Direct Synthesis of Lactams Related to UCS1025A

A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy in Organic Chemistry

Lewis Ibbotson

Exeter College

University of Oxford

June 2021

Abstract

Direct Synthesis of Lactams Related to UCS1025A

Lewis Ibbotson, Exeter College, University of Oxford.

DPhil in Organic Chemistry, 2021

Chapter I gives brief history of drug discovery and development for anticancer and antibacterial agents with discussion on the reported mode of actions for each class of compounds. In the search for novel anticancer and antibacterial agents, UCS1025A is introduced, with a detailed review for all the published total synthesis, biosynthesis and SAR of analogues of UCS1025A.

Chapter II focuses on expanding methodology for imide synthesis successfully employing solventless reactions conditions with quantitative conversions. The latter section explores esterification of acid containing imides and problems associated with Michael addition.

Chapter III expand on the use of TBDMSiOTf, by subjecting ester containing maleimides and phthalimides to silyl triflate-mediated soft-enol cyclisations to form both bi- and tricyclic systems, while giving comprehensive structural analysis. This chapter also explores the potential stability, solubility and potential for elaboration of these systems.

Chapter IV expands the chemistry introduced in chapter III by incorporating substituted maleimides and phthalimides to TBDMSiOTf-mediated cyclisations and starts to explore the possibility of elaboration on the lactam ring. Nitriles are shown to be a worthy replacement for esters in a novel modification to these cyclisations. Part of this chapter focus on the synthesis of a tricyclic system *via* the elimination of the silyl appendaged group to afford a unique and completely flat pyrrolidone.

Chapter V looks at manipulating the alkene previously synthesised by various methods such as epoxidation and hydrogenation to remove the flatness seen in these compounds to aid the lack of solubility. Lastly, this chapter attempts to further diversify these compounds by Suzuki couplings and attempts at CH arylation using bi-dentate directing groups.

Chapter VI reports biological activity for the compounds tested, when applicable, for their potential anticancer and antibacterial activity.

Acknowledgment

Firstly, I would like to give my complete appreciation and thanks to my supervisor, Professor Mark Moloney, for giving me the opportunity to prove myself. This project was full of highs and lows, despite all the complications and roadblocks that appeared during my journey, Mark's support and guidance ensured that I successfully got to this point in my life. Not only did Mark help guide me to grow into the chemist I am today, he also was instrumental in changing my mindset when facing hard challenges and difficulties that help me to better myself.

Numerous members of the CRL staff that have given their time and patience in helping to educate me that contributed to this thesis to be written, with special thanks being given to Nader for all his work in helping with the chemical assignment of compounds, Amber and Kirsten for their X-ray analysis, even when I took them the most challenging of samples, as well as the mass spec team.

During my time here at Oxford, I have been lucky to meet many great people, but I particularly want to thank Jonny and Halima for taking the time to make me feel welcome in the Moloney group, as well as all other past members of the group, with an extra little thank you to Adam for allowing me to put him under my wing during his Part II. There are many others that I have befriended over these years, such as Ana, from the first day meeting you in the teaching lab, you have been a great friend and a great proof-reader, as well as Curt and Sue for their support.

A big part of my acknowledgments is reserved for my family whose unwavering support and devotion never faltered, despite my constant belly aching and complaining about failed reactions, always happy to pretend they understood what I am saying. In particular, Mum and James, Dad and Jaqy.

Without the help of Sylvia and Peter, this thesis would have never been written, and they are owed a huge debt for their support and encouragement over many years.

Last but not at all the least, I want to thank Charlotte, for being a rock, without whom I would never have taken my first steps on this journey, you have taken the rough with the smooth and deserve a huge amount of credit for supporting me through my goals, I will even forgive you if you don't actually read any of this.

Contents

Abstract i

Acknowledgment ii

Contents iii

Abbreviations vii

Nomenclature ix

Chapter I: Introduction 1

1.1. Disease 1
1.2. Drug Discovery 2
1.2.1. Target Lead Drug Discovery (TDD) 2
1.2.2. High Throughput Screening (HTS) 3
1.2.3. Fragment Based Drug Discovery (FBDD) 4
1.2.4. Computer Aided Drug Discovery (CADD) 5
1.2.5. Phenotypic Lead Drug Discovery (PDD) 6
1.2.6. High Throughput Screening Part II 6
1.2.7. Natural Product Inspired Drug Discovery 6
1.3. An Introduction to Cancer and Anticancer Drugs 7
1.3.1 A Brief History of the Development of Anticancer Chemotherapeutics 7
1.3.2. How to Treat Cancer 9
1.3.3. Drugs Used for the Treatment of Cancer 9
1.3.3.1. Covalent DNA Binding Drugs 9
1.3.3.2. Non-covalent DNA Binding Drugs 11
1.3.3.3. Inhibitor Based Drugs 12
1.3.3.4. Antimetabolites 14
1.4. Introduction to Infectious Diseases 16
1.4.1. What are bacteria 17
1.4.2. How to Treat Bacterial Infections 18
1.4.3. A Brief History of the Discovery and Development of Antibiotics 18
1.4.4. Drugs Used in the Treatment of Bacteria 20
1.4.4.1. β-Lactams 20
1.4.4.2. Oxazolidinones 21
1.4.4.3. Macrolides 23
1.4.4.4. Quinolones 24

1.4.4.5. Tetracyclines 25
1.4.4.6. Aminoglycosides 26
1.4.4.7. Glycopeptides 27
1.5. A Need for New Antibiotics 28
1.6. Introduction to UCS1025A and UCS1025B 29
1.6.1. Characterisation and Assignment for UCS1025A and UCS1025B 30
1.7. Introduction to CJ-16,264, CJ-16,367 and Pyrrolizilactone 32
1.8. Antibacterial and Anticancer Activity for Pyrrolizidine Containing Drugs 33
1.9. Biosynthesis of UCS1025A 36
1.10. Total Synthesis of UCS1025A 37
1.11. Methods for the Synthesis of Decalin Systems 37
1.11.1 Diels-Alder Mediated Cyclisation 38
1.12. Methods for the Synthesis of Pyrrolizidine 41
1.13. Structure and Reactivity (SAR) of CJ-16,264 46
1.14. Structurally Related Compounds to the Pyrrolizidines 47
1.15. A Summary of the Direction This Thesis Will Take 49

Chapter II: Imide Formation and Esterifications 50

2.1. Introduction to Imides and Imide Formation 50
2.2. Maleimide Formation 51
2.2.1. Esterification of *N*-Maleoyl-4-aminobutyric Acid 55
2.3. Esterification of GABA 56
2.4. Solventless Imide Formation of Maleimides 57
2.4.1. Formation of Imides from Substituted GABA Derivatives 63
2.4.2. Formation of Imides from L-Glutamic Acids 65
2.4.3. Synthesis of Maleimides Using Anilines 68
2.5. The Introduction to Phthalimides 68
2.5.1. Synthesis of Substituted Phthalimides 70
2.5.2. Synthesis of 5-(1-methoxy-1-oxobutyl)-6,13-dioxoisoindoline-9-carboxylic Acid 74
2.5.3. Synthesis of Phthalimides using Glutamic Acids 75
2.5.4. Synthesis of Phthalimides using L-Glutamic Acid 5-Benzyl Ester 78
2.5.5. Synthesis of Phthalimides using Anilines 79
2.5.6. Synthesis of 2.2.1-Bicycloimide 80
2.6. Esterification of Maleimides 80
2.6.1. Esterification of Glutamic Acid Containing Maleimides 82
2.6.2. Esterification of phenyl Maleimides 83
2.7. Esterification of Phthalimides 84
2.7.1. Synthesis of Methyl-1-(9-bromo-6,13-dioxoisoindolin-1-yl)butanoate 86
2.7.2. Esterification of Glutamic Acid Containing Phthalimides 87
2.7.3. Esterification of Phenylacetic Acid Containing Phthalimides 88

2.7.4. Esterification of 2.2.1-Bicycloimide Appended Acid 89
2.7.5. *O*-alkylation of Glutamic Acid Containing Phthalimides 89
2.8. Benzylation of Glutamic Acid Containing Phthalimides 90
2.9. Summary for Chapter II 92

Chapter III: Investigation into TBDMSiOTf-mediated Cyclisations 93

3.1. Review of TBDMSiOTf Mediated Soft-Enol Cyclisation of Maleimide 93
3.1.1. Scope and Limitations for TBDMSiOTf Cyclisation 97
3.2. Identification, Isolation and Characterisation for the Unknown Product of Cyclisation 101
3.3. Optimisation and Control for the Silyl-mediated Cyclisation of Phthalimides 105
3.3.1. *In situ* Generation of TBDMSiOTf for a One-pot Cyclisation Method 105
3.3.2. Reagent Based Control on the Product of Cyclisation 106
3.4. TBAF Mediated Desilylation 110
3.5. Acidic Desilylation 111
3.6. Review of Literature for the Synthesis of Compounds Similar to 77 and 165 112
3.7. Summary for Chapter III 116

Chapter IV: Silyl-mediated Cyclisation of Substituted Imides 117

4.1. Cyclisation of Substituted Maleimides. 117
4.2. Iodolactonization of Substituted Cyclised Maliemides 123
4.3. Cyclisation of L-Glutamic Acid Dimethyl Ester 123
4.5. Cyclisation of Substituted Phthalimides 127
4.5.1. Cyclisation of Benzyl Ester Containing Phthalimides 135
4.6. Cyclisation of L-Glutamic Acid Containing Phthalimide 136
4.6.1. Cyclisation of Benzyl Ester Containing Glutamic Acid Phthalimides 137
4.7. Cyclisation of Phenylacetic Methyl Ester Phthalimide 139
4.8. Cyclisation of 2.2.1-Bicycloimide 140
4.9. Cyclisation of Amides Appended Imides 140
4.10. Cyclisation of Nitrile Appended Imides 141
4.11. Pyrrolidinone Synthesis 1443
4.11.1. Direct Synthesis of Phthalic Based Pyrrolidinone from Phthalimides 146
4.11.2. Synthesis of Saturated Nitrile Containing Pyrrolidones 150
4.12. Summary of Chapter IV 152

Chapter V: Alkene Manipulation, Suzuki, Hydrogenation and CH-Activation 153

5.1. Epoxide Formation 153
5.2. Hydrogenation of the Alkene Containing Pyrrolidones 159
5.3. Suzuki Couplings 165

5.4. Introduction of Functionality at C3 *via* β-Arylation 166
5.4.1. Use of 8-Hydroxyquinoline as a Possible Bidentate Directing Group 168
5.4.2. Amide Formation Using 8-Aminoquinoline Post-Cyclisation 170
5.4.3. Amide Formation Using 8-Aminoquinoline and Pyrrolidone 174
5.5. Summary of Chapter V 189

Chapter VI: Antibacterial and Anticancer Screening 190

6.1. Antibacterial Screening 190
6.2. Anticancer Screening 196
6.3. Summary of Chapter VI 199

Chapter VII: Experimental Techniques and Results 200

Appendix I: X-ray Crystallography Data 342

References and Bibliography 345

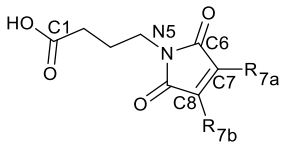
Abbreviations

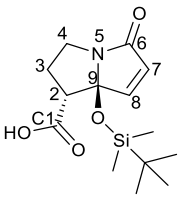
^{1}H-^{1}H DQF-COSY	proton to proton double quantum filtered-correlation spectroscopy
AcOH	acetic acid
aq.	aqueous
Ar	aromatic
Bn	benzyl
C	carbon
CADD	computer aided drug discovery
COSY	correlation spectroscopy
Da	dalton
DA	Diels-Alder
DCC	*N*-*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DHFR	dihydrofolate reductase
DIPEA	diisopropyl ethylamine
DMAP	4-dimethylaminopyridine
DNA	deoxyribonucleic acid
d.r.	diastereomeric ratio
E. coli	*Escherichia coli*
e.e.	enantiomeric excess
EMA	European Medicines Agency
ESI	electrospray ionisation
Et_2O	diethyl ether
FBDD	fragment based drug discovery
FDA	Food and Drug Administration
g	grams
GABA	γ-aminobutyric acid
H	hydrogen/proton
H. influenzae	*Haemophilus influenzae*
HeLa cells	human cell lines
hERG	human ether-à-go-go related gene
HMBC	heteronuclear multiple bond correlation
HRFAB-MS	high resolution fast-atom bombardment mass spectrometry
HSQC	heteronuclear single quantum coherence
HTS	high throughput screening
IC_{50}	half maximal inhibitory concentration
IR	infrared

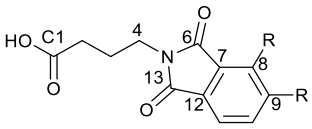
IMDA	intramolecular Diels-Alder
L	litre
LHMDS	lithium hexamethyldisilazide
***m*CPBA**	*meta*-chloroperoxybenzoic acid
MDR	multi-drug resistant
MeOH	methanol
MeCN	acetonitrile
mg	milligram
MIC	minimum inhibitory concentration
mL	millilitre
m/z	mass spectrometry
NMR	nuclear magnetic resonance
MRSA	methicillin-resistant *Staphylococcus aureus*
NOESY	nuclear Overhauser effect spectroscopy
PDD	phenotypic lead drug discovery
RNA	ribonucleic acid
***r*RNA**	ribosomal ribonucleic acid
rt	room temperature
SAR	structure activity relationship
TADA	transannular Diels-Alder
TBAF	*tetra*-n-butylammonium fluoride
TDD	target lead drug discovery
TEA	triethylamine
THF	tetrahydrofunran
***t*RNA**	transfer ribonucleic acid
$SOCl_2$	thionyl chloride
TBDMSiOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
tert	tertiary
UV	ultraviolet light
µM	micromolar
°C	degree Celsius
+	positive
-	negative

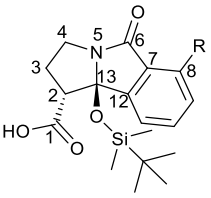
Nomenclature

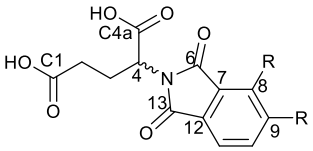
The following non-systematic number systems have been used throughout this thesis in order to provide direct compatibility of spectroscopic data.











Chapter I: Introduction

1.1. Disease

The term "disease" can be used to describe an abnormal condition that affects either part of, or all of the functions or structure of an organism, that is not due to any external injury.[1] In humans, "disease" is used more ambiguously to include disorders, disabilities, syndromes, isolated symptoms and infections. Any of the previously listed can result in distress, social problems, dysfunction, pain and even death to the person afflicted. It is possible to categorise diseases into 4 areas; deficiencies, infectious, physiological and hereditary (both genetic and non-genetic) disease. Most of the above-mentioned diseases are capable of being treated with drugs.

A few examples of each disease are listed below:

- **Deficiency disease**; Malnutrition (both overnutrition and undernutrition),[2,3] Kwashiorkor,[4,5] Marasmus,[6] and Rickets.[7]
- **Infectious disease**; Viral (such as hepatitis), fungal (such as Candidiasis) and bacterial (such as MRSA).[8]
- **Physiological disease**; Glaucoma,[9] diabetes[10,11] and asthma.[12]
- **Hereditary disease**; Sickle cell anaemia,[13] cystic fibrosis[14,15] and Down's syndrome.[16]

Some of the above known diseases still have no cure, such as cystic fibrosis, estimated in the UK to afflict over 7000 people.[15] In addition to the plethora of known existing diseases, even before the consideration for potential drug resistance to occur, such as MRSA,[17] the need for new drugs is evident.

Thankfully, chemistry is providing such drugs with 48 novel drugs approved in 2019, culminating in the largest class of approvals in 25 years.[18] In order to achieve this feat, a multitude of approaches for discovering drugs have been developed and implemented over recent years.

1.2. Drug Discovery

A significant and unavoidable issue with drug discovery is the high cost and lengthy process time. It has been estimated to cost between $800 million - $1.3 billion[19] for each drug over a period of 10 years with no guarantee of a return in profit for the manufacturer. Therefore, choosing the most effective method, or methods in the discovery of a new drug, is critical. If great care and thought is not given to the best method of discovery, then the likelihood of a costly failure is greatly increased. The first steps in discovery for a new drug will often start with generating data to support a hypothesis that inhibition or activation of a protein or specific pathway, often referred to as the so-called target, will afford a therapeutic effect.[20] The methods used for discovering new drugs are as plentiful and diverse as those being discovered, with a selection of currently used techniques discussed below.

1.2.1. Target Lead Drug Discovery (TDD)

Target lead drug discovery (TDD) uses either unknown or established targets, with the latter having a firm foundation of scientific understanding with a solid literature history.[20] In most cases, pharmaceutical companies will choose established targets, since assay methodology is likely to have already been established, and the path for drug development should be straightforward with shorter development times.[21] During the development phase, hit compounds which inhibit the target are identified. These hit compounds are often further evolved and modified to increase their effectiveness, while removing possible binding sites on major biological receptors in the body, such as hERG,[22,23] which create unwanted off-target effects.[22] The key question then becomes, how are these hit compounds identified.

1.2.2. High Throughput Screening (HTS)

High Throughput Screening (HTS) is a method often employed in the pharmaceutical sector[24] as a key process for rapid identification of "hit" compounds from a library of known small molecules, which may later become lead compounds for optimisation by medicinal based chemistry.[25] The process for HTS involves screening as many compounds as possible directly against a suitable bioassay (Figure **1.1**).[26] HTS uses complex laboratory equipment for the automation and is therefore expensive,[27] but the rapid and consistent testing of large collections of compounds (typically between 10,000 and 100,000 a day) can bring rewards by identifying the emergence of important chemical motifs.[27] Testing in such a way often assumes no prior knowledge about the target, instead relying upon chemical diversity in the compound library for discovery of novelty.

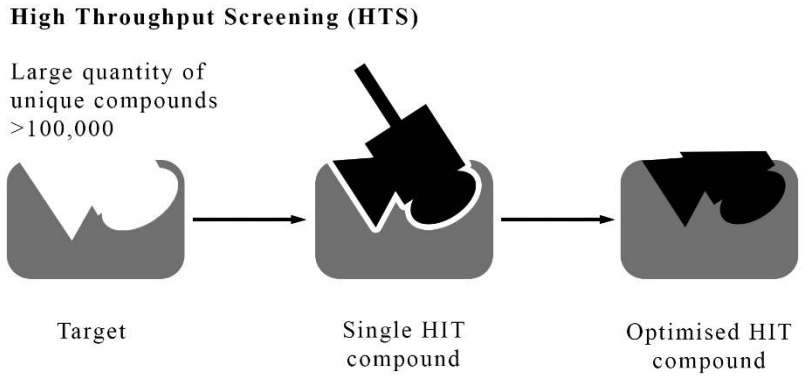


Figure 1.1. A pictorial view of a single specific compound fitting a target, followed by optimisation of the hit

Alternative strategies to HTS that have been designed to be specific in their method of discovery are *Focused* or *knowledge-based* screenings, which initially require more information being known about the target. Both of these approaches are usually based on prior literature or patents which identify the potential target for the drug. Libraries that have been prepared for *focused* or *knowledge-based* screening are significantly smaller than those used for HTS, resulting in shorter and cheaper screenings.[28] However, one of the major disadvantages to screening for hit compounds using either of these modified methods is the low success rate; for example, a

collection of compounds of ~500,000 from SmithKline-Beecham was screened against antibacterial targets, with a return of only 5 hit compounds.[29] Another problem is that these approaches may result in a lack of chemical diversity in compound libraries, as they often contain materials which are prepared with single or limited number of synthetic steps as time and cost saving measures.[29]

1.2.3. Fragment Based Drug Discovery (FBDD)

FBDD uses the same concept as HTS drug discovery along with some small but important changes.[30] Fragments are considered to be small organic molecules with low molecular weight[31] which are suitable for finding promising lead compounds for further development.[32] The aim of FBDD is to identify small chemical fragments that bind to a biological target, even if only weakly, with an example of this in Figure **1.2**. It may possible for multiple fragments to bind to different regions of the target that can then be coupled together *via* a linkage with the intention of increasing activity over a single fragment.[33] The latter step of this process focuses on metamorphosing the linked fragments into a usable drug that has desirable properties, such as low toxicity.

In contrast to HTS that may use up to millions of compounds, FBDD libraries contain a few thousand fragments with their molecular mass around 200 Da. In addition to the "rule of 5" for bioavailability,[34] these fragments should also follow the "rule of 3" that states molecular weight < 300, ClogP < 3, the number of H bond donors and acceptors each should be < 3, and the number of rotatable bonds < 3 so as to permit growth in molecular size during the optimisation process.[35]

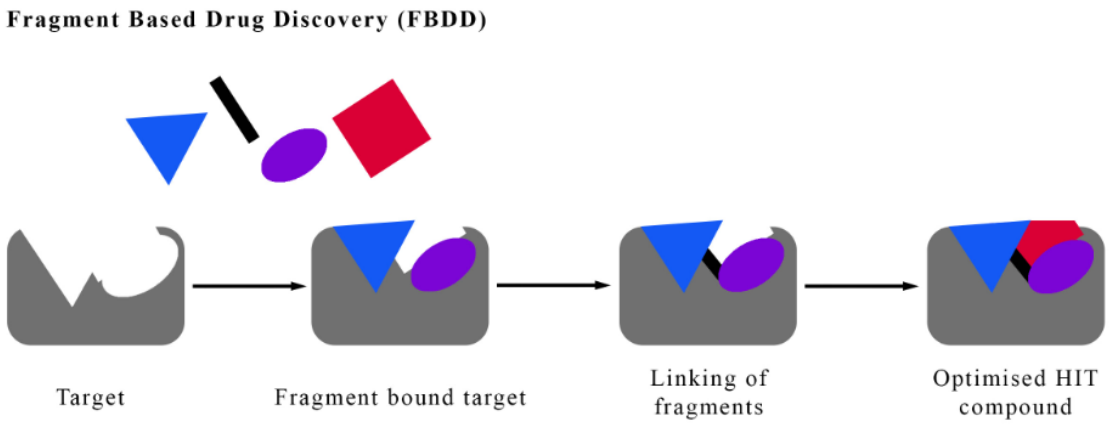


Figure 1.2. An example of small fragments binding to a specific target, followed by the development to an optimised hit compound

1.2.4. Computer Aided Drug Discovery (CADD)

Computer-aided drug discovery (CADD) has proved to be an important tool to maximise the efficiency of conventional methods of drug discovery.[27] One of the most popular CADD methods that is complementary to physical methods, is virtual (*in silico*) HTS, that takes advantage of multiple computational methods such as docking, to identify compounds with desirable properties.[36] Structure-based drug discovery (SBDD) can be applied when the three-dimensional structure of the target is known, with ligands being designed based on the known point of interactions inside the target structure. Molecular docking and *de novo* ligand design[37] are the most common methods for SBDD and have assisted directly in the discovery of FDA approved drugs such as Saquinavir and Amprenavir.[36] This approach can be further assisted by machine learning for CADD, utilising algorithms that can be trained in the identification of patterns in the drug discovery data.[38]

All the above discussed methods require the identification of a target in which to test potential drugs against, however, this is not always the case with modifications and variations in the validation process needed.

1.2.5. Phenotypic Lead Drug Discovery (PDD)

In contrast to target lead drug discovery, PDD does not rely on prior knowledge of the specific target or a hypothesis about its role in disease, instead the primary focus is on elaborating already known compounds. PDD techniques have seen a resurgence in use as a result from the diminishing returns when using HTS and FBDD methods for drug discovery.[39,40]

1.2.6. High Throughput Screening Part II

The same process used in HTS drug discovery may also be used when the target is not specified. The advantage of this style of drug discovery is that when diseases do not have a full history and understanding of the cellular processes can still be targeted.[41] A way that phenotypic lead HTS can be undertaken is to find a compound that is active, and to optimise it by a structure reactivity relationship (SAR) study.

1.2.7. Natural Product Inspired Drug Discovery

The concept of turning to nature for help in the discovery of new drugs is not new, for example, salicylate-rich plants such as the bark of the willow tree, were used to help with relieving pain and have been referenced as early as ancient Sumer and Egypt.[42]

When considering that a third of European Medical Agency (EMA) and/or Food and Drug Administration (FDA) approved drugs over the past 20 years have been based on natural products or their derivatives,[43,44] the importance of the role that nature plays in the discovery of drugs should not be understated.

Some crucial drugs that were discovered through natural products include the antibiotic Penicillin G, along with painkillers like morphine and the anticancer compound, Taxol. As these are specific named compounds, it should be also be reinforced that entire families of compounds that all share common motifs have been found in nature, such as tetramates.[45–48]

1.3. An Introduction to Cancer and Anticancer Drugs

Cancer is not a single disease, instead, it should be considered to be more of a collection of diseases classified under a generic group. There are four main types of cancers; Carcinomas, sarcomas, leukaemias and lymphomas, with over 100 different cancers filling these four categories. However, cancer does have 6 hallmarks that may be used to help define it;[49]

- Sustains proliferative signalling
- Evades growth suppressors
- Resists cell death
- Enables replicative immortality
- Induces angiogenesis
- Activates invasion and metastasis

When considering the various methods for drug discovery, it should be no surprise that anticancer compounds make up the largest share of drugs approved, at 23% for 2019.[18] Even with this supply of fresh anticancer chemotherapeutics, the survival rates can be significantly different, varying from 98% (for testicular cancer) to 1% (for pancreatic cancers).[50,51] If these percentages are coupled with the statistic suggesting that 1 in 2 people will be affected by cancer in their lifetime,[52,53] the need for novel anticancer drugs is still abundantly clear.

1.3.1 A Brief History of the Development of Anticancer Chemotherapeutics

The term "chemotherapy" or "chemo" was originally employed by Ehrlich[54] to describe the treatment of any disease using chemical agents. However, chemo is now more commonly associated with the treatment of cancers using a "cocktail" of toxic drugs. An example of one of these chemical cocktails is *MOPP*, that contains *Mustine*, *Oncovin*, *Procarbazine* and *Prednisolone* that is used in the treatment of Hodgkin's desease.[55]

Early techniques for the removal and treatment of cancers used a combination of radiotherapy and surgery, but despite small advancements, the survival rates plateaued at around 33%.[56] It was not

till the late 1960's that further understanding of micrometastases led to the development of a combination of drugs and surgery/radiotherapy to treat breast cancer that ushered in a new era of therapy.

Micrometastases occurs when a small cluster of cancerous cells migrate from a primary tumour, to more distant sites in the body where they can establish a secondary tumour.[57–59] Due to their small size and quantity, it may be nearly impossible to discover them, leading to relapse (regrowth of cancer) with metastases attributed to 90% of cancer deaths.[58] By introducing chemicals that act at the cellular level, the likelihood for all cells to be killed increases significantly.[60] With this discovery, the modern field of anticancer chemotherapy became possible.[56]

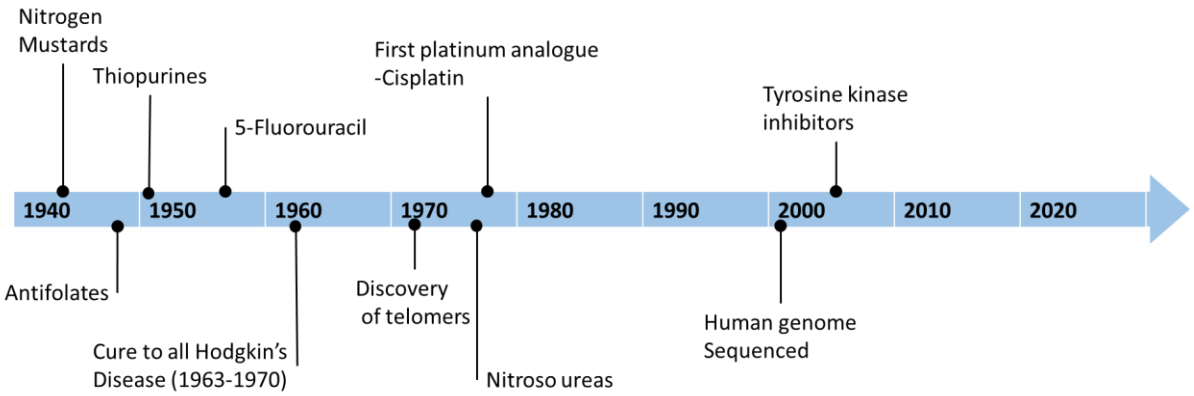


Figure 1.4. A timeline of major events in the discovery of anticancer compounds (adapted from the original source)[56]

Figure **1.4** shows some of the most important points in drug discovery against the war on cancer, from the early discovery of nitrogen mustards to nitroso ureas. One of the major breakthroughs during the mid-2000s saw the human genome sequenced, 9 years after the first full genome sequenced in 1995 (*H. influenzae*).[61]

Understanding a disease is the first part of the puzzle that needs to be solved, however, it is equally important to understand how to treat and cure cancer.

1.3.2. How to Treat Cancer

As it had already been mentioned, treating cancers can be difficult depending on the type of cancer, and in particular, where the cancer is located, since this can dictate how receptive the cancer is to specific treatments, as well as drug delivery to the cancerous cells.

This thesis will focus solely on drugs that are used to treat cancer, with no attention to radiotherapy or surgery.

1.3.3. Drugs Used for the Treatment of Cancer

There are 4 major families of anticancer chemotherapeutics that will be outlined which are covalent and non-covalent DNA binding drugs, drugs that act by inhibiting core processes in cancer and antimetabolites.

1.3.3.1. Covalent DNA Binding Drugs

One of the first major classes of anticancer compounds that will be briefly outlined are: covalent DNA binding drugs or alkylating agents. There are several subcategories of alkylating agents, exemplified in Figure **1.5**;

- Nitrogen Mustards – mechloroethamine, cyclophosphamide and bendamustine.
- Aziridines – mitomycin C, thiotepa, altretamine.
- Alkyl sulfonates – busulfan.
- Nitrosoureas – carmustine, lumustine, semustine.
- Platinum compounds – cisplatin, carboplatin, oxaliplatin.
- Methylating agents – dacarbazine, procarbazine.

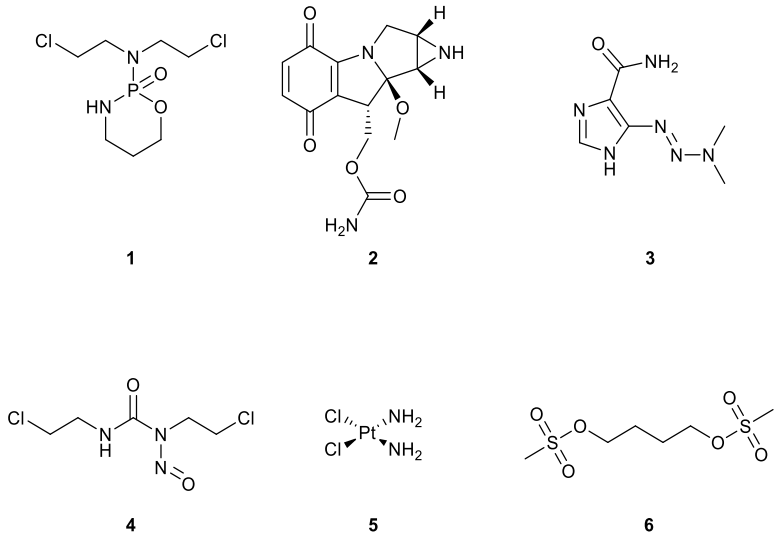
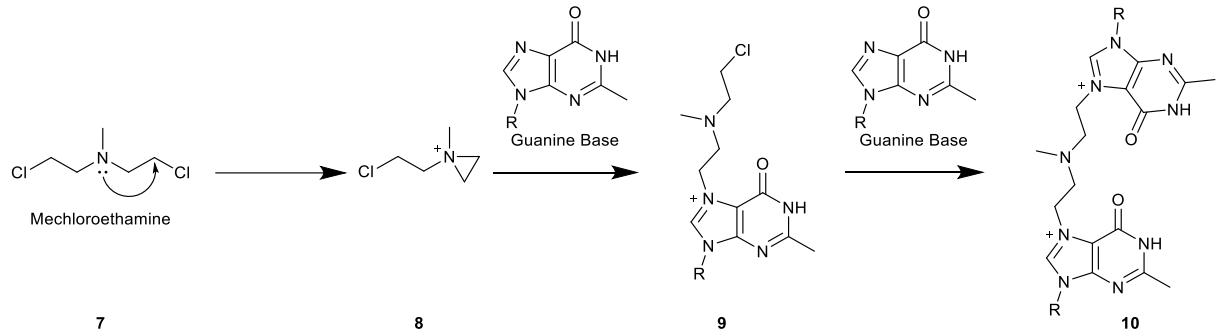


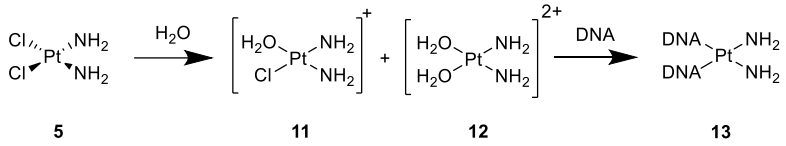
Figure 1.5. 1) cyclophosphamide,[62] **2**) mitomycin C, **3**) dacarbazine, **4**) carmustine, **5**) cisplatin,[63] and **6**) busulfan

From the aforementioned list of covalent DNA binding drugs, the first chemical compound that was implemented as a chemotherapeutic agent for the treatment of cancer were the nitrogen mustards.[64] While these early nitrogen mustards are no longer clinically used due to their high levels of toxicity and chemical weapon designations, newer and more effective compounds having been developed for therapeutic application such as cyclophosphamide **1** (1952) as shown in Figure **1.5**.[65,62] It is understood that these compounds form covalent linkages between DNA bases (usually the 7-nitrogen in Guanine) within the helical structure, forming interstrand and/or intrastrand cross linking of the DNA[66] as shown in Scheme **1.0**.



Scheme 1.0. Formation of aziridine ring **8** in nitrogen mustards leading to the alkylation of Guanine base and subsequentially cross-linking of DNA **10**[67]

The modes of action for alkylating agents are similar[68], for example, cisplatin must initially go through a series of aquation reactions, sequentially replacing the *cis*-chloro ligands for water molecules.[63,69] This yields a positively charged ligand that binds to DNA (Scheme **1.1**), impairing replication and subsequently leading to cell death.



Scheme 1.1. A simplified version of how cisplatin binds to DNA[63,69]

Tumours may be more susceptible to targeted toxins than normal tissue, since their replication is occurring at a faster rate, hence the treatment of cancerous cells by selective chemical attack becomes feasible.[64]

1.3.3.2. Non-covalent DNA Binding Drugs

Non-covalent DNA binding drugs such as intercalators are molecules that insert perpendicularly into the DNA helix, without forming any covalent bonds, being held in place *via* van der Waals, hydrogen bonding, and hydrophobic forces as well as charge transfer processes.[70] These systems are usually very planar, with their aromatic ring systems inserting themselves fully, or partly when bulky substituents are present.[71]

The resulting effect from insertion of these compounds in-between the base pairs found in the DNA strand forces the base pairs apart, distorting and destroying the helical structure making DNA replication impossible and eventually leading to cell death.[70,71] A few examples of intercalating agents are shown in Figure **1.6**.

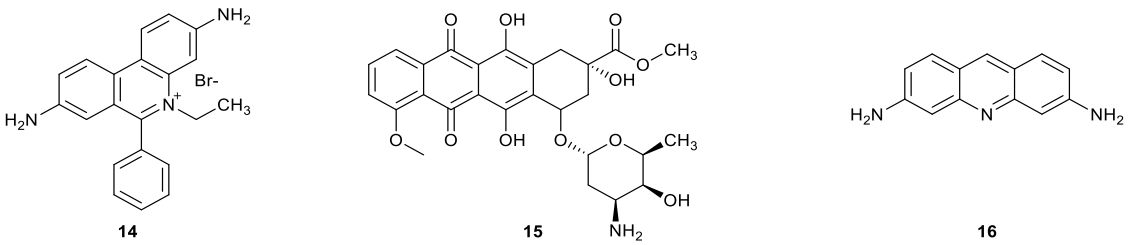


Figure 1.6. **14**) Ethidium bromide, **15**) Doxorubicin, **16**) Proflavine [72]

1.3.3.3. Inhibitor Based Drugs

Inhibitor-based anticancer chemotherapeutics, such as telomerase inhibitors, have been receiving more attention[73] due to the part they plays in cell immortality, being one of the 6 hallmarks of cancer.[49] Another reason for this interest stems from the frequency of telomerase-positive tumours, reported to be between 80-90%.[73]

A telomere is a distinct part of noncoding DNA that is found at the end of the DNA strand and used to correctly identify and distinguish the true end, rather than a break in the DNA.[8] During normal successive cell division (mitosis) in eukaryotic cells, the length of the DNA strand shortens over time. Each time replication occurs, a section of the telomere is lost, hence shortening of the newly replicated DNA strand. When shortening drops below a critical length, the cell can no longer divide, and therefore dies; this is senescence. The number of repetitive divisions is between 50 and 70 times before cell death occurs and is referred to as the Hayflick limit.[74]

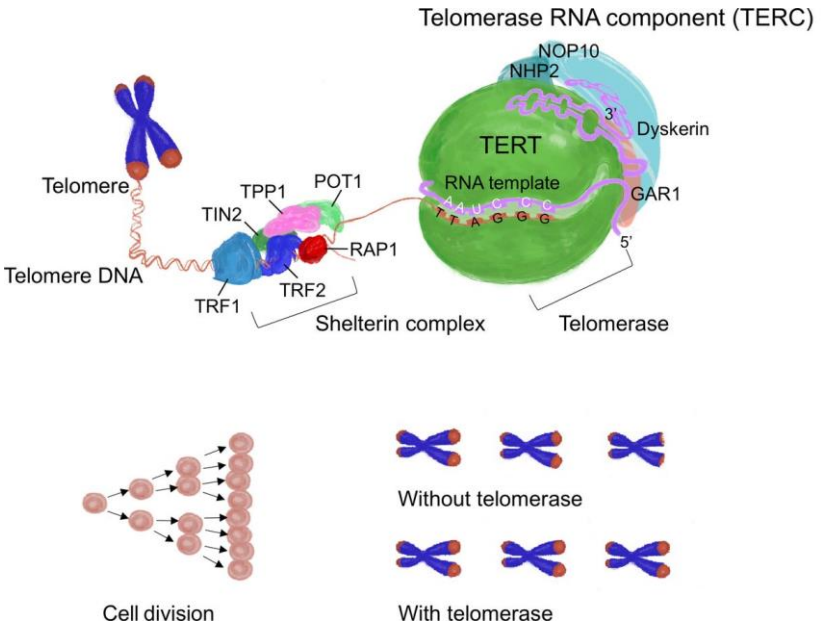
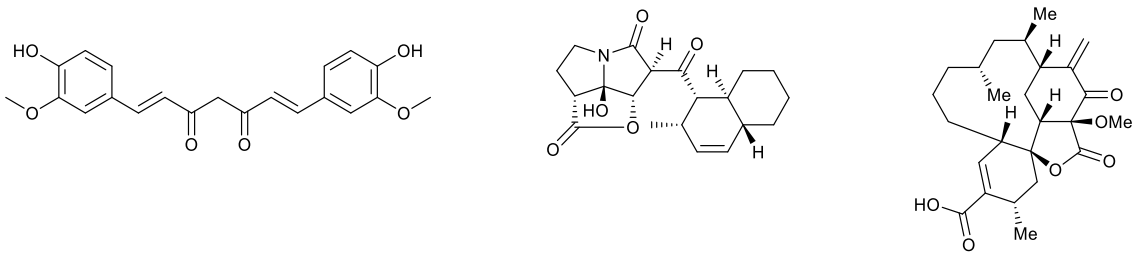


Figure 1.6b. The process of telomere lengthening *via* telomerase complex. Reprinted by permission from *Basic to Transl. Sci.*, 2019, **4**, 855–865[75]

In contrast to mammalian cells during replication, the DNA of prokaryotic cells, for example cancer cells, do not shorten and therefore do not become senescent (Figure **1.6b**.).

This can result in uncontrolled cell reproduction and "immortality."[76] Thus, since uncontrolled cell replication facilitated by telomerase is often seen in cancerous cells,[77] telomerase inhibition has become an area for potential advancements in the fight against cancer.[78] One advantage of targeting telomerase over other cancer targets is its universality, criticality and specificity to cancer cells.[73]

Telomerase inhibitors act by targeting the enzyme and their catalytic components or their RNA,[77–79] with defining modes of actions still unclear. A collection of compounds that have been shown to inhibit telomerase are shown in Figure **1.7**.



17 **18** **19**

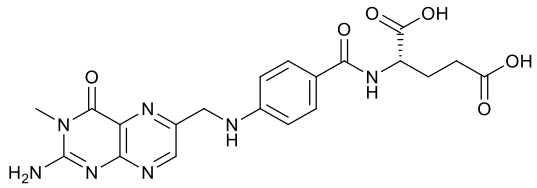
Figure 1.7. **17**) Curcumin,[79] **18**) UCS1025A,[80,81] **19**) Chrolactomycin[82]

1.3.3.4. Antimetabolites

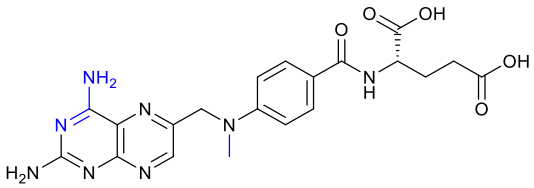
A metabolite is a small molecule that participates in normal metabolism in a cell, and a compound that inhibits metabolite action is referred to as an antimetabolite. Antimetabolites may interfere with the production of nucleic acids that are synthesised during the *de novo* pathway. As this pathway is often heavily used in tumours, it makes it an attractive therapeutic target. The major classes of nucleic acid synthesis inhibitors are;

- Folate antagonists.
- Pyrimidine antagonists.
- Purine antagonists.
- Sugar modified analogues.
- Ribonucleotide reductase inhibitors.

One of the first examples was discovered in 1937 when it was found that folic acid was deficient in patients with megaloblastic anaemia[83] and would stimulate proliferation of *Acute Lymphoblastic Leukaemia* (*ALL*) cells. The first antifolate analogues were synthesised in 1947, and methotrexate (fig **1.8**.) gave brief remission when administered to children with *ALL* cells.[84]



20

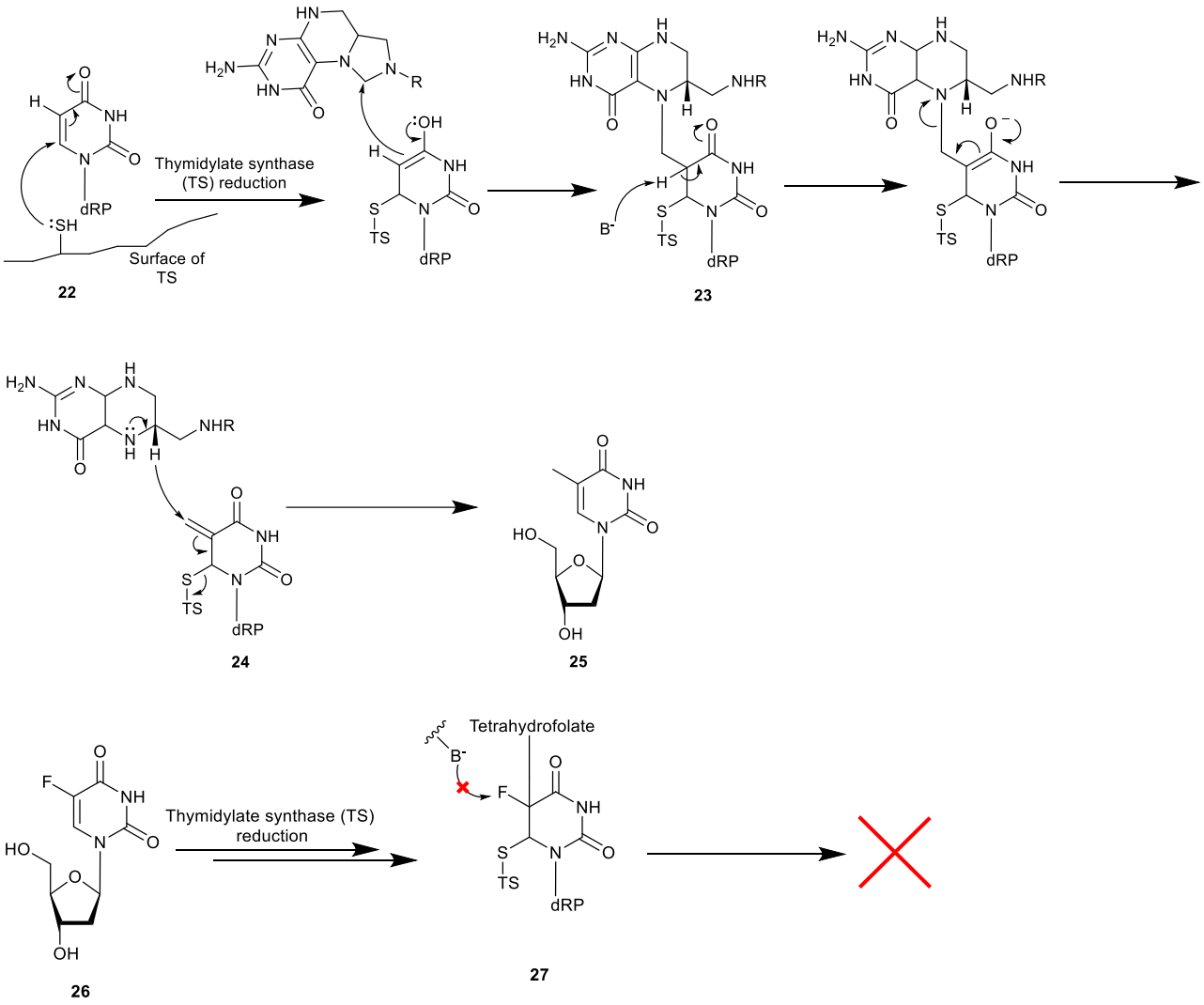


21

Figure 1.8. Folic acid **20** and its antimetabolite methotrexate **21** with changes highlighted[84,85]

It was found that the primary mode of action for antifolates is to inhibit dihydrofolate reductase (DHFR)[86] specifically during DNA and RNA synthesis, having the greatest effect on rapidly dividing cells, as seen in malignant and myeloid cells.

Thymidine biosynthesis inhibitors such as 5-fluorouracil and 5-fluorodeoxyuracil work by blocking thymidylate synthase (TS).[87] TS acts in the cell by assisting in the reduction of uridine[88] to thymidine by 5,10-methylenetetrahydrofolate (see Scheme **1.2**.). The simple addition of a fluorine resulting in the missing proton needed for the reduction to occur as shown in Scheme **1.2**, hence blocking the biosynthesis of thymidine that is used in DNA synthesis.[87]



Scheme 1.2. Thymidine **25** synthesis from uridine **22**, 5-fluorodeoxyuracil **26** forming a stable complex with TS and tetrahydrofolate (bottom)

As previously mentioned, methotrexate inhibits DHFR, and with 5-fluorodeoxyuracil inhibiting thymidine biosynthesis, combining these drugs provides a complementary action to one another.[87]

1.4. Introduction to Infectious Diseases

Infectious diseases typically arise from viral, fungal and bacterial infections while also including parasites (e.g. malaria), arthropods such as ticks and lice (e.g. Lyme disease) and worms (e.g. Schistosomiasis). Bacterial infections and their treatment with antibacterial agents form a key part of the work described in this thesis, and their early discovery along with the emergence of

bacterial resistance, and the potential for discovering new antibacterial agents, is discussed below.

1.4.1. What are bacteria

Cells can be divided into two distinct categories: eukaryotic (mammalian) cells and prokaryotic (bacterial) cells. At the centre of a eukaryotic cell is the nucleus that contains DNA, surrounded by the cytoplasm where proteins are synthesised and energy is generated, all being held in place by the cell membrane (Figure **1.9**.).[89] Prokaryotic cells have notable physiological differences, with the cell wall being the most noteworthy; this is constructed from peptidoglycan, that provide the cell with additional protection (Figure **1.10**).[90]

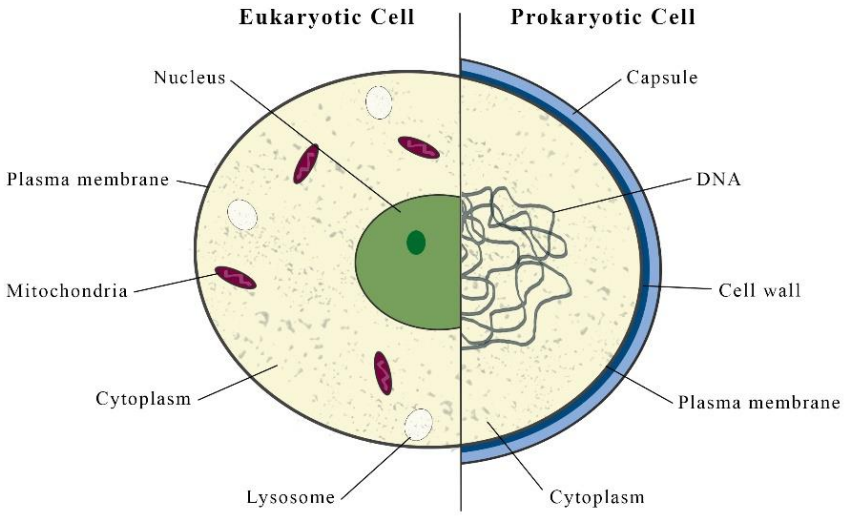


Figure 1.9. A side-by-side simplified comparison of eukaryotic and prokaryotic cells

Bacterial cells can be further divided into two types, Gram+ and Gram- strains, which differ in the organisation of the cell wall structures outside of the plasma membrane; for Gram+ bacteria, the "cell envelope" is less complex and thinner, and in Gram- bacteria, the "cell wall" is thicker and more complex.[91] One of the key additions to Gram- bacteria is an extra outer membrane structure that is covalently linked to the peptidoglycan chains, changing its responses to external stresses, included heat and more importantly, antibiotics.[90,92]

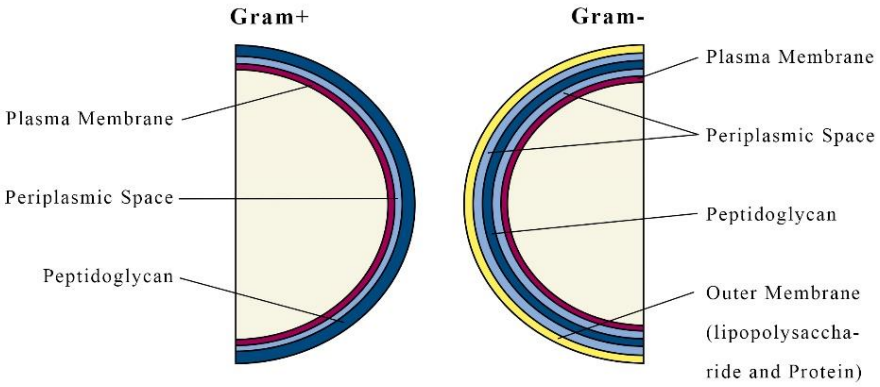


Figure 1.10. A side-by-side comparison of the different layers that form the cell wall for both Gram+ and Gram- bacteria

1.4.2. How to Treat Bacterial Infections

Treatment of bacterial infections is achieved *via* use of antibacterial drugs that selectively target bacterial and fungal infections, but not viruses.[17] As already demonstrated, the structure and complexity of bacteria is such that a substantial library of drugs is needed to target all aspects and functions in the bacterial cell. Currently, there are antibiotics which inhibit a range of processes inside the bacterial cell, and these drugs may be categorised based on their structural groups, including β-lactams (inhibition of the cell wall biosynthesis),[93] oxazolidinones (protein synthesis inhibitor),[94] macrolides (protein synthesis inhibitor),[95] quinolones (DNA gyrase inhibitor),[96] tetracyclines (protein synthesis inhibitor),[97] and lastly aminoglycosides (protein synthesis inhibitor).[98] However, all these antibiotics are now reported to have resistant strains, and the emergence of widespread bacterial resistance could threaten all areas of human life and plunge coming generations in to another "pre-antibiotic era." [99]

1.4.3. A Brief History of the Discovery and Development of Antibiotics

The year 1907 marked a critical and defining point in the history of medicine when Paul Ehrlich discovered that particular chemical dyes could selectively colour bacteria cells while leaving

mammalian cells undyed.[54] Shortly after, Ehrlich and Bertheim synthesised asphenamine[100] that could be used to cure syphilis. This was one of the first modern chemotherapeutic agents used as an antibacterial drug, starting a new age of medicine. The next major chemotherapeutic breakthrough did not come until 1928 when Alexander Fleming discovered penicillin,[101] which emerged over time as one of the most important discoveries in the history of antibiotics. Initially, only small quantities of penicillin could be isolated with the then-current technologies, and it was not until 1944 that supply was able meet the demand of the ending days of World War Two.[102] With the discovery of penicillin being mostly down to good observation, followed by diligent and careful scientific development, and some luck, other scientists at the time started to explore systematic methods that could be used to identify possible antibiotics.

Selman Waksman played a pivotal part in discovering more antibiotics, by devising a technique for the identification of natural substances with antibacterial properties.[103] The early pioneering work carried out by Waksman and his laboratory was responsible for the discovery and isolation of more than 15 antibiotics, the most famous of these being streptomycin in 1944.[104] The early pioneering work conducted by Fleming and Waksman led to a flourish of emerging antibiotics during what is now classified as the "golden era" for antibiotic discovery (see Figure **1.11**).

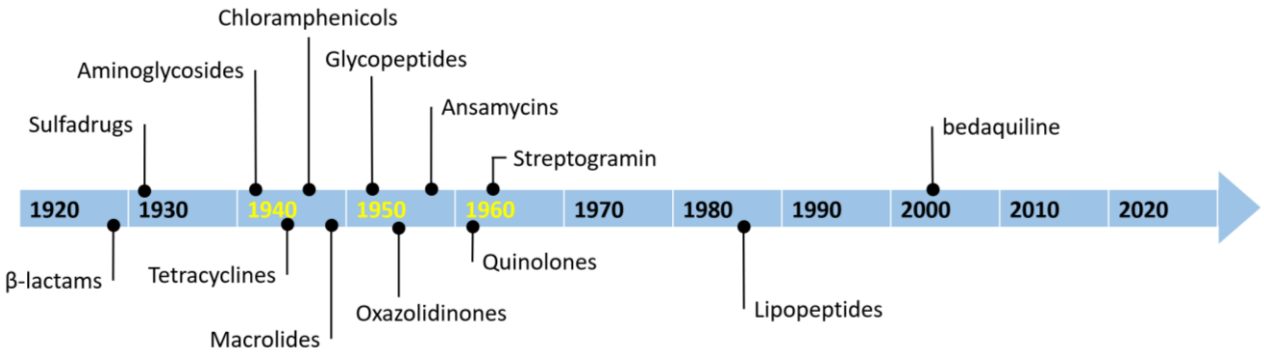


Figure 1.11. Timeline for major antibiotic discoveries with the "golden era" occurring between 1940-1960s adapted from the original source[105]

During the noticeable void in drug discovery spanning from the mid 1960's to the present day, only two new families of antibiotics have been developed: lipopeptides and bedaquiline. This void may have arisen from the belief that the effectiveness of all previously discovered drugs had been

fully optimised, and antibacterial drug development was de-prioritised especially as drug discovery programmes increasingly focused on cancer chemotherapy.[56]

1.4.4. Drugs Used in the Treatment of Bacteria

The aforementioned list (Section **3.2.2.**) of antibacterial agents will be briefly described for each category, aimed at describing their structure, activity, mode of action and finally the emergence of bacterial resistance.

1.4.4.1. β-Lactams

Of all the antibacterial drugs, the β-lactams are the most well-known, and it was reported in 2003 that they make up around 65% of all world market total sales for antibiotics.[106]

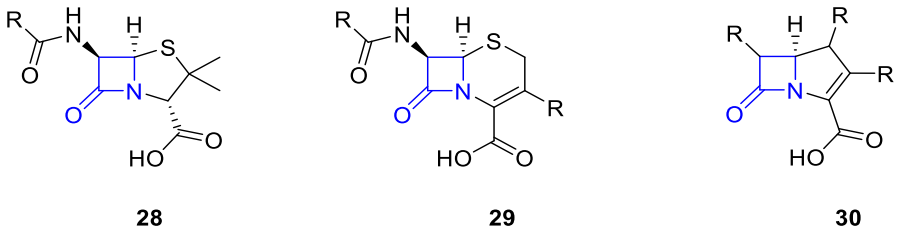


Figure 1.12. β-Lactam skeletons penicillin **28**, cephalosporin **29** and carbapenem **30**

At the core of this family of compounds is a highly strained 4-membered cyclic amide, commonly referred to as a lactam, that is essential to their activity.[93] Variations of the ring adjacent to the β-lactam ring further splits this family of drugs. For example, penicillins **28** belong to the penams characterised by their thiazolidinic[93] ring as seen in Figure **1.12**. Penams inherently suffer from acid liability, a consequence of the highly strained system, that under acidic environments and room temperature result in the protonation of the lactam nitrogen, proceeded by nucleophilic attack *via* the lateral carbonyl chain.[107] The early β-lactams were used in the treatment of Gram+ bacteria[108] due to the additional protection and functionality of the Gram- bacteria outer cell wall

affording resistance. It should be noted that a small collection of broad-spectrum β-lactams has been developed.[109,110]

β-Lactams are successful in killing bacteria by disrupting bacterial cell wall biosynthesis, by specifically targeting and inhibiting the enzyme *transpeptidase*,[93] leading to incomplete biosynthesis of the cell wall and subsequently leading to cell death.[93] During cell wall biosynthesis, *transpeptidase* couples peptide chains forming a lattice of cross-linked units.[111] The β-lactam drug enters the active site of the enzyme, and due to its susceptibility to hydrolysis, hydroxyl residues on the surface attack the lactam moiety, binding irreversibly, result in the active site being blocked as shown in Fig **1.13**.

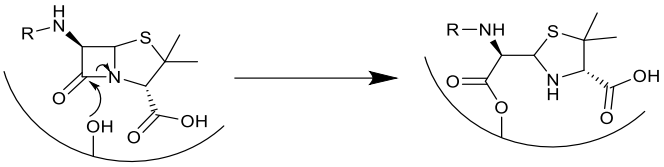
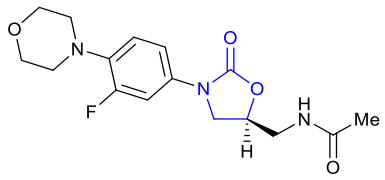


Figure 1.13. Penicillin undergoing nucleophilic attack from a hydroxyl residue on the surface on *transpeptidase*

Antibiotic resistance is a major problem with β-lactams.[99] One of the vital mechanisms in which bacteria protect themselves is by synthesising an enzyme *β-lactamase*, designed to open the drug as previously shown (Figure **1.13**.). By opening the lactam, all reactivity for the drug is lost. This can be countered with drugs specifically designed to be resistant to *β-lactamase*,[112] or even coupling lactams with other drugs, such as clavulanic acid that acts as a suicide inhibitor for *transpeptidase*.[112]

1.4.4.2. Oxazolidinones

The oxazolidinones are the only family of totally synthetic antibacterial agents resulting from the discoveries during the "golden era" of antibiotic discovery. At the core is a 5-membered cyclic carbamate, called a 1,3-oxazolidinone highlighted in Figure **1.14**.[113] The structure has changed since oxazolidinones were first used to treat tuberculosis in 1956 in the form of cycloserine.



31

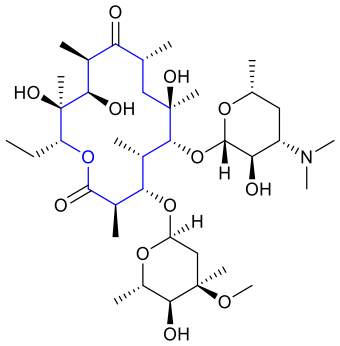
Figure 1.14. Linezolid **31**[114]

Oxazolidinones were shown to be broadly active against Gram+ bacteria that have resistance to other drugs, while also being orally active.[114,115] Interestingly, linezolid has been shown to have the same effectiveness against methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria as vancomycin does when prescribed to patients in a hospital study. [115]

It is understood that the mechanism of action for oxazolidinones is unique, binding to the 50S subunit found in the enzyme *peptidyl transferase*.[116] This section has not been shown to bind any other antibiotic suggesting the mechanism of action is novel. Once inserted into the binding site, it is believed that these drugs interfere with the processing of *N*-formylmethionyl-*t*RNA,[94,114,116] inhibiting bacterial protein synthesis.

Even though oxazolidinones are a new synthetic class of antibiotics, strains of resistant bacteria have emerged recently, after first being seen in patents in 2001.[117] It should be no surprise that one of the major mechanisms for resistance to oxazolidinone-based compounds starts with mutations in the 23S *r*RNA gene, the site where the 50S subunit is located.[117–119] This change in structure to the active site reduces or removes key residues that interact with the drug.[119]

1.4.4.3. Macrolides



32

Figure 1.15. Erythomycin **32**[120]

At the heart of the macrolides structure is a macrocyclic lactone between 14- and 16-membered-ring highlighted in Figure **1.15**. In the case of erythromycin, two deoxy (-OH group being replaced with H) containing sugar units are fused to the macrocyclic ring. Due to the number of stereocenters (10), the synthesis of erythromycin is challenging.[121] Most doses of erythromycin are a mixture of 4 different forms of the natural compound, from A-D with erythromycin A the most active antibiotic and C and D showing about 50% the levels of activity of that of A. One drawback to administering macrolides is poor bioavailability if taken orally, with erythromycin degrading when under acidic conditions, producing inactive byproducts.[122]

Macrolides exhibit a diverse biological activity that includes the ability to modulate inflammation and immunity in eukaryotic cells,[123] in particular infections caused by Gram+ bacteria with limited Gram- activity. Macrolides spectrum of activity is similar to the penicillins with a few extra additions, such as *Legionella pneumophilia,* and often used when patients show allergies to penicillins.[123]

The target site for the macrolides is the 23S region of ribosomal DNA found in the 50S ribosomal subunit. In doing so, they stimulate the dissociation of peptidyl *t*-RNA, when the bacterial cell attempts to initiate protein sysnthesis.[95,121] Binding to the active site is achieved *via* a series of

hydrogen bonds from the hydroxyl groups to the surface of the ribosomal subunit, in addition to the dimethylamino- group involved in hydrogen bonding.[95]

Bacteria develop protection against macrolides by a combination of mechanisms that involve efflux pumps to remove the drug from the cell, modification to the drug's target or use of additional enzymes that detoxify the cell by degrading the macrolide.[95]

1.4.4.4. Quinolones

Nalidixic acid **33** was one of the first quinolones developed and used only in the treatment of uncomplicated urinary tract infections and for this reason remained rather undeveloped until the emergence of the fluoroquinolones in the late 1970's (Figure **1.16**).[124]

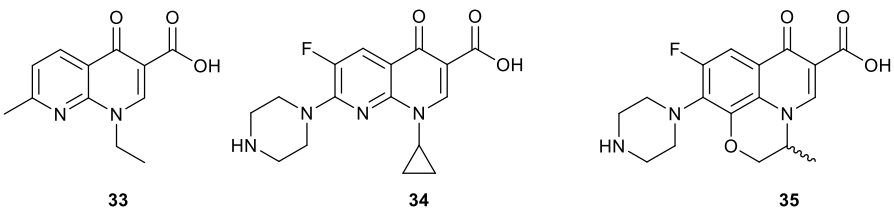


Figure 1.16. Nalidixic acid **33**, Ciprofloxacin **34** and Ofoxacin **35**[96]

The second-generation fluoroquinolones **34-35** showed significant benefits over the previous generation, not only in breadth of activity but also improved pharmacokinetics. Their main area of usage consists in the treatment of a variety of Gram- and Gram+ strains of bacteria attributed to their broad spectrum of activity.[96]

Fluoroquinolones typically target enzymes that includes bacterial type II topoisomerase, gyrase and topoisomerase IV.[125]

These enzymes participate in DNA synthesis by helping to remove strain on the DNA helix within the cell by "cutting" the DNA removing strain and reattaching the strands for DNA replication to occur. Fluoroquinolone's mode of action is to form a ternary complex that incorporates both DNA

and enzyme along with the drug. Interfering with DNA transcription, replication and repair along with promoting cleavage of the DNA leads to rapid cell death.[125]

Multiple methods of resistance for bacteria are available, with mutations to the gyrase complex reducing the affinity for binding to occur being one of the more obvious.[126] Additional protections may arise from reduced drug uptake and excretion of the drug in the form of efflux pumps.[127]

1.4.4.5. Tetracyclines

Tetracyclines are another class of the golden generation of antibiotics in the late 1940's with a key characteristic being four 6-membered rings fused together, and hence the name tetracyclines. The four rings are given letters to easily distinguish particular sections shown in Figure **1.17**, with each having functional groups that are imperative for the activity of tetracyclines.[97] In addition to the maintenance of the linear ring system seen in Figure **1.17**, other vital functionality is the α-configuration at 4a and 12a (points at which ring A and B intersect), C4 dimethylamino group and the conservation of areas that undergo enol-keto tautomerisation.[97]

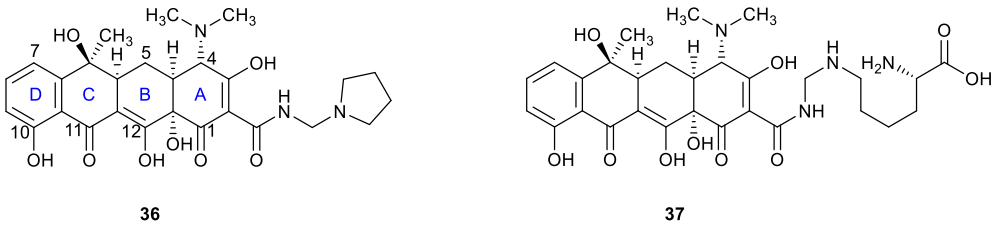


Figure 1.17. Rolitetracycline **36** and Limecycline **37**[128]

Tetracyclines are used in the treatment of Gram+ and Gram- bacteria due to their broad spectrum of activity,[128] but due to their over-use, some early discovered tetracyclines are used only when bacterial susceptibility to this drug is confirmed. New interest led to the synthesis of semi-synthetic systems with improved potency for the treatment of emerging multidrug-resistant (MRD) Gram+/- bacteria.[128,129]

It is understood that tetracyclines inhibit protein synthesis within the bacterial cell, by preventing the association of aminoacyl-*t*RNA with the bacterial ribosome.[97,129] Further specificity on the

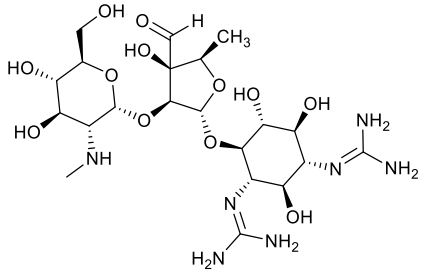
precise area that tetracyclines bind is harder to give, with studies indicating a single, high-affinity binding site in the ribosomal 30S subunit,[97] while other reports point out that this may not be correct.[130]

Tetracyclines have many attractive properties; since they are active against many common pathogens, show good oral absorption, low toxicity, low level of allergic reactions and are relatively inexpensive, it has led to extensive use in humans and animals that has contributed to large levels of bacterial resistance.[97,128,130]

Resistance to tetracyclines can be due to many factors such as mutations within the ribosomal binding site acquired *via* gene transfer, production of enzymes that deactivate the drug, or use of efflux pumps.[97,127,130,131]

1.4.4.6. Aminoglycosides

Aminoglycosides can be both natural and semisynthetic systems, sharing common features such that are typical for this family of drugs, with the core chemical structure consisting of several (usually three) rings.[132] 5- or 6-Membered sugars units are linked *via* glycosidic bonds to each other,[132] and the presence of amino- groups on these sugars, are implied given their nomenclature. Streptomycin, possibly one of the more recognised aminoglycosides, is shown in Figure **1.18**.



38

Figure 1.18. Streptomycin **38**[95]

Aminoglycosides are one of the few examples of antibiotics that are active against Gram- bacteria, as a result of their broad spectrum of activity.[98] The activity they exert is attributed to the fact these

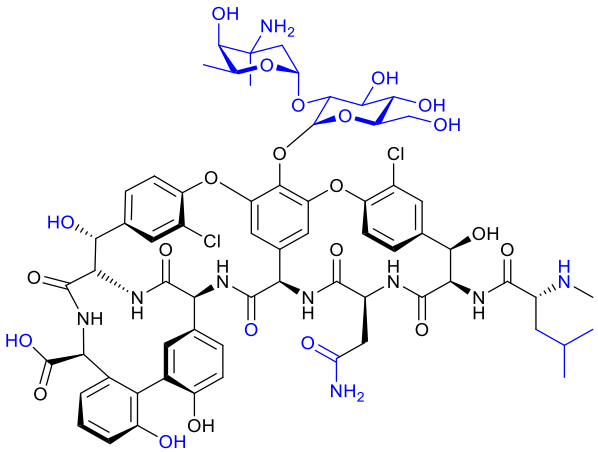
compounds have bactericidal properties, that is to say, they have the ability to kill bacteria and not only inhibit growth.[132]

Aminoglycosides are inhibitors of protein synthesis within the bacterial cell, achieved by impairing bacterial protein synthesis through binding to the prokaryotic 30S ribosome interfering with the ability to read codons in the DNA.[98] Being active against Gram- bacteria is dependent on a drug's ability to pass through the additional outer membrane, which is possible with aminoglycosides, possibly through drug induced disruption of ion channels such as Mg^{2+} channel.[133]

Resistance for aminoglycosides can occur in two different ways; a decreased uptake in to the bacterial cell possibly *via* a mutation in the ion channels, or by the production of bacterial enzymes that target aminoglycosides modifying their shape or structure rendering the compound inactive.[98,127,132–134]

1.4.4.7. Glycopeptides

Lastly to be discussed, but by no means the least important are the glycopeptides, that have the largest chemical structures formed from unique tri- or tetracyclic heptapeptide cores.[135] The glycopeptides could be considered to be the most structurally diverse of the aforementioned antibiotics with plenty of potential areas for functionalisation. Vancomycin as seen in Figure **1.18a** is one of the key glycopeptides with the areas of additional functionalisation highlighted.[136]



39

Figure 1.18a. Vancomycin **39**[136]

Glycopeptide antibiotics have been referred to as "last resort" drugs for treating severe Gram+ bacterial infections such as *Staphylococcus aureus*, *Enterococcus* spp., and *Clostridium difficile*.[135,137,138] Glycopeptides are often a go-to drug for treatment of MRSA, and also used when resistance to other antibiotics is easily achieved.[137]

They appear to act by hydrogen bonding at five different points to the C-terminal L-lys-D-Ala-D-Ala subunit found on the peptidoglycan lipid.[139] This inhibits transglycosylation and/or transpeptidation, two processes that are essential for cell wall biosynthesis.[135]

One mechanism in which bacteria form a resistance to glycopeptides, especially for *enterococci* is mutations to the lipid binding site, achieved by changes to the terminating muropeptide. Replacing the D-Ala-D-Ala with D-Ala-D-Lac reduces the frequency in which hydrogen bonding occurs in the pocket.[136] In fact, this addition adds a repulsive lone pair-lone pair interaction hypothesised to result in a 1000 fold loss in affinity for glycopeptides drugs binding.[135]

1.5. A Need for New Antibiotics

A common recurring theme for all the aforementioned family of drugs is antibacterial resistance and, in some cases, multidrug resistance. For this reason, the development of new antibiotics is paramount for the preservation of human health. The WHO describes antibiotic resistant bacteria

as one of the biggest threats to global health, food supply[140] and development.[141] Bacterial infections arising from resistant strains can occur in any person at any stage of their lives, with the CDC stating that every year in the U.S, 2.8 million people are infected with antibiotic-resistant bacteria, of whom 1.25% die as a result. The emergence of high levels of resistant infections is likely to arise from persistent use of antibiotics to treat mild infections and from drugs being over-prescribed. It is interesting that the DDD (defined daily dose) for antibacterial therapy has increased by 65% between the years of 2000 and 2015.[142] Given that the aforementioned compounds are all still clinically used as antibacterial agents, a recurring theme was a pre-established mechanism for resistance to each drug listed. For this reason, it is critical that novel series of antibiotics are developed before our current stock of drugs sees a surge in resistant bacteria, leaving these compounds redundant for use.

1.6. Introduction to UCS1025A and UCS1025B

UCS1025A **18** and its analogue UCS1025B **40** belong to a novel class of compounds that feature a lactam-containing pyrrolizidine core fused to a transdecalin moiety (see Figure **1.19**.), first isolated in 2000[80] from the fungus *Acremonium* sp. KY4917, with UCS1025A exhibiting both antibacterial and antiproliferative properties.[82]

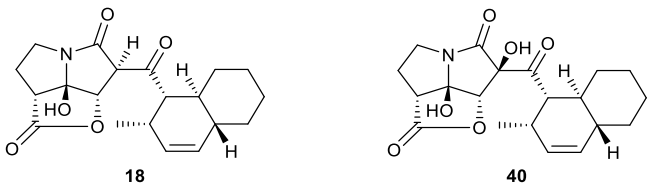


Figure 1.19. UCS1025A **18** and UCS1025B **40**[80]

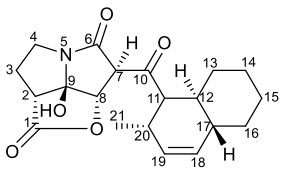
These compounds can be split into two distinct substructures; the first component of interest is a decalin moiety connected *via* a ketone. The second structurally unique section contains a tricyclic skeleton with a pyrrolizidine core, appended to a fused lactone which forms the left-hand side of the natural product. UCS1025A and UCS1025B are only differ from the replacement of a proton

with a hydroxyl group, with the addition of inversion of the stereochemistry, that blocks keto-enol tautomerisation.

The isolation of both these compounds started with batches of fungi grown on different agar media, and the cultured colonies analysed; for those exhibiting antimicrobial activity, separation and characterisation of the active compound was performed.[80] The initial fermentation medium used a mixture consisting of glucose (10%), dried mash potato (3%) and yeast extract of 3% in deionized water adjusted to a pH of 6.5. This was inoculated with a mature strain of KY4917 and incubated for 6 days at 25°C on a rotary shaker. After separation by silica gel column chromatography, extraction and further recrystallisation, UCS1025A and UCS1025B with a mass of 131 mg and 4.8 mg (no yield given) respectively were obtained.

1.6.1. Characterisation and Assignment for UCS1025A and UCS1025B

The first step in the determination of the structure of the isolated natural product was to determine the molecular weight *via* high resolution fast atom bombardment mass spectrometry (HRFAB-MS), with the exact mass reported as *m/z*= 360.1799 [MH+] (ESI^+), calculated for $C_{20}H_{26}NO_5$.[81] UV and IR analysis in addition to NMR spectroscopy was used to further elucidate the structure.



18

Figure 1.20. UCS1025A **18** and numbering of key carbons and protons[81]

Initial ^{13}C NMR analysis showed twenty carbon signals (confirming the molecular formula), and alongside DEPT and HSQC spectroscopy, Agatsuma *et al.* concluded that the product contained one methyl, six methylene, seven methine, two olefinic carbons, along with three carbonyl groups and one quaternary sp^3 carbon;[81] this all supported the original M/S data.

^{1}H-^{1}H DQF-COSY spectroscopy identified interactions between H_2-H_{3a}-H_{4a} and suggests a concaved shape giving rise to axial and equatorial protons. Similar analysis of H_{21}-H_{20}-(H_{19}-H_{18})H_{11}-H_{12}-H_{13A} along with ^{13}C NMR spectroscopic data signalled the position of an alkene between C_{18}-C_{19}. No specific NOESY correlation between H_{12} and H_{17} was seen, suggesting a *trans*-arrangement. However, NOESY NMR spectroscopy did show correlation between H_{12} and H_{21} as well as H_{17}-H_{11}. ^{13}C NMR data indicated the presence of three carbonyls that could be assigned via HMBC NMR spectroscopy. A ^{1}H-^{13}C interaction was seen from H_{3B}-C_1 and H_8-C_1. The amide carbonyl C6 also gave interactions from H_8 in addition to H_7. The proton for H_7 also saw C_{10} carbonyl as expected that could be assigned due to ^{1}H-^{13}C interactions from H_{11}. It should be noted that tautomerisation of compound **18**,[81] where the enol would formed between C_7 and C_{10} and causing the loss of H_7 proton, was observed. A visual representation for all the above correlations and interactions can be seen in Figure **1.21**. UCS1025B **40** was also identified and characterised by using the same technique and methods explained above.[81]

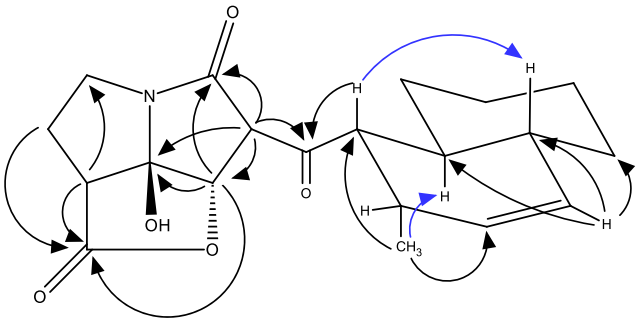


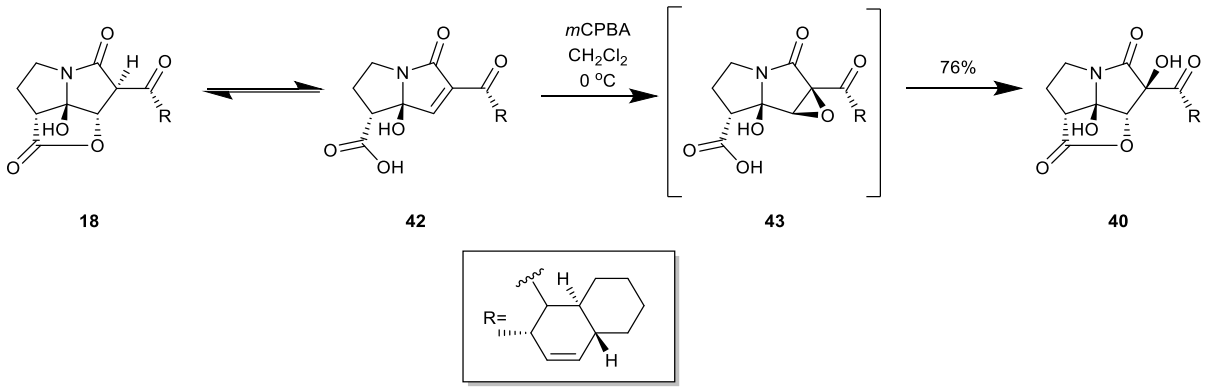
Figure 1.21. Structure of UCS1025A showing HMBC (black arrows) correlations and selected NOESY (blue arrows) interactions[81]

After recrystallisation of UCS1025A from *n*-hexane/acetone x-ray diffraction analysis was used to show that UCS1025A undergoes enol-keto tautomerisation to give the enol variant of UCS1025A (Scheme **1.3**).[81]



Scheme 1.3. Tautomeric structures of UCS1025A **36**[81]

UCS1025A was subsequently treated with *m*CPBA resulting in the formation of UCS1025B **40**. During this conversion **42** was observed by ^{1}H NMR and IR spectroscopy. Agatsuma *et al.* concluded that **42** was epoxidised to give intermediate **43** followed by the epoxide opening to form the hydroxyl at the C7 position (Scheme **1.4**.).[81]



Scheme 1.4. Conversion of UCS1025A **18** to UCS1025B **40** *via* epoxidation using *m*CBPA[81]

1.7. Introduction to CJ-16,264, CJ-16,367 and Pyrrolizilactone

UCS1025A and UCS1025B are not the only members of this novel and unique family of compounds. They are joined by two additional structures and their analogues; CJ-16,264 and CJ-16,367,[143] as well as pyrrolizactone.[144]

At first glance, the structural differences between all members of the pyrrolizidine family are subtle, as seen in Figure **1.22** that may attribute to the differences in their biological activity that will be highlighted later in this chapter. Firstly, the tricyclic lactam skeleton remains mostly identical, with CJ-16,367 **45** existing as the open lactone with the notable inclusion of a methyl on

the previously free alcohol. This may be necessary to ensure the stability of the lactam under acidic or basic conditions. The second major difference seen across this family of drugs is the *cis*-decalin rather than the *trans*-decalin as seen with UCS1025A/B.

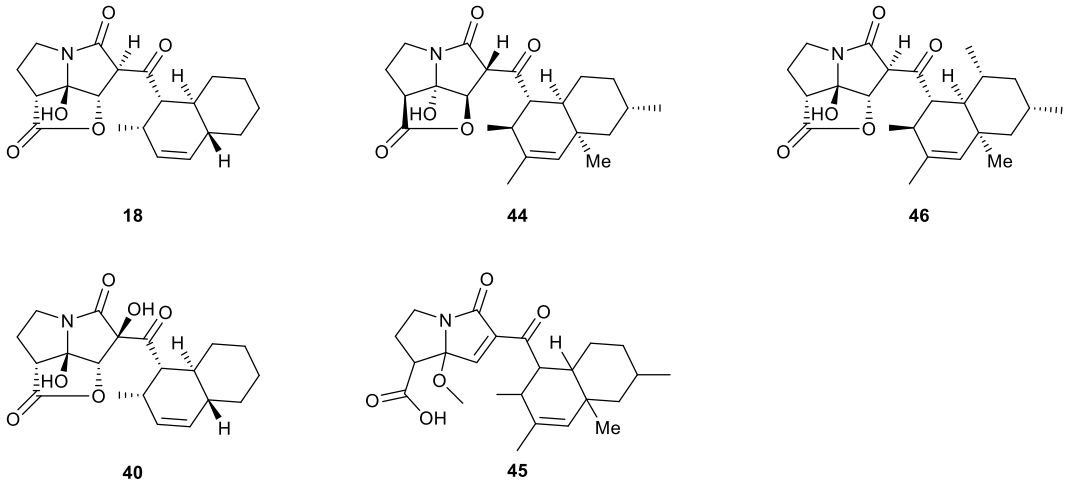


Figure 1.22. UCS1025A **18** and B **40**,[80] CJ-16,264 **44** and CJ-16,367 **45**,[143] and Pyrrolizilactone **46**[144]

The other small but impactful changes that CJ- and pyrroliziactone feature is a Me group in favour of a proton at the C15 position on the decalin ring. Additional Me groups can also be seen at the C13 and C17 positions. With pyrrolizilactone also featuring a Me at C11, making it safe to classify this as the most structurally complex from the previously mentioned families.

1.8. Antibacterial and Anticancer Activity for Pyrrolizidine Containing Drugs

The antibacterial and anticancer data for the UCS- series, CJ- series and pyrrolizilactone will be presented, summarised, and discussed together, with comparisons made when possible. UCS1025A was shown to be potent antibacterial agent (**Table 1.1**) against both Gram+ and some Gram- bacterial strains. The addition of a hydroxyl group on UCS1025B caused a large decrease in antibacterial activity. As the only structural difference between both UCS1025A and UCS1025B is the addition of a single hydroxyl group at C7, it suggests that the amide-ketone

structure might be key to antibacterial activity. Without such a group, enol tautomerisation can occur accounting for the antibacterial activity of UCS1025A.

Table 1.1. A comparison of MIC values for UCS1025A and B for different bacterial types

Bacteria tested	MIC µM/mL		Bacteria type
	UCS1025A	UCS1025B	(+ or -)
***Staphylococcus aureus subsp. Aureus* ATCC 6538 P**	1.3	42	+
***Bacillus subtilis* No. 10707**	1.3	83	+
***Enterococcus hirae* ATCC 10541**	1.3	42	+
***Proteus vulgaris* ATCC 6897**	5.2	83	-

The presence of the *trans*-decalin system and the possible importance to biological activity of both UCS1025A and UCS1025B may also be significant. There are many natural products containing decalin systems[145–147] which are primarily biosynthesised by fungi and bacteria that originate from either of two biosynthetic pathways, namely polyketides and isoprenoids.[148]

UCS1025A exhibits much more potent antiproliferative activity against human tumour cell lines,[80] with IC_{50} values ranging from 21 µM to 58 µM, with UCS1025B having no values below 100 µM. However, the IC_{50} values that UCS1025A displays are nonetheless poor compared to other antitumour agents such as etoposide (VP-16) that range from 0.31 µM to 1.3 µM.[80]

Table 1.2. Values for UCS1025A and UCS1025B with Etoposide (VP-16) for comparison of IC_{50} values

Cell Lines	IC_{50} values/µM		
	UCS1025A	UCS1025B	Etoposide (VP-16)
ACHN	58	>100	0.31
A431	55	>100	0.27
MCF-7	21	>100	0.57
T24	51	>100	1.3

CJ-16,264 also was shown to have good activity against Gram+ bacteria that included Gram+ MDR strains and additionally Gram- bacteria, such as *E. coli* (with improved membrane permeability or *imp*) displayed in Table **1.3**.

Table 1.3. A comparison of MIC values for CJ-16,264 and CJ-16,367 for different bacterial types

Bacteria tested	MIC µM/mL		Bacteria Type
	CJ-16,264	CJ-16,367	(+ or -)
Staphylococcus aureus	1.56	12.5	+
S. haemolyticus	3.12	12.5	+
S. pneumoniae	12.5	50	+
Moraxella catarrhalis	0.39	1.56	-
***E. coli* (*imp*)**	6.25	50	-

Available biological data for pyrrolizilactone did not report any antibacterial activity, but did show moderate cytotoxicities against HeLa cells with IC_{50} values of 1.1 and 3.1 µM/mL^{-1}.[144] Interestingly, pyrrolizilactone appeared to be a proteasome inhibitor when the 20S proteasome was incubated with the natural product. Chymotrypsin-like, trypsin-like and caspase-like activities were measured for the inhibited proteasome. The results are shown in Table **1.4** with UCS1025A used for comparison.

Table 1.4. IC_{50} values [µM] of pyrrolizilactone and UCS1025A for proteasomal activity

Compound	Trypsin-like	Chymotrypsin-like	Caspase-like
Pyrrolizilactone	1.6	29	84
UCS1025A	>100	>100	>100

Both UCS- series and CJ-series show a moderate level of anti-bacterial activity while pyrrolizilactone has no such data reported. In contrast, CJ-16,264 shows no inherent anti-cancer properties unlike the other pair of natural products, with UCS1025A a potential telomerase inhibitor and pyrrolizilactone inhibiting proteasomes. It is unfortunate that these compounds have

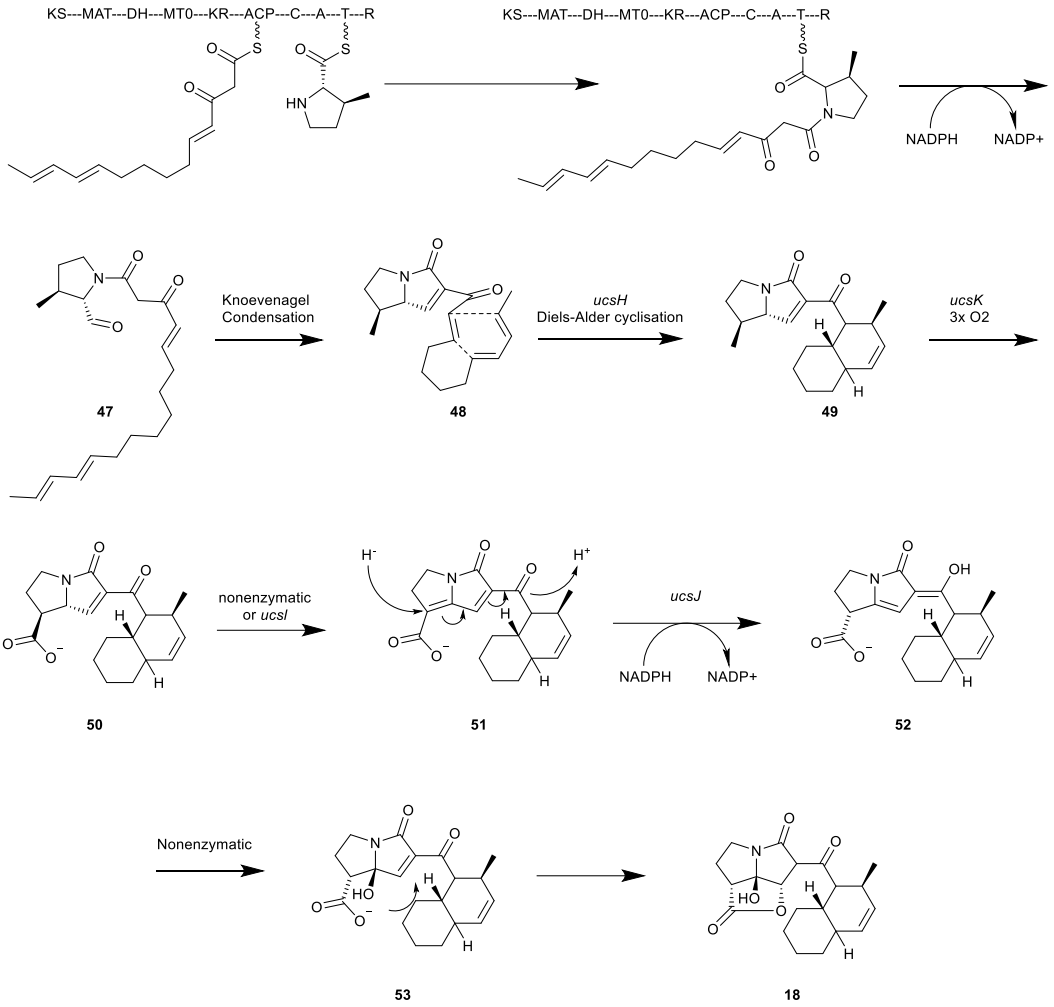
not all been tested against the same strain and typeset of bacteria in order for more conclusive assumptions on antibacterial and anticancer activity seen across this family.

This chapter will now focus on the biosynthesis and reported chemical total synthesis of UCS1025A and CJ-16,264 where applicable.

1.9. Biosynthesis of UCS1025A

The reported biosynthesis for UCS1025A[149] begin by examining the gene cluster responsible, with a collection of enzymes identified that included enoylreductase (*ucsL*), Diels-Alderase (*ucsH*), and hydrolase (*ucsC*), along with a few other enzymes controlling multiple redox reactions[149](Scheme **1.5**). It has been possible to replicate the gene cluster with alterations (such as the removal of key enzyme-controlled reactions) to produce mutations in the synthesis; for example, removal of the Diels-Alderase will stop the formation of the *trans*-decalin system **46**.[149] This approach of sequentially removing targeted enzymes, can allow the identification and isolation of specific compounds during the biosynthesis, giving confidence for the reported scheme.

A recent report on tetramic acids containing decalin systems where shown to be biosynthesised in a similar process,[150] with the relevance of pyrrolizidines and tetramic acids discussed later in this chapter.



Scheme 1.5. Proposed biosynthetic route for UCS1025A[149]

1.10. Total Synthesis of UCS1025A

As already outlined, UCS1025A and UCS1025B, as well as CJ-16,264 comprise two key structural sub-units; the transdecalin moiety, and lactam containing pyrrolizidine core. Therefore, the total synthesis of UCS1205A will be split in to two sections: Methods for the synthesis of the decalin systems (Section **1.11)** and methods for the synthesis of the pyrrolizidine core (Section **1.12**).

1.11. Methods for the Synthesis of Decalin Systems

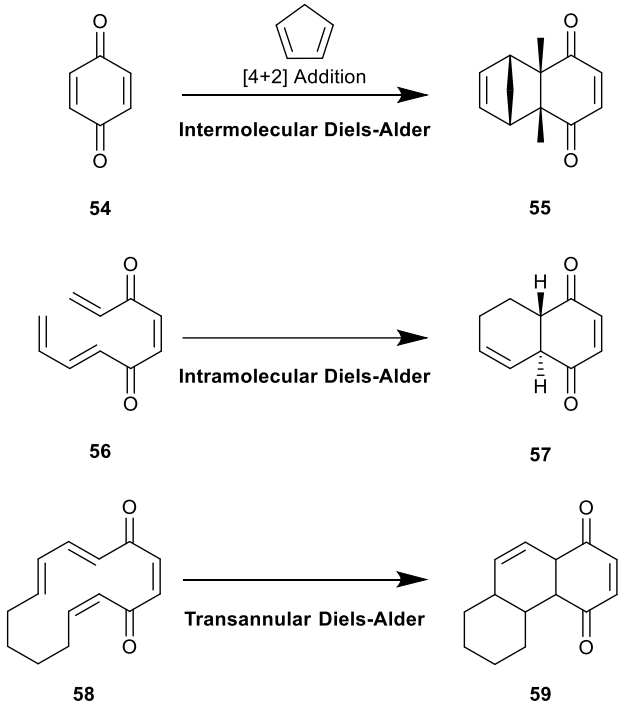
Decalin systems are bicyclic compounds that can either be in the *cis*- or *trans*- configuration and have been widely studied because of their ubiquitous occurrence in natural products.[151,152]

Methods for forming such chemical structures include inter- or intramolecular Diels-Alder reactions, and Robinson Annulation.[153]

1.11.1 Diels-Alder Mediated Cyclisation

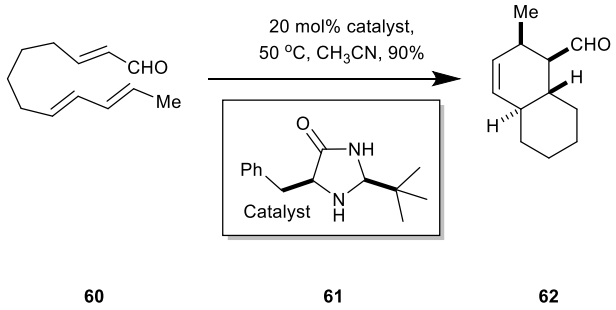
Diels-Alder (DA) cycloadditions have been developed extensively since their discovery in 1928.[154] The DA reaction allows easy access to six-membered rings with high regio-, chemo- and stereoselectivity while maintaining high atom-economy. They are currently 3 main types of DA reactions for decalin synthesis as seen in Scheme **1.6**;

- Intermolecular DA – used primarily for the synthesis *cis*-decalin systems *via* a [4+2]-cycloaddition of a conjugated diene and a dienophile.[152]
- Intramolecular DA (IMDA) – used for the stereocontrolled synthesis of *trans*-decalin systems, with the diene and dienophile connected, on the same chain.[148,152]
- Transannular DA (TADA) – similar to the IMDA reaction, with the major difference the carbon chain exists as a macrocycle (a single ring formed of 12 atoms or more).[155]



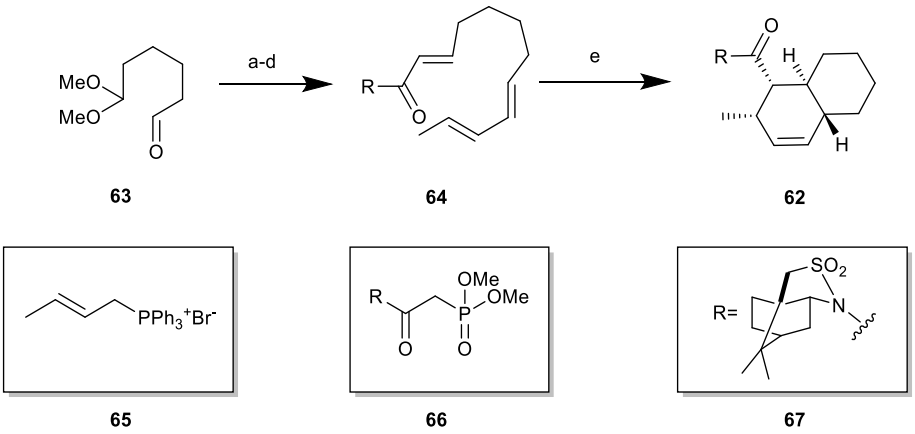
Scheme 1.6. Examples of intermolecular Diels-Alder original reaction first published by Diels and Alder, [154] intramolecular Diels-Alder and transannular Diels-Alder

The first published total synthesis of UCS1025A[156] employed the method used in the total synthesis of Solanapyrone D, where enantioselective organocatalytic IMDA using a chiral catalyst **61** was used to afford the required stereochemistry in good yield, *d.r.* and *e.e.* (71%, 20:1 and 90% respectively) (Scheme **1.7**).[157]



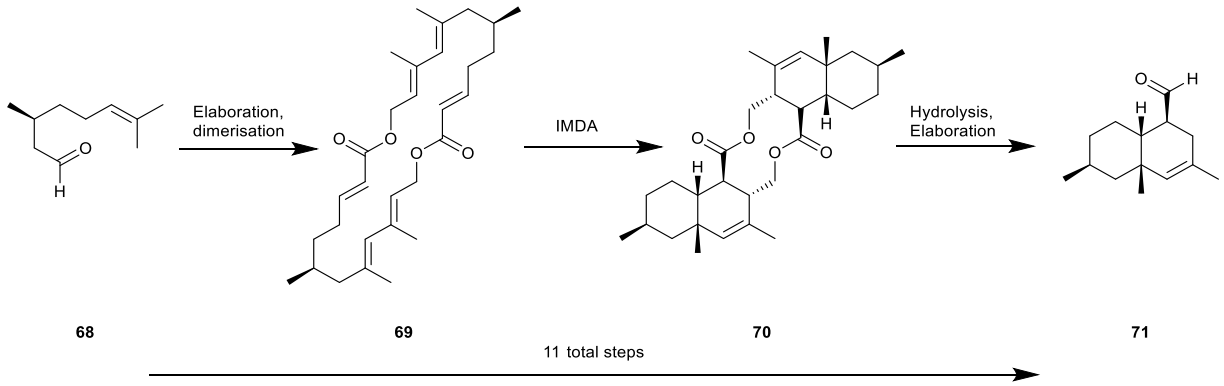
Scheme 1.7. Synthesis of the *trans*-decalin system originally used for the total synthesis of Solanapyrone D[157] and later used for the total synthesis of UCS1025A[156]

Another method that has been employed for the stereoselective synthesis of **62** used a multistep approach[158] that started with the aldehyde **63** shown in Figure **1.8**. The aldehyde compound was elongated using a phosphonium salt **65** *via* a Wittig reaction. The next step was a Horner-Wadsworth-Emmons reaction using phosphonate **66** then subsequent isomerisation of the double bond, achieved by heating in diphenyl disulfide, to afford the triene **64**. The desired product was afforded by reacting compound **64** with ethylaluminium dichloride at 0 °C that facilitated the construction of the *trans*-decalin system *via* IMDA reaction.[158]



Scheme 1.8. **a**) **65**, LHMDS, THF, 0 °C to rt, 85%; *trans*:*cis* 1:1. **b**) 1M HCl, THF. **c**) **66**, Et_3N, LiCl, MeCN, 59% over two steps. **d**) PhSSPh, THF, 65 °C, 84%. **e**) $EtAlCl_2$, CH_2Cl_2, 0 °C, 80%[158]

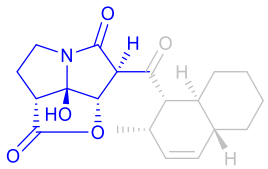
Formation of a *cis*-decalin used for the total synthesis of CJ-16,264 exploited a complex double IMDA, effectively leaving two *cis*-decalin systems fused *via* ester linkages as shown in Scheme **1.9**.[159] Simple hydrolysis was used to separate these fragments with further elaboration to give the enantiopure aldehyde. By clever choice of starting material, all the required stereochemistry can be pre-established and set, reducing the need for separation of racemic mixtures.[159]



Scheme 1.9. Synthesis employed to achieve an enantiopure transdecalin system for the total synthesis of CJ-16,264[160]

It should be noted the original publication used (*R*)-citronellal, but upon revision of the structure of CJ-16,264 (*S*)-citronellal was used.[159]

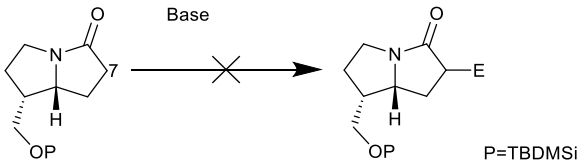
1.12. Methods for the Synthesis of Pyrrolizidine



18

Figure 1.23. The highlighted section of UCS1025A containing the pyrrolizidine core

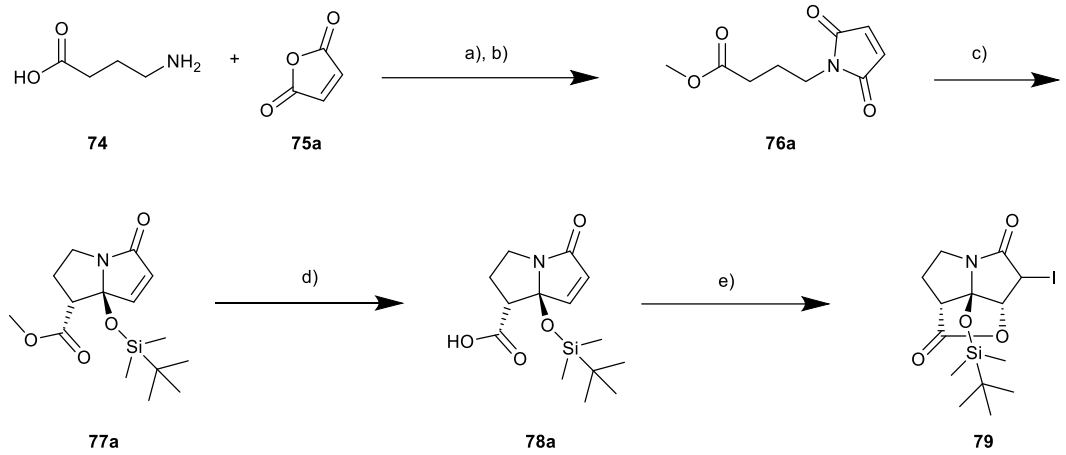
The first total synthesis of UCS1025A in 2005 by Lambert and Danishefsky attempted to employ an enantioselective route for the synthesis the of pyrrolizidine[156] with the intent to introduce functionality at C7 followed by aldol or Claisen condensation (Scheme **1.10**) to the decalin moiety.[156]



72 **73**

Scheme 1.10. Initial method proposed for the pyrrolizidine fragment[156]

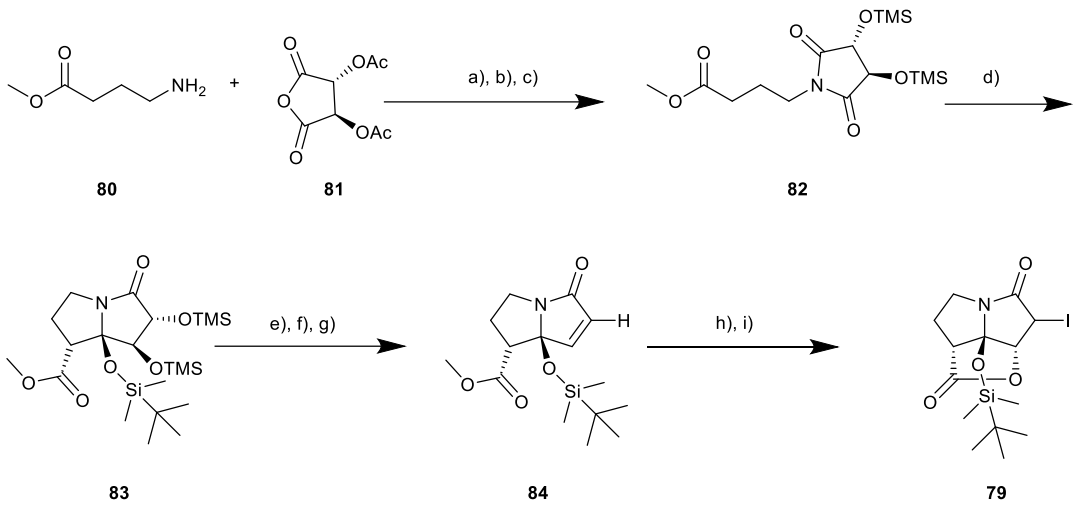
Early attempts to introduce functionality at the C7 position failed, and this was attributed to the sterically bulky silyl ether and natural 'cup' like shape of the bicyclic pyrrolizidine.[156] The first successful synthesis of a C7-functionalised lactam (Scheme **1.11**) started with γ-aminobutyric acid (GABA) and maleic anhydride to afford the corresponding maleimide which could easily be converted to ester **76a**. The next key step used *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSiOTf) as a Lewis Acid to promote a 'soft enol' cyclisation to form the pyrrolizidine **77a**. The use of TBDMSiOTf not only mediated this reaction but also trapped the free alcohol formed during cyclisation, while simultaneously controlling the stereochemistry with respect to the ester and silyl ether.[156]



Scheme 1.11. Synthetic pathway for the iodo-lactam tricycle **79**.[156] **a**) AcOH, rt for 8 hours, then toluene, Et_3N at reflux using Dean-Stark trap, 75%. **b**) $SOCl_2$, MeOH, 55%. **c**) TBDMSiOTf, Et_3N at rt for 2 hours, 80%. **d**) $LiOH{\cdot}H_2O$ 3:1 THF:H_2O, 99%. **e**) I_2, sat. $NaHCO_3$ Et_2O, THF, 84%[156]

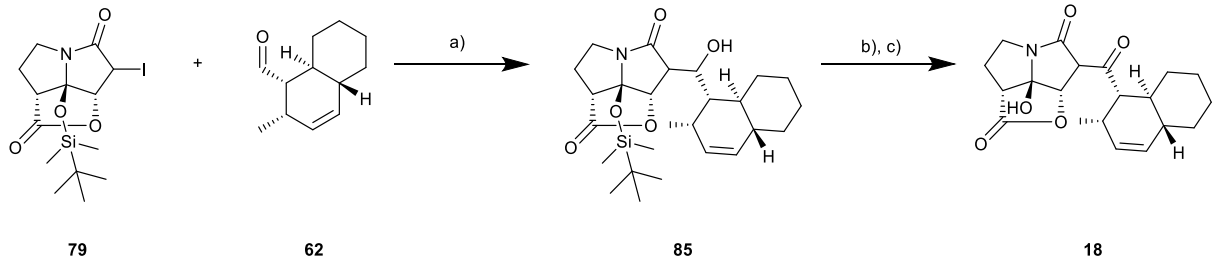
The latter steps of the synthetic route made use of basic hydrolysis followed by an iodolactonisation to give an iodo-containing tricyclic lactam **79** which could be readily coupled to the required decalin. This method gave a racemic mixture that was separable *via* chiral HPLC.

An alternative method also submitted by Lambert and Danishefsky contained additional steps but was designed to give a diastereoselective aldolisation yielding optically pure material.[156] The route started with a condensation of diacetyl tartaric anhydride **81** with 1-methyl-4-aminobutyrate **80** to afford a chiral maleimide ester **82** which upon subsequent cyclisation, following the previous method gave the desired pyrrolizidine core **79** (Scheme **1.12**).



Scheme 1.12. **a**) Et_3NH, THF then AcCl at reflux, 51%. **b**) AcCl, MeOH, 79%. **c**) TMSCl, Et_3N, CH_2Cl_2, 85%. **d**) TBDMSTf, $^{i}Pr_2NEt$, CH_2Cl_2, -78 °C to rt, 79%. **e**) AcOH, 1N HCl, THF. **f**) Tf_2O, pyridine, CH_2CH_2 -78 °C to rt. Then pyridine (76%, two steps). **g**) i) Bu_3SnH, $Pd(PPh_3)_4$, LiCl, THF, 52%. **h**) ii) $LiOH{\cdot}H_2O$ 3:1 THF:H_2O, 99%. **i**) I_2 sat. $NaHCO_3$ Et_2O, THF, 84%[156]

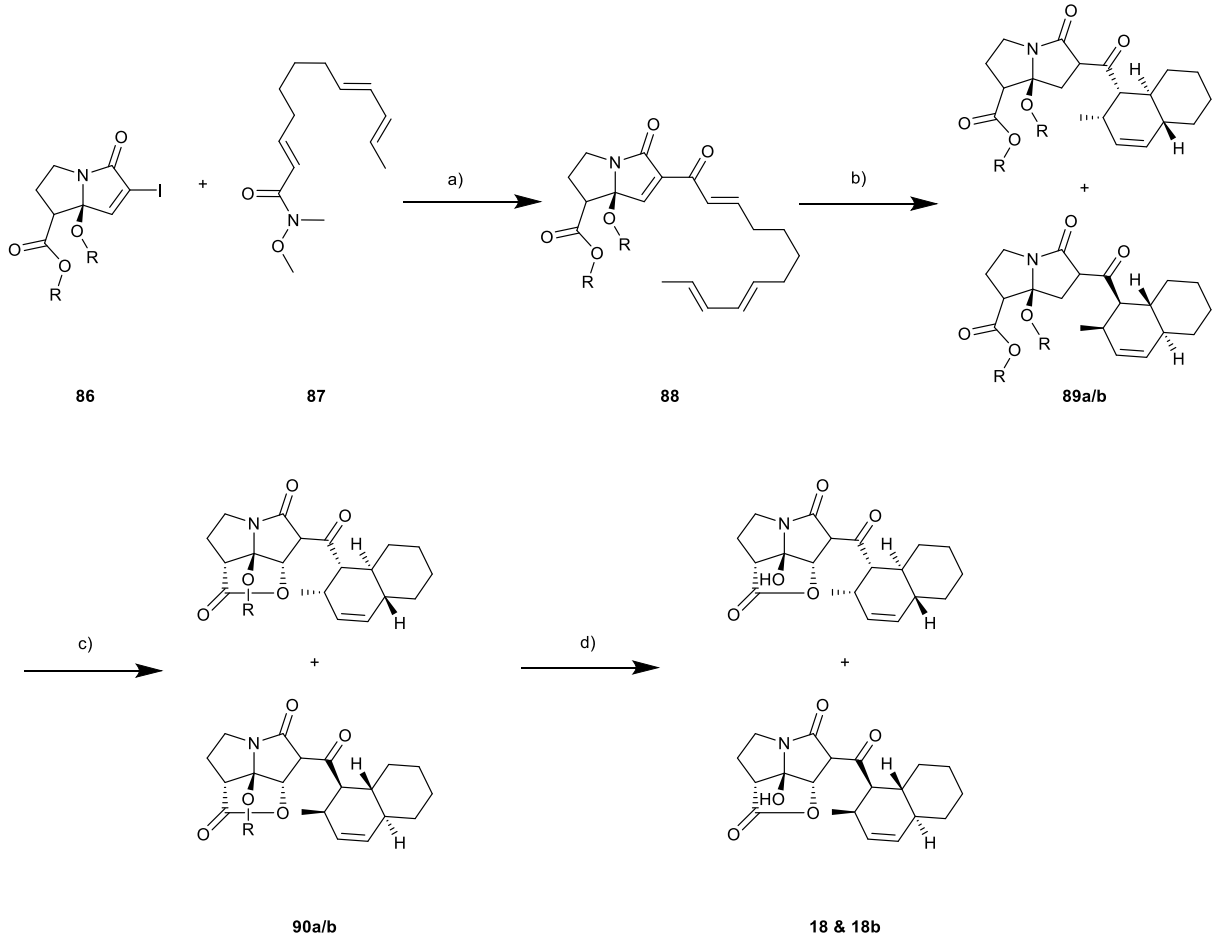
With the desired fragments available, the last steps coupled the iodo-lactam **79** to a decalin containing aldehyde **62** using a Reformatsky-type reaction[161] followed by TBAF deprotection and Dess-Martin periodinane oxidation to finally yield the natural product (Scheme **1.13**).



