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Scalzullo, Stefania Margherita

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Synthesis of lamellarin alkaloid analogues from enaminone precursors

Stefania Margherita Scalzullo

A thesis submitted to the Faculty of Science,

University of the Witwatersrand,

Johannesburg

In fulfilment of the requirements for the Degree of Doctor of Philosophy

October 2013

Declaration

I declare that the work presented in this thesis was carried out exclusively by myself under the supervision of Professor Joseph P. Michael and assisted by Professor Willem A. L. van Otterlo. It is being submitted for the Degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

Stefania Margherita Scalzullo
October 2013

Abstract

The synthesis of alkaloids from enaminones has been used extensively in the University of the Witwatersrand's organic chemistry laboratories. In this thesis enaminone precursors are one of the main ways of accessing lamellarin analogues. The lamellarin alkaloids are an important family of marine alkaloids, owing to their vast biological properties. A brief background to marine alkaloids and their general potential is given, followed by a review of lamellarin alkaloids, their structural and biological properties and some of the major syntheses carried out over the past few years.

Two novel features form the basis of the synthetic methods described in the thesis. The first is an approach to forming the lamellarin alkaloids from enaminone precursors, which are prepared through the Eschenmoser sulphide contraction. The second method uses a novel pyrrole formation, which was initially conceptualized by Garreth L. Morgans in his PhD thesis (2008). The main target of the investigation was lamellarin G trimethyl ether.

In *Chapter 3*, the syntheses of a range of mono-, di- and tetra-substituted phenacyl halides are discussed. The phenacyl halides were used in the preparation of various enaminone precursors. The tetrasubstituted phenacyl halide 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.17** is required for the synthesis of our target lamellarin G trimethyl ether. The phenacyl halides are important in both the model synthesis described in *Chapter 4* and the synthesis toward lamellarins in *Chapter 5*.

Chapter 4 deals mainly with the synthesis of pyrrolizine systems. Methodology is described for the preparation of a variety of enaminones, pyrroles and tetracyclic lamellarin analogues. The closest pyrrolizine system to lamellarin G trimethyl ether, 11-(3,4-dimethoxyphenyl)-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.52**, was the final and most complex tetracyclic model structure analogous to lamellarin G trimethyl ether. Indolizine and pyrroloazepine adaptations were also demonstrated and tetracyclic systems 10,11-dihydro-8*H*-chromeno[3,2-*a*]indolizin-12(9*H*)-one **4.39** and 9,10,11,12-

tetrahydrochromeno[3',2':3,4]pyrrolo[1,2-*a*]azepin-6(8*H*)-one **4.40** were successfully prepared, even though the pyrrole formed in an unexpected way.

Finally in *Chapter 5*, the methodology established in the model study was used in the attempted synthesis of lamellarin G trimethyl ether. A second method was also investigated. Thus, various *N*-alkylated and N-H enaminones were successfully synthesized, from which novel and unexpected pyrrole-containing products 8-(3,4-dimethoxyphenyl)-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1]isoquinolin-14(6*H*)-one **5.28** and (3-ethoxy-8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.37** were formed, even though our desired product lamellarin G trimethyl ether could not be attained from either method.

This thesis is dedicated to

my parents,

Roberto and Rita

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Chapter 1
Introduction

Lamellarin alkaloids are the main focus of this PhD thesis. The lamellarin alkaloids are a subclass of marine alkaloids. An overview of alkaloid chemistry as well as some of the main classes of the marine alkaloids will be discussed in this Chapter. An outline of the lamellarin alkaloids and their structural, biological interest, as well as some selected syntheses of lamellarin alkaloids will also be discussed.

1.1 Alkaloid chemistry: History and background

Alkaloids are generally defined as naturally occurring nitrogen-containing biologically active heterocyclic compounds. They therefore constitute one of the widest classes of natural products.[1,2] Many definitions have been posed over the years.[3] Originally a true alkaloid was described by the following criteria:

- *The nitrogen is basic and part of a heterocyclic system;*
- *They exhibit complex molecular structure;*
- *They manifest significant pharmacological activity;*
- *They are restricted to the plant kingdom.*

Although most alkaloid substances are isolated from plant material (over 10 000 species have been investigated), many animal, marine, fungal and bacterial species are considered plentiful sources of alkaloids and have been known to possess much medicinal value.[4] The primary description mentioned above in introducing this section on alkaloids is thus a more commonly accepted definition of modern alkaloids.

The use of alkaloids dates back to 1200BC in the Middle East, where the opium poppy (*Papaver*) was used medicinally. Similarly, the piperidine alkaloid coniine **1.1** (also the first alkaloid

synthesized), shown in *Figure 1.1*, is a well-known toxin that causes paralysis of motor nerve endings. It is known for being the cause of death to the Greek philosopher Socrates in 339 BC. Many modern alkaloids have names that have become well known, such as caffeine **1.2** and nicotine **1.3** (central nervous system stimulants), as well as poisons made popular by *Agatha Christie* novels such as strychnine **1.4**. Medicinal analgesics (painkillers) such as codeine **1.5** and morphine **1.6** have also become well known alkaloids (*Figure 1.1*). Morphine **1.6** was the first alkaloid isolated in its pure form by Sertürner in 1805 from the cut seed capsule of the opium poppy.[3,5,6]

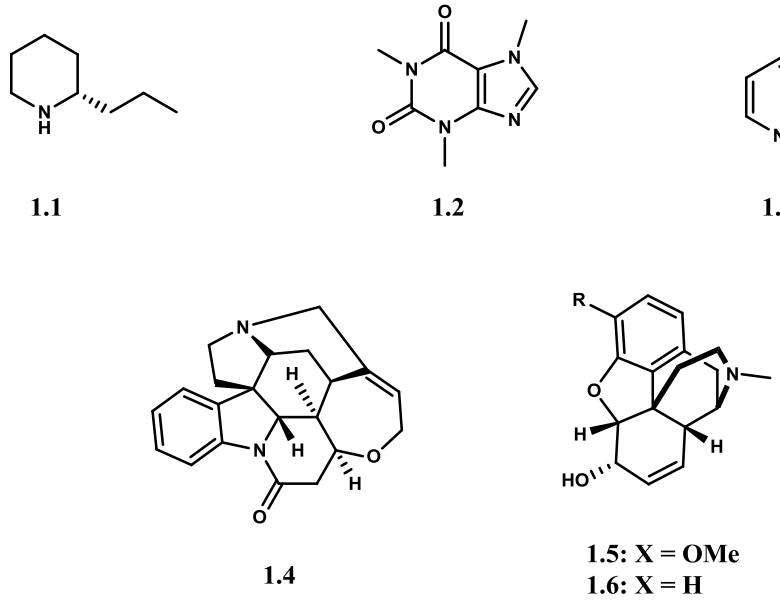
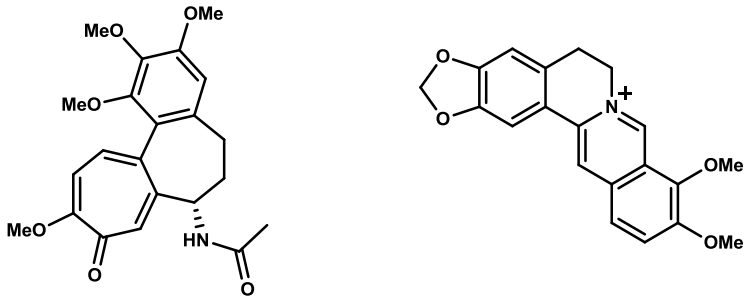


Figure 1.1: Examples of some common ancient and modern alkaloids.

The majority of alkaloids are colourless, crystalline solids, and it was often found that alkaloids had a bitter taste, which is usually considered a defence mechanism against ingestion of potentially toxic compounds.[7] Numerous harmful and repulsive substances, including xenobiotic salts, rancid fats, fermentation products, and secondary plant metabolites contain alkaloids. Alkaloids are infamous for their strong and often deadly toxicity toward animals and humans. Most of the deadly alkaloids fall into the class of neurotoxins. A cytotoxic effect can be generated through leaks in the cell membranes (saponins or steroidal alkaloids) or when elements of the cytoskeleton are inhibited. The spindle poisons colchicine **1.7**, shown in *Figure 1.2*, is

particularly famous. DNA can also be a target for alkaloids, for instance, planar and lipophilic alkaloids such as berberine **1.8** (shown in *Figure 1.2*) are intercalating compounds that assemble between stacks of paired nucleotides in the DNA double helix. Pyrrolizine and furoquinoline alkaloids are known to form covalent adducts with DNA bases which results in mutation and tumour formation. DNA alkylation and ribosomal protein biosynthesis inhibition has also been reported.[4]



1.7 **1.8**

Figure 1.2: Cytotoxic colchicine **1.7** and DNA-targeting berberine **1.8**.

The alkaloids discussed in this Chapter will mainly target the groups relevant to this PhD thesis. A brief background and review of some of the main classes of marine alkaloids, with specific interest in sponge, tunicate and mollusc sources, will be given, along with their biological applications. A brief background and review will then be done on some pyrrole-containing alkaloids systems, with particular interest in pyrrolizine, indolizine, pyrroloazepine and the isoquinoline alkaloids. Particular attention will be given to the lamellarin alkaloids, which will be discussed separately. A detailed literature review of the lamellarin alkaloids will also be presented.

1.2 A brief background to some of the main classes of marine alkaloids

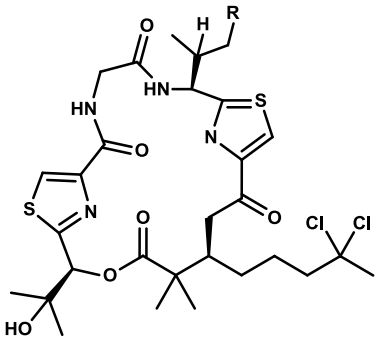
The chemical diversity of marine life, which is estimated to include about two million species of plants and animals, remains largely unexplored. The substances found in marine organisms are not the familiar alkaloid structures found in the terrestrial environment.[4,8,9] Organisms living in marine environments are subject to high salinity, high pressure, poor nutrition, low temperature (or local high temperature), and complex relations with other creatures. Over 18000 compounds have been isolated from marine sources, most with diverse biological activity such as antimicrobial, anti-inflammatory, antimalarial, antioxidant, anti-HIV and anticancer activity. Thus, marine organisms offer a wonderful resource for the discovery of new compounds and compounds with new activity.[10] Marine alkaloids frequently contain pyridoacridine, indole, pyrrole, pyridine, isoquinoline, guanidine and steroidal components. Only the pyrrole-containing marine alkaloids will be discussed in this Section. Representative marine alkaloids from different sources such as phytoplankton, fungi, algae and marine invertebrates will be discussed in this Section along with some structural and pharmacological properties.

1.2.1 Marine alkaloids from bacteria, fungi and algae

1.2.1.1 Cyanobacteria

The rich array of bioactive compounds isolated from large colonies of cyanobacteria, make this group interesting targets. About 300 marine cyanobacteria alkaloids have been reported.[1] They are often isolated from the benthic, filamentous cyanobacterium *Lyngbya majuscula* and *Lyngbya symploca*, and are typically synthesized by blue-green algae, which mostly produce potent toxins against predators. Lyngbyabellins A **1.9** and B **1.10**, are not direct examples of alkaloids but are nevertheless interesting structures containing similar structural traits to alkaloids. The cyclic depsipeptides are shown in *Figure 1.3* they exhibit a thiazole carboxylic acid unit within the structure, which is thought to play an important pharmacological role. They have shown remarkable anticancer properties in cytotoxicity testing. The lyngbyabellins are known to target the actin filaments of cells and displays anti-proliferative mechanisms. Lyngbyabellin A **1.9** is a

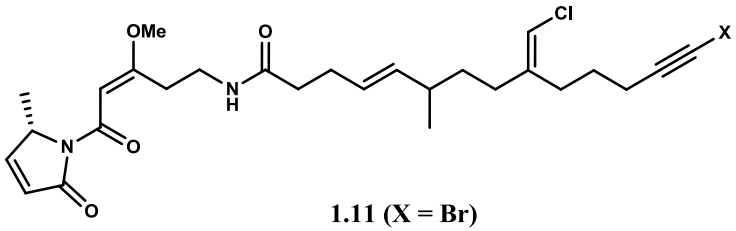
potent disruptor of the cellular microfilament network and shows cytokinesis in colon carcinoma cells causing apoptosis of the cancerous cells.[11,12] Similarly, lyngbyabellin B **1.10** has also shown potential as an anticancer drug. It has however also been found to be highly toxic to brine shrimp and the fungus *Candida albicans*.[12-14]



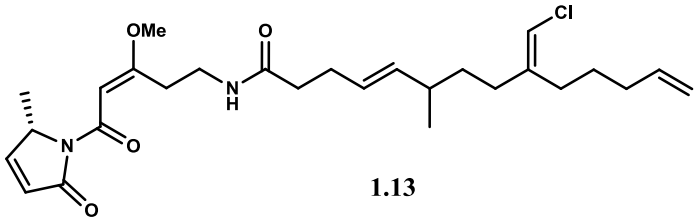
1.9 (R = CH_3)
1.10 (R = H)

Figure 1.3: Cyclic depsipeptides lyngbyabellins A **1.9** and B **1.10**.

Jamaicamides A **1.11**, B **1.12** and C **1.13** (*Figure 1.4*) are isolated from the *Lyngbya majuscula* cyanobacterium, which is found in Hector's Bay in Jamaica. They are lipopeptide alkaloids containing a high degree of functionality within the structure, which contributes greatly to its mode of action and biosynthesis. They possess an unique acetylenic bromide functionality, which has only been observed once before in nature. They also possess a vinyl chloride, β-methoxy eneone system, and pyrrolinone ring. They are moderately neurotoxic and have also shown cytotoxicity to the human lung carcinoma cell line. Finally, they exhibit low micromolar levels of sodium channel-blocking activity.[4,15]



1.11 (X = Br)
1.12 (X = H)

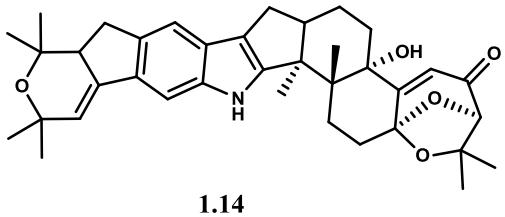


1.13

Figure 1.4: *Lipopeptide alkaloids* jamaicamide A **1.11**, B **1.12** and C **1.13**.

1.2.1.2 Fungi

Shearinine A **1.14**, shown in *Figure 1.5*, is the parent compound to a growing group of indole triterpenoid alkaloids. Thus far shearinines A to K have been isolated. Shearinine A **1.14** and its related compounds are found in the marine fungus *Penicillium janthinellum*, which are often associated with mangrove plants. Shearinine A **1.14** and other shearinine alkaloids have shown to cause apoptosis in human promyelocytic leukemia cancer cells. They have also shown significant *in vitro* blocking activity on large-conductance calcium-activated potassium channels.[1,12]



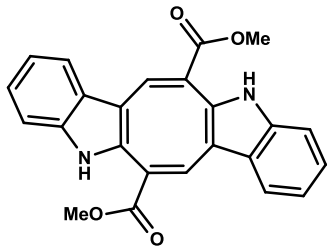
1.14

Figure 1.5: Fungus-derived alkaloid shearinine A **1.14**.

1.2.1.3 Algae

A diversity of seaweeds such as blue-green algae (Cyanophyta), green algae (Chlorophyta), red algae (Rhodophyta), and the brown algae (Phaeophyta) have become an interesting area for researchers, owing to the potential structural and pharmacological value of this peculiar and under-studied source. In sea water, many algae grow as phytoplankton (especially the dinoflagellates and certain blue-green algae). Other marine algae grow as benthos and epiphytes on other algae, and as parts of higher plants, rocks, stones, gravels, sand and mud.[16,17]

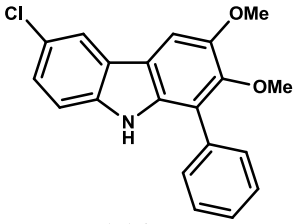
Caulerpin **1.15** (*Figure 1.6*), also known as CLP I is isolated from green and red algae. It was first extracted from *Caulerpa racemosa* but later found in *Caulerpa lamourouxii*, *Caulerpa sertularioides*, and *Caulerpa taxifolia* species. Caulerpin **1.15** is widely distributed in the Phillippines. It is also known to cause a mild anaesthetic action when placed in the mouth (the algae are often eaten as a 'salad'), which results in numbness of the lips and tongue. In some people it produces toxic effects. Some cytotoxicity and moderate antibacterial and antifungal activity have been found. Investigation of the antiviral activity of caulerpin **1.15** has shown an interesting inhibitory effect *in vitro* toward the feline immunodeficiency virus, a valid model for studying AIDS.[16-18]



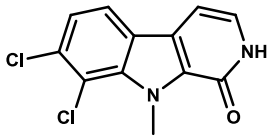
1.15

Figure 1.6: Caulerpin **1.15**, isolated from green and red algae.

Chlorohyellazole **1.16** in *Figure 1.7* is an example of a halogenated carbazole. It is produced by the blue-green algae *Hyella caespitosa*. It has shown potent monoamine oxidase inhibition. Similarly, baurerine C **1.17** in *Figure 1.7* is an example of a chlorinated β-carboline. It was isolated from the blue-green algae *Dichothrix baueriana*. It has shown activity against the herpes simplex virus type 1 and 2.[4,18]



1.16



1.17

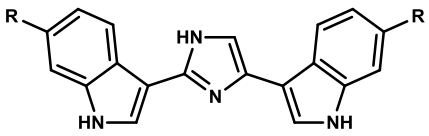
Figure 1.7: Chlorohyellazole **1.16** and baurierine C **1.17**, isolated from blue-green algae.

1.2.2 Marine alkaloids from sponges, molluscs and tunicates

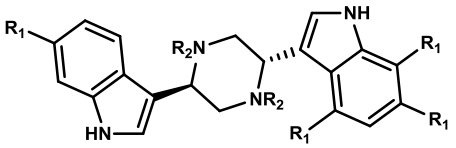
1.2.2.1 Sponges

Approximately 5000 living sponge species are classified in the phylum Porifera, also known as the 'pore bearers'. Bergman and Feeney discovered a novel bioactive nucleoside from the marine sponge *Cryptotethya crypta* in the early 1951. This started the vast interest, and subsequent extraction and isolation of marine natural products. Marine alkaloids from sponges represent approximately 14% of all the marine natural products.[4,16,19]

Nortopsentins A to D **1.18** (*Figure 1.8*), with an imidazole ring between two indole units, are isolated from the Caribbean deep water marine sponge *Spongsorites ruetzleri*. Dragmacidins A to F **1.19** (*Figure 1.8*) are characteristic bromoindoles, isolated from the pacific sponge *Hexadella* sp. and the mediterranean sponge *Halicortex* spp. Both the dragmacidins and nortopsentins exhibited *in vitro* cytotoxicity against P388 leukemia cell lines with IC50 values between 7.8 and 0.9 μg/mL.[1,16,18,19]



1.18: R = H, Br



1.19: R_1 = H, Br
R_2 = H, Me

Figure 1.8: Nortopsentin A – D **1.18** and dragmacidin A –F **1.19** exhibit cytotoxicity with P388 cell lines.

Manzamine alkaloids, shown in *Figure 1.9* have a unique polycyclic ring system. They have shown a range of bioactivities including cytotoxicity, antimicrobial, pesticidal, anti-inflammatory effects and have shown the potential to act against HIV and malaria. Manzamine A **1.20** was the first alkaloid extracted from an Okinawan sponge *Haliclona sp.* More recently *β*-carboline alkaloids, 6-hydroxymanzamine A **1.21** and 3,4-dihydromanzamine A **1.22** were isolated from the marine sponge *Amphimedon sp.* collected from the Kerama Islands, Okinawa, Japan. These were found to be cytotoxic *in vitro* against L-1210 (lymphocytic leukemia cells). Similarly, manadomanzamines A and B **1.23**, which show significant rearrangement to the manzamine skeleton, were isolated from the Indonesian sponge *Acanthostrongylophora* spp. These compounds exhibited activities against HIV-1.[1,4,6,18]

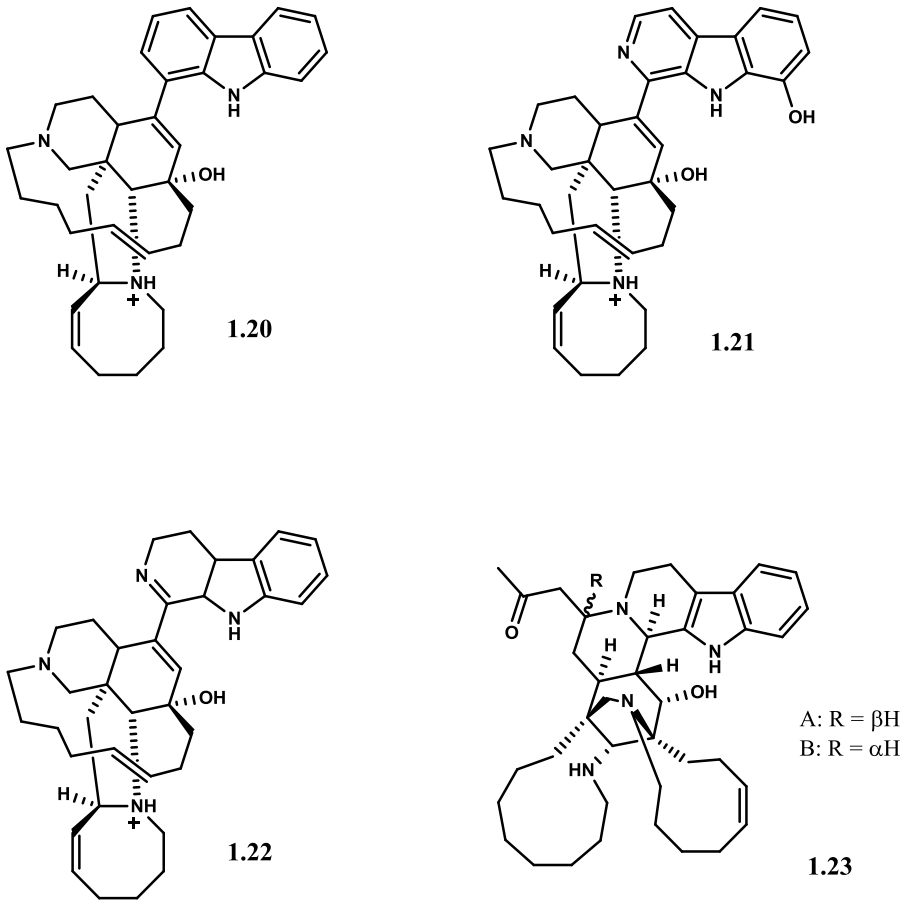
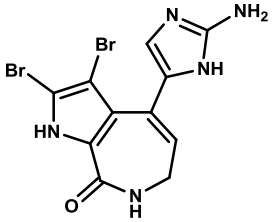
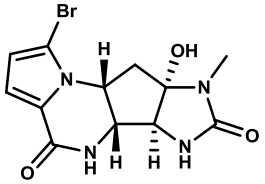


Figure 1.9: Manzamine A **1.20**, 6-hydroxymanzamine A **1.21** and 3,4-dihydromanzamine A **1.22**, manadomanzamines A and B **1.23**.

Finally, pyrrololactams form an intrinsic part of the alkaloids derived from sponges. Some important examples are stevensine **1.24** (*Figure 1.10*), isolated from the Great Barrier Reef sponge *Phakellia flabellata*. The genus has furnished many interesting bromine-containing alkaloids, which generally show broad spectrum antibiotic activity. However, most of them are toxic. The bromopyrrole agelastatin A **1.25** (*Figure 1.10*) is another example of a pyrrololactam and a naturally occurring oroidin alkaloid, isolated from the sponge *Agelas dendromorpha*. Agelastatin A **1.25** has been found to be a novel inhibitor of osteopontin-mediated adhesion, invasion, and colony formation, and it has also shown powerful antitumor effects.[4,6,16,20]



1.24



1.25

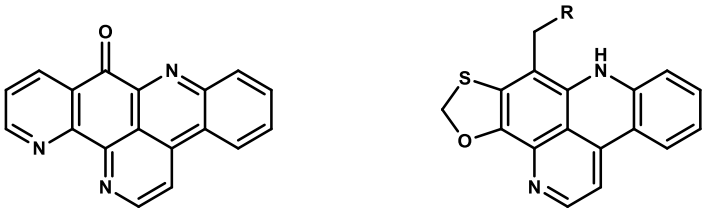
Figure 1.10: Important pyrrololactam alkaloids stevensine **1.24** and agelastatin A **1.25**.

1.2.2.2 Tunicates (ascidians)

Tunicates and ascidians belong to the phylum Chordata and the subphylum Tunicata. They are sac-like marine filter feeders. They are commonly referred to as sea squirts or tulips. The ascidians are generally considered to have a tougher structure than tunicates but they are generally similar in appearance and biology. There are approximately 3,000 living species of tunicates. The ascidians are considered the most biologically and chemically interesting marine species and many biologically active metabolites with unusual structures and significant bioactivities have been isolated.[12,14,21]

The pentacyclic pyridoacridines alkaloid ascididemin **1.26** (*Figure 1.11*) was first isolated in 1988 from the brown-coloured tunicate species of *Didemnum*, collected at Kerama Islands in Okinawa. Ascididemin **1.26** has demonstrated potent cytotoxicity as an anticancer agent. Mechanistically, it is thought to behave as a DNA intercalating agent that causes inhibition of topoisomerase II and its catalytic activity, therefore having an apoptotic effect. Ascididemin **1.26** has been tested *in vivo* at the National Cancer Institute, USA against twelve human tumour cell lines such as leukaemia, breast, colon, lung, prostate and bladder cancers, and was shown to exhibit significant activity against six of the cell lines. Ascididemin **1.26** has also shown activity against *Escherichia coli*, *Bacillus subtilis*, *Candida albicans*, and *Cladisporium resinae*.[12,21,22]
The related alkaloids, lissoclinidine A and B **1.27** (*Figure 1.11*), containing a benzoxathiole moiety, have shown moderate selective activity towards colon tumour cell lines. Lissoclinidines **1.27** are isolated from marine ascidian of the *Lissoclinum genus*. They have also shown potential

in a novel anticancer approach in which the activity of p53 tumour suppressor gene is restored. The gene is significant in preventing the transformation of normal cells into cancer cells.[12,16,21,23]

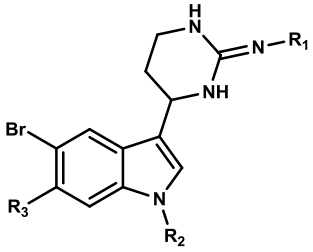


1.26 **1.27**

R = NH_2, NHCOMe

Figure 1.11: Pentacyclic pyridoacridines ascididemin **1.26** and lissoclinolides A and B **1.27**.

Aplicyanins **1.28** (A–F), shown in *Figure 1.12*, are extracted from the tunicate *Aplidium cyaneum*, which is collected in Antarctica. They all contain a 3-(2-imino-1,4,5,6-tetrahydropyrimidin-4-yl)-5-bromoindole nucleus with different substituents on the imine, *N*-indole and sometimes a second bromine at the 6-position of indole is present. Aplicyanins **1.28** (A–F) have been tested for cytotoxicity against three human tumour cell lines, including human tumour cell lines MDA-MB-231 (breast adenocarcinoma), A549 (lung carcinoma), and HT-29 (colorectal carcinoma) and also exhibit antimitotic activity. The cellular arrest in mitosis may involve interaction of the drug to either tubulin or microtubule formation, which usually leads to apoptosis.[1,16,24]



1.28

A: R_1= R_2=R_3=H
B: R_1=Ac; R_2=R_3=H
C: R_1=R_3=H; R_2=OMe
D: R_1=Ac; R_2=OMe; R_3=H
E: R_1=H; R_2=OMe; R_3=Br
F: R_1=Ac; R_2=OMe; R_3=Br

Figure 1.12: Aplicyanins **1.28** (A–F) from the tunicate *Aplidium sp*.

Finally, the alkaloids known as eudistomins, shown in *Figure 1.13*, contain either a substituted β-carboline system or a condensed β-carboline and an oxazepine in the ring system. They are thought to be biosynthetically derived from tryptophan and cysteine. The eudistomins are isolated from the tunicates *Eudistoma olivaceum, glaucus, gilboverde* and *album*, which are responsible for most of the halogenated β-carbolines. Eudistomin A, E, G and K (**1.29–1.32**) exhibit antitumour activity against L-1210, A-549, HCT-8 and P-388 cell lines. Although all the isolated eudistomins exhibited some antimicrobial and/or antiviral activity, the tetracyclic eudistomins with the unique oxathiazepine ring exhibited significant antiviral activity against *Herpes simplex* virus type (HSV-1).[1,4,6,14,16]

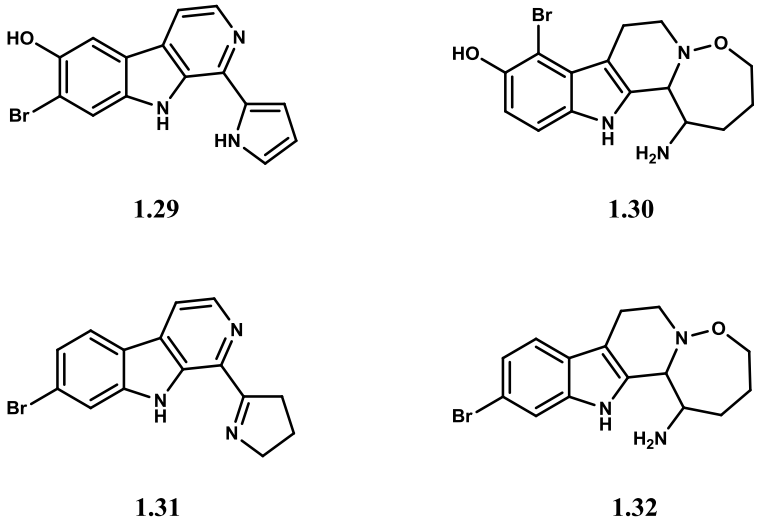
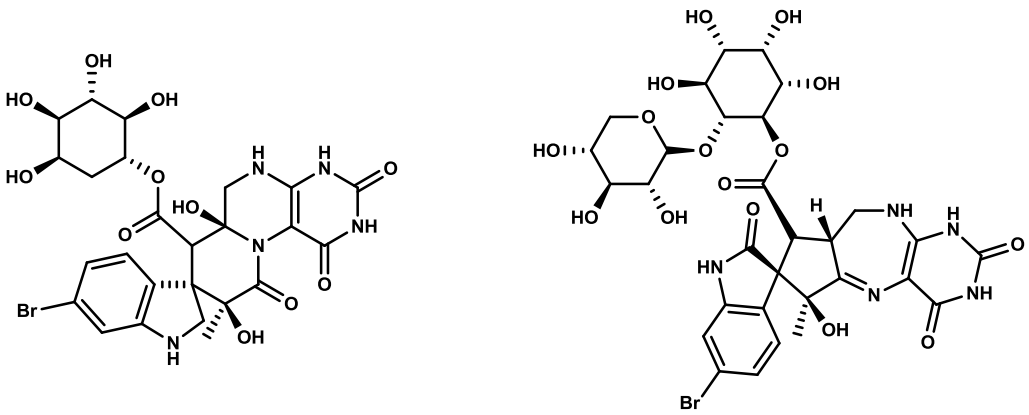


Figure 1.13: Halogenated β-carbolines, eudistomin A, E, G and K (**1.29–1.32**).

1.2.2.3 Molluscs

Molluscs are marine invertebrates of the phylum Mollusca. They make up the largest marine phylum, consisting of around 23% of the marine organisms. Marine snails of the family Conidae have been known to synthesize potent toxins which they inject into their prey by means of a hollow tooth. In 1965, food poisoning occurred due to ingestion of a carnivorous Japanese ivory mollusc, *Babylonia japonica*, which was captured in the Shizuoka district of Suruga Bay. The patients complained of visual deficiencies, such as mydriasis (the dilation of the pupils) and

amblyopia (lazy eye), speech defects, dryness of mouth, gastric distension, constipation, vomiting and dysuria (painful urination). The poisoning was apparently due to toxins, which were later discovered to have originated in the mid-gut gland of the mollusc. The two toxin were later isolated as surugatoxin **1.33** and neosurugatoxin **1.34** (*Figure 1.14*). Surugatoxin **1.33** evoked mydriasis in mice at a minimum dose of 0.05 μg/g body. Neosurugatoxin **1.34** evoked mydriasis in mice at a minimum dose of 3 μg/g body. Neosurugatoxin **1.34** has been thus been identified as the main cause of the potent poison (approximately 60 times more toxic than surugatoxin **1.33**). It was also found to be extremely unstable in alkaline medium and fairly heat labile. Neosurugatoxin **1.34** was found to be a potent antagonist of nicotinic agonists and is over 5,000 times more active as a ganglion blocking agent than existing drugs; it specifically blocks only nicotinic receptors in the ganglion.[16,25,26]

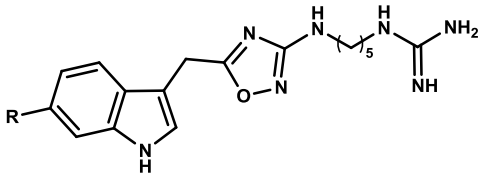


1.33 **1.34**

Figure 1.14: Marine mollusc toxins surugatoxin **1.33** and neosurugatoxin **1.34**.

The 3-substituted indole alkaloids, phidianidines A **1.35** and B **1.36**, illustrated in *Figure 1.15*, are the first example of marine natural products bearing a 1,2,4-oxadiazole scaffold, which is extremely rare in nature. Phidianidines A **1.35** and B **1.36** are isolated from the shell-less mollusc, *Phidiana militaris* belonging to the family Glaucidae. They have been extensively used in the design of potent, metabolically stable and bioavailable compounds and possess a broad range of biological properties including tyrosine kinase inhibition, muscarinic receptor agonist, histamine H_3 receptor antagonist, anti-inflammation activity, monoamine oxidase inhibition, and anticancer activity. Furthermore, they show significant cytotoxicity against cervical, cardiac

myoblast, and colorectal adenocarcinoma cell lines. Initial screening has indicated that the bromine on the indole is necessary for activity.[14,27,28]



1.35: R = Br
1.36: R = H

Figure 1.15: 1,2,4-Oxadiazole-bearing marine natural products, phidianidines A **1.35** and B **1.36**.

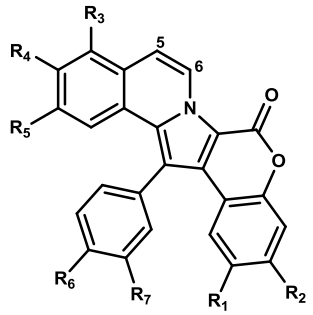
1.3 Lamellarin alkaloids

The lamellarin alkaloids were originally isolated from molluscs but were later found in many ascidian species. Lamellarins have become an important area of interest both synthetically and biologically. They will be reviewed more extensively in this section as they form an integral part of the thesis. Several important reviews describing the isolation, structure, synthesis and biological activity of lamellarins have been published.[4,29-32] These have been very helpful in the organisation of the material in the following section.

1.3.1 Background

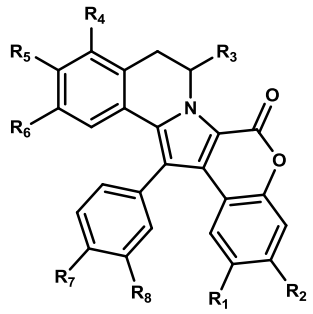
Lamellarins have attracted interest owing to their complex mechanism of action and structural originality. The lamellarins were originally extracted from a Palauan marine prosobranch mollusc *Lamellaria sp*. in 1985 by Faulkner and co-workers. Four metabolites were isolated from the mollusc, lamellarins A to D.[33] Subsequently, lamellarins have also been isolated from primitive chordate ascidian (tunicate) sources. In 1988, Fenical and co-workers[34] obtained lamellarins E–H from the marine ascidian *Didemnum chartaceum*, and in 1993 Bowden and co-workers[35] obtained lamellarins I–N from a similar *Didemnum* ascidian species. The lamellarins are a continually growing family and to date at least 70 lamellarins and other related pyrrole

products have been isolated.[9,36] The ascidian species that produce the lamellarin metabolites are known to produce many bioactive metabolites and it has been suggested that they are likely to be the original producer of lamellarins as they are the main dietary source of the *Lamellaria* mollusc. However, it has also been suggested that lamellarins are produced from microorganisms symbiotic to the ascidians and molluscs.[4] Lamellarins are generally pentacyclic and can be characterized by a central pyrrole ring fused to adjacent rings, which include isoquinoline and lactone functionality. The isoquinoline moiety at position 5 and 6 can be either unsaturated (Type I, *Figure 1.16*) or saturated (Type II, *Figure 1.17*). In some cases, the central pyrrole ring can also be isolated from the adjacent rings (Type III, *Figure 1.18*) forming simple pyrrole lamellarins. Derivatives include the phenolic hydroxyl groups substituted with methoxy, sulphate and acetate groups.[4,37]



Unsaturated	R_1	R_2	R_3	R_4	R_5	R_6	R_7
B	OMe	OH	OMe	OMe	OMe	OMe	OH
B diacetate	OMe	OAc	OMe	OMe	OMe	OMe	OAc
B 20-sulphate	OMe	OSO_3^-	OMe	OMe	OMe	OMe	OH
D	OMe	OH	H	OMe	OH	OMe	OH
D triacetate	OMe	OAc	H	OAc	OMe	OMe	OAc
H	OH	OH	H	OH	OH	OH	OH
M	OMe	OH	OH	OMe	OMe	OMe	OH
M triacetate	OMe	OAc	OAc	OMe	OMe	OMe	OAc
N	OMe	OH	H	OMe	OMe	OH	OMe
N triacetate	OMe	OAc	H	OAc	OMe	OAc	OMe
W	OMe	OH	OMe	OMe	OMe	OH	OMe
X	OMe	OH	OH	OMe	OMe	OH	OMe
X triacetate	OMe	OAc	OAc	OMe	OMe	OAc	OMe
α	OMe	OSO_3Na	OMe	OMe	OMe	OH	OMe
α 20-sulphate	OMe	OSO_3Na	H	OMe	OMe	OH	OMe
α 13,20-disulphate	OMe	OSO_3Na	H	OMe	OMe	OSO_3Na	OMe
ε	OMe	OH	OH	OMe	OMe	OMe	OMe
ζ	OMe	OH	OMe	OMe	OMe	OMe	OMe
η	OMe	OH	H	OMe	OMe	OMe	OMe
ϕ	OMe	OAc	OMe	OMe	OAc	OMe	OAc

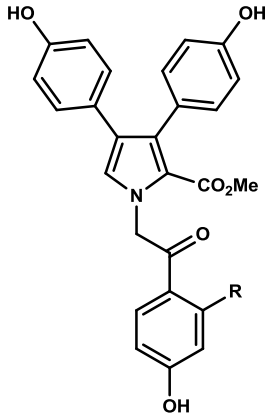
Figure 1.16: Type I unsaturated pentacyclic lamellarins.[29-31]



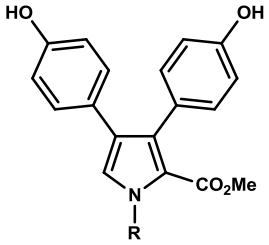
Saturated	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
A	OMe	OH	OH	OMe	OMe	OMe	OMe	OH	H
A triacetate	OMe	OAc	OAc	OMe	OMe	OMe	OMe	OAc	H
C	OMe	OH	H	OMe	OMe	OMe	OMe	OH	H
C diacetate	OMe	OAc	H	OMe	OMe	OMe	OMe	OAc	H
C20-sulphate	OMe	OSO_3^-	H	OMe	OMe	OMe	OMe	OH	H
E	OMe	OH	H	OH	OMe	OMe	OH	OMe	H
F	OMe	OH	H	OH	OMe	OMe	OMe	OMe	H
G	OH	OMe	H	H	OH	OMe	OH	OMe	H
G 8-sulphate	OH	OMe	H	H	OSO_3^-	OMe	OH	OMe	H
I	OMe	OH	H	OMe	OMe	OMe	OMe	OMe	H
I acetate	OMe	OAc	H	OMe	OMe	OMe	OMe	OMe	H
J	OMe	OH	H	H	OH	OMe	OMe	OMe	H
K	OMe	OH	H	OH	OMe	OMe	OMe	OH	H
K diacetate	OMe	OAc	H	OH	OMe	OMe	OMe	OAc	H
K triacetate	OMe	OAc	H	OAc	OMe	OMe	OMe	OAc	H
L	OMe	OH	H	H	OH	OMe	OH	OMe	H
L triacetate	OMe	OAc	H	H	OAc	OMe	OAc	OMe	H
L 20-sulphate	OMe	OSO_3^-	H	H	OH	OMe	OH	OMe	H
S	OH	OH	H	H	OH	OMe	OH	OH	H
T	OMe	OH	H	OMe	OMe	OMe	OH	OMe	H
T diacetate	OMe	OAc	H	OMe	OMe	OMe	OAc	OMe	H
T 20-sulphate	OMe	OSO_3Na	H	OMe	OMe	OMe	OH	OMe	H
U	OMe	OH	H	H	OMe	OMe	OH	OMe	H
U 20-sulphate	OMe	OSO_3Na	H	H	OMe	OMe	OH	OMe	H
V	OMe	OH	OH	OMe	OMe	OMe	OH	OMe	H
V 20-sulphate	OMe	OSO_3Na	OH	OMe	OMe	OMe	OH	OMe	H
Y	OMe	OH	H	H	OMe	OH	OH	OMe	H

Y 20-sulphate	OMe	OSO_3Na	H	H	OMe	OH	OH	OMe	H
Z	OH	OMe	H	H	OH	OMe	OH	OH	H
β	OH	OH	H	H	OH	OH	OH	OMe	H
γ	OMe	OH	H	OH	OMe	OMe	OMe	H	OMe
χ	OMe	OAc	H	H	OAc	OMe	OMe	OAc	H

Figure 1.17: Type II saturated pentacyclic lamellarins.[29-31]



Lamellarin O, R = H
Lamellarin P, R = OH



Lamellarin Q, R = H
Lamellarin R, R = C_6H_4-p-OH

Figure 1.18: Structures of isolated type III lamellarins.[29-31]

Several lamellarins have attracted a large amount of interest owing to their wide range of biological potential especially with some important cytotoxic activities.[4,29,30,32,37-42] The next section will describe some of the important biological implications and studies reported for numerous lamellarins.

1.3.2 Biomedical aspects of the lamellarins

The different biological properties of lamellarins include multidrug resistance (MDR) modulation activities, antioxidant properties, HIV integrase inhibition and cytotoxicity against tumour cells.[7] Many lamellarins have been tested against activity for numerous ailments. Several deductions

have been drawn based on the structural relationship and its influence on the biological activity. It has been found that free phenolic groups at position R_2, R_4 and R_6; methoxy groups at R_5 and R_7; and the double bond at R_5 = R_6 all generally increase the activity of the lamellarin (*Figure 1.19*).

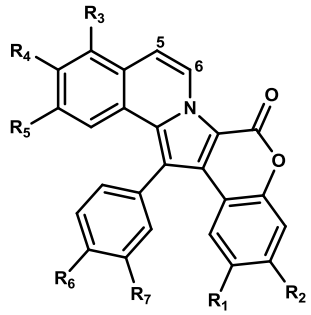


Figure 1.19: The general structures of a pentacyclic lamellarin, indicating the biologically potent sites.

1.3.2.1 Cytotoxicity and antitumor activity

The most common properties of the lamellarins are their cytotoxic activities and their capacity to inhibit the proliferation of cancer cells. The cytotoxic effect of lamellarins was first reported in 1993 by Carroll and co-workers.[35] Lamellarin D is one of the most cytotoxic compounds of the family (10–110 nM) and is thus an important contributor for potential synthetic analogues. Lamellarin D has shown good results against DU-145, LNCap (human prostate cancer) and K562 (leukemia) cell lines.[43,44] Lamellarins I, L and K exhibited good results against P388 (murine leukemia) and A549 (human lung carcinoma) cell lines, and lamellarins C and U have demonstrated potent cytotoxicity against 10 human tumour cell lines. Correspondingly, lamellarins D-triacetate E, F, H, K-triacetate, L-triacetate, M and N-triacetate, O, ***α, β,*** and ***ζ*** have also shown high activities toward a series of cell lines, including P388 (murine leukemia), A549 (human lung carcinoma), HT29 (human colon carcinoma), MEL28 (human melanoma), COLO-205 (colorectal cancer), HL-60 (human promyelocytic leukemia) and MDA-MB-231 (breast cancer) cells.[4,30,31,45,46]

1.3.2.2 Multidrug resistance (MDR) reversal activity

Multidrug resistance (MDR) is a term used to characterize the ability of a tumour to exhibit simultaneous resistance to various chemotherapeutic agents and has become one of the major obstacles to long-term cancer chemotherapy. Alteration of the activity of the target enzyme (such as glutathione-S transferase and topoisomerases), changes in apoptotic processes, and modification of drug efflux, implicating ABC (ATP-binding cassette) transporters (MDR proteins, MRP) explain the behaviour based on different mechanisms. Lamellarin L and I, with known cytotoxicity against certain cancer cell lines, have also demonstrated the reversal of MDR by inhibiting P-glycoprotein (P-gp) membrane (mediates the ATP-dependent drug efflux from cells) at non-cytotoxic concentrations thus resensitizing the resistant malignant cells to frontline therapeutics.[4,30,31,47]

1.3.2.3 Inhibition of HIV 1 integrase

Inhibition of HIV-1 integrase has become a promising target for antiretroviral chemotherapy, which is one of the most important areas of biological interest due to the prevalence of AIDS remaining extremely high. Despite the efficacy of the highly active antiretroviral therapy (HAART) and the continuous development of chemotherapeutic agents targeting HIV-1 reverse transcriptase and protease, newer effective drugs are still required. HIV-1 integrase promotes the integration of proviral DNA into the host cell chromosomal DNA. A few members of the lamellarin family displayed integrase inhibition activities. In 1999, Faulkner and co-workers reported that lamellarin α 20-sulphate is a selective inhibitor of HIV-1 integrase and is able to act at two different steps of the catalytic cycle, namely it inhibits terminal cleavage (IC_{50} = 16 μM) and strand transfer (IC_{50} = 22 μM) of the HIV-1 virus.[48,49] Moreover, this compound inhibits viral replication at nontoxic doses. Although lamellarins H and α 13,20-disulphate have also shown potent inhibition, the sulphate group is thought be an important structural factor for these biological results.[4,30,31]

1.3.2.4 Topoisomerase I inhibition

Topoisomerases are fundamental enzymes that relax the supercoils, which are generated during DNA replication, transcription, or recombination. The inhibition of the enzyme results in single-strand and thus double-strand DNA breakages, causing lethal DNA damage and the induction of apoptosis. Therefore topoisomerase inhibitors, which stabilize the topoisomerase I-DNA cleavage, are promising drugs for cancer therapies. In 2003, Bailly and co-workers discovered the potential of lamellarin D as a topoisomerase I inhibitor.[50] Lamellarin D binds relatively weakly to DNA, presumably via the insertion of its planar pentacyclic chromophore between DNA base pairs, exposing the perpendicular methoxyphenol moiety toward the DNA where enzymes can be trapped. It is also stabilized by the ternary complex by forming stacking interactions and hydrogen bonding. This DNA interaction, although relatively weak, provides the stabilization of the DNA-enzyme complex. Lamellarin H has also shown some potential as a topoisomerase I inhibitor. Lamellarin analogues with the saturated C5–C6 bond (type II) were shown to be approximately 50 times less cytotoxic than their unsaturated analogues, which suggests that the non-planar conformation prevents the intercalation of the compound to the DNA strand.[4,31,51]

1.3.2.5 Miscellaneous biological properties

Inhibition of protein kinases such as cyclin-dependant kinases (CDKs), dual-specificity tyrosine-phosphorylated and -regulated kinase 1A (DYRK1A), casein kinase 1 (CK1), glycogen synthase kinase-3 (GSK-3), and proto-oncogene serine/threonine protein kinase (PIM-1) have been tested on several lamellarins including lamellarins D, H, L, and N. Lamellarin N was found to have selectivity against some of the mentioned protein kinases, including those related to Alzheimer's disease. A good correlation between inhibition of protein kinases by lamellarins and cell death could thus lead to important antitumour effects. However, further studies are required in this section of study.[31,45]

Antioxidants are chemicals that inhibit the rate of oxidation resulting in the formation of different chemicals. Antioxidants protect cells against the effects of free radicals are are important for the chemistry and biology of the body. They can become toxic to cells through lesions caused to lipids, proteins, and DNA. Mitochondria are the main source of energy in the cell and naturally produce reactive oxidant species (ROS). When deficient ROS production arises, cancer, arteriosclerosis, or neurodegeneration occurs. The antioxidant activity of several lamellarins including lamellarins C-diacetate, I, K, U, γ, γ-monoacetate were tested, which demonstrated weak free radical scavenging activity at the millimolar range.[4,30,31]

Many lamellarins including lamellarins A, B, C, D triacetate, I, J, K, L, M, N triacetate and Q have also been tested for antibiotic and antibacterial activity against gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* and *Micrococcus luteus*. No activity was found.[4,30,31]

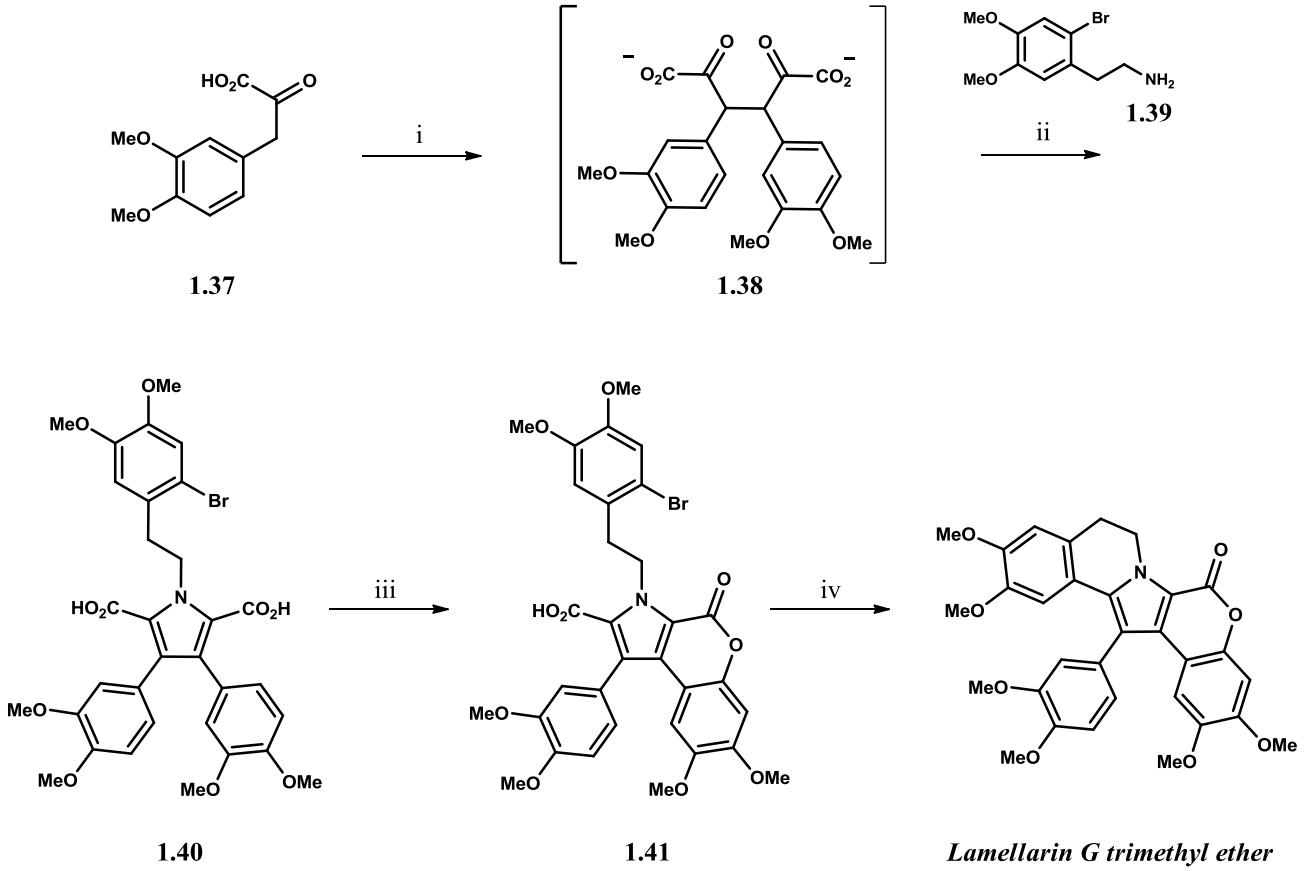
Thus, the introduction to lamellarins shown in this Section illustrates the wide range of biological activities along with the interesting structural features of lamellarins that have attracted considerable interest from the synthetic community. A brief review will be given for the synthesis of various lamellarins, indicating key synthetic points and novel directions taken in the reported syntheses.

1.4 A selection of reported syntheses of lamellarin alkaloids[4,29-32]

Although lamellarins have been isolated from natural sources, in terms of medicinal studies, the synthesis of lamellarins is a more viable and eco-friendly means of obtaining these sought-after compounds. Several synthetic approaches have been conceived for these natural products. In general, lamellarins have been synthesized using two main strategies: (i) by pyrrole formation as the key step of the synthesis and (ii) by transformation of a pre-existing pyrrole derivative through cross-coupling reactions. An assessment on the synthesis of only the pentacyclic lamellarins will be covered in this Section as they pertain directly to this PhD project.

1.4.1 Synthesis by Steglich *et al.*

In 1997, Steglich and co-workers[52] completed the first biomimetic synthesis of lamellarin G trimethyl ether (*Scheme 1.1*). The main attribute of the synthesis was the coupling of two 3-(3,4-dimethoxypheny)pyruvic acid **1.37** units by treating the acid with *n*-butylithium followed by iodine to give the 1,4-dicarbonyl **1.38**. The 1,4-dicarbonyl **1.38** was then directly transformed into the pyrrole **1.40** by reacting it with amine **1.39**, which afforded the pyrrole **1.40** in 62% yield. Selective oxidative cyclization was then achieved by treating the dicarboxylic acid **1.40** with lead tetraacetate in refluxing ethyl acetate which afforded the lactone **1.41**. Finally, an intramolecular Heck reaction gave the dihydroisoquinoline unit which afforded lamellarin G trimethyl ether in 74% yield. The synthesis was carried out in 33% overall yield.

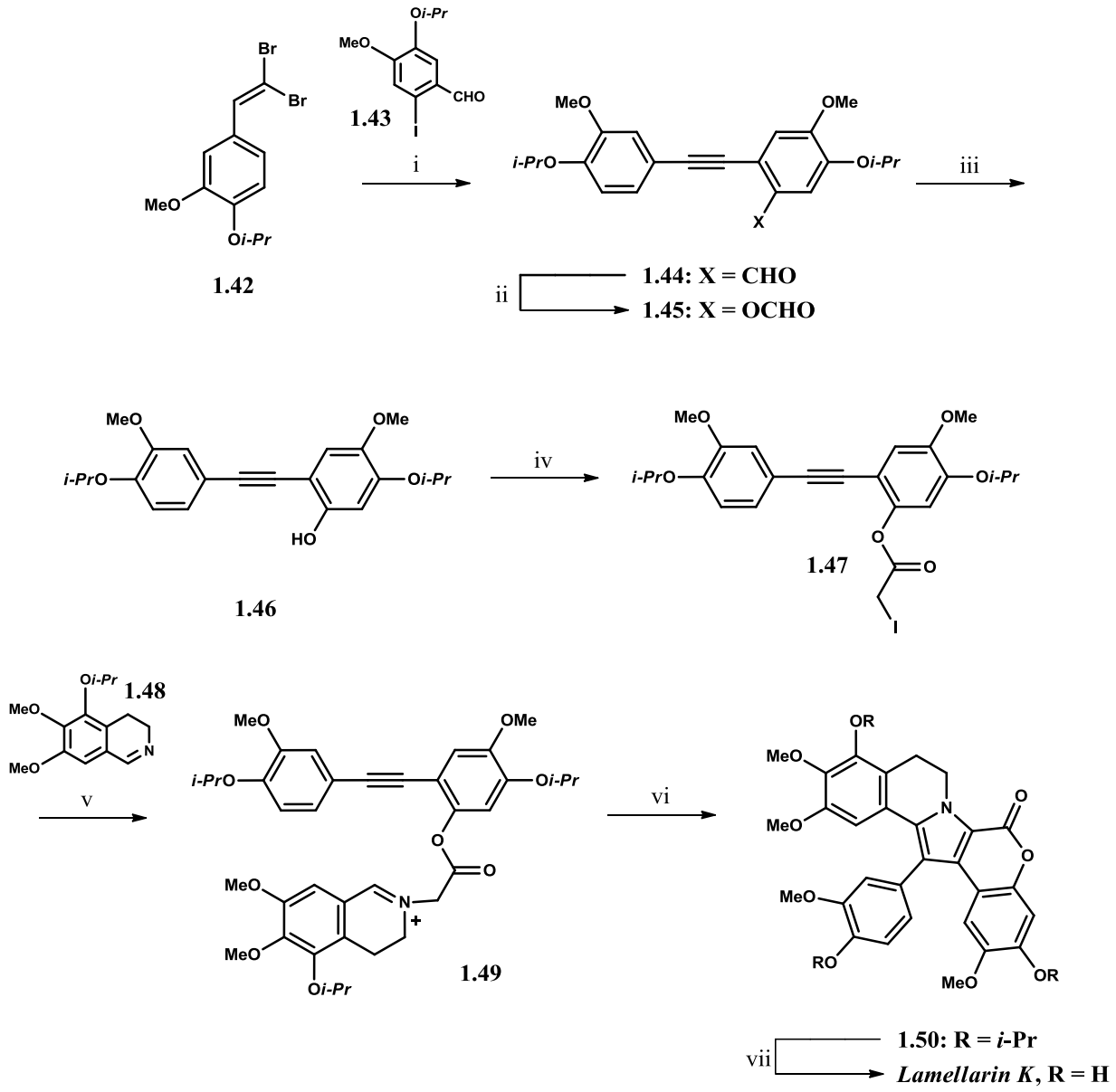


Scheme 1.1 *Synthesis by Steglich et al.*[52]: i.a. BuLi; b. I_2; ii. **1.39**, molecular sieves, 62% (3 steps); iii. $Pb(OAc)_4$, 71 %; iv. $Pd(OAc)_2$, Ph_3P, Et_3N, MeCN, 74%.

In 2000, Steglich and co-workers[53] were the first to synthesize lamellarin L by using similar methodology to that shown in *Scheme 1.1*. However, instead of using 3-(3,4-dimethoxypheny)pyruvic acid **1.37** as a coupling agent, aryl pyruvates prepared from vanillin were used. The synthesis was completed over six steps in an overall yield of 38%.

1.4.2 Syntheses by Banwell *et al.*

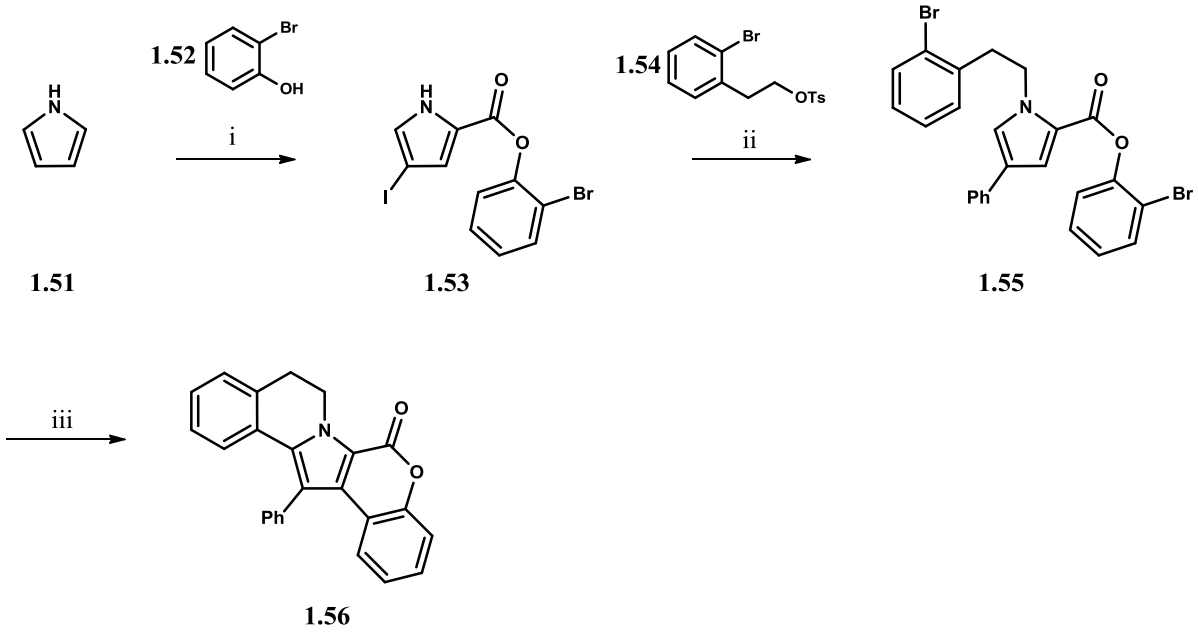
In 1997, Banwell and co-workers{{Banwell, 1997 #118;Banwell, 1997 #119} developed an intramolecular 1,3-dipolar cycloaddition synthesis for the key formation of the pyrrole core (*Scheme 1.2*). The dibromostyrene **1.42** was involved in a palladium-mediated cross-coupling reaction between the intermediate alkynylzinc chloride and the aryl iodide **1.43**, which yielded the alkyne **1.44**. A Baeyer-Villiger reaction with *meta*-chloroperoxybenzoic acid resulted in the formation of the formate ester **1.45**, which was readily hydrolysed to the phenol **1.46**. *N*,*N*'-Dicyclohexylcarbodiimide-mediated condensation with iodoacetic acid afforded the ester **1.47**, which reacted with 3,4-dihydro-6,7-dimethoxy-5-isopropoxyisoquinoline **1.48** to give the ammonium salt intermediate **1.49**. The salt was immediately treated with Hünig's base (*N*,*N*-diisopropylethylamine) and refluxed in 1,2-dichloroethane to give lamellarin K triisopropyl ether **1.50**. Deprotection of the isopropyl group with aluminium trichloride provided the target compound lamellarin K.



Scheme 1.2 *1997 Synthesis by Banwell et al.*[54]*:* i. **1.43**, BuLi, $ZnCl_2$, $Pd(Ph_3P)_4$, 18, 84%; ii. *m*CPBA, $KHCO_3$; iii. NH_3, MeOH; iv. ICH_2CO_2H, DCC, DMAP, 89% (3 steps); v. **1.48**; vi. Hünig's base ($C_8H_{19}N$), 81%; vii. $AlCl_3$, CH_2Cl_2, 96%.

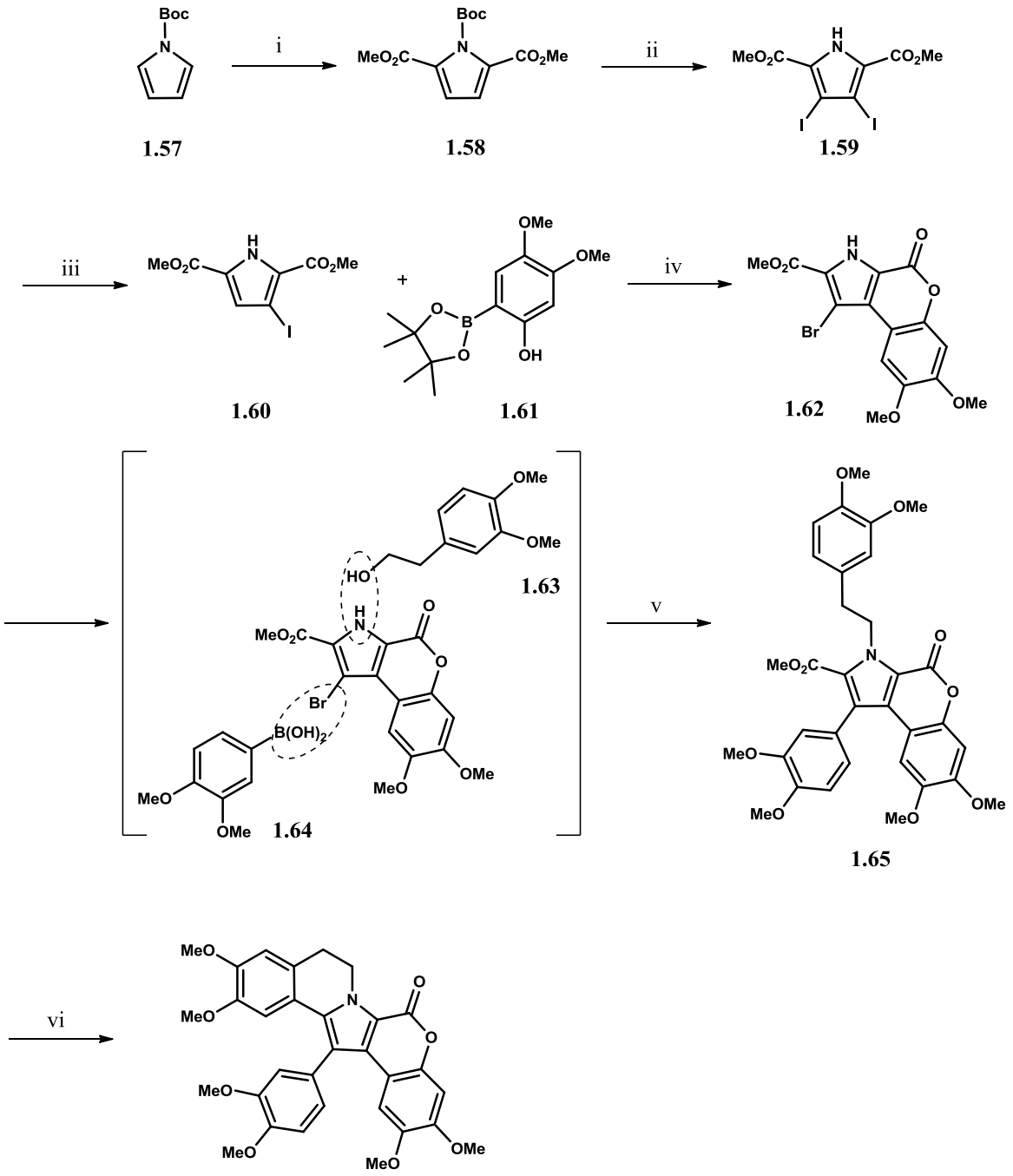
In 1999, Banwell and co-workers[55] synthesized the basic lamellarin skeleton using a key double Heck cyclization approach (*Scheme 1.3*). Pyrrole **1.51**, a commercially available starting material, was used in a reaction with methyl chloroformate to give an acylated intermediate, which could then be iodinated, substituted and reacted with **1.52** to give product **1.53**. Compound **1.55** was prepared by coupling product **1.53** with reactant **1.54** using phenylzinc

chloride and tetrakis(triphenylphosphine)palladium(0). Finally, the lamellarin skeleton **1.56** was synthesized in 16% yield by reacting compound **1.55** with palladium(II) acetate and triphenylphosphine.



Scheme 1.3 *Double Heck approach by Banwell et al.*[55]*:* i.a. **1.51**, $ClCO_2CH_3$, 80%; b. I_2, AgOTFA, 82%; c. aq. K_2CO_3, 92%; c. oxalyl chloride; d. 41, 92%; ii.a. **1.54**, K_2CO_3, DMF, 89%; b. PhZnCl, $Pd(Ph_3P)_4$, 95%; iii. $Pd(OAc)_2$, Ph_3P, NaOAc, 135°C, 16%.

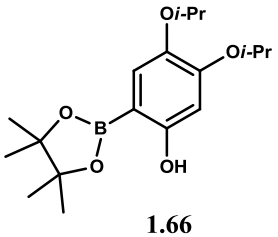
In 2011, Banwell and co-workers[56] described the synthesis of lamellarin G trimethyl ether (*Scheme 1.4*). A commercially available *N*-Boc protected pyrrole **1.57** was reacted with *tert*-butyllithium and methyl chloroformate to afford the diester **1.58**. The Boc group was then deprotected by heating with DMF and the 3- and 4-positions of the pyrrole were iodinated with *N*-iodosuccinimide (NIS) to afford the product **1.59** in 97% yield. Activated zinc powder in *N*,*N*-dimethylacetamide (DMA) at 120°C were then used to afford the mono-iodinated product **1.60**. Using previously described methodology adapted by Banwell and his colleagues, boronic ester **1.61** was coupled to **1.60** and following a spontaneous lactonization a tricyclic lactone **1.62** was afforded. A second coupling reaction with boronic acid **1.64** and a condensation reaction with prepared alcohol **1.63** to lactone **1.62** afforded tricyclic product **1.65**. A saponification of the remaining ester in product **1.65** followed by a decarboxylative Heck reaction using palladium diacetate afforded lamellarin G trimethyl ether in 48% yield.



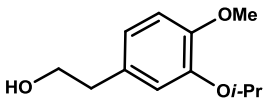
Lamellarin G trimethyl ether

Scheme 1.4 *2011 synthesis by Banwell et al.*[56]*:* i.a. NBS; DMF b. *t*-BuLi, MeOCOCl, 50% (2 steps); ii. NIS, DMF, 130°C, 12 h, 97%; iii. Zn, DMA 18–120°C, 69%; iv.a. K_2CO_3, TBAB, **1.61**, $Pd(PPh_3)_4$,THF/H_2O, 150W, 60°C, 1 h; b. NBS, DMF, 59%; v.a. **1.63**, DIAD, PPh_3, THF, 62%, b. K_2CO_3, TBAB, **1.64**, $Pd(PPh_3)_4$,THF/H_2O, 150W, 90°C, 1 h; vi.a. KOH, then HCl, 0°C, then *p*-TsOH, toluene, 57%; b. $Pd(OAc)_2$, MeCN, 19–80°C, 48%.

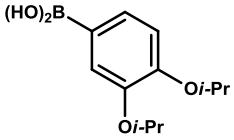
Lamellarin S was then prepared using the established methodology described above and in the previous syntheses reported by Banwell *et al*. However, several variants of the phenylethanol, boronic acid and boronic ester were prepared that encompassed the groups required for the coupling reactions (*Figure 1.20*). Therefore, di-*iso*-propoxy derivatives of the arylboronic ester **1.66**, β-phenethyl alcohol **1.67** and arylboronic acid **1.68** were prepared and applied to the previously described methodology. Lamellarin S was obtained in a 97% yield as a pale-brown solid.



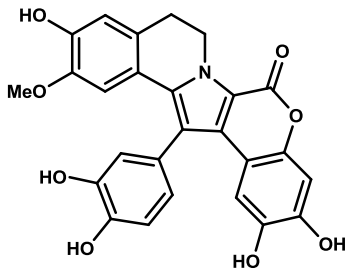
1.66



1.67



1.68

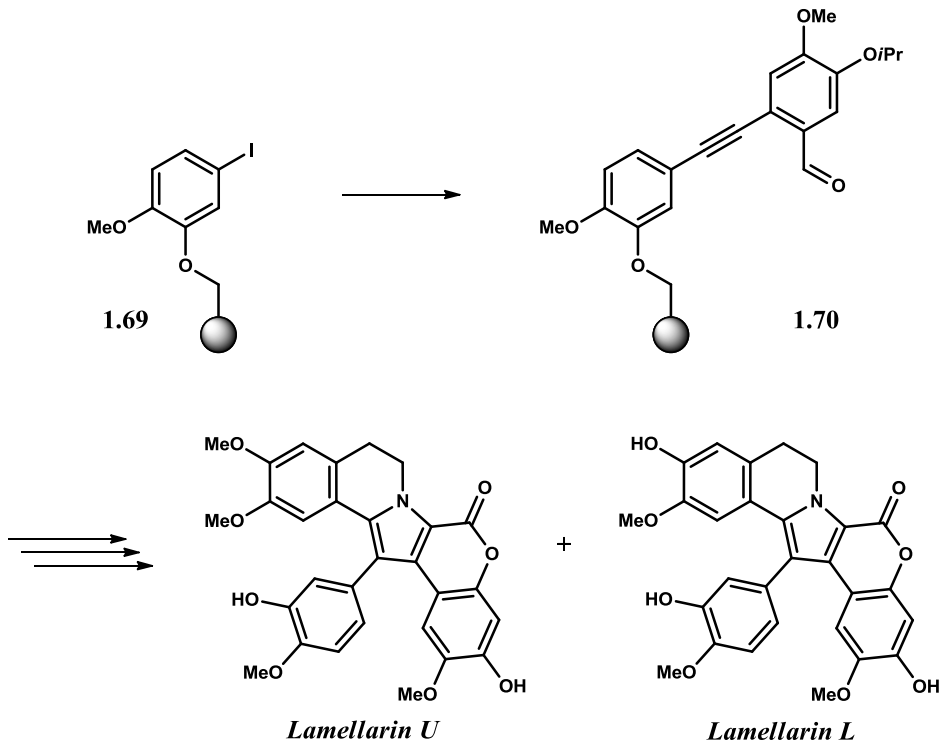


Lamellarin S

Figure 1.20: Coupling reagent used in the preparation of lamellarin S.

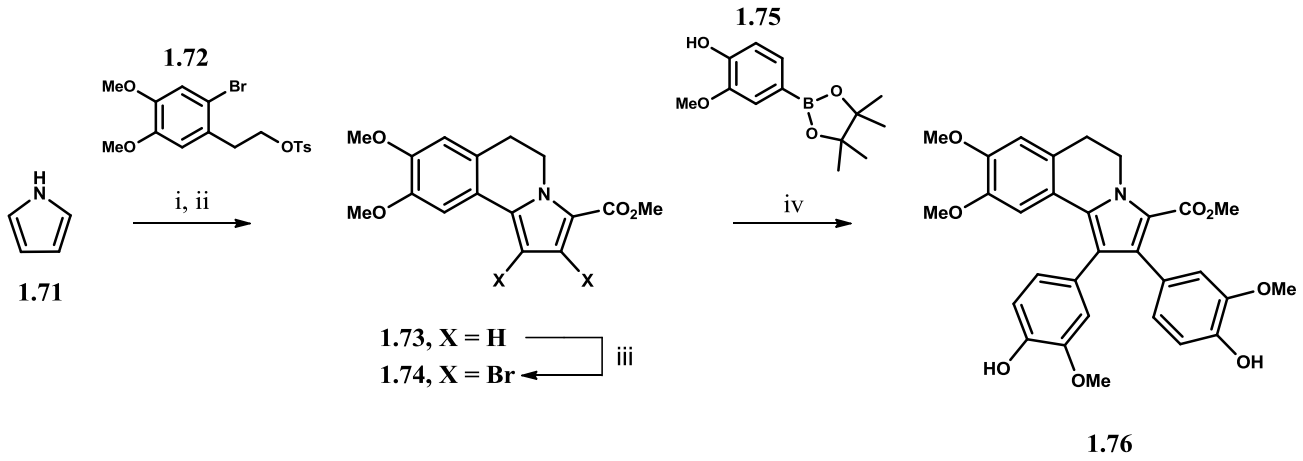
1.4.3 Syntheses by Álvarez, Albericio *et al.*

In 2004, Álvarez, Albericio and co-workers[29,57,58] adapted the synthesis described by Banwell in 1997[54] to include solid-phase methodology (*Scheme 1.5*). Aryl iodide **1.69** was used to prepared the alkyne **1.70**, from which Lamellarins U (10% overall yield), and L (4% overall yield) were obtained. The final products were cleaved from the Merrifield resin with aluminium trichloride in dry dichloromethane.



Scheme 1.5: **Á**lvarez's solid phase approach to synthesizing lamellarins U and L.

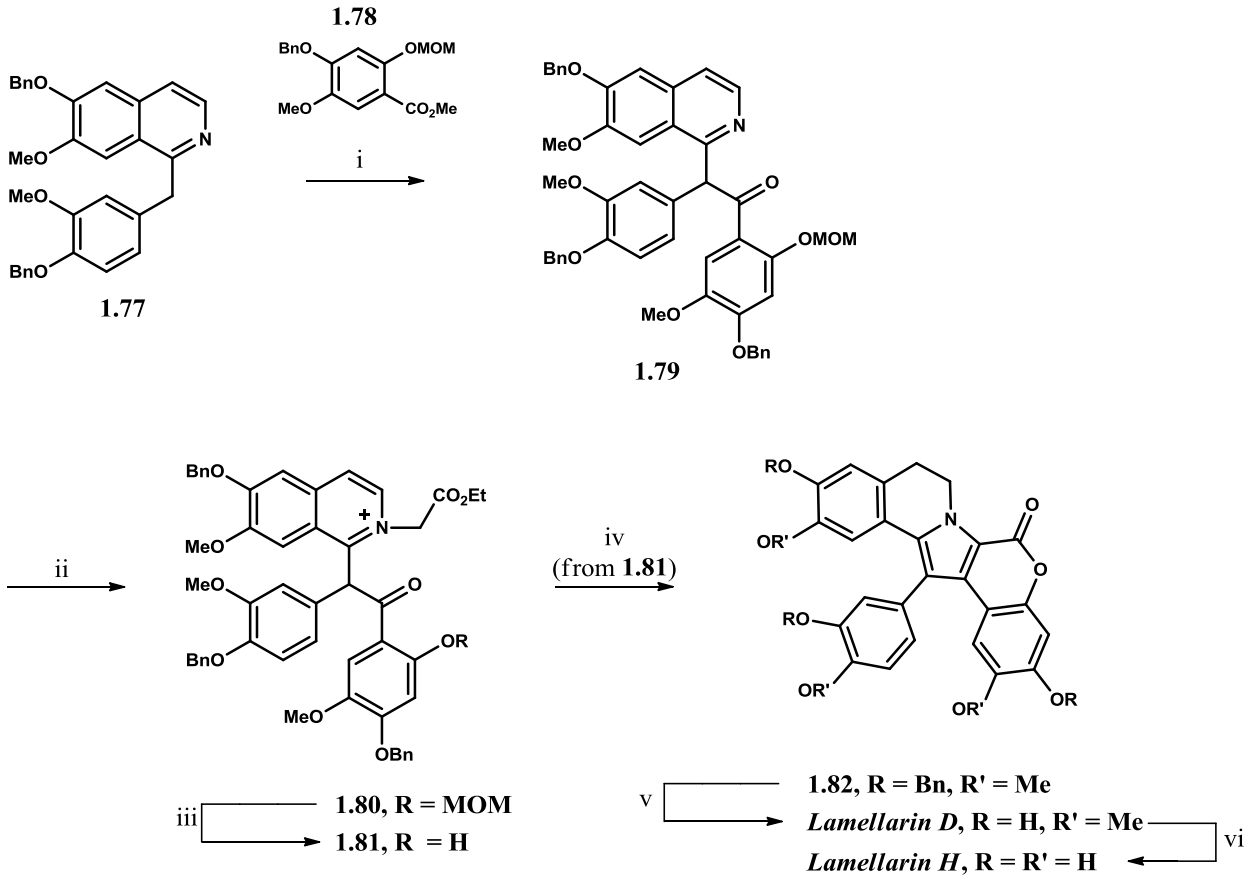
In 2005, Álvarez and co-workers[59,60] improved on the methodology for the Heck coupling approach for producing the lamellarin structures (*Scheme 1.6*). The approach involved the alkylation of the pyrrole ester **1.71** with the tosylate **1.72**. The Heck reaction proceeded with bis(triphenylphosphine)palladium(II) dichloride [$PdCl_2(Ph_3P)_2$], triphenylphosphine and potassium carbonate in *N*,*N*-dimethylformamide to afford the dihydroisoquinoline **1.73** in 81% yield. A dibromination with *N*-bromosuccinimide afforded the product **1.74**, which then underwent a Suzuki coupling with **1.75** to give the lamellarin-based skeleton **1.76** in 80% yield.



Scheme 1.6 *2005 approach by Alvarez et al.*[59]*:* i. **1.72**, NaH, DMF, 77%; ii. $PdCl_2(Ph_3P)_2$, Ph_3P, K_2CO_3, DMF, 81%; iii. NBS; 92%; iv. **1.75**, $Pd(Ph_3P)_4$, aq. Na_2CO_3, DMF, 80%.

1.4.4 Syntheses by Ishibashi, Iwao *et al*.

In 1997, Ishibashi and co-workers[38] accomplished the first total synthesis of lamellarin D and H, using *N*-ylide-mediated cyclization for the key pyrrole formation (*Scheme 1.7*). The two starting materials used (**1.77** and **1.78**) were coupled to give the product **1.79** as a mixture of keto/enol tautomers. *N*-Alkylation with ethyl bromoacetate to give product **1.80** followed by the removal of the MOM protecting group under catalytic acidic conditions afforded deprotected product **1.81**. Pyrrole formation and lactonization to give product **1.82** were accomplished by treatment of compound **1.81** with triethylamine to afford the product in 34% optimal yield, owing to the observation of significant decomposition. Deprotection of the benzyl groups by hydrogenation with Pd/C afforded lamellarin D, and further deprotection of the methyl ethers afforded lamellarin H.

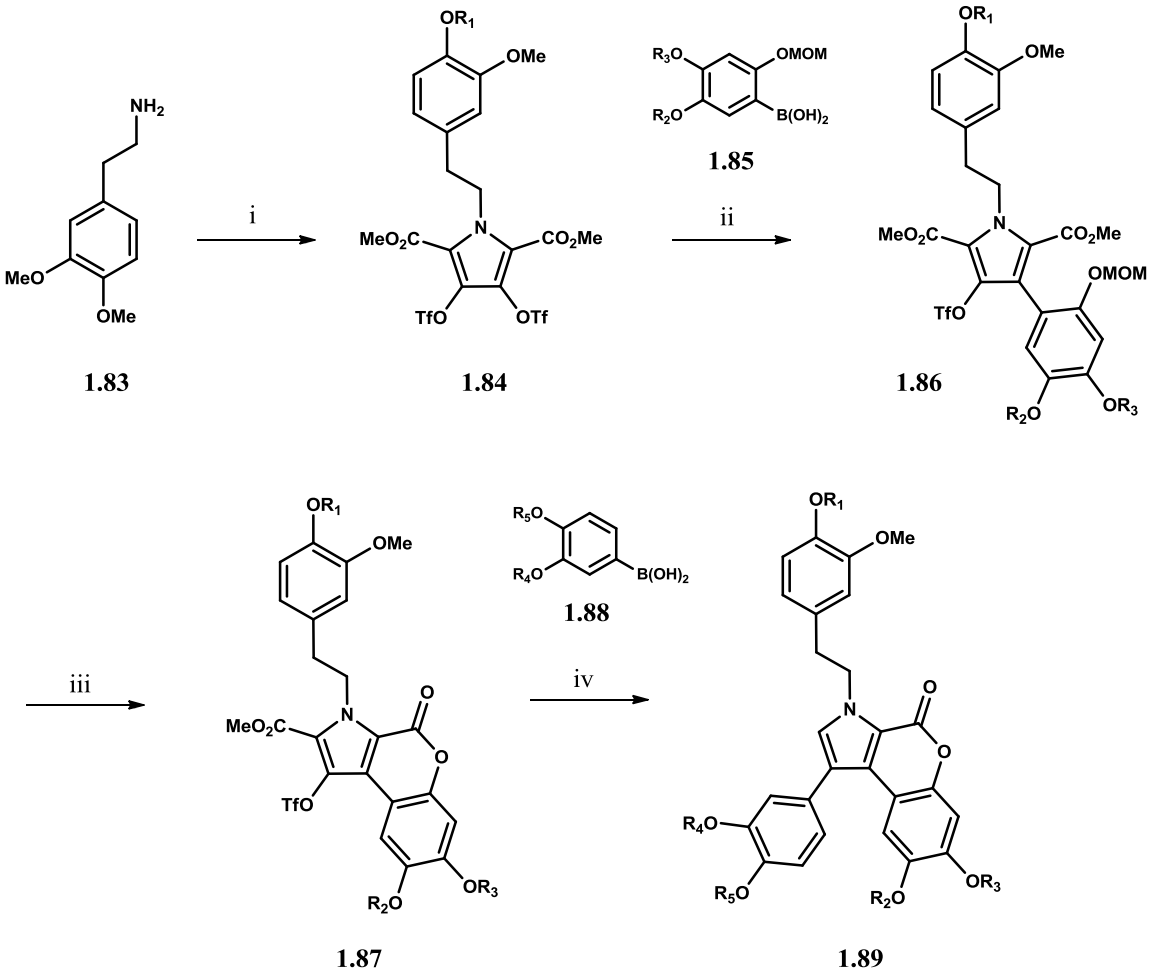


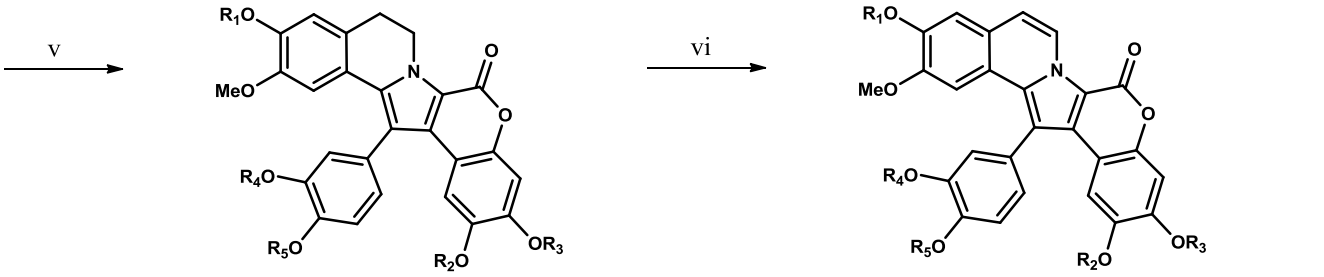
Scheme 1.7. *1997 approach by Ishibashi et al.*[38]*:* i. **1.78**, LDA, 63%; ii. $BrCH_2CO_2Et$; iii. cat. HCl, MeOH; iv. Et_3N, CH_2Cl_2, 34% (3 steps); v. H_2, Pd/C, EtOAc, 82%; vi. BBr_3, 68%.

In 2003, Ishibashi, Iwao and co-workers[61] synthesized lamellarin G trimethyl ether from amine **1.83** in an overall yield of 39% (*Scheme 1.8*). The bistriflate **1.84** was prepared in three steps from the amine **1.83**. A Suzuki coupling was then done on **1.84** with boronic acid **1.85** to afford product **1.86**. Lactonization of one of the methyl esters afforded product **1.87** in a 90% yield. A second Suzuki coupling was then done with boronic acid **1.88**. The remaining methyl ester then underwent a saponification and the carboxylic acid was then removed by a decarboxylation to afford compound **1.89**, using copper(I) oxide in hot quinoline. Lamellarin G trimethyl ether was afforded by the application of Kita's oxidative coupling conditions in a yield of 86%.

Lamellarin G trimethyl ether was the first compound prepared by these workers, and although slight modifications to the method have occurred throughout their subsequent publications, the

general method remains the same. In 2006,[62] the synthesis was expanded to include lamellarin D and N, which were afforded by creating the unsaturated bond (at the 5,6 position) with DDQ. The respective protecting groups were then removed with boron trichloride. Lamellarin D and N were afforded in quantitative yields. Finally in 2010,[49,63] lamellarin α, α-13-sulphate, α-20-sulphate, and α-13,20-sulphate were prepared by selectively deprotecting and reprotecting R_3 and R_4 to afford the products in 69–99% yields.





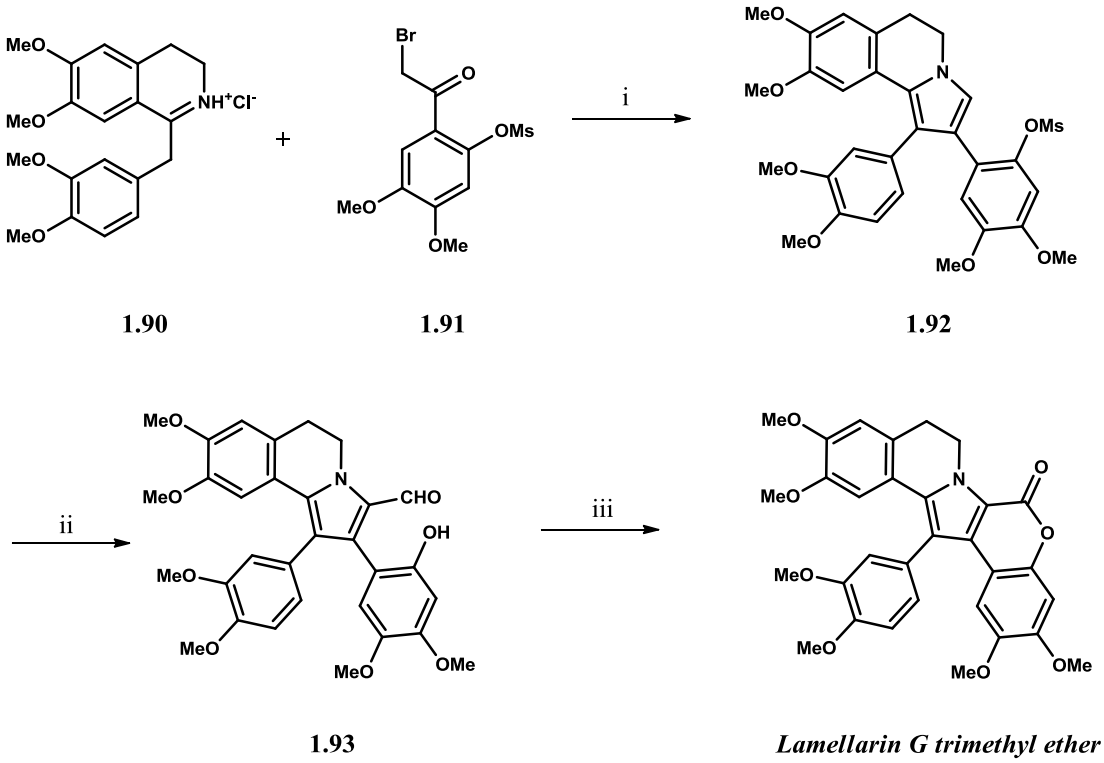
***Lamellarin G trimethyl ether*:**
R_1, R_2, R_3, R_4, R_5 = Me
***Lamellarin L*:**
R_1, R_3, R_4 = H; R_2,R_5 = Me

***Lamellarin D*: R_1, R_3, R_5 = H; R_2, R_4 = Me**
***Lamellarin N*: R_1, R_3, R_4 = H; R_2,R_5 = Me**
***Lamellarin α*: R_3, R_4 = H**
***Lamellarin α 20-sulphate*: R_3 = SO_3Na, R_4 = H**
***Lamellarin α 13-sulphate*: R_3 = H, R_4 = SO_3Na**
***Lamellarin α 13,20-sulphate*: R_3, R_4 = SO_3Na**
(all *Lamellarin α* R_1, R_2, R_5 = Me)

Scheme 1.8 *Synthesis of various lamellarin by Ishibashi et al.:* i.a. $BrCH_2CO_2Me$, $NaHCO_3$, MeCN, reflux, 91%; b. $(MeO_2C)_2$, NaOMe, MeOH, reflux, 49%; c. Tf_2O, Pyridine, 87%; ii. **1.85**, $Pd(Ph_3P)_4$, aq. Na_2CO_3, THF, reflux, 74%; iii.a. HCl, MeOH, reflux, 90%; b. *p*-TsOH, CH_2Cl_2, reflux, 93%; iv.a. **1.88**, $Pd(Ph_3P)_4$, aq. Na_2CO_3, THF, reflux, 95%; b. 40% aq. KOH, EtOH, reflux, 76%; b. PPTS, CH_2Cl_2, reflux, 61%; c. Cu_2O, quinoline, 220°C, 83%; v. PIFA, BF_3OEt, CH_2Cl_2,–40°C, 62%; vi. DDQ, CH_2Cl_2, reflux, 87%
(all the variations in substituent i.e. protections and deprotections have not been indicated)

1.4.5 Syntheses by Ruchirawat *et al.*

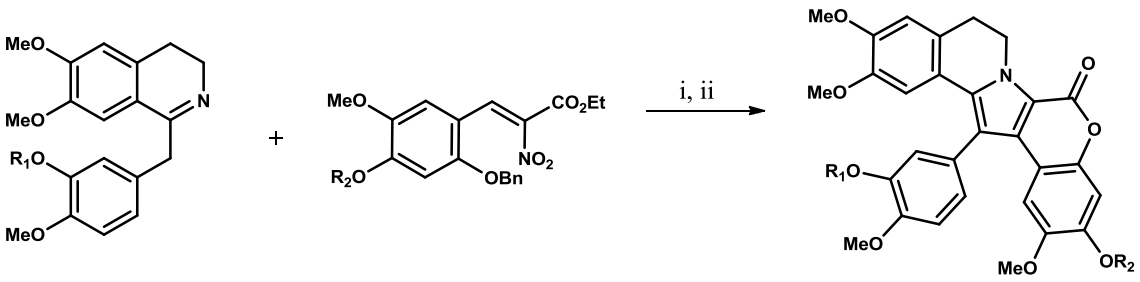
In 2001, Ruchirawat and Mutarapat[64] synthesized lamellarin G trimethyl ether in 33% yield over four steps using a condensation of 3,4-dihydropapaverine hydrochloride **1.90** with *o*-mesyloxyphenacyl bromide **1.91** in an intramolecular reaction between the enamine and the ketone (similar to the Knorr pyrrole synthesis) to afford the pyrrole[2,1-*a*]isoquinoline precursor **1.92** (*Scheme 1.9*). The pyrrole was then formylated with phosphorus oxychloride in a Vilsmeier reaction. The aldehyde **1.93** was formed in 85% yield. The mesylate group was then deprotected to expose phenol **1.93**. The phenol analogue was then reacted with bromobenzene, palladium acetate and triphenylphosphine to afford lamellarin G trimethyl ether in 80% yield.



Scheme 1.9 *2001 approach by Ruchirawat et al.*[64]*:* i. K_2CO_3, CH_3CN, reflux, 63%; ii.a. $POCl_3$, DMF, rt, 82%; b. KOH, EtOH, 81%; iii. $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, PhBr, 120°C, 80%.

Likewise in 2004, Ruchirawat and co-workers[41] adapted the above synthesis using a range of prepared papaverines and phenacyl halides (i.e. R = H, OH, OMe, OAc) from readily available starting materials such as vanillin, isovanillin and veratraldehyde. Lamellarin K was successfully synthesized in 93% yield and lamellarin L was synthesized in 87% yield over two steps. In 2006,[42] they also prepared lamellarins C, E, F, G, I, J, K, L, T, U, Y, α, χ (see *Figure 1.16* and *1.17* in *Section 1.3*) as well as some acetates of these and various unnatural lamellarin analogues in moderate to good yields of 45–71%.

In 2008, Liermann and Opatz[65] adapted this synthesis by preparing lamellarins G trimethyl ether and U with dihydroisoquinolines **1.94** and nitrocinnamates **1.95** (*Scheme 1.10*).



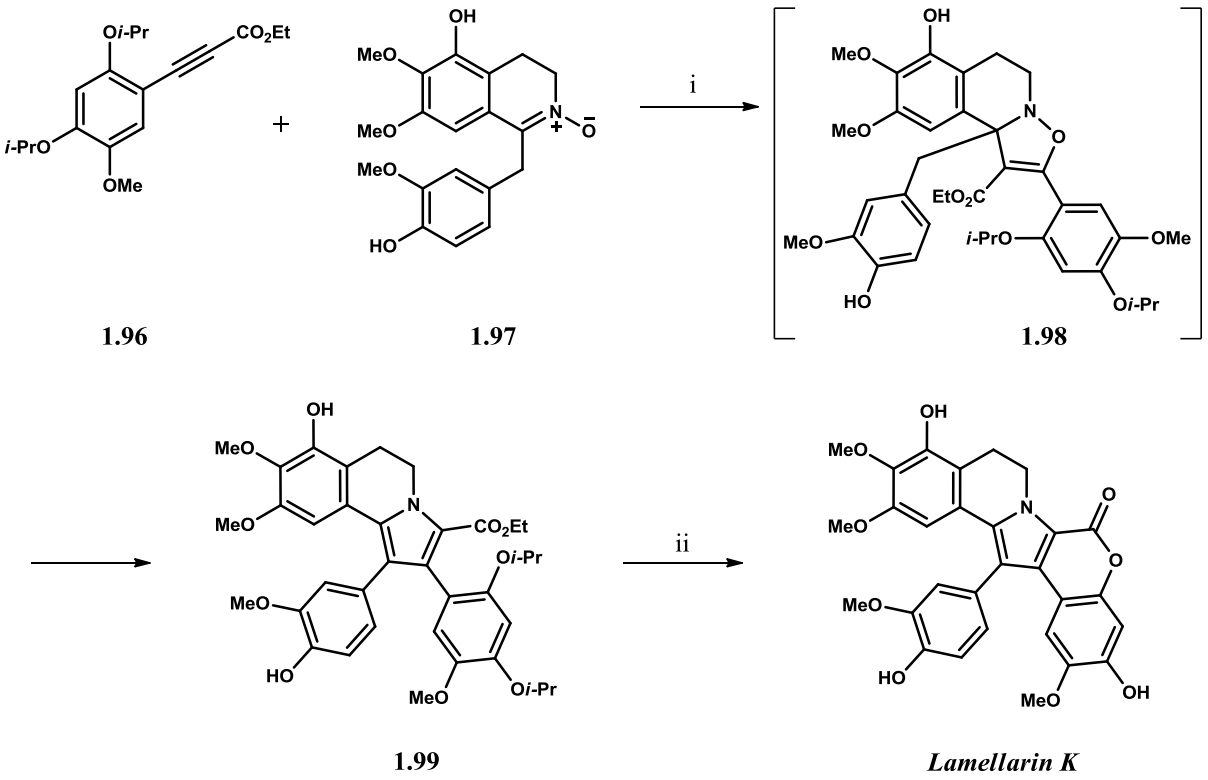
1.94 **1.95**

***Lamellarin G trimethyl ether*: R_1, R_2 = OMe**
***Lamellarin U*: R_1, R_2 = OH**

Scheme 1.10 *2008 synthesis by Liermann and Opatz[65]:* i. 2,6-di-*tert*-butyl pyridine, dioxane, 90°C, 42% (*Lamellarin G trimethyl ether*) or pyridine 90°C then HCl, EtOH, rt, 41% (*Lamellarin U*); ii.a. H_2, Pd/C, EtOH, HOAc, rt; b. DBU, toluene, 80°C, 79% (*Lamellarin G trimethyl ether*) and 85% (*Lamellarin U*).

1.4.6 Synthesis by Guitian, Diaz and Castedo

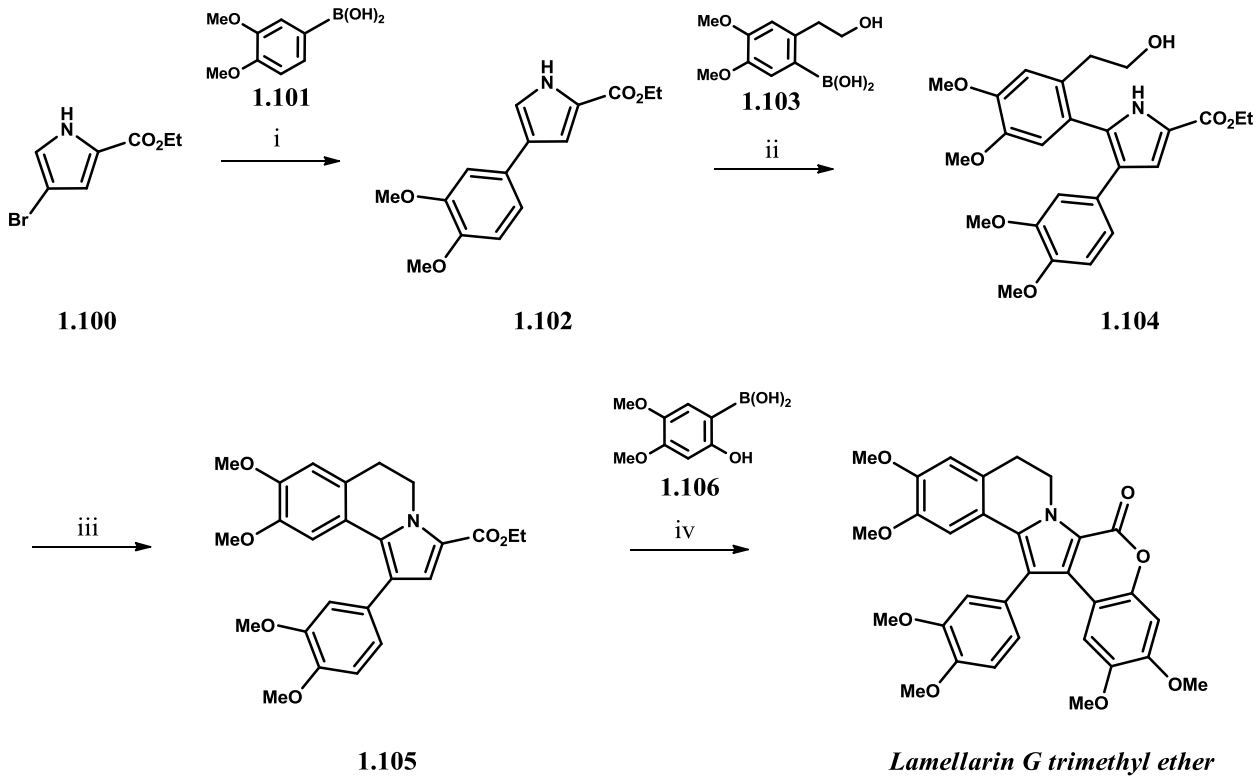
In 2001, Guitan and co-workers[66] prepared lamellarin K by using a key cyclization that was based on the 1,3-dipolar cycloaddition of an alkyne **1.96** to a nitrone **1.97** to produce the intermediate isoxazoline **1.98** (*Scheme 1.11*). Upon heating, the intermediate rearranged to form the pyrrole **1.99**. Finally, the removal of the isopropyl protecting groups followed by lactonization yields the expected lamellarin K product.



