, H-7b); δC (100 MHz, CDCl₃) 66.4 (CH, C-9), 65.6 (CH₂, C-10), 54.0 (CH₂, C-3), 52.5 (CH₂, C-5), 44.2 (CH, C-8), 28.9 (CH₂, C-1), 27.3 (CH₂, C-7), 24.9 (CH₂, C-6), 20.6 (CH₂, C-2); m/z (ESI) 156 [MH⁺]; [HRMS (ESI): calcd. for C₉H₁₈NO, 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 Et₃N (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. NaHCO₃ (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 (Na₂SO₄), then concentrated in vacuo to afford a brown oil which was purified by column chromatography (SiO₂, 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); \([\alpha]_{D}^{20} \) −55.6 (c 0.35, CHCl₃); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2951, 1713, 1435, 1260, 1100, 1036; \( \delta_H \) (400 MHz, CDCl₃) 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); \( \delta_C \) (100 MHz, CDCl₃) 166.3 (CO, C-10), 137.4 (CH, C-7), 132.2 (C, C-8), 58.7 (CH, C-9), 52.5 (CH₂, C-3), 51.5 (CH₃, C-11), 44.9 (CH₂, C-5), 29.8 (CH₂, C-1), 24.4 (CH₂, C-6), 22.3 (CH₂, C-2); \( m/z \) (ESI) 182 [MH⁺]; [HRMS (ESI): calcd. for C₁₀H₁₆NO₂, 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)methanol¹⁶⁹ 288: To a stirred solution of ester 409 (394 mg, 2.17 mmol, 1.0 equiv.) in THF (30 mL) at 0 °C 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 °C for 30 min., then warmed to rt and held for 2 h. The reaction was cooled to 0 °C 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 (MgSO₄), 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); \([\alpha]_{D}^{20} \) −54.6 (c 1.03, CHCl₃); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3352 (br), 2909, 2875, 1458, 1062, 1018; \( \delta_H \) (400 MHz, CDCl₃) 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, \( J = 10.5, 8.9, 7.9, H-5_b \)), 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-1a), 1.89 (1 H, ddddd, J = 12.8, 10.5, 8.1, 7.9, 3.6, H-2a), 1.75 (1 H, dddd, J = 12.8, 9.5, 8.9, 7.3, 3.8, H-2b), 1.54 (1 H, ddd, J = 12.1, 10.5, 10.5, 7.3, H-1b); δC (100 MHz, CDCl3) 139.4 (C, Ck8), 120.5 (CH, Ck7), 64.7 (CH2, C-10), 60.4 (CH, C-9), 52.9 (CH2, C-3), 46.6 (CH2, C-5), 28.0 (CH2, C-1), 25.0 (CH2, C-6), 22.1 (CH2, C-2); m/z (ESI) 154 [MH]+; [HRMS (ESI): calcd. for C9H16NO, 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-Methycyclohex-2-enone105 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. NaHCO3 (20 mL). The aqueous phase was separated, then extracted with Et2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO4), then concentrated in vacuo to afford a brown oil which was purified by column chromatography (SiO2, PE/EtOAc, 9:1) to give the title compound 87 (510 mg, 46%) as a pale yellow oil; Rf 0.32 (PE/EtOAc, 4:1); [α]21D +70.4 (c 0.52, CHCl3), (Lit.105 −74.6 (c 0.50, CHCl3, 80% ee)); δH (400 MHz, CDCl3) 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-6a), 2.45-2.37 (1 H, m, H-4a), 2.29-2.15 (1 H, m, H-5), 2.11 (1 H, dd, J = 15.9, 12.3, H-6b), 2.03 (1 H, dddd, J = 18.5, 9.8, 2.6, 2.5, H-4b), 1.06 (3 H, d, J = 6.5, H-7).
Lab Book Ref. = JDC/14/30
Data were consistent with those published.105
3-[(1R,2S,5R)-2-Isopropyl-5-methyleclohexyloxy]-5-methyleclohex-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. NaHCO₃ (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 (MgSO₄), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO₂, 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/Et₂O, 1:1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2954, 2871, 1655, 1600, 1377, 1208; δ$_H$ (400 MHz, CDCl₃) 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, 14', 16, 16'), 2.28-1.89 (10 H, m, H-6, 6', 10, 10', 14, 14, 15, 15', 16, 16'), 1.72-1.63 (4 H, m, H-3, 3', 4, 4'), 1.50-1.31 (4 H, m, H-2, 2', 5, 5'), 1.06 (3 H, d, $J = 1.8$, CH₃), 1.05 (3 H, d, $J = 1.7$, CH₃), 0.91-0.86 (12 H, m, CH₃), 0.73 (3 H, d, $J = 4.4$, CH₃), 0.72 (3 H, d, $J = 4.4$, CH₃); δ$_C$ (100 MHz, CDCl₃) 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 × CH₂, C-14), 39.4 (CH₂, C-10), 38.9 (CH₂, C-10), 37.7 (CH₂, C-16), 37.5 (CH₂, C-16), 34.2 (2 × CH₂, 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 (CH₂, C-4), 23.7 (C-4), 21.9 (2 × CH₃, C-1), 20.9 (CH₃), 20.8 (CH₃), 20.5 (CH₃), 20.4 (CH₃), 16.7 (CH₃), 16.6 (CH₃); m/z (ESI) 265 [MH]$^+$; [HRMS (ESI): calcd. for C₁₇H₂₉O₂, 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 Et3N (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. NaHCO3 (10 mL) then the aqueous phase was extracted with DCM (4 × 10 mL). The combined organic extracts were washed with sat. aq. NaHCO3 (20 mL) and brine (20 mL), dried (Na2SO4), then concentrated in vacuo to afford the title compound 172 (137 mg, 88%) as a yellow oil which was used immediately without further purification; Rf 0.28 (DCM/MeOH, 9:1); δH (400 MHz, CDCl3) 9.41 (1 H, s, Hk10), 6.84 (1 H, ddd, J = 4.0, 3.9, 1.7, Hk7), 3.45-3.37 (1 H, m, Hk9), 2.97-2.90 (1 H, ddd, J = 10.1, 7.9, 4.8, Hk3a), 2.74 (1 H, ddd, J = 10.1, 8.5, 7.3, H-3b), 2.68-2.61 (1 H, m, H-5a), 2.61-2.51 (1 H, m, H-6a), 2.48-2.38 (1 H, m, H-6b), 2.40-2.31 (1 H, m, H-1a), 1.94-1.75 (2 H, m, H-2), 1.45 (1 H, ddd, J = 12.8, 10.2, 9.4, 7.6, H-1b).

