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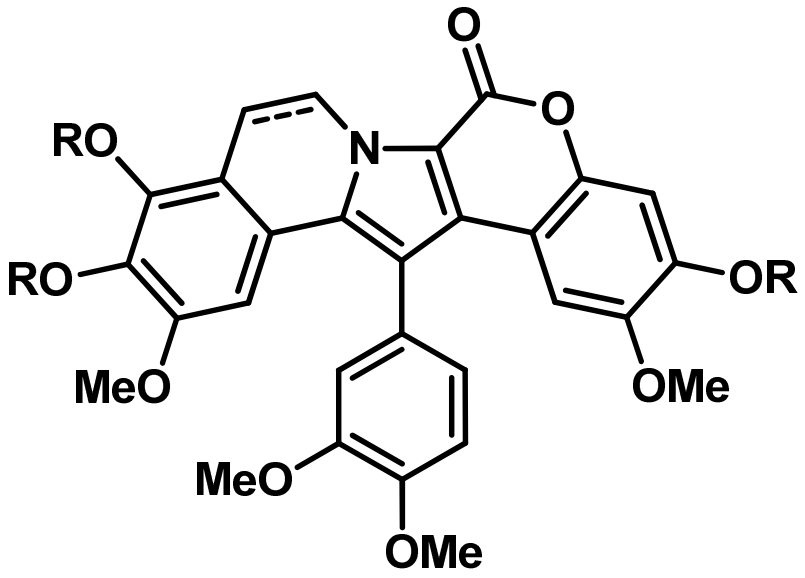
Enaminones as Precursors for Lamellarin Alkaloids and Related Heterocycles



By Robin Klintworth

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

August 2020

Declaration

I declare that the work presented in this thesis was carried out exclusively by me, unless stated otherwise, under the supervision of Professor Joseph P. Michael and Professor Charles B. de Koning. 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.



Robin Klintworth

7 October 2020

Abstract

The synthesis of alkaloids at the University of the Witwatersrand (Wits) has been led by Professor Joseph Michael for more than thirty years now. Throughout this time he has pioneered the use of enaminones as building blocks to provide alkaloids and other nitrogen-containing heterocycles. The ambident nucleophilicity and electrophilicity of the enaminone scaffolds makes them particularly suited to annulation reactions, allowing these positions to be chemically stitched together with suitable linkers to provide nitrogen-containing rings. In this thesis, we present the successful application of this kind of strategy to the synthesis of pyrrolizines and indolizines, as well as a variety of natural and synthetic lamellarin alkaloids.

Chapter 1 provides some background into alkaloids, concentrating on the lamellarins themselves, including a selection of some of the most significant contributions to their synthesis published thus far. Thereafter, the Wits enaminone strategy for the construction of heterocyclic alkaloids is discussed in greater detail, alongside a selection of pertinent examples that have been published by the group. This leads up to *Section 1.3.3*, in which previous Wits contributions to this lamellarin project are described. *Chapter 2* summarizes the preliminary investigations carried out during the first year of this project, beginning with a methodological study into the cyclization of simple *N*-(ethoxycarbonyl)methylpyrrolidine-derived enaminones to pyrrolizines under acidic conditions. This reaction was discovered almost twenty years ago in our laboratories and ever since then it has been investigated as a potential route to making the pyrrole component of lamellarins. The culmination of this work, past and present, paved the way for the development of our [4 + 1] cycloaddition strategy that is introduced in *Section 2.3.2.* The strategy entails the reaction of suitable enaminones with ethyl bromoacetate, which respectively contribute NC_3 and C_1 units to the newly formed pyrrole.

This reaction serves as a key step in all three of the relevant publications that constitute *Chapters 3, 4* and *5* of this thesis, and is arguably one of the most reliable and convenient methods for the preparation of these kinds of pyrrole systems now available. *Chapter 3* details the successful application of our [4 + 1] enaminone cycloaddition strategy to the synthesis of lamellarin G trimethyl ether, during a collaborative green chemistry project with Professor Till Opatz at the Johannes-Gutenberg University in Mainz, Germany. This

approach from an enaminone precursor was an exceptionally efficient method for the preparation of lamellarins, providing the target alkaloid in the second-highest yield ever reported at the time. *Chapter 4* details how the introduction of the alkaloids' lactone ring was tackled in a unique way, using a late-stage demethylative lactonization reaction between an aryl methyl ether and a nearby carboxylic acid. This reaction, in combination with the [4 + 1] cycloaddition strategy, allowed the completion of the synthesis of the trimethyl ethers of lamellarins G and D, as well as the naturally occurring lamellarins H and A4, in overall yields of above 80%, making this by far the most efficient route to these targets ever reported. Furthermore, this was the first-ever reported synthesis of a lamellarin at the gram-scale.

Chapter 5 then describes how this game-changing methodology was successfully applied to the synthesis of the pharmacologically active, though more complex, hydroxylated lamellarins. The naturally occurring lamellarin ε as well as the synthetic dehydrolamellarin J were selected as targets, because they are representatives of the two ring-A structural variations that provide optimal cytotoxic potency. While our [4 + 1] cycloaddition strategy and the demethylative lactonization reaction remained pivotal, significant methodological adaptations were required for the synthesis of the enaminone precursors to allow for the inclusion of isopropyl-ether protecting groups of the obligatory phenols. Three unique reactions were developed, including a one-pot phenol esterification-Fries rearrangement to form the phenolic deoxybenzoin ketone precursor, a mild isothiocyanate cyclization reaction to prepare the thiolactam precursors, as well as a particularly noteworthy novel isopropyl ether deprotection method. All three of these methodologies were facilitated with the use of the topical and "green" organic acid methanesulphonic acid. During these investigations, various methodological alterations were made to avoid the use of column chromatography altogether, whilst maintaining the excellent efficiency of our strategy. The culmination of this work gave rise to the first-ever reported chromatography-free synthesis of more than 25 g of the active lamellarin analogue dehydrolamellarin J, which was prepared in two decagram-scale batches in order to prove the reproducibility of our results.

Acknowledgements

To my supervisor Professor Joseph Michael, I cannot thank you enough. You have guided me through this period and have become a dear friend. In what is an exceptionally rare occurrence, the entirety of this PhD has been an absolute pleasure and I am truly sad for it to have reached its conclusion. I would be more than happy to continue our synthetic adventures well into the future.

To Professor Charles de Koning, Professor Amanda Rousseau and Professor Moira Bode, I would like to thank you for inspiring me to pursue a career in organic chemistry. Your lectures were so superb that they directly influenced me to continue my study of chemistry. I could always rely on you for a satisfying answer to my questions and a renewed enthusiasm to carry on. To Professor Dr Till Opatz, for hosting me in your laboratory, as well as being instrumental in procuring the necessary funding that made the visit and German phase of the project possible. This was a life-changing experience, and I am truly grateful to have been a part of it.

To Songeziwe Ntsimango, you have been a close friend throughout this journey. Your enthusiasm and wealth of knowledge have fuelled countless synthetic discussions which were always greatly appreciated. To Kathy, Memory, Hendrik, Donald and Jean, thank you for teaching me the many things I didn't learn in class.

To Robin Ratcliffe and Marinda van Roy, without all of your help I would have never been able to finish my degree, let alone this PhD. If I am one day able to provide for someone else what you have provided for me, I'd consider my life well spent.

I would also like to express my gratitude to the National Research Foundation and the University of the Witwatersrand for providing me with the necessary postgraduate funding that made this PhD possible.

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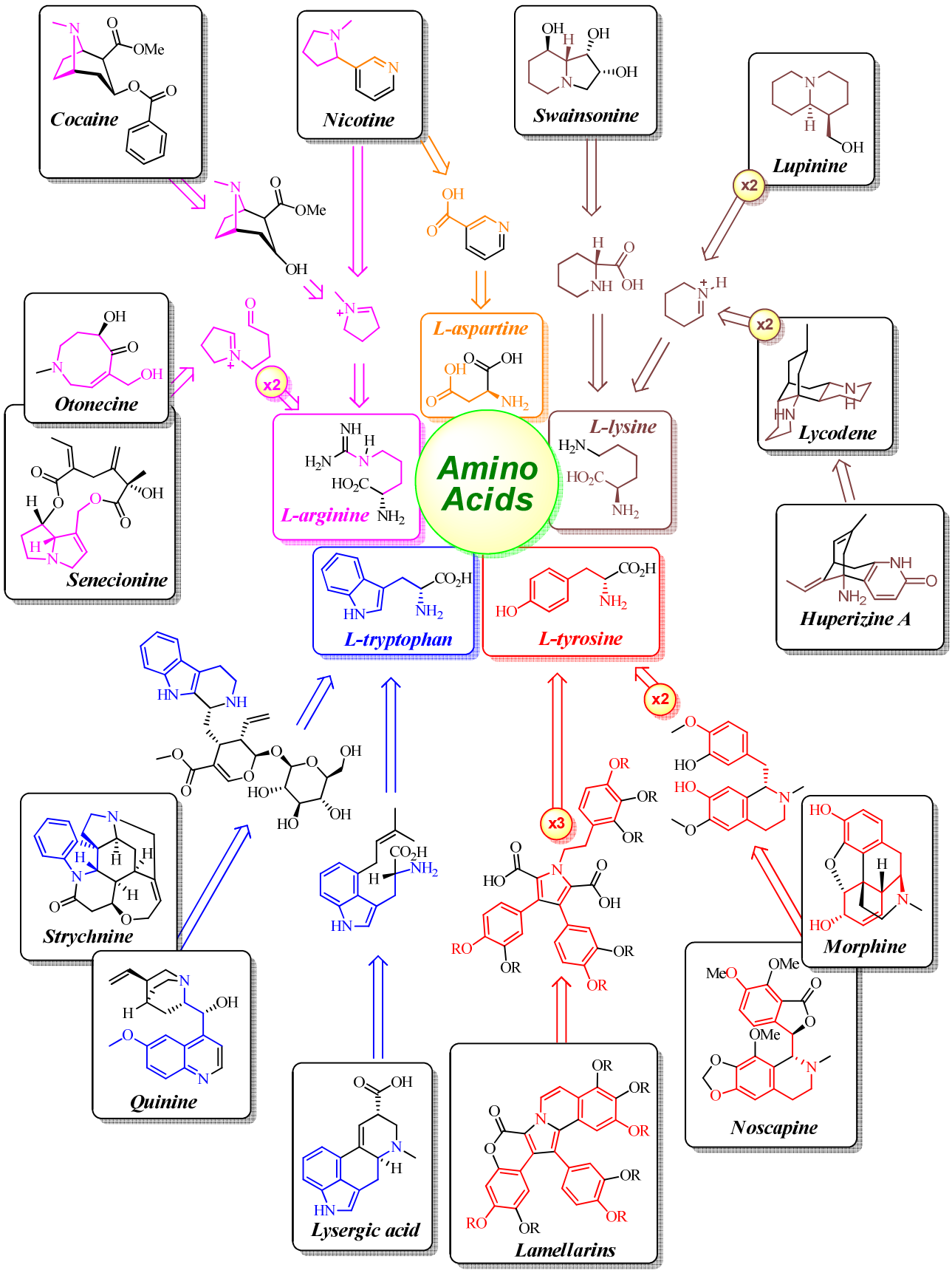
Chapter 1: Introduction and Background

1.1 Alkaloids

Alkaloids are a class of naturally occurring nitrogen-containing organic molecules of immense pharmacological importance. In fact, these are the only definitive features that have survived since their first unequivocal isolation 200 years ago in 1819.[1,2] Over the course of their study the defining properties of alkaloids have evolved unrecognizably, so much so that they have transcended any formal definition at all. A tongue-in-cheek definition occurs at the start of a famous series of monographs on alkaloid chemistry: "An alkaloid is like my wife. I can recognize her when I see her, but I can't define her".[3] The presence of a nitrogen atom is essential, but not all nitrogen-containing natural products are alkaloids. Amino acids and biological amides are universally not considered alkaloids.[1] It is worth mentioning that across the astonishing diversity of accepted natural alkaloids, they are almost exclusively derived from the 20 natural amino acids that serve as their nitrogenous precursors.[4] Some examples are given in *Figure 1.1*. The latest definition for an alkaloid found in the Oxford dictionary is quoted as: "any of a class of nitrogenous organic compounds of plant origin which have pronounced physiological actions on humans".[5] What defines a "pronounced" physiological action is inherently vague. Still further, the claimed necessity of plant origin stems from now outdated definitions and the very alkaloids discussed in this text are found in various marine animal species.[1,6,7] An attempt at an updated definition of an alkaloid from IUPAC is as follows: **"**Alkaloids: Basic nitrogen compounds (mostly heterocyclic) occurring mostly in the plant kingdom (but not excluding those of animal origin)".[8]

The fallacy of an exclusive plant origin stems from the fact that plants have served as the principal source of medicines since the very birth of our species, and potentially even earlier. 60 000 year old Neanderthal remains were recently shown to contain pollen traces of seven non-nutritional plants, all of which are still used by humans as herbal medicines today.[9] The earliest recorded use of medicinal plants comes at the very beginning of recorded history itself, around 2000 BCE, and details the use of opium by the ancient Egyptians.[10] Almost 4000 years later, in 1804, a crude extract of the opium poppy was shown to produce an intense dream-like state characteristic of the plant.[11] This extract marked the first documented alkaloid extraction in human history and was named *Morphium*, after Morpheus, the Greek God of dreams. Over the coming centuries the use of this alkaloid, now known as morphine,

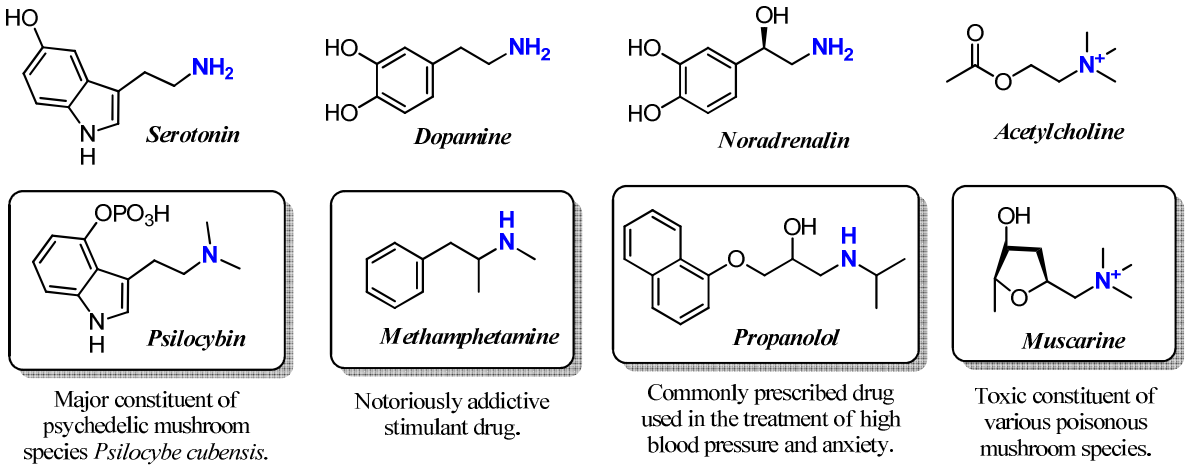
Figure 1.1. The nitrogenous components of natural alkaloids are derived from simple amino acid precursors.



continued, and today it and the derivatives thereof are considered essential for even the most rudimentary healthcare systems.[12] In 1874, the product obtained after boiling morphine in acetic anhydride was shown to have significantly increased potency compared to the parent compound. This was one of the first examples of the directed chemical manipulation of a natural product to improve its pharmacological properties.[13] The di-acetylated morphine derivative was marketed by Bayer as Heroin, eponymous with *heroine*, named for its saviour-like properties.[14] Many such isolates, most of which were alkaloids, were appropriately named after heroes and gods, because they provided us with an unprecedented ability to control pain, suffering, and even life itself. Although today this kind of pharmacological power is often taken for granted, at the time it was viewed as nothing less than divine. Today, the pharmaceutical industry is one of the most profitable in the world, with some of the largest companies turning annual revenues that rival the total GDP of most countries.[15] Since capitalism itself can be thought of as a modern religion,[16,17] our reverence for drugs today is no less profound.

Whilst the plant kingdom is still the dominant source of novel alkaloids, they have since been discovered across the animal kingdom and indeed all amino acid-utilizing organisms (and thus all recognized forms of life on earth) can produce alkaloids.[18,19] Alkaloids were originally so named because nitrogen-containing organic molecules often tend to be alkaline when the nitrogen lone pair is available for protonation. In the earliest years of their study acid-base extraction was the only means to isolate many of these bioactive plant constituents, and as such the field was limited to the study of only the isolatable alkaline bioactive constituents.[20] The fact that only the alkaline constituents of medicinal plants could be successfully isolated at the time explains their original naming, and why amino acids and most natural amides are not considered alkaloids.[21] This alkaline property of many medicinal compounds is no coincidence, and the ability to undergo protonation is in fact essential for the activity of many medicinal alkaloids, particularly those of a psychoactive nature. Much like the neurotransmitters dopamine, serotonin and noradrenaline (*Figure 1.2*), *in vivo* amine protonation leads to cation formation at nitrogen, which facilitates receptor binding, usually to a negatively charged carboxylate terminal of an aspartate amino acid.[22] This strong ionic interaction is pivotal for the natural activation of these receptors. For this reason most currently prescribed medicines that bind to the active sites of these primary neurotransmitter receptors contain at least one alkaline nitrogen atom capable of mimicking this interaction.[23,24]

Figure 1.2. Primary mammalian neurotransmitters and structurally similar psychoactive alkaloid drugs.



The actual number of these drugs is truly staggering, and probably defies tangible quantification. All of the typical serotonergic antidepressants fall into this class.[8,9,22,25] So too do the dopaminergic drugs used to treat Parkinson's disease and Attention Deficit Hyperactivity Disorder (ADHD).[26] Schizophrenia and other mental disorders are almost universally treated with at least one serotonergic or dopaminergic drug.[27] The binding properties of every one of these drugs has of course not been studied in detail, but of those that are known, a strong ionic "salt bridge" between a protonated (and hence alkaline) amine and a deprotonated carboxylate (of aspartate) is pivotal.[28,29] The small fraction of such drugs that are not alkaloids or alkaloid derivatives rely on allosteric modulation, binding to a site that is not the active site and thus does not require amine protonation for the binding interaction.[23] Shown in *Figures 1.3a* and *1.3b* are the line drawings and crystal structures of four of the most widely prescribed selective serotonin reuptake inhibitors used to treat anxiety, depression and a plethora of other mood related disorders.[22] In each case a strong ionic salt bridge is observed to facilitate drug binding of these amines. The observed non-covalent bond lengths are also of the shortest (and hence strongest) of all interactions observed.

Figure 1.3a. Molecular structures of four of the most commonly prescribed serotonergic drugs, highlighting key alkaline amines

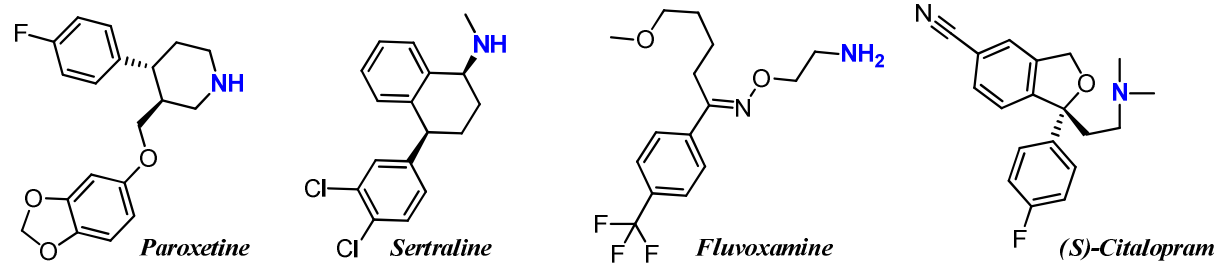
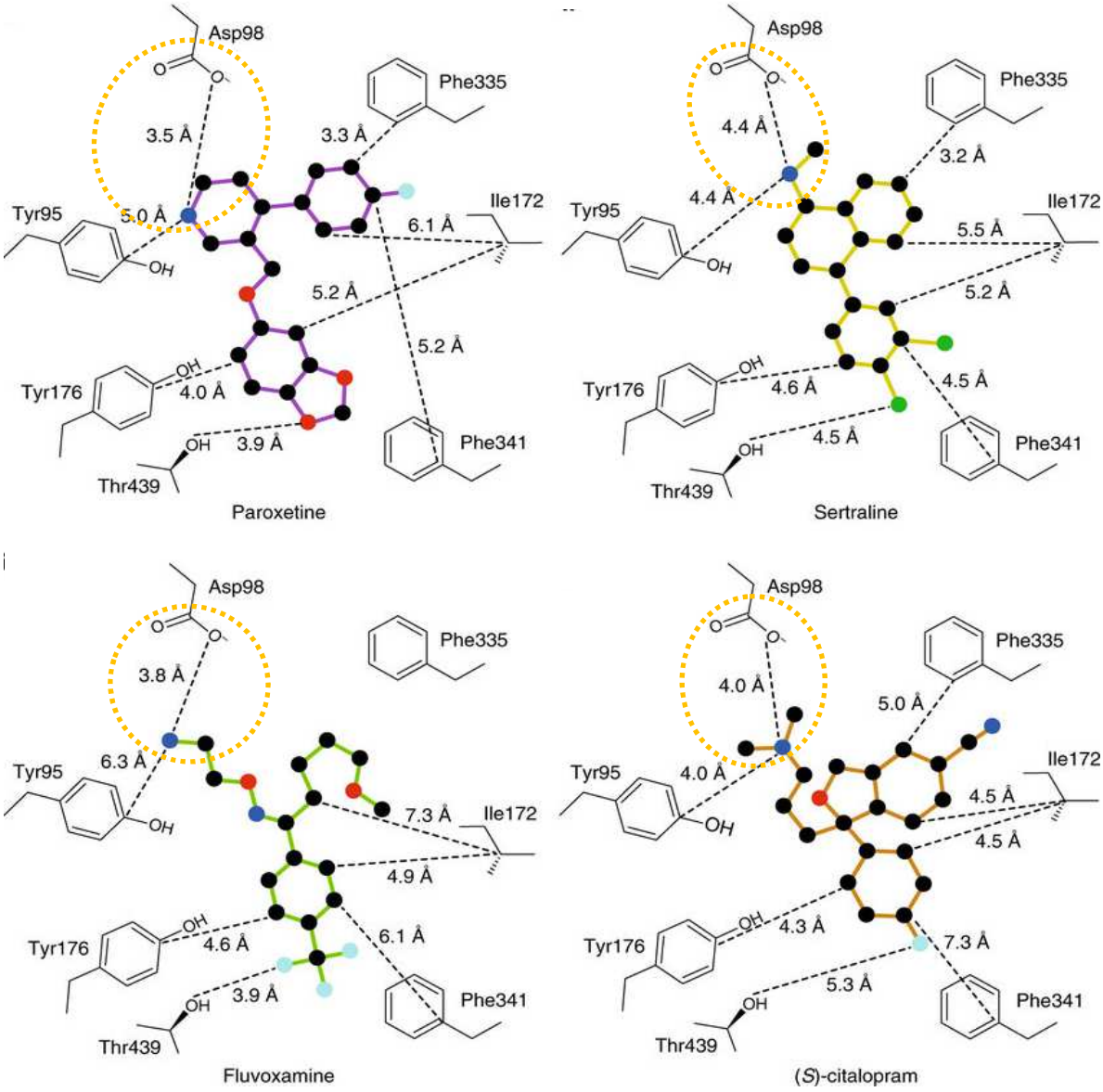


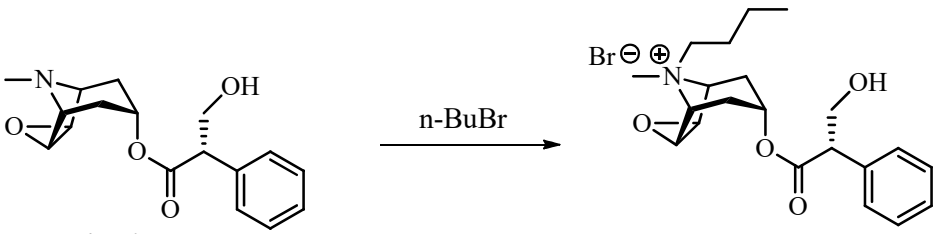
Figure 1.3b: Crystal structures of drugs depicted in *Figure 1.3a* bound to the serotonin receptor, showing key salt bridge binding interaction between protonated amine and aspartate (Asp98) residues.[22]



Another quirk of these alkaline molecules is the fact that their ionization is pH dependent, and hence reversible. In the ionized form, no passage into the bloodstream through the intestinal mucosa would occur. Likewise, no passage across the blood-brain barrier is possible in this state, which provides an incredible tool for pharmaceutical manipulation. Consider the commonly prescribed medication Buscopan®, for example (*Scheme 1.1*). The lead compound scopolamine is a structurally interesting alkaloid isolated from various plants of the nightshade family.[30] It possesses powerful antispasmodic properties and can reliably treat stomach cramps, which affect almost everybody on earth at some point in their life, with

many suffering from it daily. However, scopolamine is also powerfully psychoactive and produces intense and disorientating hallucinations.[28] By simply treating this alkaloid with butyl bromide one obtains the quaternary ammonium salt analogue (*n*-butylscopolamine, from which the name Buscopan® is derived). This salt cannot be absorbed as a consequence of its polarity, and in this form the molecule can be safely taken orally by people of all ages as an effective and non-psychoactive antispasmodic.

Scheme 1.1. Preparation of Buscopan® from scopolamine.



scopolamine ***Buscopan***

1.2 The lamellarin alkaloids

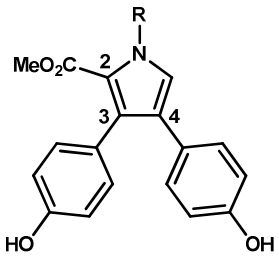
1.2.1 Isolation and characterization

After having built up the etymological definition of the alkaloids, it is now time to destroy it with the very molecules focused on in this work. The lamellarins are a diverse family of pyrrole alkaloids found in a variety of marine invertebrate species, including molluscs, ascidians and sponges.[6,31] The first isolation of these marine metabolites was reported by Faulkner and co-workers in 1985, and they were so named after the genus of "slug-like" snails they were extracted from, the *Lamellaria*.[32] Pyrrole rings contain a completely non-alkaline nitrogen, a consequence of the participation of the lone pair in aromatic conjugation.[33] Clearly, their activity stems from an entirely different property, but they are nonetheless regarded as alkaloids. Whilst the lamellarins have been proven to possess a variety of potentially useful pharmacological actions including HIV-1 integrase inhibition and immuno-modulation,[34] their anticancer potential is what sets them aside as some of the most topical novel drugs in the field.[31,35–37] Some prominent members of the lamellarin family have been shown to be exceptionally potent cytotoxins, with the additional unique property of also being capable of reversing multi-drug resistance in various cancer cell lines.[6,34] Structurally, compounds considered part of the lamellarin family possess a central pyrrole ring with at least two decorating aromatic rings on positions 3 and 4 (*Figure 1.4*), and

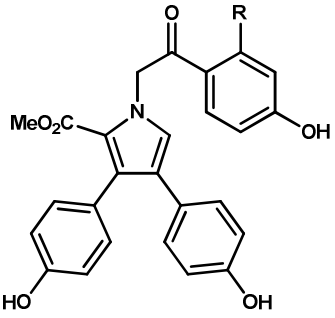
some kind of carboxyl substitution at position 2. The simple open form analogues (Type II) are believed to be intermediates in the biosynthesis of the more complex polycyclic fused analogues (Type-I).[34] Whilst the simple Type II lamellarins have shown some interesting bioactivity, they are overshadowed in most respects by the polycyclic Type-I members of the series.[34] The activity of the Type-I lamellarins can be further subdivided depending on the specific oxidation pattern of rings A, B, E and F (*Figure 1.5*). The aroyl substituents R_1-R_7 (*Figure 1.4*) have been found to possess various combinations of phenols (R = OH), methoxy substituents (R = OMe) and sulphonates (R = OSO_3H), depending on the organism from which they are isolated.[31,34] As a consequence of this structural diversity, more than seventy unique lamellarin alkaloids have now been characterized.[34]

Figure 1.4. Structural classification of lamellarin alkaloids.

Type-II Lamellarins:

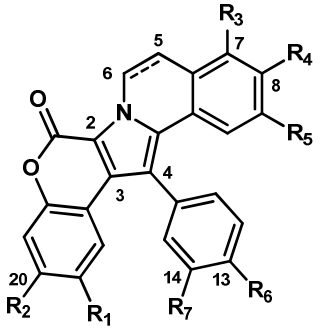


Lamellarin Q, R = H
Lamellarin R, R = C_6H_4-*p*-OH



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

Type-I Lamellarins:

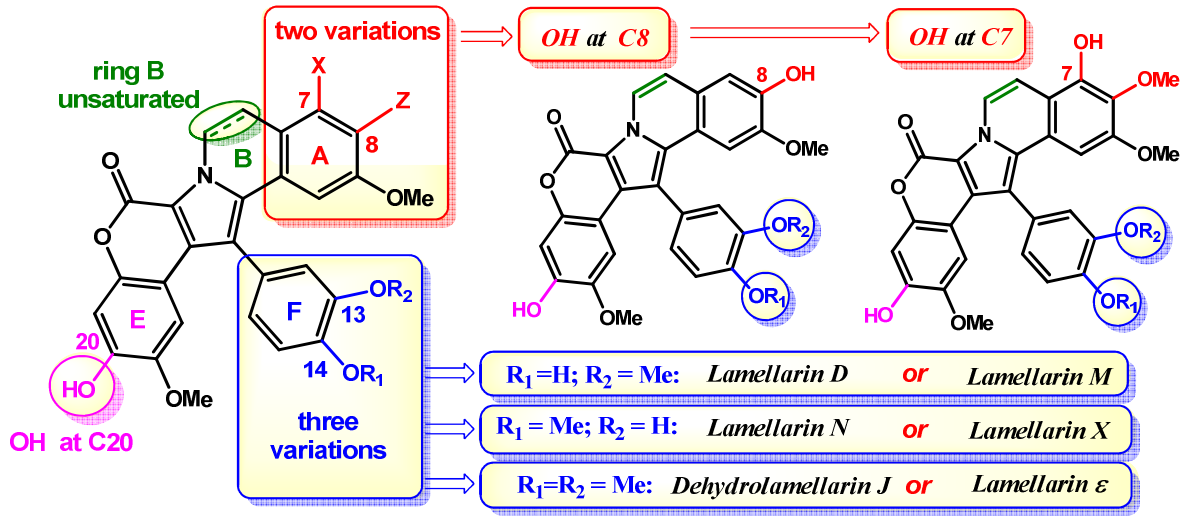


70+ Lamellarins, R = H, OH, OMe

In general, structure-activity relationship studies have elucidated the following understood structural necessities for cytotoxic potency of the lamellarins:[34–36,38]

- They must be Type-I lamellarins, with a fully fused pentacyclic structure (*Figure 1.4*).
- The isoquinoline ring (C5-C6, *ring B, Figure 1.5*) must be unsaturated. This is thought to impart planarity required for intercalative binding.
- There must be a hydroxy group at either C7 or C8. Only the two ring-A structural analogues shown in *Figure 1.5* have been shown to be effective.
- A hydroxy moiety at C20 is essential for activity.
- Ring F is amenable to change. Natural lamellarins possess either hydroxy or methoxy moieties at C13 and C14. Only the dihydroxy substitution is detrimental. All three remaining structural variations of ring F are allowed (*Figure 1.5*).

Figure 1.5. Structure-activity relationship of Type-I lamellarin alkaloids.