Scheme 1.11 *Synthesis by Guitian et al.*[66]*:* i. 120 °C, 61%; ii. $AlCl_3$, 45%.

1.4.7 Synthesis by Handy *et al.*

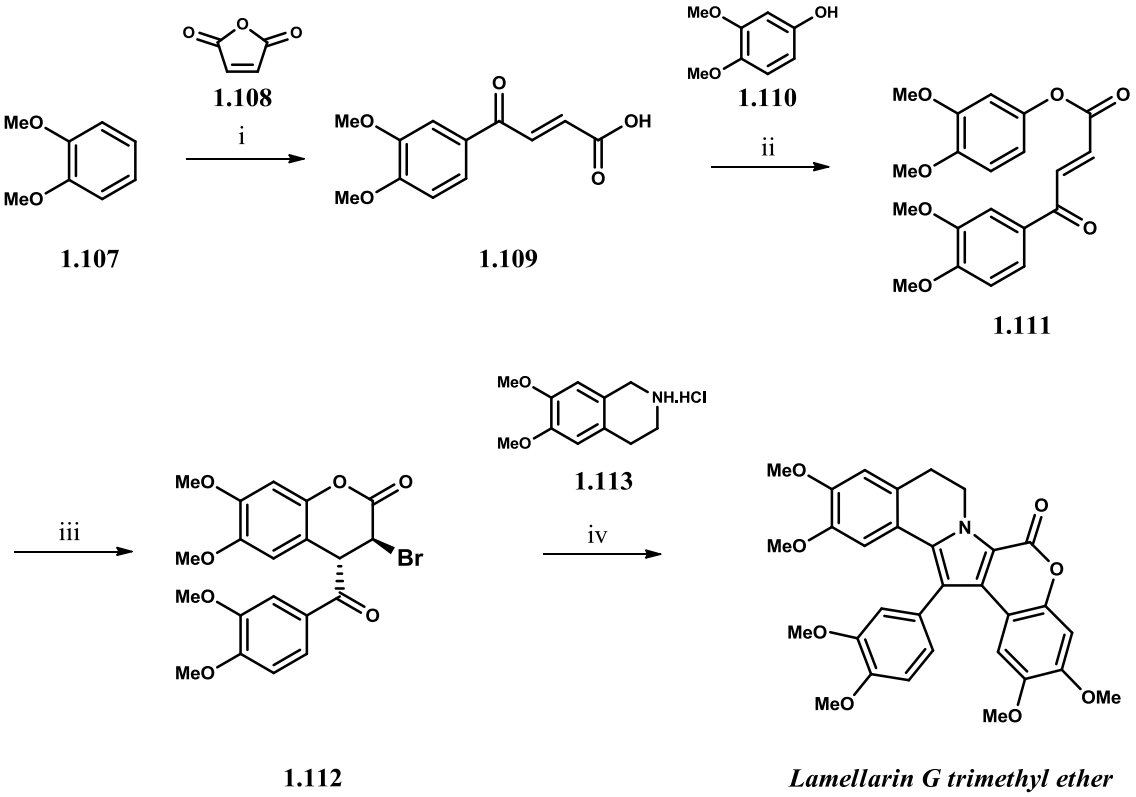
In 2004, Handy and co-workers[67] prepared lamellarin G trimethyl ether (*Scheme 1.12*) using a similar Heck/Suzuki coupling approach to that employed by Banwell (1997)[54] and Iwao (2003).[61] Using the pre-existing pyrrole **1.100**, Handy *et al.* established an efficient regioselective halogenation of the pyrrole core. Pyrrole ester **1.100** underwent a Suzuki coupling with boronic acid **1.101** to afford the biaryl product **1.102** in a 70% yield. A second bromination and Suzuki coupling with boronic acid **1.103** then afforded the trisubstituted pyrrole **1.104** in a 54% yield. The pyrrolo[2,1-*a*]isoquinoline subunit **1.105** was then obtained following an intramolecular alkylation. A final bromination and Suzuki coupling with boronic acid **1.106** (as well as a spontaneous lactonization) afforded lamellarin G trimethyl ether in a 46% yield.



Scheme 1.12 *An approach by Handy et al.*[67]*:* i.a. **1.101**, $Pd(Ph_3P)_4$, DMF/aq. Na_2CO_3, 110°C, 70%; ii.a. NBS, DMF, 0°C–rt, 100%; b. **1.103**, $Pd(Ph_3P)_4$, DMF/aq. Na_2CO_3, 110°C, 54%; iii.a. TsCl, pyridine; b. NaH, DMSO, 61%; iv.a. NBS, DMF, 0°C–rt, 100%; b. **1.106**, $Pd(Ph_3P)_4$, DMF/aq. Na_2CO_3, 110°C, 46%.

1.4.8 Synthesis by Yadav *et al.*

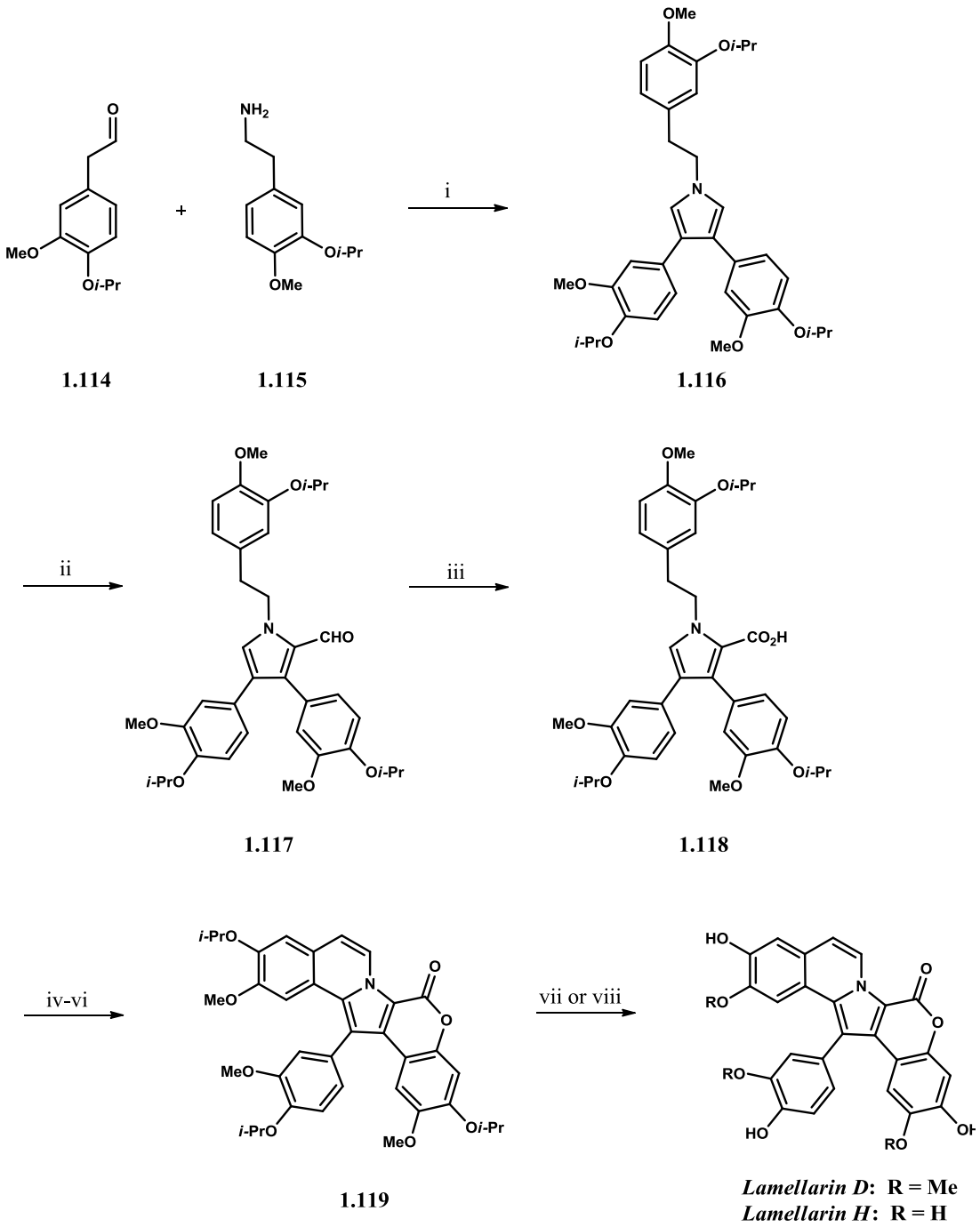
In 2009, Yadav and co-workers reported a new synthesis of lamellarin G trimethyl ether (*Scheme 1.13*).[68] In their synthesis simple 1,2-dimethoxybenzene **1.107** was reacted with maleic anhydride **1.108** using Friedel-Crafts reaction conditions, which afforded the oxobutenoic acid **1.109** in 65% yield. An esterification with 3,4-dimethoxyphenol **1.110** afforded ester **1.111**. A key intramolecular bromoarylation of the ester using samarium(III) triflate to catalyse the reaction afforded 3-bromo-3,4-dihydrocoumarin **1.112** in 93% yield. Finally, lamellarin G trimethyl ether was achieved by coupling **1.112** with tetrahydroisoquinoline **1.113**. The synthesis of the product was accomplished in four steps with an overall yield of 34%.



Scheme 1.13 *2009 approach by Yadav et al.*[68]*:* i. **1.108**, $AlCl_3$, CH_2Cl_2, 65%; ii. **1.110**, DCC, DMAP, DMF, 89%; iii. NBS, $Sm(OTf)_3$, MeCN, 20°C, 93%; iv. **1.113**, K_2CO_3, MeCN, air, reflux, 63%.

1.4.9 Synthesis by Jia *et al.*

In 2010, Jia and co-workers reported the total syntheses of lamellarin D and H (*Scheme 1.14*).[36] The synthesis of both lamellarins was achieved in 7 steps from aldehyde **1.114** (prepared from vanillin) and amine **1.115** (prepared from isovanillin). These were used in the formation of pyrrole **1.116** in a key step of the synthesis using silver acetate in a one-pot oxidative coupling reaction. A formylation of the pyrrole utilizing a microwave Vilsmeier-Haack reaction resulted in the desired formylpyrrole **1.117** in 83% yield. Aldehyde **1.117** was then oxidized to the carboxylic acid **1.118** under Lindgren oxidation conditions. Using conditions reported previously by Iwao[49,61-63] the lactone and the unsaturated isoquinoline rings were formed to afford the pentacyclic lamellarin structure **1.119**. Lamellarin D was then prepared in 98% yield from a deprotection with boron trichloride (step vii in *Scheme 1.14*), and lamellarin H was assembled in 95% yield from a deprotection with boron tribromide (step viii in *Scheme 1.14*).



1.114 **1.115** **1.116** **1.117** **1.118** **1.119**

Scheme 1.14 *2010 approach by Jia et al.*[36]*:* i. AgOAc, NaOAc, THF, 60°C, 41% (2 steps); ii. $POCl_3$, DMF, µw, 83%; iii. *t*-BuOH, H_2O, THF, 10°C, 87%; iv. $Pb(OAc)_4$, EtOAc, 68%; v. PIFA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 86%; vi. DDQ, toluene, reflux, 98%; vii. BCl_3, CH_2Cl_2, 98% (*Lamellarin D*); viii. BBr_3, CH_2Cl_2, 95% (*Lamellarin H*).

Chapter 2
Background, aims and strategies of the project

2.1. Background

2.1.1. Introduction

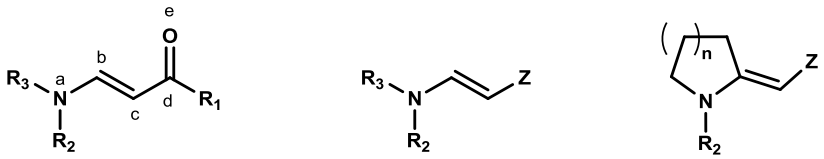
Initial studies for the novel approach toward the synthesis of the lamellarin alkaloids were conducted by a former PhD student at the University of the Witwatersrand, Garreth L. Morgans (2008).[69] In his work, he fortuitously found that acid-induced cyclization of certain enaminones resulted in the formation of pyrrole rings. The substitution pattern on the products suggested that the method might in principle be adapted for the synthesis of lamellarins. His preliminary results showed that these alkaloids were indeed feasible targets. However, his work was not taken to completion. The current PhD project will build on this work, with the intention of completing the total synthesis as well as that of various analogues.

Historically, the synthesis of alkaloids in our organic laboratories has been through the use of enaminone intermediates. A general background to enaminones will thus be discussed. Their relevance and chemical characteristics will be also be discussed and related to the proposed synthesis for this PhD thesis.

2.1.2. Enaminones and the Eschenmoser sulphide contraction

The "Wits approach" toward alkaloid chemistry dates back to the early seventies, and has centred around the use of enaminones.[70] Traditionally an enaminone is any compound containing the conjugated N–C=C–C=O system. They are structural units which most commonly comprise a nitrogen atom conjugated through a vinyl fragment to electron-withdrawing substituents on the enamine. The interest in enaminones revolves around the fact that they display both ambident

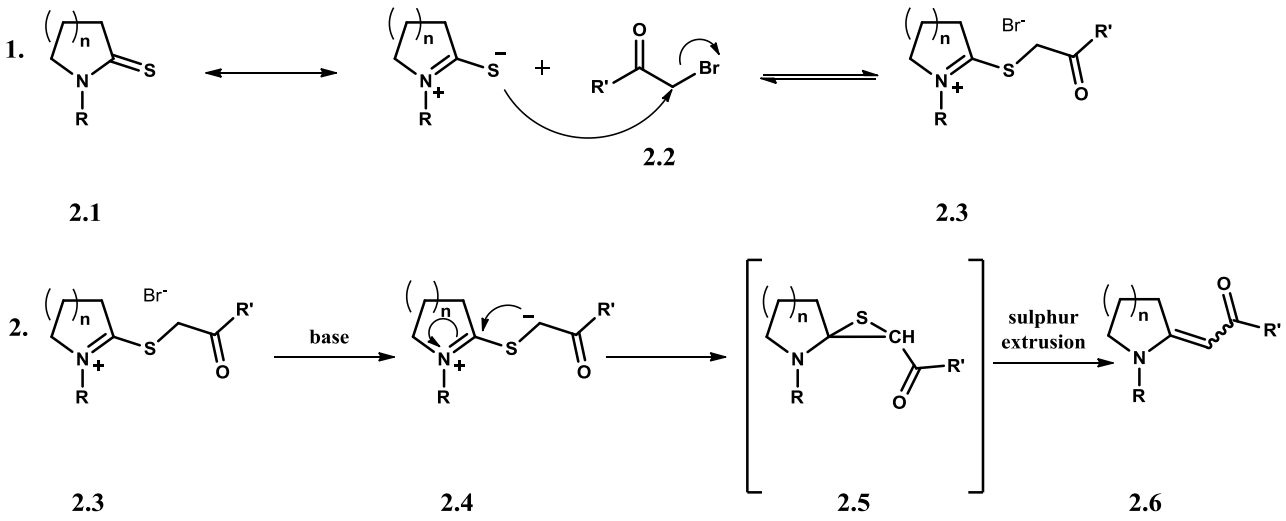
nucleophilicity through sites a, c and e and electrophilicity through sites b (1.4-addition reaction) and d (1,2-addition reaction) (*Figure 2.1*).[71,72] Primary and secondary enaminones exist in three tautomeric forms, which are obtained by the conjugation of the system and their related substituents. This allows for either the *E*- or *Z*-isomers to be formed.[73] The exocyclic enaminones typically used in the Wits University projects can be accessed through a variety of systems; with different size rings (*Structure 3 in Figure 2.1*) and different geometries of the vinyl group. The substituent groups are most commonly vinylogous amides (Z = COR) and urethanes (Z = CO_2R), however vinylogous ureas (Z = $CONR_2$), cyanamides (Z = CN), nitramines (Z = NO_2) and sulphonamides (Z = SO_2R) can also be considered for this function.



R_2, R_3 = H, alkyl, aryl
Z = COR, CO_2R, $CONR_2$, CN, NO_2, SO_2R

Figure 2.1: Nucleophilic and electrophilic sites of enaminones, also indicating variation in functionality.

The Eschenmoser sulphide contraction, also known as the Eschenmoser coupling reaction, is a common approach used for the preparation of enaminones and the route taken for most of the alkaloid syntheses in our laboratories.[74,75] The reaction occurs in two steps. The first step involves the reaction of a thiolactam **2.1** with an α-bromocarbonyl **2.2** compound to form a thioiminium salt intermediate **2.3**. The second step involves the addition of a suitable base such as triethylamine, potassium *tert*-butoxide or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); the anion **2.4** that forms undergoes a spontaneous intramolecular cyclization to form an episulphide intermediate **2.5**. The sulphur is then extruded in the presence of an appropriate thiophile such as triphenylphosphine, triethyl phosphite ($P(OEt)_3$), and mercury(II) salts, to afford the desired enaminone **2.6**.[74-78] The method for obtaining a vinyl carbon–carbon bond through sulphur extrusion was first observed in 1955 by Knott.[79] The sulphur extraction method was later established and employed synthetically by Eschenmoser in the synthesis of Vitamin B12.[78]



Scheme 2.1: Two-step Eschenmoser sulphide contraction mechanism.

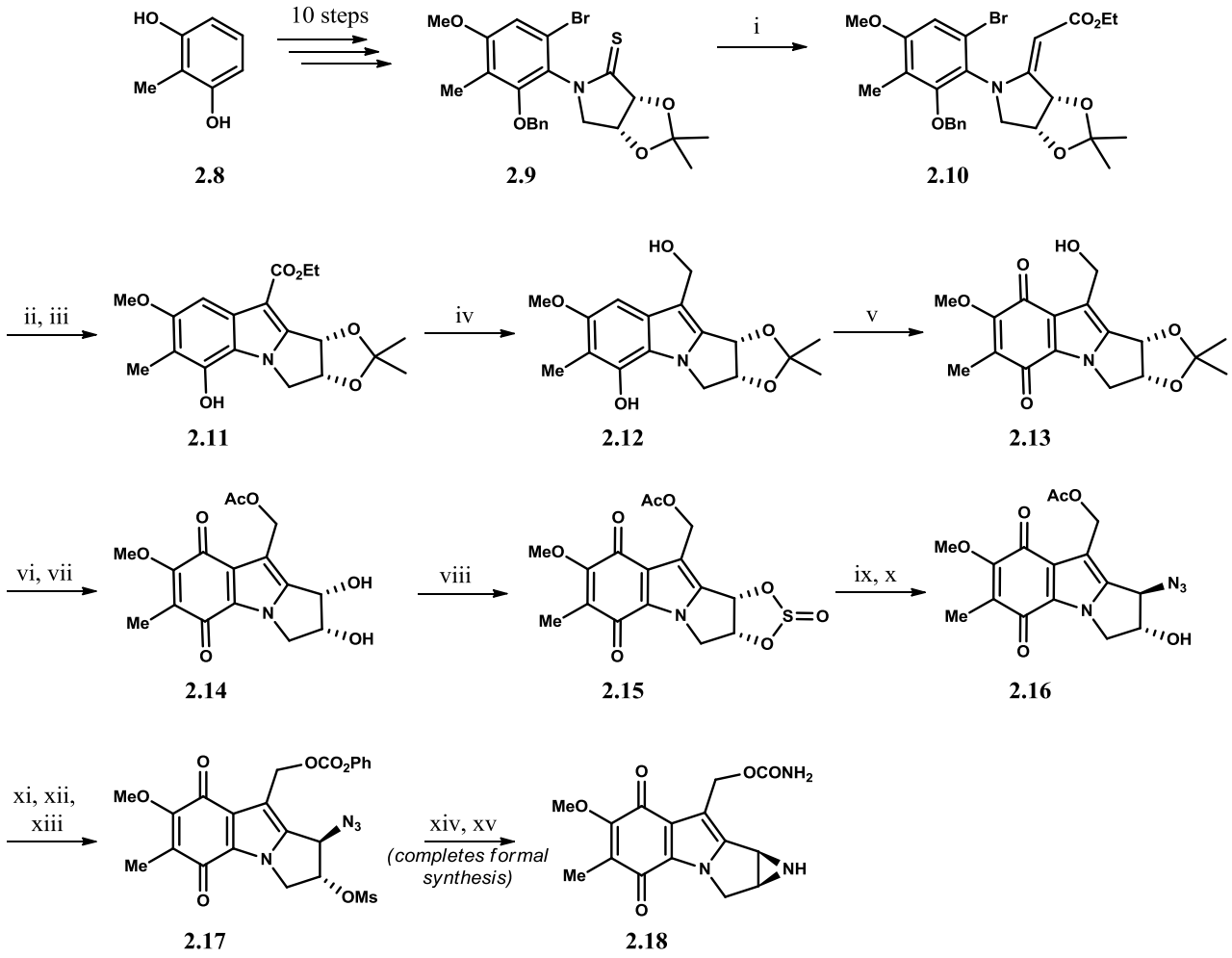
Cyclic enaminones similar to **2.7** were first prepared in 1932 by Lukeš, using a Reformatsky reaction between a lactam and ethyl 2-bromoacetate in the presence of magnesium to afford a vinylogous urethane.[80] Cyclic enaminones can also be accessed by condensation of methylthioiminium salts with acidic components such as nitromethane or β-dicarbonyl compounds.[70,81]

2.1.3. Selected syntheses performed in our laboratories using enaminone intermediates

Pyrrolizine, indolizine and quinolizidines are commonly observed in naturally occurring alkaloid systems. Enaminones have often been used in our laboratories to synthesize alkaloids and related structures containing these ring systems. A summary of a synthesis from each of these main structural groups will be highlighted, with an emphasis made on the enaminone intermediate used in the preparation of the core heterocyclic system.

The enantioselective synthesis of 7-methoxyaziridomitosene **2.18**, described in *Scheme 2.2*, is an example of a pyrrolizine-containing product described by Michael and co-workers in 2006.[82] The aziridomitosenes are analogues of the mitomycins. Both groups are known for their antitumour antibiotic activity. Thiolactam **2.9** was prepared from 2-methylresorcinol **2.8** over 10

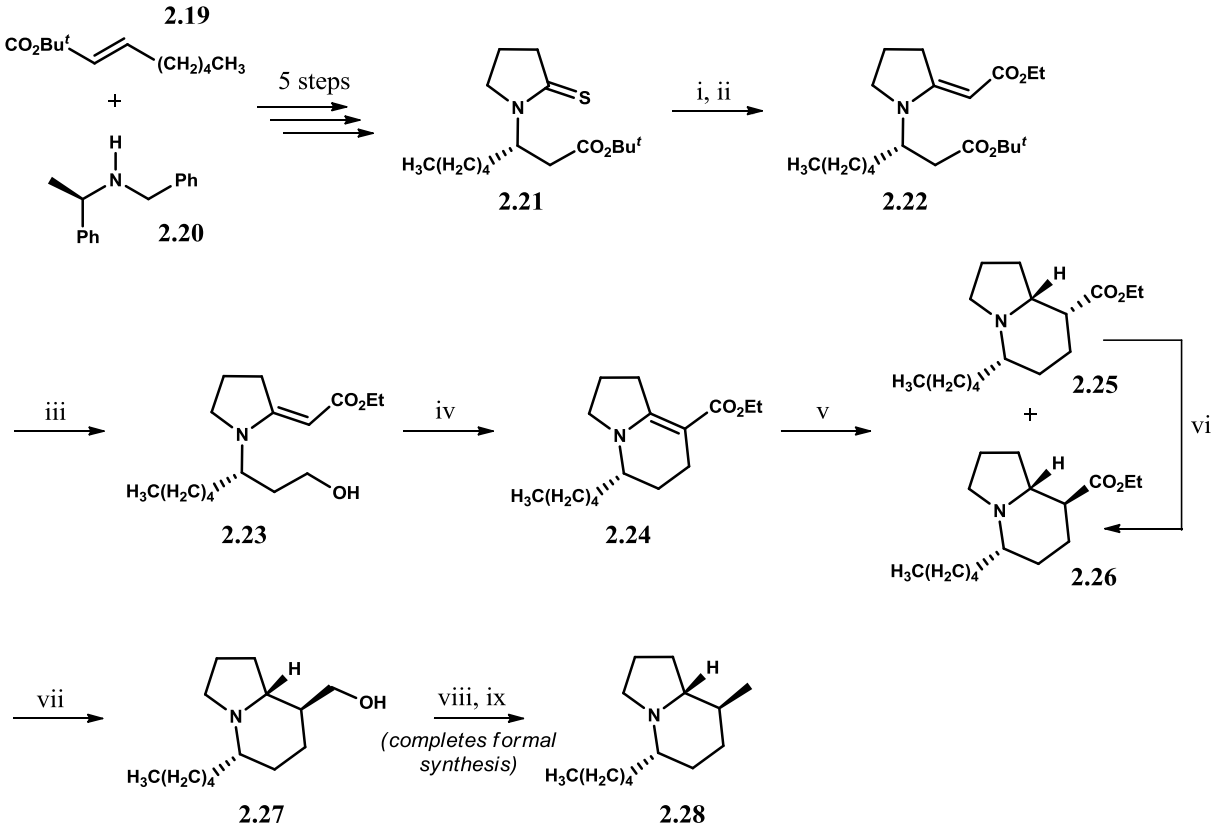
steps. The enaminone **2.10** was synthesized using a prepared organozinc reagent in boiling tetrahydrofuran. The enaminone **2.10** was isolated in 87% yield. An intramolecular Heck cyclization was then performed to afford the pyrrolizine intermediate **2.11** in 82% yield. The carboxylic ester was then reduced in the presence of lithium aluminium hydride to afford the benzylic alcohol intermediate **2.12**. The aromatic ring was then oxidized to the quinone **2.13** using salcomine. The benzylic alcohol of **2.13** was protected with an acetate group and the acetonide was hydrolysed with acetic acid to afford diol **2.14**, which was converted into the cyclic sulphite **2.15** in 76% yield. The cyclic sulphite **2.15** assisted in the formation of azido alcohol **2.16**, which was produced by reacting sodium azide in *N*,*N*-dimethylformamide at a temperature of 55°C, followed by a reaction in sulphuric acid to afford the azido alcohol **2.16** in 68% yield. The benzylic acetylated alcohol was deprotected with potassium carbonate in methanol and the alcohol was then selectively acylated with phenyl chloroformate. The remaining alcohol was then mesylated to afford **2.17** in 98% yield. This completed a formal synthesis of 7-methoxyaziridomitosene **2.18**, since Dong and Jimenez had previously reported the conversion of **2.17** into **2.18** by reaction of the carbamate with ammonia, followed by the Staudinger reaction with triphenylphosphine to form the aziridine ring.[83]



Scheme 2.2 *Reagents and conditions:* i. $BrZnCH_2CO_2Et$ (from $BrCH_2COEt$, Zn, I_2, THF, ultrasound), THF, reflux, 120 h; ii. $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, DMF, MeCN, H_2O, reflux, 4 h; iii. 10% Pd/C, H_2, EtOH, HCl, r.t., 2 h; iv. $LiAlH_4$, THF, 0°C–r.t., 25 h; v. Salcomine, DMF, O_2, r.t., 3 h; vi. Et_3N, Ac_2O, CH_2Cl_2, r.t., 18 h; vii. AcOH, THF, H_2O, 65°C, 48 h; viii. $SOCl_2$, Et_3N, THF, –15°C–r.t., 1 h; ix. NaN_3, DMF, 55°C, 2 h; x. H_2SO_4, THF, H_2O, r.t., 2 h; xi. K_2CO_3, MeOH, r.t., 1 h; xii. PhOCOCl, pyridine, CH_2Cl_2, 0°C–r.t., 3 h; xiii. MsCl. Et_3N, CH_2Cl_2, r.t., 22 h; xiv. NH_3(g), CH_2Cl_2; xv. PPh_3, Et_3N, THF/H_2O.

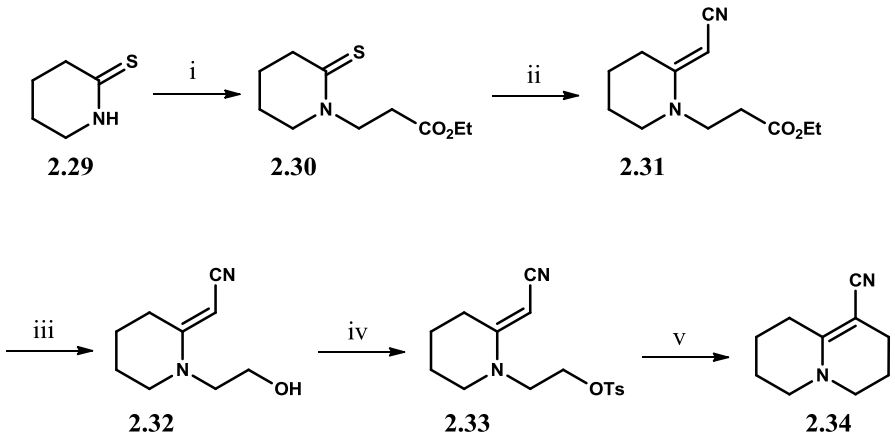
The enantioselective synthesis of (–)-indolizidine 209B (**2.28** in *Scheme 2.3*) published by Michael and Gravestock in 2000[84] is an example of an indolizine alkaloid synthesis. Thiolactam **2.21** was prepared over five steps from *tert*-butyl (2*E*)-oct-2-enoate **2.19** and (*R*)-(+)-*N*-benzyl-1-phenylethylamine **2.20**. The Eschenmoser sulphide contraction then afforded vinylogous urethane **2.22** in 94% yield in the (R)-(+) configuration. The ester was then reduced with lithium

aluminium hydride to give alcohol **2.23**. Alcohol **2.23** was cyclized by conversion into the iodide *in situ* and then reacting with imidazole and triphenylphosphine in boiling toluene to afford the unsaturated indolizidine **2.24** in 81% yield. A catalytic hydrogenation of the double bond with platinum oxide in acetic acid yielded diastereomers **2.25** and **2.26** as an 88:12 mixture (85%), respectively. Diastereomer **2.25** was then epimerized to the sought-after diastereomer **2.26** by heating with cataylic amounts of sodium ethoxide in ethanol. Finally, the ester group in **2.26** was reduced to afford alcohol **2.27** in 94% yield. This completed the formal synthesis of (–)-indolizidine 209B (**2.28**). The method designed by Holmes and co-workers[85] was used to convert alcohol **2.27** to indolizidine **2.28** by protecting the alcohol as a methanesulphonate and then reacting with lithium triethylborohydride to afford (–)-indolizidine 209B (**2.28**).



Scheme 2.3 *Reagents and conditions:* i. $BrCH_2CO_2Et$, MeCN, rt; ii. PPh_3, toluene, Et_3N, MeCN, rt; iii. $LiAlH_4$, THF, rt; iv. I_2, imidazole, PPh_3, toluene, 110°C; v. H_2 (1 atm), PtO_2, AcOH, rt; vi. NaOEt (cat.), EtOH, reflux; vii. $LiAlH_4$, THF, rt; viii. CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C; ix. :$LiEt_3BH$ (1 M in THF), THF, 0°C.

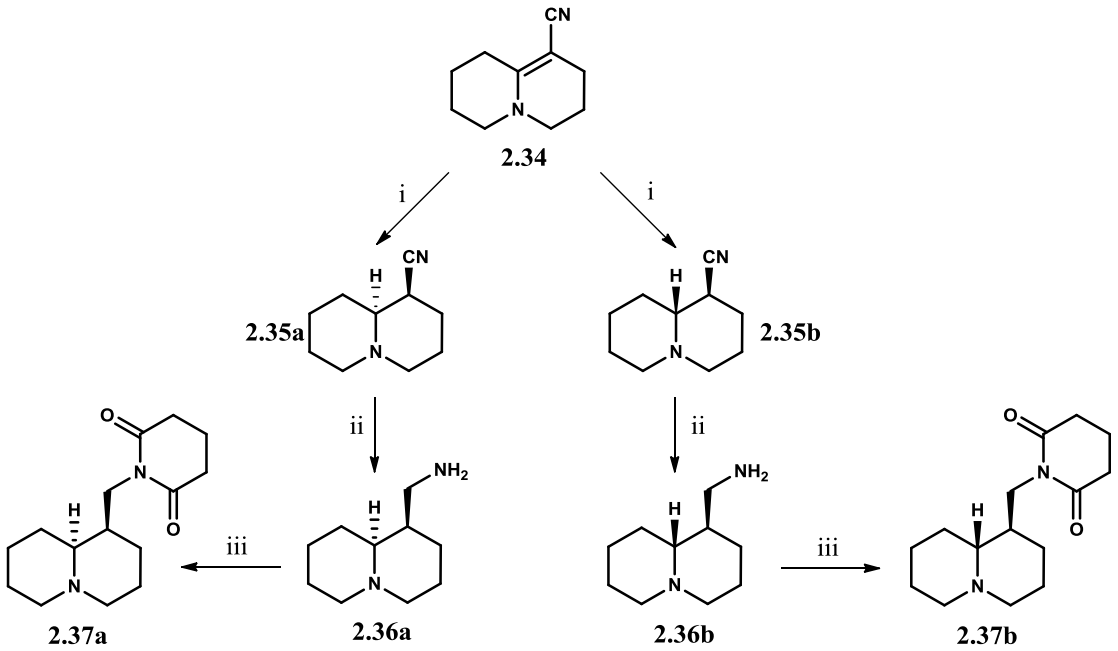
The final synthesis demonstrates the preparation of a quinolizidine alkaloid. Lamprolobine **2.37b** in *Scheme 2.5* was initially reported in 1968 as a metabolite of the Australian tree *Lamprolobium fruitcosum*. Lamprolobine **2.37b** has since been extracted from a number of flora species. Racemic lamprolobine was synthesized in our laboratories by Michael and Jungmann in 1992.[86] The thiolactam **2.29** (*Scheme 2.4*) was prepared following a procedure by Brillon.[87] Thiolactam **2.29** was then *N*-alkylated to give product **2.30** by the conjugate addition to ethyl acrylate using a catalytic amount of sodium hydroxide. The Eschenmoser sulphide contraction with bromoacetonitrile followed by triphenylphosphine and triethylamine in acetonitrile afforded vinylogous cyanamide **2.31** in 85% yield. The ester group in **2.31** was then reduced with lithium aluminium hydride, and alcohol **2.32** was furnished with a tosyl group. The quinolizidine system **2.34** was then formed by intramolecular nucleophilic displacement of the tosylate **2.33** to afford the bicyclic product **2.34** in a 70% yield over two steps.



Scheme 2.4 *Reagents and conditions:* i. ethyl acrylate, cat. NaOH, THF; ii.a. $BrCH_2CN$; b. PPh_3, Et_3N, MeCN; iii. $LiAlH_4$, THF, reflux; iv. NaH, *p*-TsCl, THF; v. MeCN, reflux.

To complete the synthesis (*Scheme 2.5*), a reduction with sodium cyanoborohydride in ethanol at a pH of 4 afforded the *trans*-isomer **2.35a** in 43% yield and the *cis*-isomer **2.35b** in 54% yield. Both products were then reduced with a nickel-aluminium alloy and sodium hydroxide in ethanol. Lupinamine **2.36a** was afforded in 99% yield from *cis*-isomer **2.35a** and epilupinamine **2.36b** was isolated in 84% yield from *trans*-isomer **2.35b**. The final products were prepared from

the amine with glutaric anhydride in refluxing acetic acid. Epilamprolobine **2.37a** was prepared from lupinamine **2.36a** in 62% yield and lamprolobine **2.37b** was prepared from epilupinamine **2.36b** in 54% yield.

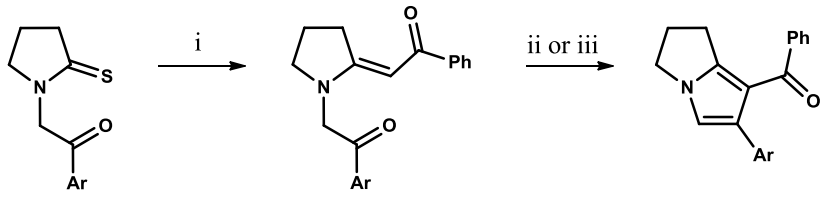


Scheme 2.5 *Reagents and conditions:* i. $NaBH_3CN$, EtOH; ii. Ni-Al, NaOH, EtOH; iii.a. glutaric anhydride; b. Ac_2O, reflux.

2.1.4. Initial studies conducted for pyrrole formation on silica gel

The concept of the pyrrole formation was first discussed by Garreth L. Morgans in his PhD thesis entitled: "New routes to arylated azabicyclic systems from enaminones, and applications to alkaloid synthesis."[69] His thesis considered the formation and manipulation of many indolizine and pyrrolizine systems. He began to explore the synthesis of lamellarin during his research on pyrrolizine systems and his work on the ambient nucleophilicity and electrophilicity of the enaminone intermediates in creating pyrrolizine systems. He initially formed the pyrrolizine systems with acetic acid in methanol. However, it was noticed that the low yields of the vinylogous amides directly correlated to the time spent on the silica gel column during purification. A test conducted using 2D TLC afforded two spots of equal intensity, which were isolated and found to be the vinylogous amide, as expected, and the ring-closed pyrrolizine

product. Various vinylogous amides **2.39** (prepared from thiolactams **2.38**) were subjected to ring-closures (to afford **2.40**) with both the acetic acid and silica gel methods and the results correlated well (*Scheme 2.6*). The silica gel method showed improved yields (52–83%) with cleaner product isolated.

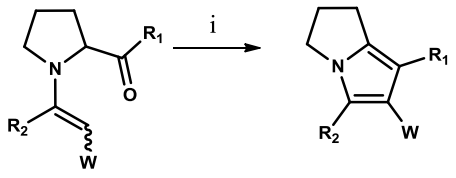


2.38 **2.39** **2.40**

Ar = Phenyl or 3,4-dimethoxyphenyl

Scheme 2.6 *Reagents and conditions:* i.a. Phenacyl iodide, MeCN; b. $P(OEt)_3$, Et_3N, MeCN; ii. AcOH, 40°C; iii. SiO_2, 90°C.

It was later revealed following a literature search that similar pyrrole formations were conducted on silica gel by Calvo and co-workers[88] in their reactions with carboxamide groups with organometallic compounds (**2.41**) to obtain a variety of 2,3-dihydropyrrolizines **2.42** (*Scheme 2.7*). However, the formation of the pyrrolizine systems with β-functionalized enaminones using silica gel was novel to our method.



2.41 **2.42**

W = CN, COPh, CO_2Et
R_1 = Me, PhC≡C, BuC≡C, HC≡C
R_2 = H, Me

Scheme 2.7 *Reagents and conditions:* i. SiO_2, $CHCl_3$ or toluene, 60–112°C, 30–60 min.

Garreth Morgans also laid the groundwork for the preparation of some of the phenacyl halides prepared in this PhD (*Chapter 3*). He also investigated both the bicylic and tetracyclic pyrrolizine systems prepared in this PhD (*Chapter 4*). In addition, some initial studies on the isoquinoline enaminones were made (*Chapter 5*). Although a ring-closure was attempted he

could not fully isolate the materials afforded and his project was ended owing to time constraints. Whenever relevant, his preliminary contributions will be mentioned in the appropriate Chapters.

2.2. Aims and strategies of the project

Pyrrolizine, indolizine and pyrroloazepine alkaloids and some of their previous syntheses have been highlighted in *Chapter 1*. The lamellarin alkaloids and their synthetic and biological properties were also discussed. The 'Wits Approach' to accessing these systems through enaminone pathways was also outlined in the previous section.

The proposed PhD project aims to prepare various lamellarin analogues via enaminone intermediates. A model synthesis has also been designed, which uses simpler pyrrolidine, piperidine and azepane systems to prepare various enaminones. These enaminones will be prepared from various phenacyl halides using methods adapted from literature and from previous studies conducted by Garreth Morgans during his PhD thesis. The enaminones will then be subjected to a ring closure to form the pyrrole ring and subsequent model analogues in the study.

An extention of the methodology will then be applied in the preparation of lamellarins. The enaminone systems will be prepared from isoquinoline thiolactams, which will be made following known literature procedures. The enaminone intermediates will be cyclised in the same manner as the model study suggests, affording a library of lamellarin alkaloid analogues.

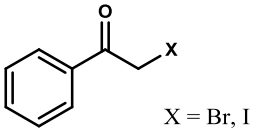
2.2.1. Preparation of phenacyl halides

The phenacyl halides are essential precursors in both the envisaged model study with pyrrolizine, indolizine and pyrroloazepine compounds and for the synthesis of lamellarins. A variety of phenacyl halides will be prepared by known literature procedures. These phenacyl halides will form the foundation of the preparation of a variety of enaminones in the thesis.

Phenacyl bromide is the simplest compound we plan to use in our synthesis. The more complex di-substituted phenacyl halides and tetra-substituted phenacyl halides will also be prepared using

various known methods. *Figure 2.2* illustrates some of the phenacyl halides to be used, where X is either bromine or iodine. *Chapter 3* focuses on the discussion of the preparation and application of the phenacyl halides in the PhD thesis.

Monosubstituted phenacyl halides



Disubstituted phenacyl halides



Tetrasubstituted phenacyl halides

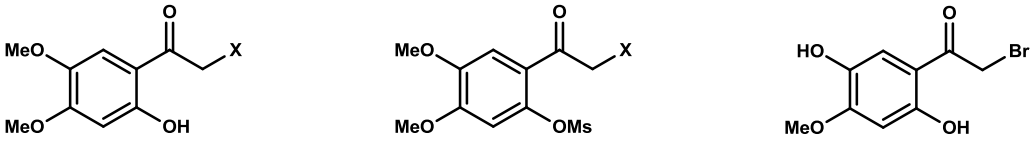
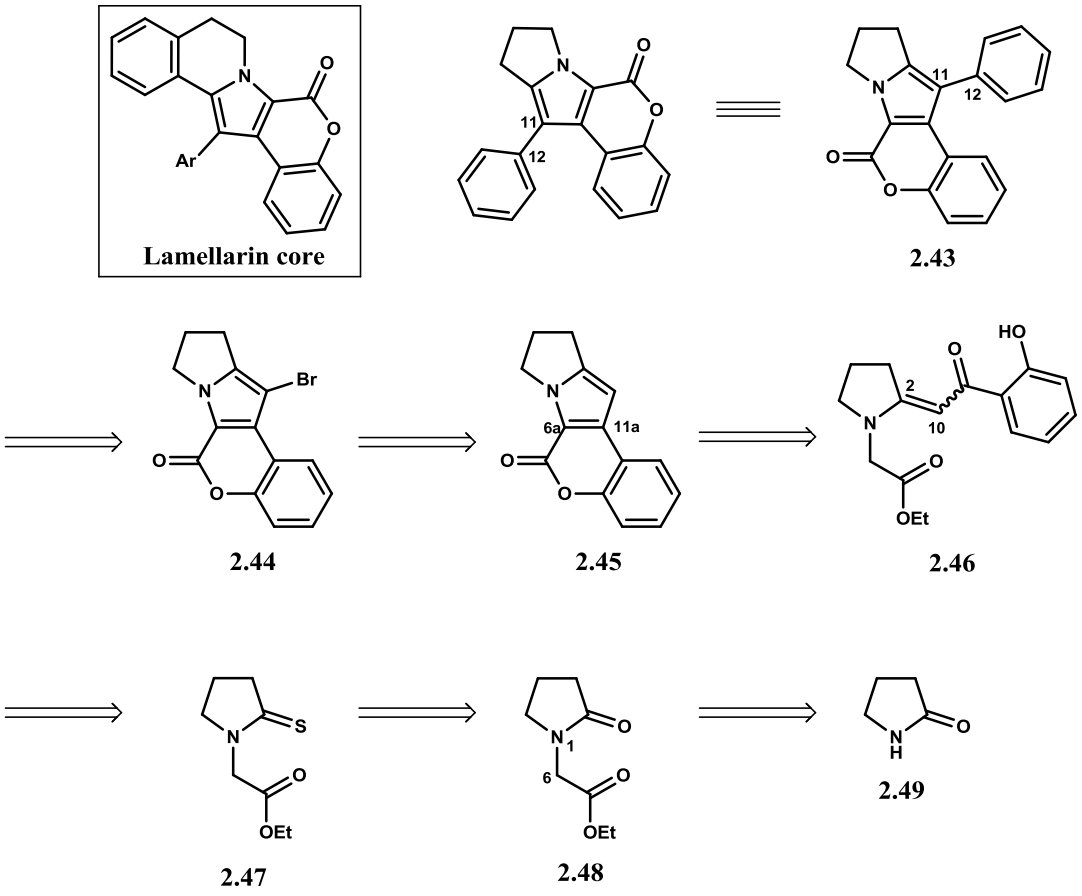


Figure 2.2: Various types of phenacyl halides to be prepared for the synthesis of enaminone.

2.2.2. Proposed strategy for the synthesis of pyrrolizines from *N*-alkylated and *N*-phenacyl analogues

We propose model studies with 5-membered pyrrole systems fused to a variety of small saturated *N*-heterocycles to test the methodology for the lamellarin synthesis and to create a diverse library of novel and potentially useful compounds. The syntheses will be discussed in *Chapter 4* of this thesis.

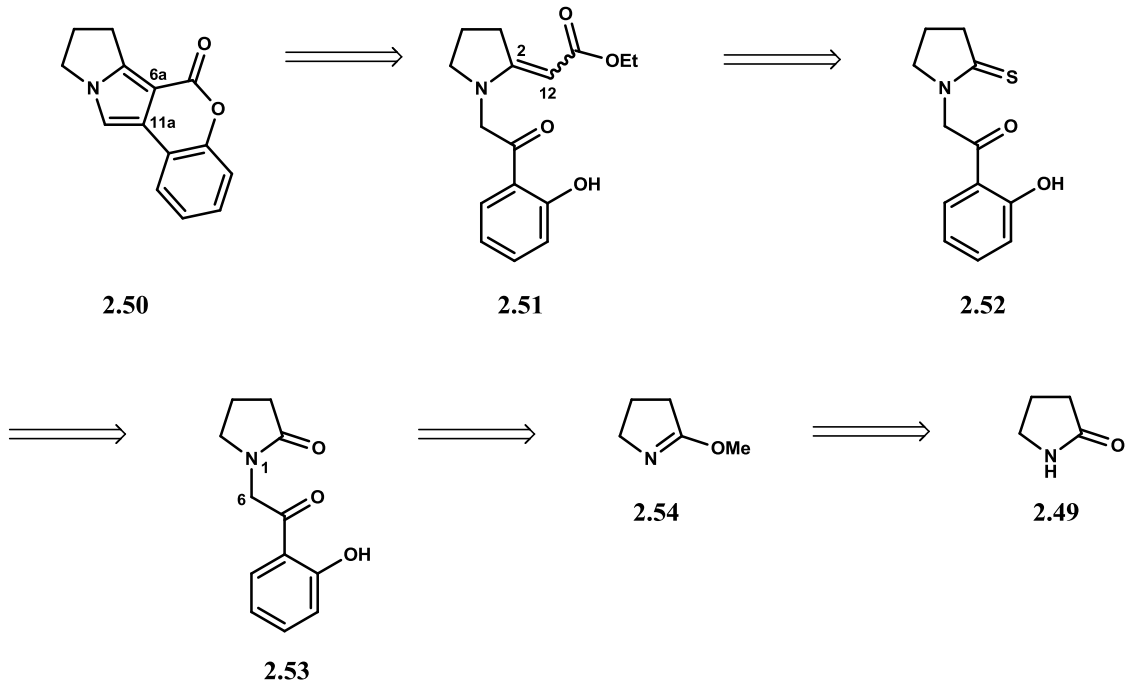
The proposed strategy is shown in the retrosynthetic route in *Scheme 2.8*. A disconnection at C11–C12 of the sought-after model analogue of lamellarin-type compound **2.43** would lead to a Suzuki-Miyaura coupling reaction strategy, which would give the brominated precursor **2.44**. A disconnection at the C6a–C11a bond of the pyrrole ring in **2.45** is an indication of the way in which the pyrrole would need to form, and leads back to the key enaminone intermediate **2.46**, which is required for the acid-catalyzed ring cyclization to form the pyrrole ring in **2.45**. The enaminone can be disconnected back to its thiocarbonyl precursor **2.47**, which would be formed from a simple thionation of lactam **2.48**. Finally, a disconnection at C1–C6 of the lactam **2.48** would give 2-pyrrolidinone **2.49** as a simple starting material for the preparation of the *N*-substituted lactam.



Scheme 2.8: Retro-synthetic analysis for the approach to *N*-alkylated enaminones and their pyrrolizine analogues.

A library of pyrrolizine compounds can therefore be prepared from thiolactam **2.47**. The Eschenmoser sulphide contraction reaction using various phenacyl halides (*Section 2.2.1*) could then be applied to the synthesis of many enaminone precursors. A diversity of ring closed pyrrole-containing systems, both bicyclic (i.e. without the lactone) and tetracyclic can be prepared, depending on whether the *ortho*-substituent on the phenacyl halide used in the reaction is a hydroxyl or not. Similarly, the Suzuki-Miyaura product can be varied with the use of different boronic acids for the formation of the biaryl axis. This will give a diversity of analogues, with interesting and potentially useful biological properties. It will also prove the flexibility of the synthesis proposed for further application to the synthesis of the lamellarin alkaloids.

The synthesis of *N*-phenacyl analogues of enaminones such as **2.46** was proposed to better ascertain the mechanism for the pyrrole ring formation. Although we were certain such precursors could also lead to pyrrolizines, owing to previous work done by G. L. Morgans in his PhD thesis, we wanted to better understand the way in which the enaminones would react using different *N*-substituents. *Scheme 2.9* shows the retrosynthesis of the proposed pyrrole formation **2.50** when the *N*- and enaminone substituents are interchanged. A disconnection of the pyrrole at C6a–C11a would give the enaminone **2.51**. The pyrrole would therefore form in a slightly different way to the *N*-alkylated enaminones discussed above. The enaminone again would be prepared from thiolactam **2.52** using the Eschenmoser sulphide contraction. A functional group interconversion from lactam **2.53** to thiolactam **2.52** using known thionating reagents would afford thiolactam **2.52**. Lactam **2.53** can be prepared with lactim ether **2.54** by a known literature procedure. Similarly, commercially available 2-pyrrolidinone **2.49** would be used to prepare lactim ether **2.54**, which Morgans found to afford the *N*-phenacylation more effortlessly.



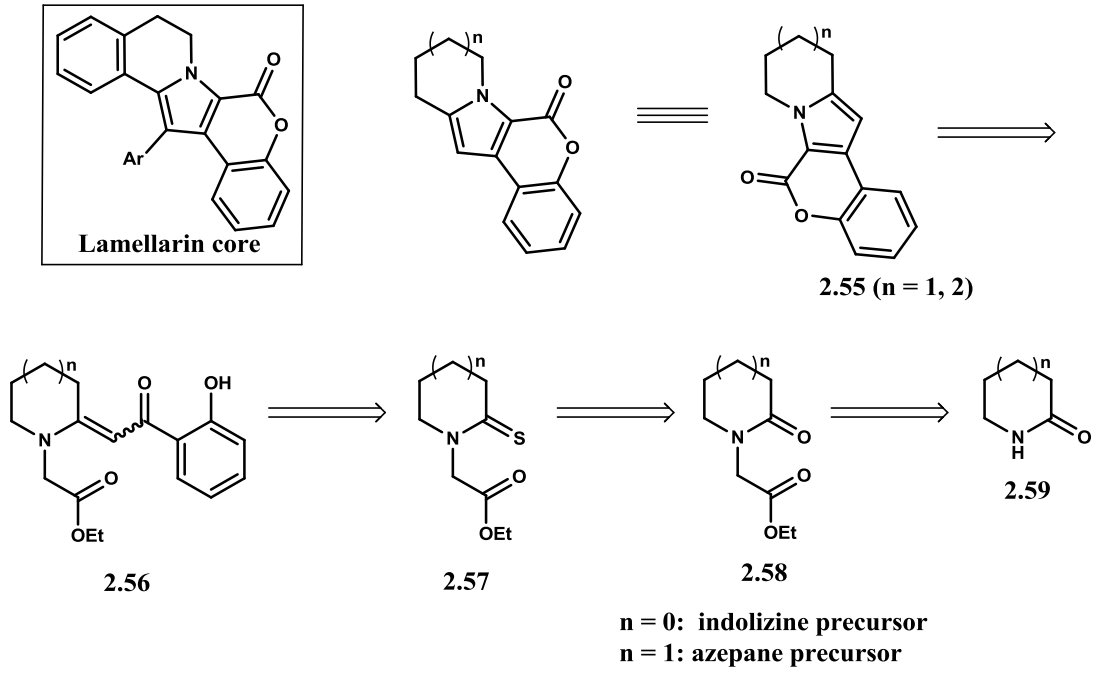
Scheme 2.9: Retro-synthetic analysis for the approach to *N*-phenacyl enaminones and their pyrrolizine analogues.

Some variation in the aromatic substituents will be made, but no Suzuki-Miyaura coupling will be attempted. The *N*-phenacyl pyrrole products are only a means to understanding the mechanism for pyrrole formation and to gain a better understanding as to how the enaminones react under these conditions.

2.2.3. Proposed strategy for the synthesis of indolizinone and pyrroloazepinone compounds

The proposed extension of the model study requires the application of the methodology mentioned in *Section 2.2.2* above, to 6-membered and 7-membered ring systems. The 6-membered piperidine analogue would more closely mimic the lamellarin isoquinoline moiety, which also possesses a 6-membered ring. The 7-membered azepane analogue would test the flexibility of the methodology and create a library of diversely sized compounds, all with unknown biological potential. These will also be discussed in detail in *Chapter 4*.

Scheme 2.10 indicates the retrosynthetic route required for the synthesis of indolizinone **2.55** (n = 0) and pyrroloazepinone **2.55** (n = 1) compounds. As described for the pyrrolizine analogues above, the tetracyclic pyrrole system **2.55** would be prepared using enaminones with an *ortho*-substituted hydroxyl phenyl group. The enaminone **2.56** would be prepared from thiolactam **2.57** using the Eschenmoser sulphide contraction, which would in turn be prepared by thionating lactams **2.58**. 2-Piperidinone **2.59** (n = 1) would be used as the starting material for the indolizine system and caprolactam **2.59** (n = 2) would be used for the synthesis of the pyrroloazepane system.



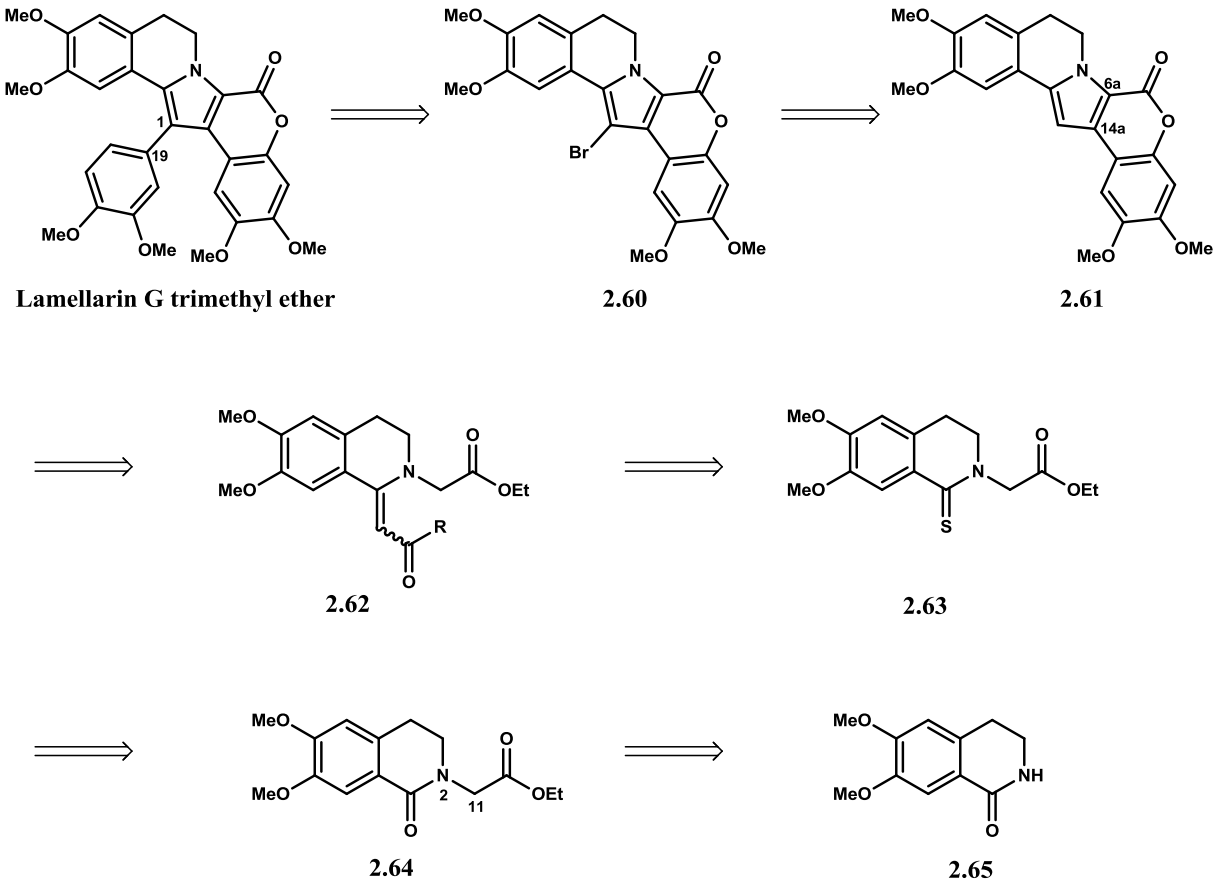
Scheme 2.10: Retro-synthetic analysis for the approach to indolizine and azepane analogues.

Only the analogues **2.55** mentioned in *Scheme 2.10* will be prepared in the synthesis. No diversification to the phenacyl groups will be made. No Suzuki-Miyaura reactions will be performed on these analogues. The extension to the pyrrolizine project is only intended to prove that the methodology is adaptable to various ring sizes.

2.2.4. Proposed strategies for the synthesis of lamellarin G trimethyl ether

A similar synthetic strategy to that in *Section 2.2.2* was adopted for the synthesis of isoquinoline lamellarins. Our main focus was to synthesize pentacyclic lamellarin G trimethyl ether because all the aromatic substituents of the compound are methoxy groups. This would help us to understand the methodology of the synthesis of these compounds before any different substituents could be used to create a library of lamellarin compounds.

Scheme 2.11 shows the disconnection of lamellarin G trimethyl ether. The biaryl axis at C1–C19 of lamellarin G trimethyl ether would be prepared through a Suzuki-Miyaura coupling reaction from the brominated precursor **2.60**. A disconnection at the C6a–C14a of the pyrrole-core ring of **2.61**, which would be formed from our developed acid-induced cyclization procedure with silica gel, would give enaminone precursor **2.62**. Enaminone **2.62** would be prepared from thiolactam **2.63** using the Eschenmoser sulphide contraction. Thiolactam **2.63** would be prepared by the thionation of the lactam **2.64** and a disconnection at the N2–C11 bond would give isoquinolinone **2.65**. Isoquinolinone **2.65** can be prepared by many known literature methods, which will be discussed in *Chapter 5*, along with the synthesis of pentacyclic lamellarin compounds.



Scheme 2.11: Retro-synthetic analysis for the approach to lamellarin G trimethyl ether.

2.3. Summary of aims

The main aims for this project can be summarized as follows:

- To prepare phenacyl halide compounds (*Figure 2.3*) using known literature methods and adopted methods to create a library of phenacyl halides with different substitution patterns and varying substituents (*Chapter 3*). These will be used in the synthesis of enaminones in *Chapters 4* and *5*.

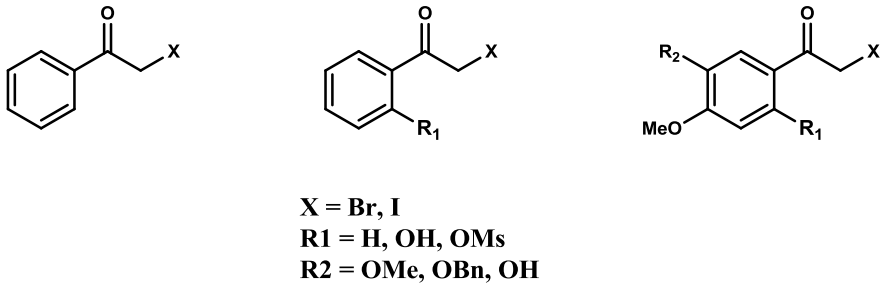


Figure 2.3: Phenacyl halides to be discussed in *Chapter 3*.

- To investigate the methodology for the synthesis of a range of 5-, 6-, and 7-membered enaminone systems using prepared phenacyl halides with the Eschenmoser sulphide contraction (*Figure 2.4*).

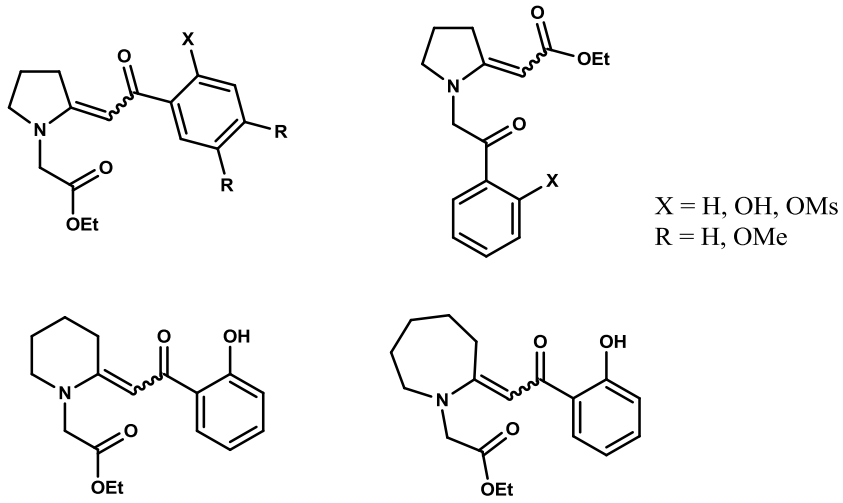


Figure 2.4: Enaminones to be discussed in *Chapter 4*.

- To prepare pyrrole ring systems, and subsequent tetracyclic pyrrolizine, indolizine and pyrroloazepane compounds (*Figure 2.5*), which mimic lamellarin alkaloids, using the previously investigated acid-induced silica gel methodology.

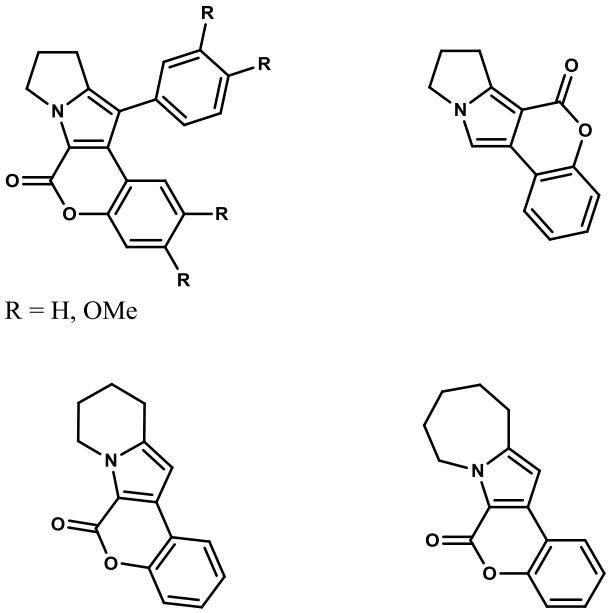
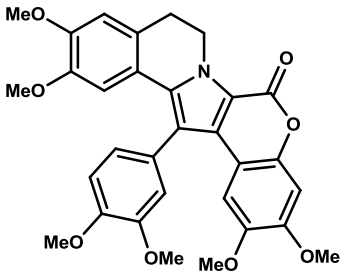


Figure 2.5: Tetracyclic pyrrole systems to be discussed in *Chapter 4*.

- To synthesize lamellarin G trimethyl ether (*Figure 2.6*) using the methodology from the model study (*Chapter 5*).



Lamellarin G trimethyl ether

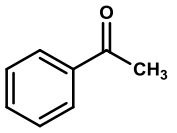
Figure 2.6: Lamellarin G trimethyl ether, the main synthetic target of the thesis.

Chapter 3
Preparation of phenacyl halides

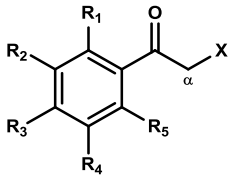
In this Chapter, the preparation of phenacyl halides will be discussed, as it pertains to both the synthesis of pyrrolizinones, indolizinones and pyrroloazepinones and related analogues (*Chapter 4*) and the lamellarins (*Chapter 5*). The synthesis of these acetophenones is being presented at this point for convenience, to facilitate the discussion in the subsequent chapters.

3.1. Introduction

Phenacyl compounds are a vast class of α-substituted acetophenones **3.1** (*Figure 3.1*). They are aromatic ketones commonly used in industry to produce resins, adhesives and fragrances, and some are used medically as hypnotics and anticonvulsants. α-Halogenated acetophenones **3.2** are especially well known for their lachrymatory effects. Chloroacetophenone is a known component of tear gas, often used by police in riot control.[89,90]



3.1



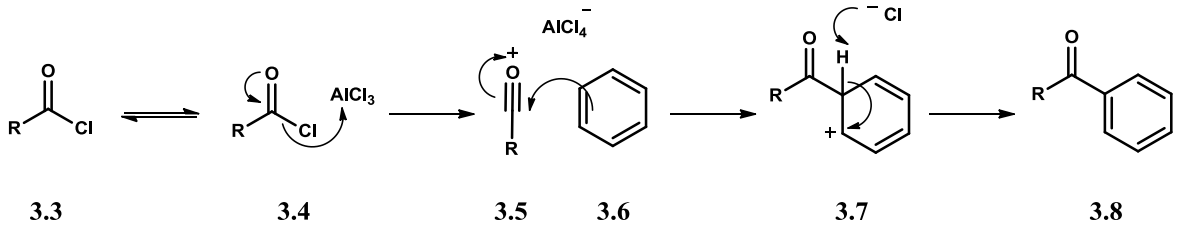
X = Br, I

3.2

Figure 3.1: The structure of acetophenone **3.1** and substituted *α*-halogenated acetophenone **3.2**.

The use of acetophenones as chiral building blocks is very important in the fine chemical and pharmaceutical industries. Variations in both the nature and the positions of the substituents (e.g. *ortho-*, *meta-*, *para-*) on the aromatic ring, as well as variation of substituents on the α–carbon (e.g. halide, methyl, methoxy, hydroxy groups) are also of major significance in industry and in organic synthesis.[91]

Classically, acetophenones and related alkyl aryl ketones have been synthesized through Friedel-Crafts acylation methodology, whereby the aromatic compound **3.6** reacts with an acyl halide **3.3** in the presence of a Lewis acid catalyst, such as aluminium trichloride,[92-94] iron trichloride and more recently zinc powder,[95] among many others. The Lewis acid assists in producing the reactive acylium ion **3.5**, which then undergoes electrophilic aromatic substitution to afford the acetophenone **3.8** (*Scheme 3.1*).[96]

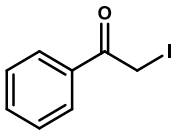


Scheme 3.1: Mechanism for the Friedel-Crafts acylation

α-Halogenated acetophenones have been synthesized from the present ketone using reagents such as bromine[92,97-99] copper(II) bromide[100] and ammonium tribromide.[64]

3.2. Outline of the synthetic strategy

This Chapter covers the preparation of four main groups of phenacyl halides. The simplest phenacyl halide, 2-iodo-1-phenylethanone **3.9** (*Figure 3.2*), bears an unsubstituted benzene ring and was prepared from commercially available 2-bromo-1-phenylethanone, as will be discussed in *Section 3.3*.

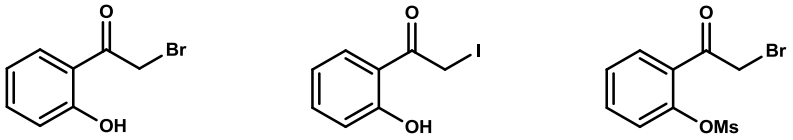


3.9

Figure 3.2: 2-Iodo-1-phenylethanone **3.9**

The second group of phenacyl halides, discussed in *Section 3.4*, contain a hydroxyl group *ortho* to the acyl group on the benzene ring (*Figure 3.3*). 2-Bromo-1-(2-hydroxyphenyl)ethanone **3.10** was prepared from anisole using the Friedel-Crafts acylation

approach mentioned above. This bromoacetophenone was iodinated to afford **3.12** and the hydroxyl group was protected with methane sulphonyl chloride to afford **3.13**.



3.10 **3.12** **3.13**

Figure 3.3: *Ortho*-hydroxy phenacyl bromide **3.10** and related phenacyl iodide **3.12** and *ortho*-mesyl phenacyl bromide **3.13** structures.

The third group of phenacyl halides of interest, discussed in *Section 3.5*, contains additional substituents on the 3- and 4-positions of the benzene ring such as **3.17**, shown in *Figure 3.4*. Synthesis of the related iodide **3.18** and methansulphonate **3.19** will also be discussed. These tetrasubstituted phenacyl halides were prepared from 3,4-dimethoxybenzaldehyde, and are closely related to the precursors required for the preparation of the lamellarin alkaloids (*Chapter 5*). This section has been expanded further to encompass phenacyl halides derived from vanillin, containing 4-methoxy-5-hydroxy substituents on the benzene ring (e.g. **3.24**).

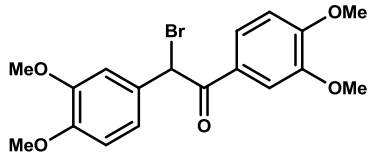


3.17: X = Br, R = H
3.18: X = I, R = H
3.19: X = Br, R = Ms

3.24

Figure 3.4: 3,4-dimethoxyphenacyl halides, **3.17**, **3.18** and **3.19**; and 4-methoxy-5-hydroxyphenacyl bromide **3.24**.

Finally, the fourth group of phenacyl halides and the most complex of the systems discussed is 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27** (*Section 3.6*)**.** This compound consists of a substituted phenacyl bromide with an additional aromatic substitution at the α–carbon (*Figure 3.5*). The phenacyl bromide was prepared from 3,4-dimethoxyphenylacetic acid by a Friedel-Crafts reaction and forms an expansion to the methodology used for the synthesis of lamellarins described in *Chapter 5*. Compounds from each of these groups will be dealt with in more detail in the sections that follow.



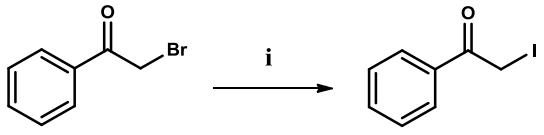
3.27

Figure 3.5: 2-Bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27**.

3.3. Preparation of 2-iodo-1-phenylethanone

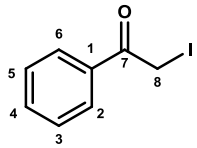
The use of established methodology for the exchange of halide groups, namely the Finkelstein reaction,[101] has been widely used in organic synthesis for the past century. The reaction uses the notion that an alkyl chloride can be converted to an alkyl bromide, while in turn can be converted into an alkyl iodide. The iodide salt is also soluble in the solvent, usually acetone, which the corresponding chloride or bromide salts form a precipitate. The increase in reactivity, nucleophilicity, and especially the difference between the solubility of the halide salts allows for this exchange to occur. The iodo-exchange was done in order to increase the reactivity of the reagent to ensure the optimization of enaminone synthesis, to be discussed in later Chapters.

2-Iodo-1-phenylethanone **3.9** was prepared from commercially available 2-bromo-1-phenylethanone (phenacyl bromide) by stirring with sodium iodide in acetone (*Scheme 3.2*).[102] The product **3.9** was obtained as a yellow oil, after purification by column chromatography and, owing to the instability of the product, was used immediately in subsequent reactions.



Phenacyl bromide **3.9**

Scheme 3.2 *Reagents and conditions:* i. NaI, acetone, 3 h.



3.9

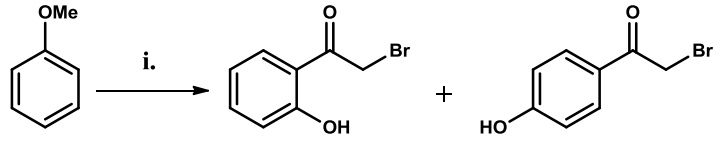
Although the iodinated and brominated compounds are very similar in structure, there were some definite shifts in peaks in the NMR spectra, which support the interconversion from acyl bromide to acyl iodide. Most significant was the presence of a signal at 2.93 ppm for C–8 CH_2 in the ^{13}C NMR spectrum, compared to 29.86 ppm for the phenacyl bromide CH_2 signal. The upfield shift of the carbon peak is commonly associated with C–I bonding. This could be explained by the difference in electronegativity between bromine and iodine (2.8 and 2.5 respectively). The increase in the electron density therefore causes the shielding effect observed in the ^{13}C NMR spectrum. The literature corresponded well with the data obtained.[102]

3.4. Synthesis of *ortho*-hydroxy acetophenones

This Section discusses the preparation of 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10** by a known literature procedure, which uses the Friedel-Crafts acylation to form both the *ortho* and *para* hydroxy substituted phenacyl bromides.[93,94] The iodinated **3.12** and mesylated **3.13** derivatives of the *ortho* substituted phenacyl bromide will also be described.

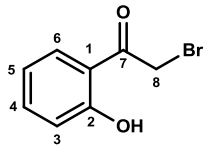
3.4.1. Preparation of 2-bromo-1-(2-hydroxyphenyl)ethanone

2-Bromo-1-(2-hydroxyphenyl)ethanone **3.10** was prepared by a known procedure using a Friedel-crafts acylation of anisole with bromoacetyl chloride, aluminium trichloride as the Lewis acid catalyst and tetrachloroethane as a solvent (*Scheme 3.3*).[93,94] The mixture was stirred under reflux for 6 hours. Various methods describe the isolation of the *ortho* and *para* isomers, however these proved quite problematic, and the isomers were generally isolated as mixtures. Column chromatography was found to be the most efficient method in separating the two isomers, and 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10** was isolated as a yellow solid in 72% yield, with a melting point of 44–45°C. The *para* product, 2-bromo-1-(4-hydroxyphenyl)ethanone **3.11**, was isolated in 18% yield, with a melting point of 129–132°C. These values were closely related to literature values of 42 and 135°C[94] for the *ortho* and *para* bromoacetophenones, respectively.

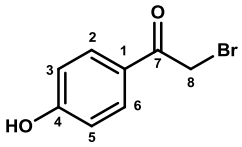


Anisole **3.10** **3.11**

Scheme 3.3 *Reagents and conditions:* i. $BrCH_2COCl$, $AlCl_3$, $Cl_2CHCHCl_2$, 0–100°C, 24 h.



3.10

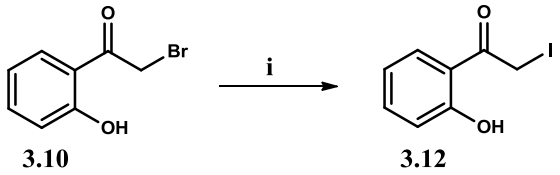


3.11

In the ^{1}H NMR spectrum, the phenol signals were observed at 11.73 ppm for **3.10** and 9.96 ppm for **3.11**. This could be explained by the additional deshielding effects of the *ortho* acyl halide on the phenol as a result of intramolecular hydrogen bonding. Additionally, the symmetry in the structure of *para* acetophenone **3.11** was observed in the NMR spectrum with the appearance of the aromatic protons as two doublets for C–3,5 ArH at 7.86 ppm (adjacent to the OH substituent) and C–2,6 ArH at 6.90 ppm (adjacent to the acetophenone substituent), with the OH contributing to the larger shielding effects on its neighbouring protons. The *ortho* acetophenone **3.10** showed four aromatic hydrogen signals in the ^{1}H NMR spectrum, as was expected for this product.

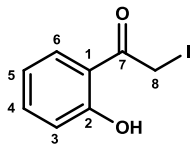
3.4.2. Preparation of 1-(2-hydroxyphenyl)-2-iodo-1-ethanone

2-Bromo-1-(2-hydroxyphenyl)ethanone **3.10** was treated with sodium iodide in acetone, using the Finkelstein reaction discussed previously. A change in the colour of the reaction mixture from a clear yellow solution to an opaque dark orange solution with the white solid precipitation of sodium bromide observed, indicating that the halide exchange had taken place. Once the reaction was complete, a recrystallization from ethanol furnished 1-(2-hydroxyphenyl)-2-iodo-1-ethanone **3.12** (*Scheme 3.4*) as bright yellow crystals, which were used immediately in subsequent reactions owing to the relatively rapid rate of decomposition of the product.



3.10 **3.12**

Scheme 3.4 *Reagents and conditions:* i. NaI, acetone, 3 h.



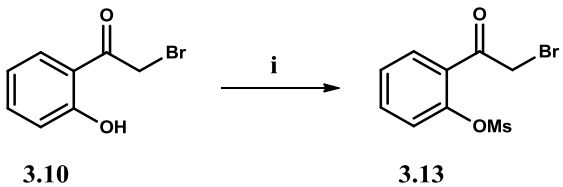
C3

The ^{1}H NMR spectrum showed a slight upfield shift for the CH_2 signal from 4.45 ppm for the brominated **3.10**, to 4.37 ppm for the iodinated product **3.12** as expected from the exchange of a bromide to an iodide. Similarly, and more significantly, the C–8 signal shifts from 29.88 to 0.58 ppm in the ^{13}C NMR spectrum, correlating with the value obtained in the iodination of 2-bromo-1-phenylethanone **3.9** that was described in *Section 3.3*. Spectroscopic data agrees with the reported literature.[102]

3.4.3. Preparation of 2-(2-bromoacetyl)phenyl methanesulphonate

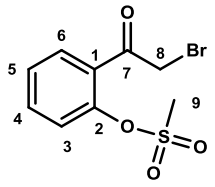
The use of mesylates as protecting groups was initially conducted for several reasons: (i) to protect the phenolic group from undesirable reactions during the synthesis; (ii) to assist in lactonization in the synthesis of the final lamellarins, by spontaneously forming the lactone during the deprotection of the mesyl group.[103] These points will be explained further in later chapters.

As shown in *Scheme 3.5*, 2-(2-bromoacetyl)phenyl methanesulphonate **3.13** was prepared from a solution of 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10** in tetrahydrofuran. Deprotonation of the phenol using triethylamine as a base, followed by the dropwise addition of methanesulphonyl chloride, afforded the product **3.13** in a quantitative yield as a yellow oil.



3.10 **3.13**

Scheme 3.5 *Reagents and conditions:* i. MsCl, Et_3N, THF, 0°C–rt , 2 h.



3.13

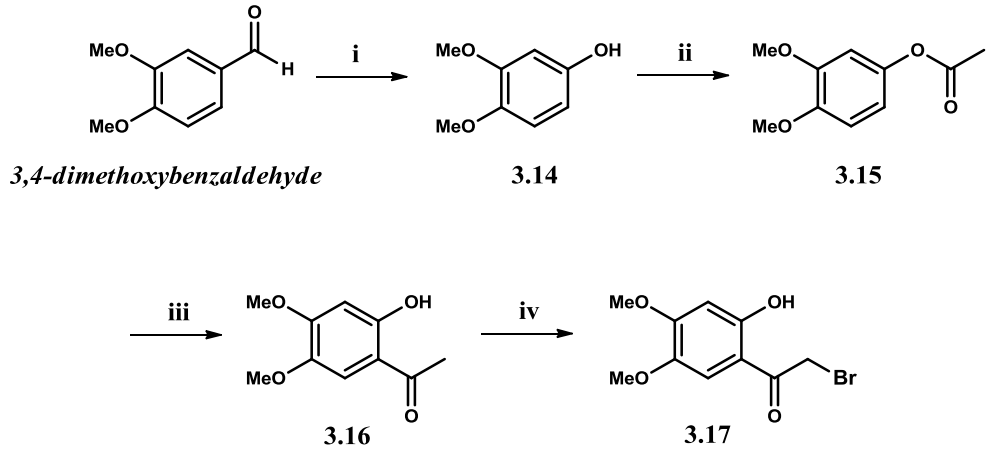
The absence of the OH peak in both the IR and ^{1}H NMR spectra was observed. In the ^{1}H NMR spectrum, a C–9 CH_3 singlet at 3.26 ppm for the new sulphonyl group was observed, as well as some significant S=O and S–O stretches at 1155 and 976 cm^{-1} in the IR spectrum. The data was in agreement with the findings of Morgans in his PhD thesis.[69]

3.5. Synthesis of tetrasubstituted acetophenones

The following Section examines the preparation of *ortho*-oxygenated phenacyl bromides with 3,4-dimethoxy and 4-methoxy-5-hydroxy substitution on the benzene ring, using methodology adapted from Zhang and Botting[104] and Ploypradith and co-workers.[103] The iodination and mesylation of the 3,4-dimethoxyphenacyl bromides will also be discussed.

3.5.1. Preparation of 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone

2-Bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.17** (*Scheme 3.6*) was prepared by a four-step synthesis from 3,4-dimethoxybenzaldehyde. The first step of the synthesis required the use of the Baeyer-Villiger oxidation to convert 3,4-dimethoxybenzaldehyde into 3,4-dimethoxyphenol **3.14**.[105] The reaction occurs in the presence of 30–35% aqueous hydrogen peroxide in methanol. A catalytic amount of sulphuric acid was then added to the mixture, and after stirring for 20 hours, the alcohol 3,4-dimethoxyphenol **3.14** was produced in 80% yield.



3,4-dimethoxybenzaldehyde **3.14** **3.15**

3.16 **3.17**

Scheme 3.6 *Reagents and conditions:* i. H_2O_2, H_2SO_4, MeOH, –15°C–rt, 18 h; ii. Ac_2O, pyridine, 0°C–rt, 18 h; iii. $BF_3 \cdot Et_2O$, 0°C–reflux 20 h; iv. $CuBr_2$, EtOAc : $CHCl_3$ (1:1), reflux, 96 h.

Product **3.14** was easily distinguishable from the starting material by comparing the ^{1}H NMR spectra. In particular, loss of the aldehyde peak at 9.82 ppm for the starting material and the appearance of the OH signal at 5.83 ppm for phenol **3.14** were observed. The alcohol was then deprotonated with pyridine and acetylated with acetic anhydride to afford 3,4-dimethoxyphenyl acetate **3.15** in a quantitative yield.[104] The product **3.15** was identified by both IR and NMR spectroscopic techniques. The disappearance of the OH group was evident in the analysis of the IR spectrum, with the broad alcohol stretch at 3334 cm^{-1} clearly absent and replaced by the C=O stretch at 1758 cm^{-1}. Similarly, the ^{1}H NMR spectrum of the product **3.15** showed the absence of the broad OH signal at 5.83 ppm, and the appearance of a CH_3 singlet at 2.28 ppm. The ^{13}C NMR spectrum also showed the presence of a C=O signal at 169.80 ppm.

3,4-Dimethoxyphenyl acetate **3.15** was used without further purification in a boron trifluoride-catalysed Fries rearrangement.[106,103,107] In this rearrangement, a boron complex is initially formed with the carbonyl oxygen. This complex then dissociates to form an acylium carbocation, which undergoes electrophillic aromatic substitution with the benzene ring. The product is then obtained after hydrolysis, and depending on the temperature used and the polarity of the solvent, the *para*- (low temperatures and polar solvents) or *ortho*- (high temperatures and non-polar solvents) product is favoured.

In our synthesis, neat boron trifluoride etherate was used and the reaction was heated to 110°C, over 5 hours. Water was then added to the reaction mixture which caused a brown solid to precipitate out of the solution. This was collected and recrystallized from methanol to afford the product 1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.16** as dark yellow crystals. An XRD crystal structure was obtained for this compound (*Figure 3.6a*), which gave an orthorhombic unit cell with Z = 4, an R-factor of 0.032, and was crystallised into the polar space group $Pca2_1$. Intramolecular hydrogen bonding was noted between the phenol and acetyl groups. Two C–H…π and several C–H...O interactions act to stabilize the structure (*Figure 3.6b*). The anticipated OH singlet peak was also observed in the ^{1}H NMR spectrum at 12.19 ppm and IR spectrum at 3020 cm^{-1}.

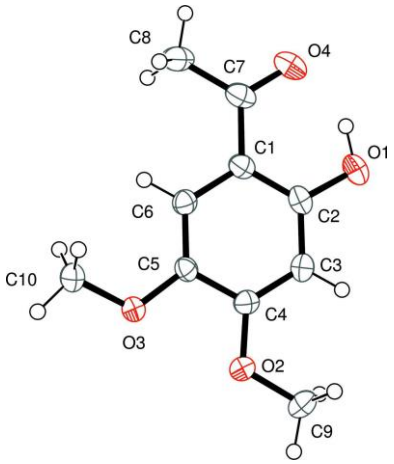


Figure 3.6a: XRD ORTEP diagram for 1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.16**

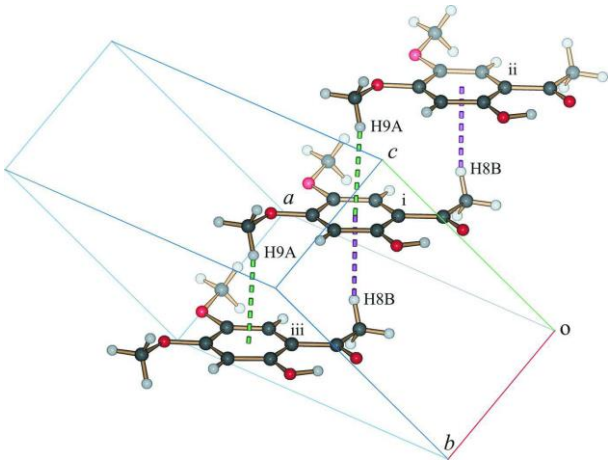
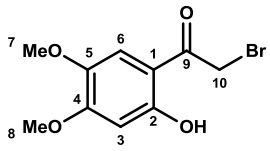


Figure 3.6b: XRD ORTEP diagram showing phenyl and acetyl interactions between 1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.16** structures

Hydroxyacetophenone, 1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.16**, was then brominated at the α-carbon by adding a suspension of copper(II) bromide in a 1:1 solution of chloroform and ethyl acetate, and heated under reflux.[108] It has been established that under these conditions the bromination is highly selective toward monobromination at the α-carbon. The reaction proceeds with the evolution of hydrogen bromide and the conversion of black copper(II) bromide to white copper(I) bromide. The colour of the solution also changes from deep emerald green to dark orange in appearance. The crude product isolated from this reaction was purified by flash column chromatography and was recrystallized from diethyl ether and ethanol to afford 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.17** as yellow crystals in 84% yield.



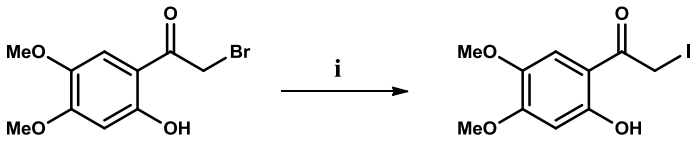
3.17

The formation of the product was confirmed by the appearance of a sharp C–Br stretch at 683 cm^{-1} in the IR spectrum and a singlet peak at 4.36 ppm, integrating for two protons on C–10 in the ^{1}H NMR spectrum. The HRMS of the product **3.17** also attested to the presence of the product. The molecular ion peak was observed at 273.9828 for the ^{79}Br isotope, which had an exact mass of 273.9841. The ^{81}Br isotope was also accounted for at 92% relative abundance, with an *m/z* value of 275.9811.

All spectroscopic data obtained for compounds **3.14** to **3.17** was corroborated with literature.[104-107,109,110]

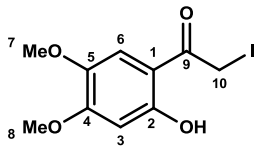
3.5.2. Preparation of 1-(2-hydroxy-4,5-dimethoxyphenyl)-2-iodoethanone

1-(2-Hydroxy-4,5-dimethoxyphenyl)-2-iodoethanone **3.18** was then prepared from 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.17**, shown in *Scheme 3.7* below, using the established procedure for iodination discussed in *Section 3.3*.



3.17 **3.18**

Scheme 3.7 *Reagents and conditions:* i. NaI, acetone, 3 h.

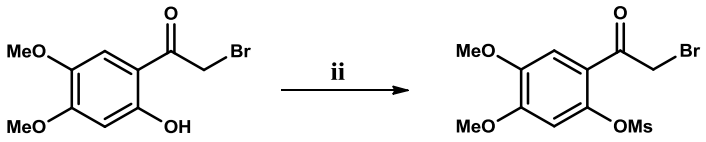


3.18

The C–10 CH_2 signal was observed at 0.75 ppm in the ^{13}C NMR spectrum for the product **3.18**, compared to 29.85 ppm for the starting material **3.17**. Once again, this illustrates the shielding effects observed on the CH_2 group, owing to the replacement of bromine with iodine. Similarly, the NMR spectra of the product **3.18** compared well with the previously prepared phenacyl iodide **3.12**, with the proton signal for C–10 CH_2 appearing at 4.30 ppm compared to 4.37 ppm for **3.12**; and the carbon signal appearing at 0.75 ppm compared to 0.58 ppm for **3.12**. The IR spectrum showed a C–I stretch at 632 cm^{-1} compared to 612 cm^{-1} for the previously prepared **3.12**.

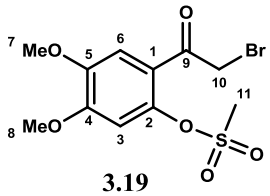
3.5.3. Preparation of 2-(2-bromoacetyl)-4,5-dimethoxyphenyl methanesulphonate

Using the established procedure for the protection of phenolic groups with a mesylate discussed in *Section 3.4.3*, the product 2-(2-bromoacetyl)-4,5-dimethoxyphenyl methanesulphonate **3.19**(*Scheme 3.8*) was afforded in a quantitative yield as a white powder.



3.17 **3.19**

Scheme 3.8 *Reagents and conditions:* i. MsCl, Et_3N, THF, 0°C–rt , 2 h.

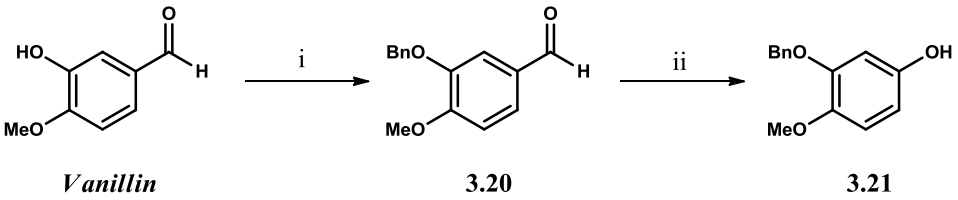


3.19

The ^1H NMR spectrum compared well with the previously prepared 2-(2-bromoacetyl)phenyl methanesulphonate **3.13** (*Section 3.4.3*). The chemical shifts for the C–11 CH_3 signal were observed to be similar (3.26 ppm for **3.13** and 3.19 ppm for **3.19**), and the S=O and S–O stretches were also observed in the IR spectrum of both compounds (1155 and 976 cm^{-1} for **3.13** and 1179 and 953 cm^{-1} for **3.19**).

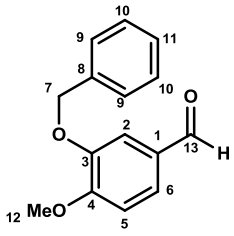
3.5.4. Preparation of 2-bromo-1-(2,4-dihydroxy-5-methoxyphenyl)ethanone

2-Bromo-1-(2,4-dihydroxy-5-methoxyphenyl)ethanone **3.24** (*Scheme 3.10*) was prepared by a five-step synthesis from vanillin. The reaction scheme is similar to the previously described preparation of 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.17**, with an additional step required to protect the aromatic alcohol in this case. The synthesis proceeded with the protection of the aromatic OH of vanillin using benzyl bromide, potassium carbonate as a mild base to deprotonate the OH group, and acetone as the solvent.[111] After purification by column chromatography, the product 3-(benzyloxy)-4-methoxybenzaldehyde **3.20** (*Scheme 3.9*) was obtained as an off-white crystalline solid.



Vanillin **3.20** **3.21**

Scheme 3.9 *Reagents and conditions:* i. BnBr, K_2CO_3, acetone, 70°C, 18 h; ii. H_2O_2, H_2SO_4, MeOH, –15°C–rt, 18 h.

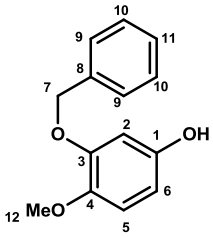


3.20

The IR and ^{1}H NMR spectra for product **3.20** confirmed the formation of the desired product showing loss of the OH peak. The ^{1}H and ^{13}C NMR spectra further supported this by showing the presence of additional aromatic proton and carbon signals: In the ^{1}H NMR spectrum it was observed that an overlap in signal peaks gave a multiplet in the region of 7.51–7.26 ppm, which integrated for seven of the aromatic hydrogen peaks present in the structure. An additional aromatic doublet signal was observed at 6.97 ppm. This was assigned to C–5, owing to its *ortho* coupling to C–6 (J = 8.2 Hz).

A Baeyer-Villiger oxidation reaction, using hydrogen peroxide in methanol with a catalytic amounts of acid, was used to convert 3-(benzyloxy)-4-methoxybenzaldehyde **3.20** into 3-(benzyloxy)-4-methoxyphenol **3.21**, using the methodology already established for the preparation of 3,4-dimethoxyphenol **3.14**. The purified product was collected as a dark orange solid in a yield of 68%. TLC for the reaction showed a change in R_f from 0.64 (for

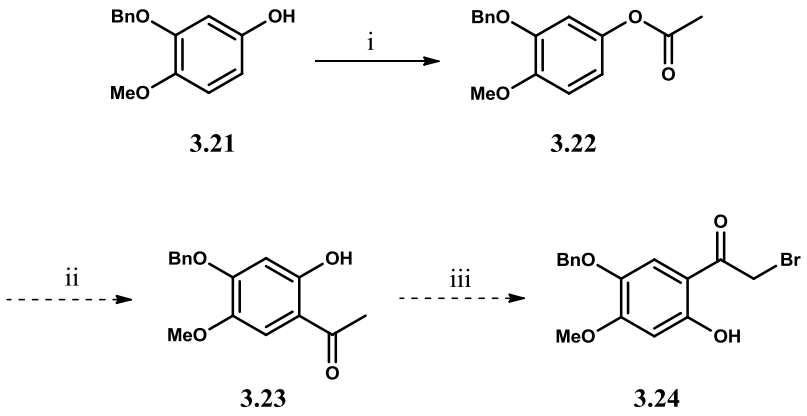
3.20) to 0.31 (for **3.21**) using 30% ethyl acetate in hexane as a mobile phase. This attests to the change in polarity of the structure from the less polar aldehyde to the more polar phenol.



3.21

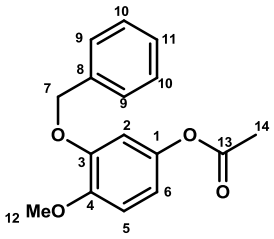
In the IR spectrum of the newly synthesized alcohol **3.21**, a broad OH stretch was observed at 3347 cm^{-1}. Similarly, the absence of the C–1 CH aldehyde **3.20** singlet at 9.81 ppm in the ^{1}H NMR spectrum and 190.87 ppm in the ^{13}C NMR spectrum, as well as the appearance of an OH singlet for the product **3.21** at 2.04 ppm in the ^{1}H NMR spectrum, confirmed that 3-(benzyloxy)-4-methoxyphenol **3.21** had formed.

The alcohol **3.21** was then protected with an acetyl group using the procedure established in the preparation of 3,4-dimethoxyphenyl acetate **3.15**, to afford 3-(benzyloxy)-4-methoxyphenyl acetate **3.22** (*Scheme 3.10*) as a pale orange oil, which was carried through to the next step without further purification.



3.21 **3.22** **3.23** **3.24**

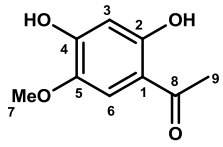
Scheme 3.10 *Reagents and conditions:* i. Ac_2O, pyridine, 0°C–rt, 18 h; ii. $BF_3{\cdot}Et_2O$, 0°C–reflux 20 h; iii. $CuBr_2$, (1:1) EtOAc : $CHCl_3$, reflux, 96 h.



3.22

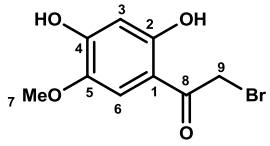
In the ^{1}H NMR and ^{13}C NMR spectra, signals for C–14 CH_3 were observed at 2.25 ppm, in the ^{1}H NMR spectrum, and 21.07 ppm in the ^{13}C NMR spectrum. The presence of the acyl group was further confirmed by a signal for C–13 C=O at 169.77 ppm in the ^{13}C NMR spectrum and 1759 cm^{-1} in the IR spectrum. Analysis of the product by high resolution mass spectrometry showed a mass of 273.1128 for 3-(benzyloxy)-4-methoxyphenyl acetate **3.22**, which was in good agreement with the expected mass of 273.1128.

The Fries rearrangement with boron trifluoride etherate using a procedure similar to that discussed for the preparation of 1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.16** was envisioned for the next step. Although the Fries rearrangement was observed, a spontaneous deprotection of the benzyl protecting group unexpectedly occurred. The product 1-(2,4-dihydroxy-5-methoxyphenyl)ethanone **3.23**, was isolated and recrystallized from methanol as a yellow powder in an unoptimized yield of 13%. The dihydroxy product could then be used in the subsequent step to form the bromoacetophenone **3.24**, without the need to deprotect the benzyl group at a later stage.



3.23

The IR spectrum of product **3.23** showed an alcohol peak at 3352 cm^{-1}, as well as confirming the presence of a ketone with a peak at 1643 cm^{-1} for C=O. In the ^{1}H NMR spectrum, the presence of the strongly hydrogen-bonded C–2 OH at 12.50 ppm (confirmed by comparisons made with previously synthesized **3.16** and vanillin starting material), the C–4 OH at 5.28 ppm, and a singlet at 2.53 ppm from C–9 CH_3 were observed. The ^{13}C NMR spectrum showed a peak at 202.66 ppm due to the ketone carbonyl.

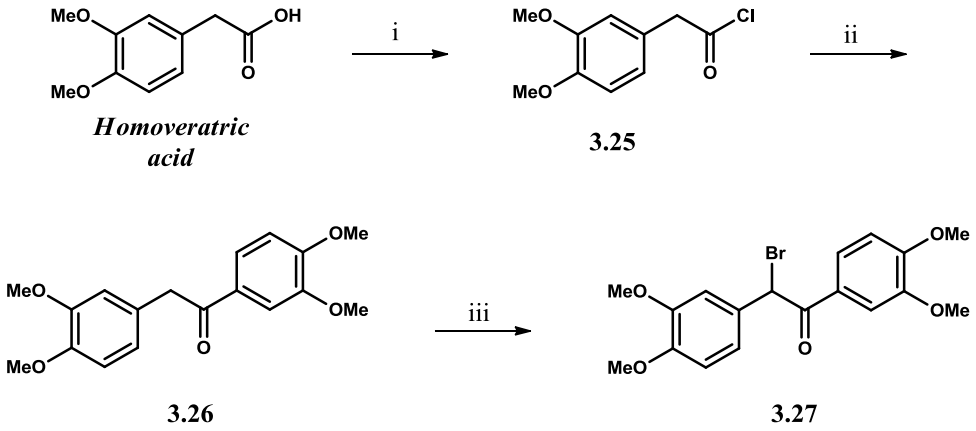


3.24

Finally, copper(II) bromide was used to brominate at the α-carbon, as described previously in the synthesis of **3.17**. 2-Bromo-1-(2,4-dihydroxy-5-methoxyphenyl)ethanone **3.24** was obtained as a yellow solid in 66% yield. In the IR spectrum, a C–Br stretch was observed at 537 cm^{-1}. The ^{1}H NMR spectrum contains a singlet peak at 4.34 ppm integrating for two protons (C–9 CH_2) illustrating the presence of the monobrominated acetophenone product **3.24**. Correspondingly, in the ^{13}C NMR spectrum, the C–9 signal was observed at 56.36 ppm. The spectroscopic data for prepared compounds **3.20–3.24** compared well with literature. [104-107,109,110]

3.6. Preparation of 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone

As discussed in *Section 3.2.*, the last and most complex of the bromoacetophenones, 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27**, was synthesized from 3,4-dimethoxyphenylacetic acid (homoveratric acid) (*Scheme 3.11*) using the established Friedel-Crafts acylation reaction. This complex bromoacetophenone was synthesized for the preparation of enaminones to be discussed in *Chapter 5*.