**Lab Book Ref. = JDC/14/18**

Data were consistent with those published.35

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(5S,6S)-6-[(8aS)-1,2,3,5,6,8a-Hexahydroindolizin-8-yl(hydroxy)methyl]-5-methylcyclohex-2-en-1-one 287: To a stirred solution of diisopropylamine (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 (K₂CO₃) then extracted with DCM (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), then concentrated in vacuo to afford an orange oil which was purified by column chromatography (SiO₂, DCM/MeOH/NH₃, 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; [α]₂⁰ −20.4 (c 0.99, CHCl₃); υₛₒₚ/cm⁻¹ (thin film) 3399 (br), 2957, 2918, 1676, 1389, 1026, 730; δH (400 MHz, CDCl₃) 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-3a), 2.84 (1 H, ddd, J = 11.3, 5.7, 5.7, H-5a), 2.72-2.63 (1 H, m, H-3b), 2.56 (1 H, dddd, J = 19.7, 5.6, 2.8, 2.6, H-15a), 2.50 (1 H, ddd, J = 11.3, 5.6, 5.3, H-5b), 2.38 (1 H, dd, J = 9.5, 3.2, H-11), 2.44-2.11 (4 H, m, H-1a, 6, 16), 2.07 (1 H, dddd, J = 19.7, 5.2, 2.3, 1.5, H-15b), 2.00-1.86 (1 H, m, H-2a), 1.82-1.67 (2 H, m, H-1b, 2b), 1.07 (3 H, d, J = 7.1, H-17); δC (100 MHz, CDCl₃) 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 (CH₂, C-3), 46.3 (CH₂, C-5), 30.1 (CH, C-16), 30.0 (CH₂, C-15), 29.6 (CH₂, C-1), 25.5 (CH₂, C-6), 22.3 (CH₂, C-2), 19.9 (CH₃, C-17); m/z (ESI) 262 [MH⁺]; [HRMS (ESI): calcd. for C₁₆H₂₄NO₂, 262.1802. Found: [MH⁺], 262.1799 (1.1 ppm error)].

(5R,6R)-6-[(8aS)-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; Rᵣ 0.35 (DCM/MeOH/NH₃, 40:9:1); [α]°D −65.4 (c 0.55, CHCl₃); υₛₒₚ/cm⁻¹ (thin film) 3340 (br), 2956, 2915, 1668, 730; δH (400 MHz, CDCl₃) 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-3a), 2.76 (1 H, ddd, J = 11.3, 5.7, 5.7 H-5a), 2.63-2.48 (2 H, m, H-3b, 15a), 2.47 (1 H, ddd, J = 11.3, 5.6, 5.6, H-5b), 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-1a, 15b), 1.93-1.80 (1 H, m, H-2a), 1.78-1.66 (1 H, m, H-2b), 1.53-1.42 (1 H, m, H-1b), 1.02 (3 H, d, J = 7.0, H-17); δC (100 MHz, CDCl3) 201.0 (CO, C12), 147.6 (CH, C14), 139.6 (C, C8), 128.5 (CH, C13), 122.1 (CH, C7), 73.4 (CH, C10), 60.1 (CH, C9), 57.5 (CH, C11), 52.7 (CH2, C3), 46.3 (CH2, C5), 30.8 (CH, C16), 30.4 (CH2, C15), 28.2 (CH2, C1), 25.4 (CH2, C6), 22.0 (CH2, C2), 19.9 (CH3, C17); m/z (ESI) 262 [MH]+; [HRMS (ESI): calcd. for C16H24NO2, 262.1802. Found: [MH]+, 262.1803 (0.5 ppm error)].

Lab Book Ref. = JDC/14/52

(5S,6R)-6-[(8aS)-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 Et3N (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. NaHCO3 (20 mL), then the aqueous phase was extracted with DCM (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na2SO4), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO2, DCM/MeOH/NH3, 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; Rf 0.69 (DCM/MeOH/NH3, 40:9:1); [α]22D
+73.7 (c 0.10, MeOH), (Lit.25 +65.7 (c 0.09, MeOH)); \( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 2959, 1676, 1656, 1390, 1190; \( \delta_{\text{H}} \) (400 MHz, DMSO-\( \text{d}_6 \)) 10.37 (1 H, br s, NH\(^+\)), 7.35 (1 H, dd, \( J = 3.8, 3.8, \text{H-7} \)), 7.16 (1 H, ddd, \( J = 9.9, 5.5, 2.2, \text{H-14} \)), 5.97 (1 H, dd, \( J = 9.9, 2.1, \text{H-13} \)), 4.40 (1 H, dd, \( J = 8.7, 8.7, \text{H-9} \)), 4.33 (1 H, d, \( J = 11.5, \text{H-11} \)), 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, \( J = 6.2, \text{H-17} \)); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( \text{d}_6 \)) 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.\(^{10,25}\)

