Towards the Total Synthesis of Domoic Acid and the Isodomoic Acids.

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Engineering and Physical Sciences

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Simon Sedehizadeh
School of Chemistry
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Abstract

This thesis describes advances in the development of a divergent synthetic route towards the isodomoic acids, employing a dearomatising cyclisation reaction as a key step.

The dearomatising cyclisation of methoxy substituted benzamides A, are discussed in section 2.1 along with the extensive work on the optimisation of these reactions.

To obtain a divergent synthesis a common late stage intermediate is considered in the form of alkyne B. Section 2.2 describes a synthetic route towards this intermediate via an Eschenmoser fragmentation reaction to introduce the alkyne functionality. Conditions are developed to overcome problems in chemoselectivity of an amide protection and arene oxidation issues surrounding a resistant aromatic ring are achieved.

Section 2.3 discusses an alternative route towards alkyne B using a regioselective Baeyer-Villiger oxidation reaction to introduce further functionality.

Finally, in section 2.4 a strategy towards alkyne B involving a silicon-mediated fragmentation is explored. Successful optimisation of a silylcupration is described, as well as addressing problems surrounding the fragmentation. Advances in the alkyne functionalisation and side chain couplings are also covered.
Declaration.

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Preface.

The Author graduated from the University of Sheffield in July 2006 with First Class Honours degree of Master of Chemistry with Year in Industry. From October 2006 until December 2009 the Author undertook a period of original research in the School of Chemistry at the University of Manchester, under the supervision of Professor Jonathan Clayden. The results of these investigations are outlined in this thesis.

Acknowledgments.

Firstly, I would like to thank Prof. Jonathan Clayden for the opportunity to carry out research within the group and for his help and support during my Ph.D. Thanks also to Dr. Neil Barnwell and co. at AstraZeneca, Loughborough for their constructive contribution to the project and for making my stay on-site an enjoyable and memorable one.

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I am grateful to the past and present members of the JPC group. A special mention to Gilles, whose contribution to the project has been priceless but has been rewarded with endless English lessons. Also thanks Abby, for proofreading this thesis and the many interesting discussions. Thanks to James², Morgan, Toma, Steve², Jordi, Mike, Julien, Beckii, Rob, Nadia, Anne, Paul, Jemma, Tetlow, Alex, Alberto, Uli and Molly.

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**Abbreviations.**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>Acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>(\text{tert-})butoxycarbonyl</td>
</tr>
<tr>
<td>Boc-ON</td>
<td>2-((\text{tert-})butoxycarbonyloxyimino)-2-phenylacetonitrile</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees celsius</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>C.D.</td>
<td>Circular Dichroism</td>
</tr>
<tr>
<td>CI(^+)</td>
<td>chemical ionisation (positive ionisation)</td>
</tr>
<tr>
<td>CN</td>
<td>Nitrile</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>COD</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>Conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>(\delta)</td>
<td>chemical shift (parts per million); partial charge</td>
</tr>
<tr>
<td>d</td>
<td>density, days</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCE</td>
<td>dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAIH</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>(N,N)-Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>(N,N)-dimethylformamide</td>
</tr>
</tbody>
</table>
DMPU: \(N,N'-\text{dimethyl-}N,N'-\text{propylene urea}\)
DMS: dimethyl sulfide
E: electrophile
e.e.: enantiomeric excess
EI\(^+\): electron impact (positive ionisation)
equiv.: equivalent(s)
ES\(^+\): electrospray (positive ionisation)
Et: ethyl
et. al.: and others
GC: gas chromatography
h: hour(s)
HMD: Hexamethyldisilane
HMDS: 1,1,1,3,3,3-hexamethyldisilazide
HMPA: hexamethylphosphoramide
HPLC: high performance liquid chromatography
HRMS: high resolution mass spectrometry
i: iso
IC1: iodine monochloride
imid: imidazole
IR: infrared
K: Kelvin
k: rate constant
\(\lambda\): wavelength
LC: liquid chromatography
LDA: lithium diisopropylamide
lit.: literature value
m: molar; unspecified metal; molecular mass (mass spectrometry)
\(m\)CPBA: \textit{meta-}chloroperoxybenzoic acid
Me: methyl
Mes: Mesitylenesulfonyl
s  secondary
sat.  Saturated
SEM  2-(trimethylsilyl)ethoxy)methyl
soln.  solution
Super-H  Lithium triethylborohydride
t  tertiary
TBAF  tetrabutylammonium fluoride
TBAT  Tetrabutylammonium triphenyldifluorosilicate
TBDMS  tert-butyldimethylsilyl
TBDPS  tert-butyldiphenylsilyl
tert  tertiary
Tf  trifluoromethanesulfonyl
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TIPS  triisopropylsilyl
TLC  thin layer chromatography
TMS  tetramethylsilane; trimethylsilyl
Tol.  Toluene
triflate  trifluoromethanesulfonate
Triton B  benzyl(trimethyl)azanium hydroxide
Ts  Tosyl
UV  ultraviolet
VT  Variable Temperature
wt%  weight percentage
Chapter 1: Introduction.

1.1 The Kainoid Family.

The kainoid family is a group of structurally related compounds containing a functionalised pyrrolidine dicarboxylic nucleus with three contiguous stereogenic centres (Fig. 1).¹

![Figure 1: Core Structure of the Kainoid Family](image)

The parent member, kainic acid ¹ (originally known as digenic acid), was first isolated from a Japanese marine alga, *Digenea simplex*, in 1953 (Fig. 2).² The C4 epimer of kainic acid, (+)-allokainic acid ², was also isolated from this alga.

(−)-Domoic acid ³ was isolated in 1958 from the Japanese marine warm water alga, *Chondria armata*³ and was later found to be present in *Pseudo -nitzschia*.⁴ Domoic acid differs from kainic acid by possessing an octadienoic side chain (containing a (cis -, trans -) diene⁵) at the C4 position on the pyrrolidine ring.⁶ This warm watered alga has also been proven to be the source of a number other members of the kainoid family, including isodomoic acids A to F (⁵ - ¹⁰),⁷ domoilactones A and B (¹³ and ¹⁴)⁸, nordomoic acid (lacking the C5′ methyl group) and the C5′ domoic acid diastereomer ⁴.⁹ Diatoms have also recently been found to be responsible for production of isodomoic acids A and B (*Nitzschia navis-varingica*) and isodomoic acid C (*Phragmites australis*).

The acromelic acids A ¹⁵ and B ¹⁶ were isolated from a poisonous Japanese mushroom, *Clitocybe acromelalgia*, in 1983.¹⁰ The quantities of these acids were low and therefore only ¹H NMR, C.D and UV spectral data was acquired for characterisation. Synthesis has since confirmed the structure of these acids. Seven years later the acromelic acids C, D and E (¹⁷ – ¹⁹), were isolated from the same alga.¹¹
Identifying remaining members of the kainoid family proved difficult until 1989. It was in this year that a reverse-phase HPLC analysis reported rapid, sensitive identification of the kainoids. Other techniques surfaced, including LC-MS, GC-MS and electrophoresis that were also able to successfully identify the kainoid amino acid series in various shellfish and phytoplankton. These techniques enabled the discovery of isodomoic acids E and F (9 and 10) from the edible mussels *Mytilus edulis* from Canadian waters in 1990, and isodomoic acids G and H (11 and 12) from re-examination of *Chondria armata* in 1997.
Chapter 1: Introduction

1.2 Biological Properties.  

A considerable amount of interest has been drawn to the kainoid amino acids due to their insecticidal, anthelmintic (anti-intestinal worm) and neuroexcitatory properties.

Insecticidal properties of domoic acid and kainic acid have been utilised for fly-killing purposes in Yakushima Island, Japan. Research has reported that domoic acid and isodomoic acids A-C are the most potent insecticides and that the potency is dependent on the nature of the octadienoic side chain at the C4 position.

*Digenea simplex* was used for eliminating parasites from humans and animals (anthelmintic properties) for thousands of years in Japan before it was discovered that the potent component was kainic acid. The *cis*-stereochemistry
of the C3 and C4 substituents appears to be a contributing factor as comparison with the C4 epimer, allokainic acid 2, shows weaker anthelmintic effects.\textsuperscript{27} 

Most investigations have concentrated on the neuroexcitatory properties of the kainoid family.\textsuperscript{28} The amino acids have been shown to stimulate nerve cells in the mammalian central nervous system (CNS) which results in symptoms that mimic those of Alzheimer’s disease, epilepsy,\textsuperscript{29} Huntington’s Chorea\textsuperscript{28(a),30} and senile dementia.\textsuperscript{31} This means that the kainoids are a powerful tool in neuropharmacology to study the neurochemical pathways to the brain. The mode of biological action is thought to be due to their conformationally restricted structural similarity to glutamic acid, 20,\textsuperscript{32} a major excitatory neurotransmitter in the mammalian CNS (Fig. 3).\textsuperscript{33} Although L-glutamic acid does not have a pyrrolidine ring or additional stereochemistry at C3 and C4, it is thought that these additional features assist in extra binding ability to the receptor site. It is also thought that the ring pre-orders the molecule, therefore reducing the entropy lost upon binding.

![Figure 3: Structural Similarity Between Kainoids and Glutamic Acid](image)

Structural-activity investigations have confirmed the C4 stereochemistry\textsuperscript{32(b)} the nature of the C4 substituent\textsuperscript{26,28(c),32(c)} and the molecular confirmation\textsuperscript{32(c)} plays a crucial role in binding and activation at the recognition site. Alkene configuration in the C4 side-chain seems to be particularly critical, with the Z-configuration of a C1’ mono-alkene 400 times more active than the E-configuration, and the potency of domoic acid more than 5,000 times that of tetrahydrodomoic acid.\textsuperscript{34,35,36} 

Domoic acid bioaccumulates in marine organisms that feed on the phytoplankton, such as shellfish, anchovies, and sardines.\textsuperscript{37} The toxin does not
bioaccumulate in the classic sense because it is quickly excreted by fish and shellfish that ingest it. It only accumulates in high numbers in these plankton feeders when the diatom itself is high in number in the surrounding waters. An outbreak of ‘amnesic shellfish poisoning’ in Prince Edward Island, Canada in 1987 was due to high levels of domoic acid in the edible blue mussels, *Mytilus edulis*. This resulted in three deaths and 153 casualties suffering from symptoms of nausea, vomiting, headaches, diarrhoea and memory loss. Canadian scientists discovered that domoic acid (which is more potent than kainic acid) had entered the food chain when the mussels fed on a toxic algal bloom of the pinnate diatom *Pseudonitzschia pungens* forma *multiseries*.

As a result of this outbreak, extensive monitoring techniques have been introduced to analyse levels of domoic acid so that it does not exceed the legal limit, 20 mg/kg. This legal limit has since been employed in Europe, as domoic acid and its analogues have been discovered in Scottish waters, Irish waters and waters surrounding Portugal. This can also be a perennial problem in areas of the world’s oceans where essential nutrients are brought up from deep water to levels penetrated by light, such as the western coast of North America. Other methods of protection employed by the shellfish industry include delaying mussel harvest until after ice-cover in Canada, processing shellfish with constant water changes and the ongoing research into isolation of bacteria that can break down domoic acid.
1.3 Biosynthesis of Domoic Acid.

Wright et al. worked on the biosynthesis of domoic acid using $^{13}$C labelling experiments. They showed that a geranyl diphosphate derivative and an activated glutamic acid derivative performed a condensation reaction that yields a precursor to the cyclisation to give a proline ring (Scheme 1).

During their research they discovered that a sample from the cultured mussel *Mytilus edulis* L. contained more than 90% domoic acid, with isodomoic acids D, E and F at just 5%, 2% and 1% respectively. They were able to make more of these isomers by exposing a dilute aqueous sample of domoic acid to 254 nm light for nine to twelve minutes. This yielded domoic acid and isodomoic acids D, E and F in a 0.28: 0.12: 0.27: 0.13 ratio respectively per unit of starting material. This finding may suggest that only domoic acid is biosynthesised by the mollusc and that the isodomoic acids present are the result of later processes.
1.4 Previous Domoic Acid Synthesis.

The synthetic challenge of the kainoid family is to address the formation of a pyrrolidine-2-carboxylic acid with defined stereochemistry at three adjacent centres with additional attention to the cis-stereochemistry. There have been numerous approaches to the synthesis of kainic acid and allokainic acid, including ene reactions, Claisen rearrangements, free-radical cyclisations, azomethane ylide cycloadditions, Pauson-Khand cyclisations and iminium ion cyclisations.

Domoic acid has only been previously synthesised once, by Ohfune and Tomita in 1982, aiming to prove the absolute stereochemistry. The synthesis began with an advanced N-tert-butoxycarbonyl-L-pyroglutamic acid intermediate, a derivative of (L)-glutamic acid (Scheme 2), performing a Diels-Alder reaction with diene to yield the bicyclic product.

\[
\begin{align*}
{22} & \quad \text{Me}_3\text{SiO} \quad \text{Me}_3\text{SiO} \\
{23} & \quad \text{NBoc} \quad \text{OTBDMS} \\
{24} & \quad \text{NBoc} \quad \text{OTBDMS} \\
\text{Reagents and conditions:} & \quad (a) \ 135 \degree C, \text{sealed tube, 3 days}
\end{align*}
\]

Scheme 2: Diels-Alder Reaction to Form Pyrrolidinone Core

This key step was used to set the stereochemistry at the C3 and C4 positions and this is achieved remarkably well by the favoured steric and electronic interactions between the starting materials. The reaction is consistent with the Woodward-Hoffmann rules, along with second order effects. Stereochemistry of the ring junction is set by the endo rule relative to the methyl group on the six membered ring. The diene approaches from above to avoid steric interactions with the bulky tert-butyldimethylsilyl group. Finally regiochemistry was set by the favourable diene-dienophile orbital overlap resulting in the trimethylsilyl group in the para position.

Adduct without isolation was treated to ozonolysis to open the six-membered ring. The carboxylic acid was converted to the ester and the aldehyde was protected as the ethylene ketal in subsequent steps (Scheme 3).
amide and the ester were reduced using borane-dimethyl sulphide complex. The TBDMS was selectively deprotected and the diol was oxidised using pyridinium dichromate and then converted to the diester 27 with diazomethane.

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{a} \quad 40\% \quad \text{MeO}_2\text{C} \\
\text{24} & \quad \text{b} \quad 70\% \quad \text{26}
\end{align*}
\]

Reagents and conditions: (a) i. \( \text{O}_3 \), DCM, -78 °C, DMS, R.T.; ii. \( \text{CH}_2\text{N}_2 \); iii. 2-methyl-2-ethyl-1,3-dioxolane, p-TsOH, R.T.; (b) \( \text{BH}_3\cdot\text{DMS} \), 70%; (c) i. MeOH, p-TsOH, ii. PDC, DMF, iii. \( \text{CH}_2\text{N}_2 \).

Scheme 3: Towards the Total Synthesis of Domoic Acid

Treating 27 with acetic acid yielded the unprotected aldehyde 28. It was reported that under these conditions the compound epimerised at the C1’ centre to give a 1:1 mixture of products (Scheme 4). Wittig chemistry was used to introduce the methoxy methylene group to give 29, then hydroxyselenation to produce \( \alpha \)-selenoaldehyde 30.
Reagents and conditions: (a) 60% AcOH; (b) Ph₃P(Cl)CH₂OCH₃, t-AmONa, benzene; (c) PhSeCl, THF, Et₃N, H₂O.

Scheme 4: Towards the Total Synthesis of Domoic Acid

Two methods were developed for the production of the enal 31 (Scheme 5), both of which give moderate yields and control of stereochemistry (Table 1).

Reagents and conditions: (a) see table 1

Scheme 5: Towards the Total Synthesis of Domoic Acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Total Yield of 31</th>
<th>Ratio E-31 : Z-31</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O₃, DCM, –78 °C; Et₃N</td>
<td>33%</td>
<td>10 : 1</td>
</tr>
<tr>
<td>2</td>
<td>NBS, THF, R.T., 2 min; NaOAc (aq.), 15 min</td>
<td>67%</td>
<td>1 : 2</td>
</tr>
</tbody>
</table>

Table 1: Conditions for Deselenation
A Wittig reaction was used to introduce the side chain with the C5' stereocentre (Scheme 6). Jones’ reagent was used to oxidise the alcohol and then diazomethane was used for the formation of the methyl ester. These steps yielded the protected products \((E, E, S)\)-32 and \((E, E, R)\)-32 which did not correspond to the 360 MHz \(^1\text{H}\) NMR spectroscopic data of the protected \((-)\)-domoic acid. X-ray crystallography experiments were then performed on \((-)\)-domoic acid which showed that the side chain is in fact \((Z, E, R)\). The synthesis was modified to obtain the correct stereochemistry.
Reagents and conditions: (a) (S)-33, n-BuLi (2 eq.), THF, -78 °C, 2 min; 0 °C, 10 min; (b) (R)-33, n-BuLi (2 eq.), THF, -78 °C, 2 min; 0 °C, 10 min; (c) Jones’ reagent, 0 °C, 1 h; (d) CH$_2$N$_2$; (e) Boc-ON (34), Et$_3$N; (f) CH$_2$N$_2$; (g) 2.5 % KOH (aq.), R.T., 24 h; (h) TFA, R.T., 15 min; NaOH (1 eq.)

Scheme 6: Towards the Total Synthesis of Domoic Acid
1.5 Semisynthesis: Isopropenyl Extension of Kainic Acid.

Mertes et al. investigated how the substitution of the isopropenyl ring of kainic acid would affect the binding ability to the kainate receptor site. Utilising a previous synthesis of kainic acid and employing a metal-coupling reaction to introduce a number of different side chains (Scheme 7) would be an attractive way of making other members of the kainoid family.

![Scheme 7: Semi-Synthesis of the Kainoid Family](image)

Mertes et al. only studied aryl couplings to the isopropenyl group, resulting in low yields and a mixture of isomers (Scheme 8).

![Scheme 8: Isopropenyl Aryl Coupling Reactions](image)

*Reagents and conditions:* (a) Pd(OAc)$_2$, 3-nitroaniline, MeCN, 60 °C; t-butylnitrite, 60 °C, portionwise over 3 h; 60 °C, 4 h; 25 °C, o/n; Pd(OAc)$_2$, 3-nitroaniline, t-butylnitrite, 60 °C, 2 h; 25 °C, 2 days

Investigations into the side chain additions were also reported. They discovered that the π-allyl palladium complex 37 intermediate was susceptible to nucleophilic attack (Scheme 9).
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Since this publication there have been no attempts to apply this chemistry to the synthesis of domoic acid or the isodomoic acids. It is thought that due to the low yields, lack of selectivity and sensitivity to the aryl-coupled substituent the route to the kainoid amino acids would not be efficient.

1.6 Isodomoic Acid G and H Synthesis.

The first total synthesis and stereochemical definition of isodomoic acid G was achieved by Montgomery et. al in 2003. The approach was to utilise a previous synthesis to kainic acid and introduce a key nickel-catalysed alkyne-alkenylzirconium coupling of 41 with 42 (Scheme 10). This key step enabled the formation of the exocyclic double bond, characteristic of isodomoic acids G and H and also complete control of the stereochemistry at the C2 and C3 positions.

\[
\text{Reagents and conditions: (a) Cp}_2\text{ZrHCl, THF, R.T.; (b) Ni(COD)}_2 \text{ (10 mol %), ZnCl}_2 \text{ (20 mol %), THF, 0 °C}
\]

Scheme 10: Towards the Total Synthesis of Isodomoic Acid G
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The selective formation of compound 44 as a single isomer proved difficult by partial epimerisation at the C2 centre in an earlier step. This was resolved by using a chiral oxazolidinone so that the two epimers could be separated (Scheme 11).

Deprotection using tetrabutylammonium fluoride and oxazolidinone opening followed to yield diol 45, which was oxidised to the corresponding diacid with Dess-Martin periodinane and NaClO₂. Ion-exchange chromatography was used to separate the products and afford 5'(R)-isodomoic acid G in 38% yield. Experimental data was compared with that of isodomoic acid G’s original isolation report from Arakawa which confirmed the structure.

Reagents and conditions: (a) MeOMgBr, MeOH, R.T, 80%; (b) i. MeONa, MeOH, R.T.; ii. TBAF, THF, R.T.; (c) i. Dess-Martin periodinane, DCM, R.T.; ii. NaClO₂, NaH₂PO₄, 2-methyl-2-butene, t-BuOH, H₂O, R.T.; iii. NaOH, MeOH, H₂O, R.T.; (iv) ion-exchange chromatography.

Scheme 11: Towards the Total Synthesis of Isodomoic Acid G
The synthesis was modified to synthesise 5′ (S) isodomoic acid G, 48 (Scheme 12).

![Scheme 12: Modified Synthesis Towards 5′ (S) Isodomoic Acid G](image)

In 2009, Denmark et. al. published a general approach to both isodomoic acids G and H using a stereodivergent alkenylsilane iodination which allows the preparation of both exocyclic alkene isomers. 60

The synthesis begins with the formation of the alkyne 52, the precursor to the key carbonylative silylcarbocyclization (Scheme 13). Lactone 49, which is derived by L-methionine, was opened using TMSI and after esterification and N-alkynylation gives the iodinated amino ester, which is converted to the corresponding selenium substrate 50 using sodium phenylselenide. N-alkylation followed by oxidative elimination then gave the N-methylpropargyl L-vinylglycine ester 52.

![Scheme 13: Towards the Total Synthesis of Isodomoic Acid H](image)

Reagents and conditions: (a) i. TMSI; ii. SOCl₂, MeOH 90%; (b) NaBH₄, Ph₂Se₂ 88%; (c) 2-butyn-1-ol, PPh₃, DEAD; (d) 30% H₂O₂.

Performing a carbonylative silylcarbocyclisation using Rh(acac)(CO)₂ on alkyne 52 gave the cyclised product 53 as an inseparable mixture of 2,3-trans and 2,3-cis-diastereoisomer in an 8:1 ratio. To obtain the desired trans isomer it was necessary to reduce the aldehyde using NaBH₄, which enabled the separation of
the two diasteroisomers in 85% yield of the desired trans diasteroisomer 53 (Scheme 14).

![Scheme 14: Total Synthesis of Isodomoic Acid H](image)

Reagents and conditions: (a) HSiMe₂Ph, Rh(acac)₂(CO)₂ (5 mol %), CO (500 psi), 120 °C, 77%, trans/cis 8:1; (b) NaBH₄ 85%; (c) i. CrO₃, H₂O₂; ii, CH₂N₂ 81%; (d) I₂, 86%; (e) 57, Pd₂(dba)₃, CHCl₃ (5 mol %), TBAF·8H₂O, 92%; (f) i. LiOH.; ii. 20% Na/Hg, NaH₂PO₄.

Alcohol 53 was converted to the methyl ester 54 using CrO₃ and CH₂N₂, followed by the iododesilylation using I₂ resulting in the complete inversion of the double bond configuration to afford Z-alkenyl iodide 55 in 86% yield. The sterochemical outcome was rationalised by an anchimeric participation of the C7 carbonyl group trapping the iodonium ion intermediate which enables bond rotation making the silyl group antiperiplanar to the oxocarbenium CO bond.

Cross-coupling of vinyl silyl 57 using Pd₂(dba)₃.CHCl₃ and TBAF·8H₂O resulted in 92% yield of the protected (−)-isodomoic acid H 56 which was deprotected over two steps to give (−)-isodomoic acid H, 12 in 56% yield.

The synthesis was modified to make the iodination retentive by employing a nonparticipating substrate in the C7 position. Alcohol 53 was protected with TIPSCI and the iodination reaction became retentive, therefore making it possible to synthesise (−)-isodomoic acid G, 11 (Scheme 15).
Reagents and conditions: (a) TIPSCl, imidazole, 91%; (b) i. IC1, ii. HF, 73%; (c) i. CrO_3, H_3IO_6, ii. CH_2N_2, 79%; (d) 57, Pd_2(dba)_3, CHCl_3 (5 mol %), TBAF:8H_2O; (e) LiOH; (f) 20% Na/Hg, NaH_2PO_4.

Scheme 15: Modification Towards the Synthesis of Isodomoic Acid G

In 2009, Montgomery et. al. published a full paper of the previously discussed total synthesis of (–)-isodomoic acid G which included a modification enabling the synthesis of (–)-isodomoic acid H. The article describes that it was necessary to convert the vinyl zirconium reagent 41 to the E-vinyl iodide, 60, using N-iodosuccinimide to obtain the desired stereochemistry (Scheme 16).

Reagents and conditions: (a) Cp_2ZrHCl, THF, R.T.; and then N-iodosuccinimide, 71%.

Scheme 16: Towards the Synthesis of Isodomoic Acid H

A Sonogashira coupling of vinyl iodide 60 and terminal alkyne 61 proceeds in 83% yield giving conjugate enyne 62 which when exposed to dimethylzinc with 10% mol Ni(COD)_2 cyclises to give 63 in 77% as a single isomer (Scheme 17).
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After assembly of the key pyrrolidine framework the protecting oxazolidinones and TIPS groups were removed giving ester 64 in 75% yield over two steps. Oxidation using Dess-Martin periodinane and a global deprotection completed the synthesis of (–)-isodomoic acid H, 12.

Scheme 17: Total Synthesis of Isodomoic Acid H

Reagents and conditions: (a) Pd(PPh₃)₂Cl₂, CuI, iPr₂NH, THF, 0 °C, 83%; (b) Ni(COD)₂, Me₂Zn, THF, 0 °C, 77%; (c) MeOMgBr, MeOH, R.T., 70%; then MeONa, MeOH, R.T.; and then TBAF, THF, R.T., 75% over two steps; (d) Dess-Martin periodinane, CH₂Cl₂, R.T.; and then NaClO₂, NaH₂PO₄, 2-methyl-2-butene, t-BuOH, H₂O, R.T.; and then NaOH, MeOH, H₂O, R.T.; ion-exchange chromatography, 21%.
1.7 Domoic Acid Analogue Synthesis: Cobalt-Mediated Cyclisation.\textsuperscript{62}

Baldwin \textit{et. al.} used a cobalt-mediated radical cyclisation, which has been previously used for the synthesis for kainic acid,\textsuperscript{63} to form an analogue of domoic acid structurally similar to isodomoic acid C, \textit{7}. The cyclisation involves homolysis followed by $\beta$-elimination of the cobalt species to form the pyrrole ring (Scheme 18).

Scheme 18: Cobalt-Mediated Radical Cyclisation Reaction

The synthesis begins with the introduction of the side chain to \textit{67} by a reductive amination with citral \textit{68} which was then protected with phenyl chlorofomate to form carbamate \textit{70}. DIBAIH was used for the reduction of the ester to the aldehyde, which was converted to alcohol \textit{71} by addition of \textit{tert}-butyllithioacetate (Scheme 19).
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Scheme 19: Towards the Synthesis of a Domoic acid Analogue

Alcohol 71 was converted to oxazolidinone 72 in 56% yield, prior to the secondary alcohol displacement with iodine as an undesired cyclisation reaction were observed with the amide (Scheme 20). The free alcohol was then converted to the iodine using triflic anhydride and sodium iodide yielding precursor 73. The alkene configuration of 73 was a cis, trans mixture due to the configuration of citral 68, which is only available as a 95:5 mixture. However, this was shown to have little effect on the cyclisation in model studies.

Scheme 20: Towards the Synthesis of a Domoic Acid Analogue

Reagents and conditions: (a) p-TsOH, MeOH; ii. K₂CO₃, H₂O, MeOH; (b) (CF₃SO₂)₂O, NaI
The key cobalt-mediated cyclisation step results in a mixture of products. The major products being the desired cyclised pyrrolidine 74 and an elimination product 75. The remaining products, 76-79, were isolated in a total of 13% yield. (Scheme 21).

Reagents: (a) Co(I), MeOH

Scheme 21: Colbolt-Mediated Cyclisation Reaction

Compound 74 was treated with aqueous sodium hydroxide to open the carbamate and hydrolyse the ester (Scheme 22). After amine protection with di-tert-butyl dicarbonate and esterification, the primary alcohol was converted to the methyl ester using pyridinium dichromate and diazomethane to give ester 81 in 61% yield.
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Scheme 22: Towards the Synthesis of a Domoic Acid Analogue

The final stage in the synthesis involves hydrolysis of the ester followed by a deprotection (Scheme 23). This yields two products, the desired alkene 82 that was present in trace amounts and the major product 83 in 72% yield as a result of an electrophilic addition with trifluoroacetic acid.

Scheme 23: Towards the Synthesis of a Domoic Acid Analogue

Baldwin et. al. wanted to apply this chemistry to the synthesis of other members of the kainoid amino acid family, however to date there have been no developments in the synthesis of other isodomoic acids. Research has concentrated on 4-aryl sulfanyl analogues 84 and 4-aryl, alkenyl and alkynyl analogues of the acromelic acids 15-19 (Fig. 4).
1.8 Previous Research Within the Clayden Group.

1.8.1 Anionic Dearomatising Cyclisation Reaction.

In the mid-1990s research was carried out on an anionic dearomatising cyclisation reaction of naphthamides and benzamides.\textsuperscript{66} The cyclisation involves the lithiation of a benzamide at the $\alpha$ position followed by a diastereoselective dearomatising cyclisation resulting in a product that contains three new stereogenic centres.

Lithiating compound\textsuperscript{85} yields two products, \textsuperscript{86} as the major compound in 40% and \textsuperscript{87} in 20% yield as a mixture of atropisomers (Scheme 24).\textsuperscript{67, 68}

\begin{align*}
\text{Reagents and conditions:} & \quad (a) s$-$BuLi, THF, $-78$ °C; (b) Mel \\
\text{Scheme 24: Anionic Dearomatizing Cyclisation Reaction}
\end{align*}

Upon this discovery the scope of the cyclisation reaction was explored which revealed that the use $\textit{tert}$-butyl group or cumyl groups gave good yields.\textsuperscript{59}
Attempts to cyclise tert-butylcarboxylate protected benzamides resulted in a rearrangement reaction described by Hamada.\textsuperscript{70,71} It was also discovered that the cyclisation can tolerate either electron-withdrawing (CN) or donating (OMe) groups on the dearomatising arene ring (Scheme 25).\textsuperscript{72}

\begin{equation*}
\text{Reagents and conditions: (a) } \text{t-BuLi; (b) HMPA; (c) NaH}_4\text{Cl, MeI, BnBr or } n\text{-BuBr}
\end{equation*}

**Scheme 25: General Dearomatising Cyclisation**

### 1.8.2 Mechanism of the Dearomatising Cyclisation.

Mechanistic experiments have suggested that the dearomatising cyclisation reaction is pericyclic rather than an intramolecular conjugate addition process.\textsuperscript{73,74} As the cyclised products have the aromatic group on the \textit{exo} face this suggests a conjugate addition process but would be a Baldwin-disfavoured 5-\textit{endo-trig} reaction (Scheme 26).\textsuperscript{75}

\begin{equation*}
\text{Scheme 26: Intramolecular Addition 5-\textit{endo-trig}}
\end{equation*}

In a pericyclic cyclisation the phenyl group would have to be \textit{trans} to the cumyl group which could be possible as the \textit{cis} conformation experiences steric interactions (Fig.5).
To confirm the type of mechanism a modified cyclisation reaction was developed in which the starting benzamide 85 was fixed in the cis conformation by introducing a small ring (Scheme 27).

\[ \text{Reagents and conditions: (a) } \text{s-BuLi, DMPU, THF, } -78^\circ \text{C to } 0^\circ \text{C}, \text{ ii. MeI; (b) } 2 \text{ M HCl, MeOH}. \]

Scheme 27: Modified Dearomatising Cyclisation Reaction

The reaction resulted in the formation of the cis isomer 97a which epimerised under mild conditions to give the more stable trans isomer 97b. The stereochemistry of the product shows that the reaction is not a conjugate addition process and is a result of a thermal electrocyclic six-electron disrotatory ring closure according to the Woodward-Hoffman rules (Scheme 28).

\[ \text{Reagents and conditions: (a) ortho-lithiation; (b) anion translocation; (c) disrotatory electrocyclic ring closure; (d) work-up.} \]

Scheme 28: Suggested Anionic Dearomatising Cyclisation
1.8.3 Synthesis of (±)-Kainic Acid.

Modifications to the dearomatising cyclisation reaction included the protecting group of the amide which was changed to a cumyl protecting group as tert-butyl group proved difficult to remove.\textsuperscript{69} Also, by using a methoxy substituted benzamide it was possible to produce methyl enol ether products that can be hydrolysed to the thermodynamically stable enone without isolation of the methyl ether intermediate (Scheme 29).\textsuperscript{72}

\begin{equation}
\begin{array}{c}
\text{MeO} \\
\text{N} \\
\text{PhH}
\end{array}
\xrightarrow{a}
\begin{array}{c}
\text{MeO} \\
\text{Li} \\
\text{Ph}
\end{array}
\xrightarrow{b}
\begin{array}{c}
\text{MeO} \\
\text{Li} \\
\text{Ph}
\end{array}
\xrightarrow{94\% \text{ (from 92)}}
\begin{array}{c}
\text{MeO} \\
\text{Ph}
\end{array}
\text{(±)-104}
\end{equation}

Reagents and conditions: (a) t-BuLi, HMPA; (b) HCl, H\textsubscript{2}O–MeOH

Scheme 29: Dearomatising Cyclisation of Methoxy Substituted Benzamide
Enone 104 was used as an intermediate in the racemic synthesis of kainic acid by the Clayden group in 2000 (Scheme 30).

\[
\text{(±)-104} \xrightarrow{a} \text{(±)-105} \xrightarrow{b, c} \text{(±)-106} \xrightarrow{d} \text{(±)-107} \xrightarrow{e} \text{(±)-108}
\]

(±)-kainic acid, 1

**Scheme 30: Total Synthesis of (±)-Kainic Acid**

Reagents and conditions: (a) Me₂CuLi, TMSCl, THF, –78 °C, 1 h; (b) TFA, reflux, 6 h; (c) Boc₂O, Et₃N, DMAP, DCM; (d) i. NaIO₄, cat. RuCl₃, 1:1 acetone:H₂O; ii. Me₃SiCHN₂, PhH, MeOH; (e) mCPBA, DCM; (f) i. NaOH (2.2 eq.), MeOH, reflux, 2 h; ii. Me₃SiCHN₂, PhH, MeOH; (g) o-NO₂C₆H₄SeCN, Bu₃P, THF, R.T.; (h) H₂O₂, py, THF, –40 °C; (i) NaBH(OMe)₃ (2 eq.), THF, reflux; (j) 10:1 TFA : H₂O, reflux, 4 h

Functionalisation of the bicyclic structure was achieved by a regioselective Baeyer-Villiger reaction giving lactone 108 as a single isomer. The subsequent steps involved opening the lactone by treatment with sodium hydroxide and formation of the isopropenyl group by elimination. The final steps required the reduction of the lactam using sodium trimethoxy borohydride and finally deprotection to complete the synthesis of (±)-Kainic acid, 1.

**1.8.4 Asymmetric Dearomatising Cyclisation & (–)-Kainic Acid Synthesis.**

The dearomatising cyclisation was developed into an enantioselective reaction by introducing a chiral base to perform an asymmetric deprotonation. Research into an enantioselective cyclisation highlighted two chiral lithium amides (111 and 112) that give good enantioselectivity (Scheme 31).
Using chiral amide 112 it was possible to obtain an enantiomeric excess of 73% which after recrystallisation gave enantiopure material with a moderate 34% yield. Chiral amide 111 gave a good enantiomeric excess of 81% and in an improved 52% yield after recrystallisation. Therefore amide 111 was chosen for the total synthesis of (−)-kainic acid, 1 in 2002.

1.8.5 Acromelic Acid Analogue Synthesis.

The Clayden group also published the synthesis of an acromelic acid analogue, known to have biological activity, in 2001. This synthesis involved the same key steps applied to the synthesis of (−)-kainic acid, 1, including the dearomatising cyclisation and a regioselective Baeyer-Villiger oxidation reaction (Scheme 32).
The aromatic side chain at the C4 position was present in naphthamide 113 prior to the dearomatising cyclisation with tert-butyllithium. The Baeyer-Villiger oxidation followed producing lactone 116, which was then opened using sodium methoxide in methanol giving alcohol 117. The lactam was reduced in a two step process using Na(OMe)3BH and then triethylsilane/boron trifluoride. Kainoid 118 was finally synthesised by performing a deprotection using aqueous HCl solution.

1.8.6 Isodomoic Acid C Synthesis.

The synthesis of isodomoic acid C was published by the Clayden group in 2005.\textsuperscript{81} This was achieved by employing the developed enantioselective dearomatising cyclisation reaction and introducing the characteristic side chain at an early stage in the synthesis (Scheme 33).
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Reagents and conditions: (a) p-anisoyl chloride, Et₃N, DCM, 0 °C, 12 h; (b) BnBr, NaH, DMF; (c) 111, n-BuLi, THF, −78 °C - R.T., 5 h; sat. aq. NH₄Cl soln.; (d) 3 M aq. HCl soln.; recrystallisation from EtOAc; (e) 120, Et₂O, −78 °C, 2 h; (f) HCO₂H, reflux, 30 min; (g) Boc₂O, DMAP, Et₃N, DCM, R.T., 18 h; (h) NaIO₄, RuCl₃, MeCN, H₂O, EtOAc, R.T., 18 h; (i) TMS–CHN₂, PhMe, MeOH, R.T., 5 min; (j) 1 M aq. NaOH, MeOH, −78 °C, 1 h; (k) TBDPSCl, imidazole, DCM, R.T., 18 h; (l) mCPBA, DCM, R.T., 72 h; (m) NaOMe, MeOH, −78 °C; (n) O₂, SeCN, n-Bu₃P, THF, R.T., 2 h; (o) H₂O₂, py, THF, −40 °C to R.T., 12 h; (p) DIBAlH, THF, −78 °C, 1 h; MeOH; (q) Et₃SiH, BF₃·Et₂O, DCM, −78 °C, 2.5 h; (r) TBAF, THF, R.T., 2 h; (s) Dess-Martin periodinane, DCM, R.T., 30 min; (t) 133, DBU, LiCl, MeCN, R.T., 1 h; (u) LiOH, MeOH, 12 h, R.T.; (v) TFA, reflux, 2 h

Scheme 33: Total Synthesis of Isodomoic Acid C
After the enantioselective synthesis of enone 104 using chiral amide 111, it was necessary to introduce the side chain using a conjugate cuprate addition to give compound 121 in 79% yield. The TIPS and cumyl protecting groups were unstable during the arene oxidation and so needed to be removed and replaced with a formate ester and Boc protecting groups respectively, giving product 123. It was then possible to perform the phenyl oxidation and esterification reactions using TMS-diazomethane to give methyl ester 124 in 64% yield. The formate group was then removed and replace with TBDPS which would be stable for the remaining steps in the synthesis. Utilising a regioselective Baeyer-Villiger oxidation enabled further functionalisation giving lactone 127 as a single isomer in quantitative yield, which was opened with NaOMe to give the corresponding primary alcohol 128 in 60%. A selenium-mediated elimination reaction gave the desired alkene 130 in 41% yield. The final steps of the synthesis removed the TBDPS group and converted the resulting alcohol into the aldehyde 132 in order to perform a Wittig reaction using ylid 133 to give the protected (−)-isodomoic acid C 134 in 50% yield. A successful deprotection completed the synthesis of (−)-isodomoic acid C, 7 in 86% yield.

This was an efficient synthetic route but one that was limited to the synthesis of (−)-isodomoic acid C (i.e. the 1, 1-disubstituted alkene) and does not tackle the issues of the other isodomoic acids which have trisubstituted alkenes.
1.9 Research Towards the Synthesis of Isodomoic Acids: Approaches to a Trisubstituted Alkene.

With the successful synthesis of (–)-kainic acid and (–)-isodomoic acid C, the Clayden group focused on applying the dearomatising cyclisation to a divergent route to multiple members of the kainoid family. The strategy was aimed at developing a synthesis that introduces a trisubstituted alkene at the C4 position, so that it could be functionalised as a late stage intermediate.

1.9.1 Tin-Mediated Fragmentation.

Initial attempts to develop a route to a trisubstituted alkene were carried out by K. Hebditch, based on using a tin-mediated fragmentation to control the stereochemistry of a trisubstituted double bond 139 (Scheme 34).\textsuperscript{82}

![Scheme 34: Proposed Synthetic Route to Isodomoic Acid B](image)

R’ = Side chain of desired isodomoic acid

The proposed route presented a number of chemoselective problems, however prior to completing a proposed synthetic route, model systems were used to validate the tin-mediated fragmentation. Unfortunately initial experiments resulted in poor yields of the desired alkene (Scheme 35).\textsuperscript{83}
Stereospecific fragmentations demonstrated by Iose et al.\textsuperscript{83(b)} were also applied to model systems (Scheme 36). As predicted this resulted in an $E$-alkene on treatment with lead tetracetate giving alkene 146. The reaction was faster for model 145a and required one equivalent of the oxidant and 145b required 1.25 equivalents. The higher yields obtained (up to 47%) were explained by the presence of calcium carbonate, which was thought to remove acetic acid and prevent decomposition and protodestannylation.

Reagents and conditions: (a) Pb(OAc)$_4$, PhH, reflux

Scheme 36: Model Fragmentation Reactions
The stereochemistry of the alkene was characterised by $^1$H NMR and was consistent with anti elimination of tin by a radical\textsuperscript{84} or an ionic mechanism\textsuperscript{83(a)} involving acetate (Scheme 37 and 38).

Scheme 37: Radical Fragmentation Mechanism

Scheme 38: Ionic Fragmentation Mechanism
1.9.2 Oxazolidine Cyclisation Towards the Synthesis of Isodomoic Acid B.\textsuperscript{85}

More recent work into the synthesis of isodomoic acids has been carried out by B. Read.\textsuperscript{86} The aim of this project was to extend the work on the $N$-benzoyloxazolidine cyclisation\textsuperscript{87} and continue fragmentation studies towards a synthetic route to isodomoic acid B. The proposed route is shown in scheme 39.

\textit{Reagents and conditions:} (a) LiAlH$_4$; (b) (CH$_2$)$_2$O; (c) $p$-anisoyl chloride; (d) $t$-BuLi, DMPU; sat. aq. NH$_4$Cl soln. (e) HCl; (f) Me$_2$CuLi; (g) Pd(OAc)$_2$; (h) R′SnLi or R′SiLi; (i) RBr; (j) TMSCN; (k) Ca, NH$_3$; (l) Boc$_2$O; (m) NaBH$_4$; (n) Pb(OAc)$_4$ (M = Sn) or PhI(OAc)$_2$/I$_2$ (M = Si); (o) NaBH$_4$; (p) base, H$_2$O; (q) DIBAlH; (r) Et$_3$SiH, BF$_3$, Et$_2$O; (s) LiHMDS

Scheme 39: Towards the Total Synthesis of Isodomoic Acid B
This route would have been an attractive synthesis towards isodomoic acid B as it would avoid the challenging arene oxidation used in previous syntheses. Instead it would involve opening of the oxazolidine ring with cyanide which could be easily converted into the desired carboxylic acid.

Large amounts of research centred on the dearomatising cyclisation of benzamide 149, the stability of the products formed and the ‘metal’ used for the fragmentation. Little success was reported due to difficulties in generating the fragmentation precursor and poor results in model fragmentation reactions.

1.10 Project Aims.

The aim of this project is to extend the work of B. Read86 and K. Hebditch82 in the studies towards isodomoic acid series, based on an efficient way of diastereoselectively obtaining the desired trisubstituted double bond. Due to the little success reported in using a fragmentation reaction, the main aim would be to synthesise to a common intermediate that could be regio- and stereoselectively functionalised at a late stage to complete the total synthesis of the isodomoic acids and numerous analogues of the kainoid family. The target would be an alkyne intermediate (at the C4 position) which is known to be a good functional group for carbometallation chemistry in order to selectively obtain the desired cis and trans alkenes (Scheme 40).

Scheme 40: Initial Research Points
The key step in the synthesis was to apply the unique dearomatising cyclisation to the synthesis of an alkyne intermediate. The initial research of the project was to concentrate on the dearomatising cyclisation reaction and the functional group interconversions to yield the desired alkyne (Scheme 41). This included the removal of the protecting group, reduction of a sterically hindered amide, oxidation of an aromatic ring and ring cleavage to introduce the required ester and alkyne.

Once a reliable, robust synthesis to an enantiopure alkyne intermediate had been developed, another investigation point was the functionalisation of the alkyne.
Chapter 2: Research Towards the Synthesis of Domoic Acid and the Isodoimoic Acid Family.

2.1 Dearomatising Cyclisation Reaction.

As previously discussed, the synthesis of the kainoid family is based around a key dearomatising cyclisation to introduce the desired stereochemistry. The initial research focussed on benzamides 160, 162 and 165 as these had been extensively researched within the Clayden group for the cyclisation reaction (Scheme 42).

Reagents and conditions: (a) amine 166, Et$_3$N, DCM; (b) oxalyl chloride, DMF, 12 h

Scheme 42: Synthesis of Benzamides for the Dearomatising Cyclisation

Sections 2.1.1, 2.1.2 and 2.1.3 detail the previous work with these three benzamides and the optimisation of the dearomatising cyclisation reactions.
2.1.1 Cyclisation of ortho-Methoxy Benzamides.

The cyclisation reaction using ortho-methoxy benzamide 160 was originally studied by K. Hebditch and was reported to result in poor yields of 166a with trace amounts of the endo epimer 166b and an aromatised by-product 167 (Scheme 43). It was also discovered that the cyclisation would not proceed without the presence of DMPU, which was thought to promote anion translocation.

Attempts to optimise the production of methyl ether 166a by performing the reaction under various conditions were unsuccessful in controlling the amount of 167 produced, which was thought to be formed due to regioselectivity issues (Scheme 44).

It was possible to hydrolyse the methyl ether 166a by introducing an acid wash in the workup procedure, enabling the isolation of enone 170 (Scheme 45).
2.1.2 Cyclisation of para-Methoxy Benzamides.

The cyclisation of para-methoxy benzamide 162 has been reported during the research towards the synthesis of (−)-kainic acid and (−)-isodomoic acid C (Scheme 46).\(^{79,81}\)

The reaction procedure was repeated a number of times but proved difficult to produce consistent yields. Due to the importance of this reaction in the synthesis of the kainoid family an optimisation study was carried out at AstraZeneca, Loughborough to monitor the reaction profile using a mid-IR probe, a UV probe and internal and external temperature probes. The cyclisation studies were carried out using para-methoxy benzamide 92 (Scheme 47).

Cumylamine was first alkylated with benzylbromide in DMF in 66% yield and the resulting amine 173 was coupled with \(p\)-anisoylchloride in DCM in 80% yield to give benzamide 92. The dearomatising cyclisation was performed using LDA at 0 °C and allowed to warm to room temperature over 2 hours, at which point the reaction was quenched with saturated ammonium chloride solution. Hydrolysis using aqueous HCl solution gave enone 104 in 43% yield with trace amounts of the re-aromatised by-product 174 (Scheme 48).
The data obtained from this reaction showed a number of changes in the IR profile, which proved difficult to characterise. The UV spectrum obtained is shown in figure 6.

![UV Spectrum](image)

**Figure 6: UV Spectrum Showing the Reaction Profile Between 0 °C and R.T.**

The spectra in figure 6 shows a UV scan every minute, represented by the different coloured lines. The peak at 431 nm developed immediately after adding benzamide 92 and was fully formed over thirty minutes. The peak remained until the reaction was quenched with ammonium chloride solution. It was proposed that the peak at 431 nm could be the desired lithium enolate 103 intermediate generated after cyclisation. To confirm the presence of the lithium enolate 103 an NMR study was performed on a sample of the reaction at −30 °C (Fig. 7).
Chapter 2: Results and Discussion

Figure 7: Crude $^1$H NMR Spectrum of the Lithium Enolate Intermediate

$^1$H NMR data shows the resonance at 6.27 (H6), 4.44 (H7), 4.24 (H3), and 3.26 (H4) ppm, which when compared with predicted ppm data values strongly suggests the presence of intermediate 103 (Fig. 8).^90

This sample was allowed to warm slowly to -10 °C recording the $^1$H NMR spectra, which showed minor changes in the aromatic region due to conformational effects or restricted rotation of the molecule at lower temperatures.

This initial result suggests that the cyclisation is complete in 30 minutes at 0 °C as there was no further formation of the lithium enolate intermediate 103. In order to investigate the cause for the inconsistent yields the reaction was performed at lower temperatures to slow the cyclisation. The reaction was repeated at -78 °C and the temperature was slowly ramped and fixed at 10 °C.
intervals until the UV spectrum showed no further formation of the intermediate 103 at 431nm (Fig. 9, Scheme 48).

This graph represents the reaction profile at different temperatures which shows that the production of the lithium enolate 103 (line of triangles) fits 1º kinetics (light blue line) and the rate clearly increases as the temperature increases. Based on this data, performing the reaction at -40 ºC was concluded as a suitable rate of reaction for the cyclisation to be complete in approximately 2 hours. The dearomatising cyclisation was repeated at a fixed temperature of -40 ºC and the reaction profile was recorded (Scheme 49, Fig. 10).
The reaction profile shows the cyclisation was complete after 2 hours and so was quenched shortly after with saturated ammonium chloride solution. The solution yield assay calculated a yield of 94% and after purification it was pleasing to obtain a greatly improved 79% yield of the methyl ether 95 with no trace of the re-aromatised by-product 174 (Scheme 49).

Scheme 49: Modified Dearomatising Cyclisation Reaction

By introducing a 1M hydrochloric acid wash in the work-up, it is possible to perform the hydrolysis and obtain the more stable enone 104 in an excellent 85% yield from benzamide 92. The amended procedure has been repeated on up to a six gram scale using either the cumyl benzamide 92 or the tert-butyl benzamide 162 with reproducible yields (Scheme 50).
In conclusion, this study has shown that the lithium enolate is an unstable species if left for prolonged periods of time at high temperatures and that it is possible to obtain a substantial increase in yield with the elimination of re-aromatisation, by performing the reaction at -40 °C for 2 hours.

### 2.1.3 Cyclisation of ortho,para-Methoxy Benzamides.

The dearomatising cyclisation using *ortho,para*-methoxy benzamide 165 has been previously reported by K. Hebditch to result in 40% yield of the enone 177 (Scheme 51).

![Scheme 51: Dearomatising Cyclisation of ortho,para-Methoxy Benzamide](image)

Reagent and conditions: (a) i. LDA, THF, 0 °C, 2 h; ii. NH₄Cl; iii. HCl aq.

The reaction was performed with an internal UV probe using *ortho,para*-methoxy benzamide 178. The results showed the progressive formation of the intermediate lithium enolate 179, at 401nm, over a 2 hour period giving a yield of 62% (Scheme 52, fig. 11).