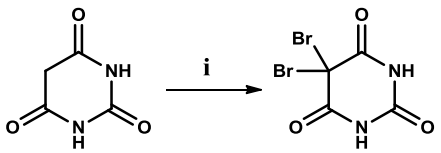
Scheme 3.11 *Reagents and conditions:* i. $(COCl)_2$, CH_2Cl_2, 0°C–rt , 18 h; ii. veratrole, $AlCl_3$, CH_2Cl_2, reflux, 3 h; iii. ***Reagent 3.28*** (*Scheme 3.12*), $CHCl_3$, 0°C–rt, 3 h.

Commercially available, 3,4-dimethoxyphenylacetic acid was reacted with oxalyl chloride in dichloromethane to give 2-(3,4-dimethoxyphenyl)acetyl chloride **3.25** as a reddish-brown oil in a quantitative yield.[112] The acyl chloride **3.25** was carried through to the next step without further purification. The IR spectrum showed the absence of the acid group and presence of the C–Cl stretch at 626 cm^{-1}. A C=O stretch was also observed at 1711 cm^{-1} for the newly formed acyl chloride **3.25**. In the ^1H NMR spectrum the absence of the OH peak at 10.49 ppm was also noted. The data agreed with the literature.[112]

2-(3,4-Dimethoxyphenyl)acetyl chloride **3.25** then underwent a Friedel-Crafts acylation with veratrole in dichloromethane, using aluminium trichloride as the Lewis acid catalyst. After 3 hours of heating under reflux, and purification by recrystallization from ethanol, the product 1,2-bis(3,4-dimethoxyphenyl)ethanone **3.26** was obtained as an off-white crystalline solid in 73% yield. In the ^1H NMR spectrum, it was observed that peaks in the aromatic region (7.67–6.78 ppm) integrated for six protons. It was also noted that four singlet signals each

integrating for three protons were present at 3.94, 3.92, 3.86, and 3.85 ppm, this indicates the incorporation of a second aromatic ring into the pre-existing structure **3.25**. Moreover, interpretation by mass spectrometry indicated that the molecular ion peak found at 316.1290 was in good agreement with the exact mass value of 316.1311 for 1,2-bis(3,4-dimethoxyphenyl)ethanone **3.26**. The literature compared well with our findings.[112,113]

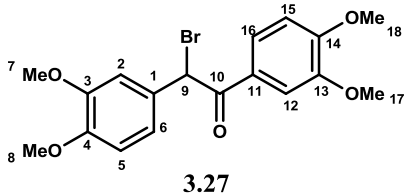
Finally, 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27** was prepared by brominating 1,2-bis(3,4-dimethoxyphenyl)ethanone **3.26** with 5,5-dibromopyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **3.28**. 5,5-Dibromopyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **3.28** was prepared from barbituric acid and bromine (*Scheme 3.12*),[114] in 67% yield as a white crystalline powder. Several other bromination methods were attempted, including the use of bromine, and the use of copper(II) bromide, but these reagents either failed to work or formed the dibrominated acetophenone as the major product.



Barbituric acid **3.28**

Scheme 3.12 *Reagents and conditions:* i. Br_2, H_2O, rt, 2 h.

The ^{1}H NMR spectrum for **3.28** depicted a singlet for the two NH protons present in the reagent, which integrated for two protons, at 10.77 ppm. No CH_2 or CH signals were present. The dibrominated reagent **3.28** was then reacted with 1,2-bis(3,4-dimethoxyphenyl)ethanone **3.26** in chloroform to afford 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27** as a yellow solid in 94% yield. The data was in agreement with literature.[114]



3.27

The IR spectrum for **3.27** showed a C–Br stretch at 639 cm^{-1}. In the ^{1}H NMR spectrum, it was observed that the C–9 CH_2 singlet at 4.19 ppm for the unbrominated starting material **3.26** had been replaced with a C–9 CH singlet at 6.41 ppm. The shift of the signal to a downfield position suggests that the product is more deshielded due to the effects of the electronegative bromine group on C–9. Similarly, inspection of the ^{13}C NMR spectrum shows a downfield shift of the C–9 C–Br signal from

44.74 ppm for **3.26** to 51.52 ppm for **3.27**, indicating that the product had formed. Mass spectrometry studies of the compound found the parent ion peak for the ^{79}Br isotope to be 394.0140, which was in good agreement with the exact mass of the compound, 394.0146. The ^{81}Br isotope showed a mass of 396.0142 and was found in 70% abundance.

3.7. Conclusions for Chapter 3

The phenacyl halides described in this Chapter form an integral part in the synthesis of enaminones using Eschenmoser sulphide contraction. They form the groundwork for the novel library of compounds discussed in the remaining chapters of this thesis.

Simple bromoacetophenones **3.10**, substituted bromoacetophenones **3.17** and **3.24**, and the brominated biaryl system, 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27** were prepared. The α–carbon of the acetophenone was brominated or iodinated, giving variation to the halide group and allowing for a diversity of reaction conditions to be applied in the subsequent syntheses. The *ortho*-substituted hydroxyl group was also protected in certain compounds to create a range of phenacyl halides and to assist in the ease of the synthesis in subsequent steps. The preparation of 4-methoxy-5-hydroxy acetophenone **3.24** illustrated the versatile application of the methodology in creating diversely substituted acetophenones for the synthesis of many analogues, in this thesis and in future adaptations. Thus, a collection of readily available and widely functionalized phenacyl halides was prepared.

Chapter 4
Towards tetracyclic pyrrolizinone, indolizinone and pyrroloazepinone analogues of lamellarins

This chapter serves as a model study toward the synthesis of pentacyclic lamellarins (*Chapter 5*). The methodology envisioned for the preparation of these simpler tetracyclic systems serves as a means of elaborating the potential importance of lamellarins. Many of the systems prepared in this Chapter are novel and could demonstrate potential biological importance. Testing of the products synthesized was delayed due to problems experienced with the biochemical facilities and the time constraints of the project; they will therefore not appear in this thesis.

4.1. Introduction

As discussed in *Chapter 1* of this thesis, lamellarins are a group of predominantly pentacyclic compounds, exhibiting a variety of structurally interesting features, which make them appealing both synthetically and biologically. There are many known lamellarins both in nature and those that have been prepared synthetically. For the purposes of the project lamellarin G trimethyl ether (*Figure 4.1*) was chosen as the main target molecule, owing to the simplicity of the substituents on the aromatic rings (i.e. OMe groups only). Lamellarins themselves constitute a much larger group containing substituents of varying number and vast diversification. This Chapter will therefore discuss only the reactions and substitution relevant to a model study of lamellarin G trimethyl ether.

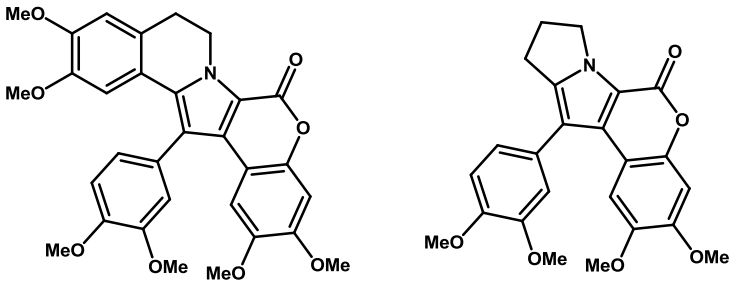
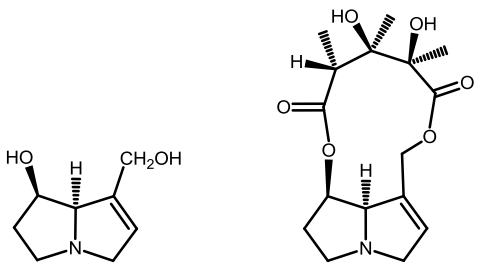


Figure 4.1: Lamellarin G trimethyl ether and corresponding pyrrolizine analogue.

The pyrrolizine alkaloids have been studied extensively in the Wits organic laboratories and some of the chemistry used in the previous syntheses were modified and used as a basis for this project. Pyrrolizines form an extensive part of this Chapter, which demonstrates that novel and interesting products can be formed from these systems. *Figure 4.1* illustrates one of the pyrrolizine analogues expected from our model synthesis, with direct reference to lamellarin G trimethyl ether.

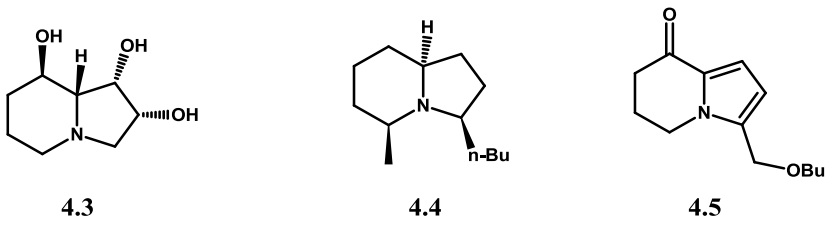
Pyrrolizine consists of a 5,5-fused ring system with a bridgehead nitrogen atom and was first reported in 1915. This system and its fully reduced analogue (pyrrolizidine) forms the core of a large class of natural products with a diversity of biological properties, including mutagenic, carcinogenic, teratogenic, anticancer and neuroactive properties. They are mainly isolated from flowing plants, especially Asteraceae (e.g. daisy and sunflower), Leguminosae (e.g. legumes and beans) and Boraginaceae (e.g. shrubs, trees, herbs such as forget-me-not). Plants containing pyrrolizines have been used medicinally since the Middle Ages. Retronecine **4.1** and monocrotaline **4.2** are two examples of pyrrolizine alkaloids (*Figure 4.2*).[115-117]



4.1 **4.2**

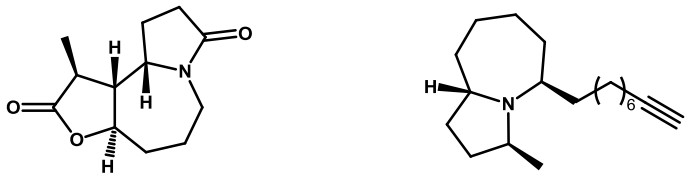
Figure 4.2: Pyrrolizine alkaloids, retronecine **4.1** and monocrotaline **4.2**.

As an extention to the methodology describing the preparation of pyrrolizine analogues; indolizine and pyrroloazepine analogues were also prepared. The indolizine framework (5,6-fused ring system with a bridgehead nitrogen) is a common substructure in a number natural products and pharmaceuticals. Indolizines are associated with a wide spectrum of biological activities including anticancer, antibacterial, antifungal, anti-inflammatory, antihistaminic, antimicrobial, antioxidant, and analgesic activity. Some important indolizine alkaloids include swainsonine **4.3**, monomorine I **4.4** and kinganone **4.5** (*Figure 4.3*).[118-121] More recently, the pyrroloazepines (5,7-fused ring system with a bridgehead nitrogen) have become more important, and they have been found in many marine, plant and animal species. They also have potential in many biological and pharmaceutical areas. Some important pyrroloazepine alkaloids include stemoamide **4.6** and lehmizidine 275A **4.7** (*Figure 4.4*).[122,123]



4.3 **4.4** **4.5**

Figure 4.3: Indolizine alkaloids, swainsonine **4.3**, monomorine I **4.4** and kinganone **4.5**.



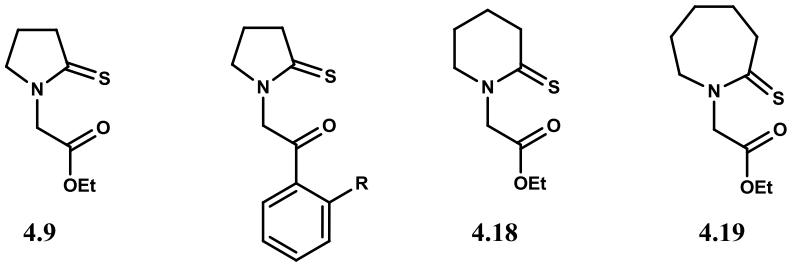
4.6 **4.7**

Figure 4.4: Pyrroloazepine alkaloids, stemoamide **4.6** and lehmizidine 275A **4.7**.

A library of tetracyclic analogues of varying ring sizes was thus prepared, which attested to the fact that the method using prepared enaminones in a novel ring closure to form pyrrole systems could be adapted to further organic systems.

4.2. Outline of the synthetic strategy

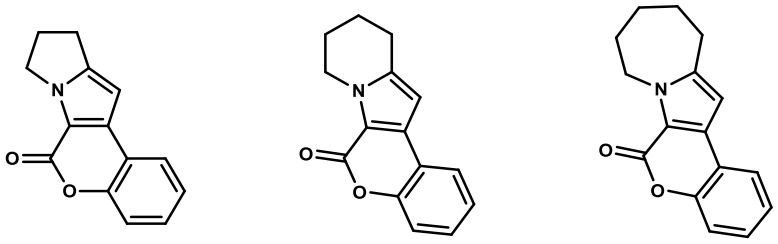
The targets to be described in the following sections were prepared by two focal methods. The first is the "Wits" approach, which has been used extensively to access alkaloid systems through enaminone intermediates via thiolactams. The preparation of relevant thiolactams will be discussed in the *Section 4.3*. 5-Membered, 6-membered and 7-membered varieties of thiolactam precursors were prepared (*Figure 4.5*). These will form the basis for the diversification of the project and will eventually produce a library of pyrrole-containing tetracyclic lamellarin analogues. Several of the initial studies in this Chapter were carried out previously by fellow colleagues;[69,124] nonetheless, certain adaptations to the methodology were necessary to facilitate improvements to the purification, characterization and yields of the enaminone products. The Eschenmoser sulphide contraction was then carried out on the thiolactam precursors (*Section 4.4*).



4.9 **4.14: R = H** **4.15: R = OH** **4.18** **4.19**

Figure 4.5: 5-Membered **4.9**, **4.14** and **4.15**, 6-membered **4.18** and 7-membered **4.19** thiolactams.

The second focal experimental point was the novel and somewhat serendipitous method for the formation of the pyrrole rings, which will be discussed in *Section 4.5*. The methodology was discovered by a previous PhD student, Garreth Morgan;[69] a related method was also employed by Calvo and co-workers.[88] The method has since been adapted and optimized for this thesis. The pyrrole formation forms an integral part of the project, and is the basis for the preparation of the tetracyclic pyrrolizinone (**4.32**), indolizinone (**4.38**) and pyrroloazepinone (**4.40**) systems (*Figure 4.6*).



4.32 **4.38** **4.40**

Figure 4.6: Simple tetracyclic pyrrolizinone **4.32**, indolizinone **4.38** and pyrroloazepinone **4.40** compounds.

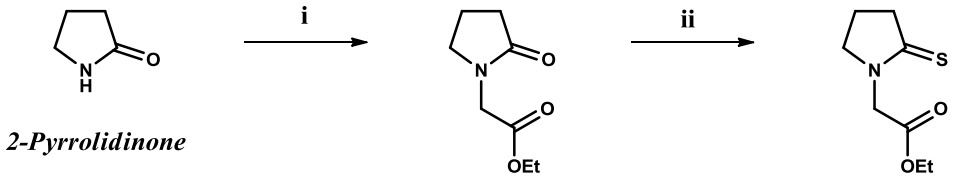
Lastly, the chapter will cover numerous experimental investigations of the chemistry on the formed pyrrole ring, with the envisaged lamellarin target model in mind. Therefore various Suzuki-Miyaura coupling reactions were accomplished (*Section 4.6*), to attest to the methodology required in the Chapter concerning the synthesis toward lamellarins. Other adaptions will also be discussed, such as the use of protecting groups and the attempt to induce the formation of the lactone in these alkaloid systems (*Section 4.7*).

4.3. Preparation of thiolactam precursors

This section explores the synthesis of thiolactams from various commercially available starting materials. Pyrrolidine thiolactams will be prepared by first *N*-alkylating with ethyl 2-bromoacetate and then thionating the resulting 2-pyrrolidinone with Lawesson's reagent or phosphorus pentasulphide. *N*-Phenacyl substituted pyrrolidine thiolactams with an inverse substitution patterns to that described above, will also be discussed. Finally, thiolactams prepared from 2-piperidinone and caprolactam will be examined. The thiolactams will be utilized as reagents in the Eschenmoser sulphide contraction reaction, which will be discussed in *Section 4.4*.

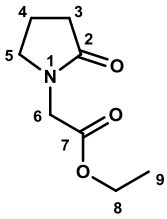
4.3.1. Preparation of ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate

2-Pyrrolidinone was added dropwise to an emulsion of sodium hydride, in 60% dispersion of mineral oil, stirred in anhydrous tetrahydrofuran. The solution was stirred at ambient temperature until analysis of the TLC plate showed activity at the baseline, indicating a salt had formed. Ethyl 2-bromoacetate was then added to the opaque white mixture and after hydrolysis and purification by column chromatography the *N*-alkylated product ethyl 2-(2-oxo-1-pyrrolidinyl)acetate **4.8** was isolated in 77% yield (*Scheme 4.1*).[84,125]



2-Pyrrolidinone **4.8** **4.9**

Scheme 4.1 *Reagents and conditions:* i. NaH (60%), ethyl 2-bromoacetate, THF, rt, 20 h; ii. Lawesson's reagent, toluene, 80°C, 20 h or P_4S_{10}, $((CH_3)_3Si)_2O$, CH_2Cl_2, reflux–rt, 48 h.

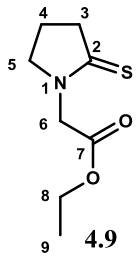


4.8

The substituted acetate branch of compound **4.8** was represented by three signals in the ^{1}H NMR spectrum for *N*-alkylated product **4.8**; a triplet at 1.28 ppm for C–9, a singlet at 4.06 ppm for C–6 and a quartet at 4.19 ppm for C–8. The coupling constant of the C–8 CH_2 quartet and the C–9 CH_3 triplet showed a correlating value of 7.0 Hz. The ester group was also confirmed by a C–O–C stretch at 1191 cm^{-1}, in the IR spectrum. The ^{13}C NMR spectrum showed two carbonyl signals at 175.23 ppm for C–2 and at 168.23 ppm for C–7. Similarly, the IR spectrum confirmed the presence of the two carbonyls with stretches at 1741 and 1672 cm^{-1}.

Ethyl 2-(2-oxo-1-pyrrolidinyl)acetate **4.8** was then thionated using Lawesson's reagent in toluene.[76,126] The deep yellow reaction mixture was heated under reflux and after 20 hours the TLC indicated that the reaction was complete. The product was purified by flash column chromatography, in 20% ethyl acetate in hexane mixture, to afford the thiolactam ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate **4.9** (*Scheme 4.1*) as a yellow oil. Similarly but less efficiently, when phosphorus pentasulphide and hexamethyldisiloxane in dichloromethane were used to

thionate the amide,[77,126] the product could only be produced in 45% yield and contained a large amount of polymeric residue.



4.9

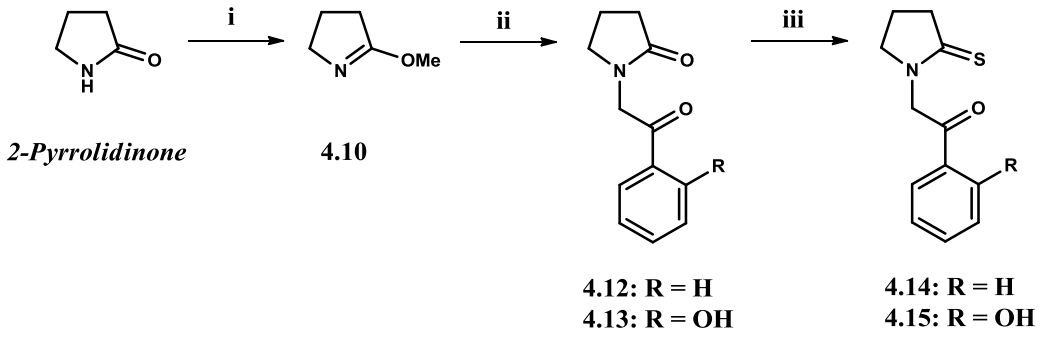
In both the ^{1}H and ^{13}C NMR spectra of product **4.9**, some distinct downfield shifts were noted. This could be explained by the difference in the electronegativity between oxygen (3.5) and sulphur (2.5). The deshielding effect of the sulphur on the surrounding protons was observed by the signal at 3.07 ppm for C–3 CH_2, adjacent to the C=S functionality, when compared to the chemical shift at 2.42 ppm observed for the starting material **4.8**. A shift was also observed in the ^{13}C NMR spectrum, at 203.60 ppm for C–2, and the ester carbonyl C–7 was observed 167.14 ppm. The IR spectrum showed strong absorbance in the region of 1503 cm^{-1} for a C=S stretch and 1196 cm^{-1} for a C–S stretch, and a C=O ester stretch at 1739 cm^{-1}.

The product was stable and could be produced in relatively large amounts (approximately 9 g). It was stored at ambient temperature or in a refrigerator to be used as needed for the preparation of a variety of enaminones, which will be discussed in *Section 4.4.1*.

4.3.2. Synthesis of thiolactams with *N*-phenacyl substitution

The synthesis of the thiolactams with the phenacyl bonded to the nitrogen rather than the ester was an experimental adaptation to the project. It was envisioned that a better understanding of the mechanism for pyrrole formation, to be discussed later in this Chapter, would be obtained through these systems. The feasibility of the synthesis when the ester group was interchanged with a phenacyl group was therefore explored.

It was previously found by G. L. Morgans in his PhD thesis, that the *N*-phenacylation was best performed with lactim ethers rather than directly from 2-pyrrolidinone.[69] The lactim ether **4.10** was therefore formed by methylation of the carbonyl in 2-pyrrolidinone using dimethyl sulphate (*Scheme 4.2*).[127] The product was highly visible when the TLC plate was stained with iodine. The crude liquid was purified by vacuum distillation (36–41°C, 21 mmHg) to afford the product as a volatile colourless liquid.



Scheme 4.2 *Reagents and conditions:* i. $(CH_3)_2SO_4$, 60°C, 17 h; ii. phenacyl bromide (*Figure 4.7*), DMF, reflux, 20 h; iii. Lawesson's reagent, toluene, 80°C, 18 h or P_4S_{10}, HMDSO, CH_2Cl_2, reflux–rt, 48 h.

In the ^{1}H NMR and ^{13}C NMR spectra of 5-methoxy-3,4-dihydro-2*H*-pyrrole **4.10**, a clear singlet signal integrating for three protons was observed at 3.81 ppm in the ^{1}H NMR spectrum and at 23.29 ppm in the ^{13}C NMR spectrum, indicating the CH_3 group was present. All characterization was in good agreement with the literature.[69]

Two different phenacyl bromides were considered for the *N*-phenacylation reaction; the simple and commercially available 2-bromo-1-phenylethanone (phenacyl bromide), which would act as an easily accessible model study to these systems; and the prepared 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10** (*Figure 4.7*), which most closely resemble the precursors required for the preparation of the tetracyclic system. The *N*-phenacyl reactions were done by refluxing the lactim ether **4.10** with the phenacyl bromide in *N*,*N*-dimethylformamide.[127] This afforded the lactam products 1-(2-oxo-2-phenylethyl)pyrrolidin-2-one **4.12** in 73% yield and 1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-one **4.13** in 57% yield.

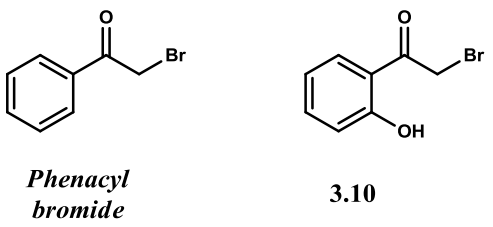
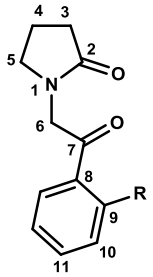


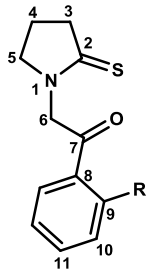
Figure 4.7: Commercially available, 2-bromo-1-phenylethanone (phenacyl bromide) and previously prepared 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10**.



4.12: R = H
4.13: R = OH

The ^{1}H NMR spectrum of lactams **4.12** and **4.13** confirmed that the phenacyl groups were incorporated into the pyrrolidinone structure. No NH peaks were observed, suggesting that *N*-protection had occurred. The signals in the aromatic region (7.96–7.48 ppm) of the ^{1}H NMR spectrum, integrated for five protons for lactam **4.12** and four protons for lactam **4.13**. A C–6 CH_2 signal was observed in the ^{1}H NMR spectrum, at 4.74 ppm for **4.12** and 4.77 ppm for **4.13**, attesting to the formation of the *N*-phenacyl lactams. In the ^{13}C NMR spectrum of the lactams, two C=O peaks are noted at 193.88 and 175.80 ppm for **4.12** and 199.45 and 176.01 ppm for **4.13**. Additionally, for lactam **4.13**, an OH signal was observed as a broad OH stretch at 3217 cm^{-1}, in the IR spectrum; a singlet signal at 11.77 ppm, in the ^{1}H NMR spectrum; and the C–9 C–OH peak at 162.53 ppm, in the ^{13}C NMR spectrum.

Lactam **4.12** was then subjected to a thionation reaction using Lawesson's reagent to afford 1-phenyl-2-(2-thioxopyrrolidin-1-yl)ethanone **4.14** in 73% yield; and lactam **4.13** was thionated using phosphorus pentasulphide to afford 1-(2-hydroxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone **4.15** in 46% yield, both as yellow solids.

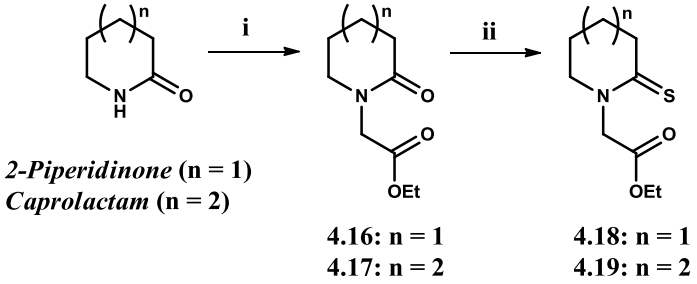


4.14: R = H
4.15: R = OH

The analysis of the thiolactams through IR spectroscopy showed that the C=O amide stretches for lactams **4.12** and **4.13** were no longer present, and instead a C=S stretch at 1514 cm^{-1} for **4.12** and 1509 cm^{-1} for **4.13** was noted. The C=O for the ketone at 1689 cm^{-1} (for **4.14**) and 1642 cm^{-1} (for **4.15**) remained unchanged. The ^{1}H NMR spectrum for both lactams remained largely unchanged except for the downfield shift of signals adjacent to the new C=S bond of the lactam. More apparent was the C=S signal in the ^{13}C NMR spectrum, observed at 203.11 ppm (for **4.12**) and 204.15 ppm (for **4.13**), which was in agreement with the expected value for a C=S thiolactam signal and has been discussed previously for the preparation of *N*-alkylated thiolactam **4.9**. Finally, the HRMS determined that a molecular ion at 219.0708, was observed for phenyl-2-(2-thioxopyrrolidin-1-yl)ethanone **4.14**, which has an exact mass of 219.0718. Similarly, the HRMS for 1-(2-hydroxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone **4.15** was found at 235.0675, which was in good agreement with the expected value of 235.0667.

4.3.3. Preparation of thiolactams from piperidinone and caprolactam

Ethyl 2-(2-oxopiperidin-1-yl)acetate **4.16** and ethyl 2-(2-oxoazepan-1-yl)acetate **4.17** were prepared from 2-piperidinone and caprolactam, respectively, using the methodology described for the preparation of ethyl 2-(2-oxo-1-pyrrolidinyl)acetate **4.8** in *Section 4.3.1*. The amide carbonyl was then thionated to furnish ethyl 2-(2-thioxopiperidin-1-yl)acetate **4.18** in 89% yield as a clear pale yellow oil, and ethyl 2-(2-thioxoazepan-1-yl)acetate **4.19** in 86% yield as a clear colourless oil (*Scheme 4.3*).



Scheme 4.3 *Reagents and conditions:* i. NaH (60%), ethyl 2-bromoacetate, THF, rt–reflux, 20 h; ii. Lawesson's reagent, toluene, 80°C, 20 h or P_4S_{10}, HMDSO, CH_2Cl_2, reflux–rt, 48 h.

TLC analysis for the reaction showed thiolactam **4.18** with an R_f of 0.46, compared to starting material **4.16** at 0.61, in 50% ethyl acetate in hexane mobile phase. The thionated products stained as dark brown spots in iodine. The IR and NMR spectra of the compounds correlated with the peaks and values observed in the previous *N*-alkylated **4.8** and thionated **4.9** products. The ^{1}H NMR spectrum for ethyl 2-(2-oxopiperidin-1-yl)acetate **4.16** confirmed that the ester group was attached to the nitrogen by chemical shifts at 4.19, 4.11 and 1.28 ppm. Similarly in the ^{13}C NMR spectrum, two clear C=O peaks at 170.43 and 169.15 ppm were evidence the desired acetate **4.16** had been made. The thionated product was confirmed by IR spectroscopy through the absorbance peaks observed at 1510 and 1107 cm^{-1} for C=S and C–S stretches, respectively, and in the ^{13}C NMR spectrum for C=S at 201.84 ppm. Mass determination by high resolution mass spectrometry was in good agreement for both the compounds synthesized.

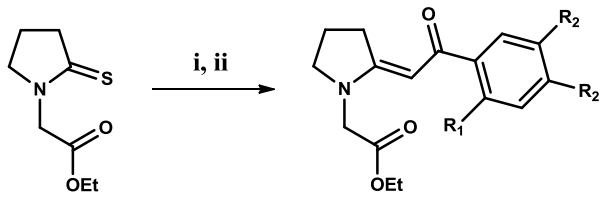
Correspondingly the *N*-alkylated product **4.17** showed IR and ^{13}C NMR spectra signals for two carbonyls, namely the ester and the amide. The ^{1}H NMR spectrum also gave signals for the acetate, quartet, singlet and triplet signals. Analysis of the compound by mass spectrometry afforded an accurate mass of 199.1210, which correlated well to the expected mass of 199.1208. The thionated product **4.19** showed C=S stretches at 1502 cm^{-1} in the IR spectrum and a C=S signal at 208.59 ppm in the ^{13}C NMR spectrum. The mass spectrum possesses an ion at *m/z* 215.0975 (100%) and the parent ion of $C_{10}H_{17}NO_2S$ requires 215.0980.

4.4. Preparation of enaminones through the Eschenmoser sulphide contraction[74,76,128,129]

This Section describes the preparation of enaminones though the Eschenmoser sulphide contraction, using the thiolactams examined in in *Section 4.3*. The synthesis of pyrrolidine, piperidine and azepane enaminones from various phenacyl bromides and iodides will be described. Eschenmoser sulphide contraction reactions utilizing ethyl-2-bromoacetate with the prepared *N*-phenacyl pyrrolidine thiolactams from *Section 4.3.2* will also be examined. The Eschenmoser sulphide contraction reaction for each of the reactions mentioned above and all the corresponding variations will be thoroughly discussed, owing to the delicate intricacies and manipulations required for the optimization of each reaction.

4.4.1. Synthesis of enaminones from ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate

Ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate **4.9** was used to prepare a number of enaminone analogues (*Scheme 4.4*) from bromo and iodo acetophenones described in *Chapter 3*. These phenacyl halides were exploited for their varied substituents to create a library of enaminones, with the potential to act as analogues toward the synthesis of lamellarins, and to discover optimum conditions for the synthesis of lamellarins themselves.



4.9

4.20: R_1 = H, R_2 = H
4.21: R_1 = OH, R_2 = H
4.22: R_1 = OMs, R_2 = H
4.23: R_1 = OH, R_2 = OMe
4.24: R_1 = OMs, R_2 = OMe

Scheme 4.4 *Reagents and conditions:* i. phenacyl halide, $CHCl_3$ or MeCN; ii. PPh_3, Et_3N, $CHCl_3$ or MeCN (see *Table 4.1* for specific reaction conditions).

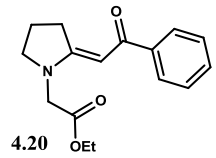
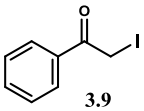
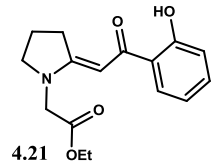
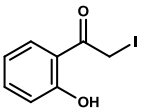
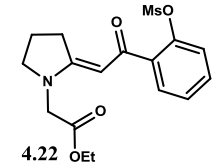
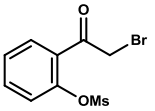
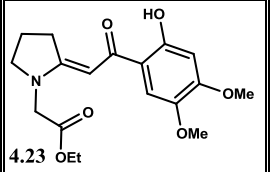
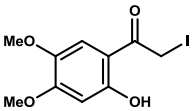
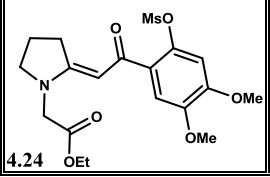
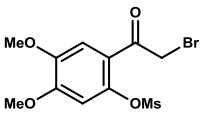
The Eschenmoser reaction is a two-step process; the first step is the formation of the thioiminium salt and is often recognised by a baseline spot on the TLC plate, with eventual loss of starting materials observed. The reaction mixture is often differentiated by its opaque appearance. Salt formation is highly dependent on the type of reaction conditions and reagents used, for instance, it may be necessary to slow the process of salt formation down by performing the reaction at ice-cooled temperatures, so the rate at which the salt is formed takes preference over the rate at which dehalogenation of the phenacyl halide (especially iodide) in the reaction mixture occurs. For this reason it may also be necessary to add the phenacyl halide in excess and/or add further phenacyl halide as the reaction progresses. Likewise, the salt formation may be very slow; the reaction can then be done at higher temperature. The *in situ* addition of sodium iodide to the reaction mixture can often catalyse the formation of the salt when the mixture is not particularly reactive. The solvent used therefore also plays a very important role in the formation of the salt. It has been observed that non-polar and aprotic polar solvents such as chloroform, dichloromethane, acetonitrile and even tetrahydrofuran and diethyl ether have been used to facilitate the salt formation process.[78,128] The concentration of solvent used in this step also plays a detrimental role to the salt forming (i.e. the solution should not be too dilute). The exact conditions used to produce the unique enaminones for this Section can be seen in *Table 4.1* below.

The second step of the reaction requires the addition of a thiophile and a base. In this section only triphenylphosphine and triethylamine were utilized. A prepared solution of

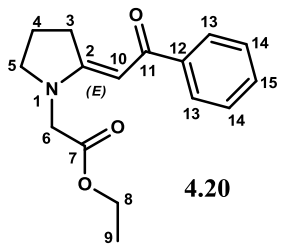
triphenylphosphine and triethylamine in either chloroform or acetonitrile was added dropwise to the opaque salt mixture. It is sometimes necessary to add these two components separately, however that depends on the reactivity and accessibility of the reactive site on the reagents involved in the Eschenmoser reaction.[76] Triphenylphosphine was used as the thiophile in this Section and although results indicate that the enaminone forms comfortably, triphenylphosphine contaminants (triphenylphosphine oxide in particular) remains after the reaction is complete and can be difficult to remove by most analytical techniques. It may also affect the purity of the product in some cases.

It can therefore be deduced that the Eschenmoser sulphide contraction reaction is highly selective to the materials, the reaction conditions and the structure of the thiolactams, used in the reaction. The reaction is also highly solvent, reagent and temperature sensitive and thus has been meticulously adjusted for each individual reaction. In *Table 4.1* below, a summary of selected reaction conditions for each prepared pyrrolidine enaminone has been illustrated. A comparison of the most significant characterization aspects will be discussed separately for each generated enaminone.

Table 4.1: Selected reaction conditions and reagents for the preparation of pyrrolidine enaminones

Product	***Phenacyl halide used***	***Part one reaction conditions***	***Part two reaction conditions***	***Appearance and yield***
 **4.20**	 **3.9**	MeCN, 0°C–rt, 2 h	PPh_3, Et_3N, MeCN, rt, 18 h	Pale brown oil 92%
 **4.21**	 **3.12**	MeCN, rt, 18 h	PPh_3, Et_3N, MeCN, 0°C–rt, 18 h	Bright yellow powder 73%
 **4.22**	 **3.13**	$CHCl_3$, NaI, rt, 18 h	PPh_3, Et_3N, $CHCl_3$, rt, 20 h	Yellow oil 82%
 **4.23**	 **3.18**	$CHCl_3$, rt, 5 h	PPh_3, Et_3N, $CHCl_3$, rt, 20 h	Yellow crystals 85%
 **4.24**	 **3.19**	MeCN, NaI, rt, 30 h	PPh_3, Et_3N, MeCN, rt, 18 h	Yellow solid 62%

The characterisation of enaminone (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)pyrrolidin-1-yl]acetate **4.20** will be discussed extensively in view of the simplicity of the structure. This enaminone was formed by introducing the simplest phenacyl halide, iodoacetophenone **3.9**, to the thiolactam. The phenacyl consists of a simple monosubstituted benzene ring with an adjacent ketone that is in conjugation with the newly formed vinylogous amide. These structural traits will be discussed comprehensively and the remaining enaminones will be corroborated through their distinctive features, over and above the features mentioned for (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)pyrrolidin-1-yl]acetate **4.20**.

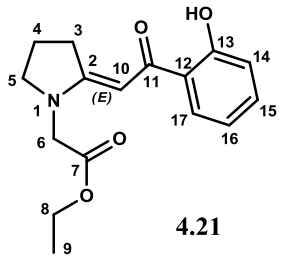


4.20

The completion of the Eschenmoser sulphide contraction for enaminone **4.20** was noted by the distinctive formation of a deep yellow spot with an R_f of 0.14 (in 40% ethyl acetate in hexane as a mobile phase) on the TLC plate. This feature was often observed during the formation of these enaminones. The thiolactam starting material **4.9** gradually disappeared during the salt formation step of the reaction. The R_f of thiolactam **4.9** was calculated to be 0.34 in the same mobile phase. In the ^{1}H NMR spectrum, two signals at 7.84 ppm (integrating for 2 protons) and 7.44–7.34 ppm (integrating for 3 protons) verified the presence of the aromatic ring in product **4.20**. Similarly, a signal at 5.66 ppm, integrating for one hydrogen suggested that the enamine-like C–10 =CH had formed. An upfield shift of the C–10 signal is caused by the increased electronegativity at C–10 because of the resonance with nitrogen's lone pair. The presence of two C=O signals at 188.24 ppm (C–11 for the ketone) and 168.15 ppm (C–7 for the ester), distinctive signals for the aromatic CH carbons at 130.64, 128.16, 127.36 ppm, and the upfield enamine C–10 =CH at 87.28 ppm, in the ^{13}C NMR spectrum corroborated data obtained. All signals pertaining to the pyrrole and ester functionalities of **4.20** were accounted for and found to be in good agreement when compared to the spectra of starting material **4.9**. Analysis of the IR spectrum for enaminone **4.20** was used in confirming that the phenacyl was introduced from the thiolactam. Distinguishing stretches for aromatic C–H and C=C were identified at 3053 and 1612 cm^{-1}, respectively. Furthermore, C=O stretches were observed for both the ester C–7, at 1732 cm^{-1}, and the ketone C–11, at 1530 cm^{-1}. A $CH_{E\text{alkene}}$ stretch at 927 cm^{-1} also suggests that the vinyl group exists as an *E*-isomer. However, additional exploration was necessary to confirm the configuration. Since enaminone **4.20** has only one vinyl hydrogen, traditional ^{1}H NMR spectrum coupling constant analysis could not be employed to assist in assigning the conformation of the alkene. A crystal structure of the product was previously achieved by Garreth Morgans,[69] in his PhD thesis, which assisted in illustrating the *E*-isomer was present. A NOESY spectrum was also used to aid in ascertaining this information. The C–10 =CH signal in the NOESY spectrum was found to interact with two signals, the C–6 CH_2 singlet of the acetate functionality at 4.06 ppm and the C–13 CH signal of the phenacyl aromatic ring at 7.84 ppm. This suggested that the C–10 =CH was in close proximity to the two groups. In order for this to occur the C–10 =CH needed to be in the *E*-conformation, otherwise interactions with the lactam C–3 CH_2 and the alkene C–10 =CH would be observed. The *E*-geometry can be further substantiated by through-space deshielding effects on the C–3 CH

proton (δ value of 3.56 ppm for **4.20** versus 3.07 ppm for starting material **4.9**) by the C–11 C=O. Thus the isolation of enaminone (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)pyrrolidin-1-yl]acetate **4.20** was confirmed.

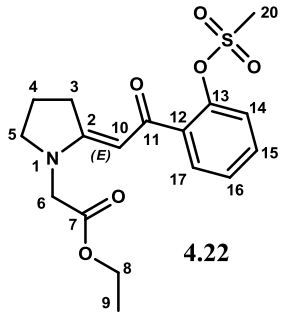
2-{2-[(*E*)-2-(2-Hydroxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}acetate **4.21** was prepared using *o*-hydroxyphenacyl iodide **3.12**. The structure differs from the previously examined enaminone **4.20** through an additional *ortho* substituted phenol on the aromatic ring.



4.21

The most notable feature in both the IR, ^{1}H NMR and ^{13}C NMR spectra of enaminone **4.21** was an OH signal observed as a broad OH stretch at 2583 cm^{-1} and a strong sharp signal at 1285 cm^{-1} for the C–O stretch of the alcohol, in the IR spectrum; a singlet signal at 13.96 ppm, in the ^{1}H NMR spectrum; and a C–13 C–OH singlet signal at 162.78 ppm, in the ^{13}C NMR spectrum. The remaining spectroscopic data compared well with the previously examined enaminone **4.20**. The presence of the *ortho* OH group in enaminone **4.21** changed the aromatic region in the ^{1}H NMR spectrum. A doublet of doublet signal at 7.63 ppm with J = 8.0 Hz (for the *ortho* interaction) and 1.4 Hz (for the *meta* interaction) was assigned to H–14, owing to the deshielding effects of the adjacent OH group on the hydrogen and because the H–14 and H–17 protons were the only signals that produced a doublet of doublet signal (*para* coupling of these protons was too small to detect). By elimination the doublet of doublet signal at 6.92 ppm belonged to H–17. Similarly, a doublet of doublet of doublet signal at 7.32 ppm was assigned to H–16, owing to the similarities in the coupling constant (1.4 and 1.6 Hz), indicating a direct relationship between the interactions of protons H–16 and H–14. The signal at 6.79 ppm was therefore assigned to H–15. The NOESY and IR spectra of 2-{2-[(*E*)-2-(2-hydroxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}acetate **4.21** showed results indicating the product was isolated in the *E*-conformation.

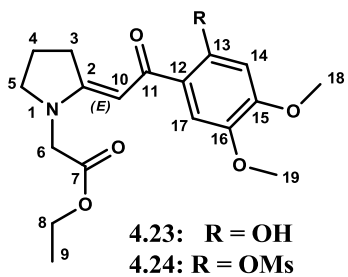
Enaminone (*E*)-ethyl 2-(2-{2-[2-(methylsulphonyloxy)phenyl]-2-oxoethylidene}pyrrolidin-1-yl)acetate **4.22** was prepared using the mesylated phenacyl bromide **3.13**. This afforded a product which was identical to **4.21** above but with the phenol having been mesyl protected.



4.22

The absence of the OH group in the spectra and the appearance of the unambiguous C–20 CH_3 singlet at 3.09 ppm was the most notable feature in the ^{1}H NMR spectrum for enaminone **4.22** when compared to enaminone **4.21**. The aromatic region in the ^{1}H NMR spectrum for enaminone **4.22** appeared slightly more overlapped but showed similar coupling constants to enaminone **4.21**, it also integrated for four protons. The HSQC spectrum showed that the C–20 CH_3 signal, for the sulphonyl group, at 3.09 ppm in the ^{1}H NMR spectrum correlated with the signal at 37.59 ppm in the ^{13}C NMR spectrum. The IR spectrum also showed a S=O stretch at 1339 cm^{-1}, and a S–O stretch at 1153 cm^{-1}, in addition to the C–$H_{E\text{alkene}}$ bend at 990 cm^{-1}, which confirmed that (*E*)-ethyl 2-(2-{2-[2-(methylsulphonyloxy)phenyl]-2-oxoethylidene}pyrrolidin-1-yl)acetate **4.22** was isolated.

The preparation of enaminones **4.21** and **4.22** attested to the fact that *ortho* substituted alcohol and mesylate aromatic compounds could be accessed from the Eschenmoser sulphide contraction reaction. The methodology was thus expanded to produce products, which would mimic the reagents needed to produce lamellarin G trimethyl ether. Therefore phenacyl iodide **3.18** was used to produce the *ortho*-hydroxyl enaminone, (*E*)-ethyl 2-{2-[2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate **4.23**; and phenacyl bromide **3.19** was used to produce the *ortho* mesylate enaminone, *(E)*-ethyl 2-(2-{2-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2-oxoethylidene}pyrrolidin-1-yl)acetate **4.24**. The characterization of these products will be discussed based on the new substituents on the aromatic ring. Any deviations from the spectral information of the *ortho*-hydroxyl enaminone **4.21** and the *ortho* mesylate enaminone **4.22** will be mentioned.



4.23: R = OH
4.24: R = OMs

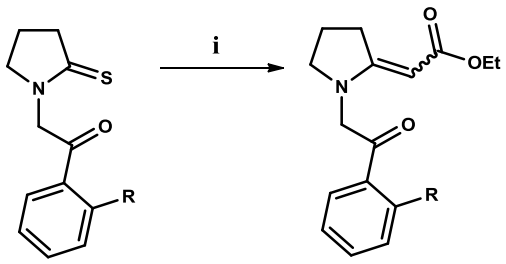
In the IR, ^{1}H NMR and ^{13}C NMR spectra, distinctive signals for the aromatic methoxy groups were observed. The ^{1}H NMR spectrum showed two singlet signals both integrating for three protons, at 3.87 and 3.84 ppm (for **4.23**) and as overlapping signals at 3.91 ppm (for **4.24**). The ^{13}C NMR spectrum indicated the presence of two methoxy groups at 57.22 and 55.95 ppm (for **4.23**) and at 56.16 and 55.96 ppm (for **4.24**). Similarly, the IR spectrum showed absorbance stretches for aromatic ethers (C–O–C stretch) at 1193 and 1126 cm^{-1}, for enaminone **4.23** and

4.24, respectively. The aromatic C–14 and C–17 CH groups of the tetrasubstituted enaminone appeared as two singlet signals in the ^{1}H NMR spectrum, suggesting that the dimethoxy aromatic substitution was present. (*E*)-Ethyl 2-{2-[2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate **4.23** was observed to have an OH stretch at 2583 cm^{-1} in the IR spectrum and an OH singlet at 14.26 ppm in the ^{1}H NMR spectrum. Similarly, *(E)*-ethyl 2-(2-{2-[4,5-dimethoxy-2-(methylsulphonyloxy) phenyl]-2-oxoethylidene}pyrrolidin-1-yl)acetate **4.24** was verified by the presence of S=O and S–O stretches at 1359 and 1155 cm^{-1}, in the IR spectrum and a sulphone CH_3 signal at 3.01 and 36.74 ppm, in the ^{1}H NMR and ^{13}C NMR spectra, respectively. HRMS found the molecular ion at 349.1525 for enaminone **4.23** ($C_{18}H_{23}NO_6$) with an actual mass of the same value. Similarly, a molecular ion peak at 427.1294 was found, with an exact mass of 427.1301 required, for enaminone **4.24** ($C_{19}H_{25}NO_8S$).

4.4.2. Synthesis of *N*-phenacyl enaminones

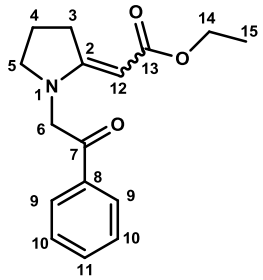
The Eschenmoser sulphide contraction with the *N*-phenacyl thiolactams allowed for a better understanding as to how different α-halocarbonyl compounds would perform under similar reaction conditions. Two thiolactams were discussed in *Section 4.3.2*, 1-phenyl-2-(2-thioxopyrrolidin-1-yl)ethanone **4.14**, containing a simple unsubstitued phenacyl and 1-(2-hydroxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone **4.15**, containing an *ortho*-substituted hydroxyl group. The Eschenmoser reaction using ethyl 2-bromoacetate as a reagent to produce novel enaminone compounds ethyl 2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]acetate **4.25** and ethyl 2-{1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-ylidene}acetate **4.26** will be discussed in this section.

The thioiminium salt was formed by reacting thiolactam (**4.14** or **4.15**) with ethyl 2-bromoacetate and sodium iodide in chloroform (*Scheme 4.5*). The completion of the salt formation was monitored by TLC. Once the salt formed, triphenylphosphine and triethylamine in chloroform were added dropwise to the reaction mixture.



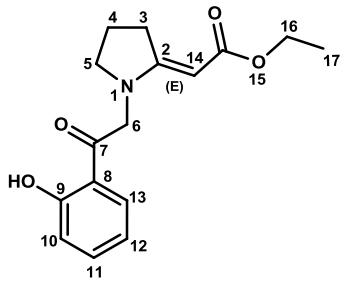
4.14: R = H **4.25: R = H**
4.15: R = OH **4.26: R = OH**

Scheme 4.5 *Reagents and conditions:* i.a. ethyl 2-bromoacetate, $CHCl_3$, rt, 4–20 h; i.b. PPh_3, Et_3N, $CHCl_3$, rt, 18–20 h.



4.25

Ethyl 2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]acetate **4.25** was purified by flash column chromatography (in 30–50% ethyl acetate in hexane solvent system) and two unmistakable products were isolated. First, (*E*)-ethyl 2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]acetate **4.25*E*** was isolated in 50% yield as a yellow solid, with an R_f of 0.28. Upon further elution a second product was collected, (*Z*)-ethyl 2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]acetate **4.25*Z*** in 33% yield as an dark orange solid, with an R_f of 0.14. In the ^{1}H NMR spectrum for both isomers formed, the acetate functionality was accounted for as a C–14 CH_2 quartet at 4.24 ppm (*E*) and 4.00 ppm (*Z*), and a C–15 CH_3 triplet at 1.33 ppm (*E*) and 1.07 ppm (*Z*), with the enaminone C–12 CH singlet accounted for at 6.28 ppm (*E*) and 5.86 ppm (*Z*). Similar observations were made in the ^{13}C NMR spectrum to confirm the addition of the acetate and thus the formation of the enaminone. In the IR spectrum, an acetate C–O–C stretch was observed for both isomers at 1176 cm^{-1} (*E*) and 1188 cm^{-1} (*Z*). A C–H bend at 886 cm^{-1} for *E*-alkenes in the IR spectrum, for the product isolated first, suggested this product was the *E*-isomer and the presence of a C–H bend at 694 cm^{-1} in the IR spectrum, for the product isolated second, suggested this product was the *Z*-isomer. An additional NOESY study of the isomers confirmed that the product isolated first was the *E*-isomer, based on interactions of C–12 CH singlet of the enaminone, with C–6 CH_2 singlet of the phenacyl moiety. Similarly, the product isolated second was confirmed as the *Z*-isomer based on interactions of C–12 CH singlet of the enaminone, with C–3 CH_2 signal of the lactam, observed in the NOESY spectrum.



4.26

Ethyl 2-{1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-ylidene}acetate **4.26** was purified in a similar manner to **4.25**, but only one product was isolated. The ^{1}H NMR, ^{13}C NMR and IR spectra confirmed the presence of the acetate group and showed that the enaminone had formed with the *N*-phenacyl lactam. All the data captured were compared to the previously discussed *N*-alkylated pyrrolidine enaminones (*Section 4.4.1*) and **4.25** above. However, an examination of the stereochemistry of the product through NOESY suggested the compound was the *E*-isomer, (*E*)-ethyl 2-{1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-ylidene} acetate **4.26**. Through space interactions between C–6 and C–14 protons were observed, no interaction between C–14 and C–3 were observed, which would be expected in the *Z*-isomer. The interpretation of HRMS showed a molecular ion at 289.1304 and the calculated exact mass as 289.1314, for the product **4.26**.

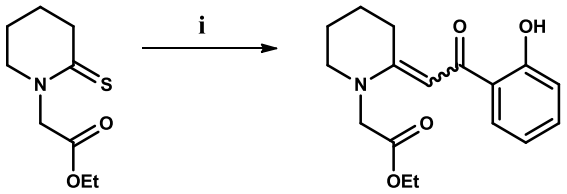
The *N*-phenacyl enaminones were formed with acetate groups in reasonable yields. The presence of only the *E*-isomer in enaminone **4.26** suggested that these pyrrolidines should chemically and mechanistically perform similarly to the *N*-alkylated enaminones. Further analysis of these systems will be discussed in *Section 4.5.3*.

4.4.3. Synthesis of piperidine and azepane enaminones

Section 4.4.1 illustrated the application of the Eschenmoser sulphide contraction methodology using a range of unsubstituted and substituted phenacyl systems. This methodology was extended to incorporate the 6-membered piperidine and the 7-membered azepane systems. The Eschenmoser reaction was used with only one acetophenone, namely 1-(2-hydroxyphenyl)-2-bromo-1-ethanone **3.10** with the purpose of establishing that the Eschenmoser reaction could be utilized not only with a variety of phenacyl groups and even an acetate group, but also with a wide range of thiolactams. These diversifications form the basis for the hypothesis toward accessing lamellarins through similar synthetic pathways.

The piperidine enaminone **4.27** was prepared from ethyl 2-(2-thioxopiperidin-1-yl)acetate **4.18** and 1-(2-hydroxyphenyl)-2-bromo-1-ethanone **3.10** (*Scheme 4.6*). To assist in the

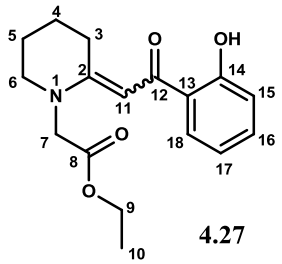
formation of the thioimium salt, sodium iodide was added, which encouraged the *in situ* halogen exchange from bromine to iodine as well as acting to promote the salt formation between these reagents. Acetonitrile was found to be the most suitable solvent. It was also necessary to cover the reaction vessel in foil, so as to prevent light-induced decomposition of the phenacyl iodide. The vessel was also cooled to 0°C for 10 to 15 minutes while adding the reagents and then gradually allowed to warm to ambient temperature. Once the salt had formed, albeit never to completion, the reaction vessel was again cooled to 0°C and triethyl phosphite was added, followed by triethylamine. The reaction vessel was again gradually allowed to warm to ambient temperature. The product ethyl 2-[2-(2-oxo-2-phenylethylidene)piperidin-1-yl]acetate **4.27** was only produced in 8% yield.



4.18 **4.27**

Scheme 4.6 *Reagents and conditions:* i.a. 1-(2-hydroxyphenyl)-2-bromo-1-ethanone **3.10**, NaI, MeCN, 0°C–rt, 18 h; i.b. $P(OEt)_3$, Et_3N, MeCN, 0°C–rt, 18 h.

Several methods were attempted to increase and optimize these results, including using triphenylphosphine as the thiophile; triethylamine and potassium *tert*-butoxide as bases and chloroform, tetrahydrofuran, diethyl ether and *tert*-butanol as solvents. None of these methods proved effective in forming the desired enaminone **4.27**.

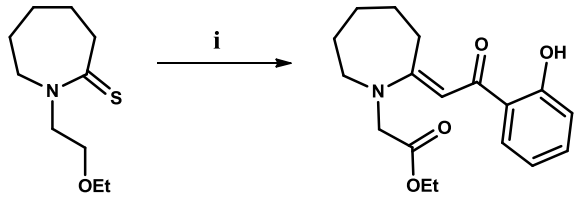


4.27

The ^{1}H NMR spectrum was the only technique used to characterize the compound due to unavoidable contamination in the sample and the rate at which it decomposed. The sample was often carried directly through to the next synthetic step with the impurities. The most notable features of the ^{1}H NMR spectrum for enaminone **4.27**, were: (i) the appearance of the aromatic region, given by four signals at 7.55 ppm (dd) for C–15, 7.30 ppm (ddd) for C–17, 6.90 ppm (dd) for C–18 and 6.76 ppm (ddd) for C–19; (ii) the chemical appearance of the OH singlet at 13.90 ppm. The data corresponded to the

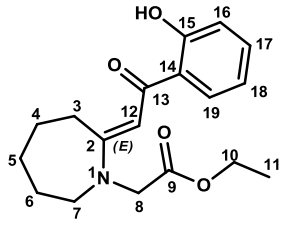
previously prepared pyrrolidine enaminone **4.21**, with the same substituted phenacyl group. The enaminone singlet C-11 =CH at 5.63 ppm; the presence of four CH_2 signals (C–3,4,5,6) with coupling constants averaging 6.2 Hz; and the confirmation of the acetate moiety, suggest the piperidine enaminone ethyl 2-[2-(2-oxo-2-phenylethylidene)piperidin-1-yl]acetate **4.27** was prepared. Although no direct techniques were used in resolving the conformation of the enaminone isomer, it was surmised that the *E*-isomer was more likely, based on the previous pyrrolidine systems. However, owing to this discrepancy, no conformation was stipulated for this compound.

As shown in *Scheme 4.7*, the previously prepared thiolactam ethyl 2-(2-thioxoazepan-1-yl)acetate **4.19** was reacted with 1-(2-hydroxyphenyl)-2-bromo-1-ethanone **3.10** and sodium iodide, in chloroform to form the thioiminium salt over 4 hours of stirring at room temperature. A solution of triphenylphosphine and triethylamine in chloroform was added to the bright yellow emulsion in a dropwise fashion. After purification by flash column chromatography in 20% ethyl acetate in hexane, the product was isolated as a yellow oil, in 20% yield. Although some improvements were noted in the preparation of azepane enaminone **4.28**, when compared to the piperidine enaminone **4.27**, the methodology was shown to be less flexible with larger rings compared to the 5-membered pyrrolidine systems. The Eschenmoser sulphide contraction was also performed using acetonitrile as a solvent and triethyl phosphite as a thiophile in an attempt to improve the yield of the product **4.28**. However these adaptions proved unsuccessful, with (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)azocan-1-yl]acetate **4.28** forming in only 20% yield.



4.19 **4.28**

Scheme 4.7 *Reagents and conditions:* i.a. 1-(2-hydroxyphenyl)-2-bromo-1-ethanone **3.10**, NaI, $CHCl_3$, 4 h, rt, 4 h; i.b. PPh_3, Et_3N, $CHCl_3$, rt, 24 h.



4.28

The IR spectrum for enaminone **4.28** showed an expected broad OH stretch at 2720 cm^{-1}, an aromatic C=C stretch at 1613 cm^{-1}, and two C=O stretches at 1744 cm^{-1} for the C–9 ester and at 1540 cm^{-1} for the C–13 ketone. Correspondingly, the ^{1}H NMR spectrum corroborated these findings, the azepane CH_2 signals (C–3 to C–7) at 3.68 to 3.47 ppm and the important C–12 CH proton signal at 5.54 ppm were observed. The C–12 CH carbon signal was also observed in the ^{13}C NMR spectrum at 91.24 ppm as expected for the enaminone formation. The presence of a CH bend at 925 cm^{-1} in the IR spectrum, and the through-space deshielding of the C–3 protons (3.68 ppm in **4.28** and 3.19 ppm in **4.19**) by the C–13 C=O in the ^{1}H NMR spectrum suggests the product is in the *E*-conformation. All the data achieved for this structure were in good agreement when compared to the previously examined enaminones **4.21** and **4.27**. The outcome of the mass spectral analysis showed a molecular ion peak at 317.1629, which correlates well to the expected mass of 317.1627 for enaminone **4.28**.

4.5. Pyrrole synthesis by acid-induced ring closure of enaminones

The synthesis of compounds that model the lamellarin core structure involves an acid-induced formation of pyrrole rings from precursors described in *Section 4.4*. A lactone ring can form spontaneously when the *ortho*-hydroxy phenacyl groups are used in the reaction. The mechanism of the reaction will be discussed when relevant. This section will look at the preparation of simple bicyclic pyrrole system from the pyrrolidine enaminone precursors discussed in *Section 4.4*. Similarly, the synthesis of tetracyclic lactone-containing systems from the pyrrolidine, piperidine and azepane enaminones will be discussed.

As discussed in *Chapter 2, Section 2.1.4*, the procedure for the acid-induced pyrrole formation was initially discovered serendipitously in our laboratories by Garreth Morgans,[69] when an enaminone precursor was pre-absorbed onto silica gel. The reaction mixture was dissolved in ethyl acetate or dichloromethane and silica gel was added to the mixture. The solvent was then slowly evaporated under vacuum using a rotary evaporator; this caused the pyrrole ring to form. The procedure discovered by Calvo and his co-workers[88] showed a similar method

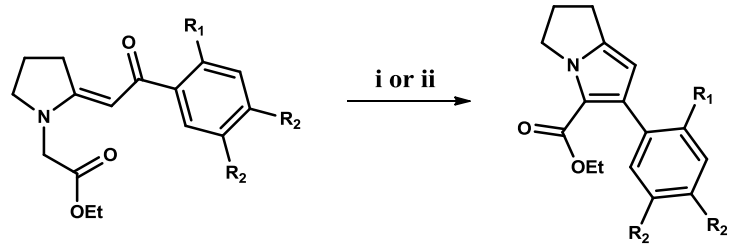
for obtaining pyrrole ring-closures with silica gel. The method has since been adapted and optimized for the purposes of this project.

The pyrrole rings were initially formed by conventional methods, by stirring the prepared enaminones with silica gel (particle size 0.063–0.2 mm, mesh 70–230, 5–10 times, the mass of the starting material) under reflux in toluene or xylene, overnight. The reaction mixture was then filtered, rinsed and purified by flash column chromatography. The method was later adapted by using microwave conditions; the reaction times were reduced and the product yields improved. The enaminone was irradiated in a silica gel and xylene slurry at 150 W, with a temperature of 180–200°C for 15–20 minutes.

The procedure for these ring closures was very versatile and generally worked well. Any adaptions and reaction specific observations will be discussed in the following sections. The most notable characterisation aspects for the products achieved will also be discussed.

4.5.1. A model study of bicyclic systems

The formation of the pyrrole ring forms an integral part of this thesis. A model study was done to better understand the mechanism by which the pyrrole ring is formed. The model study incorporates a discussion of all the simple and mesyl-protected pyrrolidine enaminone precursors, namely (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)pyrrolidin-1-yl]acetate **4.20**, (*E*)-ethyl 2-(2-{2-[2-(methylsulphonyloxy)phenyl]-2-oxoethylidene}pyrrolidin-1-yl)acetate **4.22** and *(E)*-ethyl 2-(2-{2-[4,5-dimethoxy-2-(methylsulphonyloxy) phenyl]-2-oxoethylidene}pyrrolidin-1-yl)acetate **4.24** (*Scheme 4.8*).

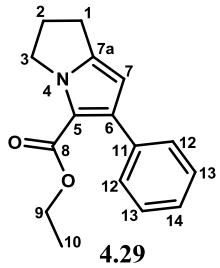


4.20: R_1 = H, R_2 = H
4.22: R_1 = OMs, R_2 = H
4.24: R_1 = OMs, R_2 = OMe

4.29: R_1 = H, R_2 = H
4.30: R_1 = OMs, R_2 = H
4.31: R_1 = OMs, R_2 = OMe

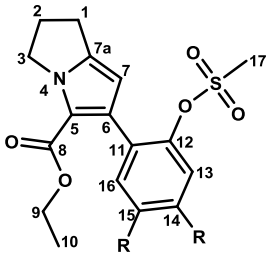
Scheme 4.8 *Reagents and conditions:* i. Conventional. Silica gel, xylene, reflux, 18 h; ii. Microwave. Silica gel, xylene, 200°C, 150 W, 15 min.

The ring closure was carried out using the general methodology mentioned above. Ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.29** was prepared using both conventional and microwave methods, followed by purification by flash column chromatography (in 5% ethyl acetate in hexane eluent). The product was isolated as a pale yellow oil in 85% yield, using the conventional method and 94% yield using the microwave method.



4.29

Analysis of the IR and ^{13}C NMR spectra for product **4.29** showed the carbonyl signals for the enaminone ketone **4.20** were no longer present. Signals were observed for the C–8 ester carbonyl at 1675 cm^{-1} in the IR spectrum and at 161.37 ppm in the ^{13}C NMR spectrum. The carbon signal for the C–8 C=O peak showed some expected shifting when compared to the precursor enaminone **4.20** at 168.15 ppm, owing to the carboxylate group's direct proximity to the aromatic ring. The aromatic ring therefore has a slight shielding effect on the adjacent ester. The ^{1}H NMR spectrum showed a pyrrole singlet at 5.94 ppm for C–7 CH, which was complemented by the signal at 103.51 ppm in the ^{13}C NMR spectrum. Although only slight variations between the enaminone precursor and pyrrolizine product were noted, it was surmised that the product had indeed formed. Mass determination by HRMS confirmed that a molecular ion peak at 255.1261 for product **4.29**, with a molecular formula of $C_{16}H_{17}NO_2$ was found, in good agreement with the calculated mass of 255.1259.



4.30: R = H
4.31: R = OMe

Similar observations were distinguishable in the spectra of the mesylate products ethyl 6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.30** and ethyl 6-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.31**. All previously discussed fragments of the compound, namely the ester, aromatic and saturated pyrrole groups, were accounted for in the evaluation of the spectra. A slight shifting pattern was observed in the ^{1}H and ^{13}C NMR spectra of both products **4.30** and **4.31**, the aromatic region remains generally unchanged, the pyrrole C–7 CH, 'lactam' C–3 and acetate C–9 signals all experience some downfield shifting, owing to the effect of the new aromatic pyrrole ring. In a similar manner, the C–1,2 CH_2 pyrrole, the C–10 CH_3 ester, and the C–17 CH_3 sulphonyl signals all experience significant upfield shifting, probably due to the shielding effects of their surrounding counterparts. Finally, the structure and orientation of the bicyclic pyrrolizine structures was accessed by X-ray diffraction of the pale off-white cuboidal crystals, which confirmed that the pyrrolizine product **4.31** had been produced (*Figure 4.8*).

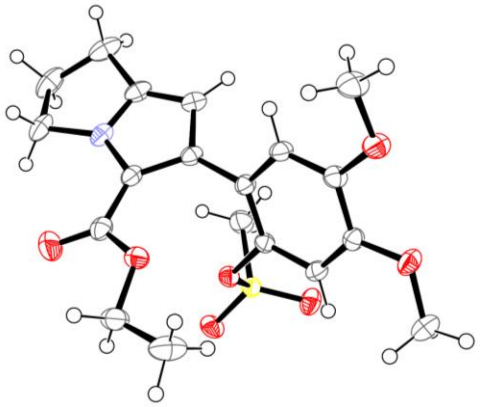


Figure 4.8: An ORTEP diagram of ethyl 6-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.31**, confirming the formation of the bicyclic pyrrolizine systems.

The proposed mechanism of these systems, shown in *Figure 4.9*, suggests that the enaminone transforms to the *Z*-configuration to facilitate the reaction between the ester and the enaminone branches of the structure. Under acidic conditions provided by the silica gel, the ester tautomerises to the 'enol', which attacks the electrophilic site of the enaminone in a 5-*exo*-trig cyclization to produce the hydroxy intermediate. This spontaneously aromatizes to form the desired bicyclic pyrrolizine systems.

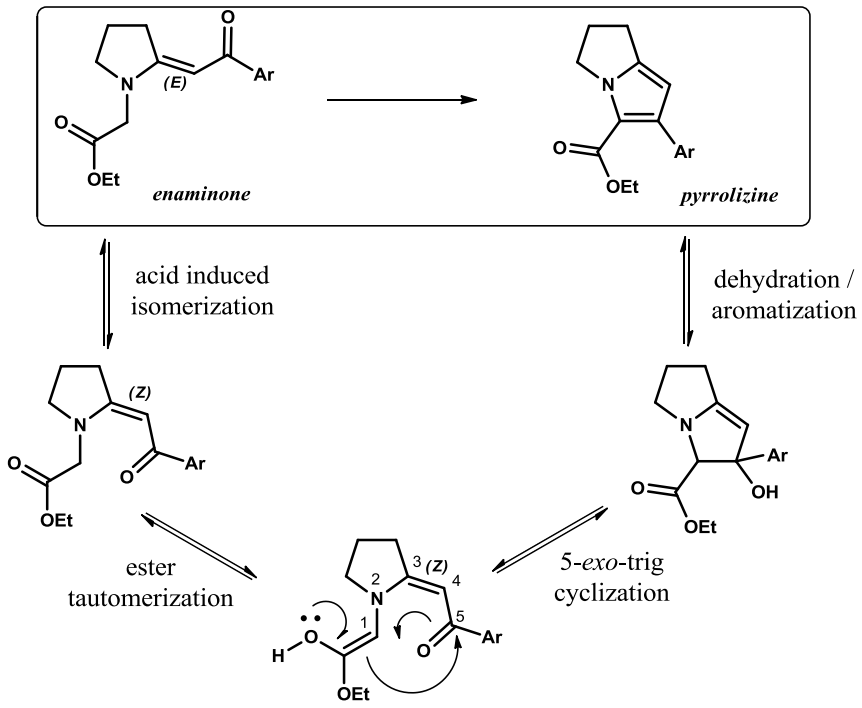
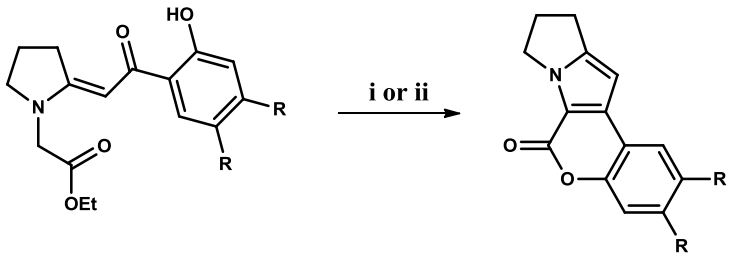


Figure 4.9: The proposed mechanism for the synthesis of bicyclic pyrrolizines **4.29, 4.30, 4.31**.

The mechanism leads to a greater understanding toward the way these pyrrolizines form. Further mechanistic studies will be discussed for pyrrolizines prepared from *N*-phenacyl enaminone (*Section 4.5.3*). Through these mechanistic studies we hoped to achieve a deeper understanding of the chemistry and structure of these systems.

4.5.2. Synthesis of tetracyclic pyrrolizinones

The methodology discussed for the acid-induced cyclization was applied to the enaminone precursors with *ortho*-hydroxylated aromatics. Under these conditions, nucleophilic attack of the phenol onto the ester spontaneously formed a lactone. The preparation and characterization of pyrrolizinones 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.32** and 2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.33** from their relative enaminone precursors will be discussed in this section (*Scheme 4.9*).

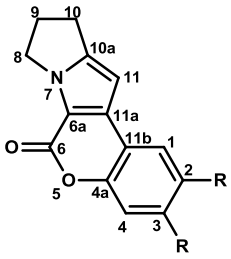


4.21: R = H
4.23: R = OMe

4.32: R = H
4.33: R = OMe

Scheme 4.9 *Reagents and conditions:* i. Conventional. Silica gel, xylene, reflux, 18 h; ii. Microwave. Silica gel, xylene, 200°C, 150 W, 15 min.

9,10-Dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.32** was purified by flash column chromatography, in 10–20% ethyl acetate in hexane mixture. The product was then recrystallized from dichloromethane and hexane to afford the desired pyrrolizinone as pale off-white filamentous crystals. Using the conventional method, the tetracyclic product was synthesized in 63% yield, and using the microwave method the product was synthesized in 74% yield.



4.32: R = H
4.33: R = OMe

The absence of the OH signal from the hydroxyl-substituted aromatic rings of starting materials **4.21** and **4.23** was observed in the ^{1}H NMR and IR spectra of pyrrolizinones **4.32** and **4.33**. Similarly, the absence a second C=O signal, namely that of the enaminone phenacyl branch of the starting materials **4.21** and **4.23**, was also noted. In the IR spectrum for **4.32**, the lactone C–6 C=O stretch at 1692 cm^{-1} and the C–O stretch at 1198 cm^{-1}, were observed. A clear indication that the product formed was the comparison between the melting point of the starting material **4.21**, at 91–92°C, and the product **4.32**, at 232–233°C. This suggested that the highly stable and rigid tetracyclic pyrrolizinone had been produced. Analysis of the ^{1}H NMR spectrum indicated that the ethoxy, OCH_2CH_3 functionality was absent, and the C–11 CH singlet signal at 6.31 ppm was present, which suggested that the pyrrole and lactone had formed. The ^{13}C NMR spectrum also corroborates these findings; the observation of six quaternary carbons also suggested that the tetracyclic product had formed. The HRMS found the molecular ion to be 255.1261, this was in good agreement with the expected value of 255.1259 for 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.32**.

In a similar way, 2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.33** was synthesized using both conventional and microwave methods. The melting point of the product was 218–220°C, which coincided to the range achieved for the simpler adduct **4.32**. The IR, ^{1}H NMR and ^{13}C NMR spectra corresponded to the results achieved for **4.32**. The OCH_3 singlet signals at 3.88 and 3.84 ppm and aromatic CH singlet signals at 6.97 and 6.82 ppm, in the ^{1}H NMR spectrum, corresponded to the results described previously in the synthesis of enaminone **4.23** in *Section 4.4.1*. The ^{13}C NMR spectrum showed an expected eight quaternary signals, as well as the C–11 CH pyrrole signal at 93.76 ppm. Similarly in the ^{1}H NMR spectrum, the C–11 CH pyrrole singlet signal was observed at 6.16 ppm. Finally, the results of the mass spectral analysis for 2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.33**, showed the molecular ion at 285.1007 correlated well to the expected mass of 285.1001.

4.5.3. Attempted synthesis of pyrrolizines from *N*-phenacyl enaminones

The *N*-phenacyl enaminones were discussed in *Section 4.4.2*. It was discovered that the *E*-isomer was not always the major isomer produced. An examination of the mechanism of the reactions of the pyrrolizine systems, when compared to the previously discussed reactions of pyrrolizines in this Section, was of foremost importance to our understanding of pyrrolizine systems as a whole. This section will describe the proposed mechanistic outcomes of these systems and describe the methods used toward the synthesis of the pyrrolizines from *N*-phenacyl enaminone precursors.

Based on the diversity of the chemical properties and the ambident nucleophilicity and/or electrophilicity of enaminones, different postulations for the mechanism could be made. *Figure 4.10* illustrates the plausible mechanism for an enaminone behaving as a nucleophile, while *Figure 4.11* illustrates the plausible mechanism for an enaminone behaving as an electrophile. Standard organic principles and logic suggest that the mechanism shown in *Figure 4.10* is the more plausible route; the ketone is more reactive than the ester and under acidic conditions the conjugation of the vinylogous urethane would prefer to act as a nucleophile and attack the ketone. However, observations of the mechanism (*Figure 4.9*) from the synthesis of the previously prepared pyrrolizines (with *N*-alkylated substitution), suggest that the mechanism in *Figure 4.11* is just as likely.

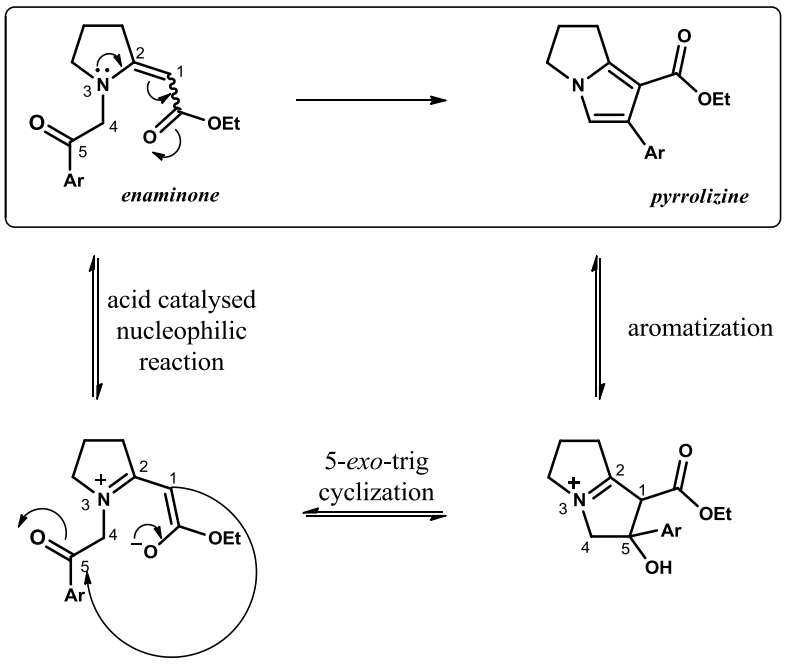


Figure 4.10: The proposed mechanism for the synthesis of pyrrolizines from *N*-phenacyl enaminones with the vinylogous urethane acting as the nucleophile.

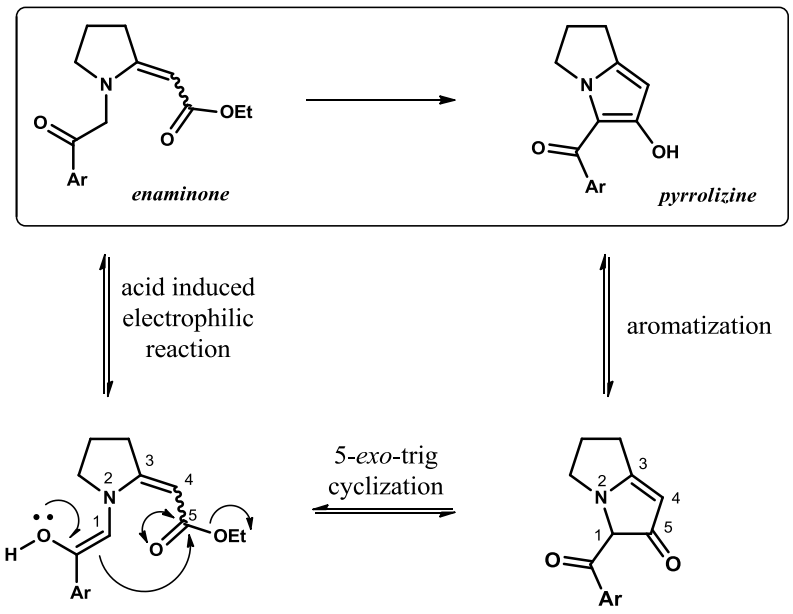
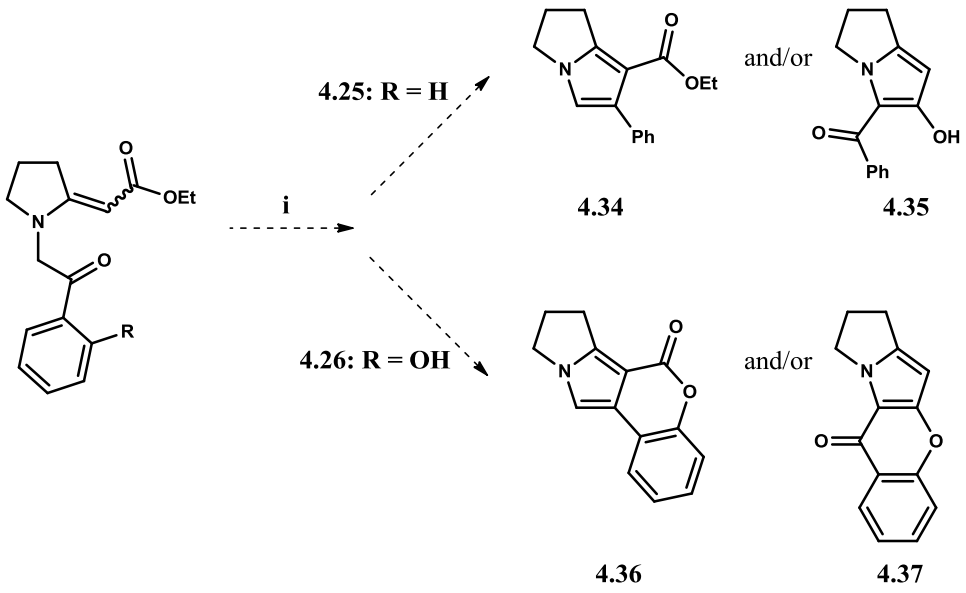


Figure 4.11: The proposed mechanism for the synthesis of pyrrolizines from *N*-phenacyl enaminones with the vinylogous amide acting as the electrophile.

Reaction using enaminones ethyl 2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]acetate **4.25** and (*E*)-ethyl 2-{1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-ylidene}acetate **4.26**, shown in *Scheme 4.10*, were attempted both conventionally and using the microwave conditions mentioned in *Section 4.5.1*. Products **4.34** and **4.35** were expected from enaminone **4.25**, based on the proposed mechanism of action given in *Figure 4.10* and *4.11* above. Similarly, products **4.36** and **4.37** were expected form enaminone **4.26**. However, the NMR for the isolated material collected from chromatography showed that only starting material was present. Under harsher conditions only decomposition was observed. The ring closure was then attempted using acetic acid in methanol at 40°C for 4 hours. The temperature was then increased to 60°C for an additional 4 hours and then finally to 80°C for 18 hours. The reaction was monitored by TLC and although several new spots were observed and collected by column chromatography, no distinguishable product was observed by NMR characterisation of the isolated material. A final method described by Junjappa and his colleagues[130] used *N*,*N*-dimethylformamide to produce pyrrole systems. The reaction was stirred in *N*,*N*-dimethylformamide under reflux or irradiated in the microwave reactor at 150 W at a temperature of 180°C for 30 minutes. Once more the results were unfavourable.

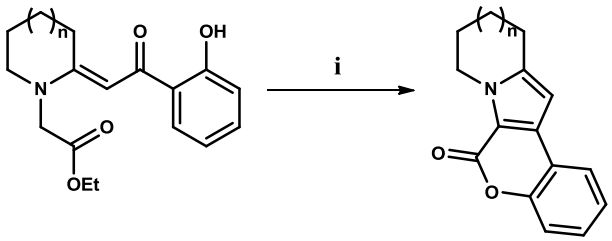


Scheme 4.10 *Reagents and conditions:* i. Silica gel, xylene, 180–200°C, 150 W, 15 min or AcOH, MeOH, 40–80°C, 26 h or DMF, 180°C, 150 W, 30 min.

Despite the undesirable results achieved in the attempt to synthesize pyrrolizine analogues from *N*-phenacyl-containing enaminones **4.25** and **4.26**, some understanding of the overall mechanism of the pyrrolizine was achieved. The phenacyl substituent on the nitrogen and the enaminone could be acting in a non-favourable way toward the electronic and chemical formation of pyrrole ring systems and the importance of the *N*-alkylated systems has been determined.

4.5.4. Synthesis of tetracyclic indolizinone and pyrroloazepinone analogues

The mechanism for the synthesis of tetracyclic indolizinone and pyrroloazepinone analogues was thought to progress in a similar manner to that described in Section *4.5.1*. A slurry was prepared with either (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)piperidin-1-yl]acetate **4.27,** or (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)azocan-1-yl]acetate **4.28** precursor enaminone, using silica gel in xylene (*Scheme 4.11*). The reaction mixture was irradiated in the microwave reactor at 150 W at a temperature of 180°C for 20 minutes.



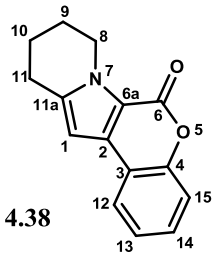
4.27: n = 1
4.28: n = 2

4.38: n = 1
4.40: n = 2

Scheme 4.11 *Reagents and conditions:* i. Silica gel, xylene, 180°C, 150 W, 15 min.

The reaction with enaminone precursor **4.27** was monitored by TLC and two prominent spots, other than the starting material, were observed with an R_f at 0.72 and 0.53, in 50% ethyl acetate in hexane mixture. The two products were separated by flash column chromatography, in 20% ethyl acetate in hexane mixture. The first spot (**4.39**) was isolated as a yellow oil in 21% yield and the second spot (**4.38**) was isolated as an orange oil in 34% yield.

The two spots were fully characterized by NMR spectroscopy, and the data obtained were compared thoroughly to the previously prepared pyrrolizine products. It was deduced that the second spot was the desired lactone product 8,9,10,11-tetrahydro-6*H*-chromeno[4,3-*b*]indolizin-6-one **4.38** (*Scheme 4.12*).

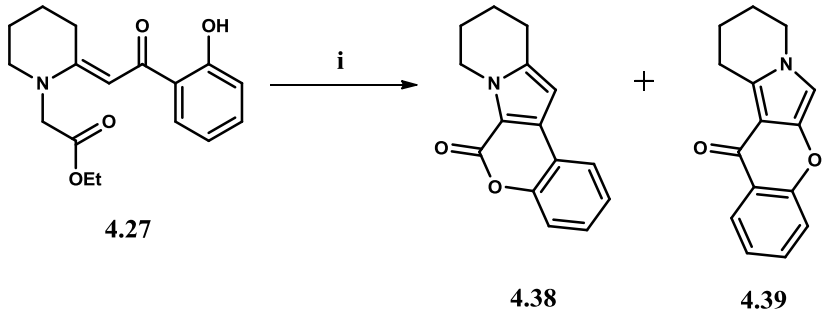


4.38

In the IR spectrum for 8,9,10,11-tetrahydro-6*H*-chromeno[4,3-*b*]indolizin-6-one **4.38**, the absence of the OH stretch and the presence of only one C=O was a distinguishing feature. The presence of a C=O stretch at 1696 cm^{-1} and a C–O stretch at 1134 and 1109 cm^{-1} suggested that the lactone had formed. Analyses of the ^{1}H and ^{13}C NMR spectra suggested that the pyrrole ring formed, owing to the occurrence of the C–1 CH pyrrole singlet at 6.48 ppm (in the ^{1}H NMR spectrum) and at 100.36 ppm (in the ^{13}C NMR spectrum). A sizeable downfield shift of the singlet peak, amongst other noticeable shifts in the aromatic and piperidine peaks, suggest deshielding effects from the newly formed pyrrole ring. The absence of the OCH_2CH_3 quartet and triplet peaks also confirmed the formation of the lactone and subsequent tetracyclic product **4.38**. A C=O signal appeared at 155.06 ppm in the ^{13}C NMR spectrum. This was similar to the values obtained with the previously synthesized pyrrolizine ring-closed products **4.32** and **4.33**. In the NOESY spectrum for lactone **4.38**, a through-space interaction of the pyrrole proton on C–1 with C–11 (piperidine ring CH_2) and C–12 (aromatic CH) confirmed the regiochemistry of the lactone formation. Similar HMBC interactions proved the lactone formation and assisted in the assignment of the quaternary carbons. The HRMS revealed a molecular ion at 240.1024 for **4.38** with the molecular formula $C_{15}H_{13}NO_2$, the calculated exact mass was 240.1025.

The product corresponding to the first spot could not be recrystallized and despite several considerations based on the mechanistic studies, the structure could not be definitively deduced. Only through an XRD studies of a lamellarin pyrrole analogue **5.28** synthesized and discussed later in *Chapter 5*, did we realise that the product formed in this related six-membered analogue (**4.39**), which correlated directly to the compound formed in the studies conducted in *Chapter 5* (**5.28**). A comprehensive NMR analysis of the product obtained in *Chapter 5* confirmed that the first product isolated during column chromatography of the reaction mixture was 10,11-dihydro-8*H*-chromeno[3,2-*a*]indolizin-12(9*H*)-one **4.39** (*Scheme 4.12*). A more comprehensive discussion and the mechanism of the reaction will be

discussed in *Chapter 5*; however, it can be clearly seen that in this case the mechanism illustrated in *Figure 4.9* (enaminone acting as acceptor) is not operating, and that, instead, it is the ester that is the acceptor (enaminone acting as a nucleophile) (*Figure 4.12*).



Scheme 4.12 *Reagents and conditions:* i. Silica gel, xylene, 180°C, 150 W, 15 min.

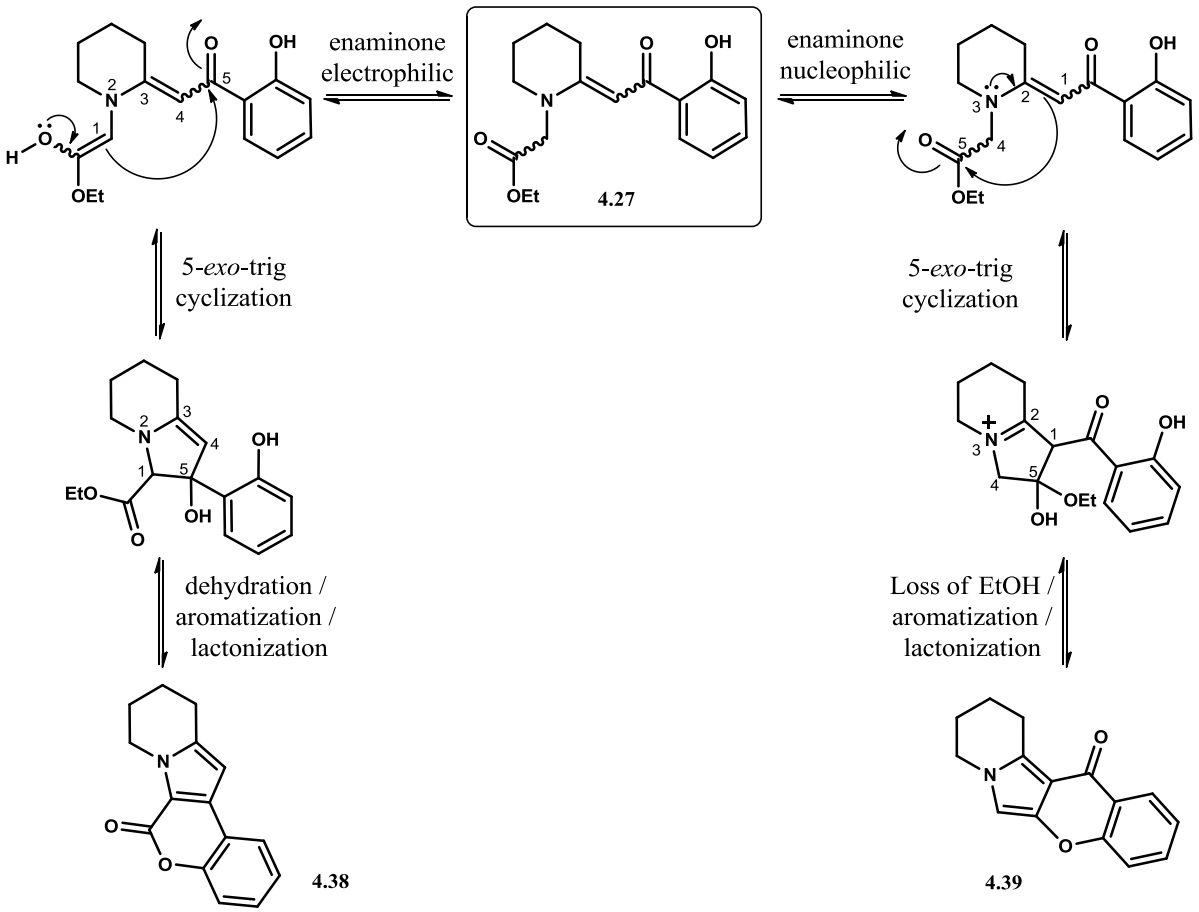
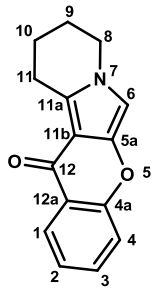


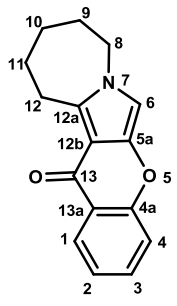
Figure 4.12: The proposed mechanism for the synthesis of indolizines **4.38** and **4.39**.



4.39

An analysis of the ^{1}H NMR spectrum for **4.39** showed that four aromatic signals, two doublets of doublets (C–1 and 4) and two doublet of doublet of doublets (C–2 and 3) were present. A singlet at 6.48 ppm (in the ^{1}H NMR spectrum) and at 100.36 ppm (in the ^{13}C NMR) was present for the pyrrole proton at C–6. When compared to the pyrrole protons in **4.38** and pyrrolizines **4.32** and **4.33**, it was found that, although the values were similar, they were slightly lower, in the range of 6.16–6.38 in the ^{1}H NMR spectrum and in the range of 99.47–93.76 for the ^{13}C NMR spectrum. The C=O appeared at 175.49 ppm, which is expected for a biaryl ketone, and shows that the product formed does not coincide to the previously observed and expected lactone-containing pyrrole products (such as pyrrolizines **4.32** and **4.33**, and indolizine **4.38**). A comparison was also drawn between the known product **5.28**, which will be discussed in *Chapter 5*, the C=O and other notable features in the NMR spectra correlated well with the product 10,11-dihydro-8*H*-chromeno[3,2-*a*]indolizin-12(9*H*)-one **4.39**.

The findings for the six-membered analogues suggested that the 7-membered analogues may also form two separate pyrrole products, owing to the steric changes of the larger ring systems. The reaction with the azepine enaminone **4.28** only produced one visibly dominant product **4.40** with an R*f* at 0.68 (in 50% ethyl acetate in hexane mixture). The NMR data were compared to both the pyrrolizine product **4.32** and the two isolated indolizine products **4.38** and **4.39** mentioned above. It was concluded that the only product isolated was 9,10,11,12-tetrahydrochromeno[3',2':3,4]pyrrolo[1,2-*a*]azepin-6(8*H*)-one **4.40** as an off-white powder in 41% yield.



4.40

The spectroscopic analysis for 9,10,11,12-tetrahydrochromeno [3',2':3,4]pyrrolo[1,2-*a*]azepin-6(8*H*)-one **4.40** verified that a tetracyclic product similar to **4.39** formed. No OH peak and no ethoxy signals were present in the IR and NMR spectra. The ^{13}C NMR spectra showed a C=O signal at 176.14 ppm, which correlated to the expected biaryl ketone and not a lactone carbonyl. All the data obtained for the tetracyclic pyrrole product correlated well with the data acquired for the indolizine **4.39** and lamellarin

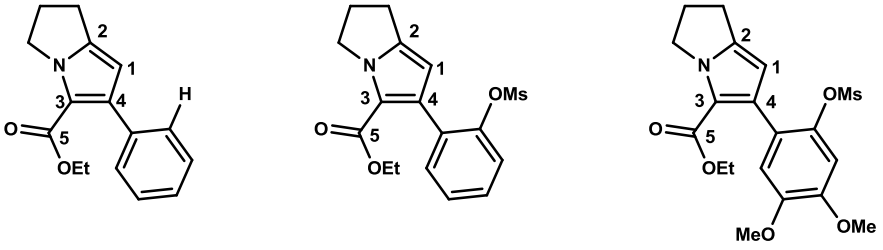
analogue **5.28** in *Chapter 5*. In the HRMS a molecular ion peak was found at 253.1107; the exact mass for product **4.40** with the molecular formula $C_{16}H_{15}NO_2$ was calculated as 253.1103.

A summary of the pyrrole-containing products formed during this project, which have been described in this Chapter is shown in *Table 4.2* below. Some selected data have been given indicating important comparative correlations for our newly formed pyrrole products. *Figure 4.13* depicts the structure of the compounds formed and their representative number, which is indicated in the table for referral purposes. Specific carbon numbers have been assigned to indicate important details. These have been adapted to encompass all the structures and do not correlate with the numbering system depicted in the rest of Chapter. Also, ^{1}H and ^{13}C NMR spectra have been added (*Figure 4.14*), for tetracyclic products **4.32**, **4.38** and **4.39**, to allow for a better ease of comparison and understanding of the results achieved in this Section.

Table 4.2: A comparison of selected data summarizing the pyrrole products synthesized in this project.

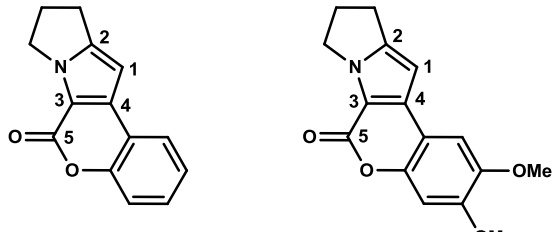
Carbon number	**Pyrrole products**							
	Biaryl products			**Tetracyclic lactone products**			**Tetracyclic chromenones**	
	4.29	**4.30**	**4.31**	**4.32**	**4.33**	**4.38**	**4.39**	**4.40**
^{1}H NMR Spectrum (ppm):								
C–1	5.94	5.98	5.99	6.31	6.16	6.38	6.48	6.51
^{13}C NMR Spectrum (ppm):								
C–1	103.51	104.16	104.13	94.54	93.76	99.47	100.36	102.25
C–2	142.33	142.48	142.37	148.96	149.00	141.73	145.26	146.14
C–3	137.40	130.50	130.21	151.47	149.17	115.28	122.77	122.77
C–4	136.70	130.24	121.99	134.08	134.67	118.03	107.70	119.22
C–5	161.37	161.14	161.00	155.10	155.41	155.06	175.49	176.14
IR spectrum (cm^{-1}):								
C–5	1675	1683	1684	1692	1704	1696	1705	1719

Pyrrolizine biaryl products



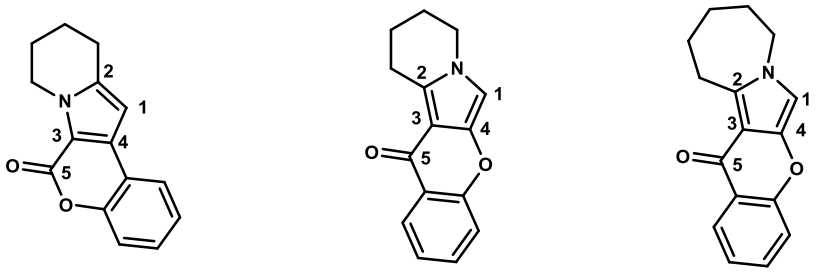
4.29 **4.30** **4.31**

Pyrrolizine tetracyclic products



4.32 **4.33**

Indolizine and pyrroloazepine products



4.38 **4.39** **4.40**

Figure 4.13: A summary of the pyrrole products synthesized in this Chapter.

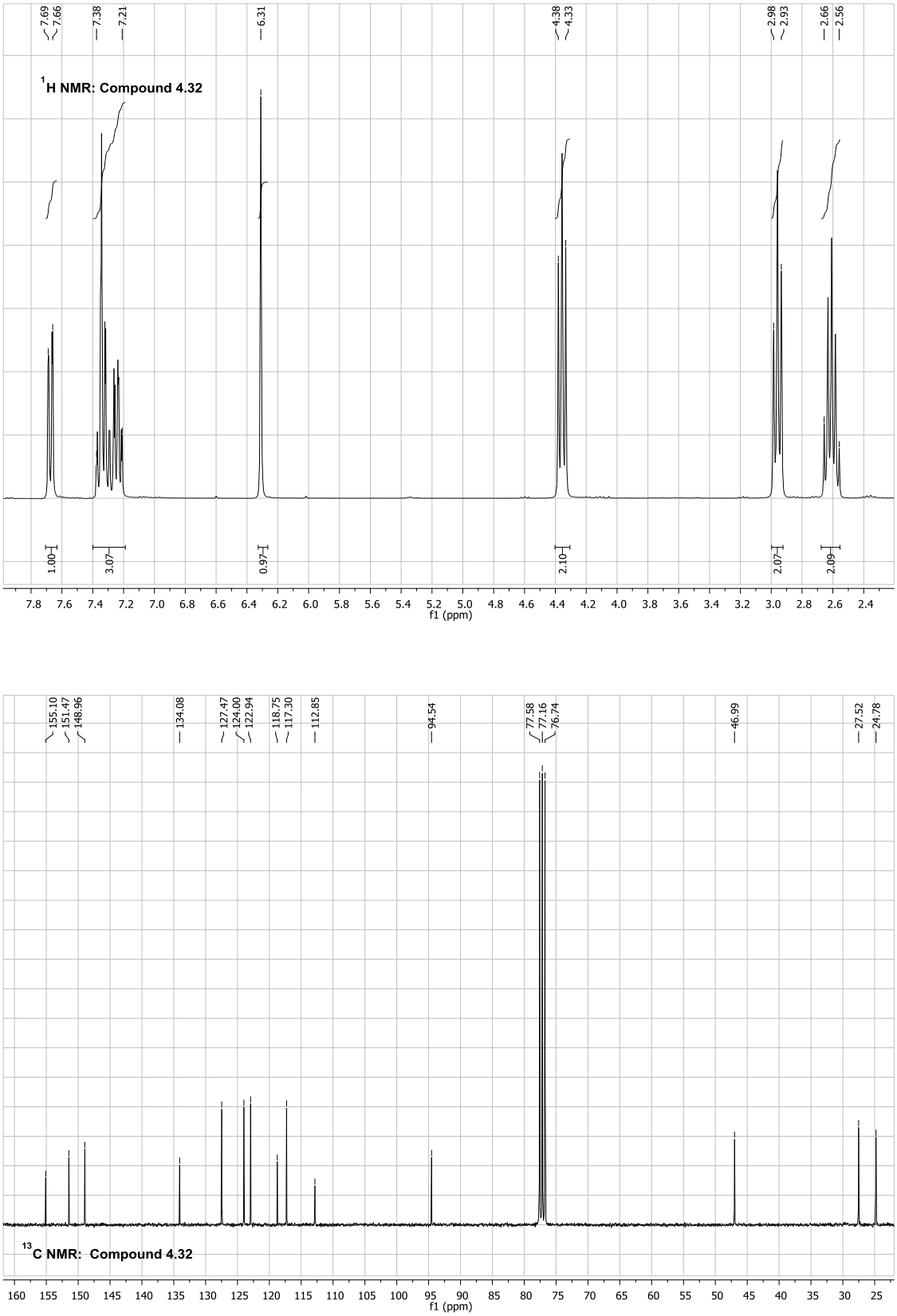


Figure 4.14a: ^{1}H and ^{13}C NMR spectra for 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.32**.