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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 °C was added dropwise 35% aq. NH\(_3\) (1 mL, ca. 18 mmol). The yellow solution was held at 0 °C 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\(_2\)SO\(_4\)), 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; \( R_{\text{f}} \) 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)); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2954, 2872, 1730, 1578, 1341, 1102; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 6.41 (1 H, ddd, \( J = 4.2, 4.2, 1.5, \text{H-7} \)), 4.63 (1 H, dddd, \( J = 3.6, 3.3, 1.8, 1.8, \text{H-14} \)), 3.70-3.63 (1 H, m, H-9), 3.55 (1 H, d, \( J = 3.1, \text{H-11} \)), 2.92 (1 H, ddd, \( J = 10.2, 7.7, 4.7, \text{H-3} \)), 2.87 (1 H, ddd, \( J = 11.0, 3.2, 3.2, \text{H-5} \)), 2.77 (1 H, ddd, \( J = 10.2, 7.7, 4.7, \text{H-3} \)).
= 10.2, 8.2, 7.5, H-3b), 2.64 (1 H, ddd, J = 11.0, 7.0, 5.1, H-5b), 2.47-2.36 (1 H, m, H-6a), 2.36-2.24 (2 H, m, H-1a, 6b), 2.16 (1 H, ddd, J = 18.8, 3.3, 2.7, H-13a), 2.06 (1 H, dd, J = 18.8, 1.8, H-13b), 2.00-1.92 (1 H, m, H-15a), 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-1b), 1.27 (1 H, ddd, J = 12.6, 4.5, 1.8, H-15b), 1.06 (3 H, d, J = 7.0, H-17); δC (100 MHz, CDCl3) 208.9 (CO, Ck12), 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 (CH2, C-3), 45.2 (CH2, C-5), 40.0 (CH2, C-13), 32.2 (CH2, C-15), 30.0 (CH2, C-1), 29.2 (CH, C-16), 24.9 (CH2, C-6), 22.4 (CH2, C-2), 21.2 (CH3, C-17); m/z (ESI) 259 [MH]+; [HRMS (ESI): calcd. for C16H23N2O, 259.1805. Found: [MH]+, 259.1810 (2.1 ppm error)].

Lab Book Ref. = JDC/14/56

Data were consistent with those published.\textsuperscript{9,55}

1-{[(8aS)-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 °C was added Fe(acac)\textsubscript{3} (3 mg, 0.008 mmol, 0.04 equiv.). The orange solution was held at 0 °C for 5 min., then propyl magnesium bromide (2.0 M in Et\textsubscript{2}O, 145 µL, 0.29 mmol, 1.4 equiv.) was added dropwise. The resulting black solution was held at 0 °C for 30 min., then quenched with sat. aq. NH\textsubscript{4}Cl (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\textsubscript{2}SO\textsubscript{4}), then concentrated \textit{in vacuo} to afford an orange oil which was purified by column chromatography (SiO\textsubscript{2}, DCM/MeOH, 98:2-9:1) to give the title compound 57 (16 mg, 39%) as a colourless oil; \textit{Rf} 0.16 (DCM/MeOH, 9:1); \nu_{max}/cm\textsuperscript{-1} (neat) = 2961, 2875, 1666, 1461, 1395, 1201; δH (400 MHz, CDCl3) 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-3a), 3.01-2.94 (1 H, m, H-3b), 2.89-2.84 (2 H, m, H-5), 2.68-2.53 (1 H, m, H-6a), 2.63 (1 H, dt, J = 16.4, 7.3, H-11a), 2.58 (1 H, dt, J = 16.4, 7.3, H-11b), 2.52-2.42 (2 H, m, H-1a, 6b), 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-1b), 0.91 (3 H, t, J = 7.4, H-13); δC (100 MHz, CDCl3) 199.8 (CO, C-10), 280
139.9 (C, C-8), 136.3 (CH, C-7), 58.6 (CH, C-9), 52.9 (CH\textsubscript{2}, C-3), 44.8 (CH\textsubscript{2}, C-5), 39.1 (CH\textsubscript{2}, C-11), 29.4 (CH\textsubscript{2}, C-1), 24.6 (CH\textsubscript{2}, C-6), 21.9 (CH\textsubscript{2}, C-2), 17.9 (CH\textsubscript{2}, C-12), 13.7 (CH\textsubscript{3}, C-13); \textit{m/z} (ESI) 194 \textsuperscript{[MH]}\textsuperscript{+}; [HRMS (ESI): calcd. for C\textsubscript{12}H\textsubscript{20}NO, 194.1539. Found: [MH]\textsuperscript{+}, 194.1541 (0.9 ppm error)].