![Scheme 52: Dearomatising Cyclisation of ortho,para-Methoxy Benzamide](image)

Reagent and conditions: (a) i. LDA, THF, 0 °C, 2 h; ii. NH₄Cl; iii. HCl aq.
Figure 11: UV Spectrum for the Dearomatising Cyclisation of ortho,para-Methoxy Benzamide

In an attempt to further optimise the yield of the reaction, various reaction temperatures were tested which resulted in poor yields and recovery of the starting benzamide 178. This was thought to be due to poor rates of cyclisation (at low temperatures) and decomposition of intermediate 179 (at higher temperatures).
2.2 Eschenmoser Fragmentation Route.

The first strategy towards the alkyne intermediate previously discussed in section 1.12, was to employ an Eschenmoser fragmentation reaction to generate an alkyne in the C4 position of the pyrrolidine ring. This work has been carried out in collaboration with Dr. J. Toueg.

This strategy had been previously explored by K. Hebditch with limited success performing the fragmentation.\textsuperscript{82} It was reported that under acidic conditions no reaction was observed and only starting material was recovered. When using basic conditions the reaction resulted in the decomposition of the starting epoxide 182 (Scheme 53).

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (a) \ i. \ \text{LDA, DMPU, THF, 0°C; ii. NH}_4\text{Cl; iii. TFA, chloroform, reflux; (b) 5M NaOH, H}_2\text{O}_2, \text{MeOH; (c) i. mesitylene-2-sulfonyl hydrazine, AcOH, DCM or; ii. 2,4-dinitrobenzenesulfonylhydrazine, pyridine, THF or; iii. Benzenesulfonyl hydrazine, AcOH, DCM.}
\end{align*}
\]

Scheme 53: Previous Attempts to Perform an Eschenmoser Fragmentation

The observed decomposition using basic conditions was thought to be due to the acidity of the ring junction hydrogen (highlighted in red) being deprotonated prior to fragmentation. Therefore, the initial research of this project was aimed at introducing a lactam reduction in order to reduce the acidity at the ring junction and prevent decomposition. The retrosynthetic route is shown in scheme 54.
Chapter 2: Results and Discussion

Scheme 54: Retrosynthetic Route

It was envisaged that alkyne A could be formed from employing the fragmentation reaction on the epoxide precursor B. This could be synthesised by performing multiple functional group interconversions from enone D, which is derived from the dearomatising cyclisation reaction using either ortho-methoxy benzamide or ortho,para-methoxy benzamide, F. The plan was to work on two synthetic routes. The first route used ortho-methoxybenzamide 160/184 as the starting material (Scheme 55).

Scheme 55: Proposed Synthesis of the Desired Alkyne from ortho-Methoxy Benzamide

Reagents and conditions: (a) dearomatising cyclisation; (b) lactam reduction and alcohol oxidation; (c) protecting group removal and replacement; (d) epoxidation; (e) arene oxidation; (f) Eschenmoser fragmentation
As discussed in section 2.1.1, it is possible to obtain enone 170/185 by performing the cyclisation reaction with an acidic work-up using either the cumyl protected benzamide 184 or tert-butyl protected benzamide 160 (step a).

Reduction of the lactam could then be attempted followed by oxidation to obtain the desired enone functionality. Removal of the protecting group and replacement with a more stable group, which is necessary in order to perform the arene oxidation could then be completed (steps b - c). Enone 187 could then be epoxidised followed by phenyl oxidation to give the ester 189 (Step d - e), which using basic conditions should fragment to give the desired alkyne 190 (step f).

An alternative route was to use ortho,para-methoxy benzamide 165/178 as the starting material for the synthesis (Scheme 56). The same or similar steps would apply as described previously but the advantage of using enone 177/180 would be the ability to generate the enone 187 via an elimination reaction after lactam reduction.

\[
\begin{align*}
\text{R'} = \text{Me (165)} & \quad \text{or Ph (178)} \\
\text{P} = \text{Protecting group} & \\
\text{R} = \text{alkyl chain}
\end{align*}
\]

*Reagents and conditions:* (a) dearomatising cyclisation; (b) lactam reduction; (c) protecting group removal and replacement; (d) enone formation; (e) epoxidation; (f) arene oxidation; (g) Eschenmoser fragmentation.

Scheme 56: Proposed Synthesis of the Desired Alkyne from ortho,para-Methoxy Benzamide
2.2.1 Lactam Reduction Attempts.

After successfully synthesising the dearomatised products 166, 170 and 177 (described in sections 2.1.1 and 2.1.3), several lactam reduction attempts were performed. Initial reactions were carried out on methyl ether 166 using the conditions detailed in table 2 (Scheme 57).

![Scheme 57: Lactam Reduction Attempts](image)

Reagents and conditions: (a) conditions in table 2; ii. Et₃SiH, BF₃.OEt₂, THF, -78 °C, 2 h (entries 1-3 only)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp.</th>
<th>Equiv.</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BH₃, THF</td>
<td>Reflux</td>
<td>3</td>
<td>2</td>
<td>166 recovered</td>
</tr>
<tr>
<td>2</td>
<td>BH₃, Me₂S, THF⁵⁶</td>
<td>Reflux</td>
<td>2</td>
<td>1</td>
<td>166 recovered</td>
</tr>
<tr>
<td>3</td>
<td>DIBAIH, THF</td>
<td>Reflux</td>
<td>4</td>
<td>18</td>
<td>Decomposition of 166</td>
</tr>
<tr>
<td>4</td>
<td>LiAlH₄, THF</td>
<td>-78 °C</td>
<td>4</td>
<td>18</td>
<td>Decomposition of 166</td>
</tr>
<tr>
<td>5</td>
<td>LiAlH₄, AlCl₃, THF</td>
<td>-10 °C</td>
<td>2</td>
<td>18</td>
<td>166 recovered</td>
</tr>
<tr>
<td>6</td>
<td>AlH₃, THF</td>
<td>R.T.</td>
<td>2</td>
<td>18</td>
<td>166 recovered</td>
</tr>
<tr>
<td>7</td>
<td>Red Al™, Toluene</td>
<td>Reflux</td>
<td>2</td>
<td>48</td>
<td>166 recovered</td>
</tr>
<tr>
<td>8</td>
<td>LiAlH₄, THF</td>
<td>Reflux</td>
<td>5</td>
<td>18</td>
<td>Decomposition of 166</td>
</tr>
</tbody>
</table>

Table 2: Lactam Reduction Attempts

The lactam proved resistant to borane reagents and starting material was recovered on each attempt (entries 1 and 2). Using harsher conditions, including LiAlH₄ at reflux, were also unsuccessful causing decomposition of the starting material (entries 3, 7 and 8).
Various reduction conditions were also used in an attempt to reduce the lactam in enone 170 (Scheme 58, table 3).

Reagents and conditions: (a) conditions in table 3; ii. Et₃SiH, BF₃·OEt₂, THF, -78 °C, 2 h (entries 1, 5 and 6 only)

Scheme 58: Lactam Reduction Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp.</th>
<th>Equiv.</th>
<th>Time (hours)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIBAlH, THF</td>
<td>-78 °C</td>
<td>5</td>
<td>18</td>
<td>82% 195</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH₄, THF</td>
<td>-78 °C</td>
<td>5</td>
<td>18</td>
<td>66% 195</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH₄, THF</td>
<td>R.T.</td>
<td>5</td>
<td>18</td>
<td>90% 196</td>
</tr>
<tr>
<td>4</td>
<td>LiAlH₄, THF</td>
<td>Reflux</td>
<td>5</td>
<td>6</td>
<td>Decomposition of 170</td>
</tr>
<tr>
<td>5</td>
<td>BH₃, THF</td>
<td>Reflux</td>
<td>3</td>
<td>2</td>
<td>Decomposition of 170</td>
</tr>
<tr>
<td>6</td>
<td>BH₃, Me₂S, THF</td>
<td>Reflux</td>
<td>3</td>
<td>1</td>
<td>Decomposition of 170</td>
</tr>
</tbody>
</table>

Table 3: Lactam Reduction Attempts

Unfortunately, reduction of the lactam was not observed using DIBAlH, borane complexes or LiAlH at -78 °C, resulting in the reduction of the alkene to give ketone 195 (entry 1 and 2). At room temperature, LiAlH₄ gave complete reduction of the enone and alcohol 196 was isolated in 90% yield (entry 3).

Lactam reduction of enone 176 was also researched using the conditions detailed in table 4 (Scheme 59).

Reagents and conditions: (a) conditions in table 4; ii. Et₃SiH, BF₃·OEt₂, THF, -78 °C, 2 h (used in entries 1, 2, 3 and 8)

Scheme 59: Lactam Reduction Attempts
### Table 4: Lactam Reduction Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp.</th>
<th>Equiv.</th>
<th>Time (hours)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BH₃, THF</td>
<td>Reflux</td>
<td>3</td>
<td>2</td>
<td>76% 198</td>
</tr>
<tr>
<td>2</td>
<td>BH₃, Me₂S, THF</td>
<td>Reflux</td>
<td>3</td>
<td>1</td>
<td>82% 198</td>
</tr>
<tr>
<td>3</td>
<td>DIBAlH₄, THF</td>
<td>Reflux</td>
<td>5</td>
<td>6</td>
<td>44% 198</td>
</tr>
<tr>
<td>4</td>
<td>LiAlH₄, THF</td>
<td>-78 °C</td>
<td>5</td>
<td>18</td>
<td>62% 198</td>
</tr>
<tr>
<td>5</td>
<td>LiAlH₄, THF</td>
<td>0 °C</td>
<td>5</td>
<td>4</td>
<td>32% 199</td>
</tr>
<tr>
<td>7</td>
<td>LiAlH₄, THF</td>
<td>Reflux</td>
<td>5</td>
<td>6</td>
<td>Decomposition of 176</td>
</tr>
<tr>
<td>8</td>
<td>Super-H, THF</td>
<td>Reflux</td>
<td>4</td>
<td>6</td>
<td>Decomposition of 176</td>
</tr>
</tbody>
</table>

Lactam reduction in enone 176 was unsuccessful using the conditions detailed in table 4. LiAlH₄ at -78 °C or borane complexes resulted in the reduction of the enone only, giving allylic alcohol 198 (entry 1, 2 and 4). Using LiAlH₄ at 0 °C resulted in the over-reduction of enone 176 giving substrate 199 in 32% yield (entry 5). Under harsher conditions, including LiAlH₄ or Super-H (LiEt₃BH) at reflux resulted in complete decomposition of the starting material (entry 7 and 8).

The limited success in the lactam reduction was thought to be due to the substrates considerably confined bicyclic structure preventing initial hydride attack, as the hemiaminal was never observed. Literature searches showed that there are a limited number of publications reporting lactam reductions in bicyclic systems, but this transformation can be made easier by introducing a Boc protecting group and reducing a more reactive carbamate protected amide. Therefore research concentrated on the cleavage of the protecting group and replacement with a Boc group.
2.2.1.1 tert-Butyl Group Cleavage.

During the development of the dearomatising cyclisation it became clear that for successful results the use of a tert-butyl or a cumyl group was needed as the amide protecting group.\textsuperscript{69} tert-Butylamine was a readily available starting material and so methods to cleave the tert-butyl group from the dearomatised products were explored.

A recent publication by Alterman and co-workers\textsuperscript{92} reported the use of scandium triflate to cleave tert-butyl groups from acyclic benzamides (Scheme 60).

\[
\text{Reagents and conditions: (a) Sc(OTf)}_3 \text{ (1.5 eq.), CH}_3\text{NO}_2, \text{ reflux}
\]

Scheme 60: tert-Butyl Cleavage

These conditions were tested on acyclic benzamide 160 and dearomatised products 170 and 176 (Scheme 61).

\[
\text{Reagents and conditions: (a) Sc(OTf)}_3 \text{ (1.5 eq.), CH}_3\text{NO}_2, \text{ reflux}
\]

Scheme 61: tert-Butyl Cleavage Attempts
Acyclic benzamide 160 was successfully cleaved with scandium triflate and free amide 202 was obtained in 97% yield. However, the bicyclic amides were unsuccessfully deprotected and resulted in recovery of the starting material or decomposition after prolonged reaction times.

The publication does not comment on the use of scandium triflate for the removal of tert-butyl group from cyclic amide, but it has been shown in our bicyclic substrates that it was not possible to cleave the tert-butyl group.

Other published examples of tert-butyl removal involve harsh acidic conditions, including conc. H$_2$SO$_4$, which were tested on enone 176 (Scheme 62 and table 5).

![Scheme 62: tert-Butyl Cleavage Attempts](image)

**Reagents and conditions:** (a) conditions in table 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA Reflux</td>
<td></td>
<td>16</td>
<td>176 recovered</td>
</tr>
<tr>
<td>2</td>
<td>H$_2$SO$_4$</td>
<td>55</td>
<td>3</td>
<td>70% 204</td>
</tr>
<tr>
<td>3</td>
<td>HBr R.T.</td>
<td></td>
<td>3</td>
<td>trace 204</td>
</tr>
</tbody>
</table>

Table 5: tert-Butyl Cleavage Attempts

Surprisingly, it was possible to perform the deprotection and isolated amide 204 in 70% yield using concentrated sulfuric acid (H$_2$SO$_4$). Due to the successful deprotection of enone 176, it was decided to concentrate exclusively on the ortho, para-methoxybenzamide 165 route (Section 2.2, Scheme 56).

### 2.2.1.2 Reprotection.

It had been decided to introduce a Boc protecting group as it had been previously shown to be stable during the phenyl oxidation reaction and it is also known that reducing a Boc protected amide requires milder reduction conditions, as the protecting group increases the susceptibility of hydride attack.
Previous research within the Clayden group has shown that protecting these types of substrates using Boc anhydride can be problematic.\textsuperscript{89} Research carried out during the synthesis of $\alpha$-methyl kainic acid has shown that the protection of amide \textbf{205} using standard conditions can result in the formation of the enol carbamate \textbf{206} (Scheme 63).

\[ \textit{Reagents and conditions: } (a) \text{Boc}_2\text{O}, \text{DCM}, \text{Et}_3\text{N}, \text{DMAP}, 12 \text{ h.} \]

\textbf{Scheme 63: Previously Reported Boc Protection}

Considering this problem, various conditions were tested in an attempt to protect amide \textbf{204} with Boc anhydride. Crude $^1\text{H}$ NMR analysis was used to determine the ratio of the products produced (Scheme 64, table 6).

\[ \textit{Reagents and conditions: } (a) \text{conditions in table 6} \]

\textbf{Scheme 64: Boc Protection Attempts}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Equiv. of Boc$_2$O</th>
<th>Time (hours)</th>
<th>Ratio by crude NMR (204:208:209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc$_2$O, NaHCO$_3$, DCM</td>
<td>1.05</td>
<td>18</td>
<td>8:1:1</td>
</tr>
<tr>
<td>2</td>
<td>Boc$_2$O, Et$_3$N, DCM</td>
<td>2</td>
<td>18</td>
<td>5:1:3</td>
</tr>
<tr>
<td>3</td>
<td>Boc$_2$O, DMAP (cat.), CH$_3$CN</td>
<td>1.05</td>
<td>18</td>
<td>6:2:3</td>
</tr>
<tr>
<td>4</td>
<td>Boc$_2$O, DMAP (cat.), DCM, Et$_3$N</td>
<td>0.95</td>
<td>1</td>
<td>5:1:2</td>
</tr>
<tr>
<td>5</td>
<td>Boc$_2$O, NaH, THF</td>
<td>1</td>
<td>2</td>
<td>5:4:1</td>
</tr>
</tbody>
</table>

\textbf{Table 6: Boc Protection Attempts}

The results in table 6 suggest that it would be challenging to obtain the desired protected product \textbf{208} without the formation of the unwanted enol carbamate \textbf{209}. Using Boc anhydride with triethylamine in DCM suggests the preferential formation of the enol carbamate \textbf{209} (entries 2 and 4). However,
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When sodium bicarbonate or catalytic amounts of DMAP are used there is no clear favoured formation of the desired product 208 (entries 1 and 3). A good ratio of the desired product 208 was obtained when using sodium hydride in THF (entry 5). As a result of the improved ratio of products using NaH, a study was carried out to determine what effect the reaction time has on the ratio of products. Three reactions were performed under the same conditions but with varying reaction times (Scheme 65, table 7).

![Scheme 65: Boc Protection Attempts](image)

Reagents and conditions: (a) Boc₂O, NaH, DCM.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of NaH</th>
<th>Equiv. of Boc₂O</th>
<th>Time (mins)</th>
<th>Ratio by crude NMR (204:208:209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>8:2:0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>20</td>
<td>5:3:2</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>30</td>
<td>3:4:3</td>
</tr>
</tbody>
</table>

Table 7: Boc Protection Attempts

The results suggest that the initial stages of the reaction involve the formation of the desired product 208 and once this has formed it then reacts further to give the unwanted enol carbamate 209. An explanation for this observation was that after the initial protection on the nitrogen the t-butoxide ions which are generated as a by-product, could deprotonate the product 208 to form a nucleophilic enolate which reacts with remaining Boc anhydride. In an attempt to avoid this, the source of the Boc protecting group was changed from Boc anhydride to 2-(Boc-oxyimino)-2-phenylacetonitrile 34 (Boc-ON) as this reagent generates non-basic by-products.
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The reaction was repeated with varying equivalents of Boc-ON (34) and sodium hydride (Scheme 66, table 8).

*Scheme 66: Boc Protection Attempts using Boc-ON*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of NaH</th>
<th>Equiv. of Boc-ON</th>
<th>Time (hours)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>18</td>
<td>40% 204, 48% 208, 0% 209</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>1.2</td>
<td>2</td>
<td>15% 204, 59% 208, 10% 209</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>5</td>
<td>2</td>
<td>5% 204, 36% 208, 30% 209</td>
</tr>
</tbody>
</table>

*Table 8: Boc Protections Attempts using Boc-ON*

By using one equivalent of Boc-ON and sodium hydride, 48% of the desired product 208 was isolated with recovered starting material (entry 1). Unfortunately, attempting to increase the yield by increasing the equivalents of either Boc-ON or sodium hydride resulted in formation of the enol carbamate 209 (entries 2 and 3).

An alternative explanation for the formation of the enol carbamate was that there may only be partial deprotonation of the free amide 204 using sodium hydride in solution. This could cause competing deprotonation with the preferential formation of the enol carbamate. To ensure complete deprotonation of the starting amide 204 a strong, bulky base was employed prior to the addition of Boc-ON (Scheme 67, table 9).

*Scheme 67: Boc Protection Attempts using Boc-ON*
Table 9: Boc Protection Attempts using Boc-ON

Pleasingly, the formation of the enol carbamate was stopped by using LDA and the desired product was obtained in 30% yield with 60% recovered starting material (entry 1). The reaction was optimised further by using 1.5 equivalents of base to obtain 87% yield of the desired protected amide 208. These results suggest that the use of a sterically hindered base prevents the formation of the nucleophilic enolate during the reaction.

2.2.2 Reduction of Lactam 208.

As previously discussed in section 2.2.1, the reduction of the lactam in bicyclic substrates has proved difficult. With the introduction of the Boc protecting group, the amide carbonyl group is more electrophilic than the previous t-butyl amide, therefore should require milder conditions to reduce. Table 10 shows the conditions used in an attempt to reduce lactam 208 (Scheme 68).

Reagents and conditions: (a) i. conditions in table 10; ii. Et₃SiH, BF₃·OEt₂, THF, -78 °C, 2 h (used in entries 1-5)
Enone 208 was resistant to lactam reduction using borane complexes, DIBAIH at low temperatures or LiAlH₄ at low temperature and only reduction of the enone was observed in alcohol 211. However, it was found that using LiAlH₄ at a higher temperature led to the partial reduction of the amide carbonyl resulting in a mixture of hemiaminals 212 and 212’ (entry 7 and 8). Furthermore, heating this reaction to 50 °C led to the complete reduction of the amide but also the reduction of the Boc group giving the N-methyl substrate 213 in 47% yield (entry 9).

Purification of hemiaminal 212 proved difficult and so an elimination reaction was performed on the crude material using mild acidic conditions (Scheme 69, table 11).

Reagents and conditions: (a) i. LiAlH₄, THF, 0 °C- R.T., 24 h; ii. PTSA, conditions in table 11.

Scheme 69: Elimination Reaction Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp./Time (hours)</th>
<th>210 (%)</th>
<th>211 (%)</th>
<th>212 (%)</th>
<th>213 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BH₃, THF</td>
<td>-78 °C to R.T./18 h</td>
<td>0%</td>
<td>quant.</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>BH₃.DMS, THF</td>
<td>-78 °C to R.T./18 h</td>
<td>0%</td>
<td>quant.</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>DIBAIH, THF</td>
<td>-78 °C/1h</td>
<td>0%</td>
<td>quant.</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>DIBAIH, THF</td>
<td>-78 °C to R.T./18 h</td>
<td>/*</td>
<td>/*</td>
<td>/*</td>
<td>/*</td>
</tr>
<tr>
<td>5</td>
<td>DIBAIH, DCM</td>
<td>-78 °C/3 h</td>
<td>0%</td>
<td>quant.</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>LiAlH₄, THF</td>
<td>-78 °C/1h</td>
<td>0%</td>
<td>quant.</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>LiAlH₄, THF</td>
<td>0°C/3 h</td>
<td>0%</td>
<td>¥</td>
<td>¥</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>LiAlH₄, THF</td>
<td>0 °C to R.T./24 h</td>
<td>0%</td>
<td>0%</td>
<td>quant.</td>
<td>0%</td>
</tr>
<tr>
<td>9</td>
<td>LiAlH₄, THF</td>
<td>R.T/24 h - 50 °C/3 h</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>47%</td>
</tr>
</tbody>
</table>

* Decomposition of starting material, ¥ Mixture of 211 and 212

Table 10: Carbamate Reduction Attempts

Table 11: Elimination Reaction Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>214 (%)</th>
<th>215 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>10</td>
<td>/</td>
</tr>
</tbody>
</table>

Table 11: Elimination Reaction Attempts
In THF, the elimination product 214 was observed in 10% yield with the formation of an unwanted elimination product 215 in 18% yield (entry 1). To avoid the undesired elimination the reaction was repeated in methanol, which was successful, however the yield was poor, 10% (entry 2).

The cause for the poor yields was thought to be the use of LiAlH₄ in the reduction step, as it proved difficult to remove from the reaction mixture and so product may have been lost. The initial reduction was repeated using LiEt₃BH (Super-H), which was easier to remove from the reaction mixture. After performing the elimination and the hemiaminal cleavage on the crude material, the desired amine 216 was purified in 32% yield over the 3 steps (Scheme 70).

\[
\begin{align*}
\text{NBoc} & \quad \text{Ph} \\
H & \quad H \\
\text{MeO} & \quad O
\end{align*}
\]

\[
\begin{align*}
\text{208} & \quad \xrightarrow{a \quad 32\%} & \quad \text{216}
\end{align*}
\]

Reagents and conditions: (a) i. LiEt₃BH, THF, 0°C-R.T., 24 h; ii. PTSA, MeOH; iii. Et₃SiH, BF₃·OEt₂, -78 °C, 2 h.

Scheme 70: Optimised Lactam Reduction and Elimination Procedure

2.2.3 Enone Epoxidation.

The remaining steps to the Eschenmoser precursor include the oxidation of a phenyl ring and epoxidation of the enone. The arene oxidation could not be performed in the presence of the enone as it would be destroyed by an unwanted oxidation. Therefore it was decided to perform the epoxidation prior to the phenyl oxidation to prevent unwanted reactions. The Clayden group has previously shown that using Sharpless’s oxidation conditions, it was possible to perform an arene oxidation reaction in the presence of epoxide functionality. ⁸⁹,⁹⁴ Enone 216 was subjected to various epoxidation conditions detailed in table 12 (Scheme 71).

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

\[
\begin{align*}
\text{a} & \quad \text{216} & \quad \text{217}
\end{align*}
\]

Reagents and conditions: (a) conditions in table 12

Scheme 71: Epoxidation Attempts
Table 2: Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Base (equiv.)</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O₂</td>
<td>NaOH</td>
<td>THF, 0°C - R.T., 2 h</td>
<td>216</td>
</tr>
<tr>
<td>2</td>
<td>H₂O₂</td>
<td>NaOH (1.5)</td>
<td>MeOH, -5°C, 0.5 h</td>
<td>42%, 217</td>
</tr>
<tr>
<td>3</td>
<td>H₂O₂</td>
<td>NaOH (0.45)</td>
<td>MeOH, 0°C, 1.5 h</td>
<td>216</td>
</tr>
<tr>
<td>4</td>
<td>H₂O₂</td>
<td>K₂CO₃ (2)</td>
<td>THF/MeOH/H₂O, 0°C - R.T., 2 h</td>
<td>54%, 217</td>
</tr>
<tr>
<td>5</td>
<td>H₂O₂</td>
<td>K₂CO₃ (1.1)</td>
<td>THF/MeOH/H₂O, 0°C, 0.5 h</td>
<td>59%, 217</td>
</tr>
<tr>
<td>6</td>
<td>H₂O₂</td>
<td>Triton B (4)</td>
<td>THF, 0°C, 2 h</td>
<td>216</td>
</tr>
</tbody>
</table>

Table 12: Epoxidation Attempts

It was possible to obtain the desired epoxide 217 in a moderate 42% yield using hydrogen peroxide with excess NaOH (entry 2). The yield was successfully increased to 59% by replacing the base with K₂CO₃ and performing the reaction in a mixed solvent system of THF, methanol and water (entry 5).

In all the successful examples shown in table 12, the epoxidation was diastereoselective with the attack of the oxidant on the exo face. It was possible to obtain an X-ray crystal structure to confirm the exo-exo configuration.

Figure 12: X-ray Crystal Structure
2.2.4 Phenyl Oxidation.

With the successful epoxidation of enone 216 it was then possible to perform the phenyl oxidation reaction. The oxidation was performed on epoxide 217 using Sharpless’s oxidation conditions (Scheme 72).93

![Image of the reaction]

Reagents and conditions: (a) i. RuCl₃, NaIO₄, EtOAc/H₂O/CH₃N, 24 h, R.T.; ii. TMS-CHN₂, MeOH/Toluene, R.T.

Scheme 72: Phenyl Oxidation Attempts

The phenyl ring in epoxide 217 proved resistant to the oxidation conditions and only starting material was recovered. The reaction was repeated with prolonged reaction times and increased equivalents of sodium periodate with little success.

In order to perform the desired oxidation, the arene ring would need to be more electron rich making it more susceptible to oxidation.95 Prior to research into an appropriate arene ring to perform the oxidation, model studies into conditions needed for the Eschenmoser fragmentation using epoxyketone 217 were explored.

2.2.5 Eschenmoser Fragmentation Model Studies.

The Eschenmoser fragmentation reaction was first discovered in 1967 by Albert Eschenmoser and involves an α, β-epoxy ketone and an aryl sulfonylhydrazine to give an alkyne and aldehyde products.96 Under acidic conditions the fragmentation is catalysed by electrophilic activation of the epoxide and using basic conditions initiate the fragmentation by deprotonation of the hydrazone (Scheme 73).
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Epoxyketone 217 was subjected to a number of different conditions to form the hydrazone, followed by fragmentation (Scheme 74, table 13).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>Result/comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-nitrobenzenesulfonyl hydrazide, pyridine, EtOH/THF&lt;sup&gt;97&lt;/sup&gt;</td>
<td>R.T.</td>
<td>4</td>
<td>217 recovered</td>
</tr>
<tr>
<td>2</td>
<td>TsHN-NH&lt;sub&gt;2&lt;/sub&gt;, EtOH, AcOH&lt;sup&gt;98&lt;/sup&gt;</td>
<td>50</td>
<td>4</td>
<td>Intermediate 224 followed by recovery of 217</td>
</tr>
<tr>
<td>3</td>
<td>TsHN-NH&lt;sub&gt;2&lt;/sub&gt;, EtOH, Pyridine&lt;sup&gt;97&lt;/sup&gt;</td>
<td>50</td>
<td>4</td>
<td>Intermediate 224 followed by recovery of 217</td>
</tr>
<tr>
<td>4</td>
<td>TsHN-NH&lt;sub&gt;2&lt;/sub&gt;, AcOH, DCM&lt;sup&gt;97, 99&lt;/sup&gt;</td>
<td>R.T.</td>
<td>8</td>
<td>31% 225</td>
</tr>
<tr>
<td>5</td>
<td>Mesitylenesulfonyl hydrazide, AcOH&lt;sup&gt;100&lt;/sup&gt;</td>
<td>R.T.</td>
<td>36</td>
<td>21% 223</td>
</tr>
</tbody>
</table>

Table 13: Eschenmoser Fragmentation Attempts

The results show that using an electron poor p-nitrobenzenesulfonyl hydrazine resulted in no reaction (entry 1). Using tolenesulfonyl hydrazine in ethanol gave intermediate 224, which when subjected to acidic and basic conditions resulted in the regeneration of ketone 217 (entries 2 and 3). To avoid
this unwanted intermediate 224, the solvent was changed to DCM and in acidic conditions the fragmentation was observed and gave alkyne 225 in 31% yield (entry 4). Alkyne 225 bears an unwanted toluenesulfonyl hydrazone and was thought to have formed because of competing rates of hydrazone formation between the ketone and the newly formed aldehyde. To overcome this problem it was decided to use a more hindered hydrazine to slow down the rate of hydrazone formation. Mesitylsulfonyl hydrazine gave a successful fragmentation reaction and the desired alkyne 223 was isolated in 21% yield (entry 5).

2.2.6 Arene Oxidation.

As discussed in section 2.2.4, the phenyl ring in epoxyketone 217 proved resistant to the oxidation conditions. Previous research within the group has shown that increasing the electron density of the arene ring enhances the susceptibility of oxidation and was reported in the synthesis of arylkainoid 229 (Scheme 75). 101

\[
\begin{align*}
\text{H} & \text{O} & \text{N} & \text{Boc} \\
\text{Ph} & \text{H} & \text{H} & \text{Ph} \\
\text{MeO} & \text{2} & \text{C} & \text{Me2} \\
\text{H} & \text{N} & \text{Boc} \\
\text{Ph} & \text{H} & \text{H} & \text{MeO} & \text{2} & \text{C} & \text{Me2} \\
\text{H} & \text{N} & \text{Boc} \\
\text{Ph} & \text{H} & \text{H} & \text{MeO} & \text{2} & \text{C} & \text{Me2} \\
\end{align*}
\]

Reagents and conditions: (a) i. cat. RuCl₃, NaIO₄ (100 equiv), EtOAc/H₂O/CH₃N (1:34:1); ii. TMS-CHN₂, MeOH/Benzene.

Scheme 75: Oxidation Reaction of Electron Rich Aromatic Ring

To achieve the desired oxidation, the phenyl group was replaced with methoxy-substituted aromatic rings and benzamides 232, 236 and 240 were synthesised (Scheme 76).
Chapter 2: Results and Discussion

There were concerns that changing the electronic properties of the benzamides may affect the dearomatising cyclisation reaction but this was only slightly observed in the yields obtained. Using benzamide 232, enone 233 was isolated in 37% yield. However, performing the cyclisation with benzamide 236 resulted in enone 237 in an improved 64% yield. With a highly increased electron rich benzamide 240, enone 241 was isolated in a poor 14% yield, which was thought to be due to the addition electron density affecting the acidity of the benzylic protons (caused by electron donation from the para-methoxy substituent).

The next step in the synthesis was to remove the tert-butyl group with conc. H$_2$SO$_4$ but this proved unsuccessful on enone 233. A number of attempts were made resulting in decomposition of starting material after prolonged reaction
times. This prompted the use of enone 237 as the cyclisation yield was high and the cumyl group could be easily removed in 86% yield using TFA (Scheme 77)

![Scheme 77: Steps Towards the Desired Epoxyketone](image)

*Reagents and conditions:* (a) TFA, reflux, 1.5 h; (b) LDA, Boc-ON, THF, 0 °C, 5 h; (c) i. LiEt₃BH, THF, 0 °C-R.T., 24 h; ii. PTSA, MeOH; iii. Et₃SiH, BF₃·OEt₂, DCM, -78 °C; (d) t-BuOOH, DBU, THF, 0 °C, 30 mins.

The free amide 242 was protected with the optimised Boc-ON conditions (discussed in section 2.2.1.2) and successfully gave 243 in 80% yield. Enone 243 was then subjected to the reduction and elimination procedure developed in section 2.2.2, to give amine 244 in an improved 48% yield over 3 steps. Performing the epoxidation with hydrogen peroxide gave epoxyketone 245 in a reduced yield of 38%. However, performing the epoxidation with *tert*-BuOOH resulted in an improved 68% yield.¹⁰² The arene oxidation reaction was then attempted using the newly synthesised epoxyketone 245 (Scheme 78, table 14).

![Scheme 78: Arene Oxidation Attempts](image)

*Reagents and conditions:* (a) i. conditions in table 14; ii. TMS-CHN₂, toluene/methanol

---

¹⁰² The arene oxidation reaction was then attempted using the newly synthesised epoxyketone 245 (Scheme 78, table 14).
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Table 14: Arene Oxidation Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temp.</th>
<th>Time (mins)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuCl₃, NaIO₄, CH₃CN, H₂O, EtOAc</td>
<td>R.T</td>
<td>10</td>
<td>1:1 mixture</td>
</tr>
<tr>
<td>2</td>
<td>RuCl₃, NaIO₄, CH₃CN, H₂O, EtOAc</td>
<td>0 °C</td>
<td>120</td>
<td>42% 218</td>
</tr>
</tbody>
</table>

Epoxyketone 245 was successfully oxidised at room temperature giving methyl ester 218 after esterification with TMS-diazomethane. However, an undesired product formed which was thought to be an oxidation α to the nitrogen in hemiaminal 246, which was inseparable to the product (entry 1).¹⁰³ This was not surprising as it has been reported that these conditions can oxidise at the α position to the nitrogen.¹⁰³ To avoid the undesired oxidation the reaction performed at 0 °C which gave the epoxyketone 218 in 42% yield with no traces of the undesired hemiaminal 246 (entry 2).

2.2.7 Eschenmoser Fragmentation Studies.

Having successfully synthesised the desired precursor to the Eschenmoser fragmentation⁹⁵, epoxyketone 218 was subjected to the fragmentation conditions discussed in section 2.2.5 (Scheme 79, table 15).

\[
\begin{align*}
\text{NBoc} & \quad \text{H} & \quad \text{H} & \quad \text{O} \\
\text{H} & \quad \text{H} & \quad \text{CO₂Me} & \quad \text{H} & \quad \text{H} & \quad \text{CO₂Me} \\
\text{218} & \quad \xrightarrow{\text{a}} & \quad \text{247}
\end{align*}
\]

Reagents and conditions: (a) i. conditions in table 15

Scheme 79: Eschenmoser Fragmentation Attempts
Chapter 2: Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar (Hydrazine)</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Time</th>
<th>Result/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mes</td>
<td>AcOH/DCM</td>
<td>R.T.</td>
<td>4 d</td>
<td>&lt; 29% 247</td>
</tr>
<tr>
<td>2</td>
<td>Mes</td>
<td>AcOH/DCM</td>
<td>40 °C</td>
<td>2h30</td>
<td>3% 247</td>
</tr>
<tr>
<td>3</td>
<td>Mes</td>
<td>AcOH</td>
<td>R.T.</td>
<td>4 d</td>
<td>&lt;21% 247</td>
</tr>
<tr>
<td>4</td>
<td>Mes</td>
<td>AcOH</td>
<td>R.T.</td>
<td>7 d</td>
<td>(to finish 40 °C for 30 min) &lt;11% 247</td>
</tr>
<tr>
<td>5</td>
<td>Tol</td>
<td>AcOH/DCM</td>
<td>R.T.</td>
<td>2 d</td>
<td>Decomposition of 218</td>
</tr>
<tr>
<td>6</td>
<td>p-NO₂Ph</td>
<td>THF</td>
<td>R.T.</td>
<td>24 h</td>
<td>218</td>
</tr>
</tbody>
</table>

Table 15: Eschenmoser Fragmentation Attempts

Fragmentation was observed using mesitylenesulfonyl hydrazine in acetic acid at room temperature but due to purification difficulties the resulting aldehyde was isolated in less than 29% yield (entry 1). Different hydrazines were tested, including toluenesulfonyl hydrazide (entry 5) and p-nitrobenzenesulfonyl hydrazide (entry 6) with no observed fragmentation.

In an attempt to increase the yield by trapping the apparently unstable aldehyde as a hydrazone (cf. 225). The reaction was repeated using an additional equivalent of mesitylenesulfonyl hydrazine but resulted in a complex mixture of products. With little success isolating the hydrazone, reactions were performed using the solvent as the trapping agent (Scheme 80, table 16).

![Scheme 80: Fragmentations using a Solvent Trapping Agent]

**Reagents and conditions:** (a) mesitylenesulfonyl hydrazine, EtOH, AcOH, R.T. (see table 16)

Table 16: Eschemoser Fragmentation Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (hours)</th>
<th>Additives</th>
<th>Conc.</th>
<th>Result/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>N/A</td>
<td>0.1 M</td>
<td>15% 248</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>N/A</td>
<td>0.1 M</td>
<td>11% 248</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>4 Å MS</td>
<td>0.1 M</td>
<td>218</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>AcOH</td>
<td>0.1 M</td>
<td>Mixture of 248 and 247, trace</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>N/A</td>
<td>0.5 M</td>
<td>11% 248</td>
</tr>
</tbody>
</table>

Table 16: Eschemoser Fragmentation Attempts
Performing the reaction for 4 hours at room temperature gave the desired product 248 in 15% yield (entry 1). Attempts to increase the yield using additives were unsuccessful and resulted in the recovery of starting material (entry 3) or low yielding mixtures of the desired 247 and 248 (entry 4).

2.2.8 Enantioselective Dearomatising Cyclisation.

Previous work within the Clayden group in developing enantioselective dearomatising cyclisations has highlighted two chiral lithium amides that give good enantioselective reactions (Scheme 81).

![Reagents and conditions:](a) i. n-BuLi, Chiral amide 111/112, -78 °C - R.T.; ii. NH₄Cl; iii. HCl aq;](image)

Scheme 81: Enantioselective Dearomatising Cyclisations

Developing an enantioselective cyclisation reaction using ortho-methoxybenzamide 249 has proven difficult using chiral amine 111, obtaining a maximum e.e. of 48% (Scheme 82).

![Reagents and conditions:](a) i. n-BuLi, -78 °C - R.T; ii. HCl aq.](image)

Scheme 82: Enantioselective Dearomatising Cyclisation using Chiral Amide 111
Variable temperature NMR has shown restricted rotation in benzamides containing ortho-methoxy substituents, which is observed in the splitting of the cumyl methyl peaks (Fig. 13). This rotation was assigned to the CO-Ar bond rather than amide bond as the observed splitting was not observed in benzamide that did not contain an ortho substituent.

\[
\begin{align*}
\text{O} & \text{-} \text{N} \\
\text{Ph} & \text{-} \text{H} \\
\text{OMe} & \text{-} \text{H}_2
\end{align*}
\]

These experiments showed coalescence of the methyl signals between 338K and 343K. Based on this data, the free energy of activation was calculated using Eyring equation \(\Delta G^\ddagger = aT_c[10.319+\log (T_c/k)]\) at 340 ± 2 K \((T_c)\) to be \(\Delta G^\ddagger = 68.4 \pm 0.4 \text{ kJmol}^{-1}\).

Figure 13: VT $^1$H NMR Spectra of Cumyl Peaks in Benzamide 249

This restricted bond rotation was also observed in ortho, para-methoxybenzamide 177. The variable temperature spectra shows coalescence of
the methyl signals between 308 K and 313 K and the free energy of activation was calculated at 311 ± 2 K to be $\Delta G^\ddagger = 62.4 \pm 0.3 \text{ kJmol}^{-1}$ (Fig. 14).

The rational for the lower barrier to rotation was due to the additional para-methoxy group providing enhanced stability by resonance and lowering the activation energy (Scheme 83).
2.2.8.1 Enantiomeric Excess Explanations.

A possible explanation for the poor enantiomeric excess was rationalised by restricted rotation at low temperatures. Substrates bearing ortho substituents are forced to have undesired dihedral angles due to steric hindrance. Therefore benzamides 177 and 249 can experience atropisomerism and exist as two amide enantiomers at low temperatures (Scheme 84).

Once asymmetrically deprotonated, the organolithium diastereoisomer B can cyclise to give the desired product but diastereoisomer B' cannot cyclise due to the ortho-methoxy substituent. This organolithium enantiomer (B') would have to epimerise in order to cyclise, therefore giving a poor enantiomeric excess.

A related explanation for the poor enantiomeric excess is based on a “match-missmatch” effect. This theory is based on the chiral base asymmetrically deprotonating one amide enantiomer successfully and unable to access the correct proton in the remaining enantiomer and is therefore forced to take the undesired proton resulting in a poor enantiomeric excess.

An alternative explanation was that anion epimerisation occurs due to the higher activation energy for the cyclisation onto a more electron rich arene ring or that the generated amide organolithium is deprotonating starting benzamide resulting in the observed poor enantiomeric excess.

Further studies into the behaviour of ortho substituted benzamide 177 at low temperatures (-80 °C) revealed additional restrictions in rotation causing the presence of diastereoisomers in NMR analysis. This was not believed to
contribute to the poor enantioselectivity as the asymmetric deprotonation does not occur at -80 °C.

Little was understood of the stability of the intermediate amide organolithium and the rate of cyclisation. Therefore, the explanations for the observed enantiomeric excess were speculative and further experiments, including deuterium quenching, would have given a better understating to the reaction process.

2.2.8.2 Enantioselective Dearomatising Cyclisation Attempts.

Based on the variable temperature calculations, the ortho, para-methoxy benzamide enantiomers (177) racemise more rapidly than the ortho-methoxy benzamide enantiomers (249) and so enantioselective dearomatising cyclisation reactions were performed using chiral amide 111 (Scheme 85, table 17)

![Scheme 85: Enantioselective Dearomatising Cyclisation Attempts](image)

Reagents and conditions: (a) i. conditions in table 17

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>e.e.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF, -78 °C – R.T.</td>
<td>52%</td>
<td>36% 179</td>
</tr>
<tr>
<td>2</td>
<td>THF – 30 °C</td>
<td>14%</td>
<td>15% 179</td>
</tr>
<tr>
<td>3</td>
<td>THF 0 °C</td>
<td>23%</td>
<td>18% 179</td>
</tr>
<tr>
<td>4</td>
<td>THF R.T.</td>
<td>27%</td>
<td>21% 179</td>
</tr>
<tr>
<td>5</td>
<td>Et₂O/10%THF -30 °C</td>
<td>/</td>
<td>177</td>
</tr>
<tr>
<td>6</td>
<td>Et₂O/10%THF 0 °C</td>
<td>/</td>
<td>177</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>/</td>
<td>177</td>
</tr>
</tbody>
</table>

Table 17: Enantioselective Dearomatising Cyclisation Attempts
The results in table 17 show that it would be difficult to obtain high enantiomeric ratios using chiral amine 111 as the highest obtained was 52% e.e. by performing the reaction in THF at -78 °C and warming to room temperature (entry 1).

Chiral amide 112 was also tested under different conditions (Scheme 86, table 18).

![Scheme 86: Enantioselective Dearomatising Cyclisation Attempts]

Reagents and conditions: (a) i. conditions in table 18

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>e.e.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF, -78 °C – R.T.</td>
<td>48%</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>THF, - 30 °C, 0.5 equiv of chiral amine</td>
<td>73%</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>THF - 20 °C, 2 h</td>
<td>7%</td>
<td>26%</td>
</tr>
<tr>
<td>4</td>
<td>THF 0 °C, 2 h</td>
<td>53%</td>
<td>24%</td>
</tr>
<tr>
<td>5</td>
<td>THF 10 °C, 2 h</td>
<td>44%</td>
<td>22%</td>
</tr>
<tr>
<td>6</td>
<td>THF R.T., 2 h</td>
<td>23%</td>
<td>18%</td>
</tr>
<tr>
<td>7</td>
<td>Et₂O/10%THF -30 °C, 2 h</td>
<td>&lt;10%</td>
<td>20%</td>
</tr>
<tr>
<td>8</td>
<td>THF/Et₂O 0 °C, 2h</td>
<td>3%</td>
<td>15%</td>
</tr>
<tr>
<td>9</td>
<td>Et₂O/10%THF 0 °C, 2 h</td>
<td>20%</td>
<td>12%</td>
</tr>
<tr>
<td>10</td>
<td>THF/Toluene 0 °C, 2 h</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>11</td>
<td>Toluene, 0 °C, 2 h</td>
<td>SM</td>
<td>/</td>
</tr>
</tbody>
</table>

Table 17: Enantioselective Dearomatising Cyclisation Attempts

Disappointingly, it was not possible to obtain a high e.e using chiral amine 112. It was possible to obtain a 53% e.e. in 24% yield by performing the reaction in THF at 0 °C (entry 4).

In an attempt to gain a further understanding of the asymmetric deprotonation, the reaction was performed with half an equivalent of base. The result gave an improved e.e. of 73% suggesting that the chiral amide selectively deprotonates the amide enantiomer that can cyclise preferentially. This result
would promote the restricted rotation explanation for the observed e.e rather than anion epimerisation (see 2.2.8.1).

As enone 179 was not crystalline, it was not possible to increase the e.e. by recrystallisation and so these results confirmed doubts that it would be difficult to obtain a high yielding enantioselective dearomatising cyclisation using an ortho substituted benzamides.
2.2.9 Summary.

In summary it has been shown that using ortho,para-methoxy benzamide it was possible to synthesise the desired alkyne using an Eschenmoser fragmentation (Scheme 87).

Reagents and conditions: (a) 3-methoxybenzyl bromide, K₂CO₃, DMF, R.T., 18 h; (b) 2,4-dimethoxybenzoyl chloride, Et₃N, DCM, R.T., 18 h; (c) i. LDA, DMPU, THF, 0 °C; ii. 1M HCl; (d) i. TFA, reflux, 1.5 h, quant; ii. LDA, Boc-OH, THF, 0 °C, 5 h; (e) i. Super-H, THF, 0 °C - R.T., 24 h; ii. PTSA, MeOH, R.T., 1.5 h; iii. Et₃SiH, BF₃·OEt₂, DCM, -78 °C, 2 h; (f) t-BuOOH, DBU, THF, 0 °C, 30 mins; (g) RuCl₃, NaIO₄, EtOAc/H₂O/CH₃N, 0 °C, 2 h; (h) mesitylsulfonyl hydrazine, EtOH, reflux, 4 h.

However, it was decided to develop an alternative route to the desired alkyne intermediate that avoids the use of an ortho-substituted benzamides due to the problems encountered with performing an enantioselective reaction. It was also decided to avoid using the Eschenmoser fragmentation as only poor, irreproducible yields were observed.
2.3 Baeyer-Villiger Oxidation Route.

An alternative strategy towards the synthesis of the alkyne intermediate was based around introducing functionality using a Baeyer-Villiger oxidation reaction. The retrosynthetic route is shown in scheme 88.

**Scheme 88: Retrosynthetic Route**

It was envisaged that alkyne A could be made via a formal dehydrogenation of alkene B, which could be synthesised via an elimination reaction on primary alcohol C. Primary alcohol C could be the product of hydrolysis and lactam reduction reactions of unsaturated lactone D. Lactone D can be made by performing a regioselective Baeyer-Villiger oxidation on enone E which is the product of the dearomatising cyclisation using para-methoxy benzamide F. The proposed synthesis is shown in scheme 89.
Chapter 2: Results and Discussion

2.3.1 Baeyer-Villiger Oxidation Studies.

The Baeyer-Villiger oxidation reaction was discovered in 1899 and is an oxidative cleavage of a carbon-carbon bond adjacent to a carbonyl, which converts a ketone into an ester or a cyclic ketone into a lactone.\(^{106}\) The general mechanism is shown in scheme 90.

Since the discovery in 1899 the reaction has been a regularly used transformation in organic synthesis.\(^ {107}\) The popularity of the reaction is based on the uniqueness of the transformation, the stereospecificity and the predictable regioselectivity, which is dependant on the substituents adjacent to the carbonyl
group and their ability to migrate. With few exceptions, the literature permits the generalisation that substituents that are able to stabilize a developing positive charge migrate preferentially. Mechanistic studies by W. von E. Doering and L. Speers, concluded that the migration aptitude supports a mechanism in which the migrating group is electron deficient in the transition state. The rearrangement requires the correct antiperiplanar alignment of the O-O bond of the leaving group and the migrating group ($R_m$), which is classed as the primary stereoelectronic effect. The secondary effect is the antiperiplanar alignment of the migrating group ($R_m$) and the oxygen lone pair (Fig. 15).

![Figure 15: Stereoelectronic Effects in the Baeyer-Villiger Reaction](image)

Counter to the generalised migration argument, Kishi et.al. have explored the effects of conformation on the Baeyer-Villiger oxidation in bicyclic structures and contend that the bond that is anti-periplanar to the dissociating peroxide bond is always and exclusively the bond that migrates, even when electronically disfavoured from doing so. Despite the many investigations on the mechanism of the Baeyer-Villiger oxidation, the migratory pattern and the nature that influences migration is still not fully understood.

The Baeyer-Villiger oxidation reaction was previously shown to be regioselective in the total synthesis of (±)-kainic acid published by the Clayden group (Scheme 91).

![Scheme 91: Baeyer-Villiger Oxidation Reaction Towards the Synthesis of (±)-Kainic Acid](image)

The regioselectivity was explained through an $ex$-face peracid attack together with steric interactions with the axial methyl group favouring the
intermediate conformation A (Scheme 91). The more favourable migration was where the breaking carbon–carbon bond is antiperiplanar to the breaking oxygen–oxygen bond (shown as bold bonds).