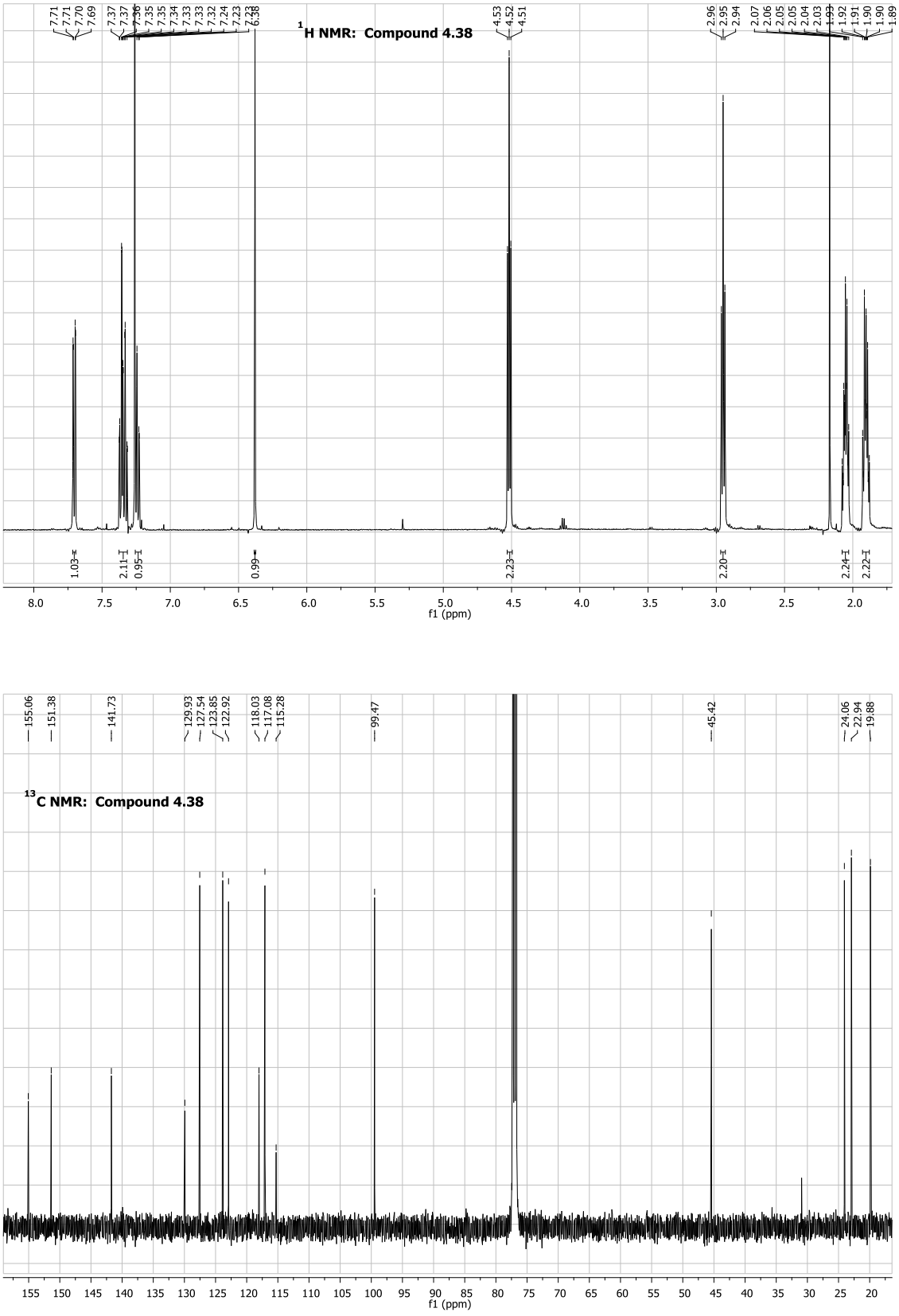


Figure 4.14b: ^{1}H and ^{13}C NMR spectra for 8,9,10,11-tetrahydro-6*H*-chromeno[4,3-*b*]indolizin-6-one **4.38**.

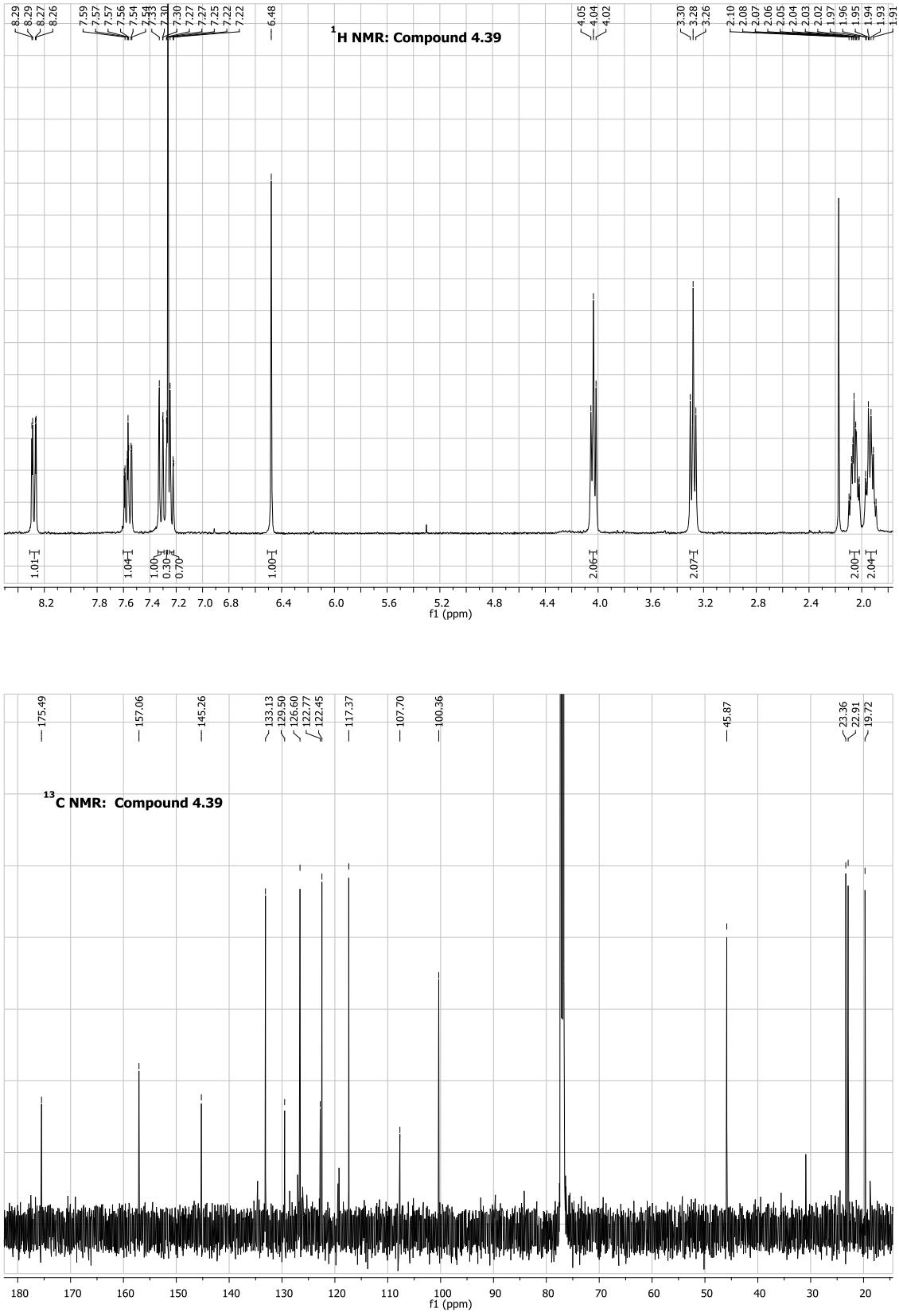


Figure 4.14c: ^{1}H and ^{13}C NMR spectra for 10,11-dihydro-8*H*-chromeno[3,2-*a*]indolizin-12(9*H*)-one **4.39**.

4.6. Brominations and Suzuki-Miyaura coupling reactions

The motivation for inserting an additional aromatic ring onto the tetracyclic compounds through a series of Suzuki coupling reactions was to create a biaryl axis that would mimic the appearance of the lamellarin alkaloids, which are the main desirable products of this project and will be discussed in the next chapter of this thesis.

The Suzuki-Miyaura reaction has been used extensively in chemistry since 1979. A halide (or triflate) is coupled to a boronic acid with the help of a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0).[131,132] The Suzuki-Miyaura coupling works through an organometallic mechanism (*Figure 4.15*).[133,134] The palladium(0) catalyst undergoes oxidative addition with the halide (***1***), followed by a transmetallation with the palladium complex and a base (***2***), usually $NaHCO_3$, K_2CO_3, Cs_2CO_3 or CsF. The boronic acid is then activated with the base (***3***) and a transmetallation forms a palladium complex of the product. The product forms when the palladium catalyst is restored by a reductive elimination (***4***).

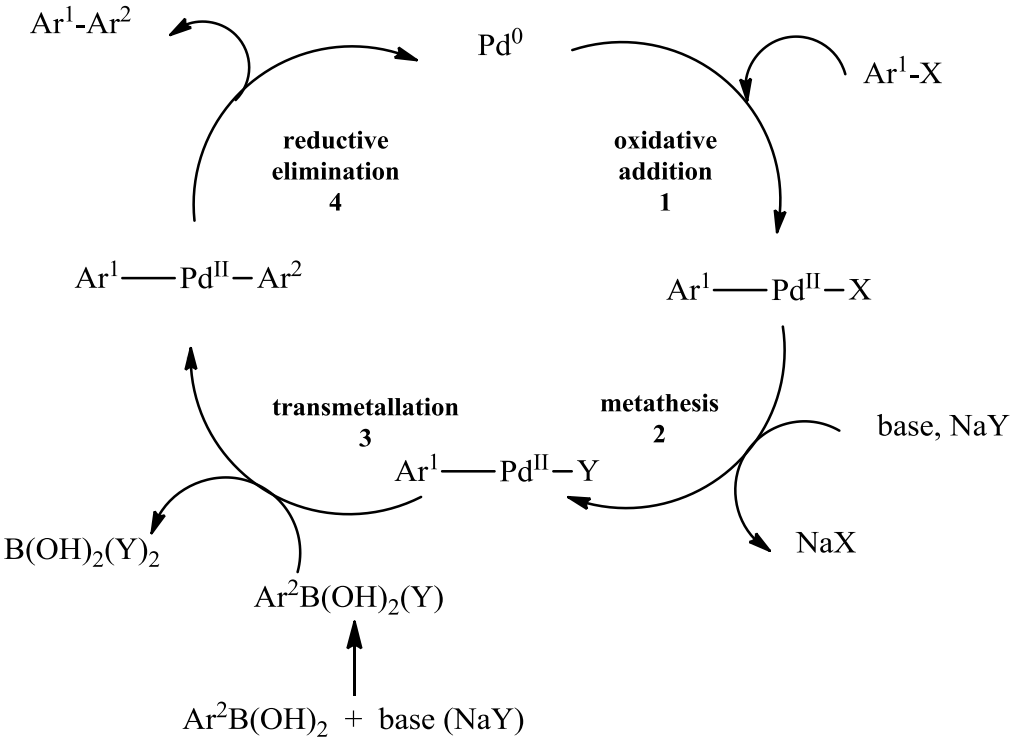
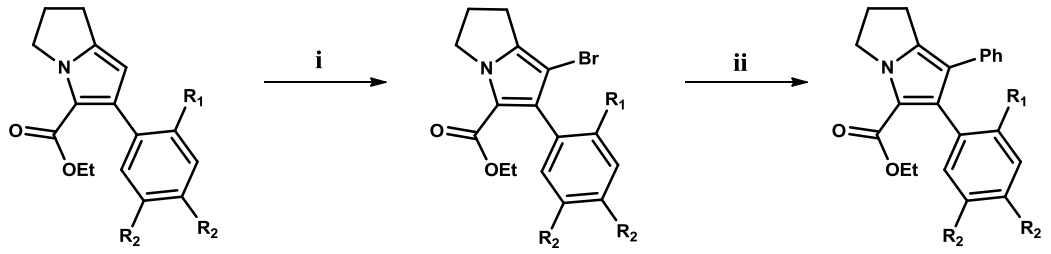


Figure 4.15: The catalytic cycle of the Suzuki-Miyaura coupling reaction showing the formation of biaryl compounds.

The Suzuki-Miyaura coupling has become a useful tool in organic synthesis, owing to the importance of carbon–carbon bond synthesis, which is highly useful in the preparation of many natural and bioactive compounds. Boronic acids are also relatively stable and possess low toxicity when compared to other organometallic substrates. Also, many are now commercially available. The reaction is versatile under many reaction conditions and reagents and shows promising results even for sterically demanding substrates.[96,133,134]

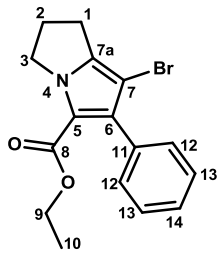
4.6.1. Brominations and Suzuki coupling on simple bicyclic compounds

The formation of simple pyrrolizine compounds was discussed in *Section 4.5.1*. The newly formed pyrrole products ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.29**, ethyl 6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.30** and ethyl 6-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.31** were brominated by stirring the pyrrole products in an ice-cold solution of *N*,*N*-dimethylformamide, then adding a solution of *N*-bromosuccinimide in *N*,*N*-dimethylformamide dropwise to the solution (*Scheme 4.13*).[67,135] The opaque reaction mixture was allowed to warm to room temperature and stirred overnight. The products were isolated after column chromatography and recrystallization.



4.29: R_1 = H, R_2 = H **4.40: R_1 = H, R_2 = H** **4.43: R_1 = H, R_2 = H**
4.30: R_1 = OMs, R_2 = H **4.41: R_1 = OMs, R_2 = H** **4.44: R_1 = OMs, R_2 = H**
4.31: R_1 = OMs, R_2 = OMe **4.42: R_1 = OMs, R_2 = OMe** **4.45: R_1 = OMs, R_2 = OMe**

Scheme 4.13 *Reagents and conditions:* i. NBS, DMF, 0°C–rt, 18 h; ii. $Pd(PPh_3)_4$, $PhB(OH)_2$, Na_2CO_3, DME and EtOH or DMF, rt–reflux, 20h.



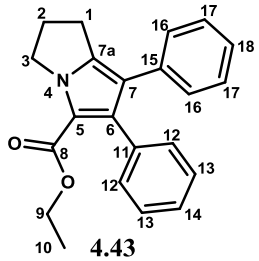
4.40

The infrared and NMR spectrum of product ethyl 7-bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.40**, was compared with the pyrrole starting material **4.29**. The ^{1}H NMR spectrum of product **4.40** very nearly paralleled the spectrum of the starting material **4.29**. The only noteworthy feature was the absence of the C–7 CH singlet from the ^{1}H NMR spectrum for **4.40**, which attested to the presence of the newly formed C–Br bond. In the IR spectrum, the presence of a C–Br stretch at 672 cm^{-1} proved the product had indeed formed. Mass determination by high resolution mass spectrometry possessed an ion at m/z 333.0361 (100%) for the ^{79}Br isotope, with an expected value of 333.0364. The ^{81}Br isotope possessed an ion at *m/z* 335.0375 (98%), which was in good agreement with the expected mass.

In a similar way, the spectra of mesylate products ethyl 7-bromo-6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.41** and ethyl 7-bromo-6-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.42** were compared to the spectra of precursors **4.30** and **4.31**, respectively. The IR spectra of the products showed a C–Br stretch at 670 cm^{-1} (for **4.41**) and at 649 cm^{-1} (for **4.42**); the ^{13}C NMR spectra showed a C–Br signal at 91.59 ppm (for **4.41**) and at 90.21 ppm (for **4.42**); and the absence of the C–7 CH peak was confirmed in the ^{1}H NMR spectra, indicating the brominated products had formed. In the ^{1}H NMR spectra of mesylated products **4.41** and **4.42** signals for C–1 and C–3 CH_2 protons appeared as non-equivalent. Thus each proton appeared as a doublet of triplet signal in the spectrum, indicating that they interacted with one proton from the same carbon to give a doublet with a *J* value of approximately 12.0 Hz, and interacted with two equivalent protons from the adjacent C–3 CH_2 carbon to give a triplet with a *J* value of approximately 7.2 Hz. The presence of the bromine on the pyrrole appears to have added additional electronic and steric effects to the structure, perhaps causing atropisomerism of the compound.

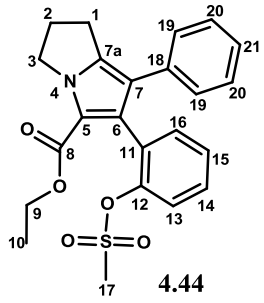
The Suzuki reaction was carried out using several methods, shown in *Scheme 4.13*.[67,134,136] Ethyl 6,7-diphenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.43** was prepared by meticulously adding the reagents to the reaction vessel making sure the atmosphere was free of water and oxygen, by degassing after each addition and operating under an atmosphere of argon. Phenylboronic acid and the brominated pyrrole **4.40** in a mixture of 1,2-

dimethoxyethane and ethanol were added to tetrakis(triphenylphosphine)palladium(0). Finally a 2M aqueous solution of sodium carbonate was added and the mixture was stirred under reflux overnight. Ethanol was added to the solution due to dissolution problems with the starting material. A second method was found that used *N*,*N*-dimethyformamide, which dissolved the reagents more readily. Suzuki product **4.43** was prepared using this method, whereas Suzuki product ethyl 6-[2-(methylsulphonyloxy)phenyl]-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.44** showed higher yields when 1,2-dimethoxyethane and ethanol were used as solvents.



4.43

Ethyl 6,7-diphenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.43** was isolated after column chromatography and recrystallization from ethanol, as a dark red crystalline solid, in 76% yield, with a melting point of 89–91°C. The ^{1}H NMR spectrum of the product showed an additional aromatic multiplet signal (when compared to the precursor **4.40**), integrating for five protons C–16, 17, 18 at 7.13–7.01 ppm; a downfield shift was also observed for the C–1 CH_2 triplet signal, from 2.76 ppm for **4.40** to 3.03 ppm for **4.43**, probably due to the steric and electronic effects of the aromatic group. The corresponding carbon CH signals were assigned to peaks at 128.66, 128.12 and 125.44 ppm, in the ^{13}C NMR spectrum. The quaternary C–7 signal was observed at 135.87 ppm and the quaternary C–15 signal was observed at 117.25 ppm, in the ^{13}C NMR spectrum. The HRMS found the molecular ion peak at 331.1574, with a calculated mass of 331.1572 for product **4.43**, with the molecular formula $C_{22}H_{21}NO_2$.



4.44

Product ethyl 6-[2-(methylsulphonyloxy)phenyl]-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.44** was isolated in 95% yield, using 1,2-dimethoxyethane and ethanol as solvents, and in 67% yield, using *N*,*N*-dimethyformamide as a solvent. In the ^{1}H NMR spectrum, the aromatic peaks showed extensive overlapping, but integrated for nine protons, indicating the Suzuki coupling had taken place. A shift in the sulphonyl C–17 methyl peak from 2.73 ppm for precursor **4.41** to a more shielded position at 2.65 ppm for product **4.44**, suggested the sulphonyl was affected both sterically and electronically by the addition of the phenyl group onto the structure, limited rotation probably forced the *ortho* substituent into a position furthest from the phenyl group. Protons C–1 and

C–3 were once again observed to be non-equivalent, the limited rotation of the biaryl axis probably forming atropisomers of the product **4.44**. The ^{13}C NMR spectrum accounted for 5 new signals (two overlapping) for the newly inserted phenyl group. X-ray crystallography diffraction of the pale orange cuboidal crystals for Suzuki product **4.44** was obtained (*Figure 4.16*). This confirmed the product was formed and illustrated the preferred conformation of the sterically hindered substituents.

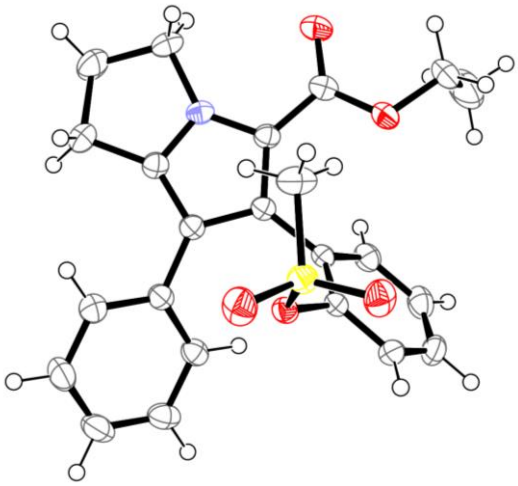
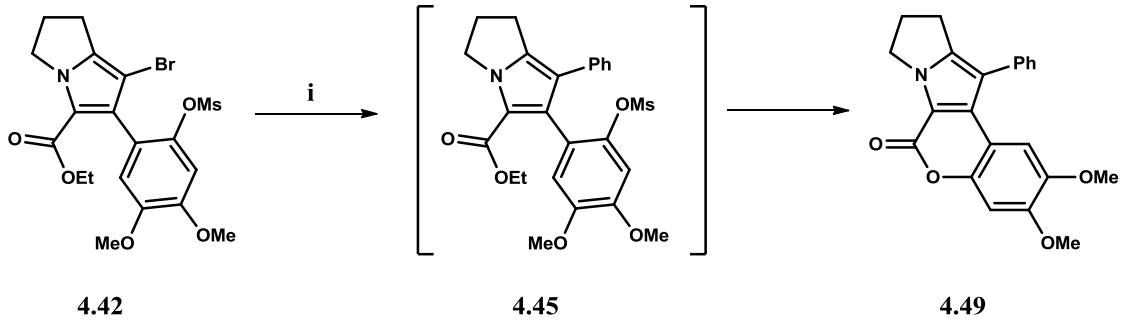


Figure 4.16: An ORTEP diagram for brominated Suzuki product **4.44**, showing the alignment of the biaryl substituents.

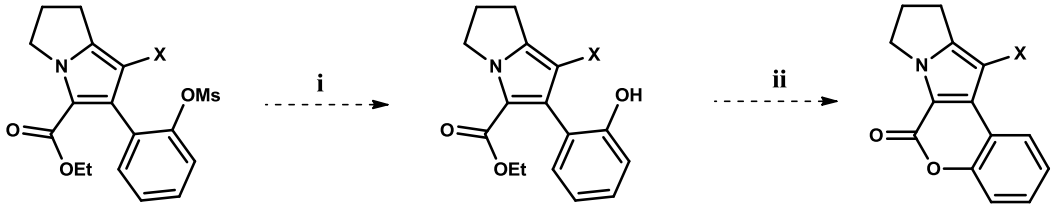
Several attempts using different Suzuki coupling reactions methods were performed in an attempt to form ethyl 6-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.45** from precursor **4.42**. Different solvent systems such as 1,2-dimethoxyethane, ethanol and *N*,*N*-dimethyformamide were used;[67,134] different bases, such as $NaHCO_3$, Na_2CO_3 and Cs_2CO_3 were used;[135,137] and the reaction was attempted using both conventional and microwave conditions.[135,138] In all the instances, boronic acid residues and starting material **4.42** were isolated. Lactone product **4.49** was also isolated in 26% to 54% yield in many of the reactions (*Scheme 4.14*), which indicated that a spontaneous deprotection of the mesyl group and formation of the lactone were occurring under these conditions to produce the tetracyclic product **4.49**, which will be discussed in more detail in the next Section.



4.42 **4.45** **4.49**

Scheme 4.14 *Reagents and conditions:* i. $Pd(PPh_3)_4$, $PhB(OH)_2$, (Na_2CO_3/$NaHCO_3$/Cs_2CO_3), (DME/EtOH/DMF), conventional (rt–reflux, 20h) or microwave (150°C, 150 W, 15 min).

A short mention of the attempts at deprotecting the mesyl group using known methods must be made.[64] The initial purpose of synthesising the mesylated adducts was to eventually form the tetracyclic products by inducing lactonization through the deprotection of the mesyl group (*Scheme 4.15*). The deprotections were attempted in a potassium hydroxide and ethanol mixture; and in a sodium hydroxide (2M solution), methanol and tetrahydrofuran mixture. The deprotections were carried out on pyrrolizines **4.30** and **4.44**, which both showed discouraging results when analysed by NMR spectroscopy. The mesylate thus proved surprisingly uncooperative under simple hydrolysis conditions.



4.30: X = H
4.44: X = Ph

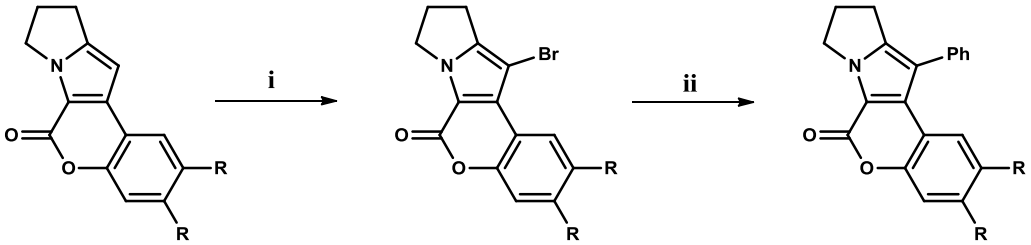
4.32: X = H
4.48: X = Ph

Scheme 4.15 *Reagents and conditions:* i. KOH, EtOH or 2M NaOH, THF, MeOH, rt–reflux, 2–20 h; ii. NaH(60%), THF, 0°C–reflux, 18h.

It was originally hypothesized that a phenolic group would have been too reactive to withstand many of the synthetic steps of this project. However the phenolic structures produced in this project formed the tetracyclic products without problems. The mesylates structures were therefore not necessary to the synthesis but formed interesting analogues for the project.

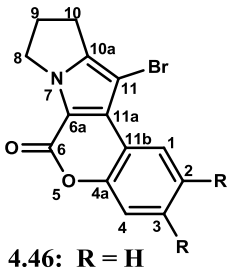
4.6.2. Brominations and Suzuki couplings of tetracyclic compounds

The tetracyclic compounds prepared in *Section 4.5.2* were subjected to brominations using the same methodology described for the preparation of the bicyclic pyrrolizines above. Brominated pyrrolizinones 11-bromo-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.46** and 11-bromo-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.47** were prepared, as shown in *Scheme 4.16*, in 59% and 72% yield, respectively.



4.32: R = H, **4.46: R = H,** **4.48: R = H,**
4.33: R = OMe **4.47: R = OMe** **4.49: R = OMe**

Scheme 4.16 *Reagents and conditions:* i. NBS, DMF, 0°C–rt, 18 h; ii. $Pd(PPh_3)_4$, $PhB(OH)_2$, (Na_2CO_3 or Cs_2CO_3), DME and EtOH or DMF, conventional (rt–reflux, 20h) or microwave (150 W, 150°C, 15 min).



4.46: R = H
4.47: R = OMe

In the IR spectrum, a C–Br stretch was observed at 660 cm^{-1} for **4.46** and at 668 cm^{-1} for **4.47**. In the ^{1}H and ^{13}C NMR spectrum the absence of the C–11 CH peak attested to the formation of the products. Some downfield shifting of the pre-existing aromatic signals suggests that the bromine has an effect on the adjacent aromatic signals. An XRD crystal structure was obtained for pyrrolizinone 11-bromo-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.46** (*Figure 4.17*), confirming the pyrrole was brominated.

A Suzuki-Miyaura coupling reaction using 1,2-dimethoxyethane and ethanol as solvents, as discussed in *Section 4.6.1*, was carried out on brominated pyrrolizinone **4.46**. The product 11-phenyl-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.48** was isolated as a white cuboidal crystalline solid following purification by column chromatography and recrystallization from ethanol. An XRD crystal structure was obtained for the product showing the somewhat rigid pyrrolizinone core and the newly formed biaryl axis (*Figure 4.17*).

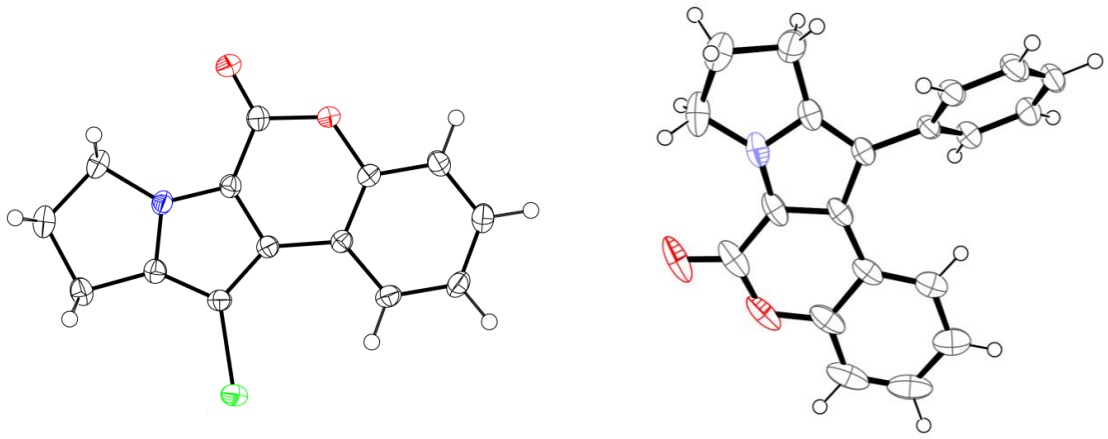
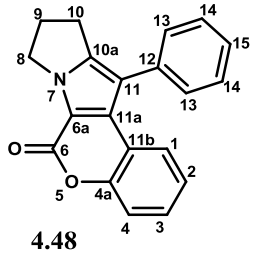


Figure 4.17: ORTEP diagrams for brominated product **4.46** and Suzuki product **4.48**.



4.48

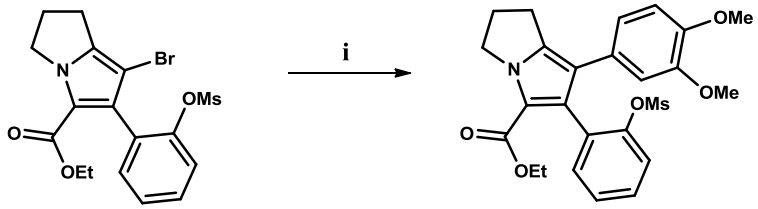
The aromatic region in the ^{1}H NMR spectrum integrated for nine protons. Correspondingly, the ^{13}C NMR spectrum showed three CH signals for carbons C–13, 14 and 15, and two quaternary carbons for C–11 at 134.69 ppm and C–12 at 113.47 ppm. The lactone C–6 C=O signal appeared at 1715 cm^{-1} in the IR spectrum and at 155.37 ppm in the ^{13}C NMR spectrum. All the data obtained were compared to brominated precursor **4.46** and previously prepared bicyclic pyrrolizines **4.43** and **4.44**, and found to be in good agreement to those results.

2,3-Dimethoxy-11-phenyl-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.49** was prepared by a Suzuki coupling using microwave conditions.[135] Several other Suzuki reactions were attempted, all showing no results. It was supposed that additional steric hindrance was caused by the 3,4-dimethoxy substituent. Brominated pyrrolizinone **4.47**, phenylboronic acid, tetrakis(triphenylphosphine)palladium(0), and caesium carbonate in 1,2-dimethoxyethane were irradiated in the microwave at 150 W, to a temperature of 150°C for 15 minutes. Following purification by flash column chromatography and recrystallization from ethanol, the product was isolated as a white powder in 28% yield. All data and characterization for the Suzuki product **4.49** were comparable to the previously discussed brominated precursor **4.47** and the Suzuki product for **4.48** above. The HRMS showed a molecular ion peak at 361.1297, with a calculated exact mass of 361.1314 for the product.

4.6.3. Suzuki reactions using 3,4-dimethoxyphenylboronic acid

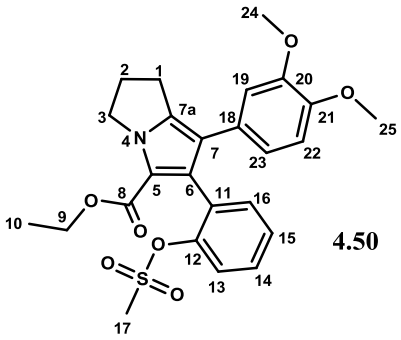
The application of the Suzuki coupling reaction to the pyrrolizine compounds was expanded to include 3,4-dimethoxyphenyl groups into the pyrrole structure. This was the final obstacle in the attempt to create model systems that paralleled lamellarin G trimethyl ether. The Suzuki-Miyaura coupling reactions were expectedly difficult to achieve, owing to steric hindrance of the 3,4-dimethoxyphenyl reagent.

The Suzuki reaction was achieved by combining ethyl 7-bromo-6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.41**, 3,4-dimethoxyphenylboronic acid, tetrakis(triphenylphosphine)palladium(0), and sodium hydrogen carbonate, in a mixture of *N*,*N*-dimethylformamide and water (1:1) in a sealed microwave vessel (*Scheme 4.17*). The reaction was irradiated at 150 W at a temperature of 150°C for 15 minutes. Following purification, the product ethyl 7-[3,4-dimethoxyphenyl)-6-(2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.50** was isolated as white crystals in 69% yield. The product possessed a slightly higher R_f value of 0.69 when compared to the phenyl Suzuki product **4.44** with an R_f value of 0.62, both in 50% ethyl acetate in hexane mobile phase. The melting point of the product was observed at 151–152°C, whereas the phenyl Suzuki product **4.44** was found to have a melting point at 117–119°C. These findings coincide with what was expected given the additional dimethoxy substituents on the phenyl ring.



4.41 **4.50**

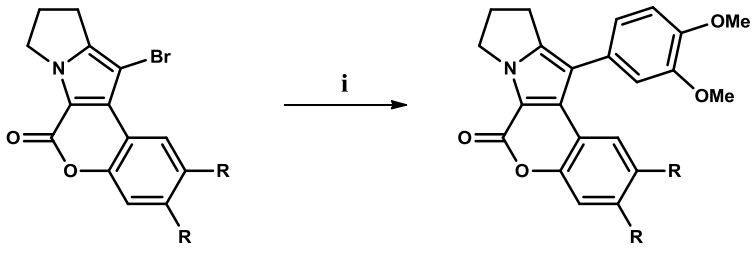
Scheme 4.17 *Reagents and conditions:* i. $Pd(PPh_3)_4$, 3,4-$(MeO)_2C_6H_3B(OH)_2$, $NaHCO_3$, DMF:H_2O (1:1), 150 W, 150°C, 15 min.



4.50

In the IR spectrum of product **4.50**, noticeable peaks were observed for the aromatic ether C–O–C stretch at 1139 and 1195 cm^{-1}. The ^{1}H and ^{13}C NMR spectrum were analysed separately and by cross referencing the data with the HSQC and COSY spectra a relationship between all the signals observed was related to the expected structure. The aromatic C–19, 22, 23 CH protons for the newly inserted aromatic were distinguishable in the ^{1}H NMR spectrum by a multiplet signal at 6.76–6.79 ppm and a singlet signal at 6.52 ppm, integrating for three protons. Analysis by HSQC gave the corresponding carbon signals at 116.25, 111.75 and 111.06 ppm for C–19, 22 and 23. The ^{1}H NMR spectrum also showed two OCH_3 singlet signals at 3.85 and 3.48 ppm, these corresponded to carbon signals at 55.76 and 55.45 ppm. This attested to the presence of the biaryl dimethoxy aromatic product **4.50**.

Using the same methodology, 11-(3,4-dimethoxyphenyl)-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.51** was prepared in 54% yield (*Scheme 4.18*). The data were analysed using IR, ^{1}H and ^{13}C NMR, HSQC and COSY spectra. Similar findings to those described above were observed. The spectra were also compared to the previously discussed 11-bromo-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.46** and 11-phenyl-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.48**, and the data correlated well. Analysis by HRMS showed a molecular ion peak at 361.1317 with an expected exact mass of 361.1314 for the product **4.51**.



4.46: R = H
4.47: R = OMe

4.51: R = H
4.52: R = OMe

Scheme 4.18 *Reagents and conditions:* i. For **4.51**: $Pd(PPh_3)_4$, 3,4-$(MeO)_2C_6H_3B(OH)_2$, $NaHCO_3$, DMF:H_2O (1:1), 150 W, 150°C, 15 min. For **4.52**: $Pd(PPh_3)_4$, 3,4-$(MeO)_2C_6H_3B(OH)_2$, CsF, Ag_2O, DME, 80°C, 22 h.

11-(3,4-Dimethoxyphenyl)-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.52** was the final, most complex, and closest tetracyclic model resembling lamellarin G trimethyl ether. The previously discussed methods for the Suzuki-Miyaura coupling reaction were attempted with 3,4-dimethoxyphenylboronic acid on brominated pyrrolizinone 11-bromo-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.47**. However, no product was formed and only starting material and phenyl by-products were observed, probably because of the steric hindrance from the dimethoxy substituents on both aromatic systems. A procedure by Korenaga and co-workers[139] and Qui and co-workers[140] using silver(I) oxide as a promoter in the Suzuki reaction, for highly congested substrates, was found. The brominated pyrrolizinone **4.47** was reacted with 3,4-dimethoxyphenylboronic acid, tetrakis(triphenylphosphine)palladium(0), caesium fluoride and silver(I) oxide, in 1,2-dimethoxyethane (*Scheme 4.18*). The reaction mixture was degassed several times and stirred under an atmosphere of argon gas at a temperature of 80°C for 22 hours. After the normal work-up the crude product was purified by flash column chromatography, in 20–50% ethyl acetate in hexane solution, and the product was isolated as a pale yellow solid in 50% yield. An x-ray crystallographic structure was obtained for the final and most sought-after product **4.52** (*Figure 4.18*). The crystal was found in the triclinic crystal system, in the *P*-1 space group with a *Z* value of 2. The crystal was afforded in an excellent goodness-of-fit of 0.894.

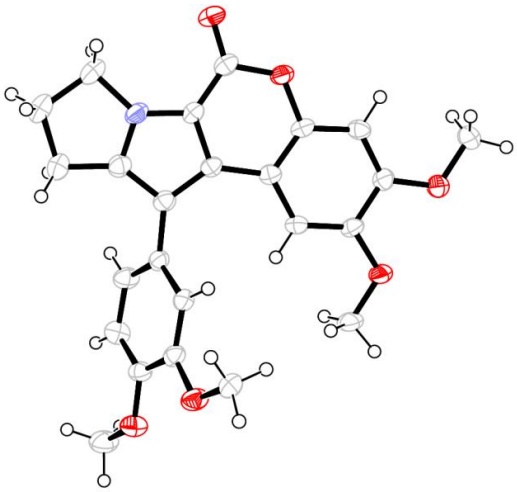
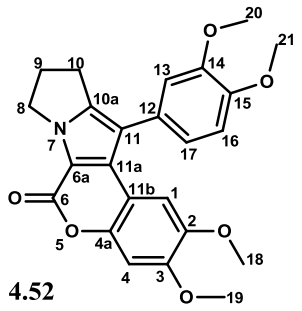


Figure 4.18: An ORTEP diagram, following XRD, showing the final Suzuki product **4.52**, showing the tetracyclic products and the newly formed biaryl axis.



4.52

In the ^{1}H NMR spectrum of product **4.52**, a distinctive aromatic multiplet integrating for three protons was observed at 7.05–6.98 ppm. Two additional C–20,21 OCH_3 signals were also observed at 3.89 ppm (overlapping), in the ^{1}H NMR spectrum and at 56.08 and 56.04 ppm, in the ^{13}C NMR spectrum. All the aromatic, lactam and methoxy environments were interpreted in the ^{1}H NMR spectrum. Similarly, the ^{13}C NMR spectrum accounted for 12 quaternary, three CH_2, four CH_3 and five ArCH signals expected for the product. Analysis of the product by high resolution mass spectrometry found the molecular ion at 422.1609, which required an exact mass of 422.1604.

4.7. Novel methods for introducting lactones into the bicyclic systems

A literature review on lamellarins and other related pyrrole compounds led to the discovery of a procedure that forms lactones with lead tetra-acetate and carboxylic acids.[36,52,53,141,142] The lead(IV) acetate reacts with the carboxylic acid to form free radical intermediates and oxidative lactonization of the acid occurs (*Figure 4.19*).

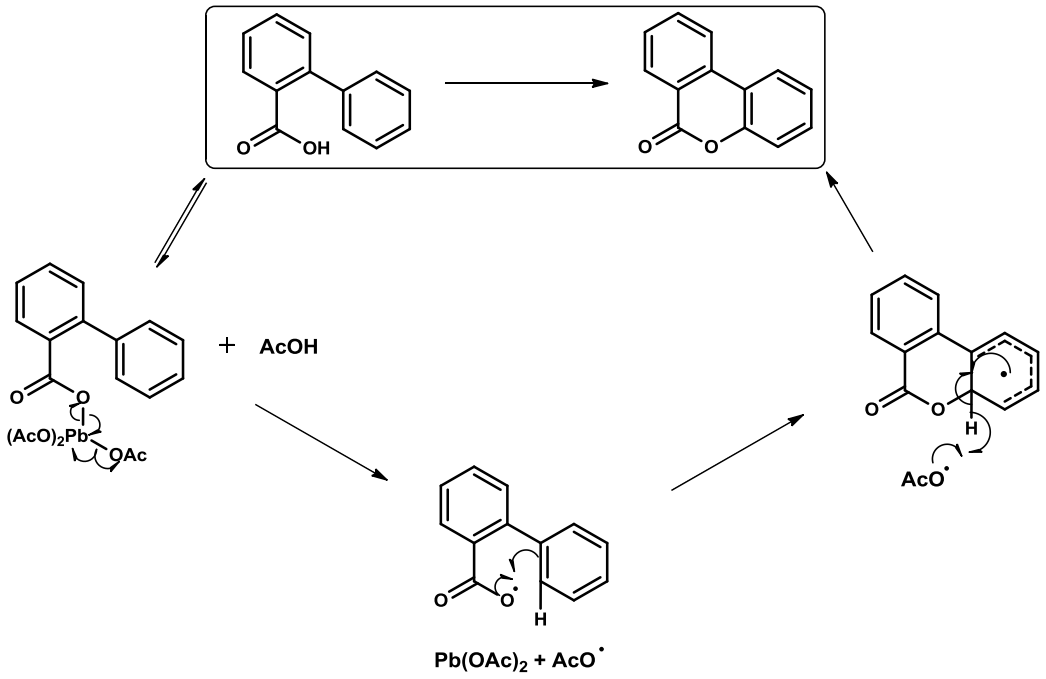
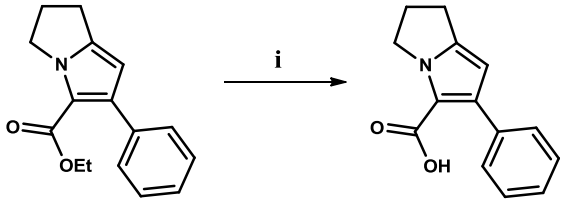


Figure 4.19: The radical cyclization reaction with lead(IV) acetate showing the lactonization between two bicyclic aromatic rings.

We decided to apply the method to the prepared bicyclic pyrrolizines in a possible alternative route to access the sought-after tetracyclic pyrrolizinones. The ester groups of the pyrrolizines were saponified to access the carboxylic acid and then submitted to the lead(IV) acetate radical reaction.

4.7.1. Preparation of 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylic acid

Pyrrolizine compound ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.29** was used in the application of the lead(IV) radical methodology to illustrate that the method could be applied to our systems. The ester group was subjected to a saponification with potassium hydroxide in methanol, shown in *Scheme 4.19*.[143] After 5 hours of stirring the mixture with slow ramping of the temperature, the product was extracted out of the solution and the crude brown solid was recrystallized from ethyl acetate to afford 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylic acid **4.53** as a white solid in 78% yield.



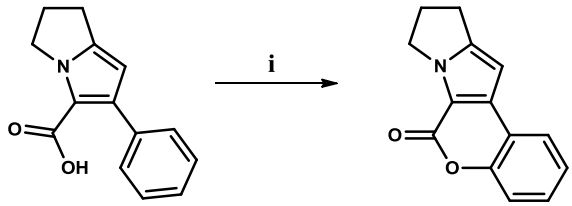
4.29 **4.53**

Scheme 4.19 *Reagents and conditions:* i. KOH, MeOH, 30–100°C, 5 h.

The most distinctive feature in the IR and ^{1}H NMR spectra was the very broad OH stretch at 3054–2440 cm^{-1} and the broad OH singlet at 11.89 ppm, respectively. In the ^{1}H NMR spectrum, absence of the CH_2 quartet and the CH_3 triplet suggested that the saponification had worked. Correspondingly in the ^{13}C NMR spectrum, the absence of the ethoxy group was observed. The HRMS showed a molecular ion at 228.1021, which is in agreement with the expected molecular formula $C_{14}H_{13}NO_2$ (exact mass 228.1025).

4.7.2. Alternative preparation of 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one

The carboxylic acid **4.53** was then subjected to the lead(IV) acetate method in an attempt to prepare 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.32**, which was previously prepared in *Section 4.5.2* of this Chapter using the hydroxyl-containing phenacyl enaminone **4.21** as a precursor to the formation of the lactone spontaneously. The carboxylic acid was treated with lead(IV) acetate in ethyl acetate at room temperature for 1 to 2 hours (*Scheme 4.20*). Following purification by flash column chromatography, in 5–20% ethyl acetate in hexane solution, the product was isolated in 34% yield.



4.53 **4.32**

Scheme 4.20 *Reagents and conditions:* i. $Pb(OAc)_4$, EtOAc, rt, 2 h.

The low yield was not optimized further as the reaction was only attempted out of interest as a possibility for future reactions on these systems. It was surmised that the reaction could be optimized by using recrystallized lead(IV) acetate, since the bottle used was relatively old and the reagent was slightly discoloured. The reaction time and temperature could also be adapted to further optimize the conditions of this reaction. A ^{1}H NMR spectrum was run for the product **4.32** and compared to the same compound prepared previously from hydroxyl phenacyl **4.21**; all the data corresponded and showed that the compound was prepared using this method.

4.8. Conclusions for Chapter 4

This Chapter discussed the preparation of bicyclic and tetracyclic pyrrolizine, indolizine and pyrroloazepine compounds, as a model synthesis toward the preparation of lamellarins, with lamellarin G trimethyl ether being especially important in our synthetic objectives.

The synthesis and characterisation of enaminones prepared from thiolactam precursors was discussed. The synthesis of enaminones with *N*-alkylated and *N*-phenacyl substituted pyrrolidine systems and *N*-alkylated piperidine and azepane adaptions were discussed. The Eschenmoser sulphide contraction was shown to be diverse in its ability to access various substrates and structural adaptions. However, it was also observed to be a highly sensitive and somewhat problematic reaction to perfect and often produced contaminated products which required extensive purification. Despite these drawbacks, a library of enaminones was fashioned, which were used to form pyrrole ring systems.

The examination into the formation of pyrrole rings using the silica gel method through an acid-induced cyclization was used to construct bicyclic pyrrolizine compounds; and tetracyclic pyrrolizinones, indolzinone and pyrroloazepinone compounds. The products formed effortlessly using this methodology and were furnished in favourable yields. A greater understanding of the mechanism for these products was reached, albeit with certain adverse findings. The synthesis of pyrroles from *N*-phenacyl enaminones proved to be ineffective despite the favourability shown in the proposed mechanisms toward the chemistry

and reactivity of these compounds. Further evaluation into these systems could be considered and repeated in future syntheses.

Many of the prepared bicyclic pyrrolizines and tetracyclic pyrrolizinones were subjected to Suzuki-Miyaura coupling reactions with phenylboronic acid and 3,4-dimethoxyphenylboronic acid. The biaryl axis of these compounds was formed by first brominating the pyrrole and then undertaking the Suzuki reaction using several known and adapted procedures. Most importantly, a pyrrolizine-containing direct analogue of lamellarin G trimethyl ether was successfully made (*Figure 4.20*).

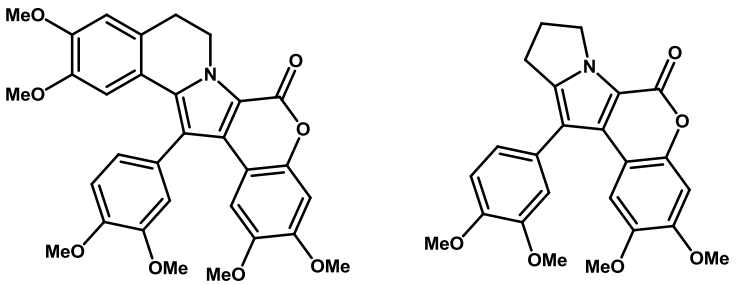


Figure 4.20: Lamellarin G trimethyl ether and corresponding pyrrolizine analogue **4.52**.

Finally, a novel procedure using lead(IV) acetate in a radical reaction was performed on simple bicyclic pyrrolizine ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.29**. The ester group was removed by a saponification and the carboxylic acid was subjected to the radical reaction to afford the tetracyclic product 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.32**, which was previously isolated in the silica gel pyrrole formation reactions using an hydroxyl phenacyl enaminone precursor to spontaneously form the lactone.

This concludes the Chapter on the preparation of tetracyclic pyrrolizinone, indolizinone, and pyrroloazepinone alkaloid compounds. The synthesis of these compounds forms a model study toward the synthesis of lamellarins, which will be discussed in Chapter 5 of this thesis. The methodology accomplished and adapted in this Chapter will be reproduced and re-explored in the Chapter concerning the synthesis toward lamellarin alkaloids.

Chapter 5
Towards lamellarin alkaloids

5.1 Introduction

Lamellarins have some interesting structural and biological traits, which have made them highly desirable targets in a variety of syntheses. There are many groups of lamellarins, not only with pentacyclic structures, but many contain only a pyrrole or indolizine-type core. The pentacyclic lamellarins are the main focus of this project, with lamellarin G trimethyl ether as the main target of the overall synthesis (*Figure 5.1*). Structurally the pentacylic lamellarins are made up of a basic isoquinoline, with the fusion of a pyrrole across the C_1–N bond of the isoquinoline. There is then a lactone fused to the pyrrole and an aromatic ring attached to the lactone.

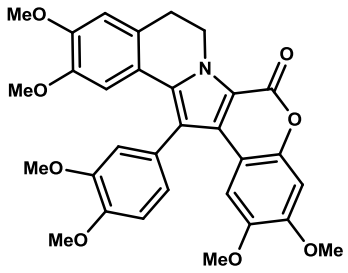


Figure 5.1: Lamellarin G trimethyl ether, illustrating the structurally interesting pentacyclic core.

Many lamellarins have been isolated and extracted, mainly from marine sources such as molluscs, sponges and ascidians. A number of synthetic lamellarins have also been produced. The accessibility of these analogues comes from the ability to manipulate the aromatic substituents. The isoquinoline core can also be saturated or unsaturated. Biologically lamellarins have been shown to be potentially useful in reversing cytotoxicity and multi-drug resistance; in inhibition of HIV-1 integrase and topoisomerase 1, and they also exhibit immunomodulatory activity, which make them highly sought-after as synthetic targets. A more elaborate introduction to the lamellarin alkaloids was given in *Chapter 1* of the thesis.

In our retrosynthesis of the lamellarin structure (*Figure 5.2*) it was observed that possible enaminone precursors, synthesized through the Eschenmoser sulphide contraction reaction,

which have been widely used in the organic laboratory at the University of the Witwatersrand, could be used to prepare the target systems. We thus have to develop a novel synthetic route to access these lamellarins.

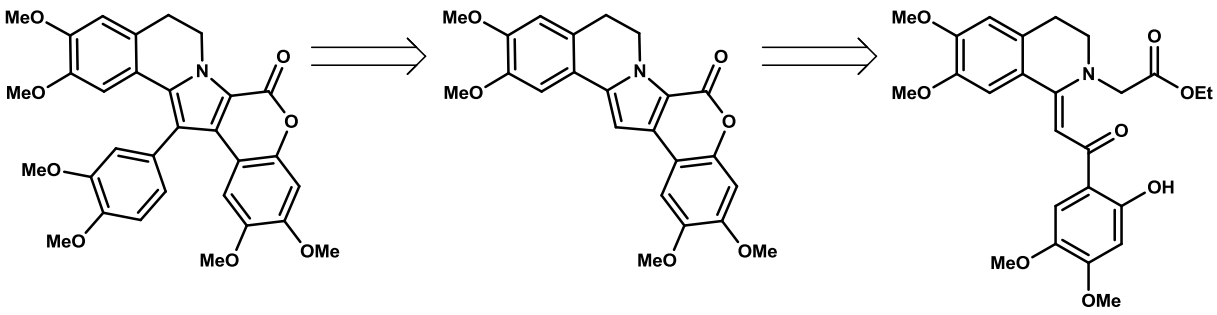


Figure 5.2: Retrosynthesis of lamellarin G trimethyl ether, illustrating the pivotal role of enaminone precursors.

The previous Chapter described the development of a model study. The methodology was tested on various simple ring sizes to produce tetracyclic pyrrolizinone, indolizinone and pyrroloazepinone structures. That methodology will be discussed with an isoquinoline-containing precursor in this Chapter. Simpler unsubstituted analogues will also be produced to help gain a better understanding of the way these isoquinoline structures behave both mechanistically and chemically with regard to the previously tested methodology. It was hoped that an improved synthesis for lamellarin alkaloids would be achieved.

5.2 Outline of the synthetic strategy

This Chapter considers the synthesis of lamellarins through two main synthetic pathways. However, it was first necessary to prepare the 3,4-dihydroisoquinolinone core (Figure 5.*3*). The synthesis of these systems has been covered extensively in the literature. Some of the routes used to optimize the synthesis of the isoquinolinone will be discussed in *Section 5.3*.

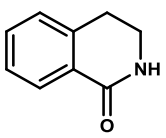


Figure 5.3: 3,4-Dihydroisoquinolinone core structure.

The isoquinolinones will then be thionated to form the precursors to the Eschenmoser sulphide contraction, used for synthesising our enaminones. The pathway diverges at this point; with the preparation of unprotected thiolactam **5.2** and *N*-alkylated thiolactam **5.10** (*Figure 5.4*).

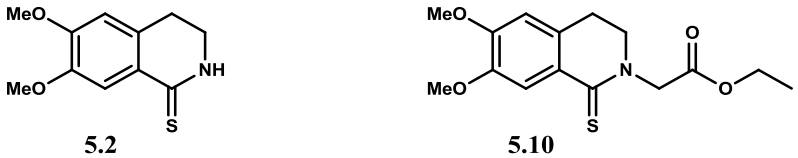
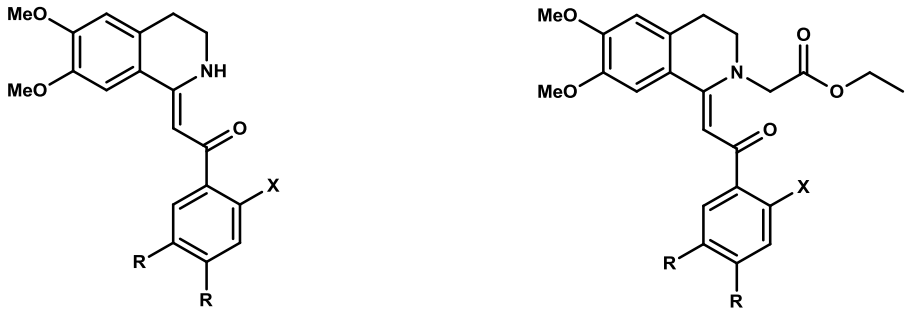


Figure 5.4: Secondary and tertiary isoquinoline-1-thione precursors **5.2** and **5.10**.

Two clear routes for the preparation of vinylogous amides will therefore be discussed (*Figure 5.5*), which will lead to two separate synthetic pathways for the preparation of the lamellarin alkaloids. The enaminones were produced following the methodology discussed in *Chapter 4*, using the previously discussed phenacyl halides (*Chapter 3*) in the Eschenmoser sulphide contraction reaction.



5.31: X = H; R = H
5.32: X = OH; R = H
5.33: X = OH; R = OMe

5.14: X = H; R = H
5.15: X = OH; R = H
5.16: X = OH; R = OMe

Figure 5.5: Unprotected and *N*-alkylated enaminones from thiolactam precursors **5.2** and **5.10**.

Section 5.4 will deal with syntheses based on the *N*-alkylated thiolactam **5.10**, with a similar synthetic pathway to that discussed in *Chapter 4*, which used the silica gel acid-catalysed ring closure to form the pyrrole ring systems. *Section 5.5* will describe routes using the unprotected thiolactam **5.2** in a synthesis adapted from studies by Junjappa and his co-workers.[130] The ester (ethyl 2-bromoacetate) is added *in situ* during the reaction to attain the ring-closed product. Similar bromination and Suzuki-Miyaura coupling reactions to those

discussed in *Chapter 4* will also be described in *Section 5.4 and 5.5* with respect to the divergent syntheses (*Figure 5.6*).

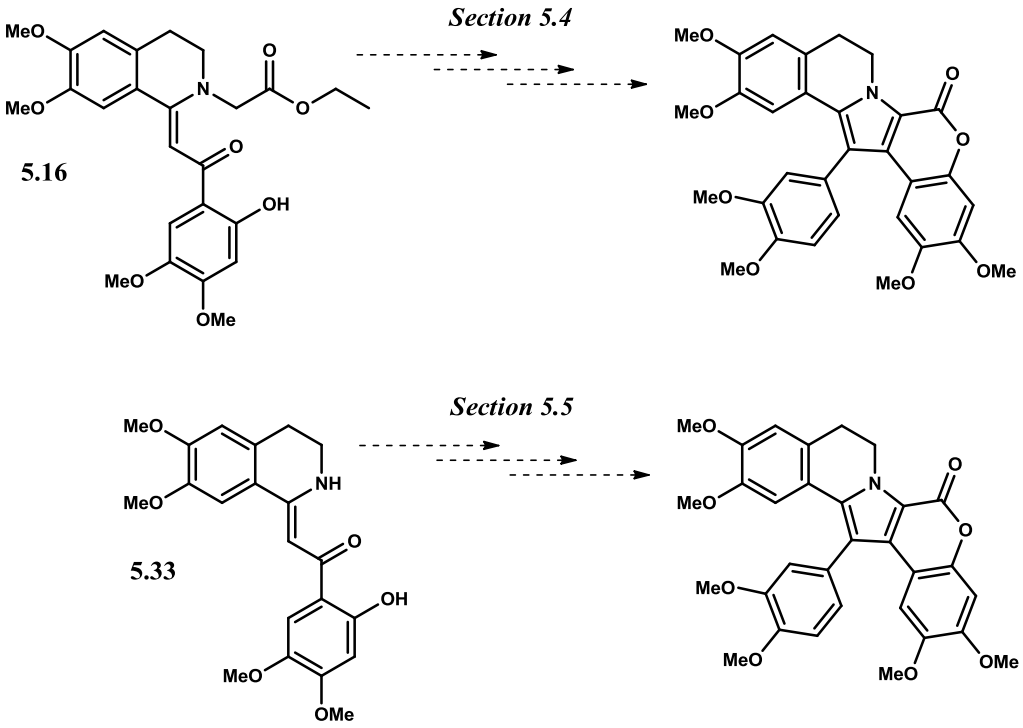


Figure 5.6: Synthesis toward lamellarins G trimethyl ether, with protected enaminone **5.16**, using silica gel method, and with unprotected enaminone **5.33**, using the Junjappa method.

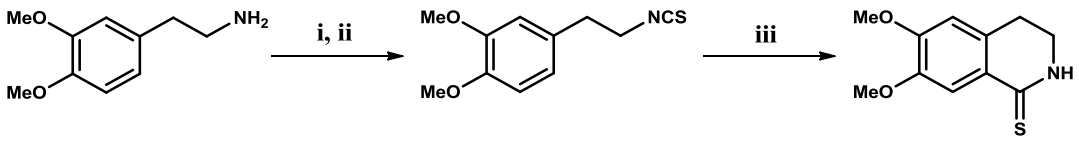
5.3 Preparation of dihydroisoquinoline-1-thiones

3,4-Dihydroisoquinolines have been synthesized in a variety of ways, owing to interest in the biological activity of this group of compounds. 3,4-Dihydroisoquinolines have been used for the treatment of schizophrenia and as potential cardiovascular and pressor agents.[144,145] 3,4-Dihydroisoquinoline is also found in many natural products that show biologically activity and have interesting chemical properties.[146]

5.3.1 Preparation of 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione[144,146]

Our primary study was to access thiolactam 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** from commercially available 3,4-dimethoxyphenylethylamine. Thiolactam **5.2** was prepared via intermediate 1-(2-isothiocyanatoethyl)-3,4-dimethoxybenzene **5.1** (*Scheme 5.1*).

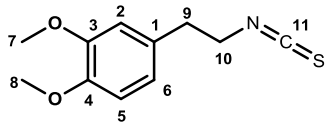
Treatment of 3,4-dimethoxyphenylethylamine (homoveratrylamine) with carbon disulphide in the presence of triethylamine forms a dithiocarbamic acid salt. This was then decomposed into the isothiocyanate **5.1** with ethyl chloroformate. The reaction mixture was then made alkaline with an aqueous solution of sodium hydroxide (2M) and after a standard extraction with dichloromethane the intermediate was isolated as a yellow oil in a quantitative yield. The isothiocyanate could either be isolated or used immediately in the next step.



Homoveratrylamine **5.1** **5.2**

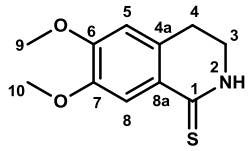
Scheme 5.1 *Reagents and conditions:* i. CS_2, Et_3N, CH_2Cl_2, 0°C–rt, 1 h; ii. EtOCOCl, Et_3N, 0°C–reflux, 2h; iii. PPA, 80°C, 4 h.

Without further purification isothiocyanate **5.1** was dissolved in a minimum of dichloromethane and added dropwise to vigorously stirring polyphosphoric acid, which had been heated to approximately 80°C. The product immediately began to precipitate on contact with the viscous polyphosphoric acid. The mixture was stirred for an additional 2–4 hours. On cooling, water was added to the reaction and the precipitate was filtered and washed. The crude solid was recrystallized from methanol, and thiolactam 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** was isolated as a pale off-white powder in 91% yield.



5.1

The presence of a distinctive stretch at 2091 cm^{-1} for isothiocyanates R–N=C=S and a C=N stretch at 1707 cm^{-1}, in the IR spectrum, as well as an unmistakeable absence of a broad amine NH_2 peak for the starting material suggested the isothiocyanate **5.1** had indeed formed. Similarly, the ^1H NMR spectrum showed no NH_2 signal, but three aromatic protons at 6.84–6.74 ppm (for C–2,5,6); two singlet signals integrating for 6 protons for the two methoxy groups at 3.90 and 3.86 ppm; and two triplets both integrating for two protons at 3.69 ppm (for C–10) and 2.93 ppm (for C–9), which was expected for the isothiocyanate product. In the ^{13}C NMR spectrum, the expected C–11 signal was observed at 130.62 ppm.



5.2

The R_f of the isothiocyanate **5.1** was calculated as 0.66, in a 50% ethyl acetate in hexane mixture, when compared to the thiolactam product **5.2** with a R_f of 0.32 in the same solvent system. This was expected as the thiolactam would be more polar due to the thioamide group. TLC could thus be used as a clear indication of reaction completion. The IR and ^{1}H NMR spectra, unambiguously showed signals for the NH group, a broad N–H stretch at 3350 cm^{-1}, in the IR spectrum and a NH singlet integrating for one proton, in the ^{1}H NMR spectrum. The aromatic signals were also observed as two singlet signals, indicating that tetra-substitution of the product had occurred. A peak at 193.38 ppm for C–1 in the ^{13}C NMR spectrum, and a C=S stretch at 1514 cm^{-1} in the IR spectrum, showed that thiolactam **5.2** was isolated. The data obtain were in agreement with the data in the literature.[144]

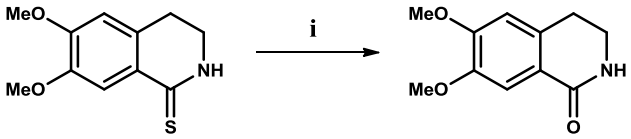
Thiolactam 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** was used directly in the synthesis of enaminones in *Section 5.5*. It was also used to prepare the *N*-alkylated thiolactam **5.10**, which was required for the preparation of enaminones in *Section 5.4*, albeit through a longer and less efficient overall pathway. This route will be discussed further in the next section along with alternative syntheses.

5.3.2 Methods for the preparation of precursor 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one

Several methods for the preparation of lactam 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **5.3** will be discussed in this Section. Several methods were attempted with the intention of optimising the overall yield of product **5.3**.

Following the discussion in *Section 5.3.1*, the prepared thiolactam 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** was used to synthesise 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **5.3** through a known oxidation reaction using basic hydrogen peroxide (*Scheme 5.2*).[147] Thiolactam **5.2** was added to a cooled solution of methanol, aqueous potassium hydroxide and hydrogen peroxide. After three hours, the mixture was cautiously acidified with hydrochloric acid and an extraction with dichloromethane was performed. The product **5.3** was isolated in 79% yield as a white solid, with an overall yield from 3,4-dimethoxyphenylethylamine to lactam **5.3** of 71%. The characterisation of the

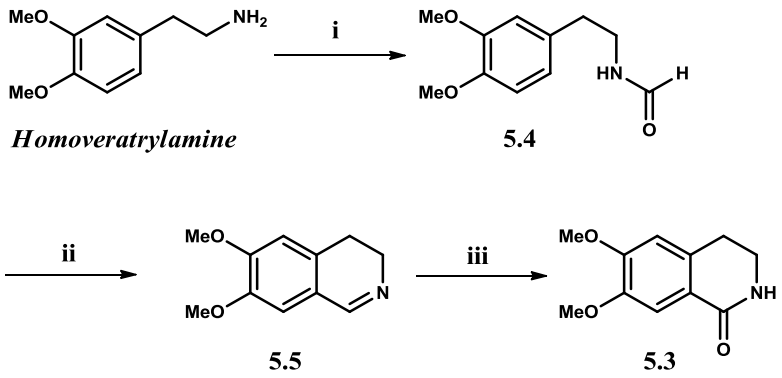
lactam will be discussed later in this Section, after all the methods for accessing lactam **5.3** have been described.



5.2 **5.3**

Scheme 5.2 *Reagents and conditions:* i. KOH, H_2O, H_2O_2, MeOH, 0°C, 3 h.

An alternative approach began with 3,4-dimethoxyphenylethylamine, the same starting material used for the previous synthesis, in a Bischler-Napieralski reaction to form intermediate **5.5**.[148-150] This isoquinoline can then be oxidized to afford isoquinolinone **5.3** (*Scheme 5.3*).



Homoveratrylamine **5.4** **5.5** **5.3**

Scheme 5.3 *Reagents and conditions:* i. Methyl formate, rt, 19 h; ii. $POCl_3$, toluene, reflux, 2 h; ii. $NaClO_2$, NaH_2PO_4, THF, rt, 42 h.

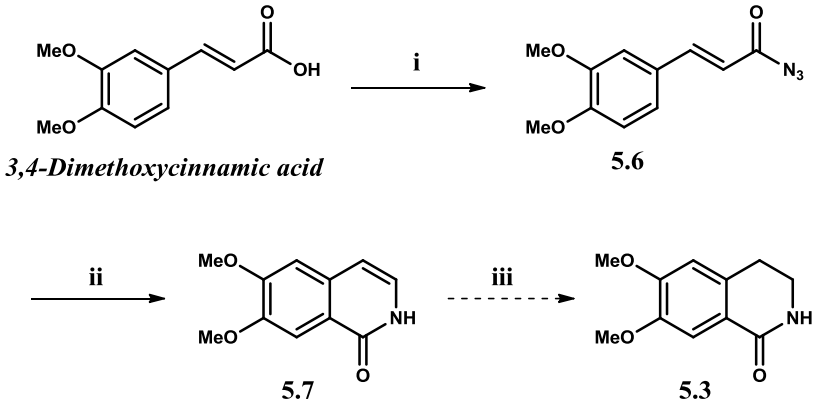
3,4-Dimethoxyphenylethylamine was formylated with methyl formate to give *N*-[2-(3,4-dimethoxyphenyl)ethyl]formamide **5.4** in a quantitative yield as a yellow oil. Formamide **5.4** was then subjected to Bischler-Napieralski conditions, by heating it under reflux with phosphoryl chloride. On completion of the reaction, the mixture was cautiously made alkaline with aqueous sodium hydroxide (2M solution). Subsequently, imine **5.5** was isolated as an orange oil in 87% yield.

In the ^{1}H NMR spectrum of *N*-[2-(3,4-dimethoxyphenyl)ethyl]formamide **5.4**, a singlet signal at 8.11 ppm was observed for the formyl unit. A second broad singlet, integrating for one

proton, was observed at 6.02 ppm, which unmistakeably showed the NH was present in the structure. Similarly, in the ^{13}C NMR spectrum, a C=O carbon signal was observed at 161.26 ppm. All the data observed corresponded to literature.[149] The data for formamide **5.4** and imine 6,7-dimethoxy-3,4-dihydroisoquinoline **5.5** were compared and the NH signal of the formamide was no longer observed in the IR and ^{1}H NMR spectra. Some other characteristic signals noted for imine **5.5** were a $R_2C=N–R$ imine observed in the IR spectrum, a singlet signal in the ^{1}H NMR spectrum at 8.24 ppm, for the imine CH and two aromatic signals at 6.81 and 6.68 ppm, suggesting a tetra-substituted compound had formed; and a significant carbon signal for the imine HC=N was noted at 159.61 ppm in the ^{13}C NMR spectrum.

6,7-Dimethoxy-3,4-dihydroisoquinoline **5.5** was then oxidized using sodium dihydrogenphosphate and sodium chlorite in an oxidation referred to as the Pinnick oxidation.[151,152] Following purification by flash column chromatography, the lactam **5.3** was isolated in 64% yield. The overall yield achieved by pursuing this route, from 3,4-dimethoxyphenylethylamine to lactam **5.3**, using the Bischler-Napieralski reaction was 56% yield.

The next approach to forming lactam **5.3** started with commercially available 3,4-dimethoxycinnamic acid (*Scheme 5.4*). The acid was treated with oxalyl chloride and sodium azide to produce the acyl azide **5.6** in a quantitative yield as a pale yellow solid. The acyl azide **5.6** was subjected to the Curtius rearrangement by heating the azide with mercuric acetate in *o*-dichlorobenzene. 6,7-Dimethoxyisoquinolin-1(2*H*)-one **5.7** was isolated as a pale brown powder in 53% yield. Several attempts to hydrogenate the double bond using different reduction methods[111,153] were unsuccessful and lactam **5.3** was not formed.

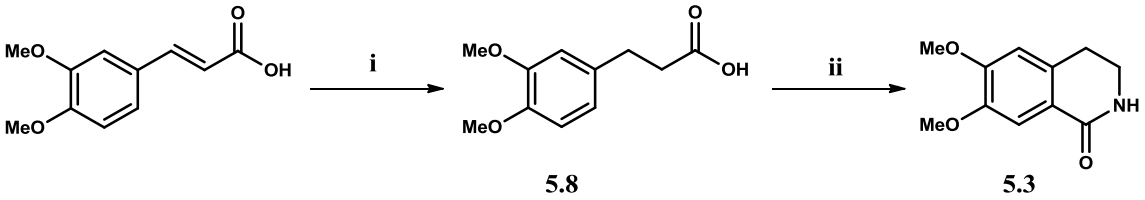


3,4-Dimethoxycinnamic acid **5.6** **5.7** **5.3**

Scheme 5.4 *Reagents and conditions:* i. $(COCl)_2$, toluene, reflux, 4 h then NaN_3, acetone, 0°C–rt, 18 h; ii. $Hg(OAc)_2$, *o*-dichlorobenzene, reflux, 5 h; iii. H_2(g), 10% Pd/C, MeOH/CH_2Cl_2 (1:1), rt, 24 h.

The IR spectrum of (2*E*)-3-(3,4-dimethoxyphenyl)prop-2-enoyl azide **5.6** showed a distinctive azide stretch at 2131 cm^{-1}, and no OH stretches were observed. In the ^{1}H NMR spectrum, two CH alkene peaks were observed at 7.69 and 6.29 ppm with a *J* value of 15.8 Hz, suggesting the compound was isolated as the *E*-isomer, also no OH signal was observed. The Curtius rearrangement product 6,7-dimethoxyisoquinolin-1(2*H*)-one **5.7** was confirmed by the NH signal observed at 1555 cm^{-1} in the IR spectrum, and at 11.37 ppm in the ^{1}H NMR spectrum. The formation of the tetra-substituted isoquinoline was also established, by two aromatic C–H singlet signals at 7.79 and 7.13 ppm, integrating for one proton each, in the ^{1}H NMR spectrum with the corresponding ^{13}C NMR spectrum signals at 106.75 and 106.16 ppm. The melting point of product **5.7** was found to be 255–256°C (the literature value was 244–245°C) all other data were in good agreement to the literature.[154]

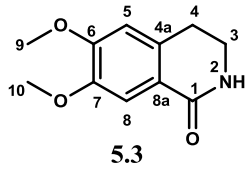
The timing of the synthesis was changed so that double bond in 3,4-dimethoxycinnamic acid was first reduced with hydrogen gas, using 10% palladium on carbon in a methanol and dichloromethane solution (1:1), to give the saturated acid **5.8** (*Scheme 5.5*). The acid was subjected to a modified Curtius rearrangement by reacting 3-(3,4-dimethoxyphenyl)propanoic acid **5.8** with triethylamine and diphenylphosphoryl azide in toluene. This was followed by the addition of boron trifluoride diethyl etherate to generate the lactam **5.3** through the one-pot synthesis in 96% yield. 6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **5.3** was therefore produced from 3,4-dimethoxycinnamic acid in two steps, in 94% overall yield.



5.8 **5.3**

Scheme 5.5 *Reagents and conditions:* i. H_2(g), 10% Pd/C, MeOH/CH_2Cl_2 (1:1), rt, 24 h; ii. $(PhO)_2PON_3$, Et_3N, toluene, 100°C, 2 h then $BF_3{\cdot}OEt_2$, 0°C–rt, 18 h.

In the ^{1}H NMR spectrum for 3-(3,4-dimethoxyphenyl)propanoic acid **5.8**, two CH_2 triplet signals for the hydrogenated compound were observed at 2.91 and 2.67 ppm, with a *J* value of 7.6 Hz, attesting to the removal of the double bond from 3,4-dimethoxycinnamic acid. The OH was observed in both the IR and ^{1}H NMR spectra and all other data correlated well with the expected structure, verifying the formation of acid **5.8**. The melting point of acid **5.8** corresponded well to the literature value of 96–98°C, and all spectral data were found in good agreement to that observed in the literature.[155]



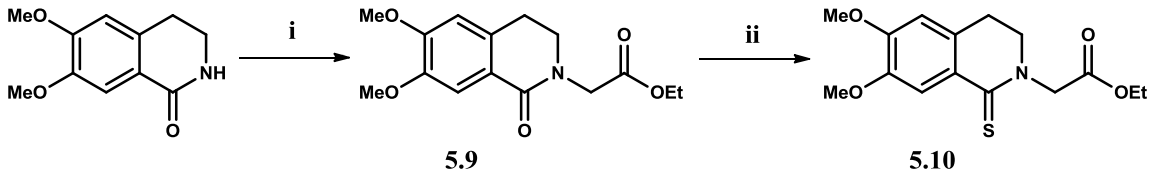
5.3

Characterization of 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **5.3** was achieved for each of the methods described above. All the data were inspected and compared thoroughly and the records correlated well. A NH stretch at 3184 cm^{-1} and a C=O stretch at 1655 cm^{-1} were observed in the IR spectrum. The ^{1}H NMR spectrum showed two aromatic C–H singlet signals at 7.57 and 6.68 ppm (for C–5,8); two OCH_3 singlet signals integrating for three protons at 3.93 ppm; and two CH_2 signals at 3.56 ppm (for C–3) and at 2.92 ppm (for C–4). All the ^{1}H NMR spectrum signals correlated well with the eleven ^{13}C NMR spectrum signals. All the data obtained were in good agreement with the literature.[69,156]

The preferred method for the preparation of lactam **5.3** was the final method described in this Section. The method was shown to be versatile and the lactam could be synthesized in relatively large amounts, ranging from 0.5 to 10 grams. The lactam was used to form the *N*-alkylated thiolactam **5.10**, required for the synthesis of enaminones in *Section 5.4*. Thiolactam **5.2** was prepared for the purpose of making enaminones in *Section 5.5*.

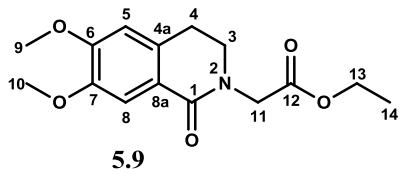
5.3.3 Preparation of ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate

The synthesis of the *N*-alkylated derivatives of previously prepared lactam **5.3** will be discussed in this Section. The *N*-alkylated thiolactam **5.10** was required for the synthesis of enaminones in *Section 5.4*. 6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **5.3** was deprotonated with sodium hydride (60% in paraffin oil) in tetrahydrofuran and ethyl 2-bromoacetate was added to the solution (*Scheme 5.6*).[84,125] Following purification by flash column chromatography (in 60% ethyl acetate in hexane) the product ethyl 2-(6,7-dimethoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.9** was isolated as white crystals in 90% yield.



5.9 **5.10**

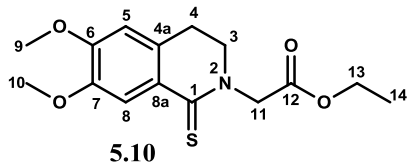
Scheme 5.6 *Reagents and conditions:* i. Ethyl 2-bromoacetate, NaH (60%), THF, 0°C–reflux, 20 h; ii. Lawesson's reagent, toluene, reflux, 18 h.



5.9

Two distinctive signals for the amide C–1 C=O and the ester C–12 C=O were observed at 1644 and 1734 cm^{-1}, respectively in the IR spectrum and at 165.00 and 169.36 ppm, respectively in the ^{13}C NMR spectrum. The acetate moiety of compound **5.9** was observed by C–11 CH_2 singlet signal at 4.31 ppm, a quartet C–13 CH_2 signal at 4.21 ppm and a triplet C–14 CH_3 signal at 1.28 ppm, in the ^{1}H NMR spectrum. The ^{13}C NMR signals for the corresponding acetate carbons were found using the HSQC spectrum; signals were observed at 61.14 ppm (for C–13), 49.21 ppm (for C–11) and 14.15 ppm (for C–14).

Ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.10** was prepared by reacting 2-(6,7-dimethoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.9** with Lawesson's reagent in toluene and heating the reaction mixture under reflux overnight.[76,126] The thiolactam **5.10** was isolated as a yellow oil in 87% yield, following purification by column chromatography.



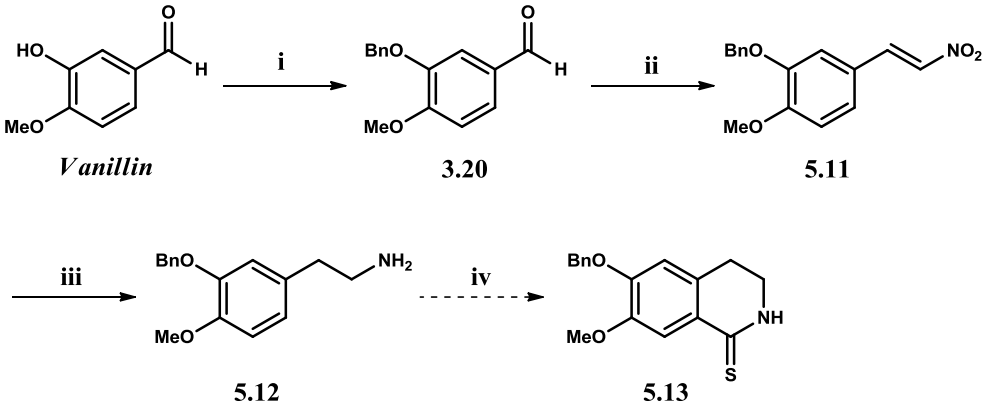
5.10

A comparison of the spectra for lactam **5.9** with thiolactam **5.10** showed that the C–1 signal had significantly changed. In the IR spectrum of thiolactam **5.10**, only one C=O stretch was observed for ester C–12 at 1733 cm^{-1}, however a C=S stretch was observed at 1495 cm^{-1}. Similarly in the ^{13}C NMR spectrum, an ester C–12 C=O signal was noted at 167.89 ppm and a C=S signal was observed at 192.98 ppm. This downfield shift was expected for the sulphur-substituted atom. Similar downfield shifts were observed for C–8, C–3 and C–11, in both the ^{1}H and ^{13}C NMR spectra, owing to their proximity to the C=S bond.

5.3.4 Initial studies for alternative aromatic substituents on the dihydroisoquinoline core

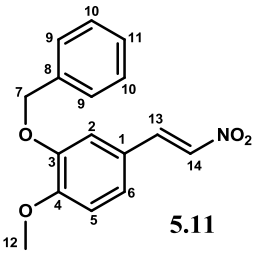
The methodology required for the preparation of 3,4-dihydroisoquinolines was also expanded to include vanillin derivatives, which would allow for the preparation of a range of lamellarins compounds. Variation to the phenacyl halides was briefly described in *Chapter 3* of this thesis, and the benzyl-protected 3-(benzyloxy)-4-methoxybenzaldehyde **3.20** was previously described in the discussion of these vanillin derivatives.

The aldehyde of the benzyl-protected vanillin **3.20** was subjected to a Henry reaction by reacting aldehyde **3.20** with nitromethane and ammonium acetate in glacial acetic acid (*Scheme 5.7*).[36,44] The reaction mixture was heated under reflux for 18 hours and then purified to afford nitroalkene (*E*)-3-(benzyloxy)-4-methoxy-1-(2-nitrovinyl)benzene **5.11** as a bright yellow powder in 90% yield.



Vanillin **3.20** **5.11** **5.12** **5.13**

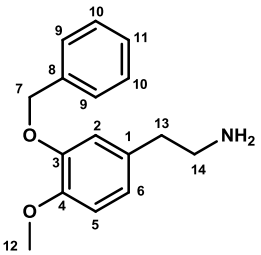
Scheme 5.7 *Reagents and conditions:* i. BnBr, K_2CO_3, acetone, 70°C, 18 h; ii. CH_3NO_2, NH_4OAc, AcOH, 120°C, 18h; iii. $LiAlH_4$, THF, 0–80°C, 20 h; iv.a. CS_2, Et_3N, CH_2Cl_2, 0°C–rt, 1 h; iv.b. $C_3H_5ClO_2$, Et_3N, 0°C–reflux, 2h then PPA, 80°C, 4 h.



5.11

The formation of nitroalkene **5.11** was demonstrated by a NO_2 stretch at 1511 and 1386 cm^{-1} in the IR spectrum; by alkene C–13,14 CH signals at 7.91 and 7.51 ppm, in the ^1H NMR spectrum, with corresponding ^{13}C NMR signals at 139.31 and 136.15 ppm. The alkene C–13 and C–14 CH signals were observed as doublets with *J* values of 13.6 Hz, suggesting the compound was isolated as the *E*-isomer. The HRMS of (*E*)-3-(benzyloxy)-4-methoxy-1-(2-nitrovinyl)benzene **5.11** was in good agreement with the expected value. All data obtained were in good agreement to literature values.[157]

Finally, a reduction of the nitro to an amine, and the reduction of the double bond were carried out by reacting (*E*)-3-(benzyloxy)-4-methoxy-1-(2-nitrovinyl)benzene **5.11** with lithium aluminium hydride in tetrahydofuran.[158] The product 2-[3-(benzyloxy)-4-methoxyphenyl]ethanamine **5.12** was isolated as a pale orange solid in 91% yield.



5.12

The formation of reduced product **5.12** was confirmed through changes observed in the R_f values and melting points when compared to nitroalkene **5.11**. The R_f for the nitroalkene **5.11** was calculated as 0.63, in 30% ethyl acetate in hexane mobile phase, whereas the R_f for amine **5.12** was calculated as 0.11 in the same solvent system, which is expected for the polar amine. The melting point of nitroalkene **5.11** was found to be 106–110°C, whereas amine **5.12** had a value of 43–46°C. In the IR spectrum, distinctive N–H stretches were observed at 3361 and 1510 cm^{-1}. A NH_2 singlet

integrating for two protons was also observed at 3.71 ppm in the ^{1}H NMR spectrum. The formation of the saturated bond was corroborated by C–13 and C–14 CH_2 triplet signals at 2.85 and 2.75 ppm, each integrating for two protons, in the ^{1}H NMR spectrum. These signals were also observed in the ^{13}C NMR spectrum at 43.45 and 39.28 ppm. Analysis of 2-[3-(benzyloxy)-4-methoxyphenyl]ethanamine **5.12** by HRMS showed a molecular ion peak of 258.1499, with a calculated exact mass of 258.1495.

Regrettably due to the time constraints of the project, no further reactions were attempted. However, isoquinoline compound **5.13** could in principle be made using the previously described methods for forming thiolactams[144,146] and lactams[148-150] with amines. Deprotection of the benzyl group would be carried out at a later stage of the synthesis toward lamellarins, using hydrogen gas and a 10% palladium on carbon catalyst to perform the hydrogenation.[111]

5.4 Attempted synthesis of lamellarins with ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate

The methodology for the synthesis of enaminones with *N*-alkylated amines was discussed in the model study for the synthesis of pyrrolizinone, indolizinone and pyrroloazepinone analogues in *Chapter 4* of this thesis. These enaminones were then subjected to an acid-induced ring closure using silica gel, to form the pyrrole ring and subsequent tetracyclic structure. The mechanism was also discussed to ascertain a better understanding of how the pyrrole ring was formed under these conditions. The method will be extended in this Section to encompass the isoquinoline structures and in turn produce the sought-after pentacyclic lamellarins. Finally, bromination and Suzuki-Miyaura coupling reactions, also discussed in the previous Chapter, will be carried out in attempts to complete the synthesis of the lamellarin alkaloid.

5.4.1 Preparation of *N*-alkylated enaminones

The methodology for each intermediate enaminone in this Section will be described, owing to the particularly unique aspects that were essential to the optimization of each enaminone synthesized. The synthesis of the isoquinoline enaminones was more challenging than for the

previously described pyrrolizine precursors, and the difficulties met when preparing the indolizine enaminones were paralleled. This led to the assumption that the six-membered ring posed some steric and electronic complications. No mesylated phenacyl halides will be discussed in this Chapter as their requirement in the synthesis was previously shown to be unnecessary. Only the simple commercially available phenacyl bromide, *ortho*-substituted hydroxyl phenacyl halides 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10** and 1-(2-hydroxy-4,5-dimethoxyphenyl)-2-iodoethanone **3.18**, and benzoin-derived phenacyl halide 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27**, will be discussed (*Figure 5.7*).

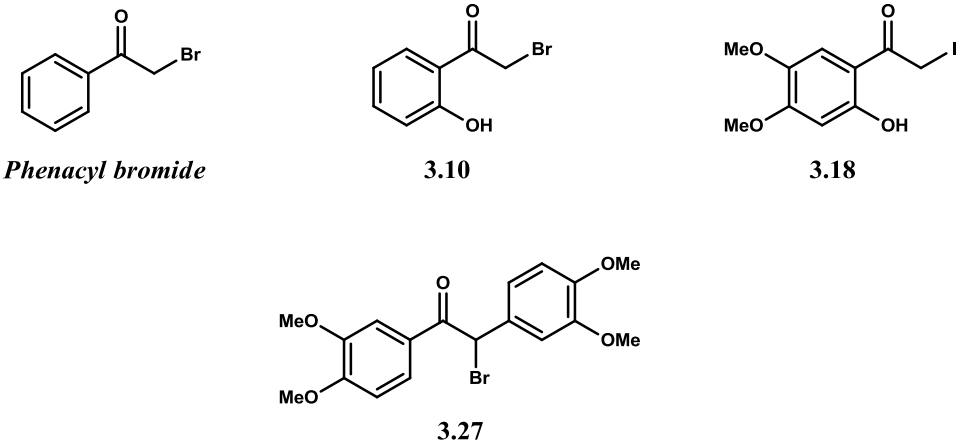
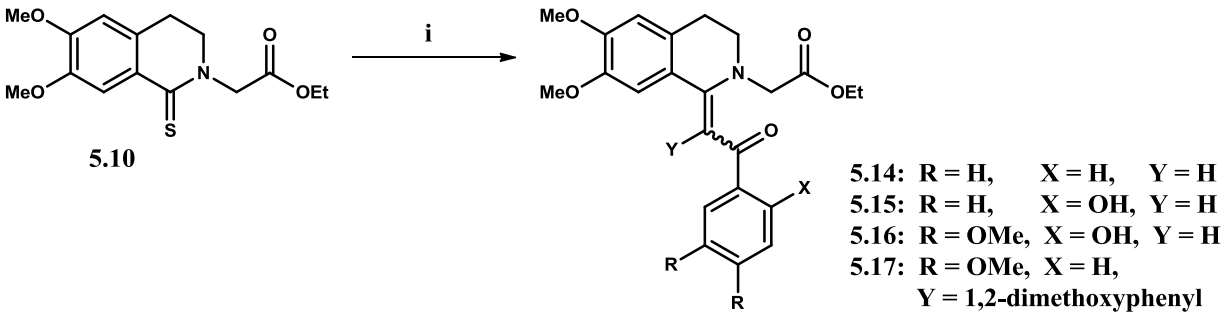


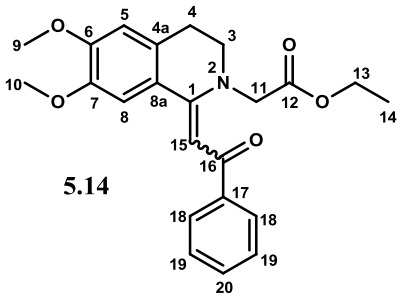
Figure 5.7: Phenacyl bromides used in the Eschenmoser sulphide contraction with isoquinoline-2-thiones.

Thiolactam ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.10** was dissolved in a minimum of acetonitrile with phenacyl bromide and sodium iodide (*Scheme 5.8*). The reaction vessel was covered in aluminium foil to avoid light-induced decomposition of the halogenated reagent. The mixture was monitored by TLC, and the thioiminium salt only formed completely after 60 hours of stirring at room temperature. Neither cooler nor warmer conditions worked in improving this outcome. The foil was then removed and the reaction vessel was cooled to 0°C, triphenylphosphine was added to the reaction mixture portionwise and after 15 minutes of stirring triethylamine was added with a second addition of acetonitrile. The reaction mixture was stirred for 21 hours. Following a thorough extraction in ethyl acetate and on occasion diethyl ether, and purification by column chromatography, the product ethyl 2-[6,7-dimethoxy-1-(2-oxo-2-phenylethylidene)-3,4-dihydroisoquinolin-2(1*H*)-yl] acetate **5.14** was isolated as a dark orange oil in 84% yield. Often meticulous extractions and cleaning methods were adopted to remove triphenylphosphine contaminants. Stirring the mixture in non-polar solvents, and even

recrystallization of the contaminant were attempted; however, the problem was highly persistent with regard to these enaminones. The high polarity of the products was the main reason for this ensuing problem. Enaminone **5.14** possessed a calculated R_f value of 0.07 in 50% ethyl acetate in hexane mobile phase. Purification of the product by flash column chromatography was necessary to remove enaminone from the column rapidly to avoid the material from immediately forming the ring closed product (to be discussed in the next section); some decomposition was also noted during the purification procedure.



Scheme 5.8 *Reagents and conditions:* i.a. Phenacyl halide (*Figure 5.7*), NaI, MeCN, rt, 20–70 h; i.b. PPh_3, Et_3N, MeCN, 0°C–rt, 4–20 h.

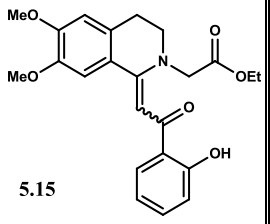
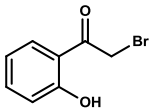
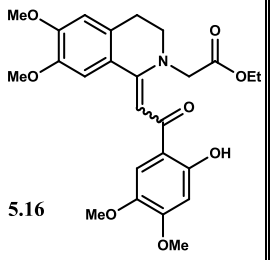
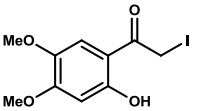
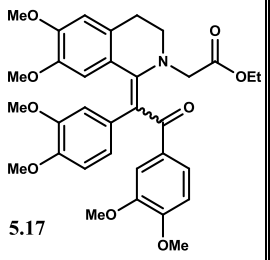
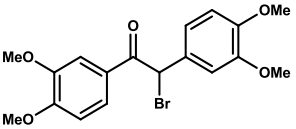


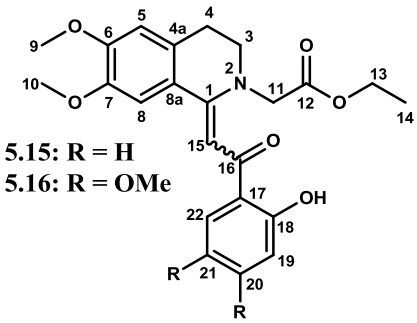
In the ^{1}H NMR spectrum of ethyl 2-[6,7-dimethoxy-1-(2-oxo-2-phenylethylidene)-3,4-dihydroisoquinolin-2(1*H*)-yl]acetate **5.14**, aromatic signals in the range of 7.90 to 7.38 ppm, integrating for five protons, and a broad =CH singlet for C–15 at 5.99 ppm were observed, which suggested that the enaminone was present in the structure. An upfield shift, for the isoquinoline aromatic proton on C–8, from 8.12 ppm (for thiolactam **5.10**) to 7.27 ppm for the enaminone product was observed, owing to the extended conjugation observed in the structure, expanding the electron cloud density throughout the entire structure and causing a slight shielding effect. The ^{13}C NMR spectrum substantiated the observations made in the ^{1}H NMR spectrum: ketone C–16 and ester C–12 C=O signals at 185.88 and 169.94 ppm, C–17 quaternary signal at 125.84 ppm, aromatic C–H C–18,19,20 signals at 128.45, 128.09, 127.68 ppm, and C–15 =CH signal at 91.18 ppm, were all identified. All the data were in good agreement with the previously examined thiolactam starting material **5.10**. No conclusions could be drawn on the configuration of these

enaminones. The NOESY spectrum was ambiguous, although through space interactions between H–11 and H–15 were observed, which suggested the *E*-isomer was more likely to have formed.

Table 5.1 summarizes the experimental adaptations and outcomes of the remaining enaminone products, **5.15**, **5.16** and **5.17**. Ethyl 2-{1-[1,2-bis(3,4-dimethoxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate **5.17** was an interesting variant in the synthesis, because the final bromination and Suzuki coupling reaction would be unnecessary and the number of steps in the synthesis would be reduced, optimizing the overall synthesis. The concept for the design of compound **5.17** was inspired by observations made when surveying a synthesis by Junjappa and co-workers.[130] This will be discussed more comprehensively in *Section 5.5*, owing to its direct relevance to the Section.

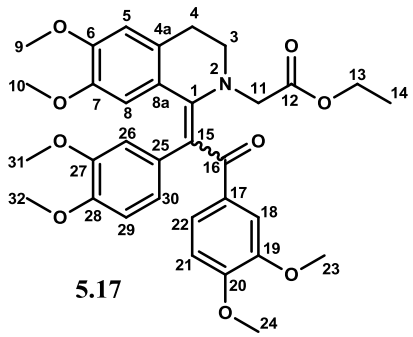
Table 5.1: Selected reaction conditions and reagents for the preparation of *N*-alkylated dihydroisoquinoline enaminones

Product	*Phenacyl halide used*	*Reaction time for salt formation*	*Reaction time for sulphur extrusion*	*Yield and appearance*
 **5.15**	 **3.10**	67 hours	20 hours	32% Bright yellow oil
 **5.16**	 **3.18**	20 hours	4 hours	66% Yellow-orange gum
 **5.17**	 **3.27**	45 hours	18 hours	68% Bright yellow solid



An unmistakeable OH peak was observed in the IR spectrum at 3051 cm^{-1} and in the ^{1}H NMR spectrum at 13.80 ppm, for ethyl 2-{1-[2-(2-hydroxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate **5.15**. Similar observations were made for ethyl 2-{1-[2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate **5.16**, with an O–H stretch at 3056 cm^{-1} in the IR spectrum, and a singlet signal at 14.06 ppm, in the ^{1}H NMR spectrum. In the aromatic region, for the ^{1}H NMR spectrum of the *ortho*-substituted enaminone **5.15**, two doublet of doublet signals for C–19 and C–22 Ar–H signals at 7.73 and

6.92 ppm, and two doublet of doublet of doublet signals for C–20 and C–21 Ar–H signals at 7.33 and 6.81 ppm, were identified. The aromatic region for tetrasubstituted enaminone **5.16** was identified by two singlet signals at 7.31 and 6.46 ppm, for C–22 and C–19 Ar–H signals, respectively. Both enaminone **5.15** and **5.16** showed characteristic singlet signals in the ^{1}H NMR spectrum for C–15 =CH at 6.01 and 5.88 ppm, respectively, with corresponding signals, in the ^{13}C NMR spectrum for C–15 at 88.60 and 88.59 ppm, respectively. All data correlated well when compared to starting material **5.10** and enaminone **5.14**.



5.17

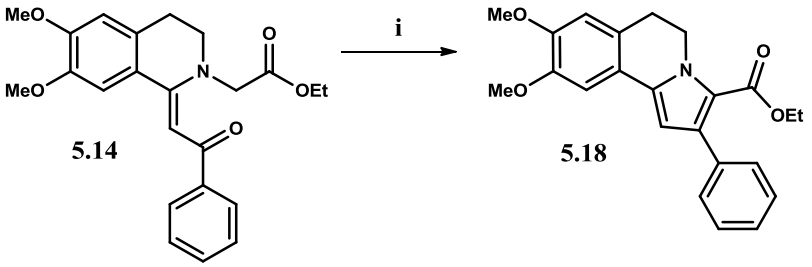
In the analysis of the ^{1}H NMR spectrum of ethyl 2-{1-[1,2-bis(3,4-dimethoxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate **5.17**, two multiplet signals, both integrating for three protons, were observed in the aromatic region, two singlet signals for isoquinoline aromatics C–5 and C–8 were also noted. Six methoxy signals, integrating for three protons each, were also observed in the ^{1}H NMR spectrum. Similar signals in the ^{13}C NMR spectrum substantiated these findings suggested that the enaminone had formed. The vast number of quaternary signals in compound **5.17** caused some difficulties in interpreting the structure. However, the evidence discussed does confirm that enaminone **5.17** was produced. Moreover, the analysis by high resolution mass spectrometry found the molecular ion peak (591.2471) in good agreement to the expected value (591.2468). However, although the compound appeared to be a single geometric isomer, its configuration could not be determined.

5.4.2 Pyrrole formation through silica gel-mediated ring-closure

The formation of the pyrrole ring, with silica gel as an acid catalyst, was discussed in *Chapter 4*, with regard to the synthesis of tetracyclic pyrrolizinone, indolizinone and pyrroloazepinone systems.