Scheme 1.13 Final steps for the synthesis of UCS1025A.[156] **a**) BEt_3, toluene, -78 °C , 99%. **b**) TBAF, THF, 85%. **c**) Dess-Martin periodinane, CH_2Cl_2, 84%

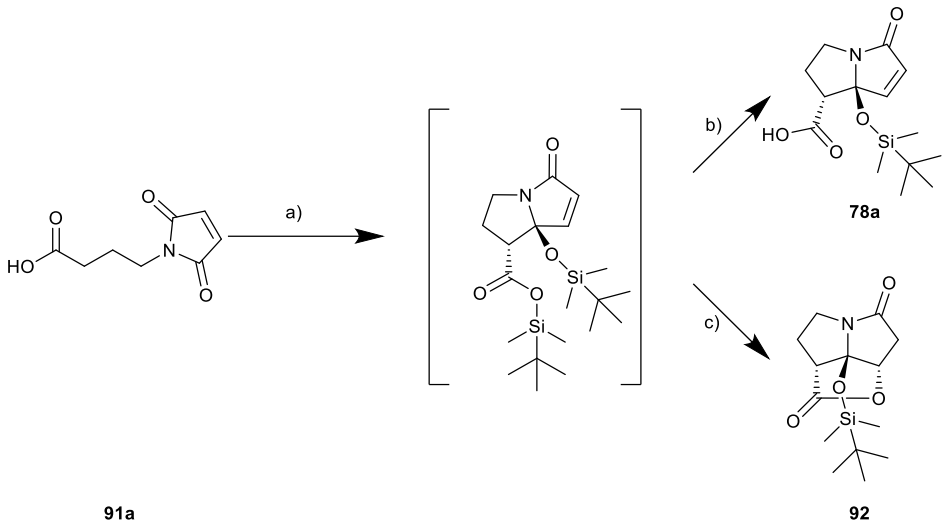
Hoye's and Dvornikov's approach to the total synthesis of UCS1025A followed a similar concept as previously described, *via* silyl-mediated soft enol addition cyclisation of **76** as a Mukaiyama-like addition, *via* the formation of a ketene acetal on the methyl ester carbonyl.[162] Base hydrolysis followed by iodo-lactonisation afforded silyl-containing iodolactam **79**. A silylative ring opening produced **86** was then treated with *i*-PrMgCl to facilitate magnesium-iodine exchange, followed

by acylation with a Weinreb amide **87**.[162] Formation of the *trans*-decalin ring **89a/b** *via* IMDA could be performed before or after a secondary iodo-lactonisation to form the pyrrolizidine core and subsequently UCS1025A (Scheme **1.14**).



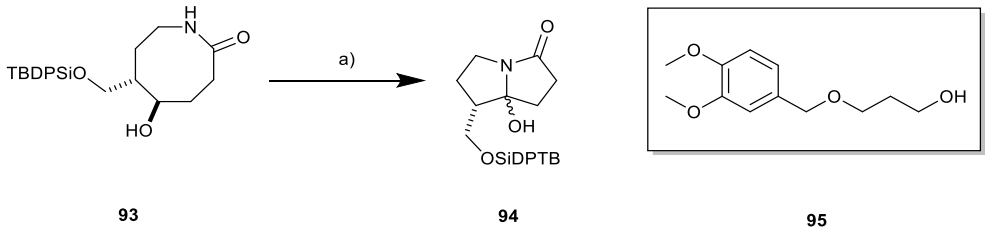
Scheme 1.14. **a**) ^{i}PrMgCl, THF/Et_2O, -50 °C, 10 mins, then **84**, -50 °C to rt, 35%. **b**) $CDCl_3$, 64 °C, 2 days, 69%. **c**) KF, MeOH, rt, 5 mins, 70-100%. **d**) HF•py, MeCN, rt, 2 days, 56%[162]

Christmann *et al.*[163] focused on a different approach by moving away from the idea of ester activation *via* TBDMSiOTf. The group hypothesised that the free carboxylic acid **91a** could undergo bis-silylketene acetal formation (Figure **1.15**). This method was based on the assumption that a bis-silylketene acetal would be a compromise between reactivity and lability to undergo soft-enolisation without the need for esterification. The group used the above-mentioned approach to achieve the desired silylated *trans*-pyrrolizidine core and even achieved completely regioselective and diastereoselective results when using unsymmetrical substituted maleimide.



Scheme 1.15 A shorter synthetic path affording either the pyrrolizidine **78a** or lactone **92**. **a**) Et_3N, TBDMSiOTf, $CHCl_3$. **b**) K_2CO_3, MeOH, 84%. **c**) SiO_2, 71%[163]

A completely unique strategy employed by Kan *et al.* focused on forming the pyrrolizidine core from an 8-membered ring **93** containing the amide as seen in Scheme **1.16**, by implementing a TPAP-mediated oxidation of the alcohol spontaneously invoking transannular cyclisation.[158]



Scheme 1.16. Reaction used to afford the bicyclic system. a) TPAP, NMO, CH_2Cl_2[158]

The group then focused on achieving the needed stereochemistry by a series of reactions, firstly by protection of the alcohol with a bulky substituent (Scheme **1.16**, compound **95**) affording the isomer of the natural product. Removal of the silyl was followed by protection with a benzyl group and lastly inversion of stereochemistry *via* MeOH addition to an acyliminium intermediate to afford the desired *trans* configuration.

1.13. Structure Activity Relationship (SAR) of CJ-16,264

In an attempt to increase activity for CJ-16,264, a small SAR study was used to further elaborate and explore if any major structural and chemical changes could be tolerated.[159] No changes were carried out to the pyrrolizidine moiety, with all the attention directed at changes to the *trans*-decalin system, or moving away from it entirely. A total of 26 compounds were synthesised with a few of these compounds outlined below, with addition of the biological data recovered for the chosen compounds.[159]

Table 1.5. Given data for the above shown compounds (Figure **1.24**), all values for MIC are in μg/mL[159]

Compound	*B. subtilis 168*	*E. faecalis S613*	*E. faecium 105*	*MRSA 371*
44 (CJ-16,264)	0.5	8	2	1
96	0.5	1	2	1
97	0.25	1	1	1
98	1	4	4	2
99	0.5	4	1	1
100	1	8	4	2

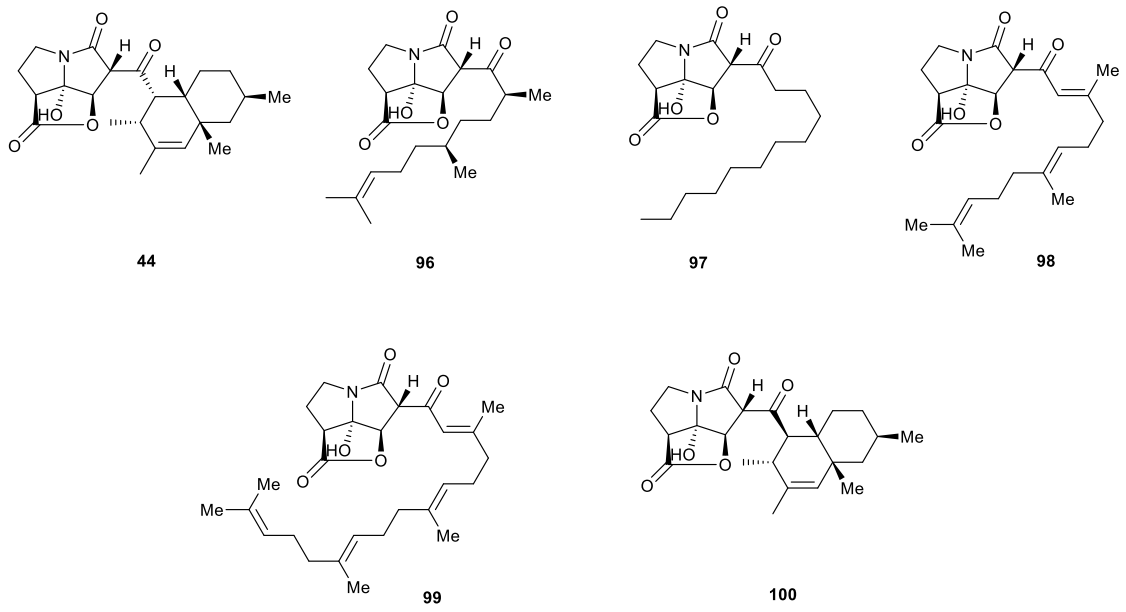


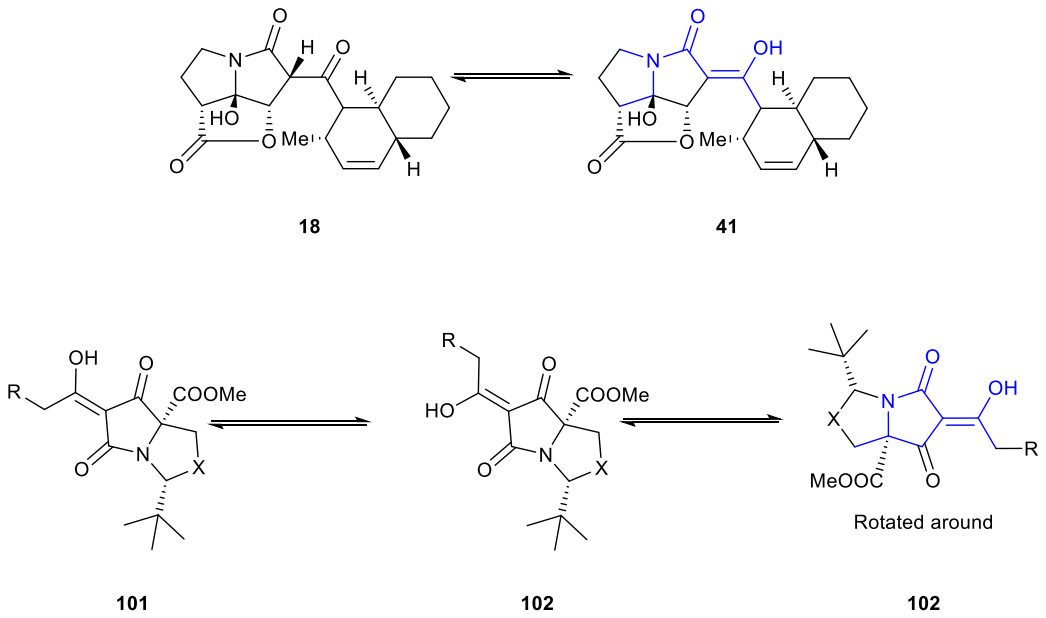
Figure 1.24. CJ-16,264 **44** with a collection of synthetic analogues which showed the highest levels of biological activity[159]

This small SAR scope shows that major chemical changes to the decalin system are not tolerated, with the greatest activity seen with compounds containing long carbon chains with roughly the same atom count as the decalin system seen in CJ-16,264 **44**. The use of more polar tethers, such as morpholine gave very poor results (all values >64 µg/mL) with hydrophobic carbon chains giving the best results.

1.14. Structurally Related Compounds to the Pyrrolizidines

A closely related structural motif to UCS1025A and other compounds previously mentioned, is the tetramic acid unit (Scheme **1.17**). This structural class of compounds occurs widely in antibiotic natural products[164] even though the core has little to no activity.[165] The key to their activity appears to be their ability to undergo enol-keto tautomerisation, providing an excellent point for chelation and/or ligand binding.[166,167] However, this is also detrimental to their *in vivo* activity, as their high affinity to iron also includes the heme group[45] found in red blood cells.

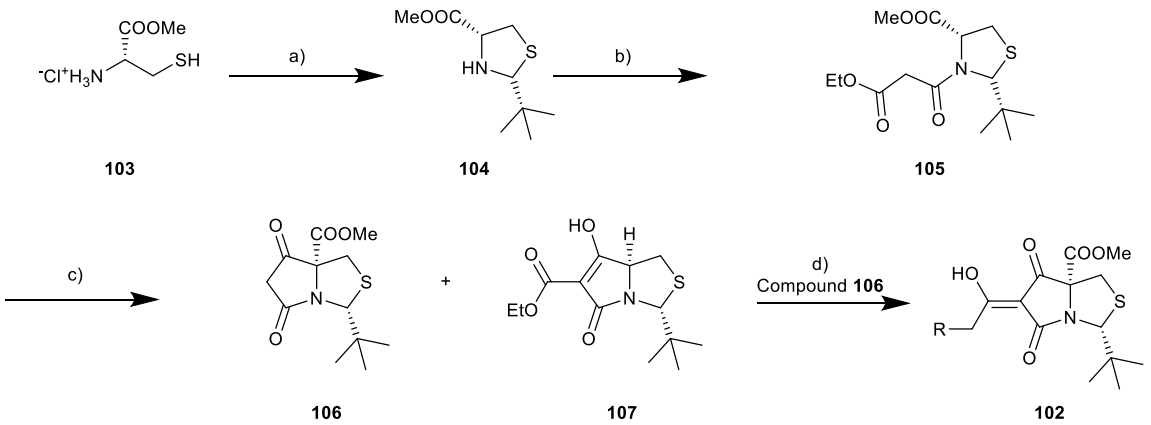
All the key areas in which UCS1025A and tetramic acids are similar can be seen in Scheme **1.17**.



Scheme 1.17. Tautomers for UCS1025A and a tetramic acid (X=O, N, S) with key similarities in blue

There has been an extensive collection of work on variations to these tetramic acid cores in the Moloney group focusing on new methodology for their synthesis while also varying different R groups to improve antibacterial activity by a series of SAR studies.[165,168–170]

The synthesis of tetramic acids has been developed and streamlined down to a direct three-step synthetic pathway from cheap and commercially available starting materials. The work conducted by the Moloney group has afforded a successful and convenient asymmetric synthesis for these chiral compounds, while also having numerous points for diversity introduction around the skeletal structure.



Scheme 1.18. Synthesis for the sulfur containing tetramic acid. **a**) NEt_3, pivaldehyde, petrol, reflux, 18 hours, 89%. **b**) Ethyl hydrogen malonate, DCC, DMAP, DCM, 5 hours, 83%. **c**) KO^tBu, ^tBuOH, reflux, 3 hours, 78%. **d**) RCH_2COOH, DCC, DMAP, rt, 16 hours, ~30%[171]

The desired compound **106** can be separated and further used to synthesise **102** which can subsequently be employed in a series of reactions, such as S_N2 displacements, when R=Cl, Br. One recurring problem is their affinity to bind to metals, particularly iron. This metal chelation was observed by ^1H NMR spectroscopy. Upon treatment of tetramic acids with various metals (Mg^{2+}, Zn^{2+}, Fe^{2+} and Fe^{3+}), their ^1H NMR spectra showed a significant broadening of peaks with the Fe samples (Fe^{3+}) being so broad as to give completely unrecognisable spectra.[171] These unique compounds with their high affinity for metal chelation is a trait that has not been seen with any members of the pyrrolizidines and has directed our interest to attempt to further expand and report the possibilities for pyrrolizidines.

1.15. A Summary of the Direction This Thesis Will Take

This thesis will start with discussing and reproduction of the work published by Lambert and Danishefsky with the aim of elaborating on different anhydrides that can be tolerated in this synthetic route. An early worry was the sensitivity of the silyl ether and which conditions would be tolerated when this group is featured.

Due to the published results from the SAR studies of CJ-16,264, it is apparent that limited chemical difference can be tolerated while keeping antibacterial activity, so we aimed to move away from targeting this section as our main area of investment.

An appealing option was to try to incorporate different anhydrides, such as the aromatic based phthalic anhydride, with numerous sites for substitutions available. All previous work conducted in the Moloney group was examined and integrated into the approach with antibacterial and anticancer activity always in-mind.

As no published work has considered adding additional functionality on the GABA chain, this made up a large section of the project, with attempts to introduce functionality and explore new and diverse chemical techniques to achieve this goal.

Lastly, this project will remain mindful of how we can tweak the synthetic routes to access a series of novel compounds with the hope of being either promising antibacterial or anticancer agents.

Chapter II: Imide Formation and Esterifications

This chapter will initially focus on highlighting a handful of different methods that have been employed for either a single, or two step synthesis of imides while further elaborating on these reported methods by describing unique and underdeveloped methodology that not only improves on current yields, but also removes need for any purifications. This alternative method will be shown to be effective at synthesising both maleimides and phthalimides providing access to various nitrogen substituents.

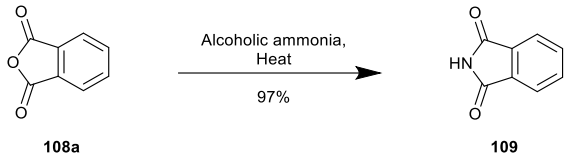
The latter sections of this chapter will then shift attention on to esterification of the carboxylic acids appended to the imide to test the scope and limitation of ester formation for these compounds, while also looking at benzylation as a credible method to selectively protect the free carboxylic glutamic acid.

2.1. Introduction to Imides and Imide Formation

The imide group is a simple organic functional group with the basic formula $(RCO)_2NR$ and can be considered to be a di-amide, that is structurally related to the acid anhydrides while being significantly more resistant towards hydrolysis. [172] When compared to amides, imides such as phthalimide **109,** display some unique properties with the N-H centre being weakly acidic, allowing easy *N*-alkylation when deprotonated with potassium hydroxide or other bases. Halogenation is also possible affording the *N*-halo derivative (such as *N*-bromosuccinimide)[172]. Imides are a very important functional group in drugs, and as a pharmacophore, they can be found in multiple families of drugs; such as antiepileptic,[173] anticancer,[174,175] anxiety[176,177] and antipsychotics.[178,179]

Some imides are commonly prepared on an industrial scale by heating dicarboxylic acids or their related anhydride, with ammonia or a primary amine, resulting in the desired imide *via* a

condensation reaction where the only expected by-product formed is water (Scheme **2.0**).[172] Comparable approaches use ammonium carbonate or urea *via* a similar mechanism.



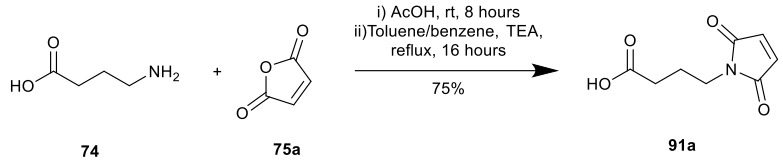
Scheme 2.0. Formation of phthalimide by heating alcoholic ammonia with phthalic anhydride[172]

In contrast to the above, a plethora of reported methodology for imide formation requires the addition of solvents with long periods of refluxing, often accompanied by additional purifications, such as slow and laborious flash column chromatography.

A key requirement for the work described in this thesis is imide formation that incorporates side chain amino acids, using methodology suitable for introducing a selection of different anhydrides in a reliable manner on a laboratory scale.

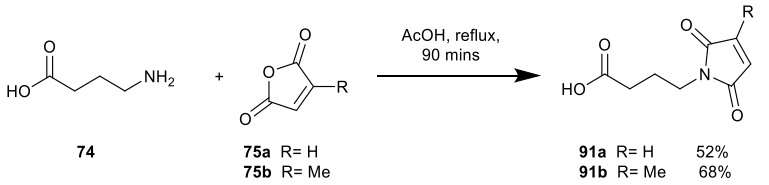
2.2. Maleimide Formation

4-Maleimidobutyric acid **91** has been shown[156,162] to be an ideal starting material for the pyrrolizidine fragment, which is one of the key structures for the synthesis of UCS1025A, and this was considered to be the optimal starting point for the work described in this thesis. For the synthesis of UCS1025A, Lambert and Danishefsky implemented a literature method that used 2.0 equivalents of GABA **74** with respect to maleic anhydride **75a** stirred in acetic acid at room temperature which proceeded to reflux in either toluene or benzene with triethylamine, giving a yield of 40% after recrystallisation from $CHCl_3$-*n*-hexane.[180] Lambert and Danishefsky[156] further modified these conditions by stirring the anhydride and GABA in acetic acid at room temperature for 8 hours prior to refluxing in toluene for 16 hours, while also using in a Dean-Stark set-up to remove the expected water by-product (Scheme **2.1**). Purification was achieved *via* flash column chromatography to afford the desired product **91a** with an isolated yield of 75%.



Scheme 2.1. Formation of the maleimide used in the total synthesis of UCS1025A[156]

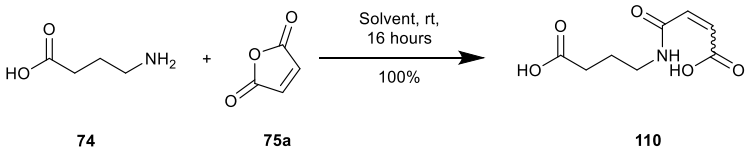
Both methods favoured a change in solvent from a more polar to a less polar solvent for the closing of the ring to afford the imide, but no explanation for this procedure was provided in the publication; subsequent work *(vide infra*) suggest that this was required for reasons of solubility. Using a single solvent for the entirety of the reaction had already been considered by Philip *et al*. who used 1.0 equivalent of amino acid to the anhydride, stirring in acetic acid for 8 hours followed by refluxing for an additional 16 hours, to afford **91a** with a yield of 63% after flash column chromatography. Christmann *et al.*[181] further refined these conditions, reporting a single step procedure for refluxing GABA with either maleic- or methylmaleic anhydride, giving isolated yields after flash column chromatography of 52 and 68% respectively (Scheme **2.2**). However, for this simple conversion, reported yields for the formation of **91a** varied from as high as 75%[156] to as low as 27%[182] with no obvious reason for the varying return on the yield.



Scheme 2.2. Conditions using AcOH in the synthesis of maleimide and methylmaleimide derivatives[181]

Rich *et al.* reported that stirring both maleic anhydride and GABA in acetic acid at room temperature initially forms the amide **110** (Scheme **2.3**), with similar amino acids (from carbon chains from 1-11 in length) reported to give yields varying from 90-100% conversion.[180] The conclusion was made that complications were occurring during the ring closure from the amide **110** to the imide **91a**, but no details were provided.

It therefore seemed to be prudent to re-examine literature procedures for forming maleimides, by reacting GABA and maleic anhydride in a given solvent to assess the effectiveness and efficiency of the above reported methods. In our hands, replication of these conditions gave a solid white precipitate forming over the course of 8 hours that was filtered under vacuum and subsequently washed with acetic acid followed by ice-cold water then dried in an oven at 45 °C to give the amide **110** in quantitative yields, in which the cyclisation had not occurred.



74 **75a** **110**

Scheme 2.3. Formation of the amide **110** using reported methodology[180]

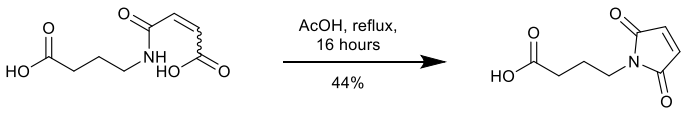
The presence of **110** was confirmed *via* LRMS and HRMS (ESI^+), with the ^1H NMR spectrum clearly indicated two distinct doublets at 6.45 and 6.25 ppm with a coupling constant of 12.6 Hz in MeOD at 200 MHz. This showed that **110** had formed rather than the potential ring-closed imide **91**. In all other reported methods where **110** was isolated, the *cis*- isomer was reported, although no reason or evidence for a *cis* configuration was stated. This may have been assumed since it is necessary in order for imide formation to occur, since the *trans*- alkene would fail to undergo ring closure. The ^1H NMR spectrum for **110** clearly indicated the presence of a single stereoisomer but did not conclusively confirm *cis*- or *trans*- isomer because the coupling constants between the alkene protons were not definitive.

An attempt to use other solvents, in order to avoid using large quantities of acetic acid, was explored, with the results displayed in Table **2.1**. These solvents were chosen as they are readily available, while also being easier to remove *via* roto-evaporation when compared to acetic acid, that proved to be difficult to completely remove even after washing with water, probably as a result of the polarity of the product.

Table 2.1. Comparison of solvents for the formation of **110** according to Scheme **2.3**

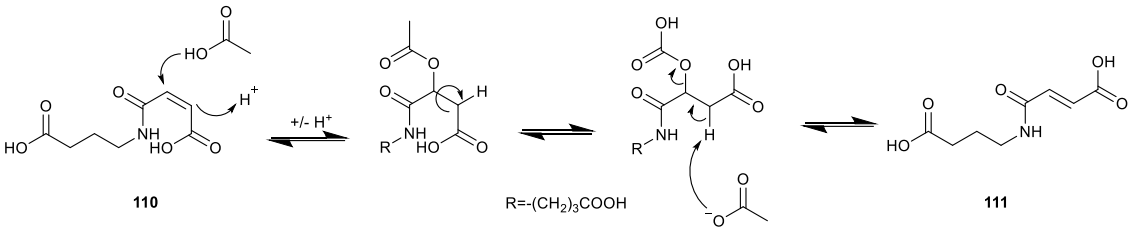
Solvent	Yield %
AcOH	100
$CHCl_3$	0
THF	0

Chloroform and THF gave no discernible product, probably as a result of the starting materials being completely insoluble in both solvents. On the other hand, GABA and maleic anhydride were readily soluble in acetic acid due to its higher polarity confirming acetic acid as the optimal solvent. An attempt was then made to convert the isolated amide **110** through to imide **91a** by extended reflux as shown in Scheme **2.4**. Thus, **110** was heated at reflux in acetic acid for an additional 16 hours with prep TLC showing some, but incomplete conversion. The crude mixture was then purified using flash column chromatography (5% AcOH in DCM) to afford the desired maleimide **91a** as a white coloured solid with a recovered yield of 44%.



Scheme 2.4. Formation of the desired cyclic imide from the amide

One reason that such a simple ring closure would give such low yields is that isomerisation may be occurring (*cis* to *trans*-) as a result of the high temperatures along with the presence of excess acetic acid. A Michael addition-elimination mechanism seemed to be the most obvious possibility from using the above conditions, as has been proposed in Scheme **2.5**. Christmann *et al* also concluded that addition-elimination was possible, reporting that Michael addition of AcOH was observed (but not isolated) after 90 mins of refluxing in acetic acid.[181] If this occurred, ring closure to the imide product would not be possible. Such isomerisation has not been discussed in any earlier publications referenced on maleimide formation but may be responsible for the low return of desired product.



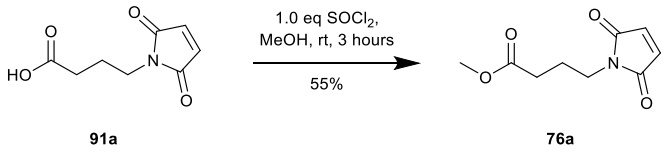
Scheme 2.5. AcOH assisted isomerization of **110** to give **111**

In our hands, no other compounds were isolated or identified when purified using flash column chromatography. A simple explanation is that imide **91a** is very polar with an R_f= 0.13 (5% AcOH in DCM), as is amide **111** containing an additional carboxylic acid as well as an amide resulting in the compound being far too polar to move on a normal phase column when using the stated solvent mixture.

Due to the unforeseen issues while trying to preform simple imide formation by using literature procedures already outlined, attention was diverted to exploring what should be a relatively simple esterification of 4-maleimidobutyric acid **91a**.

2.2.1. Esterification of *N*-Maleoyl-4-aminobutyric Acid

The synthetic route developed by Lambert and Danishefsky for their total synthesis of UCS1025A[156] esterified 4-maleimidobutyric acid **91a** opting to use $SOCl_2$ in methanol to afford the desired methyl ester **76a** with a reported yield of 55%. Once again, this simple conversion was reported to give sub-optimal yields with no explanation or identifiable side reactions/products discussed. For this reason, optimisation of the synthesis of ester **76a** was explored at this point.

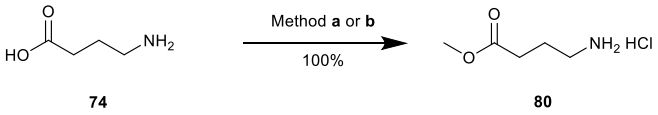


Scheme 2.6. Esterification of **91a** to afford the required methyl ester **76a**[156]

The reaction was repeated with additional equivalents of $SOCl_2$ being used and the reaction left to stir at room temperature for 16 hours; the solvent was then removed and the residue azeotroped using dichloromethane. ^{1}H NMR spectroscopic analysis strongly suggested that, along with the desired product, Michael addition to the alkene had also occurred, since at least two different methoxy peaks were identifiable. The crude material was purified via flash column chromatography and the desired product isolated with a yield of 37%. It was apparent that in order to achieve high yields throughout the synthetic pathway to **76a**, any chemistry that could interfere with the alkene region needed to be avoided, or minimised. Therefore, it was decided that the above method would not be further examined, and another method developed.

2.3. Esterification of GABA

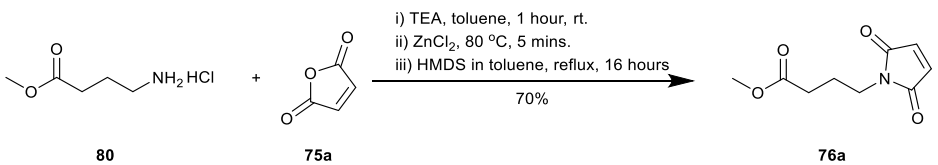
The alternative synthetic route, by reversing the two steps outlined above, began with esterification of GABA to afford γ-aminobutanoate.HCl, followed by the addition to maleic anhydride.[183] Amino ester **80** could be readily and reliably synthesised using two different methods.



74 **80**

Scheme 2.7. Method **a**) 3.0 eq $SOCl_2$, MeOH, rt, 16 hours.[184] Method **b**) 2.0 eq acetyl chloride, MeOH, rt, 16 hours[185]

Both methods of esterification gave complete and clean conversion to the methyl ester **80** with yields of 100%. **80** could then be used for the direct synthesis of imide **76a** as shown in Scheme **2.8**, by direct reaction with maleic anhydride.



80 **75a** **76a**

Scheme 2.8. Formation of methyl ester containing maleimide[183]

When considering the conditions used in Scheme **2.8,** TEA is essential to "free base" the amine **80** to allow nucleophilic attack, opening the anhydride and yielding the expected amide. Upon heating to 80 °C, $ZnCl_2$ was added as one portion to the mixture and left for 5 minutes. It is suggested that the addition of $ZnCl_2$ leads to chelation with the amide and carboxylic acid, holding the *cis*-configuration presented in Figure **2.1**, and facilitating ring closure to the imide function.[183] Due to the basic conditions used to free-base the amine, it is hypothesised that HMDS acts as a silylating agent to encourage amide formation by forming a silyl alcohol as a favourable leaving group.

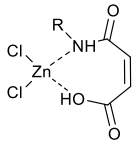


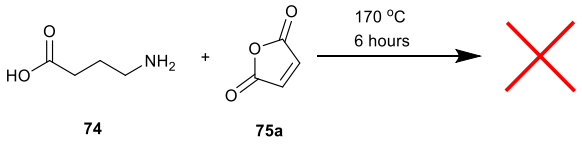
Figure 2.1. $ZnCl_2$ complexation with the free NH- amide and the carboxylic acid

Formation of the maleimide **76** using the conditions shown in Scheme **2.8** was an improvement over the aforementioned methods, with yields over two steps significantly higher and with the added bonus of one fewer purification step needed to afford the desired product. Another advantage was the removal of acetic acid from the synthetic pathway. Compared to earlier results, imide formation of 70% was a big improvement over previously attempted methods, but still required long reaction times. It was decided that an attempt to further improve maleimide formation by using less traditional synthetic methods should be explored.

2.4. Solventless Imide Formation of Maleimides

A literature search for the most reliable, high yielding and rapid synthesis led us to consider the formation of phthalimides, in which GABA and phthalic anhydride were heated neat at 170 °C for 6 hours, followed by a simple acid wash (0.5 N HCl), with the product being extracted with dichloromethane.[186] This method would provide a few advantages over all previously discussed

approaches to imide formation. Firstly, the reported quantitative conversion would avoid the need for laborious flash column chromatography purifications and use of harsh solvent mixture already outlined (Section **2.1**). Secondly, reaction times would be drastically reduced and thirdly, yields are significantly improved over all other reported methods for any maleimide synthesised. With these three main reasons in mind, these conditions were subsequently applied to maleic anhydride (Scheme **2.9**).

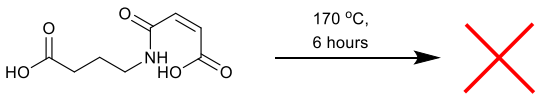


74 **75a**

Scheme 2.9. Attempted synthesis of **91a** using solventless conditions[186]

During the reaction maleic anhydride started to melt around 65 °C which also led to the dissolution of GABA. When the reaction reached close to 100 °C, the molten mixture started to darken, and this continued until 170 °C where the molten reaction mixture appeared black in colour. Cooling of the reaction mixture gave a black coloured solid that was then dissolved in dichloromethane and washed using 0.5 N HCl with the organic layer concentrated by reduced pressure. However, ^{1}H NMR and mass spectrometric analysis gave no evidence for the successful formation of the desired product **91a**.

The same conditions were applied to the amide **110** (Scheme **2.10**) hoping that the intermediate would survive the high temperatures needed for solventless imide formation. However, this reaction gave the same conclusion as the previous attempt (Scheme **2.9**).

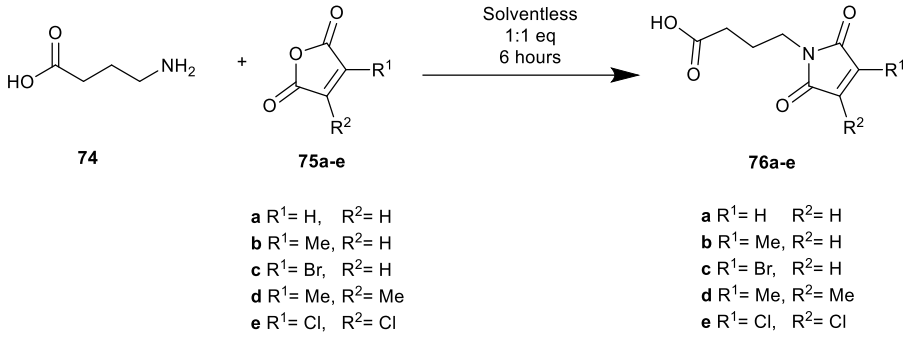


110

Scheme 2.10. Failed attempt at imide synthesis for the ring closure of **110**

From the earlier work conducted, it was becoming evident that maleic anhydride is a less than ideal starting material suffering from low solubility, along with high reaction temperatures which

led to degradation; despite the failed attempts, a solventless strategy seemed to offer a way around this difficulty, and to try to establish whether synthesis of maleimides using these conditions is possible, a collection of mono- and di-substituted maleic anhydrides was examined (Scheme **2.11**).



Scheme 2.11. Reaction of GABA with substituted maleic anhydrides (see Table **2.2**)

All of the substituted anhydrides **75b-e** were commercially available, with two examples being unsymmetrical, and the other two anhydrides being symmetrical. The original hypothesis was that the low melting point of maleic anhydride resulted in thermal degradation at high temperatures, evident from the blackening of the reaction mixture. For this reason, anhydrides with substantially lower melting points (**75b,c**) as well as those with higher melting points (**75d,e**) compared to maleic anhydride, were examined to see if this was correct (see Table **2.2** for their corresponding melting points). In the case of **75b,c** which are liquids, no additional solvent was used. After the poor results observed for maleic anhydride, it was a surprising result to see all other substituted maleimides tested gave successful conversion to the desired product with high yields that are compared in Table **2.2**.

Table 2.2. Formation of substituted maleimides from maleic anhydrides

Compound number	Anhydride melting point °C	R^1	R^2	Reaction temp °C	Yield %
91e	51-56	H	H	150	0
91b	<0	Me	H	150	83
91c	4-8	Br	H	150	86
91d	93-96	Me	Me	150	100
91e	120-122	Cl	Cl	150	83

Methyl- and bromomaleic anhydrides gave very good results, forming their corresponding maleimides **91b,c** despite their low melting points. During the formation of **91b,** the mixture darkened to a dark brown/black colour that was also seen for **91a**, but in this case the reaction was successful. Solventless formation of **91b** gave significantly better yields without any purification, unlike the other reported method for this compound.[181] For **91b-e**, excellent yields were obtained even though in some cases (**91b,c,e**) noticeable sublimation of the anhydride was observed (confirmed *via* ^{1}H NMR spectroscopy of the sublimate). During the reaction, periodic checks where conducted, with the sublimate being carefully removed from the neck of the flask and re-added to the molten reaction mixture in an attempt to further enhance the yields.

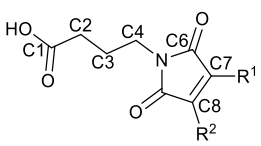
Confirmation of the complete conversion to the desired imide, rather than the amide, was established using ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry and IR analysis. With compound **91b,c**, only a single peak for the C8 alkene proton was seen, as well as the C7 methyl group, consistent with formation of the imide and no amide. Additionally, both LRMS and HRMS saw no mass ion for the amide structure. The structure of **91d** was also confirmed using ^{1}H NMR spectroscopy, with both alkene methyl groups appeared as singlets consistent with the symmetry in the compound, while also integrating at 6 protons, confirming that no amide was present. Due to the lack of noticeable and distinct protons, ^{1}H NMR spectroscopy was not as helpful in determining the conversion and synthesis of **91e**. Instead, ^{13}C NMR spectroscopy was

heavily relied upon for confidence in complete imide formation. This was achieved by identifying the peak for C=**C**-Cl found at 133.48 ppm and observing only a single peak present for this carbon. Other characteristic peaks were the single carbonyl peak at 178.22 ppm, with the addition of a peak at 163.14 ppm that represents the symmetrical imide carbonyls (N-**C**=O).

When using ^{13}C NMR spectroscopy for the analysis of **91b,c** it was interesting to see three peaks between 178 and 165 ppm. The C1 carboxylic acid carbonyl is easily identifiable due to the relative intensity and similar values situated around 178 ppm (see Table **2.3**). The other two peaks found in this region represent the imide carbonyls, with the differences in their reported values a consequence of the lack of symmetry across the imide. The difference is subtle when R=Me, but much more significant when R= Br.

Below is a complete collection of all the characteristic peaks for the maleimides mentioned in this section (Table **2.3**).

Table 1.3. Comparison for all the key characteristic proton and carbon peaks used in the characterisation of **91a-e**



91a-e

a R^1= Me, R^2= H
b R^1= Me, R^2= H
c R^1= Br, R^2= H
d R^1= Me, R^2= Me
e R^1= Cl, R^2= Cl

	^{1}H NMR characteristic peaks (ppm)					^{13}C NMR characteristic peaks (ppm)						
	H2	**H3**	**H4**	**R^1**	**R^2**	**C1**	**C2**	**C3**	**C4**	**C6/9**	**C7**	**C8**
91a	2.38	1.93	3.60	6.78	6.78	178.43	31.24	23.66	37.09	170.90	134.28	134.28
91b	2.34	1.88	3.54	2.05	6.31	178.19	31.25	23.72	37.11	171.04 171.97	145.81	127.43
91c	2.39	1.94	3.64	n/a	6.89	178.39	31.18	23.17	38.08	168.72 165.47	131.56	132.00
91d	2.35	1.98	3.55	1.90	1.90	178.28	31.33	23.91	37.12	172.33	137.35	137.35
91e	2.41	1.96	3.68	n/a	n/a	178.22	31.14	23.52	38.65	163.14	133.48	133.48

With all data acquired for **91b-e** (Table **2.3**), while also comparing with the data for **91a** it was abundantly clear that maleimide formation was successful using these solventless conditions.

It was stated earlier in this chapter that an imide could be considered to be a "diamide" however, with the removal of symmetry across the alkene, we envisioned that this may cause a change in electronics within the ring system, causing the amide carbonyls to act more like an amide and ketone. It was also hypothesised that unsymmetrical stretching from the amide carbonyls would also give the same effect. To assess this theory, **91a-e** were analysed using IR spectroscopy. Below is a table (Table **2.4**) of key characteristic IR peaks that were used to further reinforce this statement.

Table 2.4. Comparison of characteristic IR (ν_{max} (KBr) cm^{-1}) peaks used in the characterisation of **91a-e**

Compound	C6/9 symmetric	C6/9 asymmetric
91a	1713	1688
91b	1769	1696
91c	1777	1702
91d	1764	1693
91e	1793	1726

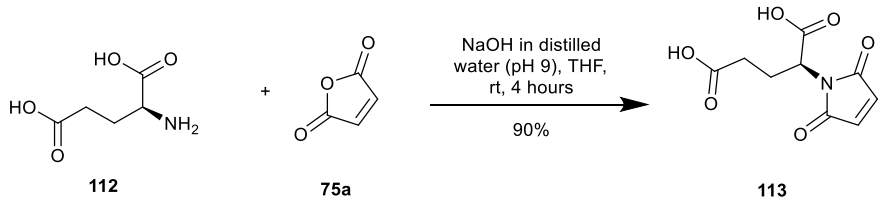
The strongest peak was for the imide carbonyl (N-**C=O**) found from 1688-1702 cm^{-1} that can be defined as strong and distinct that broadens near the base of the peak. In all cases, the major peak would also have two minor peaks appearing close to halfway down the main peak. This is due to symmetric stretching of the carbonyls and a shift in electronics of the system, appearing as a ketone and amide simultaneously. It was refreshing to see that IR values matched or were similar to those reported elsewhere.[156,181]

In this section, the reaction of GABA and substituted maleic anhydrides has been developed to synthesise maleimides in a more reliable, greener and efficient method with higher yields than any previously reported methods.[180–182,187] The above conditions seem to be optimal for acquiring

substituted maleimides. One advantage of forming imides *via* the above route (Scheme **2.11**) is that no additional purification in the form of flash column chromatography is needed, unlike all other discussed methodology. With great success seen when combining GABA and substituted maleic anhydrides *via* solventless conditions, other amino acids were examined.

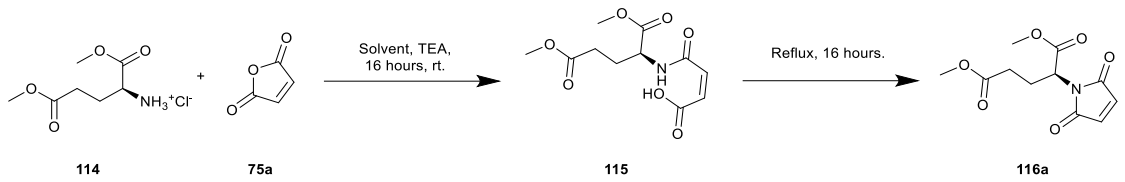
2.4.1. Formation of Imides from Substituted GABA derivatives

It was decided that glutamic acid would be an ideal replacement for GABA as a simple and cheap amino acid that would introduce chirality and further chemical functionality to these systems. A reported method in the literature described dissolving L-glutamic acid in water with the pH adjusted to 9, with the anhydride dissolved in THF, being added to the basic water and stirred as a biphasic mixture with the precipitate forming filtered then washed using pet-ether (Scheme **2.12**).[188] The next step for **113** would be to perform a double esterification, however, due to complications when attempting to esterify **91a**, which has already been discussed earlier in this chapter, this method was not explored.



Scheme 2.12. Use of L-glutamic acid with maleic anhydride to synthesise chiral maleimide **113**[188]

With L-glutamic acid dimethyl ester hydrochloride being commercially available, the obvious way forward was to form the amide at ambient temperatures, then proceed to the ring closed imide at reflux as shown in Scheme **2.13**.



Scheme 2.13. Attempted formation of the amide **115** followed by the ring closure to the desired imide **116a**

L-Glutamic acid dimethyl ester hydrochloride and maleic anhydride were dissolved in a few different solvents (Table **2.5**) and stirred for 16 hours at room temperature with an aliquot taken from each mixture and analysed by ^{1}H NMR spectroscopy to determine the rough percentage conversion to the intermediate amide **115**. If successful conversion was observed, the reaction was then refluxed for an additional 16 hours in an attempt to afford the desired imide **116**, with the results of this small investigation reported in Table **2.5**.

Table 2.5. Comparison of different solvents used for the synthesis of **115** and **116a**

Solvent	% conversion to **115** observed *via* ^{1}H NMR	% conversion to **116a** observed *via* ^{1}H NMR
AcOH	0	n/a
Toluene	~95	63
Chloroform	~60	n/a
THF	~95	0

Analysis of the "crude" conversion to the expected intermediate **115** was achieved by identifying the pair of doublets resulting from the unsymmetrical alkene that is newly formed. The peaks were integrated and set to one, then compared directly against maleic anhydride, if still present.

When acetic acid was used as the solvent for the synthesis of **115**, it was surprising that the ^{1}H NMR spectrum of the crude product did not show any distinguishable peaks for the alkene region so acetic acid was abandoned at this stage. Toluene gave the cleanest and best conversion to the desired intermediate with amide **115** being clearly observable and identifiable in the crude proton spectra. Chloroform gave particularly poor results, with the conversion to amide **115** observed.

Moreover, an additional pair of doublets were seen at 6.52 and 5.92 ppm each with the same coupling constant of 12.2 Hz, possible evidence of isomerisation (Figure **2.2**). The newly identified peaks were integrated against the assumed desired product giving a ratio of 1.0: 0.5, for this reason, this mixture was not refluxed for an additional 16 hours.

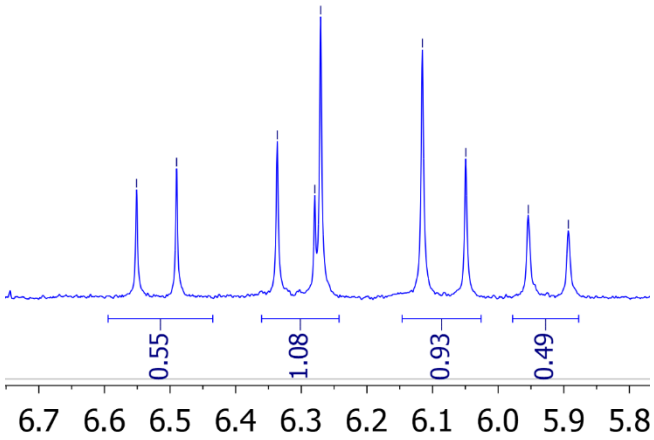
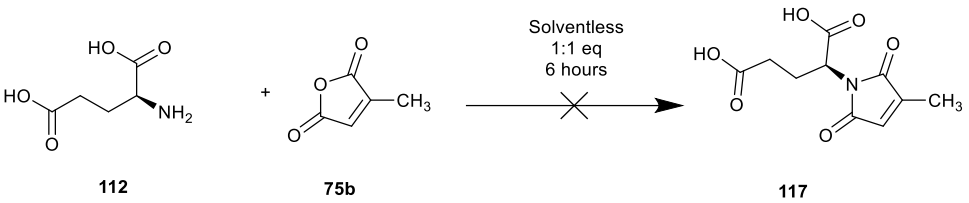


Figure 2.2. ^{1}H NMR spectrum for the *cis* and *trans* alkene protons with chloroform being used as the solvent

While THF did give good conversion to **115**, no product was observed after reflux, possibly due to the lower refluxing temperature not being high enough to facilitate imide formation. With using toluene as the solvent of choice, $ZnCl_2$ and HMDS were added using the methodology previously described[183] (Scheme **2.8**, Section **2.3.**).

2.4.2. Formation of Imides from L-Glutamic Acids

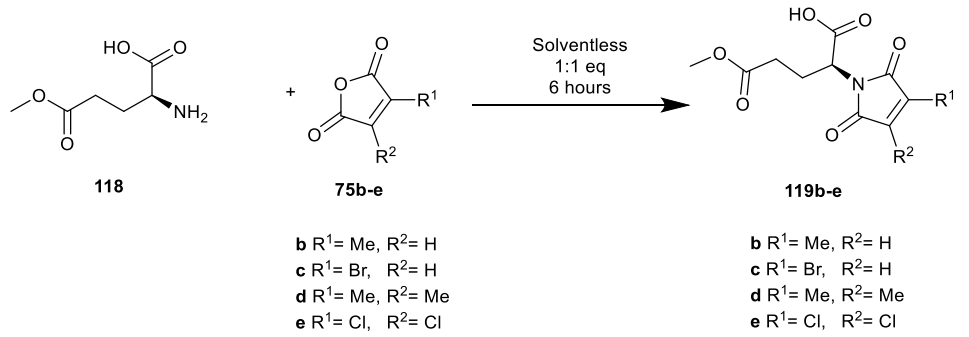
With previous results showing that solventless conditions were the optimal method for maleimide formation by reacting substituted maleic anhydrides with amino acids, application of this method using L-glutamic acid was examined (Scheme **2.14**).



Scheme 2.14. Attempted solventless formation of **117**

Methylmaleic anhydride was added to L-glutamic acid and heated to 150 °C, but the combined mixture failed to melt. The reaction temperature was increased in increments of 10 °C at which the mixture started to melt at 205 °C. The mixture darkened in colour very quickly while also appearing thicker in consistency than previously seen when using GABA. After 6 hours of heating at 205 °C the reaction was allowed to cool to room temperature before being attempted to be dissolved in dichloromethane which had little effect. The additional carboxylic acid group suggested that a more polar solvent was needed, so the dichloromethane was removed but attempted dissolution in ethyl acetate with additional drops of methanol was also unsuccessful. At this point it was decided to move away from L-glutamic acid.

L-Glutamic acid 5-methyl ester is cheap to acquire commercially and available without the hydrochloride salt reducing any possible loss of nucleophilicity for the amine. Hence the decision was made to try L-glutamic acid 5 methyl ester as the addition of an ester group reduces the melting point by 23 °C while also assisting with the problem of solubility (Scheme **2.15**).



Scheme 2.15. Solventless reaction of L-glutamic acid 5-methyl ester with substituted maleic anhydrides

Table 2.6. Formation of substituted maleimides from maleic anhydrides using L-glutamic acid 5 methyl ester

Compound	R^1	R^2	Temperature °C	Yield %	$[\alpha]_D^{25}$ (*c* 1.0 in MeOH)
119b	Me	H	150	46	-17.5
119c	Br	H	150	60	**
119d	Me	Me	150	44*	-7.1
119e	Cl	Cl	150	93	-13.5

*****Purification was needed as a noticeable quantity of anhydride remained. ******Compound not pure enough for analysis.

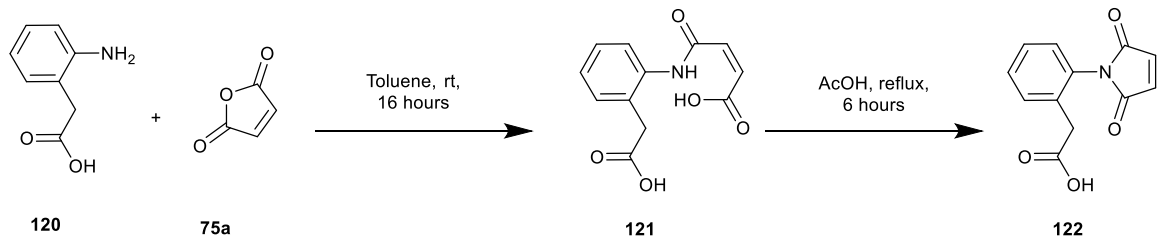
The yields for **119b-e** are given in Table **2.6**. The first major observation for the synthesis of **119b-e** was that all mixtures darkened over the course of the reaction, while also showing a decrease in solubility, often needing an increased volume of dichloromethane and the addition of ethyl acetate to assist in dissolving the desired product before acidic workup.

From reviewing the yields displayed in Table **2.6**, it is clear to see a drop in overall yields for all, apart from **119e**, when comparing against the yields when using GABA (Table **2.2**). **119d** needed to be purified as the ^{1}H NMR spectrum showed significant quantity of unreacted anhydride remaining.

The presence of the desired imides was once again confirmed mostly by using ^{1}H NMR and ^{13}C NMR spectroscopy using the same techniques previously described. The introduction of the acid at the C4 carbon made a larger influence on the proton shifts, with the protons for C2 and C3 now appearing as a multiplet of peaks from as high as 2.62 – 2.32 ppm. The remaining proton on C4 had shifted further downfield, often being seen between 4.91-4.71 ppm, confirmed when consulting the ^{13}C and HSQC NMR spectra. Polarimetry confirmed that full racemisation had not occurred during the course of the reaction, but *e.e.* was not established for these systems.

2.4.3. Synthesis of Maleimides Using Anilines

2-Aminophenylacetic acid **120** is very similar to GABA with the addition of an aromatic ring along the carbon backbone that introduces rigidity. After the early failures with GABA and maleic anhydride, it was expected that using the aniline **120** would give poor yields as the electron withdrawing effect from the aromatic ring would reduce the nucleophilicity of the amine. Contrary to this, formation of the desired amide **121** was achieved in a good yield (Scheme **2.16**). Maleic anhydride and 2-aminophenylacetic acid were taken up in toluene and stirred at room temperature for 16 hours resulting in the formation of a precipitate. The solvent was removed *via* reduced pressure, with ^{1}H NMR spectroscopic analysis confirming the conversion to the expected amide **121** immediately identifiable by the pair of distinct doublets for the alkene region found at 6.68 and 6.35 ppm. The amide **121** was then redissolved in acetic acid and refluxed for 6 hours with the reaction mixture darkening over time. Upon completion the solvent was removed *via* reduced pressure. ^{1}H NMR analysis confirmed complete cyclisation to the desired imide **122** with a yield of 53%, needing no additional purification.



Scheme 2.16. Synthesis of phenyl maleimide

2.5. Introduction to Phthalimides

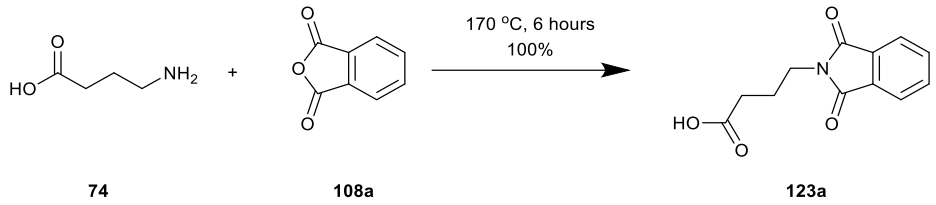
Forming phthalimides from phthalic anhydride and GABA without the needed for solvent by heating both materials together has been previously mentioned and well documented in a selection of different publications.[186,189–191] There is a plethora of reported substituted phthalimides being reacted with GABA to synthesise the corresponding imide, surprisingly none of these publications

took advantage of solventless formation, favouring a protic solvent, such as acetic acid in most cases.[192,193]

Due to the void in the literature, it seemed necessary to further explore the ability to synthesise a variety of phthalimides by using a collection of substituted phthalic anhydrides and GABA, relying upon the solventless conditions already outlined in this thesis.

To gain an understanding of the key differences in reactivity between maleic anhydrides, and phthalic anhydrides, it was decided that it would be prudent to repeat the reported procedure for phthalimide **123a** (Scheme **2.17**).[186]

Both solids were heated to 170 °C for 6 hours, during the reaction the molten mixture slowly turned to a straw yellow colour. Upon completion of the reaction, the cooled solid mass was dissolved up in dichloromethane with the apparent solubility comparable to the substituted maleimides. The organic layer was then washed using 0.5 N HCl and concentrated by reduced pressure to afford the desired product **123a** that was confirmed *via* ^{1}H NMR spectroscopy.

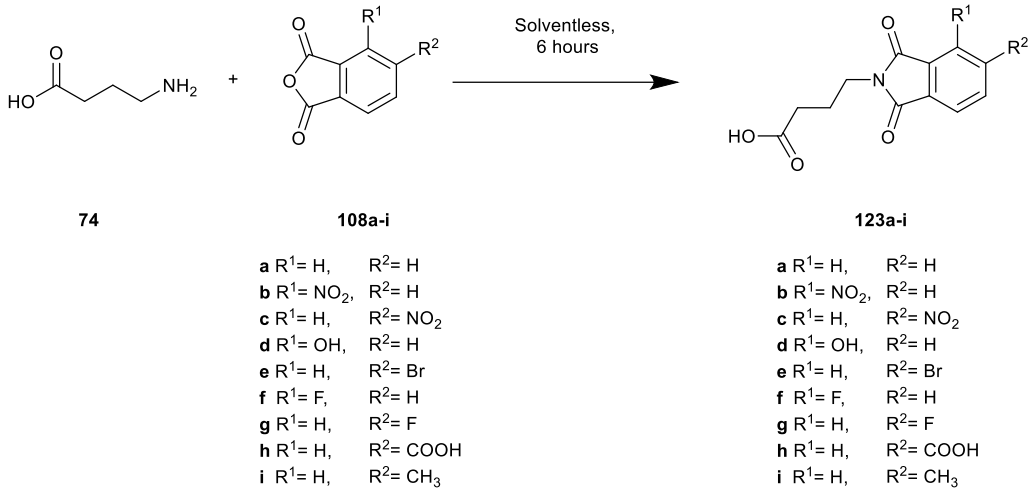


Scheme 2.17. Synthesis of the desired phthalimide *via* solventless method[186]

As expected, the resonance of the aliphatic protons were very similar to those seen in the maleic systems, however each peak was slightly more downfield in the phthalic system. The aromatic peaks appeared as a symmetrical pair of double doublets at 7.85 and 7.72 ppm. The aromatic protons clearly indicated the existence of symmetry in the system, supporting the complete cyclisation to the imide **123a**. This conclusion was also reinforced when consulting the ^{13}C NMR spectrum as well as both LRMS and HRMS.

2.5.1. Synthesis of Substituted Phthalimides

Attention moved to testing the scope and limitations of using substituted phthalic anhydrides (Scheme **2.18**), with all of the anhydrides tested being cheap and commercially available, with the results displayed in Table **2.7** and compared against phthalic anhydride.



Scheme 2.18. Synthesis of substituted phthalimides *via* solventless method.

Table 2.7. Comparison of yields of different R groups on substituted phthalic anhydrides with GABA

Compound	R^1	R^2	Temperature °C	Yield %
123a	H	H	170	100
123b	NO_2	H	175	100
123c	H	NO_2	175	100
123d	OH	H	195	95
123e	H	Br	170	84
123f	F	H	170	100
123g	H	F	170	100
123h	H	COOH	205	55
123i	H	CH_3	170	100

All substituted anhydrides reacted comparably to phthalic anhydride with near excellent yields throughout, with one exception, **123h**. The solubility of these compounds was comparable to **123a**, except for the nitro containing compounds that took longer to fully dissolve but did so in the same volume of solvent. **123h** was also problematic taking more time and gentle heating in dichloromethane in order to fully dissolve.

All reactions were carried out between 170-175 °C with the exception of **123d,h**, with higher temperatures being required to melt the anhydrides. The high melting temperature of trimellitic anhydride **123h** was the major reason for the diminishing return on yield, with some of the molten reaction mixture solidifying on the cooler parts of the flask, needing to be melted to be incorporated back into the reaction, *via* a heat gun. It was assumed that the formation of the intermediate amide had a melting point significantly higher than all other components of the reaction mixture and hence the solidifying. Due to the large percent of unreacted starting material or amide present, **123h** was purified *via* flash column chromatography using 5% methanol in ethyl acetate with a drop of acetic acid to decrease smearing on the column.

The method of analysis for **123b-i** was identical to that used for **123a**, with ^{1}H NMR spectroscopy being the main tool for confirmation of the complete ring closure, with ^{13}C NMR and HSQC to assign all aromatic protons where possible.

In addition, for the fluorinated compounds **123f,g**, ^{19}F NMR spectroscopy was used to identify the ArC-**F** bond at -112.76 ppm. When interpreting the ^{13}C NMR for both **123f,g**, it was observed that all aromatic carbons appeared as doublets as well as one of the imide carbonyl peaks being split. One additional peak was seen that was initially unexpected, later attributed to the complex nature[194] of F-C bonds in ^{13}C NMR. This phenomenon is due to the strong and long-range F-C couplings throughout these two compounds. Trying to accurately assign the Ar**C**-F was difficult, as the 4 peaks in question were at 167.34, 165.17, 158.95 and 156.31 ppm for **123f** (see Figure **2.3** for example). Using the data already acquired for other phthalimides, the peak at 167.34 ppm was assumed to be an imide carbonyl that appeared as a doublet, and due to the similar nature, the peak

at 165.17 ppm would be the remaining imide carbonyl. The last two peaks at 158.95 and 156.31 ppm would be the Ar**C**-F with a coupling constant of 264.80 Hz, a number similar to other examples in the literature.[194–196] Fluorine decoupled ^{13}C NMR was used and compared to the original ^{13}C NMR, that mostly removed or reduced the coupling seen, as well as the combining of the peaks at 158.95 and 156.31 ppm to a single peak centred at 157.94 ppm (See Figure **2.3**).

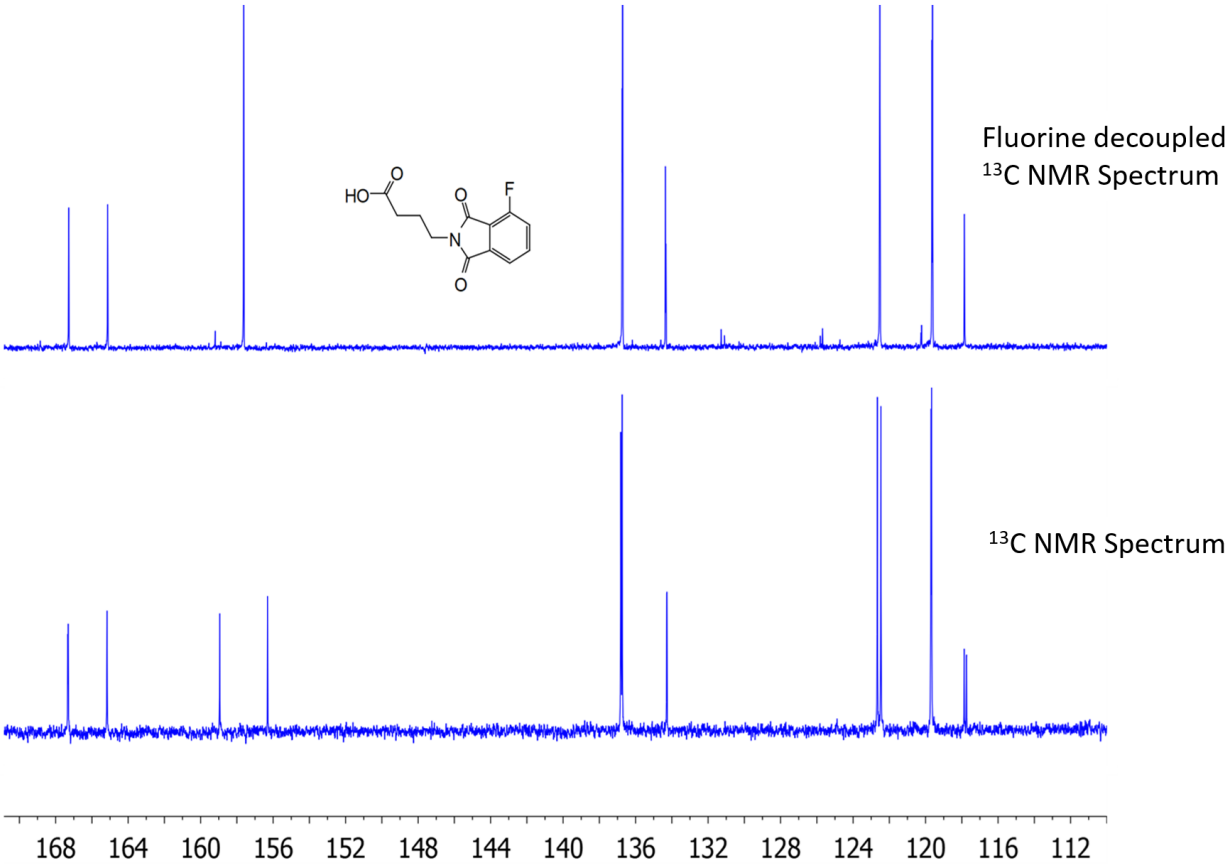
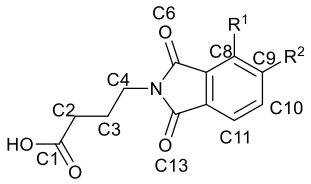


Figure 2.3. Stacked spectra for the fluorine decoupled ^{13}C NMR (top) and ^{13}C NMR spectra for **123f**

These data, along with all other characteristic proton and carbon peaks have been tabulated and can be seen in Table **2.8**.

Table 2.8. Comparison of the characteristic proton and carbon peaks for substituted and non-substituted phthalimides



123a-i

a R^1= H, R^2= H
b R^1= NO_2, R^2= H
c R^1= H, R^2= NO_2
d R^1= OH, R^2= H
e R^1= H, R^2= Br
f R^1= F, R^2= H
g R^1= H, R^2= F
h R^1= H, R^2= COOH
i R^1= H, R^2= CH_3

^{1}H NMR characteristic peaks (ppm) in $CDCl_3$

	H2	H3	H4	R^1	R^2	H10	H11
123a	2.42	2.02	3.77	7.85	7.72	7.85	7.72
123b	2.38	1.98	3.76	n/a	8.21	8.08	7.99
123c[1]	2.38	1.99	3.79	8.65	n/a	8.61	8.08
123d	2.35	1.94	3.68	n/a	7.14	7.31	7.59
123e[2]	2.26	1.80	3.58	8.02	n/a	7.75	7.93
123f	2.44	2.02	3.77	n/a	7.39	7.63	7.80
123g	2.40	1.99	3.74	7.50	n/a	7.37	7.84
123h[1]	2.37	1.98	3.76	8.49	n/a	8.35	7.94
123i	2.40	2.05	3.73	7.70	n/a	7.48	7.62

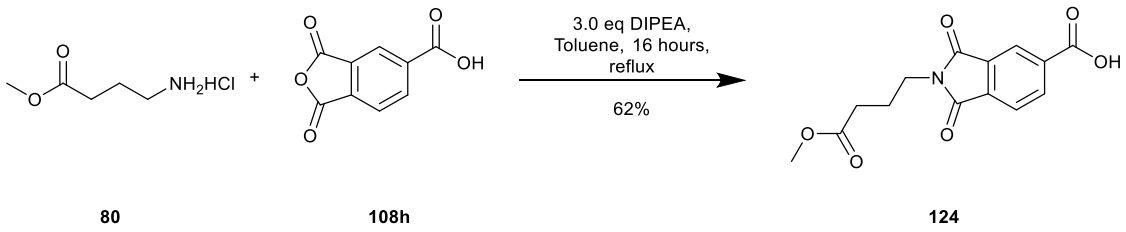
^{13}C NMR characteristic peaks (ppm) in $CDCl_3$

	C1	C6	C13	C8	C9	C10	C11
123a	177.42	168.46	168.46	123.31	134.08	134.08	123.31
123b	176.41	167.63	164.81	146.30	129.39	127.66	136.84
123c	176.47	167.75	167.98	119.10	153.22	130.38	125.39
123d	176.52	169.48	169.76	156.38	115.64	137.02	124.11
123e	174.06	167.42	166.85	125.95	127.95	137.07	124.94
123f	178.61	167.32 *J*=3.1 Hz	165.17	157.48 *J*= 264.8 Hz	122.56 *J*= 19.8 Hz	136.78 *J*= 7.8 Hz	119.68 *J*= 3.5 Hz
123g	178.71	167.08 *J*= 3.1 Hz	167.42	111.30 *J*= 24.7 Hz	166.48 *J*= 258.0 Hz	121.42 *J*= 23.5 Hz	125.80 *J*= 9.0 Hz
123h	174.98	167.59	167.59	124.82	137.77	136.56	124.18
123i	178.37	168.69	168.58	123.98	145.41	134.64	123.34

[1] NMR ran in MeOH, [2] NMR ran in DMSO

2.5.2. Synthesis of 5-(1-Methoxy-1-oxobutyl)-6,13-dioxoisoindoline-9-carboxylic Acid

124 is an interesting phthalimide as it has two different places where functionality may be introduced: C1 carboxylic acid as well as the C9 benzoic acid. Selective protection of the C1 acid was simply achieved by refluxing γ-aminobutanoate hydrochloride **80** and trimellitic anhydride **108h** in toluene and DIPEA for 16 hours (Scheme **2.19**). This approach was chosen due to previous problems associated with the high melting temperatures of **108h**. The crude material was purified *via* flash column chromatography using 1% acetic acid and 10% methanol in dichloromethane to afford the desired product with a yield of 62%. The reaction should have gone to completion with a large percentage of material being lost when attempting to purify *via* flash column chromatography with smearing being seen on the TLC plate, a consequence of the high polarity resulting from the benzoic acid.



80 **108h** **124**

Scheme 2.19. Synthesis of **124** by refluxing in toluene and DIPEA for 16 hours

124 was confirmed to be the desired product *via* ^{1}H NMR spectroscopy that clearly indicated complete imide formation due to the 3 single aromatic peaks at 8.38, 8.31 and 7.90 ppm, similar to the spectrum for **123h**. In addition to the ^{1}H NMR spectrum, ^{13}C NMR, LRMS and HRMS all confirmed that none of the intermediate amide was present. **124** can be easily converted to the acyl chloride (see experimental for details) for further functionalisation, although this was not explored. From the above results, it is evident that substituted phthalimides can be synthesised *via* solventless conditions, achieving quantitative conversions in nearly all examples. Phthalimide

formation using the chemistry developed in this thesis has many advantages over other published methods, given greater yields with no purification.

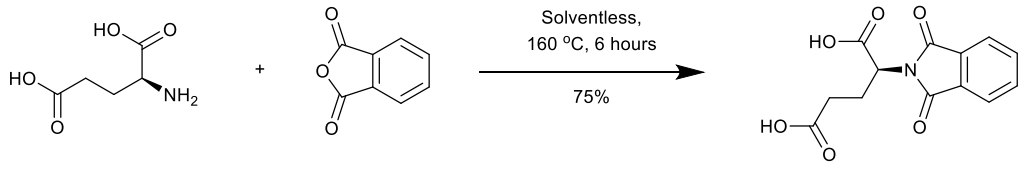
At this point, it seemed fitting to review the reactivity of glutamic acids with phthalic anhydride to see if the same trends in reactivity would be observed, as previously seen with maleic anhydrides (Section **2.4.2.**).

2.5.3. Synthesis of Phthalimides Using Glutamic Acids

To ensure that reactivity and the behaviour of phthalic and maleic anhydrides were constant, all chemistry attempted with the maleic anhydrides was repeated with phthalic anhydride, with additional methods of formation investigated.

As to be expected, the addition of glutamic acid to phthalic anhydride is not a novel reaction, with a handful of different methods incorporating solvents at reflux, for example: triethylamine at 85 °C for 5 hours giving 92%,[197] dimethyl sulfoxide and acetic acid at 120 °C for 16 hours giving 92%[198] and in acetic acid at 145 °C for 1 hour giving 85%.[199]

Once again solventless formation had been neglected and not considered. In light of this it was decided that this would a good place to start the investigation of the reactivity of glutamic acids.



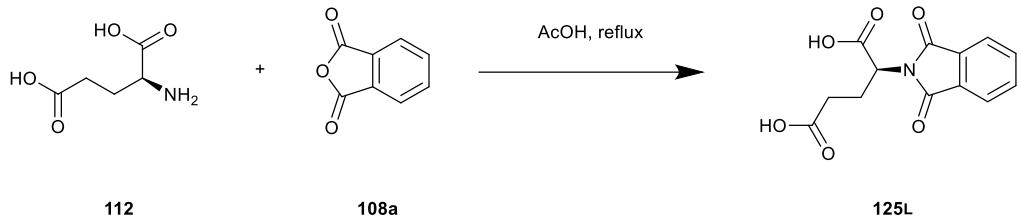
112 **108a** **125L**

Scheme 2.20. Addition of L-glutamic acid to phthalic anhydride to afford the desired phthalimide *via* solventless conditions

As anticipated, solubility was an issue, with ethyl acetate being used as a replacement for dichloromethane, with methanol being added dropwise to encourage solubility. The organic layer was subsequently washed using 0.5 N HCl and concentrated by reduced pressure with the ^{1}H NMR spectrum showing successful formation of **125L** with a yield of 75%.

The yield for **125L** was significantly lower than that reported in the literature with the only caveats for using the above conditions being the removal of solvents and the absence of any purification. In order to be able to make in informed reason for using solvents, the above reaction was repeated in the presence of acetic acid. Note that the same result was seen for D-glutamic acid **125D**, not shown above for simplicity.

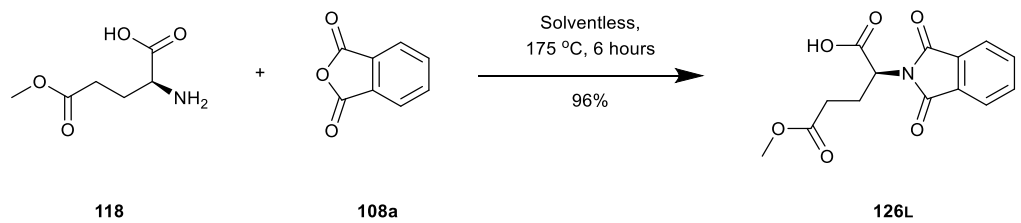
L-Glutamic acid and phthalic anhydride were heated at reflux reflux in acetic acid for 4 hours with an aliquot taken and analysed *via* ^{1}H NMR spectroscopy that showed the presence of the amide intermediate, so the reaction was refluxed for a further 4 hours (Scheme **2.21**). Upon completion, the ^{1}H NMR spectrum showing starting material and residual acetic acid remaining. Therefore, an accurate yield was hard to determine for these conditions.



Scheme 2.21. Addition of L-glutamic acid to phthalic anhydride to afford the desired phthalimide via reflux in AcOH

As with the maleic systems, the next step was to try to introduce additional solubility by using L-glutamic acid 5-methyl ester (Scheme **2.22**).

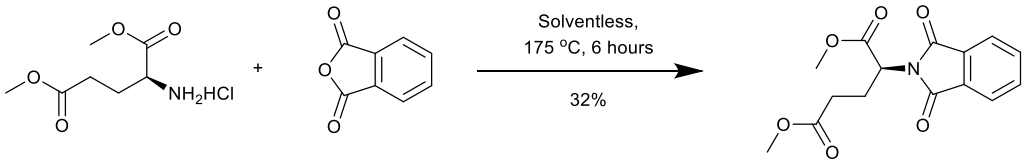
Both solids were heated together neat with the mixture darkening over time to afford a brown coloured oil **126L**, with the ^{1}H NMR spectrum showing trace amounts of unreacted anhydride with a total recovered yield of 96%.



Scheme 2.22. Addition of L-glutamic acid 5-methyl ester to phthalic anhydride to afford the desired phthalimide **126L** using solventless conditions

It should be noted that this reaction has been performed on multigram scale retaining the high yields. L-Glutamic dimethyl ester hydrochloride was previously discarded as a possible nucleophile due to the presence of the hydrochloride salt, not only increase melting temperatures but reducing the -NH_2 nucleophilicity required to initiate imide formation. Therefore, it was deemed necessary to ensure that this assumption was correct.

L-Glutamic dimethyl ester hydrochloride and phthalic anhydride were heated at 175 °C for 6 hours (Scheme **2.23**) with the mixture darkening over the course of the reaction. After the solid mass had cooled to room temperature, the crude was dissolved in dichloromethane, with a noticeable improvement in solubility over both **125L** and **126L**. ^{1}H NMR spectroscopy confirmed substantial unreacted starting materials and possibly intermediate amide with the crude material needing to be purified *via* flash column chromatography, using 30% ethyl acetate in pet-ether 40:60 to afford the desired product with a disheartening yield of 32%, confirming the original assumption was indeed correct.



114 **108a** **127L**

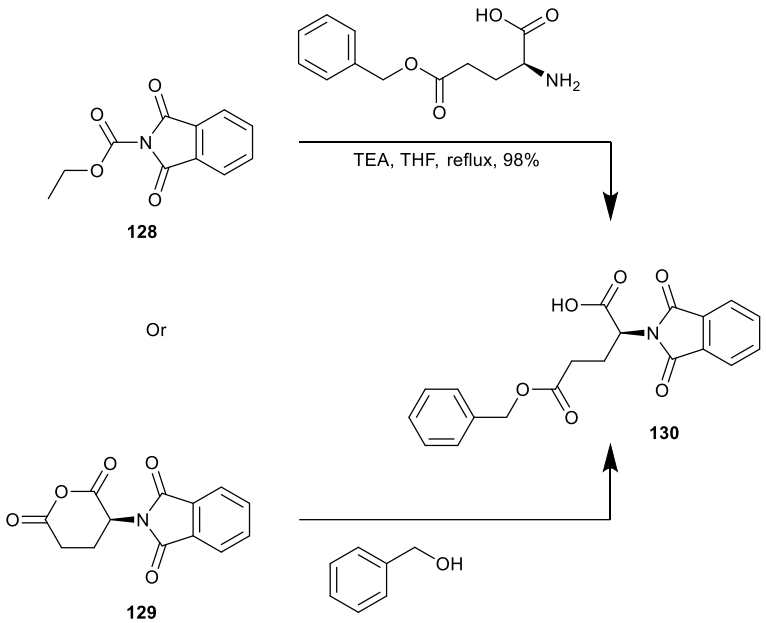
Scheme 2.23. Addition of L-glutamic dimethyl ester to phthalic anhydride to afford the desired phthalimide using solventless conditions

To see if this issue could be addressed, 1 equivalent portion of K_2CO_3 was added to both phthalic anhydride and L-glutamic dimethyl ester in an attempt to "free base" the amine, with the mixture heated at 175 °C for 6 hours. The addition of K_2CO_3 caused the starting materials to clump up, never melting during the reaction. After an acidic workup, ^{1}H NMR spectroscopy did show conversion to **127L**, with an improved yield over the similar reaction without base.

So far, the primary method for protecting any carboxylic acid is *via* esterification, which may be problematic later when trying to selectively remove a singular methyl ester. For this reason, the implementation of a benzyl ester at the C1 position was explored.

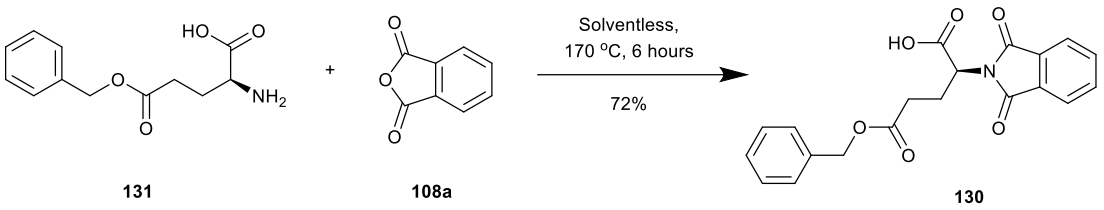
2.5.4. Synthesis of Phthalimides using L-Glutamic Acid 5-Benzyl Ester

The synthesis of **130** is not novel with a handful of published methods,[200,201] often featuring nucleophilic attack from L-glutamic acid 5-benzyl ester on a phthalimide precursor to afford the desired product (Scheme **2.24**).



Scheme 2.24. Different methods to afford **130** from a phthalimide containing precursor[200,201]

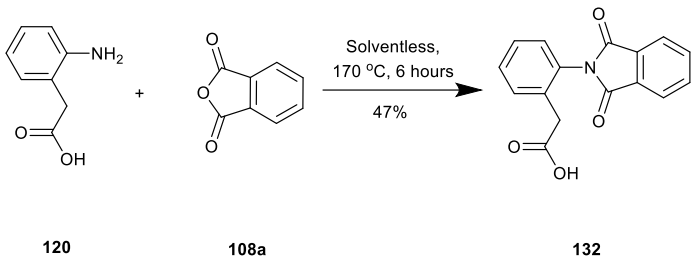
As both of these methods would require additional steps to acquire either **128** or **129**, it was decided to make use of solventless conditions established in this project. Therefore, L-glutamic acid 5-benzyl ester was added to phthalic anhydride and heated at 170 °C for 6 hours. After acidic work-up, analysis using ^{1}H NMR spectroscopy showed conversion to the desired product with a yield of 72%, with the ^{1}H NMR spectrum showing small quantity of unreacted starting materials that would be removed at later stages.



Scheme 2.25. Solventless formation of **130**

2.5.5. Synthesis of Phthalimides Using Anilines

After the unexpected success of using 2-aminophenylacetic acid with maleic anhydride, there was confidence that imide formation with phthalic anhydride and 2-aminophenylacetic acid *via* solventless conditions would attain the desired imide. Both starting materials were reacted together using standard conditions with the molten mixture appearing dark red/brown in colour. After 6 hours, the reaction was allowed to cool and subsequently dissolved in dichloromethane and washed with 0.5 N HCl with the organic layer being concentrated by reduced pressure. LRMS and HRMS did confirm the presence of **132**, however the ^{1}H NMR and ^{13}C NMR spectra showed both starting material and intermediate amide present. During the reaction, a significant quantity of sublimate had formed, greatly reducing the yield for this conversion.



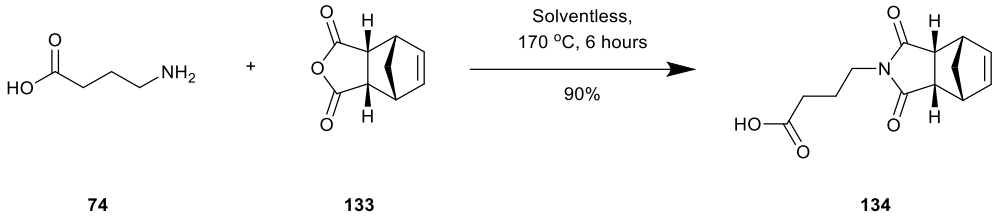
Scheme 2.26. Synthesis of the phenylphthalimide **132**

Unsurprisingly the prep TLC plate for the crude material **132** was very messy with streaking making identification for the desired product difficult.

It was decided that the corresponding methyl ester of **132** would be significantly easier to purify, as discussed below in Section **2.7.3**.

2.5.6. Synthesis of 2.2.1-Bicycloimides

So far, all solventless reactions were performed using anhydrides with sp^2-hybridised carbons adjacent to the anhydride carbonyls, with the question arising if electronic effects within these systems contributed to imide formation. Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride **133** appeared to be a very interesting anhydride, as it was hoped that the bridged ring system would remove the flatness previously seen with all phthalimides and maleimides, while simultaneously increasing solubility. It was unexpected to see that the reported synthesis of **134**[202] used solventless conditions, affording a yield of 75%, with the reported procedure requiring purification *via* flash column chromatography. Knowing that **134** could be acquired *via* solventless formation, it was hard to pass on the chance to improve on the yields of previously published methods, using the standard technique and conditions already outlined in this thesis (Scheme **2.27**).



74 **133** **134**

Scheme 2.27. Synthesis of phthalimide containing azatricyclo **134**

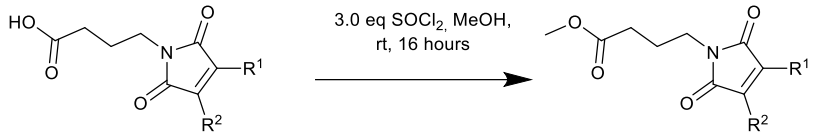
In our hands, the synthesis of **134** gave a yield of 90%, with the ^{1}H NMR spectrum suggesting no additional purification was needed. Therefore an overall improvement on the only reported synthesis[202] for **134**.

2.6. Esterification of Maleimides

Problems with the esterification of carboxylic acids appended to a maleimide have already been discussed and addressed in Section **2.2.1** as such, with a collection of substituted maleimides **91b-e** and **119b-e**, it was a high priority to ensure similar trends were not replicated in these systems.

Each substituted maleimide **91b-e** was dissolved in methanol and cooled to 0 °C using an ice bath, with thionyl chloride added dropwise over 5 minutes. After all of the thionyl chloride was added, the ice bath was removed, and the reactions were left to stir for 16 hours at room temperature. The reaction mixtures were concentrated by reduced pressure and azeotroped using dichloromethane (three times) to help remove residual thionyl chloride. When needed, compounds were purified using flash column chromatography to afford the desired products with yields compared in **Table 2.9**.

Table 2.9. Comparison of yields for the esterification of **91b-e**



91a-e

a R^1= H, R^2= H
b R^1= Me, R^2= H
c R^1= Br, R^2= H
d R^1= Me, R^2= Me
e R^1= Cl, R^2= Cl

76a-e

a R^1= Me R^2= H
b R^1= Me R^2= H
c R^1= Br, R^2= H
d R^1= Me R^2= Me
e R^1= Cl R^2= Cl

Compound Name	Yield %
76a	37
76b	58*
76c	61*
76d	84
76e	99

*Compound needed additional purification.

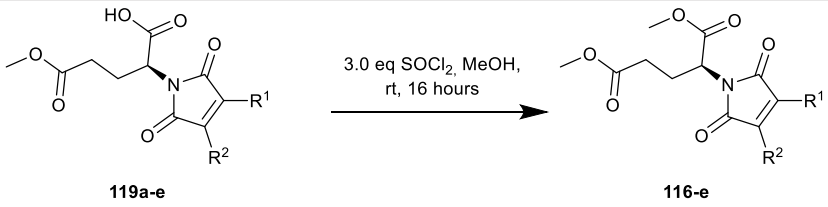
All compounds reacted well under the above conditions, with **76d & e** giving excellent yields. **76b & c** were purified *via* flash column chromatography as the starting materials had a small quantity of unreacted anhydride from the initial imide formation. It is important to note that no additional side reactions or Michael addition was detected by LRMS and ^{1}H NMR spectroscopy. When

comparing **76b-e** to the unsubstituted esterified maleimide **76a**, it is safe to assume that Michael addition is completely nullified due to the addition of any group across the alkene.

2.6.1. Esterification of Glutamic Acid Containing Maleimides

Esterification of **76b-e** gave no evidence of any problems, so the assumption was made that esterification of the glutamic acid containing substituted maleimides would also follow suit (Table **2.10**). All compounds were purified *via* flash column chromatography to ensure purity, for full analysis that included using polarimetry.

Table 2.10. Comparison of yields for the esterification of **119a-e**



a R^1= H, R^2= H
b R^1= Me, R^2= H
c R^1= Br, R^2= H
d R^1= Me, R^2= Me
e R^1= Cl, R^2= Cl

Compound Name	Yield %	$[\alpha]_D^{25}$ (c 1.0) in MeOH
116a	63	-
116b	92	-19.6
116c	60*	-18.3
116d	38*	-24.9
116e	100	-21.4

*Compounds were purified

Acids **119a-e** all reacted well despite the reported yields, with no additional side products or Michael addition detected by ^{1}H and ^{13}C NMR spectroscopy as well as LRMS. **116d** was recovered in a poor yield due to unreacted anhydride from the previous reaction remaining. If any anhydride

is present, the anhydride gets opened up and a double esterification occurs, that appears to be preferential over the glutamic acid.

When consulting the ^{1}H NMR spectra for each compound, the newly synthesised methyl ester is easily identifiable over the C1 methyl ester and exists slightly more downfield. For example, for **76b** the C1 ester is found at 3.64 ppm with **116b** found at 3.66 pm, with C4a methyl ester found at 3.73 ppm. The chemical shifts for the remaining aliphatic region were as expected and were similar to the corresponding starting materials.

Once again, polarimetry was used to confirmed that full racemisation had not occurred during the course of the reaction, with values similar to those seen for their starting materials. However, *ee* was not established for these systems.

2.6.2. Esterification of Phenyl Maleimides

As Michael addition to non-substituted maleimides had already been observed earlier in this chapter (Section **2.2.1**), confidence that the esterification of **121** would be unproblematic was low.

After stirring for 16 hours the crude mixture was tested using LRMS that showed the required mass ion for the desired product, so the crude was purified *via* flash column chromatography. However, the only discernible product collected from the purification suggested opening of the imide as the distinct alkene peaks previously seen at 6.40 ppm were not present in the ^{1}H NMR spectrum. When reconsulting the LRMS (ESI^{+}), the major mass ion present was 300 which matches **136** [MNa+] (Scheme **2.28**). Ring opening may be a consequence of addition strain through the system from the lack of flexibility caused by the aromatic ring within close proximity to the imide.



121 **136**

Scheme 2.28. Attempted esterification of **121**

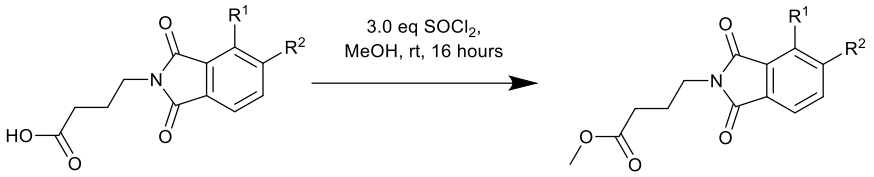
2.7. Esterification of Phthalimides

Unlike all other compounds subjected to esterification, it was envisioned that phthalimide containing acids would be the most stable for this chemistry achieving the best yields. As **123a** was the simplest of the series, it seemed logical to use this compound as a starting point for the esterification of carboxylic acid appended phthalimides.

The acquired product was analysed using ^{1}H NMR spectroscopy that showed the desired methyl ester with no additional side reactions, with the reaction proceeding to give quantitative conversion.

On the back of this success, acids **123b-i** were all subjected to the same conditions. In most cases, the functional group conversion was achieved in quantitative yields with all results compared in Table **2.11**.

Table 2.11. Comparison of yields for the esterification of **123a-i**



123a-i

a R^1= H, R^2= H
b R^1= NO_2, R^2= H
c R^1= H, R^2= NO_2
d R^1= OH, R^2= H
e R^1= H, R^2= Br
f R^1= F, R^2= H
g R^1= H, R^2= F
h R^1= H, R^2= COOH
i R^1= H, R^2= CH_3

137a-i

a R^1= H, R^2= H
b R^1= NO_2, R^2= H
c R^1= H, R^2= NO_2
d R^1= OH, R^2= H
e R^1= H, R^2= Br
f R^1= F, R^2= H
g R^1= H, R^2= F
h R^1= H, R^2= COOMe
i R^1= H, R^2= CH_3

Compound Name	Yield %
137a	100
137b	80
137c	100
137d	96
137e	0
137f	100
137g	100
137h	62
137i	100

123a,c,f,g & **i** all gave quantitative conversions to the corresponding desired methyl esters **137a,c,f,g** & **i**. Compounds **137b & d** were synthesised with good to excellent yields; with **137d** it was more important to see that the phenol was untouched, being confirmed using ^{1}H NMR and ^{13}C NMR spectroscopy as well the correct mass ion being identified in both LRMS and HRMS.

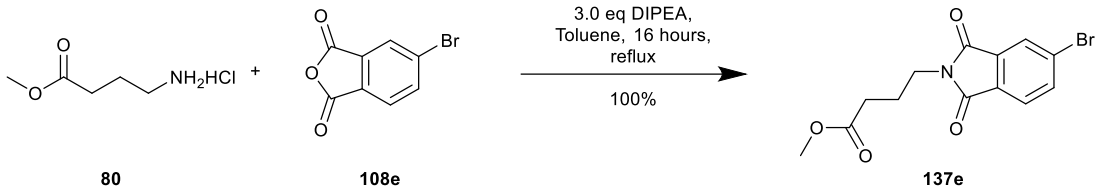
137h appeared to give poor yields when compared to the rest of the compounds tested, but it should be noted that **137h** was bought forward crude from the previous formation. It has already been discussed that the formation of **137h** saw a large presence of unreacted starting materials and intermediate amide. Therefore, the esterification would always give substantially lower yields.

137e was rather particular in the reactivity and solubility compared to all other compounds highlighted so far in this chapter. **137e** had also shown a lack of solubility with the ^{1}H NMR sample being dissolved in deuterated DMSO with additional heating required.

137e was suspended in methanol and cooled to 0 °C using an ice bath with thionyl chloride being added dropwise over 5 minutes. The ice bath was removed, and the reaction mixture was left stirring at room temperature. After 4 hours of stirring, it was apparent that the reaction was failing to work due to all the starting material failing to dissolve. The reaction mixture was warmed to 40 °C at which point all the starting material dissolved into the methanol. However, as the reaction cooled back down to room temperature, the starting material started to precipitate out of solution. It was safe to assume that the solubility of **137e** had a major impact on this reaction, so an alternative method would be explored.

2.7.1. Synthesis of Methyl-1-(9-bromo-6,13-dioxoisoindolin-1-yl)butanoate

Using γ-aminobutanoate hydrochloride to form esterified imides had proven to be a useful, and it appeared to be an excellent synthetic approach for synthesising **137e**. Hence, methyl γ-aminobutanoate hydrochloride and **123e** were suspended in toluene with DIPEA and refluxed for 16 hours (Scheme **2.29**). Upon completion the solvent was removed to afford a yellow-coloured oil with the ^{1}H NMR showing an abundance of toluene remaining. The toluene was attempted to be azeotroped using methanol, surprisingly the addition of the methanol initiated a precipitate to form. More methanol was added with the solid that had formed being filtered under vacuum and washed using ice cold methanol to quantitatively afford the desired esterified phthalimide **137e** as a white coloured solid. Subsequent solubility tests found that **137e** was highly soluble in dichloromethane and $CDCl_3$.



Scheme 2.29. Synthesis of **137e** *via* refluxing the aminobutanoate with the anhydride in toluene

Due to the lack of solubility of **137e** it was possible to crystallise the ester by using standard vapour diffusion techniques by dissolving **137e** in dichloromethane and using pet-ether 40:60 as the counter solvent with the crystallographic image acquired shown in Figure **2.4**.

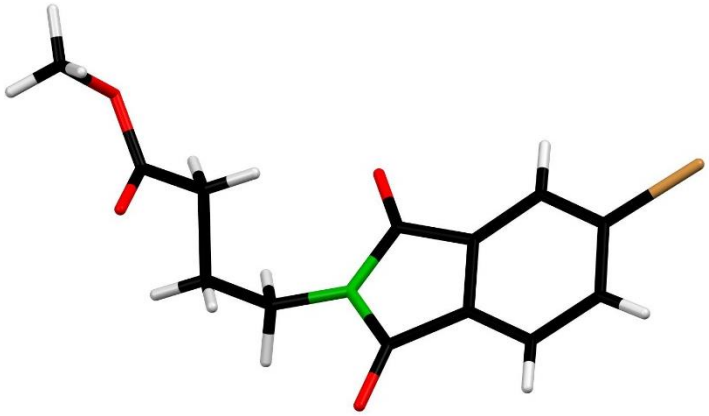
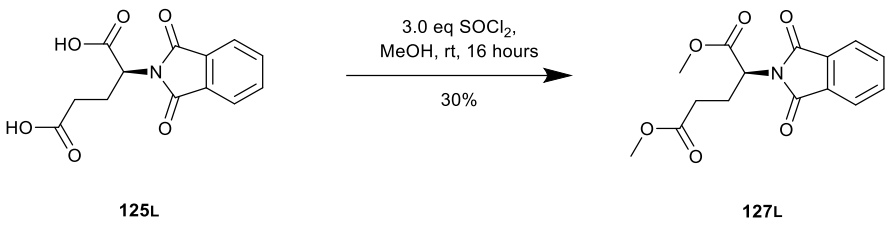


Figure 2.4. Single X-ray crystallographic data for **137e**

2.7.2. Esterification of Glutamic Acid Containing Phthalimides

It was assumed that when subjecting **125L** to esterification conditions, a double esterification of both free carboxylic acids would be the simplest route (Scheme **2.30**). the esterification of **125L** was attempted using thionyl chloride in methanol with the previously described method. ^{1}H NMR spectroscopy showed incomplete conversion to the desired dimethyl ester **127L**, so the crude was purified *via* flash column chromatography using 30% ethyl acetate in pet-ether 40:60 to afford the desired product with a poor yield of 30%.



125L **127L**

Scheme 2.30. Double esterification of **125L**

2.7.3. Esterification of Phenylacetic Acid Containing Phthalimides

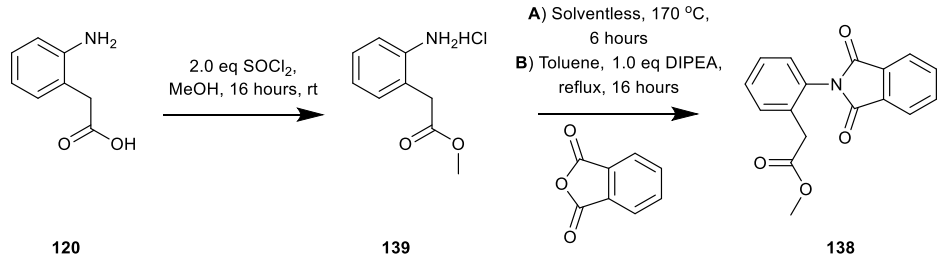
After the failure to esterify **122** where possible Michael addition cause ring opening of the maleimide, confidence in the successful esterification of the phthalimide variant **132** was minimal. Contrary to this, **132** was dissolved in methanol and cooled to 0 °C with thionyl chloride as per all other reactions. Mass spectrometer identified the presence of **132**, so the crude was purified *via* flash column chromatography using a gradient from 20-40% ethyl acetate in pet-ether 40:60 affording the desired ester **138** with a yield of 38%. This may seem low, but it should be reiterated that **132** was not pure before the esterification.



132 **138**

Scheme 2.31. Esterification of **132**

An alternative method for synthesising **138** was investigated, that started with the esterification of 2-aminophenylacetic acid, building on the experience and success of using γ-aminobutanoate.HCl. Using the procedure previously described for esterifying amino acids, **139** was afforded in quantitative yields.

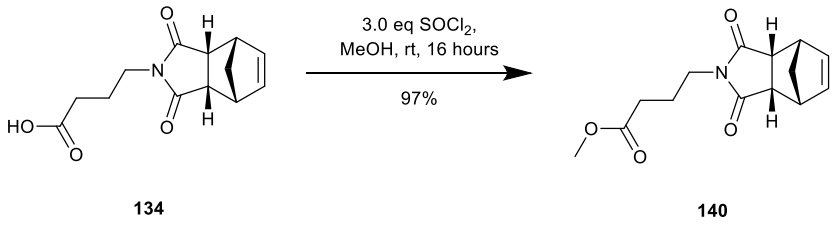


Scheme 2.32. Alternative method to afford **138**

End product **138** was generated from intermediate **139** using two different methods: Method **A** that gave a recorded yield after purification of 44%. Method **B** gave a recorded yield of 19%, also needing purification (Scheme **2.31**).

2.7.4. Esterification of 2.2.1-Bicycloimide Appended Carboxylic Acid

Esterification of **134** was not easy to predict, however, no additional side products or reactions were seen with the desired esterified product **140** being analysed *via* ^{1}H NMR spectroscopy showing complete conversion with a yield of 97% (Scheme **2.33**).



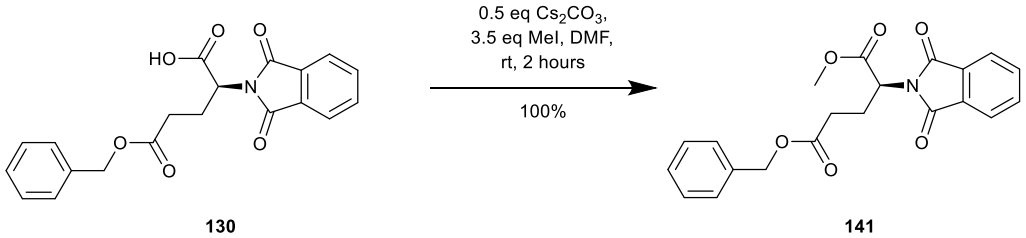
Scheme 2.33. Complete conversion to the desired esterified 2.2.1-bicycloimide **134**

2.7.5. *O*-alkylation of Glutamic Acid Containing Phthalimides

With **130** in hand and the success seen with synthesising methyl ester at the C4a position, there was confidence that no problems would occur when attempting to synthesise **141**. However, when attempting to use thionyl chloride and methanol using standard techniques used throughout this

thesis, both esterification at the C4a position, in addition to transesterification were observed leading to the formation of **127L** in quantitative yields.

O-Alkylation using MeI seemed to be a possible route to afford **141**, with a synthetic method already published,[203] it was decided to replicate these conditions.



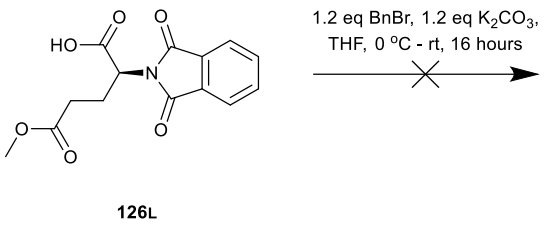
Scheme 2.34. *O*-alkylation of the C4a carboxylic acid[203]

In our hands, the above conditions worked perfectly with the only product being seen by both ^{1}H NMR and mass spectrometry being **141**.

2.8. Benzylation of Glutamic Acid Containing Phthalimides

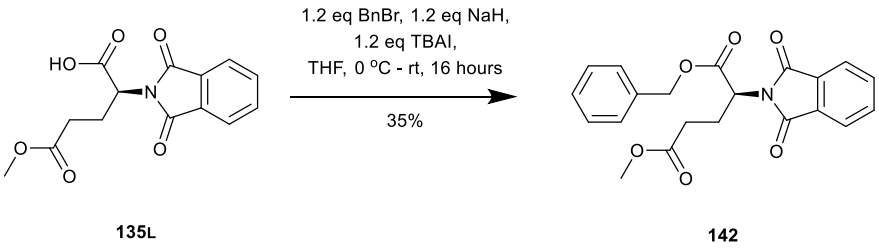
With **126L** a single esterification would be possible to afford **127L**; in lieu of this, it was proposed to use a different protecting group that would then allow selective deprotection. Conversion to the benzyl ester would be advantageous as the deprotection method (hydrogenolysis) would leave the remining methyl ester intact, while also being stable under both acidic and basic conditions.

It was assumed that standard benzylation conditions would be sufficient to perform this functional group conversion (Scheme **2.35**). After 16 hours, the reaction mixture was tested by LRMS that did not show any mass ion for the product, in addition to ^{1}H NMR suggesting the same conclusion, that the reaction did not work.



Scheme 2.35. Attempted benzylation of **126L** using K_2CO_3 as the base

As it would appear that a stronger base would be needed, the above reaction was repeated using NaH (60% dispersed on mineral oil) with TBAI also being added. This time both the LRMS and crude ^{1}H NMR spectrum showed conversion to the desired product to afford the desired benzylated product **142** with an acceptable 35% yield.



Scheme 2.36. Successful benzylation of **126L** using NaH with the addition of TBAI

Once again, the question of solubility was raised, as during the reaction the viscous consistency of the mixture most likely attributed to slower rates of reaction. In addition to this, during the flash column chromatography a white coloured solid was precipitating in the fractions and around the outlet for the column and is assumed that some product "crashed out" on the column resulting to the diminishing return on yield.

To rectify the aforementioned problems, THF was substituted for dichloromethane but the same observation of a viscous reaction mixture was still seen. Different solvent systems for purification were also tested but changes in polarity would often result in co-elution and even with the slight increase in yield would not justify a change in solvents. The best yields were achieved by using 3.0 equivalents of NaH to afford a total of 54% conversion to the desired benzyl ester **142**. It should be noted that the NaH had aged, so purity may not be guaranteed.

A collection of all reagents that were used in an attempted to synthesise **142** are displayed in Table **2.12**.

Table 2.12. Comparision of reagents for the benzylation of **142**

Reagent	Benzyl reagent	Additive	Yield %
1.2 eq K_2CO_3	BnBr	-	30
1.2 eq NaH	BnBr	1.2 eq TBAI	35
3.0 eq NaH	BnBr	1.2 eq TBAI	54
5.0 eq $SOCl_2$	BnOH	-	39
1.1 eq DCC	BnOH	0.1 eq DMAP	38

From the above data, it is clear that 3.0 equivalents of NaH gave the best yields, however this may not be ideal for large scale reactions. For the rest of the reaction conditions, there is little advantage in terms of yields suggesting that the reactivity of the glutamic acid is lower than anticipated.

2.9. Summary of Chapter II

This chapter started by reviewing the current literature on maleimide formation that primarily featured refluxing an amino acid with maleic anhydride in a given solvent for varying amounts of time. When attempting such reactions, it was discovered that isomerisation was occurring resulting in a decrease of yields. The discovery of solventless formation for imides was hugely successful in the synthesis of substituted maleimides using not just GABA, but also L-glutamic acid 5-methyl ester to achieve high yields without the need to purify. This chemistry was then expanded to include substituted phthalimides. The second half of this chapter then focused on acid esterification using $SOCl_2$ to synthesis methyl esters. A small time was also spent exploring the benzylation of L-glutamic acid 5-methyl ester containing phthalimides as a means to selectively protect and deprotect either acid group.

Chapter III: Investigation into TBDMSiOTf-mediated Cyclisations

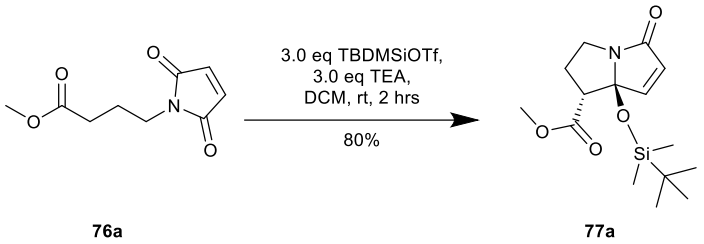
This chapter re-examines the reported method for the silyl-mediated soft enolisation reaction with maleimides and reports further optimisation of the reaction conditions. Complete characterisation and assignment for the silyl ether containing bicyclic pyrrolizidine products is reported, along with the expansion of this chemistry to phthalimides.

In this work, the report of a minor isomer formed during the cyclisation of phthalimides, as well as a discussion of the stability of the silyl enol for the removal under both basic and acidic conditions, is included.

3.1. Review of TBDMSiOTf Mediated Soft-Enol Cyclisation of Maleimide

Shifting attention back to the original publication for the total synthesis of UCS1025A, the next step was to subject the maleimido ester **76a** to ring closure to form the lactam-containing bicyclic ring system (Scheme **3.0**). Lambert and Danishefsky described a silyl mediated "soft-enolisation" *via* the use of *tert*-butyldimethylsilyl triflate (TBDMSiOTf) in the presence of a tertiary amine base,[156] a slight modification of the original conditions employed.[162] Questions arise for this cyclisation, relating to the stability of the silyl ether as well as the assigned stereochemistry. In the reported methodology, structural assignment of **77a** was achieved solely using ^{1}H NMR spectroscopy, reporting the methyl ester *trans* to the silyl ether appendage; this would be expected on steric grounds.[156]

To ensure that the original report and structural assignment was correct, as well as simultaneously investigating the stability of pyrrolizidine ester **77a**, replication of the conditions used in Scheme **3.0** was made.



Scheme 3.0. Synthesis of the bicyclic silyl containing pyrrolizidine as reported[156]

Lambert and Danishefsky describe dissolving 4-maleimidobutyrate **76a** in dichloromethane and cooling the reaction mixture to -78 °C, at which point triethylamine and TBDMSiOTf were added. The reaction was allowed to warm to room temperature while stirring over 2 hours followed by a work-up and subsequent purification *via* flash column chromatograph with an 80% yield for **77a** reported.[156] Upon replication, the reaction was tested after 2 hours using TLC, with two spots eluting close to each other, one being the starting material **76a** and the other presumed to be the desired product **77a**. Since the TLC suggested that a large quantity of starting material remained, the reaction was left stirring overnight at room temperature. The reaction mixture was worked-up and purified by flash column chromatography as reported, to yield 20% of the desired product. It should be noted that the ring-closed ester **77a** shows a significantly lower level of UV activity when viewed under a 254 nm wavelength when compared to **76a**. Hence staining of the TLC plate was performed using PMA mixture to further enhance the eluted spots (See Experimental for details).

Modifications to this procedure were attempted, initially focusing on the order of addition and the reaction temperature. With the possibility that moisture in the dichloromethane could be degrading the silyl triflate, freshly dried dichloromethane was used affording the desired product with a small increase in yield, of an additional 2%. It was decided to vary the choice of base and *N*,*N*-diisopropylethylamine was used *in lieu* of triethylamine, with all other aspects remaining the same. With these conditions, the best yield afforded was 53%, and a collection of NMR techniques[205] was used in the identification and assignment of **77a** with all values similar to those reported.[156] The alkene protons no longer appeared as a singlet, but instead as a pair of doublets, as expected,

with H7 at 6.95 (J = 5.8 Hz) and H8 at 5.97 (J = 5.8 Hz) ppm. Of interest was the decrease in the coupling constant for these protons, from 12.8 Hz in the starting maleimide, down to 5.8 Hz in the pyrrolizidinone system. The aliphatic region in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) showed signals at 3.78, 3.28, 3.12, 2.65 and 2.52 ppm. Initially, peaks at 3.78 and 3.28 ppm were arbitrarily assigned as $H4_{A/B}$, 3.12 ppm assigned as H2 with peaks at 2.65 and 2.52 ppm assigned $H3_{A/B}$. ^{13}C NMR spectrum helped to show the unique environments as expected with **77a**. Two peaks downfield at 173.89 and 171.74 ppm were initially assigned as C1 ester carbonyl and C6 lactam carbonyl. Two peaks with equal intensity were reported at 147.21 and 127.76 ppm, assigned as C7 and C8 alkene protons. A single peak at 99.89 ppm was assigned as C9 quaternary carbon. The next two peaks in question were reported at 52.98 and 51.85 ppm arbitrarily assigned as C2 and C1-OMe based on their relative intensity. Peaks at 42.09 and 31.04 ppm were assumed to be C4 and C3 based on C4 being nearer to the nitrogen and hence further downfield. The methyls from the ^{t}butyl group were reported at 25.50 ppm with the ^{t}butyl quaternary carbon reported at 17.95 ppm. Lastly, the dimethyls located on the silyl reported at -3.35 and -3.99 ppm. HSQC NMR spectroscopy was then used, and this confirmed the correct assignment for C2 (52.98), C3 (31.04) and C4 (42.09) as well as C1-OMe (51.85). HMBC NMR spectroscopy was used to accurately assign each of the carbonyl peaks. The HMBC NMR spectrum showed a clear correlation from the methyl ester, as well as H2 to the carbon peak reported at 173.89 ppm confirming this as C1. In addition to this, C6 was confirmed with correlations from H4 and H7. However, all these data do not allow for confident assignment of the stereochemistry for **77a**.