**Lab Book Ref.** = JDC/12/1

Data were consistent with those published.\textsuperscript{37}

(2\textit{E})-1-[(8\textit{aS})-1,2,3,5,6,8\textit{a}-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.) and Pd\textsubscript{2}(dba)\textsubscript{3} (2 mg, 0.002 mmol, 0.025 equiv.) in THF (1 mL, degassed) under argon (flask purged \textit{via} 5 \times vacuum/Ar cycles) at rt was added P(OEt)\textsubscript{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\textsubscript{3} (2 mL). The aqueous phase was extracted with DCM (3 \times 5 mL), then the combined organic extracts were washed with brine (5 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), then concentrated \textit{in vacuo} to afford a brown oil which was purified by column chromatography (SiO\textsubscript{2}, DCM/MeOH/NH\textsubscript{3}, 95:5:0-190:9:1) to give the title compound 421 (11 mg, 56%) as a yellow film; \(R\textsubscript{f} 0.11\) (DCM/MeOH, 9:1); \(\nu_{\text{max}}/\text{cm}^{-1}\) (thin film) 2923, 1654, 1597, 1202; \(\delta_H\) (400 MHz, CDCl\textsubscript{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\textit{a}), 3.05 (1 H, ddd, \(J = 10.7, 6.7, 6.7\), H-3\textit{b}), 3.01-2.96 (2 H, m, H-5), 2.79-2.68 (1 H, m, H-6\textit{a}), 2.63-2.52 (2 H, m, H-1\textit{a}, 6\textit{b}), 2.04-1.95 (2 H, m, H-2), 1.58 (1 H, ddd, \(J = 13.1, 9.4, 9.2\), H-1\textit{b}); \(\delta_C\) (100 MHz, CDCl\textsubscript{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 \times CH, ArCH), 128.3 (2 \times CH, ArCH), 120.6 (CH, C-11), 58.9 (CH, C-9), 53.0 (CH\textsubscript{2}, C-3), 45.0 (CH\textsubscript{2}, C-5), 29.3 (CH\textsubscript{2}, C-1), 24.3 (CH\textsubscript{2}, C-6), 21.8 (CH\textsubscript{2}, C-2); \textit{m/z} (ESI) 254 [MH]\textsuperscript{+}; [HRMS (ESI): calcd. for C\textsubscript{17}H\textsubscript{20}NO, 254.1539. Found: [MH]\textsuperscript{+}, 254.1536 (1.5 ppm error)].
(2E)-1-[(8aS)-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 Pd₂dba₃ (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. NaHCO₃ (5 mL). The aqueous phase was extracted with DCM (3 × 10 mL), then the combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), then concentrated in vacuo to afford a brown oil which was purified by column chromatography (SiO₂, DCM/MeOH, 9:1-4:1) to give the title compound 422 (102 mg, 69%) as an orange oil containing minor aromatic impurities; Rₜ 0.16 (DCM/MeOH, 4:1); vₚₓₘₐₓ/cm⁻¹ (neat) 2958, 1662, 1616, 1443, 1293, 1205; δₓ (400 MHz, CDCl₃) 6.87-6.83 (1 H, m, H₇), 6.85 (1 H, dq, J = 15.1, 6.9, H₁₂), 6.57 (1 H, dq, J = 15.1, 1.4, H₁₁), 3.71 (1 H, dd, J = 7.8, 7.5, H₉), 2.92 (2 H, dd, J = 7.2, 7.2, H₃), 2.91-2.82 (1 H, m, H₅ₐ), 2.75 (1 H, ddd, J = 11.2, 5.5, 5.5, H₅ₖ), 2.49-2.41 (2 H, m, H₆), 2.40-2.31 (1 H, m, 1ₐ), 1.91-1.79 (2 H, m, H₂), 1.87 (3 H, dd, J = 6.9, 1.4, H₁₃), 1.41 (1 H, dddd, J = 13.0, 9.8, 9.7, 7.8, H₁₅); δₓ (100 MHz, CDCl₃) 189.8 (C, C₁₀), 143.2 (CH, C₁₂), 140.9 (C, C₈), 136.5 (CH, C₇), 126.4 (CH, C₁₁), 58.5 (CH, C₉), 52.4 (CH₂, C₃), 44.7 (CH₂, C₅), 29.1 (CH₂, C₁), 24.6 (CH₂, C₆), 22.0 (CH₂, C₂), 18.3 (CH₃, C₁₃); m/z (ESI) 192 [MH]+; [HRMS (ESI): calcd. for C₁₂H₁₈NO, 192.1383. Found: [MH]+, 192.1382 (0.4 ppm error)].

Lab Book Ref. = JDC/14/47
(3S,4aS,10aS,10bR)-3-Methyldecahydropyrrolo[2,1-f][1,6]naphthyridin-1(2H)-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. NH3 (5 mL). The solution was held at 0 ºC for 30 min., then diluted with H2O (10 mL). The aqueous phase was extracted with DCM (3 × 10 mL), then the combined organics were washed with brine (10 mL), dried (Na2SO4), then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO2, DCM/MeOH/NH3, 190:9:1-90:9:1) to give the title compound 419 (28 mg, 25%) as a yellow oil containing minor diastereomeric impurities; Rf 0.16 (DCM/MeOH/NH3, 90:9:1); vmax/cm⁻¹ (neat) 2960, 2928, 2799, 1705, 1330, 1168; δH (400 MHz, CDCl3) 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-5a), 3.02 (1 H, ddd, J = 8.8, 8.6, 2.3, H-3a), 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-11a), 2.31 (1 H, ddd, J = 12.8, 6.0, 3.6, H-1a), 2.20 (1 H, dd, J = 12.8, 1.8, H-11b), 2.12 (3 H, m, H-3b, 5b, 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, 1b), 1.16 (3 H, t, J = 6.9, H-13); δC (100 MHz, CDCl3) 208.9 (CO, C-10), 62.0 (CH, C-8), 61.8 (CH, C-9), 56.1 (CH, C-7), 53.1 (CH2, C-3), 51.3 (CH, C-12), 50.4 (CH2, C-5), 49.1 (CH2, C-11), 33.1 (CH2, C-6), 29.0 (CH2, C-1), 21.7 (CH2, C-2), 19.8 (CH3, C-13); m/z (ESI) 209 [MH]+; [HRMS (ESI): calcd. for C12H21N2O, 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 $^1\text{H}/^{13}\text{C}$ Spectral Data for Grandisine D·TFA (17)