The ocean floor has proved to be a burgeoning source of novel pharmaceuticals, particularly for those of an anticancer nature.[39] It has been proposed that the reason for this is because the typically immobile organisms that inhabit these ecological niches have been continuously evolving to produce more potent cytotoxins in order to prevent cellular replication of competing species nearby.[40] Similar to how continuously taller trees have evolved in forested regions in competition for sunlight, these sea-floor organisms are in constant competition for space. In these environments nature has resorted to a kind of chemical warfare, driven by natural selection, where reproductive efficiency has become intrinsically connected to the cellular destruction of competing species, particularly those prone to rapid proliferation. As a consequence of this evolutionary battleground, the sea floor is considered the most biochemically diverse environment on earth, and is the leading source of novel cytotoxins discovered by bioprospectors.[39–43]

1.2.2 A selection of reported lamellarin syntheses

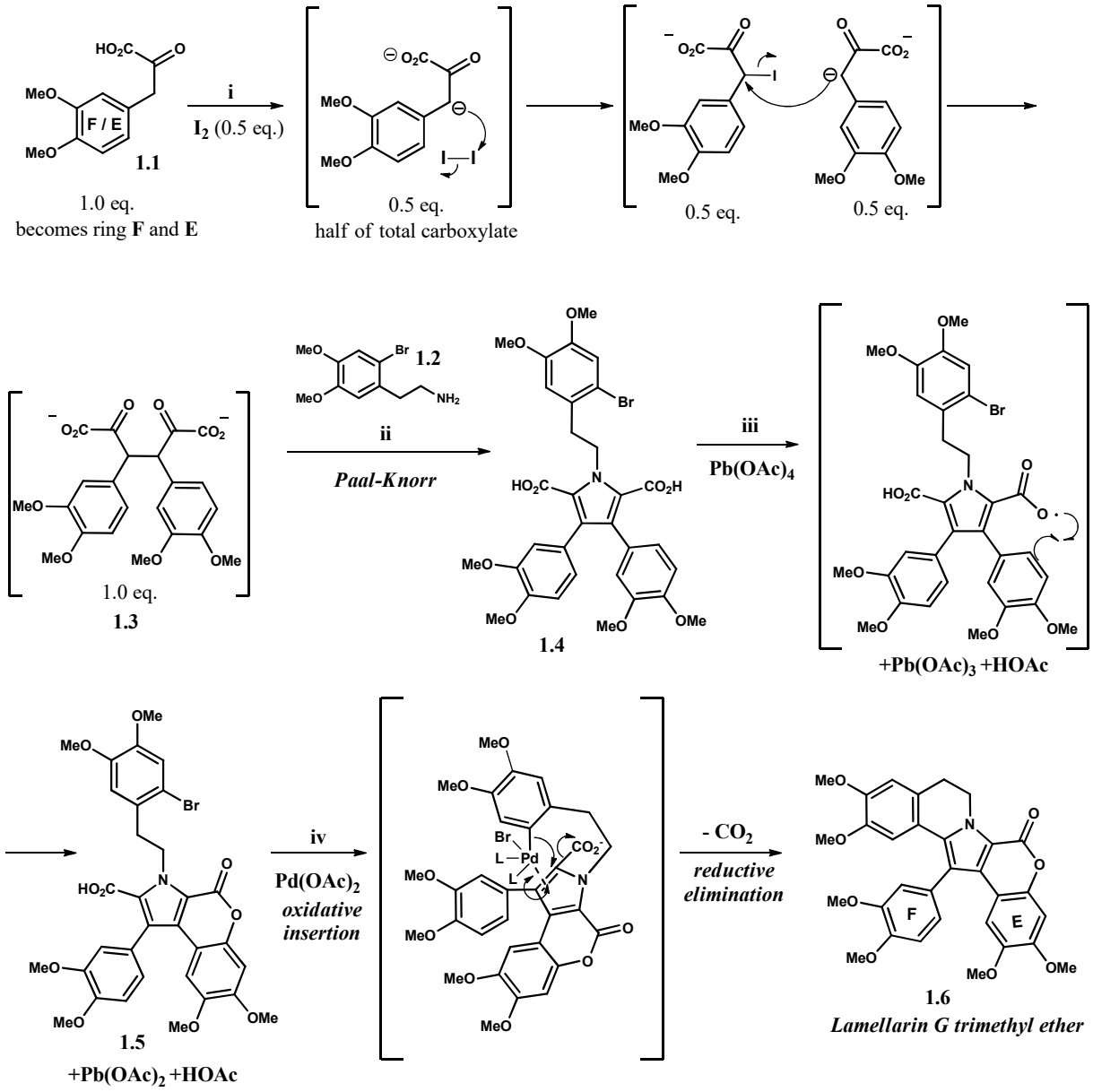
Since the first reported lamellarin synthesis in 1997 (*Scheme 1.2*), the growing international interest into their synthesis has gathered considerable momentum, and many new strategies are now published each year. There are numerous extensive reviews dedicated to both their biological activity, as well as the many methods for their synthesis.[6,31,34,44–46] A relatively small number of these, which are widely regarded as some of the front-runners in terms of efficiency and novelty, are detailed below. These routes are relatively unique from one another and have been used to illustrate both the progress that has been made in the field, as

well as the limitations of each that have prevented any from being successfully scaled up until now.

a. Syntheses by Steglich and co-workers (1997, 2000)[47,48]

The very first reported synthesis of a lamellarin analogue was by Steglich and co-workers in 1997 *(Scheme 1.2*). Their route was both short and elegant, making use of 3,4-dimethoxypyruvic acid (**1.1**) and 3,4-dimethoxyphenethylamine (**1.2**). Treating the pyruvic acid with two equivalents of *n*-butyllithium gave rapid formation of the carboxylate enol dianion by deprotonation of the carboxylic acid followed by removal of the acidic α-proton. Treating this mixture with 0.5 equivalents of molecular iodine at low temperature gave iodination of half of the total carboxylate material at the "softer" enol anion site of the dianion, to give 0.5 equivalents of the α-iodo carboxylate. Once formed, the iodinated intermediate is rapidly attacked by the remaining enol carboxylate in solution to provide the dimerized product **1.3**. Polymerization is inhibited by steric hindrance and the low temperature of the reaction. *In situ* treatment of **1.3** with the phenethylamine **1.2** and molecular sieves gave spontaneous formation of the Paal–Knorr pyrrole product, which was neutralized to give the dicarboxylic acid **1.4**. This pyrrole is thus prepared fully substituted, and hence stabilized. Treatment of **1.4** with one equivalent of lead tetraacetate then gave selective oxidation of one of the carboxylic acid termini of this symmetrical molecule to form the radical carboxylate, which then cyclized regioselectively with the electron-rich di-methoxylated aryl ring adjacent to it. In doing so (presumably by a more complicated mechanism than simple homolytic cleavage) lead(IV) is reduced to lead(II), forming two molecules of acetic acid in the process and oxidizing the carboxylic acid precursor **1.4** to the lactone **1.5**. Thereafter, treatment with palladium(II) acetate gave, in what is formally a Heck reaction, cyclization of the isoquinoline segment with concomitant decarboxylation to provide lamellarin G trimethyl ether (**1.6**), an unnatural derivative of lamellarin G. Although the synthesis is short, the overall yield for their process was only 33%. Their lactonization required a stoichiometric quantity of the oxidant, lead tetraacetate, and a stoichiometric quantity of palladium acetate was needed for the final step. Another glaring problem with this synthesis was the lack of applicability to the unsymmetrical lamellarins, because it only allowed for the synthesis of analogues with identical precursors for rings F and E (both derived from **1.1**).

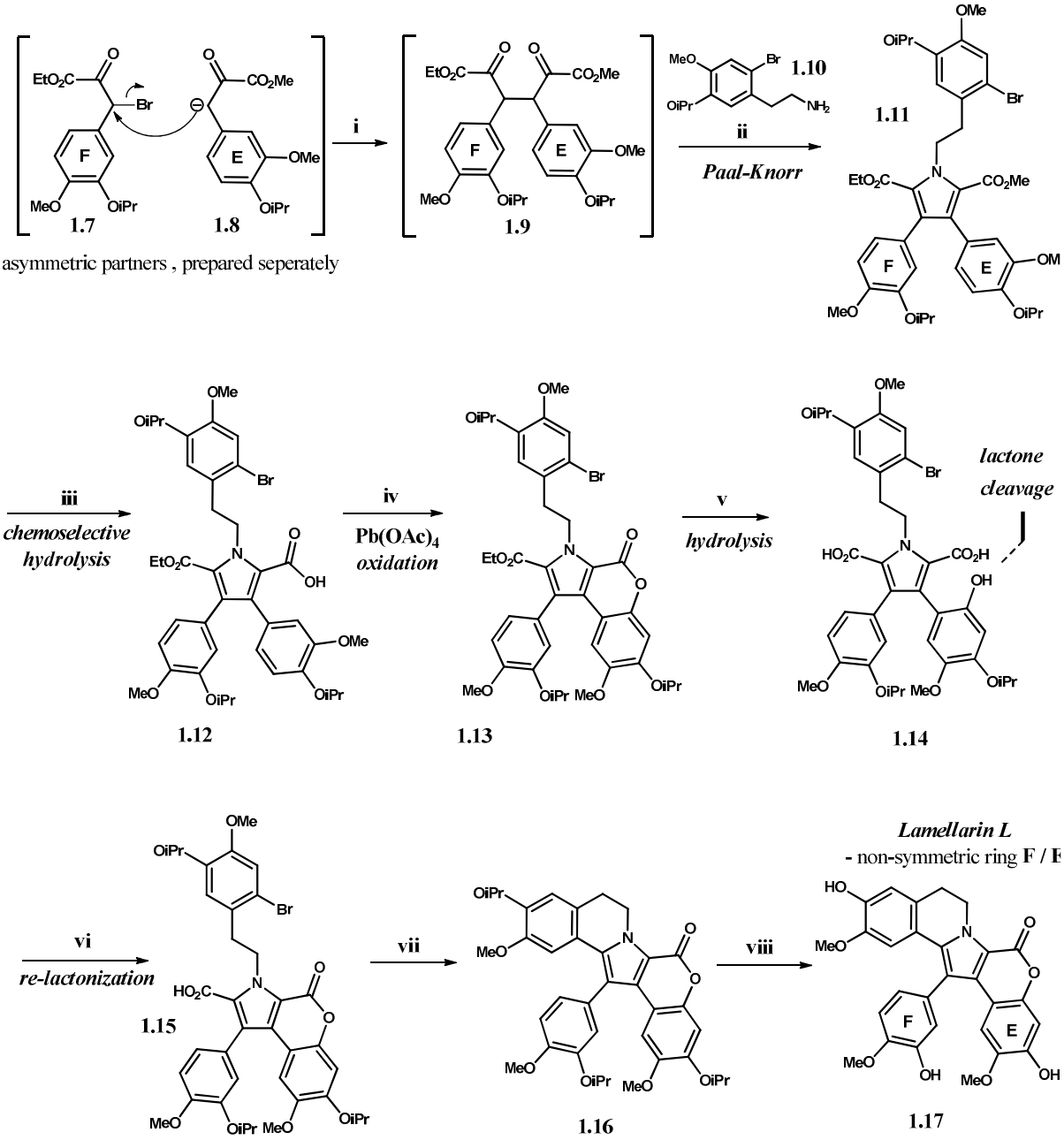
Scheme 1.2. Synthesis of lamellarin G trimethyl ether by Steglich and co-workers (1997).[40]



Reagents and conditions: i. **1.1** + BuLi, then I_2; ii. **1.2**, molecular sieves, 62% (3 steps); iii. $Pb(OAc)_4$, 71 %; iv. $Pd(OAc)_2$, Ph_3P, Et_3N, MeCN, 74%.

Steglich and co-workers then published a clever solution to this problem in 2000, in which they report the synthesis of lamellarin L (*Scheme 1.3*), a special example of an analogue with different ring F and E precursors. Instead of an *in situ* iodine-mediated oxidation, the bromopyruvate ester **1.7** for ring F was prepared separately. Treatment of **1.7** with the strong base sodium hydride then facilitated deprotonation to the enol pyruvate (*n*-butyllithium would likely be too nucleophilic for these ester pyruvates). Following a Paal-Knorr pyrrole formation reaction between diester **1.9** and amine **1.10**, they obtained the pyrrole diester **1.11**.

Scheme 1.3. Asymmetric lamellarin synthesis by Steglich and co-workers (2000).[41]



Reagents and conditions: i. **1.8** + NaH, then **1.9**, CH_2Cl_2 ; ii. 4Å molecular sieves, 5 h reflux, 53%; iii. NaCN (50 equiv), DMPU, 1 h, 98%; iv. $Pb(OAc)_4$ (1.1 equiv), PhH, reflux; v. 40% aq. KOH, 3 h; vi cat. p-TsOH, toluene, 30 min, 97%; vii $Pd(OAc)_2$ (1 equiv.), PPh_3 (2 equiv.), CH_3CN/NEt_3 (3:1), 80 min, 97%; vii. $AlCl_3$ (7.5 equiv), CH_2Cl_2 , 4 h, 96%.

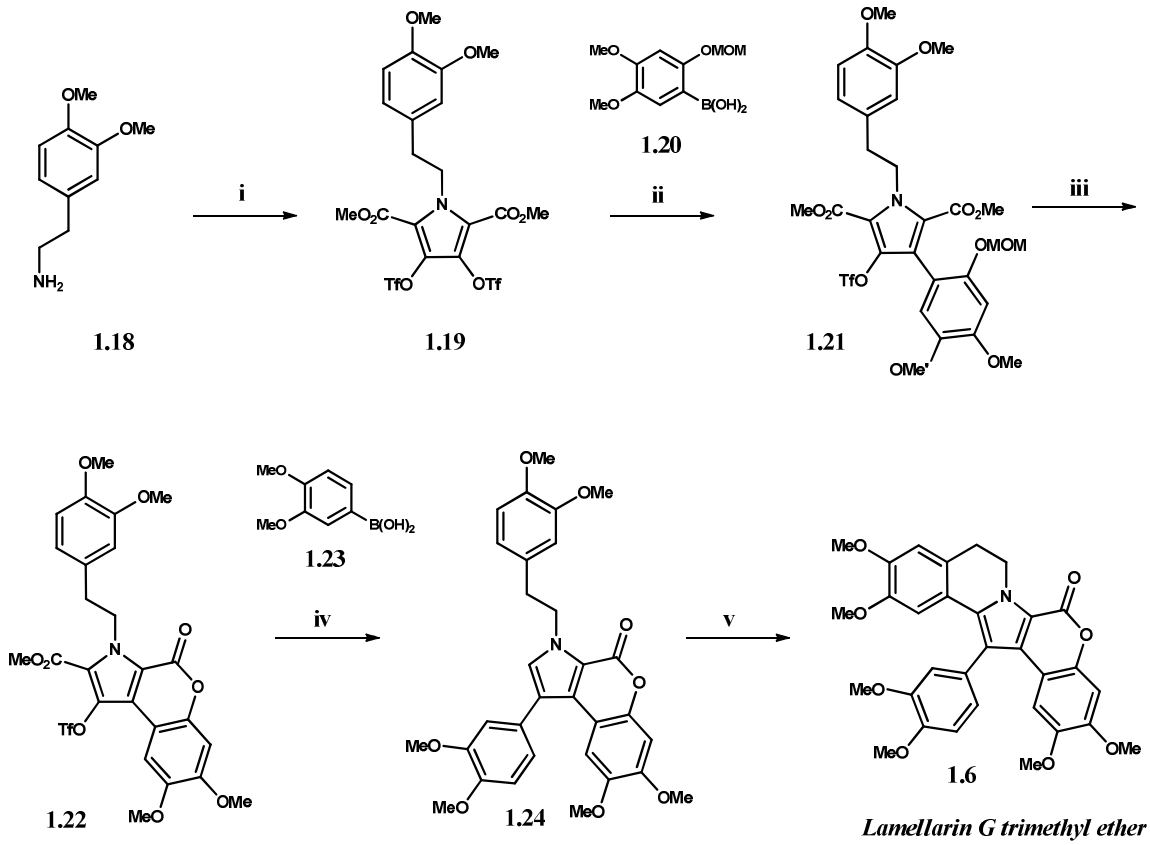
The methyl ester of **1.11** was then selectively hydrolysed preferentially to the more bulky ethyl ester by using 50 equivalents of sodium cyanide in the dipolar-aprotic solvent *N*,*N*′-dimethylpropylene urea (DMPU). Under these conditions they were able to hydrolyze the less hindered methyl ester selectively in good yield to provide the mono-acid **1.12**. The use of

DMPU as solvent was not explicitly discussed in the text, though it could provide some kind of solvent-chelation mediated steric selectivity. DMPU is relatively large, as compared to the more conventional *N,N*-dimethylformamide (DMF), and it is possible that the solvation of the precursor diester provides additional selectivity for hydrolysis of the less hindered ester. Lactonization to **1.13** was facilitated with stoichiometric lead tetraacetate and the ethyl ester was hydrolysed using potassium hydroxide to provide the di-acid **1.14**. Although cleavage of the lactone occurred under the hydrolytic conditions, the ring was easily reinstalled using catalytic *para*-toluenesulphonic acid (*p*-TsOH) in toluene to give **1.15**. Heck cyclization with decarboxylation using stoichiometric palladium acetate gave the fused isoquinoline lamellarin **1.16**, which was deprotected using aluminium trichloride to give the unsymmetrical lamellarin L (**1.17**), the unoxidized analogue of the potent cytotoxin lamellarin N, in 96% yield. Again, the overall yield for this synthesis was fairly low, at 38%, and prohibitively expensive as it required a stoichiometric amount of palladium acetate.

b. Syntheses by Ishibashi and co-workers (2003).[49]

Ishibashi and co-workers published a novel synthesis of lamellarin G trimethyl ether in 2003 which illustrates a more common approach to synthesizing fused polycyclic scaffolds, with the use of multiple cross-coupling reactions[49] (*Scheme 1.4*). In this case the pyrrole ring was constructed from the phenethylamine **1.18**, in a three-step process, after which the bis-triflate pyrrole product **1.19** was isolated in an overall yield of 39% from **1.18**. Suzuki coupling reaction between triflate **1.19** and boronic acid **1.20** installed the ring E segment to provide **1.21**. *In situ* lactonization was achieved when removing the methoxymethyl (MOM) protecting group of **1.21** using acidic hydrolysis, providing lactone **1.22**. After another Suzuki coupling reaction between this triflate **1.22** and boronic acid **1.23,** the remaining methyl ester was hydrolysed using potassium hydroxide, which also gave some concomitant lactone hydrolysis. Pyridinium *p*-toluenesulphonate (PPTS) was used to reinstall the hydrolysed lactone and the carboxylic acid was decarboxylated with cuprous oxide and quinoline at 220 °C to provide **1.24.** The isoquinoline ring B of **1.6** was formed by oxidative coupling using the hypervalent iodine reagent bis[(trifluoroacetoxy)iodo]benzene (PIFA) with boron trifluoride (BF_3) as catalyst. This provided lamellarin G trimethyl ether in an overall yield of 39%. Although relatively efficient at the time, the use of triflate-based coupling reactions and stoichiometric hypervalent iodine prohibits such syntheses from being used industrially.

Scheme 1.4. Synthesis of various lamellarins by Ishibashi and co-workers (2003).[49]

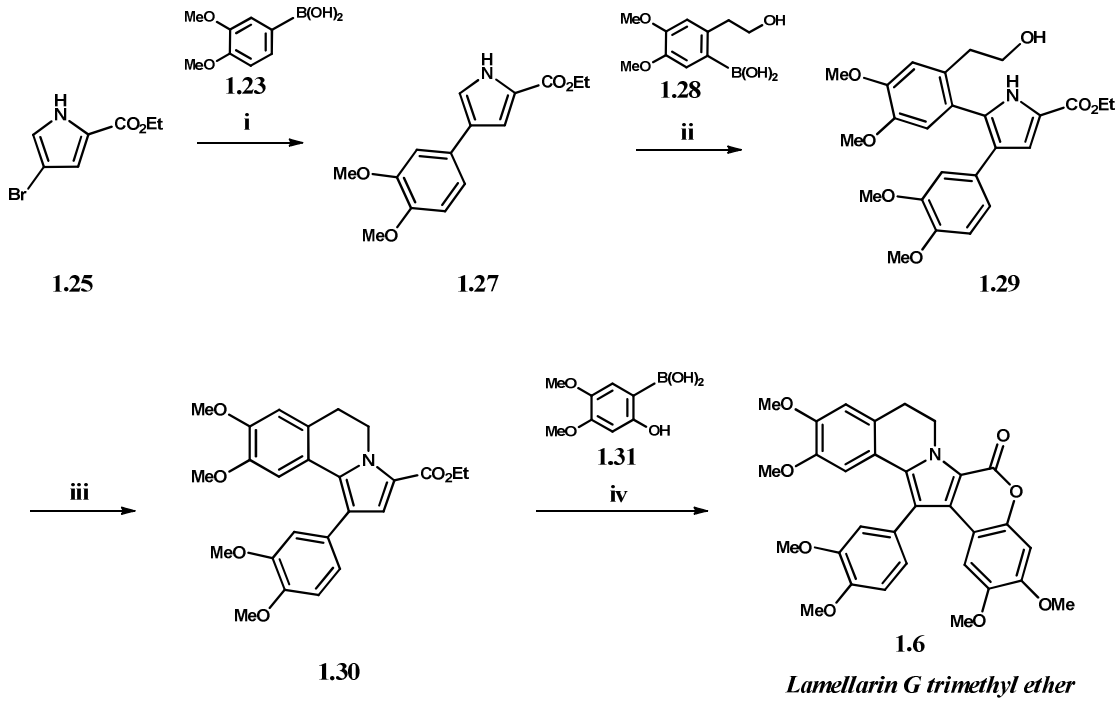


Reagents and conditions: i. (a) $BrCH_2CO_2Me$, $NaHCO_3$, MeCN, reflux, 91%; (b) $(MeO_2C)_2$, NaOMe, MeOH, reflux, 49%; (c). Tf_2O, Pyridine, 87%; ii. **1.85**, $Pd(Ph_3P)_4$, aq. Na_2CO_3, THF, reflux, 74%; iii. (a) HCl, MeOH, reflux, 90%; (b) *p*-TsOH, CH_2Cl_2, reflux, 93%; iv. (a) **1.23**, $Pd(Ph_3P)_4$, aq. Na_2CO_3, THF, reflux, 95%; (b) 40% aq. KOH, EtOH, reflux, 76%; (c) PPTS, CH_2Cl_2, reflux, 61%; (d) Cu_2O, quinoline, 220 °C , 83%; v. PIFA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -40 °C, 62%.

c. Synthesis by Handy et al. (2004).[50]

Similarly, a 2004 synthesis published by Handy and co-workers details the preparation of lamellarin G trimethyl ether from the preformed pyrrole **1.25** (*Scheme 1.5*), using three separate bromination–Suzuki coupling reaction sequences. After regioselective halogenation and Suzuki coupling of **1.25** with boronic acid **1.23**, the biaryl product **1.27** was subjected to a second bromination and Suzuki coupling with boronic acid **1.28** to give the trisubstituted pyrrole **1.29**. The hydroxyl moiety of **1.29** was converted into the tosylate and cyclization of the dihydroisoquinoline ring was facilitated by deprotonating the pyrrole N-H using sodium hydride to give **1.30**. This was then followed by a third bromination and Suzuki coupling with boronic acid **1.31** which, after *in situ* lactonization, gave lamellarin G trimethyl ether in an overall yield of only 10%.

Scheme 1.5. Approach by Handy *et al.* (2003).[50]

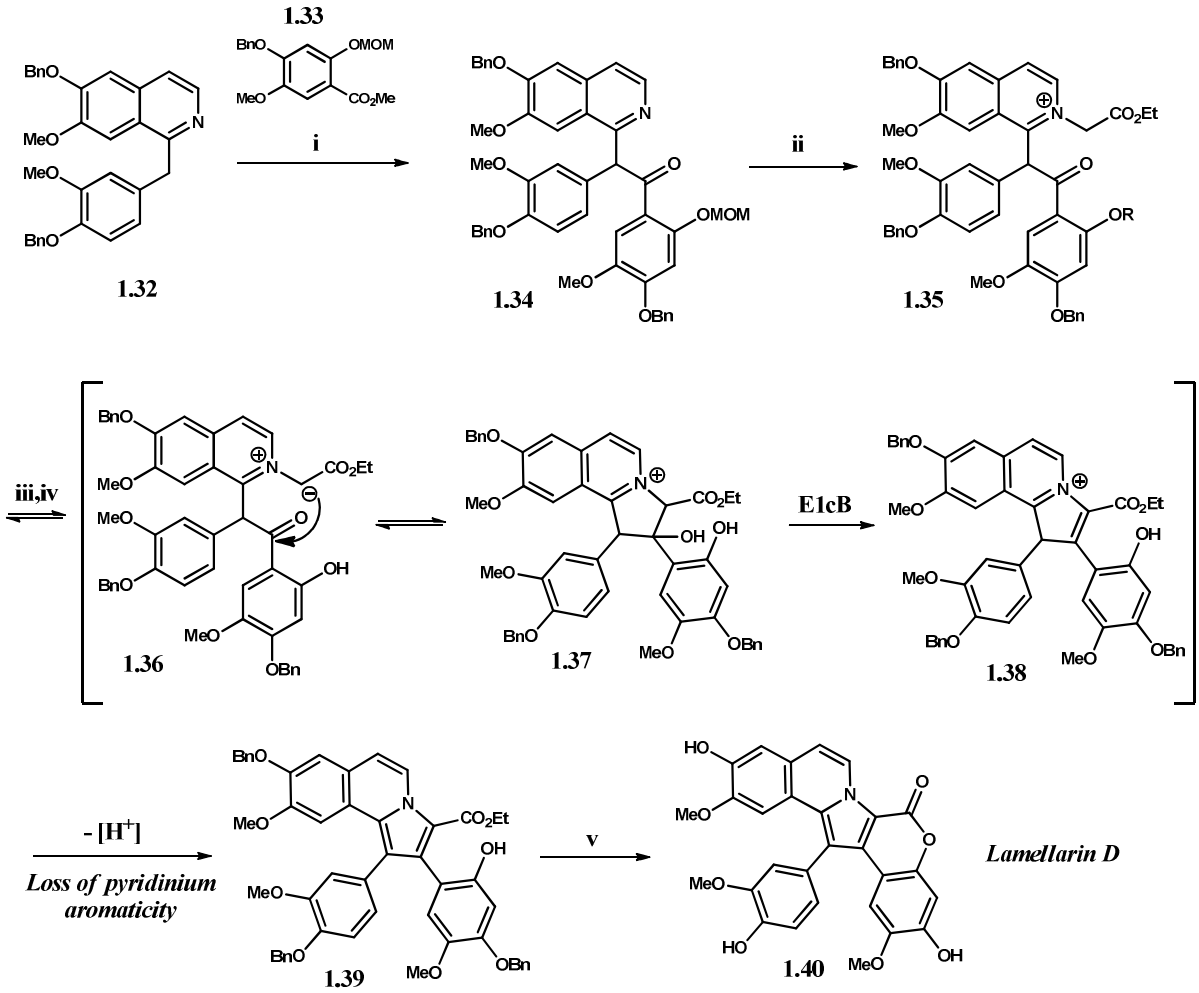


Reagents and conditions: i. **1.23**, $Pd(Ph_3P)_4$, DMF/aq. Na_2CO_3, 110°C, 70%; ii. (a) NBS, DMF, 0°C-rt, 100%; (b) **1.28**, $Pd(Ph_3P)_4$, DMF/aq. Na_2CO_3, 110°C, 54%; iii. (a) TsCl, pyridine; (b) NaH, DMSO, 61%; iv. (a) NBS, DMF, 0°C-rt, 100%; (b) **1.31**, $Pd(Ph_3P)_4$, DMF/aq. Na_2CO_3, 110°C, 46%.

d. Syntheses by Iwao and co-workers (1997).[51]

In 1997, Iwao and co-workers published the very first synthesis of the potent lamellarin D and lamellarin H. Deprotonation of papaverine (**1.32**) (*Scheme 1.6*) at the benzyl position using lithium diisopropylamide (LDA) gave *in situ* formation of the corresponding benzylic organolithium species. Acylation was facilitated with the MOM-protected methyl ester **1.33** and gave the corresponding imino-ketone **1.34**. Although tautomerism to the enaminone was observed, breaking aromaticity of the isoquinoline ring to form the enaminone tautomer is disfavoured. N-alkylation of **1.34** to form the quaternary ammonium *N*-ethoxycarbonyl species **1.35** proceeds readily. From this alkylated material deprotection of the MOM ether and subsequent treatment with triethylamine gave formation of the zwitterionic intermediate **1.36**, which underwent cyclization to the pyrrole **1.39** in a low yield of 34% from **1.34**. Hydrogenation with palladium on carbon facilitated the removal of the benzyl ether protecting groups to provide lamellarin D (**1.40**). Although inefficient, the Iwao synthesis was relatively simple and did not require any expensive or exotic reagents.

Scheme 1.6. Approach by Iwao and co-workers (1997).[51]



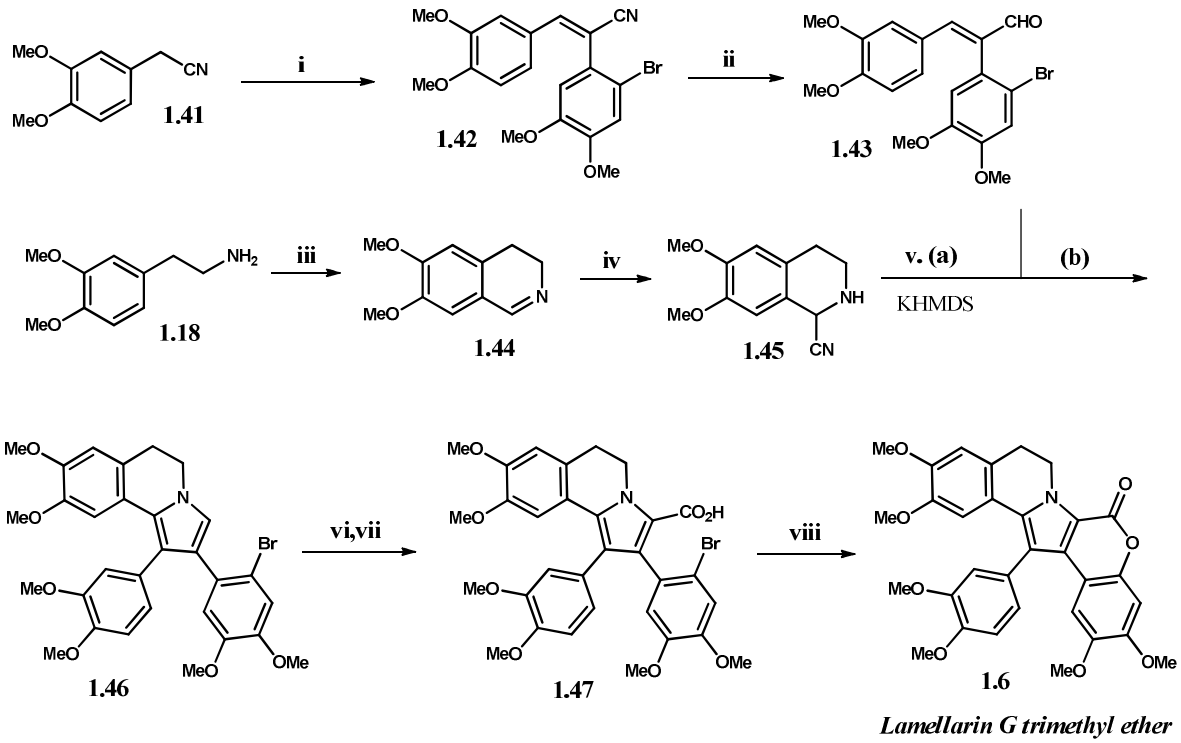
Reagents and conditions: i. **1.33**, LDA, 63%; ii. $BrCH_2CO_2Et$, 70 °C, 22 h; iii. cat. HCl, MeOH; iv. Et_3N, CH_2Cl_2, 34% (3 steps); v. H_2, Pd/C, EtOAc, 82%.

e. Synthesis by Opatz and co-workers (2013).[52]

This synopsis would not be complete without mentioning the hitherto most efficient lamellarin synthesis published until the appearance of ours (to be described in Chapter 4): that of the Opatz group in 2013. Here, the strong base potassium hexamethyldisilazide (KHMDS) is used to deprotonate aminonitrile **1.45** (*Scheme 1.7*), which reacts via conjugate addition with the electrophilic stilbene aldehyde **1.43**. *In situ* treatment with acetic acid in ethanol gives dehydrocyanation and hydrolysis/dehydration to the aromatic pyrrole **1.46**. This pyrrole is then formylated and oxidized to the corresponding carboxylic acid under carefully controlled conditions to give carboxylic acid **1.47**. Then, treatment with copper(I) thiophene-2-carboxylate (CuTC) in DMF under microwave conditions gave successful intramolecular Ullman-type coupling between the carboxylic acid and the aryl-bromide moieties of **1.47**, to

furnish the lactonized lamellarin **1.6** in high yield. Unfortunately, this process required the use of two equivalents of this exceptionally expensive copper salt, which retails for around $70 per gram. Furthermore, this methodology was not extended to the synthesis of any of the potent lamellarin scaffolds.

Scheme 1.7. Synthesis of lamellarin G trimethyl ether by Opatz and co-workers (2003).[52]



Reagents and conditions: i. (a) NBS, MeCN, TFA, 16 h, 93%; (b) veratraldehyde, NaOEt, EtOH, reflux, 5 h, ii. DIBAL-H, CH_2Cl_2, 99%; iii.) (a) HCO_2Et, reflux, 16 h; (b) PCl_5, CH_2Cl_2, 98%; iv. KCN, HCl, MeOH/H_2O, 84% v. **1.45**, KHMDS, THF, -78°C, 3 min, then **1.43,** THF, -78°C - rt, 30 min, then AcOH/EtOH, reflux, 30 min, 93;% vi. DMF, $POCl_3$, CH_2Cl_2, 0-70°C, 7.5 h; vii. $NaClO_2$, NaH_2PO_4, 1,4-dioxane/H_2O, 2,3-dimethyl-2-butene, 25 °C, 18 h, 95%; viii. CuTC, DMF, microwave, 150 °C, 30 min, 85%.

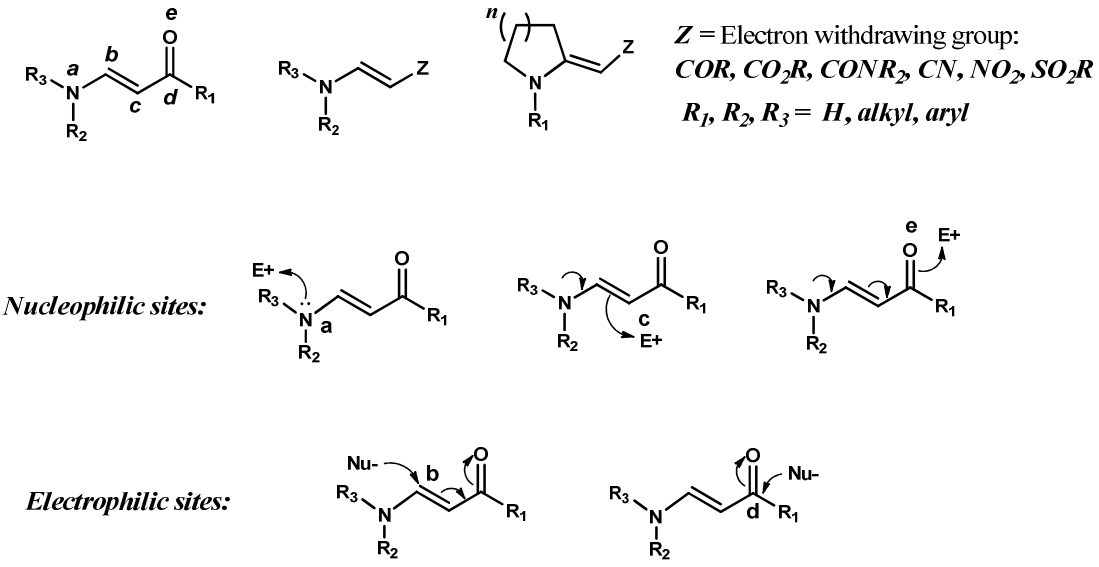
1.3 Enaminones

1.3.1 Structure, reactivity and synthesis

The synthesis of alkaloids at Wits has long been led by Professor Joseph Michael and throughout this time he has contributed significantly to their synthesis by specifically manipulating the interesting reactivity of enaminones.[53] Being essentially amides in which the nitrogen and carbonyl components are separated by an intervening conjugating vinyl group, enaminones possess some nucleophilic (and hence alkaline) tendencies characteristic

of enamines, as well as significant extension of this nucleophilicity into the carbonyl group. Because of the stabilization of the enamine's electron density into the conjugated carbonyl, they tend to be "well-behaved" and stable compounds to work with, whilst still offering the synthetic chemist various methods of selectively "unlocking" each of their respective reactive sites. The specific atomic arrangement of enaminones provides a combination of an amine, alkene, carbonyl (or other electron-withdrawing substituent), Michael acceptor and enamine functional groups. These are some of the most fundamental sources of chemical reactivity known in organic synthesis, all bottled up in a single and easy to make system. The various alternatives for enaminone reactivity are shown in *Figure 1.6*.