COSY NMR spectroscopy was used to identify connectivity between specific protons; it was not a surprise to see clear connectivity between $H4_A$-$H4_B$ with no connection to H2. $H3_A$-$H3_B$ connectivity was clear to see with weak, but real connectivity between $H3_A$-H2. NOESY NMR spectroscopy allowed the identification of atoms within close proximity to each another and was key in the assignment of **77a**. Firstly, $H3_B$ showed correlations to both $H3_A$ and $H4_A$, but not to $H4_B$. In contrast to this, $H3_A$ shows correlations to both $H4_A$ and $H4_B$ as well as $H3_B$, suggesting a

"cup-like" conformation [80] in the ring pushing $H3_B$ into a more equatorial position away from H4 protons. H2 only shows a single correlation to $H3_A$. Unsurprisingly, $H4_B$ shows correlations to $H4_A$ as well as $H3_A$. $H4_A$ can be seen to correlate with $H4_B$, $H3_A$ and $H3_B$. Due to the correlations seen around the ring, it is therefore possible to correctly assign all protons as $H4_A$ (3.78 ppm), $H3_A$ (2.65 ppm) and H2 (3.12 ppm) which all reside in the same face. In addition to this, the NMR data may be pointing to the conclusion that the methyl ester must be in a typically unfavourable axial position with H2 proton equatorial. We were keen to see if this conclusion was correct with use of x-ray crystallographic analysis, but despite attempts, **77a** failed to crystallise.

Surprisingly, the pair of methyl groups situated on the silicon showed two clear and distinct environments at 0.08 and 0.03 ppm in the ^{1}H NMR spectrum. This small but subtle shift in frequency suggested a conformation in which the silyl moiety is situated in physical space above the pyrrolizidine ring, rather than away from it.

To address this, and the previous question about the assumed stereochemistry for the methyl ester and silyl moiety, **77a** was subjected to nOe NMR spectroscopy (Figure **3.1**).[206,207] Initially, the methyl ester was irradiated but no nOe interactions were observed, suggesting that the silyl appendage must reside in a *trans* configuration with respect to the methyl ester, as expected. H2 was then irradiated and this showed a strong nOe interaction to $H3_A$ and weaker interactions to $H4_A$. Finally, the ^{t}butyl- group was irradiated and this showed an nOe to both the alkene protons, C8 being much stronger than C7, while also a nOe to H2, and in addition to weaker nOe's to both $H3_a$ and $H4_a$, that conclusively confirms the assignment of **77a**.

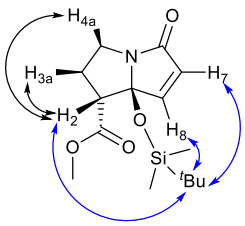
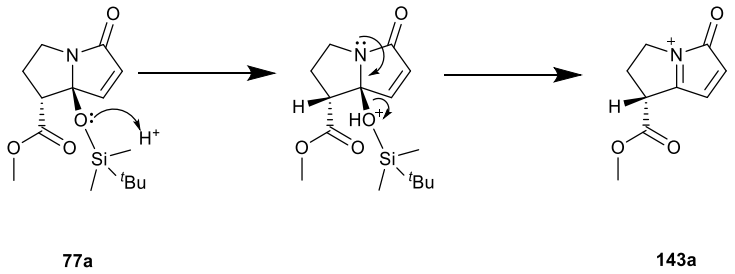


Figure 3.1. Key interactions observed in the nOe for **77**a

When **77a** was analysed using mass spectrometer, it was observed that the expected mass ion for **77a** was seen at 312 [MH+] and 334 [MNa+]. In addition to these peaks, a major peak at 180 was observed. It was assumed that under the mild acidic conditions from the solvent used during mass spectrometry analysis, protonation of the silyloxy group resulted in E1 *via* the nitrogen pushing its lone pair into the lactam resulting in desilyloxylation. When considering that the mass ion for the product **143a** of this elimination is 179, that is exactly 132 less than **77a**, which is also the exact mass of TBDMSiOH. A mechanism has been proposed in Scheme **3.1**.

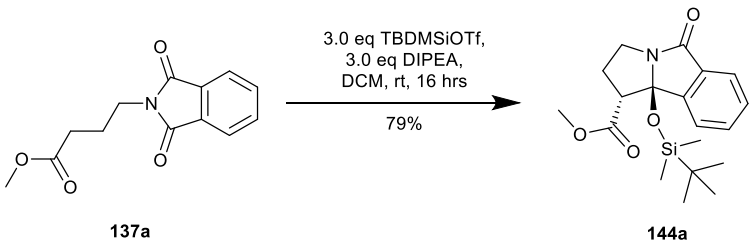


Scheme 3.1. Protonation and elimination of the silyl moiety to afford **143a**

At this point, successful cyclisation using TBDMSiOTf was welcomed, but questions remained as to its wider applicability.

3.1.1. Scope and Limitations for TBDMSiOTf Cyclisation

Having demonstrated successful reaction, **137a** was dissolved in anhydrous dichloromethane followed by the addition of *N*,*N*-diisopropylethylamine with the reaction mixture left stirring at room temperature for 1 hour. The reaction mixture was cooled and TBDMSiOTf added dropwise over 5 minutes. Over 16 hours, the reaction mixture turned to a dark orange colour. The crude mixture was worked-up and purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the silyl containing tricyclic pyrrolizidinone **144a** with an excellent yield of 79%.



Scheme 3.2. TBDMSiOTf mediated cyclisation of phthalimide **137a**

In terms of NMR characterisation, there was little difference in the aliphatic region for **144a** when compared to **77a**. The most downfield peaks for **144a** were at 7.66, 7.53-7.47 and 7.44 ppm, assigned as the 4 aromatic protons, which no longer showed the symmetry of the starting material, as expected. $H4_{A/B}$ were observed at 3.95 and 3.42 ppm respectively with H_2 at 3.30 ppm. $H3_{A/B}$ were observed from 2.73-2.66 and 2.49 ppm. Of interest were the dimethyl groups located on the silyl, that had shifted significantly more upfield to -0.08 and -0.51 ppm.

It is not uncommon to see Si-CH_3 appear very upfield in a ^{1}H NMR spectrum, since tetramethylsilane, which is reported at 0.00 ppm, is used as an internal standard.[208] However, it is less common to see peaks reside at a lower frequency than that of TMS. As **144a** features a conjugated aromatic ring, magnetic anisotropy[209] which leads to "cone-like" areas of increased and decreased shielding needs to be considered[209] for the shift in ppm.

The ^{13}C NMR spectrum was mostly as expected, with the C1-COOMe at 171.60 ppm and C6 lactam carbonyl at 170.35 ppm. The quaternary aromatic carbons were reported at 144.36 ppm, for C12 and 132.75 ppm for C7. The remaining aromatic peaks were reported at 132.20, 130.20, 123.50 and 123.26 ppm. Similar to **77a**, a peak at 99.08 was assigned as C13 quaternary carbon, with C2 at 53.05 ppm, C3 at 31.03 ppm and C4 at 42.11 ppm. The methyl ester was reported at 51.41 ppm with the trimethyls from the ^{t}butyl group at 25.41 with the quaternary ^{t}butyl carbon at 17.80. Finally, the dimethyl groups situated on the silyl were reported at -4.30 and -4.50 ppm. HSQC NMR spectroscopy was used to confirm all of the above assignments were correct.

COSY NMR spectroscopy showed connectivity between $H3_B$ with $H3_A$ and $H4_A$, but not $H4_B$. While $H3_A$ showed connectivity to both $H4_A$ and $H4_B$ in addition H2. NOESY NMR spectroscopy was useful in showing through-space interactions for **144a**. nOe interactions were seen for $H3_B$ to both $H3_A$ and $H4_A$ with a weak nOe interaction with H2. $H3_A$ reported to have nOe interaction to $H4_B$ and H2. This suggests that H2 is in an equatorial position, in order to be close enough to interact with both $H3_A$ and $H3_B$. The methyl ester showed interactions to both $H4_B$ with $H3_B$ being much weaker, but observable. H2 showed a strong nOe to $H3_A$ with a weaker interaction with $H3_B$ suggesting this distance is slightly longer. Of interest was the nOe of the ^{t}butyl group that had a weak but real interaction with $H3_A$, with stronger interactions observed for $H4_A$ and $H4_B$. This suggests that the ^{t}butyl group is located over the pyrrolizidine ring rather than away from it.

The structure of **144a** was further confirmed using LRMS and HRMS, with the major mass ions being 362 [MH+] and 384 [MNa+] along with a mass ion of 132 less than the desired product at 230 [MH+]. As with **77a**, it was assumed that under the acidity of the mass spectrometry column, desilyloxylation was occurring.

It was rewarding to find that **144a** could be recrystallised using standard vapour diffusion technique despite the bulky substituents and "greasy" nature from the quantity of methyl groups. This was achieved by dissolving **144a** in dichloromethane with pet-ether 40:60 as the co-solvent and subjected to single crystal x-ray crystallographic analysis with the image acquired displayed in Figure **3.2**; this fully confirms the structure and assures the method of analysis previously described for **144a**.

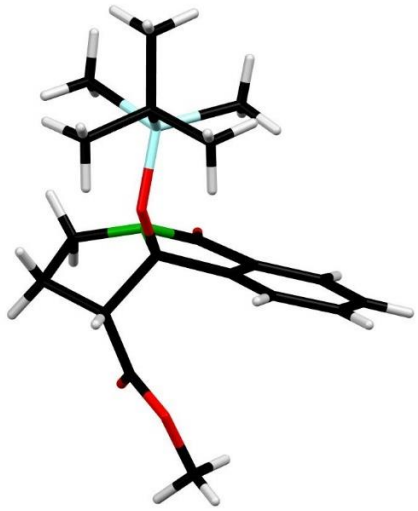
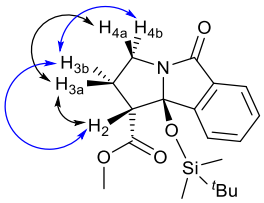


Figure 3.2. Single crystal x-ray analysis for **144a**

Figure **3.2** clearly shows the methyl ester and silyl moiety *trans*- to each other, with one of the silyl methyl groups located over the aromatic ring, accounting for the shielding observed in the NMR spectrum. It is also possible to observe the large kink in the bicyclic ring at the C2 position, which places the methyl ester underneath the aromatic ring. The x-ray image thus confirms the structure establish by NOESY analysis. It was previously stated that H2 is equatorial with the methyl ester residing in the unfavoured axial position, which is proven to be correct when studying the x-ray image. It was also hypothesised that the distance in specific protons between H4-H3-H2 may be why no COSY correlations were seen. Relevant specific bond lengths have been tabulated below in Table **3.1**.

Table 3.1. Comparison of distance between specified protons, calculated in *Mercury*, for **144a**



$H4_A$ – $H3_A$	2.289
$H4_A$ – $H3_B$	2.825
$H4_B$ - $H3_B$	2.231
$H4_B$ - $H3_A$	2.630
$H3_A$ – H2	2.579
$H3_B$ – H2	2.299

The figure of **144a** in Table **3.1** shows the connectivity observed in the COSY NMR spectrum, with those of $H3_A$ in black with $H3_B$ highlighted in blue.

It was disheartening to see that upon subsequent replication of the above conditions, **144a** was not obtained. Instead, a new product of cyclisation was formed with the isolation, properties and characterisation discussed below.

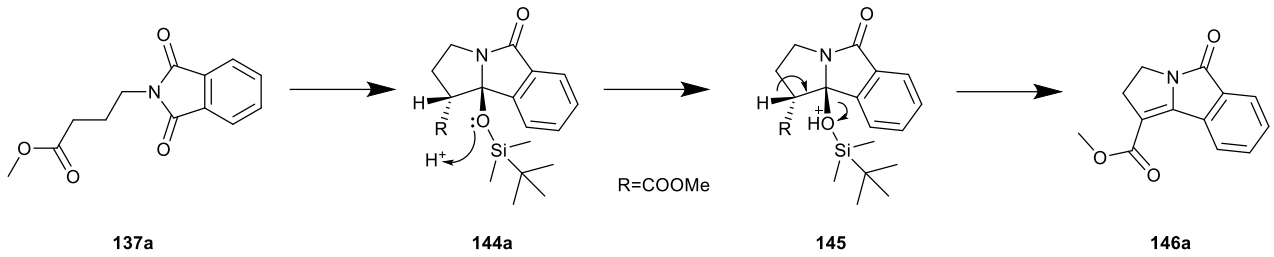
3.2. Identification, Isolation and Characterisation for the Unknown Product of Cyclisation

Upon repetition of the conditions used in Scheme **3.2**, both the crude ^{1}H NMR spectrum and LRMS did not show the presence of **144a**, with prep TLC plate also supporting this result. In the crude ^{1}H NMR spectrum, a ^{t}butyl- group was clearly visible at 0.87 ppm as well as the dimethyl group at 0.03ppm integrating at a ratio of 9:6 protons, with the dimethyl groups now appearing as a singlet. The only other peaks of interest were a pair of triplets centred at 3.99 and 3.37 ppm integrating to two protons each with a singlet integrating to three protons at 3.88 ppm. The unknown compound was tested using prep TLC and this suggested that it could be purified using 35% ethyl acetate in pet-ether 40:60 as the solvent mixture. Hence, the crude material was dissolved in a minimal quantity of dichloromethane and an attempt at purification using flash

column chromatography was made, but nothing was recovered. After multiple column volumes were collected with no sign that the unknown compound had eluted, it was assumed that the compound had precipitated on the column.

On the back of this, a second batch was synthesised using the same method already employed, and after subsequent work-up and concentration *via* reduced pressure, the solubility of the oil that remained was examined; it was soluble in chlorinated solvents (dichloromethane as well as deuterated chloroform) but not ethyl acetate/pet-ether mixture, nor in neat pet-ether 40:60. Of interest was that upon addition of neat ethyl acetate, the oil formed a precipitate. The ethyl acetate was removed and the solid was washed using another portion of ethyl acetate, with organic solvent combined and concentrated by reduced pressure then analysed using ^{1}H NMR spectroscopy that showed only two peaks, that of the ^{t}Bu- and dimethyl groups, suggesting that desilyloxylation had occurred.

Attention turned to the insoluble, yellow-coloured solid, that was attempted to be dissolved in a series of deuterated solvents for analysis *via* NMR. Surprisingly the solid was completely insoluble in MeOD and only sparingly soluble in DMSO-*d*6 with constant heating, with DMF-*d*6 seeing the same result. However, the solid was readily soluble (<80 mg/1mL) in $CDCl_3$. The solid was then analysed using LRMS which only produced a single mass ion of 230, the same seen for **144a**. As it has already been proposed that acidity from the solvent (TFA) used during LRMS had caused **144a** to eliminate to give **146a**, a similar rationale was assumed here, that an acidic species, possibly from the hydrolysis of the TBDMSiOTf, was assisting in acidic desilyloxylation of **144a** in *situ* (Scheme **3.3**). It is also hypothesised that this mechanism goes *via* an E2 elimination style reaction.



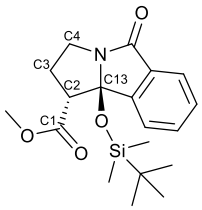
Scheme 3.3. Proposed mechanism for the *in situ* desilyloxylation of **144a** to afford **146a**

146a was obtained quantitively, suggesting the unsaturated tricyclic system is an extremely favourable product.

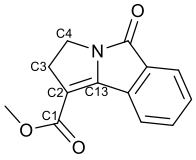
The ^{1}H NMR spectrum was simple, with the aromatic protons found at 8.52 (1H), 7.85 (1H) and 7.64 (2H) ppm proving the lack of symmetry. The triplet at 3.99 was assigned as H4, the singlet at 3.91 the methyl ester and triplet at 3.38 ppm the C3 protons. This shift further downfield for the C3 protons from 2.73-2.49 ppm for **144a** to 3.38 ppm, and for the methyl ester that had a significant shift from 3.11 to 3.89 ppm, is consistent with introduction of the new double bond.

^{13}C NMR spectroscopy also showed a shift for C1-COOMe carbonyl down to 165.09 ppm with C6 lactam carbonyl now found at 164.05 ppm. The next peak of interest was at 149.17 ppm and assigned as C13 alkene carbon. C12 quaternary carbon was now reported at 136.26 ppm and C7 at 129.62 ppm. The aromatic carbons were mostly unchanged reported at 132.26, 131.55, 126.77 and 123.52 ppm. C2 was further down field as expected at 110.31 with other significant changes being C4 at 40.9 and C3 now at 34.14 ppm. The aromatic carbon peaks along with C3 and C4 were all confirmed using HSQC NMR spectroscopy. The key NMR spectrographic data used in the assignment of **144a** and **146a** have been tabulated for comparison in Table **3.2**.

Table 3.2. Comparison for the key characteristic proton and carbon peaks for **144a** and **146a**



144a

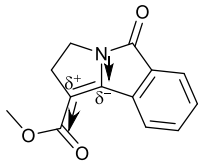


146a

	Key ^{1}H NMR peaks (ppm)	
OMe	3.11	3.89
H2	3.30	n/a
H3	2.73-2.66 & 2.49	3.37
H4	3.95 & 3.42	3.97
	Key ^{13}C NMR peaks (ppm)	
C1	171.60	165.09
C2	53.05	110.31
C3	31.03	34.14
C4	42.11	40.09
C13	99.08	149.17

While **77a** and **144a** are a "cup-like" shape with the aliphatic protons each having their own individual environment resulting from the envelope nature of the bicyclic system as clearly seen from the X-ray structure, **146a** is of course completely rigid and flat. Of interest is that **146a** is extremely UV active when excited by both shortwave (254 nm), and even appearing as a strong bright blue colour while under longwave (365 nm) radiation due to the additional conjugation throughout the system when spotted on a TLC plate. Although it was possible to crystallise **146a**, a large amount of disturbance and distortion was found in the diffraction pattern and a structure could not be obtained.

The formation of the alkene, with the lactam nitrogen and the C1 carboxylate ester at each end, forms an unusual "Push-Pull" system[210–212] with electron density simultaneously being donated into the alkene *via* the nitrogen, and being withdrawn by the ester (Figure **3.3**). This will be considered later in this thesis (Section **5.4.2** and **5.4.3**).



146a

Figure 3.3. Electron density being pushed from the amide into the alkene and being pulled into the ester

After multiple attempts of cyclising **137a**, it was apparent that it was difficult to control the formation of **144a** or **146a.** To this end, we deemed it of high importance to explore the optimisation and control for the cyclisation of phthalimides.

3.3. Optimisation and Control for the Silyl-mediated Cyclisation of Phthalimides

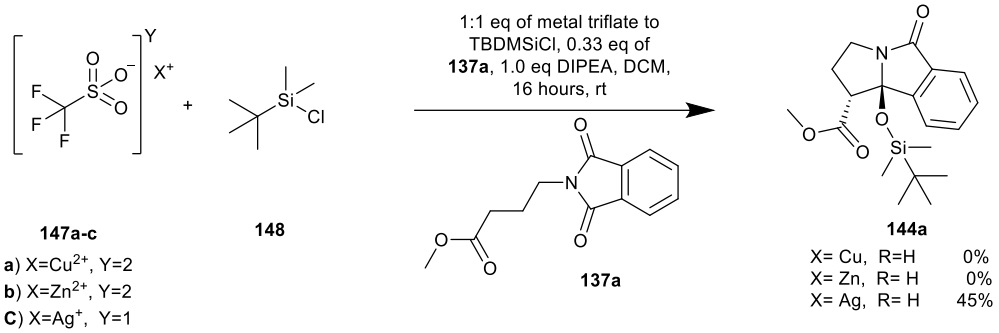
A starting point was that the smallest presence of moisture could result in the hydrolysis of the TBDMSiOTf, as it was observed that freshly opened bottles of TBDMSiOTF would afford **144a** rather than the alkene product. As only using fresh bottles of reagents was an expensive option, different approaches to introduce anhydrous TBDMSiOTf was explored.

3.3.1. *In situ* Generation of TBDMSiOTf for a One-pot Cyclisation Method

The idea was proposed that generation of the required silyl triflate *in situ*, using anhydrous reagents, might make the cyclisation process more reproducible.

A few methods for the synthesis of TBDMSiOTf have been reported, mostly using triflic acid with the corresponding silyl chloride, heated at 60 °C for up to 20 hours, with yields up to 90%.[213,214] As the main focus was to avoid the formation of acid, this approach was not suitable. An alternative method used silver trifluoromethanesulfonate **147c** and *tert*-butyldimethylsilyl chloride **148** stirred together in dichloromethane for 30 minutes,[215,216] with insoluble silver chloride salt being precipitated as the by-product. As silver trifluoromethanesulfonate is rather costly, cheaper

alternative sources of trifluoromethanesulfonate, namely copper and zinc were also examined (Scheme **3.4**).



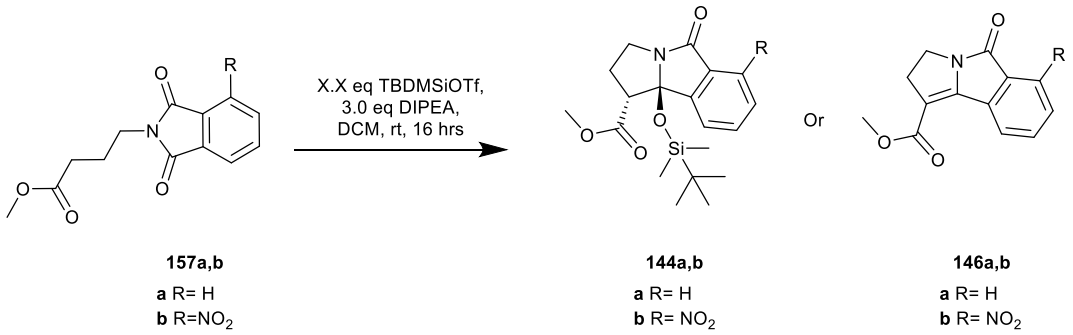
Scheme 3.4. Attempted cyclisation using TBDMSOTf generated from different metal triflates

During the reaction using silver (but not either zinc or copper) trifluoromethanesulfonate, a noticeable quantity of a white coloured solid formed. Upon work-up, each crude product was analysed by ^{1}H NMR spectroscopy, and this confirmed that only silver triflate was a viable cationic salt for *in situ* generation of TBDMSiOTf. The cost of silver triflate made this method more costly per gram then buying TBDMSiOTf, so on the back of this result, the feasibility of using TBDMSiOTf as a reagent was reassessed.

3.3.2. Reagent Based Control to Control the Product of Cyclisation

Up until this point in the project, the method of synthesis was from the work pioneered by Lambert and Danifchesky[156] with minor modifications, as it was assumed that 3.0 equivalents of TBDMSiOTf were required since the three carbonyl groups present each have the potential to co-ordinate to the reagent. Variation of the quantities of TBDMSiOTf needed for this reaction were examined. To this end, varying equivalents of TBDMSiOTf were used with two different phthalimides, **157a,b** with some unexpected results displayed in Table **3.3**.

Table 3.3. A comparison of different equivalents of TBDMSiOTf used for the cyclisation of **157a-b**



157a,b
a R= H
b R=NO_2

144a,b
a R= H
b R= NO_2

146a,b
a R= H
b R= NO_2

R	Eq. of TBDMSiOTf	Yield %	
H	1.0	**78**	0
H	1.1	**97**	0
H	2.0	0	**100**
NO_2	1.0	**64**	0
NO_2	1.1	**82**	0
NO_2	2.0	0	**100**

(Note. Regioselectivity for **144b** and **146b** will be discussed in detail in Section **4.5**).

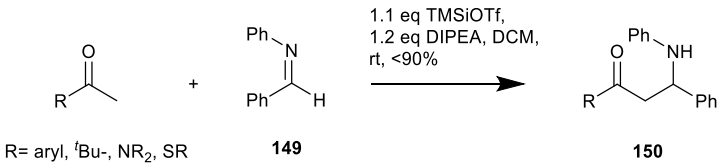
It was surprising to see that the formation of the **144a,b** was achievable in high yields, and nearly quantitative conversion for **144a** when using 1.1 equivalents of TBDMSiOTf, while 2.0 equivalents gave the pyrrolizidinone **146a,b** quantitatively. The fact that this reaction still works is contradictory to reported explanations for the cyclisation using TBDMSiOTf for these systems. Hoye described the mechanism as an intramolecular Mukaiyama-like addition in which formation of a silyl-containing acetal is followed by addition to one of the imide carbonyls *via in situ* silyl activation.[162] This was also reinforced in the publication by Christmann, with their slightly modified method employed the free carboxylic acid, forming a *bis*-silylketene acetal for their cyclisations.[181]

However, when revising the literature for Mukaiyama aldol additions, this success may be explainable.

Mukaiyama aldol addition[217] reaction allows for the cross coupling between an aldehyde and ketone, *via* an aldol, without self-condensation of the aldehyde.[218] This reaction features the

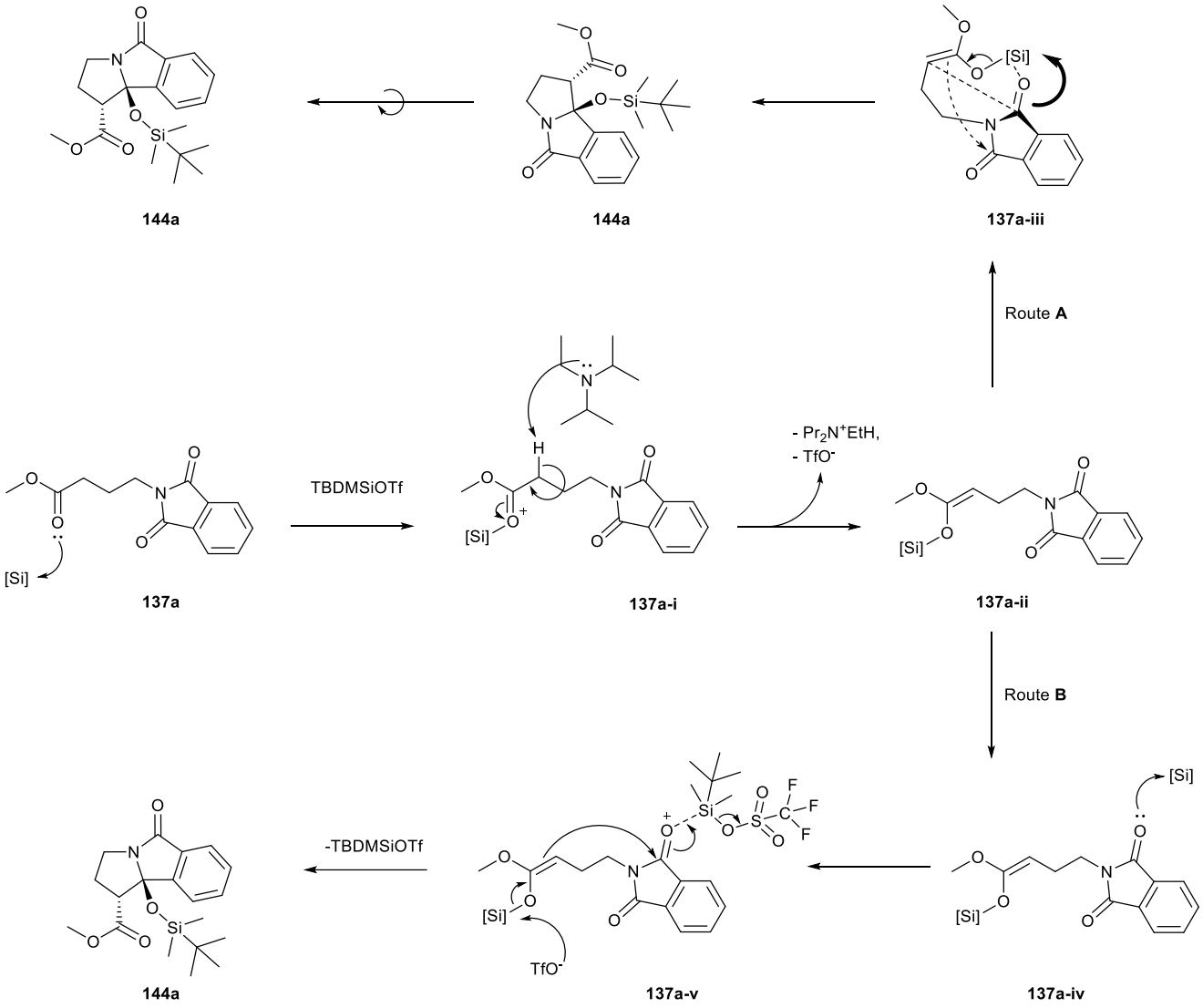
addition of a silyl ketene acetal to an aldehyde mediated by a Lewis acid.[217] The original publication used stoichiometric amounts of titanium tetrachloride[217] to mediate this addition, but over time a larger collection of catalysts have been shown to work equally as well.[218–223] This chemistry has also matured to incorporate the addition to other functional groups, such as thioacetate and amide addition to imines (Scheme **7**),[224] while also including enantioselective and diastereoselective additions.[221,225,226] To this point, a search in the literature has not shown any direct Mukaiyama additions to imides, outside of those already highlighted in this thesis.

For the most part, a pre-synthesised and purified silyl ketene acetal was used. However, it has been shown that a one-pot approach, in which formation of the silyl ketene acetal is achieved using 1.0 equivalent of trimethylsilyl chloride, with 1.0 equivalent of an amine base, such as *N*,*N*-diisopropylethylamine (Scheme **3.5**).[224] In order for Mukaiyama aldol addition to be successful, a catalytic quantity of trimethylsilyl trifluoromethanesulfonate (TMSiOTf) and a slight excess of base must be present.[224] The group concluded that TMSiOTf was recycled during the reaction with the additional base acting as a Lewis base, but could not specify the exact role played throughout the reaction.[224]



Scheme 3.5. One-pot ketene acetal-formation Mukaiyama-Mannich addition[224]

From this analysis, a mechanism for the synthesis of **144a** is proposed below.



Scheme 3.6. Proposed mechanism for the TBDMSiOTf-mediated cyclisation of **144a**

It is proposed that this reaction occurs *via* a Mukaiyama-imide aldol addition, with two routes suggested. The first step in this sequence is the formation of the silyl ketene acetal **137a-ii**. Route A shows coordination of the ketene silyl acetal to the imide carbonyl as well as the imide oxygen coordinating to the silyl group. This 5,6-membered transition state system can then undergo aldol addition *via* the C1 oxygen carbonyl reforming and the silyl group migrating onto the imide oxygen. Route B hypothesises that intramolecular Mukaiyama aldol addition proceeds through *in situ* silyl activation of an amide carbonyl, promoted by DIPEA, regenerating the catalytic quantity of TBDMSiOTf needed for this reaction to proceed.

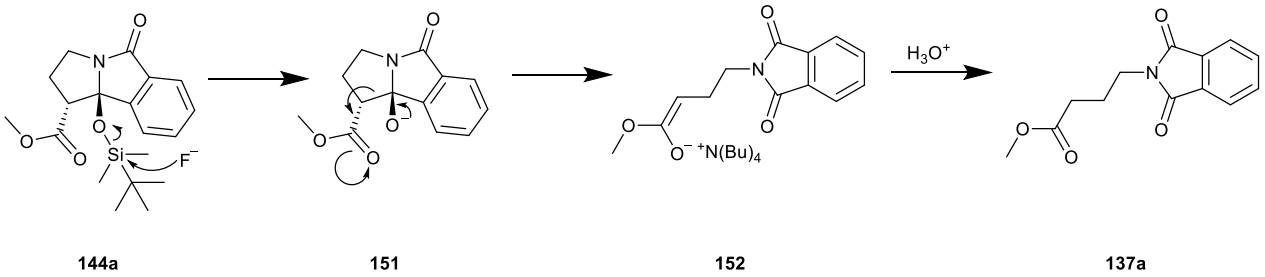
As other publications have also hypothesised, DIPEA may play a further role in this cyclisation acting as a Lewis base assisting in the bond migration *via* a pentavalent silicon.[220] The data in Table **3.3** suggests that a slight excess of TBDMSiOTf is needed for greater yields, but this may be a result of hydrolysis of the reagent over a period of time, in addition to the exact measurements of the reagent when working on small scale reactions (~0.1 g of **137a**). Alternatively, it may be that the slight excess is acting as a Lewis acid for activation of the imide. It should be noted that the maleimide **76a** has been successfully cyclised with high yields of 52% when using 1.1 equivalents of TBDMSiOTf, showing this mechanism is not specific to phthalimides.

Experimental procedures for Mukaiyama aldol additions usually feature a weak acid wash[224] that causes the release of the silyl group to afford the alcohol, but this was not attempted with **144a**.

This critical result proved to be very important for the development of this reaction, since predictable and reliable conditions that can be used to control the desired product for the cyclisation of phthalimides had been established.

3.4. TBAF Mediated Desilylation

With a rapid, reliable and efficient strategy in place for the synthesis of tricyclic pyrrolizidines, removal of the silyl protecting group affording the free alcohol was examined, with the product closely resembling UCS1025A.[80,81] To this end, a sample of **144a** was dissolved in dichloromethane and treated with TBAF, analysis after 1 minute using ^{1}H NMR spectroscopy showing complete conversion back to the starting imide **137a**. It appeared that the removal of the silyl group resulted in the expected alkoxide, which collapsed to reform the imide *via* a retro-aldol style process, breaking the previously formed pyrrolizidine ring system with a mechanism proposed in Scheme **9**.



Scheme 3.7. Retro aldol *via* TBAF deprotection

The reaction was repeated at -78 °C, and the same result was found. An attempt to trap the alkoxide using acetyl chloride with the reaction stirring at -78 °C and allowing the gentle warming to room temperature, but **137a** only was obtained quantitatively. It was apparent that removal of the silyl group was not achievable under basic conditions, such as when using TBAF, but collapse of the ring system was observed. However, this seems contradictory to a similar system where TBAF desilylation has been reported.[227]

3.5. Acidic Desilylation

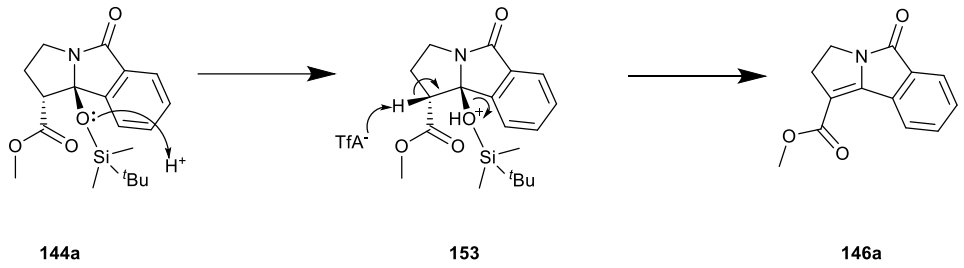
Since we were well aware that desilyloxylation was possible under acidic conditions, for example, during mass spectrometry, we hoped that acidic conditions could be better employed. Removal of the silyl moiety by using acid began by reviewing what had already been witnessed experimentally when working with these systems. Desirable was the rapid and quantitative conversion through to the alkene containing tricyclic system, hopefully without any further purification being required.

Firstly, it was observed that when certain silyl containing compounds (will be discussed later in greater depth in Chapter **4.5**) are left in an NMR tube dissolved in $CDCl_3$ overnight, while waiting for longer NMR experiments to run, such as ^{13}C NMR, partial elimination occurred.

It is known that when exposed to light, chloroform can react photochemically generating small quantities of phosgene and HCl[228,229] that can lead to the desilylation. However, this is a slow process, so it was decided not to use HCl as a possible reagent.

The use of HF in the removal of silyl protecting groups is well documented,[230–233] often giving rapid and efficient removal, but it was decided that dealing with HF as a reactive species has handling complications so it was not attempted.

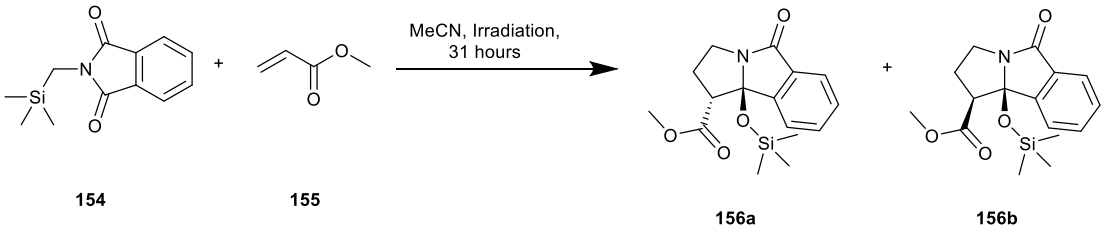
Trifluoroacetic acid (TFA) mediated desilylation reactions have been well reported[234–237] and seemed to offer a convenient way to desilylate **144a,** with most reactions reported giving near quantitative deprotection after 30 minutes of reaction. To this end, a sample of **144a** was dissolved in a mixture of TFA:H_2O 9:1 and left stirring for 30 minutes at room temperature (Scheme **3.8**). Over this period, the starting solid slowly dissolved into the solution while turning to a bright yellow colour, similar to that seen when isolating **146a** (section **3.2**). After half an hour, the solvent was removed by reduced pressure and analysed using ^{1}H NMR spectroscopy, and this showed complete silyloxy elimination to afford **146a** without any further purification needed.



Scheme 3.8. Silyl elimination *via* TFA

3.6. Review of Literature for the Synthesis of Compounds Similar to 77a and 144a

A structurally related diastereomer of **144a** has been reported,[238,239] using very different methodology. **154** was dissolved in MeCN with 10 equivalents of methyl acrylate **155** and irradiated for 31 hours giving a 6:1 mixture of isomers that was inseparable when purified using flash column chromatography with a yield of 93% based on the recovery of the starting material (Scheme **3.9**).



Scheme 3.9. Cyclisation *via* irradiation in acetonitrile to a racemic mixture of compounds

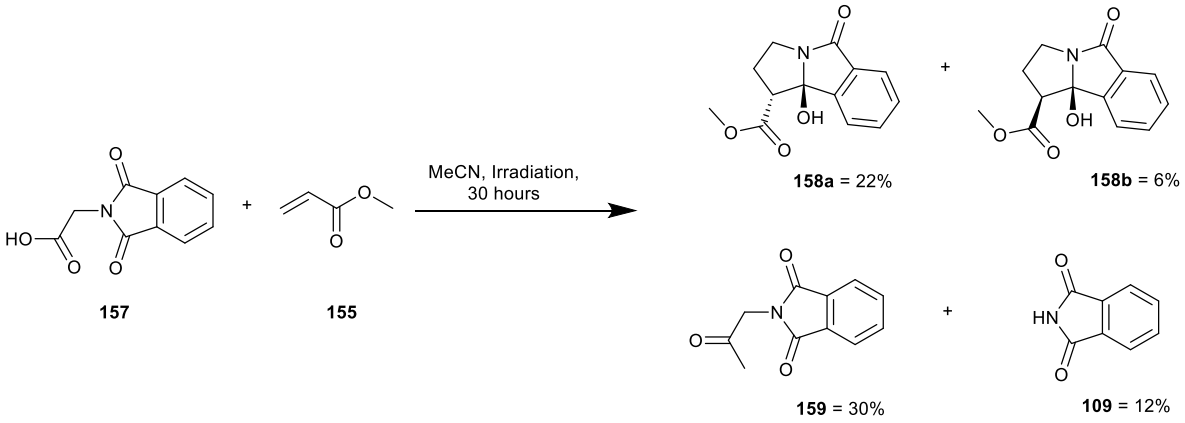
Characterisation for **156a,b** was achieved by ^{1}H and ^{13}C NMR spectroscopy with the data collected compared against closely related structures determined by X-ray analysis to prove stereochemistry. The reported data for both **156a** and **156b** differ significantly, with some of the data tabulated below in **Table 3.4**.

Table 3.4. Comparison for the reported ^{1}H NMR spectroscopic values for **156a** and **156b**

	Reported ^{1}H NMR chemical shifts (ppm)	
	Major **156a**	Minor **156b**
Si-CH_3	-0.17	0.11
OMe	3.10	3.96
H2	3.29	3.33
H3	2.49 and 2.68	2.49 and 2.68
H4	3.40 and 3.93	3.39 and 3.95

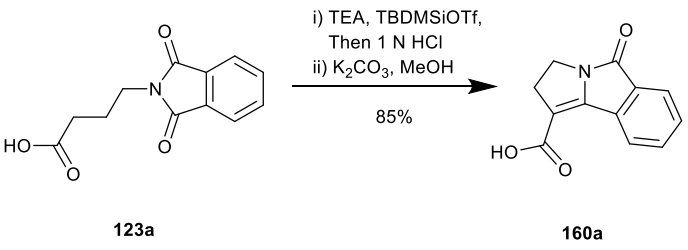
It was surprising to see such a difference in reported methyl groups situated on the silyl, as well as the difference in the methyl ester. It is also surprising to see that the configuration of the ester and silyl groups had little to no effect on the chemical shift of the aliphatic protons. However, it should be noted that the above approaches only has a limited range of substrates that can be tolerated;[240] maleimides, for example would potentially undergo 2+2 cycloaddition under these conditions[241] in addition to the active radical species reacting with acetonitrile, leading to unwanted side-reaction.

A similar strategy allowed the synthesis of the unprotected alcohol **158a,b**, albeit in low yields with inseparable side products (Scheme **3.10**).[242]



Scheme 3.10. Irradiation-mediated cyclisation to afford a racemic mixture with additional side-products shown[242]

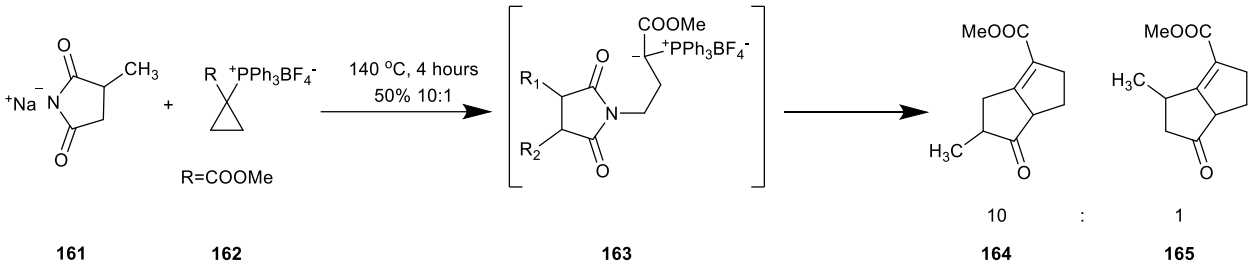
The pyrrolizidinone **146a** had also been reported by Christmann *et al.*[163], as the unprotected carboxylic acid. This used a modification of the original synthesis,[156] which skipped the esterification of the maleimidobutyric and phthalimidobutyric acids. The authors hypothesised that the carboxylic acid would attack the silyl triflate, forming a bis-silylketene acetal, before undergoing enolic addition to the imide [163]. Subsequent work-up with potassium carbonate in methanol would afford the desired bicyclic pyrrolizidine with the silyl ether *trans*- to the C1 carboxylic acid. However, they observed that when phthalimidobutyric acid was used with these conditions, the recovered product was the free carboxylic acid unsaturated lactam, after acidic work-up (Scheme **3.11**).



Scheme 3.11. Christmann *et al* approach to the synthesis of tricyclic pyrrolizinone

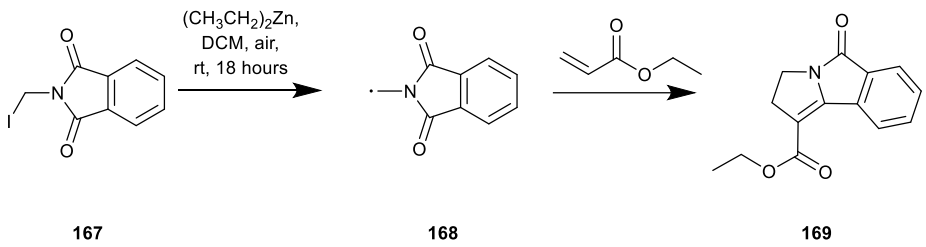
This group alluded to the fact that desilyloxylation occurs but did not propose any mechanism or indicate the point at which this happens. From the limited explanation given in the published report, and the experience of working with phthalimides in this project, it is assumed that desilyloxylation occurs upon quenching the reaction with HCl.[163]

Another approach to these systems featured intramolecular Wittig cyclisation by nucleophilic addition of a carbonyl-containing substrate, a carboalkoxycyclopropyltriphenylphosphonium species **162**,[243,244] affording cyclised pyrrolizidines.[244] Moreover, this reaction can be carried out neat, at 140 °C. The group reported that when sodium 2-methylsuccinimide was used, a 10:1 mixture of regioisomers was seen (Scheme **3.12**).[244]



Scheme 3.12. Use of cyclopropyltriphenylphosphonium **162** with 2-methylsuccinimide **161** to afford the cyclised bicyclic systems **164** and **165**[244]

The group also found that when potassium phthalimide was used, the corresponding alkene **146a** was obtained with yields of 80%, with the ethyl ester only affording 2% of the desired product.[244] The ethyl ester variant **169** has been synthesised using radical chemistry, featuring a dialkylzinc-mediated radical process.[245]

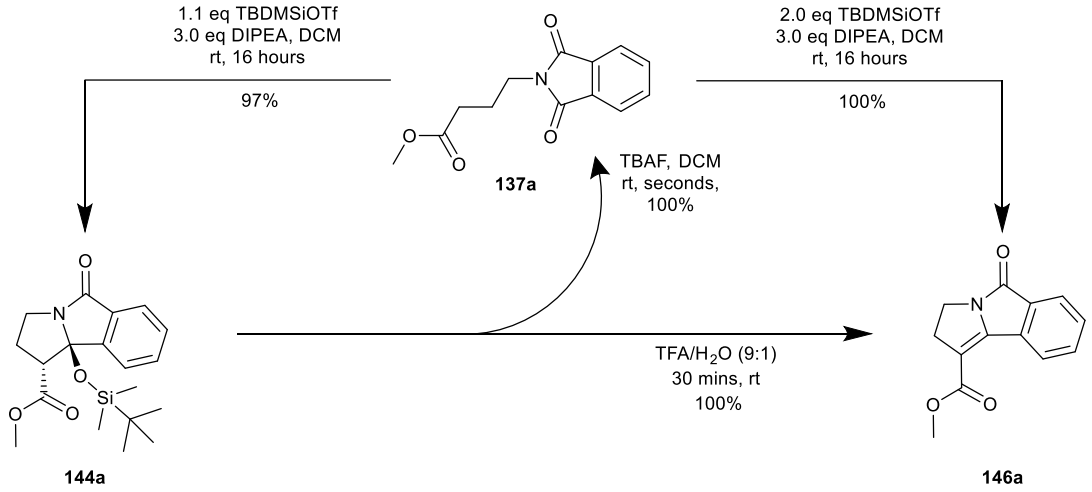


Scheme 3.13. The use of diethylzinc in the radical addition to ethyl prop-2-enoate to afford the ethyl ester containing tricyclic pyrrolizidine system[245]

3.7. Summary of Chapter III

The work reported in this chapter was critical in the development and structure for this project, giving a reliable and predictable synthetic route that could be exploited to afford two structurally different, but biologically interesting compounds.

It is assumed that the silyl-containing pyrrolizidines might give small levels of antibacterial activity that could be further elaborated and functionalised as a new building block for novel antibacterial agents. The alkene containing pyrrolizinone system would be an attractive anticancer agent, due to the flatness and conjugation seen across this system could be employed as a novel non-covalent DNA intercalator. Scheme **3.14** shows a summary of important discoveries reported in this chapter.



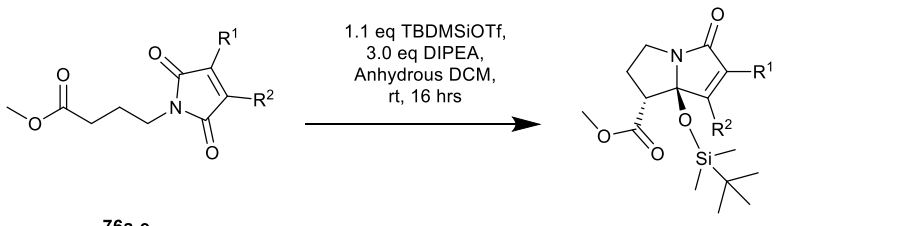
Scheme 3.14. Simplified view of the synthetic chemistry developed and described in chapter III

Chapter IV: Silyl-mediated Cyclisation of Substituted Imides

This chapter begins with a discussion of the cyclisation of mono- and disubstituted maleimides followed by glutaminyl appended maleimide to examine the role the C4 substituent might play in cyclisation. Next, this chapter will focus on all other phthalimides synthesised in Chapter 2 with the same goal of understanding the regio- and diastereoselectivity of their cyclisation reactions, followed by an expansive collection of TFA-based eliminations to afford the previously seen saturated bi- and tricyclic systems. This chapter will also detail attempts to branch away from esters and probe the reactivity of other functional groups that may be tolerated in TBDMSiOTf mediated cyclisation reactions.

4.1. Cyclisation of Substituted Maleimides

With the substituted maleimides previously synthesised now routinely available (Chapter 2, section **2.6**), the modified conditions reported (Chapter 3, Section **3.3.2**.) for silyl mediated-soft enol cyclisation were replicated (Scheme **4.1**).



76a-e

a R^1= H, R^2= H
b R^1= Me, R^2= H
c R^1= Br, R^2= H
d R^1= Me, R^2= Me
e R^1= Cl, R^2= Cl

77a-g

a R^1= H, R^2= H 53%

b R^1= Me, R^2= H 0%
c R^1= H, R^2= Me 43%
} From **76b**

d R^1= Br, R^2= H 67%
e R^1= H, R^2= Br 0%
} From **76c**

f R^1= Me, R^2= Me 57%
g R^1= Cl, R^2= Cl 63%

Scheme 4.1. Cyclisation of symmetrical and unsymmetrical maleimides.

Due to the symmetry of **77f,g**, the expected product of cyclisation is a single isomer, and this was confirmed by the formation of only one product in the ^{1}H NMR spectrum. The ^{1}H NMR spectrum also showed a single diastereomer, confirmed with only a single ^{t}butyl group being seen, with the silyl methyl groups appearing as two separate singlets. The resonances in the aliphatic region were near identical to those reported for **77a**[156] (non-substituted maleimide) with the obvious differences being the disappearance of the alkene protons and the inclusion of two methyl groups at 1.90 and 1.70 ppm for **77f.**

77g had no characteristic alkene groups detectable *via* the ^{1}H NMR spectrum, and all aliphatic proton resonance were similar to those seen throughout this series of compounds (Table **4.1**), and it was therefore obvious that the desired product had formed. However, **77g** was not isolated cleanly, with there being the presence of some starting material which co-eluted with the desired product *via* flash column chromatography.

When attempting to cyclise both unsymmetrical maleimides **76b-c**, it was expected that a mixture of isomers (formed from closure onto either of the different maleimide carbonyl groups) would be present and visible *via* preparative chromatography, but this was not the case and it was initially assumed that both isomers were co-eluting. When the crude mixture of **76b/c** was purified *via* flash column chromatography and the product analysed using ^{1}H NMR spectroscopy, it was surprisingly evident that only a single isomer was present. The only other material that was identified and isolated during the purification was confirmed to be starting material. The same process was used for the crude mixture of **76d/e** affording the same conclusion.

Confirmation for the product structure, where R^1= or R^2= Me, started with the ^{1}H NMR spectrum, with the alkene proton appeared as a quartet with a coupling constant J = 1.7 Hz peak at 6.51 ppm and the methyl appeared as a doublet with the same coupling constant at 1.81 ppm. At this point, it was not possible to be confident in the positioning of the methyl and proton across the alkene. It was hoped that the symmetrical product **77f** could be used to compare the chemical shifts of the alkene groups to that of **77b/c**, but the methyl group of **77b/c** was situated exactly half-way

between those of **77f**. At this point, a ^{1}H NMR prediction of **77b/c** was made using *ChemDraw* that predicted R^1= H would appear at 6.83 ppm and if R^2= H it would appear at 5.97 ppm. As this still left some uncertainty, the ^{13}C NMR spectrum was examined, and this showed two peaks at 174.31 and 171.73 ppm responsible for both C1 and C6 lactam carbonyls. The other two peaks in question were at 140.25 for the alkene carbon with the proton, and at 136.80 for the methyl alkene carbon, deduced based on their relative intensity. Once again, predictions of the ^{13}C NMR spectra were made, which predicted that if R^1= H, C7 would be at 115.1 ppm, while if R^1= CH_3 then C7 would be at 132 ppm. Alternatively, for R_2, if R^2= H then C8 would be at 139.0 and with R^2= CH_3, C8 would be at 155.8 ppm. This prediction seemed to offer **77b** as the likely product. It was apparent that further analysis would be needed to be confident in this assignment.

HSQC NMR spectroscopy was then used and this confirmed the peak at 140.25 ppm was indeed for the alkene proton, but was not useful in confirming the selectivity in the formation of **77b,c**.

HMBC NMR spectroscopy was the next used that would be critical in the assignment of **77b,c**. It was hypothesised that if we could correctly identify and assign C1 and C6 lactam, we could subsequently find the position of the alkene proton and alkene by which group was in close proximity to the C6 lactam. As clear correlations from $H3_{A/B}$ and H2 could be seen to the carbon peak at 171.73 ppm, this was assigned as C1 and hence, the peak at 174.31 ppm was assigned as C6 lactam. It was frustrating to see correlations from both the alkene proton and the methyl group to C6 lactam, with the alkene being much more pronounced. We hoped that we could use the C9 quaternary carbon in which the silyl moiety residues to be more definitive, but unfortunately, both alkene groups also saw correlations to C9, with the proton being much stronger this time. So far the data suggested that R^1= CH_3 and R^2= H. Contrary to this, the carbon peak at 52.34 that was confirmed *via* HSQC to be C2, shows a clear correlation to the alkene methyl group, with no such interaction from the alkene proton. From this additional interaction seen, we assign that R^1= H with R^2= CH_3. A condensed version of the HMBC NMR spectrum can be seen in Figure **4.1**.

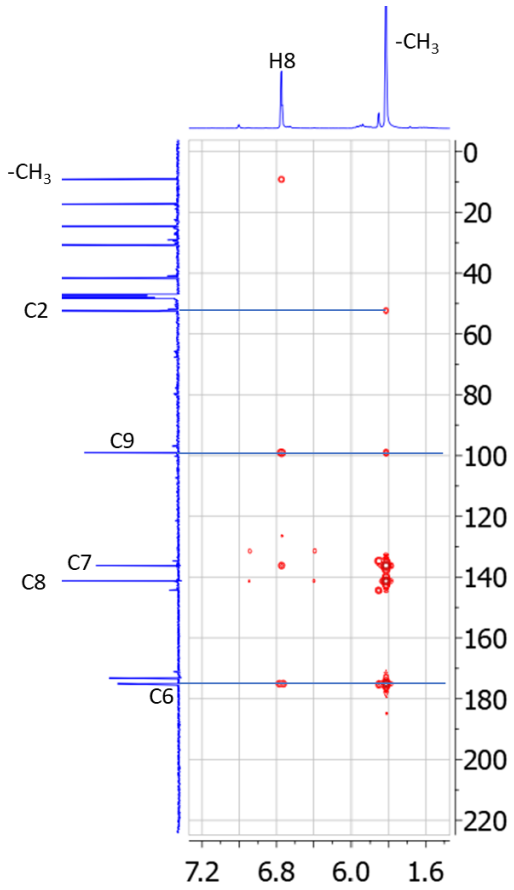


Figure 4.1. Condensed view of the key correlations observed in the HMBC NMR spectrum for **77c**

It should be noted that Christmann *et al.* have reported the carboxylic acid[163] variant of **77b,c** that was synthesised using methodology previously described in Scheme **3.11** in Section **3.6**, and the existence of the other possible regioisomer where $R^1 = CH_3$. In the publication, it is stated that they also see complete regio- and diastereoselectivity but do not indicate how they assign the selectivity. A certain area of contention comes when comparing the reported data in this publication against our own data, which appeared nearly identical (apart from the obvious changes at the C1 carbonyl and lack of ester peak), with these values reported.

For the analysis of **77d,e**, the same methodology was used, but with the addition of a bromo group, it was impossible to see interactions as with the methyl group. To this end, we attempted to crystalise **77d,e** in a minimal quantity of dichloromethane and recrystallised using standard vapour diffusion with pet-ether 40:60 used as the co-solvent but no crystals where seen to be growing. A

sample of **77d,e** was treated with a mixture of TFA:H_2O (9:1) (discussed further in Chapter 4, Section **4.12.1**) with the product successfully being crystallised using the same method and conditions as above, with the respective crystal structure shown in Figure **4.2**.

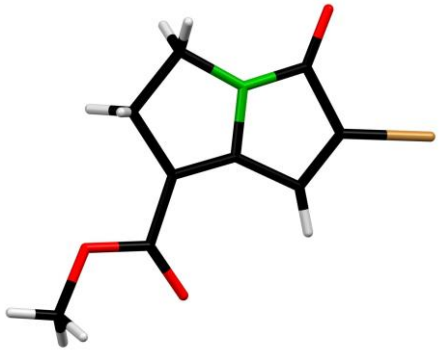
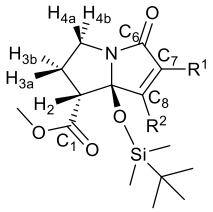


Figure 4.2. Single x-ray structure of **143d**

Figure **4.2** clearly shows that the bromo resides at the C7 position, as such we can be very confident in the same positioning for **77d**. This has shown us that these compounds exert long range coupling, and their assignment is trickier than simply affording their structure based on steric hindrance of the cyclised product.

Table 4.2. Comparision of ^{1}H and ^{13}C NMR NMR spectroscopic analysis for the cyclisation of substituted and non-substituted maleimides



77a,c,e,f,g

a R^1= H, R^2= H
c R^1= H, R^2= **Me**
d R^1= **Br**, R^2= H
f R^1= **Me**, R^2= **Me**
g R^1= **Cl**, R^2= **Cl**

^{1}H NMR characteristic peaks (ppm)

	H_2	**H_{3a}**	**H_{3b}**	**H_{4a}**	**H_{4b}**	**R^1**	**R^2**	**Si-CH_3**	**Si-CH_3**
77a[156]	3.28	2.60	2.49	3.77	3.28	6.94	5.96	0.07	0.02
77c	3.06	2.56	2.44	3.73	3.26	1.81	6.51	0.03	-0.03
77d	3.13	2.59	2.49	3.79	3.35	n/a	7.04	0.06	0.02
77f	3.03	2.55	2.42	3.75	3.27	1.90	1.70	0.05	-0.11
77g	3.16	2.59	2.44	3.83	3.38	n/a	n/a	0.07	0.00

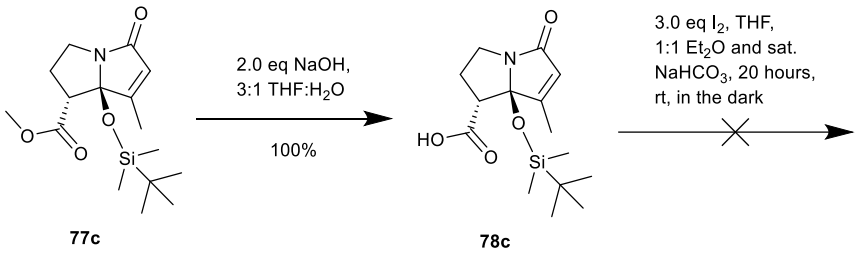
^{13}C NMR characteristic peaks (ppm)

	C_1	**C_6**	**C_7**	**C_8**
77a[156]	171.36	173.37	127.89	147.83
77c	171.73	174.31	136.80	140.25
77d	171.05	168.14	120.52	144.67
77f	171.43	174.92	130.02	150.50
77g	170.82	166.31	127.00	145.27

By the reviewing the above set of data, it is possible to say that all key characteristic protons and carbons have been correctly assigned by the obvious trends in the reported values as seen in the NMR spectra. In addition to NMR spectroscopy, the presence of **77c,d,f,g** were all confirmed using LRMS and HRMS analysis. On closer inspection for the positive LRMS (ESI^+) three major peaks were detected, MH+, MNa+ and another peak always 132 less than the product as expected, supporting that desilyloxylation also occurs for **77c,d,f,g**.

4.2. Iodolactonization of Substituted Cyclised Maliemides

With the thought of elaborating the ring closed systems to analogues of UCS1025A **18**, it was an attractive idea to attempt an iodolactonisation and coupling to simple aldehydes to gain some systems potentially likely to exhibit biological activity. First, **77c** would need to be converted to the carboxylic acid before undergoing iodolactonisation (Scheme **4.2**).

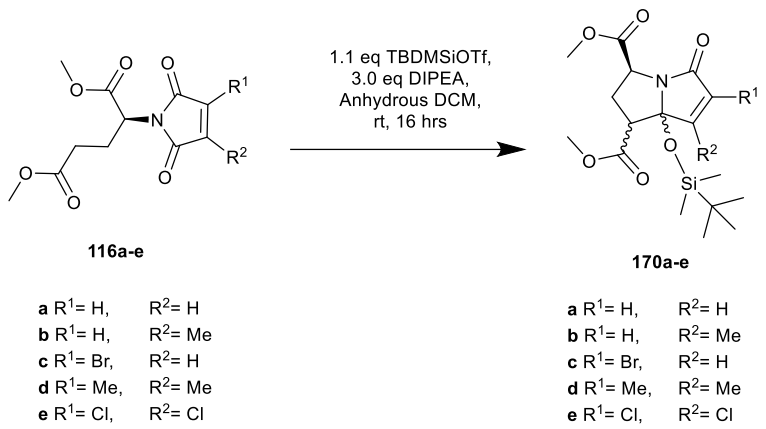


Scheme 4.2. Attempted iodolactonisation[156] of **78c**

With **78c** in hand, iodolactonisation was attempted following the procedure reported for the total synthesis of UCS1025A,[156] but upon analysis of the LRMS and crude ^{1}H NMR spectrum, it appeared that the reaction had failed. It is suggested that the addition of the methyl on the alkene is causing too much hindrance for cyclisation to occur.

4.3. Cyclisation of L-Glutamic Acid Dimethyl Ester

After the success of cyclising substituted maleimides, with yields comparable to the non-substituted maleimides, of interest was whether the inclusion of the bulky methyl ester substituent at the C4 position would hinder the reaction. To this end, of synthesised L-glutamic dimethyl ester containing maleimides were subjected to TBDMSiOTf mediated cyclisation (for comparable yields and *d.r*, see Table **4.3**).



Scheme 4.3. Cyclisation of **116a-e** using standard TBDMSiOTf mediated cyclisation

Table 4.3. Comparison for yields and *d.r.* for **170a-d**

Compound	Yield %	*d.r.*
170a	0	n/a
170b	54	1: 0.13
170c	39	1: 0.20
170d	19	1: 0.08
170e	>8	n/a

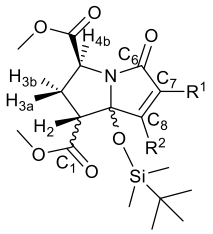
It was rewarding to see that the addition of steric bulk at the C4 position was tolerated and cyclisation still occurred. Noteworthy, though, was the decline in yield for the isolated products, not solely due to material not cyclising, but also impacted by the similar retention times of **116b-d** and **170b-d** when attempting to purify. It should be noted that **170a,d** did show possible formation in the crude ^{1}H NMR spectra but were not isolated clean, or at all, with a crude conversion less than 8%. **170b-d** gave much more complicated ^{1}H NMR spectra than **78a-h** as expected, but the formation of either regioisomers or stereoisomers added to this complexity.

The possibility of regioisomers was easy to discard as a possibility, for example, with **170b**, it was assumed that if R^1 and R^2 could both be -CH_3, then a substantial difference in ppm for these peaks would been seen. However, this was not the case, with the methyl group residing as a doublet centred at 1.82 ppm. In addition to this, it was possible to identify two different environments for

each of the methyl ester groups, which would be minimal if regioisomers were present. It seemed that the stereochemistry at the C4 position was retained but could not say definitely at this point. Analysis of **170b** began with ^{1}H NMR spectroscopy, with the alkene proton C8 appearing as separate peaks at 6.91 (q, J = 1.7 Hz) and 6.78 ppm (q, J = 1.7 Hz) that integrated at 1.0 to 0.13 giving a diastereomeric ration of 1: 0.3. As just mentioned, the CH_3- group appeared to be unaffected with regards to chemical shift between the two isomers, and it presumed the angle in which is sits of the alkene, is not being affected from the silyl moiety as much as the C7 proton. The C4 proton was found at 4.55 (major) and 4.24 (minor) ppm but as a triplet (J = 9.1 Hz) and a doublet of doublets (J = 8.4, 3.4 Hz) respectively, suggesting that these protons are being affected by other substituents, reinforcing the idea of stereoisomers over regioisomers. For the major isomer, C4 methyl ester was found at 3.75 and C1 methyl ester at 3.56 ppm. The minor isomer was similar, at 3.70 and 3.62 ppm. C1 methyl ester was assigned based on the similar chemical shift of the GABA variant **170b**. H2 was also similar to **170b**, found at 3.25 (minor) and 3.15 (major) ppm. H3 was less clear to distinguish, with $H3_A$ (minor) clear to identify at 2.92 ppm with the other remaining protons clustered together from 2.84 – 2.76 ppm. As previously mentioned, it was interesting to see the alkene CH_3 group as a singular doublet being reported at 1.82 ppm. The ^{t}butyl group was clear, reported as two singlets, very close to each other at 0.89 and 0.87 ppm. The Si-CH_3 for the major isomer were reported at 0.12 and 0.08 ppm with the minor isomers reported at 0.07 and 0.03 ppm. For all ^{1}H NMR data for **170b-d** compared, see Table **4.4**. The ^{13}C NMR spectrum also supports the conclusion that this reaction produced stereoisomers, with three separate peaks for the C6 lactam, C1 and C4 carbonyls at 175.54, 172.94 and 172.72 ppm respectively. These peaks were assigned based on their relative intensities. The minor isomer was found at 174.39, 171.43 and 171.13 ppm and assigned the same. C7 C=**C**-H carbon was reported at 141.95 ppm with C8 C=**C**-CH_3 at 138.01, assigned based on the intensity of the peaks and further confirmed *via* HSQC NMR spectroscopy. The minor isomer was reported at 145.26 (C7) and 135.74 (C8) ppm. The quaternary C9 carbon was reported at 100.61 ppm for the minor isomer

and 100.53 ppm for the major isomer. Due to the quantity of peaks from 58 ppm – 52 ppm, HSQC was used in order to ensure assignment was correct. Hence, for the major isomer, C4 was assigned as 57.17 ppm, C2 at 54.11 ppm, C4-OMe at 52.76 and C1-OMe at 52.42 ppm. C3 for the minor isomer was at 35.49 and the major was at 35.41 ppm with the ^{t}butyl reported at 26.00 ppm for the major and 25.95 ppm for the minor isomer. Only the major isomer for the quaternary ^{t}butyl carbon was observed (possibly due to concentration of the sample), with the Si-CH_3 groups at -2.97 and -3.76 for the major and -3.25 and -3.77 ppm for the minor isomer. The same analysis was also conducted for **170c,d** that gave similar results. For a comparison of key ^{13}C NMR peaks, see Table **4.4**.

Table 4.4. Comparison of ^{1}H NMR speaks used in the assignment of **170b,c,d**



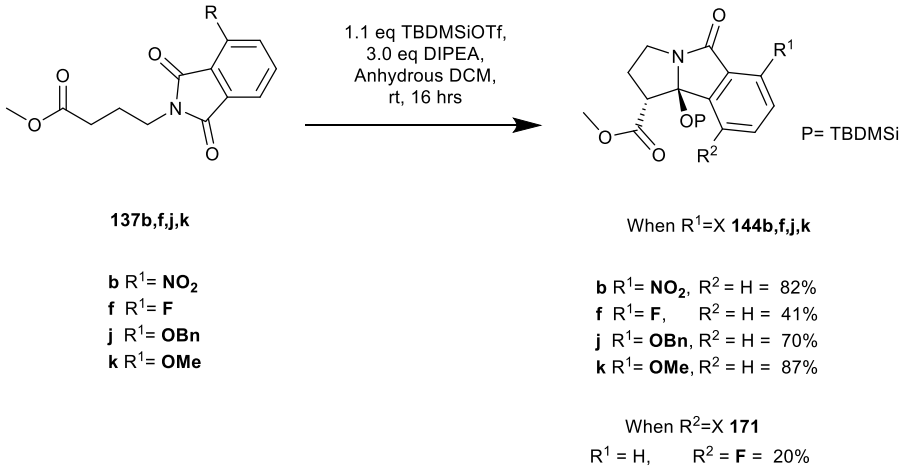
170b-d

b R^1= H, R^2= **Me**
c R^1= **Br**, R^2= H
d R^1= **Me**, R^2= **Me**

		C1-OMe	**C4-OMe**	**H4**	**H2**	**H3**	**^{t}Butly**	**Si-CH_3**	**R^1**	**R^2**
170b	Major	3.56	3.75	4.56	3.15	2.84-2.76	0.87	0.12 & 0.08	6.78	1.82
	Minor	3.62	3.70	4.24	3.25	2.92 and 2.84-2.76	0.89	0.07 & 0.03	6.91	1.82
170c	Major	3.60	3.76	4.60	3.24	2.88-2.76	0.88	0.14 & 0.10	n/a	7.45
	Minor	3.63	3.70	4.31	3.35	3.00 & 3.90	0.89	0.08 & 0.06	n/a	7.55
170d	Major	3.68	3.58	4.22	3.22	3.01 & 3.84	0.90	0.09 & -0.07	1.73	2.05
	Minor	3.75	3.55	4.60	3.16	2.84 & 2.74	0.97	0.05 & 0.02	1.97	2.01

4.5. Cyclisation of Substituted Phthalimides

Given that our earlier attempts at cyclising phthalimides gave some of the best yields, it seemed obvious to subject the remaining series of substituted phthalimides to the same silyl-mediated cyclisation conditions already employed throughout this thesis (Scheme **4.4**). After the regioselectivity seen with the nitro-containing phthalimide in Section **3.2.2** as well as with the substituted maleimides **77b-e**, it was possible to be confident that the remaining phthalimides would react similarly. It should be noted that **137j,k** were synthesised from **137d** *via* benzylation and methylation (See Experimental section for details). **137d** was protected as we suspected that the hydroxyl group would attack the silyl triflate.



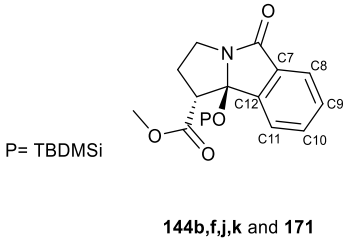
Scheme 4.4. Cyclisation of substituted phthalimides

After the reaction had been worked up and concentrated by reduced pressure, the crude material for each reaction was analysed using prep TLC and this suggested that only a single regioisomer was present for all, except when R=F. This conclusion was also supported by ^{1}H NMR spectroscopic analysis. Each of the cyclisations gave high yield, although with **144f** and **171** much lower as an attempt to purify and isolate each regioisomer resulted in impure fractions. From the crude ^{1}H NMR spectrum, the regioselectivity for **144f**/**171** was around 7:1.

The analysis of **144b** started with the ^{1}H NMR spectrum, that clearly showed the presence of a single regioisomer, with the aromatic region featuring only three separate protons at 7.85, 7.75 and

7.69 ppm. The aliphatic region was very similar to that of the unsubstituted phthalic system, with $H4_A$ at 3.99 and $H4_B$ at 3.46 ppm. H2 was reported at 3.36, the methyl ester at 3.24 and $H3_A$ at 2.76 with $H3_B$ reported at 2.53 ppm. The ^{t}butyl and silyl methyls also indicated the presence of a single isomer. The ^{13}C NMR spectrum showed two carbonyl peaks at 171.23 and 164.88 ppm assigned as C1 and C6 carbonyls respectively with two peaks of different intensities at 147.29 temporarily assigned as quaternary C12 aromatic carbon, and 145.56 ppm as the Ar**C**-NO_2. The next three peaks at 133.15, 127.44 and 124.77 were all assigned as aromatic carbons, with an additional peak at 125.37 being quaternary C7 aromatic carbon. All other peaks were very similar to that of the unsubstituted phthalic system (see Table **4.5**). NOESY NMR was rather useful in the assignment of **144b** with a through-space interaction from the ^{t}butyl group to both H3 protons, as well as H2 and a single aromatic proton at 7.75 ppm. However, a weak but real interaction from H2 to the same aromatic proton was observed, heavily suggesting that R^2 must be a proton. HMBC spectrum was first used to assign and confirm the peak at 171.23 as the C1 methyl ester, as this was seen by both H3 protons and H2. Therefore, the peak at 164.88 ppm was confirmed as C6 lactam. It was observed in the HMBC that the C6 carbonyl only saw a single aromatic proton at 7.85 ppm. It could be argued that this suggests R^1 must be H, but long range coupling in HBMC NMR for aromatic protons from 4-5 bond lengths are not rare.[246] The HMBC shows a weak correlation between the peak at 7.85 ppm and the quaternary aromatic C12, with a much stronger correlation to the quaternary aromatic C7 at 125.37 ppm. This strongly suggest that the proton at 7.85 ppm is *para* to C12 and *meta* to C7 making the assignment of the peak at 7.85 ppm as H9. The peak at 7.69 ppm saw correlations to C12, Ar**C**-NO_2 carbon, as well as weaker correlations to C7, so this carbon can be assigned as H10. More importantly, H10 also weakly saw the quaternary C13, with H11 at 7.75 seeing C13 much stronger. From all the data collected, the confident assignment of the positioning of the aromatic nitro group at the C8 position, α- to the lactam carbonyl was possible.

Table 4.5. Comparison of the key aromatic protons used in the assignment of **144b,f,j,k** and **171**



144b,f,j,k and **171**

^{13}C NMR values used in the assignment for **144b,f,j,k** and **171**

Compound	C7	C8	C9	C10	C11	C12
144b	125.37	145.56	124.77	133.15	125.37	147.29
144f	120.66	155.60	115.47	133.94	116.41	147.21
144j	135.96	119.86	132.69	119.45	157.80	130.17
144k	130.99	155.29	114.33	131.98	115.10	134.85
171	119.77	157.84	117.66	134.52	119.70	147.18

It was also possible to crystallise **144b** using standard vapor diffusion. **144b** was dissolved in the minimal quantity of dichloromethane with pet-ether 40-60°C used as the co-solvent (Figure **4.3**). It was very encouraging to see that the method employed above for the characterisation and assignment of **144b** was confirmed with the use of X-ray analysis, that gave us confidence in assigning the other remining compounds when R^1= OBn or OMe.

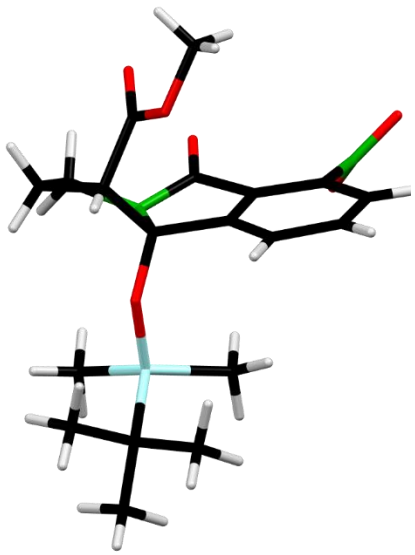


Figure 4.3 Single crystal x-ray analysis of **144b**

For the analysis of **144f/171** the question arose as to whether this mixture was of regioisomers rather than diastereoisomers. To answer this, the aliphatic region was the most useful, firstly the methyl ester appeared as a doublet centred at 3.71, which would not be the case if both *cis* and *trans* isomers were present. $H3_A$ and $H3_B$ protons appeared to be doubled up as was the case with $H4_A$ and $H4_B$. H2 proton for the minor regioisomer was slightly further downfield hidden under the $H4_B$ protons which is to be expected if it was in close proximity to a fluorine group. Secondly the ^{t}butyl group was reported as a doublet with the silyl methyl groups the same, which a larger difference in chemical shift would be expected if diastereomers were present. The aromatic region was useful as three separate environments for the major isomer were possible to identify and integrate. However, the minor isomer had only two environments visible, with the third under that of the major isomer peaks. The ^{13}C NMR was complicated by coupling arising from the presence of fluorine. An assumption was made that regioisomers would give vastly different signals when analysed using ^{19}F NMR spectroscopy, and in this case, a single peak was seen at -116.50 ppm and a second peak roughly a third of the intensity of the first peak, at -116.98 ppm.

Upon re-examination of the ^{13}C NMR spectrum, three peaks were of interest, one at 171.57 and two at 168.76 and 167.13 ppm. It was initially assumed that the peak at 171.57 was that of the C1 methyl ester, with those further upfield responsible for the C6 lactam carbonyls of the major and minor regioisomer. On closer inspection of the HMBC, clear correlations from $H3_{A,B}$ as well as H2 from both the major and minor isomer to the peak at 171.57 confirmed this as the C1 ester peak. It was possible to observe correlations from $H4_{A,B}$ to the C6 lactam peaks at 168.76 and 167.13 confirming a difference in environments for this carbonyl, and confirming the presence of regioisomers. Unfortunately, the HMBC was not concentrated enough to be able to observe all aromatic proton – carbon interactions for both the major and the minor species, but the assumption was made that if the major could be confidently assigned, then the minor should be the opposite. To this end, the proton peak centred at 7.55 ppm showed clear correlations to C13 at 99.00 ppm, but none to the C6 lactam. In addition to this, the proton at 7.33 showed very strong correlation to

C13 carbon as well as not seeing C6. The proton at 7.14 did not see C13 but did see C6 lactam very clearly, so these peaks were assigned as R^1= F, C9 at 7.14, C10 at 7.55 and C11 (R^2) at 7.33 ppm. The coupling constants were calculated, with C9 J = 19.6 Hz, C10 J = 7.5 Hz, and C11 J = 4.0 Hz. These coupling constants are as expected for ^2J, ^3J and ^4J coupling constants for fluorinated compounds.

With strong confidence that the major and minor regioisomers had been correctly assigned, we hoped that we could use X-ray analysis to reinforce this. To this end, **144f/171** was dissolved in the minimal quantity of dichloromethane and recrystallisation attempted using standard vapour diffusion technique with pet-ether 40:60 as the co-solvent. To our surprise, crystals formed and were subjected to x-ray analysis that were **171** (Figure **4.4**), where R^1= H and R^2= F, which was the assumed to be the minor regioisomer. It seemed that a substantial quantity of material had failed to crystallise, so this was taken back up into deuterated chloroform and analysed using ^{1}H NMR spectroscopy; this showed the ratio of the major to minor isomer had gone from 3:1 to 9:1, confirming **144f** as the major regioisomer. Additional attempts to crystallise the major isomer were subsequently successful with **144f** shown in Figure **4.5**.

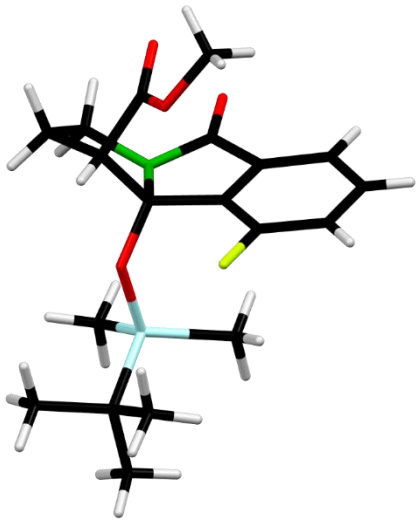


Figure 4.4. Single crystal x-ray analysis of **171**

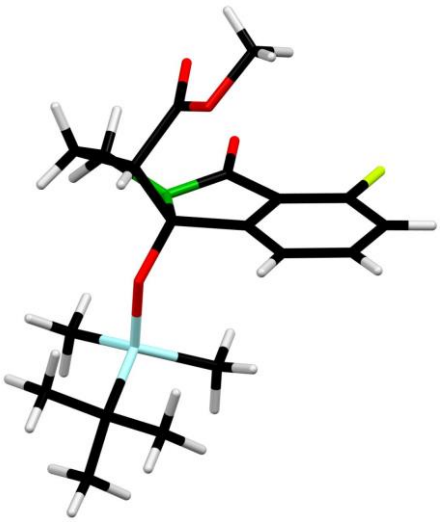
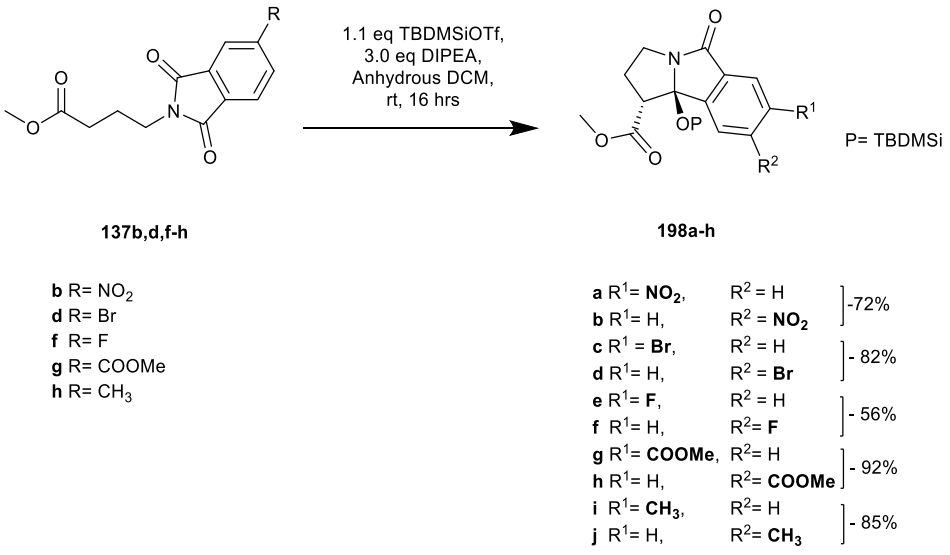


Figure 4.5. Single crystal x-ray analysis of **144f**

It appears that the cyclisation of **137f** did not proceed regioselectivity, probably due to the small size of fluorine unlike the other compounds **137b,j,k** which were affected by the sterically bulky substituents at the C8 positions.

The remaining C9 substituted phthalimides **137c,e,g-i** were subjected to the same ring-closing conditions (Scheme **4.5**).



Scheme 4.5. Cyclisation of **158b,d,f-h**

The cyclisation of **137b,d,f-h** gave excellent yields throughout, with **137g** giving particularly good yields. The yields displayed in Scheme **4.5** represents the total mass of all product collected, but

should be stated that for **172e,f**, the minor isomer started to co-elute with unreacted starting material so all possible product was not isolated cleanly, hence the lower yields seen.

Prep TLC did suggest that a mixture of regioisomers was present with some of the products, although their R_f values were very similar (for retention values, see Experimental). ^{1}H NMR analysis on the crude mixtures suggested that the cyclisation of **137b,d,f-h** had all yielded regioisomers, close to a 1:1 ratio. It was only possible to purify the mixtures and isolate the regioisomers in order to be able to fully characterise and assign them when R= NO_2, Br and F. Table **6** compares combined yields and *r.r* for both isomers.

Table 4.6. Comparison for the yields and *r.r* of **172a-h**

Compound	Yields%	*r.r*
172a,b	72	1: 0.82
172c,d	82	1: 081
172e,f	56	1: 079
172g,h	92	1: 0.83
172i,j	85	1: 0.72

For these substituents, the yields for the above cyclisations were excellent and the *r.r.* for the cyclisations of **137b,d,f-h** gave very similar values.

As the only cyclisations in which both regioisomers were isolated cleanly were for **172c,d**, and **172e,f**, accurate assignment for the position of the bromo group started with ^{1}H NMR spectroscopy. The aromatic region for **172c** showed three clear proton environments as expected at 7.67 (d), 7.62 (dd) and 7.56 (d) ppm, with the rest of the spectra near identical to the other regioisomer. The ^{13}C NMR showed a peak at 146.35 ppm that was assumed to be C12, a peak at 131.83 ppm assumed to be C7 as this followed previous trends. Other than the three obvious aromatic carbons at 133.36, 127.08 and 124.89 ppm, another peak at 126.99 was assigned as the Ar**C**-Br. The HMBC showed that the aromatic peak at 7.56 showed a clear correlation to the C6

lactam carbonyl, allowing this to be assigned as H8. In addition to this, H8 also showed correlation to the carbon peak at 146.48 ppm, suggesting this was actually C7. The aromatic peak at 7.67 ppm showed a clear correlation to the quaternary C13 peak and was assigned as C11 whilst also seeing the carbon peak at 131.83 suggesting this was C12. The C12 was also seen by the proton at 7.62 which was assigned as H10. To confirm that H11 was correct, a nOe was used to irradiate the peak that showed interactions with H2, C1 methyl ester as well as the ^{t}butyl group and the silyl methyl group at -0.44 ppm. From the above data we have assigned **172c** that was the first compound to elute with an R_f of 0.43.

The exact same analysis was conducted for **172d** that was the second compound to elute with an R_f of 0.34. Recrystallisation was attempted with the goal of confirming the above assignment *via* single crystal X-ray analysis, but **172c,e** both failed to crystallise. The same NMR analytical approach was used for **172a** with only one single isomer isolated cleanly, with this method confirmed by use x-ray analysis, after **172a** was able to be recrystallised from the minimal quantity of dichloromethane with pet-ether 40:60 as the co-solvent while using standard vapour diffusion techniques (See Figure **4.6**).

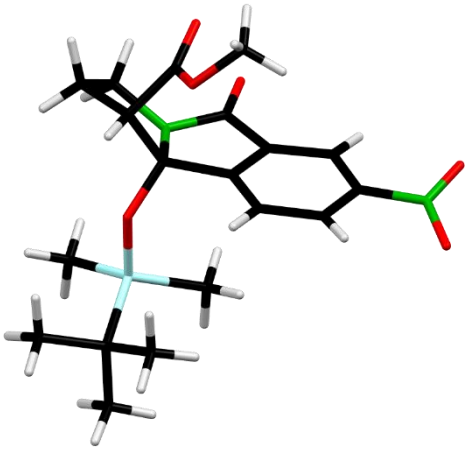
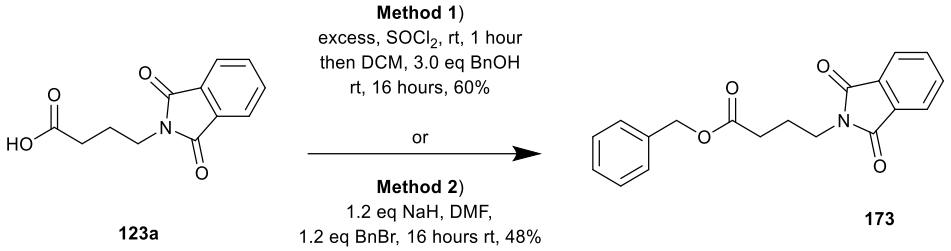


Figure 4.6. Single x-ray analysis of **172a**

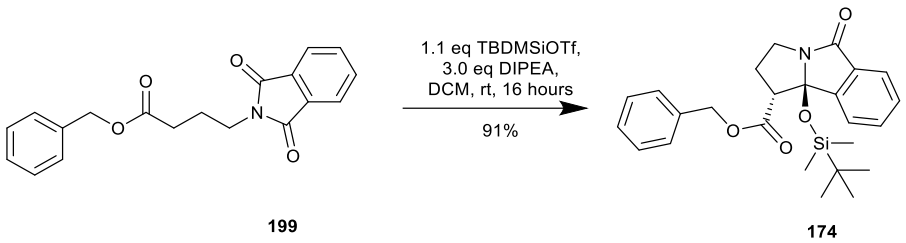
4.5.1. Cyclisation of Benzyl Ester Containing Phthalimides

While it was obvious that cyclisations using methyl esters were very high yielding and reliable reactions, of interest was whether reactions of substrates with bulkier esters, such as a benzyl ester, would also be as reliable and high yielding. Hence, we immediately looked at forming the benzyl ester variant, with two different methods employed (Scheme **4.6**).



Scheme 4.6. Benzyl protection of **123a**

Of the two methods tested, Method **1** worked the best. **173** was then subjected to standard silyl mediated cyclisation (Scheme **4.7**).

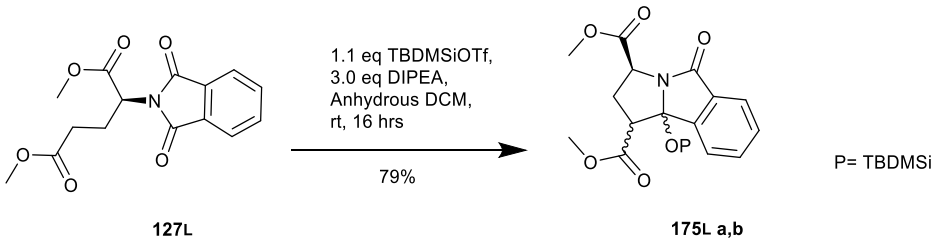


Scheme 4.7. Cyclisation of **173**

It was rewarding to find the formation of **174** with an excellent yield of 91%. The ^{1}H NMR spectrum was near identical to the methyl ester variant with the obvious inclusion of the benzylic protons that were clearly diastereotopic, at 4.66 and 4.59 ppm. It should be noted that the ^{1}H NMR and ^{13}C NMR spectra confirmed that this reaction also proceeded diastereoselectively, giving the *trans*- isomer.

4.6. Cyclisation of L-Glutamic Acid Containing Phthalimide

It was of interest to examine the effect of the presence of the glutamic methyl ester at the C4 position and whether it would also produce diastereomers under the same TBDMSiOTf mediated cyclisation. As we had previously synthesised both the D- and the L-dimethyl ester glutamic acid appended phthalimide, both of these compounds were cyclised (Scheme **4.8**).



127L **175L a,b**

Scheme 4.8. Cyclisation of **127L**

For the sake of simplicity in Scheme **4.8**, only the cyclisation of L-dimethyl ester glutamic phthalimide is shown and discussed below, but it should be noted that near identical outcome was seen for the D- variant (**127D** and **175D a,b**). It was rewarding to see that an excellent yield of 79% was recorded for the cyclisation of both enantiomers of **127**, with the presence of diastereomers confirmed by ^{1}H NMR spectroscopy. The assignment for all the key protons was achieving using ^{1}H NMR spectroscopy using previously described methodology. C6 lactam carbonyl was distinct and easy to assign at 167.54 ppm, as a correlation was seen from H4 and an aromatic proton at 7.71 ppm. Both methyl esters were found at 169.99 and 169.95 ppm. This made it very difficult to identify correlations between specific protons and a selected methyl ester. For these compounds, NOESY NMR spectroscopy was more useful, with interactions seen from H3$_A$ at 3.10-3.03 ppm to H2 and H4 with H3$_B$ at 2.92 ppm only showing very weak interactions with these protons. This heavily supports H2, H3$_A$ and H4 being in the same face resulting in both methyl esters in an axial position sticking up *cis*- to one another. In addition, the NOESY NMR spectrum also showed interactions from a silyl methyl group at -0.05 ppm to H4, H2, H3$_A$.

In attempt to ensure that this assignment was correct, **175La** was recrystallised by dissolution in a minimal quantity of dichloromethane with pet-ether 40:60 as the co-solvent (Figure **4.7**).

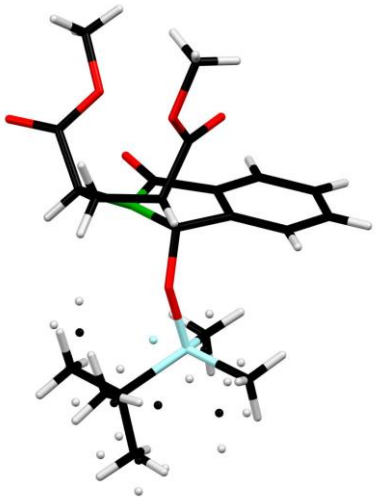


Figure 4.7. Single x-ray analysis of **175La**

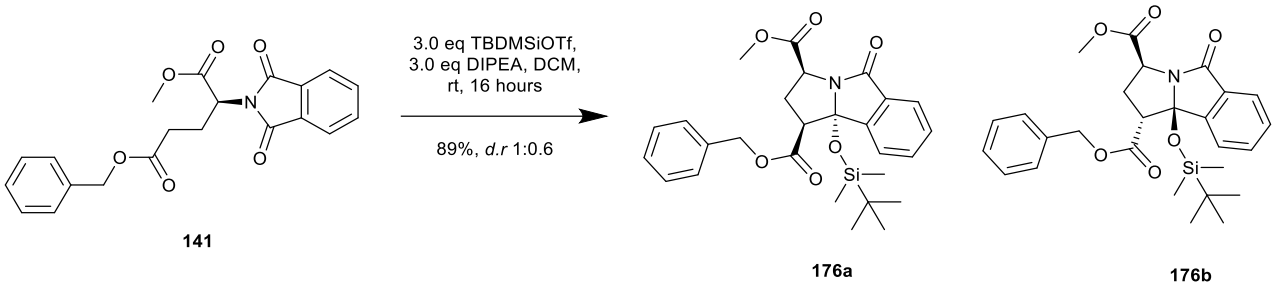
Figure **4.7** clearly shows that the methyl esters are *cis*- to one another while being axial. The carbonyl C=O group appears to line up opposite the methyl ester OMe, possible resulted from weak van der waals forces.

The minor isomer was much more difficult to assign, but from the COSY NMR spectrum for the major isomer, a correlation from the ^{t}butyl group to H4 suggested these are within close enough proximity in-order to couple, however, with the minor isomer no interaction was seen, suggesting that the ^{t}butyl group is *cis*- the C4 methyl ester group. From the data collected for the minor isomer **175Lb**, it is not possible to be conclusive in the exact assignment, but we hypothesise that the C1 methyl ester must be *trans* to both C4 methyl ester and ^{t}butyl group simply based on steric hindrance that may occur.

4.6.1. Cyclisation of Benzyl Ester Containing Glutamic Acid Phthalimides

As we had previously synthesised glutamic appended phthalimides with the benzyl ester at the C1 or C4 position, the question was raised whether the increased steric bulk would help dictate diasteroselectivity, or even nullify it. To this end, **141** and **142** where subjected to TBDMSiOTf mediated cyclisations. It should be noted that both of these compounds gave poor yields of around 35% when using 1.1 eq of TBDMSiOTf, while giving much higher yields when using 3.0 eq of

TBDMSiOTf, with the presence of the alkene product never seen when using these conditions (Scheme **4.9** and **4.10**) possibly due to the additional ester that can be activated when additional quantities of the silyl is present.



Scheme 4.9. Cyclisation of **141** to afford a mixture of diastereomers

Phthalimide **141** cyclised well to give an excellent yield of 89% with a mixture of inseparable diastereomers instantly recognisable with a calculated *d.r* of 1: 0.6. **176a** was assumed to be the major isomer as this would follow that previously seen with the glutamic series. For the major isomer, the peaks of interest were the diastereotopic protons centred at 4.60 with H4 reported as a double doublet at 4.37 ppm. It was interesting to see that for the minor isomer, both of these peaks had shifted further downfield, and sat upon each other at 4.78 ppm, confirmed *via* HSCQ. It is assumed that the presence of the benzyl group is actually having a larger impact on diastereoselectivity, with a typical *d.r.* for the dimethyl ester variant at 1: 0.2. Following this result, **142** was also cyclised (Scheme **4.10**).



Scheme 4.10. Cyclisation of **142**

The cyclisation of **142** did not give any diastereomers from the ^{1}H NMR spectrum, and this simply may be due to the steric interactions that would occur having both the benzyl and silyl moiety in the same face. In addition to NMR spectroscopy, **177** was also analysed using single crystal

diffraction, with **177** recrystallised from a minimal quantity of dichloromethane with pet-ether 40:60 used as the co-solvent (Figure **4.8**).

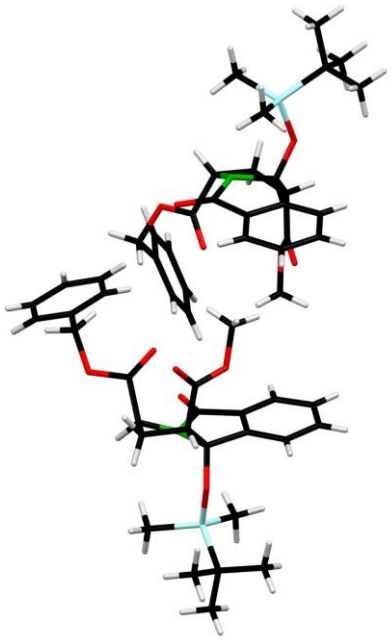
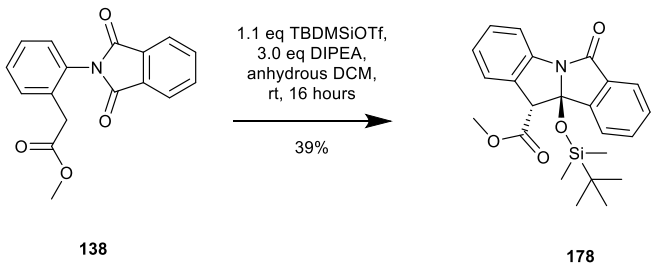


Figure 4.8. Single x-ray crystal of **177**

4.7. Cyclisation of Phenylacetic Methyl Ester Phthalimide

From the effects of a sterically bulky substituent at the C4 position on stereochemistry, of interest was what other factors may influence the product or products of cyclisation. As we had previously synthesised phenylacetic methyl ester appended phthalimide, it was decided to cyclise this compound. Initially, there was worry that the addition of the phenyl ring may cause additional strain throughout the ring changing the angles for C2 and C3, but compound **138** was subjected to our standard cyclisation conditions (Scheme **4.11**).

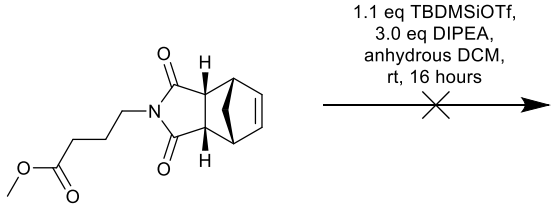


Scheme 4.11. Cyclisation of **138**

It was found that not only **138** was capable of undergoing cyclisation to afford **178**, but **178** also survived column chromatography to afford the desired product as a single stereoisomer with a satisfying yield of 39%. The most downfield silyl methyl, normally reported closer to -0.05 ppm, was now observed at -0.28 ppm. Both of these results suggest that the additional aromatic region has increased the anisotropy affect[209] across this compound.

4.8. Cyclisation of 2.2.1-Bicycloimide

Compound **140** was unique within all the maleimides and phthalimides reported in this thesis as it is the only example where the imide is not engaged in further delocalisation, whether from an aromatic ring or an alkene. It was disheartening to see that **140** failed to cyclise (Scheme **4.12**) with little evidence from the crude ^{1}H NMR spectrum and LRMS. It is suggested that the absence of delocalisation between the carbonyls reduce the imides reactivity, meaning they cannot be activated as seen with other compounds in this thesis.

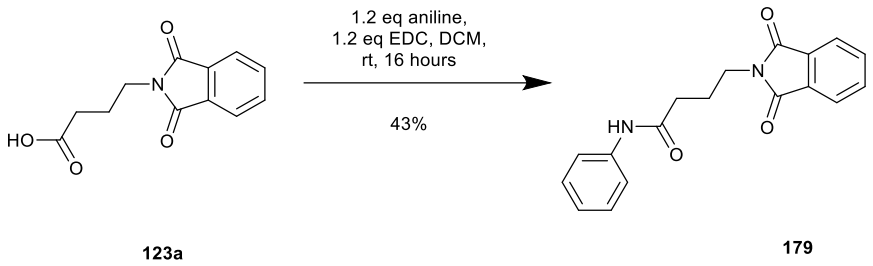


140

Scheme 4.12. Attempted cyclisation of **140**

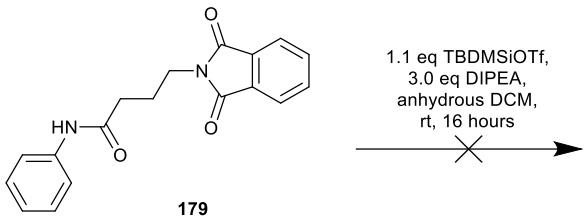
4.9. Cyclisation of Amides Appended Imides

The question was raised if other functional groups at the C1 position could be tolerated, rather than methyl esters or carboxylic acids.[163] To this end, it was decided that aniline would be reacted with **123a** to afford the benzyl amide that could then be subjected to silyl mediated ring closure.



Scheme 4.13. Amide formation of **123a** using aniline

It was decided that aniline would make the perfect amide as the electron withdrawing effect from the aromatic ring would mean that the amide carbonyl would act more like a ketone than a typical amide. It was assumed that with the above amide in place, ketene acetal formation would still occur with H2 protons acidic enough to form the required enol. To this end, **179** was subjected to our standard silyl cyclisation conditions, but was not successful.

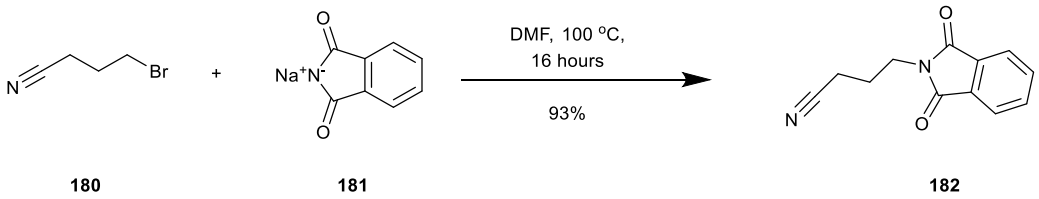


Scheme 4.13. Attempted cyclisation of **179**

We hypothesised that this style of reaction may be possible, as it has been shown that amides can undergo ketene acetal formation and subsequent Mukaiyama additions[224] but due to time constraints this chemistry was not further pursued.

4.10. Cyclisation of Nitrile Appended Imides

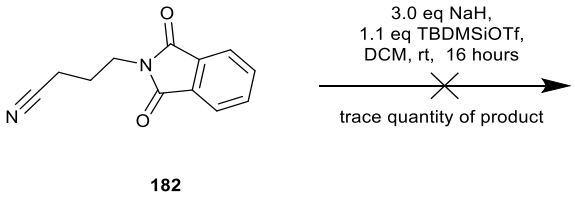
Nitriles were considered in an attempt to expand on the limited functionality tolerated for silyl mediated cyclisations. Synthesis of the required phthalimide was required, and as a synthetic route for **182** had already been published,[247] we opted to follow this method (Scheme **4.14**).



Scheme 4.14. Synthesis of **182**

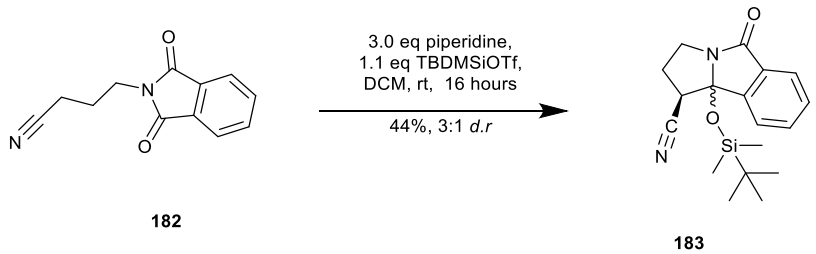
182 was synthesised by heating **180** with sodium phthalimide at 100 °C overnight, followed by purification using flash column chromatography to afford the desired product.[247]

With **182** in hand, it was subjected to TBDMSiOTf mediated cyclisation. However, a concern that DIPEA would not be nearly nucleophilic enough to facilitate this reaction, so sodium hydride was used as the base in question (Scheme **4.15**).



Scheme 4.15. Attempted cyclisation of **182** using NaH

The crude mixture was worked-up and analysed by ^{1}H NMR spectroscopy, and although this showed a trace quantity of potential product, there was not enough to warrant a purification. On review of the above conditions, it is more than possible that the formation of the sodium salt after the attack of the hydride is resulting in the lack of reactivity. Hence, a base which would be nucleophilic enough to facilitate the deprotonation while also removing the possibility of salt formation was needed. To this end, piperidine was chosen *in lieu* of NaH (Scheme **4.16**).



Scheme 4.16. Cyclisation of **182** to afford the nitrile containing tricyclic **183**

It was very rewarding to see the formation of **183**, initially confirmed *via* LRMS and ^{1}H NMR spectroscopy on the crude product. **183** appeared to be very stable and was able to be purified using flash column chromatography to afford an inseparable mixture of diastereomers. It was apparent from the ^{1}H NMR spectrum that a mixture of diastereomers were present, with separate environments for the silyl methyl groups, as well as the ^{t}butyl groups. It was unexpected to see the different chemical shifts for each isomer of **183** (See Table **4.7**). There was a large chemical shift seen for H2 in the minor isomer, shifting very upfield, that was confirmed *via* HSQC NMR spectroscopy. The ^{13}C NMR spectra for both isomers were very similar to other compounds already highlighted throughout this thesis, with the exception of the nitrile carbon, with the major *trans*- isomer at 117.31 ppm and the minor *cis*- isomer at 121.67 ppm.

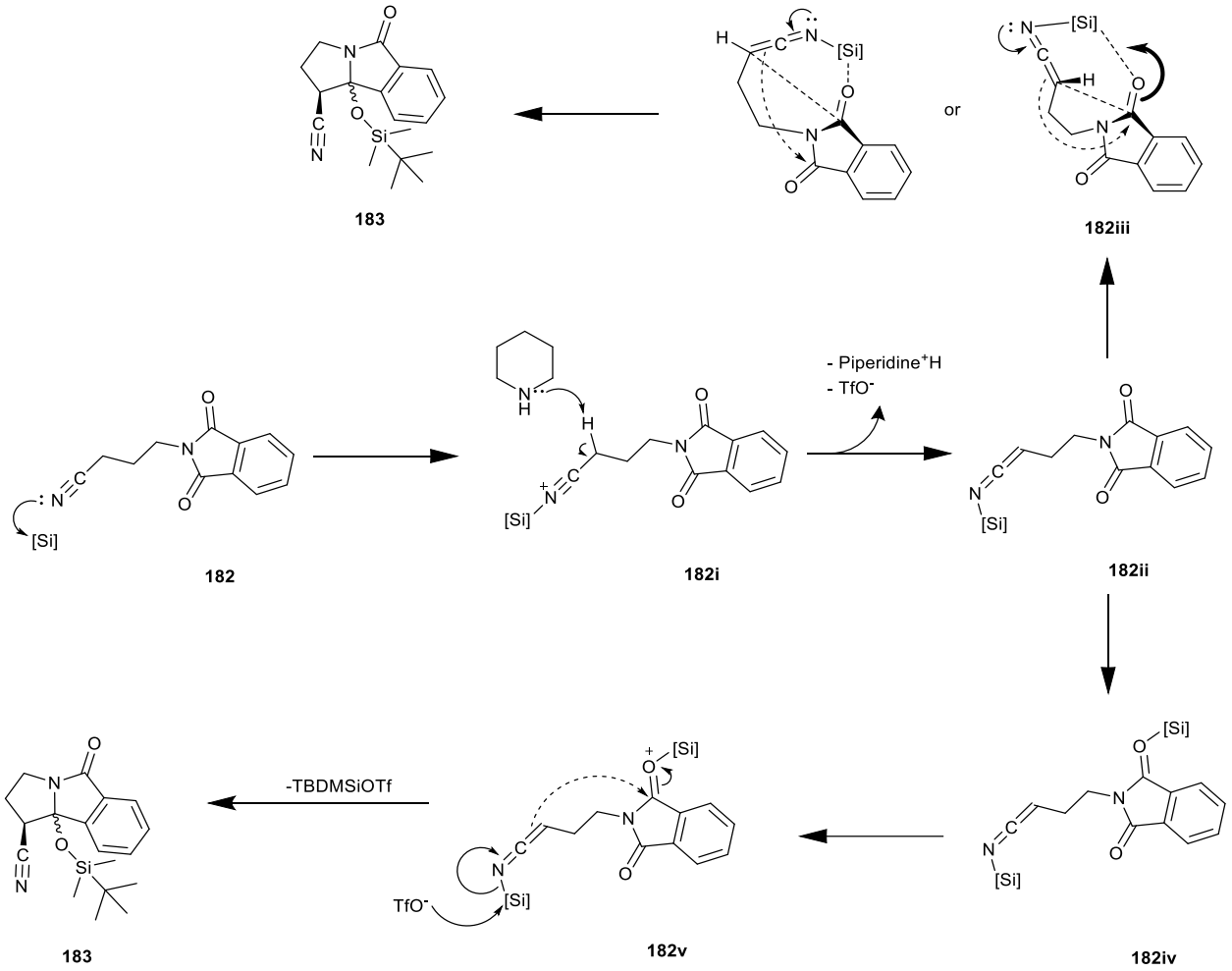
It should be noted that a similar compound has been previously reported in the literature, as the trimethylsilyl ether. It should also be mentioned that this variant was synthesised using irradiation of compound **154** (Section **3.6**) in the presence of acrylonitrile with the reported spectroscopic data in agreement with those reported in this thesis (see Table **4.7**).[248]

Table 4.7. Comparison for the characteristic peaks for the major and minor isomers of **183**

	^{1}H NMR peaks (ppm)							
	H4$_A$	**H4$_B$**	**H3$_A$**	**H3$_B$**	**H2**	**Si-CH$_3$**	**Si-CH$_3$**	**^{t}butyl**
Major	3.93	3.50	2.89	2.62	3.38	-0.08	-0.48	0.82
Minor	3.93	3.84	1.93	1.93	1.93	0.17	0.09	0.96

Attempts to crystallise **183** to obtain either isomer unfortunately were not successful.

It is suggested that the mechanism for this cyclisation is analogous to that already proposed for the methyl ester and may also go *via* the two methods; a mechanism has been proposed in Scheme **4.17**.