There are many examples in the literature involving the regioselective oxidation of a cyclic enone to the corresponding lactone.\textsuperscript{110} The theory for the preferential migration of the vinyl group is not fully understood, which is presumably due to the undefined reaction mechanism.\textsuperscript{111} Baeyer-Villiger oxidation reactions were performed on enone 104 using a number of different oxidants detailed in table 19 (Scheme 92).

\begin{center}
\includegraphics[width=\textwidth]{Scheme92}
\end{center}

Reagents and conditions: (a) conditions in table 19

Scheme 92: Baeyer-Villiger Oxidation Attempts with Different Oxidants

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Equiv.</th>
<th>Time (hours)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>mCPBA, DCM</td>
<td>1</td>
<td>24</td>
<td>171 recovered</td>
</tr>
<tr>
<td>2</td>
<td>mCPBA, DCM</td>
<td>3</td>
<td>48</td>
<td>20% 265, 60% 251</td>
</tr>
<tr>
<td>3</td>
<td>mCPBA, TsOH, DCM</td>
<td>1.5</td>
<td>24</td>
<td>171 recovered</td>
</tr>
<tr>
<td>4</td>
<td>Peracetic acid, DCM</td>
<td>1.5</td>
<td>24</td>
<td>171 recovered</td>
</tr>
<tr>
<td>5</td>
<td>Ozone, DCM</td>
<td>1.5</td>
<td>24</td>
<td>171 recovered</td>
</tr>
<tr>
<td>6</td>
<td>mCPBA, DCM</td>
<td>1</td>
<td>48</td>
<td>30% 171, 55% 251</td>
</tr>
<tr>
<td>7</td>
<td>mCPBA, DCE (60 °C)</td>
<td>1.5</td>
<td>24</td>
<td>Decomposition of 171</td>
</tr>
</tbody>
</table>

Table 19: Baeyer-Villiger Oxidation Conditions

The results show that the oxidation can be carried out regioselectively using mCPBA. Lactone 251 was obtained in 55\% yield using one equivalent of mCPBA for 48 hour with 30\% recovered starting material, which could be recycled (entry 6). Attempting to increase the yield by using excess equivalents of oxidant resulted in the epoxidation of the desired lactone 251 giving epoxide 265 in 20\% yield (entry 2).\textsuperscript{112}
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An X-ray crystal structure of lactone 251 was obtained confirming the isomer obtained (Fig 15).

![Figure 16: X-ray Crystal Structure](image)

A study was carried out on the Baeyer-Villiger oxidation using substrates 266 and 268 to determine what effect varying functionality has on the regioselectivity of the oxidation (Scheme 93).

![Scheme 93: Baeyer-Villiger Oxidation Model Studies](image)

Reagents and conditions: (a) TFA, reflux, 1 h; (b) mCPBA (1 equiv.), DCM, 48 h.; (c) H₂, Pd/C, EtOAc.

The results show that performing the oxidation on a free NH 266 does not affect the regioselectivity of the oxidation. More interestingly, the oxidation reaction using ketone 268 gave a 62% yield of an inseparable mixture of lactone isomers 269 and 270, in a 5:1 ratio. With the comparable substitution pattern
adjacent to the ketone, this result suggests that the conformation of the starting ketone and steric hindrance is causing preferential formation of isomer 269.

Substrates 271 and 274 were also synthesised to observe the effect on the ratio of products by changing surrounding functionality of ketone 268 (Scheme 94).

![Scheme 94: Baeyer-Villiger Oxidation Model Studies](image)

*Reagents and conditions:* (a) i. TFA, reflux, 1 h; ii. Boc₂O, DMAP (cat.), DCM, Et₃N; (b) mCPBA (1 equiv.), DCM, 48 h.; (c) i. RuCl₃, NaIO₄, EtOAc/H₂O/CH₃N; ii. TMS-CHN₂, MeOH/toluene.

Changing the surrounding functional groups in ketone 268 had minimal effect on the ratio of products suggesting that they have little effect on the conformation of the bicycle.

This study has shown that there is an inherent preference for the desired regioisomer using saturated ketone bicycles, which could be caused by conformation and steric hindrance. However, to obtain complete regioselectivity the presence of unsaturation is essential. Further understanding of the Baeyer-Villiger oxidation could be obtained by synthesising the reaction intermediate in a stable form and the crystal structure data would suggest reason for the preferential formation of isomer 251.
A summary of all the Baeyer-Villiger oxidation reactions performed within the group with bi-cyclic structures is shown in scheme 95 and table 20.

**Scheme 95: Summary of Baeyer-Villiger Oxidation Within the Clayden Group**

<table>
<thead>
<tr>
<th>Structure</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Yield</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>52%</td>
<td>1:0</td>
</tr>
<tr>
<td>B</td>
<td>Cumyl</td>
<td>H</td>
<td>/</td>
<td>55%</td>
<td>1:0</td>
</tr>
<tr>
<td>B</td>
<td>t-butyl</td>
<td>H</td>
<td>/</td>
<td>54%</td>
<td>1:0</td>
</tr>
<tr>
<td>B</td>
<td>t-butyl</td>
<td>Me</td>
<td>/</td>
<td></td>
<td>1:1*</td>
</tr>
<tr>
<td>B</td>
<td>t-butyl</td>
<td>H</td>
<td>/</td>
<td>37%</td>
<td>1:0</td>
</tr>
<tr>
<td>C</td>
<td>Boc</td>
<td>Me</td>
<td>CO2Me</td>
<td>88%</td>
<td>1:0</td>
</tr>
<tr>
<td>C</td>
<td>Cumyl</td>
<td>H</td>
<td>Ph</td>
<td></td>
<td>5:1*</td>
</tr>
<tr>
<td>C</td>
<td>Boc</td>
<td>H</td>
<td>Ph</td>
<td></td>
<td>3:1*</td>
</tr>
<tr>
<td>C</td>
<td>Boc</td>
<td>H</td>
<td>CO2Me</td>
<td></td>
<td>3:1*</td>
</tr>
<tr>
<td>C^v</td>
<td>Cumyl</td>
<td>SiMe3</td>
<td>Ph</td>
<td>99%</td>
<td>1:0</td>
</tr>
<tr>
<td>C^v</td>
<td>Boc</td>
<td>SiMe3</td>
<td>CO2Me</td>
<td>99%</td>
<td>1:0</td>
</tr>
<tr>
<td>D^v</td>
<td>Boc</td>
<td>SiMe3</td>
<td>CO2Bu</td>
<td>93%</td>
<td>1:0</td>
</tr>
</tbody>
</table>

*Ratio of inseparable isomers, determined by $^1$H NMR; ^v Reactions discussed in section 2.4; ^ Yield not determined

Table 20: Summary of Baeyer-Villiger Oxidations Within the Clayden Group
In all the examples shown in table 20 there is a preferential formation for one regioisomer. These results have concluded a generalisation that in order to obtain complete regioselectivity in our bicyclic substrates there is a requirement of either unsaturation or a substituent $\beta'$ to the carbonyl group.

2.3.2 Amide Reduction of Lactone 251.

Attempts were made to chemoselectively reduce the amide in lactone 251 without lactone reduction (Scheme 96, table 21).

![Scheme 96: Lactam Reduction Attempts](image)

Reagents and conditions: (a) conditions in table 21

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Equiv.</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIBAlH, THF, 2 h</td>
<td>6</td>
<td>-78 ºC</td>
<td>22% 278</td>
</tr>
<tr>
<td>2</td>
<td>BH$_3$,DMS, THF, 2 h</td>
<td>6</td>
<td>-78 ºC</td>
<td>32% 278</td>
</tr>
</tbody>
</table>

Table 21: Lactam Reduction Attempts

The results suggest that it would be challenging to reduce the amide in the presence of a reactive lactone. Using either DIBAlH or borane dimethylsulfide complex at low temperatures resulted in the reduction of the lactone to give alcohol 278 (entries 1 and 2).

2.3.2.1 Removal of the tert-Butyl Group.

It was previously shown in the Eschenmoser fragmentation route that introducing a Boc group increases the reactivity of the lactam, as milder conditions are required to reduce carbamate amides (section 2.2.2). Therefore, attempts were made to remove the tert-butyl group in enone 171 and lactone 251 using conc. H$_2$SO$_4$ (Scheme 97, section 2.2.1.1).
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The reaction proved unsuccessful using enone 171 and only starting material was recovered. Forcing reaction conditions using higher temperatures and prolonged reaction times resulted in complex mixtures of decomposition. tert-Butyl removal on lactone 251 resulted in decomposition of the starting material thought to be caused by hydrolysis of the lactone using acidic conditions.

Due to the little success in removing the tert-butyl group the cumyl protecting group was employed and the Baeyer-Villiger oxidation was performed on known enone 104 to give lactone 252 as a single regioisomer in 54% yield with 36% recovered starting material that can be recycled (Scheme 98).

The cumyl group was successfully removed from lactone 252 using TFA giving amide 267 in 89% yield.

Known enone 104 was also successfully deprotected using TFA at reflux to give free amide 266 in quantitative yield (Scheme 99). Performing the reaction for prolonged reaction times resulted in trace amounts of isomer 279 which was inseparable from the product 266.
Chapter 2: Results and Discussion

2.3.2.2 Boc Reprotection.

The next stage in the synthesis was to protect the free amide in preparation for the phenyl oxidation and amide reduction. Standard Boc protection conditions and Boc-ON conditions (developed in section 2.2.1.2) were used in an attempt to protect lactone 267 (Scheme 100, table 22).

Using both reaction conditions the unwanted formation of enol carbamate 281 was observed in high yields. This was disappointing as it was hoped that using the developed Boc-ON conditions would prevent enol carbonate formation.

Attempts were also made to protect free amide 266 using the conditions detailed in table 23 (Scheme 101).
Table 23: Boc Protection Attempts

Using either standard Boc anhydride or Boc-ON conditions resulted in the formation of the undesired carbonate 283. Extended enol formation was causing the unwanted reaction and to avoid this, the conjugation was removed from enone 104 and lactone 252 by hydrogenation (Scheme 102).

Scheme 102: Synthesis of Saturated Bicycles

Ketone 271 and lactone 254 were both successfully obtained in 85% and 69% yield respectively from amides 284 and 285. As the unsaturation was essential for a regioselective Baeyer-Villiger oxidation, lactone 254 was used as an intermediate in the synthesis of the desired alkyne.

2.3.3 Phenyl Oxidation.

The phenyl oxidation reaction was attempted using Sharpless’s oxidation conditions on lactone 254 (Scheme 103).
Chapter 2: Results and Discussion

The reaction was unsuccessful and oxidation of the lactone ring was observed. Triester 286 was the only isolated product in 23% yield after esterification with TMS-diazomethane.

2.3.4 Lactone Opening Studies.

2.3.4.1 Unsaturated Lactone Opening.

With the successful functionalisation of enone 104 using a Baeyer-Villiger oxidation reaction, research was carried out on the hydrolysis of the resulting lactones (251 and 252). Studies were performed using unsaturated lactone 251 (bearing a t-butyl group) to develop hydrolysis conditions (Scheme 104, table 24).

![Scheme 104: Lactone Hydrolysis](image)

Reagents and conditions: (a) conditions in table 24

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp.</th>
<th>Time (hours)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCl aq./EtOH (2:1)</td>
<td>R.T.</td>
<td>18</td>
<td>Trace 287</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N, THF/EtOH</td>
<td>R.T.</td>
<td>3</td>
<td>30% 287</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃, DCM/EtOH</td>
<td>R.T.</td>
<td>2</td>
<td>Quant. 287</td>
</tr>
<tr>
<td>4</td>
<td>Et₃N, DCM/EtOH</td>
<td>R.T.</td>
<td>18</td>
<td>Quant. 287</td>
</tr>
</tbody>
</table>

Table 24: Lactone Hydrolysis Attempts

Performing the reaction under basic conditions gave the desired product 287 in 30% yield (entry 2). By changing the solvent to a DCM/ethanol mixture or by using potassium carbonate it was possible to obtain the desired aldehyde 287 in quantitative yield in 18 hours and 2 hours respectively (entry 3 and 4). These conditions were transferred to lactone 252 (bearing a cumyl group), with reproducible results (Scheme 105).
2.3.4.2 Saturated Lactone Opening.

Performing the lactone opening on saturated lactone 254 was the next step in the proposed synthesis (Step f, section 2.3, scheme 89). The synthesis of (−)-kainic acid published by the Clayden group also involved a similar lactone opening reaction (Scheme 106). It was previously reported that using 1M sodium methoxide solution at -78 °C for two hours gave the desired product 109. At -30 °C, Boc migration to the primary alcohol (291a) was reported in quantitative yield. At 0 °C, Boc migration occurs and epimerisation at the C4 position (291b) was observed (Scheme 107).
Chapter 2: Results and Discussion

Reagents and conditions: (a) 1M NaOMe, -30 °C, 1 h; (b) 1M NaOMe, 0 °C, 1 h.

Scheme 107: Observed By-Products from Lactone Opening Reactions

With this information, attempts were made to open lactone 269 that contains a cumyl group, using 1M NaOMe at – 78 °C (Scheme 108).

Reagents and conditions: (a) 1M NaOMe, -78 °C, 2 h.

Scheme 108: Model Lactone Opening

At -78 °C the reaction successfully gave the desired primary alcohol 292 in 94% yield. These conditions were transferred to the Boc protected lactone 254, resulting in 80% yield of the desired alcohol 293 (Scheme 109).

Reagents and conditions: (a) 1M NaOMe, -78 °C, 2 h

Scheme 109: Lactone Opening

Having synthesised primary alcohol 293 it was then necessary to protect the free alcohol as it would not be possible to perform the phenyl oxidation without unwanted over-oxidation. The decision to tackle the challenging phenyl oxidation prior to the lactam reduction was due to the problems previously observed with α oxidation using the ruthenium oxidation conditions (section 2.2.6).
Scheme 110 shows the progress towards the alkyne intermediate and highlights the remaining steps.

Reagents and conditions: (a) benzyl bromide, K₂CO₃, DMF; (b) p-anisoyl chloride, DCM, Et₃N; (c) i. LDA, THF 0 °C, 2 h; (d) mCPBA, DCM, 48 h; (e) i. H₂, Pd/C, EtOAc; ii. TFA, reflux, 1 h; iii. Boc₂O, DMAP (cat.), Et₃N, DCM, 18 h; (f) 1M NaOMe, -78 °C, 2 h

Scheme 110: Summary of Progress and Remaining Steps
2.3.5 Alcohol Protection.

Previous work within the Clayden group towards the synthesis of α-methyl kainic acid (312) revealed that silyl protecting groups were too labile during the arene oxidation (Scheme 111).89

![Scheme 111: Previous Research into Stable Protecting Groups](image)

Reagents and conditions: (a) TIPS-OTf, Lutidine, DCM, 0 °C, MeOH; (b) SEMCl, DIPEA, DCM, 0 °C; (c) RuCl₃, NaIO₄, EtOAc/H₂O/CH₃CN, 4 h, ii. TMS-CHN₂, toluene/methanol (low yields reported).

Protecting primary alcohol 299 with an acetate group resulted in a substrate that proved stable to the oxidation reaction and gave partial oxidation of the aromatic ring, which could be oxidised to the acid using hydrogen peroxide (Scheme 112). However, deprotecting the acetate group (304) caused epimerisation at the C4 position to give the more stable trans-trans epimer, 304a.

![Scheme 112: Previous Research into Stable protecting Groups](image)

Reagents and conditions: (a) Ac₂O, Et₃N, DCM, DMAP (cat.). (b) i. RuCl₃, NaIO₄, EtOAc/H₂O/CH₃CN, 4 h; ii. H₂O₂, Na₂CO₃, dioxane, TMS-CHN₂; (c) Et₃N, H₂O or K₂CO₃, MeOH, mixture of isomers, low yield.
It was reported that using trichloroacetate as the protecting group was stable enough to perform the partial oxidation of the aromatic ring, but labile under a second oxidation to give the desired alcohol 306 (Scheme 113).

![Scheme 113: Previous Research into Stable Protecting Groups](image)

**Reagents and conditions:** (a) Cl$_3$CCOCl, Et$_3$N, DCM, 0 °C; (b) i. RuCl$_3$, NaIO$_4$, EtOAc/H$_2$O/CH$_3$CN, 4h; ii. H$_2$O$_2$, Na$_2$CO$_3$, dioxane, TMS-CHN$_2$

With this information, primary alcohol 293 was protected using trichloroacetyl chloride with triethylamine in DCM to give the desired product 307 in quantitative yield (Scheme 114).

![Scheme 114: Primary Alcohol Protection](image)

**Reagents and conditions:** (a) Cl$_3$CCOCl, DCM, Et$_3$N, R.T
2.3.6 Phenyl Oxidation.

The next step in the synthesis was to perform the phenyl oxidation reaction on the newly protected lactam 307 (Scheme 115).

\[
\begin{array}{c}
\text{Reagents and conditions: (a) i. RuCl}_3, \text{NaIO}_4, \text{EtOAc/H}_2\text{O/CH}_3\text{N, 24 h; ii. TMS-CHN}_2, \text{MeOH/toluene, 1 h}}
\end{array}
\]

The oxidation was complete in 24 hours and after esterification gave methyl ester 308 in 38% yield and 19% recovered starting material. The trichloroacetate group remained and it was not necessary to perform a second oxidation to give the desired acid (that also cleaves the protection group, as discussed in section 2.3.5).

2.3.7 Lactam Reduction Attempts.

The final steps towards the desired alkyne 298 needed to include the reduction of the lactam and the conversion of a primary alcohol to the alkyne (Scheme 116).
The chemoselective lactam reduction was attempted on lactam 308 prior to the elimination reaction (Scheme 117, table 25).

Reagents and conditions: (a) conditions in table 25

Scheme 117: Lactam Reduction Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing agent in THF (equiv.)</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>Result/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BH₃THF (3)</td>
<td>-78</td>
<td>6</td>
<td>308 recovered</td>
</tr>
<tr>
<td>2</td>
<td>BH₃THF (3)</td>
<td>0</td>
<td>4</td>
<td>308 recovered</td>
</tr>
<tr>
<td>3</td>
<td>BH₃THF (3)</td>
<td>R.T.</td>
<td>4</td>
<td>308 recovered</td>
</tr>
<tr>
<td>4</td>
<td>BH₃THF (3) Reflux</td>
<td></td>
<td>1</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>5</td>
<td>BH₃, Me₂S (2)</td>
<td>-78</td>
<td>6</td>
<td>308 recovered</td>
</tr>
<tr>
<td>6</td>
<td>BH₃, Me₂S (2)</td>
<td>0</td>
<td>4</td>
<td>308 recovered</td>
</tr>
<tr>
<td>7</td>
<td>BH₃, Me₂S (2)</td>
<td>R.T.</td>
<td>4</td>
<td>308 recovered</td>
</tr>
<tr>
<td>9</td>
<td>DIBAIH (5)</td>
<td>-78</td>
<td>6</td>
<td>308 recovered</td>
</tr>
<tr>
<td>10</td>
<td>DIBAIH (5)</td>
<td>0</td>
<td>4</td>
<td>308 recovered</td>
</tr>
<tr>
<td>11</td>
<td>DIBAIH (5)</td>
<td>R.T.</td>
<td>4</td>
<td>Decomposition of 308</td>
</tr>
</tbody>
</table>

Table 25: Carbamate Reduction Attempts

Performing the reaction using borane complexes or DIBAIH at low temperatures was unsuccessful and only starting material was recovered. At reflux, borane dimethylsulfide gives a complex mixture of products (entry 4) and with DIBAIH the lactam 308 was resistant at room temperature but at reflux, reduction of the methyl ester was observed in the crude ¹H NMR spectra.
2.3.8 Elimination Reaction Attempts.

Due to the difficulty in performing a chemoselective reduction of lactam 308, attempts were made to perform the elimination reaction. The elimination reaction has been previously applied in the synthesis of α-methyl kainic acid published by the Clayden group in 2003 (Scheme 118).

\[
\begin{align*}
\text{HO} & \quad \overset{\text{a}}{\longrightarrow} \quad \text{H} \\
\text{MeO}_2\text{C} & \quad \text{NBoc} \\
\text{C} & \quad \text{O}_2\text{Me} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

Reagents and conditions: (a) i. N-phenylselenylphthalimide, n-Bu₃P, R.T., 2 h; ii. H₂O₂, pyridine (1 drop), THF, R.T., 12 h, 64% over 2 steps.

Scheme 118: Previous Conditions Reported for the Elimination Reaction

The trichloroacetate group in lactam 308 was removed using pyridine in THF/Methanol. The crude material was subjected to elimination conditions using N-phenylselenylphthalimide (Scheme 119).

\[
\begin{align*}
\text{HO} & \quad \overset{\text{a}}{\longrightarrow} \quad \text{H} \\
\text{MeO}_2\text{C} & \quad \text{NBoc} \\
\text{C} & \quad \text{O}_2\text{Me} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

Reagents and conditions: (a) i. pyridine, THF, MeOH, R.T., 1h; ii. N-phenylselenylphthalimide, n-Bu₃P, R.T., 2 h; iii. H₂O₂, pyridine (1 drop), THF, R.T., 12 h.

Scheme 119: Elimination Reaction Attempt

The elimination reaction was unsuccessful giving a mixture of compounds in which alkene peaks were not observed in the crude \(^1\)H NMR spectrum.
2.3.9 Summary and Further Work.

It was not possible to extensively research and develop conditions for the final stages of this route. Therefore the synthesis has yet to be defined as a viable route to the alkyne intermediate.

In summary, it has been shown that a regioselective Baeyer-Villiger oxidation can be performed using enone 104 to generate a single lactone isomer 252, but as a synthetic route to the target alkyne (298) suffers from reduction and oxidation complications (Scheme 120).

\[
\begin{align*}
\text{119} & \xrightarrow{a} 66\% \quad \text{166} & \xrightarrow{b} 73\% \quad \text{92} & \xrightarrow{c} 85\% \quad \text{104} & \xrightarrow{d} 54\% \\
\text{307} & \xrightarrow{g} 95\% \quad \text{254} & \xrightarrow{f} 58\% \quad \text{269} & \xrightarrow{e} 93\% \quad \text{252} \\
\text{308} & \xrightarrow{h} 38\% \quad \text{298} & \\
\end{align*}
\]

Reagents and conditions: (a) benzyl bromide, K₂CO₃, DMF; (b) p-anisoyl chloride, DCM, Et₃N; (c) i. LDA, THF 0 ℃, 2 h; (d) mCPBA, DCM, 48 h; (e) H₂, Pd/C, EtOAc; (f) i. TFA, reflux, 1 h; ii. Boc₂O, DMAP (cat.), Et₃N, DCM, 18 h; (g) 1M NaOMe, -78 ℃, 2 h; (h) i. RuCl₃, NaIO₄, EtOAc/H₂O/CH₃CN, 24 h; ii. TMS-CHN₂, toluene/methanol, 1 h

Scheme 120: Summary of Baeyer-Villiger Route
2.4 Silicon-Mediated Fragmentation Route.

An alternative route to the desired alkyne was proposed by Dr. G. Lemière, who was associated to this project. This was to utilise the Baeyer-Villiger oxidation reaction and perform a Peterson olefination type fragmentation reaction to introduce alkene functionality (A). The retrosynthetic route is shown in scheme 121.

The conversion of the alkene B to the alkyne A was not addressed in the Baeyer-Villiger route but this transformation could be performed directly using a halogenation reaction, followed by a double elimination using base. Alternatively the alkene can be converted to the aldehyde and then using either the Corey-Fuchs reaction or the Seyferth-Gilbert homologation reaction to synthesise the alkyne. As the latter is more frequently used in organic synthesis, typically in natural product synthesis as it uses milder conditions, it was chosen as the primary sequence of steps to give the desired alkyne. Alkene B could be the product of a Peterson elimination type reaction of lactone C, which would be made from a regioselective Baeyer-Villiger oxidation reaction. The TMS group could be introduced by a silylcupration reaction on enone 104 which is the product of the dearomatising cyclisation with para-methoxy benzamide 92 (section 2.1.2).

Using a silicon-directed oxidative fragmentation reaction was previously studied within the Clayden group by B. Read, with the intention of incorporating a trisubstituted double bond in the isodomoic acid side chain stereospecifically.
Disappointingly, model studies proved poor yielding without adequate control of the alkene’s configuration. Fragmentation reactions using either 313a or 313b resulted in the formation of the *cis* alkene 314 (Scheme 122). It was hoped that this methodology would enable the synthesis of both *cis* and *trans* alkenes.

**Scheme 122: Previous Work Involving Silicon-Directed Fragmentations**

Due to the poor reported yields for the model fragmentations, no further fragmentation attempts were made using silicon. The use of a Peterson type elimination reaction was not explored during the oxidative fragmentation research and so was considered as a potential step towards the synthesis of the desired alkyne. The proposed forward synthesis is shown in scheme 123.

**Scheme 123: Proposed Synthetic Route to the Desired Alkyne**
This would be an attractive and concise route to the desired alkyne in which the TMS group indirectly protects the double bond in order to perform the aromatic oxidation reaction and is then reformed as a result of the fragmentation.

2.4.1 Model Studies.

The Peterson elimination reaction is a commonly used reaction in organic chemistry to form either a cis or trans alkene from a β-silylcarbanion.\textsuperscript{119} It was our aim to perform a similar type of reaction using a lactone to form the corresponding acid derivative and alkene. There are many examples of this type of fragmentation in the literature and a related reaction is shown in scheme 124.\textsuperscript{120}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme124.png}
\caption{Related Fragmentation Reaction}
\end{figure}
\end{center}

\textit{Reagents and conditions:} (a) mCPBA, DCM; (b) HCl (cat.), MeOH

Grandi \textit{et. al.} showed that it was possible to perform a regioselective Baeyer-Villiger oxidation to give lactone 323 in 86\% yield.\textsuperscript{119(b)} The formation of a single isomer was explained by the characteristic ability of silicon to stabilise a positive charge at the β position promoting preferential migration.\textsuperscript{121} The fragmentation reaction followed using acidic conditions to give alkene 324 in 71\% yield.

This chemistry was transferred to a model lactone 325 to confirm that the fragmentation was viable in our bicyclic substrates (Scheme 125).

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme125.png}
\caption{Silicon-Mediated Fragmentation Model Studies}
\end{figure}
\end{center}

\textit{Reagents and conditions:} (a) MeLi, CuCN, HMPA, HMD, -78 °C, THF, 2 h; (b) mCPBA, DCM, 48 h; (c) HCl (cat.), MeOH

120
A 1,4-addition of a silylcuprate was performed on known enone 104
(section 2.1.2) to give ketone 315 in 10% yield. It was thought that the cause for
the poor yield was due to potential decomposition of the cuprate intermediate.
The silylcupration reaction is discussed and optimised in section 2.4.2.

As discussed in section 2.3.1, performing the Baeyer-Villiger oxidation
reaction on a bicyclic substrate bearing a substitution in the β' position results in a
regioselective oxidation. With this information and the additional stability gained
from the presence of the silicon group, it was unsurprising to achieve a
regioselective Baeyer-Villiger oxidation reaction on ketone 315 to give lactone
325. The fragmentation was performed on the crude lactone 325 using
HCl/methanol conditions to successfully give alkene 326 in 77% over two steps.

2.4.2 Optimisation of the Silylcupration Reaction.

Since the late 1950’s it has been known that silyl anions undergo smooth
addition to a variety of electrophiles.122 Research by Fleming et. al has shown that
it is possible to perform silyl conjugate addition efficiently using copper cyanide
by transmetallation of the silyllithium species with copper (I) to form the more
reactive cuprate.123

In the model study shown in section 2.4.1, the 1, 4-addition reaction using
a silyl cuprate resulted in a poor 10% yield, which was unacceptable for an early
step in this total synthesis. Previous research by B. Read showed that it was
possible to perform a 1,4-addition reaction using PhMe2SiLi in a one pot, two step
protocol (Scheme 126).124, 86

![Scheme 126](image)

<table>
<thead>
<tr>
<th>Method 1</th>
<th>Method 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.53</td>
<td>0.62</td>
</tr>
<tr>
<td>0.84</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Relative amounts in crude product mixture compared with 328 as observed by proton NMR
Chapter 2: Results and Discussion

Reagents and conditions: **Method 1**: Et₂Zn, PhMe₂SiLi, THF, 0 °C, 10 min; 328, TMSCl, THF, –78 °C, 1 h; R.T., 1.5 h; sat. aq. NH₄Cl soln.; **Method 2**: Et₂Zn, PhMe₂SiLi, THF, 0 °C, 5 min; 328, THF, –78 °C, 40 min; TMSCl, –78 °C, 30 min; R.T., 1.5 h; sat. aq. NH₄Cl soln.

Scheme 126: Previous 1,4-Addition Reactions

The aim of this research was to isolate the silyl enol ether 330, but this proved unstable and susceptible to hydrolysis giving mixtures of 329 and 330. Attempts were not made to optimise a procedure for ketone 329, but this research highlighted the use of TMSCl to trap the cuprate intermediate in-situ in as the more stable silyl enol ether which could be hydrolysed to give the desired ketone 315.

The silylcupration reaction on enone 104 was performed with freshly distilled reagents, in the presence of TMSCl as the trapping agent (Scheme 127).

![Scheme 127: Optimised Silylcupration](image)

Reagents and conditions: (a) MeLi, CuCN, HMPA, HMD, -78 °C, THF, TMSCl, 2 h; (b) 3M HCl:THF

The reaction was cleaner by TLC analysis which identified two products. Using acidic conditions the crude intermediate was hydrolysed to give the desired product 315 in 86% after purification and a disilylated by-product 332 in 10% yield. It has been reported by Barrett *et. al.* that the formation of the disilylated product is as a result of an undesired reaction between newly formed Me₃SiLi (337) and unreacted HMD, 335 (Scheme 128).
The formation of the disilane can be suppressed by the use one equivalent of HMD. The importance of reaction stoichiometry on the balance between the formation of the pentamethyldisilyllithium and trimethylsilyllithium is consistent with the mechanism of lithiation in scheme 128.

The addition of the TMS group to enone 104 was diastereoselective and the stereochemistry was confirmed by X-ray crystallography of the product 315 (Fig 16). It was previously assumed that attack at this position was from the exo face which is caused by the ring junction stereochemistry.
2.4.3 Cumyl Removal and Boc Protection.

In order to perform the phenyl oxidation reaction it was necessary to remove the cumyl protecting group and replace it with one which was stable to the oxidation conditions. Therefore the next step in the synthesis was to remove the cumyl group which was achieved quantitatively using TFA (Scheme 129).

```
\[
\begin{align*}
315 & \xrightarrow{\text{quant.}} 341 \\
\text{Reagents and conditions: (a) TFA, reflux, 1 h.}
\end{align*}
\]

Scheme 129: Cumyl Removal
```

It has been previously reported that performing the phenyl oxidation reaction on a free amide results in complex mixtures of products\(^{89}\) and so protection of the amide with a Boc group was necessary.