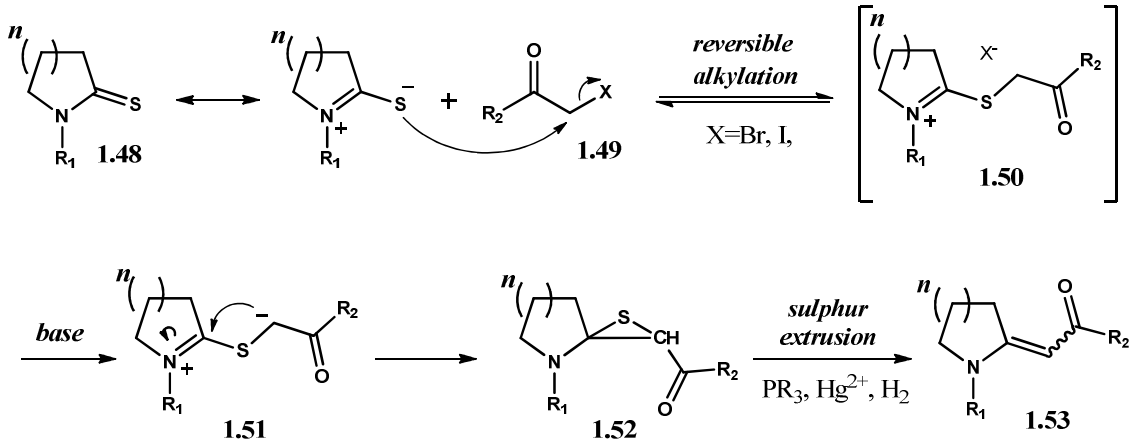
Figure 1.6. Nucleophilic and electrophilic sites of enaminones, also indicating variation in functionality.



Although there are a variety of methods available for the preparation of enaminones,[54–61] the Eschenmoser sulphide contraction is the most common for exocyclic enaminones,[62] and many variations of this approach have now been reported.[54] The first step of this reaction involves the reversible nucleophilic attack of an α-bromocarbonyl compound **1.49** *(Scheme 1.8)* by thiolactam **1.48** to form a thioiminium salt intermediate **1.50**. Once this alkylation reaction reaches completion, an appropriate base is added (alkylamines are more commonly used, though carbonates, hydroxides and potassium *tert*-butoxide have also been used).[54] This induces the deprotonation of the α-carbonyl position of **1.50** to form an anion **1.51,** which spontaneously cyclizes to form a transient episulphide intermediate **1.52**. The sulphur is then extruded in the presence of an appropriate thiophile. The actual mechanism of conversion of thioiminium ethers **1.50** into enaminones **1.53** has yet to be conclusively proven, though the

pericyclic mechanism illustrated in *Scheme 1.8*, via episulphide **1.52**, is considered the most likely.[54] The removal of sulphur occurs with concomitant formation of the π-bonded alkene functionality of the enaminone. Triphenylphosphine is commonly used, though other phosphines, phosphites, and even mercury(II) salts have also been employed. Less commonly, catalytic hydrogenation methods, typically with Raney nickel, have also been used for the desulphurization process. In some rare cases, sulphur extrusion is spontaneous, and elemental sulphur has been isolated as a by-product of these reactions.[62,63]

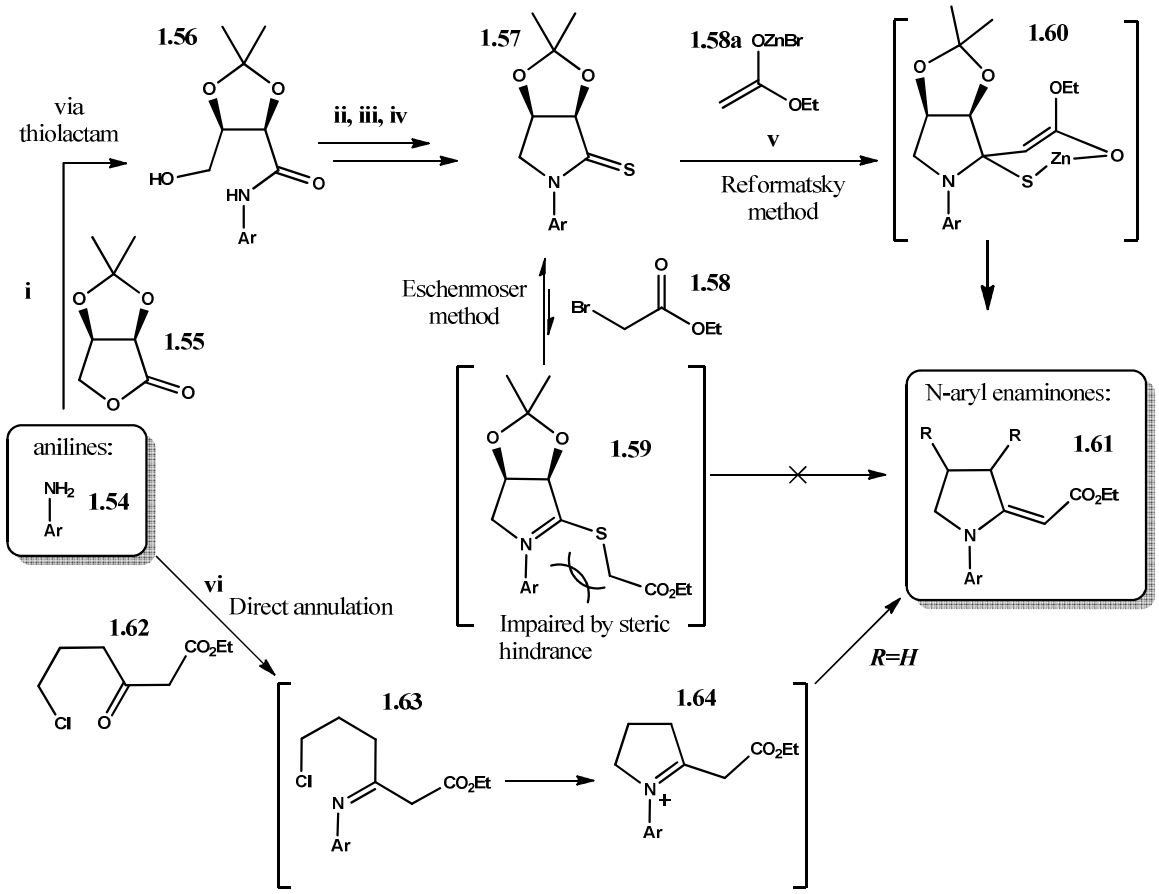
Scheme 1.8. Mechanism of the Eschenmoser sulphide contraction approach to enaminone synthesis.



The Eschenmoser sulphide contraction is typically a very reliable means of obtaining enaminones, though in certain cases, particularly when the nucleophilicity of the thiolactam **1.48** is reduced by deactivation of the nitrogen atom, or by steric hindrance induced by large R_1 groups, alternative methods are more appropriate. Fundamentally, such problems often arise due to the reversibility of the initial alkylation phase, which requires significant thermodynamic stabilization of the thioiminium intermediate **1.50**.[64] One solution to this reversibility problem is to make use of non-nucleophilic leaving groups such as triflate (X = OTf), thus making the alkylation phase irreversible.[65] Another common limitation to the reaction, specifically related to secondary six-membered thiolactam precursors **1.48** (***n = 2***), is discussed later in *Scheme 1.22*. In such cases, other available methods for the preparation of the required enaminones may be more convenient. For example, during the preparation of N-arylated enaminones such as **1.61** (*Scheme 1.9*), the Eschenmoser sulphide contraction of thiolactams **1.57** was found to be severely impaired, presumably because of the cumulative effect of conjugate deactivation of nitrogen (decreasing the nucleophilicity of sulphur), as well as the large size of the N-aryl substituents which impedes the reversible formation of intermediates **1.59**. In this case, a modified Reformatsky approach was developed by Michael

and co-workers.[66–68] The thiolactam **1.57** was treated with the zinc-enolate **1.58a**, which had been prepared separately from ethyl-bromoacetate (**1.58**) by treatment with zinc dust in the presence of catalytic iodine. After refluxing the mixture in tetrahydrofuran (THF) overnight, the corresponding enaminones **1.61** were obtained in excellent yields of 90-92%. Using this Reformatsky approach avoids the two-step Eschenmoser-sulphide contraction reaction, which requires complete alkylation of **1.57** to **1.59**, prior to the sulphur extrusion step. Instead, the Reformatsky approach makes use of a single methodological step, via **1.60**. When the unsubstituted N-aryl-pyrrolidinyl enaminones **1.61** (R = H) were sought,[69,70] a more direct approach was possible. Treatment of anilines **1.54** with 6-chloro-3-oxohexanoate **(1.62)**, in the presence of iodine as catalyst, a drying agent sodium sulphate (Na_2SO_4), and the weak base disodium hydrogen phosphate (Na_2HPO_4), provided enaminones **1.61** in a one-pot reaction. This method is, of course, limited to enaminones for which the appropriate γ-halo-ketone analogue of **1.62** is available.

Scheme 1.9. Alternative methods for preparing N-arylated enaminones developed by the Wits group.[69,70]



Reagents and conditions: i. **1.54** + EtMgBr, THF, -78°C; ii. $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0°C to rt; iii. NaH, THF, rt; iv. Lawesson's reagent, toluene, reflux; v. Zn (5 equiv.), **1.58** (3 equiv.), I_2 (0.2 equiv.), THF, ultrasound, then add **1.57**, THF, reflux; vi. Na_2SO_4, Na_2HPO_4, cat I_2, no solvent.

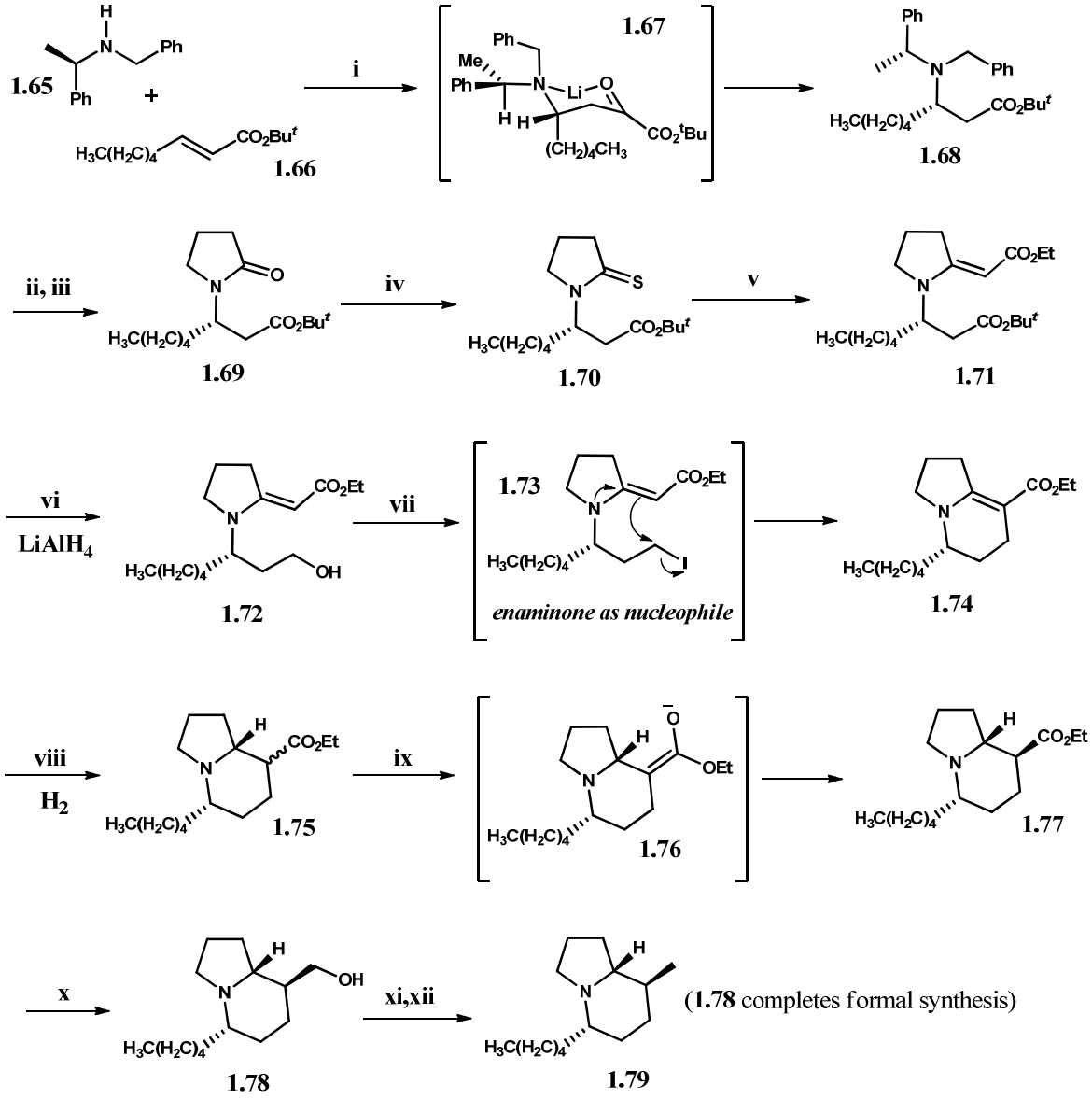
1.3.2 Use of enaminones in alkaloid synthesis at Wits University

There are numerous reviews dedicated to the interesting and often divergent reactivity of enaminones.[53,55,58] The integrated nitrogen atom is most often incorporated into the final structures, making them particularly suited to alkaloid synthesis. In general, the nucleophilic enamine segment and ambident enone electrophilic segment each provide two separate means of inducing annulation reactions with either intramolecular electrophiles or nucleophiles respectively. The combination of all of these ambident functional groups offers the potential for numerous annulation strategies: electrophilic attack of the enamine component on nitrogen and/or carbon by intramolecular electrophiles, nucleophilic attack of the enone at carbon *b* and/or *d* (*Figure 1*.6) by intramolecular nucleophiles, or even intramolecular Heck-type coupling reactions with the conjugating vinyl segment. These ambident functionalities also stabilize one another by mutual conjugation, creating what is often referred to as a "push-pull" system.[71] A few examples from the various methods of enaminone annulation developed by the Wits group are detailed below, providing unique examples of some of the major annulation strategies.

An excellent introductory example of the synthetic versatility of enaminones can be found in a synthesis of indolizidine 209B published by Michael and co-workers in 2000 (*Scheme 1.10*).[72] Here, the chiral lactam **1.69** was made stereoselectively using the lithiated amide of **1.65**. The *tert*-butyl ester was required in the Michael acceptor **1.66** to prevent nucleophilic attack of this ester by the lithiated amide. After hydrogenolysis of the two *N*-benzyl substituents of **1.68**, the lactam was built around the free primary amine using 4-chlorobutyryl chloride to give **1.69**, which was thionated to provide **1.70**. This thiolactam underwent the Eschenmoser sulphide contraction with ethyl bromoacetate to give enaminone **1.71**. Most remarkably, this enaminone is sufficiently stable to lithium aluminium hydride ($LiAlH_4$) to allow for the selective double reduction of the sterically hindered *tert*-butyl ester to the alcohol **1.72**, leaving the vinylogous urethane functionality intact. This stability arises from the conjugated electron density from the enamine component which gives the ethyl ester properties that are more akin to a urethane. Yet, in spite of the stabilization of this enamine, iodination of **1.72** results in an *in situ* nucleophilic attack by the enamine with concomitant cyclization to provide the bicyclic enaminone **1.74**. Here we see the enaminone is acting as a nucleophile at carbon (position *c*) with an intramolecular electrophile. Then, the unsaturated double bond is hydrogenated in acetic acid under standard alkene hydrogenation conditions

(although this probably occurs via the protonated imine tautomer of **1.74**) to give **1.75** The racemic centre that was generated was epimerized under alkaline conditions to give the chiral alkaloid analogue **1.77**. The ethyl ester could now be reduced with $LiAlH_4$ to give **1.78**, which was converted into the methanesulphonate and reduced with $LiEt_3BH$ to give the desired alkaloid indolizidine 209B (**1.79**).

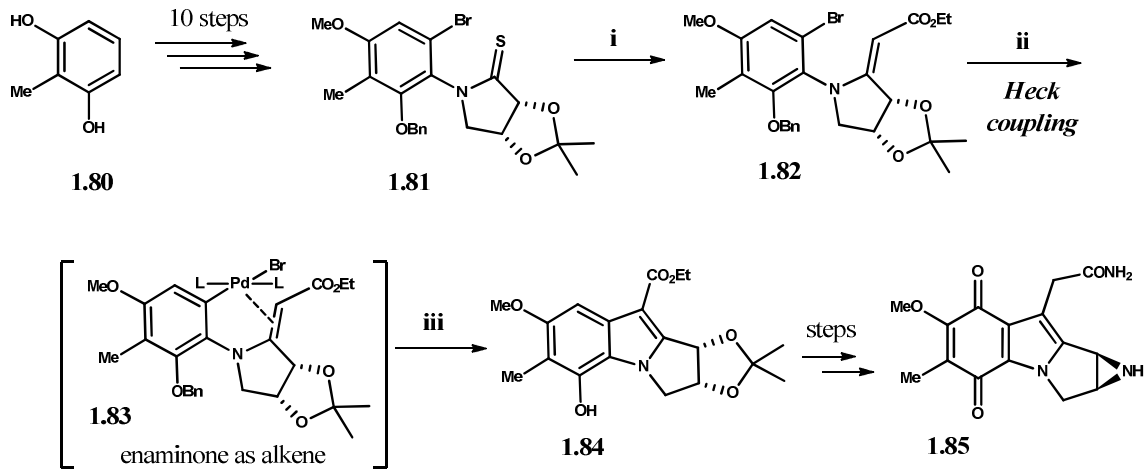
Scheme 1.10. Synthesis of Indolizidine 209B (**1.79**).[72]



Reagents and conditions: i. **1.65** + n-BuLi, THF, -78°C, then **1.66**; ii. H_2 (7 atm), 10% Pd/C, AcOH, rt; iii. (a) $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, reflux; (b) KOtBu, tBuOH, rt; iv. Lawesson's reagent, toluene, reflux; v. (a) $BrCH_2CO_2Et$, MeCN, rt; (b) PPh_3, toluene, Et_3N, MeCN, rt; vi. $LiAlH_4$, THF, rt; vii. I_2, imidazole, PPh_3, toluene, 110°C; viii. H_2 (1 atm), PtO_2, AcOH, rt; ix. NaOEt (cat.), EtOH, reflux; x. $LiAlH_4$, THF, rt; xi. CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C; xii. $LiEt_3BH$ (1 M in THF), THF, 0°C.

A completely different mode of enaminone reactivity was tapped in a 2006 publication, also by Michael *et al.*[68] The lactam ring of the thiolactam **1.81** (*Scheme 1.11*) was again constructed around a free amine (here the aniline **1.80**) using 4-chlorobutyryl chloride, in a similar manner to the previously discussed example (*Scheme 1.10*). As is detailed in *Scheme 1.9,* the Eschenmoser sulphide contraction of N-aryl thiolactams **1.81** and ethyl bromoacetate is unreliable. Instead, a modified Reformatsky reaction between **1.81** and the zinc enolate of ethyl-bromoacetate was used to provide enaminone **1.82,** which was successfully cyclized to the indole **1.84** using $Pd(OAc)_2$, by taking advantage of the alkene functionality of the enaminone. This is effectively a Heck coupling reaction, providing the heterocyclic product **1.84** in a yield of 82%. This intermediate was then successfully taken on to the mitomycin analogue **1.85**.

Scheme 1.11. Synthesis of mitomycin analogue **1.85** from enaminone **1.82** by Heck coupling reaction.[68]

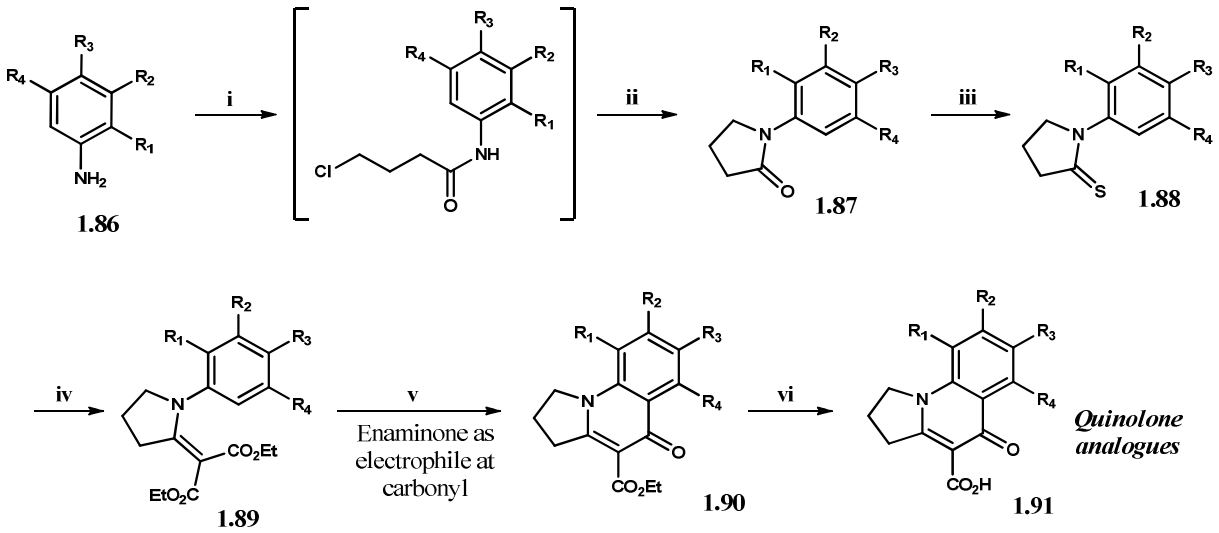


Reagents and conditions: i. $BrZnCH_2CO_2Et$ (from $BrCH_2COEt$, Zn, I_2, THF, ultrasound), THF, reflux, 120 h; ii. $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, Et_3N, DMF, MeCN, H_2O, reflux, 4 h; iii. 10% Pd/C, H_2, EtOH, HCl, r.t., 2 h;

In a 1996 publication, Michael *et al.* made use of the electrophilic properties of the enaminone functionality to synthesize the heterocyclic 2,3-dihydropyrrolo[1,2-*a*]quinolin-5 one core of various quinolone antibacterial analogues **1.91** (*Scheme 1.10*).[73] Here, the lactams **1.87** were once again constructed around the anilines **1.86** using 4-chlorobutyryl chloride. After thionation to thiolactams **1.88**, a modified Reformatsky reaction with the zinc enolate of diethyl bromomalonate was required to provide the enaminones (technically vinylogous urethanes) **1.89**. These were treated with polyphosphoric acid, which induced their

cyclization via an electrophilic aromatic acylation reaction to provide the fused quinolinone structures **1.90**.

Scheme 1.12. Synthesis of quinolone antibiotic analogues **1.91,** annulation by aryl acylation using vinylogous urethane electrophile.[73]



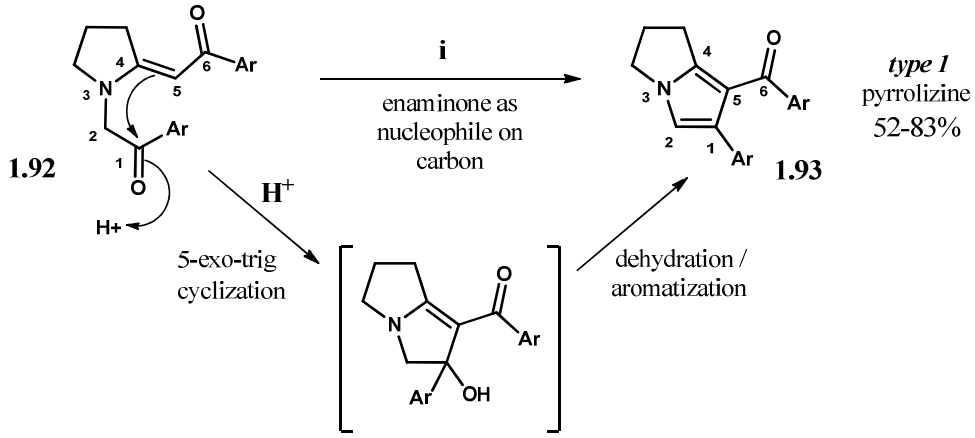
Reagents and conditions: i. $Cl(CH_2)_3COCl$, Na_2HPO_4, CH_3Cl_3; ii. NaOEt, EtOH; iii. P_2S_5,C_6H_6, ultrasound; iv. $BrCH(CO_2Et)_2$, Zn, I_2 (cat.), THF; v. PPA, 85-100C; vi. NaOH, then HCl

With these three short examples we have seen how an enaminone can serve as a nucleophile on carbon or nitrogen *(Scheme 1.10)*, as an alkene that can be hydrogenated or coupled (*Scheme 1.11*), or even as an electrophile at the enaminone carbonyl substituent (*Scheme 1.12*), facilitating annulation reactions to generate heterocyclic functionalities. The enaminones are prepared in good to excellent yields using the Eschenmoser sulphide contraction (*Scheme 1.10*), or, when incompatible, using a modified Reformatsky reaction (*Schemes 1.11* and *1.12*), from the corresponding thiolactams. The precursor lactams are all prepared in good yields, and in a similar fashion, from the corresponding amines, in a cyclization reaction with 4-chlorobutyryl chloride.

1.3.3 The origins of the present project

During work investigating the hydrogenation of *N*-phenacyl enaminones **1.92** (*Scheme 1.13*) using acetic acid as solvent, a former PhD student at Wits, Garreth Morgans, discovered that the acidic solvent system had in fact catalyzed the cyclization of the enaminone precursors **1.92** to what were eventually identified as the pyrrolizine products **1.93**. For reasons that will become apparent, this kind of cyclization pathway will be referred to as "pathway 1".[74,75]

Scheme 1.13. Acid catalyzed cyclization of N-acylmethyl ketone enaminones **1.92** via pathway 1.[74,75]

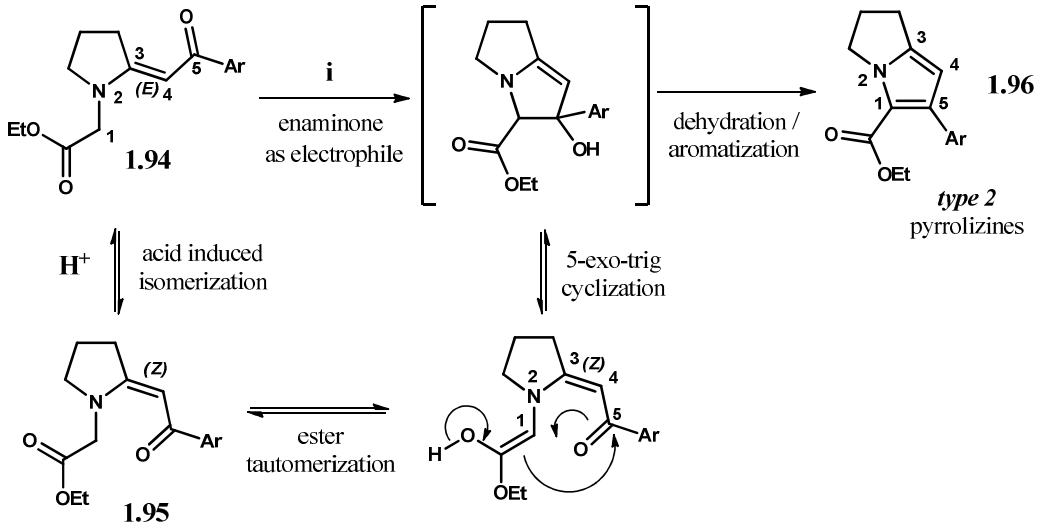


Reagents and conditions: i. AcOH (neat), 40°C or SiO_2, xylene, 90°C.

Upon further investigation it was revealed that this enaminone cyclization was also being catalyzed by the acidity of the silica gel used for chromatographic purification of the enaminone **1.92**. Indeed, further studies showed that this cyclization could be more efficiently facilitated by the use of silica gel as catalyst, especially when heated. Based on the structure of the products **1.93**, it is clear that the reaction is mediated by nucleophilic addition of the enamine vinyl carbon to the electrophilic ketone segment attached to nitrogen, followed by dehydration and aromatization to the pyrrolic core. Upon closer inspection, this outcome is essentially a modified Knorr pyrrole synthesis – one of the most versatile and general routes to pyrrole systems known.[76]

This perhaps obvious observation was then followed by something quite unusual: when the phenacyl substituent on nitrogen was replaced with an ethoxycarbonylmethyl substituent to provide **1.94** (*Scheme 1.14*), and subjected to similar acidic reaction conditions, the enaminone **1.94** indeed cyclized to a pyrrolizine, but the structure indicated a totally different mechanism. In this case the less electrophilic ester did not undergo nucleophilic attack by the enamine vinyl component and instead had itself acted as a nucleophile (presumably via the enol), attacking the electrophilic carbonyl of the enaminone.

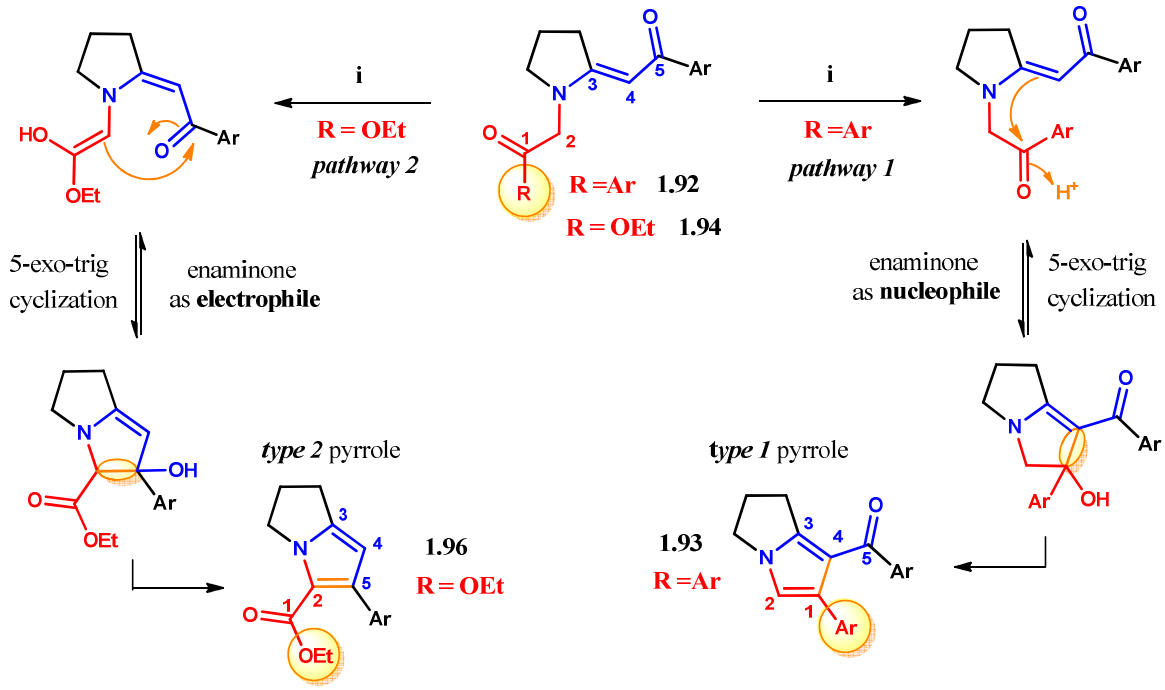
Scheme 1.14. Acid catalyzed cyclization of *N*-ethoxycarbonylmethyl enaminones **1.94** via pathway 2.



Reagents and conditions: i. AcOH (neat), 40 °C or SiO_2, xylene, 90 °C.

For this to occur, the *E*-vinyl moiety of **1.94** must first isomerize to the *Z* isomer **1.95**, a process that is also thought to be catalyzed by the acidic medium, probably through a protonation-deprotonation equilibrium. Thereafter, enolization of the ester allows for a condensation reaction between it and the now proximal enaminone ketone group, giving the unusual product **1.96,** by pathway 2. It thus became apparent that depending on the electronic properties of the acyl-methyl unit on nitrogen, one could readily select for one of the two possible cyclization modes of these enaminone systems (**1.92** or **1.94**) by either taking advantage of their nucleophilicity or their electrophilicity. When using a more electrophilic N-methylene ketone (as in **1.92**) the nucleophilic reactivity of the enamine occurs exclusively. With the less electrophilic ester (as in **1.94**), the enaminone behaves as an electrophile with the N-methylene ester taking on the role of the nucleophile. This provides two reliable methods for fusing pyrrolic rings onto five-membered cyclic enaminones to give otherwise difficult to obtain bicyclic heterocycles **1.93** or **1.96** (*Scheme 1.15*), whilst providing an excellent example of the synthetic power of the ambident functionality of enaminones.

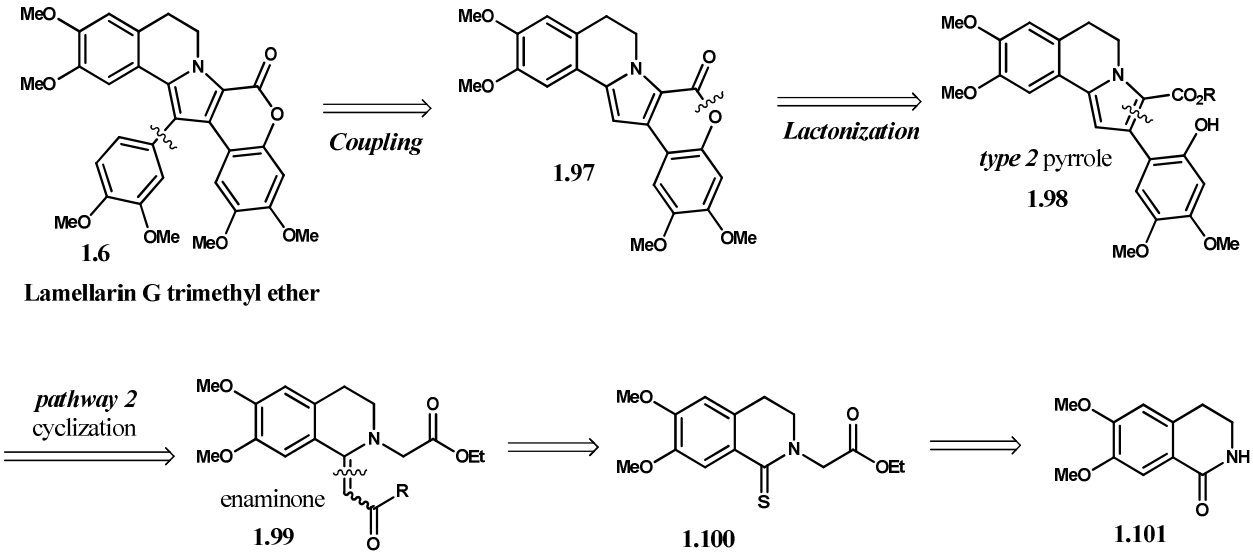
Scheme 1.15. Acid catalyzed cyclization of five membered ring enaminones by pathway 1 or 2, depending on the nature of the N-acylmethyl electrophile substituent.