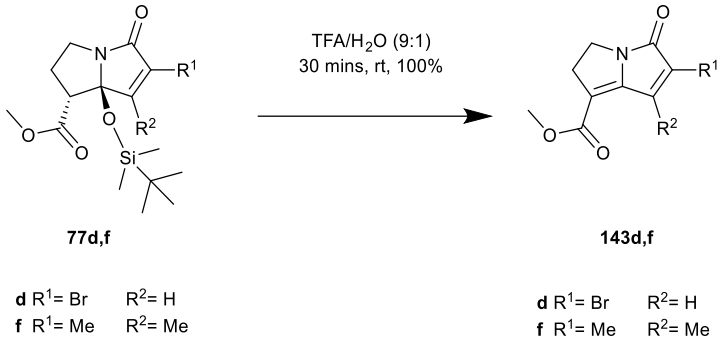
Scheme 4.17. Proposed mechanism for the cyclisation of **183**

4.11. Pyrrolidinone Synthesis

Our interest in the formation of unsaturated bi- and tricyclic systems, specifically for possible antibacterial and anticancer agents has been earlier discussed. It was also assumed that due to the flatness and delocalisation of electrons from the alkene and aromatic ring with the addition of the push-pull systems, these compounds had the potential to be a novel class of non-covalent binding DNA intracalators.[70] Another reason to pursue this avenue of exploration was the formation of the alkene *via* the acidic elimination of the oxysilyl moiety which was both rapid, efficient and clean with no need for further purification and gave the option for further chemistry in manipulating the

alkene. Alternatively, direct synthesis of the imide starting material was possible *via* cyclisation using 3.0 equivalents of TBDMSiOTf.

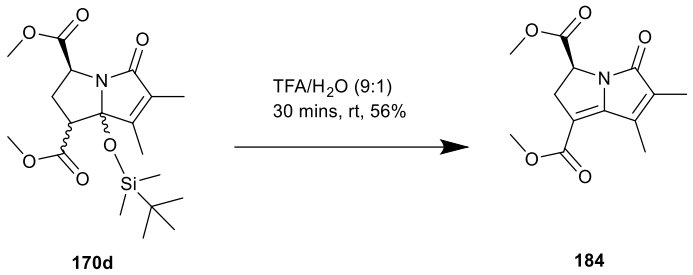
To this end, **77d,f** were dissolved in a mixture of TFA/H_2O (9:1) and left stirring at room temperature for 30 minutes with the solvent being removed and the compounds dried using reduced pressure (Scheme **4.18**).



Scheme 4.18 TFA elimination of **77d,f**

Over the first few minutes of the reaction, the starting material started to dissolve into the solvent mixture that slowly turned a strong yellow colour over the course of the reaction. After concentration of the reaction mixture, each product was readily soluble in deuterated chloroform with the ^{1}H NMR spectrum showing that only the desired product remained, with the expected eliminated silyl alcohol not present. The ^{1}H NMR spectra for these compounds were simple, for example, with **143e**, a singlet at 3.80 ppm for the ester, two triplets at 3.76 and 3.28 ppm for H4 and H3 respectively with the alkene alkyl groups at 2.25 and 1.93 ppm. It should also be noted that the melting points for both of these compounds are much higher than their silyl containing counterparts, typically over 100 °C more.

Subjecting **170d**, which contained a mixture of diastereomers, to the same conditions would remove the stereochemistry at the C1-C9 positions by the introduction of the alkene, giving only a single product.



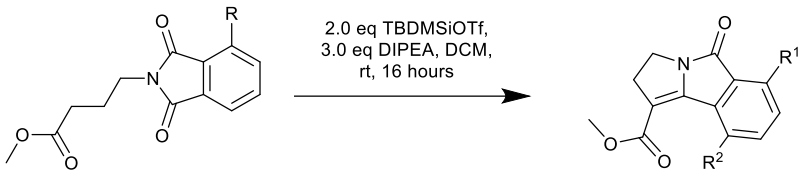
Scheme 4.19. TFA elimination of **170d**

^{1}H NMR spectroscopy was used to confirm the presence of **184**, with differences seen between **184** and **143f**, chiefly the unique environments of the three aliphatic protons with H4 reported as a double doublet at 4.66 with H3 now split, reported at 3.62 and 3.26 ppm. This was then confirmed using HSQC NMR spectroscopy. The lower yield was a result of the starting material containing impurities from previous reaction steps, namely the uncyclised maleimide due to co-elution, hence **184** was purified using flash column chromatography using a solvent mixture of 30% ethyl acetate in dichloromethane.

It is worth making a note about the unfamiliar and unusual solvent mixture used to purify these compounds. It was already mentioned in Chapter II, but due to insolubility of these saturated systems, dichloromethane is used for solubility with ethyl acetate used for polarity needed to get these compounds to move on the column. Alternatively, trituration could be used as a means of purification, however, this is dependent on solubility.

4.11.1. Direct Synthesis of Phthalic Based Pyrrolidinone from Phthalimides

It was previously discussed (Chapter **3**, Section **3.1.1**) that **157** could be directly synthesised from the starting phthalimide using 3.0 equivalents of TBDMSiOTf. This was then later refined (Chapter **3**, Section **3.3.2**) with 2.0 equivalents being successful in achieving the same outcome (Scheme **4.20**).



137a,b,e,j

a R^1= H, R^2= H
b R^1= NO_2, R^2= H
f R^1= F, R^2= H
j R^1= OBn, R^2= H

146a,b,f,j and **185**

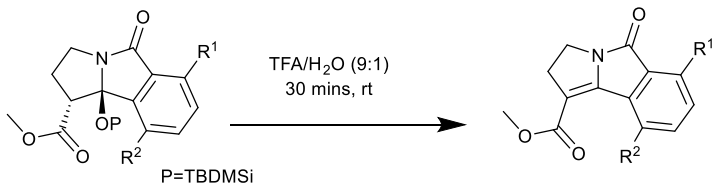
a	R^1= H,	R^2= H	100%
b	R^1= NO_2,	R^2= H	100%
f	R^1= F,	R^2= H	90%
j	R^1= OBn,	R^2= H	89%
185	R^1= H,	R^2= F	10%

Scheme 4.20. Direct synthesis of the saturated tricyclic system from **137a,b,e,j**

These compounds were synthesised using previously discussed methodology and techniques, with the only difference being the amount of silyl triflate used. However, after work up, the organic layer was concentrated using reduced pressure, with the resulting oil being triturated using pet-ether 40:60 followed by ethyl acetate. It was not a surprise to see that this reaction was also completely regioselective, followed by *in situ* desilyloxylation to afford the saturated systems.

When analysing the ^{1}H NMR spectrum for **146f** and **185**, it was possibly to identify the minor isomer with a ratio of 1.0: 0.1, however due to the similarity of the proton environments and the concentration of the samples, being able to fully characterise the minor isomer was not possible.

The TFA elimination was then carried on **144a,b,f,j** and **171** to give quantitative conversions to the desired products, with no purification required (Scheme **4.21**). **144f** and **171** were reacted as a mixture and were unable to be seperated after elimination, hence yield displayed in Figure **4.21** represents the conversion from the starting isomer for each compound.



144a,b,f,j and **171**

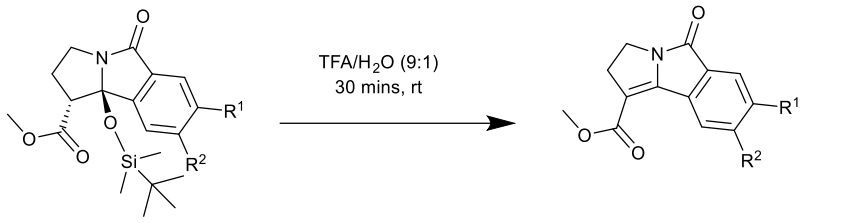
a R^1= H, R^2= H
b R^1= NO_2, R^2= H
f R^1= F, R^2= H
j R^1= OBn, R^2= H
171 R^1= H, R^2= F

146a,b,f,j and **185**

a	R^1= H,	R^2= H	100%
b	R^1= NO_2,	R^2= H	100%
f	R^1= F,	R^2= H	100%
j	R^1= OBn,	R^2= H	100%
185	R^1= H,	R^2= F	100%

Scheme 4.21. TFA elimination of **144a,b,f,j** and **171**

The remaining substituted pyrrolizidines were also subjected to the same conditions (Scheme **4.22**.). Where possible single isomers were taken forward, but if the silyl containing starting material was inseparable from the previous purification, the mixture of regioisomers was used and separation was attempted *via* flash column chromatography.



172a-j

a R^1= **NO_2**,	R^2= H	
b R^1= H,	R^2= **NO_2**	
c R^1 = **Br**,	R^2= H	
d R^1= H,	R^2= **Br**	
e R^1= **F**,	R^2= H	
f R^1= H,	R^2= **F**	
g R^1= **COOMe**	R^2= H	
h R^1= H	R^2= **COOMe**	
i R^1= **CH_3**	R^2= H	
j R^2= H	R^2= **CH_3**	

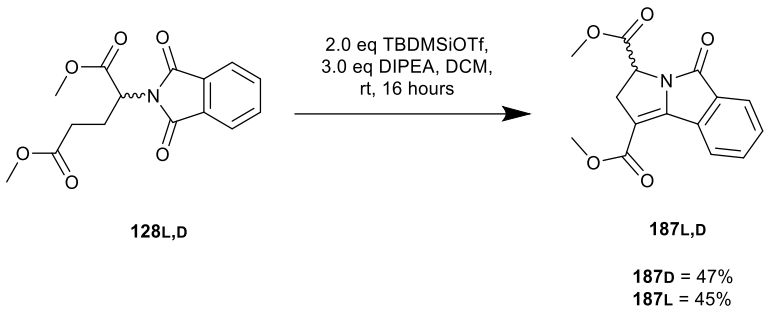
186a-j

a R^1= **NO_2**,	R^2= H	100%
b R^1= H,	R^2= **NO_2**	92%
c R^1= **Br**,	R^2= H	100%
d R^1= H,	R^2= **Br**	100%*
e R^1= **F**,	R^2= H	100%
f R^1= H	R^2= **F**	98%
g R^1= **COOMe**,	R^2= H	100%
h R^1 = H,	R^2= **COOMe**	100%
i R^1= **CH_3**,	R^2= H	100%
j R^1= H,	R^2= **CH_3**	100%

Scheme 4.22. TFA elimination to afford **186a-j**

186g,h and **186i,j** were the only mixtures that were inseparable either prior to or after TFA elimination of the silyl groups. The lower yield for **186b** was a result of starting maleimide remining that had co-eluted throughout the cyclisation steps, hence **186b** was purified using flash column chromatography with a respectable yield after collection. **186d** was anomalous as the crude ^{1}H NMR spectrum did show quantitative conversion through to the saturated system, but co-elution of the desired product along with the maleimide made it difficult to determine the isolated yield although ^{1}H NMR showed mostly the starting maleimide. **186g,h** was also difficult to determine, as during the characterisation of **186g,h**, desilyloxylation was seen in the ^{1}H NMR spectrum. However, after treating the mixture of the saturated and unsaturated systems with TFA for 30 minutes, complete conversion was seen. It should be noted that to prevent this, samples were either run in deuterated methanol (MeOD) or with the deuterated chloroform filtered through calcium carbonate prior to use.

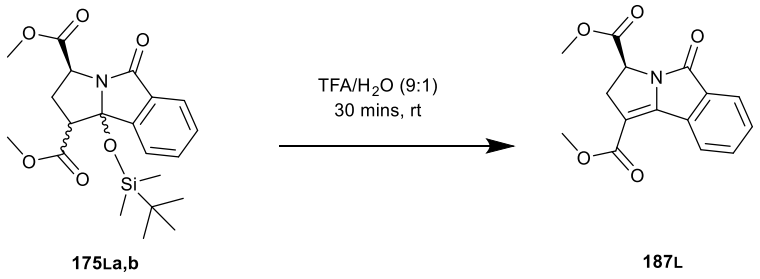
It was found that, as with **137a**, direct synthesis from the phthalimide to the unsaturated system was seen when using 3.0 equivalents of TBDMSiOTf (Scheme **4.23**).



Scheme 4.23. Direct synthesis from the phthalimide to the unsaturated system.

After purification and isolation of the desired products, determination of the optical rotation of both compounds gave values of +69.9 and -63.0 for **187D** and **187L** respectively, suggesting that the stereochemistry at the C4 methyl ester had been retained throughout. It was interesting to see that unlike the substituted phthalimides, these reactions gave lower yields with unreacted starting material still being seen and removed by purification.

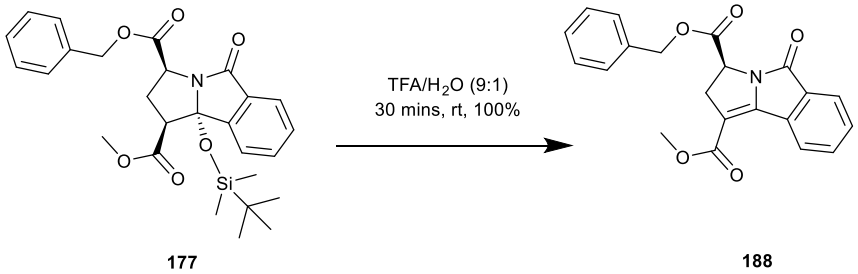
Alternatively, the silyl-containing variant could be synthesised *via* TFA elimination to afford the desired product quantitively, but if the silyl-containing product is afforded using the previous reaction, the uncyclised phthalimide co-elutes and can be removed *via* flash column chromatography at this stage. This makes it difficult to determine the recovered yields as the starting materials were impure (Scheme **4.24**).



Scheme 4.24. TFA elimination of **175La,b**.

For the sake of simplicity, only the L- variant has been shown, but should be noted that identical results were seen for **175Da,b**. For the L– variant, a recovered yield of 61% based of the weight of the crude starting mixture, with the D- variant affording 43%.

The remaining pyrrolizidine with a C4 substituent to be subjected to TFA elimination was **177** (Scheme **4.25**).

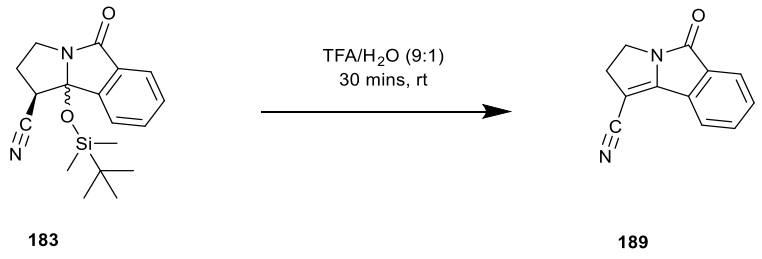


Scheme 4.25. TFA elimination of **177**

177 reacted as well as all other compounds tested to this point, giving complete conversion to the unsaturated tricyclic system, with no purification needed. From the ^{1}H NMR spectrum, the benzylic protons showed asymmetric chemical shift difference than seen with **177**. **188** was also tested with specific rotation $[\alpha]_{D}^{25}$= -63.0 which is very similar to the methyl ester variant **187L**, once again suggesting that the chiral C4 centre had been retained through this reaction.

4.11.2. Synthesis of Saturated Nitrile Containing Pyrrolidones

183 was an interesting compound to subject to TFA elimination of the silyloxy moiety, as it is the only example where the C1 methyl ester and silyl moiety are both *cis* and *trans* to one another. To this end, **183** was stirred in TFA/H_2O (9:1) for 30 mins with some surprising results (Scheme **4.26**).



Scheme 4.26. TFA elimination of **183**

Firstly, this reaction did not go to completion, with the ^{1}H NMR spectrum showing both the starting major and minor isomers remained. However, it was more surprising to see that the TFA elimination reaction had only affected the major isomer.

When consulting the ^{1}H NMR spectrum of **183**, paying particular interest to the silyl methyl groups, resonance for the minor isomer were found at 0.17 and 0.09 ppm with the major isomer showing at -0.08 and -0.48 ppm, integrating at 1:1:3:3, hence giving us the *d.r.* of 3:1 in favour of the major isomer. The ^{1}H NMR spectrum post-cyclisation shows both isomers remaining, with identical chemical shifts, with the peaks now integrating at 3:3:1:1, giving us a *d.r.* of 3:1 in favour of the *cis* isomer. Now, it is not possible to completely state that the *cis* isomer is unable to undergo TFA elimination, but it is heavily supported from this result. Moreover, since it was stated that this reaction is likely to proceed *via* E2 *syn* β-elimination, this outcome helps to cement this hypothesis, with E2 *anti* β-elimination being highly unfavourable or impossible using the above conditions.

As this result was highly unexpected, an attempt to crystallise the impure mixture was not successful. **189** did crystallise from dichloromethane using standard vapour diffusion technique with pet-ether 40:60 being used as the co-solvent with the structure acquired displayed in Figure **4.9**.

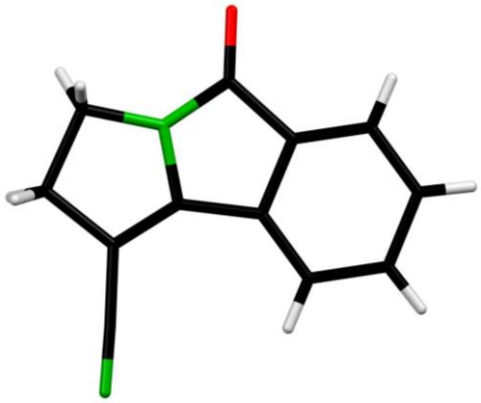


Figure 4.9. Single x-ray crystallographic image of **189**

4.12. Summary of Chapter IV

This chapter reports the assignment and characterisation of both cyclised maleimides and phthalimides and accounts for the regio- and diastereoselectivity of these reactions. This chapter also explored the possibility of the presence of bulky substituents at the C4 position, and the affect this had on controlling the diastereomer ratio of cyclisations. A small investigation was undertaken that found that any R group on the alkene hinders iodolactonisation of the maleic pyrrolizidines. The later part of the chapter discussed benzyl esters as a versatile substitution, with amides failing completely. However, it was then found that nitriles could be used to give a diastereomeric mixture of the *cis* and *trans* isomers not previously seen with these systems. lastly, TFA mediated silyloxy eliminations were explored with great success.

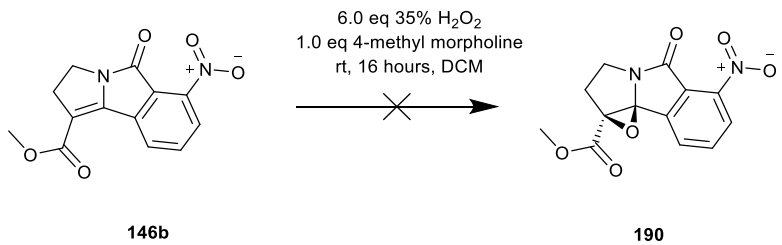
Chapter V: Alkene Manipulation, Suzuki, Hydrogenation and CH-Activation

This chapter will discuss the manipulation of the alkene of the previously synthesised saturated tricyclic systems with the intention to increase solubility and functionality. An emphasis will be placed on elaboration of the bromo-containing pyrrolizidine ring by attempting different coupling reactions. The final section of this chapter will introduce functionality at the C3 position of the tricyclic pyrrolizidine rings by attempting to use β- CH arylation to afford a collection of biologically interesting compounds that could then be used in a SAR study.

5.1. Epoxide Formation

Manipulation of the alkene might be expected to alter the solubility by removing the inherent flatness of the system, while also introducing functionality to enhance polarity. To this end, epoxidation of the alkene was explored.

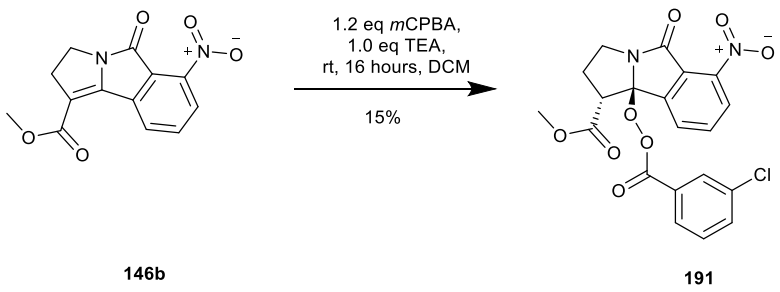
Due to the similarities of the compounds synthesised in this thesis compared to past work conducted in the Moloney group that featured lactams, there was some literature precedent,[249] using alkene-containing lactams with 35% aqueous hydrogen peroxide in the presence of 4-methyl morpholine.[250] On the back of this, **146b** was subjected to epoxidation using these reported conditions (Scheme **5.1**).



Scheme 5.1. Attempted epoxidation of a nitro-pyrrolizidinone in the presence of H_2O_2 and 4-methyl morpholine

After concentration of the organic layer, the crude mixture was analysed using ^{1}H NMR and LRMS spectroscopy, and this did not show any possible product. The above conditions were replicated using sodium hydroxide *in lieu* of 4-methylmorpholine with the same results being seen.

In an attempt to move away from hydrogen peroxide, *m*CPBA was used. **146b** was dissolved in dichloromethane with 1.2 equivalents of *m*CPBA and left stirring for 16 hours at room temperature. After this period, the reaction was checked using ^{1}H NMR spectroscopy and this did not suggest that any product had been formed. It was decided that incorporation of an organic base may help this reaction to proceed, hence 1.0 equivalent of triethylamine was added with the resulting reaction mixture left for a further 16 hours stirring at room temperature. The reaction was analysed using prep TLC that did show the emergence of a new spot, so the reaction was stopped to afford the unexpected product shown in Scheme **5.2**.



146b **191**

Scheme 5.2. Attempted epoxidation of **146b**

It was readily apparent that the isolated product was not the unreacted pyrrolizinone **146b**, and there were new splitting patterns of the H4 and H3 protons in addition to the introduction of a new peak at 5.32 ppm. It was more intriguing to see that H4 protons were now observed as a triplet of doublets at 3.98 ppm with H3 as a quartet at 2.44 ppm. The aromatic region of **191** was very clear and defined, with a total of 7 protons at 8.06, 7.93, 7.87, 7.52 and 7.36 ppm. It was apparent from the LRMS that a chlorine was present, and the ^{13}C NMR spectrum confirmed the presence of 7 aromatic carbon peaks that contained protons, with an additional 4 more peaks suggesting quaternary aromatic carbons. However, the most significant observation was the 4 potential carbonyl groups. The aliphatic region of the ^{13}C NMR spectrum had peaks at 70.98, 52.87, 35.30

and 29.59 ppm. It was at this point that *m*CPBA had indeed added into the alkene and remained present even after work-up and purification.

HSQC NMR spectroscopy confirmed that the proton at 5.32 was situated on the carbon peak at 70.98 ppm. The protons at 3.98 were confirmed as C4 with the carbon peak at 35.30, with H3 at 2.44 ppm with the corresponding carbon observed at 29.59 ppm. The question was how it could be shown that the peroxy adduct was in fact at the C13 position, rather than the C2 position. When looking at the COSY NMR spectrum, couplings were seen from H3 to H4 as expected, while also to H2. H4 only saw H3 with H2 only seeing H3. When consulting the HMBC NMR spectrum, correlations could be seen from H2 to both C3 and C4. We concluded from the data that if the proton was indeed at the C13 position, these specific correlations would not be seen. The next essential task was to assign the 4 peaks between 169.50 and 162.50 ppm. Firstly, it was seen that the peak at 169.59 ppm showed strong correlations to H2, as well as the C1 methyl ester and H3 and therefore was assigned as C1 carbonyl. The other three peaks in question that were reported at 165.66, 164.60 and 162.80 ppm were assumed to be for the C6 lactam, peroxyacid carbonyl as well as C13 quaternary carbon, however clear assignment of these carbons would prove to be very challenging. What made it trickier was that H4 saw a correlation to two different peaks, at 165.66 and 162.70 ppm, with H2 seeing correlations to the peak at 164.60 as well as C1 carbonyl. It was assumed that the peroxy moiety would be *trans* to the methyl ester and hence *cis* to H2 proton, so H2 may also be close enough in space to see the peroxy carbonyl. However, a similar argument was made for H4, as the additional bonds throughout the peroxy adduct may extend over the ring residing closer to H4. As there are similar interactions with the ^{t}butyl group to the H4 protons, it was concluded that the peak at 165.49 is for the C6 lactam with the peak at 162.70 ppm that of the peroxy carbonyl. Therefore, this leaves the peak at 164.60 as C13 quaternary carbon. The HBMC spectrum can be seen in Figure **5.1.**

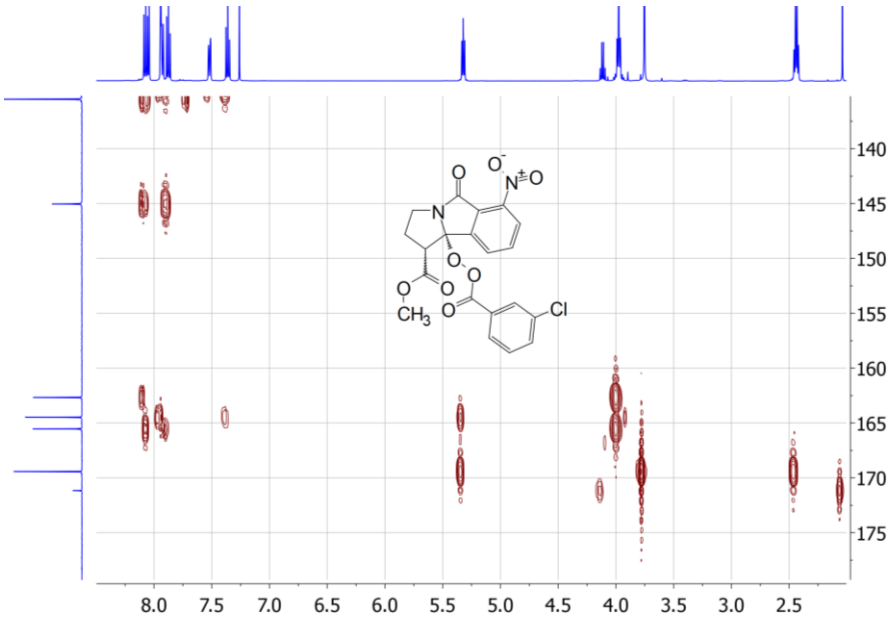
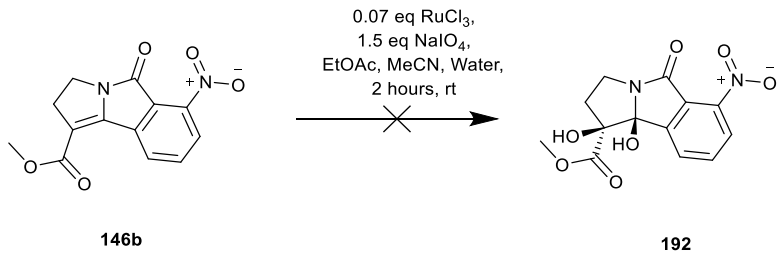


Figure 5.2. HMBC NMR spectrum for **191**

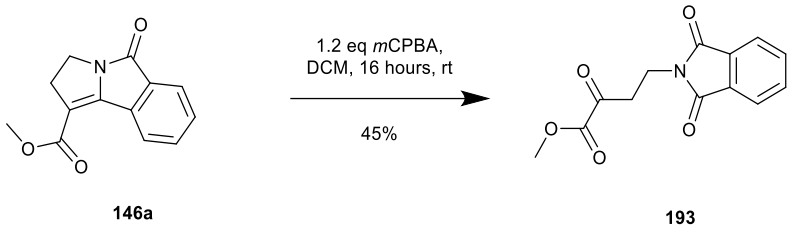
In an attempt to further explore the reactivity of **146b**, dihydroxylation of the alkene was considered since it would simultaneously increase the solubility while also increasing the attractiveness of a drug-like molecule with the hope to see biological activity. Sharpless asymmetric dihydroxylation reaction[251,252] using osmium tetroxide has been a powerful tool in organic synthesis, although it is of high cost and reagent toxicity. A milder reagent, namely ruthenium trichloride has been shown to give rapid dihydroxylations,[253] and hence **146b** was subjected to ruthenium trichloride dihydroxylation reaction (Scheme **5.3**).



Scheme 5.3. Attempted asymmetric dihydroxylation of **146b**

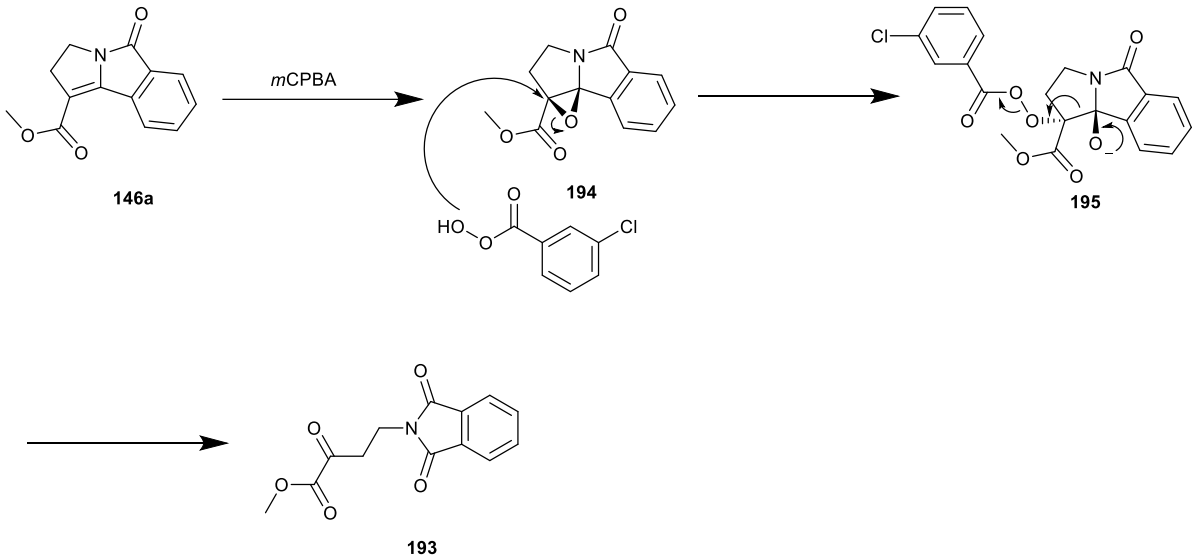
Even though it has been reported that these reactions proceed in minutes,[253] the above reaction was left stirring in the biphasic mixture for 2 hours. After this period LRMS showed no trace of the desired product. The reaction was worked-up as reported in the literature, with the organic solvent being analysed using ^{1}H NMR spectroscopy but there was no sign of any product being formed.

It was felt that the nitro group may be hindering these reactions resulting from the electron withdrawing effect of this group interfering with the electronic state of the alkene, so the non-substituted variant **146a** was examined. **146a** was dissolved in dichloromethane with *m*CPBA and left stirring for 16 hours at room temperature with completely unexpected results (Scheme **5.4**).



Scheme 5.4. Attempted epoxidation of **146a**

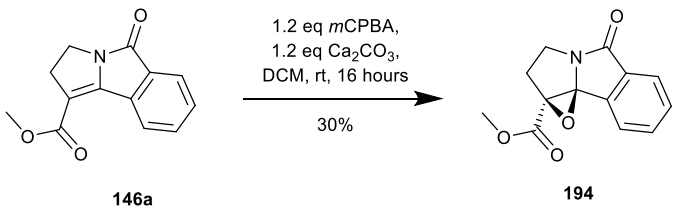
After consulting the ^{1}H NMR spectrum, it was apparent that the reaction had proceeded very differently to expected, due to the aromatic region showing two unique environments for the aromatic protons as a pair of double doublets at 7.83 and 7.72 ppm that was reminiscent of the uncyclised phthalimide compound. However, the aliphatic region showed a pair of triplets at 4.05 and 3.25 ppm with a singlet for the C1 methyl ester at 3.88 ppm. The ^{13}C NMR spectrum also reinforced this, with two aromatic regions being observed resulting from the symmetry of **193**, in addition to only three aliphatic regions being seen. The carbonyl region showed three distinct peaks, one peak at 169.81 ppm and another at 168.14 nearly double the intensity, nearly identical to the phthalimide-based compounds. Interestingly, another peak was seen at 191.25 ppm, commonly associated with aldehydes or ketones. As the ^{1}H NMR spectrum gave no hint of an aldehyde being present, the assumption that **193** containing a ketone led to the structure proposed in Scheme **4**. In addition to this, LRMS and HRMS was used to find the mass ion of **193**.



Scheme 5.5. Proposed mechanism for the formation of **193**

It is proposed that the epoxide is formed, but due to the relative acidity of *m*CPBA,[254] nucleophilic addition to C2 results in the opening of the epoxide. As seen in Section **3.4**, forming the oxygen anion results in a ring opening, but in this case, the charge is pushed through to the peroxy adduct resulting in the formation of the ketone and benzoic acid as the by-product.

The last attempt was inspired by the result seen for **146b** as this reaction, as well as the result seen in Scheme **5**, heavily suggested that addition to the alkene was occurring, even if the desired epoxide was not being seen. Calcium carbonate was added, and the reaction was repeated (Scheme **5.6**).



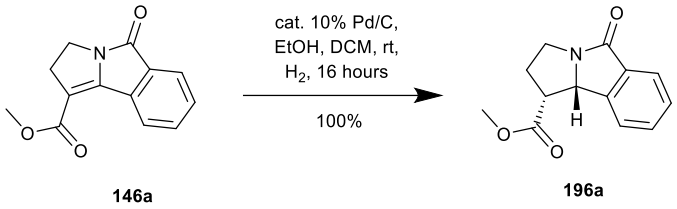
Scheme 5.6. Successful epoxidation of **146a**

It was a relief to see that **194** was obtained, and instantly recognisable from the ^{1}H NMR spectrum. H3$_{A/B}$ and H4$_{A/B}$ were now observed in singular environments for each proton supporting the hypothesis that the addition of the epoxide would introduce kink in the system.

5.2. Hydrogenation of the Alkene Containing Pyrrolidones

After the limited success seen with attempting to manipulate the alkene *via* epoxidations and dihydroxylation reactions, we aimed to explore the possibility of other chemistry that could be reliably tolerated on these unique systems.

Hydrogenation is a powerful tool in organic chemistry that has been vastly developed, with many different catalyst systems developed,[255–258] as well as the applicability to numerous functional groups.[259–261] Initially the solvent mixture was a strong yellow colour but was found that during the course of the reaction, the mixture turned colourless. The reaction was tested by LRMS and showed complete conversion to **196a** without any trace of **146a** remaining. After the solvent was removed, it was clear that **196a** was afforded in quantitative yields (Scheme **5.7**).

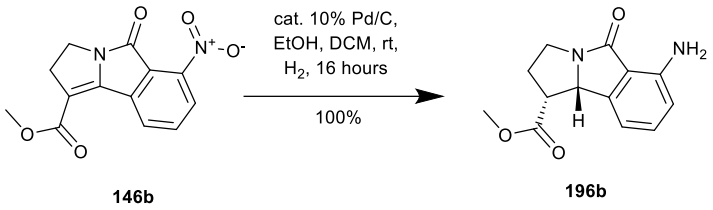


Scheme 5.7. Hydrogenation of **146a**

196a showed an increase solubility over **146a**, easily being dissolved in methanol in addition to dichloromethane. The ^{1}H NMR spectrum was very clear and clean, with the newly inserted proton at the C13 position observed as a doublet at 4.97 ppm, much higher than expected. H4$_{A/B}$ were observed at 3.98 and 3.44 ppm respectively with H2 now seen as a triplet of doublets at 3.34 ppm. For the ^{13}C NMR spectrum, it was interesting to see that the C1 methyl ester and C6 lactam had near-identical chemical shifts at 171.63 and 171.60 ppm. The only major difference seen for **196a** compared to the similar silyl containing compounds was that C13 was much further upfield at 66.31 ppm as expected.

In order to check that this chemistry would be applicable to other similar systems, such as **146b** (Scheme **5.8**). We were not unmindful to the possibility of double reduction, in fact such a process

would be welcomed it as this would introduce a location for further functionalisation, such as amide formations.



Scheme 5.8. Successful double hydrogenation of the alkene and nitro groups

The structure of **196b** was initially confirmed by LRMS that gave the desired mass ion, and further confirmed using HRMS. The ^{1}H NMR spectrum was as expected, and comparable to that seen for **196a**. An attempt to recrystallise **196b** was successful by dissolving **196b** in the minimal quantity of dichloromethane with pet-ether 40:60 used as the co-solvent *via* standard vapour diffusion techniques (Figure **5.4**).

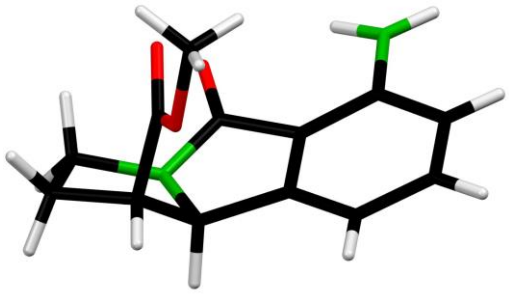
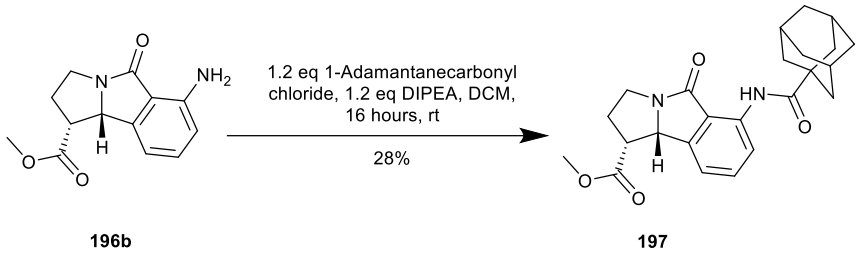


Figure 5.3. Single x-ray crystal of **196b**

It was interesting to see that in the x-ray structure obtained for **196b**, the -NH_2 group is in the plane of the aromatic ring, unlike the nitro group of its precursor (Figure **4.3**, Section **4.5**).

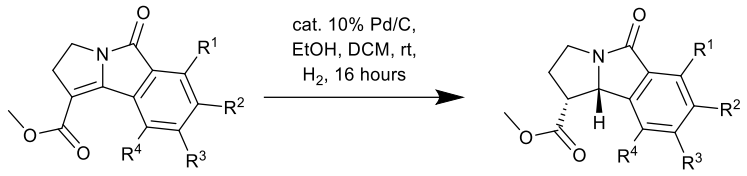
With **196b** in hand, an attempt to introduce an amide was made, in particular using 1-adamantanecarbonyl chloride (Scheme **5.9**) as this group had given some of the highest levels of antibacterial activity seen for tetramates previously synthesised in the Moloney group.[262]



Scheme 5.9. Amide formation at the C8 amine of **196b**

It was rewarding to see that **196b** could be used to form amides, albeit in low yields, and another indication of the unusual steric hindrance of this system. However, when benzyl chloride-based reagents were used, no products were seen, suggesting that the aniline suffers from low nucleophilicity.

The chemistry shown in Scheme **5.8** was then extended to the collection of pyrrolidinones previously synthesised in Chapter **IV**, Section **4.5**. When possible, single regioisomers were hydrogenated unless the mixture was inseparable from previous reaction steps (Scheme **5.10**) with the yields shown in Table **5.1**.



146a R^1= H, R^2= H, R^3= H, R^4= H,
146b R^1= **NO_2**, R^2= H, R^3= H, R^4= H,
186a R^1= H, R^2= **NO_2**, R^3= H, R^4= H,
186b R^1= H, R^2= H, R^3= **NO_2**, R^4= H,
146e R^1= **F**, R^2= H, R^3= H, R^4= H,
185 R^1= H, R^2= H, R^3= H, R^4= **F**,
186e R^1= H, R^2= **F**, R^3= H, R^4= H,
186f R^1= H, R^2= H, R^3= **F**, R^4= H,
146j R^1= **OBn**, R^2= H, R^3= H, R^4= H,
186i R^1= H, R^2= **CH_3**, R^3= H, R^4= H,
186j R^1= H, R^2= H, R^3= **CH_3**, R^4= H,

a R^1= H, R^2= H, R^3= H, R^4= H,
b R^1= **NH_2**, R^2= H, R^3= H, R^4= H,
c R^1= H, R^2= **NH_2**, R^3= H, R^4= H,
d R^1= H, R^2= H, R^3= **NH_2**, R^4= H,
e R^1= **F**, R^2= H, R^3= H, R^4= H,
f R^1= H, R^2= H, R^3= H, R^4= **F**,
g R^1= H, R^2= **F**, R^3= H, R^4= H,
h R^1= H, R^2= H, R^3= **F**, R^4= H,
i R^1= **OH**, R^2= H, R^3= H, R^4= H,
j R^1= H, R^2= **CH_3**, R^3= H, R^4= H,
k R^1= H, R^2= H, R^3= **CH_3**, R^4= H,

Scheme 5.10. Hydrogenations to afford **196a-k**

Table 5.1. Comparison of the yields for **196a-k**

Compound Name	Yield %
196a	100
196b	100
196c	100
196d	100
196e	50
196f	14
196g	100
196h	100
196i	86
196j	95
196k	95

It was rewarding to see great success in the hydrogenations for all compounds tested, with **196b-d** showing complete hydrogenation of both the alkene and the nitro group. **186d** was not completely pure as the starting material, as it contained a small percent of **186c**, but the ^{1}H NMR spectrum showed both compounds were completely reduced. **186e,f** appeared to give poor yields but it should be stated that when analysed using prep TLC, it appeared that both those compounds could be separated and isolated. To this end, **186e,f** was purified using flash column chromatography (see Experimental for details) with each product successfully isolated and separated, with any impure fractions discarded, hence the apparent drop in yield, but when looking at the ^{1}H NMR spectrum prior to purification, complete reduction was seen. It should also be noted that the fluorine group appeared to remain intact for all compounds. In addition to NMR spectroscopy for the analysis of the major and minor products collected, the structure of **196f** was also confirmed *via* x-ray analysis, recrystallised from the minimal quantity of dichloromethane with pet-ether 40:60 as the co-solvent (Figure **5.3**). Once again, double reduction of **146j** that involved the debenzylation at the C8 oxygen afforded the phenyl substituent and gave access to a

wide range of chemistry that could be used to introduce functionality at this position. For **196j,k**, the mixture was analysed using prep TLC that showed the mixture to be inseparable, so the yield displayed in Table **5.1** was calculated for the conversion of both products from the starting material.

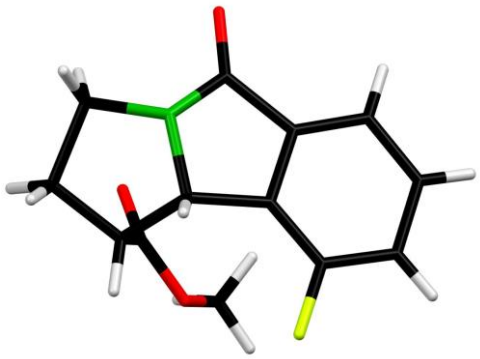
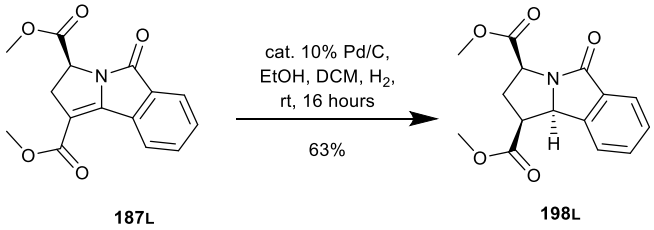


Figure 5.4. Single x-ray image for **196f**

187D,L were subjected to the same hydrogenation conditions (Scheme **5.11**) with some rather unexpected results being seen. As with other examples when both D- and L- have been used, for simplicity, only the L- variant will be shown and discussed but should be noted that identical results were seen for D-.



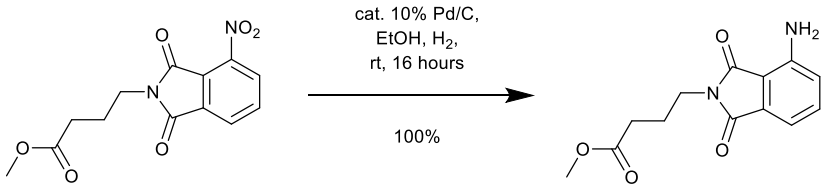
Scheme 5.11. Hydrogenation of **187L**

It was surprising to see that in the ^{1}H NMR spectrum, only a single diastereomer was present and instantly recognisable. Firstly, the proton at C13 was reported as a single doublet, with H4 proton also as a single double doublet, secondly, both the C1 and C4 methyl ester were reported as singlets with no other additional peaks being seen in this region. This was also reinforced when inspecting the ^{13}C NMR spectrum. In order to accurately assign the stereochemistry of **198L**, nOe experiments were conducted. Initially, H4 was irradiated that showed clear nOe interactions to H13, H2, and

$H3_{A,B}$. When H2 was irradiated, strong interactions were seen to H13 as expected due to the nature of *cis* addition during hydrogenation, with interactions seen to H4 and $H3_{A,B}$. When H13 was irradiated, nOe interactions were only seen to H2 and weakly to H4 and $H3_B$ at 2.86 ppm. From these data, both methyl esters are assigned as being *cis* to each other. It should be noted that the same conclusion was seen for **198D**.

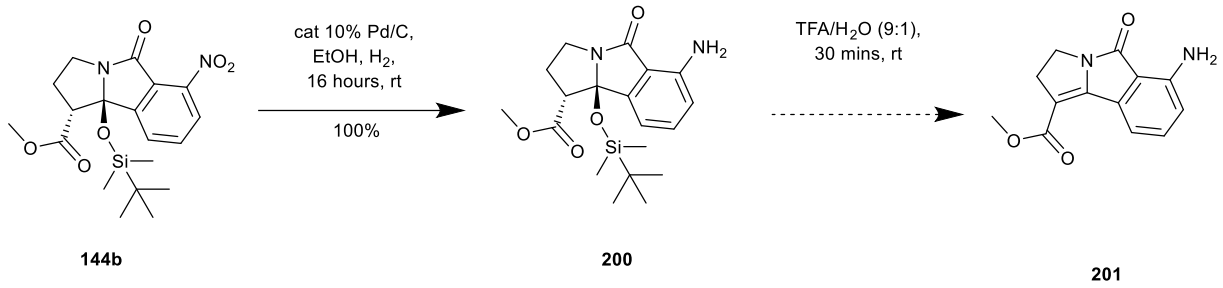
After considering this result, it is suggested that the C4 substituent is playing a crucial role in the stereoselectivity of this reduction and dictates that the compound co-ordinates to the palladium catalysts *anti*- to the ester, with the *cis* addition of the hydrogens across the alkene resulting in the selective stereochemistry shown in Scheme **5.11**.

With an interest in bioactivity for all the compounds synthesised in this project, of interest was the possibility of accessing new molecules that could be further functionalised. For example, hydrogenation conditions were used to reduce a nitro group simultaneously with the alkene for compound **146b**. We also wanted to ensure that it could be possible to do so before the alkene became present. To this end, the nitro containing maleimide **137b** was subjected to hydrogenation (Scheme **5.12**). This would also give access to the possibility of further functionalisation, such as amides, that could be used as an attractive library of drugs, as phthalimides have already discussed as potential drug-like compounds.[173–179]



Scheme 5.12. Hydrogenation of **137b**

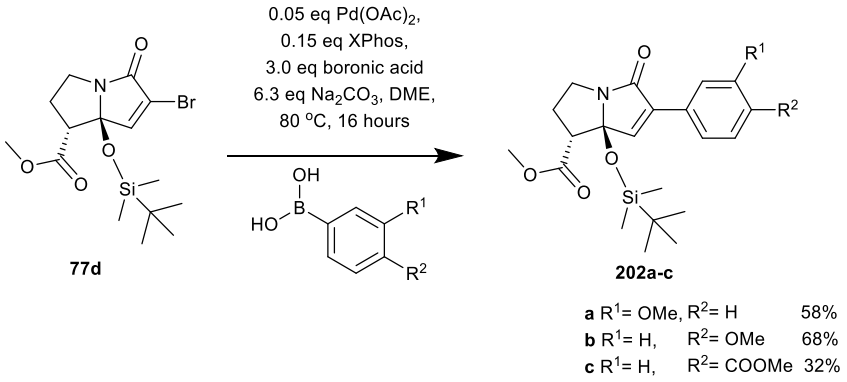
After successfully reducing the nitro group of **137b**, it seemed plausible that we could also achieve this same result after cyclisation, where the silyl moiety is in place (Scheme **5.13**). This would then allow TFA elimination of **233** to selectively afford the alkene containing aniline system **234**, however this reaction was not conducted.



Scheme 5.13. Hydrogenation of **144b** with a proposed FTA elimination to afford **201**

5.3. Suzuki Couplings

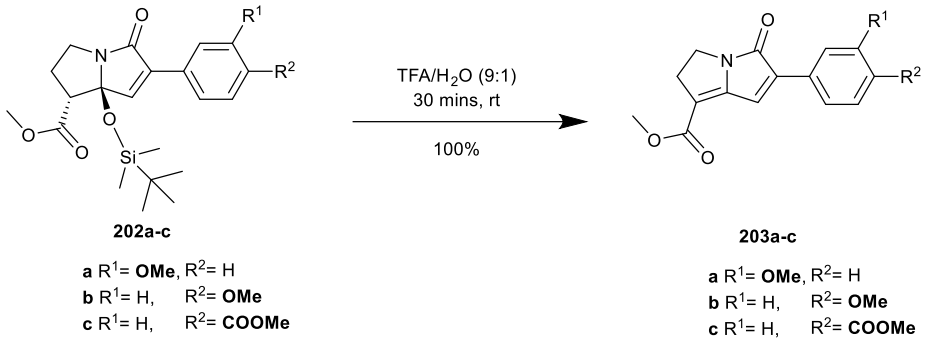
With **77d** in hand and being easily and reliably affordable, we were interested in utilising the bromo atom to undertake Suzuki couplings as a way to introduce simple functionality at the C7 position.



Scheme 5.14. Successful Suzuki couplings of **77d**

Initial attempts used triphenylphosphine but gave minimal conversion when analysed using ^{1}H NMR spectroscopy. In the development of this chemistry on **77d**, palladium acetate with XPhos as the counter catalyst proved to be a superior mixture. When coupling with less polar aromatic boronic acids, such as phenylboronic acid, the retention times of the product and starting material were far too similar to facilitate clean isolation. When phenyl groups were used with more polar substituents such as methoxy groups, careful and slower purification was still needed as these compounds co-eluted. The boronic acids gave a great return on yield, with a significant drop for **202c** simply due to co-elution with starting material and other unwanted by-products. It was also

rewarding to see that the silyl moiety remained intact, even after prolonged heating in DME. **202a-c** were all treated with TFA to afford their corresponding unsaturated systems (Scheme **5.15**).



202a-c

a R^1= **OMe**, R^2= H
b R^1= H, R^2= **OMe**
c R^1= H, R^2= **COOMe**

203a-c

a R^1= **OMe**, R^2= H
b R^1= H, R^2= **OMe**
c R^1= H, R^2= **COOMe**

Scheme 5.15. TFA elimination of **202a-c**

Compounds **203a-c** were all synthesised quantitively with no need for purification as expected. It was envisioned that these compounds would make interesting novel non-covalent binding DNA intercalators, as they are very flat with the exception of the phenyl appended group that allows for free rotation that could allow for a fit better in between the helical base pairs.

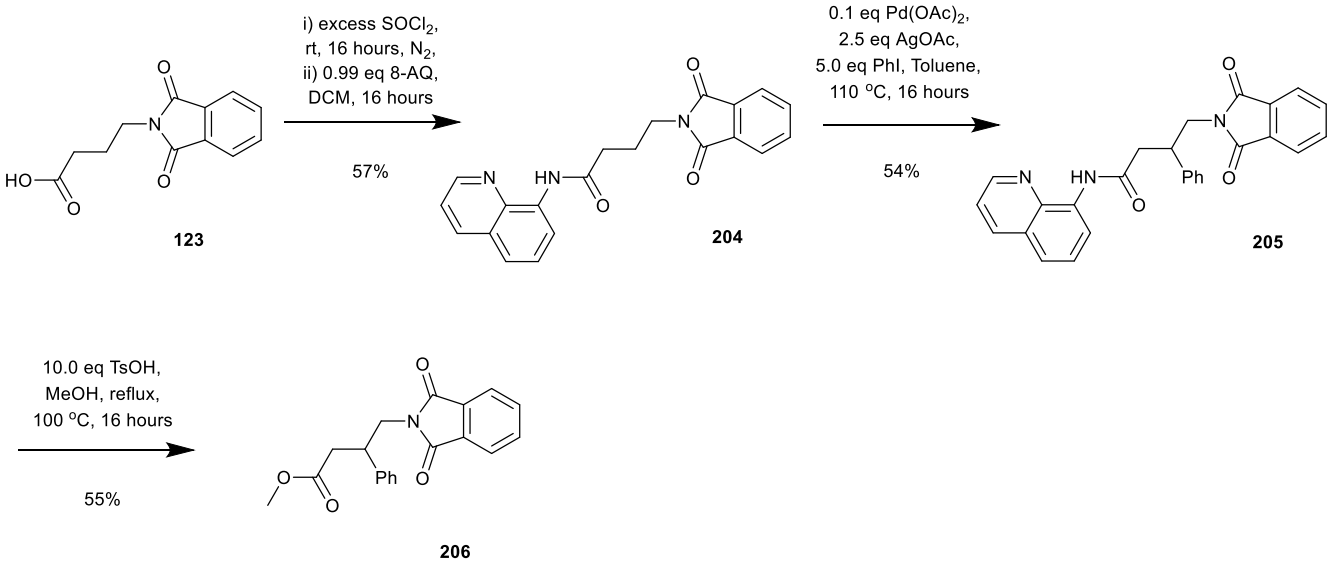
5.4. Introduction of Functionality at C3 *via* β-Arylation

Introducing substituents at the C3 position was a very attractive proposition, either as the uncyclised phthalimide, or cyclised pyrrolizidine that would then allow late-stage functionalisation. To this end, we began to explore the possibility of C3 functionalisation and with our findings detailed below.

When checking commercially available compounds for variants of GABA that incorporates any other group other than a proton at the C3 position, a few examples were found such as (*S*)-(+)-4-amino-3-hydroxybutyric acid and (±)-Baclofen.[263–267] Hydroxybutyric acid could have been an attractive option but as the hydroxy group would need to be protected prior to cyclisation, it would add additional steps to the synthesis. Baclofen is an interesting variant of GABA, as it adds a *p*-chlorophenyl substituent at the C3 position. However, Baclofen is rather expensive when comparing to GABA and a quick search of published synthesis for Baclofen shows many different

approaches that could also be used to afford a given enantiomer.[263–267] The only caveat is the 5 step procedure to afford the derivative before we could even start to incorporate into our synthetic methodology would be slow and laborious method to undertake SAR study.

A more in-depth search led to methodology that uses C-H activation, more specifically arylation of the C3 position by use of 8-aminoquinoline as a bidentate directing group.[268] The use of 8-aminoquinoline was very attractive, as not only is there a solid history of CH activation,[269–273] there are also specific examples of β-arylation of **123a**. At this point, this seemed to be the best way forward, as there would be easy access a wide range of C3 substituents. To ensure cyclisation would be possible after successful β-arylation, a single example was synthesised and tested (Scheme **5.16**).

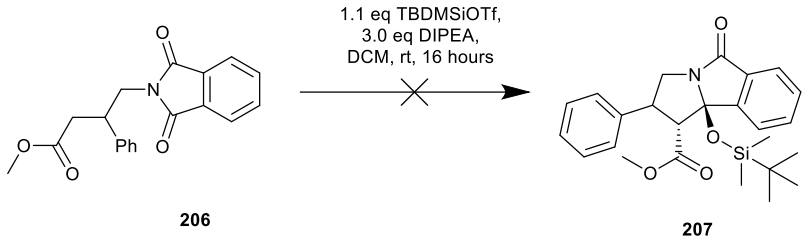


Scheme 5.16. Formation of the aminoquinoline amide followed by β-arylation to afford **206**[268]

The synthesis of the required aminoquinoline-containing amide began with the formation of the acyl chloride intermediate of **123a**, after which the solvent was removed and azeotroped using anhydrous dichloromethane. The intermediate was then dissolved in anhydrous dichloromethane and added dropwise over 5 minutes to a solution of 8-aminoquninoline dissolved in anhydrous dichloromethane with the mixture left stirring at room temperature for 16 hours. The reaction mixture was worked-up and purified *via* flash column chromatography as reported.[274]

It should be noted at this point the difficulties of working with 8-aminoqunioline. The aniline is commercially available as a black coloured solid; however, it appears that over time, oxidation occurs, darkening the material resulting in insoluble impurities. It is recommended that prior to use, an excess quantity is weighed out and purified *via* flash column chromatography using 40% ethyl acetate in pet-ether 40:60.

Formation of **205** was surprisingly straightforward, with all reagents added to a flask and suspended in toluene and heated at 110°C for 16 hours, followed by flash column chromatography to afford **205**. The functional group conversion from the amide to the required methyl ester was vital for the cyclisation and was achieved by refluxing **205** with *p*-toluenesulfonic acid in a sealed pressurised vessel at 100 °C in methanol and then purified *via* flash column chromatography to afford **206** in good yields of 55%. With **206** in hand, TBDMSiOTf mediated silyl cyclisation was attempted (Scheme **5.17**).



Scheme 5.17. Attempted cyclisation of **206**

It was disheartening to see that **206** failed to cyclise after numerous attempts made with changes to the equivalents of TBDMSiOTf being used. It was hypothesised that the addition of the steric bulk of the phenyl ring was impeding cyclisation. We envisioned that 8-aminoquinoline could be introduced post-cyclisation *via* amide formation at the C1 methyl ester.

5.4.1. Use of 8-Hydroxyquinoline as a Possible Bidentate Directing Group

When consulting the literature that uses 8-aminoquinoline as a directing group, a consensus seems to have formed that the mechanism for the CH activation requires the catalyst to be co-ordinating

to the amide nitrogen, as well as the quinoline nitrogen, followed by co-ordinating to the proton that is to be activated.[274–276] An example of this can be seen in Figure **5.4**.

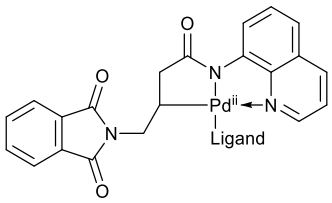
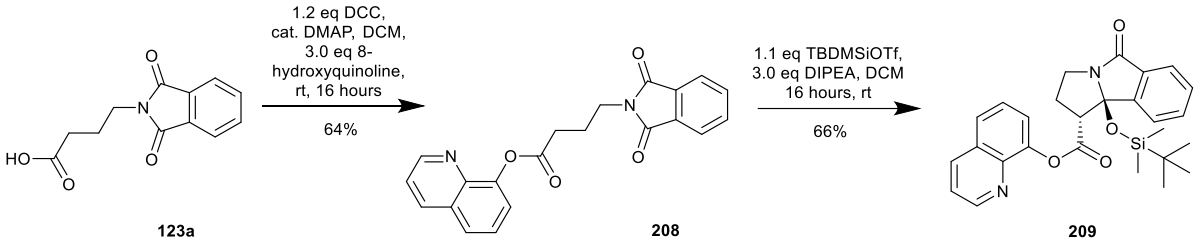


Figure 5.5. Intermediate species proposed during the activation of C3 proton[274–276]

We envisioned that the lone pair of the nitrogen amide was responsible for the co-ordination to the palladium, as deprotonation of the amide was unlikely under the conditions used in Scheme **14**. The question was asked whether an oxygen in the form of an ester would be sufficient to help facilitate this reaction. When looking at the limited reports in the literature, it seemed that this would not be possible, however, these reports often featured aromatic CH activation.[276]

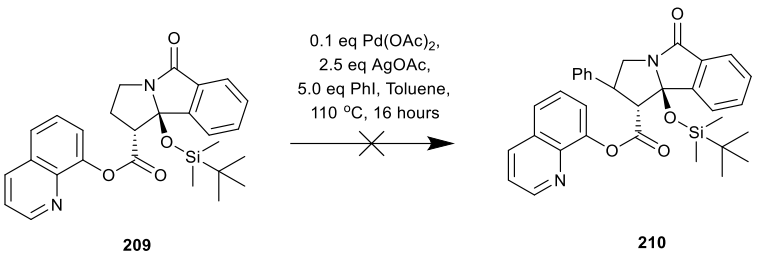
It was decided it was worth investigating this option as we were also confident that the ester variant of **204** could be cyclised, perfect for late stage functionalisation at the C3 position. (Scheme **5.18**).



Scheme 5.18. Synthesis of **209**

208 was synthesised *via N,N'*-dicyclohexylcarbodiimide coupling with 8-hydroxyquinoline with this method chosen over previously used methods that involved using thionyl chloride to avoid formation of a salt on the quinoline nitrogen. It was rewarding to see that the cyclisation of **209** was more than possible with a great yield of 66%. When analysing these compounds using prep TLC, after an hour or two after being ran, the desired products start to turn yellow, and this can be observed without the use of UV light. This is either due to oxidation occurring or 8-

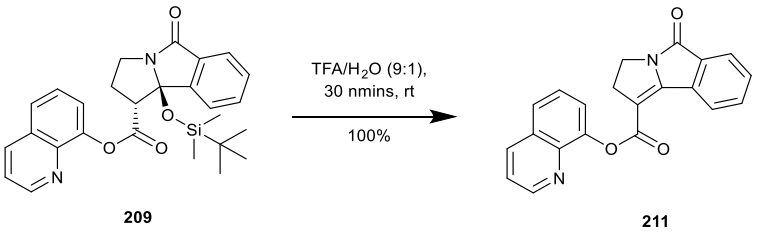
hydroxyquinoline's ability to chelate to metals,[277] as such we were hopeful that it could be used for late stage β-arylation (Scheme **5.19**).



Scheme 5.19. Attempted β- arylation of **209** at the C3 position

It was a shame to see that **209** was unable to undergo arylation as this would have meant a rapid way to introduce new functionality at the C3 position. It seemed that the amide nitrogen was essential for this activation to occur, as such we looked at introducing and forming the amide post cyclisation.

Out if interest in potential anticancer agents, **209** was treated with TFA:H_2O to afford the desired saturated system quantitively (Scheme **5.20**).

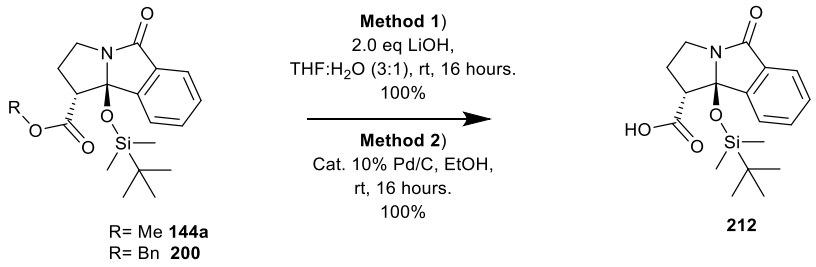


Scheme 5.20. Desilyloxylation of **209**

5.4.2. Amide Formation Using 8-Aminoquinoline Post-Cyclisation

The question that first needed to be addressed was at which point in our developed methodology should the desired amide be formed. It seemed logical to form the amide post-cyclisation where the silyl moiety is present, as we could then reform the methyl ester and follow through with our normal synthetic strategy of TFA elimination and subsequent hydrogenation producing a wide variety of interesting compounds.

To this end, the exploration of affording the carboxylic free acid was undertaken (Scheme **5.21**). As we had previously synthesised both the methyl ester **144a** and the benzyl ester **174**, two different options of deprotection were available. As this was the first time subjecting the phthalic containing pyrrolizidinones to strong basic conditions, careful observation of the reaction was needed (Scheme **5.21**).

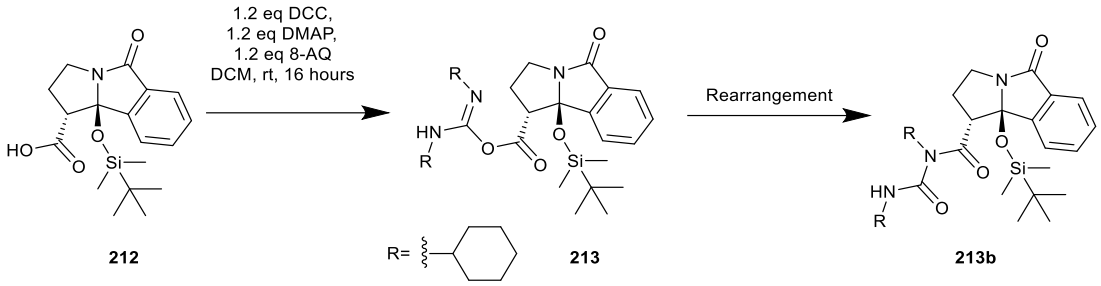


Scheme 5.21. Deprotection of the ester to afford the free carboxylic acid **212**

Two different methods were used to afford **244**. If the methyl ester **144a** was present, then basic hydrolysis using LiOH[156] was more than sufficient to afford **212** quantitatively. After the reaction was left stirring for 16 hours, the aqueous layer was concentrated to remove the THF. The material was redissolved in water and acidified using 0.5 N HCl to a pH of 3 at which point the product precipitated. It was observed that neat ethyl acetate would struggle to fully dissolved the solid, so a more polar option was explored, with a 3:1 mixture of chloroform and isopropyl alcohol being used. When the benzyl ester was present, hydrogenation was used that also afforded the desired product **212** quantitively, but extensive drying on the roto-evaporator was needed to ensure that all ethanol had been removed prior to amide formation. With **212** in hand, an attempt at amide formation using 8-aminoquinoline was made.

A standard amide formation was attempted with *N*,*N'*-dicyclohexylcarbodiimide being used as the coupling agent with 4-dimethylaminopyridine used to increase the rate of the reaction.[278] **212** was suspended in dichloromethane with *N*,*N'*-dicyclohexylcarbodiimide being added in one portion that caused the dissolution of both compounds. 4-Dimethylaminopyridine was then added with the reaction mixture left stirring at room temperature for one hour to allow the desired activated

intermediate to form. A solution of 8-aminoquinoline was then added with the resulting mixture stirred at room temperature for 16 hours (Scheme **5.22**).

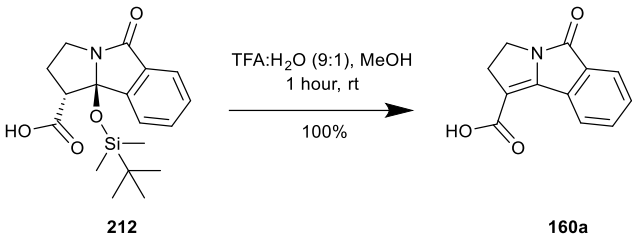


Scheme 5.22. Attempted amide formation using DCC and 8-aminoquinoline

When monitoring the prep TLC, there was no suggestion that the reaction had worked, with the LRMS also suggesting the same conclusion with no mass ions identified under positive ionisation. However, when negative ionisation was used, the major mass ions observed were 588 and 591. When subtracting the mass of chlorine from 588, the mass ion 553 is given which matches that shown for **213**, or the same mass ion for the rearrangement to the stable *N*-acylurea **213b**. We hypothesise that the carboxylic acid of **212** attacked the carbodiimide[279] affording **213**, but attack of the sterically bulky 8-aminoquinoline is hindered and in any case lacks nucleophilicity. The above conditions were repeated using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimde (EDC) with the addition of 1-hydroxybenzotriazole (HOBt) with the exact conclusion being seen with the coupling agent attached to the C1 oxygen.

The next option was to introduce the amide after TFA elimination of the silyl moiety on the saturated tricyclic system **167**. Affording the carboxylic free acid of **146a** could achieved using two different methods, deprotection of **144a** or **174** (Scheme **5.21**) followed by TFA elimination, or TFA elimination on **212** followed by basic hydrolysis.

Both these routes were explored, as concerns over the solubility of the free acid product were raised. It was decided that deprotection followed by TFA elimination would be explored first. To this end, **212** was treated with TFA (Scheme **5.23**).



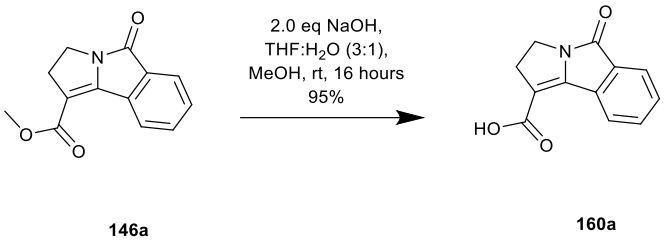
Scheme 5.23. TFA elimination to afford **212**

A solution of TFA and water (9:1) was added to **212** and stirred for 30 minutes after which it was observed that the starting material had failed to dissolve and remained as a white coloured solid. As previous experience had shown that the unsaturated systems have a bright yellow colour, it was assumed that the reaction was not proceeding with poor solubility playing a part on the reactivity of **160a**. Methanol was then added dropwise which helped with the dissolution of **160** with the reaction slowly turning yellow over the next 30 minutes with the reaction being left for a further 30 minutes to ensure complete elimination. After concentration, the crude product was tested by ^{1}H NMR and ^{13}C NMR spectroscopy and this confirmed the complete conversion to **160a**. It was found to be much easier to dissolve **160a** in deuterated dimethyl sulfoxide rather than chloroform, with substantial heating required. It should also be noted that HSQC NMR spectroscopy was used, as the natural presence of water in the NMR solvent was obscuring the area in which H4 and the methyl ester would normally be observed.

For the basic hydrolysis of **146a**, the same method was replicated as with **165** in Scheme **5.17**. **146a** was suspended in a mixture of THF:H_2O (3:1) with lithium hydroxide being added in one portion with the reaction mixture left stirring at room temperature for 16 hours. It was observed that little to no starting material had dissolved over this period, with the assumption that the reaction had failed. This was confirmed with an aliquot of the reaction mixture analysed using ^{1}H NMR spectroscopy with the mass ion of **146a** being observed when analysed using LRMS.

The reaction was repeated with sodium hydroxide being used *in lieu* of lithium hydroxide. Methanol was also added to the solvent mixture to help increase solubility. After 16 hours of stirring, all the starting material had fully dissolved, and continued to precipitate upon acidification

using 0.5 N HCl. Once again, a more polar solvent mixture was needed with a 3:1 mixture of chloroform and isopropyl alcohol being used with multiple extractions to afford the desired product with a yield of 95% (Scheme **5.24**).



146a **160a**

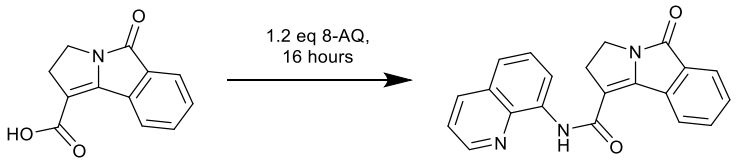
Scheme 5.24. Basic hydrolysis of **146a**

It was very interesting to see, even at this stage, the differences in reactivity of the C1 methyl ester of **144a** and **146a**, with a stronger base being needed for the hydrolysis of **146a** with **160a** in hand, extensive attempts at amide formation were attempted.

5.4.3. Amide Formation Using 8-Aminoquinoline and Pyrrolidone

It was assumed, based in the difference in reactivity already seen when trying to hydrolyse the ester, that amide formation may be very challenging, with the ideal coupling agent needing to be found. To this end, a plethora of reagents were tested with the results shown in Table **5.2**.

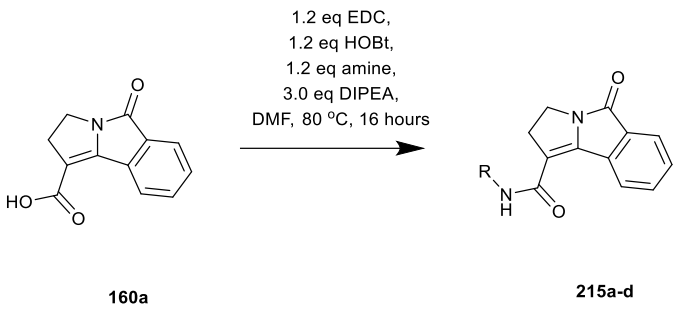
Table 5.2. Comparison of different coupling reagents and solvents attempted to afford **214**



160a **214**

Method	Reagent	Additive	Solvent	Temp °C	Yield of 214
A[278]	1.2 eq DCC	n/a	DCM	Rt	0
B[278]	1.2 eq EDC	1.2 eq HOBt 3.0 eq DIPEA	DMF	80	0
C[280]	10% mol $B(OH)_3$	n/a	Toluene	110	0
D[281]	1.5 eq CDI	10% mol $CaBr_2$	DCM	Rt	0
E[282]	2.0 eq $Si(OMe)_4$	n/a	Toluene	110	0
F[278]	Excess $SOCl_2$	3.0 eq DIPEA	DMF	80	0
G[283]	1.2 eq TBTU	3.0 eq DIPEA	DMF	Rt	0
H[284]	1.2 eq T3P	3.0 eq pyridine	DCM	Rt	0

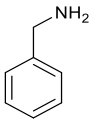
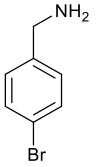
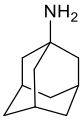
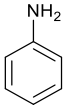
Methods **A,B,G,H** all saw the starting material dissolved after the addition of the coupling reagent and additive, but after 16 hours of stirring, the reactions were tested using LRMS and this showed the mass ion for the coupling reagent adduct situated on the C1 oxygen. When methods **C,D,E,** were all used, no apparent dissolution was seen, with only starting material seen when analysed using LRMS. **160a** appeared to fully dissolve and change colour when using method **F**, after 16 hours of stirring in an excess of thionyl chloride, the solvent was removed and azeotroped and redissolved in DMF with the 8-aminoquinoline added and left for a further 16 hours. As with other methods, the LRMS did not suggest any product as did the ^{1}H NMR spectrum of the crude material. It was at this point, there were questions about the reactivity of either the acid or amine. To try and answer this question, and attempt was made to couple **160a** with a handful of amines (Scheme **5.25**).



160a **215a-d**

Scheme 5.25. Formation of a small selection of amides using EDC, HOBt, and DIPEA in DMF (See Table **5.3** for amines and yields)

Table 5.3. Amines and yields for the synthesis of **215a-d**

Compound name	Amine	Yield
215a		35
215b		32
215c		41
215d		0

It was rewarding to see that amide formations are possible when using **160a** but the apparent drop in nucleophilicity with aniline and 8-aminoquinoline is hindering their formations. Directing groups that can be used in CH activation are plentiful,[276,285–289] however, an attempt to stay close to nitrogen based bidentate directing groups. From the possible selection of available *N,N*-bidentate directing groups that include quinoline-based, oxazole-based, triazole-based and pyrazole-based groups, the most attractive were pyridine-based directing groups, in particular 2-picolyl amine. 2-Picolyl amine and 8-aminoquinoline are very similar in their structure and positioning of the aromatic nitrogen atom (Figure **5.5**), however, the added flexibility of 2-picolyl amine resulting from the benzylic CH_2 would assist in β-arylation, and easier amide formation.

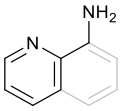
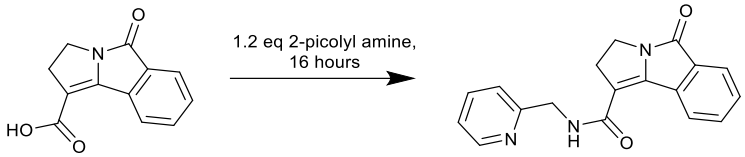


Figure 5.6. 2-picolyl amine overlaid 8-aminoquinoline

From the limited literature featuring 2-picolyl amine, it appears that in some situations it can give slightly better yields when compared to 8-aminoquinoline,[275] and seemed worth exploring.

Table 5.4. Comparison of different coupling reagents and solvents attempted to afford **216**

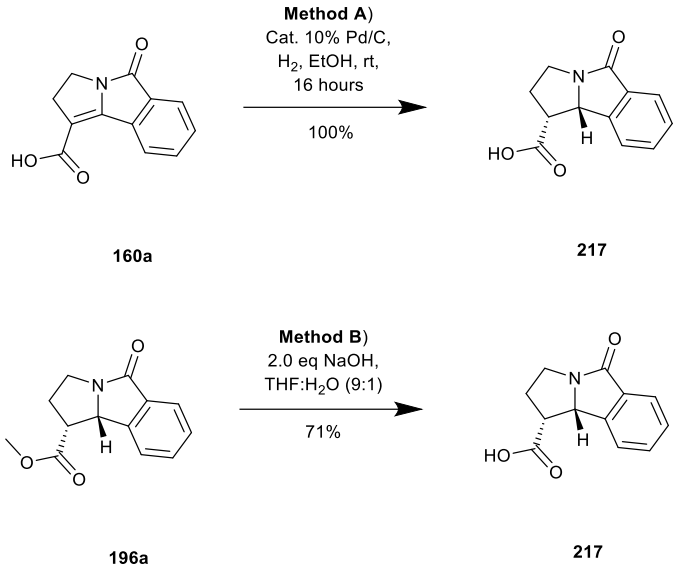


160a **216**

Method	Reagent	Additive	Solvent	Temp °C	Yield of 216
A[278]	1.2 eq DCC	n/a	DCM	Rt	0
B[278]	1.2 eq EDC	1.2 eq HOBt 3.0 eq DIPEA	DMF	80	**7**
C[280]	10% mol $B(OH)_3$	n/a	Toluene	110	0
D[281]	1.5 eq CDI	10% mol $CaBr_2$	DCM	Rt	0
E[282]	2.0 eq $Si(OMe)_4$	n/a	Toluene	110	0
F[278]	Excess $SOCl_2$	3.0 eq DIPEA	DMF	80	0
G[283]	1.2 eq TBTU	3.0 eq DIPEA	DMF	Rt	0
H[284]	1.2 eq T3P	3.0 eq pyridine	DCM	Rt	0

All previous methods for amide formations were replicated with 2-picolyl amine as the amine, with the only result being seen was using method **B**, with a poor yield of 7%. Due to the lack of material recovered, CH activation using **216** was not attempted.

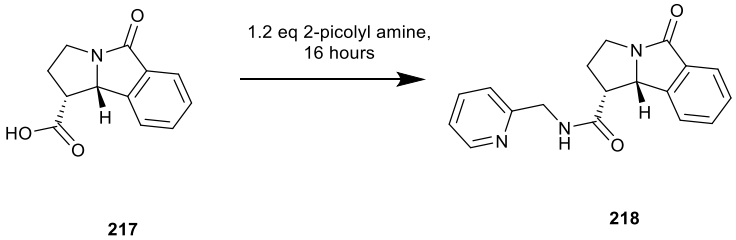
With the only option left to explore was to attempt the amide formation post-hydrogenation (Table **5.5**). Firstly, the hydrogenated free carboxylic acid needed to be synthesised and this could be accessed in a couple of ways (Scheme **5.26**).



Scheme 5.26. Formation of **217** *via* two different methods

Both methods work well to afford the desired product **217**, with Method A being the higher yielding of the two. With the reduced free carboxylic acid in hand, amide formation with 2-picolyl amine was attempted with the results displayed in Table **4**.

Table 5.5. Comparison of different coupling reagents and solvents attempted to afford **218**



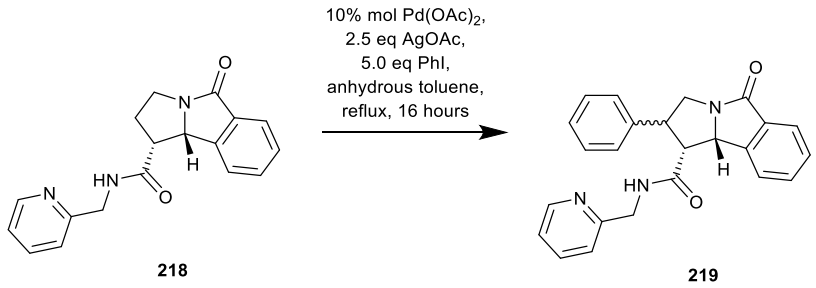
Method	Reagent	Additive	Solvent	Temp °C	Yield of 218
A[278]	1.2 eq EDC	1.2 eq HOBt 3.0 eq DIPEA	DMF	80	58
B[282]	2.0 eq $Si(OMe)_4$	n/a	Toluene	110	49
C[278]	Excess $SOCl_2$	3.0 eq DIPEA	DMF	80	52
D[283]	1.2 eq TBTU	3.0 eq DIPEA	DMF	Rt	0*

When attempting to form **218** using the above reagents, it was rewarding to see the presence of **218** when analysing each of the crude mixtures *via* LRMS and ^{1}H NMR spectroscopy. It should

be noted that for method **D**, product was observed in the crude ^{1}H NMR close to a 50% conversion, but the product was lost during flash column chromatography that will be now discussed.

The prep TLC plate for **218** (from method **D**) suggested that it could be purified using flash column chromatography using a solvent mixture of 50% ethyl acetate in dichloromethane, however, after multiple volumes of solvent had been run through the column, no product was isolated. It seemed that the acidity of the silica was causing **218** to stick to the column, even with the relatively polar solvent mixture being used. This was rather surprising as similar problems had not occurred when using 8-aminoquinoline. After looking at similar amides reported,[290] it was apparent that the column may need to be doped using base, and to this end a series of prep TLC plates were run in a mixture of solvents with the solvent mixture containing 2.5% methanol, 2.0 % triethylamine in dichloromethane appearing to give the cleanest separation. Hence, **218** was purified using these conditions that gave clean product with isolated yields from 49-58%.

With **218** in hand, β- arylation was attempted using the conditions previously used with 8-aminoquinoline directing arylations (Scheme **5.27**).



Scheme 5.27. β-Arylation of **218**

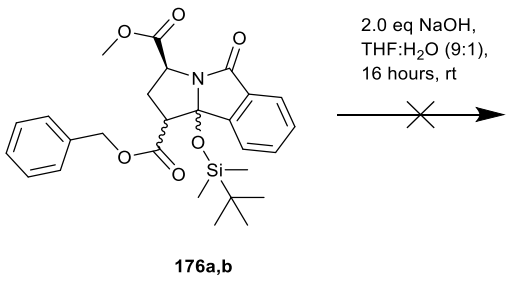
It was rewarding to observe the required mass ion of 384 [MH+] in the LRMS, with the ^{1}H NMR spectrum also supporting this, whilst suggesting roughly 50% conversion to **219**. It was tricky to be definitive in this however, as the ^{1}H NMR spectrum had a high concentration of phenyl iodide that swamped the aromatic region, in addition to residual toluene left in the reaction mixture. However, a new peak was observed as a doublet at 5.53 ppm. In addition to this, H4$_A$ for **219** was observed as a doublet of triplets at 3.82 ppm and now becoming less observable in the crude spectra

for **219** with a new multiplet peak observed at 4.32 ppm that could be responsible for $H4_A$ resulting from the additional steric bulk and interactions from the C3 phenyl group.

Unfortunately, it was not possible to isolate **219**, solely due to the high polarity and other unidentified by-products. A few other catalyst systems were also attempted to be used including $[RuCl_2(p\text{-cymene})]_2$ with triphenyl phosphine as the co-catalyst,[275] with no conversion being seen. Due to time constraints, this reaction and purification was not further examined.

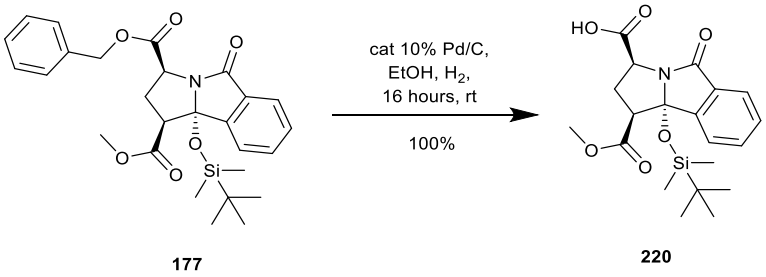
In our final attempts to introduce a bidentate directing group, we considered the possibility of C4 as a possible location, as this would also have the stereochemistry set, allowing stereoselective arylation at the C3 position.

It seemed logical to subject this compound to basic hydrolysis conditions we had previously used to expose the free acid that could be used to form the required amide (Scheme **5.28**).



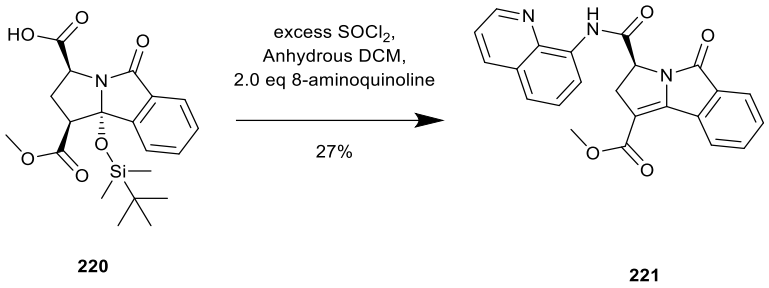
Scheme 5.28. Attempted basic hydrolysis of **176a,b**

It was surprising to see that this reaction failed, with the ^1H NMR spectrum appearing very messy with no desired product identifiable. It was hoped that the hydrogenation of the benzyl group at the C4 position of **177** would be more successful (Scheme **5.26**), while also the added benefit of a single diastereomer, unlike **176a,b**.



Scheme 5.29. Debenzylation of **177**

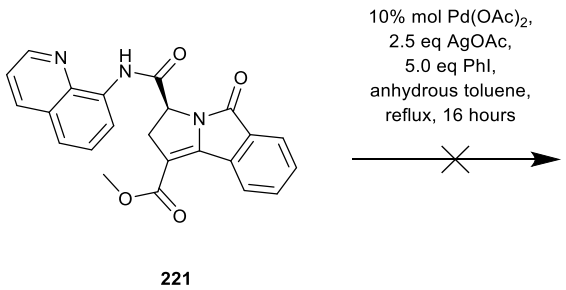
177 reacted very nicely giving quantitative conversion through to **220**. With **220** in hand, the formation the acyl chloride was attempted followed by addition of 8-aminoquinoline (Scheme **5.30**).



220 **221**

Scheme 5.30. Amide formation using 8-aminoquinoline to afford the saturated tricyclic system **221**

The crude ^{1}H NMR spectrum was very messy, with the silyl dimethyl groups not observable. The crude mixture was purified using flash column chromatography to afford **221** with a poor yield of 27%. As we had managed to isolate and purify **221**, it seemed prudent to try CH activation using the same methods already attempted with other compounds in this thesis (Scheme **5.31**).

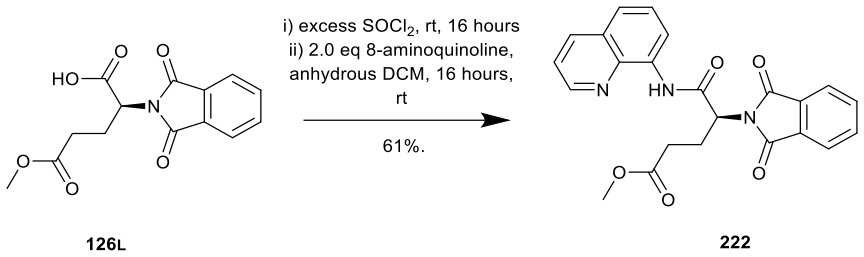


221

Scheme 5.31. Attempted β- arylation of **221**

It was disappointing to see that **221** failed to undergo CH activation, with it being hypothesised that the flatness of **221** is directly hindering the co-ordination needed to achieve arylation at the C3 position.

Our final attempt focused on the formation of the amide at the C4 position prior to cyclisation, as we have already seen that bulky benzyl ester substituents were tolerated at this position.



Scheme 5.32. Amide formation using 8-aminoquinoline to afford

The formation of **222** was surprisingly straightforward, with **126L** being dissolved and stirred in thionyl chloride for 16 hours at room temperature while under nitrogen. After this period, the solvent was removed and dissolved in anhydrous dichloromethane and added dropwise to a solution of 8-aminoquinoline dissolved in anhydrous dichloromethane. After 16 hours, the mixture was worked-up and purified using flash column chromatography to afford **222** in excellent yields. The opportunity to attempt to cyclise **222** was taken. **222** was attempted to be cyclised in 3.0 equivalents of TBDMSiOTf, with unforeseen results.

After the reaction had been stirring for 16 hours, the crude mixture was analysed using LRMS that showed the desired mass ion 532 [MH+] for the expected product. However, two other peaks where identified and questioned, one peak at 514 and 646. The crude material was subsequently purified using flash column chromatography with a single compound isolated. The ^{1}H NMR spectrum strongly suggested that **222** had successfully cyclised but with two problems, an aromatic proton was missing with an addition TBDMSi-environment being observed (Figure **5.6**).

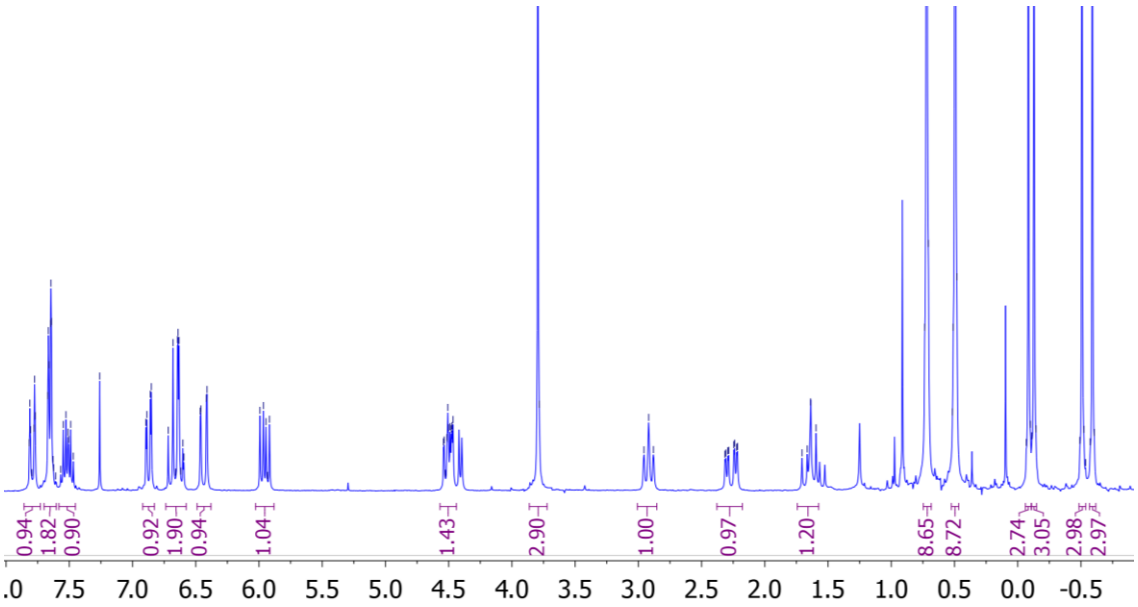
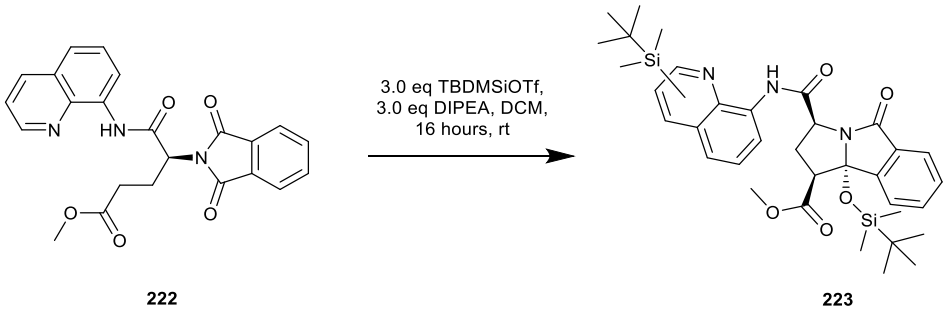


Figure 5.7. ^{1}H NMR spectrum from the cyclisation product of **222**

From a search of the literature of similar style of compounds, it was found that metal-mediated activation of aminoquinolines has been documented, with insertion *ortho* or *meta* to the amide.[291,s292] Of interest was that transition-metal-free C-H-halogenation of 8-aminoquinoline has also previously been reported[293] after stirring an 8-aminoquinoline containing amide with sodium bromide in oxone as the oxidant and dichloroethane at room temperature giving yields up to 99% conversion.[293] Moreover, the group also showed that when other aromatic species such as phenyls are present, these groups remain untouched. The group also showed *via* x-ray analysis that the addition of the halogen went *para* to the amide nitrogen, possibly due to electron donating of the amide group. However, comparing our NMR spectroscopic data to published data was not helpful. When attempting to find examples of silyl containing aromatic rings with a *para* amide being present, the aromatic peaks were not observed more upfield that 7.0 ppm, unlike with **223**.[294]

As **223** (Scheme **5.33**) appeared to be a unique structure, an attempt to assign the position of the additional silyl moiety was undertaken.



222 223

Scheme 5.33. Synthesis of **223**

The first observation would be that the resonance due to the addition dimethyl and ^{t}butyl groups in the ^{1}H NMR spectrum (Figure **6**) were possibly due to the existence of diastereomers, however, this is possible to dismiss from the single methyl ester peak that is visible in Figure **6**. It is proposed that the addition of the extra ^{t}butyl group and dimethyls with the missing aromatic protons is a consequence of the 8-aminoquinoline group performing an *in situ* metal-free CH activation, possibly helped by the presence of the TBDMSiOTf acting as a Lewis acid.

From looking at the structure proposed for **223** in Scheme **5.32**, it seemed that the silyl does not reside on the phthalic aromatic ring.

The first step in the analysis of **223** was careful observation of the ^{1}H NMR spectrum, that showed aliphatic protons at 4.50, 3.79, 2.92, 2.27 and 1.65 ppm. Based on previous chemical shift patterns, these peaks were initially assigned as H4, C1-OMe, H2, H3$_A$ then H3$_B$. In addition, it was assumed that the aromatic peaks most downfield observed from 7.79 – 7.51 were the phthalic aromatic protons. HSQC NMR spectroscopy confirmed that the peaks at 4.50, 3,79 and 2.92 where all CH with the two peaks at 2.27 and 1.65 as CH_2 protons. However these peaks seem to be much lower in their chemical shifts than similar compounds, such as **175L,D** so it was decided to tabulate the corresponding ^{1}H NMR data shown in Table **5.6**.

Table 5.6. Comparison of ^{1}H NMR data for **223** and **175L**

	223	**175L**
H4	4.50	4.34
C1 OMe	3.79	3.76
H2	2.92	3.42
$H3_A$	2.27	3.05
$H3_B$	1.65	2.91
ArH	7.79 (1H)	7.70 (1H)
ArH	7.66 (2H)	7.56 (1H)
ArH	7.51 (1H)	7.48 (2H)

From comparing ^{1}H spectroscopic data for **223** and **175L**, the chemical shifts for H4 and the methyl ester were mostly unaffected, as well as very similar chemical shifts and splitting patterns for the phthalic region of both compounds. However, rather large chemical shifts were observed for H2 and both H3 protons, possibly due to the influence of the aminoquinoline group residing in such close proximity, as well as the silyl group affecting these protons.

It was interesting to see that for the starting material **222** all quinoline aromatic protons were downfield of chloroform, while with **223**, all protons are now upfield of chloroform. When analysing the COSY NMR spectrum for **223** connectivity was seen from $H3_B$ to $H3_A$, H2 and H4, with $H3_A$ only showing coupling to $H3_B$ and H4. When analysing the coupling of H4, it was surprising to see connectivity from H4 to an aromatic proton at 5.95 ppm. With closer examination of the COSY NMR spectrum for the aromatic region, the peaks from 7.79 – 7.51 ppm show clear connectivity to each other, but no coupling to the remaining protons. The peak at 5.95 ppm showed coupling to peaks at 6.45 and 6.71 ppm. The peak at 6.45 ppm only showed coupling to the peak at 5.95 ppm. The peak at 6.89 ppm only showed connectivity to 6.65 ppm. These data suggests that the phthalic region is as expected, with the silyl moiety likely to be either *para* to the amide or the quinoline nitrogen due to the coupling patterns seen in the COSY NMR spectrum (See Figure **5.7**).

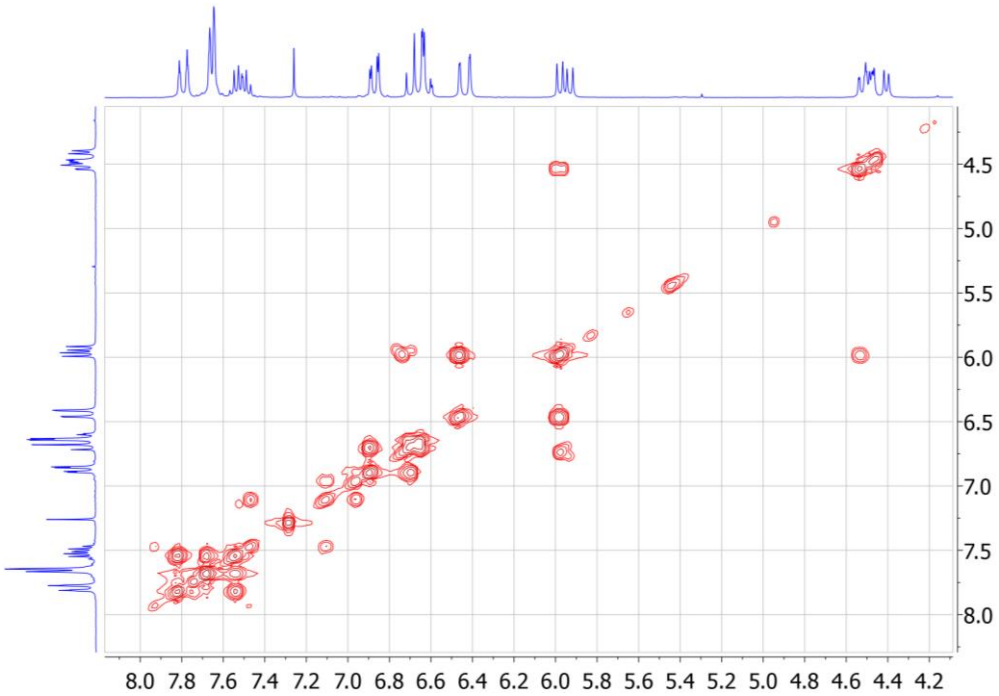


Figure 5.8. COSY NMR spectrum used in the analysis of **223**

Before the analysis of the HMBC NMR spectrum will be discussed, it is important to try and assign the aliphatic region for the ^{13}C NMR spectrum. By using the HSQC NMR spectrum, the C1 methyl ester was observed at 52.52 ppm, with C4 at 49.54, C2 at 46.61 and C3 at 28.14 ppm. Other parts of the ^{13}C NMR spectrum were very clustered and complex.

It was rather interesting to observe in the HMBC NMR spectrum correlations from $H3_A$, H2 to C4, in addition to two aromatic protons at 5.95 and 6.45 ppm, suggesting these two aromatic protons from the quinoline system is close enough in space to see C4. A weak HMBC correlation was also seen from the aromatic peak at 6.45 ppm to C2. Particular interest in correlations of H4, that were observed to two aromatic carbon peaks at 126.01 and 122.66 ppm, confirmed to correlate to the aromatic protons at 5.97 and 6.44 ppm respectively, but more importantly to a quaternary peak at 137.69 ppm. When analysing the quaternary peak at 137.69 ppm, three correlations can be seen to the protons at 6.89, 6.71 and 5.59 ppm, in addition to H4, suggesting these protons are all very close to this carbon. From the data collected and compared so for **223**, the carbon peak at 137.69 has been assigned as C13 (Table **8**), with the three protons seeing this carbon as H15, H16 and H17. H17 saw C18 as well as C19, with C19 being seen by H20. In addition to HMBC correlations,

a nOe interaction was observed from a ^{t}butyl group to H20 and also H17. This was ruled out as the C13 silyl moiety with nOe interactions being observed for this group to H4, H2 and $H3_A$. It should be noted that an unexpected nOe was seen from H2 to H16 with a very weak interaction to H15. To further collaborate our previous assignment of aromatic protons, nOe interactions were seen between H16 to both H15 and H17, with the same being seen for H20 and H21 (Figure **5.8**).

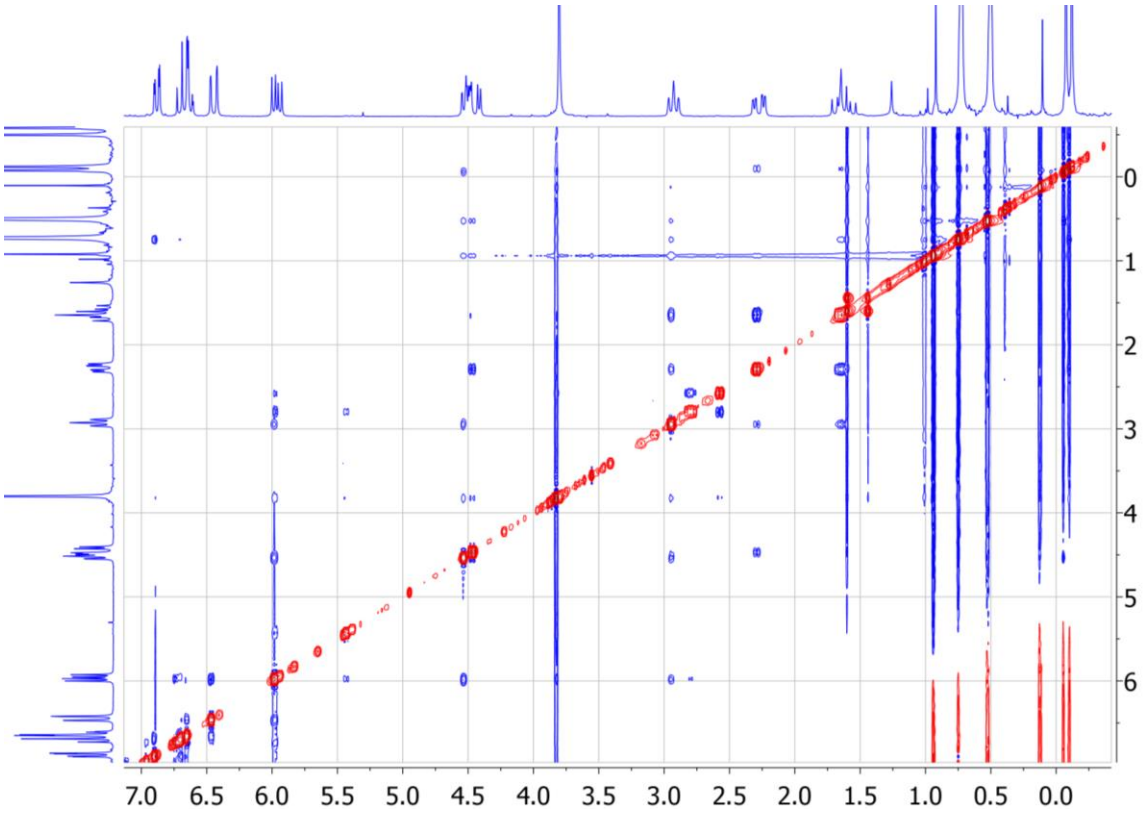
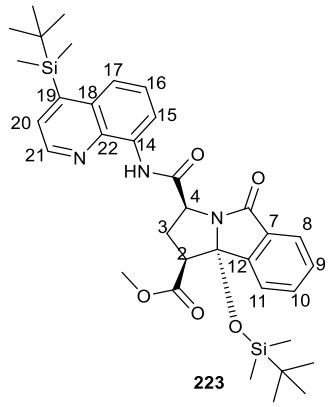


Figure 5.9. nOe NMR spectrum for **223**

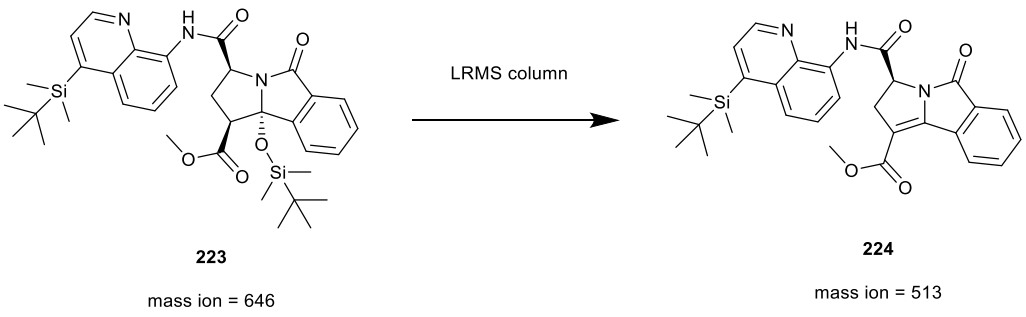
Table 5.7. ^{1}H and ^{13}C NMR data for the assigned peaks for **223**



223

Assignment C/H	^{1}H NMR peak ppm	^{13}C NMR peak ppm
2	2.92	16.61
3	2.27 & 1.65	28.14
4	4.50	49.54
7	n/a	130.55
8	7.79	124.14
9	7.66	133.54
10	7.51	130.03
11	7.66	122.85
12	n/a	148.75
14	n/a	137.76
15	6.44	122.85
16	5.95	126.24
17	6.68	119.06
18	n/a	116.58
19	n/a	131.59
20	6.87	115.46
21	6.64	123.05
22	n/a	115.27

In addition to this, the mass ion of 646 was seen when analysed during LRMS, the exact mass ion of the isolated product **233** suggested in Scheme **5.34**, with desilyloxylation being observed.



223

mass ion = 646

224

mass ion = 513

Scheme 5.34. Proposed isolated compound **223** undergoing desilyloxylation during LRMS analysis

Due to the complexity and time spent in the analysis of **256**, along with time constraints, additional exploration of this chemistry was not able to be undertaken.

5.5. Summary of Chapter V

The work discussed in this chapter has been successful in manipulating the unsaturated tricyclic alkene system *via* epoxidation or hydrogenation with the addition of some unexpected products synthesised and discussed in depth. This work also observed the effects of C4 substituents on controlling the stereochemistry when attempting to hydrogenate the C4 methyl ester containing saturated pyrrolizone. Attempted chemistry on the bromo-containing bicyclic pyrrolizidine proved to be achievable using Suzuki coupling. A small section was devoted to understanding the electronic properties of the saturated system, that was found to be difficult to predict, with a plethora of amide forming reagents attempted in reactions with aromatic, and nonaromatic amines. CH activation to access C3 substituted compounds gave mostly unwanted results, with this chemistry proving to be much more difficult than previously expected. However, this chemistry led to a proposed unprecedented metal-free CH activation with silyl triflates.

Chapter VI: Antibacterial and Anticancer Screening

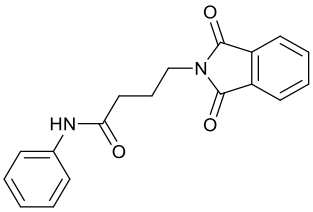
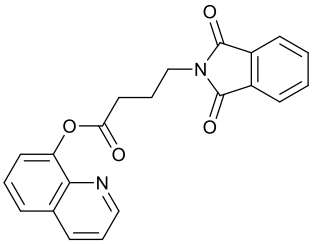
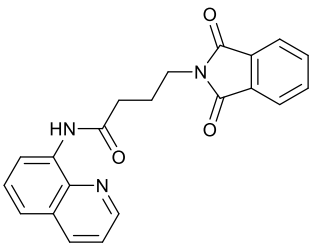
This Chapter reviews the biological data for compounds synthesised in this project and tested for their antibacterial and anticancer properties.

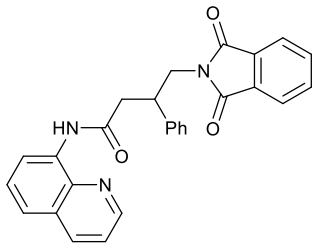
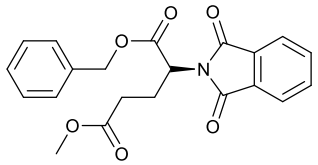
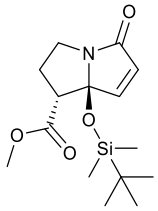
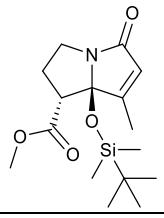
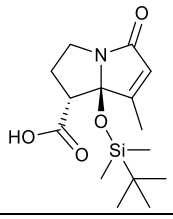
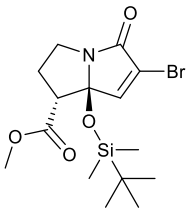
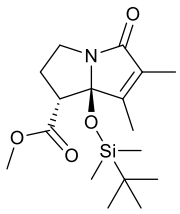
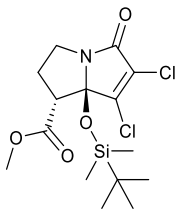
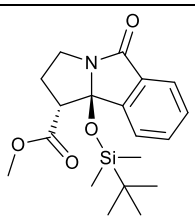
6.1. Antibacterial Screening

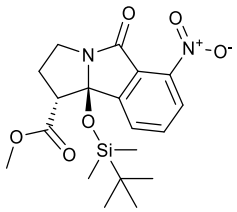
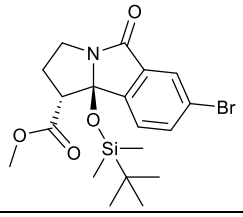
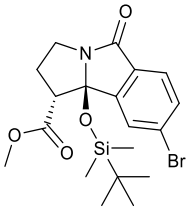
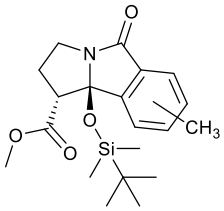
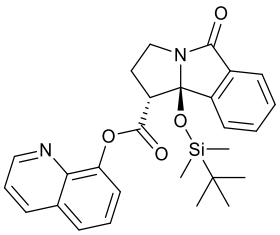
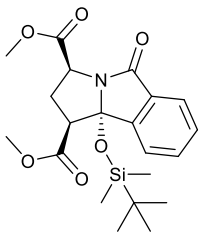
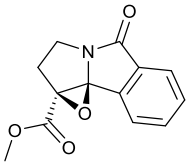
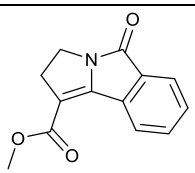
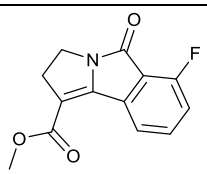
When possible, compounds that had been synthesised during this project were submitted for analysis and tested for potential antibacterial activity by the *Oxford Antibacterial Group*.