Performing the Boc protection of amide 341 using Boc anhydride gave the desired product 316 in 77% yield. Enol carbonate formation was observed in two isomeric by-products 342a and 342b in a 2:1 ratio, as an inseparable mixture in 9% yield (Scheme 130).

```
\[
\begin{align*}
341 & \xrightarrow{77\%} 316 \\
342a & \quad 342b \\
\text{Reagents and conditions: (a) Boc_2O, DCM, DMAP (cat.), Et_3N, 18 h, 342a/342b 9\%.}
\end{align*}
\]

Scheme 130: Boc Protection Reaction
2.4.4 Phenyl Oxidation.

The phenyl oxidation was then carried out using Sharpless’s oxidation conditions (Scheme 131).

![Scheme 131: Phenyl Oxidation Reaction](image)

Reagents and conditions: (a) i. RuCl₃, NaIO₄, EtOAc/H₂O/CH₂CN, 24 h; ii. TMS-CHN₂, MeOH/toluene, 1 h

The desired methyl ester 343 was successfully isolated in 76% yield over the two steps. Pleasingly, this was the highest reported yield within the Clayden group for an arene oxidation in these types of substrates.

2.4.5 Baeyer-Villiger Oxidation of Methyl Ester 343.

It has been discussed that it is possible to perform a regioselective Baeyer-Villiger oxidation reactions in these types of bicyclic structures (sections 2.3.1 and 2.4.1). The next step in the synthesis was to perform the Baeyer-Villiger oxidation on substrate 343 using mCPBA (Scheme 132).

![Scheme 132: Baeyer-Villiger Oxidation Reaction](image)

Reagents and conditions: (a) mCPBA, DCM, 48 h

The reaction successfully gave the desired lactone 344 in quantitative yield as a single regioisomer, which was identified by ¹H NMR analysis showing one set of product peaks that were assigned to isomer 344.
2.4.6 Silicon-Mediated Fragmentation of Lactone 344.

The next step in the synthesis was to perform the fragmentation reaction on silylated lactone 344. There are several conditions available to perform the desired fragmentation, most commonly used are HCl/methanol\(^{119(b)}\), boron trifluoride etherate\(^{119(c)}\) or using a fluoride source (e.g. TBAF).\(^{119(e)}\)

Various conditions using boron trifluoride and fluoride sources were explored to develop conditions for the fragmentation (Scheme 133, table 26).

![Scheme 133: Silicon-Mediated Fragmentation Studies](image)

**Reagents and conditions:** (a) i. conditions in table 26; ii. TMS-CHN\(_2\), methanol/toluene (step ii. not used in entry 7)

**Table 26: Silicon-Mediated Fragmentation Studies**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Temp.</th>
<th>345</th>
<th>346(^{1})</th>
<th>347</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBAF, THF</td>
<td>R.T.</td>
<td>0%</td>
<td>quant.</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>TBAF, THF</td>
<td>-78 °C</td>
<td>0%</td>
<td>quant.</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>TBAT, THF(^{125})</td>
<td>-78 °C</td>
<td>0%</td>
<td>86%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>BF(_3).OEt(_2), DCM</td>
<td>-78 °C</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>5</td>
<td>BF(_3).OEt(_2), DCM</td>
<td>-78 °C – R.T.</td>
<td>0%</td>
<td>0%</td>
<td>quant.*</td>
</tr>
<tr>
<td>6</td>
<td>BF(_3).OEt(_2), DCM</td>
<td>-30 °C</td>
<td>0%</td>
<td>0%</td>
<td>quant.*</td>
</tr>
<tr>
<td>7</td>
<td>HCl/MeOH</td>
<td>R.T.</td>
<td>0%</td>
<td>0%</td>
<td>32%</td>
</tr>
</tbody>
</table>

* no purification, single product by NMR analysis; \(^{1}\) single isomer obtained with undefined geometry

Fragmentation was observed using TBAF at room temperature but isomerisation of the desired product was the only product isolated as a single isomer (346, entry 1). Performing the reaction at a low temperature or using TBAT (a known non-basic fluoride source),\(^{124}\) also results in the formation of isomer 346 (entries 2 and 3). No fragmentation was observed using BF\(_3\).OEt\(_2\) at -78 °C (entry 4), but allowing the reaction to warm to room temperature gave the
desired reaction with loss of the Boc protecting group (entry 5). To avoid the loss of the Boc group the reaction was performed at -30 °C but was unsuccessful and resulted in the formation of free amide 347 (entry 6). Under HCl/methanol conditions, loss of the Boc protecting group was observed and free amide 347 was isolated in 32% yield (entry 7).

Protection of the free amide 347 was considered and attempted using either Boc anhydride or Boc-ON conditions. The protection was successful, however isomerisation of the alkene was unavoidable and methyl ester 346 was formed as a single product (Scheme 134).

![Scheme 134: Reprotection Attempts](image)

Reagents and conditions: (a) Boc₂O, DMAP (cat.), Et₃N, DCM, R.T., 18 h or Boc-ON, THF, LDA, 0 °C - R.T., 2 h

Scheme 134: Reprotection Attempts

The unwanted isomerisation was rationalised by the formation of a stable enolate intermediate which can then promote isomerisation of the alkene for increased stabilisation through conjugation (Scheme 135).

![Scheme 135: Possible Mechanism for Isomerisation](image)

Reagents and conditions: (a) i. TBAF, THF, -78 °C; ii. NH₄Cl aq.

Scheme 135: Possible Mechanism for Isomerisation

The results of this research had shown that the fragmentation reaction was working well. However, due to the presence of the amide carbonyl, isomerisation of the alkene was unavoidable.
In order to prevent this undesired isomerisation, lactam reduction was considered prior to fragmentation. Performing the lactam reduction on lactone 344 was deemed too difficult based on the similar attempts during the Baeyer-Villiger oxidation route (section 2.3.2), so it was decided to open the lactone ring and then attempt the lactam reduction prior to performing a Peterson elimination (Scheme 136).\textsuperscript{118(a)}

![Scheme 136: Peterson Elimination Mechanism](image)

Conditions to perform the methanolation of lactone 344 were studied based on the previous work carried out in section 2.3.4 (Scheme 137).

![Scheme 137: Lactone Methanolation](image)

Reagents and conditions: (a) conditions in table 27

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp.</th>
<th>351</th>
<th>352a</th>
<th>352b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOMe, MeOH, 2 h</td>
<td>-78 °C</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>2</td>
<td>NaOMe, MeOH</td>
<td>-78 °C – R.T.</td>
<td>0%</td>
<td>1*</td>
<td>1*</td>
</tr>
<tr>
<td>3</td>
<td>NaOMe, MeOH, 2 h</td>
<td>0 °C</td>
<td>0%</td>
<td>1*</td>
<td>1*</td>
</tr>
<tr>
<td>4</td>
<td>NaOMe, MeOH, 2 h</td>
<td>-30 °C</td>
<td>0%</td>
<td>60%</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>NaOMe, MeOH, 2 h</td>
<td>-60 °C</td>
<td>87%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* ratio determined by crude NMR analysis

Table 27: Methanolation Conditions

Performing the reaction at -78 °C resulted in no reaction (entry 1). Allowing the reaction to warm to room temperature gave an inseparable mixture of products 352a and 352b as a result of Boc migration and epimerisation at the
C4 position (entry 2). At -30 °C the epimerisation was stopped and only Boc migration (352a) was observed in 60% yield (entry 4). Finally the desired product was obtained by performing the reaction at -60 °C giving alcohol 351 in 87% yield.

2.4.7 Lactam Reduction.

It has been discussed in both the Eschenmoser and the Baeyer-Villiger oxidation routes that the reduction of the lactam functionality is a challenging transformation. The target of this transformation was to reduce the, evidently resistant, lactam without the undesired ester reduction. A recent publication by Jung et. al. detailing the total synthesis of (–)-kainic acid and (–)-allokainic acid via a stereoselective C-H insertion, report a similar chemoselective lactam reduction using DIBAl-H at reduced temperature followed by hemiaminal cleavage using Et₃SiH (Scheme 138).¹²⁶

![Scheme 138: Reported Lactam Reduction](image)

Reagents and conditions: (a) i. DIBAIH, THF, -78 °C, 1 h; ii. MsCl, Et₃N, iii. Et₃SiH, BF₃·OEt₂, -78 °C, 2 h

The three step procedure was used to reduce alcohol 351, which resulted in a complex mixture of products that were difficult to purify (Scheme 139).

![Scheme 139: Lactam Reduction Attempt](image)

Reagents and conditions: (a) i. DIBAIH, THF, -78 °C, 1 h; ii. MsCl, TEA, iii. Et₃SiH, BF₃·OEt₂, -78 °C, 2 h

Attempts to characterise any of the products proved difficult, however mass spectrometry data of the crude material suggested the formation of the
cyclised substrate 356 by intramolecular hemiaminal displacement. The formation of this bicycle could explain the failed mesylation and aminol cleavage attempts.

An alternative stage in the route to perform the lactam reduction was in substrate 343, as the phenyl oxidation was already completed therefore avoiding α oxidation (see section 2.2.6). Various different reducing agents were used in an attempt to reduce lactam 343 chemoselectively (Scheme 140, table 28).

![Scheme 140: Amide Reduction Attempts](image)

_**Table 28: Amide Reduction Attempts***

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing Agent (equiv.)</th>
<th>Temp.</th>
<th>Time (hours)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BH₃, Me₂S, THF</td>
<td>R.T.</td>
<td>1</td>
<td>92% 358</td>
</tr>
<tr>
<td>2</td>
<td>BH₃, THF</td>
<td>R.T.</td>
<td>1</td>
<td>88% 358</td>
</tr>
<tr>
<td>3</td>
<td>BH₃, THF</td>
<td>Reflux</td>
<td>2</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>4</td>
<td>BH₃, Me₂S, THF</td>
<td>Reflux</td>
<td>1</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>5</td>
<td>DIBAL, THF</td>
<td>0 °C</td>
<td>4</td>
<td>358*</td>
</tr>
<tr>
<td>6</td>
<td>DIBAL, THF</td>
<td>R.T.</td>
<td>2</td>
<td>359*</td>
</tr>
<tr>
<td>7</td>
<td>LiAlH₄, THF</td>
<td>-78 °C</td>
<td>6</td>
<td>47% 359</td>
</tr>
<tr>
<td>8</td>
<td>LiEt₃BH, THF</td>
<td>0 °C</td>
<td>2</td>
<td>358*</td>
</tr>
<tr>
<td>9</td>
<td>LiEt₃BH, THF</td>
<td>R.T.</td>
<td>2</td>
<td>Complex mixture of products</td>
</tr>
</tbody>
</table>

* no purification, single product by NMR analysis

Borane complexes at room temperature and DIBAIH at 0 °C gave only ketone reduction in alcohol 358 (entries 1 and 2) and decomposition under reflux. Diol 359 was observed when performing the reduction with LiAlH₄ at -78 °C or DIBAIH at R.T. (entries 6 and 7). Using LiEt₃BH (section 2.2.2) at 0 °C gave ketone reduction only (entry 8) and at room temperature resulted in a complex mixture of products which no longer contains the methyl ester by NMR analysis (entry 9).
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The results in table 28 suggest that the conditions required to reduce the lactam will also result in the unwanted reduction the methyl ester (Fig. 18).

Figure 18: Order of Carbonyl Susceptibility to Reduction

Performing a global reduction followed by alcohol protection was considered but would have involved a number of additional steps. A possible solution would be to reduce the reactivity of the ester carbonyl, enabling the use of harsher reduction conditions. This could be achieved by synthesising a more hindered ester which would decrease the susceptibility of reduction.

Literature searches revealed that performing a chemoselective lactam reduction in the presence of a tert-butyl ester group was commonly achieved. Reducing agents for this reaction include LiEt₃BH, DIBAIH and borane dimethylsulfide complex.

The tert-butyl ester 361 was synthesised by esterification of the acid which was the product of the phenyl oxidation reaction. Various conditions were explored to obtain good yields for the esterification (Scheme 141, table 30).

Reagents and conditions: (a) i. RuCl₃, NaIO₄, EtOAc/H₂O/CH₃CN, R.T., 24 h; (b) conditions in table 29

Scheme 141: tert-Butyl Esterification Attempts
Chapter 2: Results and Discussion

Table 29: tert-Butyl Esterification Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp.</th>
<th>Time (hours)</th>
<th>Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc₂O, DMAP (cat.), Et₃N, DCM&lt;sup&gt;128&lt;/sup&gt;</td>
<td>R.T.</td>
<td>18</td>
<td>44% 361</td>
</tr>
<tr>
<td>2</td>
<td>tert-butanol (1 equiv.), DCC (1 equiv.), Et₃N, DCM&lt;sup&gt;129&lt;/sup&gt;</td>
<td>0 °C</td>
<td>2</td>
<td>52% 361</td>
</tr>
<tr>
<td>3</td>
<td>tert-butanol (2 equiv.), DCC (1 equiv.), Et₃N, DCM</td>
<td>0 °C – R.T.</td>
<td>18</td>
<td>60% 361</td>
</tr>
<tr>
<td>4</td>
<td>2-methylpropene, H₂SO₄, DCM&lt;sup&gt;130&lt;/sup&gt;</td>
<td>-78 °C – R.T.</td>
<td>4</td>
<td>360</td>
</tr>
</tbody>
</table>

* % yield over two steps

The desired tert-butyl ester 361 was successfully synthesised using either Boc anhydride or tert-butanol in 44% and 52% yield respectively (entries 1 and 2). Using excess equivalents of tert-butanol gave the desired ester 361 in an improved 60% yield over 2 step (entry 3).

The tert-butyl ester 361 was subjected to various reduction conditions detailed in table 30 (Scheme 142).

Scheme 142: Lactam Reduction Attempts

Reagents and conditions: (a) conditions in table 2.29

Entry | Conditions | Temp. | Time (hours) | Result* |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc₂O, DMAP (cat.), Et₃N, DCM&lt;sup&gt;128&lt;/sup&gt;</td>
<td>R.T.</td>
<td>18</td>
<td>44% 361</td>
</tr>
<tr>
<td>2</td>
<td>tert-butanol (1 equiv.), DCC (1 equiv.), Et₃N, DCM&lt;sup&gt;129&lt;/sup&gt;</td>
<td>0 °C</td>
<td>2</td>
<td>52% 361</td>
</tr>
<tr>
<td>3</td>
<td>tert-butanol (2 equiv.), DCC (1 equiv.), Et₃N, DCM</td>
<td>0 °C – R.T.</td>
<td>18</td>
<td>60% 361</td>
</tr>
<tr>
<td>4</td>
<td>2-methylpropene, H₂SO₄, DCM&lt;sup&gt;130&lt;/sup&gt;</td>
<td>-78 °C – R.T.</td>
<td>4</td>
<td>360</td>
</tr>
</tbody>
</table>
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Table 30: Lactam Reduction Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp.</th>
<th>Equiv.</th>
<th>Time (hours)</th>
<th>Result/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BH$_3$.DMS, THF</td>
<td>0 °C</td>
<td>3</td>
<td>4</td>
<td>quant 363</td>
</tr>
<tr>
<td>2</td>
<td>BH$_3$.DMS, THF</td>
<td>R.T.</td>
<td>3</td>
<td>4</td>
<td>quant 363</td>
</tr>
<tr>
<td>3</td>
<td>BH$_3$.DMS, THF</td>
<td>50 °C</td>
<td>3</td>
<td>2</td>
<td>Complex mixture of products*</td>
</tr>
<tr>
<td>4</td>
<td>DIBAIH, THF</td>
<td>-78 °C</td>
<td>5</td>
<td>2</td>
<td>quant. 363</td>
</tr>
<tr>
<td>5</td>
<td>DIBAIH, THF</td>
<td>0 °C</td>
<td>5</td>
<td>2</td>
<td>Complex mixture of products*</td>
</tr>
<tr>
<td>6</td>
<td>LiEt$_3$BH, THF</td>
<td>-78 °C</td>
<td>3</td>
<td>3</td>
<td>quant. 363</td>
</tr>
<tr>
<td>7</td>
<td>LiEt$_3$BH, THF</td>
<td>0 °C</td>
<td>3</td>
<td>3</td>
<td>362¥</td>
</tr>
</tbody>
</table>

* ester reduction observed in crude ¹H NMR * mixture of diastereoisomers in ¹H NMR

The lactam proved resistant to borane DMS complex, DIBAIH and LiEt$_3$BH at low temperatures giving alcohol 363 (entries 1, 2, 4 and 6). At higher temperatures borane DMS and DIBAIH gave complex mixtures of products with observed ester reduction (entries 3 and 5). Pleasingly, using LiEt$_3$BH at 0 °C resulted in the chemoselective reduction of the lactam giving a mixture of diol diastereoisomers 362.

Due to purification difficulties it was not possible to purify the diol diastereoisomers 362 and so the crude material was subjected to the hemiaminal cleavage and oxidation prior to purifying ketone 364 (Scheme 143).

Scheme 143: Optimised Reduction/Oxidation Reaction

The desired amine 364 was isolated in 32% over the three step procedure. The reaction was repeated performing the LiEt$_3$BH reduction at 0 °C with a hydrogen peroxide quench to remove all traces of the borane complex, which gave the desired amine 364 in an improved 50% yield over the 3 steps.
2.4.8 Baeyer-Villiger Oxidation of Ester 364.

The Baeyer-Villiger oxidation reaction was performed on amine 364 using \( m \)CPBA (Scheme 144). The desired lactone 365 was successfully isolated in 86% yield as a single regioisomer. The over-oxidised by-product 365b was also observed in 10% yield which was inseparable from 365.

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (a) \; m \text{CPBA, DCM, R.T., 48 h} \\
\text{Scheme 144: Baeyer-Villiger Oxidation}
\end{align*}
\]

2.4.9 Silicon-Mediated Fragmentation of Lactone 365.

Having successfully synthesising lactone 365 without the lactam functionality, the product of the fragmentation reaction should not isomerise. The fragmentation reaction was performed on lactone 365 using TBAF (Scheme 145).

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (a) \; \text{i. TBAF, THF, 0 °C, 1 h;} \quad (b) \; \text{Boc}_2\text{O, DMAP, DCM, Et}_3\text{N}. \\
\text{Scheme 145: Silicon-Mediated Fragmentation Reaction}
\end{align*}
\]

The reaction gave the desired fragmentation without isomerisation and after tert-butyl esterification using \( \text{Boc}_2\text{O} \) and DMAP, amine 367 was isolated in 60% yield over two steps. The formation of the tert-butyl ester was introduced with the intention of performing a global acidic deprotection once the functionalisation of the alkyne was complete.
2.4.10 Ozonolysis of Alkene 367.

The final stages of the route to the alkyne intermediate were to convert the alkene to the alkyne via the aldehyde (as discussed in section 2.4). The ozonolysis was performed on alkene 367 using ozone generated from oxygen in THF at -78 °C (Scheme 146).\textsuperscript{131}

![Scheme 146: Ozonolysis Reaction](image)

Reagents and conditions: (a) i. O\textsubscript{3}, DCM, -78 °C, 30 min; ii. DMS, R.T., 18 h.

The reaction was complete in less than 30 minutes, indicated by the formation of a light blue solution. After the reductive quench of the trioxolane intermediate, aldehyde 368 was isolated in 98% yield.

2.4.11 Alkyne Formation.

The final step in the synthesis was to convert the aldehyde to the alkyne. Literature research highlighted two favourable reaction conditions to perform this transformation. The Corey-Fuchs reaction which uses triphenylphosphine and tetrabromomethane to make a dibromoalkene (376) that is then this is converted to the terminal alkyne (380) using butyllithium (Scheme 147).\textsuperscript{115}

![Scheme 147: Corey-Fuchs Reaction Mechanism](image)
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Alternatively, the Seyferth-Gilbert homologation reaction can be used to synthesis alkynes from aldehydes using dimethylphosphonodiazomethane with potassium tert-butoxide. These conditions generate the dimethyl (diazomethyl)phosphonate anion 382, which performs the transformation by an initial Horner-Wadsworth Emmons reaction followed by α-elimination and carbene rearrangement to give the desired alkyne (Scheme 148).

\[
\begin{align*}
R-H & \xrightarrow{\text{K}_2\text{CO}_3, \text{MeOH}, 0 \degree \text{C}, 1 \text{ h}} \text{R}^- \text{OP(OMe)}_2\text{N}_2 \xrightarrow{\text{H}_2\text{O}} \text{R}_2\text{P(O)(OMe)}_2\text{N}_2
\end{align*}
\]

This procedure has been improved by the introduction of the more stable Ohira-Bestmann reagent 386, which generates anion 382 in-situ (Scheme 149).

The main advantage of this reaction compared with the Corey-Fuchs procedure is that milder reaction conditions are used which tolerate a wider range of functional groups. Therefore, the Ohira-Bestmann conditions were chosen for the transformation using aldehyde 368 (Scheme 150).

\[
\begin{align*}
\text{NBoc} & \xrightarrow{\text{dimethyl-1-diazo-2-oxopropylphosphonate, K}_2\text{CO}_3, \text{MeOH}, 0 \degree \text{C}, 1 \text{ h}} \text{NBoc} + \text{NBoc}
\end{align*}
\]

Reagents and conditions: (a) dimethyl-1-diazo-2-oxopropylphosphonate 386, K$_2$CO$_3$, methanol, 0 °C, 1 h

Scheme 150: Ohira-Bestmann Reaction Attempt
The reaction was complete in less than one hour and after purification alkyne 387 was isolated in 66% yield. Unfortunately, due to the presence of rotamers the characterisation proved difficult and so it was not possible to prove if epimerisation at the C4 position had occurred. Therefore, a global deprotection of 387 was performed on a small scale to clarify the NMR spectrum (Scheme 151).

Reagents and conditions: (a) TFA, H₂O, R.T., 1 h

Scheme 151: Global Deprotection Reaction

The reaction was successful in giving alkyne 379 in quantitative yield. Disappointingly, NMR analysis showed two alkyne peaks at 2.79ppm and 2.68ppm in a 57:43 ratio of epimers (Fig. 19).

This confirmed the epimerisation at C4 had occurred and that new conditions were needed for the Ohira-Bestmann reaction.

Gennari et al. have also observed epimerisation in chiral aldehydes using the Ohira-Bestmann reaction. In this article it describes that epimerisation was observed due to the presence of excess potassium carbonate. To avoid the epimerisation, sodium methoxide was used to form the (diazomethyl)phosphonate anion 382 at -78 °C prior to the addition of the chiral aldehyde. This procedure
was transferred to aldehyde 368 and performed using freshly prepared sodium methoxide (Scheme 152).

Reagents and conditions: (a) dimethyl-1-diazo-2-oxopropylphosphonate 386 (5.2 eq.), NaOMe (5 eq.), THF, -78 °C, 1 h

Scheme 152: Modified Ohira-Bestmann Reaction

Pleasingly, this gave the desired alkyne 379a in 89% yield with no epimerisation (Fig. 20)

This data enabled the assignment of epimerised and the non-epimerised products, showing that epimerisation was favoured under previous conditions using potassium carbonate in methanol.
2.4.12 Enantioselective Synthesis.

The enantioselective dearomatising cyclisation reaction using para-methoxy benzamide 92 has previously been developed within the Clayden group for the total synthesis of (−)-kainic acid and (−)-isodomoic acid C.\textsuperscript{77,79} However, results from section 2.1.2 have shown the instability of the lithium enolate at high temperatures and so the procedure was modified to introduce the saturated ammonium chloride quench at 0 °C, increasing the overall yield (up to 66% after recrystallisation). The synthesis was repeated and enantiopure alkyne 379a was successfully obtained in 16 steps (Scheme 153).

Scheme 153: Enantioselective Synthesis of Alkyne Intermediate

Reagents and conditions: (a) benzyl bromide, K$_2$CO$_3$, DMF; (b) p-anisoyl chloride, DCM, Et$_3$N; (c) i. amine 112, THF, -78 °C - 0 °C; ii. 1M HCl aq.; (d) MeLi, CuCN, HMPA, HMD, -78 °C, THF, TMSCl, 2 h; ii. 1M HCl:THF; (e) i. TFA, reflux, 1 h; ii. Boc$_2$O, DCM, DMAP (cat.), Et$_3$N, 18 h; (f) i. RuCl$_3$, NaIO$_4$, EtOAc/H$_2$O/CH$_3$CN, R.T., 24 h; ii. tert-butanol (2 equiv.), DCC (1 equiv.), Et$_3$N, DCM; (g) i. LiEt$_3$BH, THF, 0 °C, 2 h; ii. Et$_3$SiH, BF$_3$OEt$_2$, THF, -78 °C, 2 h; iii. Dess-Martin period inane, DCM, R.T., 2 h; (h) mCPBA, DCM, R.T., 48 h; (i) i. TBAF, 0 °C, THF, 1h; ii. Boc$_2$O, DMAP, r-butanol; (j) i. O$_3$, DCM, -78 °C; ii. DMS, R.T., 18 h; (k) dimethyl-1-diazo-2-oxopropylphosphonate 386 (5.2 eq.), NaOMe (5eq.), THF, -78 °C, 1 h
2.4.13 Further Work.

Following the synthesis of enantiopure alkyne 387a (Scheme 153), the functionalisation was to be researched to synthesise the desired trisubstituted alkene using carbometallation chemistry (Scheme 154).

These studies have been conducted within the Clayden group by Dr. Toueg and Dr. Lemièré. Initially carboalumination chemistry developed by Negishi was considered as this is commonly used to form a trisubstituted alkene stereo- and regioselectively. Reactions were conducted on a model alkyne 390 to develop conditions prior to functionalising alkyne 387a (Scheme 155).

The reactions were unsuccessful and the lack of success was thought be due to the presence of the carbamate interfering with the functionalisation as there are limited examples of carboalumination chemistry using nitrogen containing substrates. To examine this reactivity issue a known reaction using 1-octyne was performed which showed that in the precence of the carbamate there was no observed reaction (Scheme 156).
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![Chemical structures and reactions]

Reagents and conditions: (a) i. AlMe₃, Cp₂ZrCl₂, H₂O; ii. HCl

Scheme 156: Standard Reactions

Carbomagnesiation catalysed by a Nickel complex developed by Snider was also considered for the functionalisation. However, the model alkyne proved resistant to these conditions and only starting material was recovered (Scheme 157).

![Chemical structures and reactions]

Reagents and conditions: (a) Ni(acac)₂, AlMe₃, MeMgBr, THF, 0 °C – R.T

Scheme 157: Carbomagnesiation Attempts

Due to the little success in carbometallation with nitrogen containing compounds a procedure suitable to these substrates was explored. In 1989, Lipshutz et al. reported a procedure for the formation of a trialkylstannylcuprate which can be used to functionalised alkynes. This procedure has since been applied to nitrogen protected alkynes by Capella et al. in 1991. This publication states that it is possible to perform the cupration with a methyl iodide quench to give isomers in a 95:5 ratio in 68% yield (Scheme 158).

![Chemical structures and reactions]

Reagents and conditions: (a) i. Bu₃Sn(Bu)Cu(CN)Li₂, THF, -78°C; ii. MeI, 95:5 397:398 (68% isolated 397)

Scheme 158: Regioselective Stannylcupration
This chemistry has been used in a number of different total syntheses to perform a regioselective addition of a methyl group forming a trisubstituted alkene. Therefore, attempts to functionalise model alkyne 390 were performed using Bu₃Sn(Bu)Cu(CN)Li₂ and quenching with methyl iodide (Scheme 159).

Reagents and conditions: (a) i. Bu₃Sn(Bu)Cu(CN)Li₂, THF, -78 °C; ii. Mel

Scheme 159: Stannylcupration Attempts

Pleasingly, this resulted in a regioselective cis addition giving stannane 399 as a single regioisomer in 90% yield after purification. With the success of this reaction it is envisaged to perform a Stille coupling with an appropriate halide partner (Scheme 160).

Reagents and conditions: (a) Pd catalyst

Scheme 160: Stille Coupling Reactions with Potential Coupling Partners

Initial model coupling reactions have looked promising giving the desired coupling in good yields. It is hoped that the success of the model studies can be transferred to enantiopure alkyne 387a and after a global deprotection complete the divergent synthesis to (–)-isodomoic acid B, E and F.

Depending on the success of this strategy to obtain the trisubstituted alkene, further work would need to develop the functionalisation to obtain the E isomer in order to develop the total synthesis of domoic acid and (–)-isodomoic acids A and D.
Appendix 1.

A.1 Application of Flow Chemistry to the Dearomatising Cyclisation.

Flow chemistry is a well established technique that is particularly used for large scale manufacture, in which a chemical reaction is run continuously using non-reactive tubing and pumps. There are many advantages of using flow chemistry compared to batch chemistry as reaction times and stoichiometries can be defined by the concentration of the reagents and the ratio of their flow rates. Within the field of research, Ley et al have demonstrated the use of flow chemistry to complete the total synthesis of oxomaritidine in 40% yield in 5 hours.142

Within the Clayden group, the dearomatising cyclisation of para-methoxy benzamide 92 has been extensively researched. Based on the discovery that the cyclisation can be high yielding reaction if performed at a suitable temperature (section 2.1.2), it was applied to flow chemistry in an attempt to generate large quantities of pure dearomatised methyl ether 95 (Scheme 161).

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (a) \text{ LDA, THF} \\
\text{Scheme 161: Dearomatising Cyclisation for Flow Chemistry}
\end{align*}
\]

The flow reactor was set-up using two syringe pumps containing cooled LDA in THF and benzamide 92 in THF (Fig. 21). These solutions were then pumped through a set length of stainless steel tubing at a controlled temperature (using a “cold finger”) and flow rate. Once the reaction was quenched with saturated ammonium chloride solution, the crude material was analyzed by LC-MS.
Table 31 shows the initial attempts to apply the cyclisation reaction to flow chemistry, using 5 feet of stainless steel coil (0.75 mm diameter) and performing the reaction at four different temperatures and three different flow rates.
The initial results were not encouraging as large amounts of starting benzamide 92 was recovered with poor yields of the desired methyl ether 95. The results suggest that at higher temperatures with a slow flow rate would give an acceptable percentage of the desired product (entries 11, 12 and 13). Increasing the temperature further was considered but due to the instability of the intermediate lithium enolate 103, was avoided. In an attempt to increase the

### Temperature: -20 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow Rate (mg/ml)</th>
<th>mg/ml</th>
<th>Res. Time (mins)</th>
<th>95 (%)</th>
<th>92 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fast (0.135)</td>
<td>2.39</td>
<td>2.5</td>
<td>15.35</td>
<td>79.14</td>
</tr>
<tr>
<td>2</td>
<td>Mid (0.064)</td>
<td>2.64</td>
<td>5</td>
<td>16.91</td>
<td>93.68</td>
</tr>
<tr>
<td>3</td>
<td>Slow (0.034)</td>
<td>2.44</td>
<td>10</td>
<td>15.63</td>
<td>85.11</td>
</tr>
</tbody>
</table>

### Temperature: -10 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow Rate (mg/ml)</th>
<th>mg/ml</th>
<th>Res. Time (mins)</th>
<th>95 (%)</th>
<th>92 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Fast (0.135)</td>
<td>1.94</td>
<td>2.5</td>
<td>12.44</td>
<td>80.37</td>
</tr>
<tr>
<td>5</td>
<td>Mid (0.064)</td>
<td>1.92</td>
<td>5</td>
<td>12.31</td>
<td>83.38</td>
</tr>
<tr>
<td>6</td>
<td>Slow (0.034)</td>
<td>2.10</td>
<td>10</td>
<td>13.47</td>
<td>84.15</td>
</tr>
</tbody>
</table>

### Temperature: 0 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow Rate (mg/ml)</th>
<th>mg/ml</th>
<th>Res. Time (mins)</th>
<th>95 (%)</th>
<th>92 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Fast (0.135)</td>
<td>1.97</td>
<td>2.5</td>
<td>12.64</td>
<td>78.80</td>
</tr>
<tr>
<td>8</td>
<td>Mid (0.064)</td>
<td>2.15</td>
<td>5</td>
<td>13.77</td>
<td>82.05</td>
</tr>
<tr>
<td>9</td>
<td>Slow (0.034)</td>
<td>2.06</td>
<td>10</td>
<td>13.21</td>
<td>85.04</td>
</tr>
<tr>
<td>10</td>
<td>Very Slow (0.017)</td>
<td>2.50</td>
<td>20.00</td>
<td>16.01</td>
<td>65.98</td>
</tr>
</tbody>
</table>

### Temperature: 10 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow Rate (mg/ml)</th>
<th>mg/ml</th>
<th>Res. Time (mins)</th>
<th>95 (%)</th>
<th>92 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Fast (0.067)</td>
<td>5.31</td>
<td>5</td>
<td>21.22</td>
<td>/*</td>
</tr>
<tr>
<td>12</td>
<td>Mid (0.034)</td>
<td>6.52</td>
<td>10</td>
<td>26.09</td>
<td>/*</td>
</tr>
<tr>
<td>13</td>
<td>Slow (0.017)</td>
<td>6.98</td>
<td>20</td>
<td>27.92</td>
<td>/*</td>
</tr>
</tbody>
</table>

* Actual % of SM not available

Table 31: Flow Chemistry with 5 Foot Coil (0.75 mm Diameter) at Different Temps. and Flow Rates
percentage of product the coil length was increased to 15 foot (0.75 mm diameter) and the reaction performed with reduced flow rates. Table 32 shows the results from these experiments.

**Temperature: 0 °C**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow Rate (ml/min)</th>
<th>mg/ml</th>
<th>Res. Time (mins)</th>
<th>95 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fast (0.203)</td>
<td>6.51</td>
<td>5</td>
<td>39.03</td>
</tr>
<tr>
<td>2</td>
<td>Mid (0.101)</td>
<td>5.30</td>
<td>10</td>
<td>31.78</td>
</tr>
<tr>
<td>3</td>
<td>Slow (0.050)</td>
<td>5.19</td>
<td>20</td>
<td>31.16</td>
</tr>
</tbody>
</table>

**Temperature: 10 °C**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow Rate (ml/min)</th>
<th>mg/ml</th>
<th>Res. Time (mins)</th>
<th>95 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Fast (0.203)</td>
<td>4.55</td>
<td>5</td>
<td>27.32</td>
</tr>
<tr>
<td>5</td>
<td>Mid (0.101)</td>
<td>4.20</td>
<td>10</td>
<td>25.18</td>
</tr>
</tbody>
</table>

Table 32: Flow Chemistry with 15 Feet of Coil (0.75 mm Diameter)

These results suggest that by increasing the coil length the production of product 95 increases (entry 1). However, reducing the flow rate or increasing the temperature causes a decrease in the reported percentage yield (entries 4 and 5).

The study has shown that the coil length of the reactor is a contributing factor to the amount of product produced. The reported poor conversion of benzamide 92 could be a result of a number of different factors of which the main concerns are listed below.

1. Poor mixing: the turbulence in the reactor coil may not be high enough to force the LDA and the starting material to mix adequately and the results observed are that of a reaction at the interface of these two liquid as they pass through the coil.

2. Incorrect residence time/coil length: the results suggest that a longer coil length promotes conversion and therefore 15 feet may be too short, as reducing the flow rate has proved unsuccessful.
Unfortunately, a micro-mixer was unavailable which would have eliminated the poor mixing theory, so increasing the coil length further was the only alternative. The flow reactor was altered to introduce a 33 foot Teflon tube of diameter 1.5 mm. The results are shown in table 33.

Temperature: 0 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow Rate (ml/min)</th>
<th>mg/ml</th>
<th>Res. Time (mins)</th>
<th>95 (%)</th>
<th>92 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fast (3.534)</td>
<td>7.12</td>
<td>5</td>
<td>66.50</td>
<td>1.80</td>
</tr>
<tr>
<td>2</td>
<td>Mid (1.767)</td>
<td>7.19</td>
<td>10</td>
<td>67.18</td>
<td>1.73</td>
</tr>
<tr>
<td>3</td>
<td>Slow (0.884)</td>
<td>7.07</td>
<td>20</td>
<td>66.04</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Table 33: Flow Chemistry with 33 Foot Coil (1.5 mm Diameter)

These results were more encouraging and showed that flow rate was having little affect on the conversion but by increasing the coil length had a major effect on the formation of the desired product 95, increasing the yield to 67% with <2% starting material. LC-MS data showed an increase in baseline impurities, which could be responsible for the moderate yields obtained.

Due to time limitations it was not possible to attempt further runs at lower temperature using coil lengths between 15 and 33 feet. However, this study has shown that with the correct flow reactor set-up, the dearomatising cyclisation reaction can be applied to flow chemistry to generate pure material continuous.
Appendix 2.

A.2 Alternative Approaches to the Desired Alkyne Intermediate.

Three challenging routes to synthesise the desired alkyne have been discussed in sections 2.2, 2.3 and 2.4. Described in appendix 3 are alternative routes considered for the synthesis of the alkyne.

A.2.1 Grignard Fragmentation Reaction.

A recent publication by Dudley et al. has shown the use of a Grignard reaction to perform a tandem carbanion addition which fragments to give alkyne 403 (Scheme 162).\textsuperscript{143}

\[
\begin{align*}
\text{Reagents and conditions:} & \quad \text{(a) } & \text{ Tf}_2\text{O (1.2 eq.), pyridine (2 eq.), DCM; (b) } & \text{R-M, THF, -78} ^\circ\text{C – R.T.}
\end{align*}
\]

Scheme 162: Grignard Fragmentation Reaction

These conditions were used on enone 177 (bearing a \textit{t}-butyl group) in an attempt to perform the fragmentation using phenyl magnesium bromide to initial the elimination of methoxide (Scheme 163).

\[
\begin{align*}
\text{Reagents and conditions:} & \quad \text{(a) } & \text{PhMgBr, THF, R.T. 18 h}
\end{align*}
\]

Scheme 163: Fragmentation Attempt
Subjecting enone 177 to phenyl magnesium bromide at room temperature resulted in the addition to the carbonyl group followed by enone formation to give enone 404 in 82% yield, which was thought to be a lower energy pathway compared to the fragmentation.

No further attempts were made to complete the fragmentation reaction using a Grignard reagent on enone 177. Changing the leaving group to the reported triflate was considered but required a number of addition steps to make the precursor which was disfavoured for the synthesis.

### A.2.2 Cleavage of Enone 104.

An alternative approach to the alkyne intermediate was to employ a diol cleavage reaction to give a functionalised intermediate. This reaction has been previous reported by Gonzalez et. al in the synthesis of (+)- and (−)-isocarvone (Scheme 164).

\[
\begin{array}{c}
\text{405} \\
\text{a} \quad 38\% \\
\text{406}
\end{array}
\]

*Reagents and conditions: (a) i. H^+, THF/H_2O; ii. NaIO_4, 0 °C*

Scheme 164: Alternative Route to Aldehyde Intermediate

Initial research into suitable conditions for the dihydroxylation of enone 104 were explored using osmium tetroxide (Scheme 165, table 34).

\[
\begin{array}{c}
\text{104} \\
\text{a} \\
\text{407} \\
\text{408}
\end{array}
\]

*Reagents and conditions: (a) conditions in table 34*

Scheme 165: Dihydroxylation Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>407</th>
<th>408</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OsO_4, NMO, Acetone/H_2O (8:1)</td>
<td>0%</td>
<td>82%</td>
</tr>
<tr>
<td>2</td>
<td>OsO_4, Acetone/H_2O (8:1)</td>
<td>48%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 34: Dihydroxylation Attempts
Attempting the dihydroxylation using osmium tetroxide and NMO was unsuccessful, resulting in the formation of a mono-alcohol 408 which was thought to have been as a result of intermediate enolate hydroxylation. By removing the NMO from the reaction it was possible to obtain the desired diol 407 in 48% after purification.

The next step was to perform the diol cleavage using sodium periodate to give the desired aldehyde 409 (Scheme 164).

The reaction resulted in a mixture of products thought to be that of the desired aldehyde 409 and a cyclised product 410 by crude NMR analysis. Purification proved difficult and so it was not possible to confirm the presence of either product. It was thought that in solution there could be an equilibrium between the two products and so the crude material was subjected to esterification conditions using TMS-diazomethane to promote the formation of the desired aldehyde 409. Unfortunately, this was unsuccessful and caused decomposition of the material.

Due to the little success in obtaining the desired aldehyde 409 and the concerns of epimerisation at the C4 position caused by increased acidity of the newly formed 1,3-dicarbonyl, this route was not researched further.
3.1 Experimental Procedures.

3.1.1 General Procedures.

Proton and carbon NMR spectra were recorded on Varian Unity 300, Bruker DPX 360, Varian Unity 400 or Bruker AMX 500 Fourier Transform instruments. Proton NMR data are presented as follows: chemical shift $\delta$ (in ppm relative to $\delta_{\text{TMS}} = 0$), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, hept = heptet, m = multiplet, br = broad, obs = obscured), coupling constant $J$ (in Hz, values rounded to nearest 0.5 Hz) and assignment (based on chemical shift, integration, coupling pattern and COSY, DEPT, HMQC and HMBC experiments where necessary).

Infrared spectra were recorded on an ATi Matson Genesis Series Fourier Transform spectrophotometer.

Low resolution electron impact and chemical ionisation mass spectra were recorded on a Waters Trio 2000 quadrupole mass spectrometer. Low resolution electrospray mass spectra were recorded on a Micromass Platform II mass spectrometer. High resolution mass spectra were recorded on a Thermo Finnigan MAT 95XP mass spectrometer.

Melting points were determined using Electrothermal apparatus and are uncorrected.

Analytical thin layer chromatography was carried out on pre-coated UV$_{254}$ plates, with visualisation by ultraviolet light at 254 nm, potassium permanganate, para-anisaldehyde or dodecamolybdophosphoric acid (PMA).

Flash column chromatography$^{145}$ was carried out using Fluorochem Davisil 40–63 µm 60 Å silica, under a positive pressure by means of compressed air. The use of the term in this report implies removal of the solvent under reduced pressure after purification.

Reagents and solvents were purified by standard means.$^{146}$ Dichloromethane was distilled from calcium hydride and subsequently stored under a nitrogen atmosphere; tetrahydrofuran and diethyl ether were distilled from