The method was initially tested on the simplest enaminone, ethyl 2-[6,7-dimethoxy-1-(2-oxo-2-phenylethylidene)-3,4-dihydroisoquinolin-2(1*H*)-yl] acetate **5.14**. The ring closure was carried out both conventionally and using microwave conditions. A slurry of silica gel (particle size 0.063–0.2 mm, mesh 70–230, 5–10 times the mass of the starting material) and

xylene was added to the enaminone to afford the pyrrole product, ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.18**, in 73% yield, shown in *Scheme 5.9* below. The proposed mechanism for these enaminones was established during the model study for the synthesis of pyrrolizines in *Chapter 4*, and so we expected the enaminone to act as an electrophile. *Figure 5.8* illustrates the expected mechanism with the isoquinoline system.



Scheme 5.9 *Reagents and conditions:* i. Silica gel, xylene, µw (150 W, 180°C, 30 min).

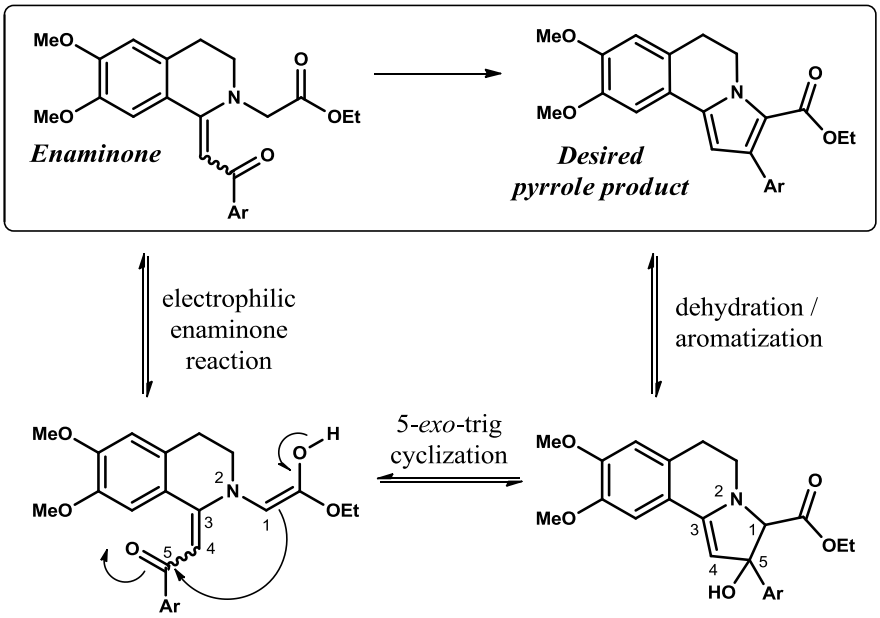
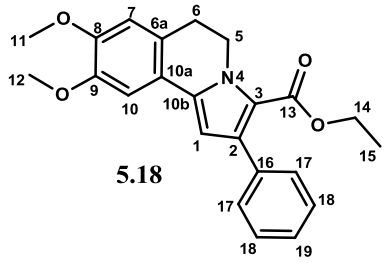


Figure 5.8: Proposed mechanism for the pyrrole ring-closure based on previously discussed pyrrolizine systems.

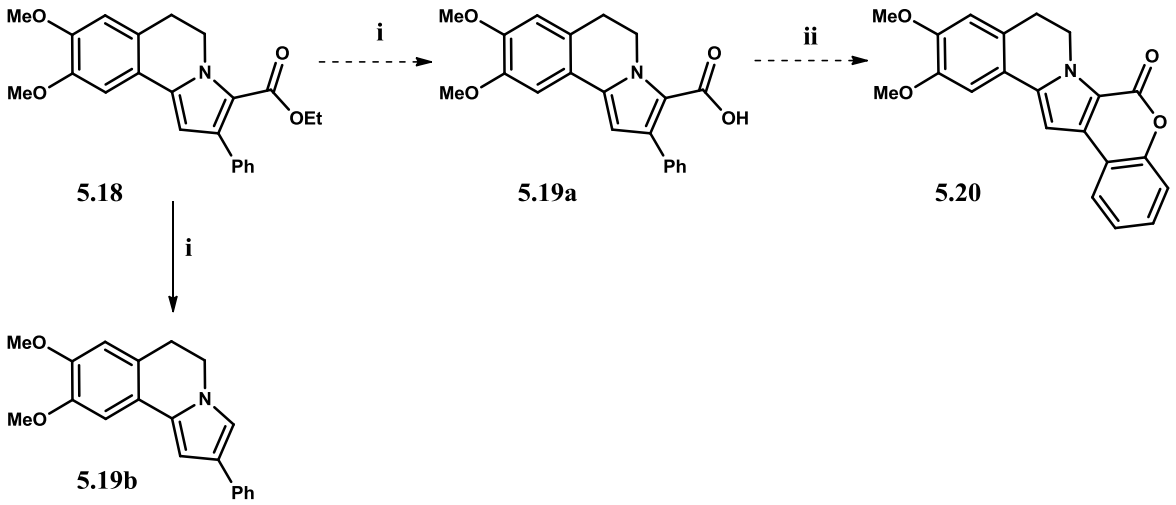


5.18

In the ^{1}H NMR spectrum of ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.18**, a shift in the C–1 =CH signal from 5.99 ppm (for enaminone **5.14**) to 6.47 ppm (for pyrrole **5.18**) for the singlet signal was expected, owing to the deshielding effect of the proton by the electrons of the aromatic ring. The acetate CH_2 singlet observed in the starting material was no longer present. The isoquinoline signals were all present in the ^{1}H NMR spectrum, all showing some downfield shifting, most probably because of the additional pyrrole ring in conjugation with the adjacent aromatic systems. The ^{13}C NMR spectrum also showed a change in the C–1 =CH signal from 91.18 ppm (for enaminone **5.14**) to 105.91 ppm (for pyrrole **5.18**). The carbonyl for the ketone in enaminone **5.14** at δ 185.88 ppm was missing, leaving only the ester C=O at 161.91 ppm (for pyrrole **5.18**), which coincides with a carboxylate in a benzylic position. The HRMS for the pyrrole product **5.18** showed a molecular ion peak at 378.1707, with a calculated exact mass of 378.1706. Isoquinoline pyrrole **5.18** was then compared to its direct pyrrolizine analogue **4.29** (examined and discussed in *Chapter 4*), and the pyrrole C–1 =CH proton signal and the carboxylate C–13 C=O carbon signal were observed at 5.94 ppm and 161.37 ppm, respectively. Similarly, a comparison of previously prepared indolizine **4.38** showed that the data were in good agreement, although the data for indolizine **4.39** still eluded us at this stage and we hoped to gain some insight into this mystery compound.

An investigation into a new method for the introduction of the lactone ring in simple systems, such as compound **4.29**, was discussed previously in *Chapter 4, Section 4.7*. We attempted a saponification of the carboxylate, using our newly formed isoquinoline pyrrole **5.18** (*Scheme 5.10*).[143,159] The carboxylate was thus reacted with potassium hydroxide in methanol (10 M solution). Analysis of the crude product using ^{1}H NMR spectroscopy showed that the carboxylic acid **5.19a** seemed to have formed as judged by the loss of the ester signals. However, several attempts to repeat the reaction appeared to yield only decarboxylated product **5.19b**. Since the carbonyl signal had vanished entirely from the ^{13}C NMR spectrum, and there appeared to be two pyrrole singlets at 6.70 ppm (overlapping) in the ^{1}H NMR spectrum, it was clear that product **5.19b** had formed. The ^{1}H and ^{13}C NMR spectra for compound **5.19b** are shown in *Figure 5.9*. The reaction was then attempted using various saponification reactions, such as sodium hydroxide,[160] lithium iodide[161] and even chlorotrimethylsilane and sodium iodide,[162] using a range of solvents under varying reaction

conditions. Hydrolysis was also attempted using hydrochloric or sulphuric acid and hydrogen bromide.[163] Transfer catalysts[164,165] and lipase enzymes[166,167] were also attempted to afford the saponification/hydrolysis of carboxylate **5.18** to carboxylic acid **5.19a**. None of these attempts at what should have been a textbook hydrolysis proved to be successful! Regrettably, the preparation of carboxylic acid **5.19a** and the subsequent radical reaction with lead(IV) acetate (*Scheme 5.10*),[36,52,53,141,142] to provide the expected pentacylic structure and lamellarin analogue **5.20**, was abandoned.



Scheme 5.10 *Reagents and conditions:* i. KOH, MeOH, 100°C, 4 h; ii. $Pb(OAc)_4$, EtOAc, 80°C, 18 h.

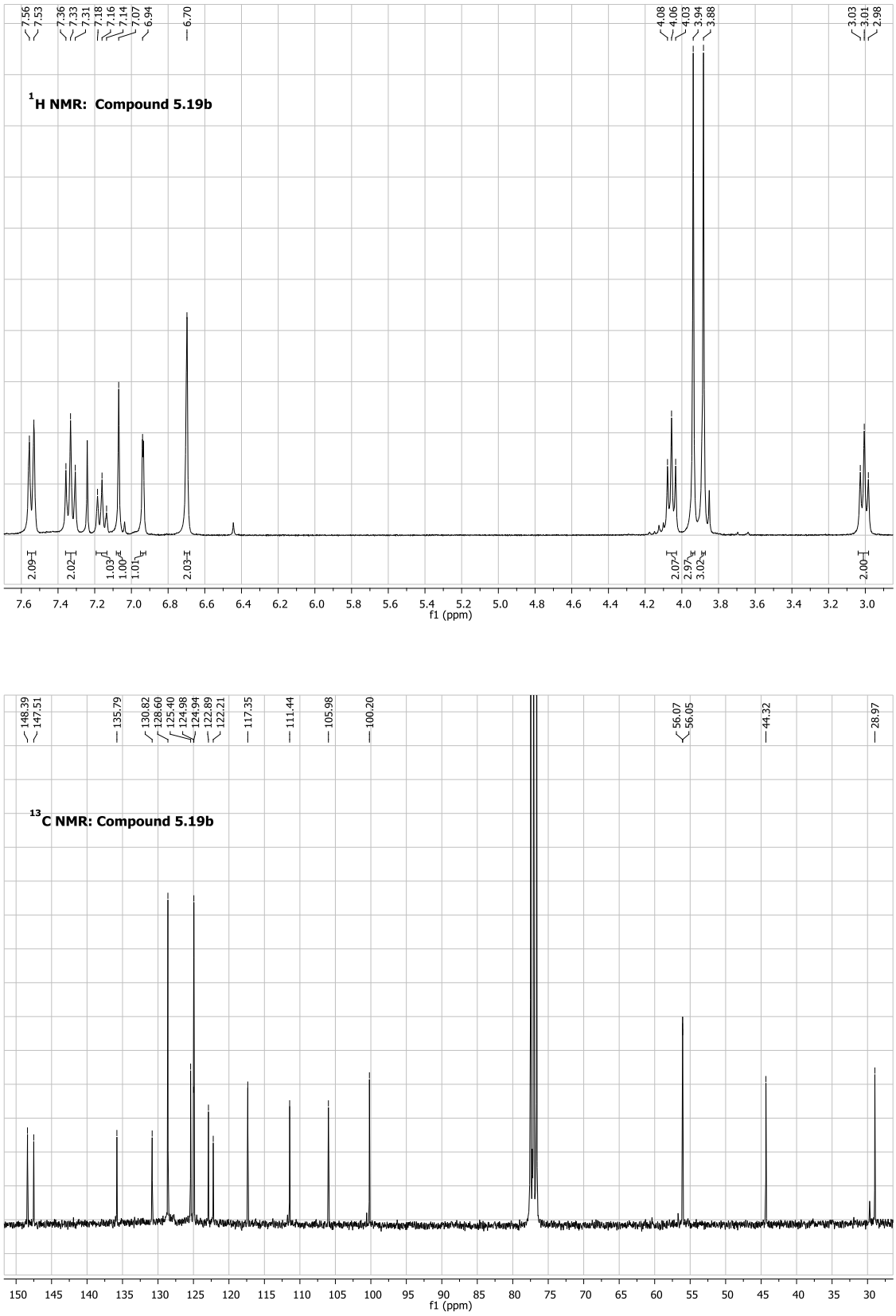
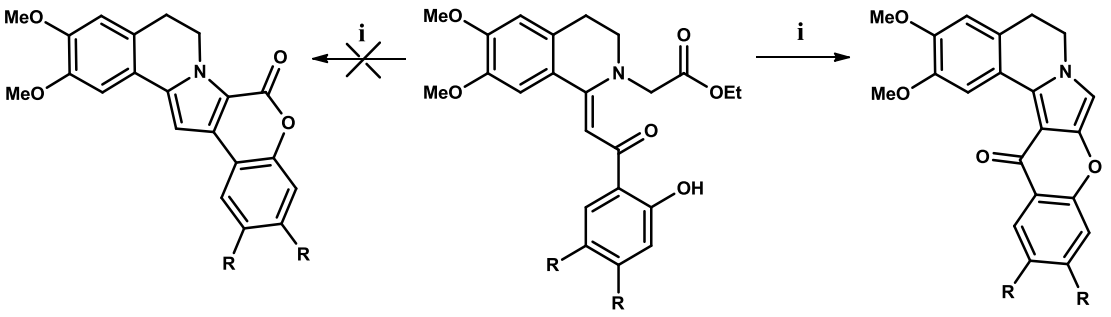


Figure 5.9: ^{1}H and ^{13}C NMR spectra for 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline **5.19b**.

The synthesis of pyrroles **5.22** and **5.23** (*Scheme 5.11*), using the silica gel method, from enaminones **5.15** and **5.16**, respectively, was undertaken in an attempt to produce pentacyclic lamellarins and their analogues through spontaneous lactonization (as observed in the pyrrolizine, indolizine and pyrroloazepine systems in *Chapter 4*). The reactions were problematic but some product was isolated. However, the results obtained were unexpected and when compared to the simpler tricyclic compound **5.18** (and related pyrrolizine pyrrole products), although they possessed certain structural similarities, some distinctive discrepancies in the results were observed. Furthermore, the results for the elusive indolizine product **4.39**, compared well with the newly prepared isoquinoline products, which we later showed to be **5.22** and **5.23**. At this stage of the project, the correct structure of these compounds was still not entirely certain. Subsequently, brominations and Suzuki-couplings were attempted on products **5.22** and **5.23**; these will be discussed in the next Section. However, mention of the reactions at this point is necessary as the identification of the actual structures was only verified once a crystal structure of the final Suzuki-Miyaura product 8-(3,4-dimethoxyphenyl)-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.28** (prepared from enaminone **5.15**) was assigned. The mechanism and structures for the remainder of the synthesis following this route will therefore be based on the structures (**5.22** and **5.23**) actually obtained (see Section *5.4.3* for further details). The mechanism in *Figure 5.10* illustrates the formation of the ring-closed product when the isoquinoline enaminone acts as a nucleophile rather than an electrophile.



5.20: R = H
5.21: R = OMe

5.15: R = H
5.16: R = OMe

5.22: R = H
5.23: R = OMe

Scheme 5.11 *Reagents and conditions:* i. Silica gel, xylene, µw (150 W, 180°C, 30 min).

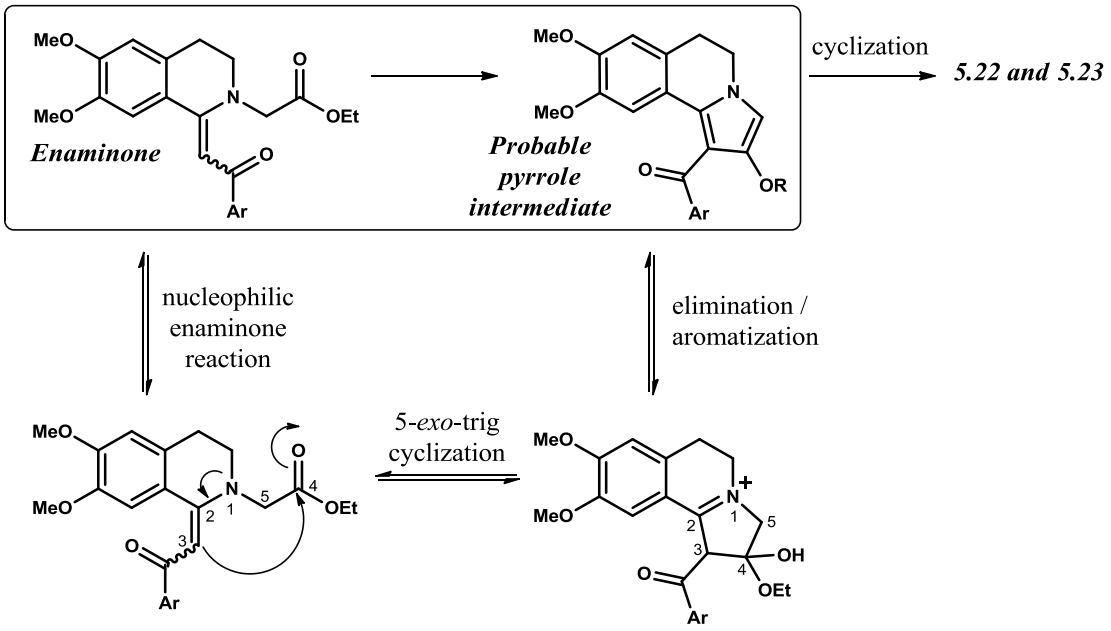
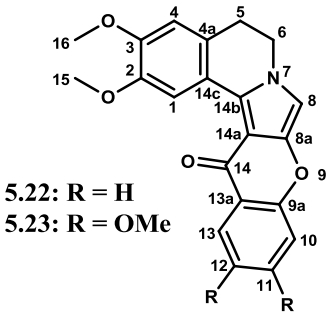


Figure 5.10: Proposed mechanism for the pyrrole products formed with isoquinoline enaminones **5.15** and **5.16**, using the silica gel method.



5.22: R = H
5.23: R = OMe

In the ^{1}H NMR spectrum of ring-closed products **5.22** and **5.23**, the pyrrolic C–8 proton singlet was observed at 6.80 ppm and 6.79 ppm, respectively. Correspondingly, ^{13}C NMR signals for C–8 were observed at 96.11 ppm and 95.36 ppm, which is expected for the pyrrole formation. A comparison of the pyrrolic =CH for compound **5.18** shows that the proton and carbon signals, 6.47 ppm and 105.91 ppm, respectively, differ, which is expected because of the proximity of the =CH to the pyrrole nitrogen. In the ^{1}H NMR spectrum for **5.22**, the aromatic region showed three aromatic singlet signals, integrating for three protons, for C–1,4 and 8. The remaining four aromatic protons in the region of 7.81–7.28 ppm were assigned to aromatic protons C–10,11,12 and 13. Analysis of the NOESY spectrum for product **5.22** showed that pyrrole C–8 C–H experienced through space interactions with the isoquinoline C–6 CH_2 and an aromatic doublet of doublets C–10, which validated the structural assignment. For pyrrole **5.23**, five aromatic singlet signals were accounted for in the aromatic region of the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, carbonyl C–14 was observed at 173.78 and 174.36 ppm, for pyrrole systems **5.22** and **5.23**, respectively. If the desired lactone of the lamellarin system had formed, the expected carbonyl signal should have been in the range of 154 to 158 ppm, which was observed with pyrrolizine products **4.32** and **4.38** as well as tricyclic isoquinoline

5.18. Analysis of pentacyclic product **5.22** by mass spectrometry afforded an accurate mass of 348.1244 with an expected mass of 348.1237; that for pentacyclic product **5.23** was also in good agreement with the expected value.

The NMR spectra of isoquinoline products **5.18**, **5.22** and **5.23** were thoroughly compared to the previously prepared pyrrolizines, indolizines and pyrroloazepines from *Chapter 4* (*Figure 5.11*), owing to the methodology being adapted from the model project. Pyrrolizines **4.29**, **4.32** and **4.33** showed no correlation to pentacylic isoquinolines **5.22** and **5.23** but related well to tricyclic isoquinoline **5.18**. Furthermore, the previously prepared indolizine **4.38** compared well to product **5.18**, and these compounds were confirmed as lactones and lactone precursors, whereas indolizine **4.39** and pyrroloazepine **4.40** more closely resemble products **5.22** and **5.23**, which confirmed these compounds as chromenones. It was therefore concluded that both lactone- and chromenone-containing products were prepared. The rearrangement of the enaminones into the chromenone seems to be highly influenced by the size of the ring. The five-membered pyrrole enaminones formed the lactone exclusively and the yields reported were predominantly high. The six-membered piperidine enaminones produced both the lactone and chromenone units with the lactone forming in slightly higher yields than the chromenone. Finally, only the chromenone was isolated when the seven-membered azepane enaminone was submitted to the ring-closure. Nevertheless, further diversification of the piperidine and azepane enaminones would assist in drawing more accurate conclusions on the matter of ring size as an influence to the ring-closure outcome. The isoquinoline systems are slightly more perplexing, however. The low yields of chromenone products **5.22** and **5.23** suggests that the lactone could have been produced during the reaction but was either converted to a water-soluble product and discarded after work-up, or it decomposed during the purification process. The presence of the bulkier hydroxyl-containing 'phenacyl' on the enaminone that underwent ring closure to form these chromenone compounds could have also influenced the mechanism of these compounds.

Figure 5.11 illustrates all the related lactone- and chromenone-containing pyrrole products discussed in the project thus far. The products indicated below will be summarized in *Table 5.2*. Selected data will be compared in the table. Significantly, different chemical shifts in the ^{13}C NMR spectrum for the carbonyl in carboxylate pyrroles **4.29** and **5.18** and lactone products **4.32** and **4.38** are compared with the carbonyl in chromenones **4.39** and **5.22** (they are highlighted in bold in *Table 5.2*). Compound numbers and atom numbering indicated in

the table correlate directly to *Figure 5.11*. The atom numbering does not depict that chosen for the remainder of the discussion and is merely indicated for the purposes of the summation. Moreover, the ^{1}H and ^{13}C NMR spectra for simple carboxylate compounds **4.29** and **5.18**, and novel isoquinoline chromenone **5.22** have been given in *Figure 5.12*. The spectra for previously presented compounds **4.32**, **4.38** and **4.39** can be referred to in *Section 4.5.4, Figure 4.14*.

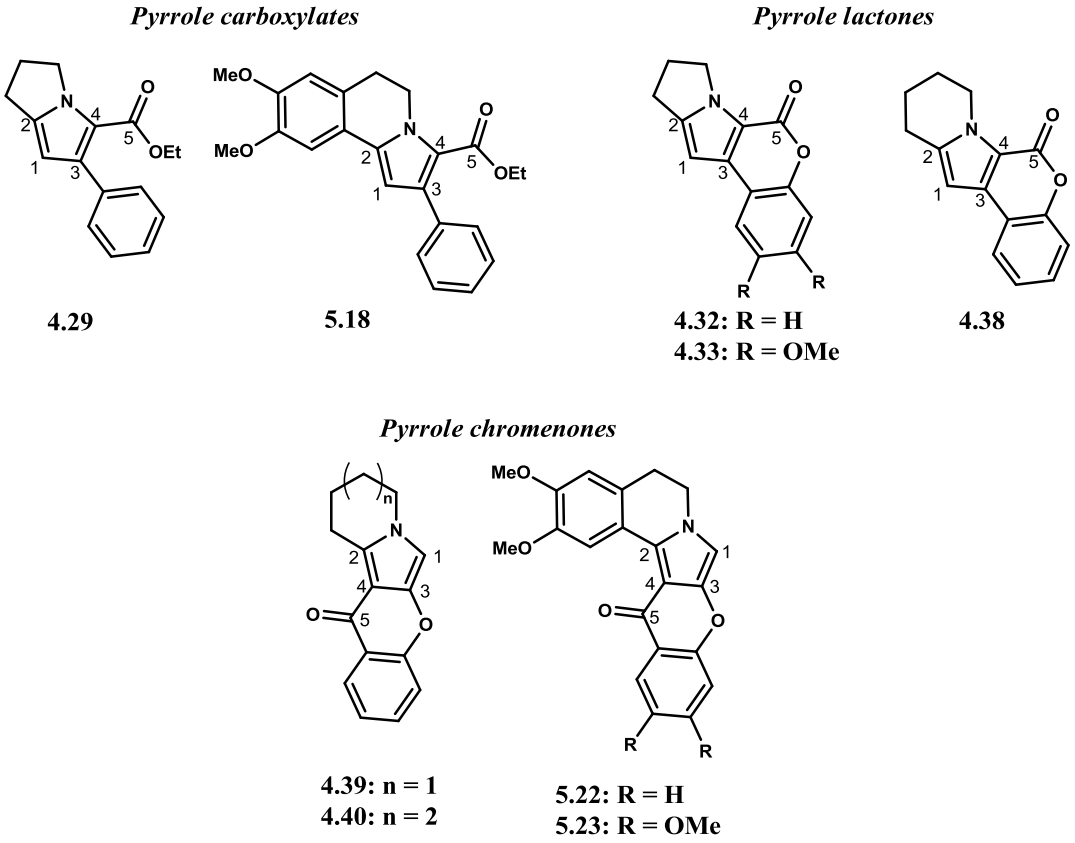


Figure 5.11: A summary of pyrrole products formed throughout the entire project thus far.

Table 5.2: A summary of several pyrrole products prepared comparing selected data.

Carbon number	**Pyrrole Products**					
	Pyrrole carboxylates		**Pyrrole lactones**		**Pyrrole chromenone**	
	4.29	**5.18**	**4.32**	**4.38**	**4.39**	**5.22**
^{1}H NMR Spectrum (ppm):						
C–1	5.94	6.47	6.31	6.38	6.48	6.80
^{13}C NMR Spectrum (ppm):						
C–1	103.51	105.91	94.54	99.47	100.36	96.11
C–2	142.33	136.96	148.96	141.73	145.26	130.59
C–3	136.70	120.80	151.47	115.28	122.77	115.85
C–4	137.40	118.24	134.08	118.03	107.70	117.95
C–5	**161.37**	**161.91**	**155.10**	**155.06**	**175.49**	**173.78**
IR spectrum (cm^{-1}):						
C–5	1675	1682	1692	1696	1705	1696

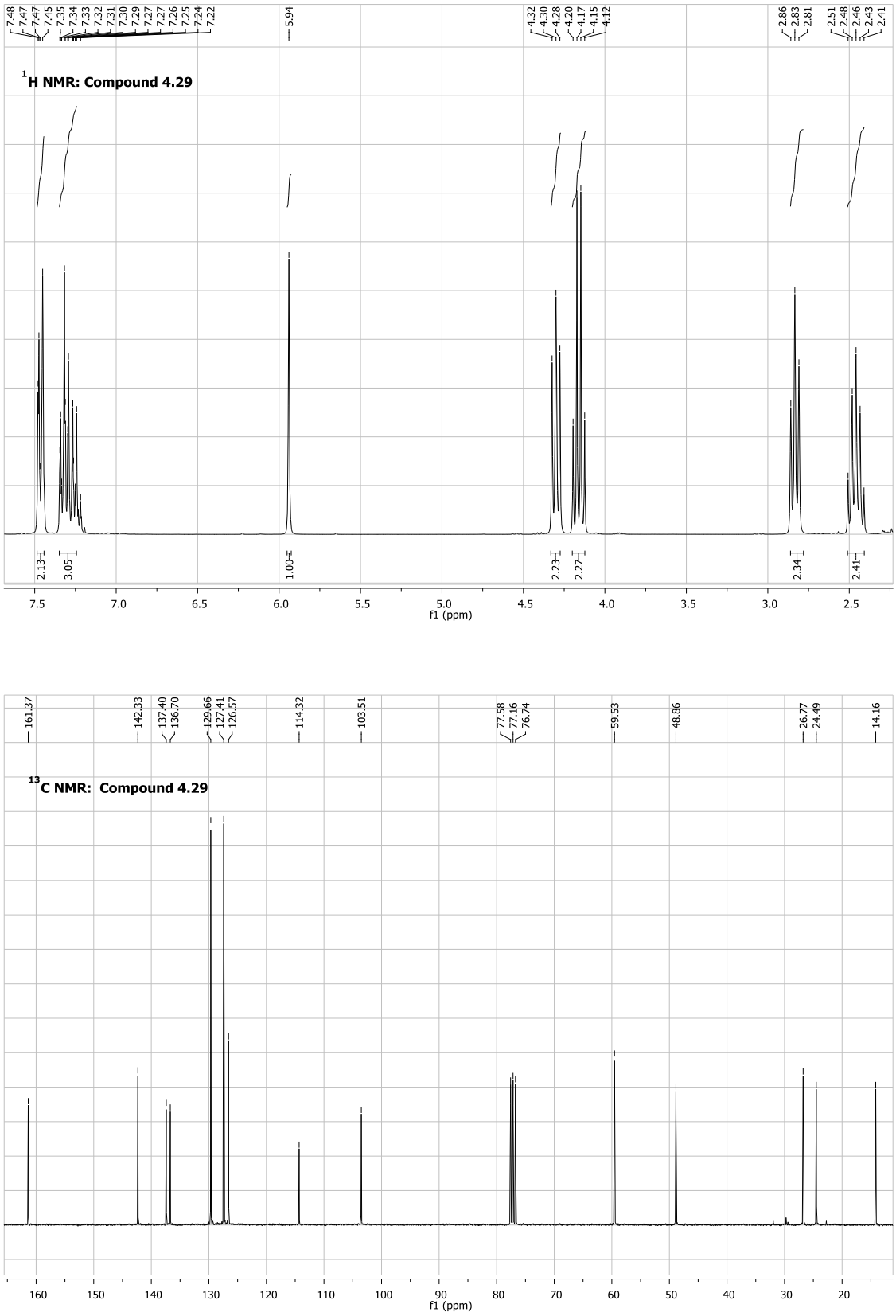


Figure 5.12a: ^{1}H and ^{13}C NMR spectra for ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.29**.

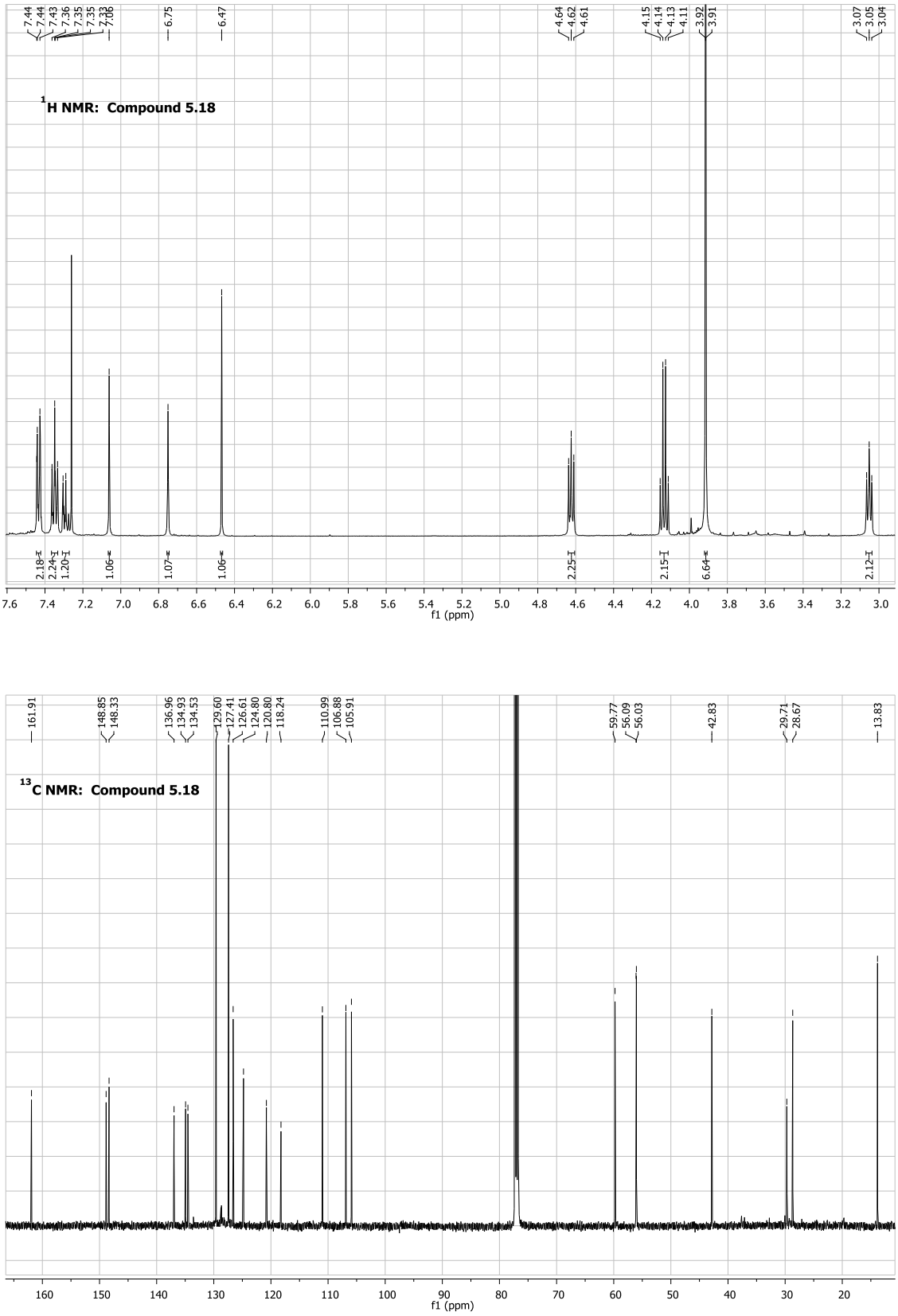


Figure 5.12b: ^{1}H and ^{13}C NMR spectra for ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.18**.

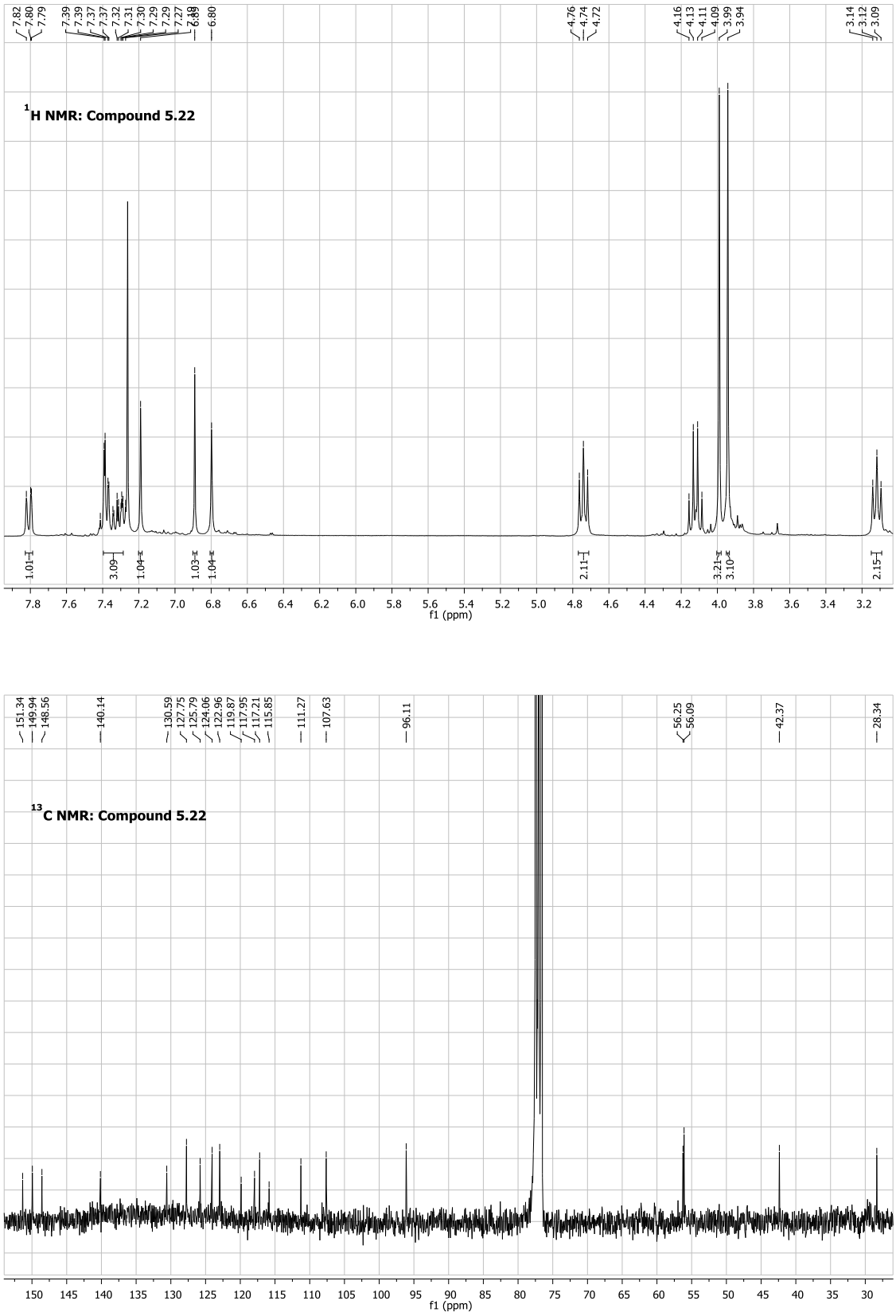
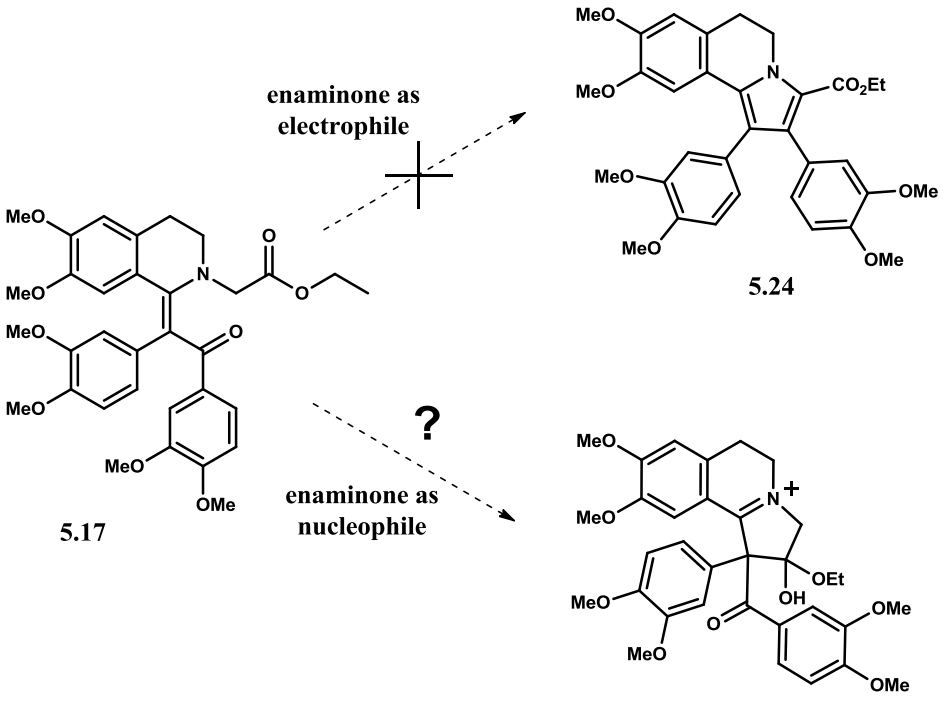


Figure 5.12c: ^{1}H and ^{13}C NMR spectra for 2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.22**.

Finally, the prepared benzoin enaminone **5.17** was also subjected to the ring closure method with silica gel (*Scheme 5.12*). Despite several attempts at forming the pyrrole ring (**5.24**), no product was ever formed, only starting material was recovered or the material decomposed. This suggested that if the enaminone alkene C–H was involved in the mechanism of cyclization, the formation of the pyrrole ring is not possible (shown in *Scheme 5.12*). Further investigation into these benzoin systems is, however, necessary.

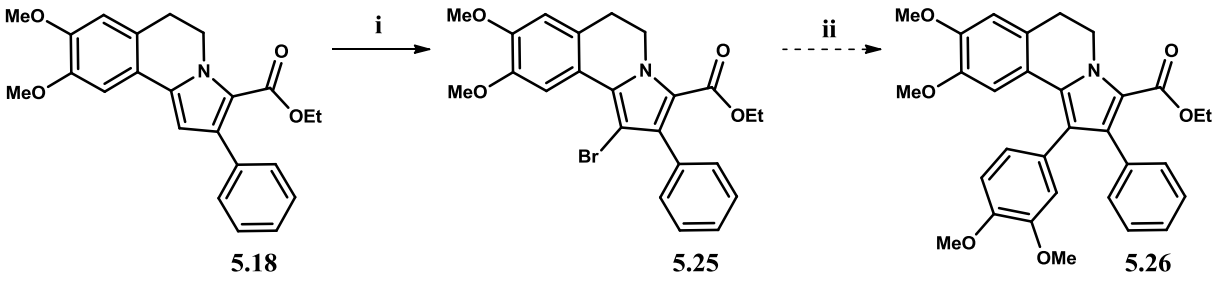


Scheme 5.12 *Reagents and conditions:* Silica gel, xylene, µw (150 W, 180°C, 30 min).

5.4.3 Bromination and Suzuki-Miyaura coupling reactions

The pyrrole products were next subjected to similar bromination and Suzuki-Miyaura coupling reactions to those discussed in *Chapter 4*. The biaryl axis construction was the final step in forming the lamellarin alkaloids and although the products formed were not in fact lamellarins, we decided to complete the synthesis in the hopes of gaining a deeper understanding as to how these compounds work and in an attempt to produce a crystal structure to prove the structure of the molecule. As mentioned previously in *Section 5.4.2*, the structure of the chromenone-containing pyrrole compounds was only confirmed unambiguously once a crystal structure was obtained for one of the Suzuki products.

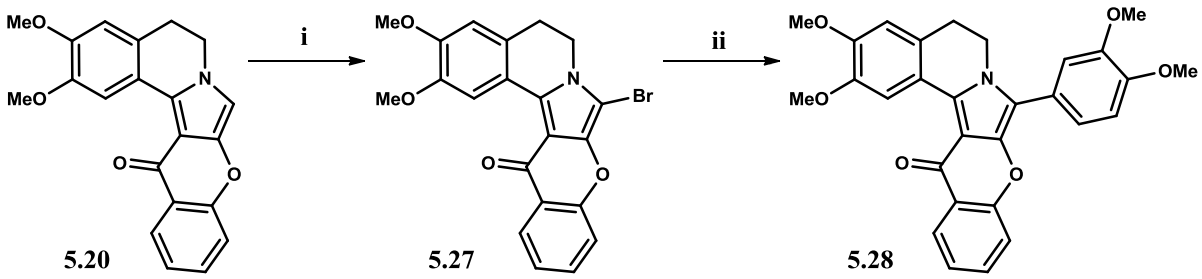
Pyrrole carboxylate **5.18** was brominated with *N*-bromosuccinimide in *N*,*N*-dimethylformamide. The reaction mixture was stirred at 0°C for 3 hours and then at room temperature for 18 hours (*Scheme 5.13*). Following purification by recrystallization from ethyl acetate in hexane, the brominated pyrrole was isolated as a pale off-white powder in 44% yield.



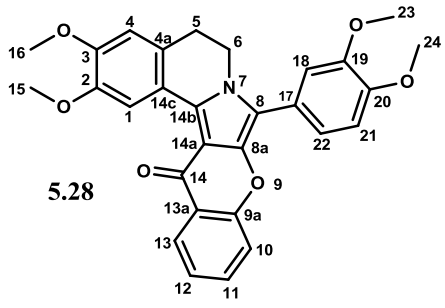
Scheme 5.13 *Reagents and conditions:* i. NBS, DMF, 0°C, 3 h; ii. $Pd(PPh_3)_4$, 3,4-$(OMe)_2C_6H_3B(OH)_2$, $NaHCO_3$, DMF:H_2O (1:1), 150 W, 150°C, 15 min or $Pd(PPh_3)_4$, 3,4-$(OMe)_2C_6H_3B(OH)_2$, CsF, Ag_2O, DME, 80°C, 18 h.

The TLC of the brominated compound showed a spot with an R_f of 0.65 in 50% ethyl acetate in hexane mixture. The starting material was found at 0.68. The completion of the reaction was therefore difficult to monitor and often only starting material was recovered from the reaction mixture. Solvents such as chloroform, dichloromethane and acetone were used in an attempt to ensure that bromination occurred. When the brominated product ethyl 1-bromo-8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.25** was eventually isolated, the absence of the pyrrole C–H singlet was evident in both the ^{1}H NMR and ^{13}C NMR spectrum. A C–Br stretch at 625 cm^{-1} in the IR spectrum indicated the bromination had worked. The product was carried through to the Suzuki reaction. However, several attempts at forming the biaryl product **5.26**, using the Suzuki-Miyaura coupling reaction, proved unsuccessful. Owing to the time constraints of the PhD, the synthesis was abandoned and the synthesis of the pentacyclic systems became the main focus of the project.

In a similar manner, pentacyclic compound **5.22** was brominated to afford 8-bromo-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.27** as a yellow-brown solid in 36% yield (*Scheme 5.14*). Analysis of the ^{1}H NMR spectrum showed the absence of the distinctive pyrrolic proton, a C–Br carbon signal was observed at 103.40 ppm, in the ^{13}C NMR spectrum, which is in the expected range for an aromatic quaternary attached to the electronegative bromine atom. Similarly in the IR spectrum, a C–Br stretch was observed at 560 cm^{-1}. The brominated product **5.27** was then subjected to a Suzuki-Miyaura coupling reaction using 3,4-dimethoxyphenylboronic acid, sodium hydrogen carbonate, and tetrakis(triphenylphosphine)palladium(0) in a *N*,*N*-dimethylformamide and water mixture (1:1). The reaction was irradiated at 150 W in a microwave reactor, at a temperature of 150°C for 20 min. Following purification by flash column chromatography (in 30% ethyl acetate in hexane mixture) and recrystallization from a chloroform, the product 8-(3,4-dimethoxyphenyl)-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.28** was isolated as fine yellow crystals in 57% yield.



Scheme 5.14 *Reagents and conditions:* i. NBS, DMF, 0°C, 3 h; ii. $Pd(PPh_3)_4$, 3,4-$(OMe)_2C_6H_3B(OH)_2$, $NaHCO_3$, DMF:H_2O (1:1), 150 W, 150°C, 15 min.



The TLC of biaryl product **5.28** showed a yellow spot with an R_f of 0.39, whereas the brominated product showed an R_f of 0.54, both in 50% ethyl acetate in hexane mobile phase. In the ^{1}H NMR spectrum of **5.28**, a distinctive downfield shift was observed for three aromatic C–H signals at 9.12, 8.39 and 7.58 ppm for new aromatic signals C–18, 21 and 22. Two additional OCH_3 signals at 4.14 and 3.97 ppm for C–23 and 24 were also observed for the newly inserted aromatic ring. In the ^{13}C NMR spectrum, a downfield shift at 142.69 ppm for the pyrrole C–8 of was observed, which is expected for the attached biaryl carbon signal. Carbonyl C–14 was also observed at 175.04 ppm, which is

expected for chromenone compounds. The distinctive pyrrolic C–H and C–Br shifts for **5.22** and **5.27** at 103.40 and 96.11 ppm, respectively, were no longer present. Finally an XRD structure for our final product **5.28** was obtained (*Figure 5.13*), which illustrated the structure formed from our investigation into the pyrrole formation of these isoquinoline enaminone systems.

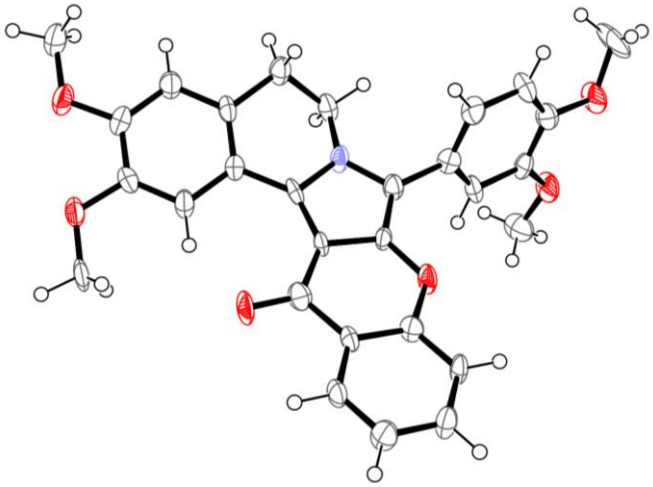
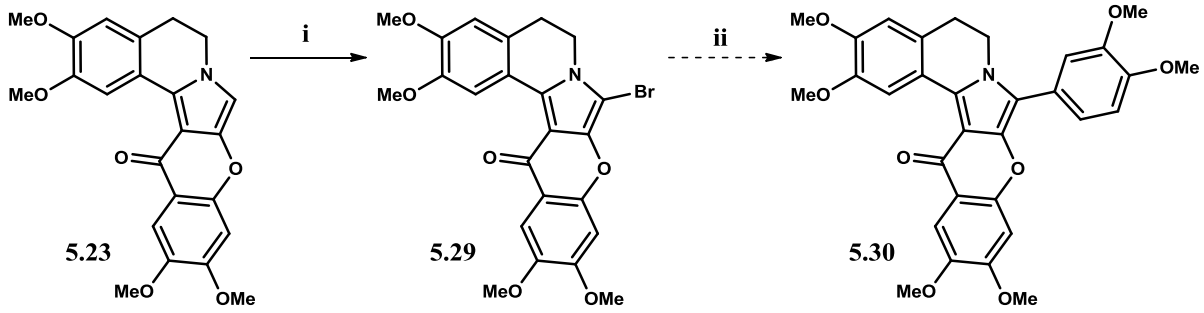


Figure 5.13: An ORTEP diagram for an XRD obtained for our unexpected final product **5.28**.

Data obtained for lamellarin G trimethyl ether[67] were compared to product **5.28**. It was shown that the isoquinoline was almost identical in character; however, the aromatic data did not coincide with the results obtained in our synthesis. The difference in aromatic ring C–10 to 13 was taken into consideration. Lamellarin trimethyl ether has a 3,4-dimethoxy substitution in this ring, and structure **5.30** would be a better model for comparison. However, a comparison of the carbonyl C–14 signals of the lactone to that of the chromenone subunit showed vast differences. For our product **5.28**, the C=O signal was found at 175.04 ppm, whereas lamellarin G trimethyl ether has a C=O signal at 155.48 ppm.[37,56,61]

In order to prepare brominated pyrrole **5.29**, pentacyclic compound **5.23** was brominated using *N*-bromosuccinimide in *N*,*N*-dimethylformamide (*Scheme 5.15*). The product 18-bromo-2,3,11,12-tetramethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.29** was formed, but some contaminants were persistent in the product, owing to the low yields (8%) obtained. However, the pyrrolic CH at 6.79 ppm for starting material **5.23** was absent. In the ^{13}C NMR spectrum, the C–H signal at 95.36 ppm for the starting material had shifted downfield to 105.35 ppm, which was in agreement with the expected C–Br of the product. Unfortunately, attempts at forming the biaryl axis (compound **5.30**) using several

Suzuki reactions were unsuccessful, probably due to the extremely small amounts of material used in the reactions. This was most unfortunate, since it would have been extremely valuable to have a compound that could be compared directly with the lamellarin G trimethyl ether target compound.



Scheme 5.15 *Reagents and conditions:* i. NBS, DMF, 0°C, 3 h; ii. $Pd(PPh_3)_4$, 3,4-$(OMe)_2C_6H_3B(OH)_2$, $NaHCO_3$, DMF:H_2O (1:1), 150 W, 150°C, 15 min or $Pd(PPh_3)_4$, 3,4-$(OMe)_2C_6H_3B(OH)_2$, CsF, Ag_2O, DME, 80°C, 18 h.

The attempted synthesis toward pentacyclic lamellarins was halted at this point. Some favourable and novel compounds were obtained using the *N*-alkylated enaminones, and pyrrole ring-closures were successful in giving pentacyclic systems with the silica gel methodology. We thus decided to attempt an alternative synthesis of the lamellarin alkaloids through an adapted synthesis, which will be described in the next Section.

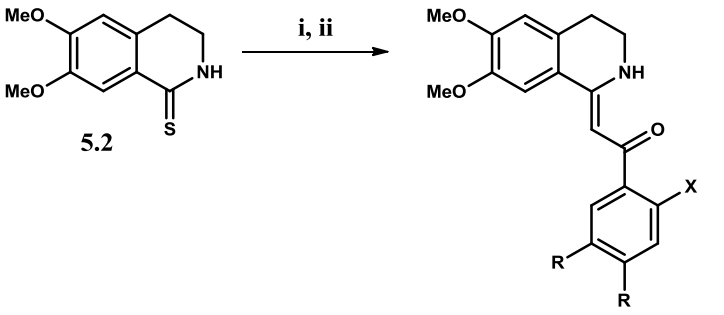
5.5 Attempted synthesis of lamellarins with 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione

The unexpected results achieved for the ring-closure reaction of the *N*-alkylated enaminones in an attempt to produce lamellarins led to the expansion of our synthetic strategy. The synthesis tested on the model systems in *Chapter 4* and used in *Section 5.4* above was therefore slightly modified to include the preparation of unprotected amines in the preparation of enaminone systems. The ring-closure procedure for the formation of the pyrrole and subsequent pentacyclic systems was adapted from the methodology described by Barun, Ila and Junjappa.[130] All other aspects of the designed synthesis remained unaltered.

5.5.1 Preparation of secondary enaminones with unprotected thioamides

The methodology for the preparation of enaminones via 'The Wits Approach' was discussed in *Chapter 4*, although the preparation of secondary enaminones with unprotected N-H groups was not examined. In this Section we explore the way the Eschenmoser sulphide contraction works with one such secondary thiolactam, namely 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2**.

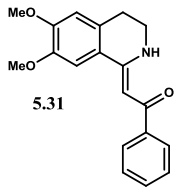
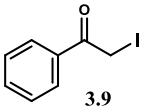
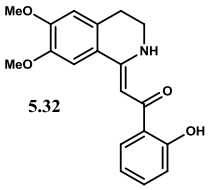
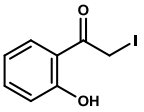
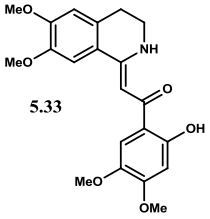
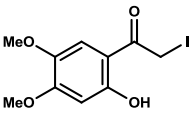
It was discovered through a number of trials that the preparation of the enaminones in this section was rather versatile and afforded the relevant N-H enaminone in good yields. The following methodology was used for the preparation of all the enaminones in this section.[76,128] Thiolactam 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** (described in *Section 5.3.1*) was dissolved in a minimum of chloroform with the relevant phenacyl halide (*see Table 5.3*). The thioiminium salt was formed over 18 hours; the completion of this transformation was monitored by TLC. Triphenylphosphine and triethylamine in chloroform were added dropwise to the opaque salt mixture and the reaction mixture was stirred at room temperature over 24 hours (*Scheme 5.16*). *Table 5.3* below describes the some of the distinguishing physical and chemical properties of the enaminones produced.



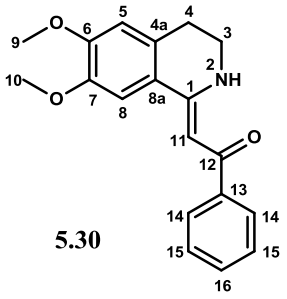
5.31: X = H; R = H
5.32: X = OH; R = H
5.33: X = OH; R = OMe

Scheme 5.16 *Reagents and conditions:* i. Phenacyl halide (*Table 5.3*), $CHCl_3$, rt, 18 h; ii. PPh_3, Et_3N, $CHCl_3$, rt, 24 h.

Table 5.3: Selected reaction conditions and reagents for the preparation of secondary enaminones

Product	***Phenacyl halide used***	***R_f and Melting point***	***Appearance***	***Yield***
 **5.31**	 **3.9**	0.17 (30% EtOAc/Hexane) 135–136°C	Bright yellow crystalline solid	87%
 **5.32**	 **3.12**	0.21 (30% EtOAc/Hexane) 206–208°C	Bright orange solid	72%
 **5.33**	 **3.18**	0.21 (30% EtOAc/Hexane) 209–212°C	Bright orange solid	91%

The interpretation and discussion of enaminone (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1-phenylethanone **5.31** will be carried out comprehensively, since this is the simplest analogue. The remaining enaminones will be discussed based on their specific structural characterisation.


5.30

The presence of the NH was an unambiguous feature in the ^{1}H NMR spectrum for enaminone **5.31**. The NH appeared as a broad singlet, in a significant downfield position at 11.83 ppm in the spectrum. This is a unique feature of these enaminone systems; the downfield shift of the NH suggests that there are strong intramolecular hydrogen-bonding interactions between the NH and the C=O of the attached phenacyl group. This is also a strong indication that enaminone **5.31** exists as the *Z*-isomer. The presence of an N–H stretch at 3174 cm^{-1} in the IR spectrum, substantiated these findings. The IR and ^{13}C NMR spectra both have C=O peaks for the ketone C–12 at 1601 cm^{-1} and 118.40 ppm, respectively. In the ^{1}H NMR spectrum, aromatic signals for the phenyl (C–14, 15, 16) were observed at 8.00–7.38 ppm, integrating for five protons. Additionally, a

distinctive signal at 6.20 ppm in the ^{1}H NMR spectrum and at 86.35 ppm in the ^{13}C NMR spectrum was observed for the C–11 enaminone alkene =CH, another significant feature of these enaminone systems. All other data were compared to the previously prepared thiolactam **5.2**, which supported the findings for enaminone **5.31**. HSQC, COSY and NOESY spectra were used to assist in assigning all hydrogens and carbons for the compound. An XRD structure for enaminone **5.31** was obtained (*Figure 5.14*), which was useful in demonstrating that only the *Z*-isomer was isolated, owing to significant hydrogen bonding observed between NH and C=O of the enaminone. The IR spectrum also confirmed these findings with a =CH bend at 697 cm^{-1}.

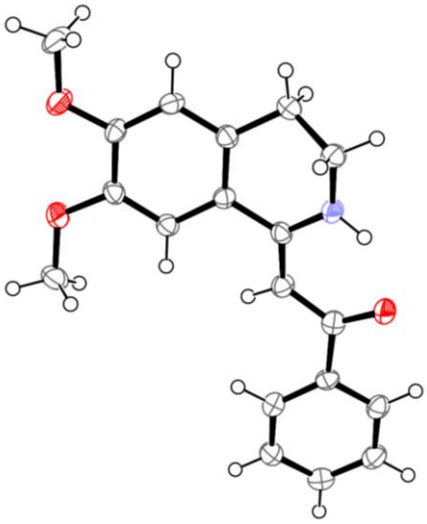
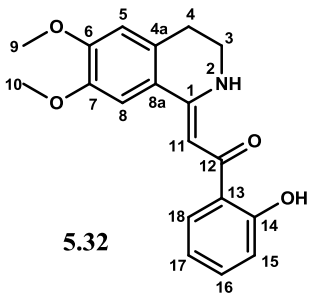


Figure 5.14: An ORTEP diagram of enaminone **5.30** showing hydrogen bonding interactions NH….O=C.



5.32

The results obtained for enaminone (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1-(2-hydroxyphenyl)ethanone **5.32** were compared to enaminone **5.31** and all the data obtained were in good agreement. The presence of an OH was explicit in the IR spectrum with an OH stretch at 3233 cm^{-1}. In the ^{1}H NMR spectrum a broad OH singlet at 13.66 ppm and a N-H singlet at 11.35 ppm, both in highly deshielded positions, suggested that intramolecular hydrogen-bonding to the C–12 C=O of both groups was occurring, and product was thus isolated in the *Z*-geometry. The *ortho*-position of the OH on the aromatic ring contributed to an expected change in the aromatic protons. Two doublet of doublet signals were observed for C–15 and C–18 at 7.73 and 6.92 ppm, and two doublet of doublet of doublet signals were observed for C–16 and C–17 at 7.32 and 7.23 ppm. In the ^{13}C NMR spectrum, a signal at 190.24 ppm was

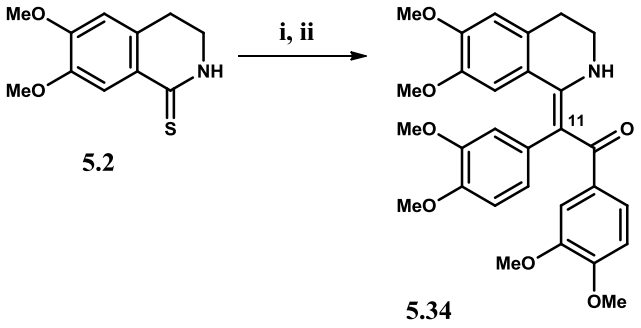
observed for C–12 C=O and a signal at 162.05 ppm was observed for C–14 C–OH, four aromatic signals were also observed for C–15,16,17,18 at 133.21, 127.39, 118.22 and 118.17 ppm. Mass determination by high resolution mass spectrometry was in good agreement with the expected value (325.1308 versus 325.1312).

The IR and ^{1}H NMR spectra for enaminone (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-3-(4-hydroxy-6,7-dimethoxyphenyl)ethanone **5.33** corresponded well with the results observed for the simple *ortho*-hydroxyl aromatic enaminone **5.32** discussed above. The aromatic region was altered due to the presence of the 3,4-dimethoxy group on the aromatic ring; this corresponded with the two proton signals in the ^{1}H NMR spectrum at 7.21 and 6.80 ppm for C–15 and 18. Four methoxy groups, integrating for three protons each, appeared at 3.98 and 3.88 ppm, attesting to the addition of the new aromatic group onto enaminone **5.33**. Similarly in the ^{13}C NMR spectrum, signals for quaternary carbons C–16 and C–17 associated with the new methoxy groups were identified at 145.70 and 141.25 ppm. Methoxy signals for C–19 and C–20 were also observed at 57.58 and 57.41 ppm. Once again the OH and NH signals (at 13.85 and 11.24 ppm, respectively) were observed in a downfield position in the ^{1}H NMR spectrum, suggesting strong intramolecular hydrogen-bonding to the C=O and Z-geometry of the compound. The HRMS showed a molecular ion peak at 385.1523, which was in agreement with the expected mass of 385.1525 (molecular formula, $C_{21}H_{23}NO_6$).

A survey of the ring closure method by Junjappa and co-workers,[130] to be discussed in the next Section, led to the design of a method whereby enaminone (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1,2-bis(3,4-dimethoxyphenyl)ethanone **5.34** would be synthesized by the Eschenmoser sulphide contraction with the previously prepared phenacyl halide 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27** (*Figure 5.7*). This method would reduce the number of overall steps required in the total synthesis of lamellarins by eliminating the bromination and Suzuki-Miyaura coupling reactions in the synthesis and therefore optimising and improving the overall synthesis. Other reasons pertaining to the mechanism of the ring-closed product will be mentioned in the next section.

The Eschenmoser sulphide contraction was accomplished using the methodology described above (*Scheme 5.17*). Enaminone (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-

ylidene)-1,2-bis(3,4-dimethoxyphenyl) ethanone **5.34** was isolated as a bright yellow powder in 69% yield.

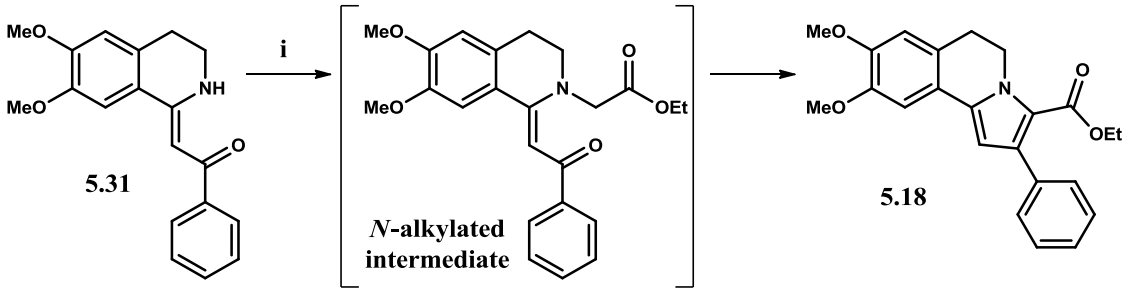


Scheme 5.17 *Reagents and conditions:* i. Phenacyl halide **3.27**, $CHCl_3$, rt, 18 h; ii. PPh_3, Et_3N, $CHCl_3$, rt, 24 h.

In the IR spectrum of (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1,2-bis(3,4-dimethoxyphenyl) ethanone **5.34**, the presence of an N–H stretch at 3074 cm^{-1} and a C–H bend for *Z*-alkenes at 707 cm^{-1}, suggests that the compound follows the same pattern observed with the previously investigated enaminones. In the ^1H NMR spectrum, a NH singlet was observed at 13.07 ppm, again suggesting strong intramolecular hydrogen-bonding and the isolation of the *Z*-isomer. The aromatic region of the ^1H NMR spectrum integrated for eight CH signals, suggesting the benzoin-containing phenacyl halide **3.27** was incorporated into the thiolactam **5.2** to form the expected enaminone **5.34**. In the ^{13}C NMR spectrum, quaternary carbon signals for six methoxy groups, six OCH_3 carbon signals, and eight aromatic CH signals, indicated the product had formed. Finally, a carbon signal for C–11 at 105.29 ppm confirmed the synthesis of desired enaminone **5.34** was accomplished.

5.5.2 A new method for the pyrrole ring formation

A method developed by Barun, Ila and Junjuppa suggested that an enaminone with an unprotected N-H moiety, such as those described in *Section 5.5.1*, could be transformed to the desired ring-closure required for the synthesis of pentacyclic lamellarin alkaloids.[130] The method proposed that the enaminone stirred under reflux in the presence of ethyl 2-bromoacetate and *N*,*N*-dimethylformamide would undergo an intramolecular *N*-alkylation and cyclization to produce lamellarin analogues (*Scheme 5.18*). The method was previously explored by Dr. Morgans in his PhD thesis; however, inconclusive results were observed.



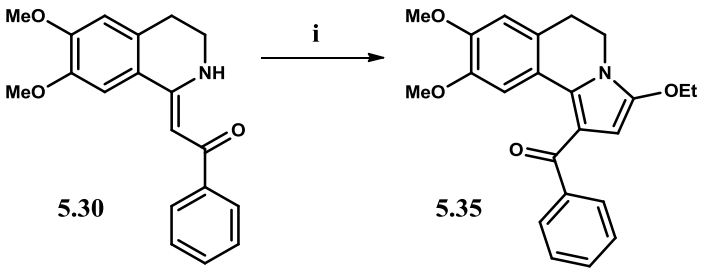
Scheme 5.18 *Junjappa's synthesis:* i. Ethyl 2-bromoacetate, DMF, reflux, 8 h.

The method was attempted using the simplest enaminone **5.31**. The reaction produced a deep emerald green solution, which after an arduous and problematic extraction with diethyl ether and ethyl acetate produced a dark green-yellow residue. The solvent was changed in an attempt to eliminate residues of *N*,*N*-dimethylformamide, which persistently contaminated any isolated compounds. *N*-Methyl-2-pyrrolidinone (NMP), acetic acid, *n*-butanol, toluene, xylene, acetonitrile, and *N*,*N*-dimethylacetamide (DMA) were used as solvents in an attempt to improve the reaction, monitor the results at different temperatures, and observe the effect of polar, non-polar, protic and aprotic solvent. *N*-Methyl-2-pyrrolidinone showed the most promising results. Following purification by flash column chromatography (20–30% ethyl acetate in hexane), Junjappa's product 'ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.18**' was isolated in 46% yield (the reason for the quotation marks will become apparent in due course). The product was isolated in 32% yield from *N*,*N*-dimethylformamide, and in 13–19% yield from *N*,*N*-dimethylacetamide, toluene, xylene and acetonitrile. Microwave conditions did not improve yields and the addition of base, such as potassium carbonate and sodium hydride, were used to induce the deprotonation of the NH but did not produce any isolatable material. Starting material was isolated in many of the reactions and extensive decomposition was also observed.

Information acquired for this reaction was critically compared to the data obtained by Junjappa and co-workers[130] for the reproduced product **'5.18'**. The product was isolated as a yellow solid in both cases. The R_f value in the Junjappa paper was reported as 0.65 and ours was calculated to be 0.69 (in 50% ethyl acetate in hexane). The melting point reported was similar; Barun, Ila and Junjappa found the melting point at 126-127°C, ours was found to be 122–125°C. Analysis of the ^{1}H NMR spectra for the two sets of data showed the aromatic

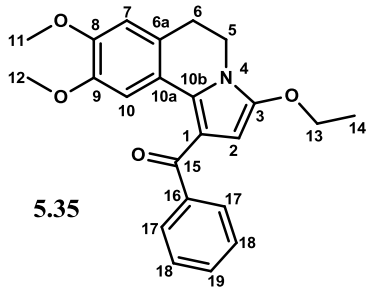
regions were very similar, only a slight downfield shift in the data was observed, this could however be attributed to the calibration of the spectra as the shift remained constant throughout the entire spectrum. The pyrrole =CH singlet was found at 5.44 ppm (in the ^{1}H NMR spectrum) and 88.11 ppm (in the ^{13}C NMR spectrum) in our analysis of the compound, and at 5.52 ppm (in the ^{1}H NMR spectrum) and 89.10 ppm (in the ^{13}C NMR spectrum) in the analysis by Junjappa *et al.* The data sets were almost identical and it was decided that we had produced the same product reported by Junjappa and co-workers. However, the data were also compared to our previous synthesis of compound **5.18**, using the silica gel method (*Section 5.4.2*). Surprisingly, it was discovered that the data for the previously prepared compound **5.18** did not correlate to our findings for **'5.18'**; nor with those of Junjappa, Barun, and Ila.

We thus began to suspect that the structure **'5.18'** as reported by Junjappa and co-workers was incorrect! In *Scheme 5.19* below, the compound that was actually formed under these reaction conditions is shown (pyrrole **5.35**). This was only discovered later in the synthesis following bromination and a Suzuki-Miyaura coupling reaction. A crystal structure was solved for Suzuki product **5.37**, which will be discussed more closely in the next Section. The similarities in the appearance, melting point and spectral information of the structure reported by Junjappa and co-workers and our newly synthesized product led to the conclusion that Junjappa *et al.* had actually prepared compound **5.35** and not product **5.18** as was expected and reported. Most probably due to the structural similarities, they, like us, assumed the product was obtained.



5.30 **5.35**

Scheme 5.19 *Reagents and conditions:* i. Ethyl 2-bromoacetate, NMP, reflux, 3 d.



5.35

With hindsight, the spectral data obtained correlated well with (3-ethoxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.35**. The main differences in the appearance in product **5.35**, compared to expected product **5.18**, were the position of the substituents on the pyrrole ring, which were expected in the 2- and 3-position of the pyrrole; the aryl ketone, which clearly was not part of a biaryl bond between the pyrrole and a benzene ring; and the ethoxy, which was expected to be part of an ester. The pyrrole =CH is expected to be more downfield in the 1- and especially the 3-position of the ring, the 2-position is expected to have a lower value. Since we had no direct comparative evidence we compared the data to the pyrrole =CH value obtained for the expected and previously synthesized product **5.18** (*Section 5.4*), in which the pyrrolic proton was in the 1-position (C–1) rather than 2-position (C–2) of the pyrrole ring (as in pyrrole **5.35**). The =CH signal for pyrrole carboxylate **5.18** was observed at 5.99 ppm, while the =CH C–2 for pyrrole **5.35** was observed at 5.44 ppm. Similarly, the pyrrolic proton in the 3-position (C–3) of the previously prepared pyrrole chromenone **5.22** was observed at 6.80 ppm. This general trend was also observed in several related compounds found in the literature.[51,64,67] Additionally, an ethoxy compared to an ethyl ester is expected to be slightly more electronegative due to the adjacent carbonyl. The ethoxy CH_2 and CH_3 signals for **5.35** were observed at 3.98 and 1.33 ppm in our ^{1}H NMR spectrum, at 4.05 and 1.41 ppm in the ^{1}H NMR spectrum reported by Barun, Ila and Junjappa, at 4.13 and 1.06 ppm for the expected pyrrole carboxylate **5.18**, and at 4.19–4.23 and 1.19–1.29 ppm for our previously discussed precursor carboxylates **5.9**, **5.10** and **5.14**. This led us to believe that the ethoxy formed in this ring-closed product more closely resembled an ether as in **5.35**, without an adjacent carbonyl group. Finally and most significantly, in the ^{13}C NMR spectrum, the C–15 carbonyl peak was observed at 191.42 ppm (in our synthesis for **5.35**), and at 192.40 ppm (in the Junjappa synthesis). The C=O signal for the expected pyrrole product **5.18** was observed at 161.91 ppm, and the precursors to pyrrole product **5.35** (compounds **5.9**, **5.10** and **5.14**) were observed at 167.88–169.94 ppm. These subtleties observed in the comparative analyses of the spectral data showed that our initial expectations and the findings suggested by Junjappa were in fact incorrect and product **5.35** was the product produced from this method.

The mechanism proposed for the formation of these pyrrole systems is illustrated in *Figure 5.15*. The mechanism suggests that the nitrogen of the enaminone does not attack the α-C of ethyl 2-bromoacetate but instead the enaminone reacts as a nucleophile through the vinyl carbon. An intramolecular cyclization between the nitrogen lone pairs (which acts as the nucleophile) and the carbonyl of the ester moiety (which acts as the electrophile) forms the 5-membered ring. Instead of the ethoxy acting as a leaving group, the carbonyl forms an alcohol which is dehydrated to encourage aromaticity of the ring, and the product **5.35** is formed.

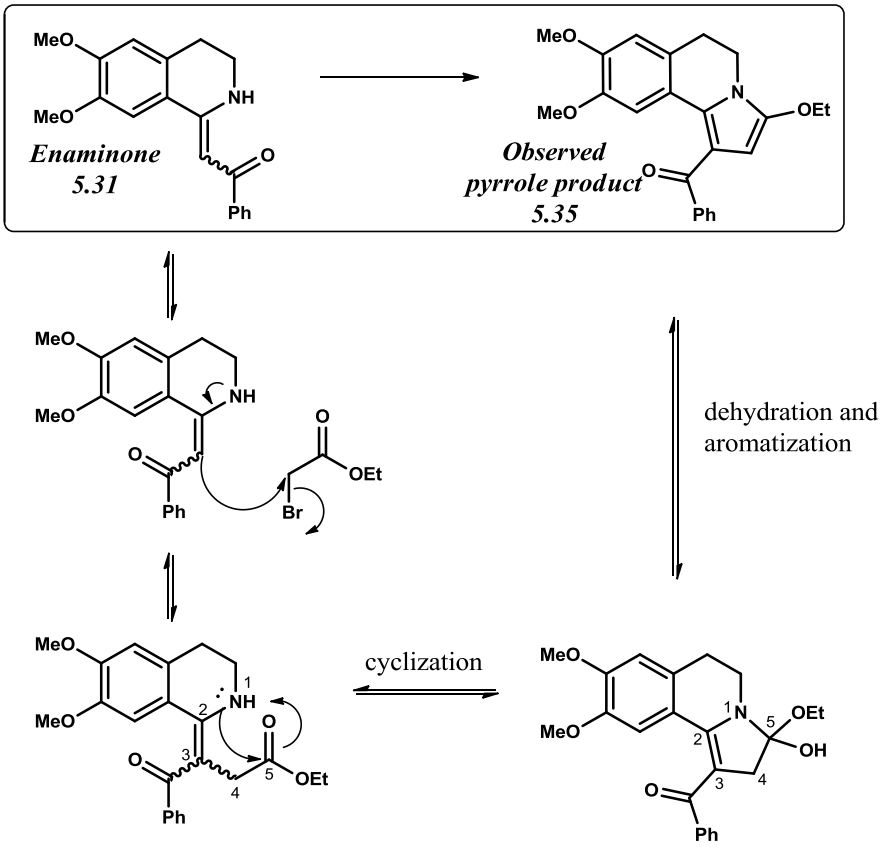


Figure 5.15: Proposed mechanism for the pyrrole product **5.35**, formed using the method by Junjappa and co-workers.[130]

An expansion of the methodology to further substantiate the results was undertaken. Several attempts to reproduce the results on enaminones **5.32** and **5.33** were unsuccessful. In some instances trace amounts of product were produced, however, not enough for any successful and uncontaminated characterization. Small amounts of starting material were recovered after purification and most of the material appeared to decompose. Although the findings were

fascinating the formation of the pyrrole product required for the synthesis of lamellarins was again unsuccessful.

A summary of the pyrrole-containing products prepared in this Chapter are shown in *Table 5.4* below. Pyrrole products **5.18** and **5.22** (from *Section 5.4.2*) and the recently discussed **5.35** will be compared, with the main focus around the pyrrole ring. The compound and aromatic numbering are shown in *Figure 5.16*, which correlates with the results represented in *Table 5.4*. The atom numbering is only meant for the table and is not a depiction of the numbering used for the discussion of products in the rest of the thesis. ^{1}H and ^{13}C NMR spectra for compound **5.35** are given in *Figure 5.17*. The spectra for compounds **5.18** and **5.22** can be refered to in *Section 5.4.2*. The NMR spectra along with *Figure 5.16* and *Table 5.4* should assist in giving a better understanding of the data presented and allow for clearer comparisons to be drawn for the compounds.

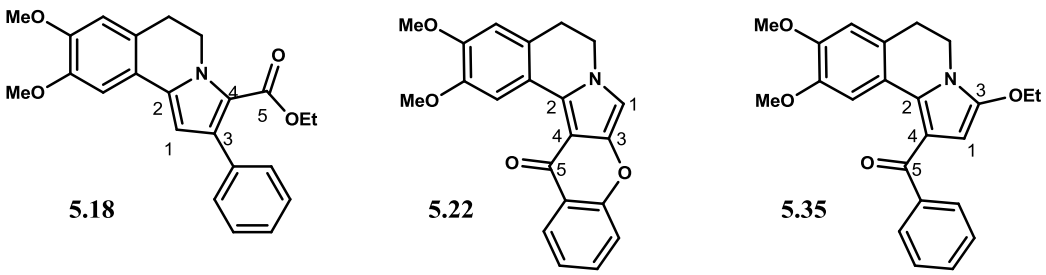


Figure 5.16: Different pyrrole derivatives formed during the project.

Table 5.4: A summary of the selected pyrrole products prepared comparing data obtained.

Carbon number	**Diverse Pyrrole Products Produced**		
	Pyrroles from *Section 5.4.2*		**Pyrrole from *Section 5.5.2***
	5.18	**5.22**	**5.35**
^{1}H NMR Spectrum (ppm):			
C–1	6.47	6.80	5.44
^{13}C NMR Spectrum (ppm):			
C–1	105.91	96.11	88.11
C–2	136.96	130.59	124.14
C–3	120.80	115.85	144.19
C–4	118.4	117.95	115.54
C–5	161.91	173.78	191.42
IR spectrum (cm^{-1}):			
C–5	1682	1696	1726

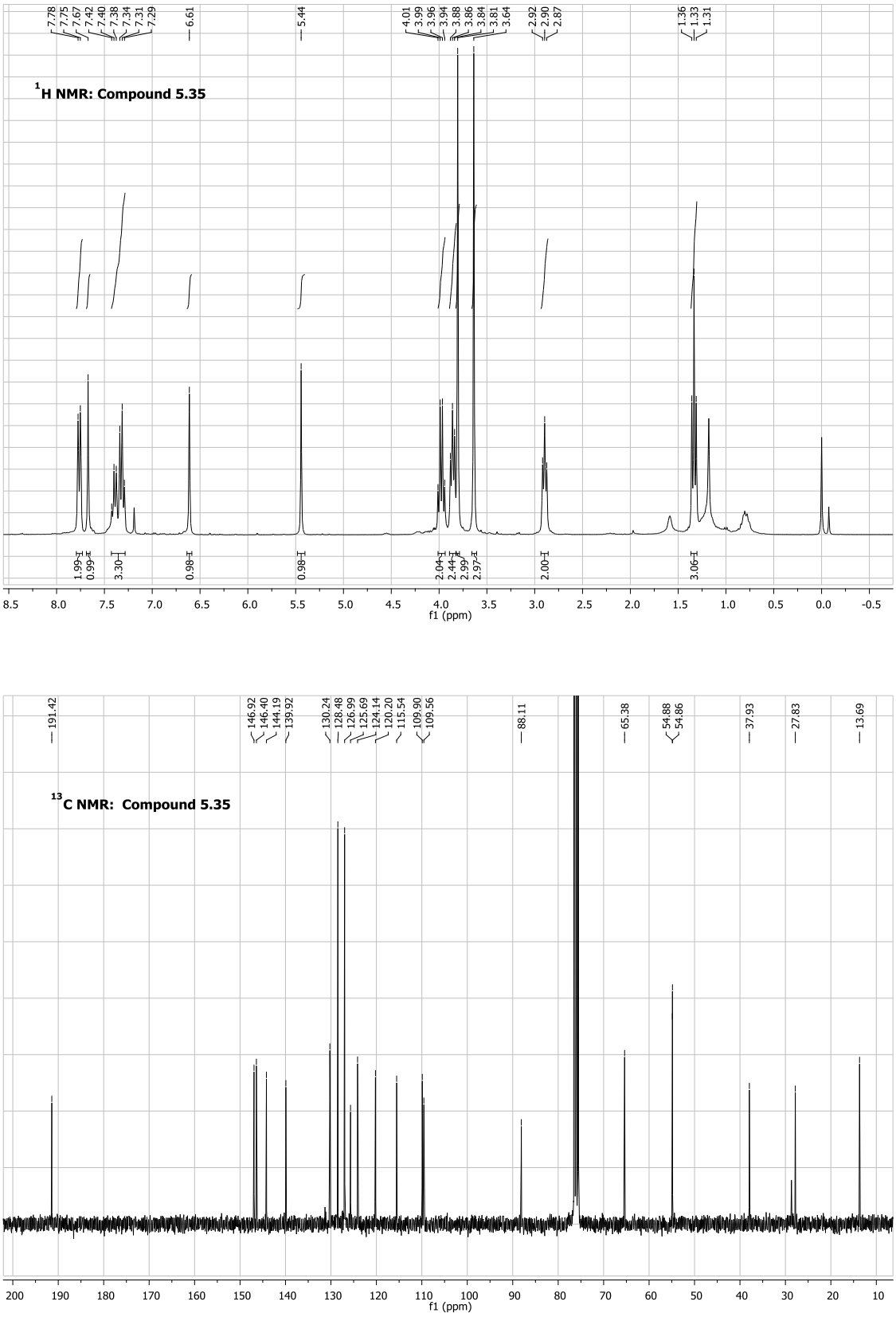
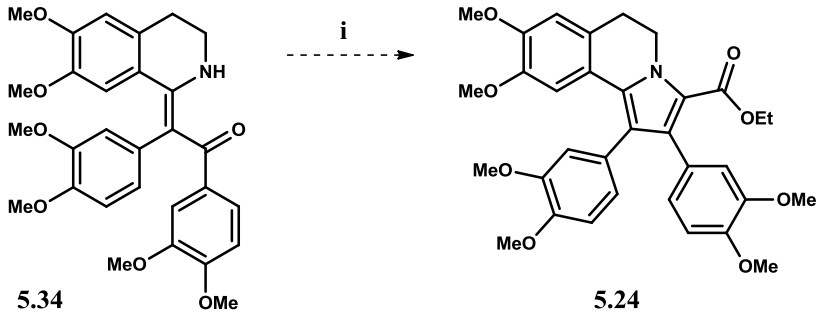


Figure 5.17: ^{1}H and ^{13}C NMR spectra for (3-ethoxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.35**.

The synthesis of enaminone (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1,2-bis(3,4-dimethoxyphenyl)ethanone **5.34** was discussed in *Section 5.5.1*. A similar structure was reported in a survey of the ring-closing method by Junjappa and co-workers.[130] Through a greater understanding of the mechanism for these systems the synthesis of **5.34** was initially designed to investigate the pyrrole formation under these conditions when the enaminone vinyl position was occupied. The pyrrole ring closure to form product **5.24** using ethyl 2-bromoacetate and *N*,*N*-dimethylformamide, was attempted (*Scheme 5.20*). Several other solvents such as *N*-methyl-2-pyrrolidinone and *N*,*N*-dimethylacetamide were used, in varying concentrations. The reaction was monitored under a variety of temperatures and both conventional and microwave techniques were used. Unfortunately, the results could not be reproduced and none of the experimental adaptions and manipulations attempted proved successful in producing any isolable material. The synthesis was therefore abandoned.

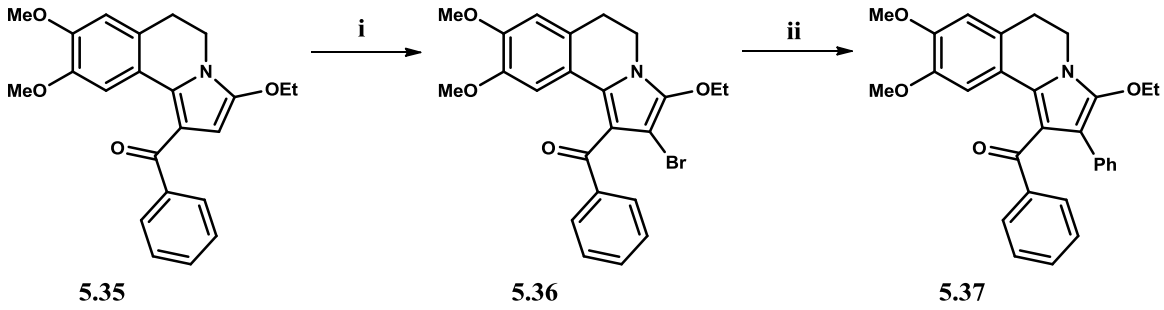


Scheme 5.20 *Reagents and conditions:* i. Ethyl 2-bromoacetate, DMF/NMP/DMA, conventional (reflux, 3 d) or microwave (80–150°C, 100–150W, 30 min).

5.5.3 Bromination and Suzuki-Miyaura coupling reactions

The synthesis of lamellarin analogues from the 'incorrect' product **5.35** was completed, despite the results obtained. Ring-closed product **5.35** was brominated in *N*,*N*-dimethylformamide with *N*-bromosuccinimide (*Scheme 5.21*). The brominated product **5.36** was isolated as a yellow solid in 95% yield. The IR spectrum of the product showed a C–Br stretch at 662 cm^{-1}. In the ^{13}C NMR spectrum, a distinctive C–Br signal was observed at 82.56 ppm. Finally, the absence of the =C–H singlet in the ^{1}H NMR spectrum (noted in **5.35**) suggested the brominated product was produced.

The brominated pyrrole **5.36** was then subjected to a Suzuki-Miyaura coupling reaction by reacting it with phenylboronic acid, caesium fluoride, silver(I) oxide and tetrakis(triphenylphosphine)palladium(0) in 1,2-dimethoxyethane. After purification, product **5.37** was isolated as yellow cuboidal crystals in 28% yield. An XRD study of Suzuki product **5.37** was achieved at this point, and the results showed that unexpected product **5.37** had formed (*Figure 5.18*). The crystallographic analysis of the structure afforded the yellow crystals in a triclinic crystal system, in the *P*-1 space group with a *Z* value of 4. As mentioned previously, it was this result that finally revealed the unexpected formation of pyrrole **5.35**, and suggested that Junjappa's reported structure of **'5.18'** was incorrect.



Scheme 5.21 *Reagents and conditions:* i. NBS, DMF, 0°C–rt, 20 h; ii. $PhB(OH)_2$, $Pd(PPh_3)_4$, CsF, AgO_2, DME, 80°C, 18 h.

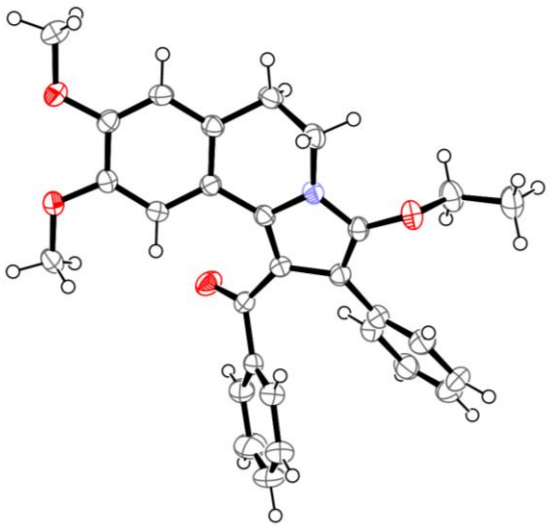
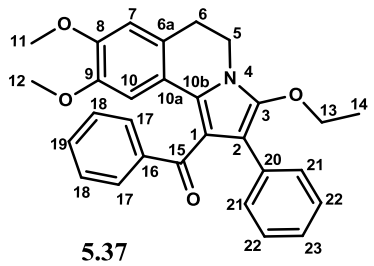


Figure 5.18: An ORTEP diagram of brominated pyrrole product **5.37** showing the unexpected ring closure.



5.37

Analysis of the ^{1}H NMR spectrum for Suzuki product (3-ethoxy-8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.37** attested to the formation of the biaryl bond in the compound. The aromatic region integrated for 12 protons. There were also two singlet signals from the isoquinoline, two phenyl rings from the enaminone moiety and the newly formed Suzuki addition. In the ^{13}C NMR spectrum, the C–Br signal, from starting material **5.36**, was replace with a quaternary signal at 133.74 ppm. All previously discussed attributes of the compound were observed in the spectral data for the product. The high resolution mass spectrum showed a molecular ion peak at 454.2002, with a calculated expected mass of the same value, for the final product **5.37**.

5.6 Conclusions for Chapter 5

The preparation of a variety of 3,4-dihydroisoquinolinones was discussed. These sub-units formed an important part of the initial investigation of the overall synthetic scheme. A variety of known and adapted procedures were used to form *N*-alkylated lactam **5.3** and thiolactams **5.2** and **5.10**, in an attempt to reduce the number of synthetic steps, form products in high yields, and be able to reproduce the products in large scales.

Thiolactams **5.2** and **5.10** were prepared and used in the Eschenmoser sulphide contraction reaction under a variety of conditions adapted for the specific reactions. The *N*-alkylated enaminones were formed in reasonable yields, despite some difficulties observed in the salt formation and subsequent purification of these systems. The enaminones containing unprotected amines were also afforded, the reaction proceeding in a versatile and facile manner in comparison to the *N*-alkylated enaminones. These enaminones were isolated readily as bright yellow or orange solids. A variety of phenacyl halide substituents were used to produce a library of both the *N*-alkylated and unprotected enaminones.

The synthesis toward lamellarin alkaloids with the *N*-alkylated enaminones was attempted with methodology adapted by Garreth Morgans[69] and Calvo and co-workers,[88] using silica gel in an acid-induced ring closure. The methodology was also successfully described in *Chapter 4* as part of a model study toward these lamellarin systems with pyrrolizine,

indolizine and pyrroloazepine analogues. The methodology showed that a pyrrole ring had indeed formed with these *N*-alkylated enaminones. The simplest tricyclic lamellarin precursor ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.18**, which resembled the bicyclic pyrrolizines discussed in *Chapter 4* was successfully prepared. However, several attempts at preparing the pentacyclic scaffold from this analogue proved unsuccessful. The subsequent pentacyclic systems were formed when a hydroxyl group was present on the *ortho*-position of the aromatic ring. However, the results gained from the experimental investigation of these systems were unanticipated, and evaluations of the spectral evidence and the crystallographic structure showed that although the pyrrole system formed, it was not as initially expected and the results obtained differed to those of the pyrrole carboxylate **5.18**. Instead the proposed mechanism for the novel structure suggested the enaminone reacted as a nucleophile with the ester group affording pyrrole products **5.22** and **5.23**. The synthesis of lamellarin G trimethyl ether was therefore not completed by this method, although very interesting analogues were obtained.

A synthesis by Barun, Ila and Junjappa[130] was then explored using secondary enaminones (with free NH units). The procedure suggested the expected pyrrole systems would form when ethyl 2-bromoacetate reacted *in situ* with these enaminones. The reactions were highly difficult to reproduce and the work-up and purification of the reaction material was unfavourable and challenging, and afforded product in very low yields. An inspection of the physical and spectral data was compared to the data achieved by Junjappa and co-workers, which suggested we had formed the same product as they did. However, a comparison with the previously prepared and expected pyrrole **5.18** (prepared using the silica gel method) and a crystal structure of the subsequent Suzuki product **5.37** showed that the pyrrole system formed was once again not that expected for the lamellarin precursor. These findings also disproved the findings of Barun, Ila and Junjappa. The proposed mechanism for these pyrrole products suggested the vinyl group of the enaminone reacted as a nucleophile, attacking the ethyl 2-bromoacetate, and the unprotected NH participated in the later cyclization and not in the initial reaction. Despite several attempts to induce the reactivity at NH site, the sought-after pyrrole ring closure was not achieved and again the synthesis toward the lamellarin alkaloids was incomplete, although a novel pyrrole product was afforded.

All pyrrole products formed in this Chapter were subjected to bromination reactions with *N*-bromosuccinimide in *N*,*N*-dimethylformamide, followed by Suzuki-Miyaura reactions with phenylboronic acid or 3,4-dimethoxyphenylboronic acid, and in general the biaryl compounds were isolated. These compounds could therefore be considered as analogues of lamellarin alkaloids, owing to similarities in the structural and chemical properties of the compounds. The compounds themselves are novel and can be considered biologically interesting. Further exploration and biological testing is required to establish the importance of these systems. The optimization and re-evaluation of the synthetic routes for these novel compounds and the lamellarin alkaloids will be explored for future syntheses.

Chapter 6
Summary and future prospects

6.1. Summary

6.1.1. Preparation of phenacyl halides

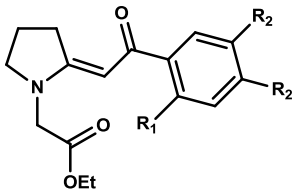
In *Chapter 3*, the synthesis of various phenacyl halides was described. The phenacyl halides were prepared as precursors required in the Eschenmoser sulphide contraction in the syntheses described in *Chapter 4* and *5* of the thesis. Two main groups of phenacyl halides were prepared, the di-substituted phenacyl halides and the tetra-substituted phenacyl halides. The specific compounds prepared in *Chapter 3* and used in *Chapters 4* and *5* were 2-iodo-1-phenylethanone **3.9**, 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10**, 1-(2-hydroxyphenyl)-2-iodo-1-ethanone **3.12**, 2-(2-bromoacetyl)phenyl methanesulphonate **3.13**, 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl) **3.17**, 1-(2-hydroxy-4,5-dimethoxyphenyl)-2-iodoethanone **3.18**, 2-(2-bromoacetyl)-4,5-dimethoxyphenyl methanesulphonate **3.19**, 2-bromo-1-(2,4-dihydroxy-5-methoxyphenyl)ethanone **3.24**, 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27**

The mesyl protected and non-substituted phenacyl halides were used in the preparation of pyrrolizine analogues (*Chapter 4*) with the intention of testing the methodology and gaining a better understanding of the way these compounds form, both chemically and mechanistically, the mesyl protected phenacyl halides were not used in the lamellarin project (*Chapter 5*). The *ortho* hydroxyl-substituted phenacyl halides formed the precursors required for the synthesis of lactones found in the lamellarins and their analogues.

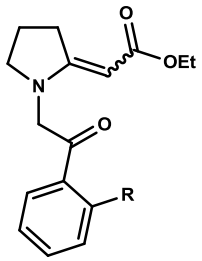
6.1.2. A model synthesis of pyrrolizines from *N*-alkylated and *N*-phenacyl analogues

The phenacyl halides prepared in *Chapter 3*, were used in a series of optimized and adapted Eschenmoser sulphide contractions with *N*-alkylated thiolactam ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate **4.9** and *N*-phenacyl thiolactams 1-phenyl-2-(2-thioxopyrrolidin-1-

yl)ethanone **4.14** and 1-(2-hydroxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone **4.15**. A library of pyrrolidine enaminones was therefore afforded (*Figure 6.1*). The *N*-alkylated enaminones were isolated as the *E*-isomer only, in yields between 72 and 92%. The *N*-phenacyl halides were isolated as both the *E* and *Z* isomers, in yields between 50 and 72%. The *N*-alkylated pyrrolidine enaminones performed more efficiently during the Eschenmoser sulphide contraction reactions and the enaminones formed in higher yields with minimal contaminations. The reaction proved to be more challenging with the *N*-phenacyl products and some experimental modifications were required.



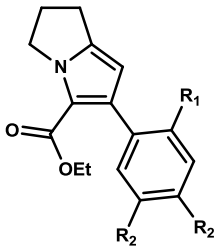
4.20: R_1 = H, R_2 = H
4.21: R_1 = OH, R_2 = H
4.22: R_1 = OMs, R_2 = H
4.23: R_1 = OH, R_2 = OMe
4.24: R_1 = OMs, R_2 = OMe



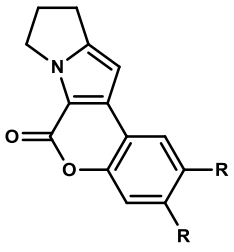
4.25: R = H
4.26: R = OH

Figure 6.1: Library of prepared *N*-alkylated and *N*-phenacyl enaminones

These enaminone compounds were then subjected to an acid-catalysed pyrrole formation with silica gel. The pyrrole formation methodology formed an intricate part of the project and a series of bicyclic pyrrolizine and tetracyclic pyrrolizinone compounds were successfully synthesized with the *N*-alkylated enaminones (*Figure 6.2*). The *N*-phenacyl enaminones showed unfavourable results for the pyrrole formation, and no product was isolated.



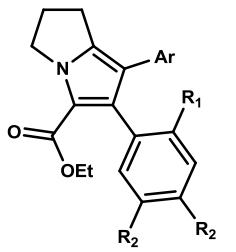
4.29: R_1 = H, R_2 = H
4.30: R_1 = OMs, R_2 = H
4.31: R_1 = OMs, R_2 = OMe



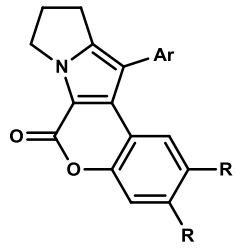
4.32: R = H
4.33: R_1 = OMe

Figure 6.2: Prepared bicyclic pyrrolizine and tetracyclic pyrrolizinone compounds.

The successful synthesis of tetracyclic compounds therefore proved that the methodology should be suitable for the synthesis of lamellarin alkaloids. A complete model of the lamellarin system was done by brominating and performing a Suzuki-Miyaura coupling reaction at the free pyrrolic site of the ring-closed products. Suzuki reactions with phenylboronic acid and 3,4-dimethoxyphenylboronic acid were performed and the model synthesis with pyrroldine compounds was completed (*Figure 6.3*).



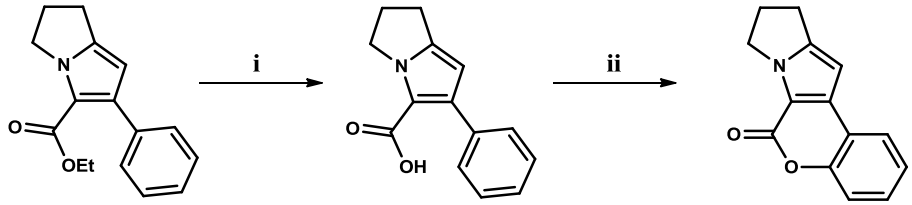
4.43: R_1 = H, R_2 = H, Ar = Ph
4.44: R_1 = OMs, R_2 = H, Ar =Ph
4.50: R_1 = OMs, R_2 = H, Ar =3,4-diOMePh
4.45: R_1 = OMs, R_2 = OMe, Ar = Ph



4.48: R = H, Ar = Ph
4.51: R = H, Ar = 3,4-diOMePh
4.49: R = OMe, Ar = Ph
4.52: R = OMe, Ar = 3,4-diOMePh

Figure 6.3: Prepared Suzuki biaryl bicyclic pyrrolizine and tetracyclic pyrrolizinone compounds.

Finally, simple bicyclic pyrrolizine **4.29** was subjected to a novel reaction using lead(IV) acetate in an attempt to induce the lactone and form tetracyclic pyrrolizinone **4.32** (*Scheme 6.1*). The reaction was successful and the saponified product **4.53** was afforded in quantitative yields. Pyrrolizinone **4.32** was then formed and the results were compared to the previously synthesized compound formed from enaminone **4.21**.



4.29 **4.53** **4.32**

Scheme 6.1 *Reagents and conditions:* i. KOH, MeOH, 30–100°C, 5 h; ii. $Pb(OAc)_4$, EtOAc, rt, 2 h

6.1.3. A model synthesis of indolizinone and pyrroloazepinone compounds

An expansion of the synthesis of pyrrolizinone **4.32** was performed on piperidine and azepane compounds to afford a variety of tetracyclic compounds with variation in size of the ring attached to the pyrrole. Thiolactam ethyl 2-(2-thioxopiperidin-1-yl)acetate **4.18** was prepared from piperidinone over two steps; and ethyl 2-(2-thioxoazepan-1-yl)acetate **4.19** was prepared from caprolactam over two steps. The thiolactams were again subjected to the Eschenmoser sulphide contraction with phenacyl halide **3.10**, and enaminone products **4.27** and **4.28** were afforded. Isolation and purification of the products was troublesome, contaminants persisted despite numerous attempts at purification; the products were therefore only isolated in 8 to 20% yield. Finally, The ring-closure reaction was attempted and the expected pyrrole product 8,9,10,11-tetrahydro-6*H*-chromeno[4,3-*b*]indolizin-6-one **4.38**, isolated in 34% yield, as well as the unexpected pyrrole products 10,11-dihydro-8*H*-chromeno[3,2-*a*]indolizin-12(9*H*)-one **4.39** in 21% yield, and 9,10,11,12-tetrahydrochromeno [4',3':4,5]pyrrolo[1,2-*a*]azepin-6(8*H*)-one **4.40**, isolated as an off-white solid in 90% yield, were afforded (*Figure 6.4*).