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

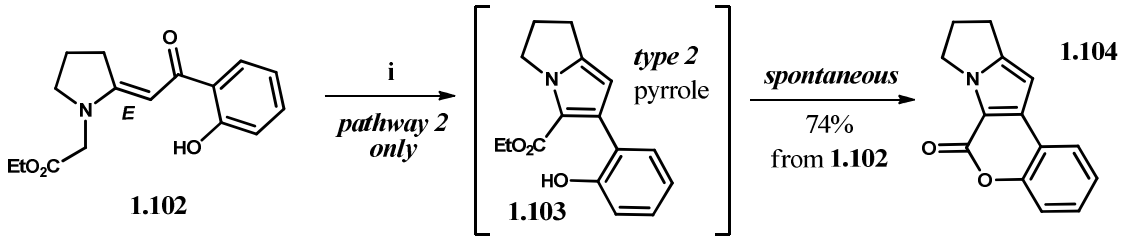
It was soon realized that this methodology had the potential to be useful in the synthesis of lamellarin alkaloids, as shown in *Scheme 1.16*.[74] It was reasoned that enaminones **1.99** should react via pathway 2 to provide type-2 pyrroles such as **1.98,** which could be structurally modified to provide lamellarins such as lamellarin G trimethyl ether (**1.6**).

Scheme 1.16. Proposed retrosynthetic strategy for the synthesis of lamellarin G trimethyl ether (**1.6**) from an enaminone intermediate **1.99**.



Preliminary investigations were carried out using the simple cyclic five-membered ring enaminone **1.102** (*Scheme 1.17*) made from a 2-hydroxyphenacyl precursor. When this compound was cyclized using silica gel as catalyst, Morgans also obtained not only pyrrolizidine formation to **1.103**, but also spontaneous cyclization to produce the lactone **1.104** in a one pot procedure. In what was effectively a single step, the basic enaminone **1.102** could be transformed into the fused chromen-2-one pyrrolizine **1.104**, which is effectively a simplified lamellarin scaffold. Most unfortunately, this methodology failed when applied to analogous systems with larger ring sizes (*Scheme 1.18*). These reactions were plagued by decomposition and, owing to time constraints, this research was left to a later PhD student, Stefania Scalzullo.[77]

Scheme 1.17. Successful one-pot cyclization of five-membered enaminone **1.102** to lamellarin lactone analogue **1.104**.[77]

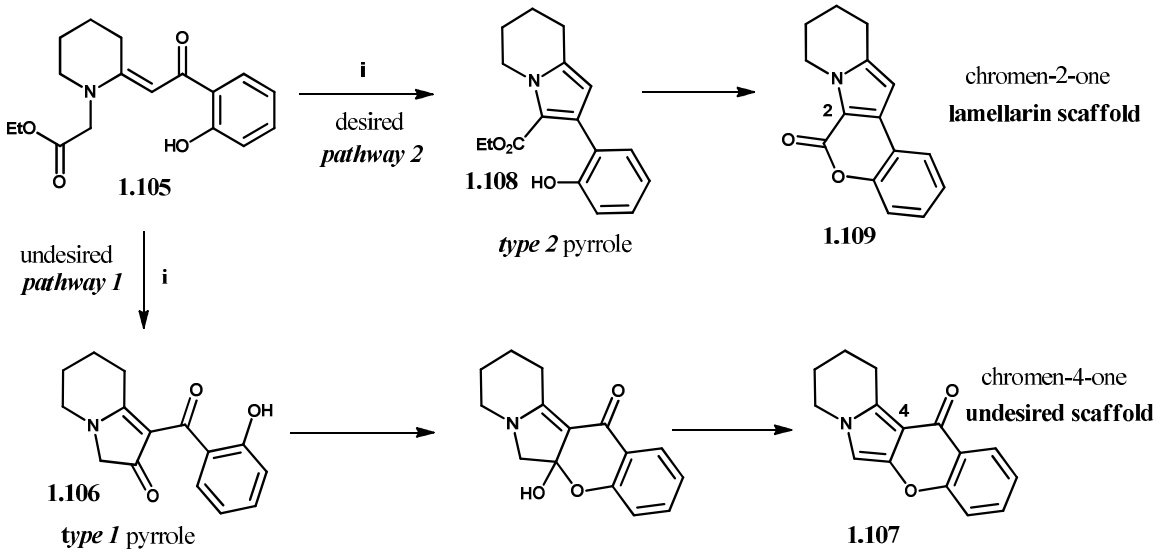


Reagents and conditions: i. Silica gel, xylene, μw (150 W, 180°C, 30 min)

During her research, she was able to replicate the success of the five-membered pyrrolidinone-derived systems, proving that they react in a reliable and predictable manner to give the desired 5-ethoxycarbonyl-6-aryl-2,3-dihydro-1*H*-pyrrolizines **1.96** (*Scheme 1.15*). She also confirmed the desirable concomitant lactone formation with 2-hydroxyphenyl-containing enaminones such as **1.102** to provide tetracyclic lactones such as **1.104** (*Scheme 1.17*). However, further investigations brought to light the peculiar finding that this methodology was not suitable for the ostensibly comparable six-membered-ring analogues like **1.105** (*Scheme 1.18*). The isolation of the pyrrolic chromen-4-one **1.107** conclusively proved that when the ring size was increased to six, the aforementioned reaction pathway 1 begins to contribute once more, with the ester acting as the electrophile and the enaminone vinyl group behaving as a nucleophile to give the intermediate 3-oxo-pyrrole **1.106** (*Scheme 1.16*). This occurred in conjunction with the desired pathway 2, providing the desired indolizine **1.109** (resulting from the ester acting as the nucleophile and the enaminone carbonyl acting as the electrophile) via the desired indolizine **1.108**. There was thus obtained

a mixture of tetracyclic products **1.109** and **1.107**, in yields of 34% and 21% respectively, alongside significant decomposition.[77]

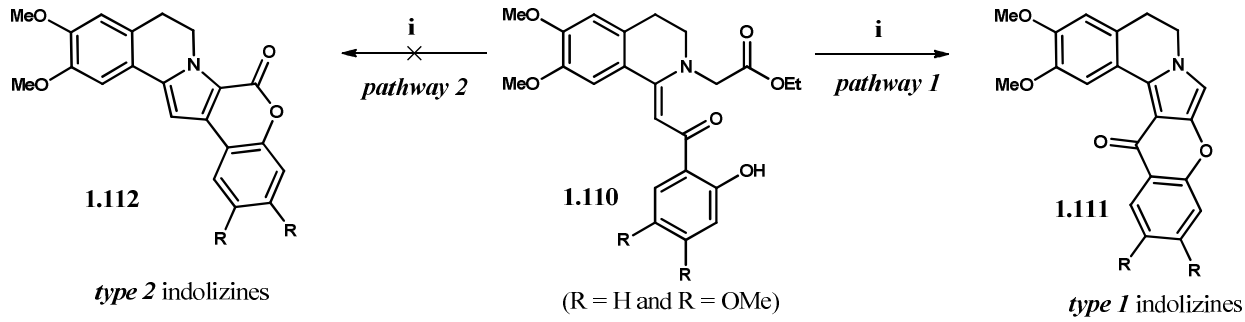
Scheme 1.18. Six-membered enaminone **1.105** cyclizes via both pathway 1 and pathway 2, giving a mixture of products **1.107** and **1.109**.



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

The analogous benzo-fused isoquinoline systems **1.110** (*Scheme 1.19*) required for the construction of the lamellarin scaffold **1.112** behaved similarly to the above mentioned unfused six-membered ring enaminone **1.105** (*Scheme 1.18*). Again, the undesired chromen-4-one product **1.111** of reaction pathway 1 was isolated, in a low yield of 31%, and significant decomposition was noted.[77] This time, no trace of the desired chromen-2-one products **1.112** of pathway 2 was isolated.

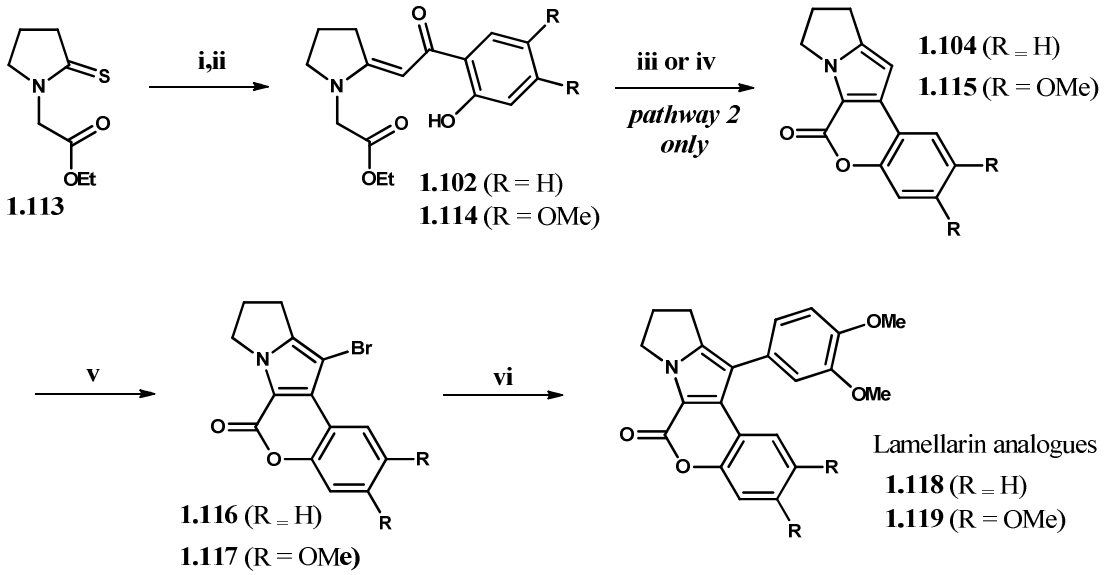
Scheme 1.19. Isoquinoline enaminones **1.110** cyclize via pathway 1 to provide the undesired type-1 products **1.111**.



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

Although interesting, the failings of this methodology when applied to these larger ring sizes prevented the completion of the synthesis of the desired lamellarin alkaloids. Scalzullo had shown that the cyclization methodology discovered by Morgans (*Scheme 1.14*) was not applicable to six-membered ring enaminone analogues, though she was able to go on to successfully apply the methodology to the simple five membered pyrrolidone-derived enaminones **1.102** and **1.114** (*Scheme 1.20*), which reacted reliably and exclusively via pathway 2 to provide lamellarin analogues **1.118** and **1.119** respectively. The project had unfortunately failed to produce a successful synthetic route to the actual isoquinoline lamellarin scaffold, and this was the state of the project when I inherited it.

Scheme 1.20. Successful application of enaminone cyclization methodology to five membered enaminones by Scalzullo.[77]



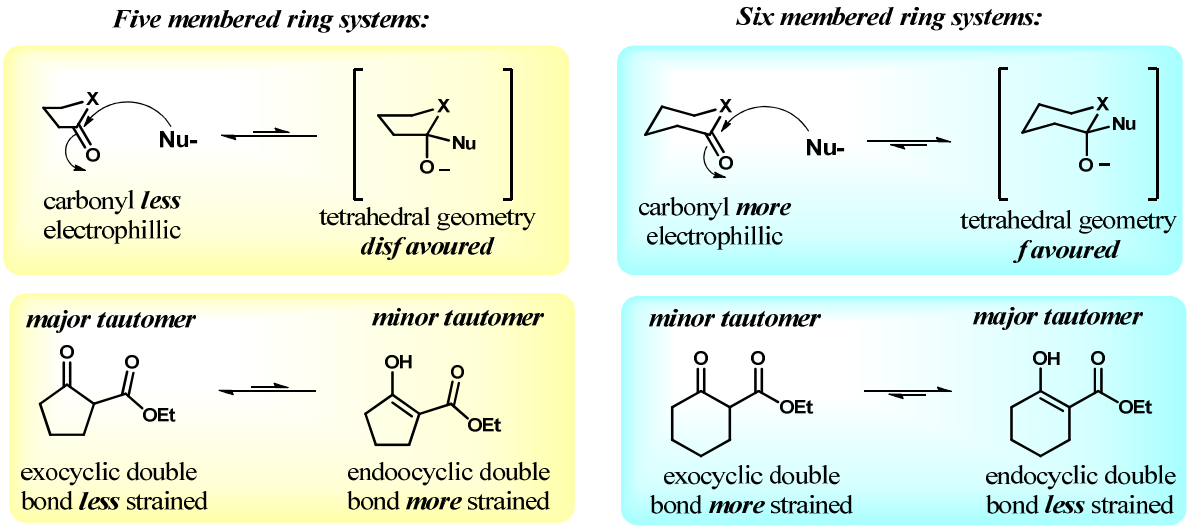
Reagents and conditions: i. Phenacyl iodide, MeCN; ii $P(OEt)_3$, Et_3N, MeCN; : iii. Conventional. Silica gel, xylene, reflux, 18 h; iv. Microwaves., Silica gel, xylene, 200 °C, 150 W, 15 min. v. NBS, DMF, 0 °C - rt, 18 h; vi. $Pd(PPh_3)_4$, $PhB(OH)_2$, (Na_2CO_3 or Cs_2CO_3), DME and EtOH or DMF, conventional (rt-reflux, 20 h) or microwave (150 W, 150 °C, 15 min).

1.3.4 Rationalizing the results of past projects.[74,77]

One can come up with a possible theoretical basis for the differences in behaviour of the five- and six-membered ring systems that was observed during previous investigations.[74,77] The electrophilicity of the ester (*Scheme 1.18*) is no different in the six-membered ring cases as compared to that of the five-membered ring analogue (*Scheme 1.17*). Instead, the change in ring size is thought to increase the nucleophilicity of the enamine carbon. This difference in reactivity between five- and six-membered rings can be explained quite elegantly as being a

consequence of an old but somewhat forgotten thermodynamic phenomenon. In a 1953 *JACS* paper H. C. Brown presented the first published analysis of the differing stabilities of exocyclic and endocyclic double bonds in five- and six-membered ring systems.[78] In this work he reviewed an impressive variety of different five- and six-membered ring systems possessing endocyclic or exocyclic double bonds, and built strong evidence that there is a universal stabilization of endocyclic double bonds for six-membered rings over exocyclic ones. Contrary to this, five-membered ring systems favour exocyclic double bonds over endocyclic ones (*Figure 1.7*).

Figure 1.7. Reactivity differences between five and six membered ring systems.[78]

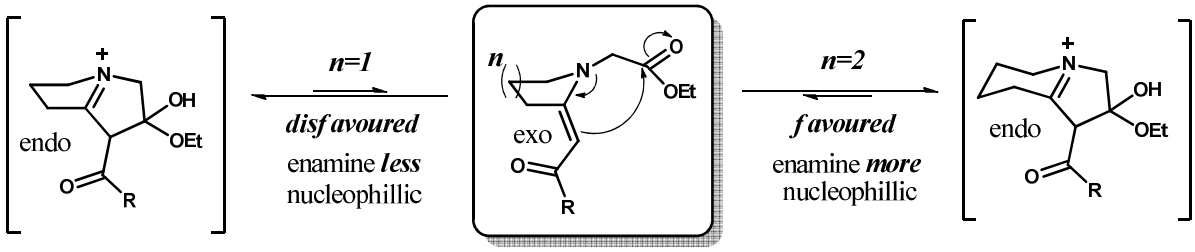


This effect is thought to arise because the more strained five-membered ring systems strongly disfavour the strained tetrahedral geometry associated with breaking exocyclic double bonds and simultaneously disfavour the formation of strained endocyclic double bonds. In other words, endocyclic double bonds (i.e., two bond angles of approximately 120°) are comparatively unfavourable for five membered rings because they impart increased strain in these smaller systems. Endocyclic double bonds are comparatively more stable for six-membered rings because in these systems endocyclic steric hindrance is less and thus the ring can efficiently accommodate unsaturation without strain. For these six membered rings exocyclic double bonds interfere with the stable chair-type conformations, giving an overall favourability for endocyclic unsaturation over exocyclic unsaturation. These results are summarised in this paper in the following generalization:

> "Reactions will proceed in such a manner as to favour the formation or retention of an *exo* double bond in the five-ring and to avoid the formation or retention of the *exo* double bond in the six-ring systems."[78]

This can be applied to enaminone systems, explaining the apparent increased nucleophilicity of the enamine component of six membered ring systems as compared to five membered rings (*Figure 1.8*).

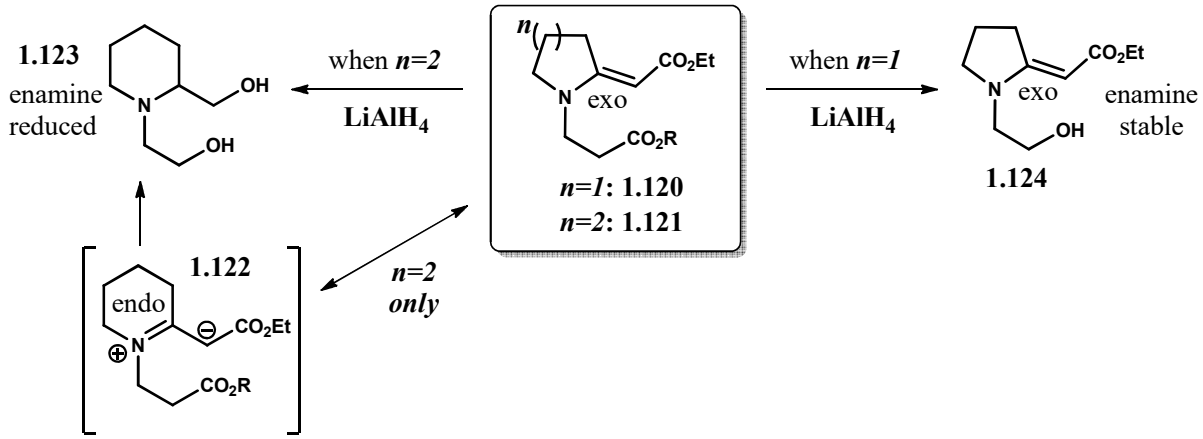
Figure 1.8. Favourability of pathway 1 cyclization of six membered enaminones explained using Brown's hypothesis.[78]



This explanation for the differing reactivities of these systems seems to have been overlooked by the general scientific community, though it provides a crucial stepping-stone to the solution of this and many other reactivity problems related to lamellarin syntheses. In fact, this simple thermodynamic property will be a major theme in this thesis, capable of explaining an impressive number of otherwise peculiar observations.

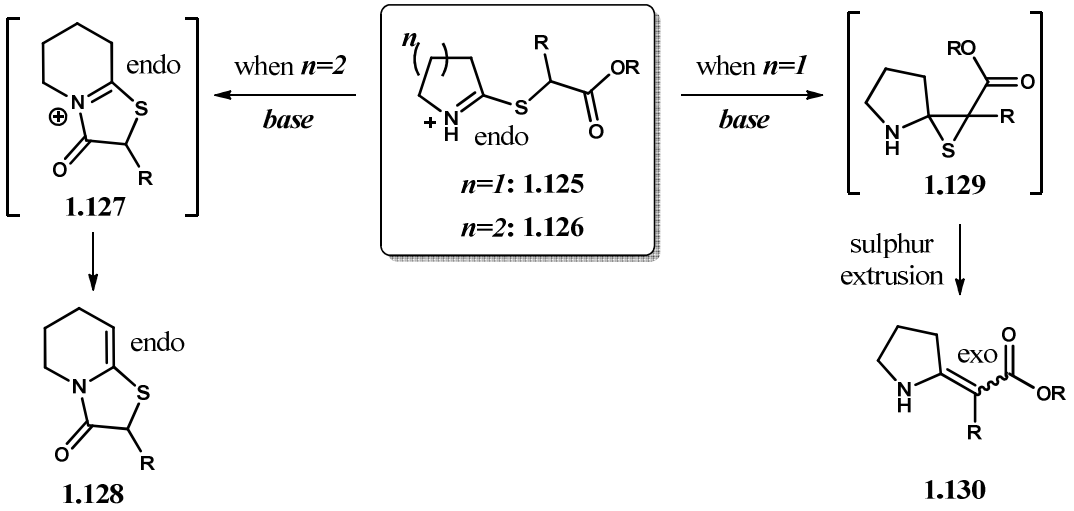
There are rather few literature examples of reactivity differences between five- and six-membered ring enaminones and related systems. Previous work from our own laboratories has provided at least two relevant examples. For example, the already mentioned stability of five-membered vinylogous urethane enaminones to reduction with lithium aluminium hydride ($LiAlH_4$), (*Scheme 1.10*), has been shown not to be true of their six membered counterparts (**1.121**, *Scheme 1.21*).[60] Instead, it is believed that the increased tendency of formation of the endocyclic unsaturated imines such as **1.122** favours the reduction of this mesomer by $LiAlH_4$ to provide completely reduced products **1.123**. This kind of mesomerism is disfavoured for five-membered systems **1.120** because the retention of the more stable exocyclic vinyl bond is favoured, ultimately giving enaminone products **1.124** which are unsaturated exo to the five-membered ring.

Scheme 1.21. Stability differences between five and six membered vinylogous urethanes explained using Brown's hypothesis.



During the preparation of enaminones (*Scheme 1.22*)[79,80] from intermediate thioethers **1.125** and **1.126,** the five-membered exocyclic enaminones **1.130** are obtained in moderate to excellent yields, while the six-membered analogues were only obtained in trace amounts. Instead, the six-membered intermediates **1.126** formed thiazolone compounds such as **1.128** as the major products of the reaction; a consequence of the favourability imparted by the retention of the endocyclic double bond that is characteristic of six membered ring systems.

Scheme 1.22. Reactivity differences of five and six membered enaminone intermediates explained using Brown's hypothesis.



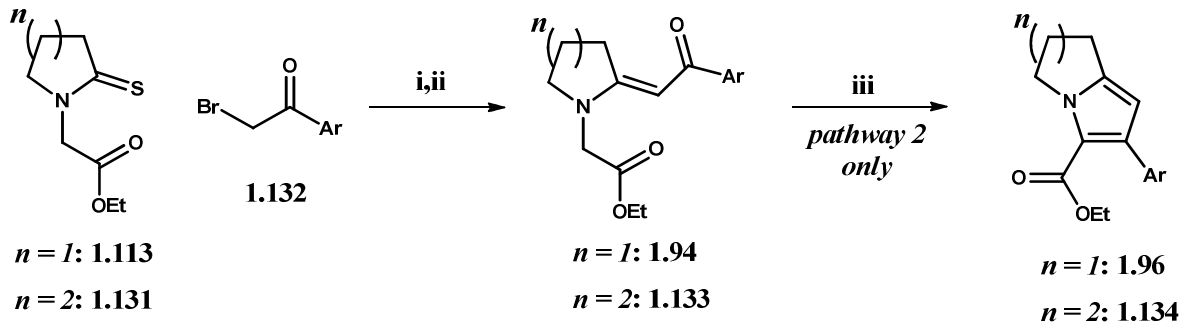
1.4 Aims and objectives for this project

The current project was devised to further explore the interesting, though unfortunate, limitations of the enaminone approach to synthesizing lamellarin analogues and related heterocycles. It was evident that the above mentioned strategy was only reliable for the five-

membered pyrrolidinone-derived enaminones **1.94** *(Scheme 1.23)*, and extension of the methodology to enaminones of different ring sizes, particularly the 3,4-dihydroisoquinoline systems **1.110** (*Scheme 1.19)* appropriate for the Type-I lamellarins, proved woefully unsuccessful. This project was thus conceived as having two halves. The first major goal was to expand upon the scope of this methodology that had been developed by Morgans and Scalzullo, with the intention of solving the problems associated with extension to higher order ring sizes. The second goal was to develop novel methodology that would provide a successful enaminone based approach for the synthesis of the lamellarin alkaloids.

1. The first aim is to explore the scope of the newly discovered enaminone cyclization reaction of simple pyrrolizine (***n* = *1***) systems (*Scheme 1.23*):

Scheme 1.23. Expanding the scope of the methodology developed by Morgans and Scalzullo.[74,77]



***n* = *1*: 1.113**
***n* = *2*: 1.131**

***n* = *1*: 1.94**
***n* = *2*: 1.133**

***n* = *1*: 1.96**
***n* = *2*: 1.134**

Reagents and conditions: i. Eschenmoser sulphide contraction: Phenacyl bromide/iodide, MeCN; ii. PR_3, Et_3N, MeCN; iii. Microwaves, silica gel.

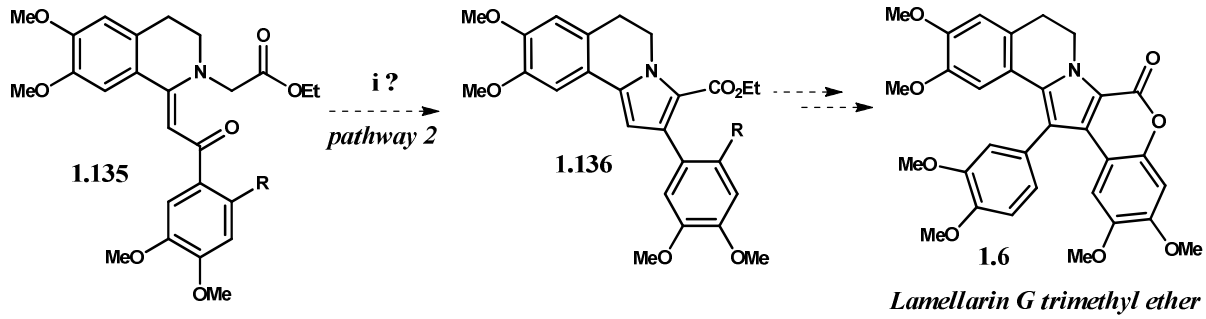
The cyclization methodology discovered and developed by Scalzullo and Morgans had already been proven effective for the five-membered (***n* = 1**) pyrrolizine systems. We intend to further the scope of this reaction by synthesizing an array of substituted pyrrolidinone-derived enaminone systems **1.94** to test this methodology. In doing so, we hoped to better understand the scope and limitations of the novel cyclization reaction when applied to a variety of aryl and heteroaryl substituted enaminones, testing the applicability of the reaction as a general route to pyrrolizines **1.96**. These investigations will be described in detail in Chapter 2.

2. The second aim is to investigate the limitations of the related six-membered enaminone precursors (***n* = 2**, *Scheme 1.23*), which are intended to produce indolizine systems **1.134**.

These six-membered ring enaminones **1.133** had been shown to exhibit dual reactivity by pathway 1 and pathway 2. We intended to investigate whether or not the reaction outcomes of these systems could be better understood and improved upon; to eventually obtain a method that was selective for the desired pathway 2 products **1.134**. These results will also be reported in Chapter 2.

3. The third, and major, aim is to expand our investigations to include the benzo-fused isoquinoline derived systems relevant to the lamellarins (*Scheme 1.24*).

Scheme 1.24. Proposed route to lamellarin alkaloids.



Reagents and conditions: i. Microwaves, Silica gel

These systems had been shown by Scalzullo and Morgans to behave similarly to the unfused six membered indolizine systems, cyclizing by both pathway 1 and pathway 2. We hoped to further explore the reactivity of these systems in an attempt to successfully develop a route to indolizines such as **1.136** *(Scheme 1.24)***,** and eventually the basic lamellarin model system, lamellarin G trimethyl ether (**1.6**). These investigations, the main features of which we have already published,[81–83] are discussed in Chapters 3 and 4.

4. The fourth aim was conceived after the timeous success of those mentioned above. It included the application of our synthetic route to the naturally occurring lamellarins, particularly one of the six most potent of the series (*Figure 1.5, page 8*).

Furthermore, we intended to produce the first multi-gram scale quantity of one of these lamellarins. Our results, the main findings of which have been published, [81–83] are presented in Chapters 4 and 5.

Chapter 2: Model Studies on the Conversion of Enaminones into Pyrrolizines and Indolizines

2.1 Cyclization of five-membered ring enaminones to pyrrolizines

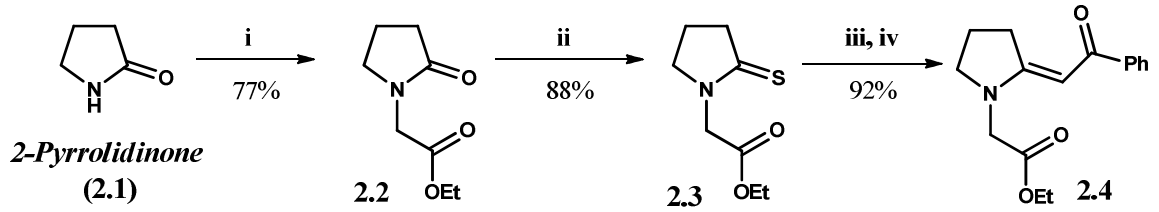
As an introductory endeavour, our initial aim was to better understand the acid-catalyzed cyclization of the five membered (*N*-acylmethylpyrrolidine) enaminones to pyrrolizines. Initially, we planned to investigate the role of the acid catalyst and thereafter explore the substrate scope of the reaction for five-membered ring systems. Thereafter, we planned to further investigate the observations made by Scalzullo and Morgans that showed that when the methodology was extended to six-membered ring systems, the reaction failed to yield pathway 2 products selectively. The eventual goal of these investigations was to eventually apply what was learned to the synthesis of the lamellarin alkaloids.

2.1.1 Synthesis of (*E*)-pyrrolidinyl enaminones

We began by studying the simple five-membered pyrrolidinone-derived ring systems that were known to react reliably. The synthesis of the parent enaminone (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)pyrrolidin-1-yl]acetate (**2.4**) was straightforward (*Scheme 2.1*). Treatment of 2-pyrrolidinone (**2.1**) with sodium hydride in tetrahydrofuran facilitates the deprotonation of this secondary lactam to the corresponding sodium salt, which precipitates from solution as a white solid. Subsequent treatment with ethyl bromoacetate then results in the solubilization of this salt as the N-alkylated product **2.2** is formed in combination with insoluble NaBr.[84] After chromatographic purification, ethyl 2-(2-oxopyrrolidin-1-yl)acetate (**2.2**) was obtained in 77% yield. It was then thionated using Lawesson's reagent in toluene, which was heated to 80 °C overnight. After 16 hours, TLC analysis showed the reaction to be complete and chromatographic purification provided the thiolactam ethyl 2-(2-thioxopyrrolidin-1-yl)acetate (**2.3**) in 88% yield as a yellow oil. Standard Eschenmoser sulphide contraction conditions were then used to convert thiolactam **2.3** into enaminone **2.4.** First, treatment of thiolactam **2.3** with 1.2 equivalents of phenacyl bromide (2-bromo-acetophenone) in acetonitrile gave complete formation of the intermediate thioether salt after 18 hours. Once TLC showed no trace of remaining thiolactam **2.3**, 1.2 equivalents of triphenylphosphine and triethylamine were added to induce the formation of enaminone (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)pyrrolidin-1-yl)acetate] (**2.4**), which was isolated in 92% yield after

chromatographic separation. The yields for these processes were all in close agreement with results previously reported by the Wits group.[74,77]

Scheme 2.1. Synthesis of five-membered (pyrrolidinyl) enaminone model system.



Reagents and conditions: i. NaH (60%), ethyl 2-bromoacetate, THF, rt, 20 h; ii. Lawesson's reagent, toluene, 80 °C, 20 h; iii. phenacyl bromide, MeCN; iv. $P(Ph)_3$, Et_3N, MeCN.

Characterization data for these materials all matched those obtained by Morgans and Scalzullo.[74,77] The successful installation of the *N*-ethoxycarbonylmethyl substituent of **2.2** was clear in the ^1H NMR spectrum, which showed the distinct methylene CH_2 singlet at 4.06 ppm, and a quartet and triplet at 4.19 ppm and 1.28 ppm respectively, as expected for the ethyl component of the ester. The coupling constants for these signals were both measured to be 7.0 Hz, confirming their mutual attachment. Integration of these peaks further confirmed that this ethyl ester group had been successfully installed. The ^{13}C NMR spectrum showed both expected carbonyl signals at 175 ppm for the ester carbonyl and 168 ppm for the lactam carbonyl.

Proving the successful thionation of lactam **2.2** to thiolactam **2.3** is straightforward. Thiocarbonyls possess very distinctly downfield ^{13}C=S nuclear resonances which typically exceed 200 ppm.[54] This observation may seem peculiar considering the fact that the more electronegative oxygen-containing carbonyl ^{13}C=O nuclei are measured at considerably lower resonant frequencies. However, the C^{13}=X (X = O, S) resonance is so uniquely downfield because of the structure of unsaturated π bonds.[85, 86] For unsaturated systems, it is the shape of the π bond that gives these molecules unusual magnetic properties. In response to the external magnetic field, circular electrical currents are generated within the π bond. These circular currents then generate their own secondary magnetic fields which, in certain regions within the molecule, add on to the magnetic field of the instrument, producing local regions of increased magnetic field strength, referred to as magnetic anisotropy (non-uniformity within the magnetic field).[85,86] The electron density of these π-bonded systems is thus directly proportional to the degree of observed anisotropy and, as such, heteroatom-containing π systems such as carbonyls and thiocarbonyls are most affected, with the less electrophilic but

more electron rich thiocarbonyls located considerably downfield of their carbonyl counterparts, because their less electrophilic nature allows for less resistance to current flow (and thus a larger degree of anisotropy). As expected, both the ^{1}H and ^{13}C NMR spectra of the thiolactam **2.3** showed specific downfield shifts of nuclei closest to the C=S moiety when compared to their C=O counterparts in the precursor lactam **2.2**. The ring CH_2 ^{1}H nuclei directly adjacent to the thiocarbonyl showed a distinct downfield shift of around 0.6 ppm. The most characteristic difference is observed in the ^{13}C NMR spectrum, where the thiocarbonyl signal is measured at 203 ppm, a 35 ppm increase compared to that measured for the precursor lactam **2.2** at 168 ppm.

The ^{13}C NMR spectrum of enaminone **2.4** confirmed the installation of the characteristic enaminone carbonyl (C=O) detected at 188 ppm, in combination with the pre-existing ester (CO_2Et) at 168 ppm. The successful formation of enaminone **2.4** was clearly evident in the ^{1}H NMR spectrum, which showed two aromatic signals at 7.8 ppm (2H) and 7.2–7.3 ppm (3H), proving the successful installation of a monosubstituted phenyl ring (see *Figure 2.1a*). A distinct ^{1}H singlet at 5.6 ppm is characteristic of the enaminone vinyl C(4) ^{1}H nucleus.[87] The simple acetophenone-derived enaminones such as **2.4** all possess a distinct vinyl proton resonance at 5.5 ppm ±0.2 ppm, and this signal can be used as a reference from which the other ambiguous peaks can be assigned, using NOESY or COSY experiments. NOESY is most convenient, as it can also be used to prove the assigned geometry of the system (see *Figure 2.1b*). The NOESY spectrum of the enaminone product **2.4** confirmed the assigned (*E*) geometric configuration by showing a weak, but distinct, correlative interaction between the distinctive enamine vinyl proton C(4)H singlet at 5.59 ppm and the methylene C(5)H_2 singlet of the nitrogen-bonded moiety at 3.99 ppm (*Figure 2.1b*). No interaction between either CH_2 triplet of the pyrrolidinone ring was observed, as would be expected for the (*Z*) geometric isomer. An additional small through-space interaction between this vinyl proton and the CH_2 pentet at 2.01 ppm was observed and was a consistent feature of the NOESY spectra obtained for related five-membered ring enaminones. This interaction between protons that appear orthogonal in two-dimensional molecular representations is well known and is, in fact, characteristic for such five-membered rings.[88] The interaction is due to the distortion from planarity of five-membered rings, which brings protons in relative (1,3)-*cis* positions into close proximity, and is thus commonly referred to as a (1,3)-*cis* coupling relationship.[88] Though this effect cannot be used as evidence for the assigned geometry of these molecules, it is nonetheless an interesting and consistent feature.