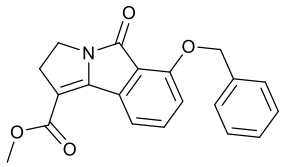
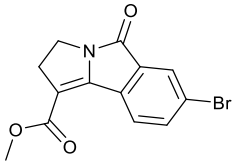
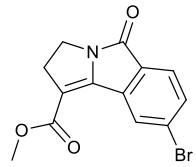
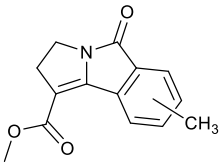
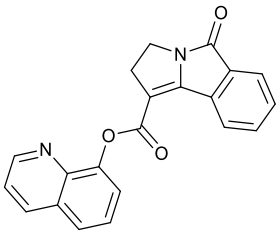
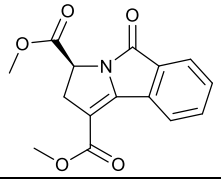
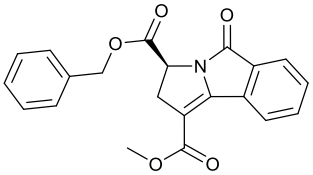
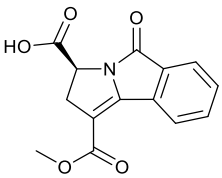
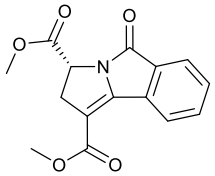
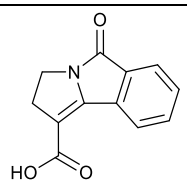
The compounds were tested using a primary 96 well plate screening assay and testing against MRSA (Gram+) and *E. coli* (Gram-) bacterial strains (See Experimental for details) with the results displayed in Table **6.1** along with the calculated molecular weights, ClogP, tPSA along with hydrogen bond donors and acceptors.

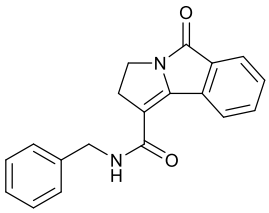
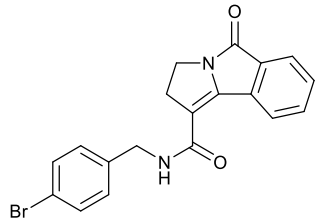
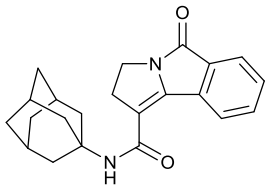
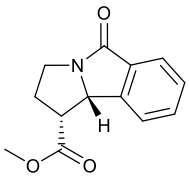
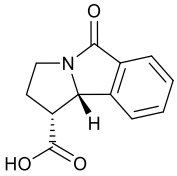
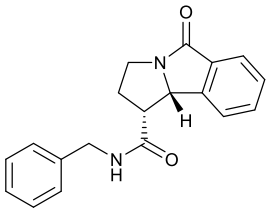
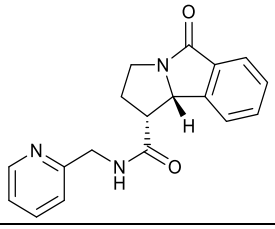
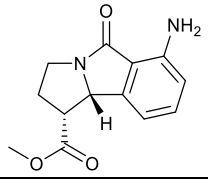
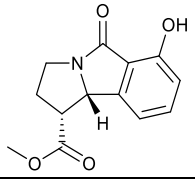
Table 6.1. Comparison for the data collected for compounds against MRSA and *E. coli*, all values for MIC are in μg/mL

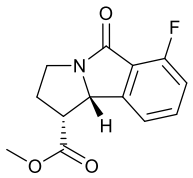
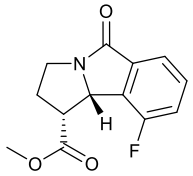
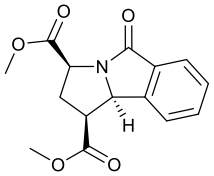
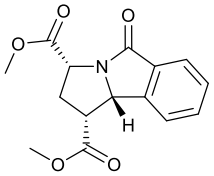
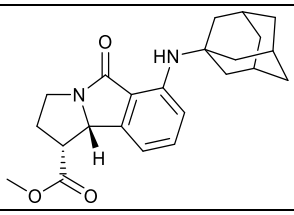
	Compound Number	MRSA	*E.coli*	Mw	Clog P	tPSA	logS	HBD	HBA
	179	n.a	n.a	308.1	2.894	66.48	-3.80	1	6
	208	7.8	7.8	360.1	3.437	76.04	-4.70	0	7
	204	n.a	n.a	351.9	3.402	78.84	-4.41	1	7

	205	n.a	n.a	435.1	4.84	78.84	-6.04	1	7
	142	n.a	n.a	381.1	2.780	89.98	4.27	0	8
	77a	n.a	n.a	311.1	2.146	55.84	-2.65	0	6
	77c	n.a	n.a	325.1	2.665	55.84	-2.78	0	6
	78c	n.a	n.a	311.1	2.196	66.84	-2.41	1	8
	77d	n.a	n.a	389.0	3.509	55.84	-3.35	0	6
	77f	n.a	n.a	339.1	3.184	55.84	-2.27	0	6
	77g	n.a	n.a	379.0	4.142	55.84	-3.61	0	6
	144a	n.a	n.a	361.1	3.401	55.84	-4.00	0	6

	144b	n.a	n.a	406.1	3.306	107.65	-4.36	0	11
	172c	n.a	n.a	439.0	4.339	55.84	-4.80	0	6
	172d	n.a	n.a	439.0	4.339	55.84	-4.80	0	6
	172j,i	125	n.a	375.1	3.900	55.84	-4.35	0	6
	209	125	125	474.2	4.906	68.20	-6.36	0	7
	175L	n.a	n.a	419.1	3.428	82.14	-4.10	0	8
	194	n.a	n.a	245.0	0.229	59.14	-1.72	0	6
	146a	n.a	n.a	229.0	0.775	46.61	-2.53	0	4
	146f	n.a	n.a	247.0	0.994	46.61	-2.77	0	4

	146j	n.a	n.a	335.1	2.763	55.84	-4.40	0	6
	186c	n.a	n.a	306.9	1.714	46.61	-3.34	0	4
	186d	n.a	n.a	306.9	1.714	46.61	-3.34	0	4
	186j,i	n.a	n.a	243.0	1.274	46.61	-2.89	0	4
	214	31.25	125	342.1	2.539	58.97	-4.92	0	5
	187L	n.a	n.a	287.0	0.853	72.91	-2.64	0	6
	188	n.a	n.a	363.1	2.564	72.91	-4.49	0	6
	226	n.a	n.a	273.0	0.527	83.91	-2.26	1	8
	187D	n.a	n.a	287.0	0.853	72.91	-2.64	0	6
	160a	n.a	n.a	215.0	0.427	57.61	-2.51	1	6

	215a	n.a	n.a	304.1	1.989	49.41	-4.01	1	4
	215b	n.a	n.a	382.0	2.852	49.41	-4.83	1	4
	215c	n.a	n.a	348.1	2.926	49.41	-4.96	1	4
	196a	n.a	n.a	231.0	0.975	46.61	-2.15	0	4
	217	n.a	n.a	217.0	0.512	57.61	-1.77	1	6
	227	n.a	n.a	306.1	1.927	49.41	-3.68	1	4
	218	n.a	n.a	307.1	0.430	61.77	-2.91	1	5
	196b	n.a	n.a	246.1	0.258	72.63	-1.87	1	5
	196i	n.a	n.a	247.0	0.849	66.84	-1.82	1	6

	196e	n.a	n.a	249.0	1.194	46.61	-2.39	0	4
	196f	n.a	n.a	249.0	1.194	46.61	-2.37	0	4
	198L	n.a	n.a	289.1	1.002	72.91	-2.26	0	6
	198D	n.a	n.a	289.1	1.002	72.91	-2.26	0	6
	197	n.a	n.a	380.2	3.684	58.64	-4.87	1	5

n.a. = not active

Noteworthy was the general lack of antibacterial activity for all compounds tested, with the exception of **208, 172i,j, 209** and **214**. Activity of **208** and **214** could be the result of their being HCl and TFA salts. It was not a complete surprise that the silyl containing compounds would show little to no activity, with **172i,j** and **209** giving the best results; in any case, these would be subject to desilylation or elimination under physiological conditions. It was hoped that a base level of antibacterial activity would be observed that could then be further built on by skeletal functionalisation. However, due to time constraints and difficulties discovered during the synthesis of these compounds that have been well documented in this thesis, further functionalisation was not achievable.

For all the compounds tested, ClogP and tPSA were calculated using *ChemDraw*, with the tPSA ranging from as low as 46 to as high as 107 that would suggest these compounds should have less of a problem permeating the cell.[295,296] ClogP is a logarithmic measurement of a compounds

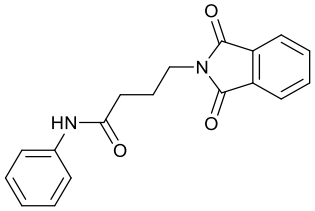
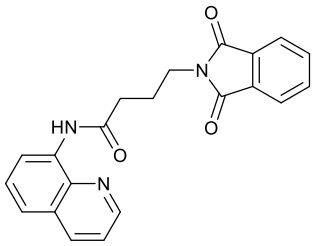
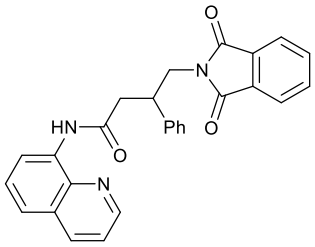
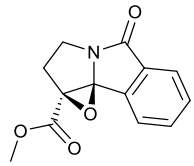
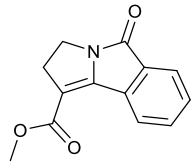
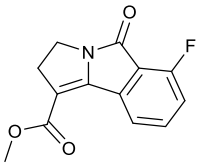
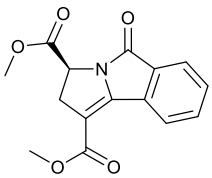
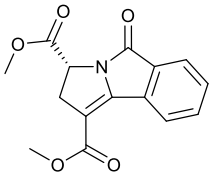
partition coefficient between *n*-octanol and water and is a well-established measurement of a compound's hydrophilicity.[297] It should be noted that these values are calculated and not compared to any values gathered experimentally.[298] When looking at these predicted values, the silyl containing pyrrolizidines had values around 3.5 suggesting that these are mostly hydrophobic, while the unsaturated variants were much lower, around 1, suggesting a preference for water solubility. However, as already demonstrated extensively in this thesis, the unsaturated systems show a great level of insolubility in nearly all solvents, even alcohol-based solvents.

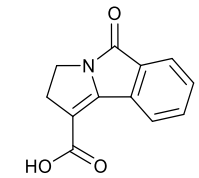
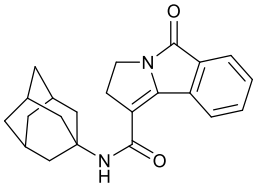
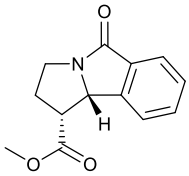
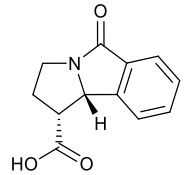
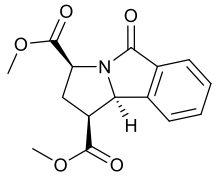
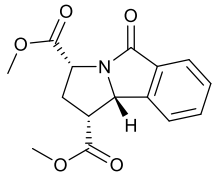
The solubility of all compounds in Table **6.1** was calculated (logS). An ideal value is greater than -4, as seen with a large share of commercial drugs, however these values do not take into account additional factors such as pH, therefore not totally accurate. An example of this is **160a**, that when it is under natural conditions, was totally insoluble in water, but predicted to be soluble when considering its logS value. It should be noted that all compounds synthesised and tested followed the rule of 5[34] with all other chemoinfomatic data suggesting these compounds form a well-rounded library to be used in determining a base level of antibacterial activity.

6.2. Anticancer Screening

When possible, compounds that had been synthesised during this project were submitted for analysis with their cytotoxicity tested by *Oxford Antibacterial Group*. The compounds were tested against four different cell lines: HeLa, HEK 293, CaCo and MDCK (see Experimental for full details) with the results displayed in Table **6.2**.

Table 6.2. Comparison of anticancer data for a collection of compounds against HeLa, HEK 293, CaCo, MDCK cell lines

Compound Structure	Compound Number	HeLa	HEK 293	CaCo	MDCK
	179	125	62.5	125	125
	204	62.5	62.5	62.5	62.5
	205	125	125	125	125
	194	62.5	62.5	62.5	62.5
	146a	62.5	62.5	62.5	62.5
	146f	62.5	31.2	62.5	62.5
	187L	62.5	62.5	125	125
	187D	125.0	62.5	62.5	62.5

	160a	62.5	62.5	125	125
	215c	15.6	15.6	31.2	31.2
	196a	62.5	62.5	62.5	62.5
	217	31.2	62.5	62.5	125
	198L	62.5	62.5	62.5	62.5
	198D	62.5	62.5	62.5	62.5

Once again nearly all the compounds that were tested showed activity that was near, or the same as, DMSO that was used as the solvent standard, suggesting these compounds are relatively inactive, but with two exceptions, **215c** and **217**.

Compound **215c** was shown to be moderately active against HeLa and HEK 293 with lesser activity against CaCo and MDCK and was **217** only weakly active against HeLa cells and inactive against the remaining cell lines.

It was observed that during testing, precipitation of the compound was seen, which is not surprising after the problems associated with solubility already discussed and explored in this thesis. Therefore, it would seem that the low solubility or insolubility is an intrinsic limitation of this type of compound class.

6.3. Summary of Chapter VI

This chapter reports values for antibacterial and anticancer activity of compounds synthesised during this thesis. It was hoped that activity would have been seen with the core pyrrolizidines core systems that could then be later functionalised by skeletal functionalisation to enhance their activity. However, nearly all compounds tested showed little to no activity making direct comparisons or being able to elucidate a conclusion on what causes activity impossible. The underlying motivation of this thesis and the strategy employed in the chemical synthesis of compounds was done in such a way to further expand on the natural product UCS1025A but manipulating the bicyclic core, while further elaborating substituents, to give greater levels of antibacterial activity. By contrast, a similar strategy in the Moloney group in which tetramates were very successfully developed for antibacterial activity, by taking a relatively inactive core skeleton and implementing system functionalisation at the ring periphery, had been highly successful, and suggests that more complex elaboration and functional group manipulation is needed to introduce activity in the UCS1025A class.[46,48,171,299–301]

Chapter VII: Experimental Techniques and Results

Commercial reagents were obtained from Acros Organics, Alfa Aesar, Apollo Scientific, Fisher Scientific, Merck or Sigma Aldrich and were used without any further purification. The only exception to this was 8-aminoquinoline that was purified using flash column chromatography (40% ethyl acetate in pet-ether 40:60) prior to use.

All reactions were performed in oven-dried glassware and under a N_2 atmosphere, unless non-anhydrous solvents were used. Anhydrous solvents were obtained from MBraun MB SPS5solvent purification system prior to use. Reactions that were concentrated, were done so with the water bath set to 40 °C while under reduced pressure using a Büchi R-114 rotatory evaporator that was attached to a Vacuubrand CVC2 pump with a pressure control system attached. When compounds were dried using reduced pressure, the water bath was set to 40 °C with the pump set to continuous, typically between 0-5 mb.

Analytical thin layer chromatography (TLC) was conducted using Merck aluminium foil backed sheets coated with 0.2 mm Kielselgel 60 F_{254}. The eluent used is specified for each compound purified using flash column chromatography. TLC spots were visualised by UV irradiation (λ 254 and 366 nm) and where necessary, staining with ninhydrin or phosphomolybdic acid (PMA) solution followed by heating by using a heat gun. Iodine chamber was also used when applicable. Retention factors (**R_f**) are quoted to two decimal places. Flash column chromatography was performed on Kielselgel 60 silica gel (230-400 mesh size).

Optical rotations were recorded at 25 °C on a Perkin-Elmer 421 polarimeter using the D line of sodium (589) and a path length of 1 dm. Concentrations (c) are reported in g/100 mL and specific rotations ($[\alpha]_D^{25}$) are quoted in 10^{-1} deg cm^2 g^{-1}.

Melting points (**Mp**) were recorded on a Stuart Scientific SMP1 melting point instrument and are uncorrected. When compounds exceeded 240 °C, the apparatus struggled to get hotter than this value so will be quoted as +240 °C.

Infrared spectra (**IR**) were recorded using a Bruker Tensor 27 FT-IR spectrometer equipped with an attached Pike Miracle attenuated total reflectance (ATR) module. Absorption maxima ($\boldsymbol{\nu_{max}}$) are reported in wavenumbers (cm^{-1}) with selected characteristic peaks assigned where possible.

^{1}H NMR spectra were recorded on any of the following instruments; Brucker DPX200 (200 MHz), AVIII HD 400 (400 MHz), AVC 500 (500 MHz), AV600 (600 MHz) and AV700 (700 MHz) and will be stated for each individual experiment. Deuterated solvents used for analysis were chloroform, methanol, dimethyl sulfoxide and water. The reference peak for each solvent was set before interpretation of the NMR spectrum was conducted. The solvent reference peak was set from the middle peak of each solvent used. Chemical shifts (δ_H) are reported in parts per million (ppm) downfield from TMS. Coupling constants (*J*) are reported in Hz. Data are reported as the following; chemical shift, intergration, multiplicity (s= singlet, d=doublet, t=triplet, q=quartet, p=quintet, dd=double doublet, dt=double triplet, m=multiplet), coupling constant, and proton assignment. Two-dimensional COSY and HSQC were recorded on a Bruker AVIII HD 400 (400 MHz) and AVC 500 (500 MHz). HMBC, NOESY and 1D nOe were recorded on AVC 500 (500 MHz). When possible, all protons were assigned according to the nomenclature set forth at the beginning of this thesis.

^{13}C NMR spectra were recorded in a Bruker AVIII HD400 at 101 MHz, AVC 500 at 125 MHz and AV600 at 150 MHz with a proton decoupling and will be stated for each individual experiment. Chemical shifts (δ_c) are reported in ppm downfield from TMS. Deuterated solvents used for analysis were chloroform, methanol, dimethyl sulfoxide and water. The reference peak for each solvent was set before interpretation of the NMR spectrum were conducted. Assignments of the spectra were made with HSQC experiments, which was performed on a Brucker AVIII 400 HD. When possible, all carbon peaks were assigned according to the nomenclature set forth at the beginning of this thesis.

Low resolution mass spectra (***m/z***) were recorded on a Fison Platform spectrometer using electrospray ionisation (ESI) with both positive and negative ESI reported when possible.

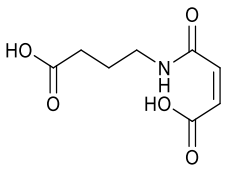
High resolution mass spectra (**HRMS**) were recorded on a Bruker microTOF (ESI), on an Agilent 7200 Q-TOF (CI) or on a Waters GCT (EI) with the predicted and observed mass ion reported to four decimal places.

Crystals for x-ray crystallography were grown from slow vapour diffusion at room temperature of petroleum either 40:60 into a solution of the requisite compound in either $CDCl_3$ or DCM.

Screening of compounds was performed by Oxford Antibiotic Group, Austria. For MIC determination by broth dilution assay, the samples were tested in a primary 96 well plate screening assay. The compounds were diluted in Mueller Hinton Broth (MHB) for bacterial screening to a stock solution of 1.0 mg/mL, serial diluted and overlaid with a microbe solution in a concentration of 104 CFU/ml. The plates were incubated for 24 h at 35 °C, after which MIC values were read from the plates.

For cytotoxicity testing, the synthesised compounds were tested against four different cell lines: HeLa, HEK 293, MDCK and CaCo. The cells were seeded in a 96 well plate and incubated until a confluence of 80% was achieved (under physiological conditions – 37 °C, 5% CO_2 and 95% humidity). The samples were tested by serial dilution in triplicates with starting concentration of 250 µg/mL. After 24 and 48 hours the survival of cells was evaluated by microscope and measured with Alamar blue. IC_{50} values were obtained from the calibration curves.

(*Z*)-4-((3-Carboxypropyl)amino)-4-oxobut-2-enoic acid[180] 110

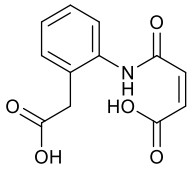


110

Maleic anhydride (0.250 g, 2.54 mmol) and 4-aminobutanoic acid (0.262 g, 2.54 mmol) were dissolved in glacial acetic acid (15 mL) and stirred at room temperature for 16 hours. The white precipitate that had formed was filtered under vacuum then washed using glacial acetic acid (20 mL) and ice-cold water (2 x 20 mL) to afford the desired product as a white coloured solid (0.523 g, quantitative).

Mp= 170-172 °C (lit. 161.5-162.5 °C)[180] . **ν_{max} (KBr) cm^{-1}** 3310 (N-H), 3053 (O-H), 2980 (C-H), 2885 (C-H), 1706 (C=O), 1681 (N-C=O), 1620 (C=O), 1518 (N-H), 1493, 1464, 1403, 1375, 1290 (C-O), 1228, 898 (C=C), 866 (C=C). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.05 (t, *J* = 5.7 Hz, 1H, *N*(5)*H*), 6.39 (d, *J* = 12.5 Hz, 1H, C(7)*H*), 6.23 (d, *J* = 12.5 Hz, 1H, C(8)*H*), 3.19 (q, *J* = 7.0, 5.7 Hz, 2H, C(4)*H*), 2.26 (t, *J* = 7.4 Hz, 2H, C(2)*H*), 1.69 (p, *J* = 7.2 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, DMSO) δ 174.06 (C(1)COOH), 165.49 (C(6,9)C=O) , 132.56 (C(8)**C**=C), 131.97 (C(7)C=**C**), 38.55 (C(4)), 30.94 (C(2)), 23.90 (C(3)). ***m/z*=** 200 [MH-] (ESI$^-$) and 224 [MNa+] (ESI$^+$). **HRMS** calculated for $C_8H_{11}NNaO_5$ requires 224.0529, found at 224.0529 [MNa+] (ESI$^+$). All data are in agreement with those found in the literature.[180]

(*Z*)-4-((2-(Carboxymethyl)phenyl)amino)-4-oxobut-2-enoic acid 121

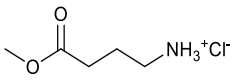


121

Maleic anhydride (0.200 g, 1.47 mmol) and 2-aminophenylacetic acid (0.200 g, 1.47 mmol) were suspended in toluene and left stirring at room temperature for 16 hours. The solvent was removed using reduced pressure to afford the desired product as an orange coloured solid (0.363 g, quantitative).

ν_{max} (KBr) cm^{-1} 3233 (N-H), 3041 (C-H), 1704 (C=O), 1682 (N-C=O), 1617 (C=O), 1524 (N-H), 1488, 1401, 1310, 1216, 1189, 1039 (C-O), 987 (C-O), 920, 851 (C=C-H), 757 (C=C-H). **^{1}H NMR** (200 MHz, Methanol-d_4) δ 7.40 – 7.21 (m, 4H, Ar-H), 6.65 (d, *J* = 12.4 Hz, 1H, C(11)*H*), 6.32 (d, *J* = 12.4 Hz, 1H, C(12)*H*), 3.71 (s, 2H, C(2)*H*). ***m/z***= 248 [MH-] (ESI$^-$) and 272 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{12}H_{11}NNaO_5$ requires 272.0529, found at 272.0530 [MNa+] (ESI$^+$).

4-Methoxy-4-oxobutan-1-aminium chloride 80



80

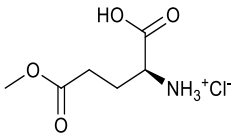
Method 1)[185] Acetyl chloride (0.689 mL, 8.77 mmol) was added to a conical flask and cooled down to 0 °C using an ice bath, with MeOH (2.5 mL) added dropwise over 5 minutes. The solution was allowed to stir for a further 5 minutes to ensure completion. The methanolic HCl solution was then added dropwise to a pre-cooled solution of 4-aminobutanoic acid (0.500 g, 4.38 mmol) in MeOH (2.5 mL) with the resulting mixture left stirring at room temperature for 16 hours. The reaction was concentrated by reduced pressure to afford the desired product as a white coloured solid (0.607 g, 107%) presumed to be the HCl salt. **Mp=** 94-98 °C (Lit. 97-101 °C).[302]

Method 2)[184] 4-Aminobutanoic acid (0.100 g, 0.97 mmol) was dissolved in MeOH (3 mL) and cooled down to 0 °C using an ice bath. An excess quantity of $SOCl_2$ (0.211 mL, 2.90 mmol) was slowly added dropwise over 5 minutes, with the reaction mixture left to warm to room temperature while stirring for 16 hours. The solution was concentrated by reduced pressure and azeotroped using DCM (3 x 10 mL) to afford the desired product as a pale yellow coloured solid (0.120 g, quantitative yield). **Mp**= 92-94 °C (Lit. 97-101 °C).[302]

ν_{max} (KBr) cm^{-1} 2953 (CH_2 and NH_2HCl), 1727 (C=O), 1588 (NH_2), 1513, 1427, 1383, 1292 (N-C), 1205 (C-O), 1152 (C-O), 1066, 758 (NH_2). **^{1}H NMR** (200 MHz, Methanol-d_4) δ 3.69 (s, 3H, OMe), 2.98 (t, *J* = 7.7 Hz, 2H, C(4)*H*), 2.49 (t, *J* = 7.1 Hz, 2H, C(2)*H*), 1.93 (p, *J* = 7.4 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, MeOD) δ 174.49 (C(1)COOMe), 52.35 (C(1)OMe), 40.14 (C(4)), 31.42 (C(2)), 23.73 (C(3)). ***m/z***= 118 [MH+] (ESI^+), 252 [MNa+] (ESI^+) and 162 [M+FA-H] (ESI^-). **HRMS** calculated for $C_4H_{10}NO_2$ requires 118.0863, found at 118.0864 [MH+] (ESI^+).

All data are in agreement with those found in the literature.[302]

L-Glutamic acid 5-methyl ester hydrochloride[303] **118**



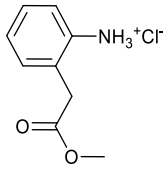
118

L-Glutamic acid (4.00 g, 27.18 mmol) was suspended in methanol (30 mL) with TMSCl (6.90 mL, 54.37 mmol) added dropwise over 5 minutes with the reaction left stirring at room temperature for 30 minutes. After this period in which all the starting material had dissolved, the solvent was removed using reduced pressure to afford the desired product as a white coloured solid (4.81 g, quantitative yield).

Mp= 183-185 °C (Lit. 180 °C). **^{1}H NMR** (400 MHz, Methanol-d_4) δ 4.06 (t, *J* = 6.6, Hz, 1H), 3.70 (s, 3H), 2.64 – 2.53 (m, 2H), 2.31 – 2.10 (m, 2H).

All data are in agreement with those found in the literature.[304]

2-(2-Methoxy-2-oxoethyl)benzenaminium chloride 139



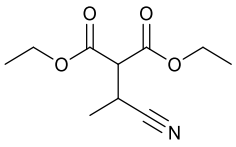
139

2-Aminophenylacetic acid (0.470 g, 3.11 mmol) was dissolved in MeOH (10 mL) in a round bottomed flask and cooled down to 0 °C using an ice bath. $SOCl_2$ (0.68 mL, 6.22 mmol) was added dropwise over 5 minutes after which the reaction was allowed to warm to room temperature and left stirring for 16 hours to ensure completion. The solvent mixture was removed by reduced pressure then azeotroped using DCM (3 x 20 mL) to afford the desired product as a beige coloured solid (0.536 g, quantitative yield).

Mp= 110-112 °C (Lit. 105-108 °C).[305] **ν_{max} (KBr) cm^{-1}** 2805 (NH_2 Salt), 1725 (C=O), 1622, 1565, 1519, 1493, 1472, 1458, 1439, 1342 (Ar-N), 1298, 1245, 1167 (C-O), 1116, 1005. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.46 (m, 4H, Ar-H), 3.92 (s, 2H, C(2)*H*), 3.75 (s, 3H, C(1)OMe). **^{13}C NMR** (101 MHz, MeOD) δ 180.04 (C(1)COOMe), 133.58 (Ar**C**-NH_3), 130.61 (ArC), 130.30 (ArC), 128.84 (ArC), 125.56 (ArC), 124.98 (ArC), 123.25 (ArC), 49.85 (C(1)OMe). ***m/z***= 199 [MCl+] (ESI$^+$). **HRMS** calculated for $C_8H_{10}NO_2$ requires 166.0863, found at 166.0864.

All data are in agreement with those found in the literature.[305]

Diethyl 2-(1-cyanoethyl)malonate 224



224

In an oven-dried round bottomed flask that had been purged with N_2, NaH (0.179 g, 4.48 mmol, 60% dispersed with mineral oil) was suspended in anhydrous THF (5 mL). In a separate oven-dried round bottomed flask that had been purged with N_2, Diethyl malonate (0.630 mL, 3.74 mmol) was dissolved in anhydrous THF (2.5 mL) and syringed into the hydride containing flask dropwise over 5 minutes that had been cooled to 0 °C prior. The reaction was left stirring at 0 °C for 1 hour. After this time, bromopropionitrile (0.77 mL, 3.74 mmol) was added dropwise over 5 minutes and left stirring at room temperature. After 16 hours a white precipitate had formed that was tested by ^{1}H NMR spectroscopy due to the low UV activity of the desired product that showed starting

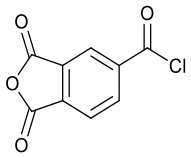
material remained. The solution was cooled down to 0°C and transferred to a separating funnel and washed using 1% Na_2CO_3 (20 mL, at 0°C) with the combined aqueous layers being extracted using diethyl ether (2 x 15 mL). The organic layers were combined and dried over $MgSO_4$ and concentrated by reduced pressure. The crude was purified by flash column chromatography (gradient from 5%-10% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a colourless oil (0.168 g, 21%).

Note that the low yield was due to reaction not going to completion and difficult purification from lack of UV activity of the desired compound.

^{1}H NMR (200 MHz, Chloroform-*d*) δ 4.37 – 4.15 (m, 4H, C(1a,3a) O-**CH_2**-), 3.53 (d, *J* = 8.4 Hz, 1H, C(2)*H*), 3.35 (dq, *J* = 8.5, 7.0 Hz, 1H, C(4)*H*), 1.41 (d, *J* = 7.0 Hz, 3H, (C(5)*H*), 1.30 (td, *J* = 7.1, 2.5 Hz, 6H, (C(1a,3a) OCH_2-**CH_3**). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.86 (C(1,3) C=O), 165.83 (C(1,3) C=O), 119.92 (C(6) C≡N), 62.17 (C(1a,3a) O-**C**H_2-, 54.24 (C(2)), 24.97 (C(4)), 15.79 C(5)), 13.74 (C(1a,3a) -CH_2-**CH_3**). ***m/z***= 214 (ESI^+) [MH+].

All data are in agreement with those found in the literature. [306]

2,9-Dioxo-2,9-dihydroisobenzofuran-5-carbonyl chloride 225



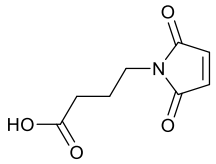
225

Trimellitic anhydride (1.00 g, 5.21 mmol) was added to an over-dried round bottom flask that had been purged using N_2 followed by an excess of $SOCl_2$ (6 mL) and heated up to 88 °C with a drop of DMF being added. The reaction was then left stirring at reflux until the gas had ceased to evolve. The reaction was allowed to cool to room temperature and concentrated using reduced pressure, with the oil azeotroped using DCM (3 x 50 mL) to afford the desired product as a yellow-coloured oil that solidified over 5 minutes (0.896 g, 82%).

Mp= 61-62 °C (Lit. 66-67 °C).[307] **ν_{max} (KBr) cm^{-1}** 1855 (C=O), 1777 (Cl-C=O), 1751 (C=O), 1427, 1263, 1191, 1151, 1109, 1086, 862 (C-Cl). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.72 (C(5a)Cl-**C**=O), 161.25 (C(9)C=O), 161.09 (C(2)C=O), 140.22 (C(5)Ar**C**-C=O), 138.07 (C(6)ArC, 135.95 (C(8)ArC), 132.22 (C(3)ArC), 128.28 (C(4)ArC), 126.49 (C(7)ArC).

All data is in agreement with that found in literature.[307]

4-(6,9-Dioxo-6,9-dihydro-5H-pyrrol-5-yl)butanoic acid[156,180] **91a**



91a

Maleic anhydride (0.500 g, 5.09 mmol) was added to 4-aminobutanoic acid in a round bottomed flask and dissolved in AcOH (10 mL) and left stirring for 16 hours at room temperature. The reaction was then heated to reflux (122 °C) and left stirring for a further 16 hours. The reaction was concentrated by reduced pressure to remove AcOH, then redissolved in DCM (5 mL) and purified *via* flash column chromatography (5% AcOH in DCM) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as an off white coloured solid (0.412 g, 44%). NMR showed residual AcOH still present with product calculated at 95.5% pure.

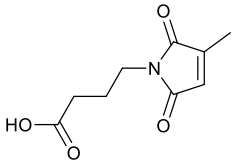
R_f =0.13. **Mp** 86-90 °C (Lit. 90-92 °C).[180] **ν_{max} (KBr) cm^{-1}** 1688 (N-C=O), 1444 (O-H), 1410, 1374 (CH), 1354, 1342, 1293, 1224, 1145. **^{1}H NMR** ^{1}H NMR (200 MHz, Chloroform-*d*) δ 6.71 (s, 2H, C(7,8)*H*), 3.60 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.38 (t, *J* = 7.3 Hz, 2H, C(2)*H*), 1.93 (p, *J* = 14.0, 7.0 Hz, 2H, C3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.43 (C(1)COOH), 170.90 (C6,9) C=O), 134.28 (C(7,8) C=C), 37.09 (C(4)), 31.24 (C2)), 23.66 (C3)).

All data are in agreement with those found in the literature.[180]

General procedure A for solventless imide formation

Substituted maleic anhydride (1.0 eq) was added to 4-aminobutanoic acid (1.0 eq) in a round bottomed flask and heated at 150 °C for 6 hours while stirring. The reaction was left to cool to room temperature with the resulting solid mass dissolved in DCM (10 mL) and transferred to a separating funnel. The organic layer was washed using 0.5 N HCl (2 x 10 mL) with the combined aqueous layers being back extracted with DCM (20 mL). The organic layers were then combined and concentrated by reduced pressure to afford the desired maleimide.

4-(7-Methyl-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)butanoic acid 91b



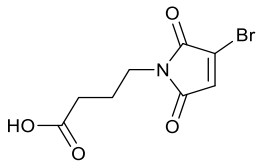
91b

91b was synthesised according to general procedure **A** using methylmaleic anhydride (0.435 mL, 4.84 mmol) and 4-aminobutanoic acid (0.500 g, 4.84 mmol) to afford the desired product as a pale orange coloured oil (0.812 g, 85%).

ν_{max} (KBr) cm^{-1} 2946 (O-H), 1769 (N-C=O), 1696 (N-C=O), 1643 (C=O), 1444, 1408 (O-H), 1379, 1189, 1129 (C-O), 1104, 1037. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.31 (q, *J* = 1.8 Hz, 1H, C(8)*H*), 3.54 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.34 (t, *J* = 7.4 Hz, 2H, C(2)*H*), 2.05 (d, *J* = 1.9 Hz, 3H, C(7a)*H*), 1.88 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.19 (C(1)COOH), 171.97 (C(6)C=O), 171.04 (C(9)C=O), 145.81 (C(7)C=**C**-CH_3), 127.43 (C(8)C=**C**-H), 37.11 (C(4)), 31.25 (C(2)), 23.72 (C(3)), 11.01 (C(7a)C=C-**C**H_3). ***m/z***= 220 [MNa+] (ESI$^+$) and 417 [2MNa+] (ESI$^+$). **HRMS** calculated for $C_9H_{11}NNaO_4$ requires 220.0580, found at 220.0583 [MNa+] (ESI$^+$).

All data are in agreement with those found in the literature.[181]

4-(7-Bromo-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)butanoic acid 91c

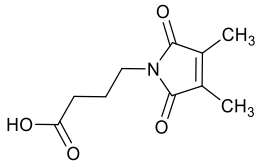


91c

91c was synthesised according to general procedure **A** using bromomaleic anhydride (0.450 mL, 4.84 mmol) and 4-aminobutanoic acid (0.500 g, 4.84 mmol) to afford the desired product dark brown coloured oil (1.03 g, 82%).

ν_{max} (KBr) cm^{-1} 2944 (O-H), 1777 (C=O), 1702 (N-C=O), 1589, 1443 (O-H), 1399, 1361, 1280, 1231 (C-O), 1137, 1088, 1001, 856, 824 (C=C), 761, 702. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.89 (s, 1H, C(8)*H*), 3.64 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.39 (t, *J* = 7.3 Hz, 2H, C(2)*H*), 1.94 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.39 (C(1)COOH), 168.72 (C(6)C=O), 165.47 (C(9)C=O), 132.00 (C(8)C=**C**-H), 131.56 (C(7)C=**C**-Br), 38.08 (C(4)), 31.18 (C(2)), 23.57 (C(3)). ***m/z***= 260 and 262 [MH-] (ESI$^-$). **HRMS** not found.

4-(7,8-Dimethyl-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)butanoic acid 91d



91d

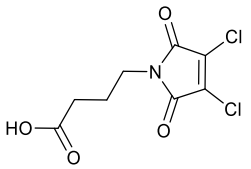
91d was synthesised according to general procedure **A** using 2,3-dimethylmaleic anhydride (0.100 g, 0.79 mmol) and 4-aminobutanoic acid (0.081 g, 0.79 mmol) to afford product as a pale yellow coloured solid (0.172 g, quant).

Mp= 68-70 °C (Lit. 43-45 °C).[308] **ν_{max} (KBr) cm^{-1}** 2983 (O-H), 1764, (C=O), 1693 (N-C=O), 1443, 1407, 1276, 1189 (C-O), 1104, 1035, 927, 733, 685. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.55 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.35 (t, *J* = 7.4 Hz, 2H, C(2)*H*), 1.98 – 1.85 (m, 8H, C(3)*H*, C(7a,8a)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.28 (C(1)COOH), 172.33 (C(6,9) C=O), 137.35

C(7,8) C=C), 37.12 (C(2)), 31.33 (C(4)), 23.91 C(2)), 8.79 (C(7a, 8a) C=C-CH_3). ***m/z***= 234 [MNa+] (ESI^+), 210 [MH-] (ESI^-). **HRMS** calculate for $C_{10}H_{13}NNaO_4$ requires 234.0747, found at 234.0737 [MNa+] (ESI^+).

All data are in agreement with those found in the literature.[308]

4-(7,8-Dichloro-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)butanoic acid 91e



91e

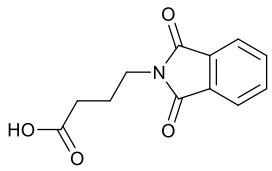
91e was synthesised according to general procedure **A** using 2,3-dichloromaleic anhydride (0.500g, 3.00 mmol) and 4-aminobutanoic acid (0.310 g, 3.00 mmol) to afford the desired product as an orange coloured solid (0.651 g, 86%).

Mp= 120-125 °C. **ν_{max} (KBr) cm^{-1}** 2980 (O-H), 1707 (N-C=O), 1693 (N-C=O), 1625 (C=O), 1452, 1435, 1397, 1358, 1334, 1298, 1237 (C-O), 1195, 1120, 1071, 1033, 995, 927, 882, 859, 734. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.68 (t, *J* = 6.9 Hz, 2H, C(4)*H*), 2.41 (t, *J* = 7.3 Hz, 2H, C(2)*H*), 1.96 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.22 (C(1)COOH), 163.14 (C(6,9)C=O), 133.48 (C(7,8)C=C), 38.65 (C(4)), 31.14 (C(2)), 23.52 (C(3)). ***m/z***= 249 and 251 [MH-] (ESI^-). **HRMS** calculate for $C_8H_6Cl_2NO_4$ requires 249.9679, found 249.9677 [MH-] (ESI^-) and requires 251.9649, found at 251.9648 [MH-] (ESI^-).

General procedure B for solventless imide formation

Phthalic anhydride (1.0 eq) was added to 4-aminobutanoic acid (1.0 eq) in a round bottomed flask and heated at 170 °C for 6 hours while stirring. The reaction was left to cool to room temperature with the resulting solid mass dissolved in DCM (10 mL) and transferred to a separating funnel. The organic layer was washed using 0.5 N HCl (2 x 10 mL) with the combined aqueous layers being back extracted with DCM (20 mL). The organic layers were then combined and concentrated by reduced pressure to afford the desired phthalimide.

4-(6,13-Dioxoisoindolin-5-yl)butanoic acid[186] **123a**



123a

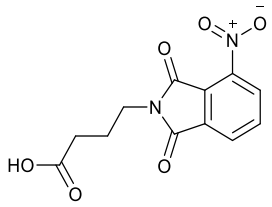
Method A) **123a** was synthesised according to general procedure **B** using phthalic anhydride (0.500 g, 3.37 mmol) and 4-aminobutanoic acid (0.435 g, 3.37 mmol) to afford the desired product as an off white coloured solid (0.793 g, quantitative yield).

Method B) **123a** was synthesised according to general procedure **B** using phthalic acid (0.500 g, 3.00 mmol) and 4-aminobutanoic acid (0.310 g, 3.00 mmol) with Phthalic acid used in replacement of phthalic anhydride afford the desired product as an off white coloured solid (0.508 g, 72%).

Mp= 112-114 °C (lit, 117 °C).[186] **ν_{max} (KBr) cm^{-1}** 2980 (O-H), 2888 (C-H), 1765 (C=O), 1698 (N-C=O), 1467 (C=C), 1357 (C-H). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H, Ar-H), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H, Ar-H), 3.77 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.42 (t, *J* = 7.4 Hz, 2H, C(2)*H*), 2.02 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 177.4 (C(1)COOH), 168.4 (C(6,13)C=O), 134.0 (ArC),132.0 (ArC), 123.3 (C(7,12)ArC), 37.0 (C(4)), 31.1 (C(2)), 23.6 (C(3)). ***m/z***= 398 [2M-H] (ESI^{+}). **HMRS** calculate $C_{12}H_{10}NO_4$ requires 232.0615, found at 232.0615 [MH^{-}] (ESI^{-}).

All data are in agreement with those found in the literature.[186]

4-(8-Nitro-6,13-dioxoisoindolin-1-yl)butanoic acid 123b



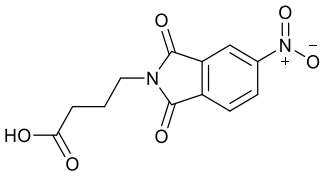
123b

123b was synthesised according to general procedure **B** using 3-nitrophthalic anhydride (0.500 g, 2.58 mmol) and 4-aminobutanoic acid (0.267 g, 2.58 mmol) to afford the desired product as an off white coloured solid (0.692 g, 93%).

Mp= 118-120 °C (Lit. 132-133 °C).[309] **ν_{max} (KBr) cm^{-1}** 2873 (C-H) 1693 (N-C=O), 1539 (N=O), 1396 (O-H), 1357 (N=O), 1331, 1308, 1287, 1206 (C-O), 1126, 1036 (C-O), 718 (C=CH). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.21 – 8.08 (m, 2H, Ar-H), 7.99 (dd, *J* = 8.1, 7.5 Hz, 1H, Ar-H), 3.76 (t, *J* = 6.8 Hz, 2H, C(4)*H*, 2.38 (t, *J* = 7.2 Hz, 2H, C(2)*H*, 1.98 (p, *J* = 7.0 Hz, 2H, C(3)*H*. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4 (C(1)COOH), 167.6 (C(13)C=O), 164.84 (C(6)C=O), 136.8 (C(8)**C**-NO_2), 135.4 (C(7,12)ArC), 129.3 (ArC), 127.6 (ArC), 38.9 (C(4)), 32.1 (C(2)), 24.6 (C(3)). ***m/z*** = 301 [MNa^+] (ESI^+) and 277 [MH^-] (ESI^-). **HRMS** calculated for $C_{12}H_{10}N_2NaO_6$ requires 301.0431, found at 301.0430 [MNa^+] (ESI^+).

All data are in agreement with those found in the literature.[309]

4-(9-Nitro-6,13-dioxoisoindolin-1-yl)butanoic acid 123c



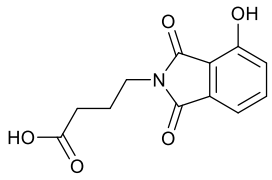
123c

123c was synthesised according to general procedure **B** using 4-nitrophthalic anhydride (0.500 g, 2.58 mmol) and 4-aminobutanoic acid (0.267 g, 2.58 mmol) to afford the desired product as a beige coloured solid (0.698 g, quantitative yield).

Mp= 164-166 °C (Lit. 165-166 °C).[310] **ν_{max} (KBr) cm^{-1}** 1700 (N-C=O), 1541 (N=O), 1396 (N=O), 1346, 1304, 1285, 1123 (C-O), 1064, 1028, 938, 865, 821, 782, 720 (C=CH). **^{1}H NMR** (500 MHz, Methanol-d4) δ 8.65 (dd, *J* = 8.1, 2.0 Hz, 1H, Ar-H), 8.61 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.08 (d, *J* = 8.1 Hz, 1H, Ar-H), 3.79 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.38 (t, *J* = 7.2 Hz, 2H, C(2)*H*), 1.99 (p, *J* = 6.9 Hz, 2H, C(3)*H*). **^{13}C NMR** (126 MHz, MeOD) δ 176.47 (C(1)COOH), 167.98 (C(13)C=O), 167.75 (C(6)C=O), 153.22 (C(9)Ar**C**-NO_2), 137.96 (C(12)ArC), 134.92 (C(7)ArC), 130.38 (ArC), 125.39 (ArC), 119.10 (ArC), 38.87 (C(4)), 32.18 (C(2)), 24.69 (C(3)). ***m/z***= 277 [MH-] (ESI$^-$). **HRMS** calculated for $C_{12}H_9N_2O_6$ requires 277.0466, found at 277.0459 [MH-] (ESI$^-$).

All data are in agreement with those found in the literature.[310]

4-(8-Hydroxy-6,13-dioxoisoindolin-1-yl)butanoic acid 123d



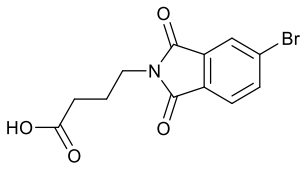
123d

123d was synthesised according to general procedure **B** using 3-hydroxyphthalic anhydride (0.900 g, 5.48 mmol) and 4-aminobutanoic acid (0.565 g, 5.48 mmol) to afford the desired product as a brown coloured solid (1.452, 92%).

Mp= 189-191 °C. **ν_{max} (KBr) cm^{-1}** 1684 (N-C=O), 1614 (C=O), 1404 (O-H), 1357 (C-H), 1286 (O-H), 1271, 1221, 1210 (C-O), 1130 (Ar-OH), 1118, 1022, 954, 885, 744 (C-H), 678, 648. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.59 (dd, *J* = 8.4, 7.2 Hz, 1H, Ar-H), 7.31 (dd, *J* = 7.2, 0.8 Hz, 1H, Ar-H), 7.14 (dd, *J* = 8.4, 0.8 Hz, 1H, Ar-H), 3.68 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.35 (t, *J* = 7.2 Hz, 2H, C(2)*H*), 1.94 (p, *J* = 7.0 Hz, 2H, (C(3)*H*). **^{13}C NMR** (101 MHz, MeOD) δ 176.52 (C(1)COOH), 169.79 (C(13)C=O), 169.48 (C(6)C=O), 156.38 (C(7)ArC), 137.02 (ArC), 134.80

(C(12)ArC), 124.11 (ArC), 115.64 (ArC), 37.96 (C(4)), 32.20 (C(2)), 24.91 (C(3)). ***m/z***= 272 [MNa+] (ESI^+). **HRMS** calculated for $C_{12}H_{11}NNaO_5$ requires 272.0529, found at 272.0529 [MNa+] (ESI^+).

4-(9-Bromo-6,13-dioxoisoindolin-1-yl)butanoic acid 123e



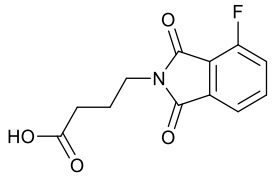
123e

123e was synthesised according to general procedure **B** using 4-bromonphthalic anhydride (0.500 g, 2.21 mmol) and 4-aminobutanoic acid (0.228 g, 2.21 mmol) to afford the desired product as a white coloured solid (0.58 g, 84%).

Mp= 139-141 °C (Lit. 103-106 °C).[192] **ν_{max} (KBr) cm^{-1}** 3331 (O-H), 1733 (C=O), 1685 (N-C=O), 1419 (O-H), 1394 (CH_2), 1374 (C=C), 1346, 1226 (C-O), 1180, 1166, 1113, 1041, 1008. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.02 – 7.93 (m, 2H, Ar-H), 7.78 – 7.70 (m, 1H, Ar-H), 3.58 (t, *J* = 6.8 Hz, 2H, C(4)*H)*, 2.26 (t, *J* = 7.2 Hz, 2H, C(2)*H*), 1.80 (p, *J* = 7.0 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, DMSO) δ 174.06 (C(1)COOH), 167.42 (C(6)C=O), 166.85 (C(13)C=O), 137.07 (C(10)ArC), 133.78 (C(12)ArC), 130.72 (C(7)ArC), 127.95 (C(9)Ar**C**-Br), 125.95 (C8)ArC), 124.94 (C(11)ArC), 37.27 (C(4)), 31.07 (C(2)), 23.33 (C(3)). ***m/z***= 310 and 312 [MH-] (ESI^-). **HRMS** calculated for $C_{12}H_9BrNO_4$ requires 309.9720 and 311.9718, found at 309.9718 and 311.9698 [MH-] (ESI^-).

All data are in agreement with those found in the literature[192]

4-(8-Fluoro-6,13-dioxoisoindolin-1-yl)butanoic acid 123f



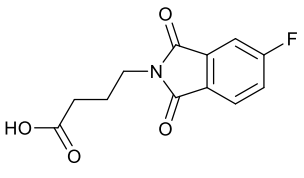
123f

123f was synthesised according to general procedure **B** using 3-fluorophthalic anhydride (0.250 g, 1.50 mmol) and 4-aminobutanoic acid (0.155 g, 1.50 mmol) to afford the desired product as a light coloured brown solid (0.378 g, Quantitive yield).

Mp= 125-126 °C. **ν_{max} (KBr) cm^{-1}** 2980 (OH), 2360, 1708 (N-C=O), 1480, 1449 (O-H), 1392 (CH_2), 1353 (Ar-F), 1314, 1282, 1257, 1122 (C-O), 1056, 1033. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.80 – 7.63 (m, 2H, Ar-H), 7.39 (ddd, *J* = 9.1, 7.6, 1.6 Hz, 1H, Ar-H), 3.77 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.44 (t, *J* = 7.4 Hz, 2H, C(2)*H*), 2.02 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.61 (C(1)COOH), 167.32 (d, *J* = 3.1 Hz, C(6)C=O), 165.17 (C(13)C=O), 157.48 (d, *J* = 264.8 Hz, C(8)Ar**C**-F), 136.78 (d, *J* = 7.8 Hz, C(10)ArC), 134.28 (C(7)ArC), 122.56 (d, *J* = 19.8 Hz, C(9)ArC), 119.68 (d, *J* = 3.5 Hz, C(11)ArC), 117.67 (d, *J* = 12.7 Hz, C(12)ArC), 37.34 (C(3)), 31.32 (C(1)), 23.57 (C(2)). ***m/z***= 250 [MH-] (ESI^-). **HRMS** calculated for $C_{12}H_{10}FNNaO_4$ requires 274.0486, found at 274.0484 [MNa+] (ESI^+).

All data are in agreement with those found in the literature.[193]

4-(9-Fluoro-6,13-dioxoisoindolin-1-yl)butanoic acid 123g



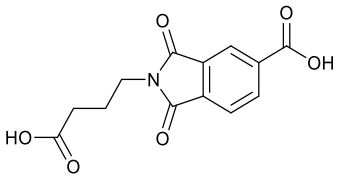
123g

123g was synthesised according to general procedure **B** using 4-fluorophthalic anhydride (0.200 g, 1.20 mmol) and 4-aminobutanoic acid (0.124 g, 1.20 mmol) to afford the desired product as beige coloured solid (0.302 g, Quantitive yield).

Mp= 125-127 °C. **ν_{max} (KBr) cm^{-1}** 1699 (N-C=O), 1613 (C=O), 1398 (CH_2), 1360 (Ar-F), 1265, 1225 (C-O), 1120, 1029. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.84 (q, *J* = 8.2, 4.5 Hz, 1H, Ar-H), 7.50 (dd, *J* = 7.0, 2.3 Hz, 1H, Ar-H), 7.37 (td, *J* = 8.5, 2.3 Hz, 1H, Ar-H), 3.74 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.40 (t, *J* = 7.4 Hz, 2H, C(2)*H*), 1.99 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.71 (C(1)COOH), 167.42 (C(13)C=O), 167.08 (d, *J* = 3.1 Hz, C(6)C=O), 166.48 (d, *J* = 257.53 Hz, C(9)Ar**C**-F), 134.90 (d, *J*= 9.4 Hz, C(7)ArC), 127.86 (d, *J* = 2.6 Hz, C(12)ArC), 125.80 (d, *J* = 9.0 Hz, C(11)ArC), 121.11 (d, *J* = 23.8 Hz, C(10)ArC), 111.30 (d, *J* = 24.7 Hz, C(8)ArC), 37.43 (C(4)), 31.33 (C(2)), 23.61 (C(3)). ***m/z***= 250 [MH-] (ESI$^-$) and 274 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{12}H_{10}FNNaO_4$ requires 274.0486, found at 274.0484 [MNa+] (ESI$^+$).

All data are in agreement with those found in the literature.[193]

4-(9-Carboxypropyl)-6,13-dioxoisoindoline-1-carboxylic acid 123h



123h

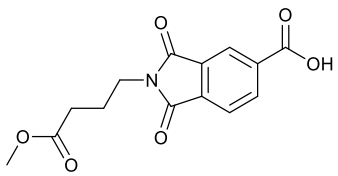
123h was synthesised according to general procedure **B** using trimellitic anhydride (0.500 g, 2.60 mmol) and 4-aminobutanoic acid (0.268 g, 2.60 mmol) at 215 °C with the crude material purified using flash column chromatography (5% Methanol in ethyl acetate with a drop of acetic acid) to afford the desired product as a white coloured solid (0.537, 74%).

ν_{max} (KBr) cm^{-1} 2955 (O-H), 1774 (C=O), 1703 (N-C=O), 1486 (O-H), 1397 (C=C), 1361 (CH_2), 1303, 1253, 1224 (C-O), 1191, 1109, 1073, 1031. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.41 (dd, *J* = 7.7, 1.4 Hz, 1H, ArH), 8.36 (m, 1H, ArH), 7.95 – 7.90 (dd, *J*=7.2, 0.6 Hz, 1H, ArH), 3.75 (t, *J*

= 6.8 Hz, 2H, C(4)*H*), 2.37 (t, *J* = 7.2 Hz, 2H, C(2)*H*), 1.99 (p, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, MeOD) δ 176.53 (C(1)C=O), 169.04 (C(9a)C=O), 169.01 (C(13)C=O), 167.75 (C(6)C=O), 137.85 (C(9)Ar**C**-COOH, 136.63 (C(7)ArC, 136.55 (C(11)ArC, 133.68 C(12)ArC), 124.85 (C(8)ArC), 124.19 (C(10)ArC), 38.53 (C(4)), 32.21 (C(2)), 24.77 (C3)). ***m/z***= 276 [MH-] (ESI$^-$). **HRMS** calculated for $C_{13}H_{10}NO_6$ requires 276.0503, found at 276.0512 [MH-] (ESI$^-$).

All data are in agreement with those found in the literature.[311]

5-(1-Methoxy-1-oxobutyl)-6,13-dioxoisoindoline-9-carboxylic acid 124



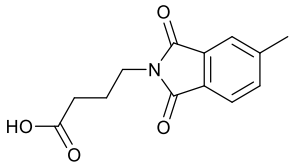
124

Compound **80** (0.283 g, 2.41 mmol) was added to Trimellitic anhydride (0.464 g, 2.41 mmol) and dissolved in toluene (20 mL) followed by the addition of DIPEA (1.26 mL, 7.42 mmol) and refluxed for 16 hours while stirring. The reaction was allowed to cool to room temperature with the reaction being concentrated by reduced pressure. The crude mixture was then purified using flash column chromatography (1% AcOH, 10% MeOH in DCM) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as pale pink coloured solid (0.438 g, 62%).

ν_{max} (KBr) cm^{-1} 3127 (OH), 1721 (N-C=O), 1695 (C=O), 1396 (C=C), 1361, 1341, 1292, 1253 (CH_2), 1201, 1179, ,1119, 1109, 1071, 1033. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.38 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar-H), 8.31 (s, 1H, Ar-H), 7.90 (d, *J* = 7.7 Hz, 1H, Ar-H), 3.73 (t, *J* = 6.7 Hz, 2H, C(4)*H*), 3.59 (s, 3H, OMe), 2.40 (t, *J* = 7.2 Hz, 2H, C(2)*H*), 1.97 (p, *J* = 6.9 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, MeOD) δ 174.98 (C(1)COOMe), 168.96 (C(9a)COOH), 167.59 (C(6,13)C=O), 137.77 (C(7,12)ArC), 136.60 and 136.56 (ArC), 133.64 (C(9)ArC), 124.82 (ArC), 124.18 (ArC),

52.09 (C(OMe)), 38.37 (C(4)), 32.01 (C(2)), 24.65 (C(2)). ***m/z*=** 290 [MH-] (ESI^-), 314 [MNa+] (ESI^+). **HRMS** calculated for $C_{15}H_{13}NO_6$ requires 292.0815, found at 292.0816 [MH+] (ESI^+).

4-(9-Methyl-6,13-dioxoisoindolin-5-yl)butanoic acid 123i



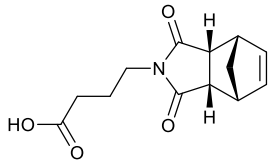
123i

123i was synthesised according to general procedure **B** using 4-methylphthalic anhydride (0.786 g, 4.84 mmol) and 4-aminobutanoic acid (0.500 g, 4.84 mmol) to afford the desired product as an off white coloured solid (1.31 g, Quantitative yield).

MP= 136-138 °C. **ν_{max} (KBr) cm^{-1}** 2941 (O-H), 1767 (C=O), 1697 (N-C=O), 1617, 1486 (O-H), 1440 (CH_3), 1393 (CH_2), 1361, 1283, 1224 (C-O), 1186, 1139, 1114, 1032. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.62 (dt, *J* = 1.5, 0.7 Hz, 1H, AR-H), 7.48 (ddq, *J* = 7.5, 1.4, 0.7 Hz, 1H, Ar-H), 3.73 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.49 (d, *J* = 0.7 Hz, 3H, C(9a)Ar-CH_3), 2.40 (t, *J* = 7.5 Hz, 2H, C(2)*H*), 2.05 – 1.93 (q, *J*=7.0 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.37 (C(1)COOH), 168.69 (C(6)C=O), 168.58 (C(13)C=O), 145.41 (C(8)ArC), 134.64 (ArC), 132.51 (ArC), 129.52 (ArC), 123.98 (ArC), 123.34 (ArC), 37.13 (C(4)), 31.38 (C(2)), 23.80 (C(3)), 22.10 (C(8a)Ar-**C**H_3). ***m/z***= 246 [MH-] (ESI^-), 270 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{13}NNaO_4$ requires 270.0731, found at 270.0739 [MNa+] (ESI^+).

All data are in agreement with those found in the literature.[193]

4-((7*R*,8*S*,11*R*,12*S*)-6,13-Dioxo-6,13,7,8,11,12-hexahydro-2H-8,11-methanoisoindol-1-yl)butanoic acid



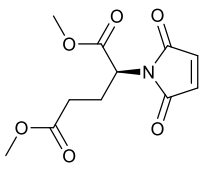
134

134 was synthesised according to general procedure **B** using *Cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (1.00 g, 6.09 mmol) and 4-aminobutanoic acid (0.628 g, 6.09 mmol) to afford the desired product a brown coloured solid (1.36 g, 90%).

Mp= 105-107 °C (Lit. 97-98 °C).[312] **ν_{max} (KBr) cm^{-1}** 2963 (O-H), 1792 (C=O), 1762 (N-C=O), 1733 (C=O), 1697, 1653, 1506, 1489, 1473 (C-H), 1337 (C-H), 1092 (C-O), 1033 (C-O), 799 (C=C), 725, 663, 639, 620. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.11 (t, *J* = 1.9 Hz, 2H, C(9,10)*H*), 3.44 – 3.34 (m, 4H, C(4,8,12)*H*), 3.25 (dd, *J* = 3.0, 1.5 Hz, 2H, C(7,12)*H*), 2.29 (t, *J* = 7.5 Hz, 2H, C(2)*H*), 1.82 – 1.67 (m, 3H, C(3,8a)*H*), 1.53 (dt, *J* = 8.8, 1.5 Hz, 1H, C(8a)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.97 (C(1)COOH), 177.95 (C(6,13)C=O) 134.64 (C(9,10)C=C), 52.43 (C(8a)), 45.89 (C(7,12)), 45.87 (C(8,11)), 37.57 (C(4)), 31.32 (C(2)), 22.98 (C(3)). ***m/z***= 286 [MNa+] (ESI^{+}). **HRMS** requires 286.1050, found at 286.1050 [MNa+] (ESI^{+}).

All data are in agreement with those found in the literature.[312]

Dimethyl (*S*)-4-(6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)pentanedioate 116a



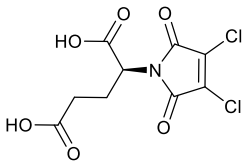
116a

Maleic anhydride (0.056 g, 0.571 mmol), L-Glutamic acid dimethyl ester HCl (0.100 g, 0.571 mmol) and TEA (0.318 mL, 2.284 mmol) were added to toluene (5 mL) and left to stir at room temperature for 1 hour. $ZnCl_2$ (0.440 g, 2.855 mmol) was added in one portion with the reaction

mixture heated to 80 °C followed by the slow addition of a solution containing HMDS (0.355 mL, 2.855 mmol) in toluene (5 mL). The reaction was heated at reflux (122 °C) for a further 16 hours. The mixture was allowed to cool to room temperature and transferred to a separating funnel, then diluted with 0.5 N HCl (75 mL). The aqueous phase was extracted using ethyl acetate (3 x 30 mL), then washed using sat. $NaHCO_3$ (30 mL), then brine (30 mL) finally being dried over Na_2SO_4. The organic layer was concentrated by reduced pressure and purified using flash column chromatography (25% ethyl acetate in pet ether 40:60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a colourless oil (0.103 g, 63%).

^{1}H NMR (200 MHz, Methanol-d_4) δ 6.93 (s, 2H, C(6,9)*H* C=C-H)), 4.87 – 4.75 (m, 1H (C(4)*H*), 3.75 (s, 3H, OMe), 3.67 (s, 3H, OMe), 2.44 – 2.32 (m, 4H, C(2)*H*, C(3)*H*).

(*S*)-4-(7,8-Dichloro-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)pentanedioic acid



113b

2,3-dichloromaleic anhydride (0.500 g, 2.99 mmol) was added to L-Glutamic acid (0.44 g, 2.99 mmol) then dissolved in AcOH (10 mL) and refluxed (120 °C) for 3 hours while stirring. The mixture was allowed to cool to room temperature with the solvent being removed by reduced pressure. A noticeable quantity of AcOH still remaining with the solvent attempted to be removed by azeotroping using toluene but due to products insolubility this didn't remove all AcOH. The desired product was collected as a pale-yellow coloured oil (1.08 g, quantitative yield). NOTE ^{1}H NMR spectrum shows product contains AcOH and toluene even after extensive drying *via* reduced pressure.

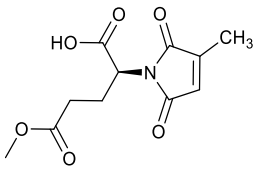
ν_{max} (KBr) cm^{-1} 3127 (COOH), 1725 (N-C=O), 1618 (C=O), 1387, 1266, 1198 (C-O), 1110 (CH_2), 887 (CH_2), 734 (C=C-Cl), 702 (C=C). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.95 – 4.87

(m, 1H, (C(4)*H*), 2.64 – 2.38 (m, 4H, C(2)*H*, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.88 (C(1)COOH), 173.18 (C(4a)COOH), 162.21 (C(6,9)C=O), 133.59 (C(7,8)C=C), 52.05 (C(4)), 30.21 (C(2)), 23.51 (C(3)). ***m/z***= 294 (ESI^-) [MH-], 296 (ESI^-) [MH-]. **HRMS** calculated for $C_9H_6Cl_2NO_6$ requires 293.9577, found 293.9577 [MH-] (ESI^-) and requires 295.9548, found 295.9546 [MH-] (ESI^-).

General procedure C for solventless imide formation

Anhydride (1.0 eq) was added to L-Glutamic acid 5-methyl ester (1.0 eq) in a round bottomed flask and were heated to 160 °C for 6 hours while stirring. The reaction was left to cool to room temperature with the resulting solid mass dissolved in a mixture of ethyl acetate in DCM (0.5:1.0) (20 mL) and transferred to a separating funnel. The organic layer was washed using 0.5 N HCl (2x 10 mL) with the combined aqueous layers being back extracted with ethyl acetate in DCM (0.5:1.0) (20 mL). The organic layers were then combined and concentrated by reduced pressure to afford the desired product.

(4*S*)-1-Methoxy-5-(7-methyl-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)-4a-oxopentanoic acid



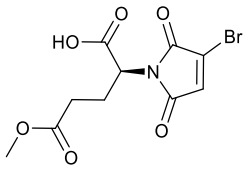
119b

119b was synthesised according to general procedure **C** using methylmaleic anhydride (0.557 mL, 6.21 mmol) and L-Glutamic acid 5-methyl ester (1.00 g, 6.21 mmol) afford the desired product as light brown coloured oil (0.742 g, 46%).

$[\alpha]_D^{25}$= -17.5 (*c* 1.0 in MeOH). **ν_{max} (KBr) cm^{-1}** 3529 (O-H), 2955 (C-H), 2362, 1707 (N-C=O),1698 (C=O), 1439 (O-H), 1401 (O-H), 1266, 1205 (C-O), 1111 (CH_2), 860 (CH_2), 770 (C=C-)**. ^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.37 (q, *J* = 1.8 Hz, 1H, C(8)*H*), 4.78 – 4.69 (m,

1H, C(4)*H*), 3.64 (s, 3H, OMe), 2.57 – 2.45 (m, 1H, C(2)H_A), 2.45 – 2.28 (m, 3H, C(2)H_B, C(3)*H*), 2.08 (d, *J* = 1.9 Hz, 3H, C(7a)C=C-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.71 (C(6)C=O), 172.83 (C(1)COOMe), 171.08 (C4a)COOH), 170.06 (C(9)C=O), 146.15 (C(7)C=**C**-CH_3), 127.75 (C(8)C=**C**-H), 52.01 (C(4a)OMe), 51.04 (C(4)), 30.72 (C(2)), 24.10 (C(3)), 11.17 (C(7a)C=C-**C**H_3). ***m/z***= 254 [MH-] (ESI^-), 278 [MNa+] (ESI^+) and 533 [2MNa+] (ESI^+). **HRMS** calculated for $C_{11}H_{13}NNaO_6$ requires 278.0635, found at 278.0637 [MNa+] (ESI^+).

(4*S*)-1-Methoxy-5-(7-bromo-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)-4a-oxopentanoic acid 119c

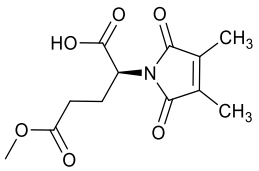


119c

119c was synthesised according to general procedure **C** using bromomaleic anhydride (0.576 mL, 6.21 mmol) and L-Glutamic acid 5-methyl ester (1.00 g, 6.21 mmol) to afford the desired product as think dark brown oil. (1.19 g, 60%).

ν_{max} (KBr) cm^{-1} 3508 (O-H), 2955 (C-H), 1711 (N-C=O), 1697 (C=O) 1589, 1428 (O-H), 1389 (O-H), 1206 (C-O), 1110 (CH_2), 1086, 762 (C-Br). **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.19 (d, *J* = 2.9 Hz, 1H, C(8)*H*), 4.81 – 4.73 (m, 1H, C(4)*H*), 3.63 (s, 3H, OMe), 2.51 – 2.30 (m, 4H, C(2,3)*H*). **^{13}C NMR** (101 MHz, MeOD) δ 174.70 (C(1)COOMe), 171.86 (C(8)C=O), 171.75 (C(4a)COOH) 166.51 (C(6)C=O), 133.85 (C(8)C=**C**-H), 132.24 (C(7)C=**C**-Br), 53.20 (C(4), 52.21 (C(1)OMe), 31.41 (C(2)), 25.13 (C(3)). ***m/z***= 317.9 and 319.9 [MH-] (ESI^-). **HRMS** calculated for $C_{10}H_9BrNO_4$ requires 319.9764 and 321.9744, found at 319.9765 and 321.9745 [MH-] (ESI^-).

(4*S*)-1-(7,8-Dimethyl-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)-4a-oxopentanoic acid 119d

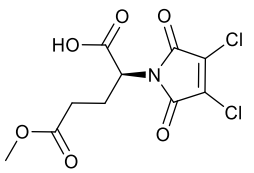


119d

119d was synthesised according to general procedure **C** using dimethylmaleic anhydride (0.783 g, 6.21 mmol) and L-Glutamic acid 5-methyl ester (1.00 g, 6.21 mmol) with the crude material purified using flash column chromatography (ethyl acetate) with the product containing fractions collected, combined and concentrated to afford the desired product as a light orange coloured oil (0.307 g, 18%).

$[\alpha]_D^{25}$= -17.1 (*c* 1.0 in MeOH). **ν_{max} (KBr) cm^{-1}** 3519 (O-H), 2956 (C-H), 2362, 1861, 1760 (C=O), 1735 (C=O), 1703 (N-C=O), 1437 (O-H), 1402 (O-H), 1274, 1205 (C-O), 1175, 1121 (C-H), 1101, 1038. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.71 (dd, *J* = 10.0, 4.8 Hz, 1H, C(4)*H*), 3.64 (s, 3H, OMe), 2.56 – 2.28 (m, 4H, C(2,3)*H*), 2.06 (s, 6H, C(7a,8a)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.88 (C(1)COOMe), 171.47 (C(4a)COOH), 166.27 (C(6,9)C=O), 137.79 (C(7,8)C=C), 51.92 (C(1)OMe), 51.21 (C(4)), 30.83 (C(2)), 24.28 (C(3)), 9.67 (C(7a,8a)C=C-**C**H$_3$). ***m/z***= 268 [MH-] (ESI$^-$) and 296 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{12}H_{16}NO_6$ requires 270.0972, found at 270.0973 [MH+] (ESI$^+$).

(4S)-1-(7,8-Dichloro-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)-4a-oxopentanoic acid 119e

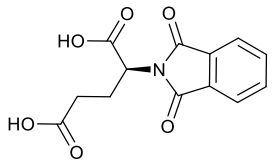


119e

119e was synthesised according to general procedure **C** using dichloromaleic anhydride (1.03 g, 6.21 mmol) and L-Glutamic acid 5-methyl ester (1.00 g, 6.21 mmol) to afford the desired product as think dark brown oil. (1.79 g, 92%).

$[\alpha]_D^{25}$= -13.5 (*c* 1.0 in MeOH). **ν_{max} (KBr) cm^{-1}** 3521 (O-H), 2956 (C-H), 1727 (N-C=O), 1619 (C=O), 1439 (O-H), 1387, 1199 (C-O), 1111 (CH_2), 1009, 738 (C-Cl). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.09 (s, 1H, O-H)), 4.91 – 4.86 (m, 1H, C(4)*H*), 3.66 (s, 3H, OMe), 2.62 – 2.50 (m, 1H, C(2)H_A), 2.49 – 2.34 (m, 3H, C(2)H_B and C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.01 (C(4a)COOH), 172.67 (C(1)COOMe), 162.46 (C(6,9)C=O), 133.81 (C(7,8)C=C), 52.41 (C(4)), 52.16 (OMe), 30.62 (C(2)), 24.05 (C(3)). ***m/z***= 310 and 312 [MH-] (ESI$^-$). **HRMS** calculated for $C_{10}H_8Cl_2NO_4$ requires 309.9880 and 311.9850, found at 309.9880 and 311.9850 [MH-] (ESI$^-$).

(*S*)-4-(6,13-Dioxoisoindolin-5-yl)pentanedioic acid 125L



125L

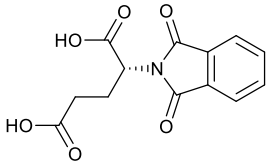
Phthalic anhydride (1.00 g, 6.80 mmol) was added to L-Glutamic acid (1.00 g, 6.80 mmol) in a round bottomed flask and were heated to 170 °C for 6 hours while stirring. The reaction was left to cool to room temperature with the resulting solid mass dissolved in ethyl acetate (10 mL) and transferred to a separating funnel. The organic layer was washed using 0.5 N HCl (2 x 10 mL) with the combined aqueous layers being back extracted with ethyl acetate (20 mL). The organic layers were then combined and concentrated by reduced pressure to afford the desired product as a beige coloured solid (1.14 g, 60%).

$[\alpha]_D^{25}$= -18.8 (*c* 1.0 in MeOH). **Mp**= 184-186 °C (lit 159-160 °C).[313] **ν_{max} (KBr) cm^{-1}** 2980 (O-H, Ar-H), 2907 (O-H, Ar-H), 2651 (Ar-H), 1773 (C=O), 1711 (C=O), 1654 (C=O), 1587, 1558, 1469 (O-H), 1457, 1419 (C=C), 1385 (C=C), 1279 (C-O), 1211 (C-O), 1114, 1088, 1070, 1027, 1006. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.88 – 7.84 (dd, *J* = 5.5, 2.7 Hz, 2H, ArH), 7.84 – 7.79 (dd, *J* = 5.4, 2.8 Hz, 2H, ArH), 4.93 (dd, *J* = 10.3, 4.8 Hz, 1H, C(4)*H*), 2.62 – 2.42 (m, 2H, C(2)*H*), 2.42 – 2.34 (m, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, MeOD) δ 176.17 (C(1)C=O), 172.20 (C(4a)C=O), 169.20 (C(6,13)C=O), 135.65(ArC), 132.01 (C(7,12)ArC), 124.38 (ArC), 52.54

(C(4)), 31.56 (C2)), 25.24 (C3)). ***m/z***= 276 [MH-] (ESI^-) and 300 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{11}NNaO_6$ requires 300.0478, found at 300.0479 [MNa+] (ESI^+).

All data are in agreement with those found in the literature.[313,314]

(*R*)-4-(6,13-Dioxoisoindolin-5-yl)pentanedioic acid 125D



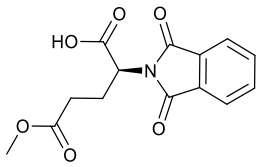
125D

Phthalic anhydride (0.500 g, 3.37 mmol) was added to D-Glutamic Acid (0.500 g, 3.37 mmol) in a round bottomed flask and were heated to 170 °C for 6 hours while stirring. The reaction was left to cool to room temperature with the resulting solid mass dissolved in ethyl acetate (10 mL) and transferred to a separating funnel. The organic layer was washed using 0.5 N HCl (2x 10 mL) with the combined aqueous layers being back extracted with ethyl acetate (20 mL). The organic layers were combined and concentrated by reduced pressure to afford the desired product as a beige coloured solid (0.709 g, 75%).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$= +17.3 (*c* 1.0 in MeOH); {Lit. $[\alpha]_D^{20}$ +45.4 (*c* 1.0 in EtOH)}.[314] **Mp**= 178-180 °C (Lit. 159-160 °C).[313] $\boldsymbol{\nu_{max}}$ **(KBr) cm^{-1}** 2980 (O-H), 2360, 1774 (C=O), 1711 (N-C=O), 1390 (C=C), 1259 (C-O), 1113, 720. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.89 (dd, *J* = 5.4, 3.6 Hz, 2H, Ar-H), 7.84 (dd, *J* = 5.6, 3.7 Hz, 2H, AR-H), 4.92 (dd, *J* = 10.3, 4.8 Hz, 1H, C(2)*H*), 2.60 – 2.41 (m, 2H, C(3)*H*), 2.40 – 2.34 (m, 2H, C(4)*H*). **^{13}C NMR** (101 MHz, MeOD) δ 174.72 (C(1)COOH), 167.79 (C(4a)COOH), 134.25 (ArC), 131.69 (C(7)), 131.02 (C(14)), 130.58 (C(8)), 128.06 (C(13)), 122.99 (ArC), 51.21 (C(2)), 30.20 (C(4)), 23.88 C(3)). ***m/z***= 276 [MH-] (ESI^-), 300 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{11}NNaO_6$ requires 300.0478, found at 300.0480 [MNa+] (ESI^+).

All data are in agreement with those found in the literature.[313,314]

(*S*)-4-(6,13-Dioxoisoindolin-5-yl)-4-methoxy-1-oxopentanoic acid 126L

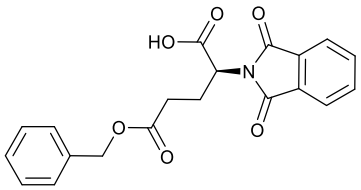


126L

126L was synthesised according to general procedure **C** using phthalic anhydride (0.100 g, 0.67 mmol) and L-glutamic acid 5-methyl ester (0.108 g, 0.67 mmol) to afford the desired product as a pale-yellow coloured oil (0.141 g, 72%).

$[\alpha]_D^{25}$= -33.0 (*c* 1.0 MeOH). **ν_{max} (KBr) cm^{-1}** 3112 (O-H), 1774 (C=O), 1708 (N-C=O), 1438 (O-H), 1387, 1263 (C=C), 1202 (C-O), 1173, 1113, 1088, 1028, 949, 885, 854, 796, 719 (C=CH), 633. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.89 (dd, 2H, Ar-H), 7.78 (dd, 2H, Ar-H), 5.01 (dd, *J* = 10.3, 5.0 Hz, 1H, C(2)*H*), 3.65 (s, 3H, OMe), 2.70 – 2.60 (m, 1H, C(4)H_A), 2.59 – 2.40 (m, 3H, C(4)H_B, C(3)*H*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.42 (C(1)COOH), 172.63 (C(4a)COOH), 167.58 (C(8)), 167.48 (ArC), 134.42 (ArC), 131.73 (ArC), 123.77 (ArC), 51.86 (C(4)), 50.91 (C(1a)OMe), 30.64 (C(2)), 24.09 (C3)). ***m/z***= 314 [MNa+] (ESI^+), 290 [MH-] (ESI^-). **HRMS** calculated for $C_{14}H_{13}NaNO_4$ requires 314.0635, found at 314.0631 [MNa+] (ESI^+).

(*S*)-1-(Benzyloxy)-4-(6,13-dioxoisoindolin-5-yl)-4-oxopentanoic acid 130



130

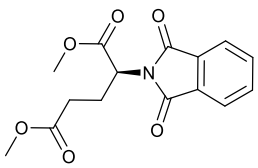
Phthalic anhydride (1.550 g, 10.47 mmol) was added to L-glutamic acid 5-benzyl ester (2.500 g, 10.47 mmol) in a round bottomed flask and heated at 170 °C for 6 hours while stirring. The reaction was left to cool to room temperature with the resulting solid mass dissolved in DCM (10 mL) and transferred to a separating funnel. The organic layer was washed using 0.5 N HCl (2x 10 mL) with the combined aqueous layers being back extracted with DCM (20 mL). The organic layers were

then combined and concentrated by reduced pressure to afford the desired product as a light brown coloured oil (2.78 g, 72%).

^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H, ArH), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H, ArH), 7.36 – 7.27 (m, 5H, ArH), 5.06 (s, 2H C(1b)ArC-C**H$_2$**-O), 4.99 (ddd, *J* = 10.5, 5.0, 1.6 Hz, 1H, C(4)*H*), 2.72 – 2.59 (m, 1H, (C(4)*H$_A$*), 2.60 – 2.49 (m, 1H, C(4)*H$_B$*), 2.49 – 2.38 (m, 2H, C(3*)H)*. ***m/z***= 366 [MH-] (ESI$^-$). **HRMS** calculated for $C_{20}H_{17}NaNO_6$ requires 390.0948, found at 390.0944 [MNa+] (ESI$^+$).

All data are in agreement with those found in the literature.[200,201]

Dimethyl (*S*)-4-(6,13-dioxoisoindolin-5-yl)pentanedioate 127L



127L

Method 1) Phthalic anhydride (0.200 g, 1.32 mmol) was added to L-glutamic acid dimethyl ester (0.236 g, 1.32 mmol) in a round bottomed flask and heated at 150 °C for 6 hours while stirring. The reaction was left to cool to room temperature with the resulting solid mass dissolved in DCM (10 mL) and transferred to a separating funnel. The organic layer was washed using 0.5N HCl (2x 10 mL) with the combined aqueous layers being back extracted with DCM (20 mL). The organic layers were then combined and concentrated by reduced pressure to afford the desired product as a colourless oil (0.166 g, 40%).

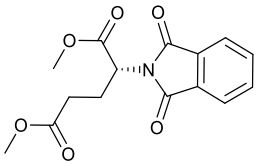
Method 2) Compound **126L** (0.936 g, 3.37 mmol) was dissolved in MeOH (10 mL) and cooled to 0 °C using an ice bath. $SOCl_2$ (2.026 mL, 10.11 mmol) was added dropwise over 5 minutes after which the reaction was allowed to warm to room temperature and left stirring for 16 hours to ensure completion. The solvent mixture was removed by reduced pressure then azeotroped using DCM (3 x 20 mL). The crude material was then purified *via* flash column chromatography (30%

ethyl acetate in pet ether 40:60) with the product containing fractions being collected, combined and concentrated to afford the desired product as a colourless oil (0.312 g, 30%).

R_f= 0.40 (30% ethyl acetate in pet-ether 40:60). $[\alpha]_D^{25}$= -35.1 (*c* 1.0 in DCM); {Lit. $[\alpha]_D^{20}$= -58 (*c* 1.0 in DMF)}.[315] **ν_{max} (KBr) cm^{-1}** 2980 (Ar-H), 2970 (Ar-H) 2956 (Ar-H), 1776 (C=O), 1736 (C=O), 1713 N-C=O), 1612, 1467 (C=C), 1436 (C=C), 1386, 1339, 1298 (C-O), 1257 (C-O), 1198 (C-O), 1172, 1112, 1029. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.90 (dd, *J* = 5.4, 3.0 Hz, 2H, Ar-H), 7.78 (dd, *J* = 5.3, 2.9 Hz, 2H, AR-H), 4.96 (dd, *J* = 10.2, 5.0 Hz, 1H, C(2)*H*), 3.77 (s, 3H, OMe), 3.64 (s, 3H, OMe), 2.73 – 2.60 (m, 1H, C(4)H_A), 2.58 – 2.46 (m, 1H, C(4)H_B), 2.45 – 2.37 (m, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.72 (C(1)COOMe), 169.36 (C(4a)COOMe), 167.64 (C(9,16)C=O), 134.42 (ArC), 131.89 (C(7,12)ArC), 123.75 (ArC), 52.96 (OMe), 51.87 (OMe) , 51.32 (C(4)), 30.79 (C(2)), 24.44 (C(3)). ***m/z***= 328 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{15}H_{16}NO_6$ requires 306.0972, found at 306.0974 [MH+] (ESI$^+$).

All data are in agreement with those found in the literature. [316]

Dimethyl (*R*)-4-(6,13-dioxoisoindolin-5-yl)pentanedioate 127D

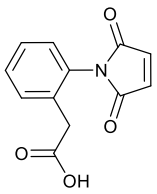


127D

Compound **125D** (0.709 g, 2.32 mmol) was dissolved in MeOH (10 mL) and cooled to 0°C using an ice bath. $SOCl_2$ (0.50 mL, 6.96 mmol) was added dropwise over 5 minutes after which the reaction was allowed to warm to room temperature and left stirring for 16 hours to ensure completion. The solvent mixture was removed by reduced pressure then azeotroped using DCM (3 x 20 mL). The crude material was then purified *via* flash column chromatography (30% ethyl acetate in pet ether 40:60) with the product containing fractions being collected, combined and concentrated to afford the desired product as a colourless oil (0.488 g, 63%).

R_f= 0.41 (30% ethyl acetate in pet-ether 40:60). **$[\alpha]_D^{25}$**= +35.5 (*c* 1.0 in DCM); {Lit. $[\alpha]_D^{25}$= +173.6 (*c* 1.4 in $CHCl_3$)}.[317] **ν_{max} (KBr) cm^{-1}** 2983 (Ar-H), 2975 (Ar-H) 2951 (Ar-H), 1776 (C=O), 1733 (C=O), 1712 (N-C=O), 1614, 1467 (C=C), 1435 (C=C), 1386, 1340, 1297 (C-O), 1257 (C-O), 1197 (C-O), 1172, 1112, 1029. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.94 – 7.81 (m, 2H, Ar-H), 7.81 – 7.69 (m, 2H, Ar-H), 4.93 (dd, *J* = 9.7, 5.2 Hz, 1H, C(4)*H*), 3.74 (s, 3H, OMe), 3.62 (s, 3H, OMe), 2.75 – 2.47 (m, 2H, C(2)*H*), 2.46 – 2.33 (m, 2H, C(3)*H*).

4-(4-(6,9-Dioxo-6,9-dihydro-5H-pyrrol-5-yl)phenyl)acetic acid 122

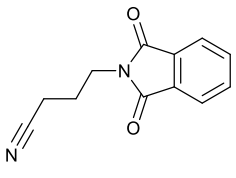


122

2-Aminophenylacetic acid (0.100 g, 0.66 mmol) was stirred in toluene (10 mL) at room temperature for 5 minutes until it was dissolved. Maleic anhydride (0.071 g, 0.72 mmol) was added in one portion and the reaction mixture was left stirring at room temperature for 16 hours. The reaction was concentrated by reduced pressure then redissolved in AcOH (5 mL) and refluxed for 6 hours while stirring. The reaction was allowed to cool to room temperature with the solvent being removed by reduced concentration to afford the desired product as a dark brown coloured solid (0.085 g, 56%).

^{1}H NMR (200 MHz, Acetic Acid-d_4) δ 7.31 – 7.15 (m, 2H, Ar-H), 7.09 – 6.91 (m, 2H, Ar-H), 6.40 (s, 2H, C(6,9)*H*), 3.61 (s, 2H, C(2)*H*).

4-(1,3-Dioxoisoindolin-2-yl)butanenitrile[247] **182**



182

Potassium phthalimide (1.00 g, 5.40 mmol) and 4-bromobutyronitrile (0.75 mL, mmol) were dissolved in DMF (5 mL) and heated at 100 °C for 16 hours while stirring. The reaction was allowed to cool to room temperature then transferred to a separating funnel and diluted with DCM (15 mL). The organic layer was washed using warm water (3 x 15 mL) with the aqueous layer back extracted using DCM (20 mL). The combined organic layers were dried over Mg_2SO_4 then concentrated by reduced pressure. The crude organic was purified using flash column chromatography (a gradient from pet-ether 40:60 up to 50% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated to afford the desired product as a white coloured solid (1.11 g, 97%).

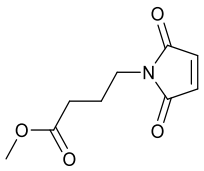
R_f = 0.5 (50% ethyl acetate in pet-ether 40:60). **ν_{max} (KBr) cm^{-1}** 2247 (C≡N), 1772, 1705 (N-C=O), 1614, 1467 (C=C), 1436, 1396, 1376, 1358 (C-H), 1188, 1172, 1122, 1089, 1026. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 5.5, 3.1 Hz, 2H, Ar-H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H, Ar-H), 3.80 (t, *J* = 6.7 Hz, 2H, C(4)*H*), 2.42 (t, *J* = 7.3 Hz, 2H, (C(2)*H*), 2.06 (q, *J* = 14.0, 7.2, 6.9 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.30 (C(6,13)C=O), 134.32 (ArC), 134.30 (ArC), 131.96 (ArC), 123.54 (ArC), 118.83 (C(1)C≡N), 36.75 (C(4)), 24.87 (C(3)), 15.21 (C(2)). ***m/z***= 215 [MH+] (ESI^+).

All data are in agreement with those found in the literature.[247,318]

General procedure D for esterification

Starting material was dissolved in MeOH (10 mL) and cooled to 0 °C with an ice bath. Thionyl chloride (3.0 eq) was then added dropwise over 5 minutes and left stirring for 16 hours at room temperature. The solvent was removed by reduced pressure then azeotroped using DCM (3 x 10 mL) to afford the desired ester. Purification *via* flash column chromatography with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired ester.

Methyl 1-(6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)butanoate 76a



76a

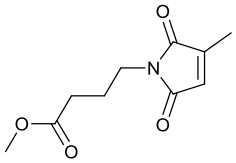
Method 1)[156] **76a** was synthesised according to general procedure **D** using **91a** (0.750 g, 4.09 mmol) with the crude material purified using flash column chromatography (30% ethyl acetate in pet ether 40:60) to afford the desired product as a colourless oil (0.302 g, 37%).

Method 2)[319] Maleic anhydride (0.500 g, 5.09 mmol) was added to **80** with TEA (0.900 mL, 20.36 mmol) and dissolved in toluene (20 mL) with the reaction left to stir for 1 hour at room temperature. $ZnCl_2$ (1.11 g, 25.45 mmol) was added in one portion with the reaction mixture heated to 80 °C followed by the slow addition of a solution containing HMDS (1.13 mL, 25.45 mmol) in toluene (5 mL). The reaction was then heated at reflux for a further 16 hours. The mixture was allowed to cool to room temperature and transferred to a separating funnel, then diluted with 0.5 N HCl (75 mL). The aqueous phase was extracted using ethyl acetate (3x 30 mL), then washed using sat. $NaHCO_3$ (30 mL), then brine (30 mL) and finally dried over Na_2SO_4. The organic layer was concentrated by reduced pressure and purified using flash column chromatography (30% ethyl acetate in pet ether 40:60) with the desired fraction being collected, combined and concentrated by reduced pressure to afford the desired product as a colourless oil (0.222 g, 70%).

R_f= 0.35 (30% ethyl acetate in pet ether 40:60). **^{1}H NMR** (200 MHz, Methanol-*d*4) δ 6.81 (s, 2H, C(7,8(*H*), 3.64 (s, 3H, OMe, *H*), 3.55 (t, *J* = 6.7 Hz, 2H, C(4)*H*), 2.33 (t, *J* = 7.2 Hz, 2H, C(2)*H*), 1.90 (p, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, CDCl3) δ 173.12 (C(1)COOMe), 170.85 (C(6,9)C=O), 134.25 (C(7,8)C=C), 51.86 (C(1)OMe), 37.22 (C(4)), 31.34 (C(2)), 23.96 (C3)). ***m/z***= 198 [MH+] (ESI^+). **HRMS** calculated for $C_9H_{12}NO_4$ requires 198.0760, found at 198.0785 [MH+] (ESI^+).

All data are in agreement with those found in the literature[156]

Methyl 1-(7-methyl-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)butanoate 76b

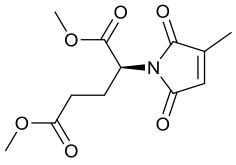


76b

Synthesised according to general procedure **D** using **91b** (0.812 g, 3.84 mmol) with the crude product then purified flash column chromatography (20% ethyl acetate in pet ether 40:60) to afford the desired product as a colourless oil (0.506, 58%).

R_f= 0.34. **ν_{max} (KBr) cm^{-1}** 2952 (C-H), 1735 (C=O), 1701 (N-C=O), 1643 (C=O), 1440, 1406, 1365, 1251, 1197 (C-O), 1173, 1128, 1104, 1040. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.30 (q, *J* = 1.8 Hz, 1H, C(8)*H*), 3.65 (s, 3H, OMe), 3.54 (t, *J* = 6.9 Hz, 2H, C(4)*H*), 2.30 (t, *J* = 7.5 Hz, 2H, (C(2)*H*), 2.06 (d, *J* = 1.9 Hz, 3H, C(7a)C=C-C**H$_3$**), 1.95 – 1.86 (q, *J*=7.0 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.16 (C(1)COOMe), 171.92 (C(9)C=O), 170.91 (C(6)C=O), 145.75 (C(7)C=**C**-CH_3), 127.39 (C(8)C=**C**-H), 51.78 (OMe), 37.22 (C(4)), 31.35 (C(2)), 24.02 (C(3)), 11.07 (C(7a)C=C-**C**H_3). ***m/z***= 234 [MNa+] (ESI$^+$). **HRMS** calculated at $C_{10}H_{13}NO_4$ requires 234.0737, found at 234.0739 [MNa+] (ESI$^+$).

Dimethyl (*S*)-4-(7-methyl -6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)pentanedioate 116b



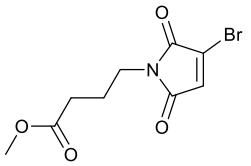
116b

116b was synthesised according to general procedure **D** using **119b** (0.741 g, 3.29 mmol) to afford the desired product as a brown coloured oil (0.723 g, 92%).

$[\alpha]_D^{25}$= -19.6 (*c* 1.0 in MeOH). **ν_{max} (KBr) cm^{-1}** 2956 (C-H), 1736 (C=O), 1708 (N-C=O), 1437, 1399, 1263 (C-O), 1111 (CH_2), 860, 705. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.38 (q, *J* = 1.9 Hz, 1H, C(8)*H*), 4.75 – 4.67 (m, 1H, C(4)*H*), 3.73 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.59 – 2.47

(m, 1H, C(2)H_A), 2.44 – 2.29 (m, 3H, C(2)H_B, C(3)*H*), 2.10 (d, *J* = 1.8 Hz, 3H, C(7a)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.75 (C(1)COOMe), 171.18 (C(6)C=O), 170.09 (C(9)C=O), 169.48 (C(4a)COOMe), 146.11 (C(7)C=**C**-CH_3), 127.78 (C(8)C=**C**-H), 52.96 (C(1)OMe), 51.94 (C(4a)OMe), 51.33 (C(4)), 30.76 (C(2)), 24.34 (C(3)), 11.22 (C(7a)C=C-**C**H_3). ***m/z***= 292 [MNa+] (ESI^+). **HRMS** calculated for $C_{12}H_{16}NO_6$ requires 270.0972, found at 270.0974 [MH+] (ESI^+).

Methyl 1-(7-bromo-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)butanoate 76c

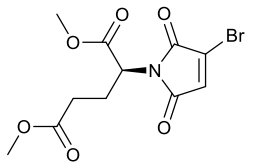


76c

76c Synthesised according to general procedure **D** using **91c** (1.02g, 3.89 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet ether 40:60) to afford the desired product as a pale yellow coloured oil (0.648 g, 61%).

ν_{max} (KBr) cm^{-1} 2953 (C-H), 1778 (C=O), 1709 (N-C=O, C=O), 1626 (C=O), 1589, 1439, 1399, 1363, 1198, 1175, 1137, 1090, 1000, 762 (C=C-Br). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.86 (s, 1H, C(8)C=C-**H**), 3.66 (s, 3H, C(1)OMe), 3.62 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 2.32 (t, *J* = 7.3 Hz, 2H, C(2)*H*), 1.93 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.98 (C(1)COOMe), 168.61 (C(9)C=O), 165.42 C(6)C=O), 131.95 (C(8)C=**C**-H), 131.48 (C(7)C=**C**-Br), 51.86 (C(1)OMe), 38.17 (C(4)), 31.22 (C(2)), 23.81 (C(3)). ***m/z***= 298 and 300 [MNa+] (ESI^+). **HRMS** calculated for $C_9H_{11}BrNO_4$ requires 275.9866 and 277.9846, found at 275.9868 and 277.9847 [MH+] (ESI^+).

Dimethyl (*S*)-4-(7-bromo -6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)pentanedioate 116c

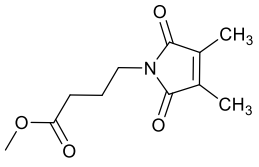


116c

116c was synthesised according to general procedure **D** using **119c** (1.19 g, 3.73 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet ether 40:60) to afford the desired product as a colourless oil (0.573 g, 46%).

$[\alpha]_D^{25}$= -18.3 (*c* 1.0 in MeOH). **R_f**= 0.26 (20% ethyl aetate in pet-ether 40:60). **ν_{max} (KBr) cm^{-1}** 2955 (C-H), 1717 (N-C=O), 1589, 1437, 1390, 1263 (C-O), 1176 (C-O), 1002. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.92 (s, 1H, C(8)*H*), 4.81 – 4.74 (m, 1H, C(4)*H*), 3.74 (s, 3H, OMe), 3.65 (s, 3H, OMe), 2.59 – 2.49 (m, 1H, C(2)H_A), 2.44 – 2.31 (m, 3H, C(2)H_B, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.56 (C(1)COOMe), 168.86 (C(4a)COOMe), 167.85 (C(9)C=O), 164.78 (C(6)C=O), 132.26 (C(8)C=**C**-H), 131.71 (C(7)C=**C**-Br), 53.14 (C(1)OMe), 52.15 (C(4)), 51.98 (C(4a)OMe), 30.65 (C(2)), 24.22 (C(3)). ***m/z***= 366 and 368 [MH+MeOH] (ESI$^+$). **HRMS** calculated for $C_{11}H_{11}BrNO_6$ requires 333.9921 and 335.9900, found at 333.9922 and 335.9901 [MH-] (ESI$^-$).

Methyl 1-(7,8-dimethyl-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)butanoate 76d



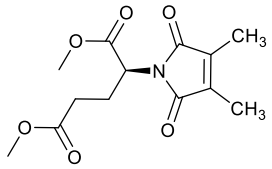
76d

76d was synthesised according to general procedure **D** using **91d** (0.160 g, 0.75 mmol) to afford the desired product as a vary pale-yellow coloured oil (0.143 g, 96%).

ν_{max} (KBr) cm^{-1} 1736 (C-N=O), 1697, (C=O), 1439, 1406, 1363, 1274 (C-O), 1196 (C-O), 1174, 1105, 1036, 733 (C=C-CH_3). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.66 (s, 3H, OMe), 3.54 (t, *J*

= 6.8 Hz, 2H, (C(4)*H*), 2.31 (t, *J* = 7.5 Hz, 2H, (C(2)*H*), 1.98 – 1.86 (m, 8H, (C(3)*H*, C(7a, 8a)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.23 (C(1)COOMe), 172.29 (C(6,9)C=O), 137.29 (C(7,8)C=**C**-CH_3), 51.76 (OMe), 37.21 (C(4)), 31.42 (C(2)), 24.16 (C(3)), 8.78 (C(7a, 8a) C=C-**C**H_3). ***m/z***= 248 [MNa+] (ESI^+). **HRMS** calculated for $C_{11}H_{16}NO_4$ requires 226.1073, found at 226.1073 [MH+] (ESI^+).

Dimethyl (*S*)-4-(7,8-dimethyl-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)pentanedioate 116d



116d

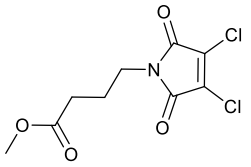
Method 1) **116d** was synthesised according to general procedure **D** using **119c** (0.732 g, 0.27 mmol) with the crude material t purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the desired product as a colourless oil (0.418 g, 54%).

Method 2) 2,3-dimethylmaleic anhydride (0.852, 6.75 mmol) was added to L-glutamic acid dimethyl ester (1.19 g, 6.76 mmol) and suspended in toluene (15 mL). DIPEA (2.38, 13.52 mmol) with the reaction being left to stir at reflux for 16 hours. The reaction was allowed to cool to room temperature with the solvent being removed using reduced pressure. The crude oil was then purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as a colourless oil. (0.410 g, 21%).

$[\alpha]_D^{25}$= -24.9 (*c* 1.0 in MeOH). **R_f**= 0.35 (20% ethyl acetate in pet-ether 40:60). **ν_{max} (KBr) cm^{-1}** 2955 (C-H), 1739 (C=O), 1706 (N-C=O), 1436, 1402, 1260, 1208 (C-O), 1173 (C-O), 1101 (CH_2). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.72 – 4.66 (m, 1H, C(4)*H*), 3.71 (s, 3H, OMe), 3.64 (s, 3H, OMe), 2.56 – 2.47 (m, 1H, C(2)H_A), 2.43 – 2.29 (m, 3H, C(2)H_B, C(3)*H*), 1.97 (s, 6H, C(7a, 8a)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.75 (C(1)COOMe), 171.45 (C(6,9)C=O), 169.65

(C(4a)COOMe), 137.77 (C(7,8)C=C), 52.88 (C(1)OMe), 51.87 (C(4a)OMe), 51.30 (C(4)), 30.78 (C(2)), 24.40 (C(3)), 8.91 (C(7a, 8a)C=C-**C**H_3). ***m/z***= 306 [MH+] (ESI^+) and 589 [2MNa+] (ESI^+).

Methyl 1-(7,8-dichloro-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)butanoate 76e

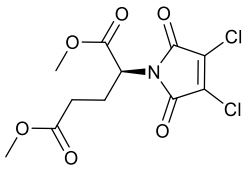


76e

76e was synthesised according to general procedure **D** using **91e** (0.100 g, 0.39 mmol) to afford the desired product as an orange-coloured oil (0.104 g, 99%).

ν_{max} (KBr) cm^{-1} 1720 (N-C=O), 1666 (C=O), 1621 (C=O), 1439, 1398, 1361, 1197 (C-O), 1117, 1033. **^{1}H NMR** (400 MHz, Chloroform-d) δ 3.71 – 3.63 (m, 5H, OMe, C(4)*H*), 2.35 (t, *J* = 7.2 Hz, 2H, C(2)*H*), 1.96 (p, *J* = 7.1 Hz, 2H, C(3*H*). **^{13}C NMR** (101 MHz, CDCl3) δ 172.89 (C(1)COOMe), 163.12 (C(6,9)C=O), 133.43 (C(7,8)C=**C**-Cl), 51.92 (OMe), 38.77 (C(4)), 31.22 (C(2)), 23.75 (C3)). **LRMS** not detected. **HRMS** calculated for $C_9H_8Cl_2NO_4$ requires 265.9981 and 267.9950, found at 265.9980 and 267.9950 [MH-] (ESI^-).

Dimethyl (*S*)-4-(7,8-dichloro-6,9-dioxo-6,9-dihydro-5H-pyrrol-5-yl)pentanedioate 116e



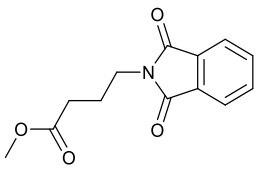
116e

116e was synthesised according to general procedure **D** using **119e** (0.556 g, 2.99 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the desired product as a colourless oil (0.664 g, 68%).

$[\alpha]_D^{25}$= -21.4 (*c* 1.0 in MeOH). **R_f**= 0.4. **ν_{max} (KBr) cm^{-1}** 2956 (C-H), 1728 (N-C=O), 1620 (C=O), 1437, 1387, 1263 (C-O), 1197 (C-O), 1111 (CH_2), 1011, 886 (CH_2), 734.67 (C=C-Cl). **^{1}H NMR**

(400 MHz, Chloroform-*d*) δ 4.87 – 4.79 (m, 1H, C(4)*H*), 3.76 (s, 3H, OMe), 3.67 (s, 3H, OMe), 2.63 – 2.50 (m, 1H, C(2)H_A), 2.47 – 2.32 (m, 3H, C(2)H_B, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.80 (C(1)COOMe), 168.84 (C(4a) COOMe), 162.84 (C(6,9)C=O), 134.11 (C(7,8)C=**C**-Cl), 53.60 (C(1)OMe), 53.07 (C(4)), 52.32 (C(4a)OMe), 30.97 (C(2)), 24.58 (C(3)). ***m/z***= 346 and 348 [MNa+] (ESI^+). **HRMS** calculated for $C_{11}H_{12}Cl_2NO_6$ requires 324.0036 and 326.0007, found at 324.0036 and 326.0003 [MH+] (ESI^+).

Methyl 1-(6,13-dioxoisoindolin-4-yl)butanoate 137a



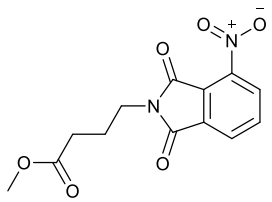
137a

137a was synthesised according to general procedure **D** using **123a** (1.49 g, 6.02 mmol) to afford the desired product as an off-white coloured solid (1.49 g, quantitative).

Mp= 86-88 °C (Lit. 89-90 °C).[320] **ν_{max} (KBr) cm^{-1}** 1770, 1733 (N-C=O), 1707 (C=O), 1437, 1396, 1363, 1191 (C-O), 1173, 1116, 1032. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H, Ar-H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H, Ar-H), 3.75 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 3.65 (s, 3H, OMe), 2.38 (t, *J* = 7.5 Hz, 2H, C(2)*H*), 2.02 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.48 (C(1)COOMe), 168.76 (C(6,13)C=O), 134.41 (ArC), 132.46 (C(7,12)Ar), 123.68 (ArC), 52.13 (C(OMe)), 37.60 (C(4)), 31.74 (C2)), 24.31 (C3)). ***m/z***= 270 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{14}NO_4$ requires 248.0917, found at 248.0917 [MH+] (ESI^+).

All data are in agreement with those found in the literature.[320,321]

Methyl 1-(8-nitro-6,13-dioxoisoindolin-4-yl)butanoate 137b

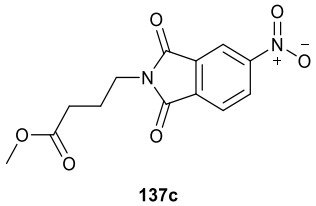


137b

137b was synthesised according to general procedure **D** using **123b** (0.690 g, 2.48 mmol)with the crude material purified using flash column chromatography (40% ethyl acetate in pet-ether 40:60) to afford the desired product as a yellow coloured solid (0.584 g, 80%).

R_f= 0.49 (40% ethyl acetate in pet-ether 40:60). **Mp**= 58-60 °C. **ν_{max} (KBr) cm^{-1}** 1778 (N-C=O), 1714 (C=O), 1540 (N-O, N=O), 1444, 1396, 1359 (N-O, N=O), 1197 (C-O), 1176, 1119, 1038, 750, 720 (CH_2). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.13 – 8.06 (m, 2H, Ar-H), 7.91 (dd, *J* = 8.2, 7.3 Hz, 1H, Ar-H), 3.77 (t, *J* = 6.9 Hz, 2H, C(4)*H*), 3.63 (s, 3H, OMe), 2.38 (t, *J* = 7.3 Hz, 2H, C(2)*H*), 2.02 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.97 (C(1)COOMe), 165.90 (C(6)C=O), 163.01 (C(13)C=O), 145.21 (C(8)Ar**C**-NO_2), 135.49 (C(11)ArC), 134.20 (C(12)ArC), 128.62 (C(9)ArC), 127.10 (C(11)ArC), 123.85 (C(7)ArC), 51.82 (OMe), 38.09 (C(4)), 31.40 (C(2)), 23.68 (C(3)). ***m/z***= 315 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{13}H_{12}NaN_2O_6$ requires 315.0587, found at 315.0581 [MNa+] (ESI$^+$).

Methyl 1-(9-nitro-1,3-dioxoisoindolin-4-yl)butanoate 137c



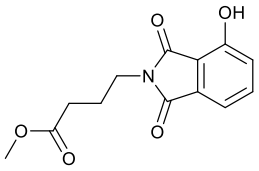
137c

137c was synthesised according to general procedure **D** using **123c** (0.288 g, 1.03 mmol) to afford the desired product as a beige coloured solid (0.302 g, quantitative yield).

Mp= 100-102 °C. **ν_{max} (KBr) cm^{-1}** 1725 (N-C=O), 1700 (C=O), 1540 (N-O, N=O), 1437, 1397, 1347 (N-O, N=O), 1290, 1195 (C-O), 1177, 1121, 1064, 1033, 994, 866, 822, 785, 720 (CH_2). **^{1}H**

NMR (400 MHz, Chloroform-*d*) δ 8.68 – 8.63 (m, 1H, Ar-H), 8.60 (d, *J* = 8.1 Hz, 1H, Ar-H), 8.04 (d, *J* = 7.8 Hz, 1H, Ar-H), 3.80 (t, *J* = 6.7 Hz, 2H, C(4)*H*), 3.64 (s, 3H, OMe), 2.39 (t, *J* = 7.1 Hz, 2H, C(2)*H*), 2.03 (p, *J* = 6.8 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.99 (C(1)COOMe), 166.28 (C6)C=O), 166.00 (C(13)C=O), 151.81 (C(9)Ar**C**-NO_2), 136.53 (C(12)ArC), 133.50 (C(7)ArC), 129.40 (C(10)ArC), 124.60 (C(11)ArC), 118.78 (C(8)ArC), 51.91 (OMe), 38.02 (C(4)), 31.30 (C(2)), 23.70 (C(3)). ***m/z***= 315 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{12}NaN_2O_6$ requires 315.0587, found at 315.0589 [MNa+] (ESI^+).

Methyl 1-(8-hydroxy-6,13-dioxoisoindolin-5-yl)butanoate 137d

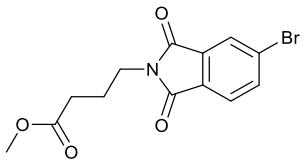


137d

137d was synthesised according to general procedure **D** using **123d** (1.291 g, 5.17 mmol) to afford the desired product as a beige coloured solid (1.31 g, 96%).

Mp= 121-123 °C. **ν_{max} (KBr) cm^{-1}** 3423 (Ar-OH), 1721 (N-C=O), 1686 (C=O), 1613, 1445 (C=C), 1407 (O-H), 1291, 1271 (C-O), 1200, 1181, 1127, 1115, 1027 (ArC-OH). **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.65 – 7.54 (m, 2H, Ar-H), 7.38 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.16 (d, *J* = 8.4 Hz, 1H, Ar-H), 3.71 (t, *J* = 6.9 Hz, 2H, (C(4)*H*), 3.66 (s, 3H, OMe), 2.38 (t, *J* = 7.4 Hz, 2H, (C(2)*H*), 2.02 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.12 (C(1)COOMe), 170.36 (C(6)C=O), 167.98 (C(13)C=O), 154.70 (C(8)Ar**C**-OH), 136.47 (C(10)ArC), 132.12 (C(12)ArC), 122.80 (C(11)ArC), 116.02 (C(9)ArC), 114.59 (C(8)ArC), 51.83 (OMe), 37.07 (C(4)), 31.32 (C(2)), 23.92 (C(3)). ***m/z***= 262 [MH-] (ESI^-) and 286 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{14}NO_5$ requires 264.0867, found at 264.0866 [MH+] (ESI^+).