sodium wire and benzophenone and subsequently stored under a nitrogen atmosphere. Triethylamine was distilled from and stored over potassium hydroxide. \( N, N'-\text{Dimethyl}-N, N'-\text{propylene urea} \) (DMPU) was distilled, under reduced pressure, from calcium hydride, and subsequently stored over molecular sieves. \( N, N'-\text{Dimethylformamide} \) (DMF) was distilled from molecular sieves, and subsequently stored under a nitrogen atmosphere. Chlorotrimethylsilane was distilled onto molecular sieves. ‘Petrol’ refers to the fraction of petroleum ether that boils between 40 °C and 60 °C, and was distilled before use. All other chemicals were used as received, except where otherwise noted in the experimental text.

All experiments were performed in anhydrous conditions under an atmosphere of nitrogen, unless otherwise noted in the experimental text. Apparatus was oven-dried and standard techniques were employed in handling air-sensitive materials.
3.1.2 Experimental Procedures for Section 2.1:

\[ \text{N-Benzyl-N-tert butyl-2-methoxybenzamide 160} \]

To a bi-phasic mixture of DCM (15 ml) and aq. sodium hydroxide (3M, 15 ml), \( N \)-\( (\text{tert}-\text{butyl}) \) benzylamine (6.22 ml, 33.6 mmol) was added. \( o \)-Anisoyl chloride (5.73 g, 33.6 mmol) was added dropwise at 0 °C. The reaction was stirred overnight at room temperature, then extracted with DCM (2 x 20 ml). The combined organic fractions were dried over magnesium sulfate and the solvents evaporated under reduced pressure. Recrystallisation from hot ethyl acetate and petrol gave the title product (9.16 g, 92 %) as a colourless solid, m.p 108-112 °C (lit.,\(^{147}\) 109-111 °C); \( R_f \) 0.47 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) 2963 and 1639 (film)/cm\(^{-1} \); \( ^1\)H NMR (300MHz; CDCl\(_3\)) \( \delta_H \): 7.34-7.17 (7H, m, ArH), 6.86-6.82 (2H, m, ArH) 4.57-4.45 (2H, bm, H3, H3'), 3.81 (3H, s, OMe), 1.50 (9H, s, \text{tBu}). All data consistent with literature\(^{147}\)

\[ \text{N-benzyl-N-tert-butyl-4-methoxybenzamide 162} \]

To a bi-phasic solution of DCM (15 ml) and aq. sodium hydroxide (3M, 15 ml), \( N \)-\( \text{-benzyl-tert-butylamine} \) 166 (6.23 ml, 33.6 mmol) was added. The bi-phasic solution was stirred vigorously and cooled to 0 °C, then \( p \)-anisoyl chloride (4.55 ml, 33.6 mmol) was added dropwise. The reaction was left to stir overnight at room temperature and then extracted with DCM (2 x 100 ml). The combined organic fractions were washed with water (100 ml), dried over magnesium sulfate and the solvent removed under reduced pressure. Purification by crystallisation from ethyl acetate and petrol gave the title compound (7.29 g, 73 %) as a colourless solid, m.p 130-132 °C (lit.,\(^{148}\) 98-99 °C); \( R_f \) 0.70 (2:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 3000 and 1609; \( ^1\)H NMR (300MHz; CDCl\(_3\)) \( \delta_H \): 7.45-7.22 (7H, m, ArH), 6.83 (2H, m,
ArH), 4.68 (2H, s, H3, H3'), 3.80 (3H, s, OMe), 1.51 (9H, s, tBu). All data consistent with literature.  

N-Benzyl-N-tert-butyl-2, 4-methoxybenzamide 165. To a round-bottom flask containing oxalyl chloride (20 ml), 2, 4-dimethoxybenzoic acid 163 (3.02 g, 16.7 mmol) and a drop of DMF was added. The solution was stirred for 12 hours. The solvents were removed under reduced pressure. The remaining yellow solid (1.74 g, 8.67 mmol) was dissolved in DCM with N-(tert-butyl) benzylamine (1.55 ml, 7.72 mmol) and triethylamine (1.61 ml, 11.6 mmol). The solution was stirred for 18 hours and then extracted with DCM (2 x 20 ml). The combined organic fractions were dried over magnesium sulfate and the solvents evaporated under reduced pressure. Purification by crystallisation from ethyl acetate and petrol (3:1 petrol/ethyl acetate) gave the title compound (2.02 g, 67 %) as a colourless solid, m.p 106-108 °C, Rf 0.62 (1:1 petrol/ethyl acetate); νmax (film)/cm⁻¹ 2976 and 1639; ¹H NMR (500MHz; CDCl₃) δH: 7.28-7.26 (2H, m, ArH), 7.21-7.17 (3H, m, ArH), 7.15-7.14 (1H, m, ArH), 6.38-6.36 (2H, m, ArH), 4.52-4.51 (2H, bm, H3, H3'), 3.79 (3H, s, OMe), 3.74 (3H, s, OMe) and 1.48 (9H, s, tBu); ¹³C NMR (75 MHz, CDCl₃) δC: 171.4 (C=O), 161.2 (COMe), 156.6 (COMe), 140.6 (Ar), 128.6 (2xAr), 128.5 (2xAr), 126.9 (Ar), 126.6 (Ar), 122.1 (Ar), 104.7 (Ar), 98.9 (Ar), 58.3 (C(CH₃)₃), 55.9 (OCH₃), 55.6 (OCH₃), 51.4 (C3) and 29.1 (C(CH₃)₂); m/z (Cl⁺) 328 (100%, MH⁺); Found MH⁺ 328.1906, C₂₀H₂₅NO₃ requires MH⁺ 328.1907.

(3R,3aR,7aR)-2-tert-Butyl-3,3a-dihydro-7-methoxy-3-phenyl-2H-isoinodol 1(7aH)-one 166a. A solution of LDA was formed by addition of n-butyllithium (1.7 M solution in diethyl ether, 2.92 ml, 5.04 mmol) to diisopropylamine (0.80 ml, 5.71 mmol) in THF (14 ml) at 0 °C. After twenty
minutes stirring at 0 °C, a yellow solution had formed and a solution of N-benzyl-N-tert-butyl-2-methoxybenzamide 160 (1.00 g, 3.36 mmol) and DMPU (2.44 ml, 20.2 mmol) in THF (16 ml) was added dropwise. The solution turned red. The reaction was quenched by addition of saturated aq. ammonium chloride solution after one hour of stirring at room temperature under nitrogen. The solution returned to pale yellow. The reaction was extracted with diethyl ether (3 x 20 ml), and the combined organics washed with brine (40 ml), dried over magnesium sulfate and concentrated under reduced pressure. Recrystallisation from hot ethyl acetate and petrol gave the title product (382 mg, 39 %) as a colourless solid, m.p. 172-174 °C (lit., 148 171-172 °C), Rf 0.54 (1:1 petrol/ethyl acetate); υmax (film)/cm⁻¹ 2963 and 1672; ¹H NMR (300MHz; CDCl₃) δH: 7.45-7.25 (5H, m, ArH), 5.98 (1H, dd, J 6.0, 2.0, H8), 5.33 (1H, dd, J 10.0, 2.0, H9), 4.98 (1H, d, J 6.0, H7), 4.81 (1H, s, H3), 3.72 (3H, s, OMe), 3.37 (1H, d, J 9.0, H5), 3.14 (1H, dt, J 9.0, 2.0, H4) and 1.39 (9H, s, tBu). Also obtained (3R,3aS,7aS)-2-tert-butyl-3,3a-dihydro-7-methoxy-3-phenyl-2H-isooindol-1(7aH)-one 166b as a side product. Purification by recrystallisation of mother liquor of above crystallisation gave a colourless solid, m.p 102-106 °C; Rf 0.33 (1:1 petrol/ethyl acetate); υmax (film)/cm⁻¹ 2970 and 1687; ¹H NMR (300MHz; CDCl₃) δH: 7.30- 6.88 (5H, m, ArH), 5.43 (1H, dd, J 9.0, 6.0, H8), 5.00 (1H, dd, J 9.0, 5.0, H9), 4.82 (1H, d, J 8.0, H7), 4.53 (1H, d, J 6.0, 2.0, H3), 3.54 (3H, s, OMe), 3.38 (1H, dd, J 13.0, 2.0, H5), 3.26 (1H, dd, J 8.0, 5.0, H4) and 1.29 (9H, s, tBu). All data consistent with literature.¹¹⁰(b),¹⁴⁸

(3R, 3aR,7aR)-2-tert-Butyl-2, 3, 3a, 4-tetrahydro-3-phenyl-7aH-isooindole-1, 7-dione 170. A solution of LDA was formed by addition of n-butyllithium (1 M solution in diethyl ether, 24.0 ml, 25.3 mmol) to diisopropylamine (3.93 ml, 28.6 mmol) in THF (70 ml) at 0 °C. After twenty minutes stirring at 0 °C, a yellow solution had formed and a solution of N-benzyl-N-tert-butyl-2-
methoxybenzamide 165 (5.00 g, 16.8 mmol) and DMPU (1.21 ml, 10.0 mmol) in THF (80 ml) was added dropwise. The solution turned red. The reaction was quenched by addition of saturated aq. ammonium chloride solution after one hour of stirring at room temperature under nitrogen. The solution returned to pale yellow. The reaction was extracted with diethyl ether (3 x 100 ml), and the combined organics washed with aq. 3M hydrochloric acid (200 ml) and brine (200 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (1:1 petrol/ethyl acetate) gave the title compound (1.43 g, 36 %) as a colourless solid, m.p 118-122 °C (lit., 80,148 119-120 °C); Rf 0.21 (1:1 petrol/ethyl acetate); νmax (film)/cm⁻¹ 2974 and 1694; ¹H NMR (300MHz; CDCl₃) δH: 7.45-7.25 (5H, m, ArH), 6.96 (1H, ddd, J 10.0, 6.0, 3.0, H8), 6.13 (1H, dd, J 10.0, 3.0, H7), 4.60 (1H, s, H3), 3.64 (1H, d, J 7.0, H5), 2.82-2.66 (2H, m, H9, H9'), 2.48-3.31 (1H, m, H4) and 1.42 (9H, s, tBu). All data consistent with literature. ¹¹⁰(b),80,148

((3S,3aS,7aR)-2-tert-butyl-3-phenyl-2,3,3a,4-tetrahydro-1H-isoxindole-1,5(7aH)-dione 171. ¹¹⁰(b) A solution of LDA was formed by addition of n-butyllithium (2.3 M solution in diethyl ether, 2.19 ml, 5.05 mmol) to a solution of diisopropylamine (0.80 ml, 5.72 mmol) in THF (14 ml) at 0 °C. The solution was left to stir for thirty minutes under an atmosphere of nitrogen. N-Benzyl-N-tert-butyl-4-methoxybenzamide (1.00 g, 2.78 mmol) in THF (16 ml) was added slowly to the LDA solution by cannula at 0 °C. The reaction turned red. It was allowed to warm to room temperature, and left the stir for one hour. Addition of saturated aq. ammonium chloride solution quenched the reaction. The mixture was extracted with diethyl ether (2 x 50 ml). The combined organic fractions were washed with aq. 6M hydrochloric acid (50 ml) then saturated aq. sodium bicarbonate solution (50 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by crystallisation from hot ethyl acetate and petrol gave the title compound (391 mg, 41 %) as a colourless solid, m.p 150-156
°C (lit., 148 151-154 °C); Rf 0.46 (2:1 petrol/ethyl acetate); ν_max (film)/cm⁻¹ 2975 and 1678; ¹H NMR (300MHz; CDCl₃) δ_H: 7.39-7.37 (2H, m, ArH), 7.32-7.29 (1H, m, ArH), 7.26-7.24 (2H, m, ArH), 6.99 (1H, dd, J 5.5, 10.5, H6), 6.11 (1H, dd, J 1.5, 10.0, H7), 4.42 (1H, s, H3), 3.62-3.59 (1H, m, H5), 2.72-2.66 (2H, m, H4, H9), 2.54 (1H, dd, J 13.5, 17.0, H9') and 1.36 (9H, s, tBu). All data consistent with literature.¹¹⁰(b),¹⁴⁸ (R)-2-tert-butyl-5-methoxy-3-phenylisoindolin-1-one 172 was isolated as a minor impurity, m.p 148-152 °C, Rf 0.7 (1:1 petrol/ethyl acetate); ν_max (film)/cm⁻¹ 1678 and 1364; (500 MHz, CDCl₃) δ_H: 7.70 (1H, d, J 10.5, ArH), 7.33-7.20 (5H, m, ArH), 6.88 (1H, dd, J 10.5, 3.0, ArH), 6.47 (1H, d, J 3.0, ArH), 5.59 (1H, s, H3), 3.72 (3H, s, OMe) and 1.44 (9H, s, tBu); (75 MHz, CDCl₃) δ_C: 169.9 (NC=O), 162.7 (C=O), 148.8 (Ar), 141.1 (Ar), 129.0 (2xAr), 127.8 (2xAr), 126.2 (Ar), 124.7 (Ar), 124.5 (Ar), 114.6 (Ar), 107.2 (Ar), 64.6 (C3), 55.8 (CH₃), 55.5 (C(CH₃)₃) and 28.6 (C(CH₃)₃); m/z (EI) 318.2 (100 %, MH⁺); Found MH⁺ 318.1470, C₁₉H₂₁NO₂ requires MNa⁺ 318.1475;

Benzyl-(1-methyl-1-phenyl-ethyl)-amine 173.⁷⁹ Benzyl bromide (3.29 ml, 27.7 mmol), potassium carbonate (3.83 g, 27.7 mmol) and cumylamine (3.20 ml, 25.1 mmol) were dissolved in dry DMF (25 ml) and left to stir for 18 hours under nitrogen. The reaction was diluted with diethyl ether (35 ml) and washed with water (2 x 35 ml). The layers were separated and the organic layer was dried over sodium sulfate and the solvents were removed under reduced pressure. Purification by flash chromatography (5:1→1:1 petrol/ethyl acetate) gave the title compound (4.17 g, 66 %) as clear oil, Rf 0.49 (3:1 petrol/ethyl acetate); ν_max (film)/cm⁻¹ 3060, 3026 and 2971; ¹H NMR (300MHz, CDCl₃) δ_H: 7.64-7.24 (10H, m, ArH), 3.56 (2H, s, H1, H1’) and 1.60 (6H, s, 2xMe). All data consistent with literature.⁷⁹
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**N-benzyl-4-methoxy-N-(2-phenylpropan-2-yl)benzamide 92.**\(^{77(a)}\) To a round-bottom flash, 2, 4-Dimethoxybenzoic acid (3.02 g, 16.6 mmol) was dissolved in oxalyl chloride (14.4 ml, 165 mmol) with a drop of dry DMF added. The reaction was left to stir for twelve hours at room temperature under nitrogen. The oxalyl chloride was removed under reduced pressure and the resulting acid chloride was dried under high vacuum. The acid chloride (1.74 g, 8.67 mmol), amine 173 (1.55 g, 7.72 mmol) and triethylamine (1.61 ml, 11.6 mmol) were dissolved in dry DCM (20 ml) and stirred for eighteen hours under nitrogen. The reaction was quenched by addition of water (20 ml). The mixture was extracted with DCM (2 x 20 ml). The combined organic fraction were dried over magnesium sulfate and concentrated under reduced pressure to give the title compound (2.48 g, 80 %) as a colourless solid which was very unstable to acid conditions, m.p. 118-119 °C (lit.,\(^{79}\) 118-119 °C); \(R_f\) 0.50 (2:1 petrol/ethyl acetate); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1639 and 1606; \(^1\text{H NMR}\) (300MHz, CDCl\(_3\)) \(\delta_H\): 7.52-7.22 (12H, m, ArH), 6.85 (2H, d, \(J\) 9.0, ArH), 4.85 (2H, s, H3, H3'), 3.81 (3H, s, OMe) and 1.75 (6H, s, 2xMe); All data consistent with literature.\(^{79}\)

\[\text{MeO} \quad \text{N} \quad \text{Ph} \]

(3S,3aS,7aR)-5-methoxy-3-phenyl-2-(2-phenylpropan-2-yl)-2,3,3a,7a-tetrahydro-1H-isodindol-1-one 95. A solution of LDA was formed by addition of \(n\)-butyllithium (2.50 M solution in diethyl ether, 10.0 ml, 25.1 mmol) to diisopropylamine (4.0 ml, 28 mmol) in dry THF (120 ml) at -40 °C. The solution was left to stir of twenty minutes under nitrogen until a pale yellow colour had formed. A solution of benzamide 92 (6.00 g, 16.7 mmol) in THF (100 ml) was then added to the LDA, dropwise at -40 °C. The solution was allowed of stir under nitrogen for two hours, and then quenched by addition of saturated aq.
ammonium chloride solution, after which the pale yellow colour returned. The product was extracted with diethyl ether (150 ml). The aqueous layer was extracted with diethyl ether (2 x 100 ml) then the combined organic fractions were dried over magnesium sulfate and the solvents removed under reduced pressure. Purification by flash column chromatography (4:1 petrol/ethyl acetate) gave the title compound (4.75 g, 79 %) as a pale yellow amorphous solid, $R_f$ 0.83 (1:1 petrol/ethyl acetate); $v_{\text{max}}$ (film)/cm$^{-1}$ 1688 and 1226; $^1$H NMR (400MHz, CDCl$_3$) $\delta$H: 7.39-7.15 (10H, m, ArH), 5.89-5.81 (2H, m, H6, H7), 4.71 (1H, d, J 3.0, H3), 4.54 (1H, m, H9), 3.60 (3H, s, OMe), 3.48 (1H, ddd, J 1.0, 4.5, 11.0, H5), 3.12 (1H, dt, J 3.0, 11.0, H4), 1.81 (3H, s, Me) and 1.38 (3H, s, Me); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 175.0 (NC=O), 153.4 (COCH$_3$), 147.2 (Ar), 143.7 (Ar), 128.9 (2xAr), 128.0 (2xAr), 127.7 (Ar or C6), 126.4 (Ar or C6), 125.7 (2xAr), 125.4 (2xAr), 124.9 (Ar), 124.2 (C7), 92.4 (C9), 60.1 (C3), 54.3 (C(CH$_3$_2)Ph), 42.9 (C5), 41.2 (C4), 29.7 (C(CH$_3$_2)Ph) and 27.3 (C(CH$_3$_2)Ph); m/z (CI) 382.2 (100 %, MH$^+$); Found MH$^+$ 360.1954, C$_{24}$H$_{25}$NO$_2$ requires MH$^+$ 360.1958

(3S,3aS,7aR)-3-phenyl-2-(2-phenylpropan-2-yl)-2,3,3a,4-tetrahydro-1Hisoindole-1,5(7aH)-dione 104.$^{77(a)}$

**Method 1:** A solution of LDA was formed by addition of $n$-butyllithium (2.40 M solution in diethyl ether, 4.8 ml, 11.5 mmol) to diisopropylamine (1.86 ml, 13.3 mmol) in dry THF (80 ml) at 0 °C. The solution was left to stir of twenty minutes under nitrogen until a pale yellow colour had formed. A solution of amide 92 (3.19 g, 8.87 mmol) in THF (70 ml) was then added to the LDA, dropwise at 0 °C. A red colour formed. The solution was allowed of stir under nitrogen for one hour, then quenched by addition of saturated aq. ammonium chloride solution, after which the pale yellow colour returned. The product was extracted with diethyl ether (150 ml) and washed with hydrochloric acid (3M, 100 ml). The aqueous layer was extracted with diethyl ether (2 x 100 ml) then the combined
organic fractions were dried over magnesium sulfate and the solvents removed under reduced pressure. Purification by flash column chromatography (3:1 petrol/ethyl acetate) gave the title compound (1.90 g, 62%) as a pale yellow solid,

**Method 2:** Amide 92 (0.25 g, 0.696 mmol) was added to a solution of chiral amide 111 (0.24 g, 0.90 mmol) and n-butyllithium (1.8 mmol) in THF (20 ml) at -78 °C. The mixture was allowed to warm to room temperature and quenched with saturated ammonium chloride solution. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with 1M HCl solution and brine, dried over magnesium sulfate and the solvents removed under reduced pressure. Purification by flash column chromatography (3:1 petrol/ethyl acetate) gave the title compound (0.205 g, 85%). Analytical HPLC (β-Gem Regis), eluting with IPA and hexane (30:70) showed it to consist of 81% e.e of a mixture of two enantiomers, \( t_R \) 8.16 and 8.95 mins. Recrystallisation from ethyl acetate gave the title compound (0.157 g, 66%) of e.e >99%; \([\alpha]_{D}^{20} = -224 \ (c = 0.17, \text{CHCl}_3)\); m.p. 125-128 °C (lit., 149-127-128 °C); \( R_f \) 0.63 (2:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1680; \(^1\)H NMR (300MHz, CDCl\(_3\)) \( \delta_H \): 7.44-7.24 (10H, m, ArH), 6.92 (1H, dd, \( J 10.0, 5.0, \) H6), 6.16 (1H, dd, \( J 10.0, 2.0, \) H7), 4.47 (1H, d, \( J 2.5, \) H3), 3.67 (1H, dd, \( J 7.0, 2.5, \) H17), 2.77-2.68 (1H, m, H4), 2.66 (1H, dd, \( J 20.0, 8.0, \) H9), 2.51 (1H, dd, \( J 20.0, 12.0, \) H9), 1.85 (3H, s, Me) and 1.52 (3H, s, Me); All data consistent with the literature.\(^{79}\)

(3S,3aS,7aS)-2-\( \text{tert}-\)butyl-2,3,3a,4-tetrahydro-7-methoxy-3-phenyl-7aH-isoinodole-1,5-dione 177. A solution of LDA was formed by addition of \( n-\)butyllithium (2.2 M solution in diethyl ether, 2.09 ml, 4.59 mmol) to diisopropylamine (0.73 ml, 5.20 mmol) in THF (14 ml) at 0 °C. After twenty minutes stirring at 0 °C, a yellow solution had formed and a solution of \( N\)-benzyl-\( N\)-\( \text{tert}-\)butyl-2- methoxybenzamide 165 (1.00 g, 3.06 mmol) in THF (16 ml) was added dropwise. The solution turned red. The reaction was quenched by addition of saturated aq. ammonium chloride solution after one hour of stirring at room
temperature under nitrogen. The solution returned to pale yellow. The reaction was extracted with diethyl ether (2 x 50 ml), and the combined organics washed with aq. 3M hydrochloric acid (50 ml) and brine (50 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (1:1 petrol/ethyl acetate) gave the title compound (410 mg, 42%) as a colourless solid, \( R_f \) 0.48 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2963, 1753 and 1639; m.p. 195-197 °C; \(^1\)H NMR (500MHz; CDCl\(_3\)) \( \delta \)H: 7.39-7.36 (2H, m, ArH), 7.32-7.29 (1H, m, ArH) 7.26-7.25 (2H, m, ArH), 5.41 (1H, s, H7), 4.49 (1H, s, H3), 3.80 (3H, s, OMe), 3.57 (1H, d, J 6.5, H5), 2.73-2.63 (2H, m, H9, H4), 2.47 (1H, dd, 12.0, 15.5, H9') and 1.38 (9H, s, tBu). All data consistent with literature.\(^{77(a)}\)

\[ \text{N-benzyl-2,4-dimethoxy-N-(2-phenylpropan-2-yl)benzamide 178. To a round-bottom flash, 2, 4-Dimethoxybenzoic acid 163 (3.01 g, 16.6 mmol) was dissolved in oxalyl chloride (14.4 ml, 165 mmol) and a drop of dry DMF added. The reaction was left to stir for twelve hours at room temperature under nitrogen. The oxalyl chloride was removed under reduced pressure and the resulting acid chloride dried under high vacuum. The acid chloride 164 (1.74 g, 8.67 mmol), amine 166 (1.55 g, 7.72 mmol) and triethylamine (1.61 ml, 11.6 mmol) were dissolved in dry DCM (20 ml) and stirred for eighteen hours under nitrogen. The reaction was quenched by addition of water (20 ml). The mixture was extracted with DCM (2 x 20 ml). The combined organic fraction were dried over magnesium sulfate and concentrated under reduced pressure to give the title compound (2.02 g, 68%) as a colourless solid, m.p. 122-126 °C (lit.,\(^{89}\) 122-123 °C); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2976 and 1639; \(^1\)H NMR (300MHz, CDCl\(_3\)) \( \delta \)H: 7.52 (2H, d, J 8.0, ArH), 7.40-7.30 (9H, m, ArH), 6.44 (2H, m, ArH), 5.79 (2H, bs, H3, H3'), 3.90 (3H, s, OMe), 3.79 (3H, s, OMe), 1.73 (3H, bs, Me) and 1.64 (3H, bs, Me); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \)C: 170.2 (NC=O), 161.1 (COMe), 156.4 (COMe), }
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148.9 (Ar), 139.8 (Ar), 129.1 (2xAr), 128.3 (2xAr), 127.9 (Ar), 126.9 (2xAr), 126.8 (2xAr), 125.8 (Ar), 124.7 (Ar), 121.0 (Ar), 104.6 (Ar), 98.5 (Ar), 62.5 (C3), 55.5 (OCH₃), 55.3 (OCH₃), 51.5 (C(CH₃)₂Ph) and 29.6 (C(CH₃)₂Ph); m/z (CI) 390 (MH⁺, 100 %), 272 (MH⁺ - cumyl, 95 %); Found M⁺ 389.1994; C₂₅H₂₇NO₃ requires M⁺ 389.1991.

(3S,3aS,7aS)-2,3,3a,4-tetrahydro-7-methoxy-3-phenyl-2-(2-phenylpropan-2-yl)-7aH-isoindole-1,5-dione 180. A solution of LD was formed by addition of n-butyllithium (2.2M solution in ether, 2.95 ml, 6.47 mmol) to a solution of diisopropylamine (1.05 ml, 7.47 mmol) in dry THF (30 ml) at 0°C and left to stir for twenty minutes under nitrogen. A solution of the amide 178 (2.00 g, 4.98 mmol) in dry THF (30 ml) was added to the LDA dropwise at 0°C and stirred for one hour under nitrogen. The reaction was quenched by addition of saturated aq. ammonium chloride solution, then diluted with water (50 ml). The mixture was extracted with diethyl ether (2 x 50 ml) and the combined organic fractions were washed with hydrochloric acid (3M aq., 100 ml), dried over sodium sulfate then the solvents were removed under reduced pressure. Purification by flash chromatography (1:1, petrol/ethyl acetate) gave the title compound (1.11 g, 62%) as a colourless solid, m.p. 174-176 °C; νₘₚₙ (film)/cm⁻¹ 2979, 1699, 1656 and 1611; ¹H NMR (300MHz, CDCl₃) δH: 7.45-7.20 (10H, m, ArH), 5.40 (1H, s, H7), 4.51 (1H, s, H3), 3.77 (3H, s, OMe), 3.68 (1H, d, J 6.0, H5), 2.67 (2H, m, H4, H9), 2.48 (1H, dd, J 17.0, 13.0, H9'), 1.88 (3H, s, Me) and 1.57 (3H, s, Me), ¹³C NMR (75 MHz, CDCl₃) δC: 196.2 (C=O), 172.1 (NC=O), 169.5 (COMe), 145.4 (Ar), 140.8 (Ar), 129.0 (Ar), 128.1 (2xAr), 128.0 (2xAr), 127.0 (Ar), 125.6 (2xAr), 125.4 (2xAr), 102.9 (C7), 66.8 (C3), 59.6 (COMe), 56.3 (C(CH₃)₂Ph), 44.7 (C5), 41.8 (C4), 38.9 (C9), 27.8 (C(CH₃)₂Ph) and 26.9 (C(CH₃)₂Ph); m/z (Cl) 375 (M⁺, 100 %) 119 (cumyl, 75 %); Found M⁺ 375.1834; C₂₅H₂₇NO₃ requires M⁺ 375.1841.
3.1.3 Experimental Procedures for Section 2.2: Eschenmoser Fragmentation Route.

(3S,3aS,7aS)-2-tert-butyl-3-phenylhexahydro-1H-isindole-1,7(7aH)-dione 195. Enone 170 (50 mg, 0.177 mmol) was dissolved in THF (2 ml) and cooled to -78 °C. Lithium aluminium hydride (2M in THF, 0.17 ml, 0.35 mmol), was added dripwise and the reaction was left to stir for 1 hour. It was quenched by dilution with ethyl acetate (1 ml) and Rochelle’s salt solution (1 ml) and left to stir for 15 mins. The organic layer was extracted with ethyl acetate (2 x 10 ml). The combined organic fractions were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (1:1 petrol/ethyl acetate) gave the title compound (0.033 g, 66 %) as an amorphous solid, $R_f$ 0.8 (1:1 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2940, 1720 and 1680; $^1$H NMR (500MHz; CDCl$_3$) $\delta_H$: 7.36-7.33 (2H, m, ArH), 7.29-7.26 (1H, m, ArH), 7.21-7.19 (2H, m, ArH), 3.58 (1H, d, J 7.0, H5), 2.42-2.37 (2H, m, H4, H7), 2.34-2.26 (1H, m, H7'), 2.19-2.16 (1H, bm, H8), 2.07-2.01 (1H, bm, H8'), 1.67 (1H, qd, J 13.5, 3.0, H9), 1.57 (1H, qt, J 13.5, 3.5 H9') and 1.38 (9H, s, tBu); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_C$: 204.9 (C=O), 169.9 (NC=O), 141.5 (Ar), 129.0 (2xAr), 127.8 (Ar), 125.4 (2xAr), 67.2 (C3), 55.7 (C7), 55.3 (C(CH$_3$)$_3$), 46.3 (C5), 40.2 (C4), 28.9 (C9 or C8), 27.8 (C(CH$_3$)$_3$) and 23.4 (C8 or C9); m/z (Cl) 308.2 (100%, MNa$^+$); Found MNa$^+$ 308.1631, C$_{18}$H$_{23}$NO$_2$ requires MNa$^+$ 308.1621.
(3S,3aS,7aS)-2-tert-butyl-octahydro-7-hydroxy-3-phenylisoindol-1-one 196. A solution of enone 170 (50.0 mg, 0.17 mmol) in MeOH (4 ml) was cooled to 0 °C. Sodium borohydride (19.7 mg, 0.52 mmol) was added slowly and the solution was allowed to stir for 2 hour. The reaction was quenched with water (2 ml). The mixture was extracted with DCM (10 ml) and washed with water (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography eluting with 3:1 petrol-EtOAc afforded the title compound (44 mg, 90%) as an amorphous solid, \( R_f \) 0.26 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2935, 1692; \( ^1H \) NMR (400MHz; CDCl\(_3\)) \( \delta \): 7.38-7.34 (2H, m, ArH), 7.30-7.28 (1H, m, ArH), 7.23-7.21 (2H, m, ArH), 4.39 (1H, s, H3), 3.61-3.54 (1H, bm, H4), 3.11 (1H, dt, J 6.0, 6.0, H5), 2.05-1.93 (3H, m, H9, H6, H7), 1.76-1.71 (1H, m, H7'), 1.36 (9H, s, tBu) and 1.31-1.12 (3H, m, H8, H8', H9'); \( ^{13}C \) NMR (75MHz, CDCl\(_3\)) \( \delta \): 177.5 (NC=O) 141.4 (Ar), 128.8 (2xAr), 127.5 (Ar), 125.3 (2xAr), 69.9 (C6), 67.2 (C3), 54.9 (C(CH\(_3\))\(_3\)), 44.2 (C5), 42.3 (C4), 33.0 (C7), 29.2 (C8 or C9), 27.9 (C(CH\(_3\))\(_3\)) and 22.6 (C9 or C8); \( m/z \) (ES\(^+\)) 288.3, 310.1 (100%, MH\(^+\), MNa\(^+\)); Found MH\(^+\) 288.1969, C\(_{18}\)H\(_{25}\)NO\(_2\) requires MH\(^+\) 288.1958.

(3S,3aS,7aS)-2-tert-butyl-5-hydroxy-7-methoxy-3-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindol-1-one 198. A solution of enone 176 (50 mg, 15 mmol) in THF (4 ml) was cooled to -78 °C. Lithium aluminium hydride (18.2 mg, 47.9 mmol) was added slowly and the solution was allowed to stir for 1 hour. The reaction was quenched with water (2 ml). The mixture was extracted with diethyl ether (10 ml) and washed with water (10 ml), dried over magnesium sulfate and concentrated under reduced pressure to give the title compound (49 mg, 97 %) as a thin-film, \( R_f \) 0.44 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3602 and 1666; \( ^1H \)
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NMR (300MHz; CDCl₃) δH: 7.36-7.33 (2H, bs, ArH), 7.28-7.23 (3H, m, ArH), 4.77 (1H, bs, H7), 4.46 (1H, s, H3), 4.35 (1H, bm, H8), 3.63 (3H, s, OMe), 3.24 (1H, d, J 6.5, H5), 2.32 (1H, dt, J 12.0, 5.0, H9), 2.17 (1H, ddd, J 13.0, 6.5, 4.0, H4), 1.59 (1H, bs, OH), 1.51-1.44 (1H, m, H9'), and 1.35 (9H, s, tBu); ¹³C NMR (75 MHz, CDCl₃) δC: 172.7 (NC=O), 153.6 (C6), 142.2 (Ar), 128.9 (2xAr), 127.6 (Ar), 125.2 (2xAr), 100.6 (C7), 66.5 (C3), 65.9 (C8), 55.0 (OC₃H₃), 54.9 (C(CH₃)₃), 43.7 (C5), 41.5 (C4), 36.9 (C9) and 27.8 (C(CH₃)₃); m/z (ES⁺) 338 (100%, MNa⁺), Found MNa⁺ 338.1732, C₁₉H₂₅NO₃ requires MNa⁺ 338.1732.

(3S,3aS,7aS)-2-tert-butyl-3,3a,4,5-tetrahydro-7-methoxy-3-phenyl-2H-isooindol-1(7aH)-one 199. A solution of enone 176 (50 mg, 0.15 mmol) in THF (4 ml) was cooled to 0°C. Lithium aluminium hydride (30.3 mg, 0.799 mmol) was added slowly and the solution was allowed to stir for 2 hour. The reaction was quenched with water (2 ml). The mixture was extracted with diethyl ether (10 ml) and washed with water (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography eluting with 3:1 petrol-EtOAc afforded the title compound (15 mg, 32 %) as an amorphous solid, Rf 0.52 (1:1 petrol/ethyl acetate); νmax (film)/cm⁻¹ 1671; ¹H NMR (300MHz; CDCl₃) δH: 7.35-32 (2H, m, ArH), 7.27-7.24 (3H, m, ArH), 4.65 (1H, bd, J 4.0, H7), 4.43 (1H, s, H3), 3.59 (3H, s, OMe), 3.24 (1H, d, J 6.5, H5), 2.17–2.03 (3H, m, H8, H8', H4), 1.95-1.92 (1H, m, H9), 1.55 (1H, ddd, J 25.0, 12.5, 6.0, H9') and 1.34 (9H, s, tBu); ¹³C NMR (75 MHz, CDCl₃) δC: 174.2 (NC=O), 151.7 (COMe), 143.1 (Ar), 129.1 (2xAr), 127.6 (Ar), 125.5 (2xAr), 95.1 (C7), 66.8 (C7), 54.8 (OCH₃), 54.8 (C(CH₃)₃), 43.9 (C5), 42.9 (C4), 28.1 (C(CH₃)₃), 26.8 (C8 or C9) and 22.5 (C9 or C8); m/z (ES⁺) 322 (100%, MNa⁺); Found MNa⁺ 322.1766, C₁₀H₂₃NO₂ requires MNa⁺ 322.1778.
**N-Benzyl-2-methoxybenzamide 202.** To a round-bottom flask, \( N \)-Benzy1-\( N \)-tert-butyl-2-methoxybenzamide 160 (50 mg, 0.16 mmol) was dissolved in \( \text{CH}_3\text{NO}_2 \) (1.5 ml) and scandium triflate (0.10 g, 0.20 mmol) was added. The solution was stirred for 4 hours at 100 °C. The reaction was allowed to cool to R.T. and the solvent removed under vacuum. The crude was dissolved in DCM and washed with water, dried over magnesium sulfate and the solvents were removed under reduced pressure. Purification by crystallisation from ethyl acetate and petrol (3:1 petrol/ethyl acetate) gave the title compound (38 mg, 97 %) as a colourless solid, \( R_f \) 0.68 (1:1 petrol/ethyl acetate); m.p 98-102 °C (lit.,\textsuperscript{150} 106-107 °C); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 3215, 2963 and 1686; \( ^1\text{H NMR} \) (500MHz; CDCl\(_3\)) \( \delta_H \): 8.15 (1H, d, \( J \) 8.0, ArH), 8.12 (1H, bs, NH), 7.35 (1H, t, \( J \) 7.5, ArH), 7.27-7.23 (4H, m, ArH), 7.18-7.16 (1H, m, ArH), 6.99 (1H, t, \( J \) 7.5, ArH), 6.87 (1H, d, \( J \) 8.5, ArH), 4.59 (2H, d, \( J \) 5.0, H3, H3') and 3.81 (3H, s, OMe); \( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta_C \): 165.2 (NC=O), 157.4 (CMe), 138.7 (Ar), 132.8 (Ar), 132.4 (Ar), 132.3 (Ar), 128.6 (2xAr), 127.4 (Ar), 127.2 (2xAr), 121.3 (Ar), 111.2 (Ar), 55.8 (OCH\(_3\)) and 43.6 (C3); \( m/z \) (Cl\(^+\)) 242 (100%, MH\(^+\)); Found M\( \text{Na}^+ \) 265.2858. \( \text{C}_{15}\text{H}_{15}\text{NO}_2 \) requires M\( \text{Na}^+ \) 265.2851.

**7-Methoxy-3-phenyl-2,3,3a,4,5,7a-hexahydro-1H-1,5-isindoledione 204.**

**Method 1:** Enone 180 (0.08 g, 0.32 mmol) was stirred in TFA at reflux for 3 h. TFA was evaporated under reduced pressure. Purification by flash chromatography, eluting with 1:2 petrol-EtOAc afforded the title compound (0.06 g, 100 %) as a colourless solid,
**Method 2:** Enone 176 (0.10 g, 0.38 mmol) was stirred in conc. H₂SO₄ (10 ml) at 55 °C for 1 h. The reaction was quenched by transferring the crude to ice water (20 ml). The mixture was extracted with ethyl acetate and concentrated under reduced pressure. Purification by flash chromatography, eluting with 1:2 petrol-EtOAc afforded the title compound (60 mg, 73 %) as a colourless film, Rₜ 0.16 (1:1 petrol/ethyl acetate); vₘₚₕ (film)/cm⁻¹ 3200, 1707, 1655 and 1603; ¹H NMR (300MHz, CDCl₃) δ_H: 7.40-7.32 (3H, m, ArH), 7.31-7.29 (2H, m, ArH), 6.40 (1H, b, NH), 5.56 (1H, s, H7), 4.38 (1H, d, J 6.5, H3), 3.79 (3H, s, OMe), 3.48 (1H, d, J 7.5, H5), 2.90-2.85 (1H, m, H4), 2.55 (1H, dd, J 17.0, 6.0, H9 [A of ABX]) and 2.48 (1H, dd, J 17.0, 5.5, H9 [B of ABX]); ¹³C NMR (75 MHz, CDCl₃) δ_C: 196.3, (C=O) 172.3 (NC=O), 170.1 (COMe), 139.1 (Ar), 129.5 (2xAr), 129.1 (Ar), 126.4 (2xAr), 104.2 (C7), 61.8 (C3), 56.9 (OCH₃), 45.0 (C5), 43.5 (C4) and 36.2 (C9); m/z (ES⁻) 256.3 (M⁻, 100 %); Found MH⁺ 258.1121, C₁₅H₁₅NO₃ requires MH⁺ 258.1125.

(1S,7aS)-**tert**-butyl 3-(**tert**-butoxycarbonyloxy)-4-methoxy-6-oxo-1-phenyl-7,7a-dihydro-1H-isooindole-2(6H)-carboxylate 209. Amide 204 (0.043 g, 0.01673 mmol) was dissolved in dry DCM (2 ml) and **tert**-butyl dicarboxylate (0.057 g, 0.0201 mmol), DMAP (0.021g, 0.1673 mmol) and triethylamine (0.023 ml, 0.1673 mmol) was added. The reaction was left the stir under nitrogen for 18 hours, and then quenched by addition of saturated ammonium chloride solution. The mixture was extracted with DCM (2 x 10 ml) and the combined organic fractions were washed with water (30 ml), dried over magnesium sulfate and the solvents were removed under reduced pressure. Purification by flash column chromatography (2:1 petrol/ethyl acetate) gave the title compound (0.007 g, 9%), as a colourless solid, m.p 170–178 °C; Rₜ 0.66 (1:1 petrol/ethyl acetate); νₘₚₕ (film)/cm⁻¹ 1793, 1732, 1665, 1610; ¹H NMR (500MHz; CDCl₃) δ_H: 7.34-7.25 (5H, m, ArH), 5.60 (1H, s, H7), 4.22 (1H, d, J 9.0, H3), 3.75 (3H, s, OMe), 3.20
(1H, ddd, 8.0, 5.5, 2.0, 5.5, H4), 2.57 (1H, dd,  J 17.5, 6.0, H9), 2.34 (1H, dd,  J 17.5, 2.0, H9), 1.44 (9H, s, tBu) and 1.06 (9H, s, tBu); $^{13}$C NMR (75MHz, CDCl$_3$); $\delta$C: 195.6 (C=O), 164.9 (COMe), 151.4 (NBoc), 148.5 (OBoc), 140.4 (COBoc), 140.0 (Ar), 129.3 (2xAr), 128.7 (Ar), 126.3 (2xAr), 106.5 (C7), 99.6 (C5), 85.0 (C(CH$_3$)$_3$), 84.2 (C(C$_3$H)$_3$), 63.5 (C3), 57.4 (OCH$_3$), 42.0 (C4), 32.8 (C9), 27.8 (C(CH$_3$)$_3$) and 27.2 (C(CH$_3$)$_3$); $m/z$ (ES$^+$) 480 (100%, M$^+$Na); Found: M, 481.1474, C$_{25}$H$_{31}$NO$_7$ requires M$^+$, 481.1471.

(1S,3aS,7aS)-$\text{tert}$-butyl 4-methoxy-3,6-dioxo-1-phenyl-3,3a,7,7a-tetrahydro-1H-isooindole-2(6H)-carboxylate 208. A solution of LDA was formed by addition of n-butyllithium (2.3 M solution in diethyl ether, 0.44 ml, 1.01 mmol) to a solution of diisopropylamine (0.16 ml, 1.17 mmol) in THF (10 ml) at 0 °C. Amide 204 (0.20 g, 0.77 mmol) was added slowly and stirred for 20 mins. Boc-ON (258 mg, 1.01 mmol) was then added and the mixture was stirred for two hours. The mixture was quenched with sat. ammonium chloride solution and extracted with diethyl ether (2 x 10 ml) and the combined organic fractions were washed with water (20 ml), dried over magnesium sulfate and the solvents were removed under reduced pressure. Purification by flash column chromatography (2:1 petrol/ethyl acetate) gave the title compound (0.239 g, 86 %), as a colourless solid, m.p 160 – 164 °C; $R_f$ 0.6 (ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2966, 1754, 1720 and 1690; $^1$H NMR (300MHz; CDCl$_3$) $\delta$H: 7.40-7.37 (2H, m, ArH), 7.34-7.31 (1H, m, ArH), 7.22-7.21 (2H, m, ArH), 5.50 (1H, s, H7), 4.81 (1H, d, J 4.0, H3), 3.79 (3H, s, OMe), 3.59 (1H, d J 7.0, H5), 2.83-2.77 (1H, m, H4), 2.68 (1H, dd, J 17.0, 6.0, H9), 2.51 (1H, dd, J 17.0, 9.5, H9) and 1.29 (9H, s, tBu); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$C: 195.5 (C=O), 169.7 (NC(O)O), 168.4 (NC=O), 149.3 (COMe), 139.2 (Ar), 129.1 (2xAr), 128.2 (Ar), 125.1 (2xAr), 103.7 (C7), 83.9 (C(CH$_3$)$_3$), 64.8 (C3), 56.6 (OCH$_3$), 45.7 (C5), 39.6 (C4), 37.5 (C9) and 27.6
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\((\text{CH}_3)_3\); \(m/z\) (ES\(^+\)) 380.2 (100%, MNa\(^+\)); Found MNa\(^+\) 380.1471, \(\text{C}_{20}\text{H}_{23}\text{NO}_5\) requires MNa\(^+\) 380.1468.

\((1S,3aS,7aS)-\text{tert}-\text{butyl} 3,3a,7,7a\text{-tetrahydro-6-hydroxy-4-methoxy-3-oxo-1-phenyl-1H-isoindole-2(6H)-carboxylate 211.}\) A solution enone 208 (50 mg, 15 mmol) in THF (4 ml) was cooled to -78 °C. Lithium aluminium hydride (18.2 mg, 47.9 mmol) was added slowly and the solution was allowed to stir for 1 hour. The reaction was quenched with water (2 ml). The mixture was extracted with diethyl ether (10 ml) and washed with water (10 ml), dried over magnesium sulfate and concentrated under reduced pressure (47 mg, 96 %) as a colourless film, \(R_f\) 0.5 (1:1 petrol/ethyl acetate); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3604, 1748 and 1692; \(^1\)H NMR (300MHz; CDCl\(_3\)) \(\delta\): 7.30-7.27 (2H, m, ArH), 7.22-7.19 (1H, m, ArH), 7.09-7.08 (2H, m, ArH), 5.79 (1H, d, \(J\) 5.0, H7), 4.88 (1H, s, H3), 4.31 (1H, bm, H8), 3.58 (3H, s, OMe), 2.87 (1H, bt, \(J\) 6.0, H5), 2.31-2.28 (1H, m, H9), 2.24-2.20 (1H, m, H4), 2.07-1.93 (1H, m, H9), 1.18 (9H, s, tBu); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)); \(m/z\) (ES\(^+\)) 382.2 (MNa\(^+\), 100%), Found MNa\(^+\), 382.163, \(\text{C}_{19}\text{H}_{25}\text{NO}_2\) requires MNa\(^+\), 382.1625.

\((3S,3aS,7aR)-7\text{-methoxy-2-methyl-3-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindol-5-ol 213.}\) Enone 208 (0.05 g, 0.14 mmol) was dissolved in THF and Lithium aluminium hydride solution (0.35 ml, 0.7 mmol) was added dropwise at -78 °C under a nitrogen atmosphere. After 30 min the cold bath was removed and the reaction mixture was stirred at R.T. for 5 h. It was then heated to 50 °C for 2 h. The reaction mixture was allowed to cool down and quenched by dropwise addition of NaHCO\(_3\) solution. The reaction mixture was then diluted with Rochelle’s salt and stirred vigorously for 1 h. The organic layer was then
extracted with EtOAc, and the combined organic extracts were washed with water and brine, dried with magnesium sulfate and evaporated. Purification by flash column chromatography (PE:EtOAc 1:1) afforded 17 mg (0.065 mmol, 47 %) of title compound as a single isomer and as a yellow oil, Rf 0.5 (1:2 PE/EtOAc); ¹H NMR (CDCl₃, 500 MHz) δH: 7.44-7.15 (5H, m, ArH), 4.81 (1H, d, J 3.5, H7), 4.41-4.33 (1H, m, H8), 3.56 (3H, s, OMe), 3.49 (1H, dd, J 7.5, 9.0, H1'), 3.15 (1H, d, J 7.0, H3), 3.01-2.86 (1H, m, H5), 2.43-2.25 (2H, m, H1', H4), 2.18 (3H, s, NMe), 2.01-1.89 (1H, m, H9) and 1.60-1.47 (1H, m, H9'); ¹³C NMR (CDCl₃, 125 MHz) δC: 158.9 (COMe), 128.6 (Ar), 128.6 (2xAr), 127.8 (Ar), 127.4 (2xAr), 98.4 (C7), 77.4 (C8), 66.7 (C3), 60.8 (C1), 54.5 (OCH₃), 45.1 (C5), 40.4 (NCH₃), 38.9 (C4) and 34.8; m/z (ES⁺) 366 (100 %, MNa⁺).

tert-Butyl (1S, 3S, 3aR, 7aS)-3-Methoxy-4-oxo-1-phenyl-1,3,3a,4,7,7a-hexahydroisoindole-2-carboxylate 214 and tert-Butyl (1S, 7aS)-4-oxo-1-phenyl-1,4,7,7a-tetrahydroisoindole-2-carboxylate 215. Enone 208 (0.1 g, 0.3 mmol) was dissolved in THF and lithium aluminium hydride solution (0.8 ml, 1.5 mmol) was added dropwise at 0 °C under a nitrogen atmosphere and the mixture was stirred for 8 h. The reaction was quenched by addition of water. 15 % wt NaOH aqueous solution was added followed by an equal volume of water. The resulting suspension was stirred at R.T. overnight. It was then filtered through a pad of celite, which was rinsed with Et₂O. The filtrate was diluted with Et₂O and water and the organic was extracted with Et₂O. The combined organic layer was dried using magnesium sulfate and reduced under vacuum. The resulting light yellow residue was dissolved in (not anhydrous) THF (3 ml) and p-toluenesulfonic acid (6 mg, 0.1 mmol) was added. The reaction mixture was allowed to stir at R.T. for 24 h. After this time further p-toluenesulfonic acid (0.03 mmol, 0.1 equiv) was added and the reaction mixture was further stirred for 48 h. The reaction was quenched by addition of a saturated aqueous solution of
NaHCO\(_3\) and extracted with Et\(_2\)O. The combined organic layers were dried using magnesium sulfate and evaporated under reduced pressure. Purification by flash column chromatography (petro/ethyl acetate 75:25) afforded 12 mg (0.035 mmol, 13 % over 2 steps) of title compound 214 as an unstable solid, and 17 mg (0.55 mmol, 18 %) of compound 215 as a white solid.

214: R\(_f\) 0.6 (7:3 PE/EtOAc); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.39-7.27 (5H, m, ArH), 7.02-6.89 (1H, m, H8), 6.24-6.10 (1H, bm, H7), 5.76-5.66 (1H, bs, H1), 4.48-4.22 (1H, m, H3), 3.66-3.52 (3H, m, OMe), 3.11-3.00 (1H, bm, H4), 2.94 (1H, d, J 6.5, H5), 2.56 (1H, dt, J 6.0, 2.5, H9), 2.52 (1H, dt, J 6.0, 2.5, H9'), 1.41 (4.5H, bs, tBu) and 1.08 (4.5H, bs, tBu); m/z (Cl) 366 (100 %, MNa\(^+\)); Found MNa\(^+\) 366.1676, C\(_{20}\)H\(_{25}\)NO\(_4\) requires MNa\(^+\) 366.1676.

215: R\(_f\) 0.3 (7:3 PE/EtOAc); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.74-7.61 (1H, m, H18), 7.46-7.20 (5H, m, ArH), 6.80 (1H, ddd, J 2.0, 6.0, 10.0, H8), 6.15 (1H, dd, J 10.0, 2.0, H7), 4.94-4.74 (1H, bm, H3), 3.42-3.27 (1H, bm, H4), 2.64 (1H, dt, J 17.5, 6.5, H9), 2.47-2.34 (1H, m, H9') and 1.57-1.04 (9H, m, tBu); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\): 184.8 (C=O), 151.8 (NBoc), 145.2 (C1), 136.0 (C8), 132.5 (C7), 128.9 (Ar), 128.6 (2xAr), 127.8 (Ar), 125.7 (2xAr), 118.2 (C5), 82.4 (C(CH\(_3\))\(_3\)), 71.0 (C3), 50.7 (C4), 31.3 (C9) and 28.0 (C(CH\(_3\))\(_3\)); m/z (Cl) 312 (100 %, MH\(^+\)).

**tert-Butyl (1S, 3aS, 7aS)- 4-oxo-1-phenyl-1,3,3a,4,7,7a-hexahydroisoindole-2-carboxylate 216.** A 1.0 M Super-Hydride\(^\circledR\) solution (1.4 ml, 1.4 mmol) in THF was added dropwise to a solution of enone 208 (0.1 g, 0.3 mmol) in THF (1.4 ml) at -78 °C under a nitrogen atmosphere. After 15 min the cold bath was removed and the reaction mixture was allowed to warm up to R.T. overnight. It was then cooled to 0 °C and carefully quenched by dropwise addition of a saturated aqueous solution of NaHCO\(_3\). The reaction mixture was extracted with EtOAc,
and the combined organic layer was washed with water and brine, dried using magnesium sulfate and evaporated. The residue was then taken up in MeOH, filtered, and the filtrate was dried under vacuum. The resulting light yellow residue was dissolved in a 9:1 mixture of (not anhydrous) THF/MeOH (2.8 mL) and p-toluenesulfonic acid (16.0 mg, 0.08 mmol) was added. The reaction mixture was allowed to stir at R.T. for 2 h, quenched by addition of a saturated aqueous solution of NaHCO₃ and extracted with EtOAc. The combined organic extracts were dried over magnesium sulfate and evaporated to afford solid 214 which was used without further purification in the next step. To a solution of the previously described residue in DCM (1.4 mL) at -78 °C under a nitrogen atmosphere was added dropwise (50 µL, 0.3 mmol) of triethylsilane and (40 µL, 0.3 mmol) of freshly distilled BF₃·OEt₂. After 15 min, another 50 µL of triethylsilane and 40 µL of BF₃·OEt₂ were added. This operation was repeated once again, and the reaction mixture was allowed to stir at -78 °C for another 1 h. The reaction was then quenched by addition of a saturated aqueous solution of NaHCO₃ and extracted with EtOAc. The combined organic layers were dried over magnesium sulfate and evaporated. Purification by flash column chromatography (petrol/ethyl acetate 7:3) afforded the title compound (28 mg, 32 % over 3 steps) as a white solid, Rₜ 0.4 (7:3 petrol/ethyl acetate); ν max (film)/cm⁻¹ 1693 and 1677; m.p. 124-126 °C; ¹H NMR (CDCl₃, 400 MHz) [2 rotamers] δH: 7.39-7.29 (3H, m, ArH), 7.23-7.12 (2H, m, ArH), 7.00-6.90 (1H, m, H8), 6.20-6.08 (1H, m, H7), 4.62-4.60 (0.35H, m, H3), 4.35 (0.65H, bd, J 7.0, H3), 4.26-4.24 (0.65, m, H1), 4.10-4.07 (0.35H, bm, H1), 3.78 (1H, dd, J 10.5, 7.0, H1'), 2.96 (1H, td, J 11.0, 5.5, H5), 2.85-2.69 (1H, m, H4), 2.69-2.56 (1H, m, H9), 2.49-2.31 (1H, m, H9'), 1.44 (3.5H, s, tBu) and 1.09 (5.5H, s, tBu); ¹³C NMR (CDCl₃, 100 MHz) [2 rotamers] δC: 196.9 (C=O), 154.1 (NBoc), 148.0 (0.5 C8), 147.6 (0.5 C8), 143.4 (Ar), 129.2 (0.5 C7), 129.1 (0.5 C7), 128.7 (Ar), 128.5 (Ar), 127.3 (Ar), 126.0 (Ar), 125.6 (Ar), 79.7 (C(CH₃)₃), 65.4 (C3), 48.8 (0.5 C1), 48.6 (0.5 C1), 47.3 (0.5 C4), 46.7 (0.5 C4), 46.5 (0.5 C5), 46.1 (0.5 C5), 28.4 (1.5 C(CH₂)₃), 28.0 (1.5 C(CH₂)₂), 25.5 (0.5 C9) and 25.0 (0.5 C9); m/z (ES⁺) 336 (100 %, MNa⁺); Found MNa⁺ 366.1570, C₁₉H₂₃NO₃ requires MNa⁺ 336.1570.