![Chemical structure of Grandisine D·TFA](image)

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<th>Carroll (ppm) ($d_6$-DMSO, 600 MHz)</th>
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Appendix II. Comparison of \(^1\text{H}/^{13}\text{C}\) Spectral Data for Grandisine B (15)

![Diagram](image)

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Grandisine D•TFA 17

400 MHz, DMSO-d$_6$
**Appendix VII. Crystallographic Data – Compound 252 (CCDC 789903)**

Identification code: 2010src0766

Empirical formula: C₉H₁₃NO₂

Formula weight: 167.20

Temperature: 120(2) K

Wavelength: 0.71073 Å

Crystal system: Triclinic

Space group: P-1

Unit cell dimensions:
- \(a = 6.60970(10) \text{ Å}\)
- \(\alpha = 95.1970(10)^\circ\)
- \(b = 10.5480(3) \text{ Å}\)
- \(\beta = 91.371(2)^\circ\)
- \(c = 12.7041(3) \text{ Å}\)
- \(\gamma = 104.645(2)^\circ\)

Volume: 852.41(3) Å³

Z: 4

Density (calculated): 1.303 Mg/m³

Absorption coefficient: 0.092 mm⁻¹

\(F(000) = 360\)

Crystal size: 0.23 x 0.11 x 0.07 mm³

Theta range for data collection: 3.19 to 27.67°

Index ranges: \(-8 \leq h \leq 8, -13 \leq k \leq 13, -16 \leq l \leq 16\)

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 [\(I>2\sigma(I)\)]: \(R1 = 0.0451, wR2 = 0.1006\)

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  \( \text{C}_9 \text{H}_{13} \text{N}_2 \text{O}_2 \)
Formula weight  167.20
Temperature  120(2) K
Wavelength  0.71073 Å
Crystal system  Monoclinic
Space group  P2(1)/c
Unit cell dimensions
\[
a = 6.9758(10) \text{ Å} \quad \alpha = 90^\circ.
\]
\[
b = 9.1944(13) \text{ Å} \quad \beta = 90.960(3)^\circ.
\]
\[
c = 13.0978(19) \text{ Å} \quad \gamma = 90^\circ.
\]
Volume  840.0(2) Å³
Z  4
Density (calculated)  1.322 Mg/m³
Absorption coefficient  0.093 mm⁻¹
\( F(000) \)  360
Crystal size  0.39 x 0.14 x 0.11 mm³
Theta range for data collection  2.71 to 28.39°
Index ranges  \(-8 \leq h \leq 9, -12 \leq k \leq 12, -17 \leq l \leq 17\)
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>2\sigma(I)]  \( R_1 = 0.0414, wR_2 = 0.1087 \)
R indices (all data)  \( R_1 = 0.0462, wR_2 = 0.1129 \)
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_{4}O_{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) Å³
Z  4
Density (calculated)  1.545 Mg/m³
Absorption coefficient  1.096 mm⁻¹
F(000)  792
Crystal size  0.30 x 0.12 x 0.07 mm³
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 F²
Data / restraints / parameters  3020 / 0 / 250
Goodness-of-fit on F²  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\textsubscript{28}H\textsubscript{28}N\textsubscript{8}O\textsubscript{15}
Formula weight              716.58
Temperature / K             110.0
Crystal system              Monoclinic
Space group                 P2\textsubscript{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\textsuperscript{3}  3004.5(4)
Z                           4
ρ\textsubscript{calc} / mg mm\textsuperscript{3} 1.584
μ / mm\textsuperscript{-1}     0.131
F(000)                      1488
Crystal size / mm\textsuperscript{3} 0.2389 × 0.0855 × 0.0853
Theta range for data collection 2.86 to 25.05\textdegree
Index ranges               -8 ≤ h ≤ 8, -20 ≤ k ≤ 20, -29 ≤ l ≤ 28
Reflections collected       29380
Independent reflections     5329 [R(int) = 0.0725]
Data/restraints/parameters  5329/6/485
Goodness-of-fit on F\textsuperscript{2} 0.960
Final R indexes [I>2σ (I)] R\textsubscript{1} = 0.0474, wR\textsubscript{2} = 0.1025
Final R indexes [all data]  R\textsubscript{1} = 0.0833, wR\textsubscript{2} = 0.1110
Largest diff. peak/hole / e Å\textsuperscript{-3} 0.268/-0.189
A Tandem Amination/Lactamisation Route to 2-Azabicyclo[2.2.2]octanones

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Received 31 August 2010

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Abstract: An efficient one-pot amination/lactamisation sequence for the preparation of 2-azabicyclo[2.2.2]octanones from 6-carbaalkoxycyclohex-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-carbaalkoxycyclohex-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 routes3 or the thermal cyclisation of aminocyclohexane carboxylic acids.4 We recently described an efficient method for preparing isoquinuclidines 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-carbaalkoxycyclohex-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.

In order to establish the viability of this approach, we initially decided to examine the cyclisation of the knowna methyl-substituted cyclohexene 3a (Scheme 2 and Table 1).

Scheme 1

Scheme 2

Table 1 Conversion of Enone 3a into 8β-Methyl-2-azabicyclo[2.2.2]octane-3,5-dione (5a)c

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<td>–</td>
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a All reactions were performed on a 0.1 mmol scale; entries 2–5 were carried out using 35% aq NH3 (0.25 mL) and solvent (0.5 mL).
b Conversion estimated by 1H NMR spectroscopy.
c A similar result was observed using CH2Cl2 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 1H NMR/13C NMR spectroscopy (characteristic bridgehead proton signals at
[Synlett, 2010, 2805–2807 © Thieme Stuttgart · New York]

δ = 4.0 and 3.1 ppm; 13C 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 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-ketoesters. The reactions generally proceeded rapidly to give the expected 2-azabicyclo[2.2.2]octane-3,5-diones in good to excellent yields. The successful cyclisation of the carvone-derived cyclohexenone (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 5 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.