Methyl 1-(9-bromo-6,13-dioxoisoindolin-1-yl)butanoate 137e

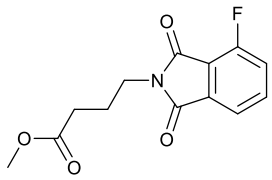


137e

Compound **123e** (1.236 g, 9.23 mmol) was added to 4-bromophthalic anhydride (2.436 g, 9.32 mmol) and dissolved in toluene (30 mL) followed by the addition of DIPEA (4.84 mL, 27.87 mmol) and left to stir for 16 hours at reflux. The reaction was allowed to cool to room temperature with the solvent being removed by reduced pressure to afford a yellow coloured oil. The impure oil was then washed using MeOH that caused the product to precipitate that was then filtered under vacuum and washed using ice cold MeOH (20 mL) to afford the desired product as a while coloured solid (3.030 g, quantitative yield).

Mp= 78-80 °C. **ν_{max} (KBr) cm^{-1}** 3399, 2945 (Ar-H), 1774 (C=O), 1728 (C=O), 1696 (N-C=O), 1603, 1436, 1416, 1394, 1362, 1301, 1196 (C-O), 1121, 1026. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.94 (dd, *J* = 1.7, 0.6 Hz, 1H, Ar-H), 7.83 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar-H), 7.68 (dd, *J* = 7.9, 0.6 Hz, 1H, Ar-H), 3.72 (t, *J* = 6.9 Hz, 2H, C(4)*H*), 3.63 (s, 3H, OMe), 2.35 (t, *J* = 7.4 Hz, 2H, (C(2)*H*), 1.99 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, CDCl3) δ 173.06 (C(1)COOMe), 167.57 (C(13)C=O), 167.04 (C(6)C=O), 137.07 (C(10)ArC), 133.73 (C(12)ArC), 130.62 (C(7)ArC), 128.98 (C(9)Ar**C**-Br), 126.72 (C(9)ArC), 124.72 (C(11)ArC), 51.83 (OMe), 37.50 (C(4)), 31.32 (C(2)), 23.83 (C(3)). ***m/z***= 325.9 and 327.9 [MNa+] (ESI^{+}). **HRMS** calculated for $C_{13}H_{12}BrNNaO_4$ requires 326.0022 and 328.0002, found at 326.0024 and 328.0004 [MNa+] (ESI^{+}).

Methyl 1-(8-fluoro-6,13-dioxoisoindolin-4-yl)butanoate 137f

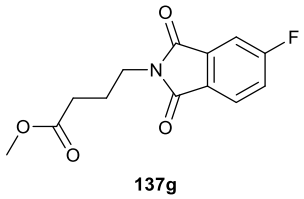


137f

137f was synthesised according to general procedure **D** using **123f** (0.370 g, 1.472 mmol) to afford the desired product as a brown coloured oil (0.393 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 1774 (N-C=O), 1708 (C=O), 1611 (N-C=O), 1481, 1446, 1396 (CH_2), 1362 (Ar-F), 1254, 1198 (C-O), 1175, 1117, 1034. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (ddd, *J* = 8.1, 7.4, 4.3 Hz, 1H, Ar-H), 7.67 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.38 (td, *J* = 8.5, 1.0 Hz, 1H, Ar-H), 3.75 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 3.66 (s, 3H, OMe), 2.38 (t, *J* = 7.4 Hz, 2H, C(2)*H*), 2.02 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.14 (C(1)COOMe), 156.35 (C(8)Ar**C**-F), 136.78 and 136.70 (d, *J*=19.9 Hz, (C(10)ArC), 122.66 and 122.46 (d, *J*=20 Hz, (C(11)ArC), 119.68 and 119.64 (d, *J*=4.2 Hz, C(9)ArC), 51.89 (OMe), 37.48 (C(4)), 31.40 (C(2)), 23.88 (C(3)). ***m/z***= 288 [MNa+] (ESI^+). **HRMS** calculate for $C_{13}H_{12}FNaNO_4$ requires 288.0642, found at 288.0641 [MNa+] (ESI^+).

Methyl 1-(9-fluoro-6,13-dioxoisoindolin-4-yl)butanoate 137g



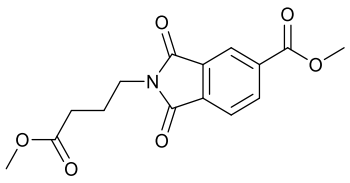
137g

137g was synthesised according to general procedure **D** using **123g** (0.302 g, 1.20 mmol) to afford the desired product as a beige coloured solid (0.320 g, quantitative yield).

Mp= 96-98 °C. **ν_{max} (KBr) cm^{-1}** 1679 (C=O), 1589, 1492, 1439, 1406 (CH_2), 1313 (Ar-F), 1286, 1265, 1186 (C-O), 1113, 1078. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.84 (dd, *J* = 8.2, 4.5 Hz, 1H, Ar-H), 7.51 (dd, *J* = 7.0, 2.3 Hz, 1H, Ar-H), 7.37 (td, 1H, Ar-H), 3.73 (t, *J* = 6.8 Hz, 2H,

C(4)*H*), 3.64 (s, 3H, OMe), 2.37 (t, *J* = 7.4 Hz, 2H, C(2)*H*), 2.00 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.11 (C(1)COOMe), 167.37 (C(13)C=O), 167.05 (d, *J* = 3.1 Hz, C(6)C=O), 166.46 (d, *J* = 256.5 Hz, C(9)Ar**C**-F), 134.94 (d, *J* = 9.5 Hz, C(12)ArC), 127.89 (d, *J* = 3.1 Hz, C(7)ArC), 125.73 (d, *J* = 9.5 Hz, C(11)ArC), 121.08 (d, *J* = 23.7 Hz, C(10)ArC), 111.25 (d, *J* = 24.8 Hz, C(8)ArC), 51.85 (OMe), 37.54 (C4)), 31.36 (C2)), 23.91 (C3)). ***m/z***= m/z=288 [MNa+] (ESI^+). **HRMS** calculate for $C_{13}H_{13}FNO_4$ requires 266.0823, found at 266.0824 [MH+] (ESI^+).

Methyl 1-(9-methoxy-9-oxobutyl)-6,13-dioxoisoindoline-9-carboxylate 137h

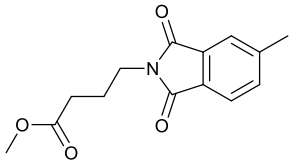


137h

137h was synthesised according to general procedure **D** using **123h** (0.288 g, 1.03 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the desired product as a white coloured solid (0.198 g, 62%).

Mp= 108-109°C. **ν_{max} (KBr) cm^{-1}** 2980 (C-H), 1742 (N-C=O), 1702 (C=O), 1439, 1400 (CH_2), 1366, 1333, 1285, 1255 (C-O), 1183 (C-O), 1113, 1075, 1033. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.43 (d, *J* = 1.2 Hz, 1H, Ar-H), 8.37 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar-H), 7.88 (d, *J* = 7.8 Hz, 1H, Ar-H), 3.95 (s, 3H, OMe), 3.74 (t, *J* = 6.9 Hz, 2H, C(4)*H*), 3.61 (s, 3H, OMe), 2.35 (t, *J* = 7.3 Hz, 2H, C(2)*H*), 2.00 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.03 (C(1)COOMe), 167.43 and 167.39 (C(6,13)C=O), 165.23 (C(9a)COOMe), 135.63 (C(12)ArC), 135.47 (C(10)ArC), 135.40 (C(9a)Ar**C**-COOMe), 132.30 (ArC), 124.38 (ArC), 123.37 (ArC), 52.94 (OMe), 51.79 (OMe), 37.54 (C(4)), 31.32 (C2)), 23.82 C(3)). ***m/z***= 328 [MNa+] (ESI^+). **HRMS** calculated for $C_{15}H_{15}NaNO_6$ requires 328.0792, found at 328.0790 [MNa+] (ESI^+).

Methyl 1-(9-methyl-6,13-dioxoisoindolin-5-yl)butanoate 137i

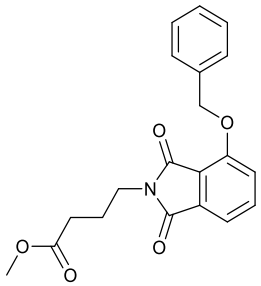


137i

137i was synthesised according to general procedure **D** using **123i** (1.311 g, 5.30 mmol) to afford the desired product as an off-white coloured solid (1.148 g, quantitative yield).

Mp= 77-79 °C. **ν_{max} (KBr) cm^{-1}** 2952 (C-H), 1768 (C=O), 1731 (N-C=O), 1703 (C=O), 1615, 1438 (CH_2), 1393 (CH_3), 1361 (CH_3), 1299, 1193 (C-O), 1172, 1117, 1030. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.68 – 7.63 (m, 1H, Ar-H), 7.51 (d, *J* = 7.2 Hz, 1H, Ar-H), 3.74 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 3.66 (s, 3H, C(1)OMe), 2.52 (s, 3H, C(9a)Ar-**CH_3**), 2.39 (t, *J* = 7.5 Hz, 2H, C(2)*H*), 2.03 (p, *J* = 7.1 Hz, 2H, (C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.19 (C(1)COOMe), 168.65 (C(13)C=O), 168.53 (C(6)C=O) 145.36 (C(9)Ar**C**-CH_3), 134.61 (ArC), 132.55 (C(12)ArC), 129.56 (C(7)ArC), 123.93 (ArC), 123.28 (ArC), 51.80 (C(1)OMe), 37.22 C(4)), 31.45 (C(2)), 24.04 (C(3)), 22.13 (C(9a)ArC-**C**H_3). ***m/z***= 284 [MNa+] (ESI$^+$).

Methyl 1-(8-(benzyloxy)-6,13-dioxoisoindolin-5-yl)butanoate 137j



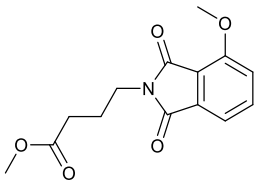
137j

Compound **123d** (0.200 g, 0.75 mmol) was dissolved in acetone (10 mL) followed by the addition of K_2CO_3 (0.126 g, 0.910 mmol) in one portion with the reaction mixture left to stir at room temperature for 5 minutes. Benzyl bromide (0.099 mL, 0.834 mmol) was then added dropwise over 5 minutes with the resulting mixture left stirring at room temperature for 16 hours. The volatiles were removed by reduced pressure then redissolved in DCM (20 mL) and transferred to

a separating funnel. The organic layer was washed using water (2 x 20 mL) then back extracted using DCM (40 mL). The combined organic layers were washed with brine (40 mL) and dried over $MgSO_4$ and concentrated by reduced pressure. The crude was purified using flash column chromatography (using a gradient from 0-30% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a white coloured solid (0.196 g, 73%).

R_f= 0.27 (30% ethyl acetate in pet-ether 40:60). **Mp**= 82-84 °C. **ν_{max} (KBr) cm^{-1}** 1730 (N-C=O), 1703 (C=O), 1608, 1438, 1396 (C-O), 1359, 1288, 1271, 1196 (C-O), 1174, 1122, 1045. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.58 (t, 1H, Ar-H), 7.51 – 7.45 (m, 2H, Ar-H), 7.44 – 7.35 (m, 3H, Ar-H), 7.35 – 7.28 (m, 1H, Ar-H), 7.19 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.33 (s, 2H, C(8a) Ar-**CH_2**-O), 3.72 (t, *J* = 6.8 Hz, 2H, C(4)*H*), 3.64 (s, 3H, OMe), 2.37 (t, *J* = 7.5 Hz, 2H, C(2)*H*), 2.01 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.22 (C(1)COOMe), 168.13 (C(13)C=O), 166.89 (C(6)C=O), 155.74 (C(8)Ar**C**-OCH_2), 136.04 (C(10)ArC), 135.90 (C(8b)Ar**C**-CH_2-O**)**, 134.35 (C(7) ArC), 128.85 (benzyl ArC), 128.24 (ArC), 126.86 (benzyl ArC), 119.50 (ArC), 118.01 (C(12)ArC), 115.87 (ArC), 70.94 (C(8a)Ar-**CH_2**-OAr), 51.78 (OMe), 37.12 (C(4)), 31.45 (C(2)), 24.00 (C(3)). ***m/z***= 376 [MNa+] (ESI^+). **HRMS** calculated for $C_{20}H_{19}NaNO_5$ requires 376.1155, found at 376.1152 [MNa+] (ESI^+).

Methyl 1-(8-methoxy-6,13-dioxoisoindolin-5-yl)butanoate 123k



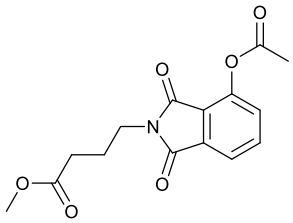
123k

Compound **123d** (0.200 g, 0.75 mmol) was dissolved in acetone (10 mL) followed by the addition of K_2CO_3 (0.126 g, 0.91 mmol) in one portion with the reaction mixture left to stir at room temperature for 5 minutes. Methyl iodide (0.052 mL, 0.83 mmol) was then added dropwise over 5 minutes with resulting mixture left stirring at room temperature for 16 hours. The volatiles were

removed by reduced pressure then redissolved in DCM (20 mL) and transferred to a separating funnel. The organic layer was washed using water (2 x 20 mL) then back extracted using DCM (40 mL). The combined organic layers were washed with brine (40 mL) then dried over $MgSO_4$ and concentrated by reduced pressure to afford the desired product as a yellow coloured solid (0.240 g, quantitative yield).

Mp 76-80 °C. **ν_{max} (KBr) cm^{-1}** 2980 (CH_3), 1766, 1733 (N-C=O), 1704 (C=O), 1612, 1487, 1441, 1398, 1361, 1282, 1170 (C-O), 1117, 1077, 1052, 1033. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.67 (dd, *J* = 8.4, 7.3 Hz, 1H, Ar-H), 7.44 (dd, *J* = 7.3, 0.8 Hz, 1H, Ar-H), 7.21 (dd, *J* = 8.5, 0.7 Hz, 1H, Ar-H), 4.03 (s, 3H, C(8a)*H*), 3.78 – 3.62 (m, 5H, C(4)*H*, C(OMe)), 2.38 (t, *J* = 7.4 Hz, 2H, C(2)*H*), 2.03 (p, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.55 (C(1)COOMe), 168.47 (C(13)C=O), 167.45 (C(6)C=O), 157.02 (C(8)Ar**C**-OMe), 136.57 (C(10)ArC), 134.59 (C(12)ArC), 117.86 (C(11)ArC), 117.67 (C(7)ArC), 115.86 (C(9)ArC), 56.75 (C(8a)ArC-O**C**H_3), 52.10 (OMe), 37.40 (C(4)), 31.73 (C(2)), 24.29 (C(3)). ***m/z***= 300 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{14}H_{15}NO_5$ requires 278.1023, found at 278.1025 [MH+] (ESI$^+$).

Methyl 1-(8-acetoxy-6,13-dioxoisoindolin-5-yl)butanoate 137l

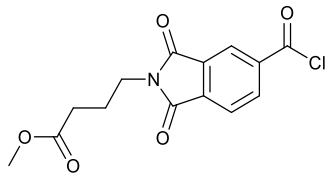


137l

Compound **123d** (0.251 g, 0.95 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C using an ice bath. Pyridine (0.084 mL, 1.04 mmol) was then added dropwise with the reaction mixture left stirring for 10 minutes at 0 °C. Acetyl chloride (0.071 mL, 1.04 mmol) was then added dropwise to the reaction mixture over 5 minutes with the resulting mixture left stirring at room temperature for 2 hours. The reaction mixture was then concentrated by reduced pressure to afford the desired product as a pale-yellow coloured oil (0.292 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 1766 (N-C=O), 1728 (C=O), 1699 (C=O), 1396, 1361, 1301, 1270, 1184 (C-O), 1032, 1008. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.76 – 7.68 (m, 2H, Ar-H), 7.38 – 7.32 (m, 1H, Ar-H), 3.70 (t, *J* = 6.9 Hz, 2H, C(4)*H*), 3.65 (s, 3H, OMe), 2.42 (s, 3H (C(8c)*H*), 2.37 (t, *J* = 7.4 Hz, 2H, C(2)*H*), 2.00 (p, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.12 (C(1)COOMe), 168.74 (C(8a)ArO-**C**=O), 167.52 (C(13)C=O), 166.04 (C(6)C=O), 146.62 (C(8)Ar**C**-O-), 135.82 (C(10)ArC), 133.68 (C(7)ArC), 128.47 (C(11)ArC), 122.92 (C(7)ArC), 121.05 (C(9)ArC), 51.81 (OMe), 37.36 (C(4)), 31.37 (C2)), 23.84 (C3)), 20.77 (C(8c) O=C-**C**H_3). ***m/z***= 328 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{15}H_{16}NO_6$ requires 306.0972, found at 306.0971 [MH+] (ESI$^+$).

Methyl 1-(9-(chlorocarbonyl)-6,13-dioxoisoindolin-4-yl)butanoate 137m



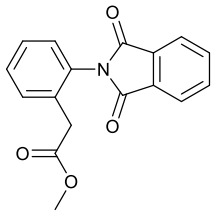
137m

Compound **124** (0.200 g, 0.68 mmol) was suspended in thionyl chloride (2 mL) in a round bottom flask and purged with N_2. The reaction was then stirred at reflux (88 °C) with a catalytic amount of DMF (1 drop) added to the mixture causing in evolution of gas. The reaction was left to stir for 5 minutes. The reaction was allowed to cool to room temperature and the solvent was removed by reduced concentrated and azeotroped using anhydrous DCM (3 x 10 mL) to afford the desired product as a dark brown coloured oil (0.213 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 2922 (CH_2), 2852 (CH_2), 1775 (O=C-Cl), 1708 (N-C=O), 1439 (C-O), 1394, 1362, 1176 (C-O), 1140, 1116, 1034. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.56 (dd, *J* = 1.6, 0.7 Hz, 1H, Ar-H), 8.52 – 8.42 (m, 1H, Ar-H), 7.99 (dd, *J* = 7.8, 0.7 Hz, 1H, Ar-H), 3.78 (t, *J* = 9.5, 6.9 Hz, 2H, C(4)*H*), 3.64 (s, 3H, OMe), 2.38 (t, *J* = 7.3, 1.9 Hz, 2H, C(2)*H*), 2.03 (p, *J* = 7.1, 2.6 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.13 (C(1)COOMe), 167.49 (C(13)C=O), 166.78 (C(6)C=O), 164.01 (C(9a)O=**C**-Cl), 138.42 (C(9)ArC, 136.81 (C(8)ArC), 125.86

(C(10)ArC), 124.89 (C(12)ArC), 123.92 (C(11)ArC), 123.44 (C(7)ArC), 51.88 (OMe), 37.90 (C(4)), 31.38 (C(2)), 23.79 (C(3)).

Methyl 1-(4-(6,13-dioxoisoindolin-4-yl)phenyl)acetate 138



138

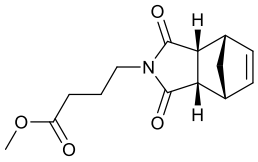
Method 1) **138** was synthesised according to general procedure **D** with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the desired product as an orange coloured solid (0.035 g, 38%).

Method 2) Compound **139** (0.300 g, 1.81 mmol) was added to phthalic anhydride (0.269 g, 1.81 mmol) in a round bottomed flask and heated at 170 °C for 6 hours while stirring. The reaction was left to cool to room temperature with the resulting solid mass dissolved in DCM (10 mL) and transferred to a separating funnel. The organic layer was washed using 0.5 N HCl (2 x 10 mL) with the combined aqueous layers being back extracted with DCM (20 mL). The crude mixture was purified using flash column chromatography (20-40% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated by reduce pressure to afford the desired product as a red/orange coloured solid (0.216 g, 44%).

Method 3) Compound **139** (0.566 g, 3.43 mmol) was added to phthalic anhydride (0.507 g, 3.43 mmol) and dissolved in toluene (15 mL) followed by the addition of DIPEA (1.79 mL, 0.98 mmol) and left to stir for 16 hours at reflux. The reaction was allowed to cool to room temperature with the solvent being removed by reduced pressure with the crude material was purified using flash column chromatography (40% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a red/orange coloured solid (0.188 g, 19%).

R_f= 0.37 (in 40% ethyl acetate in pet-ether 40:60). **ν_{max} (KBr) cm^{-1}** 3734, 1717 (C=O), 1496, 1457, 1378, 1259 (C-O), 1111 (CH_2), 1080, 763 (CH), 719 (CH), 668. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.99 (dd, *J* = 5.4, 3.1 Hz, 2H, Ar-H), 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H, Ar-H), 7.52 – 7.43 (m, 3H, Ar-H), 7.28 – 7.24 (m, 1H (Ar-H), 3.62 (s, 2H, (C(2)*H*), 3.53 (s, 3H, OMe). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.69 (C(1)COOMe), 167.29 (C(6,13)C=O), 134.42 (ArC), 133.07 (C(4)Ar**C**-phthalimide), 131.95 (ArC), 131.73 (ArC), 130.76 (ArC), 129.76 (ArC), 129.40 (ArC), 128.58 (ArC), 123.82 (ArC), 52.11 (OMe), 38.21 (C(2)). ***m/z***= 294 [MH-] (ESI^-), 318 [MNa+] (ESI^+). **HRMS** calculated for $C_{17}H_{13}NaNO_4$ requires 318.0736, found at 318.0734 [MNa+] (ESI^+). All data are in agreement with those found in the literature.[322]

Methyl 1-((*7R*,8*S*,11*R*,12*S*)-6,13-dioxo-6,13,7,8,11,12-hexahydro-2H-8,11-methanoisoindol-1-yl)butanoate 140

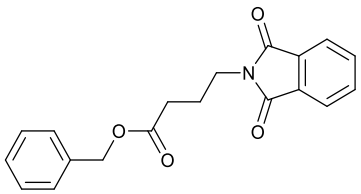


140

140 was synthesised according to general procedure **D** using **134** (1.36 g, 5.46 mmol) to afford the desired product as a brown coloured oil (1.39 g, 96%).

ν_{max} (KBr) cm^{-1} 2950 (C-H), 2873 (C-H), 1765 (C=O), 1734 (C=O), 1690 (N-C=O), 1558, 1540, 1507, 1436 (C-O), 1397 (C-O), 1363, 1337, 1197, 1099, 1050. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.09 (t, *J* = 1.9 Hz, 2H, C(9,10)*H*), 3.65 (s, 3H, OMe), 3.41 – 3.33 (m, 4H, (C(4,8,12)*H*)), 3.23 (dd, *J* = 2.9, 1.6 Hz, 2H, C(7,12)*H*), 2.24 (t, *J* = 7.6 Hz, 2H, C(2)*H*), 1.81 – 1.67 (m, 3H, C(3,8a)*H*), 1.52 (dt, *J* = 8.8, 1.5 Hz, 1H, C(8a)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.75 (C(6,13)C=O), 173.10 (C(1)COOMe), 134.60 (C(9,10)C=**C**-H), 52.38 (C(8a)), 51.78 (C(1)OMe), 45.87 (C(7,12)), 45.02 (C(8,12)), 37.62 (C(4)), 31.37 (C(2)), 23.20 (C(3)). ***m/z***= 286 [MNa+] (ESI^+). **HRMS** calculated for $C_{14}H_{17}NaNO_4$ requires 286.1050, found at 286.1050 [MNa+] (ESI^+).

Benzyl 1-(6,13-dioxoisoindolin-5-yl)butanoate 173



173

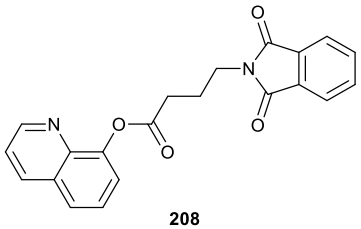
Method 1). Compound **123a** was added to a round bottomed flask that had been purged using N_2 followed by the addition of thionyl chloride (1 mL) and left stirring at room temperature for 1 hour. The solvent was removed and azeotroped using DCM (3 x 10 mL) then redissolved in anhydrous DCM (10 mL). The reaction mixture was cooled to 0 °C using an ice bath with benzyl alcohol (0.390 mL, 3.77 mmol) added dropwise of 5 minutes and left stirring at room temperature for 16 hours. The reaction mixture was concentrated by reduced pressure with the crude material being purified using flash column chromatography (DCM) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a colourless oil (0.368 g, 60%).

Method 2) NaH 60% dispersed in mineral oil (0.170 g, 5.12 mmol) was added to an oven dried round bottomed flask that was then purged with N_2 and suspended in anhydrous DMF (10 mL) and left stirring at 0 °C for 5 minutes. In a separate oven dried round bottomed flask, compound **123a** (0.995 g, 4.27 mmol) was dissolved in anhydrous DMF (5 mL) then added dropwise *via* syringe to the NaH containing flask. The reaction mixture was then left stirring for 30 minutes while at 0 °C. Benzyl bromide (0.611 mL, 5.12 mmol) was then added dropwise over 5 minutes with the reaction mixture left stirring at room temperature for 16 hours. The crude mixture was diluted with DCM (20 mL) and washed with warm water (5 x 50 mL) with the organic layer dried over $MgSO_4$ and concentrated by reduced pressure. The crude mixture was then purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a colourless oil (0.664 g, 48%).

R_f= 0.59 (DCM) and 0.27 (20% ethyl acetate in pet-ether 40:60). **ν_{max} (KBr) cm^{-1}** 1770 (N-C=O), 1707 (C=O), 1437, 1396, 1360, 1169 (C-O), 1148 (CH_2), 1030. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.88 – 7.78 (m, 2H, Ar-H), 7.75 – 7.66 (m, 2H, Ar-H), 7.39 – 7.27 (m, 5H, Bn Ar-H), 5.09 (s, 2H, C(1a)*H* O-C**H_2**-Bn), 3.76 (t, *J* = 6.9 Hz, 2H, C(4)*H*), 2.43 (t, *J* = 7.5 Hz, 2H, C(2)*H*), 2.04 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.52 (C(1)COOBn), 168.43 (C(6,13)C=O), 135.97 (Bn ArC), 134.08 (ArC), 132.18 (C(7,12)ArC), 128.67 (ArC), 128.65 (ArC), 128.35 (ArC), 123.37 (ArC), 66.51 (C(1a)O-**C**H_2-Bn), 37.31 (C(4)), 31.72 (C2)), 24.02 (C(3)). ***m/z***= 346 [MNa+] (ESI^+). **HRMS** calculated for $C_{19}H_{17}NaNO_4$ calculated for $C_{19}H_{17}NaNO_4$ requires 346.1049, found at 346.1053 [MNa+] (ESI^+).

All data are in agreement with those found in the literature.[323]

Quinolin-8-yl 1-(6,13-dioxoisoindolin-5-yl)butanoate 208

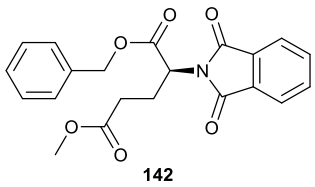


208

Compound **123a** (0.500 g, 2.14 mmol) was dissolved in DCM (5 mL) followed by the addition of DCC (0.486 g, 2.35 mmol) and a catalytic amount of DMAP and left stirring at room temperature for 5 minutes. 8-Hydroxyquinoline (0.920 g, 6.42 mmol) was added to the reaction mixture and left stirring at room temperature for 16 hours. The crude mixture was diluted with DCM (10 mL) then transferred to a separating funnel and washed using water (2 x 10 mL) and back extracted using DCM (20 mL) with the combined organic layers were combined, dried over $MgSO_4$ and concentrated by reduced pressure. The crude mix was purified using flash column chromatography (30-50% ethyl acetate in pet-ether 40:60) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as a pale yellow coloured solid (0.498 g, 64%).

Mp= 136-138 °C. **ν_{max} (KBr) cm^{-1}** 2980 (C-H), 2917 (C-H), 1759 (C=O), 1706 (N-C=O), 1499, 1468, 1437 (C-O), 1395, 1363, 1314, 1234, 1187 (C-O), 1144 (CH_2), 1111, 1082, 1053, 1027, 914, 870, 827, 789, 763, 718, 647. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.90 (dd, *J* = 4.2, 1.7 Hz, 1H, ArH), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H, ArH), 7.88 – 7.83 (m, 2H, ArH), 7.74 – 7.67 (m, 3H, ArH), 7.52 (t, *J* = 7.8 Hz, 1H, ArH), 7.47 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H, ArH), 3.92 (t, *J* = 6.9 Hz, 2H, C(4)*H*), 2.89 (t, *J* = 7.5 Hz, 2H, C(2)*H*), 2.27 (p, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.59 (C(1)ArO-**C**=O), 168.50 (C(6,13)C=O), 150.58 (ArC), 147.53 (ArC), 141.30 (ArC), 136.05 (ArC), 134.07 (ArC), 132.27 (ArC), 129.61 (ArC), 126.32 (ArC), 125.96 (ArC), 123.39 (ArC), 121.82 (ArC), 121.61 (ArC), 37.37 (C(4)), 31.75 (C(2)), 24.21 (C(3)). ***m/z***= 361 [MH+] (ESI$^+$) and 383 [MNa+] (ESI$^+$). **HMRS** calculated for $C_{21}H_{17}N_2O_4$ requires 361.1183, found at 361.1182 [MH+] (ESI$^+$).

4a-Benzyl 1-methyl (*S*)-4-(6,13-dioxoisoindolin-5-yl)pentanedioate 142



142

Method 1) In an oven dried round bottomed flash that had been purged with N_2, NaH 60% dispersed in mineral oil (0.118 g, 2.935 mmol) was dissolved in anhydrous THF (5 mL) at 0 °C using an ice bath. In a separate oven dried round bottomed flask that had been purged with N_2, compound **126L** (0.782 g, 2.68 mmol) was dissolved in anhydrous THF (5 mL) then added to the NaH containing flask *via* syringe and left to stir at 0 °C for 15 minutes. Benzyl bromide (0.35 mL, 2.68 mmol) was added dropwise followed by the addition of tetrabutylammonium iodide (0.991 g, 2.93 mmol) with the resulting reaction mixture left stirring at room temperature for 16 hours. The reaction mixture was transferred to a separating funnel and diluted with DCM (20 mL) then washed using water (2 x 20 mL) then back extracted using DCM (20 mL). The organic layers were combined and dried over $MgSO_4$ and concentrated by reduced pressure. The crude mixture was

then purified using flash column chromatography (35% ethyl acetae in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a white coloured solid (0.365 g, 35%).

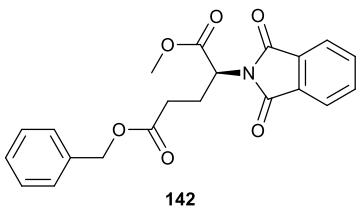
Method 2) In an oven dried round bottomed flash that had been purged with N_2, compound **126L** (0.750 g, 2.57 mmol) was dissolved in an excess of $SOCl_2$ (1 mL) and left stirring for 8 hours at room temperature. $SOCl_2$ was removed using reduced pressured and azeotroped using DCM (3 x 10 mL). The flask containing the acid chloride was then purged using N_2 and dissolved in anhydrous DCM (10 mL) and cooled to 0 °C using an ice bath followed by the addition of benzyl alcohol (0.53 mL, 5.15 mmol) dropwise over 5 minutes with the resulting mixture left stirring at room temperature for 16 hours. The solvents were removed by reduced pressure with the crude oil purified using flash column chromatography (30% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a colourless oil (0.384 g, 39%).

Method 3) Compound **126L** (6.04 g, 20.75 mmol) was added to a round bottomed flask and dissolved in anhydrous DCM (50 mL) followed by the addition of DCC (4.07 g, 22.82 mmol) and DMAP (0.253 g, 10% mol) with the resulting mixture left stirring for 1 hour at room temperature. Benzyl alcohol (2.35 mL, 22.82 mmol) was then added with the reaction mixture left stirring at room temperature for an additional 16 hours. The crude mixture was diluted with DCM (20 mL) and washed with water (2 x 50 mL) with the organic layer dried over $MgSO_4$ and concentrated by reduced pressure. The crude mixture was then purified using flash column chromatography (0-30% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a colourless oil (2.98 g, 38%).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -22.6 (*c* 1.0 in DCM). **Mp**= 103-105 °C. $\mathbf{R_f}$= 0.15 (35% ethyl acetate in pet-ether 40:60). $\boldsymbol{\nu_{max}}$ **(KBr) cm^{-1}** 1774 (C=O), 1716 (N-C=O), 1468, 1386, 1306, 1271, 1179 (C-O), 1115, 1053 (C-O), 717, 699. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.86 (ddd, *J* = 5.4, 3.0, 1.8 Hz, 2H, Ar-H),

7.75 (td, *J* = 5.5, 3.0 Hz, 3H, Ar-H), 7.37 – 7.27 (m, 4H, Ar-H), 5.18 (d, *J* = 5.5 Hz, 2H, C(4a)*H*), 4.98 (dd, *J* = 10.3, 5.1 Hz, 1H, C(4)*H*), 3.60 (s, 3H, OMe), 2.70 – 2.60 (m, 1H, C(2)H_A), 2.53 (dddd, *J* = 14.3, 10.3, 7.4, 6.1 Hz, 1H, C(2)H_B), 2.42 – 2.35 (m, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.71 (C(1)COOMe), 168.77 (C(4a)COOBn), 167.66 (C6,13)C=O), 135.26 (ArC)Bn), 134.40 (C(8,11)Ar), 131.85 (C(7,12)ArC), 128.66 (ArC)Bn), 128.47 (ArC)Bn), 128.23 (ArC)Bn), 123.72 (C(9,10)Ar), 67.74 (C(4a)Bn-**C**H_2-), 51.87 (C(4)), 51.59 (OMe), 30.80 (C(2)), 24.41 (C(3)). ***m/z***= 404 (ESI^+) [MNa+]. **HRMS** calculated for $C_{21}H_{19}NaNO_6$ requires 404.1104, found at 404.1104 [MNa+] (ESI^+).

1-Benzyl 4-methyl (*S*)-4-(6,13-dioxoisoindolin-5-yl)pentanedioate[324] **142**



142

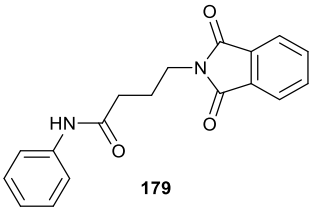
Compound **130** (3.70 g, 10.08 mmol) was suspended in DMF (20 mL) followed by the addition of Cs_2CO_3 (1.63 g, 5.04 mmol) with the reaction mixture left stirring at room temperature for 5 minutes resulting in the starting material dissolving. MeI (2.18 mL, 35.28 mmol) was slowly added over 5 minutes with the reaction mixture left stirring at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate (50 mL) and washed using warm water (40 °C, 5 x 50 mL) with the organic solvent concentrated by reduced pressure. The desired product was then azeotroped using DCM (3 x 20 mL) and concentrated by reduced pressure to afford the desired product as a colourless oil (1.64 g, 40%).

ν_{max} (KBr) cm^{-1} 3033 (C-H), 2954 (C-H), 1775 (C=O), 1713 (N-C=O), 1611, 1497 (C-H), 1467 (C-H), 1454 (C-H), 1437, 1385, 1338, 1297, 1257, 1213 (C-O), 1166 (C-O), 1111 (C-O), 1088, 1049, 1028. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.90 – 7.82 (m, 2H, ArH), 7.77 – 7.71 (m, 2H, ArH), 7.37 – 7.27 (m, 5H, ArH), 5.05 (s, 2H, C(1a)*H*), 4.94 (dd, *J* = 10.0, 5.0 Hz, 1H, C(4)*H*), 3.73 (s, 3H, C(4a)OMe), 2.70 – 2.60 (m, 1H, C(4)H_A), 2.56 – 2.47 (m, 1H, C(4)H_B), 2.47 – 2.41

(m, 2H, C(4)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.10 (C(4a)COOMe), 169.31 (C(1)BnCH_2-**C**=O), 167.60 (C(6,13)C=O), 135.78 (C(1b)CH_2-**C**Ar), 134.39 (ArC) 131.82 (C(7,12)ArC), 128.63 (ArC), 128.37 (ArC), 123.71 (ArC), 66.61 (C(1b)ArC-**C**H_2-), 52.94 (C(4a)OMe), 51.26 (C(4)), 30.95 (C(2)), 24.35 (C(3)).

All data are in agreement with those found in the literature.[324]

1-(6,13-Dioxoisoindolin-4-yl)-*N*-Phenylbutanamide 179



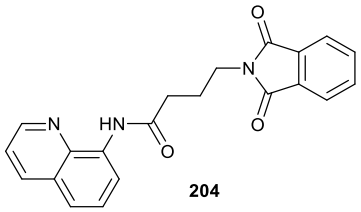
179

Compound **123a** (0.150 g, 0.64 mmol) was dissolved in DCM (5 mL) followed by the addition of EDC (0.228 g, 0.77 mmol) with the resulting mixture left stirring at room temperature for 1 hour. Aniline (0.16 mL, 0.77 mmol) was then added with the reaction left stirring at room temperature for an additional 16 hours. The reaction was then diluted using DCM (5 mL) and washed using water (10 mL) followed by an acid wash using 0.5 N HCl (10 mL). The organic layer was dried over $MgSO_4$ and concentrated by reduced pressure with the crude material being purified using flash column chromatography (40% ethyl acetate in pet-ether 40:60) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as a white coloured solid (0.085 g, 43%).

R_f= 0.28. **Mp**= 166-169 °C (Lit. 155-175 °C).[132] 3327 (N-H), 2981 (C-H), 1770 (C=O), 1706 (N-C=O), 1599, 1540, 1498, 1441, 1396, 1362, 1250, 1189 (C-O), 1111, 1030. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.92 – 7.80 (m, 2H, ArH), 7.73 (dt, *J* = 5.1, 3.5 Hz, 2H, ArH), 7.58 (d, *J* = 8.1 Hz, 2H, ArH), 7.33 (dd, *J* = 7.3, 1.8 Hz, 2H, ArH), 7.09 (t, *J* = 7.4 Hz, 1H, ArH), 3.88 – 3.75 (m, 2H, C(4)*H*), 2.44 – 2.31 (m, 2H, C(2)*H*), 2.12 (td, *J* = 11.6, 10.4, 5.5 Hz, 2H, C(3)*H*). ***m/z***= 618 [2MH+] (ESI^+). **HRMS** calculated for $C_{18}H_{17}N_2O_3$ requires 309.1234, found at 309.1238 [MH+] (ESI^+).

All data are in agreement with those found in the literature.[132]

1-(6,13-Dioxoisoindolin-4-yl)-*N*-(quinolin-8-yl)Butanamide[325] 204



204

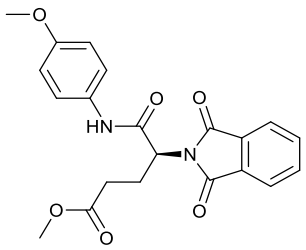
In an over-dried round bottomed flask that had been purged with N_2, compound **123a** (0.508 g, 2.17 mmol) was dissolved in an excess of $SOCl_2$ (4 mL) and left stirring at room temperature while under N_2 for 16 hours. The solvent was removed using reduced pressure and azeotroped using DCM (3 x 10 mL). The flask containing the acid chloride was then purged using N_2 and dissolved in anhydrous DCM (5 mL). The acid chloride mixture was then slowly pipetted into another round bottomed flask that containing 8-aminoquinoline (0.298 g, 2.06 mmol) and TEA (0.364 mL, 2.71 mmol) dissolved in DCM (5 mL) that had been purged with N_2. The resulting mixture was left stirring at room temperature while under an inert atmosphere of N_2 for 16 hours. The crude material was then washed using water (2 x 10 mL) and back extracted using DCM (20 mL) with the combined organic layers combined and concentrated by reduced pressure. The crude oil was then purified using flash column chromatography (40% ethyl acetate in pet-ether 40:60) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as a light brown coloured solid (0.323 g, 57%).

R_f= 0.40. **ν_{max} (KBr) cm^{-1}** 3345 (N-H), 2980 C-H), 2888 (C-H), 1977 (Ar), 1769 (N-C=O), 1699 (C=O), 1674 (N-C=O), 1527, 1488, 1464, 1430, 1393, 1356, 1325, 1289, 1253, 1166, 1119, 1084, 1072, 1029, 1018. **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.77 (s, 1H, C(1)N-*H*), 8.78 (dd, *J* = 4.3, 1.7 Hz, 1H, ArC), 8.69 – 8.63 (m, 1H, ArC), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H, ArC), 7.77 (dd, *J* = 5.4, 3.0 Hz, 2H, ArC), 7.67 – 7.61 (m, 2H, ArC), 7.47 – 7.44 (m, 2H, ArC), 7.44 – 7.40 (m, 1H, ArC), 3.85 (t, *J* = 6.7 Hz, 2H, C(4)*H*), 2.63 (dd, *J* = 8.0, 7.0 Hz, 2H, C(2)*H*), 2.26 – 2.17 (m, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.46 (C(6,13)C=O), 168.52 (C(1)N-C=O), 148.20 (ArC),

138.38 (ArC), 136.39 (ArC), 134.49 (ArC), 133.96 (ArC), 132.16 (ArC), 127.97 (ArC), 127.44 (ArC), 123.28 (ArC), 121.66(ArC), 121.49(ArC), 116.53 (ArC), 37.58 (C(4)), 35.35 (C(2)), 24.60 (C3)). ***m/z***= 360 [MH-] (ESI^-). **HRMS** calculated for $C_{21}H_{16}N_3O_3$ requires 360.1343, found at 360.1334 [MH-] (ESI^-).

All data are in agreement with those found in literature.[325]

Methyl (*S*)-4-(6,13-dioxoisoindolin-4-yl)-4a-((4-methoxyphenyl)amino)-5-oxopentanoate 228



228

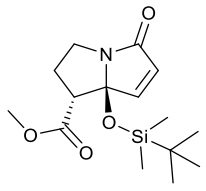
Compound **126L** (0.150 g, 0.51 mmol) was dissolved in DCM (5 mL) with the flask being purged using N_2 followed by the addition of T3P (0.153 mL, 0.51 mmol) and DIPEA (0.179 mL, 1.02 mmol) with the reaction mixture left stirring at 0 °C for 1 hour. *p*-Anisidine (0.075 g, 0.61 mmol) was added with the reaction mixture left stirring at room temperature for 16 hours. The crude mixture was transferred to a separating funnel and diluted with DCM (5 mL) and washed using water (2 x 10 mL), sat. $NaCO_3$ solution (10 mL) and brine (10 mL) with the organic layer being dried over $MgSO_4$. The crude organic material was purified using flash column chromatography (30% ethyl acetate in pet-ether 40-60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired material as an off-white-coloured film (0.005 g, 2%).

^{1}H NMR (200 MHz, Chloroform-*d*) δ 7.94 – 7.84 (m, 2H, Ar-H), 7.81 – 7.73 (m, 2H, Ar-H), 7.46 – 7.39 (m, 2H, Ar-H), 6.87 – 6.80 (m, 2H, Ar-H), 4.97 (t, *J* = 7.4 Hz, 1H, C(4)*H*), 3.77 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.64 (dd, *J* = 7.7, 6.3 Hz, 2H, C(2)*H*), 2.46 (t, *J* = 7.4 Hz, 2H, (C(3)*H*). Due to limited material available, additional characterisation was not acquired.

General procedure E for silyl-mediated cyclisation

In an oven-dried round bottomed flask that had been purged with N_2, compound (1.0 eq) was dissolved in anhydrous DCM (5 mL) followed by the addition of DIPEA (3.0 eq) and left to stir at room temperature for 1 hour. The reaction mixture was cooled to 0 °C using an ice bath with TBDMSiOTf (1.1 eq) being added dropwise over 5 minutes. The ice bath was removed with the reaction mixture allowed to warm to room temperature and left stirring for 16 hours. The crude mixture was transferred to a separating funnel and diluted with DCM (10 mL) then washed using water (2 x 10 mL) with the aqueous layers being combined and back extracted using DCM (10 mL). The combined organic layers were then dried using $MgSO_4$ and concentrated by reduced pressure. The crude oil was then purified using flash column chromatography with the product containing fractions collected, combined and concentrated to afford the desired product.

Methyl (2*R*,9*S*)-9-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,4,9-tetrahydro-1H-pyrrolizine-2-carboxylate 77a



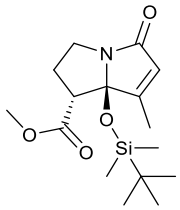
77a

77a was synthesised according to general procedure **E** using **76a** (0.292 g, 1.48 mmol) with the crude material purified using flash column chromatography (15% ethyl acetate in pet-ether 40:60) to afford the desired product as a very pale-yellow coloured oil that solidified over time (0.242 g, 57%).

R_f= 0.19. **Mp**= 51-53 °C. **ν_{max} (KBr) cm^{-1}** 2958 (C-H), 2929 (C-H), 2856 (C-H), 1738 (C=O), 1709 (N-C=O), 1437, 1357, 1049 (C-O), 1005 (O-Si), 778 (H-C=C). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.94 (d, *J* = 5.8 Hz, 1H, C(7)*H*), 5.96 (d, *J* = 5.7 Hz, 1H, C(8)*H*), 3.77 (td, 1H, C(4)H_A), 3.57 (s, 3H, OMe), 3.28 (ddd, *J* = 10.9, 9.1, 2.5 Hz, 1H, C(4)H_b), 3.11 (d, *J* = 6.7 Hz, 1H,

C(2)*H*), 2.60 (dtd, *J* = 13.2, 9.2, 6.8 Hz, 1H, C(3)H_A), 2.49 (dddd, *J* = 13.1, 8.5, 2.6, 1.4 Hz, 1H, C(3)H_B), 0.86 (s, 9H, C(CH_3)$_3$), 0.07 (s, 3H, Si-CH_3), 0.02 (s, 3H, Si-CH_3). ***m/z***= 330 [MK+] (ESI^+). **HRMS** calculated for $C_{15}H_{26}NO_4Si$ requires 312.1625, found 312.1623 [MH+] (ESI^+). All data are in agreement with those found in the literature.[156]

Methyl (2*R*,9*S*)-9-[(tert-butyldimethylsilyl)oxy]-7-methyl-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2-carboxylate 77b



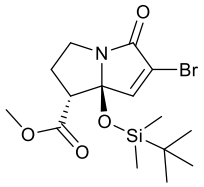
77b

77b was synthesised according to general procedure **E** using **76b** (0.506 g, 2.39 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the desired product as a pale-yellow coloured oil (0.342 g, 43%).

R_f= 0.47. **ν_{max} (KBr) cm^{-1}** 2953 (C-H), 2929 (C-H), 2900 (C-H), 2857 (C-H), 1738 (C=O), 1715 (N-C=O), 1650, 1472, 1437 (CH_3), 1408, 1360 (C-O), 1332, 1304, 1289, 1249 (Si-CH_3), 1212 (Si-C(CH_3)), 1156 (Si-O), 1084, 1045, 1007 (O-Si), 837 (CH_3-C=C), 779 (H-C=C). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.51 (q, *J* = 1.7 Hz, 1H, C(8)*H*), 3.78 – 3.69 (m, 1H, C(4)H_A), 3.53 (s, 3H, OMe), 3.26 (ddd, *J* = 10.8, 9.1, 2.5 Hz, 1H, C(4)H_B), 3.08 – 3.04 (dd, *J*=5.8, 1.1 Hz, 1H, C(2)*H*), 2.56 (dtd, *J* = 13.2, 9.1, 6.8 Hz, 1H, C(3)H_A), 2.44 (dddd, *J* = 13.1, 8.4, 2.5, 1.4 Hz, 1H, C(3)H_B), 1.81 (d, *J* = 1.7 Hz, 3H, C=C-**CH_3**), 0.84 (s, 9H, C(CH_3)$_3$), 0.03 (s, 3H, Si-CH_3), -0.03 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.31 (C(6)C=O), 171.73 (C(1)C=O), 140.25 (C(8)H-**C**=C), 136.80 (C(7)CH_3-**C**=C), 99.02 (C(9)), 52.98 (C(2)), 51.85 (C(1)OMe), 42.16 (C(4)), 31.04 (C(3)), 25.60 (C(**C**H_3)$_3$), 17.93 (Si-**C**(CH_3)$_3$), 10.79 (C(7)C=C-**C**H_3), -3.35 (Si-**C**H_3), -3.96 (Si-**C**H_3). ***m/z***= 326 [MH+] (ESI^+) and 348 [MNa+] (ESI^+). **HRMS** calculated for $C_{16}H_{28}NO_4Si$ requires 326.1782, found at 326.1786 [MH+] (ESI^+).

All data are in agreement with those found in the literature.[181]

Methyl (2*R*,9*R*)-7-bromo-9-[(tert-butyldimethylsilyl)oxy]-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2-carboxylate 77d

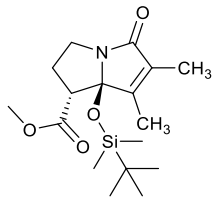


77d

77d was synthesised according to general procedure **E** from **76c** (1.42 g, 5.16 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the desired product as a yellow coloured solid (1.35g, 67%).

R_f= 0.63. **Mp**= 51-53 °C. **ν_{max} (KBr) cm^{-1}** 2953 (C-H), 2930 (C-H), 2857 (C-H), 2359, 1731 (N-C=O), 1599, 1472, 1437, 1357 (C-O), 1329, 1257 (Si-CH_3), 1196 (Si-C(CH_3)), 1174 (Si-O), 1140, 1091, 1079, 1051 (C-O), 1023, 1007 (Si-O), 835 (Br-C=C), 780 (H-C=C). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.04 (s, 1H, C(8)*H*), 3.79 (dt, *J* = 11.0, 8.9 Hz, 1H, C(4)H_A), 3.58 (s, 3H, OMe), 3.35 (ddd, *J* = 11.2, 9.1, 2.5 Hz, 1H, C(4)H_B), 3.13 (dd, *J* = 6.7, 1.3 Hz, 1H, C(2)*H*), 2.63 – 2.54 (m, 1H, C(3)H_A), 2.53 – 2.44 (m, 1H, (C(3)H_B), 0.85 (s, 9H, C(CH_3)$_3$), 0.06 (s, 3H, Si-CH_3), 0.02 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.05 (C(1)COOMe), 168.14 (C(6)C=O), 144.67 (C(8)C=**C**-H), 120.52 (C(7)C=**C**-Br), 99.30 (C(9)), 53.18 (C(1)OMe), 52.25 (C(2)), 43.06 (C(4)), 30.70 (C(3)), 25.53 (C(**C**H_3)$_3$), 17.94 (Si-**C**(CH_3)$_3$), -3.42 (Si-**C**H_3), -3.99 (Si-**C**H_3). ***m/z***= 412 and 414 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{15}H_{25}BrNO_4Si$ requires 390.0731 and 392.0710, found at 390.0732 and 392.0711 [MH+] (ESI$^+$).

Methyl (2*R*,9R)-9-((tert-butyldimethylsilyl)oxy)-7,8-dimethyl-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2-carboxylate 77f

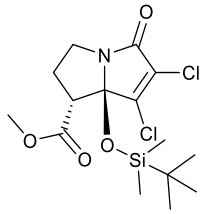


77f

77f was synthesised according to general procedure **E** using **76d** (0.500 g, 2.21 mmol) with the crude material purified using flash column chromatography (15% ethyl acetate in pet-ether 40:60) to afford the desired product as an off-white coloured solid (0.430 g, 57%).

R_f= 0.38. **Mp**= 77-81 °C. **ν_{max} (KBr) cm^{-1}** 2954 (CH_2), 2927 (CH_2), 2856 (CH), 1734 (N-C=O), 1699 (C=O), 1380, 1328, 1311, 1251 (Si-CH_3), 1204, 1193 (Si-C(CH_3)), 1174 (O-Si), 1144 (O-Si), 1119 (O-Si), 1085, 1061, 1034, 1005, 886, (C=C), 856 (=C-H), 759 (C=C-CH_3). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.80 – 3.71 (m, 1H, C(4)H_A), 3.50 (s, 3H, OMe), 3.27 (ddd, *J* = 10.8, 9.2, 1.8 Hz, 1H, C(4)H_B), 3.03 (dt, *J* = 6.6, 0.7 Hz, 1H, C(2)*H*), 2.60 – 2.49 (m, 1H, C(3)H_A), 2.46 – 2.37 (m, 1H, C(3)H_B), 1.90 (q, *J* = 1.2 Hz, 3H, C(7)C-CH_3), 1.70 (q, *J* = 1.2 Hz, 3H, C(8)C-CH_3), 0.86 (s, 9H. C(CH_3)$_3$), 0.05 (s, 3H, Si-CH_3), -0.11 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.92 (C(1)COOMe), 171.43 (C(6)C=O)), 150.50 (C(8)C=**C**-CH_3), 130.02 (C(7)C=**C**-CH_3), 100.49 (C(9)), 51.96 (C(2)), 51.44 (C(1)OMe), 42.47 (C(4)), 30.51 (C(3)), 25.42 (C(**C**H_3)$_3$), 17.78 (Si-**C**(CH_3)$_3$), 10.73 (C(8a)C=C-**C**H_3), 8.16 (C(7a)C=C-**C**H_3) , -4.49 (Si-CH_3), -4.77 (Si-CH_3). ***m/z***= 362 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{17}H_{30}NO_4Si$ requires 340.1938, found 340.1934 [MH+] (ESI$^+$).

Methyl (2*R*,9*R*)-9-((tert-butyldimethylsilyl)oxy)-7,8-dichloro-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2-carboxylate 77g

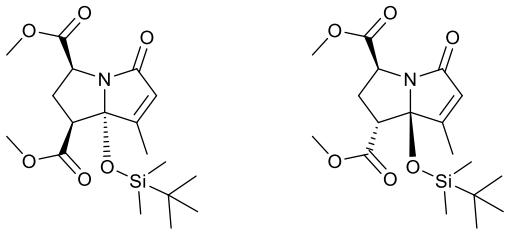


77g

77g was synthesised according to general procedure **E** using **76e** (0.498 g, 1.87 mmol) with the crude material purified using flash column chromatography (10% ethyl acetate in pet-ether 40:60) to afford the desired product as a light orange coloured solid (0.406 g, 57%). NMR shows product co-elutes with the starting material, so yield is not exact.

R_f= 0.51. **ν_{max} (KBr) cm^{-1}** 2980 (C-H), 2888 (C-H), 2858 (C-H), 1724 (N-C=O), 1620 (C=O), 1470, 1435, 1351, 1323, 1302, 1252 (Si-CH_3), 1210 (Si-C(CH_3)), 1174 (Si-O), 1128, 1102, 1058, 1044, 852, 837 (C-Cl), 810 (C-Cl), 777 (C-Cl), 735. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.83 (td, *J* = 10.4, 8.3 Hz, 1H, C(4)H_A), 3.59 (s, 3H, C(OMe)), 3.38 (ddd, *J* = 10.9, 9.1, 1.9 Hz, 1H, C(4)H_B), 3.16 (d, *J* = 6.6 Hz, 1H, C(2)*H*), 2.66 – 2.52 (m, 1H, C(3)H_A), 2.51 – 2.39 (m, 1H, C(3)H_B), 0.87 (s, 9H, C(CH_3)$_3$), 0.07 (s, 3H, Si-CH_3), -0.00 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.82 (C(1)COOMe), 166.31 (C(6)C=O), 145.27 (C(8)C=**C**-Cl), 127.00 (C(7)C=**C**-Cl), 98.26 (C(9)), 52.29 (C(1)OMe)) 52.13 (C(2)), 43.85 (C(4)), 30.47 (C(3)), 25.57 (C(**C**H_3), 18.07 (Si-**C**(CH_3)$_3$), -4.15 (Si-CH_3), -4.43 (Si-CH_3). ***m/z***= 402 and 404 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{15}H_{24}Cl_2NO_4Si$ requires 380.0846 and 382.0816, found at 380.0848 and 382.0818 [MH+] (ESI$^+$).

1,4a-Dimethyl (2*S*,4a*S*,9*R*)-9-[(tert-butyldimethylsilyl)oxy]-7-methyl-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2,4-dicarboxylate 170ba and **1,4a-Dimethyl (2*S*,4a*S*,9*S*)-9-[(tert-butyldimethylsilyl)oxy]-8-methyl-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2,4-dicarboxylate 170bb**



170ba 170bb

170ba and **170bb** were synthesised according to general procedure **E** using **116b** (0.723 g, 2.68 mmol) with the crude material purified using flash column chromatography (40% ethyl acetate in pet-ether 40:60) to afford the desired product as a pale-yellow coloured oil (0.635 g, 54%). Regioisomer mixture calculated at 10:1 for **170ba**:**170bb**.

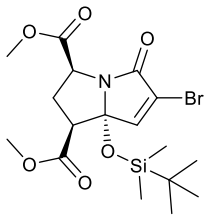
R_f= 0.41. **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 2857, 1736 (N-C=O), 1720 (C=O), 1651 (C=O), 1436, 1359, 1309, 1250 (Si-CH_3), 1198 (Si-C(CH_3)), 1174 (Si-O), 1087 (C-O), 1037, 1006. ***m/z***= 384 [MH+] (ESI^+) and 406 [MNa+] (ESI^+). **HRMS** calculated for $C_{18}H_{30}NO_6Si$ calculated for $C_{18}H_{29}NO_6Si$ requires 384.1837, found at 384.1837 [MH+] (ESI^+).

170ba) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 6.78 (q, *J* = 1.7 Hz, 1H, C(8)*H*), 4.59 – 4.52 (m, 1H, C(4)*H*), 3.75 (s, 3H, OMe), 3.56 (s, 3H, OMe), 3.16 – 3.14 (m, 1H, C(2)*H*), 2.84 – 2.75 (m, 2H, (C(3)*H*), 1.82 (s, 3H, C(7)CH_3), 0.87 (s, 9H, C(CH_3)$_3$), 0.12 (s, 3H, Si-CH_3), 0.08 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 175.54 (C(6)C=O), 172.94 (C(1)COOMe), 172.72 (C(4a)COOMe), 141.95 (C(8)C=**C**-H), 138.01 (C(7)C=**C**-CH_3), 100.53 (C(9)), 57.17 (C(4)), 54.11 (C(2)), 52.76 (OMe), 52.42 (OMe), 35.80 (C(3)), 26.08 (C(**C**H_3)$_3$), 18.66 (Si-**C**(CH_3)$_3$), 10.52 (C(7a)C=C-**C**H_3), -2.79 (Si-CH_3), -3.63 (Si-CH_3).

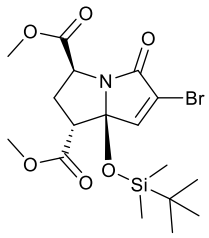
170bb) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 6.91 (q, *J* = 1.7 Hz, 1H, C(7)*H*), 4.24 (dd, *J* = 8.4, 3.4 Hz, 1H, C(4)*H*), 3.70 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.25 (dd, *J* = 7.7, 2.7 Hz, 1H, C(2)*H*), 2.92 (dt, *J* = 13.8, 8.2 Hz, 2H, C(3)*H*), 1.82 (s, 3H, C(8)CH_3), 0.89 (s, 9H, C(CH_3)$_3$)), 0.07 (s, 3H,

Si-CH_3), 0.03 (s, 3H, Si-CH_3).**^{13}C NMR** (101 MHz, MeOD) δ 174.39 (C(6)C=O), 171.43 (C(1)COOMe), 171.13 C(4a)COOMe), 145.26 C(7)C=**C**-H), 135.74 (C(8)C=**C**-CH_3), 100.51 (C(9)), 58.31 (C(4)), 56.92 (C(2)), 53.59 (OMe), 52.79 (OMe), 35.73 (C(3)), 26.07 (C(**C**H_3)$_3$), 18.37 (Si-**C**(CH_3)$_3$), 10.59 C(8a)C=C=**C**H_3), -3.10 (Si-CH_3), -3.63 (Si-CH_3).

1,4a-Dimethyl (2*S*,4a*S*,9*R*)-9-[(tert-butyldimethylsilyl)oxy]-7-bromo-6-oxo-2,3,5,9-tetrahydro-1H-pyrrolizine-2,4-dicarboxylate 170ca and **1,4a-Dimethyl (2*S*,4a*S*,9*S*)-9-[(tert-butyldimethylsilyl)oxy]-8-bromo-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2,4-dicarboxylate 170cb**



170ca



170cb

170ca and **170cb** were synthesised according to general procedure **E** using **116c** (0.573 g, 1.71 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the desired product as an orange coloured solid (0.298 g, 39%). Regieoisomer mixture calculated at 1.0: 0.20 for **170ca**:**170cb**.

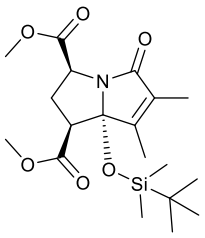
R_f= 0.36. **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 2857 (C-H), 1734 (N-C=O), 1713 (C=O), 1598, 1437, 1357, 1308, 1255 (Si-CH_3), 1202, 1176 (Si-C(CH_3), 1095 (C-O), 1038, 1007, 940, 910, 836, 781, 733 (C=C-Br), 676. ***m/z***= 470 and 472 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{17}H_{26}BrNO_6Si$ requires 470.0605 and 472.0585, found at 470.0604 and 472.0583 [MNa+] (ESI$^+$).

170ca) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.45 (s, 1H, C(8)*H*), 4.60 (td, *J* = 9.1, 0.8 Hz, 1H, C(4a)*H*), 3.76 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.24 (dt, *J* = 6.1, 1.0 Hz, 1H, C(2)*H*), 2.91 – 2.76 (m, 2H, C(3)*H*), 0.89 (s, 9H, C(CH_3)$_3$), 0.14 (s, 3H, Si-CH_3), 0.10 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 172.36 (C(1)COOMe), 172.27 (C(4a)COOMe), 169.42 (C(6)C=O), 146.78

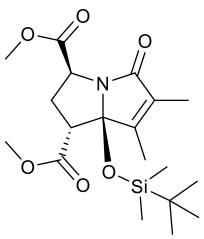
(C(8)C=**C**-H), 121.07 (C(7)C=**C**-Br), 100.82 (C(9)), 57.91 (C(4)), 54.18 (C(2)), 52.92 (OMe), 52.70 (OMe), 35.41 (C(3)), 26.00 (C(**C**H_3)$_3$), 18.77 (Si-**C**(CH_3)$_3$), -2.97 (Si-CH_3), -3.76 (Si-CH_3).

170cb) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.55 (s, 1H, C(7)*H*), 4.31 (dd, *J* = 8.9, 2.2 Hz, 1H, C(4a)*H*), 3.70 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.35 (dd, *J* = 7.7, 1.7 Hz, 1H, C(2)*H*), 3.00 (ddd, *J* = 13.9, 8.8, 7.7 Hz, 1H, C(3)*H*), 0.89 (s, 9H, C(CH_3)$_3$), 0.08 (s, 3H, Si-CH_3), 0.06 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 171.21, (C(1(COOMe), 170.92 (C(4a)COOMe), 170.49 (C(6)C=O), 150.15 (C(7)C=**C**-H), 129.72 (C(8)C=**C**-Br), 100.81 (C(9)), 57.32 (C(4)), 53.75 (C(2)), 53.00 (OMe), 52.62 (OMe), 35.49 (C(3)), 25.95 (C(**C**H_3)$_3$), 18.77 (Si-**C**(CH_3)$_3$), -3.25 (Si-CH_3), -3.77 (Si-CH_3).

1,4a-Dimethyl (2*S*,4a*S*,9*S*)-9-[(tert-butyldimethylsilyl)oxy]-6,7-dimethyl-6-oxo-2,3,5,9-tetrahydro-1H-pyrrolizine-2,4-dicarboxylate 170da and **1,4a-Dimethyl (2*R*,4a*S*,9*R*)-9-[(tert-butyldimethylsilyl)oxy]-6,7-dimethyl-6-oxo-2,3,5,9-tetrahydro-1H-pyrrolizine-2,4-dicarboxylate 170db**



170da



170db

170da and **170db** were synthesised according to general procedure **E** using **116d** (0.410 g, 1.44 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the desired product with additional impurities. The crude mixture was then purified using flash column chromatography (10% ethyl acetate in DCM) to afford the desired product as a white coloured solid (0.107 g, 19%). Regioisomer mixture calculated at 1.0: 0.08 for **170da**:**170db**.

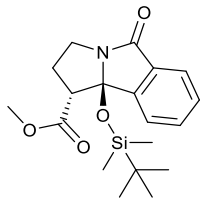
R_f= 0.30 (20% ethyl acetate in pet-ether 40:60) and 0.45 (10% ethyl acetate in pet-ether 40:60). **$[\alpha]_D^{25}$**= +53.8 (*c*. 1.0 MeOH). **Mp**= 66-68 °C. **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 2928 (C-H), 2856 (C-

H), 1739 (C=O), 1707 (N-C=O), 1435, 1402, 1254 (Si-CH_3), 1205 (Si-CH_3), 1173 (Si-C(CH_3), 1102, 1066 (Si-O), 1045, 1006, 890, 856, 838, 779, 734, 668. ***m/z***= 420 [MNa+] (ESI^+). **HRMS** calculated for $C_{19}H_{31}NO_6Si$ requires 398.1993, found at 398.1986 [MH+] (ESI^+).

170da) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 4.21 (dd, *J* = 8.8, 2.0 Hz, 1H, C(4)*H*), 3.68 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.22 (dd, *J* = 7.7, 1.6 Hz, 1H, C(2)*H*), 3.01 (ddd, *J* = 13.8, 8.8, 7.7 Hz, 1H, C(3)H_A), 2.84 (dt, *J* = 13.8, 1.8 Hz, 1H, C(3)H_B), 2.05 (d, *J* = 1.2 Hz, 3H, C(8a)C=C-CH_3), 1.73 (d, *J* = 1.2 Hz, 3H. C(7a)C=C-CH_3), 0.90 (s, 9H, C(CH_3)$_3$), 0.09 (s, 3H, Si-CH_3), -0.07 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 174.94 (C(6)C=O), 171.84 (C(1)COOMe), 170.72 (C(4a)COOMe, 156.28 (C(8)C=**C**-CH_3), 130.10 (C(7)C=**C**-CH_3), 102.10 (C(9), 56.92 (C(4)), 52.80 (OMe), 52.47 (C(2)), 52.34 (OMe), 36.15 (C(3)), 26.12 (C(**C**H_3)$_3$), 18.77 (Si-**C**(CH_3)$_3$), 12.60 (C(8)C=C-**C**H_3), 8.38 (C(7)C=C-**C**H_3), -3.93 (Si-CH_3), -4.11 (Si-CH_3).

170db) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 4.60 (m, 1H, C(4)*H*), 3.75 (s, 3H, OMe), 3.55 (s, 3H, OMe), 3.16 (d, *J*= 6.24 Hz, 1H, C(2)*H*), 2.84 (m, 1H, C(3)H_A), 2.74, (ddd, *J*= 13.4, 8.2, 0.7 Hz, 1H, C(3)H_B), 2.01, (d, *J*= 1.5 Hz, 3H, C(8a)C=C-CH_3), 1.97, (d, *J*= 1.5 Hz, 1H, C(7a)C=C-CH_3), 0.97 (s, 9H, C(CH_3)$_3$), 0.05 (s, 3H, Si-CH_3), 0.02 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 177.16 (C(6)C=O), 172.85 (C(1)COOMe), 172.72 (C(4a)COOMe, 131.77 (C(7)C=**C**-CH_3), 102.79 (C(9)), 58.29, (C(4)), 53.33 (OMe), 52.73 (OMe), 52.39 (C(2)), 35.02 (C(3)), 26.26 (C(**C**H_3)$_3$), 19.04 (Si-**C**(CH_3)$_3$), 11.84 (C(8a)C=C-**C**H_3), 8.27 (C(7a)C=C-**C**H_3), -3.54 (Si-CH_3), -3.65 (Si-CH_3). Note that C8 alkene peak not identified, due to the low concentration of the minor isomer in the ^{13}C NMR

Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-1H-benzo[a]pyrrolizine-2-carboxylate 144a



144a

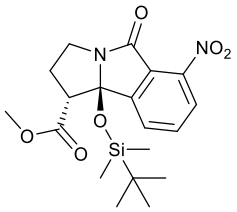
Method 1) **144a** was synthesised according to general procedure **E** using **137a** (2.86 g, 11.57 mmol) with the crude material purified using flash column chromatography (30% ethyl acetate in pet-ether 40:60) to afford the desired product as an off-white coloured solid (3.91 g, 97%).

Method 2) In an oven dried round bottomed flash that had been purged with N_2 with Silver triflate (0.312 g, 1.214 mmol) and TBDMSiCl (0.182 g, 1.214 mmol) was dissolved in anhydrous DCM (5 mL) and left stirring at room temperature for 10 minutes. A solution of **137a** (0.100g, 0.404 mmol) was dissolved in anhydrous DCM (5 mL) with the addition of DIPEA (0.211 mL, 1.214 mmol) then slowly added dropwise over 5 minutes to the triflate containing solution. The resulting mixture was left stirring at room temperature for 16 hours. The crude reaction was transferred to a separating funnel and washed with water (2 x 10 mL) and then back extracted using DCM (20 mL) with the combined organic layer washed using brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated by reduced pressure followed by purification using flash column chromatography (20% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a white coloured solid (0.066 g, 45%).

R_f= 0.31 (20% ethyl acetate in pet-ether 40:60). **Mp**= 86-88^o C. **ν_{max} (KBr) cm^{-1}** 2954 (Ar C-H), 2930 (Ar C-H), 2899 (C-CH_3), 2857 (C-H), 1737 (C=O), 1718 (N-C=O), 1467, 1436, 1360, 1328, 1251 (Si-CH_3), 1215 (Si-CH_3), 1193 (Si-C(CH_3)), 1173 (Si-O), 1141, 1110 (Si-O), 1081 (C-O), 1043, 780 (C=C-H), 757, 693 cm^{-1}. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.66 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar-H), 7.53 – 7.47 (m, 2H, Ar-H), 7.44 (ddd, *J* = 7.5, 6.9, 1.5 Hz, 1H, Ar-H), 3.95 (dt, *J*

= 10.7, 8.5 Hz, 1H, C(4)H_A), 3.42 (ddd, *J* = 11.0, 9.5, 2.2 Hz, 1H, C(4)H_B), 3.30 (d, *J* = 6.8 Hz, 1H, C(2)*H*), 3.11 (s, 3H, OMe), 2.73 – 2.66 (m, 1H, C(3)H_A), 2.49 (dddd, *J* = 13.1, 8.5, 2.2, 1.0 Hz, 1H, C(3)H_B), 0.82 (s, 9H, C(CH_3)$_3$), -0.08 (s, 3H, Si-CH_3), -0.51 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.60 (C(1)COOMe), 170.35 (C(6)C=O), 144.36 (C(12)ArC), 132.75 (C(7)ArC), 132.20 (ArC), 130.03 (ArC), 123.50 (ArC), 123.26 (ArC), 99.08 (C(13)), 53.05 C(2)), 51.41 (C(1)OMe), 42.11 (C(4)), 31.03 (C(3)), 25.48 (C(**C**H_3)$_3$), 17.80 (Si-**C**(CH_3)$_3$), -4.30 (Si-CH_3), -4.50 (Si-CH_3). ***m/z***= 384 [MNa+] (ESI^+). **HRMS** calculated for $C_{19}H_{27}NaNO_4Si$ requires 362.1782, found at 362.1781 [MNa+] (ESI^+).

Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-8-nitro-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 144b



144b

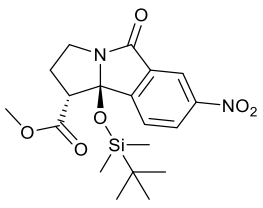
Method 1) **144b** was synthesised according to general procedure **E** using **137b** (0.490 g, 1.67 mmol) with the crude material purified using flash column chromatography (30% ethyl acetate in pet-ether 40:60) to afford the desired product as a yellow coloured solid (0.433 g, 82%).

Method 2) In an oven dried round bottomed flash that had been purged with N_2 with Silver triflate (0.263 g, 1.02 mmol) and TBDMSiCl (0.153 g, 1.02 mmol) was dissolved in anhydrous DCM (5 mL) and left stirring at room temperature for 10 minutes. A solution of **137b** (0.100 g, 0.34 mmol) was dissolved in anhydrous DCM (5 mL) with the addition of DIPEA (0.178 mL, 1.02 mmol) then slowly added dropwise over 5 minutes to the triflate containing solution. The resulting mixture was left stirring at room temperature for 16 hours. The crude reaction was transferred to a separating funnel and washed with water (2 x 10 mL) then back extracted using DCM (20 mL) with the combined organic layer washed using brine (20 mL). The organic layer was dried over

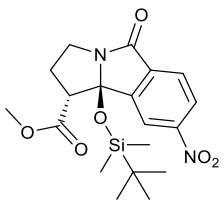
$MgSO_4$ and concentrated by reduced pressure followed by purification using flash column chromatography (30% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated by reduced pressure to afford the desired product as a white coloured solid (0.018 g, 13%).

R_f= 0.51 (30% ethyl acetate in pet-ether 40:60). **ν_{max} (KBr) cm^{-1}** 1726 (C=O), 1535 (N-O_2), 1358, 1326, 1241 (Si-CH_3), 1217 (Si-CH_3), 1190 (Si-C(CH_3)), 1107 (Si-O), 1072. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 7.8, 1.1 Hz, 1H, Ar-H), 7.75 (dd, *J* = 7.7, 1.1 Hz, 1H, Ar-H), 7.69 (t, *J* = 7.6 Hz, 1H, Ar-H), 3.99 (dt, *J* = 11.5, 9.0 Hz, 1H, C(4)H_A), 3.46 (ddd, *J* = 11.4, 9.4, 2.1 Hz, 1H, C(4)H_B), 3.38 – 3.34 (d, *J*=6.7 Hz, 1H, C(2)*H*), 3.24 (s, 3H, OMe), 2.76 (dtd, *J* = 13.3, 9.4, 7.1 Hz, 1H, C(3)H_A), 2.53 (dddd, *J* = 13.4, 8.5, 2.2, 1.0 Hz, 1H, C(3)H_b), 0.85 (s, 9H, C(CH_3)$_3$), 0.03 (s, 3H, Si-CH_3), -0.44 (s, 3H, Si-CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.23 (C(1)COOMe), 164.88 (C(6)C=O), 147.29 (C(12)ArC), 145.56 (C(8)Ar**C**-NO_2), 133.15 (C(10)ArC), 127.44 (C(9)ArC), 125.37 (C(7)ArC), 124.77 (C(11)ArC), 97.83 (C(13)), 53.11 (C(2)), 51.89 (C(1)OMe), 42.94 (C(4)), 31.13 (C(3)), 25.64 (C(**C**H_3)$_3$, 17.89 (Si-**C**(CH_3)$_3$), -4.12 (Si-CH_3), -4.21 (Si-CH_3). ***m/z***= 407 [MH+] (ESI^+). **HRMS** calculated for $C_{19}H_{27}N_2O_6Si$ requires 407.1632, found at 407.1634 [MH+] (ESI^+).

Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-9-nitro-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 172a and **Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-10-nitro-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 172b**



172a



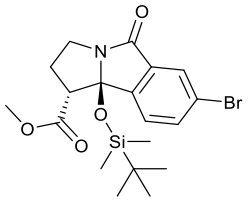
172b

172a and **172b** were synthesised according to general procedure **E** using **137c** (0.100 g, 0.342 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) concentrated in two separate flasks to afford the desired products. Only **172a** was cleanly isolated (0.015 g) with the sample containing **172b** also containing **172a** due to how closely these compounds eluted giving a total conversion from the starting material to afford 0.90 g, 72%. **172a**) $\mathbf{R_f}$= 0.36. **Mp** 104-106 °C. $\mathbf{\nu_{max}}$ **(KBr) cm^{-1}** 2958 (Ar-H), 2927 (Ar-H), 2902 (Ar-H), 2857 (Ar-H), 1730 (C=O), 1714 (N-C=O), 1625, 1597 (N-O_2), 1481, 1435, 1358, 1315, 1300, 1247 (Si-CH_3), 1217 (Si-CH_3), 1193 (Si-C(CH_3)), 1123 (Si-O), 1075 (C-O). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.53 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.43 (dd, *J* = 8.3, 2.1 Hz, 1H, Ar-H), 7.69 (d, *J* = 8.3 Hz, 1H, Ar-H), 3.99 (dt, *J* = 11.2, 8.8 Hz, 1H, C(4)H_A), 3.49 (ddd, *J* = 11.3, 9.4, 2.1 Hz, 1H, C(4)H_B), 3.40 – 3.34 (m, 1H, C(2)*H*), 3.22 (s, 3H. C(1)OMe), 2.76 (dtd, *J* = 13.2, 9.4, 7.1 Hz, 1H, C(3)H_A), 2.55 (ddt, *J* = 13.3, 8.2, 1.7 Hz, 1H, C(3)H_B), 0.85 (s, 9H, Si-C(C**H**$_3$)$_3$), -0.00 (s, 3H, Si-CH_3), -0.48 (s, 3H, Si-CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.23 (C1)COOMe), 167.79 C(6)C=O), 150.29 (C(12)ArC), 149.71 (C(9)Ar**C**-NO_2), 134.70 (C(7)ArC), 127.41 (ArC), 124.61 (ArC), 119.01 (ArC), 98.57 (C(13)), 52.95 (C(2)), 51.91 (C(1)OMe), 42.63 (C(4)), 31.20 (C(3)), 25.51 (Si-C(**C**H_3)$_3$), 17.89 (Si-**C**(CH_3)$_3$), -4.11 (Si-CH_3), -4.13 (Si-CH_3). ***m/z***= 814 [2M+H+] (ESI$^+$) and 836 [2M+Na+] (ESI$^+$). **HRMS** calculated for $C_{19}H_{27}N_2O_6Si$ requires 407.1632, found at 407.1629 [MH+] (ESI$^+$).

172b). $\mathbf{R_f}$= 0.33. $\mathbf{\nu_{max}}$ **(KBr) cm^{-1}** 2954 (Ar-H), 2857 (Ar-H), 2360, 1726 (C=O), 1619 (N-C=O), 1535 (N-O_2), 1472, 1436, 1341, 1252 (Si-CH_3), 1214 (Si-CH_3), 1194 (Si-C(CH_3)), 1122 (Si-O), 1097 (C-O), 924, 838, 802, 779, 737, 722, 695. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.41 – 8.33 (m, 2H, Ar-H), 7.88 (d, *J* = 8.1 Hz, 1H, Ar-H), 4.05 – 3.92 (m, 1H, C(4)H_A), 3.50 (ddd, *J* = 11.3, 9.4, 2.1 Hz, 1H, C(4)H_B), 3.39 (t, *J* = 7.1 Hz, 1H, C(2)*H*), 3.23 (s, 3H, OMe), 2.78 (dtdd, *J* = 13.8, 9.3, 7.0, 4.6 Hz, 1H, (C(3)H_A), 2.61 – 2.51 (m, 1H, C(3)H_B), 0.86 (d, *J* = 2.3 Hz, 9H, C(CH_3)$_3$), -0.01 (d, *J* = 7.2 Hz, 3H, Si-CH_3), -0.48 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.28 (C(1)COOMe), 167.82 (C(6)C=O), 150.57 (C(12)ArC) ,145.93 (C(10)Ar**C**-NO_2), 138.14

(C(7)ArC), 125.87 (C(9)ArC, 124.57 (C(8)ArC), 118.98 (C(11)ArC), 98.42 (C(13)), 52.72 (C(2)), 51.90 (C(1)OMe), 42.55 (C(4)), 31.25 (C(3)), 25.50 (C(**C**H_3)$_3$), 17.88 (Si-**C**(CH_3)$_3$), -4.12 (Si-CH_3), -4.14 (Si-CH_3). ***m/z***= 814 [2M+H+] (ESI^+) and 836 [2M+Na+] (ESI^+). **HRMS** calculated for $C_{19}H_{27}N_2O_6Si$ requires 407.1632, found at 407.1628 [MH+] (ESI^+).

Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-9-bromo-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 172c



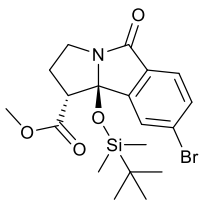
172c

172c was synthesised according to general procedure **E** using **137e** (0.501 g, 1.54 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the desired products as off-white coloured solid (0.206 g, 30%).

R_f= 0.43. **Mp**= 87-89 °C. **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 2929 (C-H), 2899 (C-H), 2857 (C-H), 1736 (C=O), 1722 (N-C=O), 1462, 1436, 1419, 1359, 1329, 1252 (Si-CH_3), 1214 (Si-CH_3), 1193 (Si-C(CH_3)), 1174 (C-O), 1126 (Si-O), 1089 (C-O), 913, 859, 839, 801, 779 , 721, 702 (C-Br), 613. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 1.9 Hz, 1H, C(8)ArC), 7.67 (dd, *J* = 8.0, 1.8 Hz, 1H, C(10)ArC), 7.39 (d, *J* = 8.0 Hz, 1H, C(11)ArC), 3.96 (dt, *J* = 11.2, 8.8 Hz, 1H, C(4)H_A), 3.44 (ddd, *J* = 11.4, 9.5, 2.2 Hz, 1H, C(4)H_B), 3.31 (dd, *J* = 7.0, 1.0 Hz, 1H, C(2)*H*), 3.22 (s, 3H, C(1)OMe), 2.72 (dtd, *J* = 13.2, 9.3, 7.1 Hz, 1H, C(3)H_A), 2.52 (dddd, *J* = 13.2, 8.6, 2.3, 1.1 Hz, 1H, C(3)H_B), 0.85 (s, 9H, Si-C(CH_3)$_3$), -0.04 (s, 3H, Si-CH_3), -0.44 (s, 3H, Si-CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.56 (C(1)COOMe), 168.84 (C(6)C=O), 143.26 (C(9)Ar**C**-Br), 135.32 (C(10)ArC), 134.86 (C(12)ArC), 126.72 (C(8)ArC), 125.12 (C(11)ArC), 124.35 (C(7)ArC), 98.88 (C(13)), 53.02 (C(2)), 51.77 (C(1)OMe), 42.36 (C(4)), 31.21 (C(3)), 25.58 (Si-C(**C**H_3)$_3$), 17.93 (Si-**C**(CH_3)$_3$), -4.12 –(Si-CH_3), -4.16 (Si-CH_3). ***m/z***= 462 and 464 [MNa+] (ESI^+). **HRMS**

calculated for $C_{19}H_{27}BrNO_4Si$ requires 440.0887 and 442.0867, found at 440.0887 and 442.0866 [MH+] (ESI^+).

Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-10-bromo-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 172d

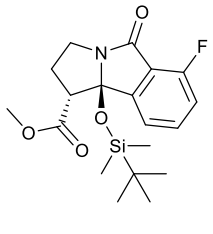


172d

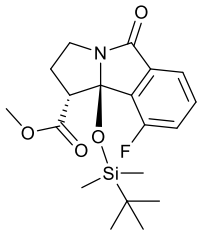
172d was synthesised according to general procedure **E** using **137e** (0.501 g, 1.54 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford the desired products as off-white coloured solid (0.168 g, 25%).

R_f= 0.34. **Mp**= 88-90 °C. **ν_{max} (KBr) cm^{-1}** 2952 (C-H), 2919 (C-H), 2884 (C-H), 2851 (C-H), 1774 (C=O), 1715 (N-C=O), 1607, 1438, 1418, 1392, 1361, 1254 (Si-CH_3), 1171, 1119 (Si-O), 1089 (C-O), 742 (C-Br). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 1.7 Hz, 1H, C(11)Ar-H), 7.62 (dd, *J* = 8.1, 1.7 Hz, 1H, C(9)Ar-H), 7.56 (d, *J* = 8.0 Hz, 1H, C(8)Ar-H), 3.95 (dt, *J* = 11.1, 8.8 Hz, 1H, C(4)H_A), 3.43 (ddd, *J* = 11.4, 9.5, 2.3 Hz, 1H, (C(4)H_B), 3.30 (dd, *J* = 7.0, 1.1 Hz, 1H, C(2)*H*), 3.22 (s, 3H, OMe), 2.71 (dtd, *J* = 13.2, 9.3, 7.1 Hz, 1H, C(3)H_A), 2.51 (dddd, *J* = 13.2, 8.5, 2.2, 1.1 Hz, 1H, C(3)H_B), 0.85 (s, 9H, Si-C(CH_3)$_3$), -0.04 (s, 3H, Si-CH_3), -0.44 (s, 3H, Si-CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.50 (C(1)COOMe), 169.46 (C(6)C=O), 146.36 (C(10)Ar**C**-Br), 133.56 (C(9)ArC), 131.83 ((C(7)ArC), 127.08 (C(11)ArC), 126.99 (C(12)ArC), 124.89 (C(8)ArC), 98.60 (C(13)), 53.04 (C(2)), 51.74 (C(1)OMe), 42.33 (C(4)), 31.11 (C(3)), 25.58 (Si-C(**C**H_3)$_3$), 17.92 (Si-**C**(CH_3)$_3$), -4.13 (Si-CH_3), -4.22 (Si-CH_3). ***m/z***= 462 and 464 [MNa+] (ESI^+). **HRMS** calculated for $C_{19}H_{27}BrNO_4Si$ requires 440.0887 and 442.0867, found at 440.0888 and 442.0865 [MH+] (ESI^+).

Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-8-fluror-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 144f and **Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-11-fluoro-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 171**



144e



171

144e and **171** were synthesised according to general procedure **E** using **137f** (0.389 g, 1.46 mmol) with the crude material purified using flash column chromatography (25% ethyl acetate in pet-ether 40:60) to afford the desired product as a mixture of isomers as an off-white coloured solid (0.349 g, 61%). *d.r*= 1:0.3 **144f**:**171**.

Recrystallisation was attempted with **171** and confirmed *via* x-ray analysis (see Appendix I, compound 7210). The oil that remined was analysed using ^{1}H NMR spectroscopy that showed the major isomer **144f** remining with the ratio now at 9:1 strongly suggesting that **144f** is the major regioisomer. **144f** was also able to be crystallised when pure (see Appendix I, compound 7210).

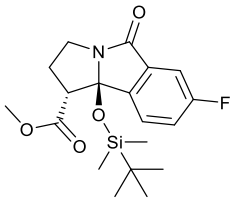
R_f= 0.40. **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 2857 (C-H), 1724 (N-C=O), 1625 (C=O), 1482, 1360, 1327, 1252 (Si-CH_3), 1195, 1117 (Si-O), 1074 (C-O), 920, 854, 839, 780, 692 (Ar-F). ***m/z***= 380 [MH+] (ESI^+). **HRMS** calculated for $C_{19}H_{27}FNO_4Si$ requires 380.1687, found at 380.1685 [MH+] (ESI^+).

144f) **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.55 – 7.44 (m, 1H, Ar-H), 7.32 – 7.28 (d, *J*= 7.3 Hz, 1H, Ar-H), 7.14 – 7.08 (t, *J*=17.6, 8.2 Hz, 1H, ArH), 4.03 – 3.87 (m, 1H, C(4)H_A), 3.46 – 3.39 (m, 1H, C(4)H_B), 3.31 (dd, *J* = 7.0, 1.0 Hz, 1H, (C(2)*H*), 3.22 (s, 3H, OMe), 2.72 (ddtd, *J* = 16.5, 13.3, 9.4, 7.1 Hz, 1H, C(3)H_A), 2.58 – 2.47 (m, 1H, C(3)H_B), 0.84 (s, 9H, Si-C(CH_3)$_3$), -0.03 (s, 3H, Si-CH_3), -0.43 (s, 3H, Si-CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.55 (C(1)COOMe), 167.13 (d, *J*=1.8 Hz, C(6)C=O), 157.84 (d, *J*= 262.4 Hz, C(8)Ar**C**-F), 147.18 (d, *J*= 2.2 Hz, C(12)ArC),

134.52 (d, *J*= 7.5 Hz, C(10)ArC), 119.70 (d, *J*= 4.0 Hz, C(11)ArC), 117.66 (d, *J*= 19.8 Hz, C(9)ArC), 98.67 (d, *J*= 1.8 Hz, C(13) , 53.24 (C(2)), 51.72 (C(1)OMe), 42.47 (C(4)), 31.10 (C(3)), 25.59 (Si-C(**C**H_3)$_3$), 17.92 (Si-**C**(CH_3)$_3$), -4.13 (Si-CH_3), -4.36 (Si-CH_3).

171) **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.55 – 7.44 (m, 2H, Ar-H), 7.20 (ddd, *J* = 8.9, 7.9, 1.1 Hz, 1H), 4.03 – 3.87 (m, 1H, C(4)H_A), 3.46 – 3.39 (m, 1H, (C(4)H_B), 3.31 (dd, *J* = 7.0, 1.0 Hz, 1H, C(2)*H*), 3.21 (s, 3H), 2.72 (ddtd, *J* = 16.5, 13.3, 9.4, 7.1 Hz, 1H, C(3)H_A), 2.58 – 2.47 (m, 1H, C(3H_B), 0.84 (s, 9H, Si-C(CH_3)$_3$), -0.04 (s,3H, Si-CH_3), -0.42 (s, 3H, Si-CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.58 (C(1)COOMe), 168.76 (d, *J*= 2.3 Hz, C(6)C=O), 157.75 (d, *J*= 262.4 Hz, C(11)Ar**C**-F), 135.96 (d, *J*= 3.6 Hz, C(7)Ar), 132.69 (d, *J*= 6.6 Hz, C(9)ArC), 130.17 (d, *J*= 16.5 Hz, C(12)ArC), 119.86 (d, *J*= 4.7 Hz, C(8)ArC), 119.45 (d, *J*= 3.8 Hz, C(10)ArC), 97.70 (C(13)), 52.60 (C(2)), 51.72 (C(1)OMe, 41.88 (C(4)), 30.95 (C(3)), 25.49 (Si-C(**C**H_3)$_3$), 17.96 (Si-**C**(CH_3)$_3$), -4.17 (Si-CH_3), -4.81 (Si-CH_3).

Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-9-fluoro-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 172e



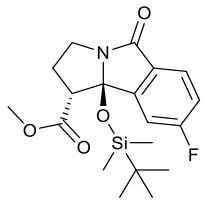
172e

172e was synthesised according to general procedure **E** using **137g** (0.798 g, 3.01 mmol) with the crude material purified using flash column chromatography (25% ethyl acetate in pet-ether 40:60) to afford the desired product as a white coloured solid (0.476 g, 41%).

R_f= 0.61. **Mp**= 104-106 °C. **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 2933 (C-H), 2907 (C-H), 2852 (C-H), 1771 (C=O), 1719 (N-C=O), 1616, 1479, 1431, 1396, 1360, 1330, 1270, 1255 (Si-CH_3), 1212 (Si-CH_3), 1195 (Si-C(CH_3)), 1174, 1156 (C-O), 1139 (Si-O), 1110, 1082 (C-O), 1036, 1006. **^{1}H NMR** (500 MHz, Methanol-d_4) δ 7.63 (dd, *J* = 8.3, 4.5 Hz, 1H, C(11)ArC), 7.42 (ddd, *J* = 9.2, 8.3, 2.4

Hz, 1H, C(10)ArC), 7.36 (dd, *J* = 7.6, 2.4 Hz, 1H, C(8)ArC), 3.90 (dt, *J* = 11.1, 8.9 Hz, 1H, C(4)H_A), 3.46 (ddd, *J* = 11.4, 9.6, 2.1 Hz, 1H, C(4)H_B), 3.35 (d, *J* = 6.9 Hz, 1H, C(2)*H*), 3.20 (s, 3H, C(1)OMe), 2.77 (dtd, *J* = 13.3, 9.4, 7.0 Hz, 1H, C(3)H_A), 2.56 (dddd, *J* = 13.3, 8.5, 2.1, 0.9 Hz, 1H, C(3)H_B), 0.88 (s, 9H, C(CH_3)$_3$), -0.02 (s, 3H, Si-CH_3), -0.42 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 173.16 (C(1)COOMe), 170.95 (d, *J* = 3.2 Hz, C(6)C=O), 165.51 (d, *J* = 249.5 Hz, C(9)Ar**C**-F), 141.62 (d, *J* = 2.8 Hz, C(12)ArC), 136.29 (d, *J*= 8.7, C(7)ArC), 127.21 (d, *J* = 8.8 Hz, C(11)ArC), 121.05 (d, *J* = 23.8 Hz, C(10)ArC), 110.78 (d, *J* = 24.3 Hz, C(8)ArC), 100.19 (C(13)), 53.79 (C(2)), 52.04 (C(1)OMe), 43.22 (C(4)), 32.11 (C(3)), 25.96 (C(**C**H_3)$_3$), 18.68 (**C**(CH_3)), -3.99 (Si-CH_3), -4.02 (Si-CH_3). ***m/z***= 380 [MH+] (ESI^+). **HRMS** calculated for $C_{19}H_{27}FNO_4Si$ requires 380.1688, found at 380.1687 [MH+] (ESI^+).

Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-10-fluoro-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 172f



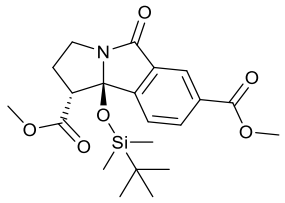
172f

172 was synthesised according to general procedure **E** using **137g** (0.798 g, 3.01 mmol) with the crude material purified using flash column chromatography (25% ethyl acetate in pet-ether 40:60) to afford the desired product as a white coloured solid (0.165 g, 14%).

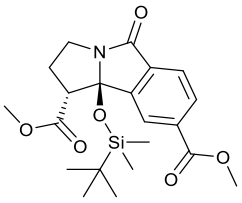
R_f= 0.48. **Mp**= 84-86 °C. **ν_{max} (KBr) cm^{-1}** 2955 (C-H), 2931 (C-H), 2900 (C-H), 2858 (C-H), 1772 (C=O), 1718 (N-C=O), 1617, 1481, 1437, 1396, 1360, 1331, 1269, 1256 (Si-CH_3), 1214 (Si-CH_3), 1194 (Si-C(CH_3)$_3$), 1174, 1157 (C-O), 1141 (Si-O), 1111, 1082 (C-O), 1036, 1006. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.73 – 7.66 (m, 1H, C(8)ArC), 7.38 – 7.28 (m, 2H, C(9,11)ArC), 3.89 (dt, *J* = 11.1, 8.5 Hz, 1H, C(4)H_A), 3.45 (ddd, *J* = 11.3, 9.5, 2.1 Hz, 1H, C(4)H_B), 3.36 (d, *J* = 6.9 Hz, 1H, C(2)*H*), 3.22 (s, 3H, C(1)OMe), 2.76 (dtd, *J* = 13.3, 9.4, 7.0 Hz, 1H, C(3)H_A), 2.55

(dddd, *J* = 13.3, 8.5, 2.1, 1.0 Hz, 1H, C(3)H_B), 0.89 (s, 9H, C(CH_3)$_3$), 0.00 (s, 3H, Si-CH_3), -0.42 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 173.02 (C(1)COOMe), 171.40 (C(6)C=O), 167.08 (d, *J* = 252.8 Hz, C(10)Ar**C**-F), 148.69 (d, *J* = 9.4 Hz, C(7)ArC), 130.04 (d, *J* = 2.4 Hz, C(12)ArC), 126.63 (d, *J* = 10.1 Hz, C(8)ArC), 118.98 (d, *J* = 23.8 Hz, C(9)ArC), 112.44 (d, *J* = 24.5 Hz, C(11)ArC), 99.87 (d, *J* = 2.6 Hz, C(13), 53.78 (C(2)), 52.09 (C(1)OMe), 43.33 (C(4)), 31.92 (C(3)), 25.94 (C(**C**H_3)$_3$), 18.66 (**C**(CH_3)$_3$), -4.01 (Si-CH_3), -4.16 (Si-CH_3). ***m/z***= 380 [MH+] (ESI^+). **HRMS** calculated for $C_{19}H_{27}FNO_4Si$ requires 380.1688, found at 380.1688 [MH+] (ESI^+).

Dimethyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,9-dicarboxylate 172g and **Dimethyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,10-dicarboxylate 172h**



172g



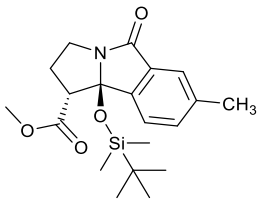
172h

172g and **172h** were synthesised according to general procedure **E** using **137i** (0.100 g, 0.33 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and concentrated to afford an inseperable mixture of the desired products as a colourless oil (0.132 g, 92%).

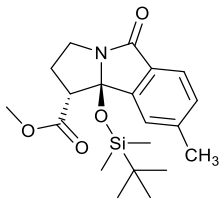
R_f= 0.41 (ethyl acetate in pet-ether 40:60). **ν_{max} (KBr) cm^{-1}** 2953 (C-H), 2857 (C-H), 1720 (N-C=O), 1624 (C=O), 1435, 1360, 1328, 1288 (Ar-C=O), 1254 (Si-CH_3), 1215 (Si-CH_3), 1194 (Si-C(CH_3)), 1172 (C-O), 1123 (Si-O), 1081 (C-O). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.37 (dd, *J* = 1.5, 0.7 Hz, 1H, ArH), 8.26 (dd, *J* = 7.9, 1.5 Hz, 1H, ArH, 8.18 (d, *J* = 7.2 Hz, 2H, ArH), 7.80 – 7.73 (m, 1H, ArH), 7.60 (dd, *J* = 7.9, 0.7 Hz, 1H, ArH), 4.03 – 3.98 (m, 2H, C(4)H_A), 3.97 (s, ArC-COOMe), 3.95 (s, ArC-COOMe), 3.47 (ddd, *J* = 11.4, 9.4, 2.2 Hz, 2H, C(4)H_B), 3.36 (t, *J* = 6.6

Hz, 2H C(2)*H*), 3.17 (d, *J* = 0.8 Hz, 6H, C(1)OMe), 2.75 (dqd, *J* = 13.1, 9.1, 7.3 Hz, 2H, C(3)H_A), 2.53 (ddd, *J* = 13.3, 8.6, 2.1 Hz, 2H, C(3)H_B), 0.85 (d, *J* = 3.5 Hz, 18H, C(CH_3)$_3$), -0.05 (d, *J* = 10.8 Hz, 6H, Si-CH_3), -0.49 (d, *J* = 3.9 Hz, 6H, Si-CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.57 (C(1)OMe), 171.50 (C(1)OMe), 169.38 (C(6)C=O), 169.23 (C(6)C=O), 166.17 (C(9)OMe), 166.11 (C(10)OMe), 148.76 (ArC), 144.66 (ArC), 136.83 (ArC), 133.86 (ArC), 133.72 (ArC), 133.46 (ArC), 132.43 (ArC), 131.76 (ArC), 124.87 (ArC), 124.85 (ArC), 123.76 (ArC), 123.47 (ArC), 98.94 C(13)), 53.14 (OMe), 53.00 (OMe), 52.77 (OMe), 52.65 (OMe), 51.75 (C(2)), 51.72 (C(2)), 42.44 (C(4)), 42.36 (C(4)), 31.28 (C(3)), 31.15 (C(3)), 25.61 (C(**C**H_3)$_3$), 25.59 (C(**C**H_3)$_3$), 17.95 (Si-**C**(CH_3)$_3$), -4.10 (Si-CH_3), -4.15 (Si-CH_3), -4.23 (Si-CH_3). ***m/z***= 862 [2MNa+] (ESI^+). **HRMS** calculated for $C_{21}H_{30}NO_6Si$ requires 420.1836, found at 420.1829 [MH+] (ESI^+).

Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-9-methyl-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 198i and **Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-10-methyl-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 198j**



172i



172j

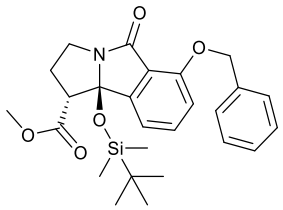
172i and **172j** were synthesised according to general procedure **E** using **137i** (0.500 g, 1.91 mmol) with the crude material purified using flash column chromatography (25% ethyl acetae in pet-ether 40:60) with the product containing fractions collected combined and concentrated. ^{1}H NMR spectroscopy showed starting material and an unknown impurity remaining, assumed that all components co-eluted. The crude material was attempted to be purified using flash column chromatography (100% DCM) with the product containing fractions collected, combined and concentrated by reduced pressure to show the same conclusion (0.596 g, 85%). ^{1}H NMR did show

that the majority of the collected product was the desired product, but starting material remaining and after the ^{13}C NMR had run, the compound had degrading *via* desilylation to the alkene variant. **R_f**= 0.54 (25% ethyl acetate in pet-ether 40:60) and 0.20 (DCM). ***m/z***= 376 [MH+] (ESI^+) and 398 [MNa+] (ESI^+). **HRMS** calculated for $C_{20}H_{30}NO_4Si$ requires 376.1938, found at 376.1937 [MH+] (ESI^+).

172i) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.49 (dq, *J* = 1.7, 0.8 Hz, 1H), 7.45 – 7.36 (m, 1H, Ar-H), 7.35 – 7.29 (m, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 3.98 – 3.90 (m, 1H (C(4)H_A), 3.42 (dddd, *J* = 11.7, 9.4, 2.3, 0.8 Hz, 1H, C(4)H_B), 3.36 – 3.27 (m, 1H, C(2)*H*), 3.16 (s, 3H, C(1)OMe), 2.70 (dtdd, *J* = 13.1, 9.3, 7.1, 1.3 Hz, 1H, C(3)H_A), 2.41 (s, 3H, C(C9)Ar-CH_3), 2.52 (m, 1H, C(3)H_B), 0.84 (d, *J* = 1.6 Hz, 9H, Si-C(CH_3)$_3$), -0.07 (d, *J* = 0.9 Hz, 3H, Si-CH_3), -0.48 (d, *J* = 1.2 Hz, 3H, Si-CH_3).

172j) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.39 – 8.33 (m, 1H, Ar-H), 7.56 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.45 – 7.36 (m, 1H, Ar-H), 7.35 – 7.29 (m, 1H, Ar-H), 3.98 – 3.90 (m, 1H (C(4)H_A), 3.42 (dddd, *J* = 11.7, 9.4, 2.3, 0.8 Hz, 1H, C(4)H_B), 3.36 – 3.27 (m, 1H, C(2)*H*), 3.16 (d, *J* = 1.2 Hz, 3H, C(1)OMe), 2.70 (dtdd, *J* = 13.1, 9.3, 7.1, 1.3 Hz, 1H, C(3)H_A), 2.43 (d, *J* = 0.9 Hz, 2H, C(C10)Ar-CH_3), 2.52 (m, 2H, C(3)H_B), 0.84 (d, *J* = 1.6 Hz, 9H, Si-C(CH_3)$_3$), -0.07 (d, *J* = 0.9 Hz, 3H, Si-CH_3), -0.48 (d, *J* = 1.2 Hz, 3H, Si-CH_3).

Methyl (2*R*,13*R*)-8-(benzyloxy)-13-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,5,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 144j

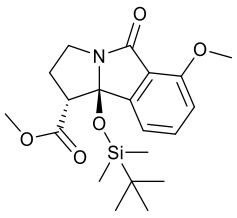


144j

144j was synthesised according to general procedure **E** from **137j** (0.678 g, 1.92 mmol) with the crude material purified using flash column chromatography (30% ethyl acetate in pet-ether 40:60) to afford the desired product as a pale yellow coloured oil (0.632 g, 70%).

R_f= 0.28. **ν_{max} (KBr) cm^{-1}** 2953 (C-H), 2929 (C-H), 2897 (C-H), 2856 (C-H), 1735 (C=O), 1713 (N-C=O), 1604, 1483, 1453, 1360, 1306, 1262 (Si-CH_3), 1213 (Si-CH_3), 1195 (Si-C$(CH_3)_3$), 1172 (C-O), 1120 (Si-O), 1074 (C-O), 1027. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.56 – 7.48 (m, 2H, ArH), 7.47 – 7.39 (m, 2H, ArH), 7.39 – 7.33 (m, 1H, ArH), 7.33 – 7.26 (m, 1H, ArH), 7.11 (dd, *J* = 7.5, 0.7 Hz, 1H, ArH), 6.95 (dd, *J* = 8.3, 0.7 Hz, 1H, ArH), 5.32 (d, *J* = 4.2 Hz, 2H, C(8b)O-C**H_2**-Ar), 4.03 (dt, *J* = 11.1, 8.9 Hz, 1H, C(4)H_A), 3.48 – 3.40 (m, 1H, C(4)H_B), 3.32 (dd, *J* = 7.1, 1.1 Hz, 1H, C(2)*H*), 3.22 (s, 3H, C(1)OMe), 2.81 – 2.64 (m, 1H, C(3)H_A), 2.52 (dddd, *J* = 13.1, 8.5, 2.3, 1.2 Hz, 1H, C(3)H_B), 0.87 (s, 9H, C$(CH_3)_3$), 0.00 (s, 3H, Si-CH_3), -0.43 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.75 (C(1)COOMe), 169.14 (C(6)C=O), 155.57 (C(8)Ar**C**-OBn), 147.19 (C(12)ArC), 136.72 (C(8c)Ar**C**-CH_2-O), 133.94 (ArC), 128.61 (ArC),127.82 (ArC), 126.95 (ArC), 120.63 (ArC), 116.40 (ArC), 115.43 (ArC), 98.37 (C(13)), 70.90 (C(8b)O-**C**H_2-Ar), 53.51 (C(2)), 51.56 (C(1)OMe), 42.52 (C(4)), 30.96 (C(3)), 25.63 (C(**C**$H_3)_3$), 17.92 (**C**$(CH_3)_3$), -4.14 (Si-CH_3), -4.40 (Si-CH_3). ***m/z***= 347 [MH+] (ESI$^+$). **HRMS** calculated for $C_{26}H_{34}NO_5$ requires 368.2201, found at 368.1299 [MH+] (ESI$^+$).

Methyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-8-methoxy-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 144k

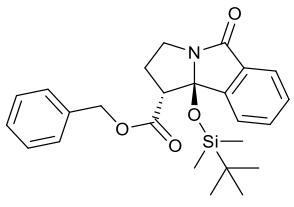


144k

144k was synthesised according to general procedure **E** using **137k** (0.080 g, 0.28 mmol) with the crude material purified using flash column chromatography (30% ethyl acetate in pet-ether 40:60) to afford the desired product as a pale yellow coloured oil (0.98 g, 87%).

R_f= 0.47. **ν_{max} (KBr) cm^{-1}** 2953 (C-H), 2928 (C-H), 2855 (C-H), 1733 (C=O), 1715 (N-C=O), 1605, 1491, 1463, 1439, 1363, 1331, 1278 (O-CH_3), 1251 (Si-CH_3), 1198 (Si-C(CH_3)$_3$), 1135 (Si-O), 1099, 1077, 1044. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.42 (dd, *J* = 8.2, 7.5 Hz, 1H, ArH), 7.28 (dd, *J* = 7.5, 0.8 Hz, 1H, ArH), 6.99 (dd, *J* = 8.2, 0.7 Hz, 1H, ArH), 3.94 – 3.84 (m, 4H, C(4)H_A and ArC-OC**H$_3$**), 3.46 – 3.36 (m, 2H, C(4)H_B and C(2)*H*), 3.17 (s, 3H, C(1)OMe), 2.74 (dtd, *J* = 13.1, 9.4, 7.0 Hz, 1H, C(3)H_A), 2.50 (dddd, *J* = 13.1, 8.6, 2.0, 0.8 Hz, 1H, C(3)H_B), 0.84 (s, 9H, C(CH_3)$_3$), -0.09 (s, 3H, Si-CH_3), -0.46 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.73 (C(1)COOMe), 169.74 (C(6)C=O), 155.29 (Ar**C**-OCH_3), 134.85 (C(12)ArC), 131.98 (ArC), 130.99 (C(7)ArC), 115.10 (ArC), 114.33 (ArC), 98.23 (C(13)), 55.36 (ArC-O**C**H_3), 52.18 (C(2)), 51.37 (C(1)OMe), 41.40 (C(4)), 31.04 (C(3)), 25.42 (C(**C**H_3)$_3$), 17.90 (**C**(CH_3)$_3$), -4.29 (Si-CH_3), -4.93 (Si-CH_3). ***m/z***= 414 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{20}H_{30}NO_5Si$ requires 392.1888, found at 392.1886 [MH+] (ESI$^+$).

Benzyl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 200

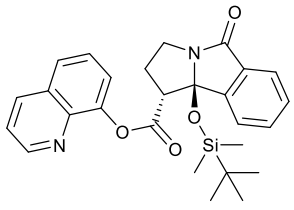


200

200 was synthesised according to general procedure **E** using **173** (0.368 g, 1.14 mmol) with the crude material purified using flash column chromatography (30% ethyl acetate in pet-ether 40:60) to afford the desired product as a colourless oil (0.418 g, 91%).

R_f= 0.35 (30% ethyl acetate in pet-ether 40:60). **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 2856 (C-H), 1716 (C=O), 1614 C=O), 1466, 1385, 1352, 1328, 1251 (Si-CH_3), 1212 (Si-CH_3), 1169 (Si-C(CH_3)), 1143 (C-O), 1108 (Si-O), 1080 (C-O), 1040. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.73 – 7.67 (m, 1H, Ar-H), 7.55 – 7.44 (m, 3H, Ar-H), 7.36 – 7.27 (m, 3H, Ar-H), 7.14 – 7.05 (m, 2H, Ar-H), 4.66 (d, *J* = 12.0 Hz, 1H, C(1a)H_A), 4.59 (d, *J* = 12.0 Hz, 1H, C(1a)H_B), 4.05 (dt, *J* = 11.0, 8.9 Hz, 1H, C(4)H_A), 3.51 (ddd, *J* = 11.3, 9.5, 2.1 Hz, 1H, C(4)H_B), 3.42 (dd, *J* = 6.9, 0.9 Hz, 1H, C(2)*H*), 2.79 (dtd, *J* = 13.1, 9.3, 6.9 Hz, 1H, C(3)H_a), 2.60 (dddd, *J* = 13.1, 8.6, 2.2, 0.9 Hz, 1H, C(3)H_B), 0.89 (s, 9H, (C(CH_3)$_3$), 0.00 (s, 3H, Si-CH_3), -0.45 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.19 (C(1)COOMe), 170.37 (C(6)C=O), 144.33 (C(12)ArC), 135.12 (C(7)ArC), 132.96 (ArC), 132.27 (C(10)ArC), 130.16 (ArC), 128.76 (ArC), 128.59 (ArC), 128.40 (ArC), 123.69 (C(8)ArC), 123.43 (C(11)ArC), 99.18 (C(13)), 66.58 (C(1a)Bn-**C**H_2-), 53.04 (C(2)), 42.26 (C(4)), 31.34 (C(3)), 25.61 (C(**C**H_3)$_3$), 17.93 (Si-**C**(CH_3)$_3$), -4.20 (Si-CH_3), -4.40 (Si-CH_3). ***m/z***=460 (ESI^+) [MNa+]. **HRMS** calculated for $C_{25}H_{32}NO_4Si$ requires 438.2095, found at 438.2096 (ESI^+) [MH+].