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**tert-Butyl (1aS, 2aR, 5S, 5aS, 6aS)-2-oxo-5-phenyloctahydro-1-oxa-4-azacyclopenta[2,3-f]indene-4-carboxylate 217.** To a solution of amine 216 (26 mg, 0.1 mmol) in 0.4 mL of a 4:4:1 mixture of THF/MeOH/H₂O under a nitrogen atmosphere at 0 °C, 35 % wt aqueous solution of H₂O₂ (0.01 ml, 0.16 mmol) and K₂CO₃ (12 mg, 0.1 mmol) was added. The reaction mixture was stirred for 45 min, and then quenched by addition of a saturated aqueous solution of NH₄Cl. It was extracted with EtOAc, and the combined organic layer was washed with water and brine, dried over sodium sulfate and evaporated. Purification by flash column chromatography (petrol/ethyl acetate 7:3) afforded the title compound (16 mg, 59 %) as a yellow oil, R₇ 0.5 (7:3 petrol/ethyl acetate); νmax (film)/cm⁻¹ 1693; m.p. 156-158 °C; ¹H NMR (CDCl₃, 400 MHz) δH: 7.36-7.28 (2H, m, ArH), 7.27-7.21 (1H, m, ArH), 7.16-7.09 (2H, m, ArH), 4.85 (1H, dd, J 11.5, 9.5, H3), 3.89-3.68 (2H, m, H1, H1'), 3.66-3.64 (1H, m, H8), 3.34 (1H, d, J 4.5, H7), 3.22-3.07 (1H, m, H5), 2.68-2.77 (1H, m, H4), 2.60-2.46 (1H, m, H9), 1.99 (1H, dd, J 15.0, 10.0, H9') and 1.60-1.05 (9H, m, tBu); ¹³C NMR (CDCl₃, 100 MHz) δC: 205.8 (0.5 C=O), 205.4 (0.5 C=O), 154.3 (NBoc), 142.2 (Ar), 128.7 (2xAr), 127.3 (Ar), 125.3 (2xAr), 80.1 (C(CH₃)₃), 66.5 (C3), 55.8 (C7), 54.8 (C8), 47.0 (C5), 44.2 (C4), 28.3 (C(CH₃)₂) and 25.4 (C9); m/z (CI) 352 (MNa⁺, 100 %); Found MNa⁺ 352.1519, C₁₉H₂₃NO₄ requires MNa⁺ 352.1520.

(1aS,2aR,5S,5aS,6aS)-tert-butyl 2-ethoxy-5-phenyl-2-(2-tosylhydrazinyl)hexahydro-1aH-oxireno[2,3-f]isoindo-4(2H)-carboxylate 224. A mixture of 217 (10 mg, 0.03 mmol) and tosyl hydrazide (6.0 mg, 0.03 mmol) in EtOH (0.3 ml) was stirred at R.T. for 30 min and then heated to 50 °C for 1 h 30 mins. The reaction mixture was then allowed to cool to R.T. and the
reaction mixture was diluted with EtOAc and brine. It was extracted with EtOAc, dried over magnesium sulfate and evaporated. Purification by flash column chromatography (petrol/ethyl acetate 7:3) afforded the title compound (9 mg, 55 %) as yellow oil, R_f 0.3 (7:3 petrol/ethyl acetate); \( ^1 \)H NMR (CDCl\(_3\), 400 MHz) [2 rotamers] \( \delta \)H: 7.88-7.72 (2H, m, ArH), 7.39-7.16 (5H, m, ArH), 7.16-7.04 (2H, m, ArH), 4.84 (0.35H, s, H3), 4.61 (0.65, s, H3), 4.11 (1H, dd, J 14.5, 7.0, H8), 3.84-3.74 (1H, m, H1), 3.64 (1H, d, J 3.0, H7), 3.55-3.39 (1H, m, H1'), 3.18-3.16 (1H, bm, H5), 3.03-2.94 (1H, m, H9), 2.91-2.80 (1H, m, H9'), 2.58-2.49 (1H, m, H4), 2.43 (3H, s, ArMe), 1.96-2.16 (2H, m, OCH\(_2\)) and 1.50-1.16 (12H, m, tBu, CH\(_2\)CH\(_3\)); m/z (ES\(^+\)) 566 (100 %, MNa\(^+\)); Found MH\(^+\) 544.2476, C\(_{28}\)H\(_{38}\)N\(_3\)O\(_6\)S\(_1\) requires MH\(^+\) 544.2476.

![1-tert-Butyl (2S, 3S, 4S)-4-ethynyl-3-(2-oxoethyl)-2-phenylpyrrolidine-1-carboxylate 223](image)

1-tert-Butyl (2S, 3S, 4S)-4-ethynyl-3-(2-oxoethyl)-2-phenylpyrrolidine-1-carboxylate 223. A mixture of 217 (10.0 mg, 0.03 mmol) and mesitylsulfonyl hydrazide (7.0 mg, 0.1 mmol) in AcOH (0.3 mL) was stirred at R.T. for 36 h. The reaction mixture was diluted with EtOAc and carefully neutralized with a saturated aqueous solution of NaHCO\(_3\). It was extracted with EtOAc, dried over magnesium sulfate and evaporated. Purification by flash column chromatography (petrol/ethyl acetatev8:2) afforded the title compound (2 mg, <21 % [impure]) as a yellow oil, R_f 0.6 (7:3 PE/EtOAc); \( ^1 \)H NMR (CDCl\(_3\), 300 MHz) [2 rotamers] \( \delta \)H: 9.86-9.75 (1H, m, CHO), 7.38-7.15 (5H, m, ArH), 4.60 (0.35H, bs, H3), 4.39 (0.65H, d, J 6.5, H3), 3.86-3.80 (1.65H, m, H1, H1'), 3.79-3.76 (0.35H, m, H1'), 3.36-3.23 (1H, m, H5), 3.07-2.95 (1H, m, H9), 2.68-2.61 (2H, m, H4, H9'), 2.21 (1H, s, H7), 1.44 (4H, bs, tBu) and 1.12 (5H, s, tBu); m/z (ES\(^-\)) 312 (100 %, M\(^-\)H).
**N-(tert-Butyl)-N-(3-methoxyphenyl)-amine 231.** Potassium carbonate (898 mg, 6.50 mmol) was added to a solution of tert-butylamine (630 µl, 6.00 mmol) and 3-methoxybenzylbromide (700 µl, 5.01 mmol) in 25 ml of anhydrous DMF. The resulting solution was stirred overnight at R.T. under a nitrogen atmosphere. The reaction mixture was then quenched with water and extracted with Et₂O. The combined organic extracts were washed with brine, dried over magnesium sulfate and evaporated. The resulting oil was then taken up in Et₂O and washed 4 times with water. The organic layer was then dried over magnesium sulfate and evaporated to yield the title compound (822 mg, 85 %) as a yellow oil, Rf 0.65 (4:1 petrol/ethyl acetate); ¹H NMR (CDCl₃, 400 MHz) δH: 7.24 (1H, t, J 8.0, ArH), 6.99-6.88 (2H, m, ArH), 6.82-6.75 (1H, m, ArH), 3.83 (3H, s, OMe), 3.72 (2H, s, H9, H9') and 1.18 (9H, s, tBu); ¹³C NMR (CDCl₃, 100 MHz); δC: 159.8 (COMe), 143.3 (Ar), 129.5 (Ar), 120.6 (Ar), 113.9 (Ar), 112.3 (Ar), 55.3 (OCH₃), 50.8 (C(CH₃)₃), 47.4 (C9) and 29.3 (C(CH₃)₃); m/z 194 (100 %, MH⁺); all data consistent with literature.⁸⁹

2, 4-Dimethoxy-N-tert-butyl N-(3-methoxyphenyl)benzamide 232. To a round-bottom flask, 2, 4-Dimethoxybenzoyl chloride (1.0 g, 5.1 mmol) was added N-tert-butyl-N-(3-methoxyphenyl) amine (822 mg, 4.25 mmol) in DCM (20 ml) at R.T. under a nitrogen atmosphere. Triethylamine (0.9 ml, 6.4 mmol) was added to the reaction mixture, which was stirred overnight. It was then quenched by addition of water and extracted with DCM. The combined organic extracts were washed with brine, dried over magnesium sulfate and evaporated. Purification by flash column chromatography (petrol/ethyl acetate 7:3) yielded benzamide 232
(1.361 g, 90 %) as a colourless wax, \( R_f \) 0.55 (6:4 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1633, 1605 and 1583; \(^1\)H NMR (CDCl\(_3\), 300 MHz) \( \delta_H \): 7.25-7.11 (1H, m, ArH), 6.89-6.68 (3H, m, ArH), 6.45-6.34 (2H, m, H3, H3\(^2\)), 3.80 (3H, s, OMe), 3.79 (3H, s, OMe), 3.76 (3H, s, OMe) and 1.51 (9H, s, \( t \)Bu); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta_C \): 171.2 (NC=O), 161.0 (Ar), 159.8 (Ar), 156.4 (Ar), 142.2 (Ar), 129.4 (Ar), 128.3 (Ar), 122.0 (Ar), 118.7 (Ar), 112.2 (Ar), 112.1 (Ar), 104.6 (Ar), 98.8 (Ar), 58.2 (C3), 55.7 (OCH\(_3\)), 55.4 (OCH\(_3\)), 55.3 (OCH\(_3\)), 51.2 (C(CH\(_3\))\(_3\)) and 29.0 (C(CH\(_3\))\(_3\)); \( m/z \) (ES\(^+\)) 358 (100 %, MH\(^+\)); Found M\(^+\) 358.2011, C\(_{21}\)H\(_{28}\)NO\(_4\) requires MH\(^+\) 358.2013.

(3S, 3aS, 7aS)-2-(tert-Butyl)-7-methoxy-3-(3-methoxyphenyl)-2,3,3a,7a-tetrahydro-4H-isoinole-1,5-dione 233. In a round-bottom flask, 2.1 M \( n \)BuLi (0.6 ml, 1.3 mmol) was added to a solution of DIPA (0.2 ml, 1.5 mmol) in THF (7 ml) at 0 °C under a nitrogen atmosphere. Then a solution of benzamide 232 (357 mg, 1.01 mmol) and DMPU (0.6 ml, 5.2 mmol) in THF (2 ml) was added dropwise via cannula to the reaction mixture at 0 °C. The reaction mixture, which turned to a deep orange colour, was stirred at 0 °C for another 1 h. It was quenched by addition of a saturated aqueous solution of NH\(_4\)Cl. The reaction mixture was then diluted with water and extracted with Et\(_2\)O. The combined organic extracts were washed with a 3M aqueous solution of HCl, dried over magnesium sulfate and evaporated. Purification by flash column chromatography (petrol/ethyl acetate 4:6) afforded the title compound (108 mg, 31 %) as a white waxy solid, \( R_f \) 0.24 (4:6 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1685, 1653 and 1605; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta_H \): 7.31 (1H, t, \( J \) 8.0, ArH), 6.86 (1H, d, \( J \) 2.0, ArH), 6.84 (1H, d, \( J \) 2.0, ArH), 6.79 (1H, t, \( J \) 2.0, ArH), 5.43 (1H, s, H7), 4.46 (1H, s, H3), 3.82 (3H, s, OMe), 3.81 (3H, s, OMe), 3.61-3.56 (1H, m, H5), 2.75-2.63 (2H, m, H9 H4), 2.54-2.41 (1H, m, H9) and 1.40 (9H, s, \( t \)Bu); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta_C \): 196.5 (C=O), 172.6 (NC=O), 170.0 (Ar), 160.4 (Ar), 142.6
(COMe), 130.4 (Ar), 117.6 (Ar), 113.2 (Ar), 111.3 (Ar), 103.1 (C7), 66.2 (C3), 56.6 (OCH₃), 55.7 (C(CH₃)₃), 55.4 (OCH₃), 45.0 (C5), 42.2 (C4), 39.5 (C9) and 27.9 (C(CH₃)₃); m/z 344 (100 %, MH⁺); Found MH⁺ 344.1864, C₂₀H₂₆NO₇ requires MH⁺ 344.1856.

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\begin{array}{c}
\text{N-(3-Methoxyphenyl)-N-(1-methyl-1-phenylethyl)amine 235.} \\
\text{Potassium carbonate (10.42 g, 75 mmol) was added to a solution of cumylamine (10 ml, 70 mmol) and 3-methoxybenzylbromide (8.1 ml, 58 mmol) in 250 ml of anhydrous DMF. The resulting solution was stirred overnight at R.T. under a nitrogen atmosphere. The reaction mixture was then quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over magnesium sulfate and evaporated. The resulting oil was purified by flash column chromatography (petrol/ethyl acetate4:1) to yield the title compound (14.09 g, 95 %) as a colourless oil, Rf 0.6 (7:3 petrol/ethyl acetate). All spectroscopic data in accordance with the literature.}^{79}
\end{array}
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\begin{array}{c}
\text{2,4-Dimethoxy-N-(3-methoxyphenyl)-(1-methyl-1-phenylethyl)benzamide 236.} \\
\text{To a round-bottom flask, 2, 4-Dimethoxybenzoyl chloride (12 g, 61 mmol) was added to a solution of N-cumyl-N-(3-methoxyphenyl) amine 235 (14 g, 55 mmol) in DCM (180 ml) at R.T. under a nitrogen atmosphere. Then triethylamine (11 ml, 83 mmol) was added to the reaction mixture, which was stirred at R.T. overnight. It was then quenched by addition of water and extracted with DCM. The combined organic extracts were washed with brine, dried over magnesium sulfate and evaporated. The resulting oil was dissolved in EtOAc and Et₂O was added until a precipitate started to form. This suspension was then evaporated.}
\end{array}
\]
The resulting solid was then recrystallized twice from EtOAc/Et<sub>2</sub>O to yield the title benzamide (19.95 g, 86 %) as a white crystalline solid, R<sub>f</sub> 0.5 (6:4 petrol/ethyl acetate); m.p. 108-110°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 7.52-7.44 (2H, m, ArH), 7.32 (2H, t, J 8.0, ArH), 7.25-7.14 (3H, m, ArH), 6.86-6.80 (2H, m, ArH), 6.77 (2H, dd, J 8.0, 2.0, ArH), 6.43-6.35 (2H, m, ArH), 4.71 (2H, bs, H<sub>3</sub>, H<sub>3</sub>'), 3.86 (3H, s, OMe), 3.80 (3H, s, OMe), 3.76 (3H, s, OMe), 1.80 (3H, bs, Me) and 1.65 (3H, bs, Me); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ<sub>C</sub>: 170.3 (NC=O), 161.3 (Ar), 159.8 (Ar), 156.6 (Ar), 149.0 (Ar), 141.6 (Ar), 129.5 (Ar), 129.2 (Ar), 128.0 (Ar), 126.0 (Ar), 124.8 (2xAr), 121.1 (Ar), 119.2 (Ar), 112.6 (Ar), 112.5 (Ar), 104.7 (Ar), 98.7 (Ar), 62.6 (C(CH<sub>3</sub>)<sub>2</sub>Ph), 55.7 (OCH<sub>3</sub>), 55.4 (OCH<sub>3</sub>), 55.3 (OCH<sub>3</sub>) and 51.6 (C3); m/z (ES<sup>-</sup>) 418 (100%, M<sup>-</sup>H); Found MH<sup>+</sup> 420.2170, C<sub>26</sub>H<sub>30</sub>NO<sub>4</sub> requires MH<sup>+</sup> 420.2169.

(3S, 3aS, 7aS)-7-Methoxy-3-(3-methoxyphenyl)-2-(1-methyl-1-phenylethyl)-2,3,3a,7a-tetrahydro-4H-isoinde-1,5-dione 237 and 5,7-Dimethoxy-3-(3-methoxyphenyl)-2-(1-methyl-1-phenylethyl)-2,3-dihydroisoindoindol-1-one 237b.

**Method 1:** A solution of LDA was formed by the addition of 2.2 M nBuLi (13.4 mL, 29.5 mmol) to diisopropylamine (4.8 ml, 34.0 mmol) in THF (100 ml) at 0 °C under a nitrogen atmosphere. Then a solution of benzamide 236 (9.50 mg, 23 mmol) and DMPU (16.4 ml, 136 mmol) in THF (40 ml) was added dropwise via cannula at 0 °C over 30 min. The reaction mixture, which turned first to a deep green colour and then dark brown, was stirred for another 1 h at 0 °C. It was then quenched by addition of a saturated aqueous solution of NH<sub>4</sub>Cl. The reaction mixture was then diluted with water and extracted with Et<sub>2</sub>O. The combined organic extracts were then washed with a 3M aqueous solution of HCl, dried over
magnesium sulfate and evaporated. The resulting solid was recrystallised from EtOAc and EtOH. The white precipitate was filtered off and dried under vacuum. The mother liquors were evaporated again and purified by flash column chromatography (petrol/ethyl acetate 7:3 then 6:4) to yield the rearomatised product 237b (179 mg, 2%) as an off-white solid and the title compound (5.81 g, 64%) as a colourless crystalline solid.

**Method 2:** Amide 236 (0.50 g, 0.12 mmol) was added to a solution of chiral amide 112 (0.01 g, 0.059 mmol) and n-butyllithium (0.9 mmol) in THF (10 ml) at -30 °C. The mixture was allowed stir for 2 hours and then quenched with saturated ammonium chloride solution. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with 1M HCl solution and brine, dried over magnesium sulfate and the solvents removed under reduced pressure. Purification by flash column chromatography (3:1 petrol/ethyl acetate) gave the title compound (0.006 g, 12%). Analytical HPLC (β-Gem Regis), eluting with IPA and hexane (10:90) showed it to consist of 73% e.e of a mixture of two enantiomers, $t_R$ 17.89 and 20.41 mins.

**237b (rearomatised product):** $R_f$ 0.35 (6:4 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1682 and 1604; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta_H$: 7.33-7.15 (5H, m, ArH), 6.83-6.74 (2H, m, ArH), 6.60-6.45 (1H, m, ArH), 6.35 (1H, d $J$ 1.5, ArH), 5.63 (1H, s, ArH), 3.89 (3H, s, OMe), 3.74 (3H, s, OMe), 3.73 (3H, s, OMe), 1.90 (3H, s, Me), 1.61 (3H, s, Me); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta_C$: 168.6 (NC=O), 164.4 (Ar), 159.9 (Ar), 158.2 (Ar), 151.0 (Ar), 147.5 (Ar), 142.3 (Ar), 129.9 (Ar), 128.1 (2xAr), 126.3 (Ar), 125.3 (Ar), 119.2 (Ar), 112.4 (Ar), 98.7 (Ar), 98.1 (Ar), 65.2 (C3), 60.1 (C(CH$_3$)$_2$Ph), 55.7 (OCH$_3$), 55.5 (OCH$_3$), 55.2 (OCH$_3$), 29.0 (C(CH$_3$)$_2$Ph) and 28.5 (C(CH$_3$)$_2$Ph) (missing 2 Ar); $m/z$ (ES$^+$) 440 (100 %, MNa$^+$).

**237:** $R_f$ 0.3 (6:4 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1701, 1654, 1648 and 1610; m.p. 224 °C; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta_H$: 7.41-7.36 (2H, m, ArH), 7.33-7.27 (3H, m, ArH), 7.25-7.20 (1H, m, ArH), 6.89-6.82 (2H, m, ArH), 6.78-6.74 (1H, m, ArH), 5.38 (1H, s, H7), 4.47 (1H, s, H3), 3.82 (3H, s, OMe), 3.74 (3H, s,
OMe), 3.67 (1H, d, J 7.0, H5), 2.71-2.60 (2H, m, H9, H4), 2.45 (1H, dd, J 12.0, 15.5, H9), 1.87 (3H, s, Me), 1.56 (3H, s, Me); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ$_C$: 196.4 (C=O), 172.2 (COMe), 169.7 (NC=O), 160.3 (Ar), 145.6 (Ar), 142.7 (Ar), 130.3 (Ar), 128.3 (Ar), 127.2 (Ar), 125.6 (Ar), 117.9 (Ar), 113.4 (Ar), 111.6 (Ar), 103.1 (C7), 67.0 (C3), 59.8 (C(CH$_3$)$_2$Ph), 56.5 (OCH$_3$), 55.4 (OCH$_3$), 44.9 (C5), 42.0 (C4), 39.2 (C9), 28.1 (C(CH$_3$)$_2$Ph) and 27.0 (C(CH$_3$)$_2$Ph); m/z (ES$^+$) 428 (100 %, MNa$^+$); Found MNa$^+$, 428.3384, C$_{25}$H$_{31}$N$_2$O$_4$ requires MNa$^+$ 428.2278.

2,4-Dimethoxy-N-tert-butyl N-(3,4-dimethoxyphenyl)benzamide 240. To a round-bottom flash, 3,4-dimethoxybenzaldehyde (1.0 g, 6.0 mmol) was added to a solution of tert-butylamine (760 µl, 7.20 mmol,) in DCM (30 ml) at R.T. under a nitrogen atmosphere. Then acetic acid (380 µL, 6.60 mmol) was added to the reaction mixture, and left to stir at R.T. for 2 h. NaBH(OAc)$_3$ (1.9 g, 9.0 mmol) was added to the reaction mixture, which was left to stir for 3 days. The reaction was quenched by addition of a saturated aqueous solution of NaHCO$_3$, extracted with DCM, and the combined organic layer were dried over magnesium sulfate and evaporated. The resulting crude amine (1.33 g, 99 %), as a colourless oil, was used in the next step without further purification. 2,4-Dimethoxybenzoyl chloride (1.32 g, 6.61 mmol) was added to a solution of N-tert-butyl-N-(3,4-dimethoxyphenyl)amine 239 (1.33 g, 6.0 mmol) in DCM (30 ml) at R.T. under a nitrogen atmosphere. Triethylamine (1.25 ml, 9.01 mmol) was added to the reaction mixture, and was stirred overnight. The reaction was quenched by addition of water and extracted with DCM. The combined organic layer was washed with brine, dried over magnesium sulfate and evaporated. Purification by flash column chromatography (petrol/ethyl acetate 45:55) yielded the title compound (859 mg, 2.22 mmol) as a colourless crystalline solid, R$_f$ 0.3 (1:1 petrol/ethyl acetate); $\nu_{\max}$ (film)/cm$^{-1}$ 1626, 1607 and 1582; m.p. 116-118 ºC; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta_H$: 7.15 (1H, d, J 9.0, ArH), 6.82-6.70 (3H, m, ArH),
(3S, 3aS, 7aS)-2-(tert-Butyl)-7-methoxy-3-(3,4-dimethoxyphenyl)-2,3,3a,7a-tetrahydro-4H-isoadole-1,5-dione 241. In a round-bottom flask, 2.0 M nBuLi (0.66 ml, 1.3 mmol) was added to a solution of DIPEA (0.21 ml, 1.5 mmol, 1.5 equiv) in THF (6 ml) at 0 °C under a nitrogen atmosphere. Then a solution of benzamide 240 (357 mg, 1.12 mmol) and DMPU (0.73 ml, 6 mmol) in THF (3 ml) was added dropwise via cannula at -15 °C. The reaction mixture, which turned to a bright orange colour, was allowed to warm up to 0 °C over 2 h. It was quenched by addition of a saturated aqueous solution of NH₄Cl. The reaction mixture was then diluted with water and extracted with Et₂O. The combined organic layer was washed with a 3M aqueous solution of HCl, dried using magnesium sulfate and evaporated. Purification by flash column chromatography (petrol/ethylacetate 1:2) afforded 234 mg (0.6 mmol, 60 %) of starting material and the title compound (52 mg, 14 %) as a colourless oil, Rf 0.23 (1:2 petrol/ethyl acetate); ¹H NMR (CDCl₃, 300 MHz) δH: 6.90-6.78 (2H, m, ArH), 6.75-6.69 (1H, m, ArH), 5.43 (1H, s, H7), 4.45 (1H, s, H3), 3.89 (6H, s, 2xOMe), 3.82 (3H, s, OMe), 3.60-3.57 (1H, m, H5), 2.74-2.62 (2H, m, H4, H9), 2.53-2.40 (1H, m, H9') and 1.40 (9H, s, tBu); ¹³C NMR (CDCl₃, 75 MHz) δC: 196.5 (C=O), 172.5 (NC=O), 169.9 (Ar or OMe), 146.9 (Ar or OMe), 148.8 (Ar or OMe), 133.3 (Ar or OMe), 117.5 (Ar), 111.6 (Ar), 108.4 (Ar), 103.1 (C7), 65.9 (C3), 56.5 (OCH₃), 56.1 (OCH₃), 55.6 (C(CH₃)₃), 45.0 (C5), 42.3 (C4), 39.4 (C9) and 27.9
(C(CH$_3$)$_3$); m/z (ES$^+$) 374 (100%, MH$^+$); Found MH$^+$ 374.1966, C$_{21}$H$_{28}$NO$_5$ requires MH$^+$ 374.1962.

(3S, 3aS, 7aS)-7-Methoxy-3-(3-methoxyphenyl)-2,3,3a,7a-tetrahydro-4H-isooindole-1,5-dione 242. Enone 237 (5.03 g, 12.4 mmol) was refluxed in TFA (31 ml) for 1 h 30 mins under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and purification by flash column chromatography (ethyl acetate to ethyl acetate/methanol 9:1) afforded the title compound (3.61 g, quant.) as a colourless crystalline solid, R$_f$ 0.2 (ethyl acetate); m.p. 158-160 °C; v$_{max}$ (film)/cm$^{-1}$ 1701, 1648, 1638 and 1602; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$H: 7.31 (1H, t, J 7.9, ArH), 6.91-6.86 (2H, m, ArH), 6.85-8.83 (1H, m, ArH), 6.31 (1H, bs, NH), 4.36 (1H, d, J 5.0, H3), 3.82 (3H, s, OMe), 3.81 (3H, s, OMe), 3.49 (1H, d, J 7.0, H5), 2.94-2.85 (1H, m, H4), 2.58 (1H, dd, J 17.0, 6.0, H9) and 2.50 (1H, dd, J 17.0, 6.0, H9$'$); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$C: 196.1 (C=O), 172.1 (NC=O), 170.0 (NBoc), 160.4 (Ar), 140.7 (Ar), 130.4 (Ar), 118.6 (Ar), 114.2 (Ar), 111.7 (Ar), 104.0 (C7), 61.6 (C3), 56.8 (OCH$_3$), 55.5 (OCH$_3$), 44.8 (C5), 43.2 (C4) and 36.2 (C9); m/z (ES$^+$) 310 (100%, MNa$^+$); Found MNa$^+$ 310.1041, C$_{16}$H$_{17}$NO$_4$ requires MNa$^+$ 310.1050.

tert-Butyl (3S, 3aS, 7aS)-7-Methoxy-3-(3-methoxyphenyl)-1,5-dioxo-1,3,3a,4,5,7a-hexahydroisoindole-2-carboxylate 243. A suspension of compound 242 (3.61 g, 12.6 mmol) in THF (60 ml) was sonicated in a water bath. It was then cooled down to 0°C under a nitrogen atmosphere and (14.9 ml, 14.9
mmol) of a 1M solution of LDA in THF was added dropwise. The suspension then turned yellow. It was stirred at 0 °C for 20 min before a solution of Boc-ON (4.44 g, 15.5 mmol) in THF (15 ml) was added dropwise via cannula at 0 °C. The reaction mixture was stirred at this temperature for another 6 h. Over this time, the reaction turned to a deep brown solution. It was quenched by addition of a saturated aqueous solution of NH₄Cl, extracted with EtOAc and the combined organic extracts were dried over magnesium sulfate and evaporated. Purification by flash column chromatography (petrol/ethyl acetate 1:1 to 1:2) yielded the title compound (3.69 g, 77 %) as a white solid, Rᶠ 0.7 (ethyl acetate); m.p. 70-72°C; νmax (film)/cm⁻¹ 1785, 1757, 1656, 1647 and 1611; ¹H NMR (CDCl₃, 400 MHz) δH: 7.30 (1H, t, J 8.0, ArH), 6.86 (1H, dd, J 8.0, 2.0, ArH), 6.82-6.79 (1H, m, ArH), 6.76-6.73 (1H, m, ArH), 5.51 (1H, s, H7), 4.80 (1H, d, J 3.5, H3), 3.81 (3H, s, OMe), 3.79 (3H, m, OMe), 3.60 (1H, d, J 7.0, H5), 2.86-2.78 (1H, m, H4), 2.69 (1H, dd, J 17.0, 6.0, H9), 2.52 (1H, dd, J 17.0, 9.5, H9) and 1.33 (9H, s, tBu); ¹³C NMR (CDCl₃, 100 MHz) δC: 195.7 (C=O), 169.9 (NC=O), 168.5 (NBoc), 160.4 (COMe), 149.5 (Ar), 140.9 (Ar), 130.3 (Ar), 117.4 (Ar), 113.6 (Ar), 111.0 (Ar), 103.8 (C7), 84.0 (C(CH₃)₃), 64.8 (C3), 56.8 (OCH₃), 55.4 (OCH₃), 45.8 (C5), 39.7 (C4), 37.7 (C9) and 27.8 (C(CH₃)₂); m/z (ES⁺) 410 (100%, MNa⁺); Found MNa⁺ 410.1570, C₂₁H₂₅NO₆ requires MNa⁺ 410.1574.

**tert-Butyl (1S, 3aS, 7aS)-1-(3-methoxyphenyl)-4-oxo-1,3,3a,4,7,7a-hexahydroisoindole-2-carboxylate 244.** To a solution of 243 (1.51 g, 4.03 mmol) in DCM (27 ml) at -78 °C under a nitrogen atmosphere, triethylsilane (0.71 ml, 4.41 mmol) and freshly distilled BF₃·OEt₂ (0.56 ml, 4.41 mmol) was added dropwise. After 20 min, a further 0.71 ml of triethylsilane and 0.56 ml of BF₃·OEt₂ were added. This operation was repeated again twice. The reaction mixture was then allowed to stir at -78 °C for another 2 h. It was quenched by
addition of a saturated aqueous solution of NaHCO₃ and extracted with EtOAc. The combined organic layer was dried over magnesium sulfate and evaporated. Purification by flash column chromatography (petrol/ethyl acetate 7:3) afforded the title compound (1.09 g, 79 %) as a white solid, Rf 0.4 (7:3 petrol/ethyl acetate); νmax (film)/cm⁻¹ 1685, 1669 and 1599; ¹H NMR (CDCl₃, 400 MHz) [2 rotamers] δH: 7.23 (1H, t, J 7.8, ArH), 6.98-6.89 (1H, m, H8), 6.84-6.64 (3H, m, ArH), 6.17-6.09 (1H, m, H7), 4.56 (0.35H, d, J 4.5, H3), 4.32 (0.65H, d, J 7.0, H3), 4.22 (0.65H, dd, J 11.0, 3.5, H1), 4.07 (0.35H, dd, J 11.0, 5.0, H1), 3.79 (3H, s, OMe), 3.79-3.70 (1H, m, H1'), 2.98-2.90 (1H, m, H5), 2.80-2.67 (1H, m, H4), 2.67-2.55 (1H, m, H9), 2.50-2.33 (1H, m, H9'), 1.42 (4.0H, s, tBu) and 1.10 (5.0H, s, H4); ¹³C NMR (CDCl₃, 100 MHz) [2 rotamers] δC: 196.9 (C=O), 159.9 (Ar [COMe]), 154.2 (NBoc), 147.6 (0.5 C8), 147.6 (0.5 C8), 145.1 (Ar), 129.8 (0.5 Ar), 129.6 (0.5 Ar), 129.2 (0.5 C7), 129.1 (0.5 C7), 118.4 (Ar), 117.9 (Ar), 112.5 (Ar), 111.7 (Ar), 80.1 (0.5 C(CH₃)₃), 79.8 (0.5 C(CH₃)₃), 65.4 (C3), 55.4 (OCH₃), 48.8 (0.5 C1), 48.5 (0.5 C1), 47.2 (0.5 C5), 46.7 (0.5 C5), 46.6 (0.5 C4), 46.2 (0.5 C4), 28.5 (4.5 C(CH₃)₃), 28.1 (0.5 C9), 25.7 (0.5 C9) and 25.2 (0.5 C9); m/z (ES⁺) 366 (100%, MNa⁺); Found MH⁺ 344.1856, C₂₀H₂₃NO₅ requires MH⁺ 344.1857.

**tert-Butyl (1aS, 2aR, 5S, 5aS, 6aS)-5-(3-methoxyphenyl)-2-oxooctahydro-1-oxa-4-azacyclopenta[f]indene-4-carboxylate 245.** To a solution of 244 (1.14 g, 3.32 mmol) in THF under a nitrogen atmosphere at 0 °C, 70 % wt aqueous solution of tert-BuOOH (1.1 ml, 6.6 mmol) and DBU (0.99 ml, 6.61 mmol) were added. The reaction mixture was stirred for 45 mins, and then quenched by addition of a saturated aqueous solution of sodium thiosulfate. It was extracted with EtOAc, and the combined organic extracts were washed with water and brine, dried over sodium sulfate and evaporated. Purification by flash column
chromatography (petrol/ethyl acetate 7:3) afforded the title compound (804 mg, 68 %) as a white solid, Rf 0.5 (6:4 petrol/ethyl acetate); ν\text{max} (film)/cm\(^{-1}\) 1695, 1602 and 1586; \(^1\)H NMR (CDCl\(_3\), 400 MHz) δ\(\text{H}\): 7.24 (1H, t, J 8.0, ArH), 6.79 (1H, dd, J 2.5, 8.0, ArH), 6.75-6.70 (1H, m, ArH), 6.68-6.65 (1H, m, ArH), 4.62-4.44 (1H, bm, H3), 3.87-3.70 (5H, m, OMe, H1, H1'), 3.68-3.63 (1H, m, H8), 3.35 (1H, d, J 4.0, H12), 3.20-3.15 (1H, m, H5), 2.77-2.69 (1H, m, H4), 2.60-2.48 (1H, bm, H9), 1.99 (1H, dd, J 15.0, 10.5, H9') and 1.56-1.13 (9H, m, tBu); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) δ\(\text{C}\): 205.6 (C=O), 202.0 (NBoc), 159.9 (Ar), 154.3 (Ar), 129.7 (Ar), 117.6 (Ar), 112.3 (Ar), 111.3 (Ar), 80.1 (C(CH\(_3\))\(_3\)), 66.4 (C3), 55.8 (C1), 55.7 (C7), 55.3 (OCH\(_3\)), 54.8 (C8), 47.1 (C5), 44.6 (C4), 28.3 (C(CH\(_3\))\(_3\)) and 25.4 (C9); m/z (ES\(^+\)) 382 (100%, MNa\(^+\)); Found MNa\(^+\) 382.1622, C\(_{20}\)H\(_{25}\)NO\(_5\) requires MNa\(^+\) 382.1622.

4-tert-Butyl 5-methyl (1aS, 2aR, 5S, 5aS, 6aS)-2-oxooctahydro-1-oxa-4-azacyclopenta[f]indene-4,5-dicarboxylate 218. In a round-bottom flash, RuCl\(_3\).xH\(_2\)O (145 mg, 0.72 mmol) was dissolved in MeCN (11.5 ml). Then distilled water was added (23 ml), followed by NaIO\(_4\) (9.0 g, 42 mmol) of. This dark mixture was stirred vigorously at R.T. for 10 min. It was then cooled down to 0 °C, and a solution of compound 245 (837 mg, 2.33 mmol) in EtOAc (11.5 ml) was slowly added dropwise. The reaction mixture turned light brown upon addition of the product. It was allowed to stir at 0 °C for 2 h. It was then filtered through a pad of celite. The filtrate was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered through a pad of celite, evaporated and dried under vacuum. The dark residue was then dissolved in toluene (40 ml) at R.T. under a nitrogen atmosphere. Anhydrous methanol (20 ml) was added, followed by 2.0 M solution of (trimethylsilyl)diazomethane (1.75 ml, 3.55 mmol) in hexanes. The reaction mixture was stirred for 15 min, and quenched by careful addition of 2
drops of acetic acid. The reaction was concentrated under vacuum and purification by flash column chromatography (petrol/ethyl acetate 7:3) afforded the title compound (304 mg, 42%) as a yellow oil, \( R_f \) 0.55 (6:4 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2367, 2340, 1747, 1707 and 1699; \(^1\)H NMR (CDCl\(_3\), 400 MHz) [2 rotamers] \( \delta_H \): 4.14 (0.65H, s, H3), 3.99 (0.35H, s, H3), 3.90-3.77 (1H, m, H1), 3.75 (3H, s, OMe), 3.67-3.63 (1H, m, H1'), 3.63-3.55 (1H, m, H8), 3.37 (1H, d, \( J \) 4.0, H7), 3.19 (1H, td, \( J \) 10.0, 8.0, H5), 2.98-2.88 (1H, m, H4), 2.59-2.49 (1H, m, H9), 2.03-1.90 (1H, bm, H9) and 1.51-1.36 (9H, m, tBu); \(^1^3\)C NMR (CDCl\(_3\), 75 MHz) [2 rotamers] \( \delta_C \): 205.2 (0.5 C=O), 204.6 (0.5 C=O), 172.1 (0.5 CO\(_2\)Me), 172.0 ((0.5 CO\(_2\)Me), 154.4 (0.5 NBoc), 153.2 (0.5 NBoc), 80.4 (C(CH\(_3\))\(_3\)), 66.4 (C3), 64.3 (0.5 C7), 63.9 (0.5 C7), 55.2 (0.5 C8), 54.6 (0.5 C8), 52.3 (0.5 CO\(_2\)CH\(_3\)), 52.2 (0.5 CO\(_2\)CH\(_3\)), 46.5 (0.5 C5), 46.3 (0.5 C5), 45.6 (0.5 C4), 44.6 (0.5 C4), 37.9 (0.5 C1), 36.7 (0.5 C1), 28.1 (0.5 C(CH\(_3\))\(_2\)), 28.1 (0.5 C(CH\(_3\))\(_2\)), 25.8 (0.5 C9) and 25.6 (0.5 C9); \( m/z \) (ES\(^+\)) 344 (100%, MNa\(^+\)); Found MH\(^+\) 329.1709, C\(_{15}\)H\(_{25}\)NO\(_5\) requires MH\(^+\) 329.1709.

1-tert-Butyl 2-methyl (2S, 3S, 4S)-4-ethynyl-3-(2-oxoethyl)-pyrrolidine-1,2-dicarboxylate 247. A mixture of compound 218 (35 mg, 0.1 mmol) and mesitylsulfonyl hydrazide (25 mg, 0.1 mmol) in a 1:1 mixture of DCM/ACOH (1.1 ml) was heated to 40 °C for 2 h 30 mins. The reaction mixture was diluted with DCM and carefully neutralized with a saturated aqueous solution of NaHCO\(_3\). It was extracted with DCM, dried using magnesium sulfate and evaporated. Purification by flash column chromatography (petrol/ethyl acetate 75:25) afforded the title compound (1 mg, <3% [impure]) yellow oil, \( R_f \) 0.6 (7:3 petrol/ethyl acetate); \(^1\)H NMR (CDCl\(_3\), 300 MHz) [rotamers present] \( \delta_H \): 9.87-9.77 (1H, m, CH\(_O\)), 4.11-3.93 (1H, m, H3), 3.88-3.67 (5H, m, Me, H1, H1'), 3.36-3.26 (1H, m, H5), 3.12-2.97 (1H, m, H9), 2.88-2.71 (2H, m, H9', H4), 2.22 (1H, s, H7) and 1.53-1.36 (9H, m, tBu); \( m/z \) (ES\(^+\)) 318 (100%, MNa\(^+\)).
1-tert-Butyl 2-methyl (2S, 3S, 4S)-3-(2,2-diethoxyethyl)-4-ethynylpyrrolidinedicarboxylate 248. A mixture of 218 (50 mg, 0.2 mmol) and mesitylsulfonyl hydrazide (36 mg, 0.2 mmol) in EtOH (1.6 ml) was refluxed for 4 h. The reaction mixture was then allowed to cool down and volatiles were removed under vacuum. Purification by flash column chromatography (petrol/ethyl acetate 8:2) afforded the title compound (9 mg, 15 %) as a yellow oil, R_f 0.7 (7:3 petrol/ethyl acetate); ν_max (film)/cm⁻¹ 3256, 2976, 2927, 2895, 1747 and 1704; ¹H NMR (CDCl₃, 300 MHz) [2 rotamers] δ_H: 4.61 (1H, dd, J 6.0, 11.5, H₈), 4.13 (0.35H, d, J 7.0, H₃), 4.03 (0.65H, d, J 8.0, H₃), 3.80-3.39 (9H, m, OCH₂, OCH₂, Me, H₁, H₁'), 3.21-3.08 (1H, m, H₅), 2.48-2.35 (1H, m, H₄), 2.19 (1H, d, J 2.5, H₇), 2.18-2.03 (2H, m, H₉), 1.92-1.77 (1H, m, H₉'), 1.50-1.36 (9H, m, iBu) and 1.29-1.14 (6H, t, J 7.0, 2xOCH₂CH₃); ¹³C NMR (CDCl₃, 75 MHz) [2 rotamers] δ_C: 173.1 (C=O), 154.3 (0.5 NBoc), 153.6 (0.5 NBoc), 101.2 (C₈), 81.4 (C(CH₃)₃ or C≡CH), 80.4 (C(CH₃)₃ or C≡CH), 72.9 (C₇), 63.2 (0.5 C₃), 62.8 (0.5 C₃), 61.8 (OCH₂CH₃), 61.5 (OCH₂CH₃), 52.3 (0.5 CO₂CH₃), 52.1 (0.5 CO₂CH₃), 51.8 (0.5 C₁), 51.6 (0.5 C₁), 42.3 (0.5 C₅), 42.3 (0.5 C₅), 33.5 (C₄), 32.9 (0.5 C₉), 32.8 (0.5 C₉), 28.5 (4.5 C(CH₃)₃), 28.3 (4.5 C(CH₃)₃) and 15.4 (2xOCH₂CH₃); m/z (ES⁺) 392 (100%, MNa⁺); Found MH⁺ 370.2229, C₁₀H₃₂NO₆ requires MH⁺ 370.2224.
3.1.4 Experimental Procedures for Section 2.3: Baeyer-Villiger Oxidation Route.

(3S,3aS,8aS,Z)-2-tert-butyl-3-phenyl-2,3a,4-tetrahydro-1H-oxepino[4,5-c]pyrrole-1,5(8aH)-dione 251. Enone 171 (0.100 g, 0.353 mmol) was dissolved in dry DCM (20 ml) and 3-chloroperoxybenzoic acid (0.079 g, 0.353 mmol) was added. The reaction was left the stir under nitrogen for 24 hours, then quenched by addition of saturated aq. sodium sulphite solution. The mixture was extracted with DCM (2 x 20 ml) and the combined organic fractions were washed with water (20 ml), dried over magnesium sulfate and the solvents were removed under reduced pressure. Purification by flash column chromatography (2:1 petrol/ethyl acetate) gave the title compound (0.045 g, 43 %) as a colourless solid, m.p 170-172 °C; \( R_f \) 0.28 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 1728 and 1690; \( ^1\text{H} \) NMR (500MHz; CDCl\(_3\)) \( \delta_{\text{H}} \): 7.39-7.36 (2H, m, ArH), 7.33-7.30 (1H, m, ArH), 7.22-7.20 (2H, m, ArH), 6.42 (1H, d, \( J \ 7.0 \), H7), 5.61 (1H, t, \( J \ 6.5 \), H6), 4.70 (1H, s, H3), 3.52 (1H, dd, \( J \ 7.5 \), 7.5 H5), 2.95 (1H, dd, \( J \ 12.5 \), 3.0, H9), 2.85 (1H, dd, \( J \ 12.0 \), 8.5, H9), 2.64 (1H, td, \( J \ 8.0 \), 3.0, H4) and 1.35 (9H, s, tBu); \( ^{13}\text{C} \) NMR (75MHz, CDCl\(_3\)) \( \delta_{\text{C}} \): 172.4 (C=O), 169.2 (NC=O), 142.2 (Ar), 139.8 (C7), 129.2 (2xAr), 128.2 (2xAr), 125.2 (Ar), 111.7 (C6), 67.4 (C(CH\(_3\))\(_3\)), 55.7 (C3), 42.2 (C5), 38.3 (C4), 27.9 (C(CH\(_3\))\(_3\)) and 27.7 (C9); \( m/z \) (ES\(^{+}\)) 322 (100%, MNa\(^{+}\)); Found MNa\(^{+}\) 322.1521, C\(_{18}\)H\(_{21}\)NO\(_3\) requires MNa\(^{+}\) 322.1521.
(1aS,4aS,5S,7aS,7bR)-6-tert-butyl-tetrahydro-5-phenyl-1aH-6,8-dioxabicyclo[5.1.0]oct-1(7)-eno[3,2-c]pyrrole-3,7(7aH,7bH)-dione 265. Enone 171 (0.100 g, 0.353 mmol) was dissolved in dry DCM (20 ml) and 3-chloroperoxybenzoic acid (0.158 g, 0.706 mmol) was added. The reaction was left the stir under nitrogen for 24 hours, and then quenched by addition of saturated aq. sodium sulphite solution. The mixture was extracted with DCM (2 x 20 ml) and the combined organic fractions were washed with water (20 ml), dried over magnesium sulfate and the solvents were removed under reduced pressure. Purification by flash column chromatography (2:1 petrol/ethyl acetate) gave the title compound (0.092 g, 83 %) as a colourless solid, m.p 178-182 °C; $R_f$ 0.22 (1:1 petrol/ethyl acetate); $\nu_{max}$ (film)/cm$^{-1}$ 1728 and 1690; $^1$H NMR (500MHz; CDCl$_3$) $\delta$H: 7.39-7.36 (2H, m, ArH), 7.33-7.30 (1H, m, ArH), 7.21-7.19 (2H, m, ArH), 5.22 (1H, d, $J$ 2.5, H7), 4.48 (1H, s, H3), 3.62 (1H, dd, $J$ 4.0, 2.5, H6), 3.48 (1H, dd, $J$ 7.5, 4.0, H5), 3.23 (1H, dd, $J$ 14.0, 11.5, H9), 2.80 (1H, dd, $J$ 14.0, 3.0, H9$'$), 2.42 (1H, ddd, $J$ 11.0, 8.5, 3.0, 8.5, H4) and 1.36 (9H, s, tBu); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$c; 171.8 (C=O), 168.7 NC=O), 142.1 (Ar), 129.6 (2xAr), 128.6 92xAr), 125.4 (Ar), 79.4 (C7), 67.8 (C(CH$_3$)$_3$), 55.9 (C6), 55.5 (C3), 40.4 (C5), 39.3 (C4), 38.9 (C9) and 27.8 (C(CH$_3$)$_3$); $m/z$ (ES$^+$) 316 (80%, MH$^+$), 338 (100%, MNa$^+$); Found MNa$^+$, 338.1363. C$_{18}$H$_{21}$NO$_4$ requires MNa$^+$ 338.1363.

(3S,3aS,7aR)-3-phenyl-2,3,3a,4-tetrahydro-1H-isooindole-1,5(7aH)-dione 266. Enone 104 (113 mg, 0.33 mmol) was dissolved in trifluoroacetic acid (5 ml) and heated at reflux for thirty minutes. The trifluoroacetic acid was removed under reduced pressure, then the compound was diluted with DCM (15 ml). The
solution was washed with saturated aq. sodium bicarbonate solution (15 ml). The organic fraction was dried over sodium sulfate then the solvent removed under reduced pressure. Purification by flash chromatography (1:1 petrol/ethyl acetate → ethyl acetate) gave the title compound (59.5 mg, 80 %) as a colourless film, $R_f$ 0.44 (ethyl acetate); $^1$H NMR (300MHz, CDCl$_3$) $\delta$: 7.39-7.28 (5H, m, ArH), 6.81 (1H, ddd, J 10.0, 3.0, 1.0, H6), 6.58 (1H, bs, NH), 6.24 (1H, dd, J 10.0, 3.0, H7), 4.33 (1H, d, J 8.0, H3), 3.47 (1H, dt, J 8.0, 3.0, H5), 2.87-2.82 (1H, m, H4) and 2.58-2.48 (2H, m, H9, H9'); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 198.6 (C=O), 175.4 (NC=O), 147.6 (C6), 143.2 (Ar), 128.8 (2xAr), 127.6 (2xAr), 126.6 (C7), 125.4 (Ar), 47.9 (C3), 44.4 (C5), 42.6 (C4) and 28.9 (C9); $m/z$ (CI) 228 (100%, MH$^+$); Found MH$^+$ 227.0947, C$_{14}$H$_{13}$NO$_2$ requires MH$^+$ 227.0946.

(3S,3aS,7aR)-3-phenyl-2-(2-phenylpropan-2-yl)hexahydro-1H-isooindole-1,5(6H)-dione 268. Enone 104 (3.0 g, 8.7 mmol) and 5 % Pd/C (5 % w/v) was dissolved in ethyl acetate (100 ml) and placed into a hydrogenator® at atmospheric pressure. The reaction was left to stir under hydrogen for 1 hour. The reaction mixture was filtered and concentrated under reduce pressure to yield the title compound (2.9 g, 96 %) as a colourless solid, $R_f$ 0.40 (1:1 petrol:ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1684 and 1696; $^1$H NMR (500MHz; CDCl$_3$) $\delta$: 7.37-7.18 (10H, m, ArH), 4.40 (1H, s, H3), 3.11-3.07 (1H, m, H5), 2.61 (1H, dd J 7.0, 15.5, H9), 2.57-2.52 (1H, m, H4), 2.38 (1H, dd, J 14.0, 8.0, H9$'$), 2.31-2.25 (1H, m, H6), 2.23-2.16 (2H, m, H7, H7$'$), 1.99-1.92 (1H, m, H6$'$), 1.80 (3H, s, Me) and 1.50 (3H, s, Me); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$: 210.9 (C=O), 174.9 (NC=O), 146.1 (Ar), 142.3 (Ar), 129.0 (2xAr), 128.1 (2xAr), 127.9 (2xAr), 126.9 (Ar), 125.7 (2xAr), 125.4 (Ar), 68.3 (CH$_3$)$_3$, 59.4 (C3), 43.4 (C5), 42.4 (C4), 38.7 (C7 or C9), 37.2 (C7 or C9), 27.9 (CH$_3$)$_2$Ph, 26.8 (CH$_3$)$_2$Ph), and 22.6 (C6); $m/z$ (ES$^+$) 370.2 (100%, M$^{Na^+}$); Found M$^{Na^+}$ 370.1778, C$_{23}$H$_{25}$NO$_2$ requires M$^{Na^+}$ 370.1778.
(3S,3aS,7aR)-3-phenylhexahydro-1H-isooindole-1,5(6H)-dione 268b. Enone 268 (0.082 g, 0.24 mmol) was stirred in TFA at reflux for 3 h. TFA was evaporated under reduced pressure. Purification by flash chromatography, eluting with 1:2 petrol-EtOAc afforded the title compound (0.071 g, quant.) as a colourless film, $R_f$ 0.07 (1:1 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1701; $^1$H NMR (400MHz; CDCl$_3$) $\delta$: 7.39-7.25 (5H, m, ArH), 6.28 (1H, bs, NH), 4.27 (1H, d, $J$ 5.0, H3), 2.91 (1H, dt, $J$ 6.5, 9.0, H5), 2.82-2.76 (1H, m, H4), 2.62 (1H, dd, $J$ 6.5, 15.5, H9 [A of ABX]), 2.50 (1H, dd, $J$ 6.5, 15.5, H9' [B of ABX]), 2.38-2.35 (2H, m, H7, H7') and 2.30-2.12 (2H, m, H6, H6'); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$: 210.3 (C=O), 178.2 (NC=O), 140.7 (Ar), 129.1 (2xAr), 128.4 (2xAr), 125.6 (Ar), 62.8 (C3), 43.8 (C5), 41.2 (C4), 38.7 (C7 or C9), 37.6 (C7 or C9) and 22.7 (C6); $m/z$ (ES$^+$) 252.2 (100%, M+Na$^+$); Found MH$^+$ 230.1178, C$_{14}$H$_{16}$NO$_2$ requires MH$^+$ 230.1102.

(3S,3aS,7aR)-tert-butyl 1,5-dioxo-3-phenylhexahydro-1H-isooindole-2(3H)-carboxylate 271. Amide 271 (50 mg, 0.218 mmol), 4-dimethylaminopyridine (DMAP) (0.003 g, 0.022 mmol), and di-tert-butyl dicarbonate (0.057 g, 0.261 mmol) were dissolved in dry acetonitrile (5 ml) and left to stir for eighteen hours. Water was added (5 ml) and the mixture extracted with ethyl acetate (3 x 5 ml). The combined organic fractions were washed with saturated aq. sodium bicarbonate solution (10 ml), and then dried over sodium sulfate and the solvents removed under reduced pressure. Purification by flash chromatography (2:1 petrol/ethyl acetate→ethyl acetate) gave the title compound (0.060 mg, 85 %) as an colourless solid, $R_f$ 0.5 (1:1 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1782, 1742
and 1718; $^1$H NMR (400MHz; CDCl$_3$) δ$_H$: 7.38-7.28 (3H, m, ArH), 7.19-7.17 (2H, m, ArH), 4.75 (1H, d, J 1.5, H3), 3.04-2.99 (1H, m, H5), 2.71-2.62 (2H, m, H9, H4), 2.50-2.37 (3H, m, H9', H7, H6), 2.31-2.24 (1H, m, H7), 2.08-1.99 (1H, m H6) and 1.30 (9H, s, H4); $^{13}$C NMR (75MHz, CDCl$_3$) δ$_C$: 209.4 (C=O), 174.4 (NC=O)), 149.5 (NBoc), 139.9 (Ar), 128.9 (2xAr), 127.9 (2xAr), 124.8 (Ar), 83.5 (C(CH$_3$)$_3$), 65.8 (C3), 42.5 (C5), 41.6 (C4), 39.7 (C7 or C9), 37.5 (C7 or C9), 27.6 (C(CH$_3$)$_3$) and 22.8 (C6); m/z (ES$^+$) 352.2 (100%, MNa$^+$); Found MH$^+$ 330.1695, C$_{19}$H$_{24}$NO$_4$ requires MH$^+$ 330.1627.

(3aR,7aS)-2-tert-butyl 1-methyl 3,6-dioxohexahydro-1H-isooindole-1,2(3H)-dicarboxylate 273. Sodium periodate (11.7 g, 3.04 mmol) was added to a solution of H$_2$O (40 ml)/acetonitrile (20 ml). RuCl$_3$.xH$_2$O (0.06 g, 0.32 mmol) was added and the mixture was stirred for 10 minutes. Lactam 271 (1.00 g, 3.04 mmol) was dissolved in EtOAc (20 ml) and added dropwise to the reaction mixture and was allowed to stir for 24 hours. The solution was then filtered over celite and extracted with EtOAc. The combined organic layer was washed with water, dried using magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography eluting with 2:1 petrol-EtOAc to yield the title compound (0.400 g, 39 %) as an amorphous solid, $R_f$ 0.60 (1:1 petrol/ethyl acetate); $\nu_{\max}$ (film)/cm$^{-1}$ 1732 and 1676; $^1$H NMR (400MHz; CDCl$_3$) δ$_H$: 4.23 (1H, d, J 1.5, H3), 3.77 (3H, s, OMe), 3.00-2.96 (1H, m, H5), 2.85-2.78 (1H, m, H4), 2.63 (1H, dd, J 15.0, 6.0, H9), 2.43-2.19 (4H, m, H6, H7, H7', H9'), 2.08-1.99 (1H, m, H6'), 1.48 (9H, s, H4); $^{13}$C NMR (75MHz, CDCl$_3$) δ$_C$: 208.4 (C=O), 184.7 (CO$_2$Me), 173.0 (NC=O), 170.4 (NBoc), 84.2 (C(CH$_3$)$_3$), 63.0 (C3), 52.8 (CO$_2$CH$_3$), 42.5 (C5), 40.4 (C4), 37.2 (C7 or C9), 35.9 (C7 or C9), 27.8 (C(CH$_3$)$_3$) and 22.4 (C6); m/z (ES$^+$) 334.1 (100%, MNa$^+$); Found MNa$^+$ 334.1257, C$_{15}$H$_{21}$NO$_6$ requires MNa$^+$ 334.1267.