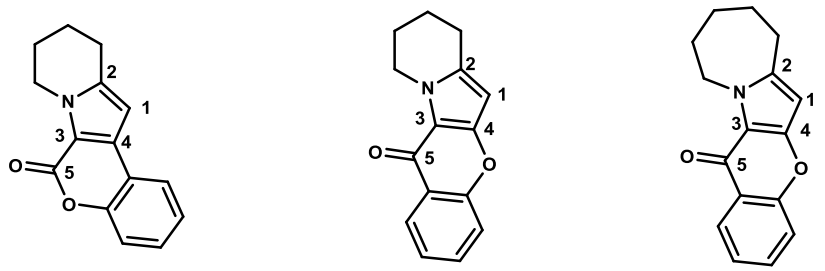
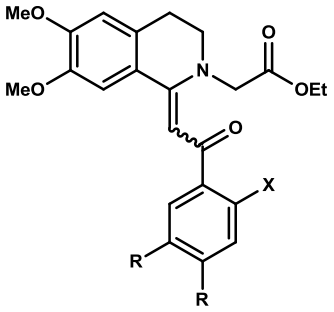


Figure 6.4: Tetracyclic indolizinone **4.38, 4.39** and pyrroloazepinone **4.40** products.

6.1.4. Synthesis toward lamellarin G trimethyl ether with the proposed silica gel method

Several syntheses for the preparation of isoquinoline systems and subsequent thiolactam ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.10** were described in *Chapter 5*. Thiolactam **5.10** was used in the synthesis on *N*-alkylated enaminones with the previously prepared phenacyl halides in the Eschenmoser sulphide contraction reaction. This reaction was very sensitive and the reagents in the salt formation were susceptible to light-induced decomposition. The reaction conditions therefore required specific manipulations for

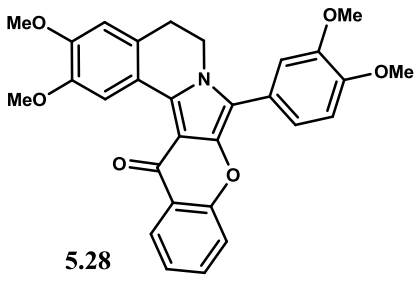
the preparation of each enaminone (*Figure 6.5*). Purification of the products was problematic and contaminants persistently affixed themselves to the enaminones. As a consequence the yields of the reactions were lower than we anticipated.



5.14: X = H, R = H
5.15: X = OH, R = H
5.16: X = OH, R = OMe

Figure 6.5: Enaminones **5.14**, **5.15** and **5.16**, prepared using the Eschenmoser sulphide contraction reaction.

Enaminones **5.14**, **5.15** and **5.16** were subjected to the acid-induced silica gel ring-closure and pyrrole products **5.18**, **5.22** and **5.23** were isolated. Although pyrrole carboxylate **5.18** successfully produced a tricyclic lamellarin precursor, which correlated with the pyrrolizines from Chapter 4, it was however discovered that the products **5.22** and **5.23** were not what we had initially anticipated. Following the bromination and Suzuki-Miyaura coupling reaction of pyrrole product **5.22**, an XRD was obtained for **5.28**, which indicated that an unexpected pentacyclic product had been isolated (*Figure 6.6*). The proposed mechanism for the formation of product **5.28** suggested that the enaminone performed as a nucleophile and reacted with the carbonyl carbon of the acetate functionality. The ring closed product therefore did not form a lactone but the novel chromenone moiety shown in *Figure 6.6*.

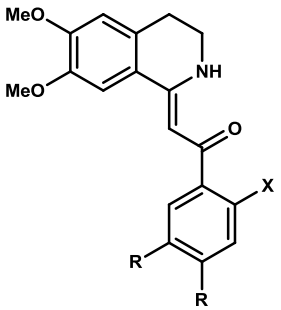


5.28

Figure 6.6: Novel pentacylic compound 8-(3,4-dimethoxyphenyl)-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.28**.

6.1.5. Synthesis toward lamellarin G trimethyl ether with the Junjappa method[130]

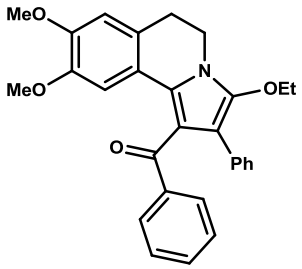
Thiolactam 1-(2-isothiocyanatoethyl)-3,4-dimethoxybenzene **5.2** was used in the synthesis of enaminones with an unprotected amine. Thiolactam **5.2** was prepared from 3,4-dimethoxyphenylethylamine in 90% yield over two steps. The thiolactam was then subjected to Eschenmoser sulphide reactions with phenacyl halides **3.9**, **3.12**, and **3.18**. The enaminones were isolated as bright yellow or orange powders with yields between 72 and 91%. The Eschenmoser sulphide contraction was versatile to these systems and readily afforded enaminones as uncontaminated and pure products. All the enaminones were isolated as *Z*-isomers due to hydrogen bonding interactions between the amine and the carbonyl of the enaminone (*Figure 6.7*).



5.31: X = H; R = H
5.32: X = OH; R = H
5.33: X = OH; R = OMe

Figure 6.7: Enaminones synthesized with unprotected amines, from phenacyl halide **3.9**, **3.12** and **3.18**.

The synthesis of the pyrrole ring was attempted using the methodology described by Junjappa and co-workers.[130] The product formed, when enaminone **5.31** and ethyl 2-bromoacetate in *N*-methyl-2-pyrrolidinone (*N*MP) were reacted under reflux, was not the pyrrole product we expected (compound **5.18**). Further investigation of the mechanism suggested that the vinyl of the enaminone reacted directly with ethyl 2-bromoacetate, this was then followed by an intramolecular cyclization to afford pyrrole product **5.35**. This product was also brominated and the Suzuki-Miyaura coupling reaction with phenylboronic acid afforded biaryl product (3-ethoxy-8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.37** (*Figure 6.8*). The unexpected product was confirmed by X-ray crystallography. Although this was not the pyrrolic structure we had hoped for, the pyrrole did form and the compound could be considered as a lamellarin analogue.



5.37

Figure 6.8: Suzuki product (3-ethoxy-8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.37**.

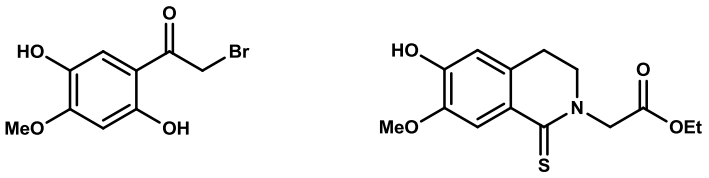
Investigation of the methodology with enaminones **5.32** and **5.33** did not afford any unambiguously characterizable products, and the synthesis was not pursued further. Also, the products isolated by Junjappa and co-workers suggested the compound isolated was not the lamellarin precursor we were hoping for. A comparison of our data to their data suggested they had isolated the same product we had (**5.35**) and their reported findings were flawed. A final attempt at gaining an understanding of the mechanism of these structures was ascertained when enaminone **5.34** was submitted to the ring-closing reactions with thiolactam **5.2** and phenacyl bromide **3.27**. The ring closure was also performed in the synthesis described by Junjappa and co-workers. The vinyl of the enaminone would be hindered by the existence of the aryl group and the ethyl 2-bromoacetate would not be able to react at this site. Unfortunately, unfavourable results were achieved and only decomposition and starting material were afforded from the reaction.

6.2. Future Prospects

6.2.1. Expansion of methodology to include diversely substituted phenacyl halides and isoquinolines

In *Chapter 3*, initial studies of tetra-substituted phenacyl halides with variation in substitution of the 4- and 5-positions of the aromatic systems were investigated using vanillin. Phenacyl bromide 2-bromo-1-(2,4-dihydroxy-5-methoxyphenyl)ethanone **3.24** was afforded. Similarly,

in *Chapter 5*, preliminary investigations into the formation of isoquinoline systems with diversity in their substitution patterns (such as the sought-after **5.38**) were observed, although with inconclusive results, owing to the time restrictions of the project (*Figure 6.9*).



3.24 **5.38**

Figure 6.9: Vanillin analogues, phenacyl bromide **3.24** and potential isoquinoline-2-thione **5.38**.

A literature review of the lamellarin alkaloids suggests that the following structural adaptions are of importance in the diverse synthesis of lamellarin alkaloids. The generalised structure of a pentacyclic lamellarin is shown in *Figure 6.10* below. R_1 represents the adaptions to the isoquinoline saturation and accessibility to substituents at this position, R_2 represents the variation on the aromatic ring of the isoquinoline and R_3 represents the adaptions available for the aromatic phenacyl and boronic acid groups in the lamellarin structure. An expansion of this methodology would include a variety of substituents, including OMe, OH, OAc, OSO_3Na, halides and other chemically accessible groups. These functionalities could be inserted onto anyone of the rings explained above in a number of different patterns to create a library of potential lamellarin analogues, with a plethora of biological potential.

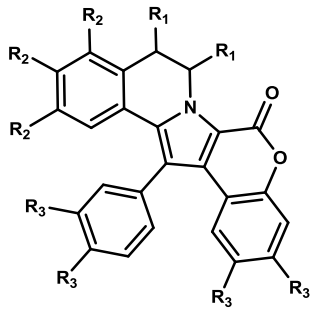


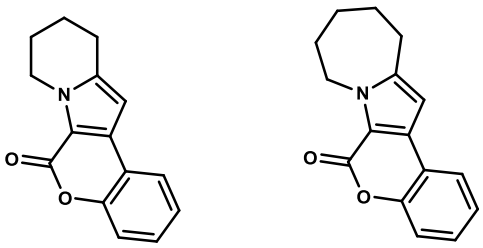
Figure 6.10: General pentacyclic lamellarin, showing the possibilities in diversification of substituents.

Vanillin and isovanillin are commercially available and affordable reagents that could be used to access most of the variations mentioned above. The expansion of the methodology would

therefore manipulate and advance on the procedures already mentioned in *Chapter 3* and *5* for the synthesis of phenacyl halides and isoquinolines with vanillin.

6.2.2. Creation of a library of indolizine and pyrroloazepine analogues

The formation of the piperidine and azepane systems was an important synthetic adaption to the model study of lamellarins. Although the 5-membered pyrrolidines resemble the simplest and more synthetically studied compounds, the piperidine and azepane systems provide a greater understanding as to how the manipulation of the molecules could affect the synthesis of lamellarins. The indolizine systems are of special interest, owing to their inherent structural relationship to the lamellarin isoquinolines (both contain 6-membered ring systems). The results afforded from the synthesis of the tetracyclic indolizine and pyrroloazepine suggested that the desired lactone could be obtained (as observed with product **4.38**). However, chromenone products **4.39** and **4.40** suggested that the chromenone compounds were more likely. It would however be of interest to formulate a synthesis, which would allow the lamellarin-type precursor pyrroles **4.38** and **4.54** (*Figure 6.11*) to be afforded. Further analysis of the piperidine and azepane systems would therefore be beneficial.

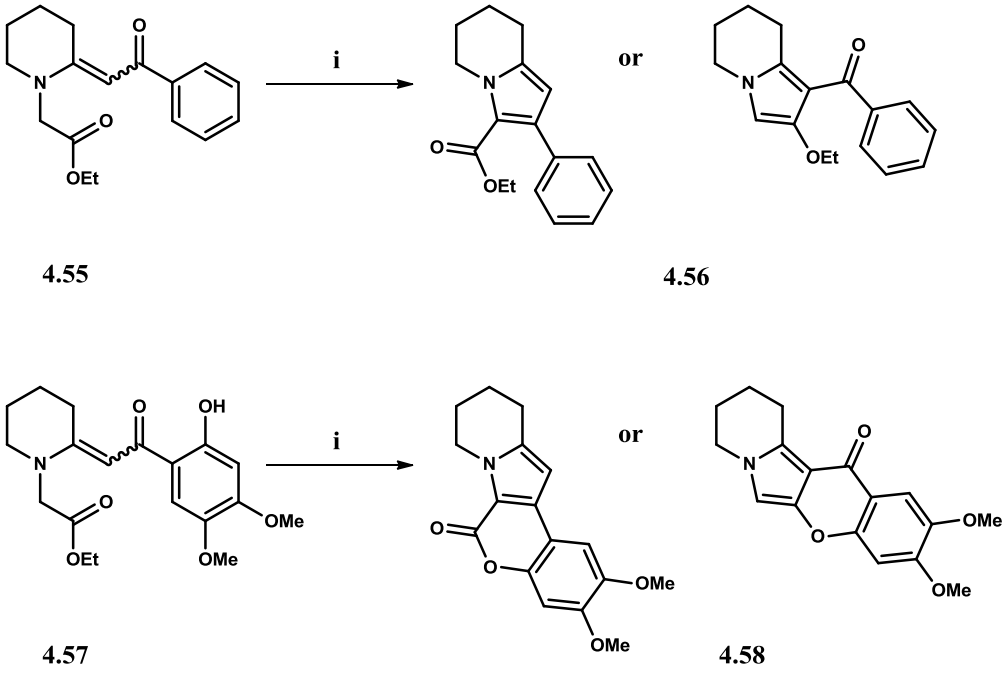


4.38 **4.54**

Figure 6.11: Tetracyclic indolizine **4.38** and pyrroloazepine **4.54**.

It would therefore be of interest to obtain more data, especially for the indolizine compounds. The preparation of enaminones with a simple phenacyl, such as 2-iodo-1-phenylethanone **3.9** and a more complex phenacyl halide such as 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl) **3.17** would be a sought- after synthetic variation to understand the way the structures perform when doing the silica gel ring closure (*Scheme 6.2*). The preparation of biaryl compounds accessed through the Suzuki reaction would also be important in affording more crystalline solids and attaining XRD structures to prove which of the structures was more likely to form.

This would afford a greater understanding of the chemical and mechanistic function of both the indolizine and isoquinoline enaminones during the pyrrole ring formation reaction.



Scheme 6.2 *Reagents and conditions:* i. Silica gel, xylene, µw (180°C, 150 W, 15 min).

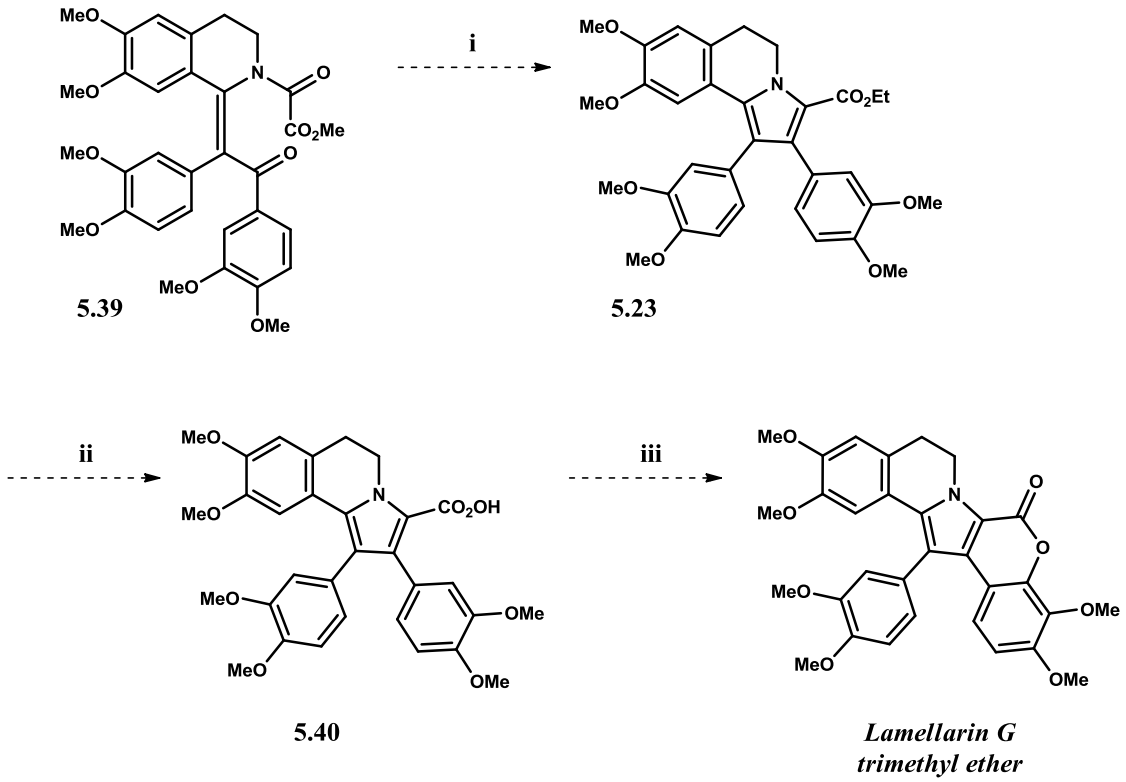
The indolizines and pyrroloazepines have important biological interest on their own and they form a great percentage of the alkaloids present in nature. An investigation into the biological activity of the prepared compounds, and similar adapted compounds would also be highly beneficial.

6.2.3. Re-evaluation of the synthetic strategy for the synthesis of lamellarin alkaloids

Two synthetic routes were designed in an attempt to synthesise lamellarin alkaloids. The first approach accessed a range of *N*-alkylated enaminones, which were ring-closed to form a pyrrole ring under acid-catalysed conditions using silica gel. It was found that the simpler enaminone **5.14** reacted as an electrophile during the ring-closure to afford the expected pyrrole lamellarin precursor. However, enaminones **5.15** and **5.16** reacted as nucleophiles rather than electrophiles; and although a pyrrole formed, it had an unexpected substitution pattern (such as **5.22**, **5.23**). The second approach toward the synthesis of lamellarins suggested that ethyl 2-bromoacetate added *in situ* to an enaminone with unprotected amine

would afford the lamellarin precursor **5.18**. Again, this was not the case and the ethyl 2-bromoacetate added to the vinyl of the enaminone, followed by a cyclization to produce another pyrrole system **5.35**, again with an unexpected regiochemistry. The major challenge in both these syntheses was the formation of the pyrrole ring and the unpredictable mechanistic behaviour of the enaminone and acetate branches in the pyrrole formation process.

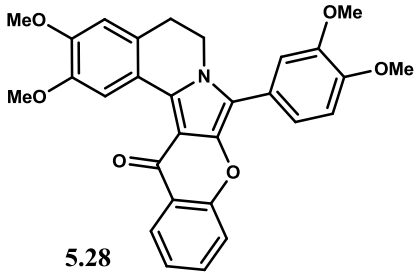
A literature review of a synthesis by Fürstner and co-workers[168,169] suggested another method for obtaining the sought-after pyrrole formation, using similar reagents and chemical principles mentioned in these projects. The pyrrole ring would therefore form using an adapted McMurry coupling technique. A reductive coupling between the ketone and the amide, also known as oxo-amide coupling, would occur in the presence of a reducing agent such as $TiCl_4$, $ZrCl_4$ or titanium on graphite. *Scheme 6.3* shows the proposed pyrrole formation under the new McMurry conditions. A necessary adaption required for this synthesis would be to use methyl 2-chloro-2-oxoacetate as an acetylating agent in place of ethyl 2-bromoacetate. This would give the sought-after pyrrole product **5.24**, the lamellarin precursor. The reaction also shows that enaminones such as **5.39** (an adapted system to **5.17**) could be further manipulated to afford lamellarin precursor **5.22**. The *N*-alkylated product could be replaced with methyl 2-chloro-2-oxoacetate and the acetate could then undergo saponification to afford **5.40**,[143] followed by the catalytic lactone formation with lead(IV) acetate[36,52,53,141,142] to afford lamellarin G trimethyl ether. *Ortho*-hydroxyl phenacyl halides related to compound **5.38** (vanillin analogues) could also be synthesized to afford the pyrrole and lactone formation in one step, without any further reactions. These proposed reaction schemes would eliminate the need for the bromination and Suzuki-Miyaura reaction in the synthesis.



Scheme 6.3 *Reagents and conditions:* i. Ti/C, THF; ii. KOH, MeOH, 30–100°C, 5 h ; iii. $Pb(OAc)_4$, EtOAc, rt, 2 h.

6.2.4. Development of new syntheses based on novel compound (5.28)

The silica gel methodology discussed in *Chapter 4* and *5* of this thesis was a novel technique developed for the formation of the pyrrole ring. Although lamellarin precursors were not produced under these conditions with the isoquinoline systems, a novel approach to achieving different pyrrole systems, such a **5.28** (*Figure 6.12*), was shown in *Chapter 5*. The pyrrole afforded is a means to accessing new and exciting ways of forming a plethora of related alkaloid analogues, with chemical, structural and biological potential.



5.28

Figure 6.12: Pyrrole product 8-(3,4-dimethoxyphenyl)-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.28**.

8-(3,4-Dimethoxyphenyl)-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.28**, has several structurally significant features, which are known to exist in many alkaloid systems and natural products. The chromanone group **A** is observed often in the synthesis of flavonoids such as cirsiliol.[170] They exhibit various biological activities, amongst them, antitumour and anti-proliferative properties. The chromenopyrrolone group **B** is observed in alkaloids such as the pyralomicinones,[171] which are isolated from micro-organism *Microtetrapora spiralis*, and are known as the aglycons of the pyralomicin antibiotics. The chromenoindolizinone group **C** is shown to possess antitumour activity and compounds incorporating **C** have shown potent cytotoxicity against several human cell lines.[172,173] *Figure 6.13* shows some examples of groups **A**, **B** and **C**. Although most of the examples given in this Section express the pyrrole nitrogen in a different position to that of compound **5.28**, the structural similarities could potentially afford analogues with interesting biological and medical properties.

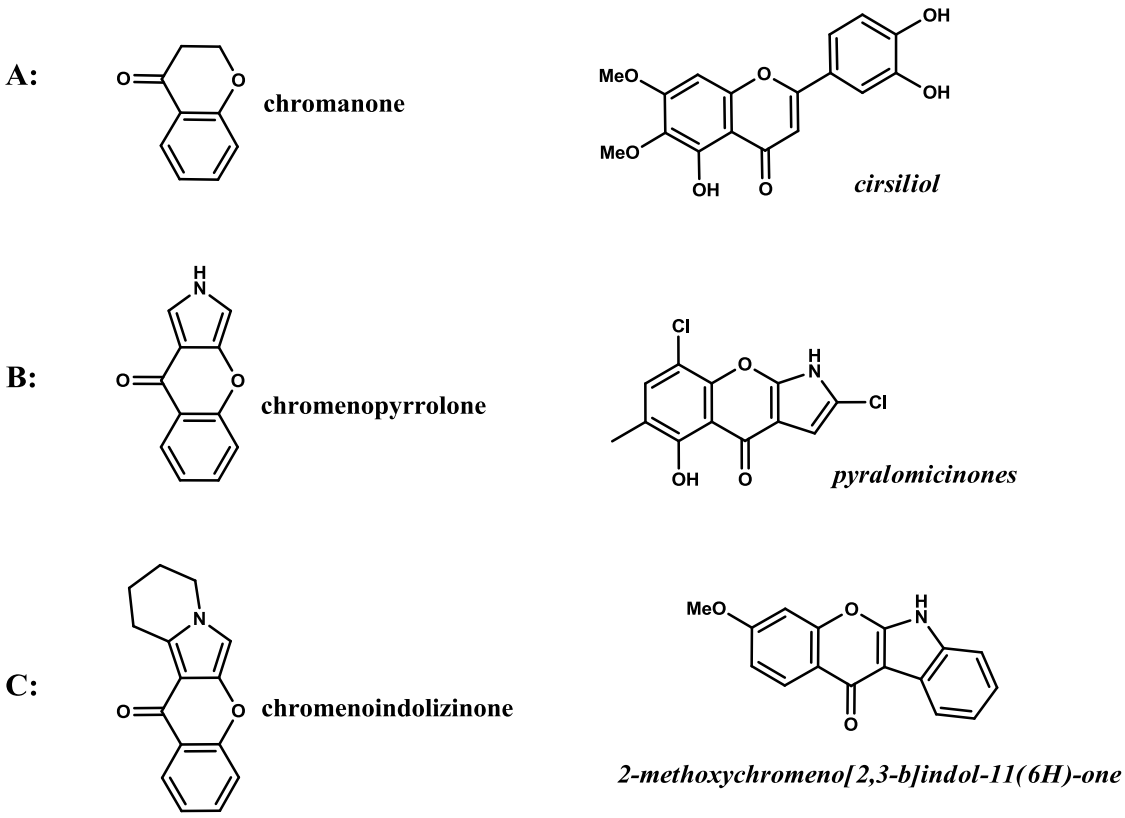
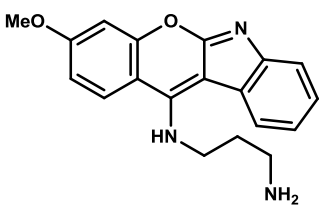
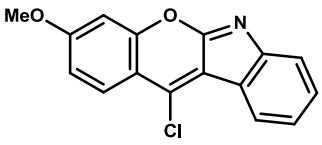


Figure 6.13: Novel and biologically interesting chromanone **A**, chromenopyrrolone **B**, and chromenoindolizinone **C** groups, showing some associated literature examples.

These chromenone compounds also give us access to other structurally similar compounds, also showing diverse biological activities. Amino- and chloro-chromenoindole analogues (attained by further reacting the carbonyl of the chromenone) (*Figure 6.14*) have shown significant anti-proliferative activity against human colon and lung cancer cell lines.[173] Some have been shown to intercalate DNA and inhibit topoisomerase II activity. Once again the nitrogen on the pyrrole (in the given examples) is in a different position to compound **5.28**, but shows the possible adaption that could be made to the chromenone unit.



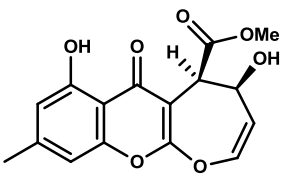
N-(3-aminopropyl)-2-methoxychromeno[2,3-b]indol-11-amine



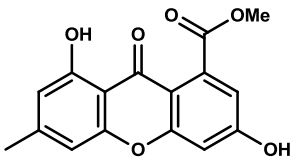
11-chloro-3-methoxychromeno[2,3-b]indole

Figure 6.14: Examples of amino-and chloro-chromenoindolizinone derivatives

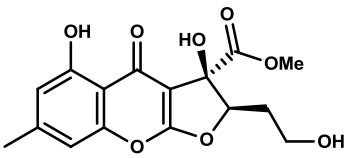
Finally, the chromenone group can be adapted to the synthesis of conioxepinols (with 7-membered rings), xanthones (with 6-membered rings) and coniofurol (with a furan instead of a pyrrole ring), examples of each group are observed in *Figure 6.15*.[174] These chromenone compounds have been isolated from a variety of fungi and exhibit biological activity, such as antimicrobial, antibacterial and anti-inflammatory effects. Nitrogen-containing regioisomers (analogues) could be of definite interest in view of the potential biological activity shown for the compounds in *Figure 6.15*.



Conioxepinol A



Conioxanthone A



Coniofurol A

Figure 6.15: Examples of 7-membered oxepine, 6-membered xanthone and 5-membered furol chromenone compounds.

Chapter 7
General Experimental Methods

7.1. Purification of solvents and reagents

Solvents used for chromatographic purposes, such as ethyl acetate and hexane, were distilled before use by means of conventional distillation procedures. Solvents used for reaction purposes were dried over an appropriate drying agent and then distilled under an argon atmosphere using the appropriate methods mentioned below:

- Tetrahydrofuran (THF) and diethyl ether (Et_2O) were pre-dried over sodium wire, and distilled from sodium metal wire using benzophenone as an indicator.
- Toluene was pre-dried over sodium wire, and distilled from sodium lumps.
- Acetonitrile (MeCN), dichloromethane (DCM), chloroform, methanol (MeOH) and *tert*-butanol (*t*-BuOH) were distilled from calcium hydride.
- Triethylamine was distilled from, and stored over potassium hydroxide.
- *N*,*N*-Dimethylformamide (DMF), dimethylacetamide (DMA) and *N*-methyl-2-pyrrolidone (NMP) were distilled from, and stored over, 4 Å molecular sieves.
- Pyridine was distilled from potassium hydroxide, and stored over potassium hydroxide or 4 Å molecular sieves.
- Acetic anhydride was distilled, and stored over 4 Å molecular sieves.
- Methanesulphonyl chloride (MsCl) was distilled over phosphorus pentoxide, and stored over 4 Å molecular sieves.

7.2. Chromatographic separations

Separation of compounds by standard column chromatography was performed using Sigma-Aldrich or Fluka silica-gel (particle size 0.063–0.20 mm, mesh 70–230), with a silica to product ratio of 30:1. Sigma-Aldrich or Fluka silica-gel (particle size 0.035–0.070 mm, mesh 220–440) was used for preparative flash chromatography. The elution solvent system was adjusted to afford an R_f of 0.20-0.30. The silica was packed into a suitable column, and the the solvent was passed through the dry silica under pressure until no air bubbles were visible

and the silica was uniformly packed and wet. Alternatively, the appropriate amount of silica gel was measured out and a slurry was made with the indicated eluent system. This was then transferred to the column and directly used. The crude product was either adsorbed onto silica, loaded onto the silica surface or the crude product was gently loaded directly onto the silica surface in a minimum of solvent. The adsorbed product was covered with a plug of cotton wool or acid-washed sand. The elution process was performed using the indicated solvent mixtures either under gravity or air pump pressure conditions. R_f values quoted are for thin layer chromatography (TLC), which was performed using Macherey-Nagel ALUGRAMSil G/UV254 pre-coated plates with 0.20 mm silica gel 60, or Merck/Fluka silica gel 60 F254 coated on aluminium sheets. Compounds on the TLC plate were viewed under a UV lamp or with prepared stains, potassium permanganate $KMnO_4$, ceric ammonium sulphate and iodine, where additional identification was required.

7.3. Spectroscopic and physical data

- All melting points were obtained using a JM 626 melting-point apparatus with microscope and a digital thermometer, and are uncorrected.
- Infrared spectra were recorded on a Bruker Tensor 27 Fourier Transform spectrometer with diamond ATR attachment. Absorptions are reported on the wavenumber (cm^{-1}) scale, in the range 400-4000 cm^{-1}. Abbreviations used in describing the signals are: s (strong), m (medium), w (weak), br (broad). Assignments were afforded with the assistance of readily available correlation tables.
- Hydrogen (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on the Bruker Avance-300, with the proton frequency at 300.13 MHz and the carbon frequency at 75.47 MHz; or on the Bruker Avance III 500, at 500.13 MHz (proton frequency) and at 125.75 MHz (carbon frequency). The probe temperature for all experiments was 300±1 K. All spectra were recorded in deuterated chloroform ($CDCl_3$) in 5 mm NMR tubes unless otherwise stated. All NMR experiments (FIDs) were processed using Topspin 3.1 and MestReNova (version 6.0.2-5475) as software platform. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as internal standard, in the case of ^{1}H NMR spectra and relative to the central signal of deuterated chloroform taken at δ 77.00 ppm, in the case of ^{13}C NMR spectra. All NMR spectra were assigned based on chemical principles of the compounds, 2D experiments such as COSY,

HSQC, NOESY and HMBC were sometimes used for complete assignment of the NMR signals. In some selected cases, external predictive programing, such as MestReNova and ChemBioDraw (version 12.0.2.1076) were used to assist in interpreting assignments. Assignments were also based on comparisons to previously prepared and related compounds where possible. Abbreviations used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

- High resolution mass spectra (ESI/EI) were recorded on a Waters Synapt G2. The polarity was positive, and the ionization employed was ESI, with a cone voltage of 15V. A Thermo Electron Corporation DFS High Resolution Magnetic Sector mass spectrometer was also used. The polarity was positive, ionization employed was EI and a mass range of 1000 amu (5 kV) was utilized. Scan rates of 6 secs/decade for magnetic fragmentation data and 30 sec/decade for a high resolution electric scans, were used respectively. Data are quoted in relative abundance (*m/z*).
- Crystal structure intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50kV, 30mA) using the APEX 2[175] data collection software. The collection method involved ω-scans of width 0.5° and 512 × 512 bit data frames. Data reduction was carried out using the program *SAINT+*[176]. The crystal structure was solved by direct methods using *SHELXTL*[177]. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL, PLATON[178] and ORTEP-3[179].

7.4. Additional general procedures and techniques

All reactions were performed under an inert argon or nitrogen atmosphere using a standard manifold line connected to a vacuum pump. The argon was passed through self-indicating silica gel. Reaction vessels were oven dried and/or flame dried while under vacuum and were allowed to cool to room temperature before reactions took place. The microwave reactor used is the CEM Discovery, and operating conditions employed are outlined in the experimental procedures. Evaporation *in vacuo* refers to the removal of solvent under reduced pressure

(20–40 mmHg, 40–50°C) on a rotary evaporator followed by removal of trace amounts of solvent using a high vacuum (oil) pump at ~ 1-2 mmHg.

7.5. Nomenclature and numbering of compounds

The compounds prepared during this PhD project are named in the following sections according to systematic nomenclature. However, the numbering system used in the diagrams of the compounds shown in the experimental section, were adopted for convenience and ease for the discussion of the relevant compounds. It is not meant to reflect systematic numbering of these compounds.

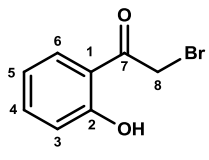
Chapter 8
Experimental procedures pertaining to Chapter 3

8.1. Preparation of di- and tetra-substituted phenacyl bromides

8.1.1. 2-Bromo-1-(2-hydroxyphenyl)ethanone (3.10) and 2-bromo-1-(4-hydroxy phenyl)ethanone (3.11)[93,94]

Anisole (14.93 g, 15.00 cm^3, 138.0 mmol) was cautiously and slowly added to an ice-cooled solution of aluminium trichloride (27.60 g, 207.0 mmol) in 1,1,2,2,-tetrachloroethane (50 cm^3). After 10 minutes, bromoacetyl chloride (23.89 g, 12.63 cm^3, 151.8 mmol) was slowly added to the mixture which was left to stir at 0ºC for an additional 20 minutes before allowing the mixture to warm to room temperature. The reaction mixture was then heated under reflux for 6 hours and then stirred at room temperature for an additional 18 hours. The product was extracted into ethyl acetate (400 cm^3) and washed with water (3 × 400 cm^3). The organic extract was then dried over sodium sulphate, filtered and evaporated under reduced pressure to afford an orange gum. Purification by column chromatography (in 30% ethyl acetate in hexane solution) afforded the *ortho* product 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10** (21.35 g, 99.27 mmol, 72%) as a pale yellow solid and the *para* product 2-bromo-1-(4-hydroxyphenyl)ethanone **3.11** (5.342 g, 24.84 mmol, 18%) as a bright yellow solid.

2-Bromo-1-(2-hydroxyphenyl)ethanone (3.10)



3.10

R_f (50% ethyl acetate in hexane): 0.76

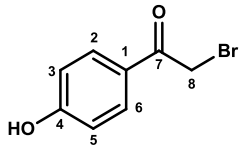
M.p.: 44–45°C (Lit.[94] 42°C)

IR (ν/cm^{-1}): 3104 (br w, OH stretch), 3047 (w, C–H stretch), 1644 (s, ketone, C=O stretch), 1613, 1388 (m, C=C stretch), 1223 (s, C–C stretch), 1155 (s, C–O stretch), 752 (s, C–H bend), 690, 634 (s, C–Br stretch)

^{1}H NMR (300 MHz, $CDCl_3$): δ 11.73 (s, 1H, OH), 7.75 (dd, J = 8.1, 1.0 Hz, 1H, H_6), 7.54 (ddd, J = 9.2, 5.2, 1.0 Hz, 1H, H_5), 7.03 (dd, J = 8.5, 0.6 Hz, 1H, H_3), 6.94 (ddd, J = 7.7, 4.5, 0.8 Hz, 1H, H_4), 4.45 (s, 2H, H_8)

^{13}C NMR (75 MHz, $CDCl_3$): δ 197.00 (C_7), 163.24 (C_2), 137.43 (C_1), 130.34 (C_3), 119.28 (C_6), 118.96 (C_5), 117.06 (C_4), 29.88 (C_8)

2-Bromo-1-(4-hydroxyphenyl)ethanone (3.11)



3.11

R_f (50% ethyl acetate in hexane): 0.38

M.p.: 129–132°C (Lit.[94] 135°C)

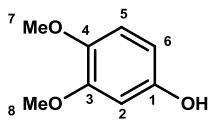
IR (ν/cm^{-1}): 3258 (br w, OH stretch), 3034 (w, C–H stretch), 1661 (s, C=O stretch), 1571, 1513 (s, C=C stretch), 1284 (m, C–C stretch), 1167 (s, C–O stretch), 843, 809 (s, C–H bend), 695 (s, C–Br stretch)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.96 (s, 1H, OH), 7.86 (d, *J* = 8.6 Hz, 2H, H_3, H_5), 6.90 (d, *J* = 8.7 Hz, 2H, H_2, H_6), 4.43 (s, 2H, H_8)

^{13}C NMR (75 MHz, DMSO) δ 189.87 (C_7), 162.94 (C_4), 131.42 (C_3, C_5), 125.54 (C_1), 115.75 (C_2, C_6), 31.21 (C_8)

8.1.2. 3,4-Dimethoxyphenol (3.14)[105]

To a solution of 3,4-dimethoxybenzaldehyde (15.94 g, 95.92 mmol) in methanol (190 cm^3) at –15ºC was added hydrogen peroxide (100 vols, 20 cm^3), followed by the catalytic amount of concentrated sulphuric acid (1.5 cm^3). The reaction mixture was stirred at –15ºC for 3 hours and then warmed to room temperature and stirred for an additional 20 hours. Activated charcoal (0.45 g) was added to the mixture and the solution was stirred for 30 minutes. The crude mixture was filtered through a column of neutral alumina and washed with an excess of methanol, the solvent was then removed by evaporation under reduced pressure. The crude product was purified by column chromatography (30% ethyl acetate in hexane) to afford the product 3,4-dimethoxyphenol **3.14** (11.79 g, 76.45 mmol, 80%) as a pale red solid.



3.14

R_f (50% ethyl acetate in hexane): 0.62

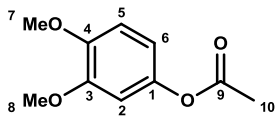
M.p.: 76–78°C (Lit.[109] 80–81°C)

IR (ν/cm^{-1}): 3334 (br w, OH stretch), 3001, 2949 (w, C–H stretch), 1673 (m, C–C stretch), 1587, 1511 (s, C=C stretch), 1242, 1017 (s, C–O–C stretch), 1137 (s, C–O stretch), 873, 733, 641 (s, C–H_{meta} bend), 802 (s, C–H_{para} bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.6 Hz, 1H, H_5), 6.47 (d, *J* = 2.7 Hz, 1H, H_2), 6.36 (dd, *J* = 8.6, 2.8 Hz, 1H, H_6), 5.83 (s, 1H, OH), 3.81 (s, 3H, H_8), 3.78 (s, 3H, H_7)
^{13}C NMR (75 MHz, $CDCl_3$) δ 150.37 (C_1), 149.84 (C_2), 142.96 (C_4), 112.64 (C_3), 106.00 (C_6), 100.72 (C_5), 56.63 (C_8), 55.76 (C_7)

8.1.3. 3,4-Dimethoxyphenyl acetate (3.15)[110]

3,4-Dimethoxyphenol **3.14** (7.068 g, 45.85 mmol) was added to an ice-cooled solution of pyridine (9.291 g, 9.5 cm^3, 117.5 mmol). Acetic anhydride (11.88 g, 11 cm^3, 116.4 mmol) was then added and the reaction mixture was stirred at 0ºC for 1 hour. The mixture was then allowed to warm to room temperature and left to stir for an additional 18 hours. The product was extracted into ethyl acetate (50 cm^3) which was washed with aqueous hydrochloric acid (2M, 3 × 50 cm^3), water (2 × 50 cm^3) and brine (50 cm^3). The organic layer was dried over sodium sulphate, filtered and the remaining residue was rinsed with additional ethyl acetate and the solvent was removed *in vacuo* to afford the pure product 3,4-dimethoxyphenyl acetate **3.15** (7.589 g, 38.68 mmol, 97%) as a dark orange oil.

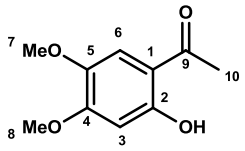


3.15

R_f (40% ethyl acetate in hexane): 0.62
IR (ν/cm^{-1}): 2961, 2834 (w, C–H stretch), 1758 (s, C=O stretch), 1602, 1508 (m, C=C stretch), 1461 (m, C–C stretch), 1282, 1262, 1125 (s, C–C(O)–C stretch), 1202, 1184 (s, ester C–O stretch), 1024 (s, ether C–O–C stretch), 923, 891, 767 (s, C–H bend)
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, 9.1 Hz, 1H, H_5), 6.67–6.61 (m, 2H, H_3, H_6), 3.86 (s, 3H, H_8), 3.85 (s, 3H, H_7), 2.28 (s, 3H, H_{10})
^{13}C NMR (75 MHz, $CDCl_3$) δ 169.80 (C_9), 149.38 (C_2), 146.86 (C_1), 144.34 (C_2), 112.83 (C_3), 111.21 (C_5), 105.75 (C_6), 56.15 (C_8), 55.93 (C_7), 21.03 (C_{10})

8.1.4. 1-(2-Hydroxy-4,5-dimethoxyphenyl)ethanone (3.16)[104,106,107]

To an ice-cooled solution of 3,4-dimethoxyphenyl acetate **3.15** (7.988 g, 40.71 mmol) was cautiously added boron trifluoride etherate, $BF_3 \cdot OEt_2$ (23.12 g, 20 cm^3, 162.9 mmol). The mixture was warmed to room temperature and then heated to 110ºC for 5 hours. It was again cooled to room temperature and stirred for an additional 18 hours. Water (50 cm^3) was added to the reaction mixture, and a brown solid precipitated out of the solution. The solid was filtered off and washed with a copious amount of water. The brown solid was then recrystallized from methanol to afford the product 1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.16** (4.898 g, 24.97 mmol, 61%) as a dark yellow crystalline solid.



3.16

R_f (50% ethyl acetate in hexane): 0.72

M.p.: 112–113°C (Lit.[180] 112–114°C)

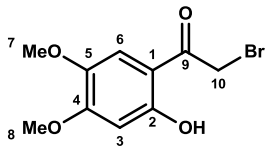
IR (ν/cm^{-1}): 3065 (w, OH stretch), 3013, 2845 (w, C–H stretch), 1632 (s, C=O stretch), 1509, 1446 (m, C=C stretch), 1335 (m. C–C stretch), 1258 (s, C–O stretch), 1204, 1160, 1064 (s, ether C–O–C stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.65 (s, 1H, OH), 7.06 (s, 1H, H_3), 6.45 (s, 1H, H_6), 3.92 (s, 3H, H_8), 3.87 (s, 3H, H_7), 2.56 (s, 3H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.04 (C_9), 160.12 (C_1), 156.82 (C_4, C_5), 141.89 (C_2), 111.72 (C_3), 100.55 (C_6), 56.69 (C_8), 56.15 (C_7), 26.34 (C_{10})

8.1.5. 2-Bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone (3.17)[100,108,181]

A solution of 1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.16** (1.326 g, 6.757 mmol) in ethyl acetate (6 cm^3) was brought to reflux. Copper(II) bromide, $CuBr_2$ (3.232 g, 14.47 mmol) in chloroform (6 cm^3) was then added and stirring under reflux was continued for 16 hours. On cooling, the reaction mixture was filtered through a plug of Celite® and rinsed with an excess of ethyl acetate. Once the solvent was removed, a crude greenish-brown solid remained which was purified by flash column chromatography (30% ethyl acetate in hexane), the product was then recrystallized from diethyl ether and ethanol to afford the product 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.17** (1.568 g, 5.699 mmol, 84%) as yellow crystals.



3.17

R_f (50% ethyl acetate in hexane): 0.38

M.p.: 118–120°C

IR (ν/cm^{-1}): 3020 (w, OH stretch), 2948, 2850 (w, C–H stretch), 1618 (s, C=O stretch), 1509, 1460 (m, C=C stretch), 1244, 1155 (s, C–O–C stretch), 1199 (s, C–O_{ketone} stretch), 970 (m, C–$O_{alcohol}$ stretch), 683 (m, C–Br stretch)

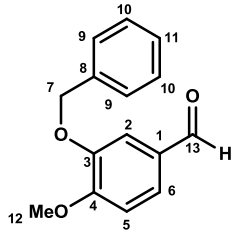
^{1}H NMR (300 MHz, $CDCl_3$) δ 12.19 (s, 1H, OH), 7.05 (s, 1H, H_3), 6.48 (s, 1H, H_6), 4.36 (s, 2H, H_{10}), 3.93 (s, 3H, H_8), 3.88 (s, 3H, H_7)

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.63 (C_9), 161.45 (C_5), 157.76 (C_4), 142.20 (C_2), 110.72 (C_3), 109.03 (C_1), 100.82 (C_6), 56.61 (C_8), 56.32 (C_7), 29.85 (C_{10})

HRMS (EI): Found M^+ = 273.9828, $C_{10}H_{11}{}^{79}BrO_4$ requires 273.9841

8.1.6. 3-(Benzyloxy)-4-methoxybenzaldehyde (3.20)[111]

To a solution of vanillin (10.03g, 65.92 mmol) in acetone (300 cm^3) was added potassium carbonate (18.24 g, 132.0 mmol). The mixture was stirred for 15 minutes at room temperature. Benzyl bromide (22.59 g, 15.6 cm^3, 131.95 mmol) was then added to the reaction vessel and the mixture was brought to reflux and stirred for 22 hours. The yellow mixture was cooled and filtered through a plug of Celite®, which was and washed with excess acetone. The solvent was evaporated under reduced pressure to give a crude yellow solid. Dichloromethane was added to dissolve the crude mixture, and the organic phase was washed with an aqueous sodium hydroxide solution (1M), followed by water and then brine. The organic layer was dried over magnesium sulphate, filtered through a sintered funnel containing Celite® and the solvent was evaporated. The crude product was purified by flash column chromatography (10–30% ethyl acetate in hexane) to afford the benzyl-protected vanillin 3-(benzyloxy)-4-methoxybenzaldehyde **3.20** (10.15 g, 41.91 mmol, 64%) as a cream crystalline solid.



3.20

R_f (30% ethyl acetate in hexane): 0.64

M.p.: 62–63°C (Lit.[112] 62–63°C)

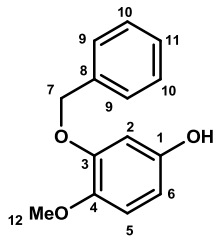
IR (ν/cm^{-1}): 2990, 2840, 2722 (w, C–H stretch), 1671 (s, C=O stretch), 1582, 1505, 1464 (m, C=C stretch), 1258, 1132, (s, ether C–O–C stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H, H_{13}), 7.51–7.26 (m, 7H, $H_{2,6,9-11}$), 6.97 (d, J = 8.2 Hz, 1H, H_5), 5.22 (s, 2H, H_7), 3.91 (s, 3H, H_{12})

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.87 (C_{13}), 153.61 (C_4), 150.08 (C_3), 136.05 (C_8), 130.32 (C_1), 128.71 (C_{10}), 128.21 (C_{11}), 127.25 (C_9), 126.53 (C_6), 112.43 (C_2), 109.43 (C_5), 70.84 (C_7), 56.01 (C_{12})

8.1.7. 3-(Benzyloxy)-4-methoxyphenol (3.21)[105]

To a solution, cooled to –15°C, of the previously prepared 3-(benzyloxy)-4-methoxybenzaldehyde **3.20** (3.006 g, 12.41 mmol) in methanol (25 cm^3) was added hydrogen peroxide (100 vols, 3 cm^3), followed by a catalytic amount of sulphuric acid (0.5 cm^3). The solution was allowed to stir at –15°C for 4 hours and then allowed to warm to room temperature and stirred for an additional 20 hours. Activated charcoal was added to the reddish-brown mixture and stirred for 30 minutes. The reaction mixture was then filtered through a plug of aluminium oxide 90 active neutral (70–230 mesh) and rinsed with methanol. The solvent was removed by rotary evaporator and the crude product was purified by flash column chromatography (30% ethyl acetate in hexane). The purified product 3-(benzyloxy)-4-methoxyphenol **3.21** (1.957 g, 8.500 mmol, 68%) was collected as an orange-brown solid.



3.21

R_f (30% ethyl acetate in hexane): 0.31

M.p.: 80–83°C (Lit.[182] 83–85°C)

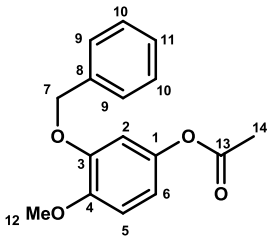
IR (ν/cm^{-1}): 3347 (m br, O–H stretch), 3085, 2939 (w, C–H stretch), 1603. 1509 (m, C=C stretch), 1212, 1192, 1028 (s, C–O–C_{ether} stretch), 1027 (s, C–$O_{alcohol}$ stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H, H_9), 7.34–7.24 (m, 3H, $H_{10,11}$), 6.68 (d, J = 8.6 Hz, 1H, H_5), 6.41 (d, J = 2.8 Hz, 1H, H_2), 6.23 (dd, J = 8.6, 2.8 Hz, 1H, H_6), 5.01 (s, 2H, H_7), 3.71 (s, 3H, H_{12}), 2.04 (s, 1H, OH)

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.15 (C_1), 150.82 (C_3), 141.79 (C_4), 137.36 (C_8), 128.48 (C_{10}), 127.88 (C_{11}), 127.68 (C_9), 116.48 (C_5), 106.27 (C_6), 101.05 (C_2), 72.48 (C_7), 55.83 (C_{12})

8.1.8. 3-(Benzyloxy)-4-methoxyphenyl acetate (3.22)[110]

Pyridine (1.956 g, 2.0 cm^3, 24.73 mmol) was added to 3-(benzyloxy)-4-methoxyphenol **3.21** (1.465 g, 6.362 mmol) at 0°C. Acetic anhydride (2.160 g, 2.0 cm^3, 21.16 mmol) was then added to the solution which was stirred at 0°C for an hour before warming the reaction vessel to room temperature and allowing a further 18 hours of stirring. The reaction mixture was then washed with an aqueous solution of hydrochloric acid (2M, 2 × 30 cm^3) was added to the reaction and the product was extracted into ethyl acetate. The aqueous layer was then washed with further portions of ethyl acetate (2 × 100) and the collected organic extracts were then washed with water and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed *in vacuo* to afford the pure product 3-(benzyloxy)-4-methoxyphenyl acetate **3.22** (1.453 g, 5.337 mmol, 84%) as a pale orange solid.



3.22

R_f (50% ethyl acetate in hexane): 0.86

M.p.: 75–77°C (Lit.[182] 76–77°C)

IR (ν/cm^{-1}): 3032, 2996, 2937 (w, C–H stretch), 1759, 1600 (m, C=O stretch), 1508 (m, C=C stretch), 1266 (m, C–C stretch), 1200, 1179, 1127 (s, C–O–C stretch), 954, 916 (s, C–O stretch)

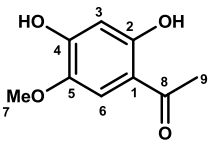
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.39 (m, 2H, H_9), 7.38–7.28 (m, 3H, $H_{10,11}$), 6.84 (d, *J* = 8.7 Hz, 1H, H_5), 6.65 (d, *J* = 2.6 Hz, 1H, H_2), 6.56 (dd, *J* = 8.7, 2.6 Hz, 1H, H_6), 5.11 (s, 2H, H_7), 3.84 (s, 3H, H_{12}), 2.25 (s, 3H, H_{14})

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.77 (C_{13}), 150.21 (C_3), 146.02 (C_1), 144.85 (C_4), 137.08 (C_8), 128.57 (C_{10}), 127.90 (C_{11}), 127.35 (C_9), 114.31 (C_5), 112.88 (C_6), 106.18 (C_2), 71.50 (C_7), 56.04 (C_{12}), 21.07 (C_{14})

HRMS (ESI+): Found $(M + H)^+$ = 273.1128 and $(M + Na)^+$ = 295.0991, $C_{16}H_{16}O_4$ requires 273.1128 and 295.0949. *M/z*: 295.0991 (50%, $(M + Na)^+$), 290.1404 (50%), 273.1128 (83%, $(M + H)^+$), 259.0968 (7%), 231.1016 (74%), 213.0888 (4%), 195.0655 (100%), 181.0971 (20%), 153.0559 (27%), 141.0648 (4%), 91.0548 (18%)

8.1.9. 1-(2,4-Dihydroxy-5-methoxyphenyl)ethanone (3.23)[104,106,107]

To an ice-cooled solution of 3-(benzyloxy)-4-methoxyphenyl acetate **3.22** (1.453 g, 7.407 mmol) was added boron trifluoride etherate (5.308 g, 4.6 cm^3, 37.04 mmol). The solution was then warmed to room temperature and heated to 110°C. After 5 hours, the reaction was cooled to room temperature and stirred for an additional 17 hours. The reaction mixture was transferred to a 600 cm^3 beaker and rinsed cautiously with saturated solutions of sodium acetate and sodium hydrogen carbonate until the reaction mixture no longer effervesced. The mixture was then extracted into ethyl acetate and the organic layer was washed with brine. The organic extract was dried over sodium sulphate and the solvent was evaporated. The crude product was then recrystallized from methanol to give the product 1-(2,4-dihydroxy-5-methoxyphenyl)ethanone **3.23** (0.1583 g, 0.9525 mmol, 13%) as a yellow powder.



3.23

R_f (50% ethyl acetate in hexane): 0.57

M.p.: 80–83°C

IR (ν/cm^{-1}): 3352 (m, br, OH stretch), 3067, 2995 (w, C–H stretch), 1643, 1614 (m, C=O stretch), 1504, 1443 (m, C=C stretch), 1267 (m, C–O stretch), 1220, 1194, 1159 (s, C–O–C_{ether} stretch), 1063 (m, C–C stretch), 1003, 963 (s, C–O stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.50 (s, 1H, C_2–OH), 7.21 (s, 1H, H_6), 6.44 (s, 1H, H_3), 5.28 (s, 1H, C_4–OH), 3.93 (s, 3H, H_7), 2.53 (s, 3H, H_9)

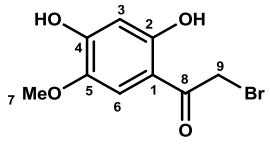
^{13}C NMR (75 MHz, $CDCl_3$) δ 202.66 (C_8), 158.90 (C_2), 153.70 (C_4), 137.98 (C_5), 113.95 (C_6), 112.50 (C_1), 99.74 (C_3), 56.19 (C_7), 26.46 (C_9)

HRMS (ESI+): Found $(M + H)^+$ = 183.0665, $C_9H_{10}O_4$ requires 183.0658.

8.1.10. 2-Bromo-1-(2,4-dihydroxy-5-methoxyphenyl)ethanone (3.24)[100,108,181]

A solution of 1-(2,4-dihydroxy-5-methoxyphenyl)ethanone **3.23** (0.0235 g, 0.129 mmol) in chloroform (2 cm^3) was brought to reflux. Copper(II) bromide (0.0720 g, 0.323 mmol) in ethyl acetate (2 cm^3) was then added and the reaction was refluxed for 43 hours. On cooling, the reaction mixture was filtered through a plug of Celite® and rinsed with ethyl acetate. The solvent was removed under vacuum and the crude product was recrystallized from methanol

to afford 2-bromo-1-(2,4-dihydroxy-5-methoxyphenyl)ethanone **3.24** (0.0223 g, 0.0854 mmol, 66%) as a yellow solid.



3.24

R_f (50% ethyl acetate in hexane): 0.48

M.p.: 108–110°C

IR (ν/cm^{-1}): 3421 (m, br, OH stretch), 2924, 2852 (w, C–H stretch), 1628 (m, C=O stretch), 1503, 1438 (m, C=C stretch), 1272, 1060 (m, C–C stretch), 1234 (m, C–O stretch), 1204, 1190, 1150 (s, ether C–O–C stretch), 1018, 989 (s, C–O stretch), 537 (C–Br stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.04 (s, 1H, C_4–OH), 7.21 (s, 1H, H_6), 6.47 (s, 1H, H_3), 5.34 (s, 1H, C_2–OH), 4.34 (s, 2H, H_9), 3.95 (s, 3H, H_7)

^{13}C NMR (75 MHz, $CDCl_3$) δ 195.11 (C_8), 160.24 (C_2), 154.72 (C_4), 138.34 (C_5), 113.18 (C_6), 109.85 (C_1), 100.07 (C_3), 56.36 (C_7), 29.98 (C_9)

8.2. Methanesulphonyl chloride protections[64]

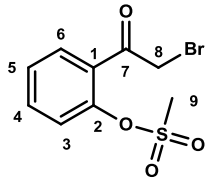
General method:

The previously prepared phenacyl bromide **3.10** and **3.17** (*Section 8.1*) (1.00 molar equivalent) was dissolved in tetrahydrofuran (2 cm^3/mmol) and stirred at –15ºC for 5 minutes. Triethylamine (1.40 molar equivalents) was then added, followed by the dropwise addition of methanesulphonyl chloride, $MeSO_2Cl$ (1.40 molar equivalents) in tetrahydrofuran (2 cm^3/mmol). The opaque mixture was allowed to stir at –15ºC for 15 minutes and then warmed to room temperature and stirred for 2 hours. The product mixture was filtered through a plug of Celite® and rinsed with additional tetrahydrofuran the solvent was then removed by means of a rotary evaporator.

8.2.1. 2-(2-Bromoacetyl)phenyl methanesulphonate (3.13)

The product was prepared from 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10** (1.58 g, 7.33 mmol), triethylamine (0.890 g, 1.2 cm^3, 8.80 mmol), methanesulphonyl chloride (1.01 g, 0.70 cm^3, 8.80 mmol) in tetrahydrofuran (20 cm^3) by the general method above. The crude orange residue obtained was purified by flash column chromatography (30% ethyl acetate in

hexane) to afford the product 2-(2-bromoacetyl)phenyl methanesulphonate **3.13** (1.99 g, 6.78 mmol, 92%) as a yellow oil.



3.13

R_f (30% ethyl acetate in hexane): 0.29

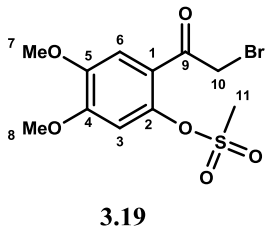
IR (ν/cm^{-1}): 3038, 2939 (w, C–H stretch), 1683 (s, C=O stretch), 1600, 1478 (m, C=C stretch), 1360, 1155 (s, S=O stretch), 1285 (s, C–O stretch), 1247 (m, C–C stretch), 976 (s, S–O stretch), 859 (S–C stretch), 795, 776 (s, C–H bend), 628 (m, C–Br stretch)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (dd, J = 7.7, 1.4 Hz, 1H, H_6), 7.61 (ddd, J = 9.0, 7.3, 1.7 Hz, 1H, H_5), 7.49–7.40 (m, 2H, H_3, H_4), 4.69 (s, 2H, H_8), 3.26 (s, 3H, H_9)

^{13}C NMR (75 MHz, d-Acetone): δ 192.13 (C_7), 147.48(C_1), 134.93(C_3), 131.67(C_5), 131.43(C_2), 128.44(C_6), 124.44(C_4), 38.57(C_9), 36.22(C_8)

8.2.2. 2-(2-Bromoacetyl)-4,5-dimethoxyphenyl methanesulphonate (3.19)

The product was prepared from 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.17** (0.771 g, 2.80 mmol) , triethylamine (0.397 g, 0.55 cm^3, 3.92 mmol), methanesulphonyl chloride (0.449 g, 0.30 cm^3, 3.92 mmol) in tetrahydrofuran (10 cm^3) using the general method. This afforded a crude gum which was purified by flash column chromatography (30% ethyl acetate in hexane) to afford the product 2-(2-bromoacetyl)-4,5-dimethoxyphenyl methanesulphonate **3.19** (0.947 g, 2.68 mmol, 96%) as a white powder.



3.19

R_f (50% ethyl acetate in hexane): 0.45

M.p.: 112–115°C

IR (ν/cm^{-1}): 3041, 2965, 2940 (w, C–H stretch), 1681 (s, C=O stretch), 1600, 1511 (m, C=C stretch), 1293 (s, C–C stretch), 1258, 1179 (s, S=O stretch), 1225 (s, C–C stretch), 1150, 1106 (s, C–O–C stretch), 1021 (m, C–O stretch), 953 (s, S–O stretch), 644 (m, C–Br stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 1H, H_6), 6.83 (s, 1H, H_3), 4.41 (s, 2H, H_{10}), 3.83 (s, 3H, H_8), 3.81 (s, 3H, H_7), 3.19 (s, 3H, H_{11})

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.60 (C_9), 153.39 (C_1), 147.65 (C_4), 141.38 (C_5), 121.14 (C_2), 112.14 (C_3), 106.54 (C_6), 56.51 (C_8), 56.30 (C_7), 48.65 (C_{11}), 34.60 (C_{10})

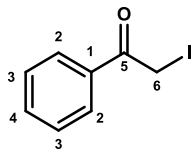
8.3. Conversion of phenacyl bromides into phenacyl iodides[102]

General method for Finkelstein iodination:

To a solution of the prepared phenacyl bromide (*Section 8.1*) (1.00 molar equivalent) in acetone (4 cm^3/mmol), was added sodium iodide (1.20 molar equivalents). The reaction was left to stir at room temperature for 3 hours. The mixture was filtered through a plug of Celite® and rinsed with excess acetone. The solvent was then removed and the crude product was extracted into ethyl acetate and washed with water and then brine. The organic extract was dried over sodium sulphate, filtered and the solvent was removed under vacuum.

8.3.1. 2-Iodo-1-phenylethanone (3.9)

The general method for iodination was used on the commercially available 2-bromo-1-phenylethanone (2.00 g, 10.1 mmol), with sodium iodide (1.81 g, 12.1 mmol) in acetone (15 cm^3). The crude brown liquid obtained was purified by flash column chromatography (20% ethyl acetate in hexane) to give the pure product 2-iodo-1-phenylethanone **3.9** (2.35 g, 9.55 mmol, 95%) as a yellow oil.



3.9

R_f (30% ethyl acetate in hexane): 0.66

IR (ν/cm^{-1}): 3059, 2974 (w, C–H stretch), 1668 (m, C=O stretch), 1597, 1579, 1492 (m, C=C stretch), 1268 (m. C–C stretch), outside area (C–I stretch)

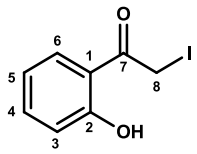
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.87 (m, 2H, H_2), 7.55–7.44 (m, 1H, H_4), 7.41–7.31 (m, 2H, H_3), 4.29 (s, 2H, H_6)

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.71 (C_5), 133.84 (C_4), 133.43 (C_3), 129.04 (C_2), 128.89 (C_3), 2.93 (C_6)

8.3.2. 1-(2-Hydroxyphenyl)-2-iodo-1-ethanone (3.12)

The product was prepared from 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10** (1.28 g, 5.91 mmol) and sodium iodide (1.06 g, 7.09 mmol) in acetone (20 cm^3) by the general method for iodination. The crude brown oil achieved was purified by column chromatography (30%

ethyl acetate in hexane) to afford the product 1-(2-hydroxyphenyl)-2-iodo-1-ethanone **3.12** (1.5376 g, 5.87 mmol, 99%) as bright yellow crystals. The product could also be purified by recrystallization from ethanol.



3.12

R_f (30% ethyl acetate in hexane): 0.72

M.p.: 59–60°C (Lit.[69] 62–63°C)

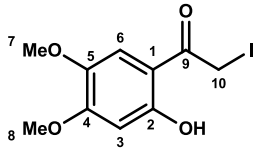
IR (ν/cm^{-1}): 3046 (w, OH stretch), 2983 (w, C–H stretch), 1610 (m, C=O stretch), 1585, 1485 (m, C=C stretch), 1249 (m. C–C stretch), 1163, 1001 (s, C–O stretch), 747 (s, C–H bend), 612 (C–I stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.86 (s, 1H, OH), 7.75 (dd, J = 8.1, 1.5 Hz, 1H, H_3), 7.51 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H, H_4), 7.02 (dd, J = 8.4, 0.9 Hz, 1H, H_6), 6.93 (ddd, J = 8.2, 7.2, 1.1 Hz, 1H, H_5), 4.37 (s, 2H, H_8).

^{13}C NMR (75 MHz, $CDCl_3$): δ 198.93 (C_7), 163.39 (C_2), 137.44 (C_3), 130.60 (C_6), 119.26 (C_4), 119.08 (C_5), 116.64 (C_1), 0.58 (C_8).

8.3.3. 1-(2-Hydroxy-4,5-dimethoxyphenyl)-2-iodoethanone (3.18)

The product was prepared from 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.17** (4.402 g, 16.00 mmol) sodium iodide (2.88 g, 19.2 mmol) in acetone (30 cm^3) using the general method for iodination. The crude product obtained was purified by flash column chromatography (40% ethyl acetate in hexane) to afford the pure product 1-(2-hydroxy-4,5-dimethoxyphenyl)-2-iodoethanone **3.18** (4.962 g, 15.41 mmol, 96%) as a bright yellow crystalline solid. Alternately, the product could be recrystallized from hot ethyl acetate, using hexane as a co-solvent.



3.18

R_f (30% ethyl acetate in hexane): 0.52

M.p.: 132–134°C

IR (ν/cm^{-1}): 3017 (w, OH stretch), 2929, 2848 (w, C–H stretch), 1631 (m, C=O stretch), 1598, 1512 (m, C=C stretch), 1275 (m. C–C stretch), 1204, 1138 (s, C–O–C_{ether} stretch), 1088, 977 (s, C–O stretch), 632 (C–I stretch)

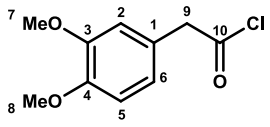
^{1}H NMR (300 MHz, $CDCl_3$) δ 12.31 (s, 1H, OH), 7.05 (s, 1H, H_3), 6.48 (s, 1H, H_6), 4.30 (s, 2H, H_{10}), 3.94 (s, 3H, H_8), 3.89 (s, 3H, H_7)

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.50 (C_9), 161.58 (C_2), 157.79 (C_4), 142.19 (C_5), 111.15 (C_1), 108.67 (C_3), 101.08 (C_6), 56.77 (C_8), 56.46 (C_7), 0.75 (C_{10})
HRMS (EI): Found M^+ = 321.9695, $C_{10}H_{11}IO_4$ requires 321.9702

8.4. Preparation of benzoin-containing phenacyl bromide

8.4.1. 2-(3,4-Dimethoxyphenyl)acetyl chloride (3.25)[112]

To a three-necked 100 cm^3 round bottom flask was added 3,4-dimethoxyphenylacetic acid (4.416 g, 22.51 mmol) in dichloromethane (45 cm^3). The reaction mixture was degassed and argon was bubbled through the solution for 10 minutes. The solution was the cooled to 0°C and oxalyl chloride (3.143 g, 2.1 cm^3, 24.76 mmol) was syringed into the reaction vessel. After 15 minutes, the ice bath was removed and the reaction was allowed to stir at ambient temperature for 18 hours. The solvent was removed and the product was carried through to the next reaction without further purification. Thus, 2-(3,4-dimethoxyphenyl)acetyl chloride **3.25** (4.828 g, 22.49 mmol, 99%) was obtained as an orange powder.

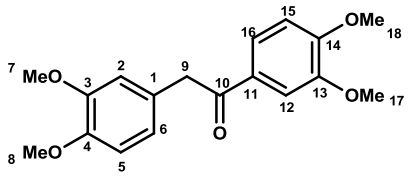


3.25

R_f (80% ethyl acetate in hexane): 0.52
M.p.: 118–120°C
IR (ν/cm^{-1}): 2941, 2839 (w, C–H stretch), 1711 (s, C=O stretch), 1592, 1541 (m, C=C stretch), 1261, 1016 (s, C–O–C_{ether} stretch), 1148 (m, C–C stretch), 626 (m, C–Cl stretch)
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87–6.73 (m, 3H, $H_{2,5,6}$), 4.06 (s, 2H, H_7), 3.86 (s, 3H, H_9), 3.85 (s, 3H, H_{10})
^{13}C NMR (75 MHz, $CDCl_3$) δ 172.16 (C_8), 149.18 (C_3), 148.95 (C_4), 123.61 (C_1), 121.99 (C_6), 112.50 (C_2), 111.39 (C_5), 55.89 (C_9), 55.85 (C_{10}), 52.58 (C_7)

8.4.2. 1,2-Bis(3,4-dimethoxyphenyl)ethanone (3.26)[112,113]

To an ice-cooled solution of 2-(3,4-dimethoxyphenyl)acetyl chloride **3.25** (4.828 g, 22.49 mmol) in dichloromethane (120 cm^3) was added veratrole (3.421 g, 3.2 cm^3, 24.76 mmol), followed by the cautious addition of aluminium trichloride (7.504 g, 56.28 mmol). The reaction was warmed to room temperature and then heated under reflux for 3 hours. On cooling to room temperature for 18 hours, the reaction mixture was quenched with an aqueous solution of hydrochloric acid (1M, 50 cm^3). The product was extracted into dichloromethane (3 × 50 cm^3) and the organic extracts were dried over sodium sulphate and the solvent was removed under reduced pressure. The crude viscous oil was purified by recrystallization from ethanol to give the benzoin product 1,2-bis(3,4-dimethoxyphenyl)ethanone **3.26** (5.174 g, 16,36 mmol, 73%) as an off-white crystalline solid.



3.26

R_f (50% ethyl acetate in hexane): 0.82

M.p.: 104–105°C (Lit.[183] 103–105°C)

IR (ν/cm^{-1}): 3080, 2834 (w, C–H stretch), 1677 (m, C=O stretch), 1585, 1516 (m, C=C stretch), 1261, 1146, 1136 (s, C–O–C stretch), 1017 (s, C–C stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.4, 2.0 Hz, 1H, H_{16}), 7.56 (d, *J* = 2.0 Hz, 1H, H_{12}), 6.88 (d, *J* = 8.4 Hz, 1H, H15), 6.83–6.78 (m, 3H, $H_{2,5,6}$), 4.19 (s, 2H, H_9), 3.94, 3.92, 3.86, 3.85 (s, 4 × 3H, $H_{7,8,17,18}$)

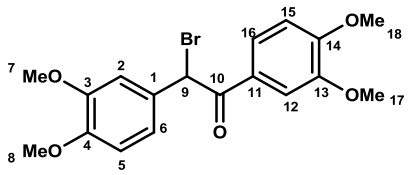
^{13}C NMR (75 MHz, $CDCl_3$) δ 196.54 (C_{10}), 153.34 (C_{14}), 149.07 ($C_{3,13}$), 147.97 (C_4), 129.75 (C_{11}), 127.50 (C_1), 123.42 (C_6), 121.45 (C_{16}), 112.46 (C_2), 111.38 (C_5), 110.70 (C_{15}), 110.01 (C_{12}), 56.04 , 55.93, 55.87, 55.85 ($C_{7,8,17,18}$), 44.74 (C_9)

HRMS (EI): Found M^+ = 316.1290, $C_{18}H_{20}O_5$ requires 316.1311.

8.4.3. 2-Bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone (3.27)[112,113]

To an ice-cooled solution of 1,2-bis(3,4-dimethoxyphenyl)ethanone **3.26** (0.141 g, 0.444 mmol) in chloroform (3 cm^3) was added 5,5-dibromopyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **3.28** (0.0825 g, 0.289 mmol). The solution was stirred at 0°C for 1 hour and then warmed to room temperature for a further 2 hours. The solvent was removed and the crude residue was washed with saturated sodium hydrogen carbonate and the organic product was

extracted into ethyl acetate (2 × 20 cm^3), the combined organic extracts were then washed with water, dried with anhydrous sodium sulphate, filtered through a sintered funnel and the solvent was extracted. The crude product was purified by flash column chromatography (10% ethyl acetate in hexane) to afford the monobrominated product 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27** (0.164 g, 0.416 mmol, 94%) as a yellow solid



3.27

R_f (50% ethyl acetate in hexane): 0.46

M.p.: 130–132°C (Lit.[183] 103–105°C)

IR (ν/cm^{-1}): 3017, 2935 (w, C–H stretch), 1659 (m, C=O stretch), 1595, 1473 (m, C=C stretch), 1264, 1011 (s, C–O–C stretch), 1138 (s, C–C stretch), 639 (s, C–Br stretch)

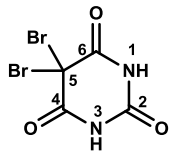
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.55 (m, 2H, $H_{12,16}$), 7.14–7.04 (m, 2H, $H_{2,15}$), 6.88–6.79 (m, 2H, $H_{5,6}$), 6.41 (s, 1H, H_9), 3.93, 3.91, 3.90, 3.86 (s, 4 × 3H, $H_{7,8,17,18}$)

^{113}C NMR (75 MHz, $CDCl_3$) δ 189.78(C_{10}), 153.82(C_{14}), 149.79(C_3), 149.40(C_{13}), 149.24(C_4), 128.62(C_{11}), 127.07(C_1), 123.68(C_6), 121.60(C_{16}), 112.00(C_2), 111.37(C_5), 111.00(C_{15}), 110.10(C_{12}), 56.12, 56.00, 55.99, 55.90($C_{7,8,17,18}$), 51.52(C_9)

HRMS (EI): Found M^+ = 394.0140, $C_{18}H_{19}{}^{79}BrO_5$ requires 394.0416

8.4.4. 5,5-Dibromopyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3.28)[114]

Bromine (16.05 g, 5.15 cm^3, 100.4 mmol) was added dropwise to a suspension of barbituric acid (5.146 g, 40.17 mmol) in water (12 cm^3). After 2 hours of stirring at ambient temperature, the reaction mixture was cooled to 0°C to allow for precipitation of the product. The crude solid was then filtered and washed with water, the product was then dried under high vacuum to afford 5,5-dibromopyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **3.28** (7.712 g, 26.98 mmol, 67%) as a white crystalline powder.



3.28

R_f (80% ethyl acetate in hexane): 0.69

M.p.: 242–246°C (Lit.[114] 235–237°C)

^{1}H NMR (300 MHz, Acetone) δ 10.77 (s, 2H, $H_{1,3}$)

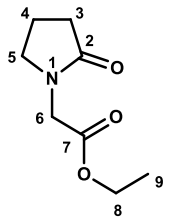
^{13}C NMR (75 MHz, Acetone) δ 163.71 ($C_{4,6}$), 148.72 (C_2), 48.16 (C_5)

Chapter 9
Experimental procedures pertaining to Chapter 4

9.1. Preparation of *N*-alkylated enaminones

9.1.1. Ethyl 2-(2-oxo-1-pyrrolidinyl)acetate (4.8)[84,125]

To a stirring solution of sodium hydride (60% dispersion in oil, 1.74 g, 43.3 mmol) in tetrahydrofuran (50 cm^3) was added 2-pyrrolidinone (3.07 g, 36.1 mmol) in tetrahydrofuran (50 cm^3) dropwise over 20 minutes. Stirring was continued at room temperature for an additional 2 hours. Ethyl 2-bromoacetate (7.23 g, 5.00 cm^3, 43.3 mmol) in tetrahydrofuran (50cm^3) was then added dropwise to the opaque white emulsion and the reaction was left to stir under an atmosphere of argon gas at room temperature for 20 hours. Water (15 cm^3) was cautiously added to the mixture and the product was then extracted into an excess of ethyl acetate (50 cm^3). The organic phase was removed and the aqueous phase was back extracted with ethyl acetate (2 × 50 cm^3). The combined organic fractions were then washed with brine (100 cm^3) and dried over anhydrous sodium sulphate. The solvent was filtered and evaporated to give a crude yellow oil which was purified using column chromatography (ethyl acetate) to afforded ethyl 2-(2-oxo-1-pyrrolidinyl)acetate **4.8** (4.76 g, 27.8 mmol, 77%) as a colourless oil. The spectroscopic data reported agreed with previously reported results.



4.8

R_f (ethyl acetate): 0.59

IR (ν/cm^{-1}): 2982 (w, C-H stretch), 1741 (s, $C{=}O_{ester}$ stretch), 1672 (s, $C{=}O_{amide}$ stretch), 1289 (C–C stretch), 1191 (s, C–O–C stretch), 1022 (s, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, J = 7.1 Hz, 2H, H_8), 4.06 (s, 2H, H_6), 3.50 (t, J = 7.0 Hz, 2H, H_3), 2.42 (t, J = 7.9 Hz, 2H, H_5), 2.16–2.03 (m, 2H, H_4), 1.28 (t, J = 7.1 Hz, 3H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.23 (C_2), 168.33 (C_7), 60.86 (C_8), 47.35 (C_3), 43.71 (C_6), 29.98 (C_5), 17.62 (C_4), 13.81 (C_9)

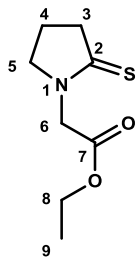
9.1.2. Ethyl 2-(2-thioxo-1-pyrrolidinyl) acetate (4.9)

Method 1:

To a solution of ethyl 2-(2-oxo-1-pyrrolidinyl)acetate **4.8** (4.76 g, 27.8 mmol) in toluene (80 cm^3) was added Lawesson's reagent (6.74 g, 16.7 mmol). On addition of the thionation reagent, the reaction mixture became bright yellow in colour. The mixture was brought to reflux and allowed to stir in an atmosphere of nitrogen for 20 hours. The solvent was evaporated *in vacuo* and the crude sample was purified, initially by column chromatography (40% ethyl acetate in hexane) and again with flash column chromatography (20% ethyl acetate in hexane) affording ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate **4.9** (4.67 g, 25.0 mmol, 90%) as a yellow oil. The spectroscopic data below was in agreement with the previously reported data.[69,76,126]

Method 2:[77,126]

To a stirring mixture of ethyl 2-(2-oxo-1-pyrrolidinyl)acetate **4.8** (2.74 g, 16.0 mmol) in dichloromethane (35 cm^3) was added phosphorus pentasulphide (1.42 g, 6.40 mmol) and hexamethyldisiloxane (3.90 g, 5.10 cm^3, 24.0 mmol). The yellow reaction mixture was left to stir at room temperature under an atmosphere of argon for 48 hours. The heterogeneous solution was then filtered thru a plug of silica gel (40 g) and the solvent was removed under reduced pressure to give the crude product as a clear yellow oil. This was then purified by flash column chromatography (40% ethyl acetate in hexane) affording the product **4.9** (1.36 g, 7.24 mmol, 45%) as a pale yellow oil.



4.9

R_f (40% ethyl acetate/hexane): 0.34

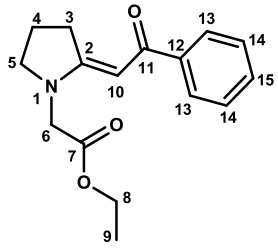
IR (ν/cm^{-1}): 2979 (w, C-H stretch), 1739 (s, C=O stretch), 1503 (s, C=S stretch) 1328(m, C–C stretch), 1223 (s, C–O–C stretch), 1196 (s, C–S stretch), 1020 (s, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (s, 2H, H_6), 4.22 (q, J = 7.1 Hz, 2H, H_8), 3.85 (t, J = 7.3 Hz, 2H, H_5), 3.07 (t, J = 7.9 Hz, 2H, H_3), 2.14 (p, J = 7.7 Hz, 2H, H_4), 1.30 (t, J = 7.1 Hz, 3H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.60 (C_2), 167.04 (C_7), 61.52 (C_8), 55.49 (C_3), 48.97 (C_6), 44.27 (C_5), 19.68 (C_4), 14.08 (C_9)

9.1.3. (*E*)-Ethyl2-[2-(2-oxo-2-phenylethylidene)pyrrolidin-1-yl]acetate(4.20)[74,76,128,129]

To an ice-cooled solution of ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate **4.9** (1.21 g, 6.46 mmol) in acetronitrile (10 cm^3) was added the previously prepared 2-iodo-1-phenylethanone **3.9** (1.93 g, 9.69 mmol). The opaque yellow reaction mixture was stirred at for 10 minutes at 0°C and then at room temperature for a further 2 hours. To a dropping funnel was added triphenylphosphine (2.68 g, 10.3 mmol) and triethylamine (1.30 g, 1.80 cm^3, 12.9 mmol) in acetonitrile (20 cm^3) which was added to the reaction mixture over 20 minutes. The reaction was then left for a further 18 hours. The solvent was removed and the product was extracted into ethyl acetate (50 cm^3) and washed with water (2 × 50 cm^3), brine (50 cm^3). The organic extracts were collected and dried over anhydrous sodium sulphate, filtered and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (40% ethyl acetate in hexane) to afford (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)pyrrolidin-1-yl]acetate **4.20** as a pale brown solid (1.62 g, 5.94 mmol, 92%).



4.20

R_f (40% ethyl acetate/ hexane): 0.14

M.p.: 81–83°C (Lit.[69] 55–57°C)

IR (ν/cm^{-1}): 3053, 2982, 2881 (w, C–H stretch), 1732 (s, C=O stretch), 1612, 1578 (m, C=C stretch), 1530 (s, C=O stretch), 1308 (m, C–C stretch), 1192 (s, C–O–C stretch), 1016 (m, C–N stretch), 927 (w, $CH_{E\text{alkene}}$ bend)

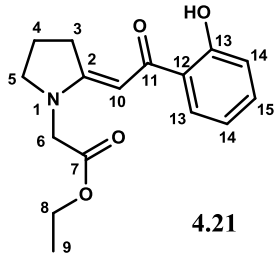
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.7, 1.8 Hz, 2H, H_{13}), 7.44–7.34 (m, 3H, $H_{14,15}$), 5.66 (s, 1H, H_{10}), 4.24 (q, *J* = 7.1 Hz, 2H, H_8), 4.06 (s, 2H, H_6), 3.56 (t, *J* = 7.3 Hz, 2H, H_3), 3.43 (t, *J* = 7.8 Hz, 2H, H_5), 2.08 (p, *J* = 7.6 Hz, 2H, H_4), 1.29 (t, *J* = 7.1 Hz, 3H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$): δ 188.24 (C_{11}), 168.15 (C_7), 167.38 (C_2), 141.77 (C_{12}), 130.64 (C_{15}), 128.16 (C_{14}), 127.36 (C_{13}), 87.28 (C_{10}), 61.73 (C_8), 53.78 (C_3), 48.26 (C_6), 33.53 (C_5), 21.30 (C_4), 14.31 (C_9).

HRMS (ESI+): Found $(M + H)^+$ = 273.1359, $C_{16}H_{19}NO_3$ requires 273.1365

9.1.4. 2-{2-[(*E*)-2-(2-Hydroxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}acetate (4.21)

The previously prepared 1-(2-hydroxyphenyl)-2-iodo-1-ethanone **3.12** (2.09 g, 7.94 mmol) was added to a stirring solution of ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate **4.9** (0.99 g, 5.29 mmol) in acetonitrile (5 cm^3). On addition of the halogenated compound the reaction mixture immediately became deep red in appearance. Stirring was continued for 18 hours at room temperature to complete the formation of the thioiminium salt. The reaction mixture was then cooled to 0°C and a dropwise addition of triphenylphosphine (2.22 g, 8.46 mmol) and triethylamine (1.07 g, 1.50 cm^3, 10.6 mmol) in acetonitrile (10 cm^3) was introduced to the salt over 10 minutes. The reaction vessel was allowed to warm to room temperature and stirring was continued for an additional 18 hours. The solvents were evaporated and the residue was extracted with ethyl acetate (100 cm^3) and washed with water (50 cm^3) and brine (50 cm^3). The organic extract was dried over anhydrous sodium sulphate, filtered and evaporated to give a red gum. Purification by flash column chromatography (30% ethyl acetate in hexane) afforded the desired 2-{2-[(*E*)-2-(2-hydroxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}acetate **4.21** (1.11 g, 3.84 mmol, 73%) as a bright yellow powder.



4.21

R_f (30% ethyl acetate in hexane): 0.28

M.p.: 91–92°C (Lit.[69] 65–66°C)

IR (ν/cm^{-1}): 2989, 2875 (w, C–H stretch), 2583 (w br, O–H stretch), 1734 (s, C=O stretch), 1613, 1576 (m, C=C stretch), 1540 (s, C=O stretch), 1342 (m, C–C stretch), 1285 (s, C–O stretch), 1192 (s, C–O–C stretch), 1018 (m, C–N stretch), 925, (m, C–$H_{E\text{alkene.}}$ bend)

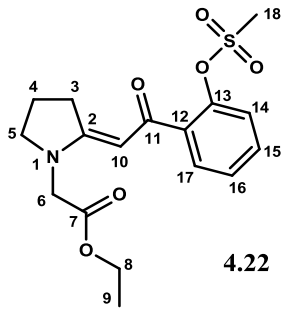
^{1}H NMR (300 MHz, $CDCl_3$) δ 13.96 (s, 1H, OH), 7.63 (dd, *J* = 8.0, 1.4 Hz, 1$H_{o,m}$, H_{14}), 7.32 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1Ho,$_{o,m}$, H_{16}), 6.92 (dd, *J* = 8.3, 0.8 Hz, 1$H_{o,m}$, H_{17}), 6.79 (ddd, *J* = 8.8, 4.7, 0.9 Hz, 1$H_{o,o,m}$, H_{15}), 5.71 (s, 1H, H_{10}), 4.26 (q, *J* = 7.1 Hz, 2H, H_8), 4.09 (s, 2H, H_6), 3.61 (t, *J* = 7.3 Hz, 2H, H_3), 3.42 (t, *J* = 7.8 Hz, 2H, H_5), 2.10 (p, *J* = 7.6 Hz, 2H, H_4), 1.31 (t, *J* = 7.1 Hz, 3H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.39 (C_{11}), 168.43 (C_7), 167.71 (C_2), 162.78 (C_{13}), 133.51 (C_{12}), 127.97 (C_{14}), 121.25 (C_{17}), 118.18 (C_{16}), 117.85 (C_{15}), 85.49 (C_{10}), 61.80 (C_8), 54.00 (C_3), 48.23 (C_6), 33.83 (C_5), 20.93 (C_4), 14.21 (C_9)

HRMS (ESI +): Calculated for $C_{16}H_{19}NO_4$ 289.1314; found $(M+H)^+$ = 289.1317

9.1.5. (*E*)-Ethyl 2-(2-{2-[2-(methylsulphonyloxy)phenyl]-2-oxoethylidene}pyrrolidin-1-yl)acetate (4.22)

Previously prepared 2-(2-bromoacetyl)phenyl methanesulphonate **3.13** (1.66 g, 5.65 mmol) was added to a stirring mixture of ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate **4.9** (0.872 g, 4.66 mmol) in dichloromethane (8 cm^3) and stirred under an atmosphere of argon gas at room temperature for 18 hours. Triphenylphosphine (1.96 g, 7.46 mmol) and triethylamine (0.943 g, 1.30 cm^3, 9.32 mmol) in dichloromethane (8 cm^3) were then added to a dropping funnel and added to the reaction mixture over 15 minutes. Stirring was then continued for 20 hours at room temperature. The reaction was quenched with water (20 cm^3) and the product was extracted and removed. The aqueous phase was further extracted with dichloromethane (2 × 20 cm^3) and the combined organic extracts were dried over anhydrous sodium sulphate. The product was then filtered and the solvent was removed by rotary evaporator. The crude product was purified by flash column chromatography (60% ethyl acetate in hexane) to afford (*E*)-ethyl 2-(2-{2-[2-(methylsulphonyloxy)phenyl]-2-oxoethylidene}pyrrolidin-1-yl)acetate **4.22** (1.40 g, 3.81 mmol, 82%) as a yellow oil.



4.22

R_f (60% ethyl acetate in hexane): 0.17

IR (ν/cm^{-1}): 3003, 2926 (w, CH stretch), 1751 (s, $C{=}O_{ester}$ stretch), 1619, 1472 (m, C=C stretch), 1526 (s, $C{=}O_{ketone}$ stretch), 1339, 1153 (s, S=O stretch), 1300 (m, $C–O_{ester}$ stretch), 1199, 1182 (m, C–N stretch),1086 (s, C–C stretch), 1022 (s, C–O–C stretch), 990 (m, $C–H_{E alkene.}$ bend)

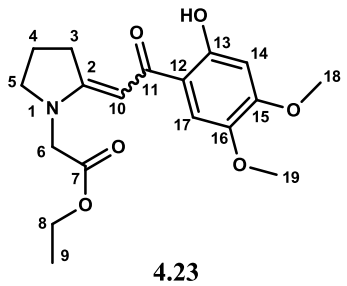
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 7.4, 1.5 Hz, 1H, H_{14}), 7.48–7.26 (m, 3H, $H_{15, 16, 17}$), 5.40 (s, 1H, H_{10}), 4.23 (q, *J* = 7.1 Hz, 2H, H_8), 4.03 (s, 2H, H_6), 3.56 (t, *J* = 7.3 Hz, 2H, H_5), 3.37 (t, *J* = 7.7 Hz, 2H, H_3), 3.09 (s, 3H, H_{20}), 2.08 (dt, *J* = 13.6, 6.8 Hz, 2H, H_4), 1.28 (t, *J* = 7.2 Hz, 3H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$): δ 186.58 (C_{11}), 175.62 (C_7), 168.68 (C_2), 145.90 (C_{12}), 137.21 (C_{13}), 130.49 (C_{17}), 129.73 (C_{14}), 127.20 (C_{15}), 123.45 (C_{16}), 91.25 (C_{10}), 61.77 (C_8), 53.76 (C_5), 44.06 (C_6), 37.59 (C_{20}), 33.71 (C_3), 20.95 (C_4), 14.11 (C_9)

HRMS (ESI+): Calculated for $C_{17}H_{21}NO_6S$: 367.1090; found $(M + H)^+$ = 367.1080. *M/z*: 361.1090 (100%, $(M + H)^+$), 278.0860 (40%)

9.1.6. (*E*)-Ethyl2-{2-[2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (4.23)

Salt formation was induced by combining ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate **4.9** (0.566 g, 3.02 mmol) and 1-(2-hydroxy-4,5-dimethoxyphenyl)-2-iodoethanone **3.18** (1.18 g, 2.82 mmol) in chloroform (5 cm^3) and stirring the dark orange mixture at room temperature for 5 hours. Triphenylphosphine (1.17 g, 4.48 mmol) and triethylamine (0.611 g, 850 µl, 6.04 mmol) in chloroform (8 cm^3) were then added dropwise to the reaction mixture over 10 minutes, which gradually began to darken in colour. Stirring was then continued at room temperature for an additional 20 hours. The solvent was then removed under vacuum and the product was extracted with ethyl acetate (50 cm^3). The organic layer was washed with saturated ammonium chloride (2 × 50 cm^3), water (2 × 50 cm^3), and brine (50 cm^3). The organic extract was then removed and dried over anhydrous sodium sulphate, filtered and the solvent was removed *in vacuo*. The crude orange oil was purified by flash column chromatography in 20% ethyl acetate in hexane to afford (*E*)-ethyl 2-{2-[2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate **4.23** (0.639 g, 2.56 mmol, 85%) as a bright yellow cuboidal crystals.



4.23

R_f (50% ethyl acetate in hexane): 0.31

M.p.: 113–115°C (Lit.[69] 79–80°C)

IR (ν/cm^{-1}): 2966, 2877 (w, C–H stretch), 2583 (w br, O–H stretch), 1735 (s, $C{=}O_{ester}$ stretch), 1615, 1578 (m, C=C stretch), 1542 (s, $C{=}O_{ketone}$ stretch), 1344 (m, C–C stretch), 1289 (s, C–O stretch), 1225, 1193, 1042 (s, C–O–C stretch), 1018 (m, C–N stretch), 927 (m, $C–H_{E alkene.}$ bend)

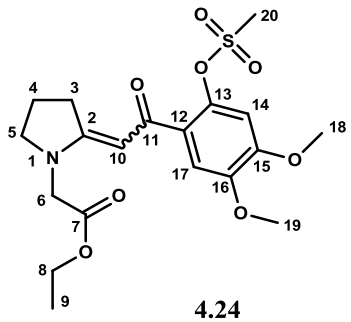
^{1}H NMR (300 MHz, $CDCl_3$) δ 14.26 (s, 1H, OH), 7.08 (s, 1H, H_{17}), 6.43 (s, 1H, H_{14}), 5.54 (s, 1H, H_{10}), 4.25 (q, *J* = 7.1 Hz, 2H, H_8), 4.08 (s, 2H, H_6), 3.87 (s, 3H, H_{18}), 3.84 (s, 3H, H_{19}), 3.59 (t, *J* = 7.3 Hz, 2H, H_3), 3.39 (t, *J* = 7.7 Hz, 2H, H_5), 2.08 (p, *J* = 7.6 Hz, 2H, H_4), 1.29 (t, *J* = 7.1 Hz, 3H, H_9).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.54 (C_{11}), 167.99 (C_7), 167.53 (C_2), 159.94 (C_{13}), 154.70 (C_{16}), 141.08 (C_{15}), 112.80 (C_{12}), 111.50 (C_{17}), 100.97 (C_{14}), 85.45 (C_{10}), 61.81 (C_8), 57.22 (C_{19}), 55.95 (C_{18}), 54.01 (C_5), 48.49 (C_6), 33.68 (C_3), 21.18 (C_4), 14.31 (C_9).

HRMS (ESI+): Found $(M+H)^+$ = 349.1525, $C_{18}H_{23}NO_6$ requires 349.1525

9.1.7. (*E*)-Ethyl 2-(2-{2-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2-oxoethylidene} pyrrolidin-1-yl)acetate (4.24)

Ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate **4.9** (0.333 g, 1.78 mmol) was dissolved in acetonitrile (3 cm^3) and 2-(2-bromoacetyl)-4,5-dimethoxyphenyl methanesulphonate **3.19** (0.817 g, 2.31 mmol) was added and stirring was continued for 30 hours at room temperature. Triphenylphosphine (0.754 g, 2.85 mmol) and triethylamine (0.547 g, 760 µl, 5.41 mmol) in acetonitrile (10 cm^3) were added to a dropping funnel and introduced to the reaction dropwise over 10 minutes with continuous stirring. Stirring was then continued for an additional 18 hours at room temperature. The solvents were evaporated and the residue was extracted with ethyl acetate (100 cm^3) and washed with saturated ammonium chloride (50 cm^3), water (50 cm^3), and brine (50 cm^3). The organic extract was dried over anhydrous sodium sulphate, filtered and evaporated to give a crude orange oil. Purification by flash column chromatography (50% ethyl acetate in hexane) afforded the desired *(E)*-ethyl 2-(2-{2-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2-oxoethylidene} pyrrolidin-1-yl)acetate **4.24** (0.473 g, 1.11 mmol, 62%) as a yellow solid.



4.24

R_f (60% ethyl acetate in hexane): 0.86

M.p.: 122–125°C

IR (ν/cm^{-1}): 2965, 2918 (w, C–H stretch), 1744 (s, $C{=}O_{ester}$ stretch), 1601, 1580 (m, C=C stretch), 1528 (s, $C{=}O_{ketone}$ stretch), 1359 (s, S=O stretch), 1301 (m, C–C stretch), 1256, 1126, 1196 (s, C–O–C stretch), 1155 (s, S–O stretch), 1069 (m, C–N stretch), 924 (m, $C–H_{E alkene.}$ bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 1H, H_{17}), 6.86 (s, 1H, H_{14}), 5.60 (s, 1H, H_{10}), 4.27 (q, *J* = 7.1 Hz, 2H, H_8), 4.06 (s, 2H, H_{10}), 3.91 (2 × s, *J* = 1.6 Hz, 6H, $H_{18,19}$), 3.57 (t, *J* = 7.3 Hz, 2H, H_5), 3.40 (t, *J* = 7.8 Hz, 2H, H_3), 3.01 (s, 3H, H_{20}), 2.10 (p, *J* = 7.6 Hz, 2H, H_4), 1.30 (t, *J* = 7.1 Hz, 3H, H_9)

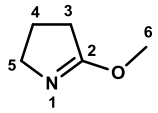
^{13}C NMR (75 MHz, $CDCl_3$) δ 184.94 (C_{11}), 168.59,167,62 (C_{15},C_{16}), 150.31 (C_7), 147.53 (C_2), 139.88 (C_{12}), 128.28 (C_{13}), 111.45 (C_{17}), 106.69 (C_{14}), 91.15 (C_{10}), 61.62 (C_8), 56.14 (C_{18}), 55.96 (C_{19}), 53.54 (C_5), 47.54 (C_6), 36.74 (C_{20}), 33.64 (C_3), 20.81 (C_4), 13.93 (C_9)

HRMS (ESI+): Found $(M + H)^+$ = 427.1294, $C_{19}H_{25}NO_8S$ requires 427.1301

9.2. Preparation of *N*-phenacyl enaminones

9.2.1. 2-Methoxy-3,4-dihydro-5*H*-pyrrole (4.10)[99,127]

A solution 2-pyrrolidinone (11.2 g, 10.0 cm^3, 132 mmol) and dimethyl sulphate (18.3 g, 14.0 cm^3, 145 mmol) was stirred at room temperature for 2 hours before increasing the temperature to 60ºC for 17 hours. The reaction was then cooled to room temperature and carefully poured into an aqueous solution of potassium carbonate (2M, 20.3 g, 0.147 mmol, in 75 cm^3 of water). After an hour of stirring the solution was transferred to a separating funnel and the organic layer was extracted with diethyl ether (3 × 200 cm^3). The combined organic fractions were dried over anhydrous sodium sulphate and filtered. The solvent was cautiously evaporated *in vacuo* at a water bath temperature not exceeding 20–30ºC to afford the crude product as a pale yellow liquid. The crude product was purified by vacuum distillation (36–41ºC, 21 mmHg) to afford 5-methoxy-3,4-dihydro-2*H*-pyrrole **4.10** (8.43 g, 85.1 mmol, 65%) as a colourless, clear liquid.



4.10

R_f (ethyl acetate): 0.39

IR (ν/cm^{-1}): 2952 (w, C–H stretch), 1670 (s, C=N stretch), 1392 (s, C–N stretch), 1258 (s, C–O–C stretch) 1202 (m, C–C stretch)

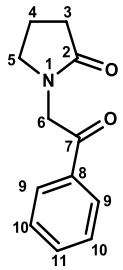
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H, CH_3), 3.66 (td, *J* = 7.2, 1.2 Hz, 2H, H_5), 2.45 (td, *J* = 8.4, 0.8 Hz, 2H, H_3), 2.03 (tdd, *J* = 8.2, 7.5, 0.6 Hz, 2H, H_4)

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.79 (C_2), 55.25 (C_5), 54.90 (C_3), 30.78 (C_4), 23.29 (CH_3)

9.2.2. 1-(2-Oxo-2-phenylethyl)pyrrolidin-2-one (4.12)[127]

To a solution of 5-methoxy-3,4-dihydro-2*H*-pyrrole **4.10** (0.647g, 6.52 mmol) dissolved in *N*,*N*-dimethylformamide (4 cm^3) was added 2-bromo-1-phenylethanone (1.30 g, 6.52 mmol). The mixture was then heated to approximately 60ºC and stirred for 20 hours. On cooling to room temperature, the reaction was quenched with an aqueous solution of sodium hydroxide (2M, 2.05 g, 100 mmol, in 50 cm^3 of water) and the organic phase extracted with ethyl acetate (3 × 50 cm^3). The organic phase was washed with water (2 × 50 cm^3), followed by brine (50 cm^3). The combined organic fractions were dried over sodium sulphate, filtered and evaporated *in vacuo* to give the crude product as an orange oil. Flash column

chromatography (50% ethyl acetate in hexane) rendered the purified product 1-(2-oxo-2-phenylethyl)pyrrolidin-2-one **4.12** (0.969 g, 4.77 mmol, 73%) as a white powder. Data agreed with previously reported results.[69,127]



4.12

R_f (ethyl acetate): 0.54

M.p.: 64–66°C (Lit.[69] 69–71°C)

IR (ν/cm^{-1}): 2961, 2876 (w, C–H stretch), 1673 (s, C=O_{ketone} stretch), 1593, 1422 (m, C=C stretch), 1446 (s, C=O_{amide} stretch), 1286 (s, C–C stretch), 1066 (m, C–N stretch)

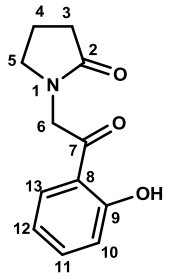
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 ($dd_{o,m}$, J = 7.4 Hz, 2H, H_9), 7.60 ($dd_{o,m}$, J = 7.4 Hz, 1H, H_{11}), 7.48 ($dd_{o,o}$, J = 7.6 Hz, 2H, H_{10}), 4.74 (s, 1H, H_6), 3.50 (t, J = 7.0 Hz, 1H, H_3), 2.48 (t, J = 8.1 Hz, 1H, H_5), 2.10 (p, J = 7.6 Hz, 2H, H_4)

^{13}C NMR (75 MHz, $CDCl_3$) δ 193.88 (C_7), 175.80 (C_2), 134.95 (C_8), 133.82 (C_{11}), 128.86 (C_{10}), 128.03 (C_9), 49.11 (C_6), 47.91 (C_3), 30.45 (C_5), 18.10 (C_4)

HRMS (EI): Found M^+ = 203.0940, $C_{12}H_{13}NO_2$ requires 203.0946. *M/z*: 203.0940 (100%, M^+), 200.9956 (4%), 194.0800 (28%)

9.2.3. 1-[2-(2-Hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-one (4.13)

To a solution of 5-methoxy-3,4-dihydro-2*H*-pyrrole **4.10** (0.817 g, 8.24 mmol) dissolved in *N*,*N*-dimethylformamide (5 cm^3) was added 2-bromo-1-(2-hydroxyphenyl)ethanone (1.79 g, 8.32 mmol). The mixture was then heated to 60–80ºC and stirred for 16 hours. On cooling to room temperature the reaction was quenched with an aqueous solution of sodium hydroxide (1 M, 0.41 g, 10 mmol, in 10 cm^3 of water) and the organic phase extracted with ethyl acetate (3 × 50 cm^3). The organic phase was washed with water (2 × 50 cm^3), followed by brine (50 cm^3). The combined organic fractions were dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to give the crude product as an yellow oil. Flash column chromatography (50–80% ethyl acetate in hexane) rendered an off white solid, which was recrystallized from ethanol to give the purified product 1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-one **4.13** (1.00 g, 4.58 mmol, 57%) as pale cream coloured flaky crystals.