Quinolin-8-yl (2*R*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 209



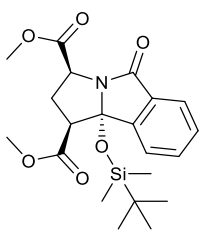
209

209 was synthesised according to general procedure **E** using **208** (0.232 g, 0.64 mmol) with the crude material purified using flash column chromatography (30% ethyl acetate in pet-ether 40:60) to afford the desired product as a white coloured solid (0.204 g, 66%).

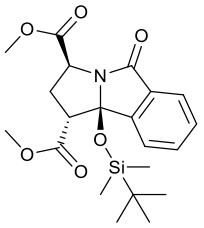
R_f= 0.20 (30% ethyl acetate in pet-ether 40:60). **Mp**= 193-195 °C. **ν_{max} (KBr) cm^{-1}** 2955 (C-H), 2929 (C-H), 2856 (C-H), 1757 (C=O), 1715 (N-C=O), 1499, 1469, 1358, 1328, 1251 (Si-CH_3),

1189 (Si-C(CH_3)), 1139 (Si-O), 1109, 1081 (C-O). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H, ArH), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H, ArH), 7.88 – 7.82 (m, 1H, ArH), 7.80 (dt, *J* = 7.5, 1.0 Hz, 1H, ArH), 7.67 (td, *J* = 7.4, 1.4 Hz, 1H, ArH), 7.62 (ddd, *J* = 8.4, 5.6, 1.4 Hz, 2H, ArH), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H, ArH), 7.32 – 7.27 (m, 1H, ArH), 6.22 (dd, *J* = 7.5, 1.3 Hz, 1H, ArH), 4.14 (dt, *J* = 11.0, 8.9 Hz, 1H (C(4)H_A), 3.89 (dd, *J* = 6.7, 0.9 Hz, 1H, (C(2)*H*), 3.61 (ddd, *J* = 11.3, 9.3, 2.1 Hz, 1H, C(4)H_B), 3.13 – 3.04 (m, 1H, (C(3)H_A), 3.03 – 2.95 (m, 1H, C(3)-H_B), 0.94 (s, 9H, (C(CH_3)$_3$), 0.07 (s, 3H, Si-CH_3), -0.38 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.34 (C(1)COOMe), 169.82 (C(6)C=O), 150.49 (C(7,12)ArC), 146.44 (ArC), 144.87 (ArC), 141.00 (ArC), 135.92 (ArC), 133.46 (ArC), 132.51 (ArC), 130.27 (ArC), 129.39 (ArC), 126.04 (ArC), 125.92 (ArC), 124.30 (ArC), 123.58 (ArC), 121.76 (ArC), 120.79 (ArC), 99.34 (C(13)), 53.15 (C(2)), 42.35 (C(4)), 31.67 (C(3)), 25.66 (C(**C**H_3)$_3$), 17.99 (Si-**C**(CH_3)$_3$), -4.12 (Si-CH_3), -4.32 (Si-CH_3). ***m/z***= 475 [MH+] (ESI^+) and 497 [MNa+] (ESI^+). **HRMS** calculated for $C_{27}H_{30}NaN_2O_4Si$ requires 475.2023, found at 475.2023 [MNa+] (ESI^+).

2,4-Dimethyl (2*S*,4*S*,13*S*)-13-[(tert-butyldimethylsilyl)oxy]-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 175La and **2,4-Dimethyl (2*R*,4*S*,13*R*)-13-[(tert-butyldimethylsilyl)oxy]-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 175La**



175La



175Lb

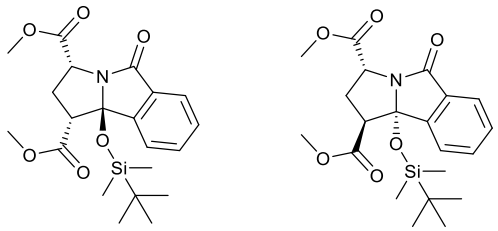
175La and **175Lb** were synthesised according to general procedure **E** using **127L** with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford an inseparable mixture of isomers with the desired products as an off-white-coloured solid that showed presence of SM remaining (0.068 g, 79%). *d.r* = 1: 0.29 for **175La**: **175Lb**.

R_f= 0.31 (20% ethyl acetate in pet-ether 40:60). ***m/z***= 420 [MH+] (ESI^+). **HRMS** calculated for $C_{21}H_{30}NO_6Si$ requires 420.1836, found at 420.1826 [MH+] (ESI^+).

175La) **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.71 (dt, *J* = 7.5, 1.0 Hz, 1H, ArH), 7.59 – 7.54 (m, 1H, ArH), 7.54 – 7.45 (m, 2H, ArH), 4.35 (dd, *J* = 8.9, 3.4 Hz, 1H, C(4)*H*), 3.77 (s, 3H, C(1)OMe), 3.43 (dd, *J* = 8.1, 2.2 Hz, 1H, C(2)*H*), 3.35 (s, 3H, C(4a)OMe), 3.10 – 3.03 (m, 1H, C(3)H_A), 2.92 (ddd, *J* = 13.6, 3.4, 2.3 Hz, 1H, C(3)H_B), 0.83 (d, *J* = 1.9 Hz, 9H, $C(CH_3)_3$), -0.07 (s, 3H, Si-CH_3), -0.55 (s, 3H, Si-CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.99 (C(1)COOMe), 169.95 (C(4a)COOMe), 167.54 (C(6)C=O), 145.55 (C(12)ArC), 132.79 (C(7)ArC), 132.47 (ArC), 129.79 (ArC), 123.90 (ArC), 123.78 (ArC), 99.29 (C(13)), 55.33 (C(4)), 52.69 (C(2)), 52.61 (C(1)OMe), 51.86 (C(4a)OMe), 36.07 (C(3)), 25.64 (C(**C**$H_3)_3$), 17.93 (**C**$(CH_3)_3$), -4.03 (Si-CH_3), -4.44 (Si-CH_3).

175Lb) **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.71 (dt, *J* = 7.4, 1.0 Hz, 1H, ArH), 7.61 – 7.55 (m, 1H, ArH), 7.54 – 7.45 (m, 2H, ArH), 4.86 (t, *J* = 9.0 Hz, 1H, C(4)*H*), 3.80 (s, 3H, C(1)OMe), 3.40 (d, *J* = 6.8 Hz, 1H, C(2)*H*), 3.14 (s, 3H, C(4a)OMe), 3.02 – 2.97 (m, 1H, C(3)H_A), 2.83 (dd, *J* = 13.4, 8.5 Hz, 1H, C(3)H_B), 0.83 (d, *J* = 1.9 Hz, 9H, $C(CH_3)_3$), -0.10 (s, 3H, Si-CH_3), -0.38 (s, 3H, Si-CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.76 (C(1)COOMe), 171.32 (C(4a)COOMe), 170.50 (C(6)C=O), 143.71 (C(12)ArC), 134.45 (C(7)ArC), 132.79 (ArC), 132.41 (ArC), 130.57 (ArC), 124.43 (ArC), 99.47 (C(13)), 53.89 (C(4)) 53.78 (C(2))), 52.61 (C(1)OMe), 51.73 (C(4a)OMe), 34.49 (C(3)), 25.73 (C(**C**$H_3)_3$), 18.13 (**C**$(CH_3)_3$), -3.41 (Si-CH_3), -4.16 (Si-CH_3).

2,4-Dimethyl (2*R*,4*R*,13*R*)-13-[(tert-butyldimethylsilyl)oxy]-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 175Da and **2,4-Dimethyl (2*S*,4*R*,13*S*)-13-((tert-butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 175Db**



175Da 175Db

175Da and **175Db** were synthesised according to general procedure **E** using **127D** (0.389 g, 1.27 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in pet-ether 40:60) to afford an inseparable mixture of isomers as an off-white coloured solid that also showed presence of SM remaining (0.432 g, 79%). *d.r*= 1: 0.2 for **175Da**: **175Db.**

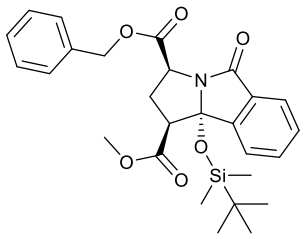
R_f= 0.31 (20% ethyl acetate in pet-ether 40:60). **Mp**= 113-115 °C. **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 2857 (C-H), 1719 (C=O), 1466 (C-H), 1436 (C-H), 1387, 1360, 1253 Si-C(CH_3), 1210 (Si-CH_3), 1174, 1110 (Si-O), 1072 (C-O), 839, 779, 722, 696. ***m/z***= 420 [MH+] (ESI^+). **HRMS** calculated for $C_{21}H_{30}NO_6$ requires 420.1836, found at 420.1833.

175Da) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.70 (dt, *J* = 7.5, 1.0 Hz, 1H, ArH), 7.60 – 7.53 (m, 1H, ArH), 7.52 – 7.44 (m, 2H, ArH), 4.34 (dd, *J* = 8.8, 3.4 Hz, 1H, C(4)*H*), 3.76 (s, 3H, C(1)OMe), 3.42 (dd, 1H, C(2)*H*), 3.35 (s, 3H, C(4a)OMe), 3.10 – 3.01 (m, 1H, C(3)H_A), 2.91 (ddd, *J* = 13.6, 3.4, 2.3 Hz, 1H, C(3)H_B), 0.82 (d, *J* = 1.5 Hz, 9H, C(CH_3)$_3$), -0.08 (s, 3H, Si-CH_3), -0.56 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.96 (C(1)COOMe), 169.90 (C(4a)COOMe), 167.50 (C(6)C=O), 145.53 (C(12)ArC), 134.42 (ArC), 132.44 (ArC), 129.76 (ArC), 123.89 (C(7)ArC), 123.75 (ArC), 99.28 (C(13)), 55.33 (C(2)), 52.68 (C(4)) , 52.57 (C(1)COOMe), 51.82 (C(4a)COOMe), 36.04 (C(3)), 25.62 (C(**C**H_3)$_3$), 17.91 (**C**(CH_3)$_3$), -4.05 (Si-CH_3), -4.46 (Si-CH_3).

175Db) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.70 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.52 – 7.44 (m, 2H), 4.85 (ddd, *J*=9.5, 8.6, 0.8 Hz, 1H, C(4)*H*), 3.79 (s, 3H), 3.41 - 3.39 (m, 1H),

3.13 (s, 3H), 3.04 – 2.97 (m, 1H), 2.82 (ddd, *J* = 13.5, 8.6, 0.7 Hz, 1H), 0.82 (d, *J* = 1.5 Hz, 9H), -0.11 (s, 3H), -0.39 (s, 3H). Note that NMR too weak to observe and report minor isomer.

4-Benzyl 2-methyl (2*S*,3*S*,13*S*)-13-((tert-butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 177



177

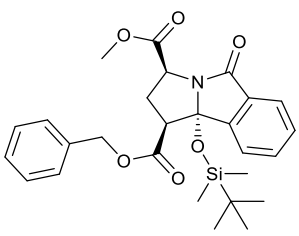
177b was synthesised according to general procedure **E** using **142** (0.100 g, 0.26 mmol) with 3.0 eq of TBDMSiOTf with the crude material purified using flash column chromatography (30% ethyl acetate in pet-ether 40:60) to afford the desired product as an pale yellow coloured solid (0.097 g, 75%).

$[\alpha]_D^{25}$= -21.2 (*c* 1.0 in DCM). **R_f**= 0.29. **Mp**= 113-115 °C. **ν_{max} (KBr) cm^{-1}** 2953 (C-H), 2856 (C-H), 1719 (C=O), 1466, 1359, 1254 (Si-CH_3), 1172 (Si-C(CH_3)), 1106 (O-Si), 1058 (C-O). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 – 7.69 (m, 1H, ArH), 7.57 (td, *J* = 7.4, 1.1 Hz, 1H, ArH), 7.53 – 7.44 (m, 2H, ArH), 7.40 – 7.27 (m, 5H, ArH), 5.24 (d, *J* = 12.3 Hz, 1H, C(4b)Ar-C**H**$_2$-), 5.15 (d, *J* = 12.3 Hz, 1H, C(4b)Ar-C**H**$_2$-)), 4.40 (dd, *J* = 9.0, 2.9 Hz, 1H, C(4)*H*), 3.41 (dd, *J* = 8.0, 1.9 Hz, 1H, C(2)*H*), 3.18 (s, 3H, C(1)OMe), 3.09 (ddd, *J* = 13.6, 9.0, 8.0 Hz, 1H, C(3)H_A), 2.93 (dt, *J* = 13.6, 2.4 Hz, 1H, C(3)H_B), 0.82 (s, 9H, C(CH_3)$_3$), -0.08 (s, 3H, Si-CH_3), -0.55 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.68 (C(1)COOMe), 169.32 (C(4a)COOMe), 167.55 (C(6)C=O), 145.68 (C(12)ArC), 135.58 (C(7)ArC), 134.39 (ArC), 132.86 (ArC), 132.42 (ArC), 129.71 (ArC), 128.59 (ArC), 128.39 (ArC), 124.02 (ArC), 123.75 (ArC), 123.68 (ArC), 99.34 (C(13)), 67.48 (Ar-**C**H_2-O), 55.42 (C(4)), 52.56 (C(2)), 51.66 (C(1)OMe), 35.97 (C(3)), 25.61 (C(**C**H_3)$_3$), 17.91 (**C**(CH_3)$_3$, -4.07 (Si-CH_3), -4.46 (Si-CH_3). ***m/z***= 496 [MH+] (ESI$^+$) and

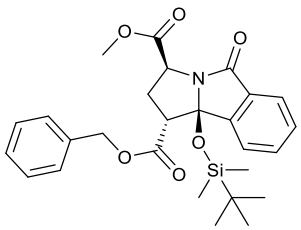
518 [MNa+] (ESI^+). **HRMS** calculated for $C_{27}H_{34}NO_6Si$ requires 496.2149, found at 496.2143 [MH+] (ESI^+).

Structure and stereochemistry confirmed *via* x-ray analysis (See Appendix I, compound 7272).

2-Benzyl 4a-methyl (2*S*,4*S*,13*S*)-13-((tert-butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 176a and **2-Benzyl 4a-methyl (2*R*,4*S*,13*R*)-13-((tert-butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 176b**



176a



176b

176a and **176b** were synthesised according to general procedure **E** using **141** (0.895 g, 2.34 mmol) with 3.0 eq of TBDMSiOTf with the crude material purified using flash column chromatography (30% ethyl acetate in pet-ether 40:60) to afford an inseparable mixture of isomers (1.038 g, 89%). *d.r*= 1: 0.6 for **176a**: **176b**.

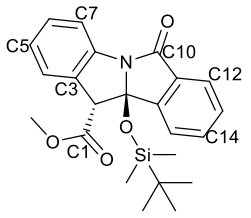
R_f= 0.48. **ν_{max} (KBr) cm^{-1}** 3034 (C-H), 2953 (C-H), 2930 (C-H), 2892 (C-H), 2856 (C-H), 1721 (C=O), 1466, 1437, 1352, 1252 (Si-CH_3), 1210 (Si-CH_3), 1174 (Si-C(CH_3)$_3$), 1109 (O-Si), 1075 (C-O), 1037 (C-O), 950, 868, 839, 801, 780, 753, 696. ***m/z***= 496 [MH+] (ESI^+). **HRMS** calculated for $C_{27}H_{34}NO_6Si$ requires 496.2150, found at 496.2145 [MH+] (ESI^+).

176a) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.57 (dt, *J* = 7.2, 1.2 Hz, 1H, ArH), 7.54 – 7.47 (m, 2H, ArH), 7.47 – 7.41 (m, 1H, ArH), 7.31 – 7.21 (m, 3H, ArH), 7.07 – 6.97 (m, 2H, ArH), 4.83 – 4.75 (m, 2H, C(1b)ArC-C**H**$_2$-O), 4.37 (dd, *J* = 9.0, 3.1 Hz, 1H, C(4)*H*), 3.66 (s, 3H, C(1)OMe), 3.55 (dd, *J* = 8.0, 2.0 Hz, 1H, C(2)*H*), 3.15 (ddd, *J* = 13.7, 9.0, 7.9 Hz, 1H, C(3)H_A), 3.03 – 2.84 (m, 1H, C(3)H_B), 0.84 (s, 9H, C(CH_3)$_3$), -0.07 (s, 3H, Si-CH_3), -0.57 (s, 3H, Si-CH_3).**^{13}C NMR** (101 MHz, MeOD) δ 172.09 (C(6)C=O), 171.17 (C(1)COOBn), 170.70 (C(4a)COOMe), 146.92

(C(12)ArC), 136.55 (C(1c)OCH_2-**C**Ar), 133.96 (ArC), 133.76 (C(7)ArC), 130.95 (ArC), 129.55 (ArC), 129.51 (ArC), 129.40 (ArC), 125.65 (ArC), 124.22 (ArC), 100.77 (C(13), 67.87 (C(1b)ArC-**C**H_2-O), 56.42 (C(4)), 54.45 (C(2)), 52.87 (C(1)OMe), 37.09 (C(3), 25.98 (**C**$(CH_3)_3$), 18.64 (**C**$(CH_3)_3$), -3.96 (Si-CH_3), -4.28 (Si-CH_3).

176b) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.64 – 7.60 (m, 1H, ArH), 7.54 – 7.47 (m, 2H, ArH), 7.47 – 7.41 (m, 1H, ArH), 7.31 – 7.21 (m, 3H, ArH), 7.07 – 6.97 (m, 2H, ArH), 4.83 – 4.75 (m, 1H, C(4)*H*), 4.66 – 4.53 (dd, *J* = 15.2, 12.1 Hz, 2H, C(1b) ArC-C**H**$_2$-O), 3.78 (s, 3H, C(1)OMe), 3.47 – 3.43 (m, 1H C(2)*H*), 3.03 – 2.84 (m, 2H, C(3)*H*), 0.84 (s, 9H, C$(CH_3)_3$), -0.11 (s, 3H, Si-CH_3), -0.35 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 172.67 (C(4a)COOMe), 172.35 (C(6)C=O), 169.49 (C(1)COOBn), 144.69 (C(12)ArC), 136.37 (C(1c)OCH_2-**C**Ar), 134.03 (ArC), 133.42 (C(7)ArC), 131.96 (ArC), 129.71 (ArC), 129.35 (ArC), 129.18 (ArC), 126.03 (ArC), 124.42 (ArC), 100.79 (C(13)), 67.70 (C(1b)ArC-**C**H_2-O), 57.98 (C(4)), 54.79 (C(2)), 53.45 (C91)OMe), 35.81 (C(3)), 26.18 (C(**C**$H_3)_3$), 18.89 (**C**$(CH_3)_3$), -3.10 (Si-CH_3), -3.86 (Si-CH_3).

Methyl (2*R*,17*R*)-17-((tert-butyldimethylsilyl)oxy)-10-oxo-3,8-dihydro-1H-carboxylate[a]pyrrolizine-2-carboxylate



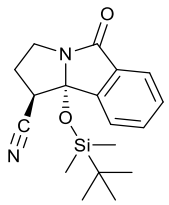
178

178 was synthesised according to general procedure **E** using **138** (0.181 g, 0.61 mmol) with the crude material purified using flash column chromatography (40% ethyl acetate in pet-ether 40:60) to afford the desired product as yellow coloured solid (0.098 g, 39%).

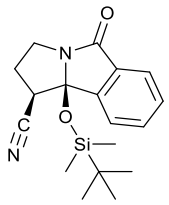
R_f= 0.82. **ν_{max} (KBr) cm^{-1}** 3434, 3293, 2953 (C-H), 2856 (C-H), 2568 (C-H), 2468, 1728 (N-C=O), 1604, 1526, 1497, 1479, 1463, 1418, 1353, 1319, 1295, 1262 (Si-CH_3), 1196 (Si-C(CH_3)), 1174 (C-O), 1135, 1107 (Si-O), 1083 (C-O), 1057, 1035, 1002, 780 (C=C-H), 747. **^{1}H NMR** (400

MHz, Methanol-d_4) δ 7.81 (dt, *J* = 7.6, 1.0 Hz, 1H, Ar-H), 7.75 (td, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 7.70 – 7.60 (m, 3H, Ar-H), 7.44 (td, *J* = 7.7, 1.3 Hz, 1H, Ar-H), 7.39 (ddt, *J* = 7.6, 1.4, 0.7 Hz, 1H, Ar-H), 7.22 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 4.37 (s, 1H, C(2)*H*), 3.18 (s, 3H, OMe), 0.74 (s, 9H, $C(CH_3)_3$), -0.28 (s, 3H, Si-CH_3), -0.38 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 170.87 (C(1)COOMe), 169.52 (C(10)C=O), 146.36 (ArC), 141.14 (ArC), 135.26 (ArC), 134.85 (ArC), 133.97 (ArC), 131.84 (ArC), 130.32 (ArC), 127.03 (ArC), 126.48 (ArC), 125.07 (ArC), 124.94 (ArC), 118.77 (ArC), 101.37 (C(17)), 60.41 (C(2)), 52.42 (C(1)OMe), 25.82 (Si-C(**C**$H_3)_3$, 18.55 (Si-**C**(CH_3)), -3.78 (Si-**C**H_3), -4.00 (Si-**C**H_3). ***m/z***= 408 [MH-] (ESI^-), 410 (MH+) (ESI^+), 432 [MNa+] (ESI^+) and 847 [2MNa+] (ESI^+). **HRMS** requires 410.1782, found at 410.1774.

(2*S*,13*R*)-13-((tert-Butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carbonitrile 183a and **(2*R*,13*R*)-13-((Tert-butyldimethylsilyl)oxy)-6-oxo-3,4,6,13-tetrahydro- benzo[a]pyrrolizine-2-carbonitrile 183b**



183a



183b

In an oven dried round bottomed flask that had been purged with N_2 compound **182** (0.100 g, 0.46 mmol) was dissolved in anhydrous DCM (5 mL) followed by the addition of piperidine (0.13 mL, 1.38 mmol) and left stirring at room temperature for 30 minutes. The reaction was cooled to 0 °C with TBDMSiOTf (0.12 mL, 0.50 mmol) added dropwise and the resulting reaction left stirring at room temperature for 16 hours. The mixture was transferred to a separating funnel and diluted with DCM (5 mL) then washed using water (2 x 10 mL) and back extracted with DCM (10 mL). The combined organic layers were combined, dried over $MgSO_4$ and concentrated by reduced pressure. The crude mixture was purified using flash column chromatography (30% ethyl acetate in pet-ether 40:60) with the product containing fractions being collected, combined and

concentrated by reduced pressure to afford a mixture of inseparable diastereomers the desired product as yellow coloured solid (0.068 g, 44%). *d.r* = 3:1 for **183a**: **183b**.

R_f= 0.60. **ν_{max} (KBr) cm^{-1}** 2955(C-H), 2928 (C-H), 2856 (C-H), 1773 (N-C=O), 1713 (N-C=O), 1614, 1467, 1396, 1348, 1322, 1253 (Si-CH_3), 1172 (Si-C(CH_3)), 1115 (O-Si), 1087, 1004. ***m/z***= 329 [MH+] (ESI^+) and 351 [MNa+] (ESI^+). **HRMS** calculated for $C_{18}H_{25}N_2O_2Si$ requires 329.1680, found at 329.1680 [MH+] (ESI^+).

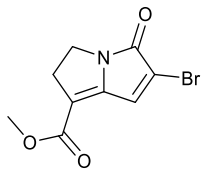
183a) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.80 – 7.75 (m, 1H, ArH), 7.66 – 7.61 (m, 1H, ArH), 7.59 – 7.53 (m, 2H, ArH), 4.00 – 3.87 (m, 1H, (C(4)H_A), 3.50 (ddd, *J* = 11.4, 8.9, 2.2 Hz, 1H, C(4)H_B), 3.38 (ddd, *J* = 6.8, 1.5, 0.6 Hz, 1H, (C(2)*H*), 2.89 (dddd, *J* = 13.2, 9.7, 8.9, 6.9 Hz, 1H, (C(3)H_A), 2.62 (dddd, *J* = 13.1, 7.9, 2.2, 1.5 Hz, 1H, C(3)H_B), 0.82 (s, 9H, C(CH_3)$_3$), -0.08 (s, 3H, Si-CH_3), -0.48 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.07 (C(6)C=O), 144.20 (C(12)ArC), 133.30 (ArC), 132.31 (C(7)ArC), 130.99 (ArC), 124.08 (ArC), 121.67 (ArC), 117.31 (C(1)C-**C**≡N), 98.20 (C(13)), 41.15 (C(4)), 39.88 (C(2)), 32.57 (C(3)), 25.50 (C(**C**H_3)$_3$), 17.84 (**C**(CH_3)$_3$), -4.36 (Si-CH_3), -4.52 (Si-CH_3).

183b) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H, ArH), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H, ArH), 4.00 – 3.87 (m, 1H, C(4)H_A), 3.84 – 3.75 (m, 1H, C(4)H_B), 2.03 – 1.84 (m, 3H, C(2)*H* and C(3)*H*), 0.96 (s, 9H, C(CH_3)$_3$), 0.17 (s, 3H, Si-CH_3), 0.09 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.29 (C(6)C=O), 134.18 (ArC), 132.31 (C(12)ArC), 132.05 (C(7)ArC), 123.45 (ArC), 121.67 (C(1)C-**C**≡N), 98.20 (C(13)), 38.13, 26.80 (C(**C**H_3)$_3$), 26.36 (C(3)) 17.52 (**C**(CH_3)$_3$), 13.69 (C(2)), -7.03 (Si-CH_3), -7.14 (Si-CH_3).

General procedure F TFA desilyloxylation

Silyl containing compound was dissolved in a solution of TFA/H_2O (9:1, 1 mL) and left stirring at room temperature for 1 hour, in which the reaction mixture turned yellow. The stirrer bar was removed and washed using water (1 mL) resulting in the mixture to turn cloudy. The solvent was removed using reduced pressure to afford the desired product without any additional purification.

Methyl 7-bromo-6-oxo-3,4-dihydro-1H-pyrrolizine-2-carboxylate 143d

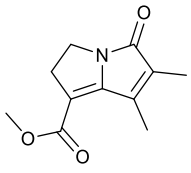


143d

143d was synthesised according to general procedure **F** using **77d** (0.136 g, 0.34 mmol) to afford the desired product as a bright yellow coloured oil (0.093 g, quantitative yield).

Mp= 148-150 °C. **ν_{max} (KBr) cm^{-1}** 3096 (C-H), 2946 (C-H), 1683 (N-C=O), 1640 (C=O), 1513, 1468 (C-H), 1439 (C-H), 1425, 1405, 1364, 1329, 1260, 1225, 1201, 1128 (C-O), 1103, 1065, 739 (C-Br). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.52 (s, 1H, C(8)*H*), 3.89 (t, *J* = 8.0, 7.0 Hz, 2H, C(4)*H*), 3.82 (s, 3H C(1)OMe), 3.23 (t, *J* = 8.1, 7.0 Hz, 2H C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.02 (C(1)COOMe), 160.87 (C(6)C=O), 149.00 (C(9)C=**C**-H), 129.51 (C(7)C=**C**-Br), 127.11 (C(8)C=**C**-H), 114.45 (C(2)**C**=C), 52.23 (C(1)OMe), 41.27 (C(4)), 33.78 (C(3)). ***m/z***= 258 and 260 [MH+] (ESI^+). **HRMS** calculated for $C_9H_9BrNO_3$ requires 257.9760 and 259.9740, found at 257.9762 and 259.9741 [MH+] (ESI^+).

Methyl 7,8-dimethyl-6-oxo-3,4-dihydro-1H-pyrrolizine-2-carboxylate 143f



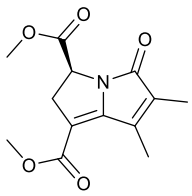
143f

143f was synthesised according to general procedure **F** using **77f** (0.051 g, 0.15 mmol) to afford the desired product as a bright yellow coloured oil (0.033 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 1695 (N-C=O), 1682 (C=O), 1629 (C-O), 1436 (CH_3), 1402, 1340, 1261, 1210 (C-O), 1181, 1128. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.80 (s, 3H, OMe), 3.76 (t, *J* = 7.6 Hz, 2H, C(4)*H*), 3.28 (t, *J* = 7.8 Hz, 2H, C(3)*H*), 2.25 (s, 3H, C(7)C=C-**CH_3**), 1.93 (s, 3H, C(8)C=C-**CH_3**). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.69 (C(1)COOMe), 164.35 (C(6)C=O), 151.02

(C(9)C=**C**), 140.07 (C(8)C=**C**-CH_3), 134.59 (C(7)C=**C**-CH_3), 114.64 (C(2)**C**=C), 52.02 (C(1)OMe), 39.42 (C(4)), 35.20 (C(3)), 12.83 (C(8a)C=C-**C**H_3), 9.50 (C(7a)C=C-**C**H_3). ***m/z***= 208 [MH+] (ESI^+). **HRMS** calculated for $C_{11}H_{14}NO_3$ requires 208.0968, found at 208.0966 [MH+] (ESI^+).

Dimethyl (*S*)-7,8-dimethyl-6-oxo-3,6-dihydro-1H-pyrrolizine-2,4-dicarboxylate 184

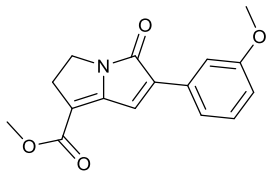


184

184 was synthesised according to general procedure **F** using **170d** with the crude material purified using flash column chromatography (30% ethyl acetate in DCM) to afford the desired product as a pale-yellow coloured film (0.031 g, 56%).

R_f= 0.65. **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 2925 (C-H), 2853 (C-H), 1752 (N-C=O), 1693 (C=O), 1632 (C=O), 1436 (C-H), 1398, 1340, 1232, 1208, 1159 (C-O), 1123, 1051, 1022. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.66 (dd, *J* = 10.5, 4.0 Hz, 1H, C(4)*H*), 3.77 (s, 3H, C(1)OMe), 3.76 (s, 3H, C(4a)OMe), 3.67 – 3.58 (m, 1H, C(3)H_A), 3.26 (ddd, *J* = 18.0, 4.0, 0.8 Hz, 1H, C(3)H_B), 2.27 (q, *J* = 1.3 Hz, 3H, C(8a)C=C-C**H**$_3$), 1.95 (q, *J* = 1.0 Hz, 3H, C(7a)C=C-C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.53 (C(4a)COOMe), 166.39 (C(1)COOMe), 163.99 (C(6)C=O), 151.68 (C(9)C=**C**), 140.48 (C(8)C=**C**-CH_3), 134.85 (C(7)C=**C**-CH_3), 109.12 (C(2)**C**=C), 52.94 (C(1)OMe), 52.78 (C(4)), 51.81 (C(4a)OMe), 40.43 (C(3)), 12.90 (C(8a)C=C-**C**H_3), 9.63 (C(7a)C=C-**C**H_3). ***m/z***= 266 [MH+] (ESI^+) and 288 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{16}NO_5$ requires 266.1023, found at 266.1022 [MH+] (ESI^+).

Methyl 7-(3-methoxyphenyl)-6-oxo-3,3,6-trihydro-pyrrolizine-2-carboxylate 203a

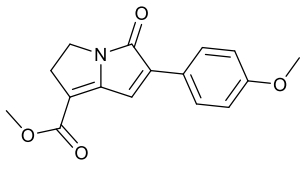


203a

203a was synthesised according to general procedure **F** using **202a** (0.070 g, 0.16 mmol) to afford the desired product as a bright yellow coloured oil (0.048 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 3082, 2952 (C-H), 2837 (C-H), 1687 (N-C=O), 1644 (C=O), 1597, 1580, 1553, 1482 (C-H), 1437 (C-H), 1407, 1360, 1324, 1307, 1286, 1253 (C-O), 1219 (C-O), 1180, 1121, 1051, 1031. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.57 – 7.49 (m, 2H, ArH), 7.46 (s, 1H, C(8)*H*), 7.34 (t, *J* = 7.9 Hz, 1H, ArH), 6.96 (dd, *J* = 8.4, 2.6 Hz, 1H, ArH), 3.92 (t, *J* = 7.4 Hz, 2H, C(4)*H*), 3.86 (s, 3H, (C(1)OMe), 3.92 (s, 3H, ArC-OMe), 3.32 (t, *J* = 7.4 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.95 (C(1)COOMe), 164.72 (C(6)C=O), 159.83 (Ar**C**-OMe), 149.91 (C(2)C=**C**), 144.51 (C(7)C=**C**-Ar), 132.19 (Ar**C**-C=C), 129.92 (ArC), 120.46 (ArC), 120.00 (C(7)C=**C**-H), 116.40 (ArC), 114.87 (ArC), 112.99 (C(2)**C**=C), 55.50 (ArC-O**C**H_3), 52.30 (C(1)OMe), 40.70 (C(4)), 34.15 (C(3)). ***m/z***= 286 [MH+] (ESI$^+$) and 308 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{16}H_{16}NO_4$ requires 286.1074, found at 286.1075 [MH+] (ESI$^+$).

Methyl 7-(4-methoxyphenyl)-6-oxo-3,4-dihydro-1H-pyrrolizine-2-carboxylate 203b



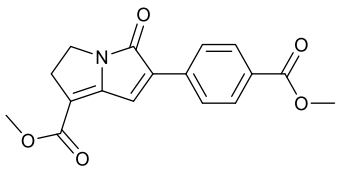
203b

203b was synthesised according to general procedure **F** using **202b** (0.080 g, 0.19 mmol) to afford the desired product as a bright yellow coloured solid (0.058 g, quantitative yield).

Mp= 176-178 °C. **ν_{max} (KBr) cm^{-1}** 2952 (C-H), 2909 (C-H), 2839 (C-H), 1709 (N-C=O), 1684 (C=O), 1641 (C-O), 1602, 1501, 1438 (C-H), 1408, 1333, 1303, 1244 (C-O), 1213, 1176 (C-O),

1116, 1039, 1023, 830, 733. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.00 – 7.95 (m, 2H, ArH), 7.34 (s, 1H, C(8)*H*), 6.98 – 6.92 (m, 2H, ArH), 3.90 (t, *J* = 7.4, Hz, 2H, C(4)*H*), 3.85 (s, 3H, C(1)OMe), 3.84 (s, 3H, ArC-OC**H$_3$**), 3.31 (t, *J* = 7.4 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.22 (C(1)COOMe), 164.91 (C(6)C=O), 161.38 (Ar**C**-OMe), 150.33 (C(9)C=**C**), 144.19 (C(7)C=**C**-Ar), 129.60 (ArC), 123.82 (C(7a)C=C-**C**Ar), 117.23 (C(8)C=**C**-H), 114.42 (ArC), 113.40 (C(2)**C**=C), 55.52 (ArC-O**C**H_3), 52.17 (C(1)OMe), 40.63 (C(4)), 34.04 (C(3)). ***m/z***= 286 [MH+] (ESI^+) and 308 [MNa+] (ESI^+). **HRMS** calculated for $C_{16}H_{16}NO_4$ requires 286.1074, found at 286.1072 [MH+] (ESI^+).

Methyl 7-(4-(methoxycarbonyl)phenyl)-6-oxo-3,4-dihydro-1H-pyrrolizine-2-carboxylate 203c

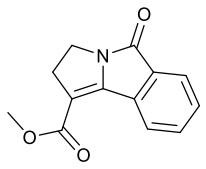


203c

203c was synthesised according to general procedure **F** using **202c** (0.070 g, 0.15 mmol) to afford the desired product as a bright yellow coloured solid (0.053 g, quantitative yield).

Mp= +240 °C. **ν_{max} (KBr) cm^{-1}** 2955 (C-H), 1715 (C=O), 1687 (N-C=O), 1641 (C=O), 1604, 1477 (C-H), 1427 (C-H), 1409, 1304, 1276 (C-O), 1240, 1214, 1187 (C-O), 1107, 1014, 963, 848, 805, 779, 750, 698, 658. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.08 (s, 4H, ArH), 7.57 (s, 1H, C(8)*H*), 3.93 (m, 5H, C(4)*H* and ArC-COOMe), 3.86 (s, 3H, C(1)OMe), 3.33 (t, *J* = 7.9 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.74 (C(1)COOMe), 164.87 (C(6)C=O), 164.57 (Ar-COOMe), 149.97 (C(9)C=**C**), 143.30 (C(7)C=**C**-CAr), 135.49 (C(7a)C=C-**C**Ar), 131.11 (Ar**C**-COOMe), 130.00 (ArC), 127.83 (ArC), 121.35 (C(8)C=**C**-H), 114.15 (C(2)**C**=C), 52.43 (ArC-COO**Me**), 52.14 (C(1)OMe), 40.66 (C(4)), 34.16 (C(3)). ***m/z***= 314 [MH+] (ESI^+) and 336 [MNa+] (ESI^+). **HRMS** calculated for $C_{17}H_{16}NO_5$ requires 314.1023, found at 314.1022 [MH+] (ESI^+).

Methyl 6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylate 146a



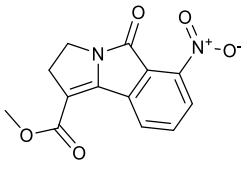
146a

Method 1) **146a** was synthesised according to general procedure **E** from **137a** (0.400 g, 1.61 mmol) and using 3.0 eq of TBDMSiOTf with the crude material purified using flash column chromatography (40% ethyl acetate in DCM), alternatively, the crude oil can be triturated using EtOAc to afford the desired product as yellow coloured solid (0.372 g, quantitative yield).

Method 2) **146** was synthesised according to general procedure **F** using **144a** (4.31 g, 11.93 mmol) to afford the desired product as a bright yellow coloured solid (3.39 g, quantitative yield).

R_f= 0.41. **Mp**= 175-177 °C. **ν_{max} (KBr) cm^{-1}** 2950 (C-H), 1688 (N-C=O), 1641 (C=O), 1585, 1470 (CH), 1436 (CH), 1400, 1341, 1308, 1291, 1251, 1224, 1181 (C-O), 1159, 1120, 1011. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.53 (d, 1H, Ar-H), 7.84 (ddd, *J* = 7.2, 1.5, 0.8 Hz, 1H, Ar-H), 7.68 – 7.57 (m, 2H, Ar-H), 3.97 (t, *J* = 7.9 Hz, 2H, C(4)*H*), 3.89 (s, 3H, OMe), 3.37 (t, *J* = 8.9 Hz, 2H, C(3)*H*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.09 (C(1)COOMe), 164.05 (C(6)C=O), 149.17 (C(13)C=**C**), 136.26 (C(12)ArC), 132.26 (ArC), 131.55 (ArC), 129.62 (C(7)ArC), 126.77 (ArC), 123.52 (ArC), 110.31 (C(2)**C**=C), 51.95 (C(1)OMe), 40.09 (C(4)), 34.14 (C(3)). ***m/z***= 230 [MH+] (ESI^+) and 252 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{12}NO_3$ requires 230.0811, found at 230.0812 [MH+] (ESI^+).

Methyl 8-nitro-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylate 146b



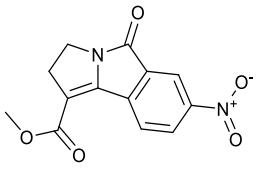
146b

Method 1) **146b** was synthesised according to general procedure **E** from **137b** (0.300 g, 1.02mmol) using 3.0 eq of TBDMSiOTf with the crude oil triturated using EtOAc to afford the desired product as yellow coloured solid (0.283 g, quantitative yield).

Method 2) **146b** was synthesised according to general procedure **F** using **144b** to afford the desired product as a bright yellow coloured solid (0.108 g, 98%).

Mp= 211-213 °C. **ν_{max} (KBr) cm^{-1}** 3096 (C-H), 2980 (C-H), 1716 (N-C=O), 1694 (N-C=O), 1645 (C=O), 1615, 1575, 1533 (NO_2), 1472, 1431, 1387, 1349 (NO_2), 1304, 1251, 1207, 1181 (C-O), 1159, 1120, 1100. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.87 (dd, *J* = 7.8, 1.0 Hz, 1H, Ar-H), 7.92 (dd, *J* = 8.1, 1.0 Hz, 1H, Ar-H), 7.78 (t, *J* = 7.9 Hz, 1H, Ar-H), 4.01 (t, *J* = 8.8 Hz, 2H, C(4)*H*), 3.90 (s, 3H, (C(1)OMe), 3.41 (t, *J* = 8.9 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.60 (C(1)COOMe), 158.79 (C(6)C=O), 146.41 (C(13)C=**C**), 145.79 (C(8)Ar**C**-NO_2), 133.06 (ArC), 131.48 (ArC), 130.60 (ArC), 127.38 (ArC), 125.88 (ArC), 113.26 (C(2)**C**=C), 52.30 (C(1)OMe), 40.63 (C(4)), 34.28 (C(3)). ***m/z***= 275 [MH+] (ESI$^+$) and 297 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{13}H_{11}N_2O_5$ requires 275.0662, found at 275.0661 [MH+] (ESI$^+$).

Methyl 9-nitro-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylate 186a



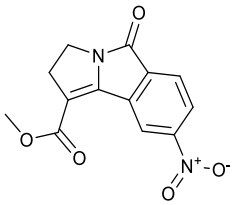
186a

186a was synthesised according to general procedure **F** using **172a** (0.126 g, 0.31 mmol) to afford the desired product as a pale yellow coloured solid (0.109 g, quantitative yield).

Mp= 206-208 °C. **ν_{max} (KBr) cm^{-1}** 3109 (C-H), 3094 (C-H), 3035 (C-H), 2955 (C-H), 2853 (C-H), 1715 (N-C=O), 1695 (C=O), 1595, 1527 (-NO_2), 1479, 1341, 1252, 1222, 1180 (C-O), 1155, 1124, 1063, 1035, 1001. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.74 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.65 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.51 (dd, *J* = 8.4, 2.1 Hz, 1H, Ar-H), 4.07 (t, *J* = 8.8 Hz, 2H, C(4)*H*), 3.93 (s, 3H, OMe), 3.45 (t, *J* = 8.8 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.33

(C(1)COOMe), 162.33 (C(6)C=O), 149.70 (C(9)Ar**C**-NO_2), 146.69 (C(13)C=**C**), 137.19 (C(12)ArC), 133.90 (C(7)ArC), 127.91 (C(11)ArC), 127.34 (C(10)ArC), 119.08 (C(8)ArC), 115.48 (C(2)**C**=C), 52.52 (C(1)OMe), 40.66 (C(4)), 34.51 (C(3)). ***m/z***= 275 [MH+] (ESI^+) and 297 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{11}N_2O_6$ requires 275.0662, found at 275.0665 [MH+] (ESI^+).

Methyl 10-nitro-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylate 186b

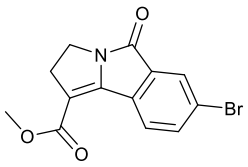


186b

186b was synthesised according to general procedure **F** using **172b** (0.119 g, 0.29 mmol) with the ^{1}H NMR spectrum showed impurities from previous reaction, so the crude material was purified using flash column chromatography (10% ethyl acetate in DCM) to afford the desired product as a yellow coloured solid (0.074 g, 92%).

R_f= 0.48. **Mp**= 209-211 °C. **ν_{max} (KBr) cm^{-1}** 3109 (C-H), 3094 (C-H), 3035 (C-H), 2955 (C-H), 2853(C-H), 1715 (N-C=O), 1695 (N-C=O), 1648 (C=O), 1595, 1527 (-NO_2), 1479, 1341, 1252, 1222, 1180 (C-O), 1155, 1124, 1063, 1035, 1001. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.33 (dd, *J* = 2.1, 0.6 Hz, 1H, Ar-H), 8.47 – 8.43 (m, 1H, Ar-H), 7.97 (dd, *J* = 8.3, 0.6 Hz, 1H, Ar-H), 4.03 (t, *J* = 7.9 Hz, 2H, C(4)*H*), 3.93 (s, 3H, OMe), 3.42 (t, *J* = 8.7 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.38 (C(1)COOMe), 161.45 (C(6)C=O), 150.49 (C(10)Ar**C**-NO_2), 146.85 (C(13)C=**C**), 140.81 (C(7)ArC), 130.35 (C(13)ArC), 126.53 (C(8)ArC), 124.36 (C(9)ArC), 122.10 (C(11)ArC), 113.05 (C(2)**C**=C), 52.34 (C(1)OMe), 40.50 (C(4)), 34.26 (C(3)). ***m/z***= 275 [MH+] (ESI^+) and 297 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{11}N_2O_6$ requires 275.0662, found at 275.0664 [MH+] (ESI^+).

Methyl 9-bromo-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylate 186c

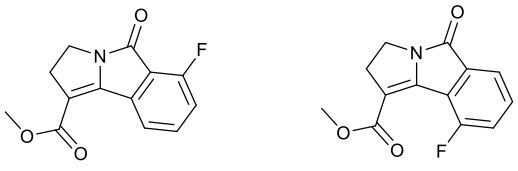


186c

186c was synthesised according to general procedure **F** using **172c** (0.164 g, 0.40 mmol) to afford the desired product as a pale yellow coloured solid (0.143 g, quantitative yield).

Mp= 197-199 °C. **ν_{max} (KBr) cm^{-1}** 3467, 2953 (C-H), 1691 (C=O), 1647 (N-C=O), 1574, 1476, 1450, 1399, 1330, 1299, 1253, 1223, 1177 (C-O), 1161, 1125, 1052, 1012, 701 (Ar-Br). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.41 – 8.34 (m, 1H, Ar-H), 7.96 (dd, *J* = 1.9, 0.5 Hz, 1H, Ar-H), 7.77 (dd, *J* = 8.2, 1.8 Hz, 1H, Ar-H), 3.98 (t, *J* = 8.7 Hz, 2H, (C(4)*H*), 3.90 (s, 3H, C(1)OMe), 3.36 (t, *J* = 8.7 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.80 (C(1)COOMe), 163.15 (C(6)C=O), 147.92 (C(13)C=**C**), 137.56 (C(12)ArC), 135.50 (ArC), 128.16 (ArC), 128.02 (Ar**C**-Br), 126.95 (ArC), 126.30 (C(7)ArC), 112.43 (C(2)**C**=C), 52.20 C(1)OMe), 40.36 (C(4)), 34.27 (C(3)). ***m/z***= 309 and 311 [M+2H+] (ESI^+), 330 and 332 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{11}BrNO_3$ requires 307.9917 and 309.9896, found at 307.9918 and 309.9897 [MH+] (ESI^+).

Methyl 8-fluoro-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylate 146f and **Methyl 9-fluoro-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylate 185**



146f **185**

Method 1) **146f** and **185** were synthesised according to general procedure **E** from **137f** (0.240 g, 0.95 mmol) using 3.0 eq of TBDMSiOTf with the crude oil triturated using pet-ether 40:60 (2 x 10 mL) followed by the addition of ethyl acetate (5 mL) resulting in precipitating to form a yellow-coloured solid. The solvent was removed and the remining solid was triturated using ethyl acetate

(20 mL) with the solid dried using reduced pressure to afford an inseparable mixture of regioisomers as a bright yellow coloured solid (0.364 g, quantitative yield). *r.r* = 1.0: 0.1 for **146f**: **185**.

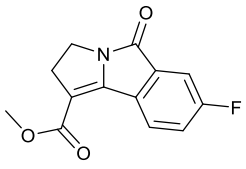
Method 2) **146f** and **185** were synthesised according to general procedure **F** from a mixture of **144f** and **171** (0.349g, 0.92 mmol) to afford an inseparable mixture of desired products as a pale yellow coloured solid (0.347 g, quantitative yield). *r.r* = 1.0: 0.33 for **146f**: **185.**

ν_{max} (KBr) cm^{-1} 2951 (C-H), 1693 (C=O), 1648 (N-C=O), 1571, 1449, 1401, 1329, 1298, 1251, 1221, 1175 (C-O), 1163, 1129, 1057, 1011, 709 (Ar-F). ***m/z***= 248 [MH] (ESI$^+$) and 270 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{13}H_{11}FNO_3$ requires 248.0726, found at 248.0719 [MH+] (ESI$^+$).

146f) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 7.4 Hz, 1H, ArH), 7.63 – 7.54 (m, 1H, ArH), 7.20 (ddd, *J* = 9.1, 8.1, 0.7 Hz, 1H, ArH), 3.92 (t, *J* = 8.7 Hz, 2H, C(4)*H*), 3.84 (s, 3H, C(1)OMe), 3.32 (t, *J* = 8.7 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.70 (C(1)COOMe), 160.63 (C(6)C=O), 157.80 (d, *J* = 261.4 Hz, C(8)Ar**C**-F), 148.09 (d, *J* = 1.2 Hz, C(13)C=**C**), 134.17 (d, *J* = 7.9 Hz, C(10)ArC), 131.66 (d, *J* = 3.8 Hz, C(12)ArC) 122.90 (d, *J*= 3.5 Hz, C(11)ArC), 119.19 (d, *J* = 19.9 Hz, C(9)ArC), 110.88 (C(2)**C**=C), 51.83 (C(1)OMe), 40.06 (C(4)), 34.03 (C(3)). NOTE C7 aromatic carbon not identified.

185) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.54 (m, 2H), 7.27 (ddd, *J* = 10.0, 8.1, 1.2 Hz, 1H), 3.92 (t, *J* = 8.7 Hz, 2H), 3.83 (s, 3H), 3.39 (t, *J* = 8.7 Hz, 1H, C(3)*H*). Note ^{13}C NMR too weak to fully assign peaks.

Methyl 9-fluoro-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylate 186e

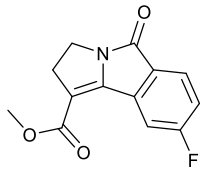


186e

186e was synthesised according to general procedure **F** using **172e** (0.476 g, 1.25 mmol) to afford the desired product as a pale yellow coloured solid (0.317 g, quantitative yield).

Mp= 201-203 °C. **ν_{max} (KBr) cm^{-1}** 1779, 1697 (C=O), 1646 (N-C=O), 1593, 1474, 1440, 1399, 1343, 1303, 1247, 1215, 1195 (C-O), 1163, 1130, 1118, 1088, 1041, 1010, 775 (ArC-F). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.52 (dd, *J* = 8.5, 4.7 Hz, 1H, ArH), 7.50 (dd, *J* = 7.5, 2.4 Hz, 1H ArH), 7.33 (td, *J* = 8.7, 2.5 Hz, 1H, ArH), 3.98 (t, *J* = 8.7 Hz, 2H, C(4)*H*), 3.89 (s, 3H, C(1)OMe), 3.37 (t, *J* = 8.6 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.95 (C(1)COOMe), 164.83 (C(6)C=O), 158.59 (d, *J* = 41.8 Hz, C(9)Ar**C**-F), 147.70 (C(13)C=**C**), 138.41 (d, *J* = 8.9 Hz, C(7)ArC), 129.01 (d, *J* = 9.2 Hz, C(11)ArC), 125.42 (d, *J* = 2.7 Hz, C(12)ArC), 119.76 (d, *J* = 23.5 Hz, C(8)ArC), 111.75 (C(2)**C**=C), 111.05 (d, *J* = 24.4 Hz, C(8)ArC), 52.18 (C(1)OMe), 40.36 (C(4)), 34.13 (C(3)). ***m/z***= 248 [MH+] (ESI$^+$) and 270 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{13}H_{11}FNO_3$ requires 248.0717, found at 248.0719 [MH+] (ESI$^+$).

Methyl 10-fluoro-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylate 186f



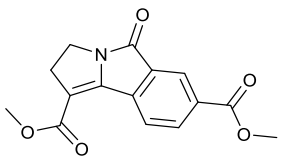
186f

186f was synthesised according to general procedure **F** using **172f** (0.165 g, 0.435 mmol) to afford the desired product as a pale yellow coloured solid (0.110 g, quantitative yield).

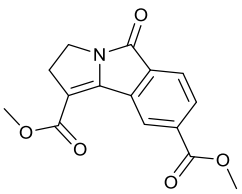
Mp= 179-181 °C. **ν_{max} (KBr) cm^{-1}** 2955 (C-H), 1712 (C=O), 1695 (N-C=O), 1649 (C=O), 1616, 1473, 1444, 1397, 1363, 1307, 1258, 1213, 1193, 1123, 1092, 747 (ArC-F). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.21 (dd, *J* = 8.7, 2.4 Hz, 1H, ArH), 7.79 (dd, *J* = 8.4, 4.9 Hz, 1H, ArH), 7.26 (m, 1H, ArH), 3.94 (t, *J* = 9.0 Hz, 2H, C(4)*H*), 3.88 (s, 3H, C(1)OMe), 3.34 (t, *J* = 9.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.57 (d, *J* = 41.7 Hz, (C(10)Ar**C**-F), 164.81 (C(1)COOMe), 162.95 (C(6)C=O), 148.14 (d, *J* = 3.2 Hz, C(13)C=**C**), 132.21 (d, *J* = 2.5 Hz, C(7)ArC), 131.64 (d, *J* = 11.2 Hz, C(12)ArC), 125.37 (d, *J* = 9.6 Hz, C(8)ArC), 118.79 (d, *J* = 23.8 Hz, C(11)ArC), 114.20 (d, *J* = 26.3 Hz, C(9)ArC), 111.10 (C(2)**C**=C), 52.00 (C(1)OMe), 40.24 (C(4)), 34.04

(C(3)). ***m/z***= 248 [MH+] (ESI^+) and 270 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{11}FNO_3$ requires 248.0717, found at 248.0719 [MH+] (ESI^+).

Dimethyl 6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2,9-dicarboxylate 186g and **Dimethyl 6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2,10-dicarboxylate 186h**



186g

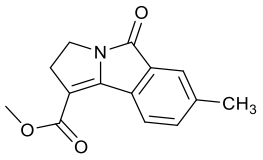


186h

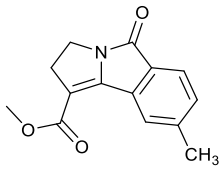
186g and **186h** were synthesised according to general procedure **F** using a mixture of **172g** and **172h** (0.130 g, 0.31 mmol) to afford the inseparable mixture of the desired products as an inseparable pale yellow coloured solid (0.090 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 2973 (C-H), 1694 (C=O), 1649 (N-C=O), 1618 (C=O), 1531, 1438 (C-H), 1346, 1304 (C-O), 1253 (C-O), 1224, 1158, 740, 669. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.03 (d, *J* = 1.4 Hz, 1H, Ar-H), 8.51 (d, *J* = 8.1 Hz, 1H, Ar-H), 8.40 (d, *J* = 1.5 Hz, 1H, Ar-H), 8.25 (ddd, *J* = 10.7, 8.0, 1.5 Hz, 2H, Ar-H), 7.83 (d, *J* = 7.9 Hz, 1H, Ar-H), 3.95 (m, 10H, C(4)*H* and (C(1)OMe), 3.89 (m, 6H, C(9,10)OMe), 3.36 (t, *J* = 8.2 Hz, 4H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.14 (C(1)OMe), 165.86 (C(1)OMe), 164.57 (C(6)C=O), 164.55 (C(6)C=O), 163.39 (C(10)OMe), 163.22 (C(9)OMe), 147.76 (C(13)C=**C**), 147.61 (C(13)C=**C**), 139.32 (ArC), 136.14 (ArC), 133.81 (ArC), 133.47 (ArC), 132.95 (ArC), 132.80 (ArC), 132.72 (ArC), 129.41 (ArC), 127.83 (ArC), 126.71 (ArC), 124.67 (ArC), 123.48 (ArC), 113.21 (C(2)**C**=C), 112.56 (C(2)**C**=C), 52.84 (C(10)OMe, 52.76 (C(9)OMe), 52.18 (C(1)OMe) 52.17 (C(1)OMe), 40.30 (C(4)), 40.28, (C(4)) 34.29 (C(3)), 34.24 (C(3)). ***m/z***= 576 [2MNa+] (ESI^+). **HRMS** calculated for $C_{15}H_{14}NO_5$ requires 288.0866, found at 288.0866 [MH+] (ESI^+).

Methyl 9-methyl-6-oxo-3,4,6-benzo[a]pyrrolizine-2-carboxylate 186i and **Methyl 10-methyl-6-oxo-3,4,6-benzo[a]pyrrolizine-2-carboxylate 186j**



186i



186j

186i and 186j were synthesised according to general procedure **F** using a mixture of **172i** and **172j** (0.596 g, 1.58 mmol) with the crude material purified using flash column chromatography (20% ethyl acetate in DCM) to afford the desired products as in inseparable mixture of isomers as a yellow coloured solid (0.330 g, 85%). Note that the purification was to remove the starting material pre-cyclisation. Note that due to both compounds' similarity in characteristic data, both compounds have been reported together.

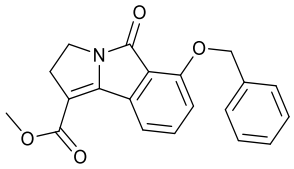
R_f= 0.54. **Mp**= 149-151 °C. **ν_{max} (KBr) cm^{-1}** 2952 (C-H), 1687 (C=O), 1643 (N-C=O), 1477, 1439, 1401, 1336, 1305, 1253 (C-O), 1231 (C-O), 1173, 1120, 1013. ***m/z***= 244 [MH+] (ESI^+) and 398 [MNa+] (ESI^+). **HRMS** calculated for $C_{14}H_{14}NO_3$ requires 244.0968, found at 244.0968 [MH+] (ESI^+).

186i) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.34 (d, *J* = 7.9 Hz, 1H, ArH), 7.61 (dt, *J* = 1.6, 0.8 Hz, 1H, ArH), 7.41 (ddd, *J* = 7.9, 1.7, 0.8 Hz, 1H, ArH), 3.92 (t, *J* = 8.9 Hz, 2H, C(4)*H*), 3.87 (s, 3H, C(1)OMe), 3.32 (m, 2H), 2.49 (s, 3H, C(9a)ArC-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.18 (C(1)COOMe), 164.05 (C(6)C=O), 149.33(C(12a)C=**C**), 142.39 (C(9/10)Ar**C**-CH_3), 136.55 (C(12)ArC), 132.93 (ArC), 127.04 (C(7)ArC, 126.47 (ArC), 123.88 (ArC), 109.12 (C(2)C=C), 51.79 (C(1)OMe, 40.01 (C(4)), 33.98 (C(3)), 22.01 C(9/10)Ar-**C**H_3).

186j) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.32 (dt, *J* = 1.6, 0.8 Hz, 1H, ArH), 7.71 – 7.66 (m, 1H ArH), 7.38 (ddd, *J* = 7.7, 1.5, 0.7 Hz, 1H, ArH), 3.92 (t, *J* = 8.9 Hz, 2H, C(4)*H*), 3.87 (s, 3H (C(1)OMe)), 3.32 (m, 2H), 2.47 (s, 3H, C(10a)ArC-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.18 (C(1)COOMe), 164.05 (C(6)C=O), 149.65 (C(12a)C=**C**), 143.00 (C(9/10)Ar**C**-CH_3), 133.72

(C(12)ArC), 132.31 (ArC), 129.26 (C(7)ArC) 127.22 (ArC), 123.24 (ArC), 109.58 (**C**=C), 51.83 (C(1)OMe), 40.01 (C(4)), 34.01 (C(3)), 22.21 (C(9/10)Ar-**C**H_3).

Methyl 8-(benzyloxy)-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylate 146j

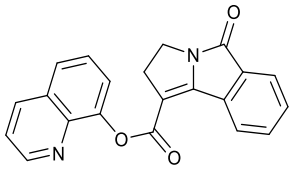


146j

Method 1) **146j** was synthesised according to general procedure **E** from **137j** (0.180 g, 0.51 mmol) using 3.0 eq TBDMSiOTf with the crude oil triturated using pet-ether 40:60 (2 x 10 mL) followed by the addition of ethyl acetate (5 mL) resulting in precipitating to form a yellow-coloured oil. The solvent was removed and the remining solid was triturated using ethyl acetate (20 mL) with the solid dried using reduced pressure to afford the desired product as a bright yellow coloured solid (0.089 g, 52%).

Method 2) **146j** was synthesised according to general procedure **F** using **144j** (0.200 g, 0.42 mmol) to afford the desired product as a bright yellow coloured solid (0.149 g, quantitative yield). **Mp**= 168-170 °C. **ν_{max} (KBr) cm^{-1}** 1678 (C=O), 1659 (N-C=O), 1256 (C-O), 1193, 1115, 1029, 926, 811, 747, 696, 637. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.19 (dd, *J* = 7.6, 0.7 Hz, 1H, Ar-H), 7.56 – 7.50 (m, 3H, Ar-H), 7.42 – 7.37 (m, 3H, Ar-H), 7.34 – 7.30 (m, 1H, Ar-H), 7.10 (d, *J* = 8.3 Hz, 1H, Ar-H), 5.36 (s, 2H, C(8b)Ar-C**H**$_2$-O), 4.00 – 3.93 (m, 2H, C(4)*H*), 3.89 (s, 3H, C(1)OMe), 3.36 (t, *J* = 9.1 Hz, 2H, (C(3)*H*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.18 (C(1)COOMe), 162.77 (C(6)C=O), 155.83 (C(8)Ar**C**-O-), 149.01 (C(13)C=**C**), 136.60 (C(8c)-CH_2-Ar**C**), 133.88 (ArC), 131.81 (C(12)ArC), 128.76 (BnC), 127.99 (ArC), 126.95 (BnC), 122.98 (C(7)ArC), 119.71 (ArC), 117.02 (ArC), 109.64 (C(2)**C**=C), 70.85 (C(8b)O-**C**H_2-Bn), 51.83 (C(1)OMe), 40.10 (C(4)), 34.04 (C(3)). ***m/z***= 336 [MH+] (ESI$^+$). **HRMS** calculated for $C_{20}H_{18}NO_4$ requires 336.1230, found at 336.1232 [MH+] (ESI$^+$).

Quinolin-8-yl 6-oxo-3,4-dihydro-1H-[a]pyrrolizine-2-carboxylate 211

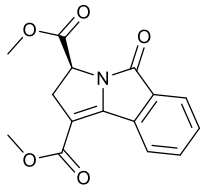


211

211 was synthesised according to general procedure **F** using **209** (0.100 g, 0.21 mmol) to afford the desired product as a pale orange coloured solid (0.091 g, quantitative yield).

Mp= +240 °C. **ν_{max} (KBr) cm^{-1}** 2983 (C-H), 1703 (N-C=O), 1641 (C=O), 1558, 1472 (C-H), 1404, 1340, 1308, 1216, 1136, 1097 (C-O), 1068, 936, 857, 760, 693. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.55 (d, *J* = 5.0 Hz, 1H, ArH), 8.86 (d, *J* = 8.3 Hz, 1H, ArH), 8.43 (d, *J* = 7.7 Hz, 1H, ArH), 8.07 (dd, *J* = 8.2, 1.3 Hz, 1H, ArH), 7.99 – 7.91 (m, 2H, ArH), 7.87 (t, *J* = 7.9, 1.1 Hz, 2H, ArH), 7.58 (dtd, *J* = 20.0, 7.5, 1.2 Hz, 2H, ArH), 4.10 (t, *J* = 8.0 Hz, 2H, C(4)*H*), 3.77 (t, *J* = 8.3 Hz, 2H, C(3)*H*). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 164.66 (C(1)COOAr), 162.84 (C(6)C=O), 152.89 (C(1b)Ar**C**), 147.10 (ArC), 144.66 (C(13)C=**C**), 142.71 (ArC), 135.90 (C(12)ArC), 134.13 (ArC), 132.57 (ArC), 132.11 (ArC), 130.24 (ArC), 129.74 (ArC), 129.25 (C(7)ArC), 127.15 (ArC), 127.04 (ArC), 126.65 (ArC), 123.78 (ArC), 122.42 (ArC), 109.04 (C(2)**C**=C), 40.52 (C(4)), 33.76 (C(3)). ***m/z*** not seen. **HRMS** calculated for $C_{21}H_{15}N_2O_3$ requires 343.1077, found at 343.1077 [MH+] (ESI^+).

1,4a-Dimethyl (4*S*)-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 187L



187L

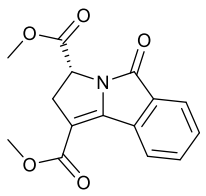
Method 1) **187L** was synthesised according to general procedure **E** using **127L** (0.095 g, 0.31 mmol) using 3.0 eq TBDMSiOTf with the crude oil purified using flash column chromatography

(45% ethyl acetate in pet-ether 40:60) to afford the desired product as a yellow coloured solid (0.040 g, 45%).

Method 2) **187L** was synthesised according to general procedure **F** from a mixture of **175La/b** with the crude mixture purified using flash column chromatography (30% ethyl acetate in DCM) to afford the desired product as a yellow coloured solid (0.127 g, 61%).

$[\alpha]_D^{25}$= -12.9 (*c* 1.0 in DCM). **R_f**= 0.39 (30% ethylacetate in DCM). **Mp**= 122-124 °C. **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 1751 (C=O), 1693 (C=O), 1649 (N-C=O), 1586, 1471, 1436, 1396, 1337, 1307, 1212 (C-O), 1185 (C-O), 1149, 1120, 1038. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.54 – 8.47 (m, 1H, Ar-H), 7.85 (ddd, *J* = 7.3, 1.4, 0.7 Hz, 1H, Ar-H), 7.69 – 7.57 (m, 2H, Ar-H), 4.88 (dd, *J* = 11.0, 4.3 Hz, 1H, C(4)*H*), 3.86 (s, 3H, C(1)OMe), 3.79 (s, 3H, C(4a)OMe), 3.72 (m, 1H, C(3)H_A), 3.37 (dd, *J* = 17.6, 4.3 Hz, 1H, C(3)H_B). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.15 (C(1)COOMe), 164.45 (C(4a)COOMe), 163.44 (C(6)C=O), 148.96 (C(13)C=**C**), 135.79 (C(12)ArC, 132.63 (ArC), 131.80 (ArC), 129.59 (C(7)ArC, 126.94 (ArC), 123.93 (ArC), 107.46 C(2)**C**=C), 53.55 (C(1)OMe), 53.09 (C(4a)OMe), 51.96 (C(4)), 39.67 (C(3)). ***m/z***= 310 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{15}H_{14}NO_5$ requires 288.0866, found at 288.0867 [MH+] (ESI$^+$).

1,4a-Dimethyl (4*R*)-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 187D



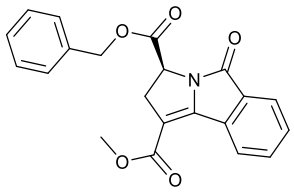
187D

Method 1) **187D** was synthesised according to general procedure **E 127D** (0.190 g, 0.62 mmol) using 3.0 eq TBDMSiOTf with the crude oil purified using flash column chromatography (45% ethyl acetate in pet-ether 40:60) to afford the desired product as a yellow coloured solid (0.085 g, 47%).

Method 2) **187D** was synthesised according to general procedure **F** from a mixture of **175Da/b** with the crude mixture purified using flash column chromatography (30% ethyl acetate in DCM) to afford the desired product as a yellow coloured solid (0.115 g, 43%).

$[\alpha]_D^{25}$= +69.9 (*c* 1.0 in MeOH). **R_f**= 0.32 (30% ethyl acetate in DCM). **ν_{max} (KBr) cm^{-1}** 2952 (C-H), 1694 (N-C=O), 1650, (C=O), 1472, 1437, 1398, 1338, 1307, 1218 (C-O), 1150, 1121. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.51 (dt, *J* = 7.6, 0.9 Hz, 1H, Ar-H), 7.85 (ddd, *J* = 7.3, 1.4, 0.8 Hz, 1H, Ar-H), 7.64 (dtd, *J* = 20.4, 7.5, 1.3 Hz, 2H, Ar-H), 4.89 (dd, *J* = 11.0, 4.3 Hz, 1H, C(4)*H*), 3.87 (s, 3H, (C(1)OMe), 3.79 (s, 3H, C(4a)OMe), 3.78 – 3.68 (m, 1H, C(3)H_A), 3.38 (dd, *J* = 17.6, 4.3 Hz, 1H, C(3)H_B). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.12 (C(1)COOMe), 164.43 (C(4a)COOMe), 163.59 (C(6)C=O), 148.92 (C(13)C=**C**), 135.79 (C(12)ArC), 132.68 (ArC), 131.82 (ArC), 129.60(C(7)ArC), 126.98 (ArC), 123.97 (ArC), 107.69 (C(2)**C**=C), 53.62 (C(4)), 53.08 (C(1)OMe), 51.96 (C(4a)OMe), 39.70 (C(3)). ***m/z***= 310 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{15}H_{13}NaNO_5$ requires 310.0685, found at 310.0687 [MNa+] (ESI$^+$).

4-Benzyl 2-methyl (*S*)-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 188



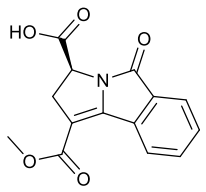
188

188 was synthesised according to general procedure **F** using **142** (0.150 g, 0.30 mmol) to afford the desired product as a yellow-coloured oil (0.110 g, quantitative yield).

$[\alpha]_D^{25}$= -63.0 (*c* 1.0 in DCM). **ν_{max} (KBr) cm^{-1}** 1697 (N-C=O), 1651 (C=O), 1471, 1438, 1397, 1337, 1307, 1242, 1189 (C-O), 1122 (C-O). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.52 (dt, *J* = 7.7, 1.0 Hz, 1H, ArH), 7.88 (dt, *J* = 7.3, 1.1 Hz, 1H, ArH), 7.74 – 7.60 (m, 3H, ArH), 7.38 – 7.32 (m, 4H, ArH), 5.23 (q, *J* = 12.2 Hz, 2H, C(4b)Ar-C**H_2**-O), 4.94 (dd, *J* = 11.0, 4.3 Hz, 1H, C(4)*H*), 3.87 (s, 3H, C(1)OMe), 3.77 – 3.69 (m, 1H, C(3)H_A), 3.36 (dd, *J* = 17.6, 4.3 Hz, 1H, C(3)H_B). **^{13}C**

NMR (126 MHz, Chloroform-*d*) δ 168.77 (C(4a)COOMe), 164.46 (C(1)COOMe), 163.76 (C(6)C=O), 148.95 (C(13)C=**C**), 135.78 (ArC), 135.04 (ArC), 134.05 (ArC), 132.76 (ArC), 131.89 (ArC), 128.80 (ArC), 128.70 (ArC), 128.67 (ArC), 127.02 (ArC), 124.04 (ArC), 123.38 (ArC), 107.78 (C(2)**C**=C), 67.98 (C(4b)Ar-**C**H_2-O), 53.75 (C(1)OMe), 52.02 (C(4)), 39.64 (C(3)). ***m/z***= 368 [MNa+] (ESI^+). **HRMS** calculated for $C_{21}H_{18}NO_5$ requires 364.1179, found at 364.1179 [MH+] (ESI^+).

(*S*)-2-(Methoxycarbonyl)-6-oxo-3,6-dihydro-1H-benzo[a]pyrrolizine-4-carboxylic acid 226

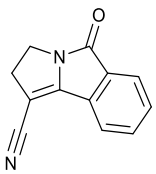


226

226 was synthesised according to general procedure **F** using **220** (0.723 g, 1.78 mmol) to afford the desired product as a yellow coloured solid (0.471 g, 96%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (dt, *J* = 7.6, 1.0 Hz, 1H, ArH), 7.85 – 7.78 (m, 2H, ArH), 7.74 (td, *J* = 7.5, 1.2 Hz, 1H, ArH), 4.86 (dd, *J* = 10.9, 4.0 Hz, 1H, C(4)*H*), 3.82 (s, 3H, C(1)OMe), 3.79 – 3.67 (m, 1H,C(4)*H*), 3.20 (dd, *J* = 17.5, 4.0 Hz, 1H, (C(H)*H*). **^{13}C NMR** (101 MHz, DMSO) δ 170.96 (C(1)COOMe), 163.90 (C(4a)COOH), 162.33 (C(6)C=O), 147.89 (C(13)C=**C**), 135.28 (C(12)ArC), 132.86 (ArC), 132.12 (ArC), 128.85 (C(7)ArC), 126.35 (ArC), 123.42 (ArC), 107.77 (C(2)**C**=C), 53.33 (C(4)), 51.83 (C(1)OMe), 39.52 (C(3)). ***m/z***= 272 [MH-] (ESI^-).

6-Oxo-3,4H-dihydro-1H-benzo[a]pyrrolizine-2-carbonitrile 189

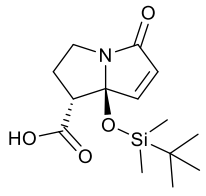


189

189 was synthesised according to general procedure **F** from **183** (0.068 g, 0.20 mmol) to afford the desired product as pale yellow solid (0.059 g). Note that ^{1}H NMR spectrum showed incomplete conversion from the mixture of starting materials to the desired product, hence a yield was not possibly to calculate. Due to the limited amount of material recovered, purification was not attempted.

ν_{max} (KBr) cm^{-1} 2955 (C-H), 2929 (C-H), 2857 (C-H), 2221 (C≡N), 1773 (N-C=O), 1712 (N-C=O), 1654, 1468, 1436, 1397, 1368, 1348, 1254, 1172, 1146, 1117, 1088, 999, 910, 838, 781, 717, 691. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.98 – 7.93 (m, 1H, ArH), 7.86 – 7.81 (m, 1H, ArH), 7.71 (dd, *J* = 5.4, 3.1 Hz, 1H, ArH), 7.65 (ddd, *J* = 7.6, 5.5, 1.4 Hz, 1H, ArH), 4.02 (t, *J* = 8.9 Hz, 2H, C(4)*H*), 3.38 (t, *J* = 9.0 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.10 (C(6)C=O), 153.08 (C(13)C=**C**), 135.75 (C(12)ArC), 132.49 (ArC), 132.22 (ArC), 128.24 (C(7)ArC), 124.05 (ArC), 123.44 (ArC), 115.53 (C-**C**≡N), 85.29 (C(2)NC-**C**=C), 40.70 (C(4)), 35.22 (C(3)). ***m/z*** not seen. **HRMS** calculated for $C_{12}C_9N_2O$ requires 197.0709, found at 197.0715 [MH+] (ESI^{+}).

(1*R*,8*S*)-9-((tert-Butyldimethylsilyl)oxy)-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2-carboxylic acid 78a



78a

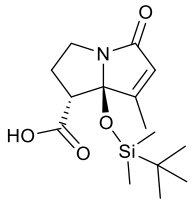
Compound **77a** (0.06 g, 0.19 mmol) was dissolved in a solution of THF in water (3:1, 5 mL) followed by the addition of LiOH (0.013g, 0.577 mmol) in one portion with the reaction mixture left stirring at room temperature for 16 hours. The reaction mixture was acidified using 0.5 N HCl to pH ~3, that caused the product to precipitate out of solution. The mixture was transferred to a separating funnel and extracted using ethyl acetate (2 x 25 mL) with the combined organic layers

being dried over $MgSO_4$ and concentrated by reduced pressure to afford the desired product as an off white coloured solid (0.032 g, 56%).

ν_{max} (KBr) cm^{-1} 2987 (C-H), 2863 (C-H), 1736 (N-C=O), 1680 (C=O), 1340 (C-O), 1296, 1209 (Si-O), 1191 (Si-CH_3), 1093 (Si-C(CH_3)), 1037, 1004, 866, 836, 816, 786, 709, 687. **^{1}H NMR** (200 MHz, Chloroform-*d*) δ 7.01 (d, *J* = 5.8 Hz, 1H, C(8)*H*), 6.00 (d, *J* = 5.8 Hz, 1H, C(7)*H*), 3.87 – 3.66 (m, 1H, C(4)H_A, 3.40 – 3.01 (m, 2H, C(4)H_B, C(2)*H*), 2.77 – 2.51 (m, 2H, C(3)*H*), 0.88 (s, 9H, C(CH_3)$_3$), 0.06 (d, *J* = 9.1 Hz, 6H, Si-CH_3). ***m/z***= 296 [MH-] (ESI$^-$), 298 [MH+] (ESI$^+$) and 320 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{14}H_{24}NO_4Si$ requires 298.1469, found at 298.1470 [MH+] (ESI$^+$).

All data are in agreement with those found in the literature.[156]

(1*R*, 9*S*)-9-[(tert-Butyldimethylsilyl)oxy]-7-methyl-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2-carboxylic acid 78c



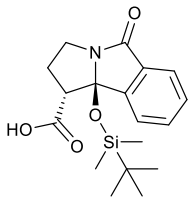
78c

Compound **77c** (0.347 g, 1.06 mmol) dissolved in a solution of THF in water (3:1, 5 mL) followed by the addition of NaOH (0.084 g, 2.12 mmol mmol) in one portion with the reaction mixture left stirring at room temperature for 16 hours. The reaction mixture was acidified using 0.5 N HCl to pH ~3, that caused the product to precipitate out of solution. The mixture was transferred to a separating funnel and extracted using ethyl acetate (2 x 10 mL) with the combined organic layers being dried over $MgSO_4$ and concentrated by reduced pressure to afford the desired product as an off-white coloured solid (0.336 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 2929 (O-H), 1716 (C=O),1698 (N-C=O), 1361, 1250 (C-O), 1216 (Si-O), 1086 (Si-C(CH_3)), 937, 836, 779, 674. **^{1}H NMR** (500 MHz, Methanol-d_4) δ 6.75 (q, *J* = 1.7 Hz, 1H, C(7)*H*), 3.68 (dt, *J* = 10.6, 8.9 Hz, 1H, C(4)H_A), 3.26 (ddd, *J* = 11.0, 9.3, 2.3 Hz, 1H, C(4)H_B),

3.01 (dd, *J* = 6.8, 1.1 Hz, 1H, (C(2)*H*), 2.60 (dtd, *J* = 13.2, 9.3, 6.8 Hz, 1H, C(3)H_A), 2.51 – 2.44 (m, 1H, C(3)H_B), 1.79 (d, *J* = 1.7 Hz, 3H, C(8a)C=C-C**H**$_3$), 0.90 (s, 9H, Si-C(CH_3)$_3$), 0.07 (s, 3H, Si-CH_3), 0.04 (s, 3H, Si-CH_3). **^{13}C NMR** (126 MHz, MeOD) δ 176.46 (C(6)C=O), 174.59 (C(1)COOH), 142.67 (C(7)C=**C**-H), 137.59 (C(8)C=**C**-CH_3), 100.47 (C(12a)), 53.73 C(2)), 42.97 (C(4)), 32.07 (C(3)), 25.98 (Si-C(**C**H)$_3$), 18.69 (Si-**C**(CH_3)$_3$, 10.59 (C(8a)C=C-**C**H_3), -3.19 (Si-CH_3), -3.80 (Si-CH_3). ***m/z***= 310 [MH-] (ESI^-) and 334 [MNa+] (ESI^+).

(1*R*,13*R*)-13-[(tert-Butyldimethylsilyl)oxy]-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylic acid 212



212

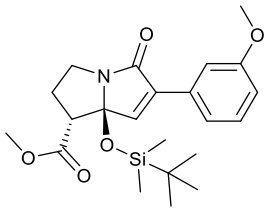
Method 1) Compound **144a** (0.330 g, 0.91 mmol) dissolved in a solution of THF in water (3:1, 5 mL) followed by the addition of NaOH (0.073 g, 1.82 mmol) in one portion with the reaction mixture left stirring at room temperature for 16 hours. The reaction mixture was acidified using 0.5 N HCl to pH ~3, that caused the product to precipitate out of solution. The mixture was transferred to a separating funnel and extracted using ethyl acetate (2 x 10 mL) with the combined organic layers being dried over $MgSO_4$ and concentrated by reduced pressure to afford the desired product as an off-white coloured solid (0.317 g, quantitative yield).

Method 2) In an oven-dried round bottomed flask that had been purged with N_2 compound **174** (0.418 g, 0.96 mmol) was added followed by a catalytic quantity of 10% Pd/C and suspended in ethanol (15 mL), with DCM being added dropwise to encourage solubility of the starting material. The flask was sealed and purged using N_2 (3x) and charged with H_2 (2x). The reaction was then fitted with two balloons pressurised with H_2 with the reaction was left stirring at room temperature for 16 hours. The reaction flask was then degassed and purged using N_2. The solvent was then

filtered through a pad of Kieselguhr under pressure. The pad of Kieselguhr was then washed using methanol (15 mL) with the combined organic solvents being concentration by reduced pressure to afford the desired product as white coloured solid (0.334 g, quantitative yield).

Mp= 186-188 °C. **ν_{max} (KBr) cm^{-1}** 2924 (O-H), 1736 (C=O), 1666 (N-C=O), 1469 (C=C), 1376, 1332, 1251 (Si-CH_3), 1218 (Si-CH_3), 1190 (Si-C(CH_3), 1143, 1114 (Si-O), 1084 (C-O), 914, 839, 781 (C=C-H), 755, 725, 694. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.70 – 7.59 (m, 3H, ArH), 7.58 – 7.52 (m, 1H, ArH), 3.90 (ddd, *J* = 11.0, 9.4, 8.5 Hz, 1H, C(4)H_A), 3.45 (ddd, *J* = 11.2, 9.5, 2.0 Hz, 1H, C(4)H_B), 3.27 (d, *J* = 6.8 Hz, 1H, C(2)*H*), 2.89 – 2.72 (m, 1H, C(3)H_A), 2.59 – 2.50 (m, 1H, C(3)H_B), 0.87 (d, *J* = 8.5 Hz, 9H, C(CH_3)), -0.04 (d, *J* = 1.3 Hz, 3H, Si-CH_3), -0.46 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 174.90 (C(6)C=O), 172.71 (C(1)COOH), 146.18 (C(12)ArC), 134.21 (C(7)ArC), 133.86 (ArC), 131.34 (ArC), 125.20 (ArC), 123.98 (ArC), 100.71 (C(13)), 53.94 (C(2)), 43.09 (C(4)), 32.42 (C(3)), 26.00 (C(**C**H_3)$_3$, 18.70 (Si-**C**(CH_3)$_3$), -4.01 (Si-CH_3), -4.13 (Si-CH_3). ***m/z***= 370 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{18}H_{25}NaNO_4Si$ requires 370.1445, found at 370.1447 [MNa+] (ESI$^+$).

Methyl (2*R*,9*S*)-9-((tert-Butyldimethylsilyl)oxy)-7-(3-methoxyphenyl)-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2-carboxylate 202a



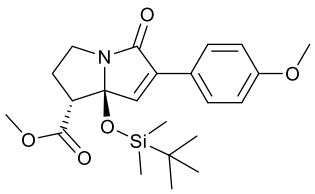
202a

In an oven dried round bottomed flask that had been purged with N_2, Compound **77d** (0.150 g, 0.38 mmol), 3-Methoxybenzeneboronic acid (0.174 g, 1.15 mmol), $Pd(OAc)_2$ (0.004 g, (0.019 mmol), XPhos (0.027 g, 0.057 mmol) and Na_2CO_2 (0.254 g, 2.39 mmol) were suspended in DME (10 mL). The flask was then purged using N_2 and sealed with a rubber septum with the reaction mixture left stirring at 85 °C for 24 hours. The reaction mixture was allowed to cool to room

temperature and filtered through a pad of Kieselguhr under pressure. The pad of Kieselguhr was then washed using ethyl acetate with the organic layer concentrated by reduced pressure. The resulting crude material was purified using flash column chromatography (gradient from 10-20% ethyl acetate in pet-ether 40:60) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as a pale yellow coloured solid (0.092 g, 58%).

R_f= 0.42. **Mp**= 85-87 °C. **ν_{max} (KBr) cm^{-1}** 2954 (C-H), 2929 (C-H), 2899 (C-H), 2857 (C-H), 1739 (N-C=O), 1712 (C-O), 1600, 1578, 1489 (C-H), 1467 (C-H), 1434 (C-H), 1360, 1335, 1285 (C-O), 1254 (Si-CH_3), 1215 (Si-CH_3), 1195, 1176, 1158, 1127 (Si-O), 1088, 1070, 1051, 1043, 1007. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.36 (dt, *J* = 2.7, 0.8 Hz, 1H, ArH), 7.33 – 7.29 (m, 2H, ArH), 7.26 (s, 1H, C(8)*H*), 6.98 – 6.93 (m, 1H, ArH), 3.84 – 3.75 (m, 4H, ArC-OC**H$_3$** and C(4)H_A), 3.52 (s, 3H, C(1)OMe), 3.38 – 3.32 (m, 1H, C(4)H_B), 3.18 (dt, *J* = 6.6, 0.9 Hz, 1H, C(2)*H*), 2.67 (dtd, *J* = 13.2, 9.3, 6.8 Hz, 1H, C(3)H_A), 2.53 (dddd, *J* = 13.2, 8.6, 2.2, 1.1 Hz, 1H, C(3)H_B), 0.91 (s, 9H, C(CH_3)$_3$), 0.10 (s, 3H, Si-CH_3), 0.05 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 174.18 (C(1)COOMe), 173.05 (C(6)C=O), 161.22 (Ar**C**-OMe), 141.57 (C(8)C=**C**-H), 138.44 (C(7)C=**C**-Ar), 132.85 (C(7a)C=C-**C**Ar), 130.72 (ArC), 120.76 (ArC), 116.05,(ArC) 113.93 (ArC), 99.61 (C(9)), 55.74 (C(1)OMe), 54.04 (C(2)), 52.39 (ArC-O**C**H_3), 43.20 (C(4)), 31.73 (C(3)), 26.00 (C(**C**H_3)$_3$), 18.73 (**C**(CH_3)$_3$), -3.04 (Si-CH_3), -3.73 (Si-CH_3). ***m/z***= 418 [MH-] (ESI^-) and 440 [MNa+] (ESI^+). **HRMS** calculated for $C_{22}H_{32}NO_5Si$ requires 418.2044, found at 418.2040 [MH-] (ESI^-).

Methyl (2*R*,9*S*)-9-((tert-butyldimethylsilyl)oxy)-7-(4-methoxyphenyl)-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2-carboxylate 202b

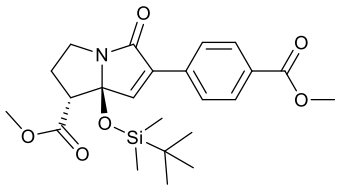


202b

In an oven dried round bottomed flask that had been purged with N_2, Compound **77d** (0.150 g, 0.38 mmol), 4-Methoxybenzeneboronic acid (0.174 g, 1.15 mmol), $Pd(OAc)_2$ (0.004 g, (0.019 mmol), XPhos (0.027 g, 0.057 mmol) and Na_2CO_2 (0.254 g, 2.39 mmol) were suspended in DME (10 mL). The flask was then purged using N_2 and sealed with a rubber septum with the reaction mixture left stirring at 85 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and filtered through a pad of Kieselguhr under pressure. The pad of Kieselguhr was then washed using ethyl acetate with the organic layer concentrated by reduced pressure. The resulting crude material was purified using flash column chromatography (gradient from 10-20% ethyl acetate in pet-ether 40:60) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as a yellow coloured solid (0.109 g, 68%).

R_f= 0.35 (20% ethyl acetate in pet-ether 40:60). **Mp**= 84-86 °C. **ν_{max} (KBr) cm^{-1}** 2955 (C-H), 2928 (C-H), 2900 (C-H), 2856 (C-H), 1738 (C=O), 1709 (N-C=O), 1606, 1575, 1488 (C-H), 1467 (C-H), 1434 (C-H), 1359, 1334, 1281 (C-O), 1251 (Si-CH_3), 1215 (Si-CH_3), 1195, 1176, 1158, 1127 (Si-O), 1088, 1070, 1051, 1043, 1007. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.77 – 7.73 (m, 2H, ArH), 7.11 (s, 1H, C(8)*H*), 6.98 – 6.93 (m, 2H, ArH), 3.85 – 3.74 (m, 4H, ArC-OC**H_3** and C(4)H_A), 3.51 (s, 3H, C(1)OMe), 3.37 – 3.32 (m, 1H, (C(4)H_B), 3.19 – 3.15 (m, 1H, C(2)*H*), 2.67 (dtd, *J* = 13.2, 9.3, 6.8 Hz, 1H, (C(3)H_A), 2.52 (dddd, *J* = 13.2, 8.5, 2.3, 1.1 Hz, 1H, C(3)H_B), 0.91 (s, 9H, C(CH_3)$_3$), 0.09 (s, 3H, Si-CH_3), 0.04 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, MeOD) δ 174.60 (C(1)COOMe), 173.12 (C(6)C=O), 162.16 (Ar**C**-OMe), 138.87 (C(8)C=**C**-H), 138.11 (C(7)C=**C**-Ar), 129.89 (ArC), 124.09 (C(7a)C=C-**C**Ar), 115.06 (ArC), 99.68 (C(9)), 55.77 (ArC-O**C**H_3), 54.09 (C(2)), 52.35 (C(1)OMe), 43.15 (C94)), 31.73 (C(3)), 26.00 (C(**C**H_3)$_3$), 18.73 (**C**(CH_3)$_3$), -3.05 (Si-CH_3), -3.73 (Si-CH_3). ***m/z***= 418 [MH-] (ESI$^-$) and 440 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{22}H_{32}NO_5Si$ requires 418.2044, found at 418.2037 [MH-] (ESI$^-$).

Methyl (2*R*,9*S*)-9-((tert-butyldimethylsilyl)oxy)-7-(4-(methoxycarbonyl)phenyl)-6-oxo-3,4,6,9-tetrahydro-1H-pyrrolizine-2-carboxylate 202c



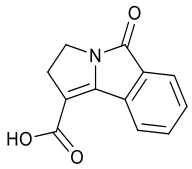
202c

In an oven dried round bottomed flask that had been purged with N_2, Compound **77d** (0.150 g, 0.38 mmol), 4-Methoxycarbonylphenylboronic acid (0.174 g, 1.15 mmol), $Pd(OAc)_2$ (0.004 g, (0.019 mmol), XPhos (0.027 g, 0.057 mmol) and Na_2CO_2 (0.254 g, 2.39 mmol) were suspended in DME (10 mL). The flask was then purged using N_2 and sealed with a rubber septum with the reaction mixture left stirring at 85 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and filtered through a pad of Kieselguhr under pressure. The pad of Kieselguhr was then washed using ethyl acetate with the organic layer concentrated by reduced pressure. The resulting crude material was purified using flash column chromatography (gradient from 10-20% ethyl acetate in pet-ether 40:60) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as a pale yellow coloured solid (0.054 g, 32%).

R_f= 0.44. **Mp**= 134-136 °C. **ν_{max} (KBr) cm^{-1}** 3067, 2953 (C-H), 2928 (C-H), 2857 (C-H), 1733 (C=O), 1719 (C=O), 1698 (N-C=O), 1608, 1436 (C-H), 1413 (C-H), 1364, 1338, 1284 (C-O), 1252 (Si-CH_3), 1206 (Si-CH_3), 1166, 1134 (C-O), 1090, 1053, 1021, 1006. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.04 (dd, *J* = 8.4, 2.0 Hz, 2H, ArH), 7.83 (dq, *J* = 8.5, 2.0 Hz, 2H, ArH), 7.11 (s, 1H, C(8)*H*), 3.91 (s, 3H, ArC-COOMe), 3.89 – 3.82 (m, 1H, (C(4)H_A), 3.50 (s, 3H, (C(1)OMe), 3.35 (ddd, *J* = 11.2, 9.2, 2.4 Hz, 1H, (C(4)H_B), 3.18 (dd, *J* = 6.7, 1.3 Hz, 1H, (C(2)*H*), 2.64 (dtd, *J* = 13.2, 9.2, 6.8 Hz, 1H, (C(3)H_A), 2.51 (dddd, *J* = 13.2, 8.5, 2.4, 1.3 Hz, 1H, C(3)H_B), 0.86 (s, 9H, $C(CH_3)_3$), 0.07 (s, 3H, Si-CH_3), -0.00 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.83 (C(1)COOMe), 171.48 (C(6)C=O), 166.77 (ArC-**C**OOMe), 141.11 (C(8)C=**C**-H), 136.70

(C(7a)C=C-**C**Ar), 134.78 (C(7)C=**C**-ArC), 130.72 (ArC), 129.95 (ArC), 127.47 (ArC), 98.16 (C(9)), 53.26 (C(2)), 52.35 (ArC-COOMe), 52.07 (C(1)OMe), 42.45 (C(4)), 30.84 (C(3)), 25.57 (C(**C**H_3)$_3$), 17.95 (**C**(CH_3)$_3$), -3.17 (Si-CH_3), -3.91 (Si-CH_3). ***m/z***= 446 [MH+] (ESI^+) and 468 [MNa+] (ESI^+). **HRMS** calculated for $C_{23}H_{32}NO_6Si$ requires 446.1993, found at 446.1988 [MH+] (ESI^+).

5-Oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxylic acid 160a



160a

Method 1) Compound **146a** (0.100 g, 0.43 mmol) was suspended in water (5 mL) with NaOH (0.035g, 0.86 mmol) being added in one portion. The reaction mixture was then left stirring for 16 hours at room temperature. The reaction mixture was then acidified to pH ~3 using 0.5 N HCl with a small quantity of precipitate forming. The aqueous layer was then extracted using a mixture of IPA in chloroform (1:3) (3 x 10 mL) with the combined organic layers combined and concentrated to afford the desired product as a pale yellow coloured solid (0.103 g, quantitative yield).

Method 2) Compound **212** (0.334 g, 0.96 mmol) was dissolved in a solution of TFA/H_2O (9:1, 1 mL) with methanol added to help solubility and left stirring at room temperature for 1 hour, in which the reaction mixture turned yellow. The stirrer bar was removed and washed using water (2 mL) resulting in the mixture to turn cloudy. The solvent was removed to afford the desired product as a yellow coloured solid (0.222 g, quantitative yield).

Mp= 234-236 °C (Lit. 229-231 °C).[163] **ν_{max} (KBr) cm^{-1}** 2917 (C-H), 2550, 1724 (C=O), 1646 (N-C=O), 1621 (C=O), 1585, 1496 (O-H), 1472, 1444, 1393, 1337, 1312, 1267, 1220, 1179, 1156 (C-O), 1120, 921, 858, 772, 752, 743, 688, 670. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.91 (s, 1H, C(1)COO-H), 8.46 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.80 – 7.70 (m, 2H, Ar-H), 7.66 (t, *J* = 7.4 Hz, 1H, Ar-H), 3.85 (t, *J* = 8.2 Hz, 2H, C(4)*H*), 3.23 (t, *J* = 8.2 Hz, 2H, C(3)*H*). **^{13}C NMR** (126 MHz,

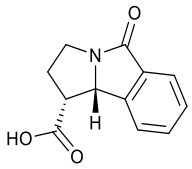
DMSO) δ 165.58 (C(1)COOH), 162.48 (C6)C=O), 147.23 (C(13)C=**C**), 135.73 (C(12)ArC), 132.12 (ArC), 131.42 (ArC), 129.14 (C(7)ArC), 126.23 (ArC), 122.86 (ArC), 111.60 (C(2)**C**=C), 34.01 (C(3)). Note that C4 resides somewhere around 39.95ppm but is hidden under DMSO, confirmed *via* HSQC NMR data. ***m/z***= 427 [2MH+] (ESI^+). **HRMS** calculated for $C_{12}H_8NO_3$ requires 214.0510, found at 214.0509 [MH-] (ESI^-).

All data are in agreement with those found in the literature.[163]

General Procedure G for hydrogenation

In an oven-dried round bottomed flask that had been purged with N_2, compound was added followed by a catalytic quantity of 10% Pd/C and suspended in ethanol (15 mL), with DCM being added dropwise to encourage solubility of the starting material. The flask was sealed and purged using N_2 (3x) and charged with H_2 (2x). The reaction was then fitted with two balloons pressurised with H_2 with the reaction was left stirring at room temperature for 16 hours. The reaction flask was then degassed and purged using N_2. The solvent was then filtered through a pad of Kieselguhr under pressure. The pad of Kieselguhr was then washed using methanol (15 mL) with the combined organic solvents being concentration by reduced pressure to afford the desired product.

(2*R*,13*S*)-6-Oxo-3,4,6,12-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylic acid 217



217

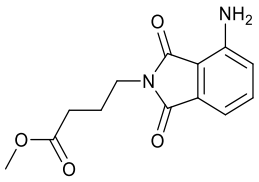
Method 1) Compound **196a** (0.051 g, 0.22 mmol) was suspended in water (5 mL) with NaOH (0.017g, 0.44 mmol) being added in one portion. The reaction mixture was then left stirring for 16 hours at room temperature. The reaction mixture was then acidified to pH ~3 using 0.5 N HCl with a small quantity of precipitate forming. The aqueous layer was then extracted using ethyl acetate

(3 x 5 mL) with the combined organic layers being combined and concentrated by reduced pressure to afford the desired product as a white coloured solid (0.032 g, 72%).

Method 2) **217** was synthesised according to general procedure **G** using **160a** (0.500 g, 2.18 mmol) to afford the desired product as white coloured solid (0.481 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 2898 (C-H), 1721 (C=O), 1644 (C-N=O), 1614 (C=O), 1469 (O-H), 1401, 1334, 1303, 1271, 1224, 1184 (C-O), 1116, 1097. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.68 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.59 (d, 2H, Ar-H), 7.49 (dt, *J* = 8.1, 4.1 Hz, 1H, Ar-H), 5.14 (d, *J* = 6.7 Hz, 1H, C(13)*H*), 3.87 (dt, *J* = 11.2, 8.7 Hz, 1H, C(4)H_A), 3.45 (ddd, *J* = 11.4, 8.1, 3.9 Hz, 1H, C(4)H_B), 3.37 (td, *J* = 6.3, 2.3 Hz, 1H, C(2)*H*), 2.63 – 2.56 (m, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, MeOD) δ 174.79 (C(1)COOH), 173.61 (C(6)C=O), 144.75 (C(12)ArC), 135.60 (C(7)ArC), 132.96 (ArC), 129.85 (ArC), 125.16 (ArC), 124.25 (ArC), 67.95 (C(13)), 42.47 (C(2)), 42.44 (C(4)), 33.52 (C(3)). ***m/z***= 435 [2MNa+] (ESI$^+$). **HRMS** calculated $C_{12}H_{12}NO_3$ requires 218.0812, found at 218.0810 [MH+] (ESI$^+$).

Methyl 1-(8-amino-6,13-dioxoisoindolin-4-yl)butanoate 199



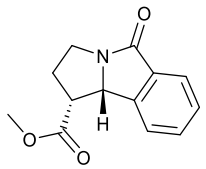
199

199 was synthesised according to general procedure **G** using **137b** (0.250 g, 0.43 mmol) to afford the desired product as a yellow-coloured oil (0.228 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 3474 (-NH_2), 3367 (-NH_2), 2951 (C-H), 1732 (C=O), 1689 (N-C=O), 1631 (-NH_2), 1595, 1482 (C-H), 1438 (C-H), 1409, 1362, 1330, 1273, 1183 (C-O), 1116 (C-N), 1027. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.37 (dd, *J* = 8.3, 7.1 Hz, 1H, ArH), 7.14 – 7.07 (m, 1H, ArH), 6.83 (d, *J* = 8.0 Hz, 1H, ArH), 3.74 – 3.62 (m, 5H, C(4)*H* and OMe), 2.36 (t, *J* = 7.5 Hz, 2H, C(2)*H*), 1.98 (p, *J* = 7.1 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.28 (C(1)COOMe),

170.25 (C(13)C=O), 168.71 (C(6)C=O), 145.37 (C(8)Ar**C**-NH_2), 135.24 (C(10)ArC), 132.83 (C(12)ArC), 121.15 (C(9)ArC), 112.76 (C(11)ArC), 111.31 (C(7)ArC), 51.76 (C(1)OMe), 36.83 (C(4)), 31.44 (C(2)), 24.09 (C(3)). ***m/z***= 285 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{14}NaN_2O_4$ requires 285.0845, found at 285.0841 [MNa+] (ESI^+).

Methyl (1*R*,13*S*)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 196a

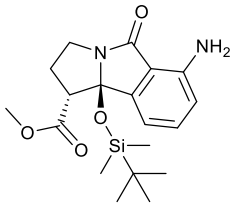


196a

196a was synthesised according to general procedure **G** using **146a** (2.36 g, 10.29 mmol) to afford the desired product as a white coloured solid (2.62 g, quantitative yield).

Mp= 116-118 °C. **ν_{max} (KBr) cm^{-1}** 2950 (C-H), 1729 (C=O), 1686 (N-C=O), 1615, 1468 (C=C), 1435, 1378, 1332, 1302, 1219, 1194, 1168, 1096 (C-O), 1067, 1040. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.75 (dt, *J* = 7.5, 1.1 Hz, 1H, ArH), 7.50 (td, *J* = 7.4, 1.2 Hz, 1H, ArH), 7.47 – 7.38 (m, 2H, ArH), 4.97 (d, *J* = 6.9 Hz, 1H, C(12a)*H*), 3.98 (dt, *J* = 11.2, 8.5 Hz, 1H, C(4)H_A), 3.44 (dtd, *J*=17.4, 9.0, 2.5 Hz, 1H, (C(4)H_B), 3.34 (td, *J* = 7.0, 1.6 Hz, 1H, C(2)*H*), 3.14 (s, 3H, C(1)OMe), 2.60 (dddd, *J* = 13.2, 8.4, 3.0, 1.6 Hz, 1H, C(3)H_A), 2.49 (dddd, *J* = 13.5, 9.4, 8.6, 7.0 Hz, 1H, C(3)H_B). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.63 (C(1)COOMe), 171.60 (C(6)C=O), 142.57 (C(12)ArC), 134.51 (C(7)ArC), 131.53 (ArC), 128.96 (ArC), 123.87 (ArC), 123.55 (ArC), 66.31 (C(13)), 51.45 (C(1)OMe), 44.56 (C(4)), 41.79 (C(2)), 32.35 (C(3)). ***m/z***= 232 [MH+] (ESI^+) and 254 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{14}NO_3$ requires 232.0968, found at 232.0966 [MH+] (ESI^+).

Methyl (2*R*,13*R*)-8-amino-13-[(tert-butyldimethylsilyl)oxy]-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 200

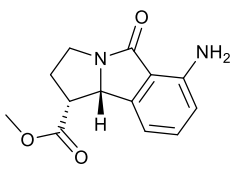


200

200 was synthesised according to general procedure **G** using **144b** (0.287 g, 0.70 mmol) to afford the desired product as a pale-yellow coloured oil (0.276 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 2981 (C-H), 1736 (C=O), 1698 (N-C=O), 1625, 1319 (Ar-NH_2), 1072. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.20 (dt, *J* = 8.2, 6.2 Hz, 1H, Ar-H), 6.72 (dd, *J* = 7.3, 0.7 Hz, 1H, Ar-H), 6.56 (dd, *J* = 8.1, 0.7 Hz, 1H, Ar-H), 5.12 (s, 1H, -NH_2) 3.90 (dt, *J* = 11.0, 8.8 Hz, 1H, C(4)H_A), 3.35 (ddt, 1H, C(4)H_B), 3.27 – 3.15 (m, 4H, C(2)*H*, C(1)OMe), 2.64 (dtd, *J* = 13.1, 9.2, 7.0 Hz, 1H, C(3)H_A), 2.49 – 2.39 (m, 1H, C(3)H_B), 0.82 (s, 9H, Si-C(CH_3)$_3$), -0.07 (d, *J* = 2.9 Hz, 3H, Si-CH_3), -0.41 (d, *J* = 10.5 Hz, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.58 (C(6)C=O), 172.01 (C(1)COOMe), 145.38 (C(8)Ar**C**-NH_2), 133.59 (ArC), 115.80 (ArC), 114.42 (ArC), 112.12 (ArC), 99.24 (C(13)), 53.19 (C(2)), 51.53 (C(1)OMe), 42.05 (C(4)), 30.90 (C(3)), 25.61 (Si-C(**C**H_3)$_3$), 17.89 (Si-**C**(CH_3)$_3$), -4.20 (Si-CH_3), -4.35 (Si-CH_3). ***m/z***= 399 [MNa+] (ESI$^+$) and 415 [MK+] (ESI$^+$). **HRMS** not found.

Methyl (2*R*,13*S*)-8-amino-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 196b

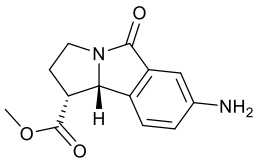


196b

196b was synthesised according to general procedure **G** using **146b** (0.100 g, 0.36 mmol) to afford the desired product as a pale yellow coloured solid (0.097 g, quantitative yield).

Mp= 153-155 °C. **ν_{max} (KBr) cm^{-1}** 3464 (N-H), 3362 (N-H), 1730 (C=O), 1672 (N-C=O), 1621 (N-H), 1482 (C-H), 1436 (C-H), 1389, 1322, 1220 (N-C), 1200, 1169 (C-O), 1053. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.21 (dd, *J* = 8.1, 7.4 Hz, 1H, Ar-H), 6.66 (dd, *J* = 7.4, 0.9 Hz, 1H, Ar-H), 6.55 (dd, *J* = 8.2, 0.8 Hz, 1H, Ar-H), 4.90 (d, *J* = 7.2 Hz, 1H, C(12a)*H*), 3.95 (dd, *J* = 11.2, 8.4 Hz, 1H, C(4)H_A), 3.37 (ddd, *J* = 11.2, 9.5, 3.2 Hz, 1H, C(4)H_B), 3.29 (dt, *J* = 7.0, 1.9 Hz, 1H, C(2)*H*), 3.25 (s, 3H, C(1)OMe), 2.55 (dddd, *J* = 13.5, 8.4, 3.2, 1.9 Hz, 1H, C(3)H_B), 2.44 (dddd, *J* = 13.5, 9.3, 8.4, 7.0 Hz, 1H, C(3)H_B). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.12 (C(6)C=O), 173.87 (C(1)COOMe), 145.93 (C(8)Ar**C**-NH_2), 143.84 (C(12)ArC), 133.04 (ArC), 116.60 (C(7)ArC), 114.54 (ArC), 111.97 (ArC), 66.33 (C(13)), 51.53 (C(1)OMe), 44.68 (C(2)), 41.79 (C(4)), 32.21 (C(3)). ***m/z***= 247 [MH+] (ESI^+). **HRMS** calculated for $C_{13}H_{15}N_2O_3$ requires 247.1077, found at 247.1075 [MH+] (ESI^+).

Methyl (2*R*,13*S*)-9-amino-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 196c



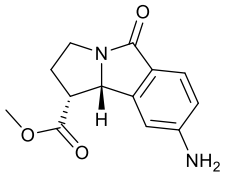
196c

196c was synthesised according to general procedure **G** using **186a** (0.109 g, 0.39 mmol) to afford the desired product as a pale yellow coloured solid (0.104 g, quantitative yield).

ν_{max} (KBr) cm^{-1} 3344 (N-H), 3025 (C-H), 2948 (C-H), 1729 (C=O), 1676 (N-C=O), 1624 (N-H), 1503, 1436, 1381, 1341, 1284, 1223 (N-C), 1195 (C-O), 1169, 1066. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.17 (dd, *J* = 8.1, 2.7 Hz, 1H, ArH), 6.94 (d, *J* = 2.3 Hz, 1H, ArH), 6.74 (dd, *J* = 8.2, 2.3 Hz, 1H, ArH), 4.87 (d, *J* = 6.9 Hz, 1H, C(13)*H*), 3.94 (dtd, *J* = 11.4, 8.5, 2.7 Hz, 1H, C(4)H_A), 3.39 (ddd, *J* = 11.6, 9.3, 2.9 Hz, 1H, C(4)H_B), 3.25 (td, *J* = 6.9, 1.5 Hz, 1H, C(2)*H*), 3.20

(s, 3H, C(1)OMe), 2.56 (dddd, *J* = 13.1, 8.5, 3.0, 1.6 Hz, 1H, C(3)H_A), 2.50 – 2.38 (m, 1H, (C(3)H_B). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.25 (C(1)COOMe), 171.94 (C(6)C=O), 149.00 (C(9)Ar**C**-NH_2), 135.63 (C(12)ArC), 131.15 (C(7)ArC), 124.05 (ArC), 117.43 (ArC), 106.12 (ArC), 66.03 (C(13)), 51.48 (C(1)OMe), 44.68 (C(2)), 41.69 (C(4)), 32.21 (C(3)). ***m/z***=247 [MH+] (ESI^+). **HRMS** calculated for $C_{13}H_{15}N_2O_3$ requires 247.1077, found at 247.1075 [MH+] (ESI^+).

Methyl (2*R*,13*S*)-10-amino-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 196d

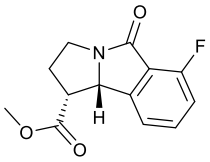


196d

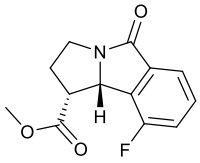
196d was synthesised according to general procedure **G** using **186b** (0.045 g, 0.16 mmol) to afford the desired product as a pale yellow coloured solid (0.062 g, quantitative yield). NMR shows impurity from other regioisomer, persisting from prior reactions and purifications.

ν_{max} (KBr) cm^{-1} 3346 (N-H), 3230 (C-H), 2952 (C-H), 2895, (C-H) 1728 (C=O), 1670 (N-C=O), 1609 (C=O), 1497, 1475, 1436, 1382, 1277, 1223 (N-C), 1199 (C-O), 1171, 1117, 1067, 1038. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 8.2 Hz, 1H, ArH), 6.69 – 6.62 (m, 2H, ArH), 4.85 (d, *J* = 7.0 Hz, 1H, C(13)*H*), 3.94 (dt, *J* = 11.0, 8.4 Hz, 1H(C(4)H_A), 3.38 (ddd, *J* = 11.6, 9.3, 3.0 Hz, 1H (C(4)H_B), 3.30 – 3.23 (m, 4H, C(2)*H* and C(1)OMe), 2.55 (ddt, *J* = 13.2, 8.3, 2.6 Hz, 1H, C(3)H_A), 2.44 (dtd, *J* = 13.5, 8.9, 7.1 Hz, 1H, C(3)H_B). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.44 (C(1)COOMe), 171.84 (C(6)C=O), 150.23 (C(10)Ar**C**-NH_2), 145.18 (C(12)ArC), 125.25 (ArC), 124.39 (C(7)ArC), 115.49 (ArC), 108.62 (ArC), 65.97 (C(4)), 51.56 (C(1)OMe), 44.86 (C(2)), 41.96 (C(4)), 32.27 (C(3)). ***m/z***= 247 [MH+] (ESI^+) and 269 [MH+] (ESI^+). **HRMS** calculated for $C_{13}H_{15}N_2O_3$ requires 247.1077, found at 247.1075 [MH+] (ESI^+).

Methyl (2*R*,13*S*)-8-fluoro-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 196e and **Methyl (2*R*,13*S*)-11-fluoro-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 196f**



196e



196f

196e and 196f were synthesised according to general procedure **G** using a mixture of **146f** and **185** (0.250 g, 1.01 mmol) with the products separated by flash column chromatography (25% ethyl acetate in pet-ether 40:60) to afford the desired products as yellow-coloured solids.