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(3R,4S,5S)-1-tert-butyl-3,4-bis(2-hydroxyethyl)-5-phenylpyrrolidin-2-one 278. A solution lactone 251 (50 mg, 0.2 mmol) in THF (4 ml) was cooled to -78 °C. DIBAL-H (1M solution in hexanes, 0.50 ml, 0.50 mmol) was added slowly and the solution was allowed to stir for 1 hour. The reaction was quenched with MeOH (2 ml). The mixture was extracted with diethyl ether (10 ml) and washed with water (10ml), dried over magnesium sulfate and concentrated under reduced pressure (32 mg, 63 %) as a colourless film, \( R_f \) 0.22 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 3260 and 1652; \(^1\)H NMR (500MHz; CDCl\(_3\)) \( \delta_H \): 7.38-7.35 (2H, m, ArH), 7.29-2.25 (3H, m, ArH), 4.84 (1H, s, H3), 3.95-3.90 (2H, m, H8 H8), 3.80 (1H, dt, \( J \) 11.0, 8.0, 4.0, H7), 3.62 (1H, td, \( J \) 10.0, 2.0, H7), 2.99-2.94 (1H, m, H5), 2.21-2.15 (1H, m, H4), 1.94-1.84 (1H, m, H6), 1.82-1.75 (1H, m, H9), 1.55-1.47 (2H, m, H9, H6) and 1.36 (9H, s, tBu); \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \( \delta_c \): 174.1 (NC=O), 140.6 (Ar), 129.2 (2xAr), 128.1 (2xAr), 125.3 (Ar), 67.1 (C7 & C8), 65.9 (C3), 55.1 (C(CH\(_3\))\(_3\)), 41.8 (C5), 40.7 (C4), 37.2 (C6 or C9), 30.9 (C6 or C9) and 27.9 (C(CH\(_3\))\(_3\)); \( m/z \) (ES\(^+\)) 328.6 (100%, MNa\(^+\)); Found MH\(^+\) 306.2643, C\(_{18}\)H\(_{27}\)NO\(_3\) requires MH\(^+\) 306.2147.

(3S,3aS,8aS,Z)-3-phenyl-2-(2-phenylpropan-2-yl)-2,3,3a,4-tetrahydro-1H-oxepino[4,5-c]pyrrole-1,5(8aH)-dione 252. Enone 104 (3.00 g, 8.31 mmol) was dissolved in dry DCM (50 ml) and 3-chloroperoxybenzoic acid (1.45 g, 8.69 mmol) was added. The reaction was left under nitrogen for 24 hours, and then quenched by addition of saturated aq. sodium sulphite solution. The mixture was extracted with DCM (2 x 20 ml) and the combined organic fractions were washed with water (20 ml), dried over magnesium sulfate and the solvents were
removed under reduced pressure. Purification by flash column chromatography eluting with 2:1 petrol/ethyl acetate, gave the title compound (2.1 g, 67 %), as an amorphous solid, Rf 0.55 (1:1 petrol/ethyl acetate); νmax (film)/cm⁻¹ 1690 and 1606; ¹H NMR (400MHz; CDCl₃) δH: 7.36-7.20 (8H, m, ArH), 7.12-7.10 (2H, m, ArH), 6.34 (1H, dd, J 8.0, 4.0, H7) 5.54 (1H, dd, J 8.0, 4.0, H6), 4.55 (1H, s, H3), 3.62 (1H, ddd, J 8.0, 4.0, 2.5, H5), 2.94 (1H, dd, J 12.0, 10.5, H9), 2.87 (1H, dd, J 17.5, 15.5, H9'), 2.64 (1H, td, J 12.5, 3.0, H4), 1.81 (3H, s, Me) and 1.54 (3H, s, Me); ¹³C NMR (75MHz, CDCl₃) δc: 172.0 (C=O), 169.3 (NC=O), 145.6 (Ar), 141.8 (Ar), 138.7 (C7), 129.1 (2xAr), 128.3 (2xAr), 128.1 (2xAr), 127.0 (2xAr), 125.8 (2xAr), 110.9 (C6), 68.5 (C3), 59.86 (C(CH₃)₂Ph), 43.3 (C5), 42.7 (C4), 38.5 (C9), 27.8 (Me) and 26.8 (Me); m/z (ES⁺) 384 (100%, MNa⁺); Found MNa⁺ 384.1576. (4aS,5S,7aS)-tetrahydro-5-phenyl-6-(2-phenylpropan-2-yl)-1aH-6,8-dioxa-bicyclo[5.1.0]oct-1(7)-en-3,7(7aH,7bH)-dione 252b, was also isolated by flash chromatography as an amorphous solid (20 mg, 18 %), Rf 0.56 (1:1 petrol/ethyl acetate); νmax (film)/cm⁻¹ 1685, 1607 and 1251; ¹H NMR (400MHz; CDCl₃) δH: 7.39-7.16 (8H, m, ArH), 7.15-7.10 (2H, m, ArH), 5.19 (1H, d, J 3.5, H6), 4.55 (1H, s, H3), 3.63 (1H, dd, J 4.5, 4.5, H7), 3.49 (1H, dd, J 12.0, 6.0, H5), 3.35 (1H, dd, J 18.5, 18.5, H9), 2.68 (1H, dd, J 18.5, 2.5, H9'), 2.46-2.36 (1H, m, H4), 1.85 (3H, s, Me) and 1.51 (3H, s, Me); ¹³C NMR (75MHz, CDCl₃) δc: 171.9 (C=O), 168.2 (NC=O), 145.7 (Ar), 141.6 (Ar), 129.1 (2xAr), 128.4 (Ar), 128.2 (Ar), 127.1 (Ar), 125.6 (Ar), 125.5 (Ar), 125.4 (Ar), 79.2, (C7), 68.6 (C(CH₃)₂Ph), 55.8 (C6), 40.2 (C3), 38.9 (C5), 38.5 (C4), 28.1 (C9) and 27.1 (C(CH₃)₂Ph); m/z (ES⁺) 400.6 (100%, MNa⁺); Found MH⁺ 378.1700, C₂₃H₂₃NO₂ requires MH⁺ 378.1705.

(3S,3aS,8aS,Z)-3-phenyl-2,3,3a,4-tetrahydro-1H-oxepino[4,5-c]pyrrole-1,5(8aH)-dione 267. Lactone 252 (0.08 g, 0.22 mmol) was stirred in TFA at reflux for 3 h. TFA was evaporated under reduced pressure. Purification by flash chromatography, eluting with 1:2 petrol-EtOAc afforded the title compound as a
colourless film, $R_t$ 0.23 (1:1 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3254, 1702 and 1665; $^1$H NMR (400MHz; CDCl$_3$) $\delta$: 7.41-7.32 (3H, m, ArH), 7.27-7.25 (2H, m, ArH), 6.65 (1H, bs, NH), 6.45 (1H, dd, J 7.0, 2.5, H7), 5.55 (1H, dd, J 7.0, 5.0, H6), 4.47 (1H, d, J 4.0, H3), 3.55-3.51 (1H, m, H5), 3.02-2.92 (2H, m, H9, H4) and 2.85-2.76 (1H, m, H9'); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$: 175.9 (C=O), 168.9 (NC=O), 140.5 (Ar), 140.1 (C7), 129.3 (2xAr), 128.8 (2xAr), 125.5 (Ar), 110.5 (C6), 63.1 (C3), 46.5 (C5), 41.2 (C4) and 36.4 (C9); $m/z$ (ES$^+$) 266.8 (100%, MNa$^+$); Found MNa$^+$ 266.0793, C$_{14}$H$_{13}$NO$_3$ requires MNa$^+$ 266.0793.

(1S,8aS,Z)-tert-butyl 3-(tert-butoxycarbonyloxy)-7-oxo-1-phenyl-8,8a-dihydro-1H-oxepino[4,5-c]pyrrole-2(7H)-carboxylate 281. Lactone 267 (70 mg, 0.194), di-tert-butyl dicarbonate (47 mg, 0.213 mmol) and 4-dimethylaminopyridine (DMAP) (2 mg, 0.019 mmol) were dissolved in dry DCM (3 ml) and stirred for 18 hours nitrogen. The reaction was quenched with water (5 ml) and extracted with DCM (2 x 10 ml). The combined organic fractions were dried over sodium sulfate and the solvents were removed under reduced pressure. Purification by column chromatography (3:1 petrol/ethyl acetate) gave the title compound (52 mg, 60 %) as a colourless film, $R_t$ 0.66 (1:1 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1756, 1742 and 1639; $^1$H NMR (400MHz; CDCl$_3$) $\delta$: 7.42-7.32 (5H, m, ArH), 6.49 (1H, d, J 7.0, H7), 5.65 (1H, d, J 7.0, H6), 4.64 (1H, d, J 7.0, H3), 3.30 (1H, ddd, J 10.5, 7.0, 3.5, H4), 2.92 (1H, dd, J 13.0, 11.0, H9 [A of ABX]), 2.82 (1H, dd, J 13.0, 3.5, H9' [B of ABX]), 1.42 (9H, s, tBu) and 1.20 (9H, s, tBu); $m/z$ (ES$^+$) 466.3 (100%, MH$^+$); Found MH$^+$ 466.1832, C$_{23}$H$_{29}$NO$_7$ requires MH$^+$ 466.1842.
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**tert-butyl (3S,3aS)-1-oxo-3-phenyl-2,3,3a,4-tetrahydro-1H-isooindol-5-yl carbonate 283.** Amide 266 (138 mg, 0.608 mmol), di-tert-butyl dicarbonate (133 mg, 0.61 mmol) and 4-dimethylaminopyridine (DMAP) (7.0 mg, 0.1 mmol) were dissolved in dry DCM (5 ml) and stirred for 18 hours nitrogen. The reaction was quenched with water (5 ml) and extracted with DCM (2 x 10 ml). The combined organic fractions were dried over sodium sulfate and the solvents were removed under reduced pressure. Purification by flash chromatography (2:1→1:2 petrol/ethyl acetate with 1 % triethylamine) gave the title compound (45 mg, 23 %) as a colourless solid, m.p. 154-157 °C; Rf 0.29 (1:1 petrol/ethyl acetate); νmax (film)/cm⁻¹ 3241, 2978, 1756 and 1692; ¹H NMR (300MHz, CDCl₃) δH: 7.39-7.31 (5H, m, ArH), 6.75 (1H, dd, J 6.0, 3.5, H6), 6.47 (1H, bs, H4), 6.04 (1H, dd, J 6.0, 3.0, H7), 4.31 (1H, d, J 7.0, H3), 3.00-2.92 (1H, m, H4), 2.68 (1H, dt, J 17.0, 2.5, H9), 2.49 (1H, dd, J 16.5, 9.5, H9') and 1.48 (9H, s, tBu); ¹³C NMR (75 MHz, CDCl₃) δc: 169.4 (NC=O), 152.8 (COBoc), 150.8 (OBoc), 140.2 (Ar), 130.0 (C6), 129.3 (2xA), 128.8 (C5), 126.4 (2xA), 123.6 (Ar), 111.8 (C7), 84.2 (C(CH₃)₃), 64.3 (C3), 44.3 (C4), 30.2 (C9) and 27.9 (C(CH₂)₃); m/z (CI) 328 (20%, MH⁺), 228 (M-Boc); Found MH⁺ 328.1545, C₁₉H₂₁NO₄ requires MH⁺ 328.1543.

**lactone 252** (5.00 g, 13.9 mmol) and 5 % Pd/C (5 % w/v) were dissolved in ethyl acetate (100 ml) and placed into a hydrogenator® at 10 bar. The reaction was left the stir under hydrogen for 3 hours. The reaction mixture was filtered and concentrated under reduce pressure to yield the title

(3S,3aS,8aR)-3-phenyl-2-(2-phenylpropan-2-yl)hexahydro-1H-oxepino[4,5-c]pyrrole-1,5(7H)-dione 269. Lactone 252 (5.00 g, 13.9 mmol) and 5 % Pd/C (5 % w/v) were dissolved in ethyl acetate (100 ml) and placed into a hydrogenator® at 10 bar. The reaction was left the stir under hydrogen for 3 hours. The reaction mixture was filtered and concentrated under reduce pressure to yield the title
compound (4.9 g, 97 %) as an amorphous solid, $R_f$ 0.50 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 1740 and 1690; \(^1\)H NMR (400MHz; CDCl\(_3\)) \( \delta \): 7.38-7.16 (10H, m, ArH), 4.36 (1H, s, H3), 4.05 (1H, ddd, \( J \) 13.5, 5.0, 2.5, H7), 3.9 (1H, dd, \( J \) 13.0, 11.5, H7'), 3.01 (1H, td, \( J \) 6.0, 2.5, H5), 2.7 (1H, dd, \( J \) 13.0, 13.0, H9), 2.61 (1H, dd, \( J \) 13.0, 3.0, H9'), 2.4-2.31 (2H, m, H6, H4), 1.83 (3H, s, Me), 1.78-1.68 (1H, m, H6') and 1.47 (3H, s, Me); \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \( \delta \): 174.1 (C=O), 172.6 (NC=O), 145.6 (Ar), 140.5 (Ar), 129.1 (2xAr), 128.7 (2xAr), 128.2 (2xAr), 127.3 (2xAr), 125.6 (Ar), 125.4 (Ar), 67.6 (C7), 65.9 (C3), 59.3 (C(CH\(_3\))\(_2\)Ph), 41.8 (C5), 40.6 (C4), 37.1 (C9), 27.8 (C6), 26.9 (C(CH\(_3\))\(_2\)Ph) and 26.1 (C(CH\(_3\))\(_2\)Ph); \( m/z \) (ES\(^+\)) 386 (100 %, MNa\(^+\)); Found MNa\(^+\) 386.1732, C\(_{23}\)H\(_{25}\)NO\(_3\) requires MNa\(^+\) 386.1732.

(3S,3aS,8aR)-3-phenylhexahydro-1H-oxepino[4,5-c]pyrrole-1,5(7H)-dione

Lactone 269 (0.08 g, 0.22 mmol) was stirred in TFA at reflux for 3 h. TFA was evaporated under reduced pressure. Purification by flash chromatography, eluting with 1:2 petrol/ethyl acetate afforded the title compound as an amorphous solid, $R_f$ 0.42 (1:2 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 1752 and 1647; \(^1\)H NMR (400MHz; CDCl\(_3\)) \( \delta \): 7.38-7.29 (5H, m, ArH), 7.19 (1H, bs, NH), 4.59 (1H, ddd, \( J \) 11.0, 7.0, 5.0, H7), 4.51-4.43 (2H, m, H3, H7'), 2.81-2.75 (2H, m, H5, H4), 2.58 (2H, dd, \( J \) 16.5, 6.5, H9), 2.41 (1H, dd, \( J \) 16.5, 7.0, H9'), 2.15-2.07 (1H, m, H6) and 1.97-1.88 (1H, m, H6'); \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \( \delta \): 179.1 (C=O), 175.8 (NC=O), 139.3 (Ar), 129.0 (2xAr), 128.4 (2xAr), 125.8 (Ar), 66.2 (C7), 61.3 (C3), 44.3 (C5), 40.7 (C4), 32.7 (C9) and 24.2 (C6); \( m/z \) (ES\(^+\)) 268.1 (100%, MNa\(^+\)); Found MH\(^+\) 246.1232, C\(_{14}\)H\(_{25}\)NO\(_3\) requires MH\(^+\) 246.1132.
(3S,3aS,8aR)-tert-butyl 1,5-dioxo-3-phenylhexahydro-1H-oxepino[4,5-c]pyrrole-2(7H)-carboxylate 254. Lactone 285 (3.00 g, 10.1 mmol), di-tert-butyl dicarbonate (2.4 g, 11 mmol) and 4-dimethylaminopyridine (DMAP) (123 mg, 1.01 mmol) were dissolved in dry DCM (25 ml) and stirred for 18 hours nitrogen. The reaction was quenched with water (5 ml) and extracted with DCM (2 x 30 ml). The combined organic fractions were dried over sodium sulfate and the solvents were removed under reduced pressure. Purification by flash chromatography (3:1 petrol/ethyl acetate) gave the title compound (2.86 g, 95 %) as a colourless solid, \(R_f\) 0.66 (1:1 petrol/ethyl acetate); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1752, 1732 and 1659; \(^1\)H NMR (400MHz; CDCl\(_3\)) \(\delta\): 7.40-7.31 (3H, m, ArH), 7.19-7.17 (2H, m, ArH), 4.88 (1H, s, H3), 4.26-4.21 (2H, m, H7, H7'), 3.04-2.98 (2H, m, H9, H5), 2.90 (1H, dd, \(J\) 13.5, 3.0, H9'), 2.61-2.56 (1H, m, H4), 2.54-2.49 (1H, m, H6), 1.98-1.89 (1H, m, H6') and 1.35 (9H, s, tBu); \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \(\delta\): 173.3 (C=O), 172.2 (NC=O), 149.6 (NBoc), 138.6 (Ar), 128.6 (2xAr), 128.2 (2xAr), 124.9 (Ar), 83.8 (C(CH\(_3\))\(_3\)), 65.7 (C7), 65.6 (C3), 41.6 (C5), 39.8 (C4), 36.8 (C9), 27.7 (C(CH\(_3\))\(_2\)) and 25.9 (C6); \(m/z\) (ES\(^+\)) 368.2 (100%, MNa\(^+\)); Found MNa\(^+\) 368.1478, C\(_{19}\)H\(_{23}\)NO\(_5\) requires MNa\(^+\) 368.1468.

(2S,3S,4R)-1-tert-butyl 2-methyl 3,4-bis(2-methoxy-2-oxoethyl)-5-oxopyrroolidine-1,2-dicarboxylate 286. Sodium periodate (0.55 g, 2.61 mmol) was added to a solution of H\(_2\)O (3 ml)/acetonitrile (1.5 ml). RuCl\(_3\).xH\(_2\)O (3.00 mg, 0.02 mmol) was added and the mixture was stirred for 10 minutes. Lactam 254 (0.05 g, 0.15 mmol) was dissolved in EtOAc (20 ml) and added dropwise to the reaction mixture and was allowed to stir for 24 hours. The solution was then
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filtered over celite and extracted with EtOAc. The combined organic layer was washed with water, dried using magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography eluting with 2:1 petrol-EtOAc to yield the title compound (0.025 g, 44 %) as a waxy film, Rf 0.34 (1:1 petrol/ethyl acetate); ν_{max} (film)/cm^{-1} 1782, 1722 and 1642; ^1H NMR (400MHz; CDCl_{3}) δ_{H}: 4.45 (1H, d, J 1.0, H3), 3.82 (3H, s, OMe), 3.72 (3H, s, OMe), 3.70 (3H, s, OMe), 3.33 (1H, ddd, J 10.0, 8.0, 4.5, H5), 3.07-3.01 (1H, m, H4), 2.91 (1H, dd, J 17.5, 5.0, H6), 2.49 (1H, dd, J 16.0, 5.0, H9), 2.39 (1H, dd, J 17.5, 10.5, H6), 2.32 (1H, d, J 16.0, 9.0, H9') and 1.48 (9H, s, tBu); ^13C NMR (75MHz, CDCl_{3}) δ_c: 172.3 (C=O), 171.6 (C=O), 171.2 (C=O), 170.6 (NC=O), 149.4 (NBoc), 84.1 (C(CH_{3})_{3}), 61.9 (C3), 52.9 (OCH_{3}), 52.3 (OCH_{3}), 52.2 (OCH_{3}), 41.8 (C5), 34.7 (C4), 33.7 (C6 or C9), 30.2 (C6 or C9), and 27.9 (C(CH_{3})_{2}); m/z (ES+)^+ 410.1 (100%, MNa^+); Found MNa^+ 410.1430, C_{17}H_{25}NO_{9} requires MNa^+ 410.1422.

**ethyl 2-((2S,3S,4R)-1-tert-butyl-5-oxo-4-(2-oxoethyl)-2-phenylpyrrolidin-3-yl)acetate 287.** Lactone 251 (0.05 g, 0.17 mmol) was dissolved in a 1:1 mixture of DCM:EtOH (6ml). Potassium carbonate (0.05 g, 0.33 mmol) was added and the mixture was stirred for 2 hours. The mixture was concentrated under reduced pressure and dissolved in DCM. The organic was washed with water (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography eluting with 2:1 petrol/ethyl acetate, gave the title compound (0.045 g, 77 %) as an amorphous solid, Rf 0.53 (1:1 petrol:ethyl acetate); ν_{max} (film)/cm^{-1} 1755 and 1684; ^1H NMR (400MHz; CDCl_{3}) δ_{H}: 9.81 (1H, s, CHO), 7.38-7.27 (5H, m, ArH), 4.70 (1H, s, H3), 4.24 (2H, q, J 7.5, OCH_{2}(CH_{3})), 3.40 (1H, dt, J 7.5, 7.5, H5) 2.93 (1H, dd, J 18.0, 6.0, H6), 2.64 (1H, ddd, J 11.0, 7.0, 4.0, H4), 2.35 (1H, dd, J 18.0, 8.0, H6), 2.33 (1H, dd, J 16.0, 4.0, H9), 2.25 (1H, dd, J 16.0, 11.0, H9'), 1.35 (9H, s, tBu), 1.32 (3H, t, J
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7.0, OCH$_2$CH$_3$); $^{13}$C NMR (75MHz, CDCl$_3$) δ$_c$: 200.2 (CHO), 174.5 (C=O), 171.9 (NC=O), 141.5 (Ar), 129.1 (2xAr), 128.8 (2xAr), 127.6 (Ar), 65.2 (OCH$_2$CH$_3$), 60.9 (C3), 54.9 (C(CH$_3$)$_3$), 42.0 (C5), 40.0 (C4), 38.0 (C6), 34.4 (C9), 27.5 (C(CH$_3$)$_3$) and 14.2 (OCH$_2$CH$_3$); m/z (ES$^+$) 346.2 (100%, MNa$^+$); Found MNa$^+$ 346.2000, C$_{20}$H$_{28}$NO$_4$ requires MNa$^+$ 346.2013.

**ethyl 2-((2S,3S,4R)-5-oxo-4-(2-oxoethyl)-2-phenyl-1-(2-phenylpropan-2-yl)pyrrolidin-3-yl)acetate 288.** Lactone 252 (0.10 g, 0.28 mmol) was dissolved in a 1:1 mixture of DCM:EtOH (10ml). Potassium carbonate (0.08 g, 0.55 mmol) was added and the mixture was stirred for 2 hours. The mixture was concentrated under reduced pressure and dissolved in DCM. The organic was washed with water (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography eluting with 2:1 petrol/ethyl acetate, gave the title compound (0.101 g, 89 %) as an amorphous solid, R$_f$ 0.44 (1:1 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1755 and 1684; $^1$H NMR (300MHz; CDCl$_3$) δ$_H$: 9.69 (1H, s, CH$_O$), 7.35-7.13 (10H, m, ArH), 4.65 (1H, s, H3), 4.14 (2H, q, J 7.0, OCH$_2$CH$_3$), 3.40 (1H, dt, J 8.0, 6.0, H5), 2.79 (1H, dd, J 18.0, 6.0, H6), 2.65-2.54 (1H, m, H6$'$), 2.27-2.10 (3H, m, H9, H9$'$, H4), 1.78 (3H, s, Me), 1.41 (3H, s, Me) and 1.24 (3H, t, J 7.0, OCH$_2$CH$_3$); $^{13}$C NMR (75MHz, CDCl$_3$) δ$_c$: 200.2 (CHO), 174.3 (C=O), 171.8 (NC=O), 146.0 (Ar), 141.6 (Ar), 128.8 (2xAr), 128.1 (2xAr), 127.7 (2xAr), 126.9 (2xAr), 125.8 (Ar), 125.4 (Ar), 65.8 (OCH$_2$CH$_3$), 60.9 (C3), 59.1 (C(CH$_3$)$_2$Ph), 41.9 (C5), 40.0 (C4), 37.9 (C6), 34.6 (C9), 28.2 (C(CH$_3$)$_2$Ph), 26.7 (C(CH$_3$)$_2$Ph) and 14.3 (OCH$_2$CH$_3$); m/z (ES$^+$) 430.3 (100%, MNa$^+$); Found MH$^+$ 407.2300, C$_{25}$H$_{29}$NO$_4$ requires MH$^+$ 407.2116.
ethyl 2-((2S,3S,4R)-5-oxo-4-(2-oxoethyl)-2-phenylpyrrolidin-3-yl)acetate 289.

Aldehyde 288 (0.06 g, 0.15 mmol) was dissolved in trifluoroacetic acid (5 ml) and heated at reflux for thirty minutes. The trifluoroacetic acid was removed under reduced pressure and the compound diluted with DCM (15 ml). The solution was washed with saturated aq. sodium bicarbonate solution (15 ml). The organic fraction was dried over sodium sulfate then the solvent was removed under reduced pressure. Purification by flash chromatography (1:1 petrol/ethyl acetate $\rightarrow$ ethyl acetate) gave the title compound (0.03 g, 71 %) as a waxy solid, $R_t$ 0.55 (ethyl acetate); $^1$H NMR (400MHz, CDCl$_3$) $\delta$: 9.79 (1H, s, CHO), 7.39-7.26 (5H, m, ArH), 6.50 (1H, bs, NH), 4.50 (1H, d, $J$ 3.5, H3), 4.13 (2H, q, $J$ 7.0, OCH$_2$CH$_3$), 3.22 (1H, td, $J$ 9.0, 5.0, H5), 2.93-2.85 (2H, m, H6, H6'), 2.58 (1H, ddd, $J$ 18.0, 8.5, 1.0, H4), 2.41 (1H, dd, $J$ 16.5, 9.0, H9 [A of ABX]), 2.34 (1H, dd, $J$ 16.5, 7.0, H9' [B of ABX]) and 1.22 (3H, t, $J$ 7.0, OCH$_2$CH$_3$); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$: 199.9 (CHO), 177.7 (C=O), 171.6 (NC=O), 140.2 (Ar), 128.9 (2xAr), 128.1 (2xAr), 125.8 (Ar), 61.1 (OCH$_2$CH$_3$), 60.9 (C3), 43.3 (C5), 40.0 (C4), 33.7 (C6), 29.7 (C9) and 14.2 (OCH$_2$CH$_3$); m/z (ES$^-$) 312 (100%, MNa$^+$); Found MNa$^+$ 312.1211, C$_{16}$H$_{19}$NO$_4$ requires MNa$^+$ 312.1212.

methyl 2-((2S,3S,4R)-4-(2-hydroxyethyl)-5-oxo-2-phenyl-1-(2-phenylpropan-2-yl)pyrrolidin-3-yl)acetate 292. Lactone 269 (100 mg, 0.28 mmol) was dissolved in a MeOH (10 ml) and cooled to -78 °C. Sodium methoxide (1M, 1.38 mmol) was added dropwise and the mixture was stirred for 2 hours. The mixture was quenched with sodium bicarbonate solution. The mixture was extracted with EtOAc (2 x 10 ml). The organic was washed with water (10 ml), dried over
magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography eluting with 2:1 petrol/ethyl acetate, gave the title compound (102 mg, 94 %) as an amorphous solid, $R_f 0.34$ (1:1 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3266 and 1652; $^1$H NMR (400MHz; CDCl$_3$) $\delta$: 7.26-7.14 (10H, m, ArH), 4.57 (1H, s, H3), 3.63 (1H, s, OMe), 3.57 (1H, dt, $J_{11.0}$, 5.0, H7), 3.44 (1H, td, $J_{9.5}$, 3.0, H7$'$), 2.91 (1H, ddd, $J_{9.5}$, 7.0, 4.5, H5), 2.47-2.37 (2H, m, H4, H9), 2.16 (1H, dd, $J_{12.0}$, 11.5, H9$'$), 1.78 (3H, s, Me), 1.71-1.62 (1H, m, H6), 1.40 (3H, s, Me) and 1.38-1.31 (1H, m, H6$'$); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$: 176.7 (C=O), 172.5 (NC=O), 145.5 (Ar), 141.0 (Ar), 128.5 (2xAr), 127.8 (2xAr), 127.4 (2xAr), 126.6 (2xAr), 125.5 (Ar), 125.1 (Ar), 66.0 (C7), 61.7 (C3), 59.0 (C(CH$_3$)$_2$Ph), 51.6 (OCH$_3$), 43.1 (C5), 42.9 (C4), 33.6 (C9), 28.5 (C6), 27.9 (C(CH$_3$)$_2$Ph) and 26.3 (C(CH$_3$)$_2$Ph); m/z (ES$^+$) 396.4 (100%, MH$^+$); Found MNa$^+$ 418.2086, C$_{24}$H$_{29}$NO$_4$ requires MNa$^+$ 418.2097.

(3R,4S,5S)-tert-buty 3-(2-hydroxyethyl)-4-(2-methoxy-2-oxoethyl)-2-oxo-5-phenylpyrrolidine-1-carboxylate 293. Lactone 254 (0.20 g, 0.58 mmol) was dissolved in a MeOH (10 ml) and cooled to -78 °C. Sodium methoxide (1M, 2.89 mmol) was added dropwise and the mixture was stirred for 2 hours. The mixture was quenched with sodium bicarbonate solution. The mixture was extracted with EtOAc (2 x 10 ml). The organic was washed with water (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography eluting with 2:1 petrol/ethyl acetate, gave the title compound (0.174 g, 80 %) as a colourless film, $R_f 0.45$ (1:1 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3643, 1752, 1732 and 1659; $^1$H NMR (400MHz; CDCl$_3$) $\delta$: 7.39-7.28 (5H, m, ArH), 4.98 (1H, s, H3), 3.81-3.68 (5H, m, OMe, H7, H7$'$), 2.96 (1H, td $J_{8.0}$, 6.0, H5), 2.75-2.69 (1H, m, H4), 2.58 (1H, dd $J$ 17.0, 4.5, H9 [A of ABX]), 2.41 (1H, dd $J$ 17.0, 11.0, H9$'$ [B of ABX]), 1.99-1.90 (1H, m, H6), 1.64-1.56 (1H, m, H6$'$) and 1.33 (9H, s, tBu); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$: 176.2 (C=O),
172.4 (NC=O), 149.6 (NBoc), 139.6 (Ar), 128.8 (2xAr), 127.8 (2xAr), 125.1 (Ar),
83.6 (C(CH₃)₃), 64.7 (C7), 61.3 (C3), 52.1 (OCH₃), 42.6 (C5), 41.1 (C4), 33.4
(C9), 28.4 (C6) and 27.7 (C(CH₃)₃); m/z (ES⁺) 378.2 (100%, MH⁺); Found MH⁺
378.1823, C₂₀H₂₇NO₆ requires MH⁺ 378.1838.

(2S,3S,4R)-tert-butyl 3-(2-methoxy-2-oxoethyl)-5-oxo-2-phenyl-4-(2-(2,2,2-
trichloroacetoxy)ethyl)pyrrolidine-1-carboxylate 307. Alcohol 293 (0.100 g,
0.265 mmol) was dissolved in DCM (5 ml). Triethylamine (0.05 ml, 0.318 mmol)
and trichloroacetyl chloride (0.058 ml, 0.318 mmol) were added and the mixture
was allowed to stir for 2 hours at R.T. The reaction was quenched with water (2
ml) and extracted with DCM (2 x 10 ml). The combined organic layers was dried
with magnesium sulfate and evaporated under reduced pressure. Purification by
flash chromatography, eluting with 6:1 petrol-EtOAc afforded the title compound
(0.135 g, 98 %) as a colourless oil, R₇ 0.61 (1:1 petrol/ethyl acetate); v_max
(film)/cm⁻¹ 1769, 1732 and 1659; ¹H NMR (400MHz; CDCl₃) δH: 7.37-7.27 (5H,
m, ArH), 5.04 (1H, s, H3), 4.51 (1H, dt, J 6.0, 11.0, H7), 4.40 (1H, ddd, J 11.0,
8.5, 5.5, H7’), 3.78 (3H, s, OMe), 2.91 (1H, dt, J 7.5, 7.0, H5), 2.78-2.73 (1H, m,
H4), 2.60 (1H, dd, J 17.0, 3.5, H9 [A of ABX]), 2.41 (1H, dd, J 17.0, 11.5, H9
[B of ABX]), 2.29 (1H, dq, J 6.0, 5.5, H6), 1.86-1.77 (1H, m, H6’) and 1.36 (9H, s,
tBu); ¹³C NMR (75MHz, CDCl₃) δc: 173.8 (C=O), 172.1 (NC=O), 161.6
(CCl₃C=O), 149.7 (NBoc), 139.4 (Ar), 128.8 (2xAr), 127.8 (2xAr), 124.9 (Ar),
89.8 (CCl₃), 83.5 (C(CH₃)₃), 67.5 (C7), 63.9 (C3), 52.1 (OCH₃), 40.7 (C5), 40.5
(C4), 33.1 (C9), 27.8 (C(CH₂)₂) and 23.9 (C6); m/z (ES⁺) 544.3 (100%, MNa⁺);
Found MH⁺ 522.0853, C₂₂H₂₆Cl₃NO₇ requires MH⁺ 522.0853.
(3S,4R)-methyl 3-(2-methoxy-2-oxoethyl)-5-oxo-4-(2-(2,2,2-trichloroacetoxy)ethyl)pyrrolidine-2-carboxylate 308. Sodium periodate (0.74 g, 3.44 mmol) was added to a solution of H$_2$O (12 ml)/acetonitrile (6 ml). RuCl$_3\cdot$H$_2$O (0.004 g, 0.019 mmol) was added and the mixture was stirred for 10 minutes. Lactam 307 (0.1 g, 0.192 mmol) was dissolved in EtOAc (6 ml) and added dropwise to the reaction mixture and was allowed to stir for 24 hours. The solution was then filtered over celite and extracted with EtOAc. The combined organic layer was washed with water, dried using magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography eluting with 2:1 petrol-EtOAc to yield the title compound (0.035 g, 36 %) and recovered starting material (10 mg, 10 %), $R_f$ 0.45 (1:1 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1752, 1732 and 1659; $^1$H NMR (400MHz; CDCl$_3$) $\delta_H$: 4.55 (1H, dt, 11.0, 5.5, H7), 4.46-4.40 (2H, m, H7', H3), 3.79 (3H, s, OMe), 3.71 (3H, s, OMe), 2.94-2.90 (2H, m, H5, H4), 2.59 (1H, dd, J 17.0, 4.0, H9), 2.35-2.21 (2H, m, H9', H6), 1.86-1.77 (1H, m, H6') and 1.47 (9H, s, tBu); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta_c$: 172.6 (C=O), 171.3 (C=O), 170.6 (NC=O), 161.8 (COCCl$_3$), 148.4 (NBoc), 89.5 (CCl$_3$), 84.2 (C(CH$_3$)$_3$), 67.7 (C7), 61.8 (C3), 52.9 (OCH$_3$), 52.3 (OCH$_3$), 42.3 (C5), 35.3 (C4), 33.3 (C9), 27.9 (C(CH$_3$)$_3$) and 22.4 (C6); $m/z$ (ES$^+$) 526.4 (100%, MH$^+$); Found MH$^+$ 526.0404, C$_{22}$H$_{26}$Cl$_3$NO$_7$ requires MH$^+$ 526.0414.
3.1.5 Experimental Procedures for Section 2.4: Silicon-Mediated Fragmentation Route.

(3S,3aS,7aR)-3-phenyl-2-(2-phenylpropan-2-yl)-7-((trimethylsilyl) hexahydro-1H isoindole-1,5(6H)-dione 315. A solution of HMPA (3.20 ml, 18.4 mmol) and HMDS (1.54 ml, 7.54 mmol) in THF (25 ml) was cooled to 0 °C. Methyl lithium (3.99 ml, 6.38 mmol) was then added in one portion and the reaction was left to stir for 15 minutes. Copper cyanide (285 mg, 3.19 mmol) was then added in one portion and the reaction was left to stir for 30 minutes. After this time the reaction was cooled to -78 °C and a solution of enone 104 (1.00 g, 2.89 mmol) and TMSCl (1.07 ml, 8.67 mmol) was added dropwise. The mixture was allowed to stir at -78 °C for 30 minutes and then quenched with NH₄OH/NH₄Cl solution. The layers were separated and the organic was washed with water (30 ml), brine (30 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (petrol/ethyl acetate 8:2) gave the title compound (1.05 g, 86 %) as a colourless solid, Rf 0.8 (1:1 petrol/ethyl acetate); m.p. 119-121 °C; [α]D24 = 58.0 (c = 1 in CHCl3); νmax (film)/cm⁻¹ 2947, 1722, 1694, 1495, 1455 and 1390; ¹H NMR (400MHz; CDCl3) δH: 7.45-7.24 (10H, m, ArH), 4.43 (1H, s, H3), 3.05 (1H, dd, J 4.0, 4.0, H5), 2.59 (1H, dd, J 12.0, 4.0, H9), 2.48-2.40 (1H, m, H4), 2.39-2.28 (2H, m, H9', H7), 2.15-2.04 (1H, m, H7'), 1.90 (3H, s, Me), 1.75-1.69 (1H, m, H6), 1.55 (3H, s, Me) and 0.00 (9H, s, 3xSiMe); ¹³C NMR (100MHz, CDCl3) δC: 211.4 (C=O), 175.6 (NC=O), 146.1 (Ar), 141.8 (Ar), 129.1 (2xAr), 128.2 (2xAr), 127.9 (2xAr), 127.0 (2xAr), 125.6 (Ar), 125.4 (Ar), 67.4 (C3), 62.3 (C(CH3)2Ph), 43.1 (C5), 42.9 (C4), 39.6 (C7), 38.7 (C9), 28.1 (C(CH3)2Ph), 27.1 (C(CH3)2Ph), 19.9 (C6) and -2.5 (Si(CH3)3)2; m/z (ES⁺) 442.2 (100%, MNa⁺); Found MH⁺ 420.2367, C26H33NO5Si requires MH⁺ 420.2353.
(3S,3aS,7aR)-7-(1,1,2,2,2-pentamethyldisilyl)-3-phenyl-2-(2-phenylpropan-2-yl)hexahydro-1H-isoinodole-1,5(6H)-dione 332 was isolated as a minor impurity (141 mg, 10%) as a colourless oil, \( R_f \) 0.82 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2947, 1719, 1690; \(^1^H\) NMR (400MHz; CDCl\(_3\)) \( \delta \): 7.42-7.22 (10H, m, ArH), 4.37 (1H, s, H3), 3.01 (1H, dd, \( J \) 7.0, 5.0, H5), 2.55 (1H, dd, \( J \) 15.0, 5.5, H9), 2.44-2.22 (3H, m, H4, H9', H7), 1.89-1.86 (4H, m, Me, H6), 1.53 (3H, s, Me) and 0.00 (15H, s, 5xSiMe); \(^1^C\) NMR (100MHz, CDCl\(_3\)) \( \delta \): 211.0 (C=O), 175.3 (NC=O), 145.9 (Ar), 141.6 (Ar), 128.9 (2xAr), 128.1 (2xAr), 127.9 (2xAr), 126.9 (2xAr), 125.5 (Ar), 125.4 (Ar), 67.2 (C3), 59.2 (C(CH\(_3\))\(_2\)Ph), 43.3 (C5), 42.9 (C7), 40.3 (C4), 39.4 (C7), 27.9 (C(CH\(_3\))\(_2\)Ph), 27.0 (C(CH\(_3\))\(_2\)Ph), 18.8 (C6) and -1.83 (Si(CH\(_3\))\(_3\)); \( m/z \) (ES\(^{+}\)) 500.3 (100%, MNa\(^{+}\)); Found MH\(^+\) 478.2601, C\(_{28}\)H\(_{39}\)NO\(_2\)Si\(_2\) requires MH\(^+\) 478.2592.

(3S,3aS,8aR)-3-phenyl-2-(2-phenylpropan-2-yl)-8-(trimethylsilyl)hexahydro-1H-oxepino[4,5-c]pyrrole-1,5(7H)-dione 325. Silylated ketone 315 (160 mg, 0.38 mmol) was dissolved in DCM (5 ml). \( m\)CPBA (131 mg, 0.76 mmol) was added and the reaction was allowed to stir for 48 hours. The reaction was quenched with sodium sulfite solution and the organic was extracted with DCM (20 ml). The organic layer was washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated under reduced pressure to yield a colourless oil. The crude was used without purification in the next step, \( R_f \) 0.44 (7:3 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1739 and 1691; \(^1^H\) NMR (400MHz; CDCl\(_3\)) \( \delta \): 7.46-7.22 (10H, m, ArH), 4.38 (1H, s, H3), 4.20 (1H, dd, \( J \) 13.5, 3.5, H7), 4.11 (1H, d, \( J \) 13.0, H7'), 2.98 (1H, d, \( J \) 6.5, H5), 2.83 (1H, dd, \( J \) 13.0, 13.0, H9 [A of ABX]), 2.64 (1H, dd, \( J \) 13.0, 3.0, H9 [B of ABX]), 2.40 (1H, ddd, \( J \), 13.0, 6.0, 3.0, H4), 1.88 (3H, s, Me), 1.85-1.82 (1H, m, H6), 1.53 (3H, s, Me) and 0.00 (9H, s, 3xSiMe); \(^1^C\) NMR (100MHz, CDCl\(_3\)) \( \delta \): 174.5 (C=O), 172.7 (NC=O), 145.5 (Ar), 140.6 (Ar), 129.1 (2xAr), 128.2 (2xAr), 127.3 (2xAr), 125.5

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**Chapter 3: Experimental Procedures**

(3S,3aS,7aR)-7-(1,1,2,2,2-pentamethyldisilyl)-3-phenyl-2-(2-phenylpropan-2-yl)hexahydro-1H-isoinodole-1,5(6H)-dione 332 was isolated as a minor impurity (141 mg, 10%) as a colourless oil, \( R_f \) 0.82 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2947, 1719, 1690; \(^1^H\) NMR (400MHz; CDCl\(_3\)) \( \delta \): 7.42-7.22 (10H, m, ArH), 4.37 (1H, s, H3), 3.01 (1H, dd, \( J \) 7.0, 5.0, H5), 2.55 (1H, dd, \( J \) 15.0, 5.5, H9), 2.44-2.22 (3H, m, H4, H9', H7), 1.89-1.86 (4H, m, Me, H6), 1.53 (3H, s, Me) and 0.00 (15H, s, 5xSiMe); \(^1^C\) NMR (100MHz, CDCl\(_3\)) \( \delta \): 211.0 (C=O), 175.3 (NC=O), 145.9 (Ar), 141.6 (Ar), 128.9 (2xAr), 128.1 (2xAr), 127.9 (2xAr), 126.9 (2xAr), 125.5 (Ar), 125.4 (Ar), 67.2 (C3), 59.2 (C(CH\(_3\))\(_2\)Ph), 43.3 (C5), 42.9 (C7), 40.3 (C4), 39.4 (C7), 27.9 (C(CH\(_3\))\(_2\)Ph), 27.0 (C(CH\(_3\))\(_2\)Ph), 18.8 (C6) and -1.83 (Si(CH\(_3\))\(_3\)); \( m/z \) (ES\(^{+}\)) 500.3 (100%, MNa\(^{+}\)); Found MH\(^+\) 478.2601, C\(_{28}\)H\(_{39}\)NO\(_2\)Si\(_2\) requires MH\(^+\) 478.2592.

(3S,3aS,8aR)-3-phenyl-2-(2-phenylpropan-2-yl)-8-(trimethylsilyl)hexahydro-1H-oxepino[4,5-c]pyrrole-1,5(7H)-dione 325. Silylated ketone 315 (160 mg, 0.38 mmol) was dissolved in DCM (5 ml). \( m\)CPBA (131 mg, 0.76 mmol) was added and the reaction was allowed to stir for 48 hours. The reaction was quenched with sodium sulfite solution and the organic was extracted with DCM (20 ml). The organic layer was washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated under reduced pressure to yield a colourless oil. The crude was used without purification in the next step, \( R_f \) 0.44 (7:3 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1739 and 1691; \(^1^H\) NMR (400MHz; CDCl\(_3\)) \( \delta \): 7.46-7.22 (10H, m, ArH), 4.38 (1H, s, H3), 4.20 (1H, dd, \( J \) 13.5, 3.5, H7), 4.11 (1H, d, \( J \) 13.0, H7'), 2.98 (1H, d, \( J \) 6.5, H5), 2.83 (1H, dd, \( J \) 13.0, 13.0, H9 [A of ABX]), 2.64 (1H, dd, \( J \) 13.0, 3.0, H9 [B of ABX]), 2.40 (1H, ddd, \( J \), 13.0, 6.0, 3.0, H4), 1.88 (3H, s, Me), 1.85-1.82 (1H, m, H6), 1.53 (3H, s, Me) and 0.00 (9H, s, 3xSiMe); \(^1^C\) NMR (100MHz, CDCl\(_3\)) \( \delta \): 174.5 (C=O), 172.7 (NC=O), 145.5 (Ar), 140.6 (Ar), 129.1 (2xAr), 128.2 (2xAr), 127.3 (2xAr), 125.5
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(2xAr), 125.4 (2xAr), 68.4 (C7), 67.5 (C3), 59.3 (C(CH$_3$)$_2$Ph), 41.9 (C5), 41.8 (C4), 37.2 (C9), 27.6 (C(CH$_3$)$_2$Ph), 27.1 (C(CH$_3$)$_2$Ph), 25.8 (C6) and -2.0 (Si(CH$_3$)$_3$); m/z (ES$^+$) 458 (100%, MNa$^+$).

**Methyl 2-((2S,3S,4R)-5-oxo-2-phenyl-1-(2-phenylprop an-2-yl)-4-vinylpyrrolidin-3-yl)acetate 326.** Lactone 325 (crude) was dissolved in 2:1 methanol/DCM. Two drops of concentrated HCl was added and the reaction was left to stir for 18 hours. The reaction was quenched with NaHCO$_3$ solution and the organic was extracted with ethyl acetate. Purification by column chromatography (petrol/ethyl acetate 4:1) gave the title compound (110 mg, 77% over 2 steps) as a colourless oil, R$_f$ 0.40 (7:3 petrol ethyl acetate); $^1$H NMR (300MHz; CDCl$_3$) $\delta$: 7.36-7.18 (10H, m, ArH), 5.62 (1H, ddd, J 17.5, 10.5, 8.5, H6), 5.16 (2H, dd, J 35.5, 10.5, H7), 4.61 (1H, s, H3), 3.70 (3H, s, OMe), 3.55 (1H, t, J 8.0, H5), 2.61-2.46 (2H, m, H9, H4), 2.22 (1H, dd, J 16.0, 11.0, H9$^\prime$), 1.83 (3H, s, Me) and 1.47 (3H, s, Me); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$: 174.4 (C=O), 172.9 (NC=O), 146.1 (Ar), 142.0 (Ar), 131.5 (C6), 128.9 (2xAr), 128.1 (2xAr), 127.7 (2xAr), 126.9 (2xAr), 126.0 (Ar), 125.5 (Ar), 121.1 (C7), 65.8 (C3), 59.3 (C(CH$_3$)$_2$Ph), 51.9 (OCH$_3$), 47.5 (C5), 44.2 (C4), 34.3 (C9), 28.2 (C(CH$_3$)$_2$Ph) and 27.0 (C(CH$_3$)$_2$Ph); m/z (ES$^+$) 400 (100%, MNa$^+$).

(3S,3aS,7aR)-3-phenyl-7-(trimethylsilyl)hexahydro-1H-isoindole-1,5(6H)-dione 341. Lactam 315 (1.23 g, 2.94 mmol) was dissolved in TFA (12 ml). The reaction was heated at reflux for 1 hour and then allowed to cool to R.T.. The TFA was removed under reduced pressure and the crude was dissolved in DCM (20 ml). The organic was washed with water (10 ml), brine (10 ml), dried over
magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (1:1 petrol/ethyl acetate) gave the title compound (0.819 g, 92%) as a colourless solid, [\(\alpha\)]\(_D\)\(^{25}\) = 95.2 (c = 1 in CHCl\(_3\)); m.p 99-101 \(^\circ\)C; \(R_f\) 0.13 (3:2 petrol/ethyl acetate); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3440, 2952, 1714, 1687 and 1651; \(^1\)H NMR (400MHz; CDCl\(_3\)) \(\delta_H\): 7.41-7.27 (5H, m, ArH), 6.92 (1H, bs, NH), 4.36 (1H, d, \(J\) 3.0, H3), 2.80-2.69 (2H, m, H5, H4), 2.61 (1H, dd, \(J\) 16.0, 6.0, H9 [A of ABX]), 2.50 (1H, dd, \(J\) 16.0, 9.5, H9'[B of ABX]), 2.40 (1H, dd, \(J\) 15.5, 5.0, H7), 2.15 (1H, dd, \(J\) 15.5, 10.5, H7'), 1.64 (1H, ddd, \(J\) 10.5, 7.5, 5.5, H6) and 0.00 (9H, s, 3xSiMe); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta_C\): 211.1 (C=O), 178.6 (NC=O), 140.3 (Ar), 128.8 (2xAr), 128.1 (2xAr), 125.5 (Ar), 61.8 (C3), 45.5 (C5), 41.7 (C4), 39.7 (C7 or C9), 39.3 (C7 or C9), 20.7 (C6) and -2.5 (Si(CH\(_3\))\(_3\)); \(m/z\) (ES\(^+\)) 324 (100%, MNa\(^+\)); Found MNa\(^+\) 324.1389, C\(_{17}\)H\(_{23}\)NO\(_2\) requires MNa\(^+\) 324.1390.

(1S,3aR,7aS)-tert-butyl 3,6-dioxo-1-phenyl-4-(trimethylsilyl)hexahydro-1H-isoinindle-2(3H)-carboxylate 316. Amide 316 (809 mg, 2.69 mmol) was dissolved in DCM (20 ml). Boc\(_2\)O (762 mg, 3.49 mmol), triethylamine (0.37 ml, 2.69 mmol) and DMAP (65.0 mg, 0.54 mmol) was added and the reaction was allowed to stir for 18 hours. The reaction was quenched with water (20ml) and extracted with DCM. The organic layer was washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (4:1 petrol/ethyl acetate) gave the title compound (830 mg, 77%) as a colourless solid, [\(\alpha\)]\(_D\)\(^{25}\) = + 93.6 [reading +0.234] (c = 1 in CHCl\(_3\)); m.p 168 \(^\circ\)C; \(R_f\) 0.71 (1:1 petrol/ethyl acetate); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1782, 1751, 1716 and 1636; \(^1\)H NMR (400MHz; CDCl\(_3\)) \(\delta_H\): 7.39-7.35 (2H, m, ArH), 7.32-7.28 (2H, m, ArH), 7.19-7.17 (2H, m, ArH), 4.79 (1H, s, H3), 2.92 (1H, dd, \(J\) 6.5, 6.5, H5), 2.66 (1H, dd, \(J\) 15.0, 5.0, H7), 2.58-2.52 (1H, m, H4), 2.46-2.38 (2H, m, H7', H9), 2.11 (1H, dd, \(J\) 15.5, 9.0, H9'), 1.73 (1H, dt, \(J\) 12.0, 6.0, H6), 1.31 (9H, s, tBu) and 0.00 (9H, s, 3xSiMe); \(^{13}\)C NMR (100MHz, CDCl\(_3\))
δ_C: 210.0 (C=O), 174.9 (NC=O), 149.6 (NBoc), 139.8 (Ar), 128.9 (2xAr), 127.9 (Ar), 124.7 (2xAr), 83.3 (C(CH_3)_3), 65.2 (C3), 42.5 (C5), 41.0 (C7), 40.8 (C4), 38.5 (C9), 27.6 (C(CH_3)_3), 19.9 (C6) and -2.7 (Si(CH_3)_3); m/z (ES^+) 424.3 (100%, MNa^+); Found MNa^+ 424.1927, C_{22}H_{31}NO_4 requires MNa^+ 424.1915.

(1S,3aR,7aS)-tert-butyl 6-(tert-butoxycarbonyloxy)-3-oxo-1-phenyl-4-(trimethylsilyl)-3a,4,7a-tetrahydro-1H-isooindole-2(3H)-carboxylate 342a and (3S,3aS,7aR)-tert-butyl 5-(tert-butoxycarbonyloxy)-1-oxo-3-phenyl-7-(trimethylsilyl)-3,3a,7,7a-tetrahydro-1H-isooindole-2(6H)-carboxylate 342b were isolated as an inseparable 2:1 mixture (120 mg, 9%) as a colourless solid, m.p 148-150 °C; R_f 0.75 (1:1 petrol/ethyl acetate); \nu_max (film)/cm^{-1} 2979, 1783, 1749, 1721 and 1698; \textsuperscript{1}H NMR (500MHz; CDCl_3) \delta_H: 7.38-7.18 (7.5H, m, ArH), 5.58 (1H, s, H9a), 5.49 (0.5H, d, J 4.0, H7b), 4.89 (1H, d, J 2.0, H3b), 4.86 (1H, s, H3a), 2.84 (1H, dd, J 2.5, 7.0, 7a), 2.81-2.76 (1H, bm, H4a), 2.70 (1H, dd, J 2.0, 7.0, H9b), 2.54-2.45 (4H, m, H7a', H9b', H5b, H4b), 2.24-2.20 (1H, m, H6b), 2.06 (1H, d, J 18.0, H5a), 1.80 (1H, d, J 8.2, H6a), 1.51 (3.5H, s, tBu[b]), 1.50 (9H, s, tBu[a]), 1.30 (18H, s, tBu[a+b]) and 0.00 (18H, s, 6xSiMe[a+b]) \textsuperscript{13}C NMR (125MHz, CDCl_3) \delta_C: 175.6 (NC=O), 175.3 (NC=O), 151.6 (OBoc), 150.7 (OBoc), 149.9 (NBoc), 149.7 (NBoc), 142.7 (OBoc), 140.9 (2xAr), 129.0 (4xAr), 128.7 (4xAr), 128.6 (4xAr), 125.2 (4xAr), 124.8 (2xAr), 114.1 (C7b or C9a), 113.6 (C9a or C7b), 83.1 (C(CH_3)_3), 82.9 (C(CH_3)_3), 65.9 (C3a or b), 65.8 (C3a or b), 53.4 (-40.4 (C5a or b), 40.2 (C5a or b), 39.5 (C4a or b), 39.1 (C4a or b), 27.7 (C(CH_3)_3), 27.5 (C(CH_3)_3), 23.7 (C7a or C9b), 23.2 (C9b or C7a), 18.9 (C6a and b), -2.5 (Si(CH_3)_3) and -2.6 (Si(CH_3)_3); m/z (ES^+) 524 (100%, MNa^+); Found MNa^+ 524.2439, C_{27}H_{39}NO_6 requires MNa^+ 524.2439.

(1S,3aR,7aS)-2-tert-butyl 1-methyl 3,6-dioxo-4-(trimethylsilyl)hexahydro-1H-isooindole-1,2(3H)-dicarboxylate 343. To a solution of NaIO_4 (7.79 g, 36.4 mmol) in distilled water (30 ml) and acetonitrile (15 ml), RuCl_3.xH_2O (38 mg,
0.182 mmol) was added in one portion. A solution of lactam 316 (730 mg, 1.82 mmol) in ethyl acetate (15 ml) was added dropwise. The reaction was allowed to stir for 24 hours. After this time the reaction was filtered over a bed of celite and the organic was extracted with ethyl acetate. The organic layer was washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated under reduced pressure. The crude acid was used in the next step without purification. The crude acid was dissolved in 2:1 toluene/methanol (20 ml:10 ml). TMS-diazomethane (2M in hexanes, 1.82 ml, 3.64 mmol) was added dropwise and the reaction was allowed to stir for 30 minutes. At this time the reaction was quenched by 2 drops of acetic acid. The reaction was concentrated under reduced pressure. Purification by column chromatography (4:1 petrol/ethyl acetate) gave recovered starting material 316 (74 mg, 10%) and the title compound (529 mg, 76%) as a colourless oil, Rf 0.77 (1:1 petrol/ethyl acetate); νmax (film)/cm⁻¹ 1783, 1744 and 1717; ¹H NMR (400MHz; CDCl₃) δH: 4.26 (1H, bs, H3), 3.81 (3H, s, OMe), 2.90 (1H, dd, J 7.0, 7.0, H5), 2.73 (1H, m, H4), 2.59 (1H, dd, J 16.0, 5.5, H9 [A of ABX]), 2.39 (1H, dd, J 16.0, 5.5, H7 [A of ABX]), 2.32 (1H, dd, J 16.0, 12.5, H9' [B of ABX]), 2.14 (1H, dd, J 16.0, 9.5 [B of ABX], H7'), 1.68 (1H, dt, J 9.5, 6.0 H6) and 1.51 (9H, s, tBu); ¹³C NMR (100MHz, CDCl₃) δC: 209.1 (C=O), 173.7 (C=O), 170.5 (NC=O), 149.5 (NBoc), 84.2 (C(CH₃)₃), 62.6 (C3), 52.9 (OCH₃), 42.0 (C5), 41.8 (C4), 38.4 (C9 or C7), 35.5 (C7 or C9), 27.9 (C(CH₃)₃), 19.8 (C6) and -2.6 (Si(CH₃)₃); m/z (ES⁺) 406.1 (100%, MNa⁺); Found MNa⁺ 406.1662, C₁₈H₂₁NO₆Si requires MNa⁺ 406.1662.

(1S,3aR,8aS)-2-tert-butyl 1-methyl 3,7-dioxo-4-(trimethylsilyl)hexahydro-1H-oxepino[4,5-c]pyrrole-1,2(7H)-dicarboxylate 344. Lactam 343 (522 mg, 1.36 mmol) was dissolved in DCM (10 ml). mCPBA (671 mg, 2.73 mmol) was added in one portion and the reaction was left to stir for 2 days. The reaction was quenched with sodium sulfite and extracted with DCM (10 ml). The organic layer
was washed with water (10 ml), brine (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (3:1 petrol/ethyl acetate) gave the title compound (543 mg, quant.) as a colourless oil, R\text{f} 0.66 (1:1 petrol/ethyl acetate); m.p. 159-161 °C; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2954, 1790 and 1732; \(^1\text{H NMR} (400MHz; \text{CDCl}_3) \delta_H: 4.32 (2H, m, H7, H7'), 4.25 (1H, s, H3), 3.82 (3H, s, OMe), 2.59 (1H, t, J 13.0, 13.0, H9 [A of ABX]), 2.89 (1H, bd, J 6.5, H5), 2.77 (1H, ddd, J 13.0, 7.0, 3.0, H4), 2.70 (1H, dd, J 13.0, 2.5, H9' [B of ABX]), 1.95-1.91 (1H, bm, H6) and 1.51 (9H, s, tBu); \(^{13}\text{C NMR} (100MHz, \text{CDCl}_3) \delta_C: 172.7 (C=O), 171.5 (\text{CO}_2\text{Me}), 169.9 (\text{NC}=\text{O}), 149.3 (\text{NBoc}), 84.5 (\text{C}((\text{CH}_3)_3), 68.0 (\text{C}7), 63.1 (\text{C}3), 53.0 (\text{OCH}_3), 44.9 (\text{C}5), 36.9 (\text{C}4), 34.6 (\text{C}9), 27.8 (\text{C}((\text{CH}_3)_2), 25.6 (\text{C}6) and -1.9 (\text{Si}((\text{CH}_3)_2); m/z (\text{ES}^+) 422.2 (100\%, \text{MNa}^+); \text{Found MH}^+ 400.1777, \text{C}_{18}\text{H}_{29}\text{NO}_7\text{Si} requires MH}^+ 400.1786.

(2S,3S)-1-tert-butyl 2-methyl 4-ethylidene-3-(2-methoxy-2-oxoethyl)-5-oxopyrrolidine-1,2-dicarboxylate 346. Lactone 344 (10.0 mg, 0.03 mmol) was dissolved in THF (1 ml). TBAF (1M in THF, 0.04 ml, 0.04 mmol) was added dropwise and the reaction was left to stir for 20 minutes. The reaction was quenched with water (1 ml) and extracted with ethyl acetate (5 ml). The organic was washed with brine (5 ml), dried over magnesium sulfate and concentrated under reduced pressure. The crude acid was dissolved in 2:1 toluene/methanol (1 ml: 0.5 ml) and TMS-diazomethane (2M in hexanes, 0.02 ml, 0.05 mmol) was added dropwise. The reaction was allowed to stir for 30 minutes and then quenched with a drop of acetic acid. The reaction mixture was concentrated under reduced pressure to give the title compound (8 mg, quant.) as a colourless oil, R\text{f} 0.52 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2925, 2855, 1786, 1742, 1703, 1677 and 1438; \(^1\text{H NMR} (400MHz; \text{CDCl}_3) \delta_H: 6.82 (1H, qd, J 7.5, 2.0, H6), 4.46 (1H, d, J 1.5, H3), 3.77 (3H, s, OMe), 3.74 (3H, s, OMe), 3.34-3.31 (1H, bm, H4), 2.56-2.53 (2H, m, H9, H9'), 1.84 (3H, d, J 7.5, H7) and 1.51 (9H, s, tBu);
\[ ^{13}\text{C NMR (100MHz, CDCl}_3 \delta\text{C}: 171.3 (C=O), 170.7 (C=O), 165.2 (NC=O), 150.0 (NBoc), 135.8 (C5), 132.6 (C6), 84.8 (C(CH}_3)_3), 61.4 (C3), 52.8 (OCH}_3), 52.2 (OCH}_3), 38.4 (C4), 34.6 (C9), 27.9 (C(CH}_3)_3)\] and 15.2 (C7); \[ m/z \text{ (ES}^+\text{)} 364.2\] (100%, MNa\text{+}); Found MNa\text{+} 364.1360, C\text{16}H\text{23}NO\text{7} requires MNa\text{+} 364.1367.