Figure 2.1. ^{1}H 42NMR spectrum of enaminone **2.4**.

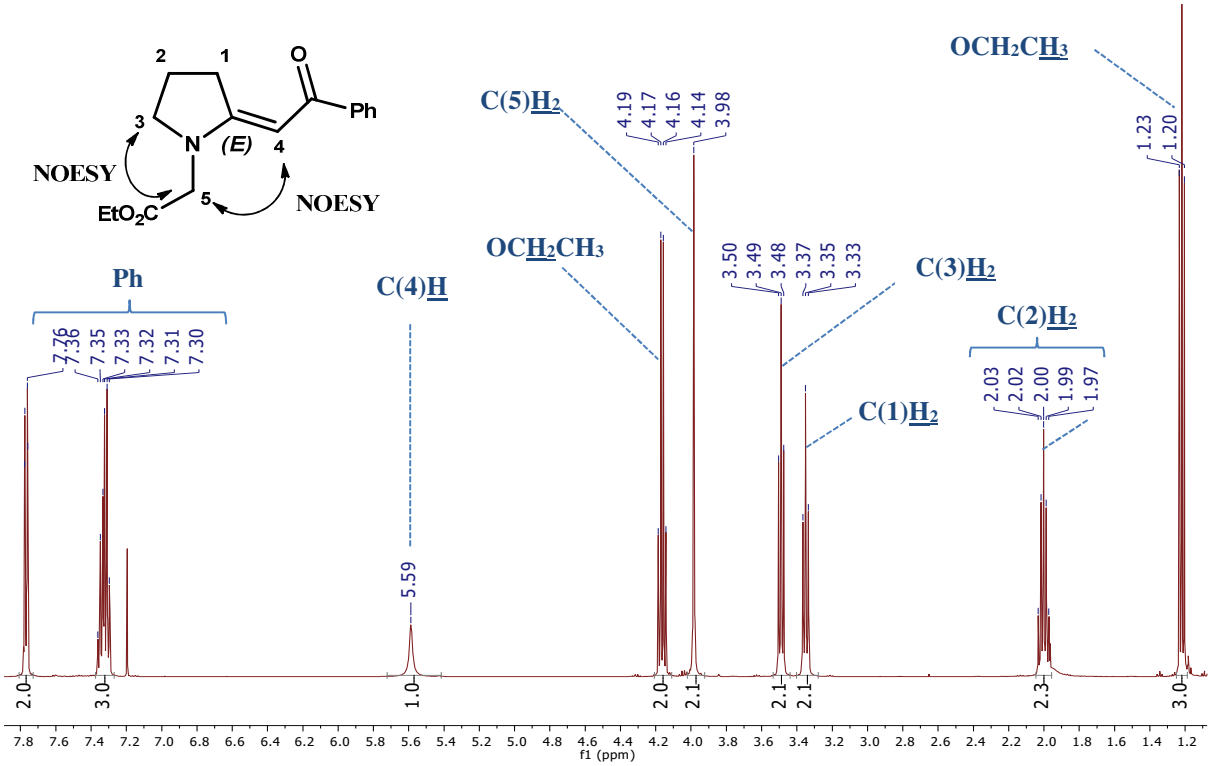
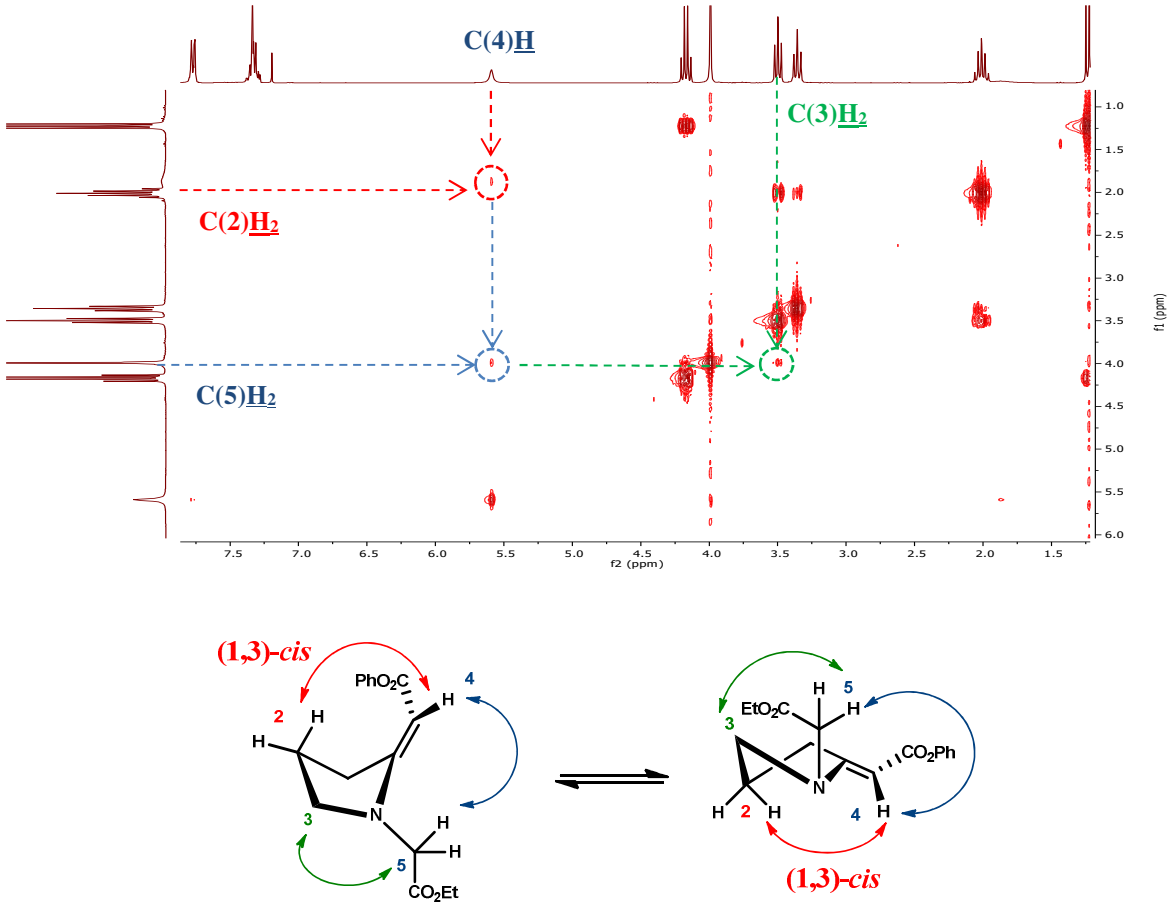


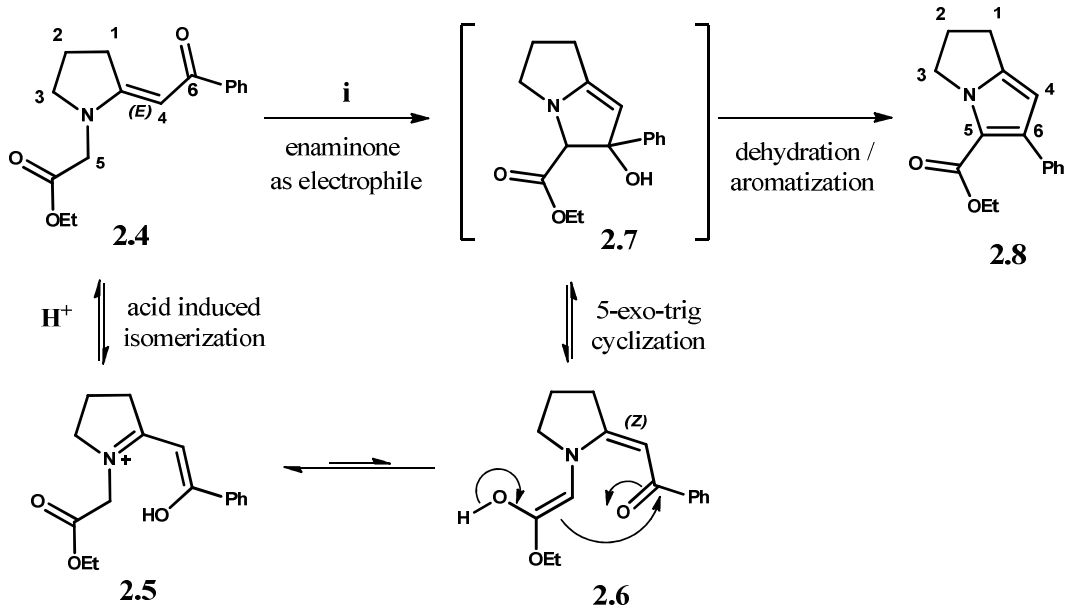
Figure 2.1b. Structural elucidation of enaminone **2.4** using NOESY spectrum, showing "(1,3)"-*cis* coupling.



2.1.2 Establishing the optimal conditions for the cyclization reaction

With the simple enaminone **2.4** in hand, it was used as a model system in determining the optimal conditions for inducing its cyclization to pyrrolizine **2.8** (*Scheme 2.2*).

Scheme 2.2. Acid catalyzed cyclization of enaminone **2.4** to pyrrolizine **2.8.**



Reagents and conditions: i. See *table 2.1* for reaction conditions explored.

We began by replicating the method developed by Scalzullo.[77] The enaminone **2.4** was dissolved in xylene, to which was added 5 mass equivalents of silica gel (relative to the starting enaminone). The reaction mixture was heated in a sealed microwave tube, under 150W of microwave irradiation, with a maximum temperature limit set to 180°C (although the actual internal temperature only reached around 150°C). After just 3.5 minutes, the reaction was complete as judged by TLC, and the residue was chromatographed to provide the desired pyrrolizine **2.8** in an excellent yield of 92%. As a prudent measure we then tested the reliance of the reaction on the acid catalyst by subjecting enaminone **2.4** to identical reaction conditions, but excluding the addition of the acid. As expected, we failed to isolate any trace of pyrrolizine **2.8**, even after extended reaction times. Indeed, heating the enaminone **2.4** in a variety of non-acidic solvents failed to give any trace of the expected pyrrolizine **2.8** or any other by-products in the absence of an acid catalyst (*Table 2.1*). We then began investigating the potential for other, more conventional, acids to facilitate the reaction. Interestingly, strong Bronsted and Lewis acids were consistently shown to be unable to induce any cyclization whatsoever. These solutions were stable at room temperature and

would simply decompose when heated. This was true even when diluted solutions of these strong acids were used. TLC analysis showed baseline spots for these reactions, and even complete conversion of the enaminone to baseline material when quantitative amounts of strong acid were added. After neutralization of the acid, the enaminone's chromatographic behaviour would return to normal. This implied that when strong acids are used, the enaminone is perpetually locked in the protonated salt form **2.5** (*Scheme 2.2*). This effect was particularly prominent when a solution of the enaminone was exposed to the strongly acidic Amberlyst-15 proton exchange resin, which is essentially a form of solid-bound sulphuric acid.[89] Within minutes, all of the dissolved enaminone disappeared from solution and was undetectable by TLC or NMR. All of the dissolved enaminone had apparently been rapidly adsorbed onto heterogeneous acid material as **2.5**, and subsequent treatments of the solid resin with aqueous bicarbonate solution rapidly liberated the unchanged and still pure enaminone **2.4**.

The weak organic acid acetic acid was the only one that was capable of facilitating the desired transformation, providing the pyrrolizine **2.8** in a good yield of 72%. The stronger analogue trifluoroacetic acid gave no reaction and instead appeared to protonate the enaminone irreversibly to **2.5**. Another weak heterogeneous acid, Montmorillonite K10 acid clay, was also shown to be an effective catalyst for the reaction, albeit at a reduced rate compared to silica. This material is also a type of silicate with some alumina inclusions. Our investigations indicated that whilst an acid was indeed required, it needed to be sufficiently weak to allow the deprotonation of the intermediate cation **2.5** to form the transient intermediate *Z*-enaminone isomer **2.6**, leading to concomitant formation of pyrrolizine **2.8**. Silica was shown to be the cheapest and most efficient candidate for the transformation, particularly when heated using microwave irradiation and in a non–polar solvent such as xylene. The combination of a non-polar solvent with a polar heterogeneous catalyst is well known to be particular effective for many microwave irradiated chemical reactions.[90,91] This is believed to be a consequence of the polar material (in our case silica) selectively absorbing the microwave energy and thus heating substantially. The non-polar solvent acts to dissipate the heat generated on the silicate surface, without absorbing significant quantities of microwave energy itself. Since the heterogeneous boundary at the silicate surface is the site of the reaction, only the reaction material in contact with the silicate surface experiences the relatively extreme conditions generated there, and the remaining bulk of the reaction material is held at a milder temperature by the non-polar, non-absorbent solvent.

Table 2.1. Optimization attempts for acid-catalyzed cyclization of enaminone **2.4** to pyrrolizine **2.8**

Acid catalyst	Solvent	Temperature*	time	Yield of 2.8
none	DMF	150 °C	10 min	**0**[a]
	xylene	150 °C	10 min	**0**[a]
	ethanol	100 °C	10 min	**0**[a]
$AlCl_3$	DCM	r.t.	18 h	**0**[a]
		50 °C	10 min	**0**[b]
$BF_3(OEt_2)$	DCM	r.t	18 h	**0**[a]
		50 °C	10 min	**0**[b]
	neat	r.t	18 h	**0**[b]
HCl	Neat (32% in H_2O)	r.t	10 min	**0**[c]
		r.t	18 h	**0**[b]
		50 °C	10 min	**0**[b]
	EtOH	r.t	10 min	**0**[a]
		r.t	18 h	**0**[a]
		100 °C	10 min	**0**[b]
MsOH	neat	r.t	10 min	**0**[c]
		r.t.	18 h	**0**[b]
		50 °C	10 min	**0**[b]
TFA	DCM	r.t.	18 h	**0**[a]
	neat	r.t.	18 h	**0**[b]
Acetic acid	neat	r.t.	18 h	**0**[a]
		140 °C	10 min	**72**
Amberlyst 15	DCM	r.t.	24 h	**0**[c]
		50 °C	10 min	**0**[c]
Montmorillonite K10	xylene	r.t.	18 h	**0**[b]
		150 °C	10 min	**84**
Silica gel	xylene	r.t.	18 h	**0**[a]
		150 °C	4 min	**92**
	toluene	140 °C	8 min	**90**

* Heating was facilitated using microwave irradiation (50W) of the sample to the specified temperature. ***a:*** no reaction with no decomposition; ***b:*** decomposition observed; ***c:*** irreversible protonation to **2.5** (*Scheme 2.2*).

Conversion of enaminone **2.4** into the pyrrole **2.8** causes two major spectroscopic changes in the material. The distinct CH_2 singlet of the N-methylene group typically found at 4.0 (±0.2) ppm, corresponding to the protons on C5 (*Scheme 2.2*), disappears as this carbon becomes incorporated into the pyrrole ring as a quaternary nucleus. The second significant distinction is that the characteristic vinyl proton found at 5.5 ppm for the enaminone **2.4** is shifted downfield to 5.95 ppm, consistent with the generated aromaticity of a pyrrole ring. Indeed, all protons sufficiently close to the generated pyrrole ring experience a significant deshielding effect because of the concomitant increase in electron withdrawal from the nitrogen electron reservoir into the aromatic ring, since the nitrogen lone pair density is required within the ring for the stabilizing effect of aromaticity. There is one unique exception to this deshielding phenomenon: the triplet at 2.86 ppm (*Figure 2.2a*). This triplet corresponds to the CH_2 group in position C1, as proven by the positive COSY correlation detected with the distinct pyrrole CH at 5.95 ppm on C4 (*Figure 2.2b*), which is significantly shielded from its position at 3.55 ppm in the parent enaminone **2.4**. The reason this proton group experiences a net shielding effect is thought to be due to the loss of an anisotropic deshielding effect of the enaminone carbonyl functionality at C6 (*Scheme 2.2*), which is lost during cyclization to form the pyrrole ring. Thus, this proton should experience a decrease in electron density associated with aromatization, but its precessional frequency is still decreased because this effect is weaker than the anisotropic deshielding effect with the enaminone carbonyl that has been lost. The ester triplet and quartet typically remain at almost identical resonances whilst aromatic ring resonances of the aryl group are typically slightly decreased. The ester carbonyl was confirmed in the ^{13}C NMR spectrum at 161 ppm (*Figure 2.2b*).

Figure 2.2a. ^{1}H NMR spectrum for pyrrolizine **2.8**.

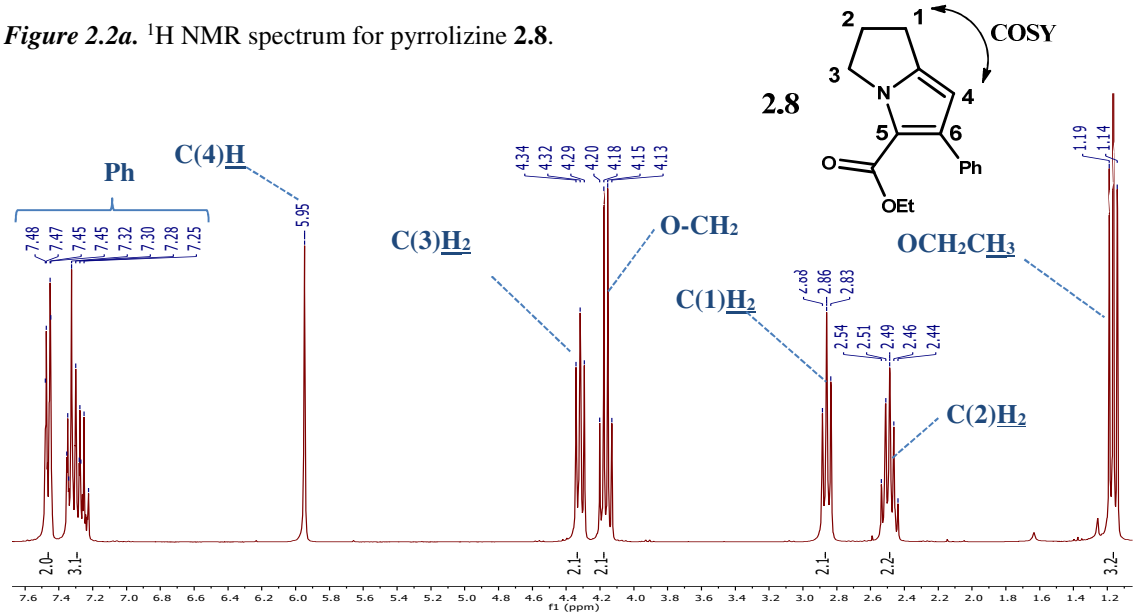


Figure 2.2b. ^{13}C NMR spectrum for pyrrolizine **2.8**.

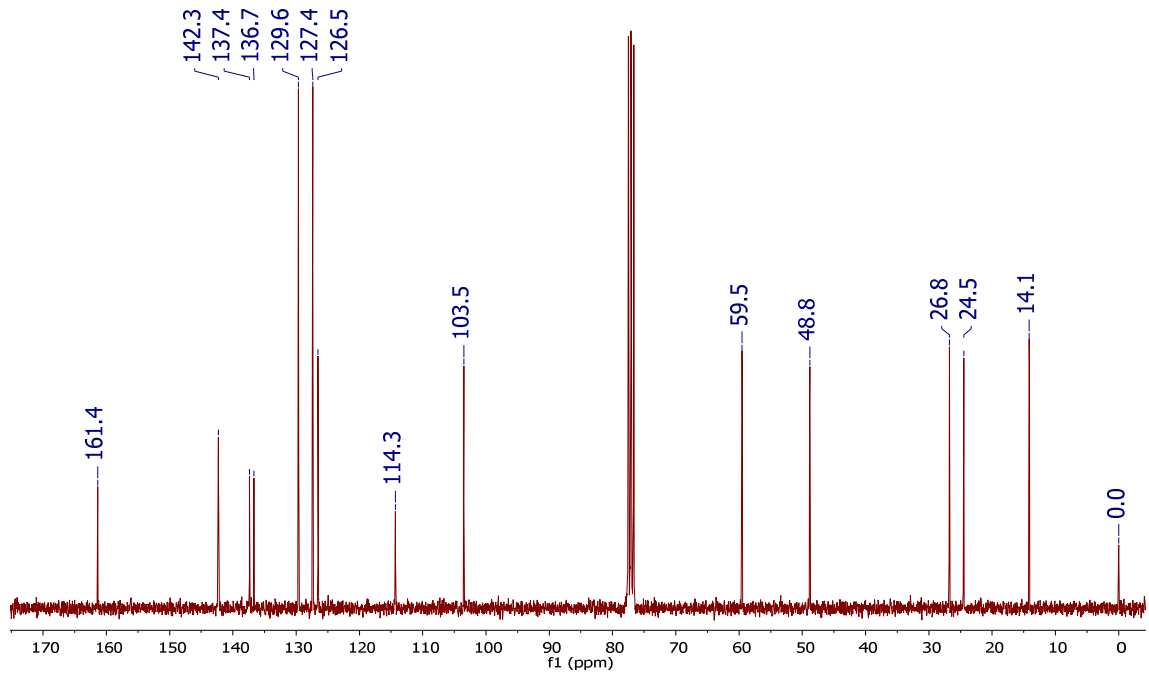
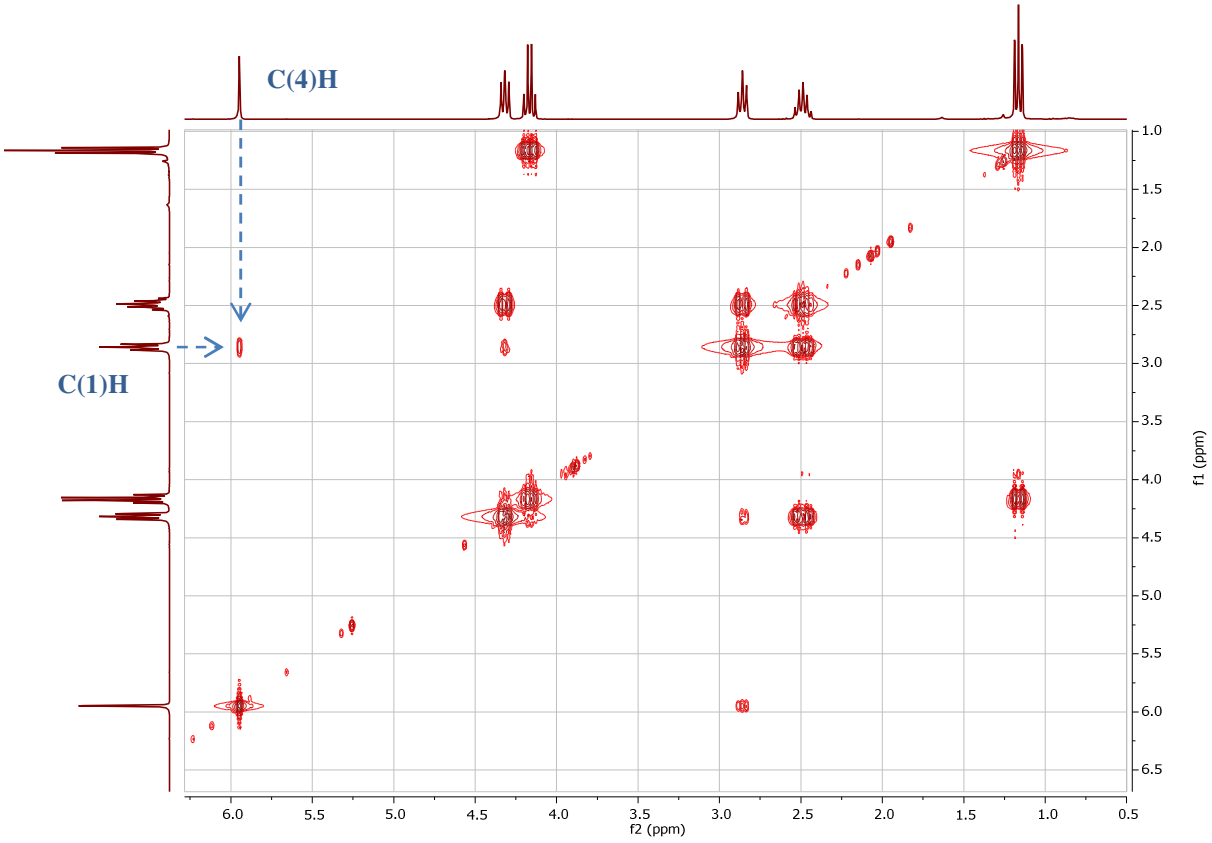


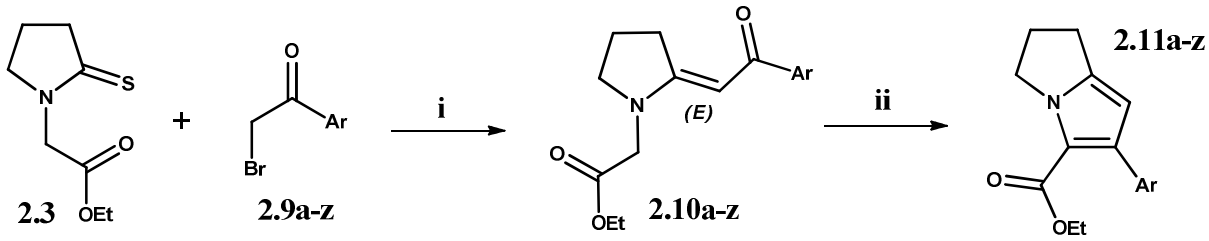
Figure 2.2c. COSY NMR spectrum for pyrrolizine **2.8**.



2.1.3 Exploring the reaction scope by varying the nature of the enaminone acyl substituent

Following this optimized method, we began the synthesis of what soon became a huge catalogue of interesting enaminones, literally from **a**-**z**, by altering the enaminone aroyl substituent. The enaminones **2.10a-z** were then subjected to the general procedure for the catalytic cyclization reaction using silica gel as catalyst to form pyrrolizine products **2.11a-z**. The synthesis of a variety of five-membered pyrrolidinone derived enaminones was achieved in good to excellent yields, using the same general procedure for the Eschenmoser sulphide contraction outlined in *Section 2.1 by* using the same thiolactam precursor **2.3**, but modifying the bromoketone aroyl group of **2.9**. The bromo-ketones **2.9a-z** were either purchased directly or prepared by brominating of the corresponding ketone using literature methods.[92–99]

Scheme 2.3. Exploring the reaction scope by varying the nature of the enaminone acyl substituent.



Reagents and conditions: i. Mix **2.3** and **2.9** (1.25 *eq.*) in MeCN, 18 hrs; ii. PPh_3 or $P(OEt)_3$, Et_3N, MeCN; iii. Silica gel, xylene, μw (150 W, 180°C, see *table 2.2*).

Triphenylphosphine and triethyl phosphite can be used interchangeably for the sulphur extrusion step, but in general triethyl phosphite was preferred because it is a liquid that can be conveniently measured volumetrically. In some cases (see *Table 2.2*) triphenylphosphine was used instead, after initial attempts using triethyl phosphite gave co-elution of the enaminones with phosphite-derived contaminants. For a small number of these cases, the observed co-elution could be avoided after replacing triethyl phosphite with triphenylphosphine, providing pure enaminones **2.10**. However, in most cases the co-elution of some enaminones **2.10** with phosphorus-derived by-products was unavoidable. This has been noted by Morgans and Scalzullo and is a widespread problem with the Eschenmoser sulphide contraction.[74,77,54] Purification of such enaminones often requires multiple chromatographic separations which unavoidably reduces the isolated yields thereof as some co-elution is often inevitable. The pyrrolizine products **2.11** are significantly less polar than the enaminones **2.10** and elute with much higher R_f values. Pyrrolizines **2.11** are thus easily separated from any phosphine/phosphite derived contaminants by chromatography. It was therefore decided that

in cases where the enaminones **2.10** could not be isolated from these phosphorus contaminants, the impure samples would be subjected to the catalytic cyclization reaction directly to form the desired pyrrolizine products. In doing so, we would be utilizing a kind of two-step process, after which the pyrrolizines could be isolated as pure spectroscopically homogenous materials. Therefore, for some cases, an overall two-step isolated yield of these pyrrolizines **2.11a-z** is reported from thiolactam **2.3**. This two-step process proved very reliable, as the contaminating by-products did not appear to hinder the reaction process in any way and the unnecessary yield reductions associated with purification attempts of these enaminones were avoided.

In general, characterization of the enaminones and pyrrolizines followed the guidelines discussed for the simple phenyl model systems **2.4** and **2.8** in *Section 2.1.1*. The completion of the cyclization reaction of enaminones **2.10** to pyrrolizines **2.11** was determined by TLC of the reaction mixture after successive time intervals, in order to provide a reasonably accurate measure of the relative time taken to reach completion for each individual system. A fairly accurate measure of the rate dependence of the reaction on the changing aroyl substituent could thus be inferred (to within approximately 30 seconds). Monitoring the completion of the reaction by TLC was straightforward as there is a significant difference in polarity between the enaminones **2.10a-z** and pyrrolizines **2.11a-z.** The enaminones typically elute at an R_f of around 0.3 (±0.1) in 50% ethyl acetate in hexane, whilst the more lipophilic pyrrolizines eluted at approximately 0.9 (±0.1) in the same solvent system. Indeed, we observed a very distinct rate dependence on both the size and the electronic properties of the aryl substituent, with more electron-withdrawing substituents giving a significantly increased reaction rate and more sterically hindered substituents giving a significantly decreased reaction rate. The possible implications of these observations are discussed in *Section 2.1.4*. In general, both the Eschenmoser sulphide contraction and the novel cyclization reaction were shown to be very reliable, with a few notable exceptions to be discussed.

Table 2.2. Acid catalyzed conversion of enaminones **2.10** to pyrrolizines **2.11** using silica gel as catalyst.

Entry	Ar	**2.10** (yield, %)*	Time (min)	**2.11** (yield, %)
a	4-MeO-C_6H_4	**84**[a]	**5**	**96**
b	4-Me-C_6H_4	**82**[a]	**4.5**	**90**
c	4-Br-C_6H_4	**93**[a]	**4.5**	**97**
d	C_6H_5	**92**[a]	**3.5**	**93**
e	4-CN-C_6H_4	**92**[a]	**3**	**98**
f	4-F-C_6H_4	**90**[b]	**5**	**98**
g	4-NO2-C_6H_4	**100**[a]	**0.5**	**78**
h	3-MeO-C_6H_4	**(-)**[b]	**3.5**	**81**[c]
i	3-NO_2-C_6H_4	**99**[a]	**3.5**	**78**
j	1-Naphthyl	**(–)**[b]	**17**	**83**[c]
k	Cinnamyl	**88**[a]	**0.5**	**82**
l	2-NO_2-C_6H_4	**88**[a]	**0.5**	**0**[d]
m	2-I-C_6H_4	**93**[a]	**10**	**0**[d]
n	2-Br-4,5-$(MeO)_2$-C_6H_2	**97**[a]	**9**	**34**[d]
o	2-Br-C_6H_4	**(–)**[a]	**9**	**46**[d]
p	2-Cl-C_6H_4	**92**[a]	**9**	**92**
q	2-MeO-C_6H_4	**92**[a]	**7**	**82**
r	2-F-C_6H_4	**(–)**[b]	**1.5**	**99**[c]
s	2-Furyl	**93**[b]	**5.5**	**100**[c]
t	2-Thienyl	**(–)**[b]	**4.5**	**99**[c]
u	2-Benzofuryl	**93**[b]	**2.5**	**96**
v	3-(*N*-Tosyl)indolyl	**88**[b]	**2**	**92**
w	2,5-$(MeO)_2$-C_6H_3	**(–)**[b]	**7**	**87**[c]
x	3,4-$(MeO)_2$-C_6H_3	**(–)**[b]	**5**	**90**[c]
y	$C(CH_3)_3$	**62**[b]	**19**	**81**
z	2-OH-C_6H_4	**89**[b]	**5**	**86**[e]

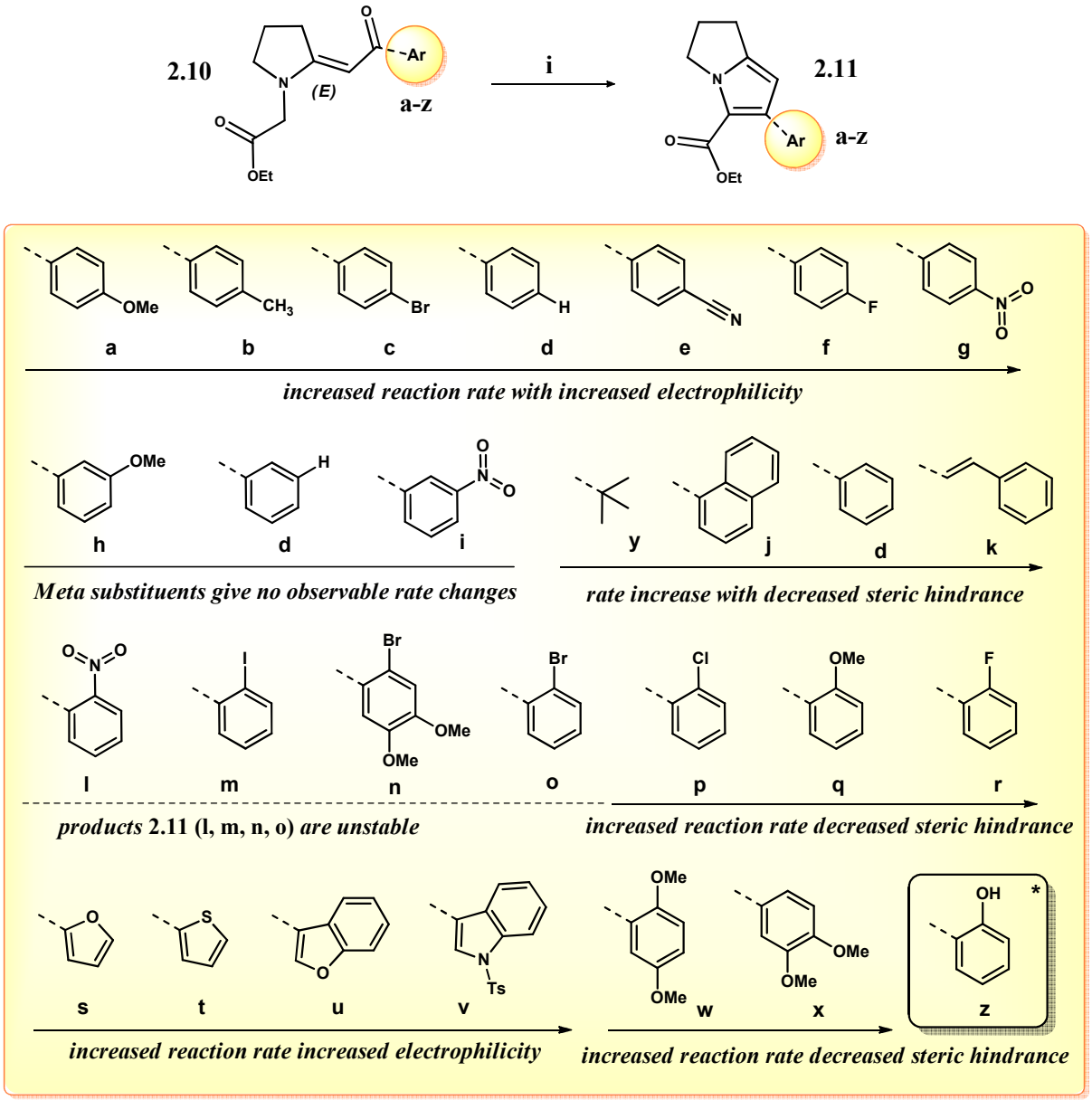
*Reaction conditions specified in *Scheme 2.3.* Yields given as "(–)" refer to instances in which the enaminones **2.10** could not be isolated from contaminating by-products, and were used without purification.

a: using $POEt_3$; **b:** using PPh_3; **c:** two-step yield (enaminone could not be isolated free from by-products); **d:** significant decomposition occurred; **e: 2.11z** spontaneously cyclized to **2.16** (*Scheme 2.14*).