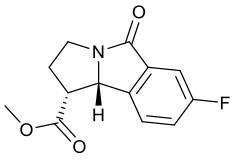
196e) 0.125 g. $\mathbf{R_f}$= 0.16. **Mp**= 143-145 °C. $\boldsymbol{\nu_{max}}$ **(KBr) cm^{-1}** 2980 (C-H), 1730 (C=O), 1694 (N-C=O), 1626 (C=O), 1592, 1479 (C-H), 1437, 1382, 1332, 1250, 1220, 1197 (C-O), 1170, 1045, 660 (Ar-F). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.48 (ddd, *J* = 8.4, 7.6, 4.7 Hz, 1H, ArH), 7.20 (d, *J* = 7.5 Hz, 1H, ArH), 7.07 (t, *J* = 17.6, 8.8 Hz, 1H, ArH), 4.97 (d, *J* = 6.9 Hz, 1H, C(13)*H*), 3.98 (dt, *J* = 11.3, 8.5 Hz, 1H, (C(4)H_A), 3.41 (ddd, *J* = 11.9, 9.3, 3.0 Hz, 1H, C(4)H_B), 3.34 (td, *J* = 7.0, 1.6 Hz, 1H, C(2)*H*), 3.23 (s, 3H, C(1)OMe), 2.59 (dddd, *J* = 13.2, 8.5, 3.0, 1.6 Hz, 1H, C(3)H_A), 2.54 – 2.45 (m, 1H, C(3)H_B). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.50 (C(1)COOMe), 168.40 (d, *J* = 2.3 Hz, C(6)C=O), 158.50 (d, *J* = 260.7 Hz, C(8)Ar**C**-F), 145.30 (d, *J* = 3.2 Hz, C(12)ArC), 133.64 (d, *J* = 7.5 Hz, C(10)ArC), 121.65 (d, *J* = 13.5 Hz, C(7)ArC), 119.60 (d, *J* = 4.1 Hz, C(11)ArC), 116.37 (d, *J* = 19.5 Hz, C(9)ArC) , 66.00 (C(13)), 51.66 (C(1)OMe), 44.59 (C(2)), 41.98 (C(4)), 32.37 (C(3)). ***m/z***= 248 [MH-] (ESI$^-$). **HRMS** calculated for $C_{13}H_{13}FNO_3$ requires 250.0874, found at 250.0875 [MH+] (ESI$^+$).

196f) 0.035 g. $\mathbf{R_f}$= 0.20. **Mp**= 144-146 °C. $\boldsymbol{\nu_{max}}$ **(KBr) cm^{-1}** 2953 (C-H), 1731 (C=O), 1698 (N-C=O), 1595, 1484, 1437 (C-H) (C-O), 1383, 1332, 1271, 1250, 1216, 1172, 1035, 756 (ArC-F). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.56 (dt, *J* = 7.5, 0.8 Hz, 1H, ArH), 7.45 (dddd, *J* = 8.1, 7.4, 4.6, 0.6 Hz, 1H, ArH), 7.20 (ddd, *J* = 8.8, 8.2, 0.8 Hz, 1H, ArH), 5.04 (d, *J* = 6.4 Hz, 1H, C(13)*H*),

4.00 – 3.91 (m, 1H, C(4)H_A), 3.48 – 3.44 (m, 1H, C(4)H_B), 3.44 – 3.40 (m, 1H, (C(2)*H*), 3.20 (s, 3H, C(1)OMe), 2.64 (dddd, *J* = 13.6, 8.4, 2.4, 1.1 Hz, 1H, (C(3)H_A), 2.53 (dtd, *J* = 13.6, 9.3, 6.8 Hz, 1H, C(3)H_B). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.30 (C(1)COOMe), 170.27 (d, *J* = 2.4 Hz, C(6)C=O), 157.84 (d, *J* = 251.5 Hz, C(11)Ar**C**-F), 137.43 (d, *J* =4.4 Hz, C(7)ArC), 131.40 (d, *J* = 6.5 Hz, C(9)ArC), 128.68 (d, *J* = 18.3 Hz, C(12)ArC), 119.90 (d, *J* = 3.6 Hz, C(8)ArC), 118.42 (d, *J* = 19.6 Hz, C(10)ArC), 63.87 (C(13)), 51.68 (C(1)OMe), 44.09 (C(2)), 41.65 (C(4)), 32.39 (C(3)). ***m/z***= 248 [MH-] (ESI^-). **HRMS** calculated for $C_{13}H_{13}FNO_3$ requires 250.0874, found at 250.0874 [MH+] (ESI^+).

Structure confirmed *via* x-ray analysis; see 7273 (Appendix I).

Methyl (2*R*,13*S*)-9-fluoro-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 196g



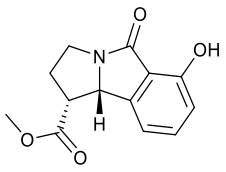
196g

196g was synthesised according to general procedure **G** using **186e** (0.317 g, 1.28 mmol) to afford the desired product as a white coloured solid (0.331 g, quantitative yield).

Mp= 139-141 °C. **ν_{max} (KBr) cm^{-1}** 3067 (C-H), 2952 (C-H), 2897 (C-H), 1729 (C=O), 1690 (N-C=O), 1620, 1602, 1484, 1439, 1380, 1333, 1267, 1244, 1219, 1196 (C-O), 1169, 1129, 1096, 1065, 1040, 971, 957, 788 (ArC-F). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.45 – 7.36 (m, 2H, ArH), 7.20 (ddd, *J* = 9.0, 8.3, 2.5 Hz, 1H, ArH), 4.95 (d, *J* = 6.9 Hz, 1H, C(13)*H*), 3.97 (dt, *J* = 11.4, 8.5 Hz, 1H, C(4)H_A), 3.44 (dddd, *J* = 11.3, 9.4, 2.9, 0.7 Hz, 1H, C(4)H_B), 3.33 (td, *J* = 6.9, 1.6 Hz, 1H, C(2)*H*), 3.19 (s, 3H, (C(1)OMe), 2.61 (dddd, *J* = 13.0, 8.4, 2.9, 1.5 Hz, 1H, C(3)H_A), 2.50 (dddd, *J* = 13.6, 9.4, 8.6, 6.9 Hz, 1H, C(3)H_B). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.47, 170.28, 163.34 (d, *J* = 248.5 Hz, C(9)Ar**C**-F), 138.00 (d, *J* = 3.0 Hz, C(12)ArC), 136.81 (d, *J* = 8.0 Hz, C(7)ArC), 125.09 (d, *J* = 8.6 Hz, C(11)ArC), 119.00 (d, *J* = 23.8 Hz, C(8)ArC), 110.74 (d, *J* =

23.5 Hz, C(10)ArC), 65.90 (C(13)), 51.58 (C(1)OMe), 44.49 (C(2)), 41.89 (C(4)), 32.36 (C(3)). ***m/z***= 248 [MH-] (ESI^-). **HRMS** calculated for $C_{13}H_{13}FNO_3$ requires 250.0874, found at 250.0872 [MH+] (ESI^+).

Methyl (2*R*,13*S*)-8-hydroxy-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 196i

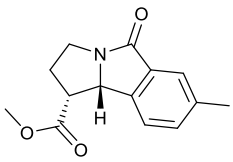


196i

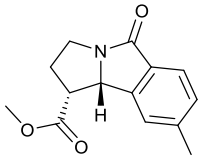
196i was synthesised according to general procedure **G** using **146j** (0.400 g, 1.19 mmol) to afford the desired product as an off-white coloured solid (0.252 g, 86%).

ν_{max} (KBr) cm^{-1} 3384 (O-H), 2895 (C-H), 1731 (C=O), 1672 (N-C=O), 1465 (C-H), 1399 (O-H), 1295, 1200 (C-O), 1170, 1051 (C-O). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.37 (dd, *J* = 8.3, 7.4 Hz, 1H, ArH), 6.91 (dt, *J* = 7.4, 0.8 Hz, 1H, ArH), 6.85 (d, *J* = 8.2 Hz, 1H, ArH), 4.98 (d, *J* = 6.9 Hz, 1H, C(13)*H*), 3.93 (dt, *J* = 11.1, 8.5 Hz, 1H, C(4)H_A), 3.40 (dtd, *J*= 17.9, 8.9, 2.9 Hz, 1H, C(4)H_B), 3.32 (td, *J* = 6.9, 1.6 Hz, 1H, C(2)*H*), 3.23 (s, 3H, C(1)OMe), 2.60 (dddd, *J* = 13.2, 8.4, 3.0, 1.6 Hz, 1H, C(3)H_A), 2.49 (dddd, *J* = 13.6, 9.4, 8.6, 6.9 Hz, 1H, C(3)H_B). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.27 (C(1)COOMe), 171.61 (C(6)C=O), 155.56 (C(8)Ar**C**-OH), 142.88 (C(12)ArC), 134.01 (C(10)ArC), 118.57 (C(7)ArC), 115.60 (C(11)ArC), 115.04 (C(9)ArC), 67.08 (C(13)), 51.59 (C(1)OMe), 44.23 (C(2)), 41.34 (C(4)), 32.46 (C(3)). ***m/z***= 246 [MH-] (ESI^-), 248 [MH+] (ESI^+) and 270 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{14}NO_4$ requires 248.0917, found at 248.0916 [MH+] (ESI^+).

Methyl (2*R*,13S)-9-methyl-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 196j and **Methyl (2*R*,13S)-10-methyl-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 196k**



196j



196k

196j and **196k** were synthesised according to general procedure **G** using a mixture of **186i** and **186j** (0.300 g, 1.35 mmol) to afford the desired products as an inseparable white coloured solid (0.318 g, 95%).

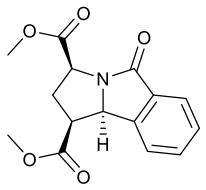
ν_{max} (KBr) cm^{-1} 2952 (C-H), 1769 (C=O), 1731 (C=O), 1683 (N-C=O), 1620, 1435, 1379, 1330, 1286, 1222 (C-O), 1193 (C-O), 1169, 1136, 1067, 1039. ***m/z***= 246 [MH+] (ESI$^+$) and 268 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{14}H_{16}NO_3$ requires 246.1125, found at 246.1125 [MH+] (ESI$^+$).

186j) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.56 (q, *J* = 1.0 Hz, 1H, ArH), 7.30 (d, *J* = 1.2 Hz, 1H, ArH), 7.26 – 7.20 (m, 1H, ArH), 4.93 (dd, *J* = 6.9, 4.4 Hz, 1H, C(13)*H*), 4.01 – 3.91 (m, 1H, C(4)H_A), 3.45 – 3.38 (m, 1H, (C(4)H_B), 3.31 (td, *J* = 7.0, 1.6 Hz, 1H, (C(2)*H*), 3.17 (d, *J* = 2.0 Hz, 3H, (C(1)OMe), 2.58 (dddd, *J* = 13.2, 8.4, 3.0, 1.6 Hz, 1H, C(3)H_A), 2.53 – 2.44 (m, 1H, C(3)H_B), 2.39 (d, *J* = 0.7 Hz, 3H, ArC-C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.82 (C(6)C=O), 171.73 (C(1)COOMe), 142.27 (C(12)ArC), 139.08 (Ar**C**-CH_3), 134.62 (C(7)ArC), 132.54 (ArC), 124.15 (ArC), 123.23 (ArC), 66.17 (C(13)), 51.48 (C(1)OMe), 44.55 (C(2)), 41.77 (C(4)), 32.36 (C(3)), 21.49 (ArC-**C**H_3).

186k) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.66 – 7.61 (m, 1H, ArH), 7.30 (d, *J* = 1.2 Hz, 1H, ArH), 7.26 – 7.20 (m, 1H, ArH), 4.93 (dd, *J* = 6.9, 4.4 Hz, 1H, C(13)*H*), 4.01 – 3.91 (m, 1H, (C(4)H_A), 3.45 – 3.38 (m, 1H, C(C4)H_B), 3.31 (td, *J* = 7.0, 1.6 Hz, 1H, (C(2)*H*), 3.17 (d, *J* = 2.0 Hz, 3H, (C(1)OMe), 2.58 (dddd, *J* = 13.2, 8.4, 3.0, 1.6 Hz, 1H, C(3)H_A), 2.53 – 2.44 (m, 1H, C(3)H_B), 2.42 (s, 3H, ArC-C**H**$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.88 (C(6)C=O), 171.67

(C(1)COOMe), 142.99 (C(12)ArC), 139.77 (Ar**C**-CH_3), 131.92 (C(7)ArC), 129.95 (ArC), 124.01 (ArC), 123.66 (ArC), 66.17 (C(13)), 51.46 (C(1)OMe), 44.63 (C(2)), 41.79 (C(4)), 32.36 (C(3)), 21.96 (ArC-**C**H_3).

Dimethyl (1*S*,4a*S*,13*R*)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 198L

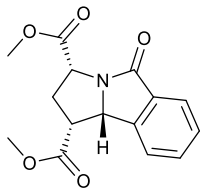


198L

198L was synthesised according to general procedure **G** using **187L** using (0.104 g, 0.36 mmol) to afford the desired product as a yellow-coloured solid (0.063 g, 63%).

Mp= 106-108 °C. **ν_{max} (KBr) cm^{-1}** 2952 (C-H), 1738 (C=O), 1692 (N-C=O), 1616 (C=O), 1435, 1392, 1365, 1328, 1288, 1206 (C-O), 1172 (C-O), 1096, 1059. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 7.6, 1.1 Hz, 1H, Ar-H), 7.54 (td, *J* = 7.5, 1.3 Hz, 1H, Ar-H), 7.47 – 7.41 (m, 2H, Ar-H), 5.03 (d, *J* = 7.2 Hz, 1H, C(4)*H*), 4.40 (dd, *J* = 9.0, 3.2 Hz, 1H (C(13)*H*), 3.76 (s, 3H, C(1)OMe), 3.42 (td, *J* = 7.6, 2.2 Hz, 1H, C(2)*H*), 3.35 (s, 3H C(4a)OMe), 3.01 (ddd, *J* = 14.0, 3.2, 2.2 Hz, 1H, C(3)H_A), 2.83 (ddd, *J* = 13.9, 9.0, 7.8 Hz, 1H, C(3)H_B). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.40 (C(1)COOMe), 169.92 (C(4a)COOMe), 168.32 (C(6)C=O), 143.35 (C(12)ArC), 134.47 (C(7)ArC), 131.67 (ArC), 128.40 (ArC), 124.20 (ArC), 123.50 (ArC), 66.09 (C(4)), 55.11 (C(2)), 52.60 (C(1)OMe), 51.83 (C(4a)OMe), 43.21 (C(2)), 37.19 (C(3)). ***m/z***= 290 [MH+] (ESI^+) and 312 [MNa+] (ESI^+). **HRMS** calculated for $C_{15}H_{16}NO_5$ requires 290.1023, found at 290.1021 [MH+] (ESI^+).

Dimethyl (1*R*,4a*R*,13*S*)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2,4-dicarboxylate 198D

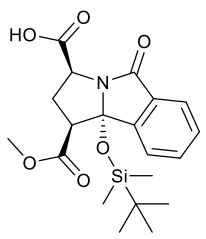


187D

198D was synthesised according to general procedure **G** using **187D** using (0.080 g, 0.27 mmol) to afford the desired product as a pale-yellow coloured solid (0.083 g, quantitative yield).

Mp= 104-106 °C. **ν_{max} (KBr) cm^{-1}** 2953 (C-H), 1742 (N-C=O), 1692 (C=O), 1435, 1391, 1211 (C-O), 1060. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (dt, *J* = 7.6, 1.1 Hz, 1H, Ar-H), 7.58 – 7.49 (m, 1H, Ar-H), 7.48 – 7.39 (m, 2H, Ar-H), 5.03 (d, *J* = 7.4 Hz, 1H, C(13)*H*), 4.40 (dd, *J* = 4.8, 3.5 Hz, 1H, C(4)*H*), 3.75 (s, 3H, C(1)OMe), 3.42 (td, *J* = 7.5, 2.2 Hz, 1H, C(2)*H*), 3.35 (s, 3H, C(4a)OMe), 3.00 (ddd, *J* = 14.0, 3.3, 2.2 Hz, 1H, C(3)H_A), 2.84 (ddd, *J* = 14.0, 9.0, 7.8 Hz, 1H, C(3)H_B). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.41 (C(1)COOMe), 169.92 (C(4a)COOMe, 168.36 (C(6)C=O), 143.35 (C(12)ArC), 134.47 (C(7)ArC), 131.70 (ArC), 128.41 (ArC), 124.21 (ArC), 123.51 (ArC), 66.15 (C(4)), 55.11 (C(2)), 52.60 (C(1)OMe), 51.83 (C(4a)OMe), 43.21 (C(2)), 37.21 (C(3)). ***m/z***= 310 [MNa+] (ESI^+). **HRMS** calculated for $C_{15}H_{15}NaNO_5$ requires 310.0685, found at 310.0687 [MNa+] (ESI^+).

(2*S*,4*S*,13*S*)-13-((tert-Butyldimethylsilyl)oxy)-2-(methoxycarbonyl)-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-4-carboxylic acid 200

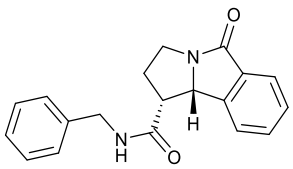


200

200 was synthesised according to general procedure **G** using **188** (0.885 g, 1.78 mmol) to afford the desired product a colourless oil (0.803 g, quantitative yield). Note that residual EtOH still remains and could not be removed on a standard roto-evaporator.

$[\alpha]_D^{25}$= +10.2 (*c* 1.0 in MeOH). **ν_{max} (KBr) cm^{-1}** 2953 (C-H), 2930 (C-H), 2895 (C-H), 2857 (C-H), 1723 (C=O), 1613 (N-C=O), 1468 (C-H), 1445 (C-H), 1361, 1252 (Si-CH_3), 1213 (Si-CH_3), 1152 (Si-C(CH_3)), 1110 (Si-O), 1076 (C-O), 1057, 1007. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.75 (dt, *J* = 7.5, 1.0 Hz, 1H, ArH), 7.60 (td, *J* = 7.5, 1.2 Hz, 1H, ArH), 7.57 – 7.47 (m, 2H, ArH), 4.57 (d, *J* = 9.9, Hz, 1H, C(13)*H*), 3.43 (dd, *J* = 7.3, 1.1 Hz, 1H, C(2)*H*), 3.31 (s, 3H, C(1)OMe), 3.18 (ddd, *J* = 14.0, 9.9, 7.3 Hz, 1H, C(3)H_A), 3.06 (ddd, *J* = 14.0, 3.1, 1.2 Hz, 1H, C(3)H_B), 0.83 (s, 9H, C(C**H**$_3$)$_3$), -0.10 (s, 3H, Si-CH_3), -0.52 (s, 3H, Si-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.38 (C(1)COOMe), 169.72 (C(4a)COOH), 167.78 (C(6)C=O), 142.97 (C(12)ArC), 133.01 (ArC), 132.61 (C(7)ArC), 130.76 (ArC), 124.36 (ArC), 123.71 (ArC), 100.56 (C(13)), 57.30 (C(4)), 52.46 (C(1)COOMe), 51.47 (C(2)), 36.44 (C(3)), 25.53 (C(**C**H$_3$)$_3$), 17.97 (**C**(CH$_3$)$_3$), -4.04 (Si-CH_3), -4.28 (Si-CH_3). ***m/z***= 403 [MH-] (ESI$^-$). **HRMS** calculated for $C_{20}H_{28}NO_6Si$ requires 406.1680, found at 406.1681 [MH+] (ESI$^+$).

(2*R*,13*S*)-*N*-Benzyl-6-oxo-2,3,5,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxamide 227



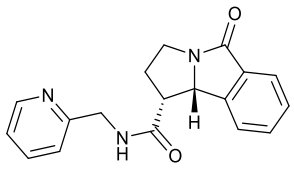
227

227 was synthesised according to general procedure **G** from **215a** (0.110 g, 0.36 mmol) to afford the desired product as an off white coloured solid (0.116 g, quantitative yield).

Mp= 184-186 °C. **ν_{max} (KBr) cm^{-1}** 3292 (N-H), 2951 (C-H), 1666 (N-C=O), 1547, 1496 (C-H), 1467 (C-H), 1454, 1387, 1333, 1303, 1275, 1237, 1155, 1081, 1027. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.61 – 7.55 (m, 1H, ArH), 7.41 – 7.28 (m, 3H, ArH), 7.19 – 7.02 (m, 4H, ArH), 6.73 – 6.64 (m, 2H, ArH), 4.93 (d, *J* = 6.5 Hz, 1H, C(13)*H*), 4.05 – 3.91 (m, 2H, C(1b)H_A and

C(4)H_A), 3.79 (dd, *J* = 14.9, 5.2 Hz, 1H, C(1b)H_B), 3.35 (ddd, *J* = 11.4, 9.4, 2.5 Hz, 1H, C(4)H_B), 3.23 (td, *J* = 6.6, 1.3 Hz, 1H, C(2)*H*), 2.55 – 2.34 (m, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.88 (C(1)N-C=O), 171.24 (C(6)C=O), 143.10 (C(12)ArC), 138.14 (ArC), 135.01 (C(7)ArC, 131.48 (ArC), 128.60 (ArC), 128.44 (ArC), 127.55 (ArC), 127.07 (ArC), 123.74 (ArC), 123.66 (ArC), 44.35 (C(2)), 42.98 (C(1b)Ar-**C**H_2-N), 42.16 (C(4)), 33.17 (C(3)). ***m/z***=307 [MH+] (ESI$^+$) and 329 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{19}H_{19}N_2O_2$ requires 307.1441, found at 307.1439 [MH+] (ESI$^+$).

(1*R*,13*S*)-6-Oxo-*N*-(pyridin-2-ylmethyl)-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxamide 218



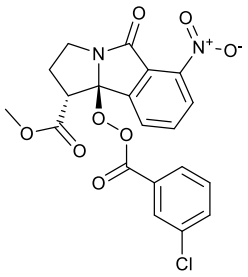
218

Method 1) In an oven dried flask that had been purged with N_2, compound **217** (0.100 g, 0.46 mmol) was suspended in $SOCl_2$ (0.33 mL, 4.60 mmol) with a few drops of anhydrous DCM to assist with solubility and left stirring under an inert atmosphere of N_2 at room temperature for 2 hours. The solvent was then removed and azeotroped with anhydrous DCM (3 x 5 mL) by reduced pressure. The oil was then redissolved in anhydrous DCM with the flask purged with N_2, followed by the addition of 2-picolylamine (0.095 mL, 0.92 mmol) added dropwise over 5 minutes. The resulting reaction mixture was then left stirring at room temperature for 16 hours. The crude mixture was diluted with DCM (10 mL) and washed using warm water (40 °C, 5 x 10 mL) with the organic layer purified using flash column chromatography (silica pre-doped using 2.0% TEA, with the solvent being using to run the column 2.0% TEA, 2.5% MeOH in DCM) with the desired fractions collected, combined and concentrated by reduced pressure to afford the desired product as a pale-yellow coloured oil (0.074 g, 52%).

Method 2) Compound **217** (0.100 g, 0.46 mmol) was suspended in DMF (3 mL) followed by the addition of EDC (0.10 mL, 0.55 mmol) and DIPEA (0.24 mL, 1.11 mmol) and left stirring for 1 hour at room temperature in which all the starting material had dissolved. HOBt (0.85 g, 0.55 mmol) was added followed by the addition of 2-picolylamine (0.056 mL, 0.55 mmol) with the resulting reaction mixture left stirring at room temperature for 16 hours. The crude mixture was diluted with DCM (10 mL) and washed using warm water (40 °C, 5 x 10 mL) with the organic layer purified using flash column chromatography (silica pre-doped using 2.0% TEA, with the solvent being using to run the column 2.0% TEA, 2.5% MeOH in DCM) with the desired fractions collected, combined and concentrated by reduced pressure to afford the desired product pale yellow coloured oil (0.083g, 58%).

R_f = 0.51 (2.0% TEA, 2.5% MeOH in DCM). **ν_{max} (KBr) cm^{-1}** 3292 (N-H), 3065 (C-H), 2894 (C-H), 1657 (N-C=O), 1591 (N-H), 1570, 1548, 1471 (C-H), 1436 (C-H), 1388, 1333, 1303, 1217 (N-C), 1148 (N-C), 1096, 1048, 995, 750, 697, 675. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.51 (dt, *J* = 4.9, 1.4 Hz, 1H, ArH), 7.81 – 7.73 (m, 1H, ArH), 7.69 (td, *J* = 7.7, 1.8 Hz, 1H, ArH), 7.50 – 7.41 (m, 3H, ArH), 7.30 (d, *J* = 7.8 Hz, 1H, ArH), 7.22 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H, ArH), 4.99 (d, *J* = 9.7 Hz, 1H, C(13)*H*), 4.70 (dd, *J* = 16.4, 5.0 Hz, 1H, C(1b)ArC-C**H**$_2$-N), 4.61 (dd, *J* = 16.4, 4.7 Hz, 1H, C(1b)ArC-C**H**$_2$-N), 3.77 (dt, *J* = 11.6, 8.7 Hz, 1H, C(4)H_A), 3.55 (ddd, *J* = 11.8, 9.5, 2.6 Hz, 1H, C(3)H_B), 2.72 (ddt, *J* = 12.9, 11.3, 9.3 Hz, 1H, C(3)H_A, 2.65 – 2.57 (m, 1H, C(3)H_B), 2.31 (ddd, *J* = 11.2, 9.7, 7.5 Hz, 1H, (C(2)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.46 (C(1)N-C=O), 170.93 (C(6)C=O), 155.77 (C(1c)CH_2-**C**Ar), 149.11 (ArC), 145.13 (C(12)ArC), 137.04 (ArC), 133.48 (C(7)ArC), 131.94 (ArC) 128.89 (ArC), 124.08 (ArC), 123.38 (ArC), 122.72 (ArC), 122.28 (ArC), 66.77 (C(13)), 49.25 (C(1b)ArC-**C**H_2-N), 44.58 (C(2)), 41.64 (C(4)), 33.86 (C(3)). ***m/z***= 306 [MH-] (ESI$^-$) and 308 [MH+] (ESI$^+$). **HRMS** calculated for $C_{18}H_{18}N_3O_2$ requires 308.1394, found at 308.1393 [MH+] (ESI$^+$).

Methyl (2*R*,13*R*)-13-(3-chlorobenzoylperoxy)-8-nitro-6-oxo-,3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 191



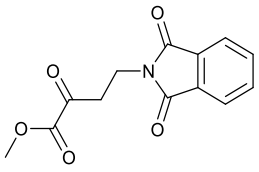
191

Compound **146b** (0.045 g, 0.16 mmol) was dissolved in DCM (10 mL) followed by the addition of *m*CPBA (0.034 g, 0.19 mmol) with the reaction mixture left stirring for 16 hours at room temperature. The crude mixture was transferred to a separating funnel and washed using water (2 x 10 mL) and back extracted using DCM (10 mL) with the combined organic layers washed using brine (20 mL). The organic solvent was concentrated by reduced pressure with the crude material was purified using flash column chromatography (40% ethyl acetate in pet-ether 60:60) with the desired fractions being collected, combined and concentrated by reduced pressure to afford the title product as a colourless oil (0.011 g, 15%).

R_f= 0.45. **ν_{max} (KBr) cm^{-1}** 2955 (C-H), 1776 (C=O), 1716 (N-C=O), 1541 (NO_2), 1438 (C-H), 1396, 1359, 1295 (C-O), 1254 (C-O), 1126 (O-O), 1088, 1073, 737 (Ar-Cl), 719 (Ar-Cl). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.06 (ddd, *J* = 15.2, 7.8, 0.9 Hz, 2H, Ar-H), 7.95 – 7.90 (m, 2H, Ar-H), 7.87 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.52 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H, PhtAr-H), 7.36 (t, *J* = 7.9 Hz, 1H, Phth-Ar-H), 5.32 (t, *J* = 6.8 Hz, 1H, C(2)*H*), 3.98 (td, *J* = 6.7, 1.9 Hz, 2H, C(4)*H*), 3.75 (s, 3H, C(1)OMe), 2.44 (q, *J* = 6.7 Hz, 2H, C(3)*H*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.56 (C(1)COOMe), 165.66 (C(14)C=O), 164.60 (C(13)), 162.80 (C(6)C=O), 145.16 (C(12)ArC), 135.62 (ArC), 134.70 (C(7)ArC), 134.06 (Ar**C**-NO_2), 133.61 (ArC), 130.87 (ArC), 129.95 (ArC), 129.86 (ArC), 128.81 (Phth Ar-C), 128.15 (Phth Ar-C), 127.22 (Phth Ar-C), 123.78 (Ar**C**-Cl), 70.98 (C(2)), 52.87 (C(1)OMe), 35.30 (C(4)), 29.59 (C(3)). ***m/z***= 916 [2MH+] (ESI^+). **HRMS**

calculated for $C_{20}H_{16}ClN_2O_8$ requires 447.0589 and 449.0560, found at 447.0589 and 449.0559 [MH+] (ESI^+).

Methyl 1-(6,13-dioxoisoindolin-4-yl)-2-oxobutanoate 192

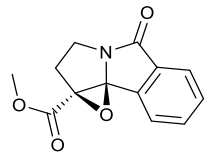


192

Compound **146a** (0.100 g, 0.43 mmol) was dissolved in DCM (3 mL) followed by the addition of *m*CPBA (0.09 g, 0.52 mmol) and left stirring at room temperature for 16 hours. The reaction mixture was diluted with DCM (5 mL) and washed using water (10 mL). The organic layer was concentrated by reduced pressure with the crude material purified using flash column chromatography (45% ethyl acetate in pet-ether) with the desired fractions collected, combined and concentrated by reduced pressure to afford the desired product as a colourless oil that solidified over 10 minutes (0.052 g, 46%). NMR showed the presence of residual *m*CPBA.

R_f= 0.39. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H, Ar-H), 7.72 (dd, 2H, Ar-H), 4.05 (t, *J* = 7.0 Hz, 2H, C(4)*H*), 3.88 (s, 3H, OMe), 3.25 (t, *J* = 6.9 Hz, 2H, (C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.25 (C(2)C=O), 169.81 (C(1)COOMe), 168.14 (C(6,13)C=O), 134.28 (ArC), 132.05 (C(7,12)ArC), 123.55 (ArC), 53.31 (OMe), 38.31 (C(3)), 32.79 (C(4)). ***m/z***=284 [MNa+] (ESI^+). **HRMS** calculated for $C_{13}H_{12}NaNO_5$ requires 262.0710, found at 262.0712 [MH+] (ESI^+).

Methyl (2*S*,13*S*)-6-oxo-3,4-dihydro-1H-12-oxa-1-azatricyclo-benzo[a]pyrrolizine-2-carboxylate 194



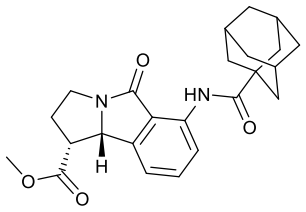
194

Compound **146a** (0.150 g, 0.65 mmol) was added to a round bottomed flask containing *m*CPBA (0.135 g, 0.78 mmol) and Ca_2CO_3 (0.083 g, 0.78 mmol) and dissolved in DCM (5 mL). The resulting mixture was then left stirring at room temperature for 16 hours. The reaction mixture was diluted with DCM (5 mL) and washed using water (2 x 10 mL) with the aqueous layers back extracted using DCM (10 mL). The organic layers were then combined and concentrated by reduced pressure with the crude material attempted to be dissolved in DCM with a white coloured solid insoluble. The DCM was removed and the solid was triturated with DCM (5 mL) with the solid being dried by reduced pressure to afford the desired product as a white coloured solid (0.048 g, 30%).

Mp= +240 °C. **ν_{max} (KBr) cm^{-1}** 2917 (C-H), 1738 (C=O), 1700 (N-C=O), 1608, 1464 (C-H), 1438, 1379, 1333, 1315, 1261 (C-O-C), 1241, 1219 (C-O), 1196, 1139, 1107, 1075, 884 (C-O-C), 758 (C-O-C). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.81 (dd, *J* = 7.7, 1.3 Hz, 1H, Ar-H), 7.63 (td, *J* = 7.6, 1.3 Hz, 1H, Ar-H), 7.51 (td, *J* = 7.5, 0.8 Hz, 1H, Ar-H), 4.35 (dd, *J* = 12.5, 9.1 Hz, 1H, C(4)H_A), 3.93 (td, *J* = 12.0, 6.1 Hz, 1H, C(4)H_B), 3.46 (s, 3H, OMe), 2.55 (dd, *J* = 14.3, 6.0 Hz, 1H, C(3)H_A), 2.24 (ddd, *J* = 14.2, 11.7, 9.2 Hz, 1H, C(3)H_B). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.95 (C(1)COOMe), 169.46 (C(6)C=O), 140.81 (C(12)ArC), 134.19 (C(7)ArC), 131.81 (ArC), 129.75 (ArC), 127.59 (ArC), 124.50 (ArC), 65.83 (C(2)), 52.46 (C(1)COOMe), 42.11 (C(4)), 35.57 (C(3)). ***m/z*** not seen. **HRMS** calculated for $C_{13}H_{12}NO_4$ requires 246.0764, found at 246.0761 [MH+] (ESI^+).

Note that the peak for C13 was not seen, it was assumed to be covered by the $CDCl_3$ peaks, but not confirmed.

Methyl (2*R*,13*R*)-8-(adamantane-1-amido)-13-[(tert-butyldimethylsilyl)oxy]-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 197



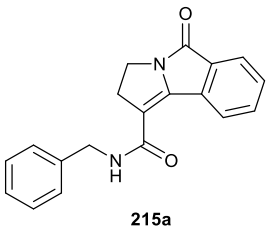
197

Compound **196b** (0.050 g, 0.20 mmol) and 1-adamantanecarbonyl chloride (0.048 g, 0.24 mmol) and dissolved in DCM (5 mL) followed by the addition of DIPEA (0.042 mL), 0.24 mmol) with the reaction mixture left stirring at room temperature for 16 hours. The crude mixture was transferred to a separating funnel and diluted with DCM (5 mL) and washed using water (2 x 10 mL) then back extracted using DCM (10 mL). The combined organic layers were combined and dried over $MgSO_4$ and concentrated by reduced pressure. The crude material was then purified using flash column chromatography (20-40% ethyl acetate in pet-ether 40:60) with the product containing fractions collected, combined and concentrated to afford the desired product as a pale-yellow coloured oil (0.023 g, 28%). Note that compound co-eluted with another by-product so yield was low.

ν_{max} (KBr) cm^{-1} 2904 (C-H), 2851 (C-H), 1734 (C=O), 1677 (N-C=O), 1621 (N-C=O), 1537 (N-H), 1478 (C-H), 1452 (C-H), 1435 (C-H), 1386, 1334, 1279, 1222 (C-O), 1198, 1169. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.51 (s, 1H, N(8a)*H*), 8.53 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.49 – 7.42 (t, *J*= 8.2 Hz, 1H, Ar-H), 7.06 (dt, *J* = 7.5, 0.8 Hz, 1H, Ar-H), 4.97 (d, *J* = 7.0 Hz, 1H, C(12a)*H*), 3.97 (dt, *J* = 11.1, 8.5 Hz, 1H, C(4)H_A), 3.44 (dddd, *J* = 11.1, 9.4, 2.8, 0.7 Hz, 1H, C(4)H_B), 3.35 (td, *J* = 6.8, 1.5 Hz, 1H, C(2)*H*), 3.24 (s, 3H, C(1)OMe), 2.63 (dddd, *J* = 13.6, 8.4, 2.8, 1.5 Hz, 1H, C(3)H_A), 2.57 – 2.45 (m, 1H, C(3)H_B), 2.02 (d, *J* = 3.1 Hz, 7H, C(Adamantane)*H*), 1.75 (t, *J* = 3.2 Hz, 7H, C(adamantane)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.70 (C(1)COOMe), 172.93 C(C6)C=O), 171.66 (C(8b)C=O), 142.54 C(12)ArC), 138.15 (C(8)Ar**C**-N), 133.46 (ArC), 119.91 (C(7)ArC), 118.86 (ArC), 117.59 (ArC), 66.45 (C(13)), 51.70 (C(1)OMe), 44.09 (C(2)), 42.16

(Adamantane C), 41.51 (C(4)), 39.16 (Adamantane C), 36.58 (Adamantane C), 32.40 (C(3)), 28.28 (Adamantane C). ***m/z***= 409 [MH+] (ESI^+). **HRMS** calculated for $C_{24}H_{29}N_2O_4$ requires 409.2121, found at 409.2118 [MH+] (ESI^+).

_N_-Benzyl-6-oxo-3,5-dihydro-1H-benzo[a]pyrrolizine-2-carboxamide 215a



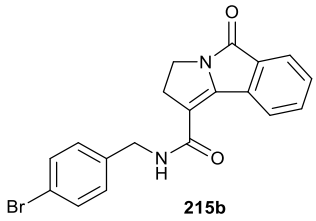
215a

Compound **160a** (0.125 g, 0.58 mmol) was suspended in DMF (3 mL) followed by the addition of EDC (0.10 mL, 0.69 mmol) and DIPEA (0.20 mL, 1.16 mmol) and left stirring for 1 hour at room temperature in which all the starting material had dissolved. HOBt (0.078 g, 0.69 mmol) was added followed by the addition of benzyl amine (0.08 mL, 0.69) with the resulting reaction mixture left stirring at room temperature for 16 hours. The crude mixture was diluted with DCM (10 mL) and washed using warm water (40 °C, 5 x 10 mL) with the organic layer purified using flash column chromatography (40% ethyl acetate in DCM) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as an off-white coloured solid (0.0.68 g, 35%).

R_f= 0.39. **Mp**= 201-203 °C. **ν_{max} (KBr) cm^{-1}** 3328 (N-H), 3060 (C-H), 2915 (C-H), 1690 (N-C=O), 1654 (C=O) 1625 (N-C=O), 1584, 1523, 1471, 1446, 1402, 1354, 1339, 1312, 1274 (N-C), 1226, 1182, 1165, 1147, 1080, 1028, 1012. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.76 (dt, *J* = 7.8, 1.0 Hz, 1H, ArH), 7.78 (td, 1H, ArH), 7.58 (dtd, 2H, ArH), 7.36 – 7.26 (m, 5H, ArH), 6.08 (t, *J* = 5.8 Hz, 1H, ArH), 4.60 (d, *J* = 5.8 Hz, 2H, C(1c)*H*), 3.95 (t, 2H, C(4)*H*), 3.28 (t, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.83 (C(1)N-C=O), 163.78 (C(6)N-C=O), 147.64 (C(13)C=**C**), 138.12 (ArC), 136.13 (C(12)ArC), 132.13 (ArC), 131.14 (ArC), 129.94 (C(7)ArC), 128.93 (ArC), 127.96 (ArC), 127.81 (ArC), 127.49 (ArC), 123.14 (ArC), 112.40 (C(2)**C**=C), 43.81 (C(1b)N-

CH_2-Ar), 39.91 (C(4)), 33.77 (C(3)). ***m/z***= 305 [MH+] (ESI^+) and [327] MNa+] (ESI^+). **HMRS** calculated for $C_{19}H_{17}N_2O_2$ requires 305.1285, found at 305.1285 [MH+] (ESI^+).

***N*-(4-Bromobenzyl)-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxamide 215b**



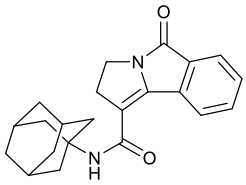
215b

Compound **160a** (0.098 g, 0.45 mmol) was suspended in DMF (3 mL) followed by the addition of EDC (0.097 mL, 0.54 mmol) and DIPEA (0.16 mL, 0.9 mmol) and left stirring for 1 hour at room temperature in which all the starting material had dissolved. HOBt (0.078 g, 0.69 mmol) was added followed by the addition of 4-bromobenzylamine (0.101 g, 0.54 mmol) with the resulting reaction mixture left stirring at room temperature for 16 hours. The crude mixture was diluted with DCM (10 mL) and washed using warm water (40 °C, 5 x 10 mL) with the organic layer purified using flash column chromatography (gradient from 50% ethyl acetate in pet-ether 40:60 to 100% ethyl acetate) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as a white coloured solid (0.068 g, 44%).

R_f= 0.37 (100% ethyl acetate). **Mp**= 208-210 °C. **ν_{max} (KBr) cm^{-1}** 3333 (N-H), 2914 (C-H), 1692 (N-C=O), 1655 (C=O), 1627 (C=O), 1524, 1487 (C-H), 1472 (C-H), 1445 (C-H), 1404, 1341, 1312, 1278 (N-C), 1226, 1183, 1165, 1147, 1071, 1012, 691 (ArC-Br). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.80 – 8.72 (m, 1H, ArH), 7.79 (d, *J* = 8.0, 1.4 Hz, 1H, ArH), 7.60 (dt, 2H, ArH), 7.45 (dd, *J* = 8.4, 2.5 Hz, 2H, ArH), 7.21 (dd, *J* = 8.4, 2.0 Hz, 2H, ArH), 6.04 (s, 1H, N(1a)*H*), 4.56 (d, *J* = 5.9, 1.7 Hz, 2H, C(1b)*H*), 3.97 (td, *J* = 8.5, 4.0 Hz, 2H, C(4)*H*), 3.30 (t, *J* = 9.0, 7.4 Hz, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.85 (C(6)C=O), 163.83 (C(1)N-C=O), 148.00 (C(13)C=**C**, 137.27 (C(12)ArC), 136.16 (ArC), 132.20 (ArC), 132.01 (ArC), 131.27 (ArC), 129.92 (C(7)ArC), 129.65 (ArC), 127.53 (ArC), 123.20 (ArC), 121.71 (Ar**C**-Br), 111.97 (C(2)**C**=C), 43.16 (C(1b)ArC-**C**H_2-, 39.95 (C(4)) 33.76 (C(3)). ***m/z***= 789 and 791 [2M+Na+]

(ESI$^+$). **HRMS** calculated for $C_{19}H_{16}BrN_2O_2$ calculated for 383.0390 and 385.0396, found at 383.0392 and 385.0370 [MH+] (ESI$^+$).

***N*-(-Adamantan-1-yl)-6-oxo-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxamide 215c**

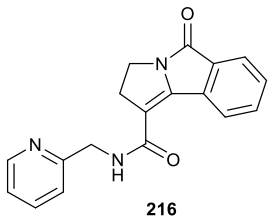


215c

Compound **160a** (0.050 g, 0.23 mmol) was dissolved in DCM (5 mL) followed by the addition of EDC (0.043 g, 0.27 mmol) and left stirring at room temperature for 1 hour. 1-Adamantylamine hydrochloride (0.052 g 0.27 mmol) and DIPEA (0.049 mL, 0.27 mmol) were added and the reaction was left stirring at room temperature for 16 hours. The mixture was then diluted with DCM (5mL) and washed using water (2 x 10 mL) and dried over $MgSO_4$ and concentrated by reduced pressure. The crude material was then purified using flash column chromatography (30% ethyl acetate in DCM) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as a pale-yellow coloured oil (0.034 g, 41%).

R_f= 0.34. **ν_{max} (KBr) cm^{-1}** 3321 (N-H), 2906 (C-H), 2852 (C-H), 1698 (N-C=O), 1655 (C=O), 1628 (N-C=O), 1510 (N-H), 1471 (C-H), 1448 (C-H), 1401, 1343, 1276, 1227 (C-O). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.81 (dd, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 7.84 (dt, *J* = 7.3, 0.9 Hz, 1H, Ar-H), 7.63 (td, *J* = 7.5, 1.3 Hz, 1H, Ar-H), 7.58 (td, *J* = 7.4, 1.2 Hz, 1H, Ar-H), 5.94 (d, *J*= 8.0 Hz, 1H, N(1a)N*H*), 4.06 (t, *J* = 8.9, 7.5 Hz, 2H, C(4)*H*), 3.38 (t, 2H, C(3)*H*), 2.09 – 2.03 (m, 2H, C(Adamantane)*H*), 1.98 – 1.56 (m, 15H, C(Adamantante)*H*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.88 (C(6)C=O), 163.07 (C(1)N-C=O), 147.34 (C(13)C=**C**), 136.18 (C(12)ArC, 132.10 (ArC), 131.08 (ArC), 130.04 (C(7)ArC, 127.56 (ArC), 123.18 (ArC), 112.83 (C(2)**C**=C), 39.91 C(4)), 37.56 (C(adamantane)), 37.24 (C(adamantane)), 33.87 (C(3)), 32.27 (C(adamantane)), 32.14 (C(adamantane)), 27.31 (C(adamantane)), 27.27 (C(adamantane)). ***m/z***= 349 [MH+] (ESI$^+$).

6-Oxo-*N*-(pyridin-2-ylmethyl)-3,4-dihydro-1H-pyrrolo[2,1-a]isoindole-2-carboxamide 216

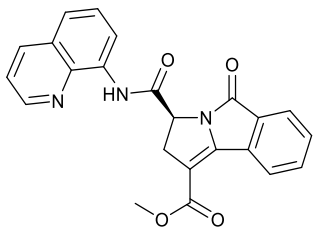


216

Compound **160a** (0.200 g, 0.93 mmol) was suspended in DMF (3 mL) followed by the addition of EDC (0.20 mL, 1.11 mmol) and DIPEA (0.19 mL, 1.11 mmol) and left stirring for 1 hour at room temperature in which all the starting material had dissolved. HOBt (0.150 g, 1.11 mmol) was added followed by the addition of 2-picolylamine (0.12 mL, 1.11 mmol) with the resulting reaction mixture left stirring at room temperature for 16 hours. The crude mixture was diluted with DCM (10 mL) and washed using warm water (40 °C, 5 x 10 mL) with the organic layer purified using flash column chromatography (40% ethyl acetate in pet-ether 40:60) with the desired fractions collected, combined and concentrated by reduced pressure to afford the desired product as a light blue coloured solid (0.020 g, 7%).

R_f= 0.19. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.46 – 8.41 (m, 1H, ArH), 7.84 – 7.79 (m, 1H, ArH), 7.61 – 7.51 (m, 2H, ArH), 7.49 – 7.35 (m, 4H, ArH), 5.33 (s, 2H, C(1b)ArC-C**H**$_2$-N), 3.96 (dd, *J* = 9.1, 7.7 Hz, 2H, (C(4)*H*), 3.39 (dd, *J* = 9.1, 7.7 Hz, 2H, (C(3)*H*). ***m/z***= 306 [MH+] (ESI$^+$) and 328 [MNa+] (ESI$^+$). **HRMS** calculated for $C_{18}H_{16}N_3O_2$ requires 306.1237, found at 306.1125 [MH+] (ESI$^+$).

Methyl (*S*)-6-oxo-4a-(quinolin-8-ylcarbamoyl)-3,4-dihydro-1H-benzo[a]pyrrolizine-2-carboxamide 221

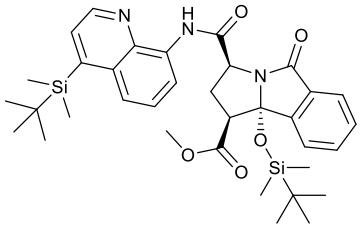


221

In an oven dried round bottomed flask that had been purged with N_2 compound **200** (0.309 g, 0.76 mmol) was dissolved in an excess of $SOCl_2$ (1 mL) with a few drops of anhydrous DCM to help with solubility and left to stir at room temperature for 3 hours. The solvent was removed and azeotroped using DCM (3 x 10 mL) with the reaction flask purged with N_2 and dissolved in anhydrous DCM (5 mL). In a separate flask, freshly purified 8-Aminoquinoline (0.219 g, 1.52 mmol) (see experimental techniques for details) was dissolved in anhydrous DCM (5 mL) and added to the acyl chloride containing mixture dropwise over 5 minutes with the resulting mixture left stirring under an inert atmosphere of N_2 at room temperature for 32 hours. The reaction mixture was diluted with DCM (5 mL) and washed using water (10 mL) with the organic layer concentrated by reduced pressure with the ^{1}H NMR showing desilylation. The crude material was then triturated using methanol (2 x 5 mL) with the resulting solid dried by reduced pressure to afford the desired product as a sandy coloured solid (0.082g, 27%).

$[\alpha]_D^{25}$= -67.2 (*c* 1.0 in DCM). **Mp**= +240 °C. ν_{max} **(KBr) cm^{-1}** 3324 (N-H), 2950 (C-H), 1692 (C=O), 1651 N-C=O), 1531 (N-H), 1488 (C-H), 1471, 1436, 1393, 1323, 1247 (N-C), 1221 (C-O), 1187 (C-O), 1168, 1122. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.70 (s, 1H, (N(4b)*H*), 8.80 (dd, *J* = 4.3, 1.7 Hz, 1H, ArH), 8.75 (dd, *J* = 6.0, 3.0 Hz, 1H, ArH), 8.59 (dt, *J* = 7.6, 1.0 Hz, 1H, ArH), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H, ArH), 7.91 (dt, *J* = 7.4, 1.0 Hz, 1H, ArH), 7.70 (td, *J* = 7.6, 1.3 Hz, 1H, ArH), 7.63 (td, *J* = 7.5, 1.2 Hz, 1H, ArH), 7.57 – 7.51 (m, 2H, ArH), 7.46 (dd, *J* = 8.3, 4.3 Hz, 1H, ArH), 5.19 (dd, *J* = 10.1, 5.2 Hz, 1H, C(4)*H*), 3.89 (s, 3H, C(1)OMe), 3.85 – 3.74 (m, 2H, C(3)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.87 (C(4a)N-C=O), 164.56 (C(1)COOMe) 164.16 (C(6)C=O), 148.57 (C(13)C=**C**), 148.47 (Ar**C**=N-ArC), 138.65 (C(12)ArC), 136.44 (ArC), 135.64 (ArC), 134.05 (ArC), 132.73 (ArC), 131.67 (ArC), 129.75 (C(7)ArC), 128.02 (ArC), 127.27 (ArC), 126.99 (ArC), 123.92 (ArC), 122.47 (ArC), 121.78 (ArC), 117.40 (ArC), 109.01 (C(2)), 56.47 (C(2)), 51.96 (C(1)OMe), 39.36 (C(3)). ***m/z***= 398 [MH-] (ESI^-) and 400 [MH+] (ESI^+). **HRMS** calculated for $C_{23}H_{18}N_3O_2$ requires 400.1292, found at 400.1274 [MH+] (ESI^+).

Methyl (2*S*,4a*S*,13*S*)-13-[(tert-butyldimethylsilyl)oxy]-4a-{[6-(tert-butyldimethylsilyl)quinolin-9-yl]carbamoyl}-6-oxo-3,4,6,13-tetrahydro-1H-benzo[a]pyrrolizine-2-carboxylate 223



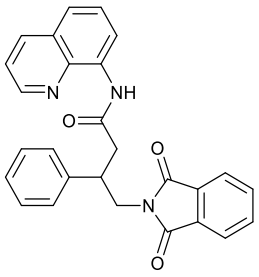
223

223 was synthesised according to general procedure **E** from **222** (0.100g, 0.23 mmol) using 3.0 eq of TBDMSiOTf with the crude material purified using flash column chromatography (15% ethyl acetate in pet-ether 40:60) to afford the desired product as very pale-yellow coloured oil (0.047 g, 30%).

R_f= 0.31. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.79 (dt, *J* = 7.5, 1.0 Hz, 1H, ArH), 7.66 (dt, *J* = 4.0, 0.9 Hz, 2H, ArH), 7.51 (dt, *J* = 7.5, 4.2 Hz, 1H, ArH), 6.87 (dd, *J* = 7.0, 1.6 Hz, 1H, ArH), 6.74 – 6.56 (m, 2H, ArH), 6.44 (dd, *J* = 9.6, 1.0 Hz, 1H, ArH), 5.95 (dd, *J* = 9.7, 5.5 Hz, 1H, ArH), 4.50 (ddd, *J* = 7.4, 4.6, 1.4 Hz, 1H, C(4)*H*), 3.79 (s, 3H, C(1)OMe), 2.92 (t, *J* = 7.5 Hz, 1H, C(2)*H*), 2.27 (ddd, *J* = 14.0, 4.5, 1.3 Hz, 1H, C(3)H_A), 1.72 – 1.56 (m, 1H, C(3)H_B), 0.72 (s, 9H, C(CH_3)$_3$), 0.50 (s, 9H, C(CH_3)$_3$), -0.08 (s, 3H, Si-CH_3), -0.13 (s, 3H, Si-CH_3), -0.51 (s, 3H, Si-CH_3), -0.59 (s, 3H, Si-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.64 (C(1)COOMe), 172.87 (C(6)C=O), 172.04 (C(4a)N-C=O), 148.75 (C(12)ArC), 137.76 (C(14)ArC) 133.54 (C(9)ArC), 131.59 (C(19)Ar**C**-Si), 130.55 (C(7)ArC), 130.03 (C(10)ArC), 126.24 (C(16)ArC), 124.14 (C(8)ArC), 123.05 (C(21)ArC), 122.85 (C(11)ArC), 119.06 (C(17)ArC), 117.75 , 116.58 (C(18)ArC), 115.46 (C(20)ArC), 115.27 (C(22)ArC), 106.68 (C(13)), 52.52 (C(1)OMe), 49.54 (C(4)), 46.61 (C(4)), 28.14 (C(3)), 25.72 (C(**C**H_3)$_3$),, 25.34 (C(**C**H_3)$_3$),, 18.25 (**C**(CH_3)$_3$),, 17.24 (**C**(CH_3)$_3$), -2.83 (Si-CH_3)., -3.83 (Si-CH_3)., -4.01 (Si-CH_3)., -4.85 (Si-CH_3). ***m/z***= 646 [MH+] (ESI^+).

4-(6,13-Dioxoisoindolin-2-yl)-3-phenyl-*N*-(quinolin-8-yl)butanamide 205



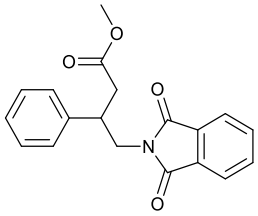
205

In a round bottomed flask compound **204** (0.150 g, 0.41 mmol) was added to $Pd(OAc)_2$ (0.010 g, 0.041 mmol), AgOAc (0.174 g, 1.04 mmol) and PhI (0.776 mL, 2.08 mmol) were all dissolved in anhydrous toluene (5 mL) and heated at 110 °C for 16 hours under a N_2 atmosphere. The mixture was then concentrated by reduced pressure and purified using flash column chromatography (35% ethyl acetate in pet-ether 40:60) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as an off-white coloured solid (0.098 g, 54%).

^{1}H NMR (400 MHz, Chloroform-d) δ 9.66 (s, 1H, ArH), 8.74 (dd, *J* = 4.6, 1.6 Hz, 1H, ArH), 8.41 (dd, *J* = 7.6, 1.3 Hz, 1H, ArH), 8.06 (dd, *J* = 8.3, 1.6 Hz, 1H, ArH), 7.59 (dd, *J* = 7.3, 3.6 Hz, 2H, ArH), 7.49 (dd, *J* = 5.5, 3.1 Hz, 2H, ArH), 7.43 – 7.33 (m, 4H, ArH), 7.33 – 7.21 (m, 3H, ArH), 7.19 – 7.12 (m, 1H, ArH), 4.05 – 3.88 (m, 3H, C(3)*H*, C(4)*H*), 3.00 – 2.88 (m, 2H, (C(3)*H*). **^{13}C NMR** (101 MHz, CDCl3) δ 169.27 (C(1)N-C=O), 168.42 (C(6,13)C=O), 148.18 (ArC), 140.99 (ArC), 138.29 (ArC), 136.27 (ArC), 134.32 (ArC), 133.82 (ArC), 131.96 (C(7,12)ArC), 128.90 (ArC), 127.89 (ArC), 127.85 (ArC), 127.37 (ArC), 127.34 (ArC), 123.19 (ArC), 121.65 (ArC), 121.38 (ArC), 116.33 (ArC), 43.50 (C(4)), 42.22 (C(3)), 41.01 (C(2)).

All data are in agreement with those found in the literature.[274]

Methyl 1-(6,13-dioxoisoindolin-4-yl)-3-phenylbutanoate 206



206

Compound **205** (0.085 g, 0.19 mmol) was suspended in MeOH (3 mL) in a pressure vial followed by the addition of TsOH (0.100 g, 1.75 mmol) with the vessel being sealed and the reaction left stirring at 100 °C 16 hours while stirring. The reaction was allowed to cool to room temperature and the solvent was removed using reduced pressure. The crude material was then purified using flash column chromatography (35% ethyl acetate in pet-ether 40:60) with the product containing fractions collected, combined and concentrated by reduced pressure to afford the desired product as a white coloured solid (0.035 g, 55%).

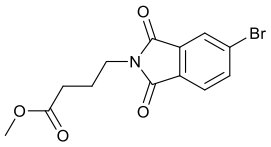
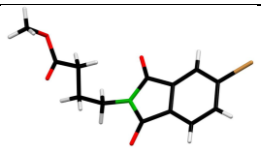
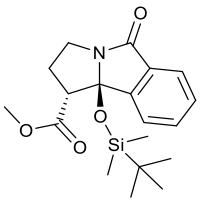
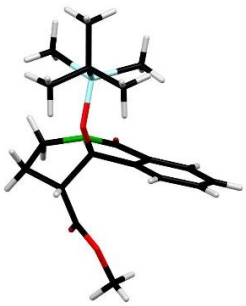
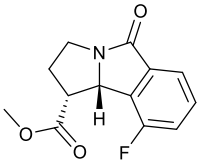
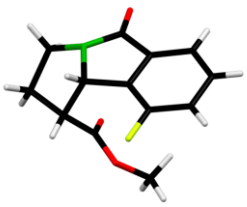
Mp= 99-101 °C (Lit. 101-103 °C). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.79 (dd, *J* = 5.4, 3.1 Hz, 2H, Ar-H), 7.68 (dd, *J* = 5.5, 3.0 Hz, 2H, Ar-H), 7.27 (d, *J* = 2.0 Hz, 4H, Ar-H), 7.23 – 7.17 (m, 1H, Ar-H), 3.89 (d, *J* = 7.8 Hz, 2H, C(4)*H*), 3.74 (p, *J* = 7.6 Hz, 1H, C(3)*H*), 3.47 (s, 3H, OMe), 2.73 (d, 2H, C(2)*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.07, C(1)COOMe), 168.24 (C(6,13)C=O), 140.53 (C(3a)ArC), 134.08 (ArC), 131.96, (C(7,12)ArC) 128.75 (ArC), 127.74 (ArC), 127.40 (ArC), 123.37 (ArC), 51.71 (C(1)OMe), 43.29 (C(4)), 40.83 (C(3)), 38.43 (C(2)). ***m/z***= 346 [MNa+] (ESI^+). **HRMS** calculated for $C_{19}H_{17}NaNO_4$ requires 346.1050, found at 346.1052 [MNa+] (ESI^+).

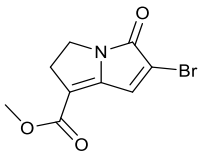
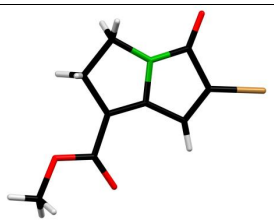
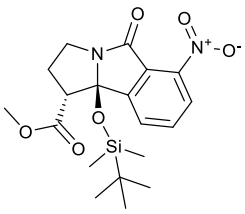
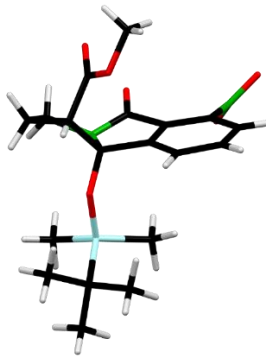
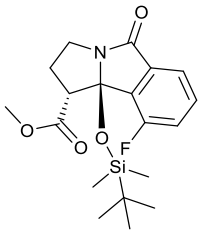
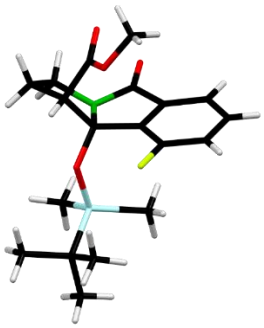
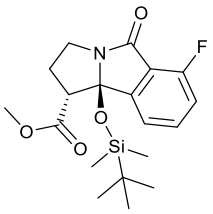
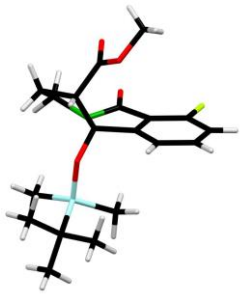
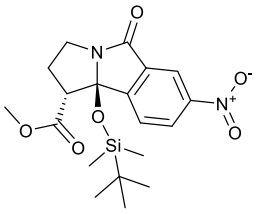
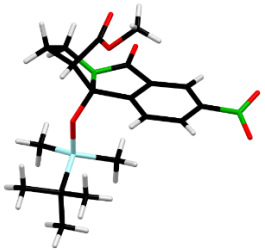
All data are in agreement with those found in the literature.[274]

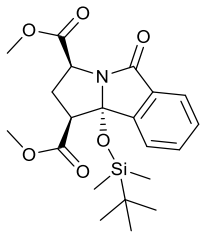
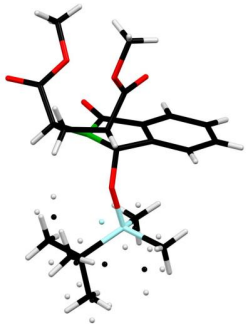
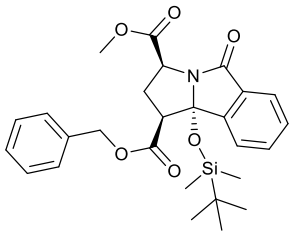
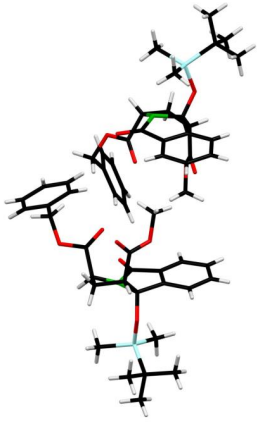
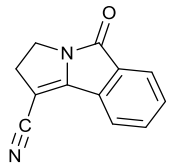
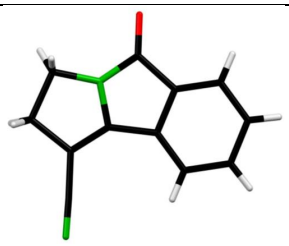
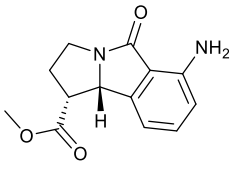
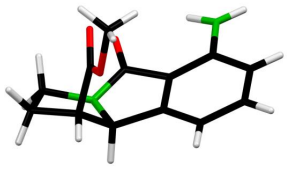
Appendix I: X-ray Crystallography Data

X-ray crystal structures for all compounds in this thesis were collected by the Oxford Chemistry Crystallographic Service. The software Mercury v3.8 was used to find stick style of the chemical structure with each imaged rendered at 3559 x 1634 pixels with a transparent background. Each atom colour coded as follows; Carbon (black), hydrogen (white), nitrogen (green), oxygen (red), silicon (light blue), fluorine (yellow). See the uploaded zip file for each related cif files as well as complete documentation for all bond lengths and calculation used in the generation of the below structures.

Table 1. List of x-ray structures with their corresponding SI, compound and file numbers

SI Number	Compound Number	Structure	Crystal Structure (Stick style)	File Name
1	**137e**			**7330**
2	**144a**			6992
3	**194f**			7273

4	**143d**			7384
5	**144a**			7049
6	**171**			DIA0413
7	**144f**			7210
8	**172**			7138

9	**175La**			7037
10	**177**			7272
11	**189**			7388
12	**196b**			7089

References and Bibliography

1 S. J. Leach, *Eur. Mol. Biol. Organ.*, 2004, **5**, 650–653.

2 R. E. Black, C. G. Victora, S. P. Walker, Z. A. Bhutta, P. Christian, M. De Onis, M. Ezzati, S. Grantham-Mcgregor, J. Katz, R. Martorell and R. Uauy, *Lancet*, 2013, **382**, 427–451.

3 K. Norman, C. Pichard, H. Lochs and M. Pirlich, *Clin. Nutr.*, 2008, **27**, 5–15.

4 J. N. P. Davies, *Lancet*, 1948, **251**, 317–320.

5 I. Trehan, H. S. Goldbach, L. N. LaGrone, G. J. Meuli, R. J. Wang, K. M. Maleta and M. J. Manary, *N. Engl. J. Med.*, 2013, **368**, 425–435.

6 K. M. Rosenthal. R, Zenilman. M, *Clinical Nutrition in Practice*, 2011.

7 M. F. Holick, N. C. Binkley, H. A. Bischoff-Ferrari, C. M. Gordon, D. A. Hanley, R. P. Heaney, M. H. Murad and C. M. Weaver, *J. Clin. Endocrinol. Metab.*, 2011, **96**, 1911–1930.

8 D. R. Ferrier, *Lippincott's Illustrated Reviews: Biochemistry*, 2014, vol. 6.

9 Y. C. Tham, X. Li, T. Y. Wong, H. A. Quigley, T. Aung and C. Y. Cheng, *Am. Acad. Ophthalmol.*, 2014, **121**, 2081–2090.

10 J. R. Gavin, K. G. M. M. Alberti, M. B. Davidson, R. A. DeFronzo, A. Drash, S. G. Gabbe, S. Genuth, M. I. Harris, R. Kahn, H. Keen, W. C. Knowler, H. Lebovitz, N. K. Maclaren, J. P. Palmer, P. Raskin, R. A. Rizza and M. P. Stern, *Diabetes Care*, 2003, **26**, 5–20.

11 G. Danaei, M. M. Finucane, Y. Lu, G. M. Singh, M. J. Cowan, C. J. Paciorek, J. K. Lin, F. Farzadfar, Y. H. Khang, G. A. Stevens, M. Rao, M. K. Ali, L. M. Riley, C. A. Robinson and M. Ezzati, *Lancet*, 2011, **378**, 31–40.

12 F. D. Martinez, *Eur. Respir. J.*, 2007, **29**, 179–184.

13 G. R. Serjeant, *Br. J. Haematol.*, 2010, **151**, 425–429.

14 B. P. O'Sullivan and S. D. Freedman, *Lancet*, 2009, **373**, 1891–1904.

15 J. C. Davies, E. W. F. W. Alton and A. Bush, *Br. Med. J.*, 2007, **335**, 1255–1259.

16 A. Asim, A. Kumar, S. Muthuswamy, S. Jain and S. Agarwal, *J. Biomed. Sci.*, 2015, **22**, 1–9.

17 K. C. Nicolaou and S. Rigol, *J. Antibiot. (Tokyo).*, 2018, **71**, 153–184.

18 A. Mullard, *Nat. Rev. Drug Discov.*, 2020, **19**, 79–84.

19 G. R. Wizemann. T, Robinson. S, *Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies*, 2nd edn., 2009.

20 J. P. Hughes, S. S. Rees, S. B. Kalindjian and K. L. Philpott, *Br. J. Pharmacol.*, 2011, **162**, 1239–1249.

21 K. H. Bleicher, H. J. Böhm, K. Müller and A. I. Alanine, *Nat. Rev. Drug Discov.*, 2003, **2**, 369–378.

22 M. Sanguinetti and M. Tristani-Firouzi, *Nature*, 2006, **440**, 463–469.

23 A. Butler, M. V. Helliwell, Y. Zhang, J. C. Hancox and C. E. Dempsey, *Front. Pharmacol.*, 2020, **10**, 1–13.

24 P. Szymański, M. Markowicz and E. Mikiciuk-Olasik, *Int. J. Mol. Sci.*, 2012, **13**, 427–452.

25 C. P. Entzeroth. M, Flotow. H, *Current Protocols in Pharmacology*, 2009.

26 S. Fox, S. Farr-Jones, L. Sopchak, A. Boggs, H. W. Nicely, R. Khoury and M. Biros, *J. Biomol. Screen.*, 2006, **11**, 864–869.

27 S. S. Phatak, C. C. Stephan and C. N. Cavasotto, *Expert Opin. Drug Discov.*, 2009, **4**, 947–959.

28 K. Boppana, P. K. Dubey, S. A. R. P. Jagarlapudi, S. Vadivelan and G. Rambabu, *Eur. J. Med. Chem.*, 2009, **44**, 3584–3590.

29 D. J. Payne, M. N. Gwynn, D. J. Holmes and D. L. Pompliano, *Nat. Rev. Drug Discov.*, 2007, **6**, 29–40.

30 D. A. Erlanson, R. S. McDowell and T. O'Brien, *J. Med. Chem.*, 2004, **47**, 1–20.

31 A. J. Price, S. Howard and B. D. Cons, *Essays Biochem.*, 2017, **61**, 475–484.

32 B. C. Doak, R. S. Norton and M. J. Scanlon, *Pharmacol. Ther.*, 2016, **167**, 28–37.

33 Q. Li, *Front. Mol. Biosci.*, 2020, **7**, 1–13.

34 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Deliv. Rev.*, 2001, **46**, 3–26.

35 M. Congreve, R. Carr, C. Murray and H. Jhoti, *Drug Discov. Today*, 2003.

36 S. P. Leelananda and S. Lindert, *Beilstein J. Org. Chem.*, 2016, **12**, 2694–2718.

37 D. B. Kitchen, H. Decornez, J. R. Furr and J. Bajorath, *Nat. Rev. Drug Discov.*, 2004, **3**, 935–949.

38 A. Lavecchia, *Drug Discov. Today*, 2015, **20**, 318–331.

39 J. G. Moffat, F. Vincent, J. A. Lee, J. Eder and M. Prunotto, *Nat. Rev. Drug Discov.*, 2017, **16**, 531–543.

40 D. C. Swinney and J. Anthony, *Nat. Rev. Drug Discov.*, 2011, **10**, 507–519.

41 H. Brito, V. Marques, M. B. Afonso, D. G. Brown, U. Börjesson, N. Selmi, D. M. Smith, I. O. Roberts, M. Fitzek, N. Aniceto, R. C. Guedes, R. Moreira and C. M. P. Rodrigues, *Cell Death Discov.*, 2020, **6**, 1–13.

42 D. Jeffreys, *Asprin the remarkable story of a wonder drug*, 2008.

43 C. G. Newman. D, *J Nat Prod*, 2012, **75**, 311–335.

44 G. T. Carter, *Nat. Prod. Rep.*, 2011, **28**, 1783–1789.

45 X. Mo, Q. Li and J. Ju, *RSC Adv.*, 2014, **4**, 50566–50593.

46 M. Anwar and M. G. Moloney, *Chem. Biol. Drug Des.*, 2013, **81**, 645–649.

47 M. M. G. Jeong. Yon-Chul, *Furture Med. Chem.*, 2015, **7**, 159–183.

48 S. W. B. Tan, C. L. L. Chai and M. G. Moloney, *Org. Biomol. Chem.*, 2017, **15**, 1889–1912.

49 D. Hanahan and R. A. Weinberg, *Cell*, 2011, **144**, 646–674.

50 K. D. Miller, L. Nogueira, A. B. Mariotto, J. H. Rowland, K. R. Yabroff, C. M. Alfano, A. Jemal, J. L. Kramer and R. L. Siegel, *CA. Cancer J. Clin.*, 2019, **69**, 363–385.

51 R. L. Siegel, K. D. Miller and A. Jemal, *CA. Cancer J. Clin.*, 2020, **70**, 7–30.

52 A. S. Ahmad, N. Ormiston-Smith and P. D. Sasieni, *Br. J. Cancer*, 2015, **112**, 943–947.

53 J. Maddams, M. Utley and H. Møller, *Br. J. Cancer*, 2012, **107**, 1195–1202.

54 R. L. Bosch F, *Pharmacology*, 2008, **3**, 171–179.

55 P. G. Corrie, *Medicine (Baltimore).*, 2008, **36**, 24–28.

56 V. T. DeVita and E. Chu, *Cancer Res.*, 2008, **68**, 8643–8653.

57 L. Gomez-Cuadrado, N. Tracey, R. Ma, B. Qian and V. G. Brunton, *Dis. Model. Mech.*, 2017, **10**, 1061–1074.

58 P. Mehlen and A. Puisieux, *Nat. Rev. Cancer*, 2006, **6**, 449–458.

59 B. Weigelt, J. L. Peterse and L. J. Van Veer, *Nat. Rev. Cancer*, 2005, **5**, 591–602.

60 R. B. Mokhtari, T. S. Homayouni, N. Baluch, E. Morgatskaya, S. Kumar, B. Das and H. Yeger, *Oncotarget*, 2017, **8**, 38022–38043.

61 C. G. Van El, M. C. Cornel, P. Borry, R. J. Hastings, F. Fellmann, S. V. Hodgson, H. C. Howard, A. Cambon-Thomsen, B. M. Knoppers, H. Meijers-Heijboer, H. Scheffer, L. Tranebjaerg, W. Dondorp and G. M. W. R. De Wert, *Eur. J. Hum. Genet.*, 2013, **21**, 580–584.

62 R. K. Singh, S. Kumar, D. N. Prasad and T. R. Bhardwaj, *Eur. J. Med. Chem.*, 2018, **151**, 401–433.

63 Z. H. Siddik, *Oncogene*, 2003, **22**, 7265–7279.

64 B. A. Chabner and T. G. Roberts, *Nat. Rev. Cancer*, 2005, **5**, 65–72.

65 Y. Xiong, W. D. Burke, J. L. Jakubczak and T. H. Eickbush, *Nucleic Acids Res.*, 1988, **16**, 10561–10573.

66 X. L. Yang and A. H. J. Wang, *Pharmacol. Ther.*, 1999, **83**, 181–215.

67 S. Mukherjee, A. Guainazzi and O. D. Schärer, *Nucleic Acids Res.*, 2014, **42**, 7429–7435.

68 Z. H. Siddik, *Cancer Handb.*, 2005, **1**, 1–16.

69 D. Wang and S. J. Lippard, *Nat. Rev. Drug Discov.*, 2005, **4**, 307–320.

70 R. Martinez and L. Chacon-Garcia, *Curr. Med. Chem.*, 2012, **12**, 127–151.

71 Nial J. Wheate, Craig R. Brodie, J. Grant Collins, Sharon Kemp and Janice R. Aldrich-Wright, *Mini-Reviews Med. Chem.*, 2007, **7**, 627–648.

72 H. K. Liu and P. J. Sadler, *Acc. Chem. Res.*, 2011, **44**, 349–359.

73 C. B. Harley, *Nat. Rev. Cancer*, 2008, **8**, 167–179.

74 L. Siegel, Are telomerse the Key to Aging and Cancer?, https://web.archive.org/web/20131201021609/http://learn.genetics.utah.edu/content/begin/traits/telomeres/, (accessed 13 April 2020).

75 J. K. Yeh, M. H. Lin and C. Y. Wang, *JACC Basic to Transl. Sci.*, 2019, **4**, 855–865.

76 K. Gerth, H. Steinmetz, G. Höfle and R. Jansen, *Angew. Chemie Int. Ed.*, 2008, **47**, 600–602.

77 B. Villeponteau, *Semin. Cell Dev. Biol.*, 1996, **7**, 15–21.

78 T. T. Andrews. L, *Methods Mol Biol*, 2008, **405**, 1–8.

79 K. Ganesan and B. Xu, *Int. J. Mol. Sci.*, 2018, **19**, 1–26.

80 Y. Yamashita and T. Mizukami, *J. Antibiot. (Tokyo).*, 2000, **53**, 2–4.

81 T. Agatsuma, T. Akama, S. Nara, S. Matsumiya, R. Nakai, H. Ogawa, S. Otaki, S. I. Ikeda, Y. Saitoh and Y. Kanda, *Org. Lett.*, 2002, **4**, 4387–4390.

82 R. Nakai, H. Ishida, A. Asai, H. Ogawa, Y. Yamamoto, H. Kawasaki, S. Akinaga, T. Mizukami and Y. Yamashita, *Chem. Biol.*, 2006, **13**, 183–190.

83 E. B. D. F. Wills. L, Clutterbuck. P. W, *Nutr. Rev.*, 2009, **36**, 215–218.

84 J. A. Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F. & Wolff, *N. Engl. J. Med*, 1948, **238**, 787–793.

85 J. C. Wright, A. Prigot, B. Wright, S. Weintraub and L. T. Wright, *J. Natl. Med. Assoc.*, 1951, **43**, 211–240.

86 A. Nzila, *J. Antimicrob. Chemother.*, 2006, **57**, 1043–1054.

87 T. Miran, A. T. J. Vogg, L. El Moussaoui, H. J. Kaiser, N. Drude, V. von Felbert, F. M. Mottaghy and A. Morgenroth, *Cancer Med.*, 2017, **6**, 1639–1651.

88 H. E. Krokan, F. Drabløs and G. Slupphaug, *Oncogene*, 2002, **21**, 8935–8948.

89 L. W, *Review of medical microbiology and immunology*, 2016.

90 R. J. M. Salton and K.-S. Kim, *Medical microbiology*, 4th edn., 1996.

91 E. Peterson and P. Kaur, *Front. Microbiol.*, 2018, **9**, 1–21.

92 A. Mai-Prochnow, M. Clauson, J. Hong and A. B. Murphy, *Sci. Rep.*, 2016, **6**, 1–11.

93 R. Fernandes, P. Amador and C. Prudêncio, *Rev. Med. Microbiol.*, 2013, **24**, 7–17.

94 B. Bozdogan and P. C. Appelbaum, *Int. J. Antimicrob. Agents*, 2004, **23**, 113–119.

95 R. Leclercq and P. Courvalin, *Antimicrob. Agents Chemother.*, 2002, **46**, 2727–2734.

96 O. N. Aldred. K. J, Kerns. R. J, *Biochemistry*, 2014, **53**, 1565–1574.

97 C. Ian and R. Marilyn, *Microbiol. Mol. Biol. Rev.*, 2001, **65**, 232–260.

98 Y. Glupczynski, *Am. Soc. Microbiol.*, 1999, **43**, 727–737.

99 N. Mobarki, B. Almerabi and A. Hattan, *Int. J. Med. Dev. Ctries.*, 2019, **40**, 561–564.

100 K. J. Williams, *J R Soc Med*, 2009, **102**, 343–348.

101 R. I. Aminov, M. Otto and A. Sommer, *Front. Microbiol.*, 2010, **1**, 1–7.

102 J. Parascandola, *The History of antibiotics: a symposium*, 1980.

103 S. A. Waksman and H. B. Woodruff, *New Jersey Agric. Exp. Stn.*, 1940, **1**, 581–600.

104 H. R. L. Kresge. N, Simoni. R. D, *Biol. Chem.*, 2004, **279**, 101–102.

105 K. Lewis, *Nature*, 2012, **485**, 439–440.

106 R. P. Elander, *Appl. Microbiol. Biotechnol.*, 2003, **61**, 385–392.

107 A. J. Long, I. J. Clifton, P. L. Roach, J. E. Baldwin, P. J. Rutledge and C. J. Schofield, *Biochemistry*, 2005, **44**, 6619–6628.

108 J. F. Fisher, S. O. Meroueh and S. Mobashery, *Chem. Rev.*, 2005, **105**, 395–424.

109 O. Mimoz, N. Grégoire, L. Poirel, M. Marliat, W. Couet and P. Nordmann, *Antimicrob. Agents Chemother.*, 2012, **56**, 2759–2760.

110 K. Bush, *Crit. Care*, 2010, **14**, 224.

111 B. Al-Dabbagh, D. Mengin-Lecreulx and A. Bouhss, *J. Bacteriol.*, 2008, **190**, 7141–7146.

112 S. M. Drawz and R. A. Bonomo, *Clin. Microbiol. Rev.*, 2010, **23**, 160–201.

113 G. E. Zurenko, B. H. Yagi, R. D. Schaadt, J. W. Allison, J. O. Kilburn, S. E. Glickman, D. K. Hutchinson, M. R. Barbachyn and S. J. Brickner, *Antimicrob. Agents Chemother.*, 1996, **40**, 839–845.

114 M. R. Barbachyn and C. W. Ford, *Angew. Chemie - Int. Ed.*, 2003, **42**, 2010–2023.

115 T. Tas, A. Kucukbayrak, I. N. Hakyemez, F. Z. Mengeloglu, H. Simavli, G. Ozyalvacli and M. Erdurmus, *Cornea*, 2013, **32**, 1052–1057.

116 D. Shinabarger, *Expert Opin. Investig. Drugs*, 1999, **8**, 1195–1202.

117 Y. Tian, T. Li, Y. Zhu, B. Wang, X. Zou and M. Li, *BMC Microbiol.*, 2014, **14**, 1–15.

118 V. G. Meka and H. S. Gold, *Clin. Infect. Dis.*, 2004, **39**, 1010–1015.

119 C. D. Doern, J. Y. Park, M. Gallegos, D. Alspaugh and C. A. D. Burnham, *J. Clin. Microbiol.*, 2016, **54**, 1289–1294.

120 T. Mazzei, E. Mini, A. Novelli and P. Periti, *J. Antimicrob. Chemother.*, 1993, **31**, 1–9.

121 S. Pal, *Tetrahedron*, 2006, **62**, 3171–3200.

122 P. Kurath, P. H. Jones, R. S. Egan and T. J. Perun, *Experientia*, 1971, **27**, 362.

123 S. Kanoh and B. K. Rubin, *Clin. Microbiol. Rev.*, 2010, **23**, 590–615.

124 A. M. Emmerson, *J. Antimicrob. Chemother.*, 2003, **51**, 13–20.

125 L. A. Mitscher, *Chem. Rev.*, 2005, **105**, 559–592.

126 X. Guan, X. Xue, Y. Liu, J. Wang, Y. Wang, J. Wang, K. Wang, H. Jiang, L. Zhang, B. Yang, N. Wang and L. Pan, *J. Int. Med. Res.*, 2013, **41**, 20–30.

127 H. Nikaido, *J. Bacteriol.*, 1996, **178**, 5853–5859.

128 T. H. Grossman, *Cold Spring Harb. Perspect. Med.*, 2016, **6**, 1–24.

129 B. S. Speer, N. B. Shoemaker and A. A. Salyers, *Clin. Microbiol. Rev.*, 1992, **5**, 387–399.

130 H. W. Schnappinger. D, *Arch Microbiol*, 1996, **165**, 359–369.

131 M. N. Alekshun and S. B. Levy, *Cell*, 2007, **128**, 1037–1050.

132 P. Beringer and M. E. Winter, *Basic Clin. Pharmacokinet. Fifth Ed.*, 2011, **5**, 3–22.

133 and G. D. W. Davies, J., *Trends Microbiol*, 1997, **5**, 234–240.

134 and G. H. M. Shaw, K. J., P. N. Rather, R. S. Hare, *Microbiol. Rev*, 1993, **57**, 138–163.

135 M. S. Butler, K. A. Hansford, M. A. T. Blaskovich, R. Halai and M. A. Cooper, *J. Antibiot. (Tokyo).*, 2014, **67**, 631–644.

136 M. A. T. Blaskovich, K. A. Hansford, M. S. Butler, Z. Jia, A. E. Mark and M. A. Cooper, *ACS Infect. Dis.*, 2018, **4**, 715–735.

137 G. L. Marcone, E. Binda, F. Berini and F. Marinelli, *Biotechnol. Adv.*, 2018, **36**, 534–554.

138 S. Jovetic, Y. Zhu, G. L. Marcone, F. Marinelli and J. Tramper, *Trends Biotechnol.*, 2010, **28**, 596–604.

139 M. A. Cooper and D. H. Williams, *Chem. Biol.*, 1999, **6**, 891–899.

140 A. K. Sarmah, M. T. Meyer and A. B. A. Boxall, *Chemosphere*, 2006, **65**, 725–759.

141 World Health Organization, Antibiotic resistance, https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance, (accessed 23 August 2020).

142 E. Y. Klein, T. P. Van Boeckel, E. M. Martinez, S. Pant, S. Gandra, S. A. Levin, H. Goossens and R. Laxminarayan, *Proc. Natl. Acad. Sci. U. S. A.*, 2018, **115**, 3463–3470.

143 Y. Sugie, H. Hirai, H. Kachi-Tonai, Y. J. Kim, Y. Kojima, Y. Shiomi, A. Sugiura, A. Sugiura, Y. Suzuki, N. Yoshikawa, L. Brennan, J. Duignan, L. H. Huang, J. Sutcliffe and N. Kojima, *J. Antibiot. (Tokyo).*, 2001, **54**, 917–925.

144 T. Nogawa, M. Kawatani, M. Uramoto, A. Okano, H. Aono, Y. Futamura, H. Koshino, S. Takahashi and H. Osada, *J. Antibiot. (Tokyo).*, 2013, **66**, 621–623.

145 S. Polyfibrospongia, P. Djura, D. B. Stierle, B. Sullivan, D. J. Faulkner, E. Arnold and J. Clardy, *J. Org. Chem.*, 1980, **45**, 1435–1441.

146 P. C. Boros. C, Dix. A, Katz. B, Vasina. Y, *J. Antibiot. (Tokyo).*, 2003, **56**, 862–865.

147 M. K. and K. S. Noriaki Hirayama, *Tetrahedron Lett.*, 1980, **21**, 2559–2560.

148 G. Li, S. Kusari and M. Spiteller, *Nat. Prod. Rep.*, 2014, **31**, 1175–1201.

149 L. Li, M. C. Tang, S. Tang, S. Gao, S. Soliman, L. Hang, W. Xu, T. Ye, K. Watanabe and Y. Tang, *J. Am. Chem. Soc.*, 2018, **140**, 2067–2071.

150 X. Wang, L. Zhao, C. Liu, J. Qi, P. Zhao, Z. Liu, C. Li, Y. Hu, X. Yin, X. Liu, Z. Liao, L. Zhang and X. Xia, *Front. Microbiol.*, 2020, **10**, 1–11.

151 V. Singh, S. R. Iyer and S. Pal, *Tetrahedron Lett.*, 2005, **36**, 9197–9227.

152 J. A. S. Dhambri, S. Mohammad, O. Nguyen Van Buu, G. Galvani, Y. Meyer, M.-I. Lannou, G. Sorin, *Nat. Prod. Rep.*, 2015, **32**, 841–864.

153 W. S. Rapson and R. Robinson, *J. Chem. Soc*, 1935, 1285–1288.

154 K. Alder and O. Diels, *Justus Liebig's Ann. der Chemie*, 1927, **31**, 98–122.

155 E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discov.*, 2008, **7**, 608–624.

156 T. H. Lambert and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2006, **128**, 426–427.

157 R. M. Wilson, W. S. Jen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 11616–11617.

158 K. Uchida, T. Ogawa, Y. Yasuda, H. Mimura, T. Fujimoto, T. Fukuyama, T. Wakimoto, T. Asakawa, Y. Hamashima and T. Kan, *Angew. Chemie - Int. Ed.*, 2012, **51**, 12850–12853.

159 K. C. Nicolaou, K. K. Pulukuri, S. Rigol, M. Buchman, A. A. Shah, N. Cen, M. D. McCurry, K. Beabout and Y. Shamoo, *J. Am. Chem. Soc.*, 2017, **139**, 15868–15877.

160 K. C. Nicolaou, A. A. Shah, H. Korman, T. Khan, L. Shi, W. Worawalai and E. A. Theodorakis, *Angew. Chemie - Int. Ed.*, 2015, **54**, 9203–9208.

161 U. K. Nozaki. K, Oshima. K, *Bull. Chem. Soc. Jpn*, 1991, **64**, 403–409.

162 T. R. Hoye and V. Dvornikovs, *J. Am. Chem. Soc.*, 2006, **128**, 2550–2551.

163 R. M. De Figueiredo, R. Fröhlich and M. Christmann, *Angew. Chemie - Int. Ed.*, 2007, **46**, 2883–2886.

164 B. J. L. Royles, *Chem. Rev.*, 1995, **95**, 1981–2001.

165 Y. C. Jeong and M. G. Moloney, *Synlett*, 2009, **15**, 2487–2491.

166 J. Markopoulos, K. C. Prousis, G. Athanasellis, V. Stefanou, D. Matiadis, E. Kokalari, O. Igglessi-Markopoulou and V. McKee, *Bioinorg. Chem. Appl.*, 2010, **2010**, 315056.

167 M. Zaghouani and B. Nay, *Nat. Prod. Rep.*, 2016, **33**, 540–548.

168 M. D. Andrews, A. G. Brewster, K. M. Crapnell, A. J. Ibbett, T. Jones, M. G. Moloney, K. Prout and D. Watkin, *J. Chem. Soc. Perkin Trans. 1*, 1998, **1**, 223–236.

169 C. A. Holloway, C. J. Matthews, Y. C. Jeong, M. G. Moloney, C. F. Roberts and M. Yaqoob, *Chem. Biol. Drug Des.*, 2011, **78**, 229–235.

170 M. G. Moloney, *Trends Pharmacol. Sci.*, 2016, **37**, 689–701.

171 J. Lockett, University of Oxford, 2018.

172 R. Wolf, B. L. Kaul, J. H. Zagal, F. Bedioui and J. P. Dodelet, *Ullmann's Encycl. Ind. Chem.*, 2012, 619–671.

173 P. N. Patsalos, *Epilepsia*, 2005, **46**, 140–148.

174 S. Belluti, G. Orteca, V. Semeghini, G. Rigillo, F. Parenti, E. Ferrari and C. Imbriano, *Int. J. Mol. Sci.*

175 I. M. M. Othman, M. A. M. Gad-Elkareem, M. El-Naggar, E. S. Nossier and A. E. G. E. Amr, *J. Enzyme Inhib. Med. Chem.*, 2019, **34**, 1259–1270.

176 P. Singh and L. Tripathi, *Asian J. Chem.*, 2018, **30**, 2193–2200.

177 N. Kushwaha and D. Kaushik, *J. Appl. Pharm. Sci.*, 2016, **6**, 159–171.

178 M. H. Norman, D. J. Minick and G. C. Rigdon, *J. Med. Chem.*, 1996, **39**, 149–157.

179 R. Van Hes, P. Smid, C. N. J. Stroomer, K. Tipker, M. T. M. Tulp, J. A. M. Van Der Heyden, A. C. McCreary, M. B. Hesselink and C. G. Kruse, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 405–408.

180 D. H. Rich, P. D. Gesellchen, A. Tong, A. Cheung and C. K. Buckner, *J. Med. Chem.*, 1975, **18**, 1004–1010.

181 R. M. De Figueiredo, P. Oczipka, R. Fröhlich and M. Christmann, *Synthesis (Stuttg).*, 2008, **8**, 1316–1318.

182 C. Bonneaud, J. M. Burgess, R. Bongiovanni, C. Joly-Duhamel and C. M. Friesen, *J. Polym. Sci. Part A Polym. Chem.*, 2019, **57**, 699–707.

183 N. Makita, Y. Kabasawa, Y. Otani, Firman, J. Sato, M. Hashimoto, M. Nakaya, H. Nishihara, M. Nangaku, H. Kurose, T. Ohwada and T. Iiri, *Circ. Res.*, 2013, **112**, 327–334.

184 R. G. Moran, P. D. Colman, R. A. Forsch and A. Rosowsky, *J. Med. Chem.*, 1984, **27**, 1263–1267.

185 L. Zhang, L. Zhang, J. Bian, Q. Jiang, J. Gao and W. Song, *Anticancer. Drugs*, 2018, **29**, 145–156.

186 E. Guénin, M. Monteil, N. Bouchemal, T. Prangé and M. Lecouvey, *Eur. J. Org. Chem.*, 2007, **20**, 3380–3391.

187 A. J. Sinclair, V. del Amo and D. Philp, *Org. Biomol. Chem.*, 2009, **7**, 3308.

188 F. Tamay-Cach, J. Correa-Basurto, L. Villa-Tanaca, T. Mancilla-Percino, M. Juárez-Montiel and J. G. Trujillo-Ferrara, *J. Enzyme Inhib. Med. Chem.*, 2013, **28**, 1026–1033.

189 A. G. Griesbeck, A. Henz, W. Kramer, J. Lex, F. Nerowski, M. Oelgemöller, K. Peters and E. M. Peters, *Helv. Chim. Acta*, 1997, **80**, 912–933.

190 F. M. Dato, M. Sheikh, R. Z. Uhl, A. W. Schüller, M. Steinkrüger, P. Koch, J. M. Neudörfl, M. Gütschow, B. Goldfuss and M. Pietsch, *ChemMedChem*, 2018, **13**, 1833–1847.

191 T. M. Gabbasov, E. M. Tsyrlina, L. V. Spirikhin and M. S. Yunusov, *Chem. Nat. Compd.*, 2018, **54**, 951–955.

192 T. J. M. Kaml, S. A. Khan, *Indian J. Hetrocyclic Chem.*, 2010, **19**, 321–324.

193 H. Wu, J. Wu, W. Zhang, Z. Li, J. Fang, X. Lian, T. Qin, J. Hao, Q. Zhou and S. Wu, *Bioorg. Med. Chem.*

Lett., 2019, **29**, 870–872.

194 F. C. Schilling, *J. Magn. Reson.*, 1982, **47**, 61–67.

195 L. Estel, F. Marsais and G. Quéguiner, *J. Org. Chem.*, 1988, **53**, 2740–2744.

196 D. Doddrell, D. Jordan, N. V. Riggs and P. R. Wells, *J. Chem. Soc. Chem. Commun.*, 1972, **0**, 1158.

197 2017, 1231.

198 S. E. Border, R. Z. Pavlović, L. Zhiquan, M. J. Gunther, H. Wang, H. Cui and J. D. Badjić, *Chem. - A Eur. J.*, 2019, **25**, 273–279.

199 W. Wang, J. Ding, C. Xiao, Z. Tang, D. Li, J. Chen, X. Zhuang and X. Chen, *Biomacromolecules*, 2011, **12**, 2466–2474.

200 M. H. Chen, O. P. Goel, J. Magano, J. R. Rubin, W. Company and A. Arbor, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1587–1592.

201 F. E. King, J. W. Clark-Lewis, R. Wade and W. A. Swindin, *J. Chem. Soc.*, 1957, **166**, 873–880.

202 I. M. Sakhautdinov and A. F. Mukhametyanova, *Russ. J. Org. Chem.*, 2019, **55**, 1280–1286.

203 US., *Pat.*, US5508272, 1996.

204 Evans pKa table, http://ccc.chem.pitt.edu/wipf/MechOMs/evans_pKa_table.pdf, (accessed 6 January 2021).

205 R. M. Silverstein, F. X. Webster, D. J. Kiemle and D. L. Bryce, *Spectrometric Identification of Organic Compounds*, 7th edn., 2014.

206 A. Kumar and R. C. Rani Grace, *Nuclear overhauser effect*, Elsevier Ltd., 3rd edn., 2016.

207 R. R. Gil and A. Navarro-Vazquez, *Modern NMR Approaches to the Structure Elucidation of Natural Products: Volume 2: Data Acquisition and Applications to Compound Classes*, 2016.

208 R. E. Hoffman, *Magn. Reson. Chem.*, 2006, **44**, 606–616.

209 M. Baranac-Stojanović, *RSC Adv.*, 2014, **4**, 308–321.

210 I. Yavari, A. Zonouzi and R. Hekmat-Shoar, *Tetrahedron Lett.*, 1998, **39**, 3841–3842.

211 E. Kleinpeter, *J. Serbian Chem. Soc.*, 2006, **71**, 1–17.

212 G. Fischer, 1991, **29**, 212–222.

213 D. L. Kuo and T. Money, *Can. J. Chem.*, 1988, **66**, 1794–1804.

214 R. F. Stewart and L. L. Miller, *J. Am. Chem. Soc.*, 1980, **102**, 4999–5004.

215 R. M. Williams, O. P. Anderson, R. W. Armstrong, J. Josey, H. Meyers and C. Eriksson, *J. Am. Chem. Soc.*, 1982, **104**, 6092–6099.

216 R. Noyori, S. Murata and M. Suzuki, *Tetrahedron*, 1981, **37**, 3899–3910.

217 T. Mukaiyama and S. Kobayashi, *Org. React.*, 1994, **46**, 1–103.

218 K. Banno, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 2284–2291.

219 H. R. Kalita, A. J. Borah and P. Phukan, *Indian J. Chem.*, 2013, **52**, 289–292.

220 C. W. Downey and M. W. Johnson, *Tetrahedron Lett.*, 2007, **48**, 3559–3562.

221 R. Mahrwald, *Chem. Rev.*, 1999, **99**, 1095–1120.

222 P. Phukan, *Synth. Commun.*, 2004, **34**, 1065–1070.

223 J. H. Han, S. B. Kim and T. Mukaiyama, *Bull. Korean Chem. Soc*, 1994, **15**, 529.

224 C. Wade Downey, J. A. Ingersoll, H. M. Glist, C. M. Dombrowski and A. T. Barnett, *European J. Org. Chem.*, 2015, **2015**, 7287–7291.

225 K. Nagatani, A. Minami, H. Tezuka, Y. Hoshino and M. Nakada, *Org. Lett.*, 2017, **19**, 810–813.

226 D. A. Evans, K. A. Scheidt, J. N. Johnston and M. C. Willis, *J. Am. Chem. Soc.*, 2001, **123**, 4480–4491.

227 N. Kise, S. Isemoto and T. Sakurai, *Org. Lett.*, 2009, **11**, 4902–4905.

228 E. Turk, *Chem. Eng. News*, 1998, **76**, 6.

229 K. E. Maudens, S. M. R. Wille and W. E. Lambert, *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.*, 2007, **848**, 384–390.

230 G. Maiti and S. C. Roy, *Tetrahedron Lett.*, 1997, **38**, 495–498.

231 A. Fürstner, M. Bindl and L. Jean, *Angew. Chemie - Int. Ed.*, 2007, **46**, 9275–9278.

232 K. C. Nicolaou and S. E. Webber, *Synthesis (Stuttg).*, 1986, **1**, 453–462.

233 P. G. M. Wuts, *Greene's Protective Groups in Organic Chemistry*, 5th edn., 2014.

234 R. H. Schlessinger, M. A. Poss and S. Richardson, *J. Am. Chem. Soc.*, 1986, **108**, 3112–3114.

235 R. Baker, W. J. Cummings, J. F. Hayes and A. Kumar, *J. Chem. Soc*, 1986, **1**, 1237–1239.

236 M. J. Robins, V. Samano and M. D. Johnson, *J. Org. Chem.*, 1990, **55**, 410–412.

237 S. F. Martin, J. A. Dodge, L. E. Burgess and M. Hartmann, *J. Org. Chem.*, 1992, **57**, 1070–1072.

238 Y. J. Lee, H. L. Ammon, P. S. Mariano, U. C. Yoon, D. U. Kim, C. W. Lee and Y. S. Choi, *J. Am. Chem. Soc.*, 1995, **117**, 2698–2710.

239 Y. Takahashi, T. Miyashi, U. C. Yoon, S. W. Oh, M. Mancheno, Z. Su, D. F. Falvey and P. S. Mariano, *J. Am. Chem. Soc.*, 1999, **121**, 3926–3932.

240 E. N. DeLaney, D. S. Lee, L. D. Elliott, J. Jin, K. I. Booker-Milburn, M. Poliakoff and M. W. George, *Green Chem.*, 2017, **19**, 1431–1438.

241 L. D. Elliott, M. Berry, B. Harji, D. Klauber, J. Leonard and K. I. Booker-Milburn, *Org. Process Res. Dev.*, 2016, **20**, 1806–1811.

242 U. C. Yoon, C. W. Lee, S. W. Oh and P. S. Mariano, *Tetrahedron*, 1999, **55**, 11997–12008.

243 P. L. Fuchs, *J. Am. Chem. Soc.*, 1974, **96**, 1607–1609.

244 J. M. Muchowski and P. H. Nelson, *Tetrahedron Lett.*, 1980, **21**, 4585–4588.

245 J. Maury, D. Mouysset, L. Feray, S. R. A. Marque, D. Siri and M. P. Bertrand, *Chem. - A Eur. J.*, 2012, **18**, 3241–3247.

246 R. Araya-Maturana, H. Pessoa-Mahana and B. Weiss-Lopez, *Nat. Prod. Commun.*, 2008, **3**, 445–450.

247 A. F. McKay, D. L. Garmaise, R. Gaudry, H. A. Baker, G. Y. Paris, R. W. Kay, G. E. Just and R. Schwartz, *J. Am. Chem. Soc.*, 1959, **81**, 4328–4335.

248 Y. J. Lee, H. L. Ammon, P. S. Mariano, U. C. Yoon, D. U. Kim, C. W. Lee and Y. S. Choi, *J. Am. Chem. Soc.*, 1995, **117**, 2698–2710.

249 I. F. Cottrell, P. J. Davis and M. G. Moloney, *Tetrahedron Asymmetry*, 2004, **15**, 1239–1242.

250 S. W. B. Tan, University of Oxford, 2014.

251 M. Schroder, *Chem. Rev.*, 1980, **80**, 187–213.

252 H. C. Kolb, M. S. VanNieuwenhze and B. K. Sharpless, *Chem. Re*, 1994, **94**, 2483–2547.

253 T. K. M. Shing, E. K. W. Tam, V. W. Tai, I. H. F. Chung and Q. Jiang, *Chem. Eur. J.*, 1996, **2**, 50–57.

254 A. S. Rao, H. R. Mohan and A. Charette, in *Encyclopedia of Reagents for Organic Synthesis*, 2005.

255 L. McEwan, M. Julius, S. Roberts and J. C. Q. Fletcher, *Gold Bull.*, 2010, **43**, 298–306.

256 R. P. Ye, J. Ding, W. Gong, M. D. Argyle, Q. Zhong, Y. Wang, C. K. Russell, Z. Xu, A. G. Russell, Q. Li, M. Fan and Y. G. Yao, *Nat. Commun.*, 2019, **10**, 1–15.

257 R. M. Mironenko, O. B. Belskaya and V. A. Likholobov, *Catal. Today*, 2020, **357**, 152–165.

258 K. Dobrezberger, J. Bosters, N. Moser, N. Yigit, A. Nagl, K. Föttinger, D. Lennon and G. Rupprechter, *J. Phys. Chem. C*, 2020, **124**, 23674–23682.

259 A. M. Smith and R. Whyman, *Chem. Rev.*, 2014, **114**, 5477–5510.

260 Z. F. Jiao, J. X. Zhao, X. N. Guo, X. L. Tong, B. Zhang, G. Q. Jin, Y. Qin and X. Y. Guo, *Catal. Sci. Technol.*, 2019, **9**, 2266–2272.

261 Y. Saito, H. Ishitani, M. Ueno and S. Kobayashi, *ChemistryOpen*, 2017, **6**, 211–215.

262 R. Zhang, X. Li, M. Genov, A. Pretsch, D. Pretsch and M. G. Moloney, *J. Org. Chem.*, 2020, **85**, 12393–12407.

263 T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119–125.

264 Y. Hayashi, D. Sakamoto and D. Okamura, *Org. Lett.*, 2016, **18**, 4–7.

265 R. Karla, B. Ebert, C. Thorkildsen, C. Herdeis, T. N. Johansen, B. Nielsen and P. Krogsgaard-Larsen, *J. Med. Chem.*, 1999, **42**, 2053–2059.

266 P. Resende, W. P. Almeida and F. Coelho, *Tetrahedron Asymmetry*, 1999, **10**, 2113–2118.

267 M. Houshdar Tehrani, M. Farnia and M. Shalchian Nazer, *Iran. J. Pharm. Res.*, 2010, **1**, 1–3.

268 R. Tomar, D. Bhattacharya and S. A. Babu, *Tetrahedron*, 2019, **75**, 2447–2465.

269 L. Nicke, P. Horx, K. Harms and A. Geyer, *Chem. Sci.*, 2019, **10**, 8634–8641.

270 A. Yokota, Y. Aihara and N. Chatani, *J. Org. Chem.*, 2014, **79**, 11922–11932.

271 Z. Huang and G. Dong, *Tetrahedron Lett.*, 2014, **55**, 5869–5889.

272 D. P. Affron and J. A. Bull, *Eur. J. Org. Chem.*, 2016, **1**, 139–149.

273 Y. Liu, Y. Zhang, X. Cao and J. P. Wan, *Beilstein J. Org. Chem.*, 2016, **12**, 1122–1126.

274 Z. Liu, Y. Wang, Z. Wang, T. Zeng, P. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2017, **139**, 11261–11270.

275 Y. Aihara and N. Chatani, *Chem. Sci.*, 2013, **4**, 664–670.

276 M. Corbet and F. De Campo, *Angew. Chemie - Int. Ed.*, 2013, **52**, 9896–9898.

277 A. Albert and J. N. Phillips, *J. Chem. Soc*, 1956, 1294–1304.

278 C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827–10852.

279 T. Schlama, V. Gouverneur and C. Mioskowski, *Tetrahedron Lett.*, 1996, **37**, 7047–7048.

280 R. K. Mylavarapu, G. C. M. Kondaiah, N. Kolla, R. Veeramalla, P. Koilkonda, A. Bhattacharya and R. Bandichhor, *Org. Process Res. Dev.*, 2007, **11**, 1065–1068.

281 R. M. de Figueiredo, J. S. Suppo, C. Midrier and J. M. Campagne, *Adv. Synth. Catal.*, 2017, **359**, 1963–1968.

282 D. C. Braddock, P. D. Lickiss, B. C. Rowley, D. Pugh, T. Purnomo, G. Santhakumar and S. J. Fussell, *Org. Lett.*, 2018, **20**, 950–953.

283 G. R. Pettit, B. E. Toki, J. P. Xu and D. C. Brune, *J. Nat. Prod.*, 2000, **63**, 22–28.

284 J. R. Dunetz, Y. Xiang, A. Baldwin and J. Ringling, *Org. Lett.*, 2011, **13**, 5048–5051.

285 S. Rej, Y. Ano and N. Chatani, *Chem. Rev.*, 2020, **120**, 1788–1887.

286 C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, *Chem. Soc. Rev.*, 2018, **47**, 6603–6743.

287 M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li and W. Su, *Org. Chem. Front.*, 2014, **1**, 843–895.

288 S. Rej, A. Das and N. Chatani, *Coord. Chem. Rev.*, 2021, **431**, 1–37.

289 Y. Xia and G. Dong, *Nat. Rev. Chem.*, 2020, **4**, 600–614.

290 S. Sunkari, S. R. Bonam, A. V. S. Rao, S. Riyaz, V. Lakshma Nayak, H. M. S. Kumar, A. Kamal and B. Nagendra Babu, *Bioorg. Chem.*, 2019, **87**, 484–494.

291 Y. Nakao, *Synthesis (Stuttg).*, 2011, 3209–3219.

292 T. Iwai and M. Sawamura, *ACS Catal.*, 2015, **5**, 5031–5040.

293 Y. Wang, Y. Wang, K. Jiang, Q. Zhang and D. Li, *Org. Biomol. Chem.*, 2016, **14**, 10180–10184.

294 S. V. Kumar and D. Ma, *J. Org. Chem.*, 2018, **83**, 2706–2713.

295 S. Prasanna and R. Doerksen, *Curr. Med. Chem.*, 2009, **16**, 21–41.

296 P. Matsson and J. Kihlberg, *J. Med. Chem.*, 2017, **60**, 1662–1664.

297 Y. Kwon, *Handbook of Essential Pharmacokinetics, Pharmacodynamics, and Drug Metabolism for Industrial Scientists*, Kluwer Adeademic Publishers, 2002.

298 I. Moriguchi, S. Hirono, I. Nakagome and H. Hirano, *Chem. Pharm. Bull*, 1994, **42**, 976–978.

299 M. Anwar, A. R. Cowley and M. G. Moloney, *Tetrahedron Asymmetry*, 2010, **21**, 1758–1770.

300 Y. C. Jeong, M. Anwar, Z. Bikadi, E. Hazai and M. G. Moloney, *Chem. Sci.*, 2012, **4**, 1008–1015.

301 Y. C. Jeong and M. G. Moloney, *Beilstein J. Org. Chem.*, 2013, **9**, 1899–1906.

302 W. D. Holroyd. S. E, Groves, P. Searle. M, Gerhard. U, *Tetrahedron*, 1993, **49**, 9171–9182.

303 S. S. More and R. Vince, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3793–3797.

304 R. L. Prestidge, D. R. K. Harding, J. E. Battersby and W. S. Hancock, *J. Org. Chem.*, 1975, **40**, 3287–3288.

305 T. H. Fife and N. W. Duddy, *J. Am. Chem. Soc.*, 1983, **105**, 74–79.

306 R. Heckendorn, *Bull. des Soc. Chim. Belg*, 1986, **95**, 921–943.

307 CN., 111072612, 2020.

308 R. D. Tressel. R, Wondrak. G, Kersten. E, *J. Agric. Food Chem.*, 1994, **42**, 2692–2697.

309 K. S. Ko, G. Park, Y. Yu and N. L. Pohl, *Org. Lett.*, 2008, **10**, 5381–5384.

310 L. R. Caswell and K. C. C. Yang, *J. Chem. Eng. Data*, 1968, **13**, 291–292.

311 A. Staubli, E. Ron and R. Langer, *J. Am. Chem. Soc.*, 1990, **112**, 4419–4424.

312 H. Koch and J. Kotlan, *Monatshefte fur Chemie*, 2004, **621**, 609–621.

313 Y. Kosdo, *Biopolymers*, 1970, **9**, 41–52.

314 F. P. Dwyer, B. Halpern and K. R. Turnbull, *Aust. J. Chem.*, 1963, **16**, 727–728.

315 G. G. Vatulina, T. N. Tuzhilkova, T. V. Matveeva, V. P. Krasnov, N. L. Burde and L. V. Alekseeva, *Pharm. Chem. J.*, 1986, **20**, 647–653.

316 A. L. V Vatulina. G. G, Tuzhilkova. T. N, Mateeva. V. P, Burde. N .L, *Pharm. Chem. J.*, 1986, **20**, 647–653.

317 J. F. Bower, R. Jumnah, A. C. Williams and J. M. J. Williams, *Perkin Trans. I*, 1997, **1**, 1411–1420.

318 T. Zou, X. Yu, X. Feng and M. Bao, *Chem. Commun.*, 2015, **51**, 10714–10717.

319 N. Makita, Y. Kabasawa, Y. Otani, Firman, J. Sato, M. Hashimoto, M. Nakaya, H. Nishihara, M. Nangaku, H. Kurose, T. Ohwada and T. Iiri, *Circ. Res.*, 2013, **112**, 327–334.

320 J. C. Richards and I. D. Spenser, *Can. J. Chem.*, 1982, **60**, 2810–2820.

321 J. G. Nathanael, J. M. White, A. Richter, M. R. Nuske and U. Wille, *Org. Biomol. Chem.*, 2020, **18**, 6949–6957.

322 K. G and K. G, *Hetrocycles*, 1997, **45**, 1979–1988.

323 Br. Pat., GB1036694, 1964.

324 J. A. Robl, *Tetrahedron Lett.*, 1994, **35**, 393–396.

325 R. Tomar, D. Bhattacharya and S. A. Babu, *Tetrahedron*, 2019, **75**, 2447–2465.