(2S,3S)-methyl 3-(2-methoxy-2-oxoethyl)-5-oxo-4-vinylpyrrolidine-2-carboxylate 347. Lactone 344 (10.0 mg, 0.03 mmol) was dissolved in DCM (1 ml) and cooled to -78 °C. Freshly distilled BF\text{3}.OEt\text{2} (0.01 ml, 0.05 mmol) was added dropwise and the reaction was allowed to stir for 30 minutes. The reaction was quenched with water (1 ml) and allowed warm to room temperature. The organic was extracted with DCM (5 ml), washed with brine (5 ml), dried over magnesium sulfate and concentrated under reduced pressure. The crude acid was dissolved in 2:1 toluene/methanol (1.0 ml: 0.5 ml) and TMS-diazomethane (2M in hexanes, 0.018 ml, 0.038 mmol). The reaction was allowed to stir for 30 minutes and then a drop of acetic acid was added to quench. The crude was concentrated under reduced pressure to give the title compound (6 mg, quant.) as a colourless oil, R\text{f} 0.15 (1:1 petrol/ethyl acetate); \[ ^1\text{H NMR (400MHz; CDCl}_3 \delta\text{H}: 6.46 (1H, bs, NH), 5.66 (1H, dt, J 16.5, 10.0, H6), 5.36-5.28 (2H, m, H7), 4.01 (1H, d, J 6.0, H3), 3.79 (3H, s, OMe), 3.69 (3H, s, OMe), 3.38 (1H, t, J 8.5, 8.5, H5), 3.12-3.05 (1H, m, H4), 3.66 (1H, dd, J 17.0, 7.0, H9 [A of ABX]) and 3.57 (1H, dd, J 17.0, 8.0, H9' [B of ABX]); m/z \text{ (ES}^+\text{)} 242 (100%, MH}\text{+}).

(2S,3S,4R)-methyl 4-(2-(tert-butoxycarbonyloxy)-1-(trimethylsilyl)ethyl)-3-(2-methoxy-2-oxoethyl)-5-oxopyrrolidine-2-carboxylate 352a. Lactone 344 (50.0 mg, 0.13 mmol) was dissolved in MeOH (5 ml) and cooled to -30 °C.
NaOMe (1M, 0.25ml, 0.25 mmol) was added dropwise and the reaction was allowed to stir for 1 hour. At this point the reaction was quenched with ammonium chloride solution (3 ml) and allowed to warm to R.T. The organic was extracted with ethyl acetate (2 x 10 ml), washed with water (10 ml), brine (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (4:1 petrol/ethyl acetate) gave the title compound (32 mg, 60 %) as a colourless oil, \( R_f \) 0.71 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2957, 2922, 2854, 1766 and 1716; \(^1\)H NMR (400MHz; CDCl\(_3\)) \( \delta_H \): 6.57 (1H, d, \( J \ 9.5, \ NH \)), 5.59 (1H, dd, \( J 9.5, 4.0, H3 \)), 4.45 (1H, t, \( J 9.0, 9.0, H7 \ [A of ABX] \)), 4.19 (1H, dd, \( J 12.0, 9.5, H7' \ [B of ABX] \)), 3.75 (3H, s, OMe), 3.70 (3H, s, OMe), 3.01-2.96 (1H, m, H5), 2.82 (1H, dd, \( J 10.0, 2.0, H4 \)), 2.57 (1H, dd, \( J 16.5, 12.0, H9 \ [A of ABX] \)), 2.56 (1H, dd, \( J 16.5, 3.0, H9' \ [B of ABX] \)), 2.13-2.06 (1H, m, H6), 1.42 (9H, s, tBu) and 0.00 (9H, s, TMS); \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \( \delta_C \): 179.5 (C=O), 172.1 (C=O), 171.1 (NC=O), 156.2 (OBoc), 79.7 (C(CH\(_3\))\(_3\)), 71.5 (C7), 55.7, (C3), 52.4 (OCH\(_3\)), 52.2 (OCH\(_3\)), 42.8 (C5), 37.3 (C4), 32.6 (C9), 28.2 (C(CH\(_3\))\(_3\)), 14.1 (C6) and -2.2 (Si(CH\(_3\))\(_3\)); \( m/z \) (ES\(^+\)) 454.2 (100%, MNa\(^+\)); Found MNa\(^+\) 454.1871, C\(_{19}\)H\(_{33}\)NO\(_8\)Si requires MNa\(^+\) 454.1868.

(2S,3S,4R)-1-tert-butyl 2-methyl 4-(2-hydroxy-1-(trimethylsilyl)ethyl)-3-(2-methoxy-2-oxoethyl)-5-oxopyrrolidine-1,2-dicarboxylate 351. Lactone 344 (50.0 mg, 0.13 mmol) was dissolved in MeOH (5 ml) and cooled to -60 °C. NaOMe (1M, 0.25 ml, 0.25 mmol) was added dropwise and the reaction was allowed to stir for 2 hour. At this point the reaction was quenched with ammonium chloride solution (3 ml) and allowed to warm to R.T. The organic was extracted with ethyl acetate (2 x 10 ml), washed with water (10 ml), brine (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (4:1 petrol/ethyl acetate) gave the title compound (46 mg, 87 %) as a colourless oil, \( R_f \) 0.48 (1:1 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \)
Chapter 3: Experimental Procedures

2982, 2901, 1768 and 1709; $^1$H NMR (400MHz; CDCl$_3$) δH: 4.41 (1H, s, H3), 3.79 (3H, s, OMe), 3.74-3.72 (5H, m, H7, H7', OMe), 3.19 (1H, t, J 7.5, 7.5, H5), 2.98-2.92 (1H, m, H4), 2.62 (1H, dd, J 16.5, 3.5, H9 [A of ABX]), 2.37 (1H, dd, J 16.5, 11.5, H9' [B of ABX]), 1.47 (9H, s, tBu) and 1.36-1.32 (1H, m, H8); $^{13}$C NMR (100MHz, CDCl$_3$) δC: 175.7 (C=O), 172.7 (C=O), 171.5 (NC=O), 149.9 (NBoc), 84.4 (C(CH$_3$)$_3$), 63.2 (C7), 62.5 (C3), 53.4 (OCH$_3$), 52.8 (OCH$_3$), 45.8 (C5), 36.2 (C4), 33.8 (C9), 27.8 (C(CH$_3$)$_3$), 14.1 (C6) and -0.7 (Si(CH$_3$)$_3$); m/z (ES$^+$) 454.4 (100%, MNa$^+$); Found MNa$^+$ 454.1879, C$_{19}$H$_{33}$NO$_8$Si requires MNa$^+$ 454.1868.

![Structure](image.png)

(1S,3aR,7aS)-2-tert-butyl 1-methyl 6-hydroxy-3-oxo-4-(trimethylsilyl)hexahydro-1H-isooindole-1,2(3H)-dicarboxylate 358. Lactam 343 (50 mg, 0.13 mmol) was dissolved in THF (5 ml) and cooled to 0 °C. BH$_3$.DMS (2M in THF, 0.66 ml, 0.66 mmol) was added dropwise and the reaction was allowed to stir for 1 hour. The reaction was quenched with NaHCO$_3$ solution and extracted with ethyl acetate (10 ml). The organic was washed with water (10 ml), brine (10 ml) and dried over magnesium sulfate. Concentration under reduced pressure gave the title compound as a 1:0.8 mixture of diastereoisomers (46 mg, 92 %) as a colourless oil, Rf 0.67 (1:1 petrol/ethyl acetate); $^1$H NMR (400MHz; CDCl$_3$) δH: 4.23 (1H, s, H3a), 4.21 (1H, d, J 3.0, H3b), 4.02-3.96 (1H, m, H8a), 3.79 (3H, s, OMe), 3.78 (3H, s, OMe), 3.64-3.55 (1H, m, H8b), 2.63-2.56 (3H, bm, H4a, H5a, H5b), 2.46 (1H, qn, J 6.0, H4b), 2.29-2.17 (1H, m, H9b), 1.93-1.86 (1H, m, H7b), 1.79-1.59 (3H, m, H7a, H9a, H9a'), 1.50 (9H, s, tBu), 1.49 (9H, s, tBu), 1.44-1.18 (4H, m, H7a', H7b', H6b, H6a), 1.23 (1H, dt, J 12.0, 11.5, H9b') and 0.05 (18H, s, Si(CH$_3$)$_3$) and 0.03 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (100MHz, CDCl$_3$) δC: 174.5 (C=O), 174.0 (C=O), 171.1 (NC=O), 170.8 (N=CO), 149.9 (NBoc), 83.7 (C(CH$_3$)$_3$), 83.5 (C(CH$_3$)$_3$), 66.4 (C8a or b), 65.8 (C8a or b), 62.6 (C3a or b), 62.1 (C3a or b), 60.4, 52.7 (OCH$_3$), 52.5 (OCH$_3$), 42.9 (C5a or
b), 41.8 (C5a or b), 38.1 (C7a and b), 35.4 (C4a or b), 34.2 (C4a or b), 33.1 (C9a or b), 32.9 (C9a or b), 28.2 (C(CH₃)₃), 27.9 (C(CH₃)₃), 19.5 (C6a or b), 18.1 (C6a or b), -1.4 (Si(CH₃)₃) and -1.9 (Si(CH₃)₃); m/z (ES⁺) 408 (100%, MNa⁺); Found MNa⁺ 408.1718, C₁₈H₃₁NO₆Si requires MNa⁺ 408.1818.

(1S,3aR,7aS)-tert-butyl 6-hydroxy-1-(hydroxymethyl)-3-oxo-4-(trimethylsilyl)hexahydro-1H-isindole-2(3H)-carboxylate 359. Lactam 343 (50 mg, 0.13 mmol) was dissolved in THF (5 ml). BH₃.DMS (2M in THF, 0.66 ml, 0.66 mmol) was added dropwise and the reaction was heated to reflux and stirred for 24 hours. The reaction was quenched with NaHCO₃ solution and extracted with ethyl acetate (10 ml). The organic was washed with water (10 ml), brine (10 ml) and dried over magnesium sulfate. Concentration under reduced pressure gave the title compound (21 mg, 47%) as a colourless oil, R_f (1:1 petrol/ethyl acetate); ¹H NMR (500MHz; CDCl₃) δH: 3.84-3.83 (2H, m, H₂0, H₃), 3.78-3.76 (1H, m, H₂0'), 3.61 (1H, tt, J 11.5, 4.0, H₈), 2.76 (1H, d, J 7.0, H₅), 2.41 (1H, qn, J 6.0, H₄), 2.25 (1H, bs, OH), 2.12-2.06 (1H, m, H₉), 1.92-1.88 (1H, m, H₇), 1.77-1.75 (1H, m, H₆), 1.46-1.39 (1H, m, H₇), 1.09 (1H, q, J 12.5, H₉'); ¹³C NMR (75MHz, CDCl₃) δC: 175.1 (NC=O), 151.3 (NBoc), 83.5 (C(CH₃)₃), 66.3 (C₈), 63.1 (C₂₀), 63.2 (C₃), 41.9 (C₅), 38.2 (C₄), 34.5 (C₇ or C₉), 33.1 (C₈ or C₇), 28.0 (C(CH₃)₃), 19.8 (C₆), and -1.4 (Si(CH₃)₃); m/z (ES⁺) 380.2 (100%, MNa⁺); Found MNa⁺ 380.1859, C₁₇H₃₁NO₆Si requires MNa⁺ 380.1869.
(1S,3aR,7aS)-di-tert-butyl 3,6-dioxo-4-(trimethylsilyl)hexahydro-1H-isouindole-1,2(3H)-dicarboxylate 361. To a solution of NaIO₄ (0.48 g, 2.25 mmol) in distilled water (4 ml) and acetonitrile (2 ml), RuCl₃.xH₂O (3.00 mg, 0.02 mmol) was added in one portion. A solution of lactam 343 (50 mg, 0.13 mmol) in ethyl acetate (2 ml) was added dropwise. The reaction was allowed to stir for 24 hours. After this time the reaction was filtered over a bed of celite and the organic was extracted with ethyl acetate (10 ml). The organic layer was washed with water (10 ml), brine (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography (4:1 petrol/ethyl acetate then methanol) was performed to recover remaining starting material (12.5 mg, 25 %). The crude acid was dissolved in DCM (2 ml). DCC (77 mg, 0.37 mmol), DMAP (36 mg, 0.3 mmol) and tButanol (0.05 ml, 0.50 mmol) were added and the reaction was allowed to stir for 18 hours. After this time the reaction was quenched with water (2 ml) and extracted with DCM (2 x 10 ml). The organic layer was washed with brine (5 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (4:1 petrol/ethyl acetate) gave the title compound (32 mg, 60%) as a colourless film, [α]ₜₒ다고 = 76.4 (c = 1 in CHCl₃); Rf 0.71 (1:1 petrol/ethyl acetate); ¹H NMR (400MHz; CDCl₃) δH: 4.13 (1H, s, H3), 2.88 (1H, dd, J 7.0, 5.5, H5), 2.70 (1H, ddd, J 12.5, 7.0, 5.5, H4), 2.57 (1H, dd, J 16.0, 5.5, H9 [A of ABX]), 2.41 (1H, dd, J 15.5, 6.5, H7 [A of ABX]), 2.28 (1H, dd, J 16.0, 12.5, [B of ABX], H9'), 2.17 (1H, dd, J 15.0, 8.0, H7' [B of ABX]) and 1.74 (1H, dt, J 7.5, 6.0, H6); ¹³C NMR (100MHz, CDCl₃) δC: 209.4 (C=O), 173.9 (CO₂Bu), 168.9 (NC=O), 149.5 (NBoc), 83.8 (C(CH₃)₃), 82.9 (C(CH₃)₃), 63.5 (C3), 42.2 (C5), 41.8 (C4), 38.4 (C9 or C7)), 36.1 (C9 or C7), 27.9 (C(CH₃)₃), 27.5 (C(CH₃)₃), 19.8 (C6) and -2.6 (Si(CH₃)₃); m/z (ES⁺) 448.5 (100%, MNa⁺); Found MNa⁺ 448.2134, C₂₁H₂₅NO₆Si requires MNa⁺ 448.2126.
(1S,3aR,7aS)-di-tert-butyl 6-hydroxy-3-oxo-4-(trimethylsilyl)hexahydro-1H-isoindole-1,2(3H)-dicarboxylate 363. Lactam 361 (50.0 mg, 0.12 mmol) was dissolved in THF (5 ml) and cooled to -78 °C. BH$_3$DMS (2M in THF, 0.66 ml, 0.66 mmol) was added dropwise and the reaction was allowed to stir for 1 hour. The reaction was quenched with NaHCO$_3$ solution and extracted with ethyl acetate (10 ml). The organic was washed with water (10 ml), brine (10 ml) and dried over magnesium sulfate. Concentration under reduced pressure gave the title compound (48 mg, quant.) as a colourless oil, $R_f$ 0.59 (1:1 petrol/ethyl acetate); $^1$H NMR (400MHz; CDCl$_3$) $\delta$: 4.08 (1H, bs, H3), 3.57 (1H, tt, $J$ 4.0, 11.5, H8), 2.57 (1H, d, $J$ 7.0, H5), 2.42 (1H, qn, $J$ 6.0, H4), 2.19-2.15 (1H, m, H9), 1.91-1.88 (1H, m, H7), 1.78 (1H, d, $J$ 6.5, H6), 1.50 (3H, s, tBu), 1.47 (3H, s, tBu), 1.42-1.32 (1H, m, H7') and 1.15-1.06 (1H, m, H9'); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$: 175.7 (C=O), 170.8 (NC=O), 151.3 (NBoc), 84.8 (C(CH$_3$)$_3$)$_3$, 83.9 (C(CH$_3$)$_3$), 67.9 (C8), 64.8 (C3), 43.2 (C5), 39.5 (C4), 37.2 (C7 or C9), 34.3 (C9 or C7), 31.1 (C(CH$_3$)$_3$), 29.3 (C(CH$_3$)$_3$), 20.8 (C6) and 0.00 (Si(CH$_3$)$_3$); m/z (ES$^+$) 450.5 (100%, MNa$^+$); Found MNa$^+$ 450.2276, C$_{21}$H$_{37}$NO$_6$Si requires MNa$^+$ 450.2277.

(1S,3aR,7aS)-di-tert-butyl 6-oxo-4-(trimethylsilyl)hexahydro-1H-isoindole-1,2(3H)-dicarboxylate 364. Lactam 361 (380 mg, 0.89 mmol) was dissolved in THF (9 ml) and cooled to 0 °C. Super-H (1M in THF, 3.5 ml, 3.7 ml) was added dropwise and the solution was allowed to stir for 1 hour. After this time the reaction was quenched with NaHCO$_3$ solution and allowed to warm to R.T. The organic was extracted with ethyl acetate (2 x 10 ml). The combined layers were washed with water (10 ml), brine (10 ml), dried over magnesium sulfate and
concentrated under reduced pressure. The crude aminol 362 was dissolved in DCM (6 ml) and cooled to -78 °C. BF$_3$·OEt$_2$ (125 µl, 0.98 ml) and Et$_3$SiH (160 µl, 0.98 ml) was added and the reaction was stirred for 30 minutes. After this time BF$_3$·OEt$_2$ (125 µl, 0.98 ml) and Et$_3$SiH (160 µl, 0.98 ml) was added and the reaction was left to stir for 2 hours. After this time the reaction was quenched with NaHCO$_3$ solution and allowed to warm to room temperature. The organic was extracted with DCM (2 x 5 ml). The combined organic layers were washed with water (10 ml), brine (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification of the alcohol was perform by column chromatography (5:3 petrol/ethyl acetate). The resulting alcohol (250 mg, 0.61 mmol) was dissolved in DCM (2 ml). Dess-Martin periodinane (0.3M in methylene chloride, 4 ml, 1.2 mmol) was added dropwise and the reaction was allowed to stir for 2 hours. After this time the reaction was quenched with NaHCO$_3$ solution and the organic was extracted with DCM (2 x 5 ml). The combined organic layers were washed with water (10 ml), brine (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (3:1 petrol/ethyl acetate) gave the title compound (181 mg, 50% over 3 steps) as a colourless oil, $\left[\alpha\right]_D^{25} = 95.2$ (c = 1 in CHCl$_3$); $R_f$ 0.55 (1:1 petrol/ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2978, 1738, 1733 and 1701; $^1$H NMR (400MHz; CDCl$_3$) $\delta_H$: 3.94 (0.3H, bs, H3), 3.84 (0.7H, dd, J 10.5, 8.0, H3), 3.78 (0.7H, dd, J 10.5, 7.5, H9), 3.68 (0.3H, dd, J 10.5, 7.5, H9), 3.29-3.25 (1H, m, H9'), 2.60-2.53 (2H, m, H4, H5), 2.46-2.42 (2H, m, H13, H3'), 2.29 (1H, dd, J 16.0, 4.5, H7 [A of ABX]), 2.10 (1H, dd, J 16.0, 12.5, H7' [B of ABX]), 1.46 (9H, bs, tBu) and 1.43 (9H, bs, tBu); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta_C$: 211.6 (C=O), 171.2 (C=O), 154.0 (NBoc), 81.6 (C(CH$_3$)$_3$), 80.3 (C(CH$_3$)$_3$), 64.8 (C3), 52.0 (C1), 43.4 (C5), 41.0 (C4), 38.7 (C7 or C9), 35.3 (C9 or C7), 28.3 (C(CH$_3$)$_2$), 28.0 (C(CH$_3$)$_3$), 23.9 (C6) and -2.9 (Si(CH$_3$)$_3$); $m/z$ (ES$^+$) 412 (80%, MH$^+$), 434.4 (100%, MNa$^+$); Found MH$^+$ 412.2505, C$_{21}$H$_{27}$NO$_5$Si requires MH$^+$ 412.2514.
(1S,3aR,4R,8aS)-di tert-butyl hexahydro-4-(trimethylsilyl)-7-oxo-1H-oxepino[4,5-c]pyrrole-1,2(7H)-dicarboxylate 365. Ketone 364 (288 mg, 0.71 mmol) was dissolved in DCM (5 mL). mCPBA (240 mg, 1.42 mmol) was added in one portion and the reaction was left to stir for 2 days. The reaction was quenched with sodium thiosulfite and extracted with DCM. The organic layer was washed twice with NaHCO₃ and brine, dried over magnesium sulfate and concentrated under reduced pressure to give 288 mg of an inseparable mixture of the title compound (86% yield) and the overoxidised product 365b (10% yield) as a colourless solid, m.p. 191-195 °C; [α]D²⁵ = -4.4° (c = 1 in CHCl₃); νₘₐₓ (film)/cm⁻¹ 2979, 2936, 1733, 1728 and 1705; ¹H NMR (400 MHz, CDCl₃), [2 rotamers] δH: 4.63-4.57 (1H, m, H7), 4.28-4.23 (1H, m, H7'), 3.99 (0.35, s, H3), 3.84 (0.65, s, H3), 3.69 (0.65H, dd, J 10.5, 8.5, H1' [A of ABX]), 3.61 (0.35H, dd, J 10.5, 8.5, H1' [A of ABX]), 3.40 (0.65H, t, J 10.5, 10.5, H1 [B of ABX]), 3.36 (0.35H, t, J 10.5, 10.5, H1 [B of ABX]), 2.99 (0.65H, t, J 13.5, 13.5, H9 [A' of A'B'X']), 2.95 (0.35H, t, J 13.5, 13.5, H9 [A' of A'B'X']), 2.75-2.69 (1H, m, H5), 2.58 (1H, dd, J 13.5, 1.5, H9' [B' of A'B'X']), 2.52 (1H, dd, J 13.0, 5.5, H4), 1.47-1.43 (18H, m, 2x tBu), 1.13 (0.65H, bs, H6) and 1.08 (0.35H, bs, H6); ¹³C NMR (100 MHz, CDCl₃, [2 rotamers] δC: 173.2 (C=O), 173.1 (C=O), 170.5 (C=O), 170.2 (C=O), 154.4 (NC=O), 154.1 (NC=O), 81.9 (C(CH₃)₃), 81.8 (C(CH₃)₃), 80.4 (C(CH₃)₃), 80.2 (C(CH₃)₃), 66.9 (C3), 66.6 (C3), 66.1 (C7), 65.9 (C7), 48.5 (C1), 48.3 (C1), 40.3 (C5), 39.3 (C5), 36.7 (4), 35.9 (C4), 35.6 (C9), 35.4 (C9), 28.2 (C(CH₃)₃), 27.9 (C(CH₃)₃), 27.8 (C(CH₃)₃), 27.3 (C(CH₃)₃), 27.2 (C6) and -2.0 (Si(CH₃)₂); m/z (ES⁺) 450 (100%, MNa⁺); Found MNa⁺ 450.2286, C₂₁H₃₇NO₆Si requires MNa⁺ 450.2282. (1S,3aR,4R,8aS)-di tert-butyl hexahydro-4-(trimethylsilyl)-3,7-dioxo-1H-oxepino[4,5-c]pyrrole-1,2(7H)-dicarboxylate 364b was observed in trace amount that was inseparable from the desired product; ¹H NMR (400 MHz; CDCl₃) δH: 4.31-4.30 (2H, m, H7, H7'), 4.14
(1H, s, H3), 2.93 (1H, t, J 12.5, 12.5, H9), 2.88 (1H, bd, J 6.5, H5), 2.83-2.68 (2H, m, H4, H9'), 1.92 (1H, bs, H6) 1.52 (9H, s, tBu) and 1.49 (9H, s, tBu); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$: 173.1 (C=O), 171.8 (C=O), 168.3 (NC=O), 149.3 (NBoc), 84.1 (C(CH$_3$)$_3$), 83.3 (C(CH$_3$)$_3$), 68.0 (C7), 63.8 (C3), 44.8 (C5), 36.8 (C4), 34.9 (C9), 28.2 (C(CH$_3$)$_3$), 27.8 (C(CH$_3$)$_3$), 25.4 (C6) and -2.0 (Si(CH$_3$)$_3$).

(2S,3S,4R)-di-tert-butyl 3-((tert-butoxycarbonyl)methyl)-4-vinylpyrrolidin-1,2-dicarboxylate 367. To a solution of lactone 365 (165 mg, 0.38 mmol) in dry THF (3.5 mL) was added Tetrabutylammonium fluoride dropwise at 0°C. The mixture was stirred for 5 min and then the cold bath was removed and stirring continued for 2 hours. The reaction was quenched with NH$_4$Cl and extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the intermediate. To a solution of the intermediate acid in tert-butanol (4 mL) was added DMAP (14.0 mg, 0.11 mmol) and Boc$_2$O (163 mg, 0.76 mmol). The reaction was allowed to stir overnight at room temperature and the mixture was concentrated under reduced pressure. Purification by column chromatography (9:1 petrol/ethyl acetate) gave the title compound (94 mg, 70% yield over 2 steps) as a colourless oil, $[\alpha]_D^{25} = -3.6^\circ$ (c = 1 in CHCl$_3$); $R_f$ 0.4 (8:2 petrol:ethyl acetate); $v_{\text{max}}$ (film)/cm$^{-1}$ 2978, 2930, 1735, 1723 and 1700; $^1$H NMR (400 MHz, CDCl$_3$), [2 rotamers] $\delta$: 5.68-5.59 (1H, m, H6), (1H, m, H7), (1H, m, H7'), 3.84 (0.35H, d, J 6.0, H3), 3.80 (0.65H, d, J 5.5, H3), 3.60 (0.65H, dd, J 11.0, 6.5, H1 [A of ABX]), 3.56 (0.35H, dd, J 10.5, 6.5, H1 [A of ABX]), 3.43 (0.65H, dd, J 11.0, 5.5, H1' [B of ABX]), 3.33 (0.35H, dd, J 10.5, 5.0, H1' [B of ABX]), 3.06-2.97 (1H, m, H19), 2.68-2.62 (1H, m, H17), 2.37-2.26 (2H, m, H9, H9') and 1.45-1.41 (27H, m, 3x tBu); $^{13}$C NMR (100 MHz, CDCl$_3$), [2 rotamers] $\delta$: 171.3 (C=O), 171.2 (C=O), 171.0 (C=O), 171.0 (C=O), 154.1 (NBoc), 153.8 (NBoc), 134.9 (C6), 134.5 (C6), 117.8 (C7), 117.7 (C7), 81.3 (C(CH$_3$)$_3$), 81.2
(C(CH₃)₃), 80.7 (C(CH₃)₃), 80.7 (C(CH₃)₃), 79.9 (C(CH₃)₃), 79.7 (C(CH₃)₃), 63.7 (C3), 63.7 (C3), 50.2 (C1), 49.5 (C1), 44.1 (C5), 44.0 (C5), 43.1 (C4), 43.0 (C4), 35.0 (C9), 34.9 (C9), 28.3 (C(CH₃)₃), 28.2 (C(CH₃)₃), 28.0 (C(CH₃)₃) and 27.9 (C(CH₃)₃); m/z (ES⁺) 434 (100%, MNa⁺); Found MH⁺ 412.2694, C₂₂H₃₅NO₆ requires MH⁺ 412.2694.

(2S,3S,4R)-di-tert-butyl 3-((tert-butoxycarbonyl)methyl)-4-formylpyrrolidine-1,2-dicarboxylate 368. In a three-neck round bottom flask, alkene 367 (130 mg, 0.32 mmol) was dissolved in dry DCM (5 mL). The solution was cooled down to -78 °C and O₃ was bubbled through for 15 min. After the appearance of deep blue colour, the mixture was allowed to stir 5 more mins. Then O₂ was bubbled for 5 min at the same temperature until the total disappearance of the blue colour. N₂ was then flushed for 5 min and Me₂S (1 mL, 15.8 mmol) was added in once. The solution was then warmed up to room temperature and allowed to stir for 24 hours. The solvents were removed under reduced pressure to give the crude aldehyde 368 (128 mg, 98% yield) as a colourless oil, [α]D²⁵ = - 3.8° (c = 1 in CHCl₃); νmax (film)/cm⁻¹ 2977, 2930, 1735, 1727 and 1703; ¹H NMR (400 MHz, CDCl₃), [2 rotamers] δH: 9.70 (1H, d, J 1.3, H6), 3.97 (0.35H, d, J 4.6, H3), 3.91 (0.65H, d, J 5.4, H3), 3.84 (0.65H, dd, J 11.5, 5.5, H1 [A of ABX]), 3.76 (0.35H, dd, J 11.0, 6.5, H1 [A of ABX]), 3.60 (0.65H, dd, J 11.5, 7.5, H1' [B of ABX]), 3.56 (0.35H, dd, J 11.0, 7.5, H1' [B of ABX]), 3.36-3.28 (1H, m, H5), 3.00-2.87 (1H, m, H4), 2.55-2.41 (2H, m, H9, H9') and 1.46-1.401 (27H, m, 3x tBu); ¹³C NMR (100 MHz, CDCl₃), [2 rotamers] δC: 199.9 (CHO), 199.9 (CHO), 170.7 (C=O), 170.6 (C=O), 170.5 (C=O), 170.5 (C=O), 154.0 (NBoc), 153.7 (NBoc), 81.8 (C(CH₃)₃), 81.8 (C(CH₃)₃), 81.5 (C(CH₃)₃), 81.4 (C(CH₃)₃), 80.4 (C(CH₃)₃), 80.3 (C(CH₃)₃), 64.5 (C3), 64.3 (C3), 51.6 (C1), 50.6 (C1), 44.9 (C5), 44.8 (C5), 42.0 (C4), 40.6 (C4), 35.1 (C9), 35.0 (C9), 28.3 (C(CH₃)₂), 28.2 (C(CH₃)₂), 28. (C(CH₃)₂), 27.9 (C(CH₃)₂) and 27.9...
Dimethyl (1-diazo-2-oxopropyl)phosphonate (Bestmann Reagent) 386. A solution of dimethyl (2-oxopropyl)phosphonate (5.01 g, 30 mmol) and p-acetamidobenznesulfonyl azide (7.96 g, 33.1 mmol, 1.1 eq) in anhydrous MeCN (100 mL) under a nitrogen atmosphere at 0°C was treated with K₂CO₃ (5.00 g, 36 mmol, 1.2 equiv). The reaction mixture was allowed to warm up to R.T. and stirred overnight. The reaction mixture was then filtered to remove the salts. Volatiles were removed under vacuum, and the residue was dissolved in CHCl₃ to recrystallize the p-acetamidobenznesulfonylamine. After stirring for 30 min, the suspension was filtered and the filtrate was evaporated. Purification by flash chromatography (Petrol/ethyl acetate 2:8) afforded 4.61 g (24 mmol, 82%) of the desired dimethyl (1-diazo-2-oxopropyl)phosphonate 386 right yellow oil; R_f: 0.3 (ethyl acetate); ^1H NMR (300 MHz, CDCl₃); δ_H: 2.27 (s, 3H, CH₃), 3.83 (s, 3H, OMe), 3.87 (s, 3H, OMe). Data consistent with the literature.

(2S,3S,4S)-di-tert-butyl 3-((tert-butoxycarbonyl)methyl)-4-ethynylpyrrolidine-1,2-dicarboxylate 387a. To a solution of Ohira-Bestmann reagent 386 (188 mg, 0.99 mmol) in dry THF (4 mL) at -78°C was added a solution of freshly prepared NaOMe (500 µL, 0.99 mmol, 2N in MeOH) in dry THF (1 mL), the solution turned yellow. To this mixture, a solution of aldehyde 368 (100 mg, 0.24 mmol) in dry THF (3 mL) was added dropwise. The reaction was allowed to stir 1 hour at the same temperature and then warmed up to room temperature over 1 hour. After this time, the reaction was quenched with NH₄Cl and extracted twice with ethyl acetate. The combined organic layers were washed...
Chapter 3: Experimental Procedures

with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (85:15 petrol/ethyl acetate) gave the title compound 387a (88 mg, 89 % yield) as a colourless oil, $[\alpha]_{D}^{25} = -4.1^\circ$ (c = 1 in CHCl$_3$); $R_f$ 0.25 (8:2 petrol:ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3273, 2980, 2932, 1738, 1732 and 1700; $^1$H NMR (400 MHz, CDCl$_3$), [2 rotamers] $\delta$: 3.93 (0.35H, d, $J$ 5.5, H3), 3.87 (0.65H, d, $J$ 5.5, H3), 3.70-3.59 (1.65H, m, H1, H1'), 3.53-3.49 (0.35H, m, H1), 3.32-3.23 (1H, m, H5), 2.77-2.72 (1H, m, H9), 2.68-2.62 (1H, m, H4), 2.47-2.40 (1H, m, H9'), 2.17 (1H, d, $J$ 2.5, H7) and 1.46-1.43 (27H, m, 3x tBu); $^{13}$C NMR (100 MHz, CDCl$_3$), [2 rotamers] $\delta$: 171.0 (C=O), 170.9 (C=O), 170.8 (C=O), 154.0 (NBoc), 153.7 (NBoc), 81.5 (C(CH$_3$)$_3$), 81.0 (C(CH$_3$)$_3$), 80.8 (C(CH$_3$)$_3$), 80.3 (C(CH$_3$)$_3$), 80.0 (C(CH$_3$)$_3$), 77.9 (C7), 72.9 (C6), 63.4 (C3), 63.3 (C3), 51.3 (C1), 50.8 (C1), 43.5 (C5), 42.3 (C5), 35.5 (C4), 35.4 (C4), 32.7 (C9), 32.0 (C9), 28.3 (C(CH$_3$)$_3$), 28.3 (C(CH$_3$)$_3$), 28.0 (C(CH$_3$)$_3$), 28.0 (C(CH$_3$)$_3$) and 27.9 (C(CH$_3$)$_3$); m/z (ES$^+$) 432 (100%, MNa$^+$); Found MNa$^+$ 432.2371, C$_{22}$H$_{35}$NO$_6$ requires MNa$^+$ 432.2357.

3.1.6 Experimental Procedures Appendix 2:

(3S,3aS,7aS)-2-tert-butyl-2,3,3a,4-tetrahydro-3,5-diphenyl-7aH-isooindole-1,7-dione 404. Enone 177 (100 mg, 0.32 mmol) was dissolved in dry THF (20 ml). Phenylmagnesium bromide was added dropwise at 0 ºC. The reaction was allowed to warm to rt and stirred for 30 minutes. The reaction was quenched with saturated ammonium chloride solution and extracted in with diethyl ether (2 x 20 ml). The combined organic fractions were washed with water (20 ml), dried over magnesium sulfate and solvent removed under reduced pressure. Purification by flash column chromatography (2:1 petrol:ethyl acetate) gave the title compound (95 mg, 82 %) as a colourless film; $R_f$: 0.91 (1:1 petrol:ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1748 and 1642; $^1$H NMR (500MHz, CDCl$_3$) $\delta$: 7.54-7.53 (2H, m, ArH), 7.45-7.43 (3H, m, ArH), 7.40-7.37 (2H, m, ArH), 7.33-7.27 (3H, m, ArH), 7.25-7.23 (6H, m, ArH).
6.46 (1H, d, J 2.5, H7), 4.66 (1H, m, H3), 3.65 (1H, d, J 6.5, H5), 3.19-3.15 (1H, m, H9), 2.84-2.74 (2H, m, H4, H9') and 1.40 (9H, s, tBu); (ES$^+$) 360.2; Found: MNa$^+$, 383.1547, $C_{24}H_{25}NO_2$ requires MNa$^+$ 383.1547.

(3S,3aR,7aS)-7a-hydroxy-3-phenyl-2-(2-phenylpropan-2-yl)-2,3,3a,4-tetrahydro-1H-isooindole-1,5(7aH)-dione 408. A solution of enone 104 (50.0 mg, 0.15 mmol) was dissolve in an 8:1 (4.5 ml). NMO (16.9 mg, 0.15 mmol) and osmium tetroxide (2.5 % in tert-butanol) (0.030 ml, 0.001 mmol) was added and allowed to stir for 18 hours. The mixture was quenched with 40 % w/v sodium hydrogen sulphate solution at 0 ºC. The acetone was removed under reduced pressure and extracted with ethyl acetate. Purification by flash chromatography afforded the title compound as an amorphous solid, $R_f$ 0.52 (1:2 petrol:ethyl acetate); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3615 and 1684; $^1$H NMR (300MHz, CDCl$_3$) $\delta$H: 7.33-7.04 (10H, m, H13, H16), 6.41 (1H, dd, J 10.5, 2.0, H7), 6.41 (1H, dd, J 10.5, 2.0, H7), 6.24 (1H, d, J 10.0, H6), 4.24 (1H, d, J 8.0, H3), 2.73-2.64 (2H, m, H9, H4), 2.39-2.30 (1H, m, H9), 1.74 (3H, s, Me) and 1.34 (3H, s, Me); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$C: 196.6 (C=O), 174.6 (NC=O), 145.9 (Ar), 143.5 (Ar), 139.6 (C6), 130.7 (C7), 128.7 (2xAr), 128.3 (2xAr), 128.0 (2xAr), 127.4 (2xAr), 126.8 (Ar), 125.0 (Ar), 71.4 (C5), 66.4 (C(CH$_3$)$_2$Ph), 61.3 (C3), 47.8 (C4), 33.0 (C9), 28.7 (C(CH$_3$)$_2$Ph) and 27.6 (C(CH$_3$)$_2$Ph); m/z (ES$^+$) 384 (100 %, MNa$^+$); Found MNa$^+$ 384.1576, $C_{23}H_{23}NO_3$ requires MNa$^+$ 384.1576.

(3S,3aS,7aS)-6,7-dihydroxy-3-phenyl-2-(2-phenylpropan-2-yl)hexahydro-1H-isooindole-1,5(6H)-dione 407. A solution of enone 104 (50.0 mg, 0.15 mmol) was dissolve in an 8:1 (4.5 ml). Osmium tetroxide (2.5 % in tert-butanol) (3.00 ml,
0.15 mmol) was added and allowed to stir for 18 hours. The mixture was quenched with 40 % w/v sodium hydrogen sulphate solution at 0 °C. The acetone was removed under reduced pressure and extracted with ethyl acetate. Purification by flash chromatography afforded the title compound as an amorphous solid, \( R_f \) 0.32 (1:2 petrol/ethyl acetate); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3622, 1752 and 1680; \(^1\)H NMR (500MHz; CDCl\(_3\)) \( \delta_H \): 7.46-7.21 (10H, m, ArH), 4.65 (1H, t, J 1.0, H6), 4.39 (1H, s, H3), 4.14-4.09 (1H, m, H7), 3.68 (1H, s, OH), 3.39 (1H, dd, J 6.0, 2.0, H5), 2.76 (1H, dd, J 10.0, 6.0, H9), 2.68-2.63 (1H, qd, J 10.0, 7.0, H4), 2.18 (1H, dd, 13.5, 11.0, H9'), 1.92 (3H, s, Me) and 1.55 (3H, s, Me); \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \( \delta_c \): 207.90 (C=O), 172.53 (NC=O), 145.37 (Ar), 140.25 (Ar), 129.03 (2xAr), 128.25 (2xAr), 128.12 (2xAr), 127.32 (2xAr), 125.66 (Ar), 125.47 (Ar), 74.63 (C7), 72.51 (C6), 67.54 (C(CH\(_3\))\(_2\)Ph), 59.41 (C3), 45.00 (C5), 43.16 (C4), 41.20 (C9), 27.73 (C(CH\(_3\))\(_2\)Ph) and 27.11 (C(CH\(_3\))\(_2\)Ph); \( m/z \) (ES\(^+\)) 402.2 (100%, MNa\(^+\)); Found MNa\(^+\) 402.1681, C\(_{23}\)H\(_{25}\)NO\(_4\) requires MNa\(^+\) 402.1681.
3.2 Detailed X-Ray Crystallographic Data.

3.2.1 Data for Epoxyketone 217.

Empirical formula \( C_{19}H_{23}NO_4 \)

Formula weight 329.38

Crystal size 0.30 x 0.20 x 0.10 mm

Temperature 100(2)K

X-Ray Wavelength 0.71073Å

\( \theta \) Range 2.03 to 28.34°

Limiting indices \(-12 \leq h \leq 24; -11 \leq k \leq 11; -24 \leq l \leq 26\)

Refinement method Full-matrix least-squares on \( F^2 \)

R Factor 0.1149

Crystal System Orthorhombic

Space Group Pbcn

Unit cell dimensions \( a = 18.768(2) \) Å \( \alpha = 90° \)

\( b = 9.0367(12) \) Å \( \beta = 90° \)

\( c = 20.034(3) \) Å \( \gamma = 90° \)

Unit Cell Volume 3397.8(8) Å³

\( Z \) 8

Calculated density 1.288 Mg/m⁻³
**Atomic Labels**

![Diagram of atomic labels]

**Atomic Coordinates**

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Chapter 3: Experimental Procedures

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C(2)–C(1)–H(1) 109.1
C(3)–C(2)–C(7) 113.32(17)
C(3)–C(2)–C(1) 111.78(16)
C(7)–C(2)–C(1) 105.43(16)
C(3)–C(2)–H(2) 108.7
C(7)–C(2)–H(2) 108.7
C(1)–C(2)–H(2) 108.7
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C(4)–C(3)–H(3A) 109.3
C(2)–C(3)–H(3A) 109.3
C(4)–C(3)–H(3B) 109.3
C(2)–C(3)–H(3B) 109.3
H(3A)–C(3)–H(3B) 108.0
O(1)–C(4)–C(5) 59.48(13)
O(1)–C(4)–C(3) 116.13(18)
C(5)–C(4)–C(3) 119.64(18)
O(1)–C(4)–H(4) 116.5
C(5)–C(4)–H(4) 116.5
C(3)–C(4)–H(4) 116.5
O(1)–C(5)–C(4) 59.42(13)
O(1)–C(5)–C(6) 116.70(17)
C(4)–C(5)–C(6) 117.50(19)
O(1)–C(5)–H(5) 116.9
C(4)–C(5)–H(5) 116.9
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O(2)–C(6)–C(5) 120.8(2)
O(2)–C(6)–C(7) 121.7(2)
C(5)–C(6)–C(7) 117.42(19)
C(6)–C(7)–C(8) 110.22(18)
Chapter 3: Experimental Procedures

\[
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C(8) - C(7) - C(2) & \quad 106.10(16) \\
C(6) - C(7) - H(7) & \quad 107.7 \\
C(8) - C(7) - H(7) & \quad 107.7 \\
C(2) - C(7) - H(7) & \quad 107.7 \\
N(1) - C(8) - C(7) & \quad 103.82(16) \\
N(1) - C(8) - H(8A) & \quad 111.0 \\
C(7) - C(8) - H(8A) & \quad 111.0 \\
N(1) - C(8) - H(8B) & \quad 111.0 \\
C(7) - C(8) - H(8B) & \quad 111.0 \\
H(8A) - C(8) - H(8B) & \quad 109.0 \\
C(10) - C(9) - C(14) & \quad 118.8(2) \\
C(10) - C(9) - C(1) & \quad 122.57(19) \\
C(14) - C(9) - C(1) & \quad 118.57(19) \\
C(9) - C(10) - C(11) & \quad 120.5(2) \\
C(9) - C(10) - H(10) & \quad 119.8 \\
C(11) - C(10) - H(10) & \quad 119.8 \\
C(12) - C(11) - C(10) & \quad 119.6(2) \\
C(12) - C(11) - H(11) & \quad 120.2 \\
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C(11) - C(12) - C(13) & \quad 120.1(2) \\
C(11) - C(12) - H(12) & \quad 119.9 \\
C(13) - C(12) - H(12) & \quad 119.9 \\
C(14) - C(13) - C(12) & \quad 119.6(2) \\
C(14) - C(13) - H(13) & \quad 120.2 \\
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C(13) - C(14) - C(9) & \quad 121.4(2) \\
C(13) - C(14) - H(14) & \quad 119.3 \\
C(9) - C(14) - H(14) & \quad 119.3 \\
O(3) - C(15) - O(4) & \quad 126.4(2) \\
O(3) - C(15) - N(1) & \quad 123.3(2) \\
O(4) - C(15) - N(1) & \quad 110.3(2)
\end{align*}
\]
O(4)-C(16)-C(17)           102.23(16)
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C(15)-N(1)-C(1)             124.52(18)
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C(15)-O(4)-C(16)            120.06(16)
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- \( \text{C(9)} - \text{C(1)} - \text{C(2)} - \text{C(3)} \): 128.76(18)°
- \( \text{N(1)} - \text{C(1)} - \text{C(2)} - \text{C(7)} \): 14.9(2)°
Chapter 3: Experimental Procedures

\[
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C(7) - C(2) - C(3) - C(4) & \quad 51.2(2) \\
C(1) - C(2) - C(3) - C(4) & \quad 170.20(17) \\
C(2) - C(3) - C(4) - O(1) & \quad 29.1(3) \\
C(2) - C(3) - C(4) - C(5) & \quad -39.0(3) \\
C(3) - C(4) - C(5) - O(1) & \quad 104.6(2) \\
O(1) - C(4) - C(5) - C(6) & \quad -106.3(2) \\
C(3) - C(4) - C(5) - C(6) & \quad -1.7(3) \\
O(1) - C(5) - C(6) - O(2) & \quad 145.2(2) \\
C(4) - C(5) - C(6) - O(2) & \quad -147.2(2) \\
O(1) - C(5) - C(6) - C(7) & \quad -37.9(3) \\
C(4) - C(5) - C(6) - C(7) & \quad 29.8(3) \\
O(2) - C(6) - C(7) - C(8) & \quad 39.9(3) \\
C(5) - C(6) - C(7) - C(8) & \quad -137.05(19) \\
O(2) - C(6) - C(7) - C(2) & \quad 161.2(2) \\
C(5) - C(6) - C(7) - C(2) & \quad -15.7(3) \\
C(3) - C(2) - C(7) - C(6) & \quad -24.9(3) \\
C(1) - C(2) - C(7) - C(6) & \quad -147.48(18) \\
C(3) - C(2) - C(7) - C(8) & \quad 98.59(19) \\
C(1) - C(2) - C(7) - C(8) & \quad -24.0(2) \\
C(6) - C(7) - C(8) - N(1) & \quad 151.21(17) \\
C(2) - C(7) - C(8) - N(1) & \quad 23.5(2) \\
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N(1) - C(1) - C(9) - C(14) & \quad 153.48(18) \\
C(2) - C(1) - C(9) - C(14) & \quad -89.1(2) \\
C(14) - C(9) - C(10) - C(11) & \quad 1.3(3) \\
C(1) - C(9) - C(10) - C(11) & \quad -175.20(19) \\
C(9) - C(10) - C(11) - C(12) & \quad 0.4(3) \\
C(10) - C(11) - C(12) - C(13) & \quad -1.6(3) \\
C(11) - C(12) - C(13) - C(14) & \quad 1.2(3) \\
C(12) - C(13) - C(14) - C(9) & \quad 0.5(3)
\end{align*}
\]
Chapter 3: Experimental Procedures

3.2.2 Data for Lactone 251.

Empirical formula \( \text{C}_{18}\text{H}_{21}\text{NO}_{3} \)
Formula weight 299.36
Crystal size 0.30 x 0.28 x 0.08 mm

Temperature \( 100(2) \) K
X-Ray Wavelength 0.71073 Å
\( \theta \) Range 2.49 to 28.28°
Limiting Indices \(-19 \leq h \leq 18; -8 \leq k \leq 7; -22 \leq l \leq 14 \)
Refinement method Full-matrix least-squares on \( F^2 \)
R Factor 0.0594
Crystal System: Monoclinic
Space Group: P2$_1$/n
Unit cell Dimensions:
- $a = 15.051(2)$ Å, $\alpha = 90^\circ$
- $b = 6.738(10)$ Å, $\beta = 113.949(3)^\circ$
- $c = 16.592(2)$ Å, $\gamma = 90^\circ$
Unit Cell Volume: $1537.9(4)$ Å$^3$
$Z$: 4
Calculated density: $1.293$ Mg/m$^{-3}$

Atomic Labels

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Chapter 3: Experimental Procedures

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Chapter 3: Experimental Procedures

\[
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C(15)-H(15) & \quad 0.9500 \\
C(16)-C(17) & \quad 1.381(2) \\
C(16)-H(16) & \quad 0.9500 \\
C(17)-C(18) & \quad 1.390(2) \\
C(17)-H(17) & \quad 0.9500 \\
C(18)-H(18) & \quad 0.9500 \\
\end{align*}
\]

**Bond Angles (°)**

\[
\begin{align*}
C(8)-C(1)-C(4) & \quad 118.52(16) \\
C(8)-C(1)-C(2) & \quad 110.87(15) \\
C(4)-C(1)-C(2) & \quad 103.08(14) \\
C(8)-C(1)-H(1) & \quad 108.0 \\
C(4)-C(1)-H(1) & \quad 108.0 \\
C(2)-C(1)-H(1) & \quad 108.0 \\
O(2)-C(2)-N(1) & \quad 126.39(18) \\
O(2)-C(2)-C(1) & \quad 124.57(17) \\
N(1)-C(2)-C(1) & \quad 109.04(15) \\
N(1)-C(3)-C(13) & \quad 113.41(15) \\
N(1)-C(3)-C(4) & \quad 102.54(14) \\
C(13)-C(3)-C(4) & \quad 113.35(14) \\
N(1)-C(3)-H(3) & \quad 109.1 \\
C(13)-C(3)-H(3) & \quad 109.1 \\
C(4)-C(3)-H(3) & \quad 109.1 \\
C(1)-C(4)-C(5) & \quad 111.00(14) \\
C(1)-C(4)-C(3) & \quad 103.20(14)
\end{align*}
\]
Chapter 3: Experimental Procedures

\[
\begin{align*}
C(5) - C(4) - C(3) & \quad 111.64(14) \\
C(1) - C(4) - H(4) & \quad 110.3 \\
C(5) - C(4) - H(4) & \quad 110.3 \\
C(3) - C(4) - H(4) & \quad 110.3 \\
C(6) - C(5) - C(4) & \quad 111.28(15) \\
C(6) - C(5) - H(5A) & \quad 109.4 \\
C(4) - C(5) - H(5A) & \quad 109.4 \\
C(6) - C(5) - H(5B) & \quad 109.4 \\
C(4) - C(5) - H(5B) & \quad 109.4 \\
H(5A) - C(5) - H(5B) & \quad 108.0 \\
O(3) - C(6) - O(1) & \quad 116.36(19) \\
O(3) - C(6) - C(5) & \quad 124.30(18) \\
O(1) - C(6) - C(5) & \quad 119.29(17) \\
C(8) - C(7) - O(1) & \quad 129.15(18) \\
C(8) - C(7) - H(7) & \quad 115.4 \\
O(1) - C(7) - H(7) & \quad 115.4 \\
C(7) - C(8) - C(1) & \quad 132.16(18) \\
C(7) - C(8) - H(8) & \quad 113.9 \\
C(1) - C(8) - H(8) & \quad 113.9 \\
N(1) - C(9) - C(10) & \quad 109.17(15) \\
N(1) - C(9) - C(12) & \quad 110.01(15) \\
C(10) - C(9) - C(12) & \quad 108.37(15) \\
N(1) - C(9) - C(11) & \quad 109.75(14) \\
C(10) - C(9) - C(11) & \quad 110.30(15)
\end{align*}
\]
C(12) - C(9) - C(11) 109.22(16)
C(9) - C(10) - H(10A) 109.5
C(9) - C(10) - H(10B) 109.5
H(10A) - C(10) - H(10B) 109.5
C(9) - C(10) - H(10C) 109.5
H(10A) - C(10) - H(10C) 109.5
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H(12A) - C(12) - H(12B) 109.5
C(9) - C(12) - H(12C) 109.5
H(12A) - C(12) - H(12C) 109.5
H(12B) - C(12) - H(12C) 109.5
C(14) - C(13) - C(18) 118.57(17)
C(14) - C(13) - C(3) 122.60(16)
C(18) - C(13) - C(3) 118.82(16)
C(15) - C(14) - C(13) 120.64(17)
C(15) - C(14) - H(14) 119.7
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C(14)–C(15)–C(16)           120.63(17)
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C(17)–C(16)–C(15)           119.14(18)
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C(16)–C(17)–C(18)           120.31(18)
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C(17)–C(18)–C(13)           120.69(17)
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C(2)–N(1)–C(3)              112.13(15)
C(2)–N(1)–C(9)              123.55(15)
C(3)–N(1)–C(9)              124.01(15)
C(6)–O(1)–C(7)              124.53(16)

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**Torsion Angles (°)**

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Chapter 3: Experimental Procedures

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C(5)-C(6)-C(7)-C(8) & \quad -137.05(19) \\
O(2)-C(6)-C(7)-C(2) & \quad 161.2(2) \\
C(5)-C(6)-C(7)-C(2) & \quad -15.7(3) \\
C(3)-C(2)-C(7)-C(6) & \quad -24.9(3) \\
C(1)-C(2)-C(7)-C(6) & \quad -147.48(18) \\
C(3)-C(2)-C(7)-C(8) & \quad 98.59(19) \\
C(1)-C(2)-C(7)-C(8) & \quad -24.0(2) \\
C(6)-C(7)-C(8)-N(1) & \quad 151.21(17) \\
C(2)-C(7)-C(8)-N(1) & \quad 23.5(2) \\
N(1)-C(1)-C(9)-C(10) & \quad -30.1(3) \\
C(2)-C(1)-C(9)-C(10) & \quad 87.3(2) \\
N(1)-C(1)-C(9)-C(14) & \quad 153.48(18) \\
C(2)-C(1)-C(9)-C(14) & \quad -89.1(2) \\
C(14)-C(9)-C(10)-C(11) & \quad 1.3(3) \\
C(1)-C(9)-C(10)-C(11) & \quad -175.20(19) \\
C(9)-C(10)-C(11)-C(12) & \quad 0.4(3) \\
C(10)-C(11)-C(12)-C(13) & \quad -1.6(3) \\
C(11)-C(12)-C(13)-C(14) & \quad 1.2(3) \\
C(12)-C(13)-C(14)-C(9) & \quad 0.5(3) \\
C(10)-C(9)-C(14)-C(13) & \quad -1.7(3) \\
C(1)-C(9)-C(14)-C(13) & \quad 174.87(19) \\
O(3)-C(15)-N(1)-C(8) & \quad -9.2(3) \\
O(4)-C(15)-N(1)-C(8) & \quad 170.89(17) \\
O(3)-C(15)-N(1)-C(1) & \quad 178.1(2) \\
O(4)-C(15)-N(1)-C(1) & \quad -1.8(3) \\
C(7)-C(8)-N(1)-C(15) & \quad 171.88(18) \\
C(7)-C(8)-N(1)-C(1) & \quad -14.8(2) \\
C(9)-C(1)-N(1)-C(15) & \quad -65.0(3) \\
C(2)-C(1)-N(1)-C(15) & \quad 173.01(18) \\
C(9)-C(1)-N(1)-C(8) & \quad 121.95(19) \\
C(2)-C(1)-N(1)-C(8) & \quad -0.1(2)
\end{align*}
\]
Chapter 3: Experimental Procedures

3.2.3 Data for Silylated Ketone 315.

Crystal Data and Structure Refinement

Empirical Formula \( \text{C}_26\text{H}_{34}\text{NO}_2\text{Si} \)
Formula Weight 428.63
Crystal Size 0.60 x 0.20 x 0.20 mm

Temperature 100(2) K
X-Ray Wavelength 0.71073 Å
θ Range 1.76 to 25.03°
Limiting Indices \(-13 \leq h \leq 11; -15 \leq k \leq 18; 15 \leq l \leq 15\)
Refinement Method Full-matrix least-squares on \(F^2\)
R Factor 0.0693

Crystal System Monoclinic
Space Group \(P2_1/n\)
Unit cell dimensions \(a = 11.549(3)\) Å \(\alpha = 90°\)
\(b = 15.630(4)\) Å \(\beta = 90.792(5)°\)
\(c = 13.138(4)\) Å \(\gamma = 90°\)
Unit Cell Volume 2371.4(11) Å³
Z 4
Calculated density 1.201 Mg/m³
Chapter 3: Experimental Procedures

Atomic Labels

Atomic Coordinates

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- Si(1)–C(3)   1.890(2)
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- O(2)–C(5)    1.216(3)
- N(1)–C(1)    1.365(3)
- N(1)–C(8)    1.470(3)
- N(1)–C(9)    1.493(3)
- C(1)–C(2)    1.524(3)
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- C(2)–C(3)    1.557(3)
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Chapter 3: Experimental Procedures

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Bond Angles (°)

C(20)–Si(1)–C(18) 111.41(12)
C(20)–Si(1)–C(19) 110.46(12)
C(18)–Si(1)–C(19) 109.09(13)
C(20)–Si(1)–C(3) 107.82(11)
C(18)–Si(1)–C(3) 109.64(11)
C(19)–Si(1)–C(3) 108.37(11)
C(1)–N(1)–C(8) 112.33(18)
C(1)–N(1)–C(9) 122.59(19)
C(8)–N(1)–C(9) 124.66(18)
Chapter 3: Experimental Procedures

\[
\begin{align*}
O(1) - C(1) - N(1) & \quad 124.7(2) \\
O(1) - C(1) - C(2) & \quad 126.8(2) \\
N(1) - C(1) - C(2) & \quad 108.5(2) \\
C(1) - C(2) - C(7) & \quad 102.42(18) \\
C(1) - C(2) - C(3) & \quad 114.2(2) \\
C(7) - C(2) - C(3) & \quad 115.53(18) \\
C(1) - C(2) - H(2) & \quad 108.1 \\
C(7) - C(2) - H(2) & \quad 108.1 \\
C(3) - C(2) - H(2) & \quad 108.1 \\
C(4) - C(3) - C(2) & \quad 110.73(19) \\
C(4) - C(3) - Si(1) & \quad 110.79(16) \\
C(2) - C(3) - Si(1) & \quad 113.95(15) \\
C(4) - C(3) - H(3) & \quad 107.0 \\
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Si(1) - C(3) - H(3) & \quad 107.0 \\
C(5) - C(4) - C(3) & \quad 111.3(2) \\
C(5) - C(4) - H(4A) & \quad 109.4 \\
C(3) - C(4) - H(4A) & \quad 109.4 \\
C(5) - C(4) - H(4B) & \quad 109.4 \\
C(3) - C(4) - H(4B) & \quad 109.4 \\
H(4A) - C(4) - H(4B) & \quad 108.0 \\
O(2) - C(5) - C(4) & \quad 122.7(2) \\
O(2) - C(5) - C(6) & \quad 121.7(2) \\
C(4) - C(5) - C(6) & \quad 115.5(2) \\
C(5) - C(6) - C(7) & \quad 114.4(2) \\
C(5) - C(6) - H(6A) & \quad 108.7 \\
C(7) - C(6) - H(6A) & \quad 108.7 \\
C(5) - C(6) - H(6B) & \quad 108.7 \\
C(7) - C(6) - H(6B) & \quad 108.7 \\
H(6A) - C(6) - H(6B) & \quad 107.6 \\
C(2) - C(7) - C(6) & \quad 111.07(19) \\
C(2) - C(7) - C(8) & \quad 103.13(18)
\end{align*}
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### Chapter 3: Experimental Procedures

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**Hydrogen Bond Length (Å)**

O(1S)–H(1O)...O(2) 0.871 O(1S)...O(2) 2.880
H(1O)...O(2) 2.05

**Hydrogen Bond Angles (°)**

O(1S)–H(1O)...O(2) 158(4)
4.1 References.

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References


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