4.13

R_f (50% EtOAc/hexane): 0.10

M.p.: 119–120°C

IR (ν/cm^{-1}): 3217 (w, OH stretch), 2943, 2717 (w, C–H stretch), 1673, 1455 (w, C=C stretch), 1644 (s, C=O$_{ketone}$ stretch), 1595 (m, C=O$_{amide}$ stretch), 1281 (m, C–C stretch), 1108 (m, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.77 (s, 1H, OH), 7.75 (d$_o$ (d$_m$), J = 7.9 Hz, 1H, H_{10}), 7.51 (d$_o$(d$_m$), J = 7.8 Hz, 1H, H_{13}), 6.95–6.92 (m, (d$_o$, J = 7.6 Hz, 2H, $H_{11,12}$), 4.77 (s, 2H, H_6), 3.51 (t, J = 7.0 Hz, 2H, H_3), 2.50 (t, J = 8.1 Hz, 2H, H_5), 2.13 (p, J = 7.5 Hz, 2H, H_4)

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.45 (C_7), 176.01 (C_2), 162.53 (C_9), 137.11 (C_8), 129.24 (C_{10}), 119.42 (C_{13}), 118.82 (C_{12}), 118.04 (C_{11}), 48.61 (C_6), 48.09 (C_3), 30.43 (C_5), 18.24 (C_4)

HRMS (EI): Found M^+ = 219.0891, $C_{12}H_{13}NO_3$ requires 219.0895

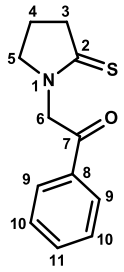
9.2.4. 1-Phenyl-2-(2-thioxopyrrolidin-1-yl)ethanone (4.14)

Method 1:

To a solution of 1-(2-oxo-2-phenylethyl)pyrrolidin-2-one **4.12** (0.481 g, 2.36 mmol) in toluene (15 cm^3) was added Lawesson's reagent (0.571 g, 1.42 mmol). The mixture was heated to 80–90ºC and allowed to stir for 18 hours. The mixture was allowed to cool to room temperature and the solvent was evaporated *in vacuo*. The crude sample was purified by column chromatography (50% ethyl acetate in hexane) affording 1-phenyl-2-(2-thioxopyrrolidin-1-yl)ethanone **4.14** (0.377 g, 1.72 mmol, 73%) as a yellow solid. The spectroscopic data below was in agreement with the previously reported data.[69,76,126]

Method 2:

To a solution of 1-(2-oxo-2-phenylethyl)pyrrolidin-2-one **4.12** (0.969 g, 4.77 mmol) in dichloromethane (10 cm^3) was added phosphorus pentasulphide (0.320 g, 1.43 mmol) and hexamethyldisiloxane (1.40 g, 1.80 cm^3, 8.59 mmol). The yellow reaction mixture was left to stir at room temperature for 20 hours. The heterogeneous solution was then filtered through a plug of silica gel (20 g) and the solvent was removed under reduced pressure to give the crude product as a yellow gum. This was then purified by flash column chromatography (40% ethyl acetate in hexane) affording the product **4.14** (0.719 g, 3.28 mmol, 69%).



4.14

R_f (50% ethyl acetate in hexane): 0.45

M.p.: 96–98°C (Lit.[69] 78–79°C)

IR (ν/cm^{-1}): 3052, 2898 (w, C–H stretch) 1689 (s, C=O_{ketone} stretch), 1596, 1449 (w, C=C stretch), 1514 (s, C=S stretch), 1326 (m, C–C stretch), 1126 (s, C–S stretch), 1062 (m, C–N stretch)

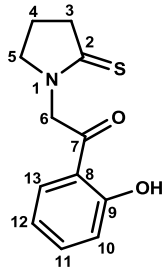
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d_o(d_m), *J* = 7.4 Hz, 2H, H_9), 7.60 (d_o(d_m), *J* = 7.4 Hz, 1H, H_{11}), 7.48 (d_o(d_o), *J* = 7.6 Hz, 2H, H_{10}), 5.27 (s, 1H, H_6), 3.81 (t, *J* = 7.3 Hz, 2H, H_3), 3.07 (t, *J* = 7.9 Hz, 2H, H_5), 2.10 (p, *J* = 7.7 Hz, 2H, H_4)

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.11 (C_2), 191.87 (C_7), 134.61 (C_8), 133.83 (C_{11}), 128.71 (C_{10}), 127.81 (C_9), 55.58 (C_3), 53.86 (C_6), 44.10 (C_5), 19.59 (C_4)

HRMS (EI): calculated for $C_{12}H_{13}NO_5$ 219.0718 found 219.0708

9.2.5. 1-(2-Hydroxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone (4.15)

1-[2-(2-Hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-one **4.13** (0.350 g, 1.60 mmol) was dissolved in dichloromethane (6 cm^3). Phosphorus pentasulphide (0.213 g, 0.958 mmol) and hexamethyldisiloxane (0.468 g, 612 µl, 2.88 mmol) were then added to the stirring mixture which was allowed to stir at room temperature for 2 days. The heterogeneous solution was then filtered through a plug of silica gel (18 g) and rinsed with an excess of dichloromethane. The solvent was removed under reduced pressure to give an orange residue which was purified by flash column chromatography (40% ethyl acetate in hexane) affording the product 1-(2-hydroxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone **4.15** (0.174 g, 0.743 mmol, 46%) as a yellow solid.



4.15

R_f (60% ethyl acetate in hexane): 0.45

M.p.: 128–130°C

IR (ν/cm^{-1}): 3050 (w, OH stretch), 2981, 2909 (w, C–H stretch), 1642 (s, C=O stretch), 1574, 1446 (w, C=C stretch), 1509 (s, C=S stretch), 1274 (m, C–C stretch), 1235 (s, C–O stretch), 1153 (s, C–S stretch), 1018 (m, C–N stretch)

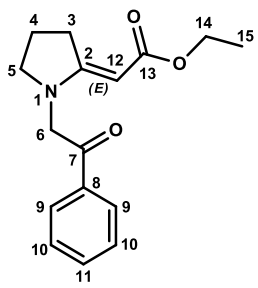
^{1}H NMR (300 MHz, $CDCl_3$) δ 11.66 (s, 1H, OH), 7.78 (d_o (d_m), *J* = 8.0, 1.2 Hz, 1H, H_{10}), 7.68–7.41 (m, 1H, H_{13}), 7.13–6.88 (m, 2H, $H_{11,12}$), 5.32 (s, 2H, H_6), 3.85 (t, *J* = 7.3 Hz, 2H, H_3), 3.15 (t, *J* = 7.9 Hz, 2H, H_5), 2.18 (p, *J* = 7.7 Hz, 2H, H_4)

^{13}C NMR (75 MHz, $CDCl_3$) δ 204.15 (C_2), 197.55 (C_7), 162.51 (C_8), 137.34 (C_9), 129.14 (C_{13}), 119.54 (C_{10}), 118.90 (C_{12}), 118.05 (C_{11}), 55.85 (C_6), 53.38 (C_3), 44.32 (C_5), 19.96 (C_4)
HRMS (ESI+): Found $(M + H)^+$ = 235.0675, $C_{12}H_{13}NO_2S$ requires 235.0667. *M/z*: 235.0675 (100%, $(M + H)^+$), 220.0931 (2%), 219.0908 (9%)

9.2.6. (*E*) and (*Z*)-Ethyl 2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]acetate (4.25)[74,76,128,129]

To a reaction vessel containing 1-phenyl-2-(2-thioxopyrrolidin-1-yl)ethanone **4.14** (1.73 g, 7.90 mmol) in chloroform (10 cm^3) was added ethyl 2-bromoacetate (1.58 g, 1.05 cm^3, 9.48 mmol). The reaction mixture was stirred at room temperature for 6 hours before adding sodium iodide (0.922 g, 6.32 mmol), and the reaction was stirred for a further 14 hours. Triphenylphosphine (2.28 g, 8.69 mmol) and triethylamine (0.959 g, 1.30 cm^3, 9.48 mmol) were dissolved in chloroform (15 cm^3) and were added dropwise to the bright orange emulsion, at 0ºC. After 30 minutes, the mixture was allowed to warm to room temperature and left to stir for an additional 20 hours. The reaction slowly began to change in appearance to a deep red colour. The reaction mixture was then poured into a separating funnel and washed with saturated ammonium chloride (2 × 50 cm^3), water (2 × 50 cm^3) and brine (50 cm^3). The organic layer was then collected and dried in anhydrous sodium sulphate, filtered and the solvent was evaporated. The crude oil was purified by flash column chromatography (30–50% ethyl acetate in hexane) to afford (*E*)-ethyl 2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]acetate **4.25*E*** (1.083 g, 3.96 mmol, 50%) as a yellow solid. After further elution by column chromatography an orange-brown solid was afforded (*Z*)-ethyl 2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]acetate **4.25*Z*** (0.709 g, 2.59 mmol, 33%).

(E)-ethyl 2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]acetate (4.25E)



4.25 (*E*)

R_f (50% ethyl acetate in hexane): 0.28

M.p.: 45– 48°C

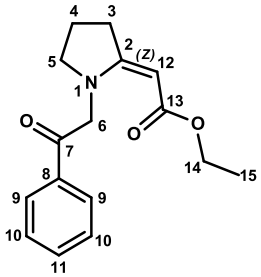
IR (ν/cm^{-1}): 2982, 2930 (w, C–H stretch), 1700 (s, $C{=}O_{ester}$ stretch), 1675 (s, $C{=}O_{ketone}$ stretch), 1579, 1480 (m, C=C stretch), 1276 (m, C–C stretch), 1176 (s, C–O–C stretch), 1057 (m, C–N stretch), 886 (s, $CH_{Ealkene.}$ bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.41 (m, 1H, H_9), 7.44–7.29 (m, 1H, $H_{10,11}$), 6.28 (s, 1H, H_{12}), 5.07 (s, 2H, H_6), 4.24 (q, *J* = 7.1 Hz, 2H, H_{14}), 3.14 (t, *J* = 7.0 Hz, 2H, H_3), 2.20 (t, *J* = 8.1 Hz, 2H, H_5), 1.74 (p, *J* = 7.4 Hz, 2H, H_4), 1.33 (t, *J* = 7.1 Hz, 3H, H_{15})

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.84 (C_7), 166.22 (C_{13}), 154.37 (C_2), 137.85 (C_8), 129.67 (C_{11}), 128.68 (C_{10}), 127.06 (C_9), 120.99 (C_{12}), 60.53 (C_{14}), 46.27 (C_3), 40.03 (C_6), 30.71 (C_5), 17.78 (C_4), 14.39 (C_{15})

HRMS (ESI+): Found $(M + H)^+$ = 273.1367, $C_{16}H_{19}NO_3$ requires 273.1365. *M/z*: 273.1367 (100%, $(M + H)^+$), 228.1028 (37%)

(Z)-Ethyl 2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]acetate (4.25Z)



4.25 (*Z*)

R_f (50% ethyl acetate in hexane): 0.14

M.p.: 54–56°C

IR (ν/cm^{-1}): 3051, 2990 (w, C–H stretch), 1723 (s, $C{=}O_{ester}$ stretch), 1684 (s, $C{=}O_{ketone}$ stretch), 1591, 1484 (m, C=C stretch), 1221, 1188 (s, C–O–C stretch), 1095 (s, C–C stretch), 996 (m, C–N stretch), 694 (s, $CH_{Zalkene.}$ bend)

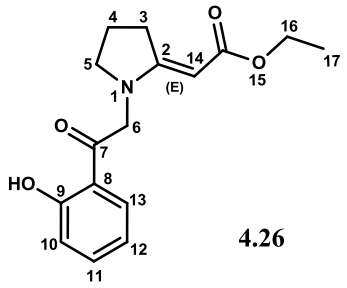
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.19 (m, 5H, $H_{9,10,11}$), 5.86 (s, 1H, H_{11}), 4.22 (s, 1H, H_6), 4.00 (q, *J* = 7.1 Hz, 2H, H_{13}), 3.32 (t, *J* = 7.0 Hz, 2H, H_3), 2.33 (t, *J* = 8.0 Hz, 2H, H_5), 2.06–1.88 (m, 2H, H_4), 1.07 (t, *J* = 7.1 Hz, 3H, H_{14})

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.06 (C_7), 165.51 (C_{12}), 152.75 (C_2), 137.10 (C_8), 133.24 (C_{11}), 128.34 (C_{10}), 127.46 (C_9), 117.77 (C_{11}), 60.10 (C_{13}), 49.41 (C_3), 47.10 (C_6), 30.46 (C_5), 17.89 (C_4), 13.88 (C_{14})

9.2.7. (*E*)-Ethyl 2-{1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-ylidene}acetate (4.26)

To a minimum of chloroform (2 cm^3) was added 1-(2-hydroxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone **4.15** (0.11 g, 0.45 mmol). Ethyl 2-bromoacetate (0.094 g, 62 µl, 0.56 mmol) was added to the reaction mixture followed by the addition of sodium iodide (0.033 g, 0.23 mmol), which immediately darkened the mixture to a dark orange colour. The mixture was stirred at room temperature for 16 hours to ensure completion of the salt formation. From deductions made from TLC, the reaction then proceeded with the dropwise addition of a

solution of triphenylphosphine (0.14 g, 0.52 mmol) and triethylamine (0.051 g, 70 µl, 0.50 mmol) in chloroform (4 cm^3) which was stirred for an additional 18 hours at room temperature. The product was then filtered through a plug of Celite® and rinsed with excess dichloromethane and the solvent was then removed *in vacuo*. The orange residues was extracted into ethyl acetate (100 cm^3) and washed with ammonium chloride (2 × 100 cm^3), water (100 cm^3) and brine (100 cm^3). The organic extract was then dried (sodium sulphate), filtered and the solvent was evaporated. Purification of the crude product was done by flash column chromatography (40–60% ethyl acetate in hexane) to afford the product (*E*)-ethyl 2-{1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-ylidene}acetate **4.26** (0.094 g, 0.32 mmol, 72%) as a white powder.



4.26

R_f (50% ethyl acetate in hexane): 0.11

M.p.: 118–120°C

IR (ν/cm^{-1}): 3671 (w, O–H stretch), 3056, 2981 (w, C–H stretch), 1708 (s, $C{=}O_{ester}$ stretch), 1654 (s, $C{=}O_{ketone}$ stretch), 1590, 1482 (m, C=C. stretch), 1287 (s, C–C stretch), 1218, 1185 (s, C–O–C stretch), 1120 (s, C–O stretch), 997 (m, C–N stretch), 939 (s, $CH_{E\text{alkene.}}$ bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H, OH), 7.21 (td, *J* = 7.9, 1.6 Hz, 1H, H_{11}), 7.09 (dd, *J* = 7.6, 1.5 Hz, 1H, H_{10}), 6.97 (dd, *J* = 8.1, 0.8 Hz, 1H, H_{15}), 6.86 (td, *J* = 7.5, 1.0 Hz, 1H, H_{12}), 6.10 (s, 1H, H_{14}), 4.83 (s, 2H, H_{14}), 4.22 (q, *J* = 7.1 Hz, 2H, H_{16}), 3.39 (t, *J* = 7.0 Hz, 2H, H_3), 2.26 (t, *J* = 8.0 Hz, 2H, H_5), 1.92–1.79 (m, 2H, H_4), 1.32 (t, *J* = 7.1 Hz, 3H, H_{17})

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.96 (C_7), 166.01 (C_{15}), 154.49 (C_2), 153.33 (C_9), 133.18 (C_8), 130.26 (C_{10}), 129.47 (C_{13}), 122.07 (C_{11}), 120.11 (C_{12}), 118.49 (C_{14}), 60.24(C_{16}), 48.69 (C_3), 43.62 (C_6), 30.75 (C_5), 18.15 (C_4), 14.26 (C_{17})

HRMS (ESI+): Found $(M + H)^+$ = 289.1304, $C_{16}H_{19}NO_4$ requires 289.1314. *M/z*: 289.1304 (36%, $(M + H)^+$), 280.0966 (18%), 278.0855 (100%)

9.3. Acid-induced pyrrole ring formations[69,88]

General experimental methods:

Method 1:

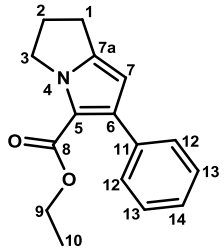
To a solution of the prepared enaminone (*Section 9.1*) in xylene (6–10 cm^3/mmol) was added silica gel (10 times the mass of the starting material). The heterogeneous mixture was heated under reflux for 18 hours under an atmosphere of argon. When the reaction was complete, as judged by TLC, the mixture was allowed to cool to room temperature. The residue was filtered through a plug of Celite® and washed with an excess of acetone. The solvents were then removed by rotary evaporation and the residue was purified by column chromatography.

Method 2:

The prepared enaminone (*Section 9.1*) was dissolved in xylene (6–10 cm^3/mmol) and silica gel (10 times mass of starting material) was added to the solution. The mixture was then irradiated under microwave conditions (150W, 200°C, 15 min). The reaction mixture was then filtered through a plug of Celite® and rinsed with acetone, until the colour was removed and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography.

9.3.1. Ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.29)

The product was prepared from (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)pyrrolidin-1-yl]acetate **4.20** (0.807 g, 2.95 mmol) and silica gel (4 g) in xylene (8 cm^3) by general method 1 and **4.20** (0.213 g, 0.779 mmol) and silica gel (2.08 g) in xylene (6 cm^3) by general method 2. The crude product obtained was purified by flash column chromatography in 5% ethyl acetate in hexane. This afforded ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.29** (0.637 g, 2.50 mmol, 85% by method 1 and 0.186 g, 0.730 mmol, 94% by method 2) as a pale yellow oil.



4.29

R_f (10% ethyl acetate in hexane): 0.25

IR (ν/cm^{-1}): 3065, 2981, 2763 (w, C–H stretch), 1675 (s, C=O stretch), 1603, 1458 (m, C=C stretch), 1177 (m, C–C stretch), 1109 (s, C–O–C stretch), 1036 (m, C–N stretch)

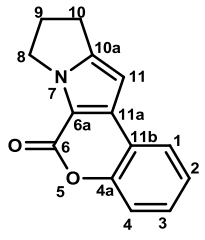
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 ($d_o d_m$, J = 5.2, 3.2 Hz, 2H, H_{12}), 7.39–7.19 (m, 3H, $H_{13,14}$), 5.94 (s, 1H, H_7), 4.30 (t, J = 7.2 Hz, 2H, H_3), 4.16 (q, J = 7.1 Hz, 2H, H_9), 2.83 (t, J = 7.5 Hz, 2H, H_1), 2.46 (p, J = 7.4 Hz, 2H, H_2), 1.16 (t, J = 7.1 Hz, 3H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.37 (C_8), 142.33 ($C7_a$), 137.40 (C_5), 136.70 (C_6), 129.66 (C_{12}), 127.41 (C_{13}), 126.57 (C_{14}), 114.32 (C_{11}), 103.51 (C_7), 59.53 (C_9), 48.86 (C_3), 26.77 (C_2), 24.49 (C_1), 14.16 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 255.1261, $C_{16}H_{17}NO_2$ requires 255.1259. *M/z*: 255.1261 (100%, $(M + H)^+$), 209.0840 (48%)

9.3.2. 9,10-Dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.32)

The product was prepared from the previously synthesized 2-{2-[(*E*)-2-(2-hydroxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}acetate **4.21** (0.12 g, 0.41 mmol) and silica gel (1.3 g) in xylene (6 cm^3) by method 1; and (0.097 g, 0.34 mmol) and silica gel (1.0 g) in xylene (3 cm^3) by method 2. The crude product obtained was purified by flash column chromatography (10–20% ethyl acetate in hexane) to afford the product which was recrystallized from a dichloromethane and hexane mixture to give 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.32** (0.058 g, 0.26 mmol, 63% by method 1 and; 0.057 g, 0.25 mmol, 74% by method 2) as pale cream filamentous crystals.



4.32

R_f (50% ethyl acetate in hexane): 0.41

M.p.: 232–233°C

IR (ν/cm^{-1}): 2987, 2742 (w, C–H stretch), 1692 (s, C=O stretch), 1614, 1486 (w, C=C stretch), 1309 (m, C–O stretch), 1260 (m, C–C stretch), 1198 (s, C–O–C stretch), 1078 (m, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, J = 7.6, 1.2 Hz, 1H, H_1), 7.36 (dd,

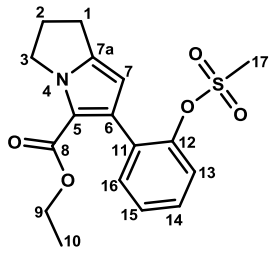
J = 8.2, 1.5 Hz, 1H, H_3), 7.31 (dd, *J* = 8.2, 1.6 Hz, 1H, H_2), 7.24 (dd, *J* = 7.5, 1.5 Hz, 1H, H_4), 6.31 (s, 1H, H_{11}), 4.37 (t, *J* = 7.2 Hz, 2H, H_8), 2.96 (t, *J* = 7.4 Hz, 2H, H_{10}), 2.60 (p, *J* = 7.5 Hz, 2H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.10 (C_6), 151.47 (C_{6a}), 148.96 (C_{10a}), 134.08 (C_{11a}), 127.47 (C_{4a}), 124.00 (C_2), 122.94 (C_4), 118.75 (C_1), 117.30 (C_3), 112.85 (C_{11b}), 94.54 (C_{11}), 46.99 (C_8), 27.52 (C_9), 24.78 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 225.0788, $C_{14}H_{11}NO_2$ requires 225.0790

9.3.3. Ethyl 6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.30)

The compound was prepared from (*E*)-ethyl 2-(2-{2-[2-(methylsulphonyloxy)phenyl]-2-oxoethylidene}pyrrolidin-1-yl)acetate **4.22** (0.66 g, 1.8 mmol) and silica gel (6.6 g) in xylene (20 cm^3) by method 1; **4.22** (0.12 g, 0.32 mmol) and silica gel (1.2 g) in xylene (3 cm^3) by method 2. The crude product obtained was purified by flash column chromatography (40% ethyl acetate in hexane) to afford the ethyl 6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.30** (0.14 g, 0.41 mmol, 23% by method 1 and; 0.081 g, 0.23 mmol, 72% by method 2) as dark orange cuboidal crystals.



4.30

R_f (50% ethyl acetate in hexane): 0.52

M.p.: 68–71°C

IR (ν/cm^{-1}): 2979 (w, C–H stretch), 1683 (s, C=O stretch), 1502, 1478 (w, C=C stretch), 1362 (s, S=O stretch), 1179 (m, C–C stretch), 1112, 1081 (s, C–O stretch), 1030 (m, C–N stretch)

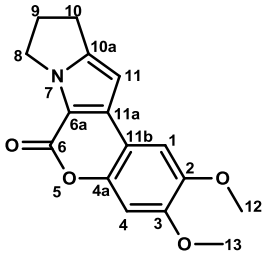
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.26 (m, 4H, $H_{12,13,14,15}$), 5.98 (s, 1H, H_7), 4.34 (t, *J* = 7.4 Hz, 2H, H_3), 4.11 (q, *J* = 7.1 Hz, 2H, H_9), 2.90 (t, *J* = 7.5 Hz, 2H, H_1), 2.68 (s, 3H, H_{17}), 2.59–2.48 (m, 2H, H_2), 1.07 (t, *J* = 7.1 Hz, 3H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.14 (C_8), 147.15 (C_{16}), 142.48 (C_{7a}), 132.52 (C_{15}), 130.50 (C_5), 130.24 (C_6), 128.50 (C_{12}), 126.70 (C_{14}), 122.93 (C_{13}), 115.80 (C_{11}), 104.16 (C_7), 59.87 (C_9), 48.69 (C_3), 37.43 (C_{17}), 26.96 (C_2), 24.60 (C_1), 14.04 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 349.0973, $C_{17}H_{19}NO_5S$ requires 349.0984. *M/z*: 349.0973 (100%, $(M + H)^+$), 303.0560 (44%)

9.3.4. 2,3-Dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.33)

The product was prepared from (*E*)-ethyl 2-{2-[2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate **4.23** (0.33 g, 0.95 mmol) and silica gel (3.5 g) in xylene (12 cm^3) by method 1; and **4.23** (0.17 g, 0.50 mmol) and silica gel (2.1 g) in xylene (7 cm^3) by method 2. The crude product was purified by flash column chromatography (40% ethyl acetate in hexane) to afford the 2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.33** (0.062 g, 0.22 mmol, 23% by method 1 and; 0.12 g, 0.41 mmol, 82% by method 2) as very fine pale brown crystals.



4.33

R_f (50% ethyl acetate in hexane): 0.36

M.p.: 218–220°C

IR (ν/cm^{-1}): 2986, 2829 (w, C–H stretch), 1704 (s, C=O stretch), 1625, 1523, 1463 (w, C=C stretch), 1231, 1181, 1136 (m, C–O–C stretch), 1060 (m, C–N stretch), 986 (s, C–C stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 1H, H_4), 6.82 (s, 1H, H_1), 6.16 (s, 1H, H_{11}), 4.29 (t, *J* = 7.1 Hz, 2H, H_8), 3.88 (s, 3H, H_{13}), 3.84 (s, 3H, H_{12}), 2.89 (t, *J* = 7.4 Hz, 2H, H_{10}), 2.54 (p, *J* = 7.3 Hz, 2H, H_9)

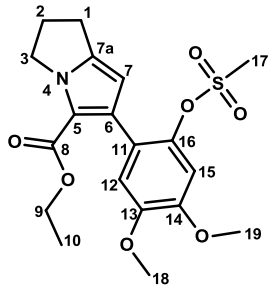
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.41 (C_6), 149.17 (C_{6a}), 149.00 (C_{10a}), 146.18 (C_3), 146.15 (C_2), 134.67 (C_{11a}), 112.09 (C_{4a}), 110.87(C_{11b}), 104.18 (C_4), 100.93 (C_1), 93.76 (C_{11}), 56.43 (C_{13}), 56.21 (C_{12}), 46.96 (C_8), 27.49 (C_9), 24.84 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 285.1007, $C_{16}H_{15}NO_4$ requires 285.1001

9.3.5. Ethyl 6-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.31)

The product was prepared by the general procedure for ring closures mentioned above, from *(E)*-ethyl 2-(2-{2-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2-oxoethylidene}pyrrolidin-1-yl)acetate **4.24** (0.24 g, 0.57 mmol) and silica gel (2.5 g) in xylene (7 cm^3) by method 1; and **4.24** (0.083 g, 0.19 mmol) and silica gel (0.90 g) in xylene (4 cm^3) by method 2. The residue afforded was purified by flash column chromatography (5-40% ethyl acetate in hexane) to give ethyl 6-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-

2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.31** (0.084 g, 0.21 mmol, 36% using method 1 and; 0.049 g, 0.12 mmol, 63% using method 2) as pale cream cuboidal crystals.



4.31

R_f (ethyl acetate): 0.86

M.p.: 115–118°C

IR (ν/cm^{-1}): 2984, 2936 (w, CH stretch), 1684 (s, C=O stretch), 1517, 1480 (w, C=C stretch), 1357, 1118 (s, S=O stretch), 1249 (m, C–O–C stretch), 1015 (m, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 1H, H_{15}), 6.86 (s, 1H, H_{12}), 5.99 (s, 1H, H_7), 4.35 (t, J = 7.1 Hz, 1H, H_3), 4.16 (q, J = 7.1 Hz, 2H, H_9), 3.94 (s, 3H, H_{19}), 3.88 (s, 3H, H_{18}), 2.91 (t, J = 7.4 Hz, 2H, H_1), 2.66 (s, 3H, H_{17}), 2.54 (dd, J = 14.5, 7.2 Hz, 2H, H_2), 1.14 (t, J = 7.1 Hz, 3H, H_{10})

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.00 (C_8), 148.50 (C_{16}), 147.16 (C_{14}), 142.37 (C_{7a}), 140.25 (C_{13}), 130.21 (C_5), 121.99 (C_6), 115.63 (C_{11}), 114.02 (C_{12}), 106.70 (C_{15}), 104.13 (C_7), 59.76 (C_9), 56.25 (C_{19}), 56.12 (C_{18}), 48.67 (C_3), 36.95 (C_{17}), 26.83 (C_2), 24.52 (C_1), 14.17 (C_{10})

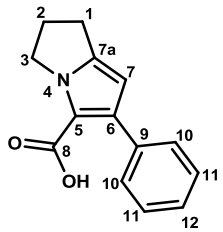
HRMS (ESI+): Found $(M + H)^+$ = 409.1179, $C_{19}H_{23}NO_7S$ requires 409.1195. *M/z*: 409.1179 (100%, $(M + H)^+$), 363.0761 (12%), 284.0901 (13%)

9.4. New method for lactone formation by ester saponification

9.4.1. 6-Phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylic acid (4.53)[143]

A prepared solution of potassium hydroxide (3.36 g, 59.9 mmol) in methanol (6 cm^3) was added to ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.29** (0.258 g, 1.01 mmol). The opaque mixture was stirred at 30°C for 1 hour; the temperature was then raised to 60°C when TLC analysis confirmed only starting material was present in the reaction mixture. Similarly, the temperature was raised to 80°C for an hour and then finally to 100°C for an hour, until it was confirmed by TLC that the product had formed. The crude mixture was extracted into diethyl ether (2 × 20 cm^3) to remove any remaining starting material. The aqueous phase was then acidified by the dropwise addition of concentrated hydrochloric acid. This was then extracted with additional diethyl ether (2 × 20 cm^3) and the collected organic phase was dried over sodium sulphate, filtered and the solvent was evaporated to afford a crude pale brown solid. The crude solid was recrystallized from ethyl acetate to afford the

product 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylic acid **4.53** (0.178 g, 0.785 mmol, 78%) as a white crystalline solid.



4.53

R_f (50% ethyl acetate in hexane): 0.64

M.p.: 160–162°C

IR (ν/cm^{-1}): 3053, 2850 (w, C–H stretch), 3049–2440 (w, br, OH stretch), 1641 (s, C=O stretch), 1603, 1488 (m, C=C stretch), 1364 (s, OH bend), 1302, 1267 (s, C–O stretch), 1172 (m, C–C stretch), 1070 (s, C–N stretch)

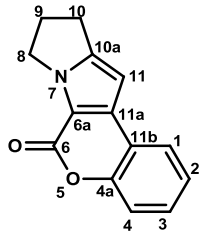
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.89 (s, 1H, OH), 7.51–7.50 (m, 2H, H_{10}), 7.38–7.27 (m, 3H, $H_{11, 12}$), 5.98 (s, 1H, H_7), 4.34 (t, *J* = 7.0 Hz, 2H, H_3), 2.89 (t, *J* = 7.3 Hz, 2H, H_1), 2.57–2.42 (m, 2H, H_2)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.87 (C_8), 143.65 ($C7_a$), 139.12 (C_5), 136.21 (C_6), 129.61 (C_{10}), 127.69 (C_{11}), 126.85 (C_{12}), 113.28 (C_9), 104.30 (C_7), 49.21 (C_3), 26.62 (C_2), 24.61 (C_1)

HRMS (ESI+): Found $(M + H)^+$ = 228.1021 and $(M + Na)^+$ = 250.0836, $C_{14}H_{13}NO_2$ requires 228.1025 and 250.0846. *M/z*: 250.0836 (10%, $(M + Na)^+$), 228.1021 (100%, $(M + H)^+$), 210.0920 (48%), 184.1129 (14%)

9.4.2. 9,10-Dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.32 from 4.53)[36,52,53,141,142]

To a solution of 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylic acid **4.53** (0.0595 g, 0.262 mmol) in ethyl acetate (6 cm^3) was added lead(IV) acetate, $Pb(OAc)_4$ (0.208 g, 0.470 mmol). The opaque white mixture was stirred at ambient temperature for 1 hour, whereby the solution darkened to a dark orange and gradually lightened to a yellow-orange opaque mixture. The reaction mixture was acidified with a 20% solution of citric acid and extracted into ethyl acetate (3 × 10 cm^3). The combined organic phase was then washed with brine (20 cm^3), collected and dried over sodium sulphate. The product was then filtered and the solvent was removed *in vacuo*. The crude product obtained was purified by flash column chromatography (5–20% ethyl acetate in hexane) to afford 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.32** (0.0198 g, 0.0879 mmol, 34%) as a pale brown solid. The ^{1}H NMR was compared to the previous method for the preparation of **4.32** to confirm the product had formed. (*see Section 9.3.2*).



4.32

R_f (50% ethyl acetate in hexane): 0.39

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.0, 1.3 Hz, 1H, H_1), 7.36–7.27 (m, 3H, $H_{2,3,4}$), 6.15 (s, 1H, H_{11}), 4.25 (t, *J* = 7.2 Hz, 2H, H_8), 2.86 (t, *J* = 7.0 Hz, 2H, H_{10}), 2.65 – 2.54 (m, 2H, H_9)

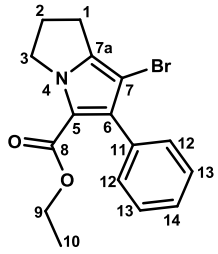
9.5. Bromination of various pyrrole ring compounds[67,135]

General method:

To an ice-cold solution of the prepared pyrrole-containing compounds (*Section 9.3*) in *N*,*N*-dimethylformamide (3–6 cm^3/mmol) was added dropwise *N*-bromosuccinimide (1.10 molar equivalent) in *N*,*N*-dimethylformamide (3-6 cm^3/mmol). The reaction mixture was stirred at 0°C for an hour and then warmed to room temperature and continued stirring for 20 hours under an argon atmosphere. The mixture was then quenched with water and extracted with diethyl ether.

9.5.1. Ethyl 7-bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.40)

The product was prepared from ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.29** (0.323 g, 1.27 mmol) and *N*-bromosuccinimide (0.338 g, 1.90 mmol) in *N*,*N*-dimethylformamide (10 cm^3) by the general method above. The crude liquid obtained was purified by flash column chromatography (5% ethyl acetate in hexane) to afford ethyl 7-bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.40** (0.354 g, 1.10 mmol, 87%) as a yellow solid.



4.40

R_f (50% ethyl acetate in hexane): 0.83

M.p.: 75–77°C

IR (ν/cm^{-1}): 3058, 2980, 2959 (w, C–H stretch), 1683 (s, C=O stretch), 1604, 1464 (w, C=C stretch), 1173 (m, C–C stretch), 1113 (s, C–O–C stretch), 1050 (m, C–N stretch), 672 (m, C-Br stretch)

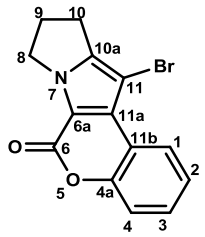
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.35 (m, 5H, $H_{12,13,14}$), 4.38 (t, *J* = 7.2 Hz, 2H, H_3), 4.09 (q, *J* = 7.1 Hz, 2H, H_9), 2.97–2.54 (m, 2H, H_1), 2.51 (d, *J* = 7.4 Hz, 2H, H_2), 1.06 (t, *J* = 7.1 Hz, 3H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.78 (C_8), 141.22 (C_{7a}), 135.05 (C_6), 134.34 (C_5), 130.60 (C_{12}), 127.41 (C_{13}), 127.25 (C_{14}), 115.72 (C_{11}), 91.36 (C_7), 59.85 (C_9), 49.99 (C_3), 26.12 (C_2), 24.35 (C_1), 14.01 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 333.0361, $C_{16}H_{16}{}^{79}BrNO_2$ requires 333.0364. *M/z*: 335.0375 (98%) for isotope ^{81}Br, 333.0361 (100%, $(M + H)^+$) for isotope ^{79}Br, 288.9957 (30%), 286.9941 (30%), 255.1258 (12%)

9.5.2. 11-Bromo-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.46)

The product was prepared by the general method for bromination described above, from 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.32** (0.062 g, 0.27 mmol) and *N*-bromosuccinimide (0.049 g, 0.27 mmol) in *N*,*N*-dimethylformamide (6 cm^3). The crude product 11-bromo-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.46** was recrystallized from dichloromethane and hexane to give white cylindrical crystals (0.049 g, 0.16 mmol, 59%).



4.46

R_f (50% ethyl acetate in hexane): 0.62

M.p.: 221–223°C

IR (ν/cm^{-1}): 3050, 2866 (w, C–H stretch), 1716 (s, C=O stretch), 1524, 1484 (w, C=C stretch), 1296 (m, C–O stretch), 1226 (m, C–C stretch), 1092 (m, C–N stretch), 660 (m, C–Br bend)

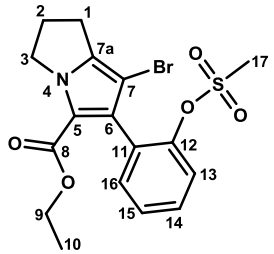
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52–8.46 (m, 1H, H_1), 7.43–7.32 (m, 2H, $H_{2,3}$), 7.33–7.23 (m, 1H, H_4), 4.46 (t, *J* = 7.2 Hz, 2H, H_8), 2.94 (t, *J* = 7.5 Hz, 2H, H_{10}), 2.65 (p, *J* = 7.6 Hz, 2H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.27 (C_6), 151.28 (C_{6a}), 147.50 (C_{10a}), 129.35 (C_{11a}), 127.95 (C_4), 123.87 (C_3), 122.50 (C_2), 118.04 (C_{4a}), 117.28 (C_1), 113.05 (C_{11b}), 83.78 (C_{11}), 48.40 (C_8), 26.59 (C_9), 24.31 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 302.9906, $C_{14}H_{10}{}^{79}BrNO_2$ requires 302.9895. *M/z*: 304.9885 (100%, for ^{81}Br isotope), 302.9895 (98%, $(M + H)^+$, for ^{79}Br isotope)

9.5.3. Ethyl 7-bromo-6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.41)

The product was prepared from ethyl 6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.30** (0.178 g, 0.510 mmol) and *N*-bromosuccinimide (0.0908 g, 0.510 mmol) in *N*,*N*-dimethylformamide (10 cm^3) by the general method. The crude product obtained was recrystallized from hot ethyl acetate with several hexane droplets to give the pure product ethyl 7-bromo-6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.41** (0.168 g, 0.392 mmol, 77%) as a white cuboidal crystalline solid.



4.41

R_f (50% ethyl acetate in hexane): 0.66

M.p.: 141–143°C

IR (ν/cm^{-1}): 3028, 2982, 2904 (w, C–H stretch), 1687 (s, C=O stretch), 1477 (w, C=C stretch), 1358 (m, S=O stretch), 1252 (m, C–N stretch), 1117, 1097 (s, C–O stretch), 1034 (m, C–C stretch), 670 (m, C-Br stretch)

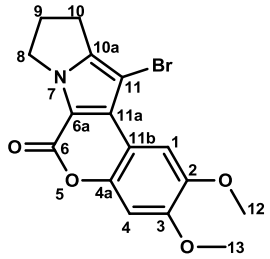
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.29 (m, 4H, $H_{13,14,15,16}$), 4.45 (dt, *J* = 12.3, 7.6 Hz, 2H, H_3), 4.15–402 (m, 2H, H_9), 2.90 (dt, *J* = 11.9, 7.8 Hz, 2H, H_1), 2.73 (s, 1H, H_{17}), 2.57 (p, *J* = 7.4 Hz, 2H, H_2), 1.02 (t, *J* = 7.1 Hz, 3H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.31 (C_8), 147.84 (C_5), 141.34 (C_{7a}), 132.82 (C_{16}), 129.29 (C_{15}), 128.48 (C_6), 128.11 (C_{16}), 126.71 (C_{14}), 122.67 (C_{13}), 117.04 (C_{11}), 91.59 (C_7), 60.18 (C_9), 49.97 (C_3), 37.30 (C_{17}), 26.26 (C_2), 24.37 (C_1), 13.88 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 427.0079, $C_{17}H_{18}{}^{79}BrNO_5S$ requires 427.0089. *M/z*: 429.0059 (100%, ^{81}Br isotope), 427.0079 (97%, $(M + H)^+$, ^{79}Br isotope), 382.9638 (49%), 380.9659 (43%)

9.5.4. 11-Bromo-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.47)

The product was prepared from 2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.33** (0.038 g, 0.14 mmol) and *N*-bromosuccinimide (0.041 g, 0.21 mmol) in *N*,*N*-dimethylformamide (2 cm^3) by the general method. The crude solid obtained was recrystallized from an ethanol and diethyl ether mixture to give the pure product 11-bromo-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.47** (0.035 g, 0.097 mmol, 72%) as a pale pink fluffy solid.



4.47

R_f (50% ethyl acetate in hexane): 0.83

M.p.: 239–241°C

IR (ν/cm^{-1}): 2954, 2838 (w, C–H stretch), 1704 (s, C=O stretch), 1624, 1592, 1530 (w, C=C stretch), 1173, 1123, (s, C–O stretch), 1040 (m, C–N stretch), 996 (s, C–C stretch), 668 (m, C–Br stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H, H_4), 6.92 (s, 1H, H_1), 4.46 (t, *J* = 7.2 Hz, 2H, H_8), 3.98 (s, 3H, H_{13}), 3.93 (s, 3H, H_{12}), 2.97 (t, *J* = 7.4 Hz, 2H, H_{10}), 2.64 (p, *J* = 7.5 Hz, 2H, H_9)

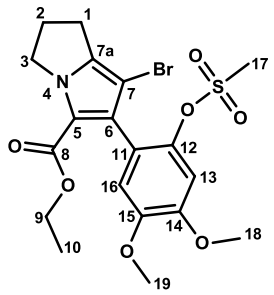
^{13}C NMR (75 MHz, $CDCl_3$) δ 162.81 (C_6), 154.79 (C_{6a}), 149.40 (C_{10a}), 147.58 (C_3), 146.37 (C_2), 145.86 (C_{4a}), 112.43 (C_{11a}), 110.29 (C_{11b}), 103.88 (C_4), 100.92 (C_1), 82.95 (C_{11}), 56.35 (C_{13}), 56.25 (C_{12}), 48.49 (C_8), 26.77 (C_9), 24.51 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 363.0111, $C_{16}H_{14}{}^{79}BrNO_4$ requires 363.0106. *M/z*: 365.0091 (98%, ^{81}Br isotope), 363.0111 (100%, $(M + H)^+$, ^{79}Br isotope)

9.5.5. Ethyl 7-bromo-6-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.42)

The product was prepared by the general method for bromination (above) from ethyl 6-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.31** (0.11 g, 0.26 mmol) and *N*-bromosuccinimide (0.10 g, 0.57 mmol) in *N*,*N*-dimethylformamide (6 cm^3). The crude product obtained from the reaction was recrystallized from hot ethyl acetate with some hexane droplets to give the pure product ethyl 7-bromo-6-[4,5-dimethoxy-

2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.42** (0.12 g, 0.25 mmol, 95%) as a pale cream solid.



4.42

R_f (50% ethyl acetate in hexane): 0.62

M.p.: 183–185°C

IR (ν/cm^{-1}): 2989, 2937 (w, C–H stretch), 1688 (s, C=O stretch), 1618, 1526 (w, C=C stretch), 1384 (s, S=O stretch), 1250 (m, C–N stretch), 1161, 1111 (s, C–O stretch), 1042 (m, C–C stretch), 649 (m, C-Br stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H, H_{15}), 6.77 (s, 1H H_{13}), 4.48 (dt, *J* = 12.2, 7.0 Hz, 2H, H_3), 4.33 (dt, *J* = 12.0, 7.4 Hz, 2H, H_3), 4.10 (q, *J* = 7.1 Hz, 2H, H_9), 2.89 (t, *J* = 7.1 Hz, 2H, H_1), 2.68 (s, 3H, H_{17}), 2.56 (p, *J* = 7.4 Hz, 2H, H_2), 1.09 (t, *J* = 7.1 Hz, 3H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.17 (C_8), 149.02 (C_5), 147.20 (C_{7a}), 141.14 (C_{15}), 141.05 (C_{14}), 128.30 (C_6), 119.43 (C_{12}), 116.97 (C_{11}), 114.12 (C_{13}), 106.52 (C_{16}), 90.21 (C_7), 60.06 (C_9), 56.23 (C_{18}), 56.18 (C_{19}), 49.93 (C_3), 36.75 (C_{17}), 26.09 (C_2), 24.26 (C_1), 13.99 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 487.0293, $C_{19}H_{22}{}^{79}BrNO_7S$ requires 487.0300. *M/z*: 490.0307 (22%), 489.0276 (100%) for ^{81}Br isotope, 488.0319 (18%), 487.0293 (90%, $(M + H)^+$) for ^{79}Br isotope

9.6. Suzuki-Miyaura couplings using phenylboronic acid

General procedure 1:[134]

Tetrakis(triphenylphosphine)palladium(0) (0.1–0.3 molar equivalent) was added to a two-necked round bottomed flask, fitted with a dropping funnel and a reflux condenser; and the system was degassed (5 × with argon gas). 1,2-Dimethoxyethane (7 cm^3/mmol of starting material), phenylboronic acid, $PhB(OH)_2$ (1.5 molar equivalent), the previously prepared brominated compound (*Section 9.5*) (1 molar equivalent) was added to the dropping funnel and degassed for an additional 10 minutes, ethanol (5 cm^3/mmol) was added to the mixture in the dropping funnel if dissolution of the mixture became problematic. The mixture was then added dropwise over 15 minutes to the palladium(0)tetrakis vessel. A 2M aqueous solution of sodium carbonate (2.5 cm^3/mmol) was then prepared and added to the dropping funnel, degassed for 10 minutes and added to the reaction vessel. The mixture was refluxed for 20

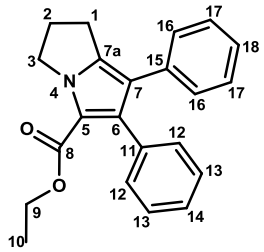
hours under an atmosphere of argon gas. On cooling, water (25–30 cm^3/mmol) was added to the reaction mixture and the organic phase was extracted with ethyl acetate. The collected organic fractions were then washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent was evaporated to give the crude product. Purification of the product was carried out by column chromatography and/or recrystallization.

General procedure 2:[67,136]

To an oven dried two-necked round bottom flask was added to a solution of the previously prepared brominated compound (*Section 9.5*) (1 molar equivalent) in *N*,*N*-dimethyformamide (14 cm^3/mmol) and degassed. Phenylboronic acid (1.2 molar equivalent) and Palladium(0)tetrakis (0.1 molar equivalents) were then added to the reaction vessel and the system was again degassed with argon. Lastly, a saturated solution of sodium carbonate (3 molar equivalents) was degassed and added to the mixture. The reaction was refluxed for 20 hours under an atmosphere of argon gas. On cooling, water was added to the vessel and an extraction of the organic phase was done with diethyl ether and ethyl acetate (2:1). The organic extract was washed with water (3 times), and the organic phase was then dried over anhydrous sodium sulphate. This was then filtered off and the solvent was evaporated *in vacuo* to give the crude product. Purification of the product was carried out by column chromatography and/or recrystallization.

9.6.1. Ethyl 6,7-diphenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.43)

Using general method 2, the product was formed from the previously brominated ethyl 7-bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.40** (0.16 g, 049 mmol), phenylboronic acid (0.074 g, 0.61 mmol), tetrakis(triphenylphosphine)palladium(0) (0.076 g, 0.066 mmol) and sodium carbonate (0.17 g, 1.6 mmol) in *N*,*N*-dimethyformamide (8 cm^3). The crude product attained was purified by flash column chromatography (10–30% ethyl acetate in hexane), it was then recrystallized from ethanol to give the pure product ethyl 6,7-diphenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.43** (0.13 g, 0.37 mmol, 76%) as an dark red cuboidal crystalline solid.



4.43

R_f (50% ethyl acetate in hexane): 0.90

M.p.: 89–91°C

IR (ν/cm^{-1}): 3083, 2971, 2844 (w, C–H stretch), 1674 (s, C=O stretch), 1602, 1464 (w, C=C stretch), 1129 (m, C–C stretch), 1093 (s, C–O stretch), 1040 (m, C–N stretch) 779, 764, 705 (m, s, C–H bend)

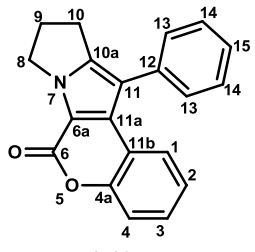
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.16 (m, 5H, $H_{12,13,14}$), 7.13–7.01 (m, 5H, $H_{16,17,18}$), 4.40 (t, *J* = 7.2 Hz, 2H, H_3), 4.10 (q, *J* = 7.1 Hz, 2H, H_9), 3.03 (t, *J* = 7.4 Hz, 2H, H_1), 2.63–2.47 (m, 2H, H_2), 1.06 (t, *J* = 7.1 Hz, 3H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.58 (C_8), 140.76 (C_{7a}), 135.87 (C_5), 135.16 (C_7), 134.24 (C_6), 131.00 (C_{12}), 128.66 (C_{16}), 128.12 (C_{17}), 127.46 (C_{13}), 126.61 (C_{14}), 125.44 (C_{18}), 117.25 (C_{15}), 115.84 (C_{11}), 59.62 (C_9), 48.94 (C_3), 26.64 (C_2), 25.13 (C_1), 14.11 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 331.1574, $C_{22}H_{21}NO_2$ requires 331.1572. *M/z*: 331.1574 (100%, $(M + H)^+$), 285.1152 (13%)

9.6.2. 11-Phenyl-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.48)

The product was prepared by general method 1 above, from 11-bromo-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.46** (0.090 g, 0.31 mmol), phenylboronic acid (0.075 g, 0.61 mmol), tetrakis(triphenylphosphine)palladium(0) (0.090 g, 0.078 mmol) and sodium carbonate (0.16 g, 1.6 mmol) in 1,2-dimethoxyethane (3 cm^3) and ethanol (3 cm^3). The crude product was purified by flash column chromatography (10–30% ethyl acetate in hexane), it was then recrystallized from ethanol to give the pure product 11-phenyl-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.48** (0.064 g, 0.21 mmol, 68%) as a white cuboidal crystalline solid.



4.48

R_f (50% ethyl acetate in hexane): 0.86

M.p.: 228–230°C

IR (ν/cm^{-1}): 3026, 2921, 2853 (w, C–H stretch), 1715 (s, C=O stretch), 1602, 1471 (w, C=C stretch), 1192 (s, C–O stretch), 1067 (s, C–N stretch), 988 (m, C–C stretch), 750, 733 (s, C–H bend)

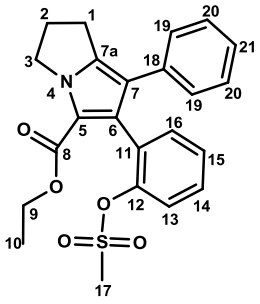
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d(d), *J* = 7.9 Hz, 1H, H_{13}), 7.47–7.45 (m, 4$H_{1,2,3,4}$), 7.45–7.22 (m, 3H, $H_{14,15}$), 7.02 (d(d), *J* = 7.6 Hz, 1H, H_{13}), 4.49 (t, *J* = 7.2 Hz, 2H, H_8), 2.95 (t, *J* = 7.4 Hz, 2H, H_{10}), 2.65 (p, *J* = 7.3 Hz, 2H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.37 (C_6), 151.62 (C_{4a}), 147.25 (C_{10a}), 134.69 (C_{11}), 129.87 (C_{13}), 129.53 (C_{11a}), 128.82 (C_{14}), 127.43 (C_{15}), 127.39(C_4), 123.70 (C_3), 123.38(C_2), 119.14 (C_{6a}), 117.55 (C_1), 113.47 (C_{11b}), 113.06 (C_{12}), 47.61 (C_8), 27.20 (C_9), 24.35 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 301.1103, $C_{20}H_{15}NO_2$ requires 301.1103

9.6.3. Ethyl 6-{2-[(methylsulphonyl)oxy]phenyl}-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.44)

The product was prepared from ethyl 7-bromo-6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.41** (0.17 g, 0.39 mmol), phenylboronic acid (0.092 g, 0.75 mmol), tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.11 mmol) and sodium carbonate (0.21 g, 1.9 mmol) in 1,2-dimethoxyethane (3 cm^3) and ethanol (2 cm^3) by method 1. The crude product was purified by flash column chromatography (10–30% ethyl acetate in hexane), it was then recrystallized from ethanol to give the pure product ethyl 6-[2-(methylsulphonyloxy)phenyl]-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.44** (0.16 g, 037 mmol, 95%) as a pale orange cuboidal crystalline solid.



4.44

R_f (50% ethyl acetate in hexane): 0.62

M.p.: 117–119°C

IR (ν/cm^{-1}): 3048, 2983, 2931 (w, C–H stretch), 1694 (s, C=O stretch), 1605, 1524, 1507 (w, C=C stretch), 1363 (s, S=O stretch), 1225 (m, C–N stretch), 1159, 1104 (s, C–O stretch), 1043 (m, C–C stretch), 879, 772, 757 (s, C–H bend)

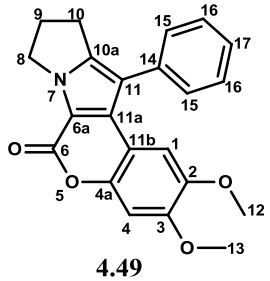
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–6.97 (m, 9H, ArH), 4.41 (dt, *J* = 12.0, 7.2 Hz, 2H, H_3), 4.09 (q, *J* = 7.1 Hz, 2H, H_9), 3.06 (t, *J* = 7.4 Hz, 2H, H_1), 2.65 (s, 3H, H_{17}), 2.57 (p, *J* = 7.3 Hz, 2H, H_2), 1.02 (t, *J* = 7.1 Hz, 3H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.26 (C_8), 147.89 (C_5), 140.81 (C_{7a}), 134.75 (C_{12}), 133.45 (C_{16}), 129.39 (C_6), 128.70 (C_{21}), 128.42 (C_{19}), 128.06 (C_{20}), 127.18 (C_{18}), 126.47 (C_{14}), 125.87 (C_{15}), 122.32 (C_{13}), 117.69 (C_{11}), 116.58 (C_7), 59.92 (C_9), 48.89 (C_3), 37.81 (C_{17}), 26.70 (C_2), 25.23 (C_1), 13.9 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 425.1307, $C_{23}H_{23}NO_5S$ requires 425.1297. *M/z*: 425.1307 (100%, $(M + H)^+$), 380.0918 (3%), 379.0885 (14%), 350.1020 (2%), 349.0885 (12%), 303.0575 (5%)

9.6.4. 2,3-Dimethoxy-11-phenyl-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.49)[135]

To a sealed microwave vessel containing 1,2-dimethoxyethane (1.5 cm^3) was added 11-bromo-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.47** (0.117 g, 0.322 mmol), phenylboronic acid (0.0666 g, 0.546 mmol), caesium carbonate, Cs_2CO_3 (0.288 g, 0.884 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.0331 g, 0.0286 mmol). The reaction was then irradiated at 150 W, at a temperature of 150°C for 15 minutes by microwave reactor. The cooled reaction mixture was then filtered through a plug of Celite® and rinsed with ethyl acetate. The solvent was then removed by rotary evaporator to afford a crude brown residue which was purified by flash column chromatography (20–50% ethyl acetate in hexane). The product was then further purified by a recrystallization from ethanol to afford 2,3-dimethoxy-11-phenyl-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.49** (0.0326 g, 0.0902 mmol, 28%) as a white powder.



4.49

R_f (60% ethyl acetate in hexane): 0.66

M.p.: 189–191°C

IR (ν/cm^{-1}): 2931 (w, C–H stretch), 1726 (s, C=O stretch), 1601, 1536, 1503 (w, C=C stretch), 1154 (s, C–O stretch), 1077, 1030 (s, C–O–C stretch), 913, 768, 704 (m, C–H bend)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.44 (m, 4H, $H_{15,16}$), 7.37 (dd, *J* = 6.9 Hz, 1H, H_{17}), 7.04 (s, 1H, H_1), 6.91 (s, 1H, H_4), 4.48 (t, *J* = 7.1 Hz, 2H, H_8), 3.89, 3.54 (s, 2 × 3H, $H_{12,13}$), 2.97 (t, *J* = 7.4 Hz, 2H, H_{10}), 2.64 (p, *J* = 7.4 Hz, 2H, H_9)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.55 (C_6), 148.78 (C_{4a}), 146.95 (C_3), 146.28 (C_2), 145.43 (C_{10a}), 134.59 (C_{14}), 130.19 (C_{11a}), 129.98 (C_{16}), 128.53 (C_{15}), 127.28 (C_{17}), 112.37 (C_{11}), 112.15 (C_{6a}), 111.02 (C_{11b}), 104.71 (C_1), 100.87 (C_4), 56.08, 55.74 ($C_{12,13}$), 47.39 (C_8), 27.11 (C_9), 24.23 (C_{10})

HRMS (EI): Found M^+ = 361.1297, $C_{22}H_{19}NO_4$ requires 361.1314

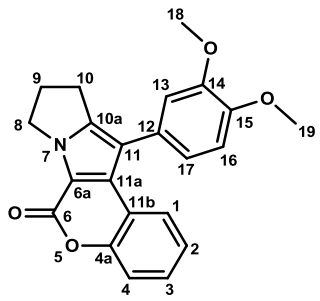
9.7. Suzuki-Miyaura couplings using 3,4-dimethoxyphenylboronic acid

General procedure:[67,134,136]

To a sealed microwave vessel was added the prepared brominated pyrrole compound (1.00 molar equivalent), 3,4-dimethoxyphenylboronic acid (1.30 molar equivalents), sodium hydrogen carbonate (3.00 molar equivalents), tetrakis(triphenylphosphine)palladium(0) (6% molar equivalents) to a *N*,*N*-dimethylformamide and water mixture (1:1) (16 cm^3/mmol of brominated compound). The reaction was then irradiated at 150 W at a temperature of 150°C for 15 min by microwave reactor. The cooled reaction mixture was then extracted into diethyl ether (50 cm^3) and washed with water (20 cm^3); the aqueous layer was then extracted further with diethyl ether (3 × 40 cm^3). The collected organic extracts were dried of anhydrous sodium sulphate, the solid was then filtered and the organic solvent was evaporated.

9.7.1. 11-(3,4-Dimethoxyphenyl)-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.51)

The product was prepared from 11-bromo-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.46** (0.11 g, 0.37 mmol), 3,4-dimethoxyphenylboronic acid (0.091 g, 0.50 mmol), sodium hydrogen carbonate (0.095 g, 1.1 mmol), tetrakis(triphenylphosphine)palladium(0) 0.025 g, 0.022 mmol) and a mixture of *N*,*N*-dimethylformamide and water (1:1) (6 cm^3) by the general method above. The crude product was purified by flash column chromatography (10–30% ethyl acetate in hexane), the product was then recrystallized form an ethyl acetate in hexane mixture to afford the pure product 11-(3,4-dimethoxyphenyl)-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.51** (0.073 g, 0.20 mmol, 54%) as a white crystalline solid.



4.51

R_f (60% ethyl acetate in hexane): 0.80

M.p.: 230–232°C

IR (ν/cm^{-1}): 3102, 2956, 2832 (w, C–H stretch), 1704 (s, C=O stretch), 1608, 1480 (w, C=C stretch), 1181 (s, C–O stretch) , 1131, 1082 (s, C–O–C stretch), 1028 (s, C–N stretch), 924 (m, C–C stretch), 817, 761, 699 (m, C–H bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.9, 1.3 Hz, 1H, H_1), 7.39 (dd, *J* = 8.3, 0.8 Hz, 1H, H_4), 7.33–7.26 (m, 2H, $H_{2,3}$), 7.09–6.98 (m, 2H, $H_{16,17}$), 6.95 (s,

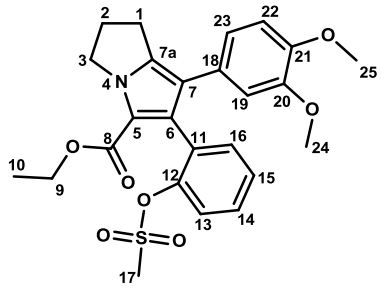
1H, H_{13}), 4.50 (t, *J* = 7.2 Hz, 2H, H_8), 3.99 (s, 3H, H_{18}), 3.89 (s, 3H, H_{19}), 2.97 (t, *J* = 7.4 Hz, 2H, H_{10}), 2.67 (dq, *J* = 14.7, 7.5 Hz, 2H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.22 (C_6), 151.48 (C_{4a}), 148.92 (C_{14}), 148.35 (C_{15}), 147.04 (C_{10a}), 129.51 (C_{11a}), 127.26 (C_1), 126.94 (C_{12}), 123.53 (C_2), 123.27 (C_3), 121.95 (C_4), 119.03 (C_{11}), 117.42 (C_{17}), 117.27 (C_{11b}), 113.05 (C_{13}), 112.71 (C_{6a}), 111.39 (C_{16}), 55.97 (C_{18}), 55.97 (C_{19}), 47.44 (C_8), 27.06 (C_{10}), 24.19 (C_9)

HRMS (ESI+): Found $(M + H)^+$ = 361.1317, $C_{22}H_{19}NO_4$ requires 361.1314. *M/z*: 361.1317 (100%, $(M + H)^+$), 225.0788 (6%)

9.7.2. Ethyl 7-(3,4-dimethoxyphenyl)-6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.50)

Using the general method, the product was prepared from ethyl 7-bromo-6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.41** (0.084 g, 0.20 mmol) , 3,4-dimethoxyphenylboronic acid (0.050 g, 0.25 mmol), sodium hydrogen carbonate, (0.052 g, 0.59 mmol), tetrakis(triphenylphosphine)palladium(0) (0.011 g, 0.0098 mmol) and a mixture of *N*,*N*-dimethylformamide and water (1:1) (3 cm^3). The orange residue obtained from the reaction was further purified by flash column chromatography (10–30% ethyl acetate in hexane), followed by a recrystallized form an ethanol and diethyl ether mixture, which afforded the pure product ethyl 7-(3,4-dimethoxyphenyl)-6-[2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate **4.50** (0.065 g, 0.14 mmol, 69%) as a white crystalline solid.



4.50

R_f (60% ethyl acetate in hexane): 0.69

M.p.: 151–152°C

IR (ν/cm^{-1}): 3017, 2836 (w, C–H stretch), 1687 (s, C=O stretch), 1609, 1520 (w, C=C stretch), 1344 (s, S=O stretch), 1214 (m, C–N stretch), 1158, 1109 (s, C–O stretch), 1024 (m, C–C stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.24 (m, 4H, $H_{13–16}$), 6.79–6.76 (m, 2H, $H_{19,22}$), 6.52 (s, 1H, H_{23}), 4.43 (dddd, *J* = 19.6, 14.9, 12.0, 7.6 Hz, 2H, H_9), 4.12 (qq, *J* = 10.7, 7.1 Hz, 2H, H_3), 3.85 (s, 3H, H_{24}), 3.48 (s, 3H, H_{25}), 3.08 (h, *J* = 16.1 Hz,

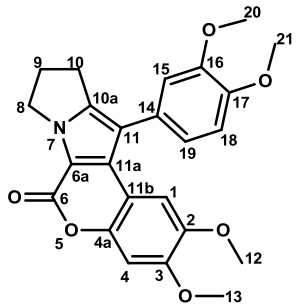
2H, H_1), 2.72 (s, 3H, H_{17}), 2.59 (dtd, J = 10.0, 7.8, 4.6 Hz, 2H, H_2), 1.05 (t, J = 7.1 Hz, 3H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.12 (C_8), 148.50 (C_{20}), 147.85 (C_5), 147.02 (C_{21}), 140.26 (C_{7a}), 133.14 (C_{13}), 129.75 (C_6), 128.39 (C_{16}), 127.22 (C_{12}), 126.72 (C_{18}), 126.50 (C_{14}), 122.65 (C_{15}), 119.73 (C_{23}), 117.28 (C_{11}), 116.25 (C_7), 111.75 (C_{19}), 111.06 (C_{22}), 59.80 (C_9), 55.76, 55.45 ($C_{24,25}$), 48.67 (C_3), 38.07 (C_{17}), 26.59 (C_1), 25.12 (C_2), 13.83 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 485.1510 $C_{25}H_{27}NO_7S$ requires 485.1508

9.7.3. 11-(3,4-Dimethoxyphenyl)-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.52)[139,140]

The product was prepared by reacting 11-bromo-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.47** (0.073 g, 0.20 mmol), 3,4-dimethoxyphenylboronic acid (0.067 g, 0.37 mmol), caesium fluoride (0.067 g, 0.44 mmol), silver(I) oxide (0.080 g, 0.35 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.047 g, 0.041 mmol) with 1,2-dimethoxyethane (4 cm^3). The reaction mixture was heated to 80°C for 22 hours. On cooling, water (10 cm^3) was added to the mixture and the product was extracted into dichloromethane (3 × 10 cm^3), the organic layer was further washed with water (10 cm^3) and brine (10 cm^3). The collected organic phase was dried over anhydrous sodium sulphate, filtered through a sintered funnel, and the solvent was removed by rotary evaporator. The crude product obtained was purified by flash column chromatography in a 30% ethyl acetate in hexane mixture. Recrystallization was then induced from an ethyl acetate in hexane mixture to afford the product 11-(3,4-dimethoxyphenyl)-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **4.52** (0.0416 g, 0.101 mmol, 50%) as a pale yellow crystalline solid.



4.52

R_f (50% ethyl acetate in hexane): 0.21

M.p.: 223–225°C

IR (ν/cm^{-1}): 3085, 2839 (w, C–H stretch), 1703 (s, C=O stretch), 1621, 1499 (w, C=C stretch), 1413 (s. C–O stretch), 1254, 1004, 1157, 1141 (s, C–O–C stretch), 1083 (m, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1H, H_1), 7.05 – 6.98 (m, 3H, $H_{13,16,17}$), 6.91 (s, 1H, H_4), 4.47 (t, J = 7.2 Hz, 2H, H_8), 3.94, 3.89 (s,

2 × 3H, $H_{21,22}$), 3.89, 3.57 (s, 2 × 3H, $H_{18,19}$), 2.96 (t, *J* = 7.4 Hz, 2H, H_{10}), 2.64 (p, *J* = 7.3 Hz, 2H, H_9)

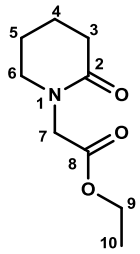
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.54 (C_6), 148.97 (C_{4a}), 148.84 (C_{1a}), 148.37 (C_3), 147.00 (C_{15}), 146.33 (C_{10a}), 145.48 (C_2), 130.22 (C_{11a}), 127.07 (C_{12}), 122.24 (C_{17}), 113.19 (C_{13}), 112.16 (C_{11}), 111.97 (C_{6a}), 111.33 (C_{16}), 111.09 (C_{11b}), 104.83 (C_1), 100.93 (C_4), 56.08, 56.04, 56.00, 55.91 ($C_{18,19,20,21}$), 47.38 (C_8), 27.09 (C_9), 24.23 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 422.1609 and $(M + Na)^+$ = 444.1487, $C_{24}H_{23}NO_6$ requires 422.1604 and 444.1425. *M/z*: 444.1487 (3%, $(M + Na)^+$), 422.1609 (100%, $(M + H)^+$)

9.8. An expansion of the methodology with piperidine and caprolactam ring systems

9.8.1. Ethyl 2-(2-oxopiperidin-1-yl)acetate (4.16)

To an ice-cooled solution of sodium hydride (60% dispersion in oil, 2.65 g, 65.9 mmol) in tetrahydrofuran (50 cm^3) was added 2-piperidinone (4.08 g, 41.2 mmol) in tetrahydrofuran (50 cm^3) dropwise over 20 minutes. The emulsion was warmed to room temperature and the refluxed for 2 hours. On cooling to room temperature, and then again to 0°C, ethyl 2-bromoacetate (8.94 g, 6.0 cm^3, 53.5 mmol) was added to the stirring emulsion which immediately became yellow and more fluid. After an additional 16 hours of stirring at room temperature water was cautiously added to the reaction mixture until the solution appeared clear. The solvent was then removed by rotary evaporator to give crude slurry which was extracted into dichloromethane (30 cm^3). The organic phase was removed and the aqueous phase was back extracted with dichloromethane (2 × 30 cm^3). The combined organic fractions were then washed with brine (80 cm^3) and dried over anhydrous sodium sulphate. The solvent was then filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (30–50% ethyl acetate in hexane) to afforded ethyl 2-(2-oxopiperidin-1-yl)acetate **4.16** (6.77 g, 36.5 mmol, 89%) as a white solid.



4.16

R_f (50% ethyl acetate in hexane): 0.61

M.p.: 75–76°C (Lit.[184] 70–71°C)

IR (ν/cm^{-1}): 2954, 2868 (w, C–H stretch), 1738 (s, C=O$_{ester}$ stretch), 1627 (s, C=O$_{amide}$ stretch), 1257 (s, C–C stretch), 1207, 1162 (s, C=O stretch), 1022 (s, C–N stretch)

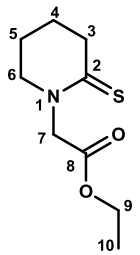
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H, H_9), 4.11 (s, 2H, H_7), 3.37 (t, *J* = 5.9 Hz, 2H, H_6), 2.43 (t, *J* = 6.9 Hz, 2H, H_3), 1.86 (dt, *J* = 5.8, 2.7 Hz, 4H, $H_{4,5}$), 1.28 (t, *J* = 7.2 Hz, 3H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.43 (C_2), 169.15 (C_8), 61.06 (C_9), 49.17 (C_6), 48.60 (C_7), 32.06 (C_3), 23.13 (C_5), 21.33 (C_4), 14.12 (C_{10})

HRMS (EI): Found M^+ = 185.1044, $C_9H_{15}NO_3$ requires 185.1052. *M/z*: 185.1044 (100%, M^+), 184.0615 (5%), 183.0543 (20%)

9.8.2. Ethyl 2-(2-thioxopiperidin-1-yl)acetate (4.18)

To a solution of ethyl 2-(2-oxopiperidin-1-yl)acetate **4.16** (3.530 g, 17.54 mmol) in toluene (80 cm^3) was added Lawesson's reagent (4.256 g, 10.52 mmol), which was allowed to heat to 80°C for 24 hours. On cooling, the solvent was removed under reduced pressure to afford the crude product as a viscous red residue which was purified by flash column chromatography (30% ethyl acetate in hexane) to afford ethyl 2-(2-thioxopiperidin-1-yl)acetate **4.18** (3.154 g, 15.67 mmol, 89%) as a clear pale yellow oil.



4.18

R_f (50% ethyl acetate in hexane): 0.46

IR (ν/cm^{-1}): 2946, 2870 (w, C–H stretch), 1739 (s, C=O$_{ester}$ stretch), 1510 (s, C=S stretch), 1349, 1257 (C–C stretch), 1194, 1162 (s, C=O stretch), 1107 (s, C–S stretch), 1023 (s, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (s, 2H, H_7), 4.22 (q, *J* = 7.1 Hz, 2H, H_9), 3.56 (t, *J* = 6.2 Hz, 2H, H_6), 3.01 (t, *J* = 6.4 Hz, 2H, H_3), 1.98 (tdd, *J* = 9.5, 6.1, 3.8 Hz, 2H, H_5), 1.79 (dtd, *J* = 8.7, 6.2, 3.9 Hz, 2H, H_4), 1.30 (t, *J* = 7.1 Hz, 3H, H_{10})

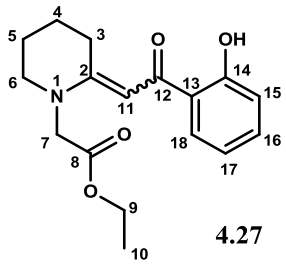
^{13}C NMR (75 MHz, $CDCl_3$) δ 201.84 (C_2), 167.23 (C_8), 61.23 (C_9), 55.98 (C_6), 52.44 (C_7), 41.30 (C_3), 22.78 (C_5), 20.48 (C_4), 14.06 (C_{10})

HRMS (EI): Found M^+ = 201.0822, $C_9H_{15}NO_2$ requires 201.0823

9.8.3. Ethyl 2-{2-[2-(2-hydroxyphenyl)-2-oxoethylidene]piperidin-1-yl}acetate (4.27)[78]

Ethyl 2-(2-thioxopiperidin-1-yl)acetate **4.18** (0.487 g, 2.42 mmol), 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10** (0.555 g, 2.58 mmol) and sodium iodide (0.371 g, 2.54 mmol) in acetonitrile (8 cm^3) was stirred in an aluminium foil-covered round bottom flask, at ambient temperature for 18 hours. The reaction vessel was then cooled to 0°C and triethyl phosphite (0.442 g, 0.46 cm^3, 2.66 mmol) was added, followed by triethylamine (0.367 g, 0.51 cm^3, 3.63 mmol). The reaction was then stirred at room temperature for 18 hours. The solvent was evaporated and the product was extracted into ethyl acetate (2 × 20 cm^3), washed with water and then brine. The combined organic fractions were then dried with sodium sulphate, filtered and evaporated. The crude brown oil was then purified by flash column chromatography (30% ethyl acetate in hexane) to afford ethyl 2-{2-[2-(2-hydroxyphenyl)-2-oxoethylidene]piperidin-1-yl}acetate **4.27** (0.0560 g, 0.185 mmol, 8%) as a brown-orange oil that was slightly contaminated with other overlapping by-products.

The following represents the most discernible peaks from the hydrogen spectrum; the sample was carried through to the next step:



4.27

R_f (50% ethyl acetate in hexane): 0.69

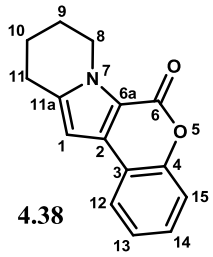
^{1}H NMR (300 MHz, $CDCl_3$) δ 13.90 (s, 1H, OH), 7.55 (dd, *J* = 8.0, 1.3 Hz, 1H, H_{18}), 7.30 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H, H_{16}), 6.90 (dd, *J* = 8.3, 1.0 Hz, 1H, H_{15}), 6.76 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H, H_{17}), 5.63 (s, 1H, H_{11}), 4.28 (q, *J* = 7.1 Hz, 2H, H_9), 4.04 (s, 2H, H_7), 3.49 (t, *J* = 6.1 Hz, 2H, H_3), 3.31 (t, *J* = 6.4 Hz, 2H, H_6), 1.95–1.84 (m, 2H, H_4), 1.81–1.71 (m, 2H, H_5), 1.33 (t, *J* = 7.1 Hz, 3H, H_{10})

9.8.4. 8,9,10,11-Tetrahydro-6*H*-chromeno[4,3-*b*]indolizin-6-one (4.38) and 10,11-dihydro-8*H*-chromeno[3,2-*a*]indolizin-12(9*H*)-one (4.39)

To a sealed microwave tube was added (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)piperidin-1-yl]acetate **4.27** (0.0558 g, 0.184 mmol), silica gel (0.97 g, 17 × mass of starting material) and xylene (3 cm^3). The mixture was irradiated at 150 W at a temperature of 180°C for 20 minutes. The brown heterogeneous mixture was then filtered through silica gel and rinsed

with an excess of acetone. The solvent was then removed by rotary evaporator and purified by flash column chromatography (10–20% ethyl acetate in hexane). The chromenone was afforded 10,11-dihydro-8*H*-chromeno[3,2-*a*]indolizin-12(9*H*)-one **4.39** (0.00885 g, 0.0369 mmol, 21%) as a dark orange oil; followed by the lactone 8,9,10,11-tetrahydro-6*H*-chromeno[4,3-*b*]indolizin-6-one **4.38** (0.0148 g, 0.0619 mmol, 34%) as a yellow oil.

10,11-Dihydro-8H-chromeno[3,2-a]indolizin-12(9H)-one (4.39)



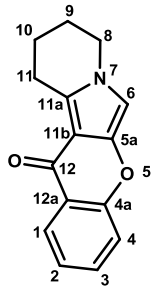
4.38

R_f (50% ethyl acetate in hexane): 0.72

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7.9, 1.7 Hz, 1H, H_1), 7.57 (ddd, *J* = 8.7, 7.1, 1.8 Hz, 1H, H_3), 7.32 (dd, *J* = 8.4, 0.7 Hz, 1H, H_4), 7.25 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H, H_2), 6.48 (s, 1H, H_6), 4.04 (t, *J* = 5.9 Hz, 2H, H_8), 3.28 (t, *J* = 6.3 Hz, 2H, H_{11}), 2.06 (tt, *J* = 8.1, 5.6, 2.8 Hz, 2H, H_9), 1.93 (tt, *J* = 11.4, 6.1, 2.4 Hz, 2H, H_{10})

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.49 (C_{12}), 157.06 (C_{4a}), 145.26 (C_{11a}), 133.13 (C_3), 129.50 (C_{12a}), 126.60 (C_1), 122.77 (C_{11b}), 122.45 (C_2), 117.37 (C_4), 107.70 (C_{5a}), 100.36 (C_6), 45.87 (C_8), 23.36 (C_{11}), 22.91 (C_9), 19.72 (C_{10})

8,9,10,11-tetrahydro-6H-chromeno[4,3-b]indolizin-6-one (4.38)



4.39

R_f (50% ethyl acetate in hexane): 0.53

IR (ν/cm^{-1}): 2921, 2852 (w, C–H stretch), 1696 (s, C=O stretch), 1612, 1493 (w, C=C stretch), 1204, 1067 (m, C–C stretch), 1134, 1109 (s, C–O stretch), 980 (m, C–N stretch), 764, 670 (s, C–H bend)

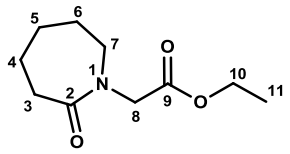
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.7, 1.4 Hz, 1H, H_{12}), 7.38 – 7.31 (m, 2H, $H_{14,15}$), 7.24 (dd, *J* = 7.0, 1.5 Hz, 1H, H_{13}), 6.38 (s, 1H, H_1), 4.52 (t, *J* = 6.2 Hz, 2H, H_8), 2.95 (t, *J* = 6.4 Hz, 2H, H_{11}), 2.08 – 2.03 (m, 2H, H_9), 1.93 – 1.88 (m, 2H, H_{10})

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.06 (C_6), 151.38 (C_4), 141.73 (C_{11a}), 129.93 (C_3), 127.54 (C_{14}), 123.85 (C_{13}), 122.92 (C_{12}), 118.03 (C_2), 117.08 (C_{15}), 115.28 (C_{6a}), 99.47 (C_1), 45.42 (C_8), 24.06 (C_{11}), 22.94 (C_9), 19.88 (C_{10})

HRMS (ESI+): Found $(M + H)^+$ = 240.1024 and $(M + Na)^+$ = 262.0849, $C_{15}H_{13}NO_2$ requires 240.1025 and 262.0846. *M/z*: 262.0849 (6%, $(M + Na)^+$), 240.1024 (100%, $(M + H)^+$)

9.8.5. Ethyl 2-(2-oxoazepan-1-yl)acetate (4.17)

To an ice-cooled solution of caprolactam (1.422 g, 12.56 mmol) in tetrahydrofuran (30 cm^3) was added sodium hydride (60% dispersion in mineral oil, 0.7537 g, 18.84 mmol). The emulsion was then stirred at 0°C for 10 minutes before warming to room temperature and refluxing for 3 hours. The reaction was then allowed to cool to room temperature for 15 minutes and then cooled to 0°C, whereby ethyl 2-bromoacetate (2.525 g, 1.7 cm^3, 15.12 mmol) was added. The reaction was stirred for 15 minutes before warming to room temperature, the reaction was then allowed to stir for an additional 18 hours. Water (5 cm^3) was cautiously added to the reaction mixture until it appeared clear, the solvent was then evaporated. The yellow residue was extracted into dichloromethane (2 × 50 cm^3) and the combined organic extracts were then washed with water (50 cm^3) and brine (50cm^3). The organic phase was then dried over sodium sulphate, filtered and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (40% ethyl acetate in hexane) to afforded ethyl 2-(2-oxoazepan-1-yl)acetate **4.17** (2.005 g, 10.06 mmol, 80%) as a clear colourless oil.



4.17

R_f (50% ethyl acetate in hexane): 0.64

IR (ν/cm^{-1}): 2931, 2858 (w, C–H stretch), 1744 (s, $C{=}O_{ester}$ stretch), 1635 (s, $C{=}O_{amide}$ stretch), 1257 (s, C–C stretch), 1185, 1148 (s, C–O stretch), 1029 (s, C–N stretch)

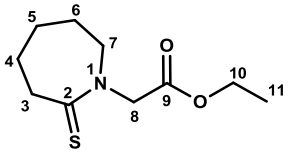
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (q, J = 6.7 Hz, 2H, H_{10}), 3.88 (s, 2H, H_8), 3.18 (dd, J = 4.8, 2.8 Hz, 2H, H_7), 2.33–2.29 (m, 2H, H_3), 1.55–1.41 (m, 6H, $H_{4,5,6}$), 1.02 (t, J = 7.1 Hz, 3H, H_{11})

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.90 (C_2), 169.40 (C_9), 60.68 (C_{10}), 50.96 (C_8), 50.20 (C_7), 36.63 (C_3), 29.72 (C_6), 27.77 (C_4), 23.00 (C_5), 13.91 (C_{11})

HRMS (EI): Found M^+ = 199.1210, $C_{10}H_{17}NO_3$ requires 199.1208. *M/z*: 199.1210 (100%, M^+), 197.9895 (5%), 193.9924 (22%)

9.8.6. Ethyl 2-(2-thioxoazepan-1-yl)acetate (4.19)

To a solution of ethyl 2-(2-oxoazepan-1-yl)acetate **4.17** (4.374 g, 21.95 mmol) in toluene (100 cm^3) was added Lawesson's reagent (2.942 g, 7.27 mmol) which was allowed to heat to 80°C for 24 hours. On cooling, the solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography (40% ethyl acetate in hexane) to afforded ethyl 2-(2-thioxoazepan-1-yl)acetate **4.19** (4.042 g, 18.78 mmol, 86%) as a clear colourless oil.



4.19

R_f (50% ethyl acetate in hexane): 0.75

IR (ν/cm^{-1}): 2979, 2929, 2856 (w, C-H stretch), 1740 (s, $C{=}O_{ester}$ stretch), 1502 (s, C=S stretch), 1241 (C–C stretch), 1184 (s, C=O stretch), 1077 (s, C–S stretch), 1004 (s, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76 (s, 2H, H_8), 4.22 (q, J = 7.1 Hz, 2H, H_{10}), 3.83–3.66 (m, 2H, H_7), 3.19 (dd, J = 6.0, 3.7 Hz, 2H, H_3), 1.85–1.72 (m, 9H, $H_{4,5,6}$), 1.29 (t, J = 7.1 Hz, 3H, H_{11})

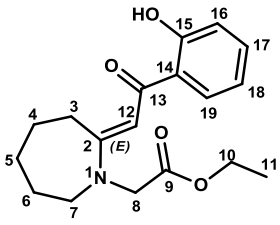
^{13}C NMR (75 MHz, $CDCl_3$) δ 208.59 (C_2), 167.75 (C_9), 61.40 (C_{10}), 58.65 (C_8), 55.93 (C_7), 46.75 (C_3), 29.25 (C_5), 26.47 (C_6), 24.59 (C_4), 14.15 (C_{11})

HRMS (EI): Found M^+ = 215.0975, $C_{10}H_{17}NO_2S$ requires 215.0980. *M/z*: 215.0975 (100%, M^+), 212.9946 (6%), 211.9865 (14%), 209.9882 (1%), 207.0333 (5%)

9.8.7. (*E*)-Ethyl 2-{2-[2-(2-hydroxyphenyl)-2-oxoethylidene]azepan-1-yl}acetate (4.28)[76]

Ethyl 2-(2-thioxoazepan-1-yl)acetate **4.19** (0.553 g, 2.57 mmol) and 2-bromo-1-(2-hydroxyphenyl)ethanone **3.10** (0.728 g, 3.39 mmol) and sodium iodide (0.543 g, 3.72 mmol) in chloroform (6 cm^3) were stirred at room temperature for 4 hours, until salt formation was complete and the mixture appeared as a bright yellow precipitate. Triphenylphosphine (1.01 g, 3.85 mmol) and triethylamine (0.520 g, 0.72 cm^3, 5.13 mmol), in chloroform (10 cm^3) were then added dropwise to the yellow mixture over 15 minutes. The reaction was then allowed to stir for 24 hours at room temperature. The solvent was evaporated and the crude residue was extracted into ethyl acetate (50 cm^3). The organic layer was washed with ammonium chloride (100 cm^3), water (2 × 50 cm^3) and brine (30 cm^3), the organic extract was then dried over

sodium sulphate, filtered and the solvent was removed under reduced pressure. The crude yellow residue was further purified by flash column chromatography (20% ethyl acetate in hexane) to afforded the product (*E*)-Ethyl 2-{2-[2-(2-hydroxyphenyl)-2-oxoethylidene]azepan-1-yl}acetate **4.28** (0.162 g, 0.509 mmol, 20%) as a clear yellow oil.



4.28

R_f (50% ethyl acetate in hexane): 0.82

IR (ν/cm^{-1}): 2980, 2930, 2857 (w, C–H stretch), 2720 (w br, O–H stretch), 1744 (s, C=O stretch), 1613, 1576 (m, C=C stretch), 1540 (s, C=O stretch), 1342 (m, C–C stretch), 1285 (s, alcohol C–O stretch), 1192 (s, C–O–C stretch), 1018 (m, C–N stretch), 925 (m, C–$H_{E\text{alkene.}}$ bend)

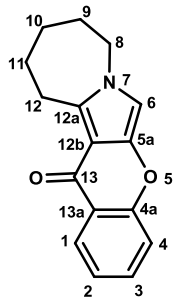
^{1}H NMR (300 MHz, $CDCl_3$) δ 13.75 (s, 1H, OH), 7.58 (dd, *J* = 8.1, 1.4 Hz, 1H, H_{16}), 7.31 (ddd, *J* = 8.5, 7.3, 1.6 Hz, 1H, H_{17}), 6.91 (dd, *J* = 8.3, 1.1 Hz, 1H, H_{18}), 6.77 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H, H_{19}), 5.54 (s, 1H, H_{12}), 4.27 (q, *J* = 7.1 Hz, 2H, H_{10}), 4.11 (s, 2H, H_8), 3.68 – 3.63 (m, 2H, H_3), 3.47–3.42 (m, 2H, H_7), 1.78–1.72 (m,, 6H, $H_{4,5,6}$), 1.32 (t, *J* = 7.1 Hz, 3H, H_{11})

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.92 (C_{13}), 170.38 (C_2), 168.75 (C_9), 162.79 (C_{15}), 133.61 (C_{17}), 128.03 (C_{16}), 122.10 (C_{14}), 118.29 (C_{19}), 117.92 (C_{18}), 91.24 (C_{12}), 61.75 (C_{10}), 55.93 (C_8), 55.07 (C_7), 29.46 (C_6), 28.31 (C_3), 27.55 (C_5), 25.26 (C_4), 14.26 (C_{11})

HRMS (EI): Found M^+ = 317.1629, $C_{18}H_{23}NO_4$ requires 317.1627

9.8.8. 9,10,11,12-Tetrahydrochromeno[3',2':3,4]pyrrolo[1,2-*a*]azepin-13(8*H*)-one (4.40)

(*E*)-Ethyl 2-[2-(2-oxo-2-phenylethylidene)azocan-1-yl]acetate **4.28** (0.0201 g, 0.0633 mmol) in xylene (2 cm^{3}l) and added silica gel (0.2 g, 10 times mass of starting material) was dissolved. The mixture was then irradiated under microwave conditions (150W, 200°C, 20 min). The reaction was then filtered through a plug of silica gel and rinsed with an excess of acetone, the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) to afford 9,10,11,12-tetrahydrochromeno [3',2':3,4]pyrrolo[1,2-*a*]azepin-6(8*H*)-one **4.40** (0.0143 g, 0.0565 mmol, 41%) as an off-white solid.



4.40

R_f (50% ethyl acetate in hexane): 0.68

M.p.: 85–88°C

IR (ν/cm^{-1}): 2923, 2853 (w, C–H stretch), 1719 (s, C=O stretch), 1607, 1459 (w, C=C stretch), 1148 (m, C–C stretch), 1250, 1073, 1029 (m, C–O–C stretch), 969 (m, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (dd, J = 7.9, 1.7 Hz, 1H, H_1), 7.80–7.66 (m, 1H, H_3), 7.61–7.50 (m, 1H, H_2), 7.31 (dd, J = 8.4, 0.7 Hz, 1H, H_4), 6.51 (s, 1H, H_6), 4.05–4.01 (m, 2H, H_8), 3.47–3.40 (m, 2H, H_{12}), 1.85–1.70 (m, 6H, $H_{9,10,11}$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.14 (C_{13}), 157.00 (C_{4a}), 146.14 (C_{12a}), 134.45 (C_{13a}), 133.19 (C_3), 126.67 (C_1), 122.77 (C_{12b}), 122.36 (C_2), 119.22 (C_{5a}), 117.34 (C_4), 102.25 (C_6), 51.12 (C_8), 31.13 (C_9), 28.84 (C_{10}), 26.64 (C_{11}), 25.90 (C_{12})

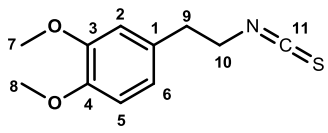
HRMS (EI): Found M^+ = 253.1107, $C_{16}H_{15}NO_2$ requires 253.1103

Chapter 10
Experimental procedures pertaining to Chapter 5

10.1. Preparation of the isoquinoline compounds

10.1.1. 1-(2-Isothiocyanatoethyl)-3,4-dimethoxybenzene (5.1)

The following compound was prepared by the literature procedure of Gittos and co-workers, and Norman and co-workers.[144,145] To an ice-cooled solution of 3,4-dimethoxyphenylethylamine (1.02 g, 5.62 mmol) in dichloromethane (3 cm^3) was added triethylamine (0.569 g, 0.78 cm^3, 5.62 mmol). The mixture was stirred for 10 minutes before adding carbon disulphide, CS_2 (0.428 g, 0.34 cm^3, 5.62 mmol) in dichloromethane (3 cm^3) dropwise to the reaction vessel over 15 minutes. The mixture was then warmed to room temperature and stirred for 1 hour. Again the mixture was again cooled to 0ºC and ethyl chloroformate (0.610 g, 0.54 cm^3, 5.62 mmol) was added dropwise, followed by a second portion of triethylamine (0.512 g, 0.71 cm^3, 5.06 mmol). The reaction vessel was then warmed to room temperature and refluxed for 2 hours. On cooling, water (15 cm^3) was added to the reaction mixture followed by a dropwise addition of an aqueous solution of sodium hydroxide (2M), until the reaction mixture became alkaline. The product was then extracted into dichloromethane (2 × 50 cm^3). The yellow organic extracts were collected and dried over sodium sulphate, filtered and the solvent was removed *in vacuo*. The isothiocynate product 1-(2-isothiocyanatoethyl)-3,4-dimethoxybenzene **5.1** (1.25 g, 5.59 mmol, 99%) was isolated as a yellow oil.



5.1

R_f(50% ethyl acetate in hexane): 0.66

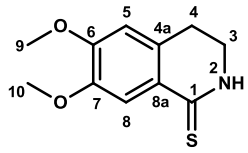
IR (ν/cm^{-1}): 2936, 2834 (w, C–H stretch), 2091 (m, R–N=C=S stretch), 1701 (w, C=N stretch), 1514, 1452 (s, C=C stretch), 1261, 1236, 1025 (s, C–O–C stretch), 1156 (s, C–C stretch), 1102 (m, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J = 8.7 Hz, 1H, H_2), 6.77–6.74 (m, 2H, $H_{5, 6}$), 3.90 (s, 3H, H_8), 3.86 (s, 3H, H_7), 3.69 (t, J = 6.8 Hz, 2H, H_{10}), 2.93 (t, J = 6.7 Hz, 2H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.05(C_4), 148.18 (C_3), 130.62 (C_{11}), 129.59 (C_1), 120.82 (C_2), 112.11 (C_5), 111.44 (C_6), 55.95 (C_8), 55.93 (C_7), 46.71 (C_{10}), 36.14 (C_9)

10.1.2. 6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (5.2)[144,146]

Isothiocyanate **5.1** (3.705 g, 16.59 mmol) in dichloromethane (10 cm^3) was added dropwise to stirring polyphosphoric acid (25 g, 8 times the mass of 3,4-dimethoxyphenylethylamine used in **5.1**), which was heated to 80–90ºC. The product immediately began to precipitate on contact with the acid and turned red. The reaction mixture was stirred for an additional 4 hours. On cooling, water (300 cm^3) was added to the reaction mixture, which caused further precipitation of the product, stirring was continued for 30 minutes. The product was then filtered through a sintered funnel and washed with additional water. The crude solid product was then dissolved in methanol and distilled for 10 minutes to ensure dissolution. On cooling, the pure product 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** (3.3851 g, 15.16 mmol, 91%) was collected as a pale pink or pale yellow powder.



5.2

R_f (50% ethyl acetate in hexane): 0.32

M.p.: 231–232°C (Lit.[144] 223°C)

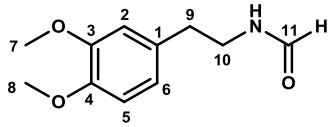
IR (ν/cm^{-1}): 3217 (m, N–H stretch), 2994, 2938 (w, C–H stretch), 1605 (m, N–H bend), 1529, 1473 (s, C=C stretch), 1514 (s, C=S stretch), 1337 (m, C–C stretch), 1250, 1227, 1033 (s, C–O–C stretch), 1050 (m, C–N stretch), 960, 939 (m, C–S, stretch), 808 (s, N–H bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H, NH), 8.08 (s, 1H, H_8), 6.62 (s, 1H, H_5), 3.97 (s, 3H, H_9), 3.94 (s, 3H, H_{10}), 3.54 (td, J = 7.0, 3.4 Hz, 2H, H_3), 2.95 (t, J = 7.0 Hz, 2H, H_4)

^{13}C NMR (75 MHz, $CDCl_3$) δ 193.38 (C_1), 153.02 (C_6), 147.95 (C_7), 127.97 (C_{4a}), 125.53 (C_{8a}), 114.54 (C_8), 109.25 (C_5), 56.25 (C_9), 56.22 (C_{10}), 42.02 (C_3), 27.70 (C_4)

10.1.3. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]formamide (5.4)[149]

3,4-Dimethoxyphenylethylamine (5.339 g, 27.46 mmol) was dissolved with methyl fomate (17.69 g, 18.16 cm^3, 294.6 mmol) and stirred at room temperature for 19 hours. The solvent was then removed by rotary evaporator and the pure product *N*-[2-(3,4-dimethoxyphenyl)ethyl]formamide **5.4** (6.144 g, 29.36 mmol, 100%) was isolated as a yellow oil.



5.4

R_f (ethyl acetate): 0.31

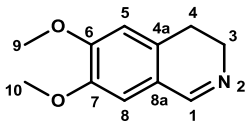
IR (ν/cm^{-1}): 3350 (br m, N–H stretch), 2936, 2837 (w, C–H stretch), 1658 (s, C=O stretch), 1591, 1463 (s, C=C stretch), 1513 (s, N–H bend), 1259, 1232, 1139 (s, C–O–C stretch), 1024 (m, C–N stretch), 854 (w, N–H bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H, H_{11}), 6.77–6.75 (m, 3H, $H_{2, 5, 6}$), 6.02 (s, 1H, NH), 3.85 (2 × s, 6H, $H_{7, 8}$), 3.53 (q, J = 6.7 Hz, 2H, H_{10}), 2.78 (t, J = 7.1 Hz, 2H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.26 (C_{11}), 149.08 (C_3), 147.77 (C_4), 131.09 (C_1), 120.67 (C_6), 111.98 (C_2), 111.49 (C_5), 55.91 (C_7), 55.87 (C_8), 39.30 (C_{10}), 35.08 (C_9)

10.1.4. 6,7-Dimethoxy-3,4-dihydroisoquinoline (5.5)[148,150]

To a solution of *N*-[2-(3,4-dimethoxyphenyl)ethyl]formamide **5.4** (1.28 g, 6.12 mmol) in toluene (25 cm^3) was added phosphoryl chloride, $POCl_3$ (9.38 g, 6.0 cm^3, 6.12 mmol). The reaction mixture was then stirred at reflux for 2 hours. The solvent was then removed under pressure and water (25 cm^3) was added to the vessel followed by the cautious addition of aqueous sodium hydroxide (2M), until the solution became alkaline. The product was extracted into diethyl ether (2 × 50 cm^3) and the collected organic extracts were dried over sodium sulphate, the product was filtered through a sintered funnel and rinsed with additional diethyl ether. The solvent was evaporated and the pure product was isolated as 6,7-dimethoxy-3,4-dihydroisoquinoline **5.5** (1.02 g, 5.33 mmol, 87%), an orange oil.



5.5

R_f(ethyl acetate): 0.08

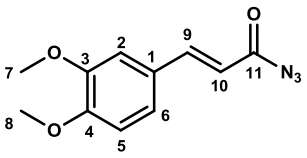
IR (ν/cm^{-1}): 2938, 2836 (w, C–H stretch), 1629 (m, R_2C=N–R imine stretch), 1604, 1462 (m, C=C stretch), 1513 (s, N–H bend), 1278, 1222, 1191 (s, C–O–C stretch), 1117 (s, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (t, *J* = 2.1 Hz, 1H, H_1), 6.81 (s, 1H, H_8), 6.68 (s, 1H, H_5), 3.92 (s, 3H, H_{10}), 3.91 (s, 3H, H_9), 3.73 (td, *J* = 8.2, 2.1 Hz, 2H, H_3), 2.68 (t, 8.0 Hz, 2H, H_4)

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.61 (C_1), 151.16 (C_6), 147.81 (C_7), 129.83 (C_{4a}), 121.54 (C_{8a}), 110.38 (C_8), 110.35 (C_5), 56.11 (C_{10}), 56.01 (C_9), 47.37 (C_3), 24.73 (C_4)

10.1.5. (2*E*)-3-(3,4-Dimethoxyphenyl)prop-2-enoyl azide (5.6)[185]

To a pale opaque solution of 3,4-dimethoxycinnamic acid (0.981 g, 4.71 mmol) in toluene (42 cm^3) was added oxalyl chloride (1.50 g, 1.1 cm^3, 11.8 mmol). The reaction was stirred at reflux temperature for 4 hours. The solvent was removed and the orange solid residue was dissolved in acetone (25 cm^3). Sodium azide (0.919 g, 14.1 mmol) was added to the solution at 0ºC and remained stirring for 15 minutes. The reaction mixture was then allowed to warm to room temperature and stir for an additional 18 hours. The mixture was filtered through a plug of Celite® and washed with excess acetone, which was then removed by rotary evaporator to give the pure product (2*E*)-3-(3,4-dimethoxyphenyl)prop-2-enoyl azide **5.6** (1.07g, 4.58 mmol, 97%) as a pale yellow solid.