2.1.4 Rate dependency on the nature of the aroyl substituent

From the results in *Table 2.2*, it clear that there is a distinct rate dependence of the reaction on both the electronic and steric properties of the enaminone's acyl substituent, as inferred from the time taken for completion of the reaction. More electron-withdrawing substituents in the conjugated *ortho* and *para* positions produced a dramatic increase in the reaction rate, whilst electron donors in these positions significantly decreased the reaction rate. This effect is well displayed in examples **a** through **g** (*Figure 2.3*) which offer minimal changes in steric hindrance and mainly electronic effects.

Figure 2.3. Rate dependence on aroyl substituents **a-z** for catalytic cyclization reactions.



Reagents and conditions: i. Silica gel, xylene, µw (150 W, 180°C, see *Table 2.2*). * **2.11z** lactonizes *in situ* to **2.16** (*Scheme 2.4*).

Both electron donating and electron withdrawing groups in the unconjugated *meta* position gave a rate that was identical to that of the unsubstituted (essentially *meta*-H) analogue (see **h** and **i** compared to **d**). This quite interesting result proves that whatever inductive or conjugative electron withdrawal that is present for these *meta*-substituted systems does not appear to be detectable within the variance of the measured time. Changes in the steric hindrance of the acyl substituent also gave dramatic changes in the reaction rates, with the most sterically hindered tertiary-butyl system **y** requiring 19 minutes to reach completion. The similarly hindered aromatic 1-naphthyl system **j** required a slightly shorter reaction time of 17 minutes as compared to the relatively unobstructed cinnamyl derivative **k**, which reached completion in only 30 seconds, with little differences in electronic contributions from the two. It is fitting to note that this same exceptionally rapid rate could be reached with the use of the highly electrophilic *para*-nitro system **g**, also requiring only 30 seconds for completion.

The smaller five-membered heterocycles **s, t, u, v** gave longer reaction times as compared to the larger phenyl substituted model system **d**, due to the increased electron densities within these heterocyclic ring systems which decreases the electrophilicity of the acyl moiety. The difference between thiophene **t** and furan **s** may seem anomalous, based on the lower electronegativity of sulphur and larger size, but the orbital size mismatch (2p for C, and 3p for S as compared to 2p for O) decreases the available electron density of the thiophenyl system, effectively decreasing the electron density of the ring via inhibited conjugation compared to the furyl system. This is essentially a mirroring of the observed rate of electrophilic aromatic substitutions of these systems, caused by the very same effect. The sterically hindered indol-3-yl derivative **v** gave a very rapid rate of reaction, presumably because of the electrophilicity increase imparted by the conjugated aromatic ring as well as the tosyl moiety. The considerable rate increase between the unsubstituted furan **s** and the aryl fused benzofuran **u** is yet another example of the reaction rate increase associated with increased conjugative electron withdrawal. The heterocycles stand out as especially promising substrates for this reaction, with all giving excellent yields, often near quantitative. The resultant biaryl bis-heterocyclic structures are also aesthetically pleasing since literature examples of such compounds are quite rare. Traditional metal-catalyzed coupling reactions are unsuitable for the synthesis of these and other bis-heteroaryl systems, owing to the difficulty in inducing oxidative addition of such electron rich aryl systems to metal catalysts, which is the rate-limiting step in most instances of these catalytic cycles.[100]

This cyclization reaction is clearly both rapid and usually efficient, but a few glaring exceptions stand out. All problems encountered occurred only for *ortho* substituted systems with chemically labile groups. In particular, the *ortho*-nitro **l** and *ortho*-iodo **m** derivatives gave almost complete decomposition, with no pure isolatable material being obtained. *Ortho*-bromo substitutions are better, but proceeded with significantly reduced yields, and decomposition was still evident. The unsubstituted *ortho*-bromo system **o** gave a disappointing yield of 46% and a long reaction time of 9 minutes, with substantial concomitant decomposition. The more electron rich dimethoxylated analogue **n** gave an even lower yield of 38%, but in the same reaction time. Our observations have indicated that for these unstable systems the reaction times are unreliable because the decomposition of the material appears faster than the rate of cyclization. The *ortho*-iodo system had completely decomposed after 10 minutes, again masking the true rate of the reaction for this especially sensitive material. The *ortho*-chloro **p** and *ortho*-fluoro **r** substituted derivatives gave good and excellent yields respectively and these systems appear relatively immune to this effect. Furthermore, the *ortho*-methoxylated systems (**q** and **w**) were all stable to the reaction conditions, giving good yields of the corresponding pyrrolizines, even with a longer duration of 7 minutes. To prove that the observed instability of these *ortho* substituted systems was not merely due to a steric effect (already somewhat indicated by the stability of all of the *ortho*-methoxylated systems) we synthesized the relatively large 1-naphthyl derivative **j**, which too gave a good yield of the corresponding pyrrolizine.

The exact cause of the instability of *ortho* substituted electrophilic groups remains a mystery. Pyrroles are well known to be notoriously reactive heterocycles, being some of the best substrates for aromatic electrophilic substitution reactions known. Could the labile group *ortho* to the newly formed biaryl axis of **2.11** (*Figure 2.3*) facilitate some kind of intramolecular oxidation of the electron-rich pyrrole ring in the products? We can be relatively sure this must be an intramolecular problem as opposed to an intermolecular one because the *para*-substituted bromo derivative **c** was a resounding success. Likewise, the *meta*- and *para*-nitro systems also gave good results. Since only *ortho*-substituted cases result in decomposition, and the enaminone precursors themselves did not appear unstable, the intramolecular oxidation theory appears to be the best explanation for these observations. Of course, this would be relatively easy to prove- by simply preparing a system with a blocked pyrrol-3-yl position. In fact, installing a methyl blocking group would simply involve treating the enaminone with methyl iodide in the presence of a base. Nucleophilic attack of the

enamine (presumably on carbon) should give, after deprotonation of the intermediate iminium salt, a methyl "protected" enaminone. If one of these enaminones was constructed with a particularly fragile aryl substituent and the proceeding cyclization worked without decomposition, then this intramolecular oxidation pathway is to blame. Owing to time constraints, further investigations into these failed reactions did not reach fruition.

Although we had initially hoped to extend the methodology beyond aroyl substituents to alkyl-ketone enaminones (Ar = CH_3, CF_3), and even pyruvates (Ar = CO_2COR), our preliminary attempts at preparing the relevant enaminones failed, and our results appeared to suggest that an alternative method for enaminone preparation might be required for these systems. Further investigations into these and other related non-aroyl systems were not explored owing to time constraints. However, application of the generalized methodology to the *tert*-butyl enaminone **2.10y** did provide a reasonable yield (61%) for the enaminone, and subsequent cyclization by our method was successful, providing **2.11y** in a good yield of 81% after a reaction time of 19 minutes. The exceptionally long reaction time for this compound is a consequence of the steric hindrance imparted by the *tert*-butyl substituent, as well as a possible electronic deactivation induced by the more electron-donating nature of the *tert*-alkyl substituent. Nevertheless, the methodology proved reliable, providing the corresponding *tert*-butyl substituted pyrrole, which is a structural motif that is otherwise difficult to obtain. The *ortho*-hydroxyphenyl enaminone **2.10z** was also prepared, and was shown to cyclize directly to the lactone **2.16** (see *Scheme 2.4*), via the intermediate pyrrolizine **2.11z**, in only 5 minutes. This confirmed the findings by Scalzullo and Morgans,[74,77] discussed *in Section 1.3.3,* showing that these five-membered (pyrrolidinyl) enaminones **2.10** can be used as precursors to lamellarin analogue scaffolds in a convenient and rapid one-pot reaction.

2.2 Cyclization of six-membered enaminones to indolizines

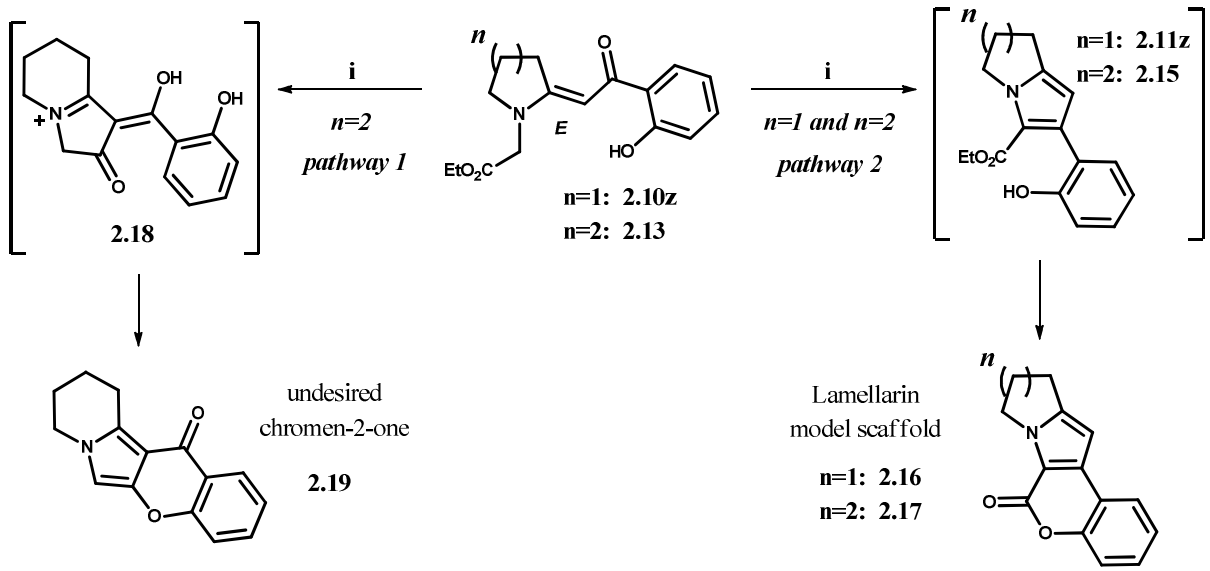
2.2.1 Recapitulation of prior work

What remained at this point was perhaps the most essential component of this initial project: fixing the six-membered ring problem encountered during previous projects related to lamellarin synthesis.[74,77] As was previously discussed in *Section 1.3.3*, this cyclization methodology had failed when the ring size of the enaminone was extended beyond five. The isolation of chromen-4-ones such as **2.19** (*Scheme 2.4*) confirmed that for these systems,

unwanted cyclization via pathway 1 was, at least partly, to blame. The increased nucleophilicity of six-membered ring enaminones such as **2.13** at the vinyl position compared to the five-membered analogue **2.10z** is thought to be a consequence of the differing thermodynamic stability of endocyclic versus exocyclic double bonds in five- and six-membered rings. The nucleophilic attack of the enamine vinyl carbon onto the ester, which initiates pathway 1 cyclization, is associated with the conversion of the exocyclic enaminone double bond in **2.13** to the endocyclic unsaturated intermediates such as **2.18**, which go on to react and form the pathway 1 product chromen-4-one **2.19**, which was isolated in 21% yield.[77] In addition, enaminone **2.13** also reacted via pathway 2 to give the desired chromen-2-one **2.17,** which was isolated in a 32% yield.[77]

The first task of the present project was thus to confirm the results obtained by Scalzullo (*Section 1.3.3*) which showed the cyclization methodology was incompatible with six membered ring enaminones, and to then direct our efforts towards improving the reaction outcome to selectively obtain the desired pathway 2 product indolizines.

Scheme 2.4. Summary of results obtained by Scalzullo showing six membered ring enaminones exhibit dual reactivity by pathways 1 and 2.



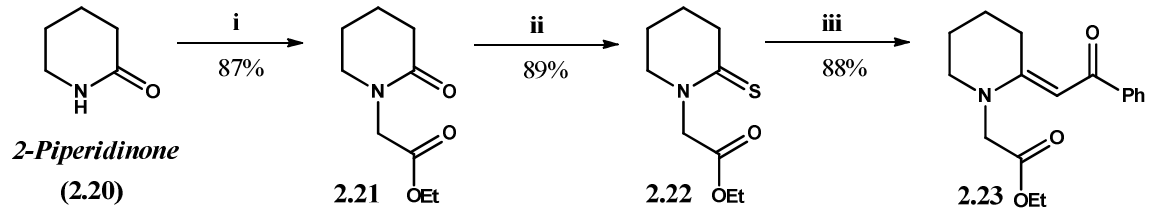
Reagents and conditions: i. Silica gel, xylene, μw (150 W, 180 °C, 30 min.)

2.2.2 Synthesis of (*E*)-piperidinyl enaminones

The preparation of the six-membered parent thiolactam, ethyl 2-(2-thioxopiperidin-1-yl)acetate (**2.22**, *Scheme 2.23*), was methodologically identical to that of the five-membered

thiolactam **2.3** described in *Section 2.1*. Ethyl 2-(2-oxopiperidin-1-yl)acetate (**2.21**) was prepared in 87% yield from 2-piperidinone (**2.20**) by treatment with sodium hydride, followed by ethyl bromoacetate. Thereafter, thionation of **2.21** using Lawesson's reagent in refluxing toluene furnished ethyl 2-(2-thioxopiperidin-1-yl)acetate (**2.22**) in 89% yield as a clear oil which, when pure, would crystallize upon refrigeration. The Eschenmoser sulphide contraction of thiolactam **2.22** with phenacyl bromide proceeded smoothly in acetonitrile. The initial alkylation phase was not associated with a crystalline salt precipitate, as was observed for the five-membered analogue, though TLC nonetheless indicated the development of a baseline compound and the complete disappearance of the thiolactam **2.22** after 18 hours. It is thought that in such cases the generated thioiminium ether salt is in fact an ionic liquid that is miscible with the reaction solvent. Thereafter, triethyl phosphite and triethylamine were added and, after 18 hours, **2.23** was isolated in 88% yield after purification by column chromatography.

Scheme 2.5. Synthesis of (*E*)-piperidinyl enaminone **2.23**.

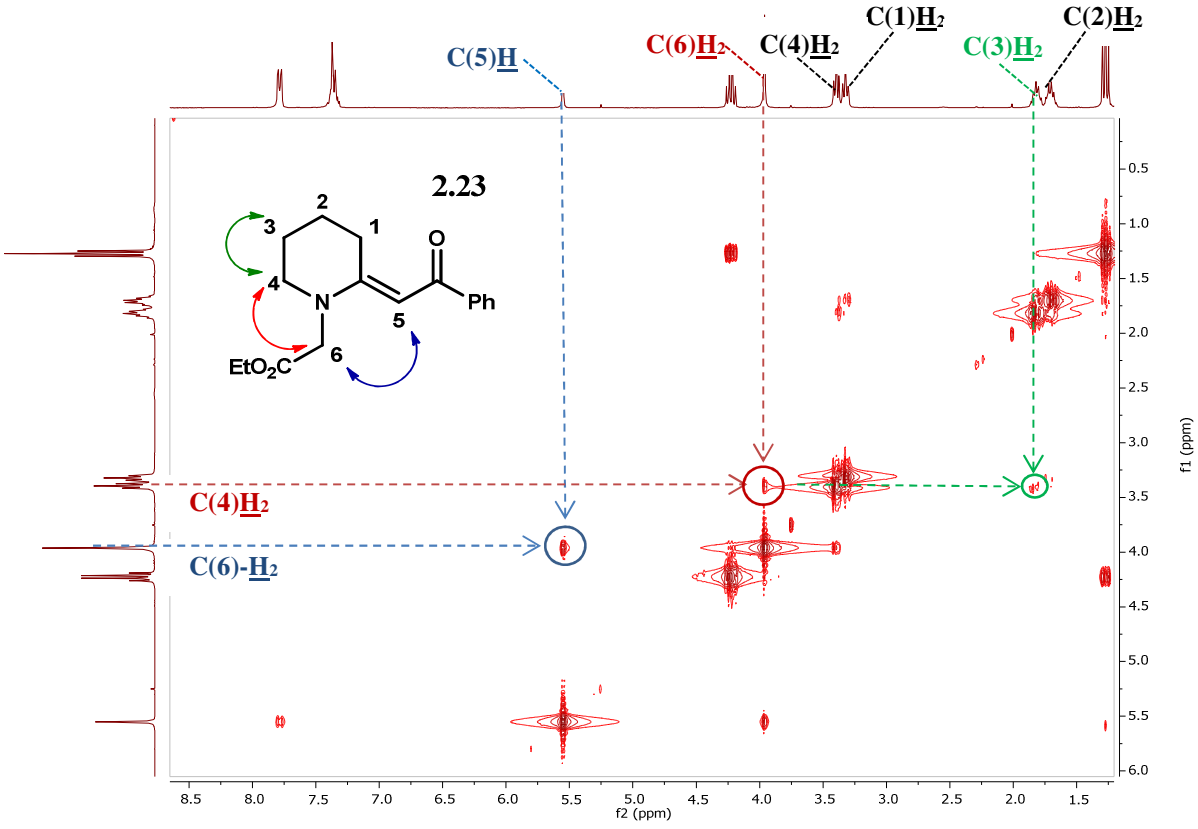


Reagents and conditions: i. NaH (60%), ethyl 2-bromoacetate, THF, rt-reflux, 20 h; ii. Lawesson's reagent, toluene, 80°C; iii. Phenacyl bromide (1.25 eq) in MeCN, 18 hrs; then $POEt_3$, Et_3N, MeCN.

Characterization data for these materials all matched those obtained by Morgans and Scalzullo.[74,77] The successful installation of the *N*-ethoxycarbonylmethyl substituent of **2.21** was clear in the ^1H NMR spectrum, which showed the distinct NCH_2 singlet at 4.1 ppm, and a quartet and triplet at 4.19 ppm and 1.28 ppm respectively, as expected for the ethyl component of the ester. These peaks were in almost identical positions to those measured for the analogous five-membered lactam **2.2.** The coupling constants for these signals were both measured to be 7.0 Hz, confirming their mutual attachment. The ^{13}C NMR spectrum corroborated this and showed two distinct C=O peaks at 170 and 169 ppm, confirming the presence of two carbonyls (the lactam and ester). Thionation of lactam **2.21** to thiolactam **2.22** was confirmed by the characteristic downfield ^{13}C=S resonance at 201 ppm (discussed in *Section 2.1*). The successful formation of the desired enaminone **2.23a** was confirmed by

the distinct ^{1}H vinyl proton at 5.5 ppm as well as the appropriately integrated 5H aromatics of the phenyl group. The ^{13}C NMR spectrum showed the expected characteristic ketone carbonyl resonance at 189 ppm. A NOESY correlation experiment (*Figure 2.4*) proved the expected (*E*)-geometry of the enaminone, showing a clear interaction between the vinyl proton singlet C(5)H at 5.5 ppm (*Figure 2.4*) and the methylene C(6)H$_2$ singlet of the ester chain attached to nitrogen at 3.96 ppm. As expected, the (1,3)-*cis* interaction that was characteristic for the five-membered ring analogues (discussed in *Section 2.1*) was not observed. The remainder of the signals could be unambiguously assigned based on the sequential NOESY correlations as shown in *Figure 2.4.*

Figure 2.4. NOESY spectrum for enaminone **2.23a** proving *E* configuration.

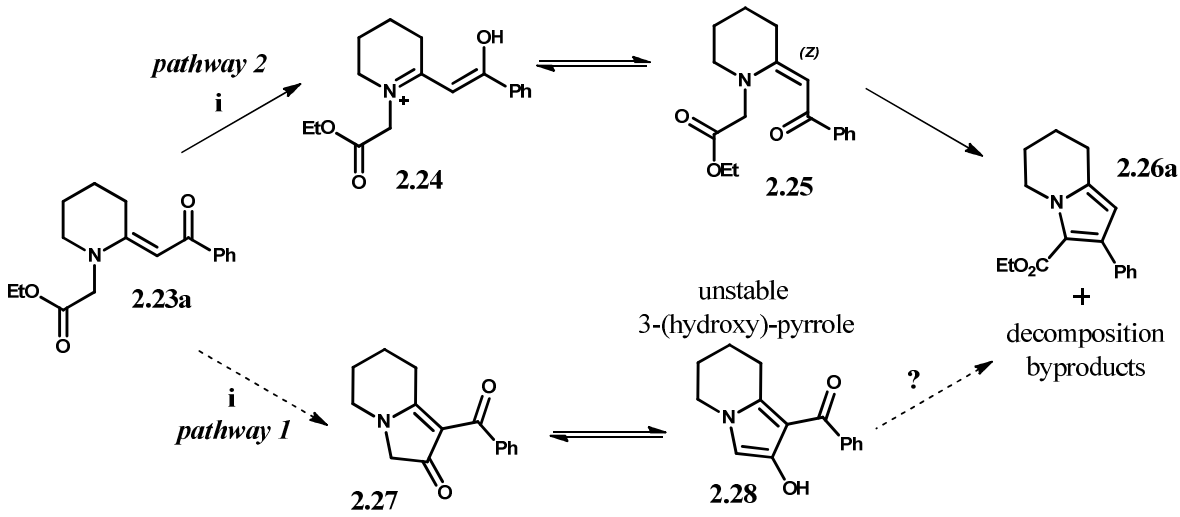


2.2.3 Selective cyclization of (*E*)-piperidinyl enaminones to indolizines

With the desired six-membered model system enaminone **2.23a** in hand, we subjected it to the general method for enaminone cyclization using silica gel and microwave irradiation (*Scheme 2.6*). As expected, the desired product **2.26a** could not be isolated in yields greater than 30% and significant decomposition was noted, even when the reaction temperature was lowered. No indication of any pathway 1 products were observed, which is believed to be a

consequence of the oxo-pyrrole intermediate **2.27** tautomerizing to form the hydroxy-pyrrole **2.28**, similar compounds to which are known to be highly unstable.[101] The rapid decomposition of **2.28** is thus thought to be a contributing factor to the poor reaction outcome. Only when the *ortho*-hydroxy aryl enaminones such as **2.17** (*Scheme 2.4*) are subjected to these conditions can these intermediate oxo-pyrroles such as **2.22** be trapped intramolecularly as stable, isolatable lactone products.

Scheme 2.6. Six-membered ring enaminones exhibit dual reactivity by pathway 1 and pathway 2.



Reagents and conditions: i. Silica gel, xylene, μw (50-150 W, 80-180°C, 0-30 min).

It soon became apparent that the increased nucleophilicity of these six-membered enaminones also extended to their alkalinity. A thin-layer chromatograph run just moments after the preparation of an acetic acid solution of the six-membered enaminone **2.23a** showed complete disappearance of the enaminone, which was replaced with a baseline spot, presumably for the protonated species **2.24** (*Scheme 2.4*). When left at room temperature this baseline spot persisted and no decomposition was observed. Interestingly, heating this solution gave no reaction whatsoever; until at very high temperatures only decomposition occurred. This seems to suggest that enaminone **2.23a** is sufficiently alkaline to be irreversibly protonated to form **2.24**, and that deprotonation required to form the desired pyrrole product **2.26a** (via **2.25**), or to re-form the unprotonated enaminone precursor **2.23a** does not occur. Irreversible protonation was not observed for the analogous five-membered enaminones **2.10** in acetic acid, which do not form an obvious baseline salt spot in acetic acid and will cyclize when heated in this solvent to provide pyrrolizines (albeit in lower yields

than with silica). Clearly, the six-membered enaminones such as **2.23a** possess an increased propensity to form the associated ionic acetate salt **2.24** as compared to their five-membered analogues **2.10**, and are hence more alkaline. Basicity is, of course, a special case of nucleophilicity with a proton as electrophile. The observed propensity for protonation of **2.23a** to form **2.24** is thus simply another observation of the increased nucleophilicity of these six-membered ring systems that was observed by Scalzullo (*Scheme 2.4*).[53] The formation of the enaminone salt **2.24** is associated with a shifting of the site of unsaturation from exocyclic to endocyclic (i.e., to $^{+}$N=C) and this exchange is so favourable that the piperidine-derived enaminones remain trapped as the associated acetate salts in acetic acid and do not undergo the necessary deprotonation required for cyclization. They also do not undergo cyclization by pathway 1 because in the salt form the enamine exists as an iminium species and is therefore unavailable for acylation. This corroborates the previous finding that when too strong an acid was added to the five-membered enaminone **2.4**, no reaction whatsoever would occur, which was also presumed to be a consequence of the necessary deprotonation step being inhibited. Here, we appear to have shown that these six-membered enaminones are more alkaline, as explained by Brown's hypothesis, and thus the acids that were appropriately strong to facilitate the isomerization and deprotonation of the five-membered systems caused irreversible protonation of these more alkaline six-membered systems. The natural implication of this was to search for milder acids to facilitate the cyclization, though silica is itself relatively mild. Attempts using another weak heterogeneous acid, montmorillonite K10, also failed, giving decomposition.

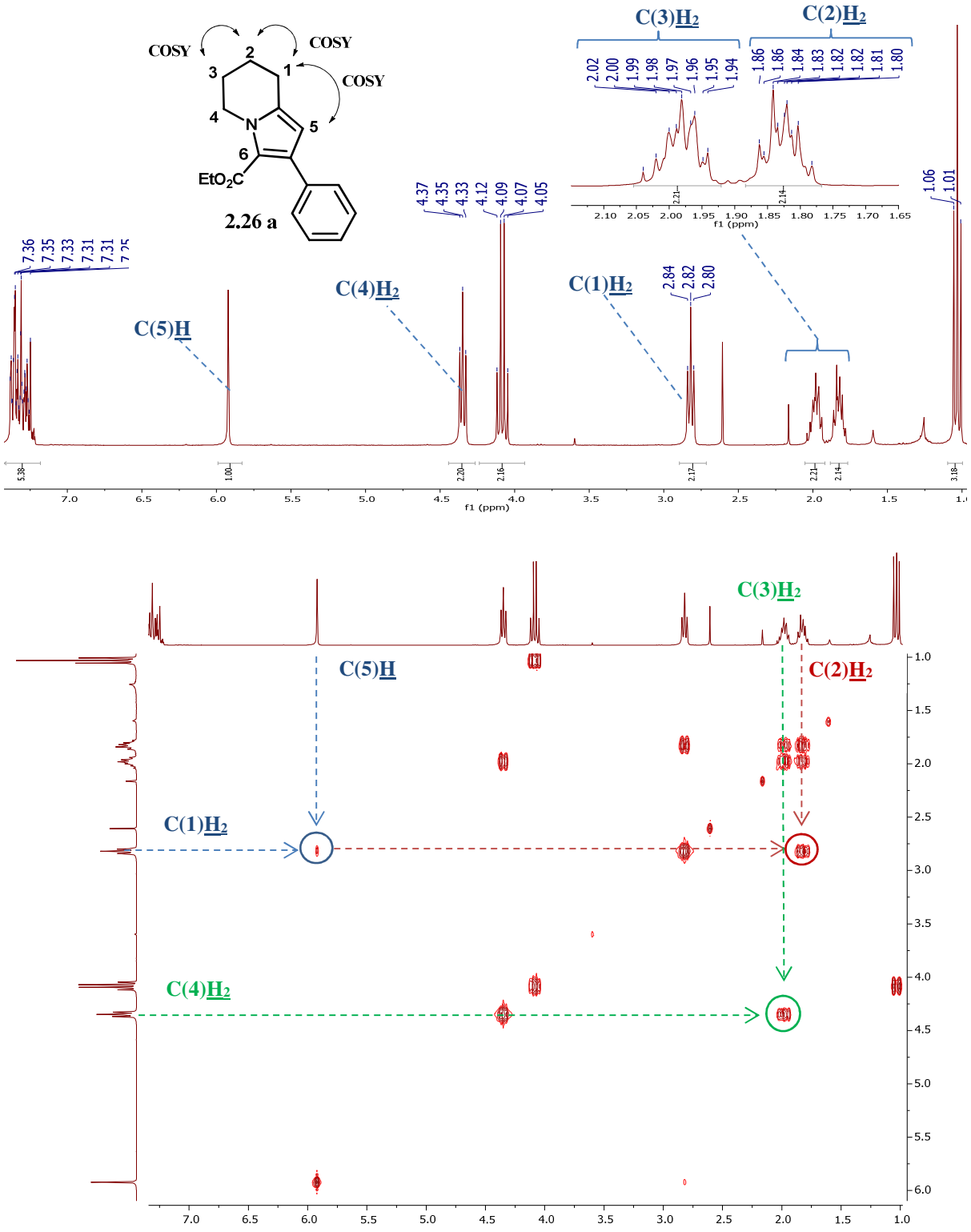
All acids and bases are defined relative to water, which has a measured pH of 7 and is (quite arbitrarily) defined as neutral. pH is simply a logarithmic scale definition of the concentration (more technically the *activity*) of hydronium ions, where $pH = -\log[H^+]$.[102] The neutrality of water stems from the fact that to water-based life forms on earth, water is subjectively "neutral". Thus, defining a protic substance as being "neutral" is also purely subjective. Taking into consideration that protonation itself is simply a special circumstance of ionic solvation, it seemed reasonable to assume that, if even weak acids caused irreversible protonation of these six-membered enaminones, a simple polar protic solvent otherwise regarded as "neutral" might provide the needed weakly protic conditions. We were most pleased to find that when a solution of the enaminone **2.23a** in neat ethanol was heated to 100 °C in a sealed microwave tube in the absence of silica gel for four hours, the desired indolizine **2.26a** was indeed selectively formed in an isolated yield of 82%, with no evidence

of any pathway 1 products **2.27** or **2.28,** nor was any significant decomposition observed. Interestingly, we found that adding silica to the reaction mixture increased the apparent rate of reaction, shortening the required reaction time from four hours to ninety minutes. The choice of ethanol in particular is not arbitrary. Not only is ester exchange possible with other alcohols, but a crucial aspect to the failure of cyclizing these six-membered ring systems that was proven by Scalzullo (*Scheme 2.4*),[77] was dual cyclization by both pathway 1 and pathway 2. Notice that the putative intermediate acylated species **2.27** (*Scheme 2.7*) can only undergo the reverse process to re-form enaminone **2.23** in the presence of ethanol, which is most improbable with only one equivalent from the ester present in solution when other solvents are used. Using ethanol as solvent allows for the potential reversibility of this unwanted pathway which would allow the desired product indolizine **2.26a** to build up selectively. It is simply a happy coincidence that ethanol can serve as solvent for the initial isomerization step to form **2.25**. As expected, the five-membered analogues **2.10** gave no reaction whatsoever under these conditions. Replacing ethanol with the aprotic polar solvent dimethylformamide (DMF) or the non-polar aprotic solvent xylene failed to provide any trace of the desired indolizine **2.26a**, proving that this was not simply a thermally induced reaction and that a unique protic solvent effect is crucial to facilitating the selective pathway 2 cyclization process. The observed rate increase when adding silica gel could arise from the catalysis of this pathway-1 reversal, though further studies are needed to better understand this phenomenon. Furthermore, a crucial additional experiment to run would be the replacement of ethanol with an analogous alcohol such as propanol. If the reversibility of pathway 1 is fundamental to the success of this reaction using ethanol as solvent, then some proportion of the product indolizine **2.26a** would have a propyl ester having been incorporated into the final structure, because the reverse process for the formation of **2.27** from **2.23a** (*Scheme 2.7*) incorporates the solvent alcohol chain into the ester functionality of the re-formed enaminone **2.23a** (where OEt would now be OPr). Owing to time constraints, and the instability of enaminones **2.23** to storage, this experiment was unfortunately not conducted.

The successful formation of the pyrrole ring of the representative indolizine **2.26a** was confirmed in the ^{1}H NMR spectrum (*Figure 2.5*), which showed the characteristic pyrrole proton C(5)H at 5.92 ppm, which is shifted downfield from 5.55 ppm for the enaminone precursor. The loss of the distinctive methylene C(6)H$_2$ singlet corresponding to the nitrogen-bonded chain was also observed, indicating its incorporation into the pyrrole ring as a quaternary nucleus. From the unambiguously defined pyrrole C(5)H signal, the remaining

ambiguous signals corresponding to positions 1-4 of the piperidinyl ring could be assigned by sequential COSY correlations as shown in *Figure 2.5b*.

Figure 2.5a and 2.5b. ^{1}H and COSY spectra for indolizine **2.26a**.



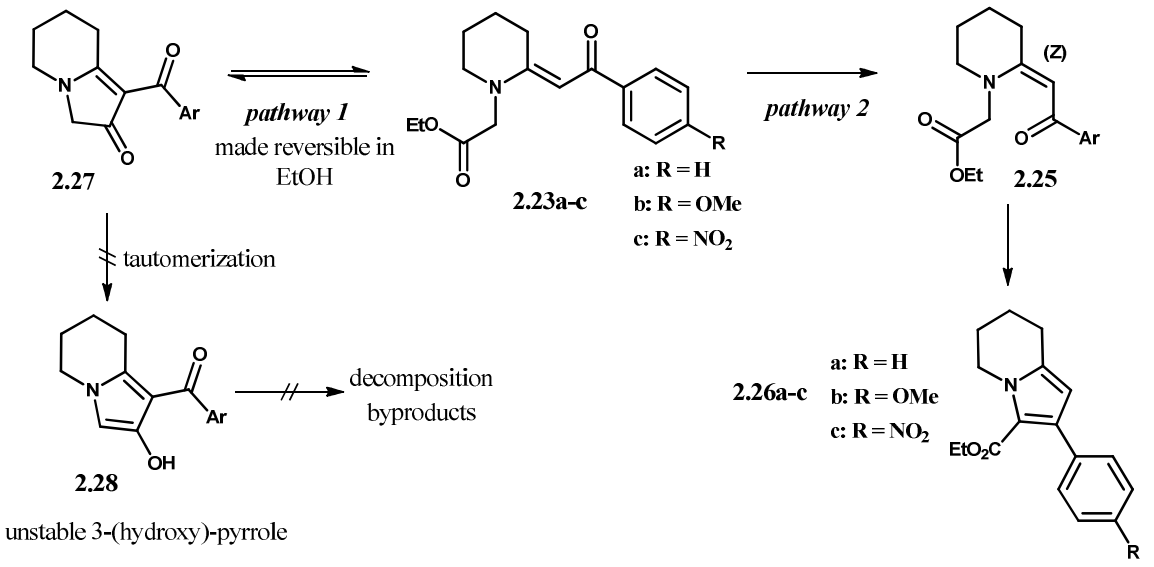
The ^{13}C NMR spectrum confirmed the presence of the ester carbonyl, measured at 162 ppm. The presence of all ten expected aromatic carbons was confirmed between 108 ppm and 137 ppm. Six carbons were detected in the aliphatic region between 10 ppm and 60 ppm. This confirms the four within the piperidinyl ring as well as the two comprising the ethyl moiety of the ester. Analysis by high resolution ESI-mass spectrometry found the desired protonated molecular ion peak $[M + H]^+$ (270.1483), which is in close agreement with the expected value (270.1489).