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-

---

Figure 1 X-ray structure of compound 5f depicted using ORTEP-3 (CCDC 789903)

Table 2 Scope of Amination/Cyclisation Sequence

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<th>Yield (§)</th>
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<td>60</td>
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</tbody>
</table>

§ All reactions were performed on a 0.25 mmol scale using 35% aq NH3 (1.0 mL) at r.t.
§ Isolated yields.
§ Diastereomeric ratio ca. 4:1
LETTER

Tandem Amination/Lactamisation Route to 2-Azabicyclo[2.2.2]octanones

![Diagram of the tandem amination/lactamisation sequence](https://example.com/diagram)

In summary, an efficient tandem amination/lactamisation route to 2-azabicyclo[2.2.2]octanones has been developed for the preparation of 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

9. Typical Procedure for the Synthesis of 8β-Methyl-2-azabicyclo[2.2.2]octane-3,5-dione (5a): A solution of ketone ester 3a (46 mg, 0.25 mmol) in 35% aqueous NH3 (1 mL) was stirred at r.t. until consumption of starting material was observed by TLC analysis (CH2Cl2–MeOH, 9:1), ca. 2 h. The reaction mixture was then concentrated in vacuo and purified by column chromatography (SiO2, CH2Cl2–MeOH, 98:2) to give the title compound 5a as a colourless crystalline solid (36 mg, 93%); mp 135–137 °C; Rf 0.40 (CH2Cl2–MeOH, 9:1). IR (thin film): 3442, 2961, 1730, 1618, 1335, 1105 cm–1. 1H NMR (400 MHz, CDCl3): δ = 7.92 (br s, 1 H, NH), 3.93–3.98 (m, 1 H), 3.03–3.11 (m, 1 H), 2.90–2.98 (m, 1 H), 2.24–2.37 (m, 1 H), 2.20 (dd, J = 18.5, 19.9 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). 13C NMR (100 MHz, CDCl3): δ = 205.1 (C), 171.8 (CO), 64.4 (CH), 47.0 (CH), 43.8 (CH2), 33.4 (CH3). MS: m/z (ESI) = 154 [M+H]+. HRMS (ESI): m/z ([M+H]+) calcd for C8H12NO2: 154.0863; found: 154.0864 (0.6 ppm error).
Synthesis of isoquinuclidinones via a tandem amination/imination sequence: application to the synthesis of (−)-mearsine

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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, due to the prevalence of such systems in natural products and pharmaceuticals/agrochemicals. Recently, we have become interested in naturally occurring isoquinuclidine alkaloids such as compounds 1–3 isolated from Daphniphyllum, Securinega and Tabernaemontana species, respectively (Fig. 1). In turn, we were attracted to the rare isoquinuclidinone alkaloids mearsine 4 and grandisine B 5 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, thermal cyclisations of 4-amino-cyclohexane carboxaldehyde derivatives, double conjugate addition of aqueous ammonia into bifunctional Michael acceptors and recently via cyclisation of silyl enol ethers onto iminium ions. 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, 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.

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-methyl-cyclohexenone 9 with LDA in THF at −78 °C and subsequent trapping with cyclohexane carboxaldehyde, followed by oxidation of the resulting β-hydroxy ketone 10 using Dess–Martin periodinane. The novel 1,3-diketone 8a exists as a mixture of diastereoisomers/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 1H/13C NMR spectroscopy revealed the product to be the desired isoquinuclidinone 6a [characteristic bridgehead proton signals at 4.5 and 3.2 ppm; 13C NMR signals at 209.0 ppm (bridging ketone) and 179.7 ppm (imine)]. Compound 6a was obtained in excellent yield.
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. 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, should also be noted; it was proposed that grandisine G 13 results from the corresponding methanol-induced ring-opening of grandisine B 5.

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, and subsequently the (+)-enantiomer of mearsine was synthesised from (+)-pulegone by Crouse and Pinder. 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-
Table 1  
Scope of amination/cyclisation sequence<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 8</th>
<th>Product 6</th>
<th>Time (h)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
</thead>
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<tr>
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<td><img src="image" alt="6d" /></td>
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<td>80&lt;sup&gt;c&lt;/sup&gt;</td>
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<td><img src="image" alt="8e" /></td>
<td><img src="image" alt="6e" /></td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>vi</td>
<td><img src="image" alt="8f" /></td>
<td><img src="image" alt="6f" /></td>
<td>8</td>
<td>50&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>vii</td>
<td><img src="image" alt="8g" /></td>
<td><img src="image" alt="6g" /></td>
<td>72</td>
<td>75&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed on 0.25 mmol scale using MeOH (1 mL), 35% aq NH₃ (0.5 mL) at 0 ºC to rt.
<sup>b</sup> Isolated yields.
<sup>c</sup> Representative experimental procedure.<sup>14</sup>
<sup>d</sup> An inseparable mixture of 6f (confirmed by <sup>1</sup>H NMR/HRMS) and by-products obtained; yield estimated using NMR spectroscopy.
<sup>e</sup> Dr = 3.4:1.

tion\textsuperscript{18} and subsequent aldol condensation. Thus, addition of 2,4-pentanediol to crotonaldehyde mediated by Jørgensen’s catalyst 14 (1 mol\%)\textsuperscript{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/amination sequence to produce \(-\text{(-)}\)-mearsine 4 in 82% yield.\textsuperscript{20} The melting point (mp 38–40 °C) with 35% aqueous ammonia in methanol initiated the required treatment of the aldehyde 15 with pTSA (10 mol%) to furnish the desired cyclohexenone 8j, which was isolated as a complex mixture of diastereoisomers/tautomers. Addition of 2,4-pentanediol to crotonaldehyde mediated by Jørgensen’s catalyst 14 (1 mol\%)\textsuperscript{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/amination sequence to produce \(-\text{(-)}\)-mearsine 4 in 82% yield.\textsuperscript{20}

Acknowledgements

We are grateful to the EPSRC and AstraZeneca for studentship support (JDC).