5.6

R_f(70% dichloromethane in hexane): 0.53

M.p.: 105–107°C (Lit.[186]105°C)

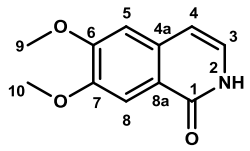
IR (ν/cm^{-1}): 3026, 2964, 2841 (w, C–H stretch), 2131 (m, azide N_3 stretch), 1672 (s, C=O stretch), 1621, 1509 (s, C=C stretch), 1264 (m, azide N_3 stretch), 1179, 1138, 1083 (s, C–O–C stretch), 1020 (s, C–N stretch)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 15.8 Hz, 1H, H_9), 7.13 (dd, *J* = 8.3, 2.0 Hz, 1H, H_6), 7.05 (d, *J* = 1.9 Hz, 1H, H_2), 6.88 (d, *J* = 8.3 Hz, 1H, H_5), 6.29 (d, *J* = 15.8 Hz, 1H, H_{10}), 3.92 (2 × s, 6H, $H_{7, 8}$)

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.07 (C_{11}), 151.95 (C_3), 149.36 (C_4), 146.72 (C_9), 126.82 (C_1), 123.59 (C_{10}), 116.69 (C_6), 111.10 (C_2), 109.91 (C_5), 56.01 (C_7), 55.92 (C_8)

10.1.6. 6,7-Dimethoxyisoquinolin-1(2*H*)-one (5.7)[185]

Mercury acetate, $Hg(OAc)_2$ (0.0704 g, 0.210 mmol) was added to a solution of (2*E*)-3-(3,4-dimethoxyphenyl)prop-2-enoyl azide **5.6** (1.63 g, 6.99 mmol) in *o*-dichlorobenzene (60 cm^3), and the reaction mixture was refluxed for 4 hours. On cooling the deep yellow solution, hexane (150 cm^3) was added to the reaction mixture to induce precipitation; the mixture was triturated for an hour to ensure product optimization. The precipitate was collected by filtration as a brown solid. Purification by column chromatography (ethyl acetate) gave the product 6,7-dimethoxyisoquinolin-1(2*H*)-one **5.7** (0.765 g, 3.73 mmol, 53 %) as a pale brown powder.



5.7

R_f (ethyl acetate): 0.19

M.p.: 255–256°C (Lit.[154] 244–245°C)

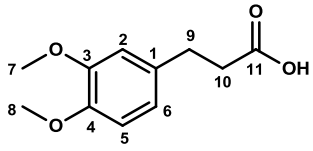
IR (ν/cm^{-1}): 3141 (w, N–H stretch), 2972, 2837 (w, C–H stretch), 1654 (s, C=O stretch), 1634, 1478 (s, C=C stretch), 1555, 1509 (s, N–H bend), 1296, 1234, 1165 (s, C–O–C stretch), 1066 (s, C–N stretch), 983, 900, (m, $C–H_{alkene.}$ bend), 874, 748 (m, $CH_{arom.}$ bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.37 (s, 1H, H_2), 7.79 (s, 1H, H_8), 7.13 (d, J = 6.4 Hz, 1H, H_3), 6.93 (s, 1H, H_5), 6.50 (d, J = 7.1 Hz, 1H, H_4), 4.04 (s, 3H, H_{10}), 4.01 (s, 3H, H_9)

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.72 (C_1), 153.91 (C_6), 149.36 (C_7), 133.99 (C_{4a}), 126.29 (C_3), 119.66 (C_{8a}), 106.89 (C_4), 106.75 (C_5), 106.16 (C_8), 56.24 (C_9), 56.11 (C_{10})

10.1.7. 3-(3,4-Dimethoxyphenyl)propanoic acid (5.8)[156]

3,4-Dimethoxycinnamic acid (1.97 g, 9.46 mmol) was dissolved in a 1:1 mixture of methanol and dichloromethane (50 cm^3) the vessel was degassed 3 times with argon gas. 10% Palladium on carbon (0.197 g, 10% of the mass of the starting material) was added to the mixture and a hydrogen balloon (1 atm) was used to introduce hydrogen to the system over 24 hours, while the mixture was stirred at room temperature. The black reaction mixture was filtered through a plug of Celite® and rinsed with excess methanol. The solvent was evaporated *in vacuo* and the pure product 3-(3,4-dimethoxyphenyl)propanoic acid **5.8** (1.94 g, 9.24 mmol, 98%) was collected as a white crystalline solid.



5.8

R_f (50% ethyl acetate in hexane): 0.45

M.p.: 96–98°C (Lit.[155] 96–98°C)

IR (ν/cm^{-1}): 2996 (w br, OH stretch), 2960, 2918 (w, C–H stretch), 1697 (s, C=O stretch), 2591, 1516 (m, C=C stretch), 1430 (m, O–H bend), 1344 (m, C–C stretch), 1236 (s, C–$O_{carboxylic\ acid}$ stretch), 1146, 1026 (s, C–O–C_{ether} stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (br s, 1H, OH), 6.89–6.69 (m, 3H, $H_{2, 5, 6}$), 3.86 (2 × s, *J* = 2.9 Hz, 6H, $H_{7, 8}$), 2.91 (t, *J* = 7.7 Hz, 2H, H_9), 2.67 (t, *J* = 7.6 Hz, 2H, H_{10})

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.85 (C_{11}), 148.92 (C_3), 147.58 (C_4), 132.77 (C_1), 120.09 (C_6), 111.66 (C_2), 111.34 (C_5), 55.91 (C_7), 55.82 (C_8), 35.87 (C_{10}), 30.26 (C_{11})

10.1.8. 6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (5.3)

Method 1 (from compound 5.2):[105,147,187]

Potassium hydroxide (3.08 g, 53.2 mmol) was dissolved in water (15 cm^3) while gently heating the solution. On cooling, the solution was added to methanol (60 cm^3) and stirred at room temperature for 10 minutes. The reaction vessel was then cooled to 0ºC before hydrogen peroxide (100 vols, 40 cm^3) was added to the stirring mixture. 6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** (4.75 g, 21.3 mmol) was added to the opaque white mixture portion wise over 20 minutes and the reaction mixture was left to stir at 0ºC for 3 hours. The product mixture was filtered through a plug of Celite® and washed with methanol until the yellow colour was no longer present. The solvent was removed and the remaining residue was extracted into dichloromethane (100 cm^3), the organic layer was washed with water (100 cm^3) and slowly acidified with concentrated hydrochloric acid. The organic layer was collected and the aqueous layer was extracted further with dichloromethane (2 × 100 cm^3). The collected organic extracts were then dried over sodium sulphate, filtered and the solvent evaporated under vacuum. The product 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **5.3** (3.47 g, 16.7 mmol, 79%) was isolated as a white crystalline solid.

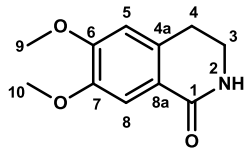
Method 2 (from compound 5.5):[151,152]

Sodium chlorite (2.26 g, 24.9 mmol) was cautiously added to a solution of 1M sodium dihydrogen phosphate (1.17 g, 7.49 mmol in 7.5 cm^3 water). The prepared solution was added to a dropping funnel and added dropwise over 15 minutes to a stirring solution of 6,7-

dimethoxy-3,4-dihydroisoquinoline **5.5** (0.953 g, 4.99 mmol) in tetrahydrofuran (20 cm^3), at room temperature. The mixture was then allowed to stir at room temperature for 42 hours. The product was then extracted into ethyl acetate (50 cm^3) and washed with concentrated sodium sulphite. The organic layer was collected and dried over sodium sulphate, filtered and the solvents were evaporated. The product was purified by flash column chromatography (in ethyl acetate) to give the product 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **5.3** (0.664 g, 3.21 mmol, 64%) as a pale yellow solid.

Method 3 (from compound 5.8):[156]

To an ice-cooled solution of toluene (20 cm^3) and triethylamine (1.96 g, 2.8 cm^3, 19.4 mmol) was added 3-(3,4-dimethoxyphenyl)propanoic acid **5.8** (3.70 g, 17.6 mmol) portionwise. The mixture was allowed to warm to room temperature and the reaction mixture was stirred for 15 minutes. Diphenylphosphoryl azide, DPPA (5.34 g, 4.2 cm^3, 19.4 mmol) in toluene (30 cm^3) was then added dropwise to the stirring reaction over 15 minutes and the mixture was heated to 100ºC for 2 hours. The reaction vessel was again cooled to 0ºC, and boron trifluoride diethyl etherate (80 cm^3) was added dropwise over 15 minutes. After a further 30 minutes, the reaction mixture was warmed to room temperature and allowed to stir for 18 hours. The reaction was quenched with aqueous sodium hydroxide (2M) until the reaction mixture became alkaline (pH 10). Ethyl acetate was then added to extract the product and the mixture was heated for an hour. The organic layer was collected and the aqueous layer was further extracted (2 × 100 cm^3). The collected organic extract was then washed with bine (100 cm^3), dried (anhydrous sodium sulphate), filtered and the solvent was evaporated. The crude solid was recrystallized from ethyl acetate to give the product **5.3** (3.50 g, 16.9 mmol, 96%) as white crystals.



5.3

R_f (ethyl acetate): 0.21

M.p.: 162–164°C (Lit.[69] 170–172°C)

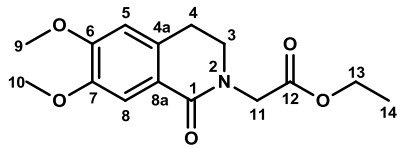
IR (ν/cm^{-1}): 3184 (w, N–H stretch), 3041, 2913 (w, C–H stretch), 1655 (s, C=O stretch), 1601, 1426, 1393 (s, C=C stretch), 1509, 1470 (s, N–H bend), 1341 (s, C–N stretch), 1217, 1122, 1049 (s, C–O–C stretch), 886, 730, 700 (m, $CH_{arom.}$ bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 1H, H_8), 7.15 (s, 1H, H_2), 6.68 (s, 1H, H_5), 3.93 (s, 3H, H_{10}), 3.93 (s, 3H, H_9), 3.56 (td, J = 6.7, 2.8 Hz, 2H, H_3), 2.92 (t, J = 6.7 Hz, 2H, H_4)

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.70 (C_1), 152.14 (C_6), 148.02 (C_7), 132.70 (C_{4a}), 121.47 (C_{8a}), 110.15 (C_5), 109.62 (C_8), 56.08 (C_9), 56.01 (C_{10}), 40.35 (C_3), 27.94 (C_4)
HRMS (EI): Found M^+ = 207.0887, $C_{11}H_{13}NO_3$ requires 207.0895

10.1.9. Ethyl 2-(6,7-dimethoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (5.9)[84,125]

To an ice-cooled solution of 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **5.3** (1.69 g, 8.17 mmol) in tetrahydrofuran (30 cm^3) was added 60% sodium hydride in paraffin oil (0.492 g, 12.3 mmol), which was stirred for 15 minutes before warming to room temperature and then heating the reaction to reflux for 2 hours. The reaction was then cooled to room temperature and once more cooled to 0ºC before adding ethyl 2-bromoacetate (1.64 g, 1.1 cm^3, 9.80 mmol). The reaction mixture was warmed to room temperature and allowed to stir for an additional 20 hours. The product mixture was quenched with water (10 cm^3), until the solution became clear. The solvent was evaporated and the crude residue was extracted into dichloromethane (2 × 50 cm^3), washed with water (50 cm^3) and brine (50 cm^3). The organic layer was collected and dried over anhydrous sodium sulphate, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (60% ethyl acetate in hexane) to give the product ethyl 2-(6,7-dimethoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.9** (2.15 g, 7.34 mmol, 90%) as white crystals.



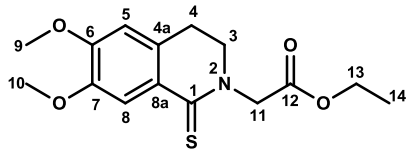
5.9

R_f (60% ethyl acetate in hexane): 0.32
M.p.: 85–90°C
IR (ν/cm^{-1}): 2994, 2826 (w, C–H stretch), 1734 (s, $C{=}O_{ester}$ stretch), 1644 (s, $C{=}O_{amide}$ stretch), 1604, 1429 (s, C=C stretch), 1278 (s, C–N stretch), 1193, (s, C–O stretch), 1114, 1023 (s, C–O–C stretch), 875, 769, 719 (m, $CH_{arom.}$ bend)
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H, H_8), 6.65 (s, 1H, H_5), 4.31 (s, 2H, H_{11}), 4.21 (q, *J* = 7.1 Hz, 2H, H_{13}), 3.92 (2 × s, 6H, $H_{9,\ 10}$), 3.65 (t, *J* = 6.5 Hz, 2H, H_3), 2.99 (t, *J* = 6.4 Hz, 2H, H_4), 1.28 (t, *J* = 7.1 Hz, 3H, H_{14})
^{13}C NMR (75 MHz, $CDCl_3$) δ 169.36 (C_{12}), 165.00 (C_1), 152.03 (C_6), 147.95 (C_7), 132.19 (C_{4a}), 121.34 (C_{8a}), 110.65 (C_8), 109.34 (C_5), 61.14 (C_{13}), 56.02 (C_9), 55.99 (C_{10}), 49.21 (C_{11}), 47.63 (C_3), 27.63 (C_4), 14.15 (C_{14})

HRMS (EI): Found M^+ = 293.1256, $C_{15}H_{19}NO_5$ requires 293.1263.

10.1.10. Ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (5.10)[76,126]

To a solution of ethyl 2-(6,7-dimethoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.9** (3.43 g, 11.7 mmol) in toluene (80 cm^3) was added Lawesson's reagent (2.83 g, 6.99 mmol). The reaction was heated to reflux and stirred for 18 hours. The solvent was evaporated under vacuum and the crude product was purified by flash column chromatography (40% ethyl acetate in hexane) to afford the product ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.10** (3.13 g, 10.1 mmol, 87%) as a yellow solid.



5.10

R_f (40% ethyl acetate in hexane): 0.35

M.p.: 125–126°C (Lit.[69] 89–90°C)

IR (ν/cm^{-1}): 2971, 2829 (w, C–H stretch), 1733 (s, C=O stretch), 1606, 1462 (s, C=C stretch), 1495 (s, C=S stretch), 1265 (s, C–N stretch), 1197, 1175 (s, C–O stretch), 1123, 1031, 1016 (s, C–O–C stretch), 866, 794, 717 (m, $CH_{arom.}$ bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H, H_8), 6.59 (s, 1H, H_5), 4.94 (s, 2H, H_{11}), 4.23 (q, *J* = 7.1 Hz, 2H, H_{13}), 3.93 (s, 3H, H_9), 3.91 (s, 3H, H_{10}), 3.75 (t, *J* = 6.7 Hz, 2H, H_3), 2.98 (t, *J* = 6.6 Hz, 2H, H_4), 1.29 (t, *J* = 7.1 Hz, 3H, H_{14})

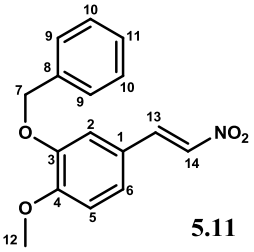
^{13}C NMR (75 MHz, $CDCl_3$) δ 192.98 (C_1), 167.89 (C_{12}), 152.30 (C_6), 147.58 (C_7), 127.05 (C_{4a}), 126.70 (C_{8a}), 115.33 (C_8), 108.68 (C_5), 61.45 (C_{13}), 57.30 (C_{11}), 56.10 (C_9), 56.05 (C_{10}), 50.45 (C_3), 27.40 (C_4), 14.17 (C_{14})

HRMS (EI): Found M^+ = 309.1028, $C_{15}H_{19}NO_4S$ requires 309.1035. *M/z*: 309.1028 (100%, M^+), 308.3335 (4%), 308.0966 (13%)

10.2. Preparation of a vanillin-derived isoquinoline structure[36,44]

10.2.1. (*E*)-3-(Benzyloxy)-4-methoxy-1-(2-nitrovinyl)benzene (5.11)

To a solution of 3-(benzyloxy)-4-methoxybenzaldehyde **3.20** (2.009 g, 8.292 mmol) in glacial acetic acid (40 cm^3) was added ammonium acetate (0.8450 g, 11.61 mmol) followed by nitromethane (1.478 g, 1.3 cm^3, 24.22 mmol). The opaque white reaction mixture was then heated to reflux and stirred for 18 hours. On cooling to ambient temperature, the maroon coloured product was extracted into dichloromethane (2 × 50 cm^3) and then washed with brine (50 cm^3), the collected organic extract was then dried over sodium sulphate, filtered through a plug of Celite® and the solvent was removed by rotary evaporator. The crude product was purified by column chromatography (20–50% ethyl acetate in hexane) to afford the pure product (*E*)-3-(benzyloxy)-4-methoxy-1-(2-nitrovinyl)benzene **5.11** (2.127 g, 7.456 mmol, 90%) as a bright yellow powder.



5.11

R_f (30% ethyl acetate in hexane): 0.63

M.p.: 106–110°C (Lit.[157] 125–127°C)

IR (ν/cm^{-1}): 3110, 3046, 2921 (w, C–H stretch), 1628, 1511, 1386 (w–s, NO_2 stretch), 1596, 1468 (s, C=C stretch), 1258, 1142, 1027 (s, C–O–C stretch), 960 (s, $CH_{E\text{alkene}}$ bend), 859, 804, 745 (m, $CH_{\text{arom.}}$ bend), 697 (s, $CH_{\text{Z-alkene}}$ bend)

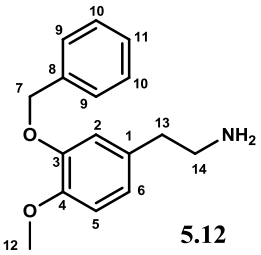
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 13.6 Hz, 1H, H_{14}), 7.51 (d, *J* = 13.6 Hz, 1H, H_{13}), 7.45–7.31 (m, 5H, $H_{9,10,11}$), 7.07 (dd, *J* = 8.3, 1.9 Hz, 1H, H_2), 7.01 (d, *J* = 1.9 Hz, 1H, H_6), 6.90 (d, *J* = 8.3 Hz, 1H, H_5), 5.19 (s, 2H, H_7), 3.90 (s, 3H, H_{12})

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.95 (C_3), 150.05 (C_4), 139.31 (C_{13}), 136.15 (C_{14}), 135.27 (C_8), 128.72 (C_{10}), 128.22 (C_{11}), 127.29 (C_9), 124.41 (C_1), 123.12 (C_6), 113.46 (C_5), 110.91 (C_2), 70.85 (C_7), 56.10 (C_{12})

HRMS (ESI+): Found $(M + H)^+$ = 286.1074, $C_{16}H_{15}NO_4$ requires 286.1080. *M/z*: 286.1074 (16%, $(M + H)^+$), 282.2814 (12%), 258.1156 (4%), 243.1024 (100%), 91.0546 (10%)

10.2.2. 2-[3-(Benzyloxy)-4-methoxyphenyl]ethanamine (5.12)[158]

To an ice-cooled solution of lithium aluminium hydride, (0.0716 g, 1.89 mmol) in tetrahydrofuran (2 cm^3) was added (*E*)-3-(benzyloxy)-4-methoxy-1-(2-nitrovinyl)benzene **5.11** (0.108 g, 0.377 mmol) in tetrahydofuran (2 cm^3) dropwise over 10 minutes. The reaction mixture was warmed to room temperature and then heated under reflux for 20 hours. On cooling to 0°C, additional tetrahydofuran (5 cm^3) followed by water (3 cm^3) and aqueous sodium hydroxide (2M, 2 cm^3) was added cautiously to the reaction mixture. The reaction mixture was then filtered and rinsed with and excess of tetrahydrofuran, and the solvent was removed by rotary evaporator to afford a crude orange-brown oil. The oil was dissolved in ethyl acetate (20 cm^3) and washed with water (20 cm^3) and brine (20 cm^3), the collected organic phase was then dried over sodium sulphate, filtered and evaporated. The crude product was recrystallized from diethyl ether to afford the product 2-[3-(benzyloxy)-4-methoxyphenyl]ethanamine **5.12** (0.0881 g, 0.342 mmol, 91%) as a pale orange solid.



5.12

R_f (50% ethyl acetate in hexane): 0.18

M.p.: 43–46°C (Lit.[157] 43–44°C)

IR (ν/cm^{-1}): 3361 (w, N–H stretch), 3002, 2928, 2858 (w, C–H stretch), 1590, 1453 (w, C=C stretch), 1510 (s, N–H bend), 1259, 1224, 1138 (s, C–O–C stretch), 1023 (s, C–N stretch), 914, 735, 696 (m, $CH_{arom.}$ bend), 805 (m, N–H bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.19 (m, 5H, $H_{9,10,11}$), 6.91–6.57 (m, 3H, $H_{2,5,6}$), 5.12 (d, *J* = 2.4 Hz, 2H, H_7), 3.85 (d, *J* = 2.0 Hz, 3H, H_{12}), 3.71 (s, 2H, NH_2), 2.85 (t, *J* = 6.3 Hz, 2H, H_{14}), 2.75 (t, *J* = 6.4 Hz, 2H, H_{13})

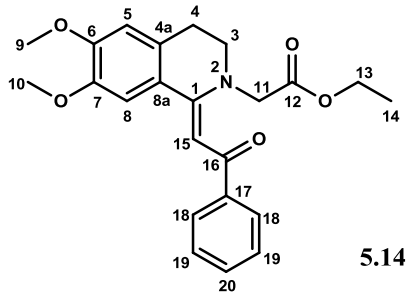
^{13}C NMR (75 MHz, $CDCl_3$) δ 149.70 (C_3), 146.69 (C_4), 137.34 (C_8), 132.82 (C_1), 128.49 ($C_{10,12}$), 127.76 (C_{11}), 127.26 ($C_{9,13}$), 120.75 (C_6), 114.36 (C_2), 112.70 (C_5), 71.19 (C_7), 55.98 (C_{14}), 43.45 (C_{14}), 39.28 (C_{13})

HRMS (ESI+): Found $(M + H)^+$ = 258.1499, $C_{16}H_{19}NO_2$ requires 258.1495. *M/z*: 258.1499 (100%, $(M + H)^+$), 241.1225 (70%), 227.1082 (78%), 208.0967 (12%), 195.0819 (25%), 91.0545 (44%)

10.3. Eschenmoser sulphide contraction with *N*-alkylated thiolactam (5.10)[74,76,84,128,129]

10.3.1. (*Z*)-Ethyl 2-[6,7-dimethoxy-1-(2-oxo-2-phenylethylidene)-3,4-dihydroisoquinolin-2(1*H*)-yl]acetate (5.14)

Ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.10** (0.397 g, 1.28 mmol) in acetonitrile (4 cm^3) was added to a 25 cm^3 round bottom flask that was covered in aluminium foil to avoid light-induced decomposition. 2-Bromo-1-phenylethanone (0.366 g, 1.84 mmol) and sodium iodide (0.287 g, 1.97 mmol) were then added, respectively and the opaque orange reaction mixture was stirred at ambient temperature for 60 hours. The reaction vessel was then cooled to 0°C and triphenylphosphine (0.523 g, 1.99 mmol) was added, and after 15 min triethylamine (0.302 g, 0.42 cm^3, 2.99 mmol) was added followed by acetonitrile (2 cm^3). The reaction was then warmed to room temperature and left to stir for 21 hours. The solvent was evaporated and the residue was extracted into ethyl acetate (2 × 20 cm^3) and washed with ammonium chloride (2 × 15 cm^3), water (2 × 15 cm^3) and brine (15 cm^3). The collected organic extracts were dried over anhydrous sodium sulphate, filtered through a plug of Celite® and the solvent was removed *in vacuo*. The crude brown oil was purified by flash column chromatography in 60% ethyl acetate in hexane to give the product (*Z*)-ethyl 2-(6,7-dimethoxy-1-(2-oxo-2-phenylethylidene)-3,4-dihydroisoquinolin-2(1*H*)-yl) acetate **5.14** (0.427 g, 1.08 mmol, 84%) as a dark orange oil.



5.14

R_f (50% ethyl acetate in hexane): 0.07

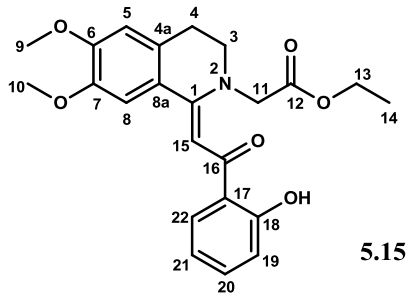
IR (ν/cm^{-1}): 2982, 2937 (w, C–H stretch), 1747 (m, $C{=}O_{ketone}$ stretch), 1685 (m, $C{=}O_{ester}$ stretch), 1635, 1602, 1478 (s, C=C stretch), 1260 (s, C–C stretch), 1231, 1164, 1017, 971 (s, C–O–C stretch), 1128 (m, C–N stretch), 941 (m, C–O stretch), 696 (s, $CH_{Zalkene}$ bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.6, 1.9 Hz, 2H, H_{18}), 7.46–7.38 (m, 3H, $H_{19,20}$), 7.27 (s, 1H, H_8), 6.65 (s, 1H, H_5), 5.99 (s, 1H, H_{15}), 4.52 (s, 2H, H_{11}), 4.19 (q, *J* = 7.1 Hz, 2H, H_{13}), 3.87 (s, 3H, H_9), 3.81 (s, 3H, H_{10}), 3.53 (t, *J* = 6.1 Hz, 2H, H_4), 2.93 (t, *J* = 6.0 Hz, 2H, H_3), 1.19 (t, *J* = 7.1 Hz, 3H, H_{14})

^{13}C NMR (75 MHz, $CDCl_3$) δ 185.88 (C_{16}), 169.94 (C_{12}), 151.61 (C_1), 142.27 (C_6), 139.45 (C_7), 128.45 (C_{20}), 128.09 (C_{18}), 127.68 (C_{19}), 127.42 (C_{4a}), 125.84 (C_{17}), 125.42 (C_{8a}), 112.49 (C_8), 110.19 (C_5), 91.18 (C_1), 65.22 (C_{13}), 58.39 (C_{11}), 56.31 (C_9), 56.05 (C_{10}), 50.51 (C_3), 28.14 (C_4), 14.17 (C_{14})

10.3.2. (*Z*)-Ethyl 2-{1-[2-(2-hydroxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate (5.15)

Ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.10** (0.117 g, 0.380 mmol) in acetonitrile (3 cm^3) was added to a 25 cm^3 round bottom covered in aluminium foil to reduce light-induced decomposition. 2-Bromo-1-(2-hydroxyphenyl)ethanone **3.10** (0.176 g,) and sodium iodide (0.135 g, 0.818 mmol) were then added and the reaction was stirred at room temperature for 67 hours. The reaction vessel was then cooled to 0°C and triphenylphosphine (0.180 g, 0.686 mmol), triethylamine (0.167 g, 0.12 cm^3, 1.65 mmol) and acetonitrile (3 cm^3) were added, respectively. After 30 min, the reaction vessel was allowed to warm to room temperature and left to stir for 20 hours. The solvent was removed and the brown residue was extracted into ethyl acetate (20 cm^3) and then washed with ammonium chloride (15 cm^3). The product was further extracted by ethyl acetate (2 × 20 cm^3) and then the combined organic extracts were washed with water (2 × 15 cm^3) and brine (15 cm^3). The organic layer was dried over sodium sulphate, filtered and the solvent was evaporated to give a dark orange oil which was purified by flash column chromatography (40% ethyl acetate in hexane) to afford the product (*Z*)-ethyl 2-{1-[2-(2-hydroxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate **5.15** (0.0492 g, 0.120 mmol, 32 %) as a bright yellow oil.



5.15

R_f (50% ethyl acetate in hexane): 0.28

IR (ν/cm^{-1}): 3051 (w, OH stretch), 2926, 2852 (w, C–H stretch), 1723 (m, $C{=}O_{ketone}$ stretch), 1674 (m, $C{=}O_{ester}$ stretch), 1632, 1600, 1485 (s, C=C stretch), 1305 (s, C–C stretch), 1247, 1156, 1192 (s, C–O–C stretch), 1020, 991 (m, C–O stretch), 724 (s, $CH_{Zalkene}$ bend).

^{1}H NMR (300 MHz, $CDCl_3$) δ 13.80 (s, 1H, OH), 7.73 (dd, *J* = 8.0, 1.3 Hz, 1H, H_{22}), 7.58 (s, 1H, H_8), 7.33 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H, H_{20}), 6.92 (dd, *J* = 8.3, 1.0 Hz, 1H, H_{19}), 6.81

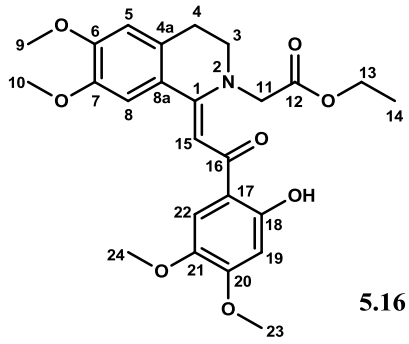
(ddd, J = 8.1, 7.1, 1.1 Hz, 1H, H_{21}), 6.64 (s, 1H, H_5), 6.01 (s, 1H, H_{15}), 4.30 (s, 2H, H_{11}), 4.20 (q, J = 7.2 Hz, 2H, H_{13}), 3.91 (s, 3H, H_9), 3.90 (s, 3H, H_{10}), 3.64 (t, J = 6.7 Hz, 2H, H_3), 2.98 (t, J = 6.7 Hz, 2H, H_4), 1.28 (t, J = 6.7 Hz, 3H, H_{14})

^{13}C NMR (75 MHz, $CDCl_3$) δ 188.50 (C_{12}), 169.39 (C_{16}), 165.05 (C_{18}), 162.59 (C_1), 152.04 (C_6), 147.97 (C_7), 133.35 (C_{20}), 132.17 (C_{22}), 131.81 (C_{4a}), 128.39 (C_{17}), 121.83 (C_{8a}), 121.36 (C_{21}), 117.99 (C_{19}), 110.69 (C_8), 109.33 (C_5), 88.60 (C_{15}), 61.19 (C_{13}), 56.06 (C_9), 56.02 (C_{10}), 49.24 (C_{11}), 47.66 (C_3), 27.68 (C_4), 14.18 (C_{14})

HRMS (EI): Found M^+ = 411.1675, $C_{23}H_{25}NO_6$ requires 411.1682

10.3.3. (*Z*)-Ethyl 2-{1-[2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate (5.16)

Ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.10** (0.323 g, 1.04 mmol) and 1-(2-hydroxy-4,5-dimethoxyphenyl)-2-iodoethanone **3.18** (0.176 g, 2.06 mmol) in acetonitrile (10 cm^3) were added to a 25 cm^3 round bottom covered in aluminium foil to reduce light-induced decomposition, and stirred at ambient temperature for 20 hours. The reaction vessel was cooled to 0°C and triphenylphosphine (0.425 g, 1.62 mmol), triethylamine (0.252 g, 0.35 cm^3, 2.49 mmol) and acetonitrile (10 cm^3) were added, respectively. The reaction was then stirred at room temperature for 4 hours. The solvent was evaporated and the residue was dissolved in ethyl acetate (20 cm^3) and washed with ammonium chloride (15 cm^3). The aqueous layer was further extracted with ethyl acetate (2 × 15 cm^3) and then the organic extracts were combined and washed with water (2 × 15 cm^3) and brine (15 cm^3). The organic layer was then dried over sodium sulphate, filtered through a sintered funnel and the solvent was then evaporated by rotary evaporator. The crude orange residue was purified by flash column chromatography (40% ethyl acetate in hexane) to give the product (*Z*)-ethyl 2-{1-[2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate **5.16** (0.322 g, 0.682 mmol, 66%) as a yellow-orange gum.



5.16

R_f (50% ethyl acetate in hexane): 0.14

IR (ν/cm^{-1}): 3056 (w, OH stretch), 3013, 2922 (w, C–H stretch), 1742 (m, C=O$_{ketone}$ stretch), 1607 (m, C=O$_{ester}$ stretch), 1589, 1436 (s, C=C stretch), 1268 (s, C–C stretch), 1189, 1118 (s, C–O–C stretch), 997 (m, C–N stretch), 753 (s, CH$_{Z\text{-alkene}}$ bend)

^{1}H NMR (500 MHz, $CDCl_3$) δ 14.06 (s, 1H, OH), 7.31 (s, 1H, H_{22}), 7.19 (s, 1H, H_8), 6.70 (s, 1H, H_5), 6.46 (s, 1H, H_{19}), 5.88 (s, 1H, H_{15}), 4.37 (s, 2H, H_{11}), 4.27 (q, J = 7.1 Hz, 2H, H_{13}), 3.93, 3.88, 3.87, 3.84 (4 × s, 3H, $H_{9,10,23,24}$), 3.64–3.59 (m, 2H, H_3), 2.98–2.92 (m, 2H, H_4), 1.31 (t, J = 7.1 Hz, 3H, H_{14})

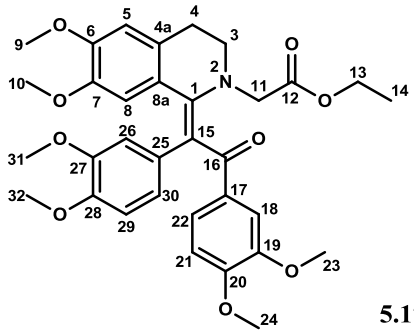
^{13}C NMR (126 MHz, $CDCl_3$) δ 188.13 (C_{12}), 171.07 (C_{16}), 169.89 (C_{18}), 159.49 (C_{20}), 158.83 (C_{21}), 154.42 (C_7), 151.93 (C_6), 147.70 (C_{15}), 141.18 (C_{4a}), 128.63 (C_{17}), 126.00 (C_{8a}), 113.29 (C_{22}), 111.22 (C_8), 110.26 (C_5), 100.90 (C_{19}), 88.59 (C_{15}), 61.26 (C_{13}), 60.34 (C_{11}), 56.88, 56.27, 56.07, 55.93 ($C_{9,10,23,24}$), 50.33 (C_3), 27.85 (C_4), 14.20 (C_{14})

HRMS (EI): Found M^+ = 471.1868, $C_{25}H_{29}NO_8$ requires 471.1893

10.3.4. (*Z*)-Ethyl 2-{1-[1,2-bis(3,4-dimethoxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate (5.17)

Ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **5.10** (0.215 g, 0.696 mmol) in acetonitrile (3 cm^3) was added to a 25 cm^3 round bottom flask that was covered in aluminium foil to reduce light-induced decomposition. 2-Bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27** (0.549 g, 1.39 mmol) and sodium iodide (0.257 g, 1.72 mmol) were then added to the reaction mixture, which was stirred at ambient temperature for 45 hours. The reaction vessel was then cooled to 0°C and triphenylphosphine (0.303 g, 1.15 mmol) was added to the stirring emulsion. After 15 minutes, triethylamine (0.144 g, 0.20 cm^3, 1.42 mmol) was added followed by additional acetonitrile (3 cm^3). The reaction was then warmed to room temperature and left to stir for 18 hours. The solvent was evaporated and the residue was extracted into ethyl acetate (3 × 20 cm^3) and washed with ammonium chloride (2 × 15 cm^3), water (2 × 15 cm^3) and brine (15 cm^3). The collected organic extracts were dried over anhydrous sodium sulphate, filtered through a plug of Celite® and the solvent was removed *in vacuo*. The crude brown residue was purified by flash column chromatography in 40% ethyl acetate in hexane to give the product (*Z*)-ethyl 2-{1-[1,2-

bis(3,4-dimethoxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate **5.17** (0.282 g, 0.476 mmol, 68%) as a bright yellow solid.



5.17

R_f (50% ethyl acetate in hexane): 0.29

M.p.: 100–102°C

IR (ν/cm^{-1}): 3076, 2931, 2834 (w, C–H stretch), 1739 (s, $C{=}O_{ketone}$ stretch), 1659 (m, $C{=}O_{ester}$ stretch), 1582, 1509 (s, C=C stretch), 1330 (s, C–C stretch), 1260, 1122, 1196 (s, C–O–C stretch), 1011 (m, C–N stretch), 638 (m, $CH_{Z\text{-}alkene}$ bend)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H, H_8), 7.63–7.45 (m, 3H, $H_{18,21,22}$), 6.92–6.78 (m, 3H, $H_{26,29,30}$), 6.58 (s, 1H, H_5), 4.96 (s, 2H, H_{11}), 4.25 (q, J = 7.1 Hz, 2H, H_{13}), 3.96 (2 × s, 6H, $H_{31,32}$), 3.95, 3.94, 3.93, 3.92 (4 × s, 12H, $H_{9,10,23,24}$), 3.76 (t, J = 6.8 Hz, 2H, H_3), 2.99 (t, J = 6.8 Hz, 2H, H_4), 1.30 (t, J = 7.1 Hz, 3H, H_{14})

^{13}C NMR (75 MHz, $CDCl_3$) δ 193.50 (C_{12}), 167.95 (C_{16}), 154.86 (C_1), 153.36 (C_{19}), 152.34 (C_{20}), 149.58 (C_{27}), 149.10 (C_{28}), 147.68 (C_6), 127.54 (C_{4a}), 126.97 (C_7), 126.81 (C_{8a}), 126.51 (C_{17}), 126.29 (C_{21}), 123.44 (C_{22}), 121.48 (C_{26}), 115.43 (C_8), 112.49 (C_{25}), 111.41 (C_{15}), 110.74 (C_{29}), 110.37 (C_{30}), 110.04 (C_{18}), 108.63 (C_5), 61.52 (C_{13}), 56.24, 56.11, 56.08, 55.97, 55.90, 55.88 ($C_{9,10,23,24,31,32}$), 50.47 (C_{11}), 44.78 (C_3), 27.49 (C_4), 14.21 (C_{14})

HRMS (EI): Found M^+ = 591.2471, $C_{33}H_{37}NO_9$ requires 591.2468

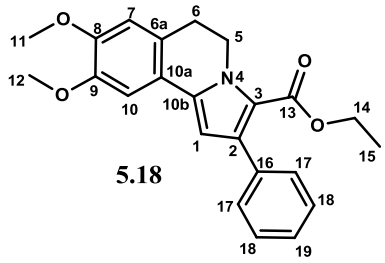
10.4. Pyrrole ring formations with silica gel

General method for the pyrrole ring-closure:[69,88]

To a sealed microwave tube was added the prepared *N*-alkylated enaminone (*Section 10.3*) dissolved in xylene (5-7 cm^3/mmol). Silica gel (3–5 times mass of starting material) was added to the solution and the mixture was then irradiated under microwave conditions (150W, 180°C, 30 min). The reaction mixture was then filtered through a plug of Celite® and silica gel and rinsed with an excess of acetone. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography.

10.4.1. Ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (5.18)

The product was prepared from (*Z*)-ethyl 2-(6,7-dimethoxy-1-(2-oxo-2-phenylethylidene)-3,4-dihydroisoquinolin-2(1*H*)-yl) acetate **5.14** (0.306 g, 0.774 mmol) by the general method for silica-induced ring closure of enaminones. The crude brown residue was purified by flash column chromatography (10–20% ethyl acetate in hexane) to afford ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.18** (0.213 g, 0.565 mmol, 73%) as a dark yellow gum.



5.18

R_f (50% ethyl acetate in hexane): 0.68

IR (ν/cm^{-1}): 3060, 2930, 2852 (w, C–H stretch), 1682 (s, C=O stretch), 1610, 1481 (w, C=C stretch), 1336 (m, C–C stretch), 1259, 1199, 1126 (s, C–O–C stretch), 1074, 1046 (m, C–N stretch)

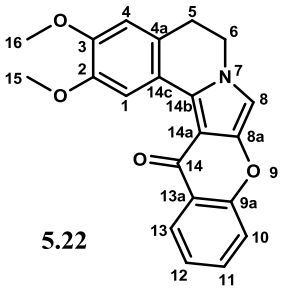
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2H, H_{17}), 7.37–7.27 (m, 3H, $H_{18,19}$), 7.06 (s, 1H, H_{10}), 6.75 (s, 1H, H_7), 6.47 (s, 1H, H_1), 4.62 (t, J = 6.8 Hz, 2H, H_5), 4.13 (q, J = 7.1 Hz, 2H, H_{14}), 3.92 (s, 3H, H_{11}), 3.91 (s, 3H, H_{12}), 3.05 (t, J = 6.8 Hz, 2H, H_6), 1.06 (t, J = 7.1 Hz, 3H, H_{15})

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.91 (C_{13}), 148.85 (C_8), 148.33 (C_9), 136.96 (C_{10b}), 134.93 (C_{16}), 134.53 (C_{6a}), 129.60 (C_{17}), 127.41 (C_{18}), 126.61 (C_{19}), 124.80 (C_{10a}), 120.80 (C_2), 118.24 (C_3), 110.99 (C_7), 106.88 (C_{10}), 105.91 (C_1), 59.77 (C_{14}), 56.09 (C_{11}), 56.03 (C_{12}), 42.83 (C_5), 28.67 (C_6), 13.83 (C_{15})

HRMS (ESI+): Found $(M + H)^+$ = 378.1707, $C_{23}H_{23}NO_4$ requires 378.1706. *M/z*: 378.1707 (100%, $(M + H)^+$), 332.1277 (3%), 320.1285 (4%), 316.3252 (2%), 270.2798 (5%)

10.4.2. 2,3-Dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one (5.22)

The product was prepared from (*Z*)-ethyl 2-{1-[2-(2-hydroxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate **5.16** (0.580 g, 1.41 mmol) by the general method for silica induced ring closure of enaminones. The crude residue was purified by flash column chromatography (20% ethyl acetate in hexane) to afford 2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.22** (0.152 g, 0.438 mmol, 31 %) as a dark yellow solid.



5.22

R_f (50% ethyl acetate in hexane): 0.52

M.p.: 248–251°C

IR (ν/cm^{-1}): 3065, 2991, 2849 (w, C–H stretch), 1696 (s, C=O stretch), 1609, 1492 (w, C=C stretch), 1331, 1211 (m, C–C stretch), 1029, 1243, 1136 (s, C–O–C stretch), 1083 (m, C–N stretch), 1029 (s, C–O stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.1, 1.3 Hz, 1H, H_{13}), 7.43–7.28 (m, 3H, $H_{10,11,12}$), 7.19 (s, 1H, H_1), 6.89 (s, 1H, H_4), 6.80 (s, 1H, H_8), 4.74 (t, *J* = 6.9 Hz, 2H, H_6), 3.99 (s, 3H, H_{15}), 3.94 (s, 3H, H_{16}), 3.12 (t, *J* = 6.9 Hz, 2H, H_5)

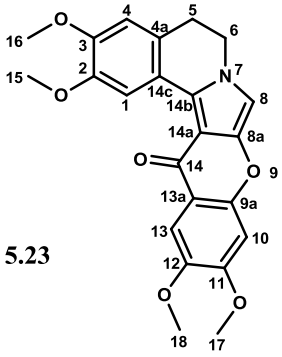
^{13}C NMR (75 MHz, $CDCl_3$) δ 173.78 (C_{14}), 151.34 (C_{9a}), 149.94 (C_3), 148.56 (C_2), 140.14 (C_{4a}), 130.59 (C_{14b}), 127.75 (C_{10}), 125.79 (C_{14c}), 124.06 (C_{12}), 122.96 (C_{13}), 119.87 (C_{13a}), 117.95 (C_{14a}), 117.21 (C_{11}), 115.85 (C_{8a}), 111.27 (C_4), 107.63 (C_1), 96.11 (C_8), 56.25 (C_{16}), 56.09 (C_{15}), 42.37 (C_6), 28.34 (C_5)

HRMS (ESI+): Found $(M + H)^+$ = 348.1244, $C_{21}H_{17}NO_4$ requires 348.1237. *M/z*: 348.1244 (100%, $(M + H)^+$), 324.1228 (5%), 312.1289 (1%), 282.2807 (3%), 274.2764 (2%)

10.4.3. 2,3,11,12-Tetramethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one (5.23)

The product was prepared from (*Z*)-ethyl 2-{1-[2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl}acetate **5.16** (0.322 g, 0.682 mmol) by the general method for silica induced ring closure of enaminones. The crude residue was purified by flash column chromatography (30% ethyl acetate in hexane) to afford

2,3,11,12-tetramethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*] isoquinolin-14(6*H*)-one **5.23** (0.0440 g, 0.108 mmol, 16 %) as a dark orange solid. The product was columned and recrystallized several times, however, contaminants were persistent in the ^{1}H NMR spectrum, all characterization was done based on visibility of potential product peaks and comparisons made to previously made compounds of similar structure.



5.23

R_f (50% ethyl acetate in hexane): 0.31

IR (ν/cm^{-1}): 2921, 2851 (w, C–H stretch), 1700 (s, C=O stretch), 1645, 1568 (m, C=N stretch), 1604, 1508 (w, C=C stretch), 1454, 1423, 1374 (m, CH bend), 1264 (m, C–C stretch), 1243, 1219, 1189, 1119 (s, C–O–C stretch), 1029 (m, C–N stretch), 1029 (s, C–N stretch), 876, 825, 798, 783, 749, 695 (s, C–H bend)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18, 6.93, 6.72, 6.66 (s, 4H, $H_{1,4,10,13}$), 6.79 (s, 1H, H_8), 4.71 (t, J = 6.8 Hz, 2H, H_6), 4.00, 3.99, 3.98, 3.97 (4 × s, 3H, $H_{15,16,17,18}$), 3.09 (dd, J = 13.7, 6.8 Hz, 2H, H_5)

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.36 (C_{14}), 154.08 (C_{11}), 152.08 (C_{9a}), 149.86 (C_3), 148.52 (C_2), 145.55 (C_{12}), 140.14 (C_{4a}), 131.12 (C_{14b}), 127.53 (C_{10}), 125.81 (C_{14c}), 124.28 (C_{13}), 121.39 (C_{13a}), 119.88 (C_{14a}), 115.41 (C_{8a}), 111.25 (C_4), 107.52 (C_1), 95.36 (C_8), 56.38, 56.34, 56.27, 55.98 ($C_{15,16,17,18}$), 42.28 (C_6), 28.74 (C_5)

HRMS (EI): Found M^+ = 407.1363, $C_{23}H_{21}NO_6$ requires 407.1369

10.5. Attempted saponification of ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (5.18)

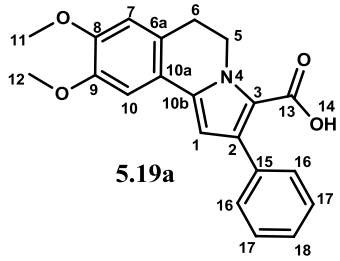
General method:

Ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.18** was added to a solution potassium hydroxide in methanol (10 M) (approximately 0.1 cm^3/mmol of **5.18**). The reaction mixture was allowed to stir at room temperature for 1 hour, while being monitored by TLC. The temperature was then ramped to 60°C for and hour, 80°C for and hour and then 100°C for 18 hours. The reaction mixture was acidified by the careful dropwise addition of concentrated hydrochloric acid. The acidified solution was then washed with a diethyl ether and ethyl acetate mixture (1:1) (3 × 20 cm^3). The organic layer was collected and dried over anhydrous sodium sulphate, followed by filtration with a sintered

funnel and removal of the solvent by rotary evaporator. The product was purified by flash column chromatography.

10.5.1. 8,9-Dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (5.19a)

The product was prepared from ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.18** (0.0188 g, 0.0498 mmol) using the general procedure described above. No further purification was performed. The crude product 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid **5.19a** (0.0164 g, 0.0469 mmol, 94% crude)was afforded as a brown gum.



5.19a

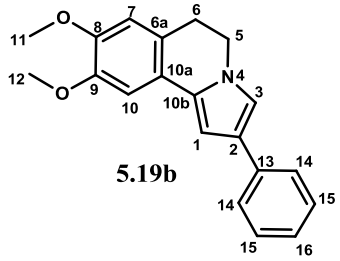
R_f (50% ethyl acetate in hexane): 0.31

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2H, H_{16}), 7.38–7.31 (m, 3H, $H_{17,18}$), 7.08 (s, 1H, H_{10}), 6.96 (s, 1H, H_7), 6.71 (s, 1H, H_1), 4.56 (s, 1H, H_{14}), 4.09 (t, J = 6.7 Hz, 2H, H_5), 3.95 (s, 3H, H_{11}), 3.90 (s, 3H, H_{12}), 3.03 (t, J = 6.6 Hz, 2H, H_6)

10.5.2. 8,9-Dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (5.19b)

Several attempts at reproducing carboxylic acid **5.19a** only yielded the decarboxylated product **5.19b**.

The decarboxylated product was prepared from ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.18** (0.1869 g, 0.495 mmol) using the general method described above. The crude product was purified by flash column chromatography (10% ethyl acetate in hexane) to afford product 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline **5.19b** (0.0552 g, 0.158 mmol, 32%) as a yellow gum.



5.19b

R_f (50% ethyl acetate in hexane): 0.79

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d (dd), *J* = 7.4 Hz, 2H, H_{14}), 7.33 (m, 2H, H_{15}), 7.16 (m, 1H), 7.07 (s, 1H, H_{10}), 6.94 (s, 1H, H_7), 6.70 (s, 2H, $H_{1,3}$), 4.06 (t, *J* = 6.7 Hz, 2H, H5), 3.94 (s, 3H, H_{11}), 3.88 (s, 3H, H_{12}), 3.01 (t, *J* = 6.6 Hz, 2H, H_6)

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.39 (C_8), 147.51 (C_9), 135.79 (C_{10b}), 130.82 (C_{13}), 128.60 (C_{15}), 125.40 (C_{16}), 124.98 (C_{14}), 124.94 (C_{6a}), 122.89 (C_{10a}), 122.21 (C_2), 117.35 (C_7), 111.44 (C_3), 105.98 (C_{10}), 100.20 (C_1), 56.07, 56.05 ($C_{11,12}$), 44.32 (C_5), 28.97 (C_6)

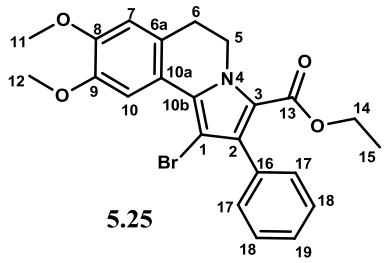
10.6. Bromination reactions for prepared pyrrole systems

General method:

To an ice-cooled solution of the previously prepared ring-closed pyrrole product (*Section 10.4*) in *N*,*N*-dimethylformamide (3–4 cm^3/mmol) was added *N*-bromosuccinimide (1.5 molar equivalents). The reaction was stirred at 0°C for 3 hours, then at room temperature for 18 hours. Water was added to the reaction mixture and the organic product was extracted into ethyl acetate, the combined organic extracts were then washed with water and brine. The organic layer was collected and dried over sodium sulphate, then filtered through a sintered funnel and the solvent was evaporated. The residue was purified by column chromatography and/or recrystallization.

10.6.1. Ethyl 1-bromo-8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (5.25)

The product was prepared from ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.18** (0.054 g, 0.14 mmol) by the general method for bromination of the pyrrole ring. The residue obtained was purified by recrystallization from ethyl acetate and hexane to afford ethyl 1-bromo-8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **5.25** (0.028 g, 0.062 mmol, 44%) as a pale off-white powder.



5.25

R_f (50% ethyl acetate in hexane): 0.65

M.p.: 168–171°C

IR (ν/cm^{-1}): 3054, 2946, 2832 (w, C–H stretch), 1682 (s, C=O stretch), 1608, 1492 (w, C=C stretch), 1335 (m, C–C stretch), 1209, 1251, 1127 (s, C–O–C stretch), 1062, 1018 (m, C–N stretch), 625 (w, C–Br stretch)

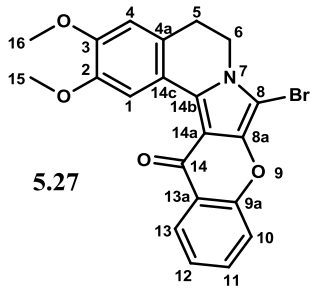
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H, H_7), 7.41–7.33 (m, 3H, $H_{18,19}$), 7.31–7.28 (m, 2H, H_{17}), 6.78 (s, 1H, H_{10}), 4.63 (t, *J* = 6.6 Hz, 2H, H_5), 4.01 (q, *J* = 7.1 Hz, 2H, H_{14}), 3.94, 3.93 (2 × s, 3H, $H_{11,12}$), 3.02 (t, *J* = 6.6 Hz, 2H, H_6), 0.88 (t, *J* = 7.1 Hz, 3H, H_{15})

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.18 (C_{13}), 148.68 (C_8), 147.67 (C_9), 135.16 (C_{10b}), 133.57 (C_{6a}), 130.54 (C_{16}), 130.47 (C_{17}), 127.44 (C_{18}), 127.13 (C_{19}), 126.32 (C_{10a}), 120.16 (C_2), 118.79 (C_1), 110.88 (C_7), 108.52 (C_{10}), 95.58 (C_3), 59.95 (C_{14}), 56.12, 55.99 ($C_{11,12}$), 43.05 (C_5), 29.23 (C_6), 13.50 (C_{15})

HRMS (ESI+): Found $(M + H)^+$ = 456.0810, $C_{23}H_{22}{}^{79}BrNO_4$ requires 456.0811. *M/z*: 458.0794 (95%, for ^{81}Br isotope), 456.0810 (100%, $(M + H)^+$, for ^{79}Br isotope)

10.6.2. 8-Bromo-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one (5.27)[67,135]

The product was prepared from 2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.22** (0.152 g, 0.438 mmol) by the general method for bromination of the pyrrole ring. The crude residue was purified by flash column chromatography (30% ethyl acetate in hexane) to afford 8-bromo-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.27** (0.0663 g, 0.156 mmol, 36 %) as a yellow-brown solid.



5.27

R_f (50% ethyl acetate in hexane): 0.54

M.p.: 261–263°C

IR (ν/cm^{-1}): 2920, 2850 (w, C–H stretch), 1700 (s, C=O stretch), 1608, 1461 (w, C=C stretch), 1579, 1534 (m, C=N stretch), 1275 (m, C–C stretch), 1212, 1045 (s, C–O–C_{diaryl} stretch), 1167, 1152, 1030 (s, C–O–C_{alkyl} stretch) 948 (m, C–N stretch), 560 (w, C–Br stretch)

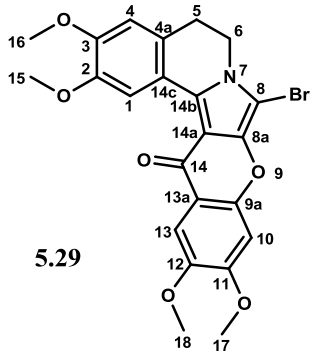
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.29 (m, 4H, H_{10-14}), 7.20 (s, 1H, H_1), 6.90 (s, 1H, H_4), 4.78 (dd, *J* = 10.9, 6.8 Hz, 2H, H_5), 3.99 (s, 3H, H_{15}), 3.94 (s, 3H, H_{16}), 3.11 (dd, *J* = 13.7, 6.8 Hz, 2H, H_6)

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.18 (C_{14}), 151.08 (C_{9a}), 149.73 (C_{11}), 148.02 (C_{4a}), 147.80 (C_{14b}), 128.14 (C_3), 127.03 (C_2), 123.93 (C_{14c}), 123.36 (C_{12}), 122.91 (C_{13}), 119.19 (C_{13a}), 117.56 (C_{14a}), 117.24 (C_{10}), 117.17 (C_4), 109.12 (C_{8a}), 108.83 (C_1), 103.40 (C_8), 56.20, 56.04 ($C_{15,16}$), 42.66 (C_6), 28.88 (C_5)

HRMS (EI): Found M^+ = 425.0190, $C_{21}H_{16}{}^{79}BrNO_4$ requires 425.0263. *M/z*: 427.0220 (90%, for ^{81}Br isotope), 425.0190 (100%, M^+, for ^{79}Br isotope)

10.6.3. 18-Bromo-2,3,11,12-tetramethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one (5.29)

The product was prepared from 2,3,11,12-tetramethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.23** (0.220 g, 0.540 mmol) by the general method for bromination of the pyrrole ring. The crude residue was purified by flash column chromatography (30% ethyl acetate in hexane) to afford 18-bromo-2,3,11,12-tetramethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.29** (0.0182 g, 0.0374 mmol, 8 %) as a brown solid. ^{1}H NMR contaminated, characterization based on visible peaks and comparison to previously prepared compounds with related structure.



5.29

R_f (50% ethyl acetate in hexane): 0.24

IR (ν/cm^{-1}): 2932, 2751 (w, C–H stretch), 1708 (s, C=O stretch), 1656, 1591 (m, C=N stretch), 1605, 1440 (w, C=C stretch), 1275 (m, C–C stretch), 1179, 1028 (s, C–O–C_{diaryl} stretch), 1161, 1120, 999 (s, C–O–C_{alkyl} stretch) 923 (m, C–N stretch), 628 (w, C–Br stretch)

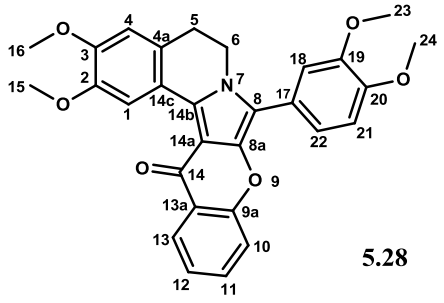
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09, 6.98, 6.74, 6.64 (s, 1H, $H_{1,4,10,13}$), 4.33 – 4.31 (m, 2H, H_5), 4.01, 3.99, 3.83, 3.82 (4 × s, 3H, $H_{15,16,17,18}$), 3.06 (t, *J* = 7.2 Hz, 2H, H_6)

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.56 (C_{14}), 115.66 (C_{10}), 113.32 (C_{13}), 110.72 (C_4), 109.36 (C_1), 105.35 (C_8), 56.78, 56.60, 56.17, 56.04 ($C_{15,16,17,18}$), 37.87 (C_6), 27.66 (C_5)

10.7. Suzuki-Miyaura couplings using 3,4-dimethoxyphenylboronic acid

10.7.1. 8-(3,4-Dimethoxyphenyl)-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one (5.28)[138]

To a sealed microwave vessel containing an *N*,*N*-dimethylformamide and water mixture (1:1) (4 cm^3:4 cm^3) was added 8-bromo-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.27** (0.0663 g, 0.156 mmol), 3,4-dimethoxyphenylboronic acid (0.0469 g, 0.258 mmol), sodium hydrogen carbonate, $NaHCO_3$ (0.0481 g, 0.574 mmol), tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$ (0.0144 g, 0.013 mmol). The reaction was irradiated by microwave reactor (150 W, 150°C, 20 min) then cooled, filtered through a plug of Celite® and washed with an excess of ethyl acetate. The solvents were then removed by rotary evaporation and the residue was purified by flash column chromatography in a 30% ethyl acetate in hexane mixture. The product was then recrystallization from a chloroform to afford the product 8-(3,4-dimethoxyphenyl)-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one **5.28** (0.0431 g, 0.0891 mmol, 57%) as bright yellow, fine crystals.



5.28

R_f (50% ethyl acetate in hexane): 0.39

M.p.: 287–288°C

IR (ν/cm^{-1}): 3056, 2922, 2835 (w, C–H stretch), 1639 (s, C=O stretch), 1592, 1466 (w, C=C stretch), 1445 (m, C=N stretch), 1276 (m, C–C stretch), 1253, 1087 (s, C–O–C_{diaryl} stretch), 1215, 1172, 1140 (s, C–O–C_{alkyl} stretch), 1026 (m, C–N stretch)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H, H_{18}), 8.39 (dd, *J* = 8.0, 1.3 Hz, 1H, H_{21}), 7.58 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H, H_{22}), 7.34–7.27 (m, 2H, $H_{10,13}$), 7.10 (d, *J* = 1.7 Hz, 1H, H_1), 7.07–7.03 (m, 2H, $H_{11,12}$), 6.74 (s, 1H, H_4), 4.18 (t, *J* = 6.7 Hz, 2H, H_5), 4.14 (s, 3H, H_{15}), 3.98, 3.97 (s, 2 × 3H, $H_{23,24}$), 3.94 (s, 3H, H_{16}), 3.02 (t, *J* = 6.7 Hz, 2H, H_6)

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.04 (C_{14}), 156.46 (C_{9a}), 149.12 (C_3), 148.90 (C_{19}), 148.69 (C_{20}), 148.15 (C_2), 142.69 (C_8), 133.37 (C_{22}), 127.60 (C_{4a}), 127.22 (C_{21}), 125.04 (C_{14b}), 122.93 (C_{17}), 122.66 (C_{10}), 122.62 (C_{13}), 121.33 (C_{14c}), 121.06 (C_{13a}), 117.30 (C_1), 114.54

(C_{14a}), 113.38 (C_{18}), 111.89 (C_{11}), 111.42 (C_{12}), 110.46 (C_4), 107.30 (C_{8a}), 56.40, 56.12, 56.05, 56.00 ($C_{15,16,23,24}$), 42.53 (C_5), 28.92 (C_6)
HRMS (EI): Found M^+ = 483.1667, $C_{29}H_{25}NO_6$ requires 483.1682

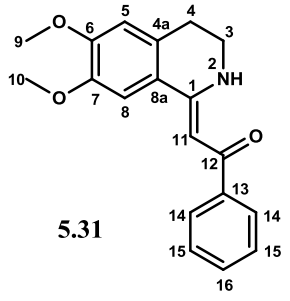
10.8. Eschenmoser sulphide contraction with thiolactam 5.2

General method for the Eschenmoser sulphide contraction:[76,128]

6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** (1.00 molar equivalent) was dissolved in a minimum of chloroform (5 cm^3/mmol). The previously prepared phenacyl iodides or mesylated phenacyl halides (*Chapter 8*) (1.50 molar equivalents) were then added to the solution and salt formation proceeded over 18 hours of stirring at room temperature. Into a dropping funnel was added triphenylphosphine (1.60 molar equivalents) and triethylamine (2.00 molar equivalents) in chloroform (7 cm^3/mmol) and the mixture was added to the reaction vessel over 15 minutes. The reaction was then left to stir at room temperature for 24 hours. The product mixture was extracted into dichloromethane and the organic layer was washed with water and then brine. The collected organic extract was dried over anhydrous sodium sulphate, filtered and the solvent was evaporated by rotary evaporator.

10.8.1. (*Z*)-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1-phenylethanone (5.31)

The product was prepared from 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** (0.410 g, 1.84 mmol), 2-iodo-1-phenylethanone **3.9** (0.680 g, 2.76 mmol), triphenylphosphine (0.772 g, 2.94 mmol) and triethylamine (0.372 g, 0.52 cm^3, 3.68 mmol) in chloroform (25 cm^3) by the general method for Eschenmoser sulphide contraction. The crude mixture obtained was purified by flash column chromatography (50% ethyl acetate in hexane) to give the pure product (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1-phenylethanone **5.31** (0.496 g, 1.60 mmol, 87%) as a bright yellow crystalline solid.



5.31

R_f (50% ethyl acetate in hexane): 0.29

M.p.: 135–136°C (Lit.[188] 135–136°C)

IR (ν/cm^{-1}): 3174 (w, N–H stretch), 3055, 2911, 2829 (w, C–H stretch), 1601 (s, C=O stretch), 1584, 1468 (s, C=C stretch), 1537, 1503 (s, N–H bend), 1334 (s, C–C stretch), 1259, 1210, 1113 (s, C–O–C stretch), 1024 (m, C–N stretch), 871, 814, 757 (m, $CH_{arom.}$ bend), 697 (s, $CH_{Zalkene}$ bend)

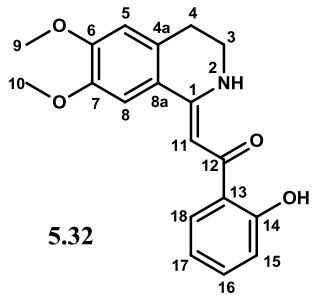
^{1}H NMR (300 MHz, $CDCl_3$) δ 11.83 (s, 1H, H_2), 8.00–7.87 (m, 2H, H_{14}), 7.50–7.38 (m, 3H, $H_{15,16}$), 7.25 (s, 1H, H_8), 6.71 (s, 1H, H_5), 6.20 (s, 1H, H_{11}), 3.95 (s, 3H, H_9), 3.93 (s, 3H, H_{10}), 3.53 (td, J = 6.7, 3.4 Hz, 2H, H_3), 2.89 (t, J = 6.6 Hz, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 188.40 (C_{12}), 158.65 (C_1), 151.76 (C_6), 148.01 (C_7), 141.26 (C_{8a}), 130.65 (C_{16}), 130.37 (C_{13}), 128.22 (C_{15}), 126.86 (C_{14}), 121.39 (C_{4a}), 110.80 (C_8), 108.57 (C_5), 86.35 (C_{11}), 56.30 (C_{10}), 56.03 (C_9), 38.71 (C_3), 27.99 (C_4)

HRMS (EI): Found M^+ = 309.1355, $C_{19}H_{19}NO_3$ requires 309.1365

10.8.2. (*Z*)-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1-(2-hydroxyphenyl)ethanone (5.32)

The product was prepared from 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** (0.599 g, 2.68 mmol), 1-(2-hydroxyphenyl)-2-iodo-1-ethanone **3.12** (0.763 g, 2.90 mmol), triphenylphosphine (0.781 g, 2.97 mmol) and triethylamine (0.576 g, 0.80 cm^3, 5.69 mmol) in chloroform (30 cm^3) by the general method for Eschenmoser sulphide contraction. The brown residue obtained was purified by flash column chromatography (30% ethyl acetate in hexane) to give the enaminone product (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1-(2-hydroxyphenyl)ethanone **5.32** (0.623 g, 1.92 mmol, 72%) as a bright orange solid.



5.32

R_f (30% ethyl acetate in hexane): 0.21

M.p.: 206–208°C

IR (ν/cm^{-1}): 3233 (w, OH stretch), 3052 (w, NH stretch), 3005, 2968, 2836 (w, C–H stretch), 1601, 1467 (s, C=C stretch) , 1581 (s, C=O stretch), 1503 (s, N–H bend), 1385 (s, C–C stretch), 1250 (s, C–O stretch), 1206, 1112, 1033 (s, C–O–C stretch), 695 (s, CH_{Z-}

$_{alkene}$ bend)

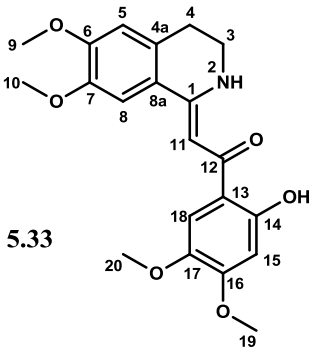
^{1}H NMR (300 MHz, $CDCl_3$) δ 13.66 (s, 1H, OH), 11.35 (s, 1H, NH), 7.73 (dd, *J* = 8.0, 1.4 Hz, 1H, H_{18}), 7.32 (ddd, *J* = 8.2, 7.1, 1.4 Hz, 1H, H_{16}), 7.23 (s, 1H, H_8), 6.92 (dd, *J* = 8.2, 0.7 Hz, 1H, H_{15}), 6.83 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H, H_{17}), 6.70 (s, 1H, H_{11}), 6.20 (s, 1H, H_5), 3.96 (s, 3H, H_9), 3.93 (s, 3H, H_{10}), 3.52 (dt, *J* = 6.5, 3.0 Hz, 2H, H_3), 2.88 (t, *J* = 6.6 Hz, 2H, H_4)

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.24 (C_{12}), 162.05 (C_{14}), 159.34 (C_1), 152.12 (C_6), 148.10 (C_7), 133.21 (C_{16}), 130.83 (C_{13}), 127.39 (C_{18}), 121.17 (C_{8a}), 121.10 (C_{4a}), 118.22 (C_{15}), 118.17 (C_{17}), 110.83 (C_8), 108.85 (C_5), 85.02 (C_{11}), 56.37 (C_{10}), 56.06 (C_9), 38.86 (C_3), 27.80 (C_4)

HRMS (EI): Found M^+ = 325.1308, $C_{19}H19NO_4$ requires 325.1312. *M/z*: 325.1305 (100%, M^+), 324.1233 (36%), 323.1155 (7%), 321.1003 (2%)

10.8.3. (*Z*)-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-3-(4-hydroxy-6,7-dimethoxyphenyl)ethanone (5.33)

The product was prepared from 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** (0.572 g, 2.56 mmol), 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone **3.17** (0.845 g, 3.08 mmol), sodium iodide (0.486 g, 3.33 mmol), triphenylphosphine (0.874 g, 3.33 mmol) and triethylamine (0.518 g, 0.72 cm^3, 5.12 mmol) in chloroform (25 cm^3) by the general method for Eschenmoser sulphide contraction. The reddish-brown residue obtained was purified by flash column chromatography (30% ethyl acetate in hexane) to give the desired product (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-3-(4-hydroxy-6,7-dimethoxyphenyl)ethanone **5.33** (0.906 g, 2.35 mmol, 91%) as a bright orange solid.



5.33

R_f (30% ethyl acetate in hexane): 0.21

M.p.: 209–212°C (Lit.[69] 143–144°C)

IR (ν/cm^{-1}): 3354 (w, OH stretch), 2978 (w, NH stretch), 2946, 2931, 2821 (w, C–H stretch), 1726 (m, C=O stretch), 1588, 1465 (s, C=C stretch), 1499 (s, N–H bend), 1389 (s, C–C stretch), 1246 (s, C–O stretch), 1208, 1154, 1033 (s, C–O–C stretch), 680 (s, $CH_{Z\text{-}alkene}$ bend)

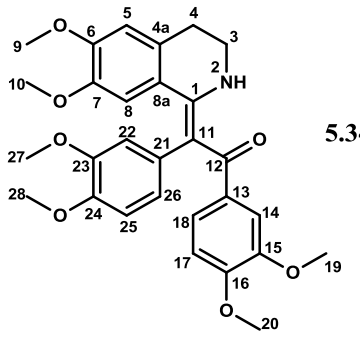
^{1}H NMR (300 MHz, $CDCl_3$) δ 13.85 (s, 1H, OH), 11.24 (s, 1H, H_2), 7.21 (s, 1H, H_{18}), 7.19 (s, 1H, H_8), 6.80 (s, 1H, H_{15}), 6.47 (s, 1H, H_5), 6.00 (s, 1H, H_{11}), 3.98 (2 × s, 6H, $H_{19,20}$), 3.88 (2 × s, 6H, $H_{9,10}$), 3.52 (dt, *J* = 6.7, 3.7 Hz, 2H, H_3), 2.87 (t, *J* = 6.6 Hz, 2H, H_4)

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.53 (C_{12}), 159.05 (C_{14}), 158.87 (C_1), 154.50 (C_6), 148.85 (C_7), 145.70 (C_{16}), 141.25 (C_{17}), 131.45 (C_{13}), 121.09 (C_{4a}), 114.25 (C_{15}), 112.54 (C_8), 111.51 (C_{8a}), 108.15 (C_{18}), 101.10 (C_5), 84.41 (C_{11}), 57.58 (C_{19}), 57.41 (C_{20}), 56.35 (C_9), 55.88 (C_{10}), 38.84 (C_3), 27.76 (C_4)

HRMS (EI): Found M^+ = 385.1523, $C_{21}H_{23}NO_6$ requires 385.1525

10.8.4. (*Z*)-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1,2-bis(3,4-dimethoxyphenyl)ethanone (5.34)

The product was prepared from 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **5.2** (0.253 g, 1.13 mmol), 2-bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone **3.27** (0.597 g, 1.51 mmol), triphenylphosphine (0.357 g, 1.36 mmol) and triethylamine (0.229 g, 0.32 cm^3, 2.26 mmol) in chloroform (12 cm^3) by the general method for Eschenmoser sulphide contraction. The crude yellow powder obtained was purified by flash column chromatography (60% ethyl acetate in hexane) to afford the product (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1,2-bis(3,4-dimethoxyphenyl) ethanone **5.34** (0.382 g, 0.755 mmol, 69%) as a bright yellow power.



5.34

R_f (50% ethyl acetate in hexane): 0.14

M.p.: 180–183°C

IR (ν/cm^{-1}): 3074 (w, N–H stretch), 2949, 2839 (w, C–H stretch), 1657 (s, C=O stretch), 1590, 1534 (s, C=C stretch), 1508 (s, N–H bend), 1327 (s, C–C stretch), 1257 , 1139, 1114 (s, C–O–C stretch), 1025 (m, C–N stretch), 707 (m, $CH_{Z\text{-alkene}}$ bend)

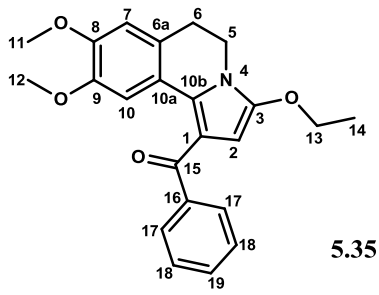
^{1}H NMR (300 MHz, $CDCl_3$) δ 13.07 (s, 1H, NH), 6.86 (s, 1H, H_8), 6.82 (dd, *J* = 8.3, 1.9 Hz, 1H, H_{18}), 6.71 (d, *J* = 1.9 Hz, 1H, H_{14}), 6.68–6.63 (m, 4H, $H_{17,22,25,26}$), 6.32 (s, 1H, H_5), 3.89, 3.81 (s, 2 × 3H, $H_{27,28}$), 3.79 (s, 3H, H_9), 3.65 (s, 3H, H_{19}), 3.64–3.56 (m, 1H, H_{3a}), 3.55 (s, 3H, H_{20}), 3.49–3.35 (m, 1H, H_{3b}), 3.21 (s, 3H, H_{10}), 3.04–2.91 (m, 1H, H_{4a}), 2.80 (dt, *J* = 14.7, 4.1 Hz, 1H, H_{4b})

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.92 (C_{12}), 159.70 (C_1), 150.21 (C_6), 148.88 (C_7), 148.43, 148.27, 147.45, 146.22 ($C_{15,16,23,24}$), 135.99, 134.40 ($C_{13,21}$), 132.13 (C_{8a}), 121.78 (C_{4a}), 120.47, 119.37, 118.21 ($C_{14,17,18}$), 115.22 (C_8), 112.16 (C_5), 110.84, 109.82 ($C_{22,25,26}$), 105.29 (C_{11}), 56.10 , 55.79, 55.70, 55.51, 55.17, 53.44 ($C_{9,10,19,20,27,28}$), 39.12 (C_3), 29.21 (C_4)
HRMS (ESI+): Found $(M + H)^+$ = 506.2192, $C_{29}H_{31}NO_7$ requires 506.2180. *M/z*: 506.2192 (100%, $(M + H)^+$), 356.1502 (8%), 279.0941 (3%)

10.9. Formation of pyrrole ring systems using the Junjappa method[130]

10.9.1. (3-Ethoxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone (5.35)

To a solution of (*Z*)-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1-phenylethanone **5.31** (0.462 g, 1.49 mmol) in *N*-methyl-2-pyrrolidinone, NMP (15 cm^3) was added ethyl 2-bromoacetate (0.299 g, 0.20 cm^3, 1.79 mmol). The reaction was then allowed to stir under reflux for 3 days. On cooling, the reaction mixture was diluted with diethyl ether (3 × 50 cm^3) and the combined organic extracts were washed with water (30 cm^3) and brine (30 cm^3). Flash column chromatography (20–30% ethyl acetate in hexane) was performed to further purify the product (3-ethoxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.35** (0.257 g, 0.682 mmol, 46%), which was collected as a dark yellow solid.



5.35

R_f (50% ethyl acetate in hexane): 0.69
M.p.: 122–125°C
IR (ν/cm^{-1}): 3016, 2926, 2871 (w, C–H stretch), 1726 (m, C=O stretch), 1621, 1521 (s, C=N stretch), 1578, 1440 (s, C=C stretch), 1285, 1025 (m, C–N stretch), 1245 (s, C–O stretch), 1208, 1152, 1109 (s, C–O–C stretch)

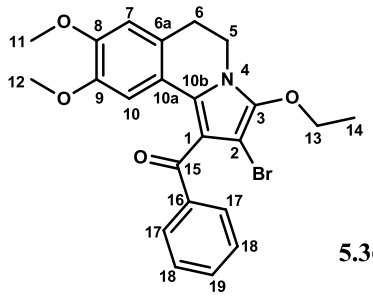
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.75 (m, 2H, H_{17}), 7.67 (s, 1H, H_{10}), 7.36–6.61 (m, 3H, $H_{18,19}$), 6.61 (s, 1H, H_7), 5.44 (s, 1H, H_2), 3.98 (q, *J* = 7.0 Hz, 2H, H_{13}), 3.90–3.83 (m, 2H, H_5), 3.81 (s, 3H, H_{12}), 3.64 (s, 3H, H_{11}), 2.90 (t, *J* = 6.5 Hz, 2H, H_6), 1.33 (t, *J* = 7.0 Hz, 3H, H_{14})
^{13}C NMR (75 MHz, $CDCl_3$) δ 191.42 (C_{15}), 146.92 (C_8), 146.40 (C_9), 144.19 (C_3), 139.92 (C_{6a}), 130.24 (C_{19}), 128.48 (C_{17}), 126.99 (C_{18}), 125.69 (C_{16}), 124.14 (C_{10b}), 120.20 (C_{10a}),

115.54 (C_1), 109.90 (C_7), 109.56 (C_{10}), 88.11 (C_2), 65.38 (C_{13}), 54.88 (C_{11}), 54.86 (C_{12}), 37.93 (C_5), 27.83 (C_6), 13.69 (C_{14})

HRMS (EI): Found M^+ = 377.1877, $C_{23}H_{23}NO_4$ requires 377.1827

10.9.2. (2-Bromo-3-ethoxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone (5.36)[67,135]

N-Bromosuccinimide (0.0458 g, 0.257 mmol) in *N*,*N*-dimethylformamide (3 cm^3) was added dropwise to an ice-cooled solution of (3-ethoxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.35** (0.0905 g, 0.240 mmol) in *N*,*N*-dimethylformamide (2 cm^3). The reaction continued to stir at 0°C for 2 hours, the ice-bath was removed and the reaction was allowed to warm to ambient temperature where it was stirred for an additional 20 hours. The product was then extracted into dichloromethane (2 × 20cm^3) and the combined organic extracts were washed with water (20 cm^3), followed by brine (20 cm^3). The organic washings were collected and dried over sodium sulphate, filtered and the solvent was evaporated to give a crude dark orange residue. Purification by flash column chromatography (5–30% ethyl acetate in hexane) afforded (2-bromo-3-ethoxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.36** (0.104 g, 0.227 mmol, 95%) as a yellow solid.



5.36

R_f (50% ethyl acetate in hexane): 0.48

M.p.: 165–169°C

IR (ν/cm^{-1}): 2971, 2932, 2837 (w, C–H stretch), 1708 (m, C=O stretch), 1632, 1530 (s, C=N stretch), 1595, 1472 (s, C=C stretch), 1277, 1024 (m, C–N stretch), 1239 (s, C–O stretch), 1210, 1159, 1119 (s, C–O–C stretch), 662 (C–Br stretch)

^{1}H NMR (300 MHz, Acetone) δ 7.92–7.87 (m, 2H, H_{17}), 7.59–7.53 (m, 1H, H_{19}), 7.47–7.40 (m, 2H, H_{18}), 6.87 (s, 1H, H_{10}), 6.69 (s, 1H, H_7), 4.28 (q, *J* = 7.1 Hz, 2H, H_{13}), 4.02 (t, *J* = 6.6 Hz, 2H, H_5), 3.77 (s, 3H, H_{12}), 3.37 (s, 3H, H_{11}), 3.04 (t, *J* = 6.5 Hz, 2H, H_6), 1.43 (t, *J* = 7.1 Hz, 3H, H_{14})

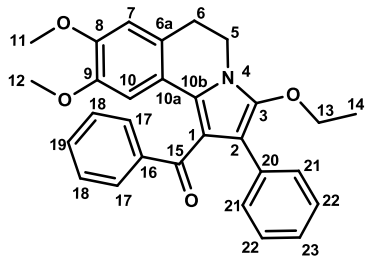
^{13}C NMR (75 MHz, Acetone) δ 192.44 (C_{15}), 149.43 (C_8), 148.72 (C_9), 142.96 (C_3), 139.86 (C_{10b}), 133.62 (C_{19}), 130.67 (C_{17}), 129.35 (C_{18}), 126.28 (C_{16}), 125.01 (C_{6a}), 120.87 (C_{10a}),

116.37 (C_1), 112.63 (C_7), 111.10 (C_{10}), 82.56 (C_2) 71.89 (C_{13}), 56.05 (C_{11}), 55.84 (C_{12}), 40.64 (C_5), 15.71 (C_{14})

HRMS (EI): Found M^+ = 455.0720, $C_{23}H_{22}NO_4{}^{79}Br$ requires 455.0732

10.9.3. (3-Ethoxy-8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone (5.37)[139,140]

To a pre-dried 25 cm^3 round bottom flask was added (2-bromo-3-ethoxy-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.36** (0.131 g, 0.287 mmol), phenylboronic acid (0.0570 g, 0.459 mmol), Caesium fluoride (0.0850 g, 0.560mmol), silver(I) oxide (0.0798 g, 0.344 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.0365 g, 0.032 mmol) followed by 1,2-dimethoxyethane (10 cm^3). The reaction mixture was degassed several times before heating the mixture to 80°C for 18 hours, the temperature was then increase to 110°C for 46 hours, and again increase to 140°C for 4 hours. On cooling, the reaction mixture was diluted with water (10 cm^3) and the product was extracted into dichloromethane (2 × 20cm^3). The combined organic extract was then washed with water (10 cm^3) and brine (10 cm^3), dried over anhydrous sodium sulphate, filtered and the solvent was evaporated. The crude product was purified by flash column chromatography (5–30% ethyl acetate in hexane) to afford the product (3-ethoxy-8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone **5.37** (0.0363 g, 0.0800 mmol, 28%) as a yellow cuboidal crystalline solid.



5.37

R_f (50% ethyl acetate in hexane): 0.55

M.p.: 175–176°C

IR (ν/cm^{-1}): 3051, 2977, 2832 (w, C–H stretch), 1713 (m, C=O stretch), 1632, 1529 (s, C=N stretch), 1599, 1497, 1450 (s, C=C stretch), 1300 (m, C–C stretch), 1260, 1205, 1107 (s, C–O–C stretch), 1020 (s, C–N stretch)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.80 (m, 2H, H_{17}), 7.40–7.27 (m, 3H, $H_{18,19}$), 7.24–7.13 (m, 4H, $H_{21,22}$), 7.12 (s, 1H, H_{10}), 7.08–6.98 (m, 1H, H_{23}), 6.69 (s, 1H, H_7), 4.03 (t, *J* = 6.4 Hz, 2H, H_5), 3.86 (s, 3H, H_{12}), 3.83 (q, *J* = 7.0 Hz, 2H, H_{13}), 3.59 (s, 3H, H_{11}), 3.02 (t, *J* = 6.5 Hz, 2H, H_6), 1.22 (t, *J* = 7.1 Hz, 3H, H_{14})

^{13}C NMR (75 MHz, $CDCl_3$) δ 195.29 (C_{15}), 147.68 (C_8), 147.59 (C_9), 141.52 (C_3), 139.11 (C_{16}), 133.74 (C_2), 132.39 (C_{20}), 130.03 (C_{17}), 129.15 (C_{22}), 127.98 (C_{18}), 127.86 (C_{21}), 125.57 (C_{19}), 124.58 (C_{23}), 123.31 (C_{10b}), 121.18 (C_{6a}), 116.05 (C_{10a}), 110.97 (C_7), 109.91 (C_1), 109.58 (C_{10}), 70.65 (C_{13}), 55.91 (C_{12}), 55.75 (C_{11}), 39.33 (C_5), 28.95 (C_6), 15.36 (C_{14})
HRMS (ESI+): Found $(M + H)^+$ = 454.2022, $C_{29}H_{27}NO_4$ requires 454.2022

Chapter 11
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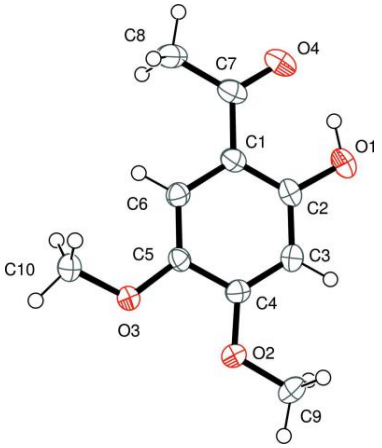
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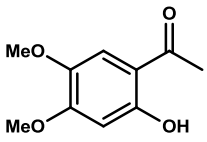
Appendix
X-ray crystallographic data

Intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50kV, 30mA) using the APEX 2[175] data collection software. The collection method involved ω-scans of width 0.5° and 512x512 bit data frames. Data reduction was carried out using the program *SAINT+*.[176]

The crystal structure was solved by direct methods using *SHELXTL*.[177] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL, PLATON[178] and ORTEP-3[179].

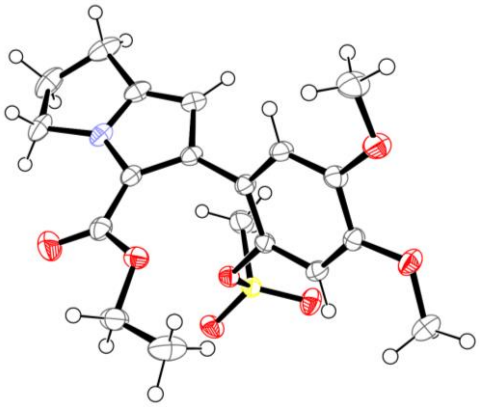
A1. 1-(2-Hydroxy-4,5-dimethoxyphenyl)ethanone (3.16)





Structure **3.16** was published in *Acta Crystallographica Section E*. *1-(2-Hydroxy-4,5-dimethoxyphenyl)-ethanone*, Stefania M. Scalzullo, Sanaz Khorasani and Joseph P. Michael, *Acta Cryst.* (2013). E**69**, o139.

A2. Ethyl 6-[4,5-dimethoxy-2-(methylsulphonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.31)



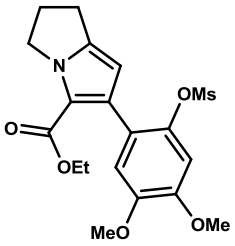
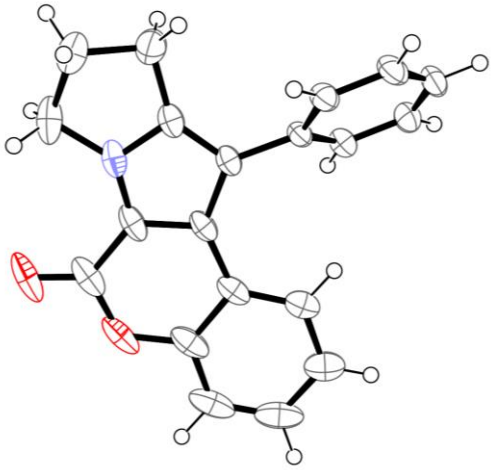


Table A1. Crystal data and structure refinement for 4.31.

Identification code	**4.31**	
Empirical formula	$C_{19}H_{23}NO_7S$	
Formula weight	409.44	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.7521(3) Å	α= 109.3170(10)°
	b = 12.3707(3) Å	β= 104.6160(10)°
	c = 16.4976(4) Å	γ = 94.7200(10)°
Volume	1970.52(9) $Å^3$	
Z	4	
Density (calculated)	1.380 Mg/m^3	
Absorption coefficient	0.205 mm^{-1}	
F(000)	864	
Crystal size	0.43 x 0.39 x 0.36 mm^3	
Theta range for data collection	1.37 to 28.00°.	
Index ranges	-12<=h<=14, -16<=k<=16, -21<=l<=21	
Reflections collected	24744	
Independent reflections	9508 [R(int) = 0.0407]	
Completeness to theta = 28.00°	99.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9508 / 0 / 513	

Goodness-of-fit on F^2	1.054
Final R indices [I>2sigma(I)]	R1 = 0.0472, wR2 = 0.1193
R indices (all data)	R1 = 0.0593, wR2 = 0.1246
Largest diff. peak and hole	0.242 and -0.528 e.Å^{-3}

A3. 11-Phenyl-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.48)



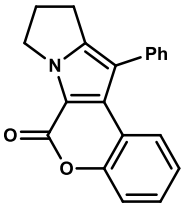


Table A2. Crystal data and structure refinement for 4.48.

Identification code	**4.48**	
Empirical formula	$C_{20}H_{15}NO_2$	
Formula weight	301.33	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 11.0368(3) Å	α= 90°
	b = 13.8450(3) Å	β= 114.3660(10)°
	c = 10.5736(3) Å	γ = 90°
Volume	1471.78(7) Å^3	
Z	4	
Density (calculated)	1.360 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	632	
Crystal size	0.33 x 0.31 x 0.06 mm^3	
Theta range for data collection	2.03 to 27.99°.	
Index ranges	-12<=h<=14, -18<=k<=18, -13<=l<=13	

Reflections collected	18423
Independent reflections	3544 [R(int) = 0.0535]
Completeness to theta = 27.99°	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3544 / 15 / 208
Goodness-of-fit on F^2	1.002
Final R indices [I>2sigma(I)]	R1 = 0.0448, wR2 = 0.1068
R indices (all data)	R1 = 0.0785, wR2 = 0.1206
Largest diff. peak and hole	0.188 and -0.264 e.Å^{-3}

A4. Ethyl 6-[2-(methylsulphonyloxy)phenyl]-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (4.44)

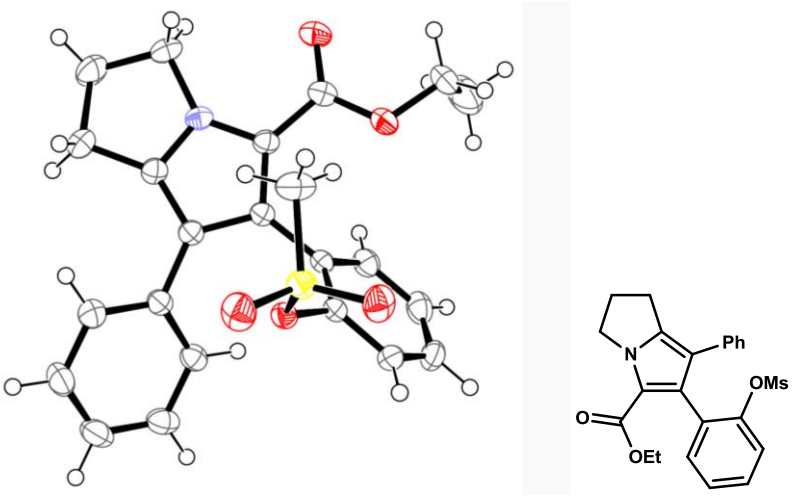
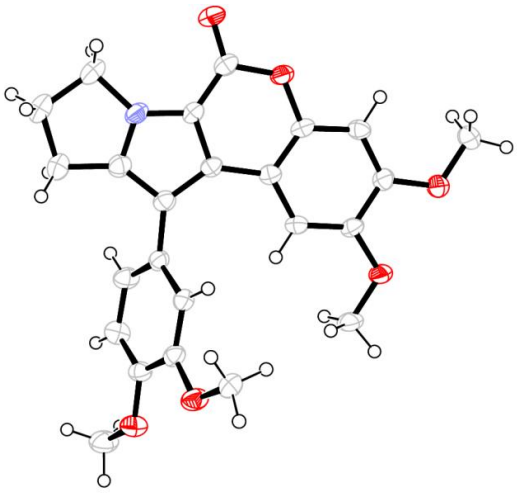


Table A3. Crystal data and structure refinement for 4.44.

Identification code	**4.44**	
Empirical formula	$C_{23}H_{23}NO_5S$	
Formula weight	425.48	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.9089(3) Å	α= 91.763(2)°
	b = 10.7207(3) Å	β= 109.983(2)°
	c = 11.2390(3) Å	γ = 112.844(2)°
Volume	1015.46(5) Å^3	

Z	2
Density (calculated)	1.392 Mg/m^3
Absorption coefficient	0.196 mm^{-1}
F(000)	448
Crystal size	0.46 x 0.25 x 0.11 mm^3
Theta range for data collection	1.96 to 28.00°.
Index ranges	-13<=h<=13, -14<=k<=14, -14<=l<=14
Reflections collected	9990
Independent reflections	4881 [R(int) = 0.0468]
Completeness to theta = 28.00°	99.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4881 / 0 / 273
Goodness-of-fit on F^2	0.980
Final R indices [I>2sigma(I)]	R1 = 0.0407, wR2 = 0.0931
R indices (all data)	R1 = 0.0601, wR2 = 0.1036
Largest diff. peak and hole	0.288 and -0.418 $e.Å^{-3}$

A5. 11-(3,4-Dimethoxyphenyl)-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (4.52)



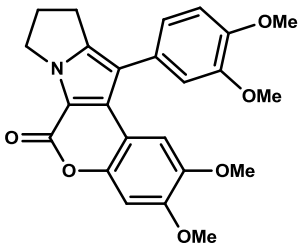
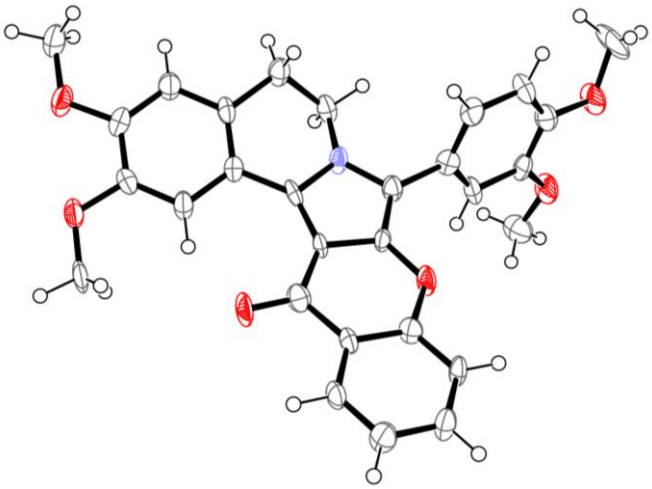


Table A4. Crystal data and structure refinement for 4.52.

Identification code	**4.52**	
Empirical formula	$C_{24}H_{23}NO_6$	
Formula weight	421.43	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.9208(4) Å	α = 115.038(2)°.
	b = 10.9572(3) Å	β = 112.240(2)°.
	c = 11.6065(4) Å	γ = 95.647(2)°.
Volume	1006.52(6) $Å^3$	
Z	2	
Density (calculated)	1.391 Mg/m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	444	
Crystal size	0.25 x 0.20 x 0.06 mm^3	
Theta range for data collection	2.16 to 26.99°.	
Index ranges	-12<=h<=11, -13<=k<=13, -13<=l<=14	
Reflections collected	11418	
Independent reflections	4382 [R(int) = 0.0859]	
Completeness to theta = 26.99°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9940 and 0.9753	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4382 / 6 / 289	
Goodness-of-fit on F^2	0.894	
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.0852	
R indices (all data)	R1 = 0.1082, wR2 = 0.1013	
Largest diff. peak and hole	0.165 and -0.219 $e.Å^{-3}$	

A6. 8-(3,4-Dimethoxyphenyl)-2,3-dimethoxy-5*H*-chromeno[3',2':3,4]pyrrolo[2,1-*a*]isoquinolin-14(6*H*)-one (5.28)



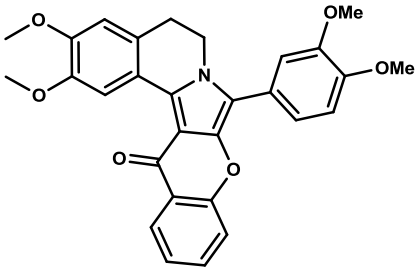


Table A5. Crystal data and structure refinement for 5.28.

Identification code	**5.28**	
Empirical formula	$C_{30}H_{25}NO_7$	
Formula weight	511.51	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.6340(9) Å	α = 68.455(5)°
	b = 11.0088(8) Å	β = 67.094(5)°
	c = 11.9446(10) Å	γ = 80.669(6)°
Volume	1197.76(17) $Å^3$	
Z	2	
Density (calculated)	1.418 Mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	536	
Crystal size	0.24 x 0.16 x 0.08 mm^3	
Theta range for data collection	1.96 to 25.00°.	
Index ranges	-12<=h<=12, -13<=k<=12, -14<=l<=14	
Reflections collected	10142	
Independent reflections	4197 [R(int) = 0.1417]	
Completeness to theta = 25.00°	99.4 %	
Absorption correction	None	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4197 / 0 / 347
Goodness-of-fit on F^2	0.932
Final R indices [I>2sigma(I)]	R1 = 0.0777, wR2 = 0.1256
R indices (all data)	R1 = 0.2416, wR2 = 0.1646
Largest diff. peak and hole	0.272 and -0.287 e.Å^{-3}

A7. (*Z*)-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-1-phenylethanone (5.31)

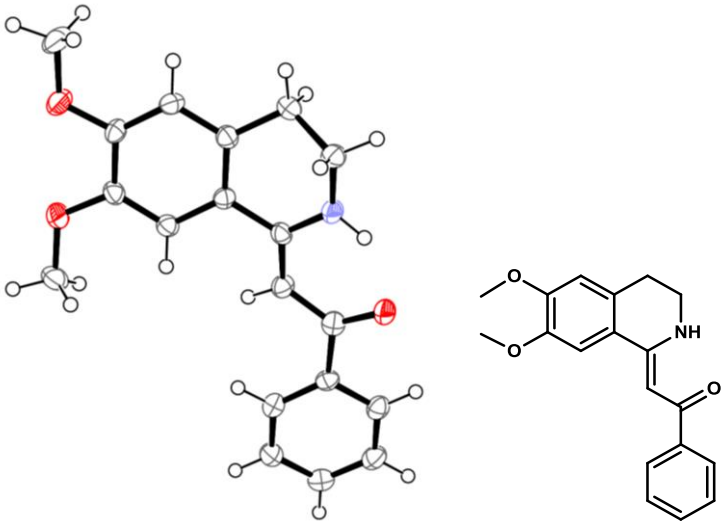


Table A6. Crystal data and structure refinement for 5.31.

Identification code	**5.31**	
Empirical formula	$C_{19}H_{19}NO_3$	
Formula weight	309.35	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	I4(1)/a	
Unit cell dimensions	a = 34.677(2) Å	α = 90°
	b = 34.677(2) Å	β = 90°
	c = 5.1572(4) Å	γ = 90°.
Volume	6201.6(8) Å^3	
Z	16	
Density (calculated)	1.325 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	

F(000)	2624
Crystal size	0.47 x 0.05 x 0.04 mm^3
Theta range for data collection	1.66 to 25.49°.
Index ranges	-42<=h<=39, -41<=k<=39, -6<=l<=6
Reflections collected	13184
Independent reflections	2881 [R(int) = 0.1382]
Completeness to theta = 25.49°	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2881 / 0 / 214
Goodness-of-fit on F^2	0.948
Final R indices [I>2sigma(I)]	R1 = 0.0529, wR2 = 0.1049
R indices (all data)	R1 = 0.1368, wR2 = 0.1374
Largest diff. peak and hole	0.218 and -0.227 $e.Å^{-3}$

A8. (3-Ethoxy-8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1-yl)(phenyl)methanone (5.37)

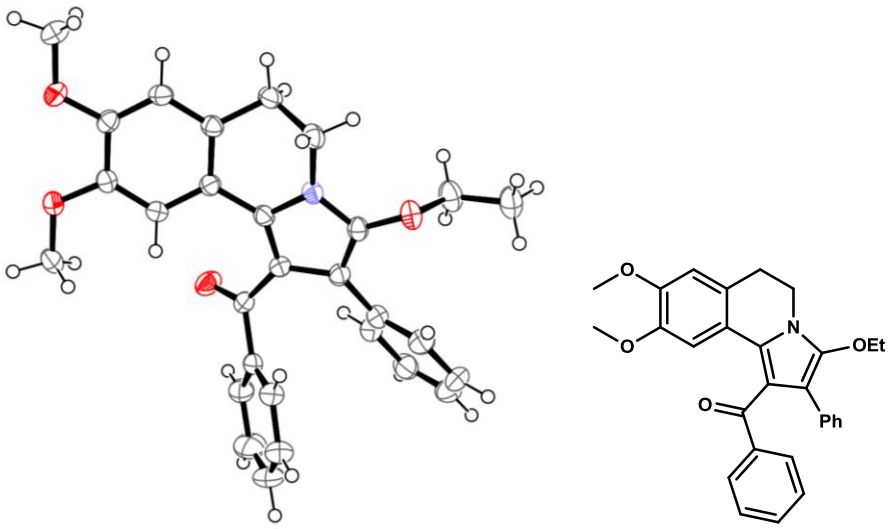


Table A7. Crystal data and structure refinement for 5.37.

Identification code	**5.37**	
Empirical formula	$C_{29}H_{27}NO_4$	
Formula weight	453.52	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.6361(2) Å	α = 85.1370(10)°
	b = 12.3935(3) Å	β = 84.8320(10)°
	c = 20.0402(4) Å	γ = 76.3010(10)°
Volume	2310.78(9) $Å^3$	
Z	4	
Density (calculated)	1.304 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	960	
Crystal size	0.39 x 0.27 x 0.16 mm^3	
Theta range for data collection	1.69 to 28.00°.	
Index ranges	-12<=h<=12, -16<=k<=16, -26<=l<=26	
Reflections collected	75827	
Independent reflections	11168 [R(int) = 0.0729]	
Completeness to theta = 28.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11168 / 7 / 619	
Goodness-of-fit on F^2	1.096	
Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.1268	
R indices (all data)	R1 = 0.0597, wR2 = 0.1347	
Largest diff. peak and hole	0.608 and -0.269 $e.Å^{-3}$	