Extending this methodology to the *para*-methoxy and *para*-nitro acetophenone-derived enaminones **2.23b** and **2.23c** (*Scheme 2.7*) was also successful, providing the relevant type-2 indolizines **2.26b** and **2.26c** in good yields (*Table 2.3*). These reactions required significantly longer times as compared to the pyrrolizine method, though rate comparisons between the five-membered and six-membered systems are inappropriate because of the lower temperature range that can be accommodated by ethanol as compared to xylene

Table 2.3. The cyclization of (*E*)-piperidinyl-enaminones **2.23** to indolizines **2.26**.

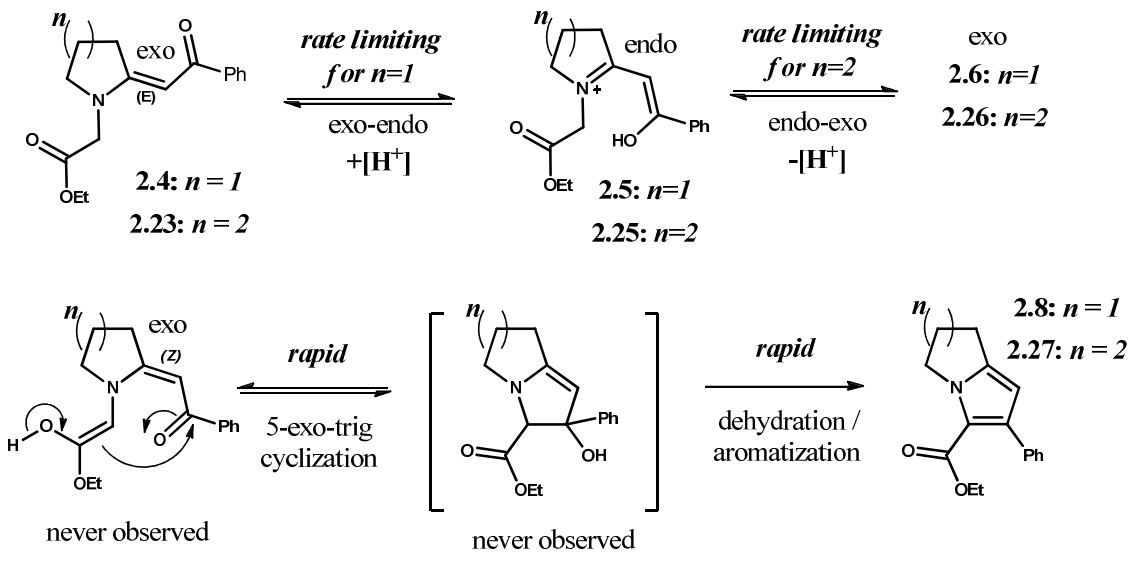
Entry	**Ar**	yield of **2.23**	**Time** (hours)	**2.26** (yield, %)
a	C_6H_5	**89**	1.5	**82**
b	4-MeO-C_6H_4	**87**	1	**74**
c	4-NO_2-C_6H_4	**86**	3	**69**

Scheme 2.7. Modified cyclization pathway of six membered enaminones using ethanol as solvent.



Interestingly, the electronic rate dependence that was observed for the five-membered ring enaminones (with more electron-withdrawing substituents resulting in more rapid cyclization) was reversed for these six-membered systems. Instead, the six-membered enaminones exhibited a clear correlation between increased aryl electron density and increased reaction rate, a stark opposite to the rate dependence observed for the five-membered systems. This immediately suggests a different rate-determining step in the pathway 2 reaction sequence for when n = 1 or n = 2 (*Scheme 2.8*). We can assume that the cyclization of the generated (*Z*)-isomers **2.6** or **2.25** to the final pyrroles **2.8** or **2.26** is not the rate determining step for either the five- or six-membered ring systems because no evidence for these intermediate (*Z*)-isomers was ever observed when studying the reaction progression by TLC or NMR. A more reasonable, though speculative, explanation for the differing rate determining steps could be that for the five-membered ring systems **2.4** (***n = 1***), it is the protonation of the exocyclic unsaturated species **2.4,** and isomerization to provide the endocyclic unsaturated (*Z*)-**2.5** that is the rate determining step. The rate of hydronium catalyzed conversion of acetophenone ketones (such as **2.4**) to enols (such as **2.5**) is well known to be significantly increased by more electrophilic aryl substituents.[103] For the six-membered systems (***n = 2***), the isomerization of the endocyclic unsaturated species *(Z)*-**2.25** to the exocyclic unsaturated *(Z)*-**2.26** is thought to be the rate-limiting step in these cases. This process would be expected to be more favourable for more electron rich aryl substituents, because increased electron density in the aryl ring increases the rate of conversion of acetophenone enols to their corresponding ketone tautomers by hydronium loss.[103] These observations also elegantly corroborate Brown's hypothesis,[78] discussed in *Section 1.3.4.*

Scheme 2.8. Rationalizing the apparent difference in kinetics for pathway 2 cyclizations of five- and six-membered ring enaminones.

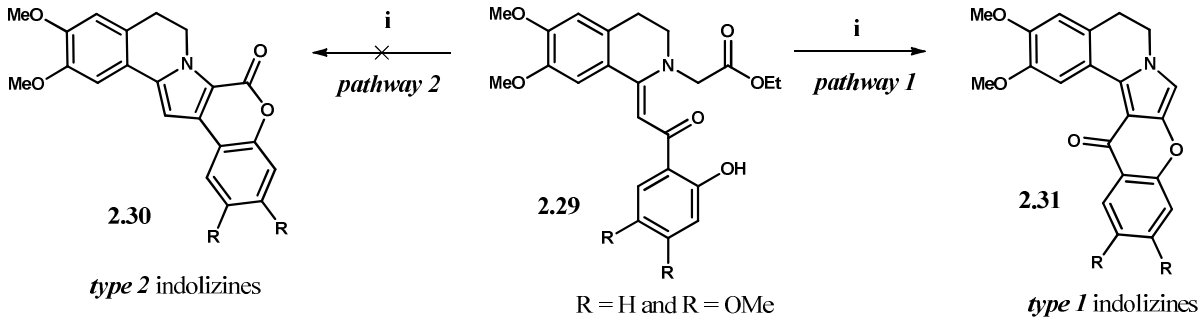


2.3 Application to enaminones derived from 3,4-dihydroisoquinolin-2-one

2.3.1. Reinvestigation of prior work

As was discussed in Chapter 1 (*Section 1.3.3*), application of this methodology to the synthesis of natural lamellarin scaffolds had failed in previous projects by Morgans and Scalzullo.[74,77] The successful isolation and characterization of chromen-4-one **2.31** (*Scheme 2.9*) by Scalzullo provided crucial evidence that competitive cyclization by pathway 1 had instead occured.[77]

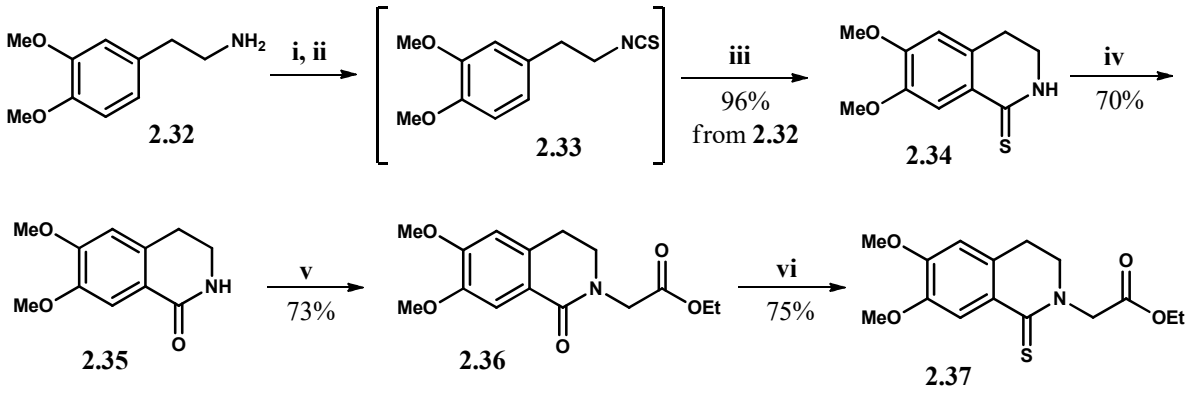
Scheme 2.9. Summary of results obtained by Scalzullo during previous investigations.[77]



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

We began by replicating this methodology, and confirmed this and several other key limitations to the route that would eventually result in the conception of an entirely new synthetic strategy. Firstly, the synthesis of enaminones **2.29** was lengthy, inefficient and inelegant (*Scheme 2.10*). Starting from commercially available homoveratrylamine (**2.32**), treatment with carbon disulphide in the presence of base, followed by the addition of ethyl chloroformate, provided the crude isothiocyanate **2.33**, which is immediately cyclized to the secondary thiolactam **2.34** using polyphosphoric acid at 80 °C for two hours, providing thiolactam, **2.34** (96% yield). Compound **2.34** is then oxidatively hydrolysed using sodium hydroxide in the presence of hydrogen peroxide to provide the lactam **2.35** (70% yield). This lactam is then deprotonated using sodium hydride and alkylated on nitrogen with ethyl bromoacetate to give the tertiary lactam **2.36** (73% yield). Thionation using Lawesson's reagent gave the desired thiolactam **2.37** (75% yield). Removing the thione functionality of **2.34**, only to reinstall a thione later at this position to generate **2.37**, is nothing short of chemical sacrilege, but was necessary because thiolactams such as **2.34** will alkylate preferentially on sulphur as opposed to nitrogen. This route provided the desired thiolactam precursor **2.37**, though after six steps and three chromatographic separations.

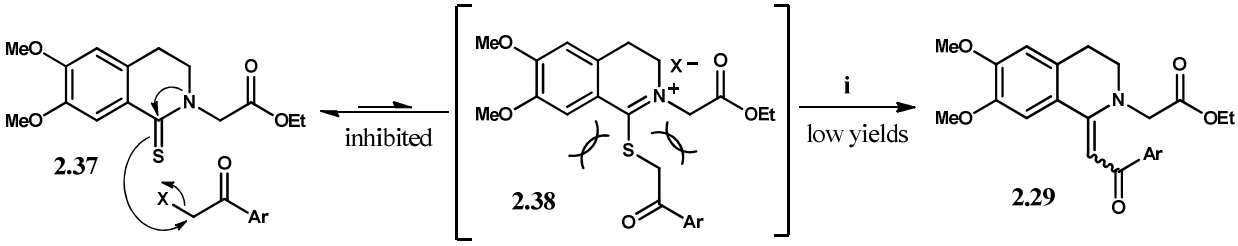
Scheme 2.10. Synthesis of thiolactam **2.37**.[77]



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, 96% from **2.32**; iv KOH, H_2O, H_2O_2, MeOH, 0 °C, 3 h, 70%; v. NaH (60%), ethyl 2-bromoacetate, THF, rt-reflux, 20 h, 73%; vi. Lawesson's reagent, toluene, reflux, 18 h, 75%;

The first severe reactivity problems were encountered during the Eschenmoser sulphide contraction of thiolactam **2.37**. Unlike for the simple unfused thiolactams (**2.3** and **2.22**), the initial S-alkylation phase was severely impaired and never reached completion. In fact, TLC and crude NMR spectroscopic analysis showed the starting materials to be the major reaction constituents even after many days. This inhibition is thought to be a result of the steric bulk imparted by the fused aryl ring and ester substituted on nitrogen on either side of the reactive thione position of **2.37** (*Scheme 2.11*). The initial alkylation phase is well known to be reversible for nucleophilic leaving groups (X = Cl, Br, I) and thus if the intermediate thioether cation **2.38** is thermodynamically less stable than the starting materials, the reaction cannot be forced to completion.[54,64] The more electrophilic, but also more unstable, iodo-acetophenones (X = I) were subsequently prepared and shown to provide a slightly improved ratio of intermediate **2.38** to **2.37**, though at the expense of increased decomposition by-products. As a consequence of these factors, the enaminones **2.29** could only be obtained in poor yields of less than 50%, always with significant decomposition being observed. Although very brief investigations into the cyclization behaviour of these enaminones did confirm Scalzullo's observation that the undesired pathway 1 chromen-4-one products **2.31** were formed as a minor component alongside decomposition by-products, isolation of these products and more extensive investigations into improving the outcome of this reaction were quickly abandoned based on the impracticality of the synthesis of the enaminones **2.29** themselves.

Scheme 2.11. Impeded alkylation phase of sterically hindered thiolactam **2.37**.

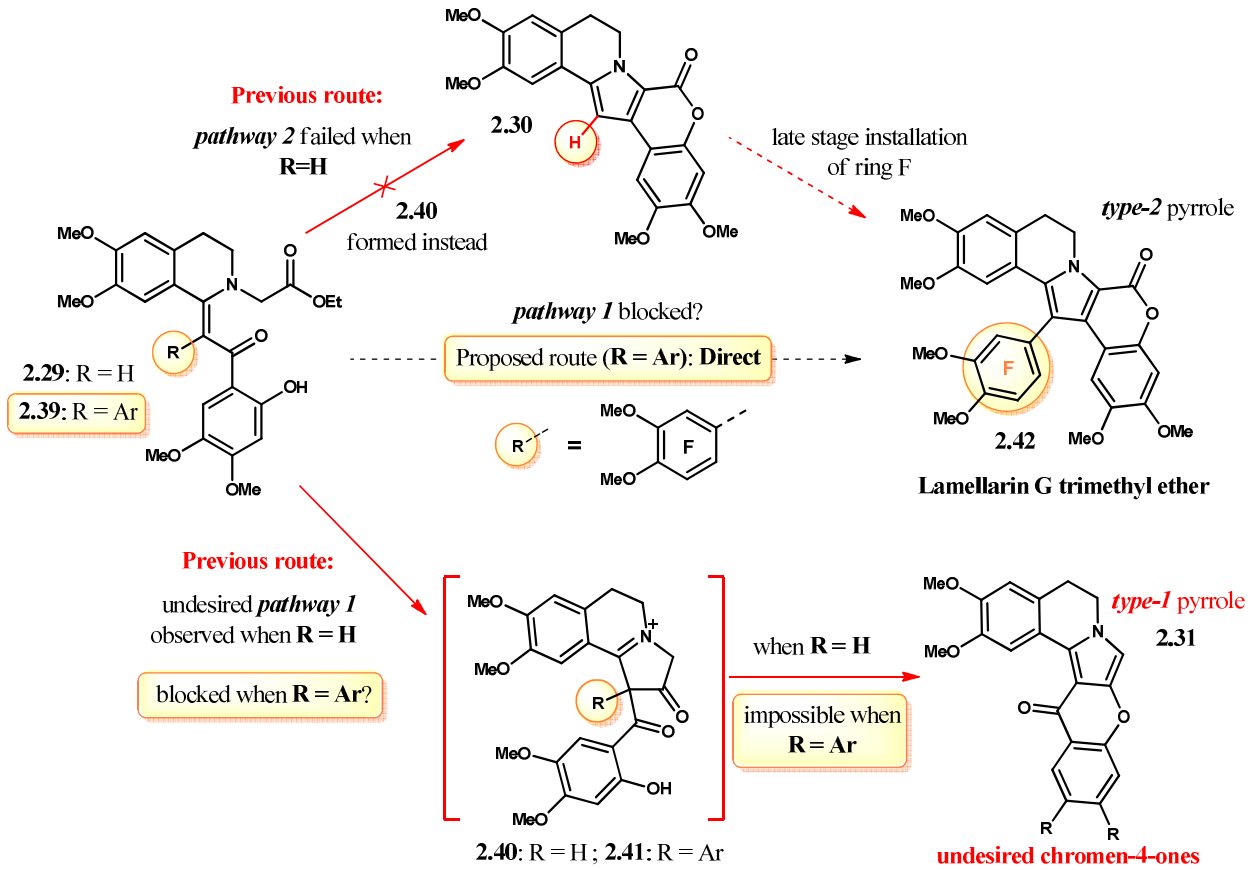


The understood flaws of the synthetic route thus far can be summarised as follows:

- The synthesis of thiolactam **2.37** is lengthy and tedious;
- Thiolactam **2.37** appeared to be too sterically hindered to provide reasonable yields of the enaminones **2.29**;
- Enaminones **2.29** exhibit uncontrolled concomitant reactivity by the undesired cyclization pathway 1, giving rise to the formation of chromen-4-ones **2.31**.

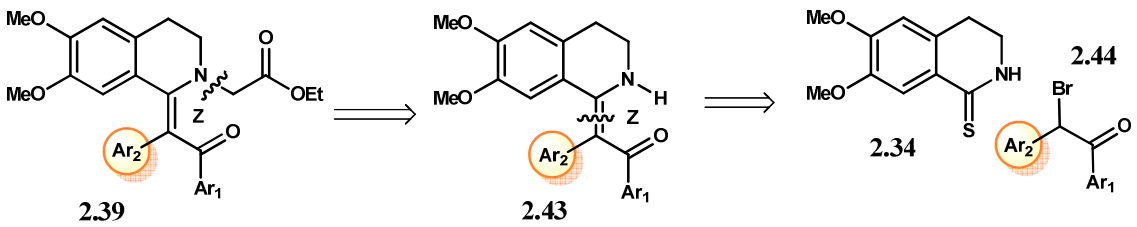
2.3.2 The solution: cyclization of 3,4-(dihydroisoquinolin-2-one)-derived enaminones to pyrrolo[1,2-*a*]isoquinolines by [4 + 1] cycloaddition

Scheme 2.12. Proposed new route to lamellarin G trimethyl ether from sterically crowded enaminones **2.39**.



Faced with these problems, a bold solution was envisaged. The initially proposed route (*Scheme 2.12*) implements a late stage coupling reaction from **2.30** to install ring F of the lamellarin framework **2.41**. However, it was realized that if we pre-install this ring F in the enaminone precursor, essentially replacing the vinyl proton of enaminones **2.29** with an aryl substituent to give enaminones **2.39**, we could sterically block the unwanted cyclization by pathway 1 to form **2.41**, whilst also making aromatization to the chromen-4-one structures **2.31** impossible. This would leave the desired cyclization pathway 2 as the only possible reaction pathway. Because the aryl ring is preinstalled in **2.39**, it would provide the fully substituted lamellarin scaffold **2.42** directly, without the need for the late stage installation of this ring via **2.30**. This in itself would not be much help, as the preparation of enaminones **2.29** (*Scheme 2.11*) had been shown to be negatively influenced by steric hindrance. The inclusion of an aryl group here as proposed for enaminone **2.39** (*Scheme 2.12*) would impart an additional steric effect. To solve the steric hindrance problem, we instead proposed to perform the Eschenmoser sulphide contraction directly on the unhindered secondary thiolactam **2.34** (*Scheme 2.13*), and add the required methylene ester group later by an N-alkylation of the resultant enaminone **2.43** (*Scheme 2.13*). The lack of an N substituent on the thiolactam **2.34** during the Eschenmoser sulphide contraction should improve the outcome of the alkylation phase that was shown to be sterically impaired for tertiary thiolactam **2.37**.

Scheme 2.13. Proposed solution to steric hindrance problem during the Eschenmoser sulphide contraction by late stage installation of *N*-ethoxycarbonylmethyl.

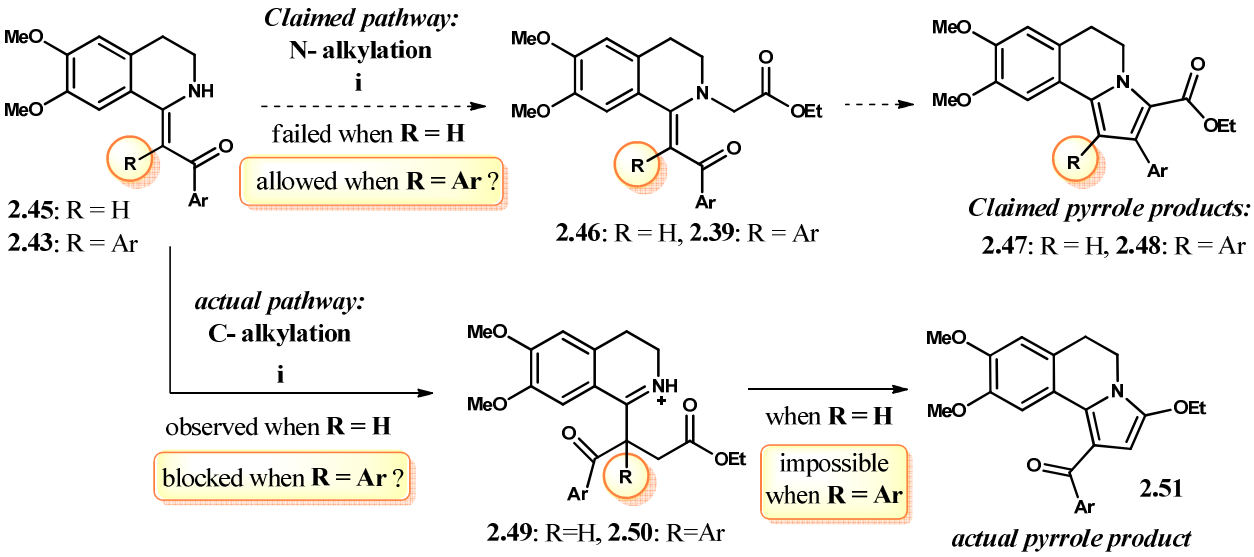


It has been well documented since Eschenmoser's first published work on the reaction[62] that this required (*Z*)-configuration of secondary enaminone products like **2.43** is ensured by hydrogen bonding between the N-H and carbonyl of the enaminone moiety when secondary (NH) thioamides such as **2.34** are used.[54,62] Thus, the necessary (*Z*)-configuration of enaminone **2.39** could be ensured because the precursor enaminone **2.43** should be formed exclusively in the *Z* configuration. As an added bonus, preparing the enaminone precursors **2.43** would make use of the simple thiolactam **2.34** directly, without the need for the tedious

dethionation-rethionation strategy used in the previous route (*Scheme 2.10*). Furthermore, this route would also negate the need for additional derivatization steps of the pyrrole core to install the final aryl ring F via **2.30** (*Scheme 2.12*).

This proposed route is actually similar to one that had been investigated by Morgans and Scalzullo, which had been based on a publication by Barun *et al.*[104] The authors of this work claimed to have facilitated the selective N-alkylation of enaminones **2.45** with ethyl bromoacetate (*Scheme 2.14*) to give the intermediate enaminones **2.46**, which they claimed had spontaneously cyclized to provide pyrrolo[1,2-*a*]isoquinolines **2.47**. Scalzullo repeated this methodology and obtained products matching their characterization data, though she was able to conclusively prove that these products were actually the isomeric pyrrolo[1,2-*a*]isoquinolines **2.51**.[77] Pyrroles **2.51** arise from alkylation of enaminones **2.45** on carbon, rather than nitrogen, via the intermediate species **2.49**. Scalzullo had thus refuted their claimed N-alkylation of enaminones **2.45**. However, our currently proposed route includes an aryl group on the vinyl position, giving enaminones **2.43**. With such a large group bonded to this position, the carbon alkylation pathway that had been proven to occur by Scalzullo should be blocked, as the resultant intermediate **2.50** would be exceptionally hindered. Indeed, blocking the unwanted reactivity of this position was the very reason we had proposed this route in the first place, as an attempt at preventing the undesired pathway 1 cyclization which results from intramolecular acylation at this position.

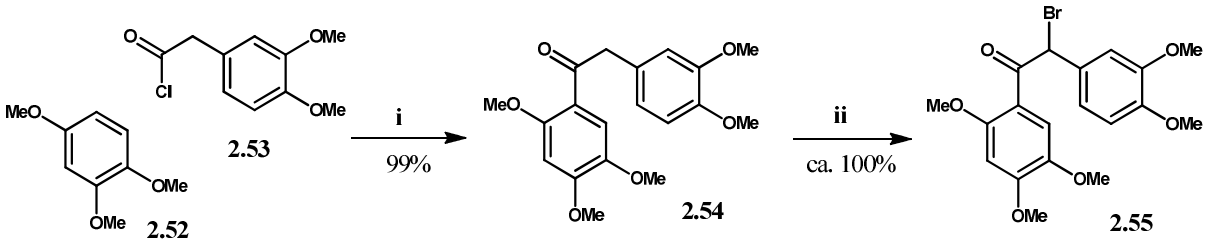
Scheme 2.14. Scalzullo's refutation of Barun *et al.*'s synthesis.[104]



Reagents and conditions: i. Ethyl 2-bromoacetate, DMF, reflux, 8 h.

We thus set our sights at preparing a sterically crowded enaminone **2.43** on which to test this idea. The synthesis of the bromoketone fragment **2.44** (*Scheme 2.13*) was tackled first as the synthesis of the required thione **2.34** was known to be straightforward. It was decided that the penta-methoxylated system **2.55** (*Scheme 2.15*) would be easy to prepare and would enable the methodology to be tested on an appropriately oxygenated enaminone model system. This material was prepared in two steps. An initial Friedel–Crafts acylation between homoveratroyl chloride **2.53** (generated *in situ* from the acid of **2.53** with oxalyl chloride or thionyl chloride) and 1,2,4-trimethoxybenzene (**2.52**) gave a remarkably pure sample of the desired ketone **2.54** directly after work-up, with no further purification being required (99% yield). This was immediately followed by enolic bromination of the resulting deoxybenzoin **2.54** with molecular bromine in chloroform (also in a practically quantitative yield). No purification was required after this step either, and no bromination of the electron-rich aromatic rings was observed when the rate of bromine addition was carefully controlled and when chloroform was used as the reaction solvent. Performing this reaction in diethyl ether failed to give selective bromination of the enol to **2.55**, and instead appeared to favour bromination of the aryl ring(s). This is thought to be a consequence of the lower solubility of the acidic by-product of the reaction, hydrogen bromide (HBr), which is required to catalyse the formation of the enol to be brominated. Instead, when using diethyl ether as solvent, the HBr gas generated was observed to bubble off, due to its insolubility.

Scheme 2.15. Preparation of bromo-deoxybenzoin **2.55**.

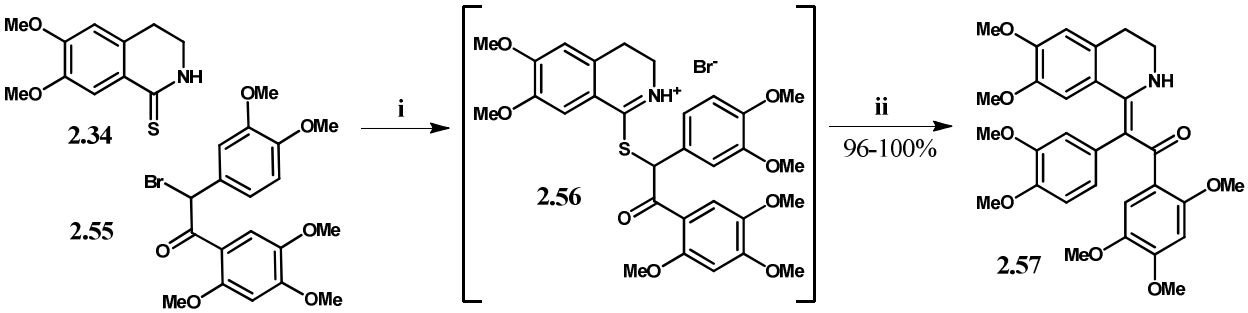


Reagents and conditions: i. $AlCl_3$, CH_2Cl_2, 0 °C; rt, 1 h; ii. Br_2 (1.0 eq.), $CHCl_3$, 0 °C, 99% (2 steps).

The proposed structure of the ketone product **2.54** obtained from the Friedel–Crafts acylation was confirmed by the ^{1}H NMR spectrum, which proved the presence of the five expected aromatic protons found between 7.41-6.50 ppm as well as a total of five aryl methyl ethers between 3.94-3.85 ppm (with a total integration of 15 protons). A characteristic 2H singlet for benzylic methylene group was observed at 4.25 ppm. ^{13}C NMR spectroscopy confirmed the presence of the ketone functionality measured at 197.6 ppm. Furthermore, analysis by

high resolution ESI-mass spectrometry found the desired $[M + H]^+$ protonated molecular ion peak (347.1490), which is in close agreement with the expected value (347.1489). The actual position of acylation corresponding to the proposed isomer was confirmed using the ^1H NMR spectrum, which distinctly shows two of the three expected aromatic singlets, with the third being incorporated into a multiplet between 6.80-6.71 ppm. Only one singlet would be expected if acylation had occurred on the alternative position 3 of precursor **2.52**. The successful bromination **2.54** to **2.55** was confirmed in the ^1H NMR spectrum, which showed the CH_2 singlet corresponding to the methylene group of the precursor **2.45** had disappeared and was replaced with a singlet integrating for 1H which was found significantly downfield at 6.45 ppm. This indicates the substitution of an electrophilic bromine at this position. The multiplicities and integration of the aromatic protons remained unchanged from the precursor ketone **2.45**, proving no aryl ring bromination had taken place. Analysis by high resolution mass spectrometry found the desired $[M + H]^+$ peak (425.0532), which is in close agreement with the expected value (425.0594). The characteristic molecular ion splitting corresponding to the two ^{79}Br and ^{81}Br isotopes was also observed.

Scheme 2.16. Successful Eschenmoser-sulphide contraction to form sterically crowded enaminone **2.57**.



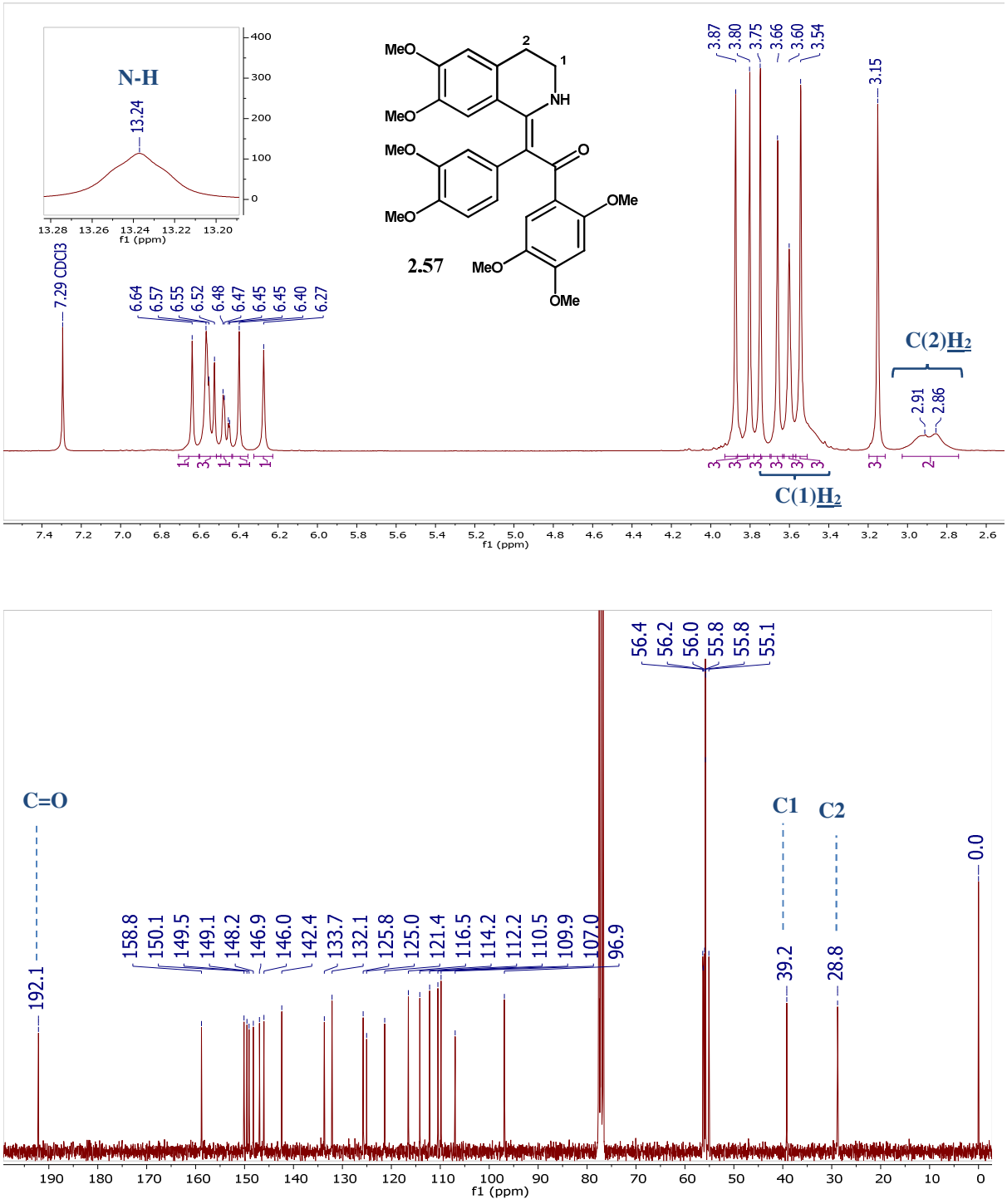
Reagents and conditions: i. **2.34** + **2.55** (1.05 eq.), MeCN, rt, 18 h; ii PPh_3, 5 min., then NEt_3, rt, 16 h, 96-100%.