References and notes

The Preparation of (−)-Grandisine B from (+)-Grandisine D; A Biomimetic Total Synthesis or Formation of an Isolation Artefact?

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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. Carroll and co-workers recently reported the isolation of the Elaeocarpus-derived indolizidine alkaloids grandisines A and B (Figure 1) from the Australian rainforest tree Elaeocarpus grandis as part of a high throughput drug discovery program. Subsequently, further studies revealed the presence of five additional members of this family, grandisines C–G (3–7). These indolizidine alkaloids have attracted considerable attention as they display human δ-opioid receptor affinity. First, Danishefsky and Maloney reported a total synthesis of (+)-grandisine A3, and then Tamura’s group published a total synthesis of (+)-grandisine D4 (as its TFA salt). Most recently, the latter group reported the conversion of grandisine B2 into grandisine D4 by the double addition of ammonia5 (following the biosynthetic proposal by Carroll2).

Our interest also focused on grandisine B2, particularly in view of its structural novelty; it contains an unprecedented combination of both indolizidine and isoquinuclidinone units linked by a Csp2–Csp2 bond. Although many indolizidine alkaloids have been isolated, isoquinuclidinone alkaloids are very rare indeed. In fact, mearsine8 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...

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‡ AstraZeneca.

methodology as part of an efficient synthesis of (−)-measrine 8. 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-methyl-cyclohexenone 10 then leads to the requirement for indolizidine 11.

Given the recent interest in the cyclization reactions of alkynyl aldehydes/acetals,11 we envisaged preparing 11 ultimately from alkyne 12 which we felt would be readily accessible from L-proline.

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 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 ([R] 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).
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 acetacetate and crotonaldehyde by an organocatalytic procedure). 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 ([α]D +73.7 (c 0.1, MeOH); published values: [α]D +34.6 (c 0.09, MeOH); [α]D +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 1H NMR spectrum.

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. 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 and the publication were consistent with those published (see Supporting Information). The isolation paper was basified with 27% NH4OH (2 x 200 mL) and partitioned with CH2Cl2. 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. 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 1; 3 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).

In addition, a tandem imination/amination sequence has been employed for the assembly of the isoquinuclidine 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 4

significantly, evidence is presented which indicates that grandisine B \( \text{B}_2 \) does not occur naturally but is formed by reaction of grandisine D \( \text{D}_4 \) 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 \( \text{B}_2 \) (CCDC815228). This material is available free of charge via the Internet at http://pubs.acs.org.
ALKYNE-ACETAL CYCLISATION REACTIONS MEDIATED BY FORMIC ACID; 3-ACYLATED-2,5-DIHYDROFURANS AND RELATED OXYGEN AND NITROGEN HETEROCYCLES

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Abstract – The utility of formic acid for the cyclisation of alkyne o-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-1H-pyrroles, tetrahydropyridines, 2H-chromenes, 1,2-dihydroquinolines and benzoxepin-5(2H)-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
As part of a natural product synthesis programme, we required ready access to a range of acylated dihydrofurans, dihydropyrroles, and higher homologues of this type. Given our interest in tandem reactions, we became attracted to approaches based on the cyclisation of o-formyl alkynes which can be mediated by both Lewis and Brønsted acids. Given that aliphatic aldehydes can be difficult to purify and prone to decomposition on storage, we explored the direct use of the corresponding alkyne o-acetals as cyclisation precursors (Scheme 1).

RESULTS AND DISCUSSION
Initial studies were carried out using the known alkynyl acetal 4a, which was readily prepared from alcohol 6 and commercially available acetal 7 using a modification of the published procedure (HMPA was omitted). 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, 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. 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 °C, 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.

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 C₁₂H₁₂NaO₄, 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td><img src="image" alt="Substrate 4a" /></td>
<td><img src="image" alt="Product 5a" /></td>
<td>98%</td>
</tr>
<tr>
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<td><img src="image" alt="Product 5b" /></td>
<td>70%$^c$</td>
</tr>
<tr>
<td>iii</td>
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<td><img src="image" alt="Product 5c" /></td>
<td>80%$^c$</td>
</tr>
<tr>
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<td><img src="image" alt="Substrate 4d" /></td>
<td><img src="image" alt="Product 5d" /></td>
<td>64%$^c$</td>
</tr>
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<tr>
<td>vi</td>
<td><img src="image" alt="Substrate 4f" /></td>
<td><img src="image" alt="Product 5f" /></td>
<td>69%</td>
</tr>
<tr>
<td>vii</td>
<td><img src="image" alt="Substrate 4g" /></td>
<td><img src="image" alt="Product 5g" /></td>
<td>97%$^d$</td>
</tr>
</tbody>
</table>

$^a$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-1H-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. 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 \([\alpha]_D -87 (c \text{ 0.97}, \text{ CHCl}_3)\). Such thioesters appear to be valuable synthetic building blocks and, indeed, thioester 5g has recently been employed by our group to prepare \((-\text{)-grandisine B and (+-grandisine D via a novel synthetic route.}\) 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 benzoexepinone 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).

\[
\begin{align*}
\text{Scheme 3}
\end{align*}
\]

In summary, a simple formic acid procedure has been developed for the conversion of alkyne \(\omega\)-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(2H)-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 (1H) and 100 MHz (13C); chemical shifts (δ) are quoted in parts per million (ppm) calibrated to residual non-deuterated solvent (1H NMR: CDCl3 at 7.26 ppm; 13C NMR: CDCl3 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, 4e, 4f, 4g and 2-(pent-1-ynyl)aniline12 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 °C (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 (SiO2, PE/EtOAc, 9:1) to give compound 5a (43 mg, 98%) as a crystalline solid; mp. 67-69 °C; Rf 0.23 (PE/EtOAc, 4:1) (other data fully consistent to published values7a).

All other products were prepared using the above procedure. Products 5e, 5f, 5g and 16 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; Rf 0.21 (PE/EtOAc, 4:1); IR (neat) 2855, 1738, 1124, 1074 cm⁻¹; 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) δ 22.6 (CH3), 32.7 (CH2), 74.4 (CH2), 76.3 (CH2), 136.3 (CH), 141.0 (C), 197.0 (C); m/z (ESI) 127 [MH]+; [HRMS (ESI): calcd. for C7H11O2, 127.0754. Found: [MH]+, 127.0757 (2.7 ppm error)].
(2-Methyl-2,5-dihydrofuran-3-yl)(phenyl)methanone 5c: purified by column chromatography (SiO₂, PE/EtOAc, 9:1) as a pale yellow oil (38 mg, 80%); Rₜ 0.33 (PE/EtOAc, 4:1); IR (neat) 2973, 2848, 1644, 1359, 1276, 1240, 1084 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 20.5 (CH₃), 74.5 (CH₂), 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 C₁₂H₁₃O₂, 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 (SiO₂, PE/EtOAc, 19:1 to 9:1) as a yellow oil (39 mg, 64%); Rₜ 0.49 (PE/EtOAc, 4:1); IR (neat) 2929, 1646, 1317, 1240, 1089 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 22.3 (2 × CH₂), 25.0 (CH₂), 34.1 (2 × CH₂), 71.9 (CH₂), 90.4 (C), 128.3 (2 × CH), 128.9 (2 × CH₂), 132.4 (CH), 139.1 (C), 139.9 (CH), 145.5 (C), 192.4 (C); m/z (ESI) 265 [MNa⁺]; [HRMS (ESI): calcd. for C₁₆H₁₈NaO₂, 265.1199. Found: [MNa⁺], 265.1192 (2.5 ppm error)].

1-(2H-Chromen-4-yl)butan-1-one 13: purified by column chromatography (SiO₂, PE/EtOAc, 9:1) as a yellow oil (29 mg, 57%); Rₜ 0.48 (PE/EtOAc, 4:1); IR (neat) 2964, 1682, 1485, 1456, 1226 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 13.8 (CH₃), 17.9 (CH₂), 41.6 (CH₃), 64.3 (CH₂), 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 C₁₃H₁₄NaO₂, 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 (SiO₂, PE/EtOAc, 9:1) as a yellow oil (54 mg, 60%); Rₜ 0.33 (PE/EtOAc, 4:1); IR (neat) 2964, 1682, 1354, 1165, 1089 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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 (ddd, J = 8.1, 1.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.7 (CH₃), 17.5 (CH₂), 21.4 (CH₃), 41.2 (CH₂), 44.8 (CH₂), 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$_3$S, 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$_2$O, 20:1 to 10:1) as a colourless crystalline solid (15 mg 39%); mp 60-62 °C; $R_f$ 0.19 (PE/Et$_2$O, 4:1); IR (thin film) 3429, 1718, 1653, 1475, 1302, 1165, 1108, 1012 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 46.2 (CH$_2$), 76.1 (CH), 120.7 (CH$_2$), 123.4 (CH), 127.8 (C), 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

7. For recent research on ω-carbonyl alkyn cyclisations see: (a) J. U. Rhee and M. J. Krische, _Org._

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).


### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tr>
<td>Ac</td>
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<tr>
<td>Ac$_2$O</td>
<td>Acetic anhydride</td>
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<td>acac</td>
<td>Acetylacetone</td>
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<td>aq.</td>
<td>Aqueous</td>
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<td>Benzyl</td>
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<td>Boc</td>
<td>tert-butoxycarbonyl</td>
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<td>Boc$_2$O</td>
<td>tert-Butyl dicarbonate</td>
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<td>br</td>
<td>Broad</td>
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<tr>
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<td>Ceric(IV) ammonium nitrate</td>
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<td>Correlation spectroscopy</td>
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<td>Cu(OTf)$_2$</td>
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<td>DIPEA</td>
<td>Diisopropylethylamine</td>
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<tr>
<td>DMAP</td>
<td>4-$N,N$-Dimethylaminopyridine</td>
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<tr>
<td>DMF</td>
<td>$N,N$-Dimethylformamide</td>
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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
KOt-Bu  Potassium tert-Butoxide
LDA  Lithium diisopropylamine
LHMDS  Lithium hexamethyldisilazane
m  Multiplet
M  Molar
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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>m/z</td>
<td>Mass to charge ratio</td>
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ppm Parts per million
PPTS Pyridinium p-toluene sulfonate
Pr Propyl
p-TsOH para-Toluenesulfonic acid
Py Pyridine
q Quartet
Quant. Quantitative
R Alkyl group (undefined)
Rf 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
TfO Trifluormethanesulfonic anhydride
TFA Trifluoroacetic acid
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<td>TFAA</td>
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