The thiolactam **2.34** (*Scheme 2.16*) needed for the Eschenmoser sulphide contraction was obtained in two telescoped steps from homoveratrylamine by following the methodology that was adapted from the literature.[105] Simply mixing thiolactam **2.34** and bromoketone **2.55** (the latter in 5% molar excess) in acetonitrile allowed for the *in situ* formation of the thioiminium ether salt **2.56**. As desired, this reaction reached completion within a few hours and was unimpeded by steric hindrance, as was observed during similar reactions with tertiary enaminones such as **2.37**. Sulphur was extruded under standard Eschenmoser sulphide contraction conditions with triphenylphosphine and trimethylamine, and the

heptamethoxylated enaminone **2.57** was obtained in an excellent yield of 96%, after purification by column chromatography. It is worth mentioning that the success of this reaction is quite exceptional, and as was previously discussed in *Section 1.3* (*Scheme 1.20, page 32*), six-membered secondary enaminones (non benzo-fused analogues of **2.34**) have been consistently shown to provide thiazolone products under conventional Eschenmoser sulphide contraction reactions, which result from deprotonation of the piperidinyl ring at position 3 of the corresponding non-benzo-fused analogues of **2.56.** In doing so, the conservation of a stable endocyclic double bond is ensured. However, as is obvious for intermediate **2.56,** the aryl ring fused to this position makes this unwanted deprotonation event impossible.

The ^{1}H NMR spectrum of the product enaminone **2.57** showed a distinctly downfield broad singlet at 13.24 ppm, which indicates intramolecular hydrogen bonding with the carbonyl substituent of the enaminone, and confirmed that the assigned (*Z*) geometric isomer had been formed. All seven methyl aryl ethers, each integrating for 3H, were accounted for between 3.87-3.15 ppm, and all seven aromatic protons with their expected multiplicities were observed in the aromatic region between 6.64-6.40 ppm. The dihydro-isoquinoline segment of the molecule was observed as two very broad multiplets at 3.55–3.40 ppm and 3.03–2.74 ppm, each integrating for the expected two protons. The significant broadening of these signals is in agreement with the fusing of the congested deoxybenzoin portion of the molecule, which slows the rate of ring flipping of the flexible non-planar six-membered ring, giving rise to the observed geminal non-equivalence of each CH_2 moiety at room temperature. The ^{13}C NMR showed the characteristic enaminone carbonyl resonance at 192.1 ppm. Analysis by high resolution mass spectrometry found the desired $[M + H]^+$ peak (536.2271), which is in close agreement with the expected value (536.2279).

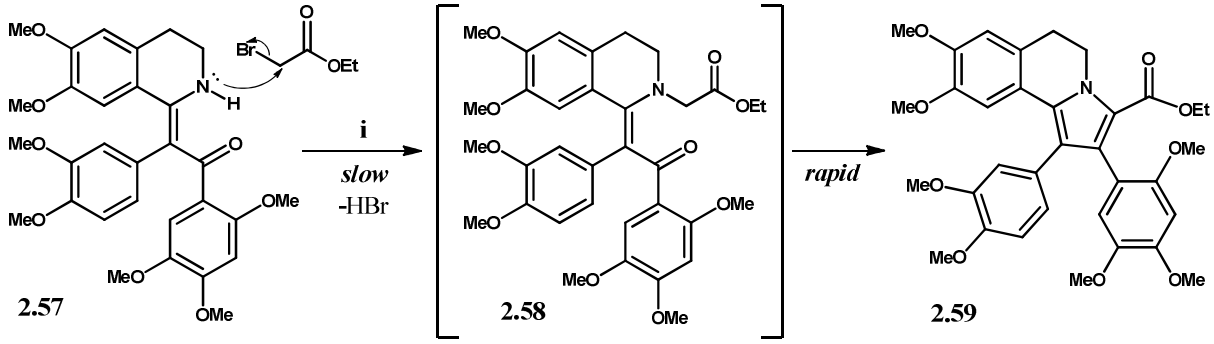
Figure 2.5. ^{1}H and ^{13}C NMR spectra of enaminone **2.57**.



We began our attempts at alkylating enaminone **2.57** with ethyl bromoacetate by preparing a solution of both in *N*,*N*-dimethylformamide (DMF), without any base. DMF is commonly used to facilitate such S_N2 alkylations as its dipolar aprotic nature effectively solvates the ionic intermediates without itself acting as a nucleophile. These conditions are similar to those reported by Barun and co-workers.[104] Once prepared, this solution was heated to reflux for 8 hours. After this time, significant decomposition was noted, though chromatographic

separation provided a small quantity (<5% yield) of desired pyrrole **2.59** as a minor component of the reaction mixture. It was thus apparent that although successful, the conditions of the reaction needed significant optimization.

Scheme 2.17. [4 + 1] Cycloaddition of ethyl-bromoacetate to sterically crowded enaminone **2.57.**



Reagents and conditions: various explored. Optimized conditions: $BrCH_2CO_2Et$ (3-10 eq.), K_3PO_4, microwaves, (120 °C, 20 W), 3-4 h.

Adding various bases to neutralize the acidic hydrogen bromide HBr by-product gave confusing results. The standard alkylamines triethylamine, pyridine, 4-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO) all failed to improve the state of the reaction and in fact promoted additional decomposition. The failure of these alkylamine bases is likely a consequence of their reaction with ethyl bromoacetate to produce the more reactive tertiary ammonium bromide species.[106] This kind of reaction usually acts to improve the alkylating capacity of the alkyl-bromide in similar reactions involving the alkylation of alcohols and amines, but it is quite possible that the resultant steric hindrance and/or altered electronic properties of the ionic alkylating agent are detrimental for alkylating these enaminone systems. Additionally, the reaction seemed highly dependent on the concentration of ethyl bromoacetate, with more concentrated solutions giving significantly faster reaction times. This is a clear sign that the rate limiting step is in fact the initial N alkylation of **2.57** to form **2.58**, and that by increasing the probability of collision between the sterically hindered and conjugately deactivated nitrogen site of enaminone **2.57** and the alkylating agent, the rate of the reaction also increased. Doing so by increasing the reaction temperature merely resulted in decomposition. It was thus decided that the best course of action was to use a neat solution of the alkylating agent, with as low a reaction temperature as was possible. The use of neat alkylating agent was not a concern as the reagent is relatively cheap, with many solvents, including DMF, being of a comparable price

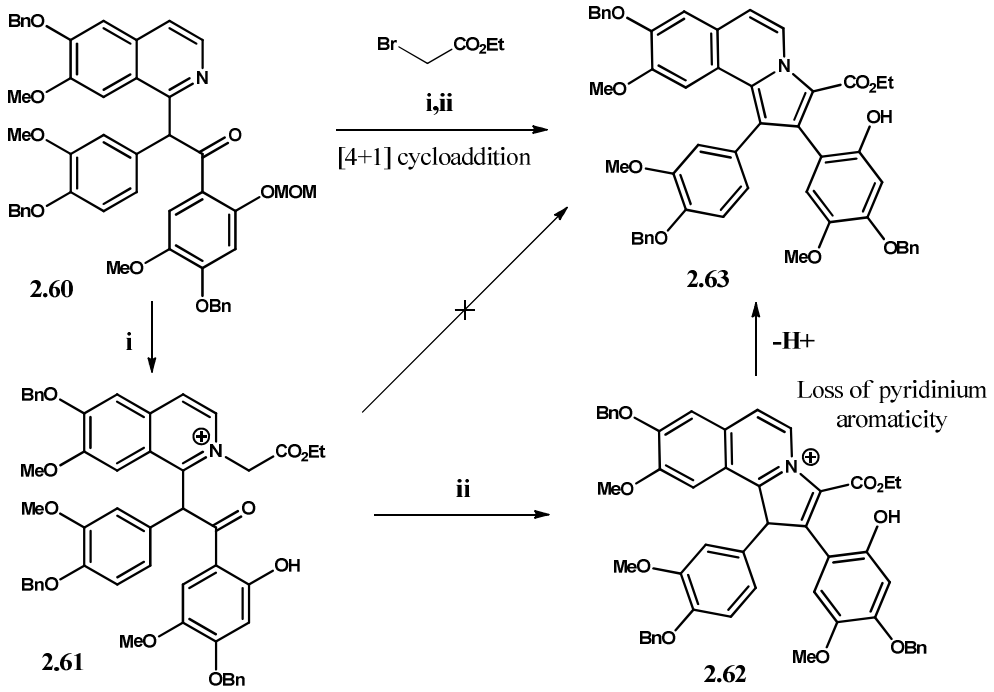
from commercial retailers. Furthermore, only around 3-5 equivalents of ethyl bromoacetate were actually needed to produce a manageable solution, giving what is (quite coincidentally) a solvent-free reaction. It was only when heterogeneous bases were tried, such as sodium or potassium carbonate (Na/KCO_3), cesium carbonate ($CsCO_3$), dipotassium hydrogen phosphate (K_2HPO_4) and particularly tripotassium phosphate (K_3PO_4), that significant improvements were noted. It is interesting to note that the heterogeneity of the base in this reaction seems particularly crucial and none of the homogenous bases tested provided any trace of the target indolizine-containing product **2.59**.

Tripotassium phosphate (K_3PO_4) was shown to particularly effective at promoting the reaction, but only when no solvent was present other than ethyl bromoacetate. It was thus found that the optimal conditions for the reaction involved dissolving enaminone **2.57** in neat ethyl bromoacetate (minimum 2–3 equivalents) with anhydrous tripotassium phosphate as base, and irradiating the mixture under a low microwave power of only 20 W, with a maximum temperature set to 120 °C, until the reaction was deemed complete by TLC. Under these conditions the reaction reached completion in 2-3 hours, after which time the bright yellow colour of the enaminone had vanished. No discolouration due to decomposition was observed. Both TLC and NMR spectroscopy indicated complete consumption of **2.57**, which can also be conveniently visualized by disappearance of the bright yellow colour of the reaction mixture, which turns to pale amber, showing no visual signs of any significant decomposition by-products. Column chromatography provided the pyrrole product **2.57** in excellent yields of between 80-90%. Throughout these investigations no sign of intermediate **2.58** was ever observed by TLC or NMR spectroscopy, implying that once formed, it rapidly and spontaneously cyclizes to form the aromatic pyrrole product **2.59**. Although the reaction is not concerted, and hence not pericyclic, the net outcome is a formal [4 + 1] cycloadittion.[21] The five-membered pyrrole ring is formed by the combination of the four atoms making up the enaminone and the single atom at the α-carbonyl position of ethyl bromoacetate, with a net reduction in the bond multiplicity of the acetate induced by deprotonation of **2.58** to **2.59**. Interestingly, ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed three peaks at δ 4.72 ppm (d, J = 11.6 Hz, 2H), 4.25 ppm (q, J = 7.1 Hz, 2H) and 1.30 ppm (t, J = 7.2 Hz, 3H). These peaks correspond to the product arising from the alkylation of the phosphate anion by ethyl bromoacetate, giving triethyl 2,2′,2″-[phosphoryltris(oxy)]triacetate, as well as mono and di-alkylated analogues.[107]

The ^{1}H NMR spectrum (*Figure 2.6*) of the isolated product **2.59** confirmed the successful incorporation of the ethoxycarbonyl moiety as a characteristic 2H quartet and 3H triplet at 4.07 ppm and 0.98 ppm respectively. The disappearance of the characteristic NH singlet at 13.24 ppm of the precursor enaminone **2.57** was also observed. All seven aromatic protons were accounted for, with the corresponding expected multiplicities that were mostly unchanged from the enaminone precursor. The geminal non-equivalence of the hydrogens in the dihydroisoquinoline ring that was characteristic for the enaminone precursor **2.37** was reduced drastically, giving rise to two distinct and characterizable triplets at 4.52 ppm and 3.06 ppm. This corroborates the fusing of the pyrrole ring thereto, as a result of the increased planarity of the newly formed dihydro-indolizine ring system, which restricts the formation of different ring conformations. The ^{13}C NMR spectrum confirmed the disappearance of the enaminone carbonyl and the presence of the characteristic ester carbonyl functionality at 162.3 ppm. Twenty-one aromatic carbons were accounted for between 97.6-151.8 ppm, confirming the installation of the additional aromatic pyrrole ring. The presence of the ethyl ester moiety was further confirmed as two signals detected at 43.2 ppm and 29.4 ppm. Analysis by high resolution ESI-mass spectrometry found the desired $[M + H]^{+}$ peak (604.2538.), which is in close agreement with the expected value (604.2541).

It is worth mentioning that a [4 + 1] cycloaddition strategy for the construction of lamellarin pyrroles is not totally unprecedented. As was discussed in in *Section 1.2.2*, Iwao and co-workers reported a similar strategy in 1997, though the overall cycloaddition occurred over two separate steps.[51] Their strategy had involved the N-alkylation of the isoquinoline **2.60**, which is essentially an unsaturated analogue of our enaminone intermediate **2.57** (*Scheme 2.17*). The unsaturation of the isoquinoline ring completely changes the chemical behaviour of their system, favouring the endocyclic unsaturated pyridinium imine intermediates **2.60**–**2.62** (*Scheme 2.18*) by aromatic stabilization induced by the pyridine ring.

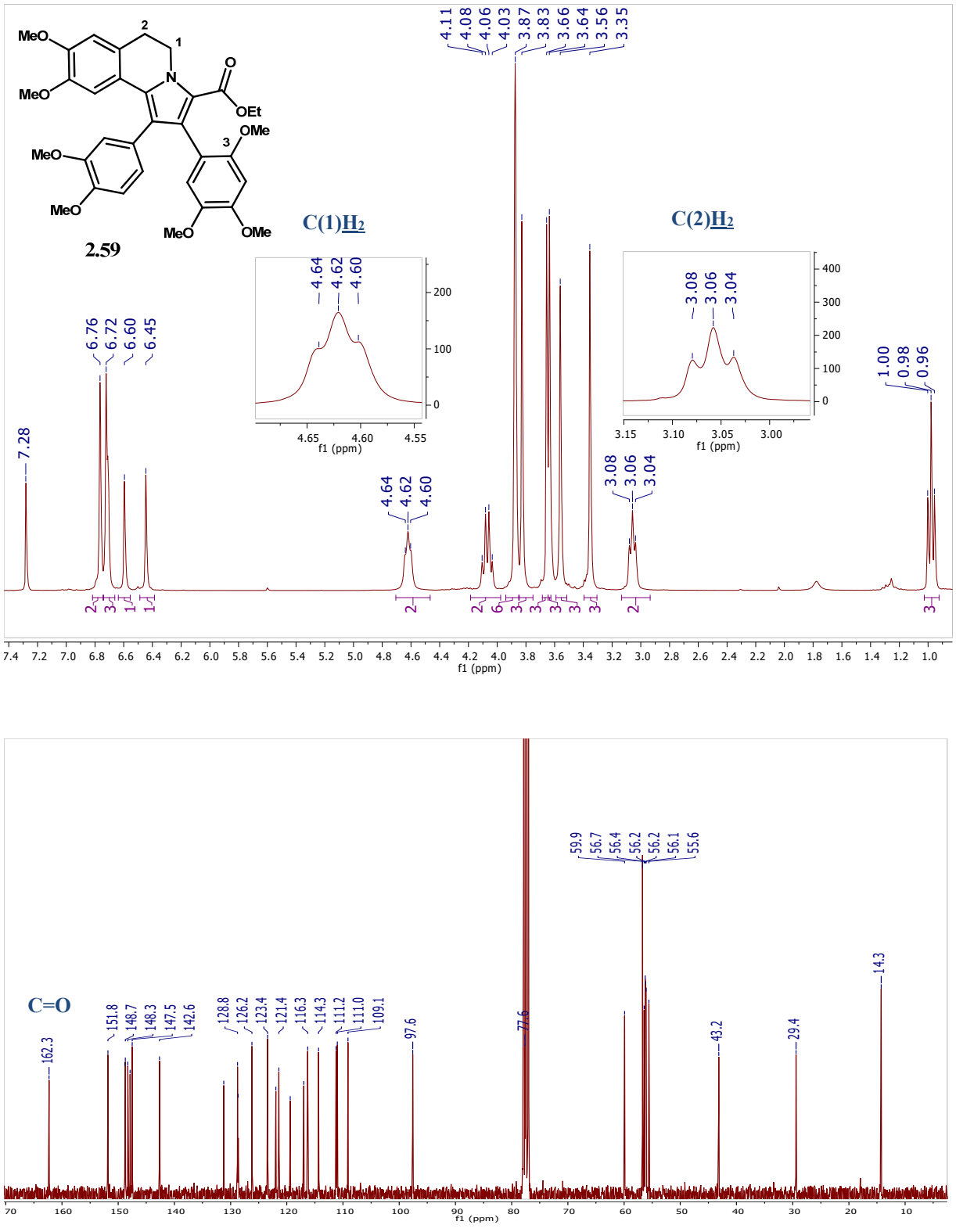
Scheme 2.18. [4+1] Two-step cycloaddition strategy implemented by Iwao *et al.* (1997).[51]



Reagents and conditions: i. $BrCH_2CO_2Et$, then cat. HCl, MeOH; ii. Et_3N, CH_2Cl_2, 34% (3 steps).

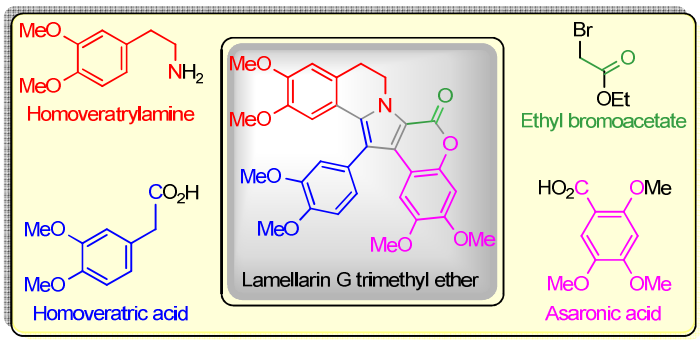
The endocyclic unsaturation of their intermediates is in stark contrast to our case, where the isoquinoline ring is saturated and the exocyclic unsaturated intermediates **2.57** and **2.58** (*Scheme 2.17*) are the most stable tautomers. N-alkylation of their pyridine system **2.60** on nitrogen was relatively ready in comparison to ours, because of the available non-conjugated nitrogen lone pair. However, subsequent cyclization of **1.61** to the desired pyrrole ring is relatively onerous, whereas ours was spontaneous. The impeded cyclization of their N-alkylated intermediates **1.61** as compared to ours, **2.58**, stems from the fact that the aromaticity of the pyrrole ring cannot be immediately established after dehydration of the carbonyl of **2.61**. Instead, the cyclic iminium product **2.62** must undergo an additional deprotonation event, at the thermodynamic expense of losing aromaticity of the pyridinium ring system. Although the resultant pyrrole **2.63** is aromatic and the isoquinoline ring product is conjugatively stabilized, the net thermodynamic stabilization of the process is lower than in our case, as it comes at the expense of losing some degree of aromaticity of the pyridine ring. Consequently, cyclization of their N-alkylated pyridinium intermediate **2.61** was slow and occurred alongside considerable decomposition, providing the target pyrrole **2.63** in a low yield of 34%. Our method circumvents these problems by making use of the non-pyridinyl enaminone **2.57**, which cyclizes spontaneously in-situ, in a single mechanistic step from **2.58**, without any loss in aromaticity.

Figure 2.6. ^{1}H and ^{13}C NMR spectra of pyrrole product **2.59**.



At this stage, the groundwork had been laid for application of this [4 + 1] cycloaddition reaction to the synthesis of the lamellarins themselves. *Chapters 3-5* to follow are comprised of three unique publications in the field of lamellarin synthesis, all of which make use of this enaminone-based approach to pyrrole formation. In *Chapter 3*, this reaction was utilized as described above, using tripotassium phosphate as base, under microwave irradiation. In *Chapters 4* and *5,* an improved method is described, with sodium bicarbonate as base and conventional heating at 80°C for 24 hours. This method circumvents the formation of the by-products arising from the alkylation of ethyl bromoacetate by the phosphate anion, thus allowing for the more effective purification of the pyrrole products, either by a short chromatographic separation, or by recrystallization. Our [4 + 1] cycloaddition reaction proved to be reliable and exceptionally high yielding, consistently providing all of the various multisubstituted pyrroles described in *Chapters 3-5* in yields of above 90%.

Chapter 3: A Xylochemically Inspired Synthesis of Lamellarin G Trimethyl Ether via an Enaminone Intermediate



3.1 Foreword

The work pertaining to this chapter was performed at the Johannes-Gutenberg University in Germany, where I spent three months working under the Supervision of Prof. Dr. Till Opatz in 2018. The main findings of this research were subsequently published in 2019, and the corresponding paper serves as *Chapter 3* of this thesis.[81] The primary goal of the project was to continue developing the enaminone approach to lamellarin synthesis that was introduced in *Section 2.3.2*, but with methodological alterations that were comparatively "green".[108,109] The most essential requirement was to make use of precursors, reagents and solvents that could be derived from xylochemical sources.[110] Furthermore, the avoidance of toxic reagents and solvents, as well as unnecessary chromatographic purifications, was desirable. Our goal was to utilize the [4 + 1] cycloaddition strategy that we had developed at Wits (described in *Section 2.3.2*), as a key reaction to prepare the pyrrolo[1,2-*a*]isoquinoline **5** (*Scheme 1* of attached publication), which had been previously synthesized by the Opatz group and others.[111,112] This was the penultimate intermediate in the successful preparation of lamellarin G trimethyl ether (**3**), after catalytic hydrogenolysis of the benzyl ether protecting group.[113,111] One of the major modifications to the synthetic strategy that we had already partially developed at Wits was to find a xylochemically based, and atom economical, route to the enaminone **4.** The Eschenmoser-sulphide contraction method we had been utilizing at Wits is unsuitable for a project related to green chemistry, because the associated use of a phosphine and non-catalytic base is not atom economical, nor can these reagents be obtained from xylochemical sources.[109,114] An important feature of the route described is that the target alkaloid was obtained in the second-highest overall yield reported to date.

3.2 Declaration

All experimental work reported within the attached publication was performed exclusively by me, without any contribution from other students. Every single experimental method detailed therein was performed by me alone. Furthermore, the initial drafts of the publication were also prepared by me.

3.3 Publication details

Title of paper: A Xylochemically Inspired Synthesis of Lamellarin G Trimethyl Ether via an Enaminone Intermediate

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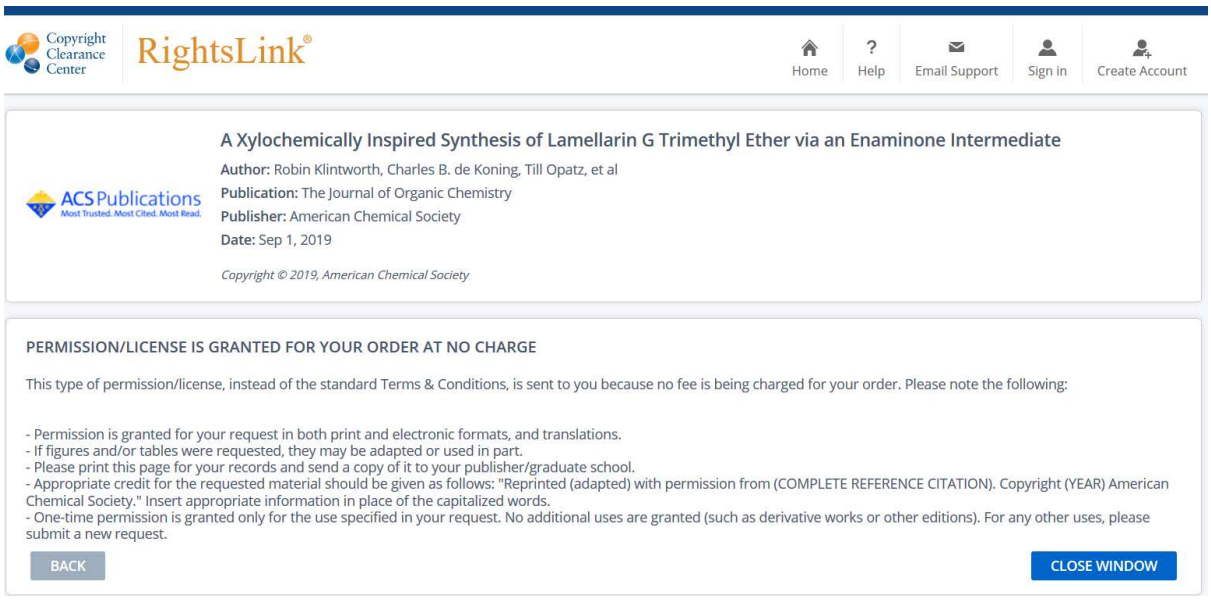

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Cite This: J. Org. Chem. 2019, 84, 11025−11031 pubs.acs.org/joc

A Xylochemically Inspired Synthesis of Lamellarin G Trimethyl Ether via an Enaminone Intermediate

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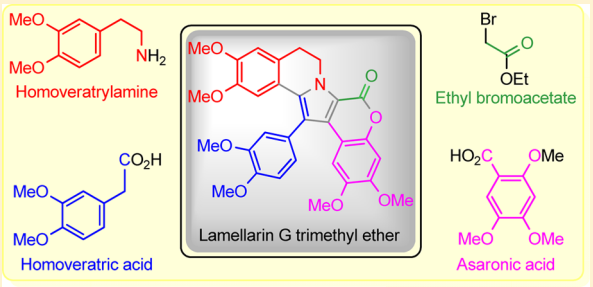
Supporting Information

ABSTRACT: A concise high yielding synthesis of lamellarin G trimethyl ether has been achieved from precursors and solvents that can in principle be derived from xylochemical (woody biomass) sources. The route is comparatively green in that some reactions are performed without solvent or with relatively benign solvents. In addition, chromatographic purification of products is avoided, and only a single aqueous workup is performed. The novelty of the synthesis lies in the intermediacy of an enaminone for the construction of the central pyrrole ring. The overall yield of the product is among the highest reported to date.



INTRODUCTION

Lamellarins are an interesting and topical group of alkaloids found in a variety of marine invertebrates, including molluscs, sponges, and tunicates.[1,2] Most of these alkaloids are characterized by a highly oxygenated fused pentacyclic skeleton containing a central pyrrole core and a pendent aromatic ring at C-1, as seen in lamellarins D (**1**) and G (**2**) (Figure 1).

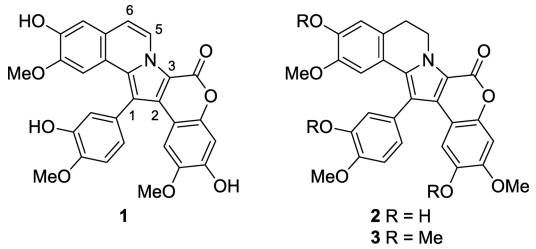


Figure 1. Lamellarin D (**1**), lamellarin G (**2**), and lamellarin G trimethyl ether (**3**).

Since many lamellarins exhibit potent cytotoxicity,[2] most notably as potential anticancer agents,[3] there has been considerable interest in the development of synthetic strategies for constructing their 1-aryl-6*H*-chromeno-[4′,3′:4,5]pyrrolo-[2,1-*a*]isoquinolin-6-one framework.[4,5] Lamellarin G trimethyl ether (**3**), although not itself a natural product, is a popular target for synthesis[6] and provides a touchstone for evaluating new approaches to the formation of the fused pentacyclic lamellarin scaffold.

In the interests of devising an environmentally responsible route to **3**, we sought a method that avoided, as far as possible, the use of noxious precursors, tedious chromatographic purifications, and undesirable (especially chlorinated) solvents. Furthermore, in pursuance of our current efforts to sidestep coal- and petroleum-derived precursors for the synthesis of natural products,[7] we have chosen to begin with oxygenated aromatic precursors ("xylochemicals") that can formally be derived from the valorization of lignin and lignocellulose.[8] In this article, we disclose a new efficient, essentially green, convergent route that yields **3** in an overall yield of 58−61% based on commercially available homoveratric acid—the second highest to date (cf. 69% overall yield based on 3,4-dimethoxyphenylacetonitrile[6e]).

RESULTS AND DISCUSSION

Most reported syntheses of the pentacyclic lamellarins proceed via precursors or intermediates already possessing a suitably functionalized pyrrole core onto which the additional rings are elaborated.[9] Less commonly, the pyrrole ring is created by cyclization involving condensation or cycloaddition between an isoquinoline precursor and moieties that supply either the C-1/C-2/C-3 or the C-2/C-3 components of the targets.[10] Even rarer are approaches in which the pyrrole ring is formed by the attachment of a building block that provides only C-3, with most or all of the lamellarin's carbon framework already in place.[11] The disconnection envisaged in the present approach is of the latter type (Scheme 1). The reason for this choice of strategy arises from our long-standing interest in the use of enaminones as intermediates for the synthesis of alkaloids and other nitrogen heterocycles.[12,13] We visualized a pivotal role for the enaminone **4** in a late-stage assembly of the pyrrole. By reacting this intermediate with a bifunctional reagent such as ethyl bromoacetate, we believed we could take advantage of the enaminone's nucleophilicity at nitrogen in displacing the halide and its electrophilicity at the carbonyl substituent by

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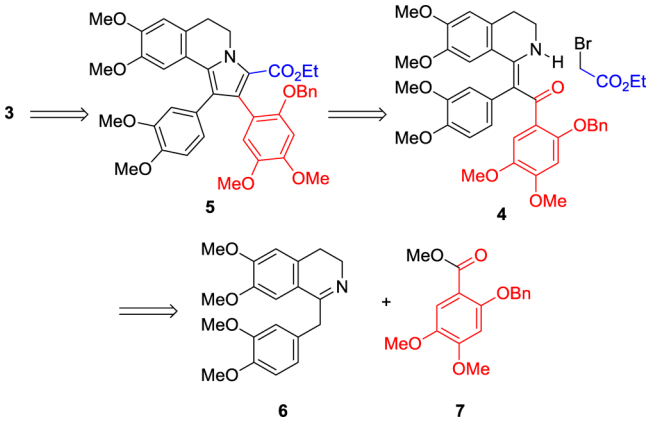
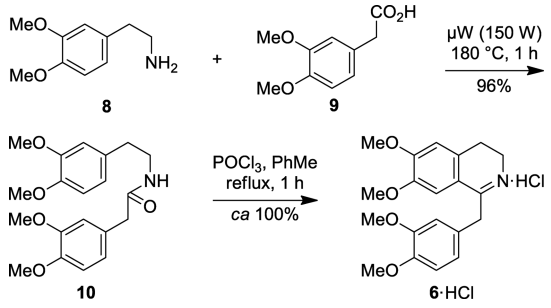
Scheme 1. Retrosynthetic Analysis for Lamellarin G Trimethyl Ether (3)



condensation with the α-methylene site of the ester. This process installs the required heterocycle in a formal [4 + 1] cycloaddition, thus forming the known intermediate **5**, which has been converted into the target **3** after hydrogenolysis of the benzyl ether.[6i] Such a route to the pyrrole hub of lamellarins via an enaminone appears to be unprecedented, although a similar but low yielding reaction between ethyl bromoacetate and a fully unsaturated isoquinoline precursor containing a small amount of enaminone tautomer was used by Iwao and co-workers in their synthesis of lamellarin D.[11b] Other syntheses of pyrroles by [4 + 1] cycloaddition between enaminones and α-halo esters are virtually unknown.[14] Enaminone **4** itself was considered to be accessible by base-mediated C-acylation of dihydropapaverine (**6**) with a functionalized benzoate such as **7** in an aza-enolate variant of a Claisen condensation, the resulting imine then equilibrating to the hydrogen-bonded enaminone tautomer **4**. The envisaged acylation of a lithiated azaenolate (ketimine α-anion) on carbon rather than on nitrogen is precedented; reactions with esters[15] or other acylating agents[16] have been reported to give various enaminones (vinylogous amides and related products) in fair to excellent isolated yields in most cases. Although dihydropapaverine is a common synthetic precursor for lamellarins,[4] its use in this manner has not been reported previously.

Our synthesis of lamellarin G trimethyl ether (**3**) began with two commercially available precursors, homoveratrylamine (**8**) and homoveratric acid (**9**). Both can be made in several steps from vanillin,[17−19] a common xylochemical derived from lignin by hydrothermal depolymerization[8a] or electrolysis.[20] Their condensation to form the amide **10** was accomplished in the absence of solvent in a slight modification of a reported procedure[21] by heating equimolar quantities of the reactants at 180 °C in a closed microwave vessel at a power setting of 150 W for 1 h (Scheme 2). After this time, NMR spectroscopy showed no trace of the precursors. Trituration of the reaction mixture with ethyl acetate afforded pure amide **10** in 96% yield. Its cyclization to the hydrochloride salt of dihydropapaverine (**6**) was accomplished by the Bischler−Napieralski reaction, which was performed by heating **10** with phosphorus oxychloride in toluene. The crude product precipitated when the hot reaction mixture was cooled, and it could be obtained in crystalline form after trituration with cold toluene followed by brief heating at the boiling point of the solvent. However, the salt was found to absorb atmospheric moisture rapidly to

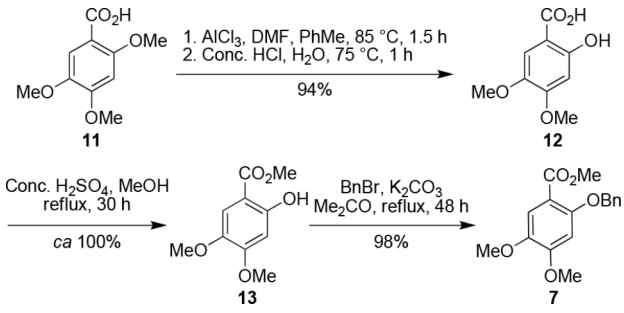
Scheme 2. Modified Synthesis of Dihydropapaverine Hydrochloride (6·HCl)



give a hydrate, traces of which were always apparent in its ^{1}H NMR spectrum at approximately 2.3 ppm. For the further reaction, the salt could be dried by heating under vacuum at 100 °C. We also found that, although dihydropapaverine itself could be released from the salt by treatment with aqueous ammonia, the free base was not easy to purify and very unstable to benzylic oxidation during storage, as has been reported previously.[22] The hydrochloride salt was therefore used in the ensuing reactions (vide infra).

The protected benzoate **7** required for the C-acylation of **6** was made in three steps from another commercially available compound, asaronic acid (**11**), which can itself be prepared from the natural product asarone by heating with potassium permanganate in a basic medium.[23] Despite the presence of three methoxy substituents in **11**, selective demethylation of the ether ortho to the carboxylic acid was accomplished in 94% yield according to a patented procedure by stirring **11** in hot toluene with aluminum trichloride solubilized in situ with dimethylformamide, followed by hydrolysis of the crude mixture with hydrochloric acid[24] (Scheme 3). Alternative

Scheme 3. Conversion of Asaronic Acid (11) into Methyl 2-Benzyloxy-4,5-dimethoxybenzoate (7)



procedures reported in the same patents and that employ either sodium bromide and boron trifluoride etherate in ethyl acetate or titanium tetrachloride in ethyl acetate reportedly gave lower yields of the desired *o*-hydroxy acid **12**. Fischer esterification of **12** with methanol and sulfuric acid afforded the ester **13** after which benzylation of the liberated phenol under standard conditions completed the synthesis of the requisite building block **7** in 92% overall yield based on asaronic acid.

With both the imine hydrochloride **6**·HCl and the substituted benzoate **7** in hand, the assembly of the key enaminone **4** was tackled. As mentioned before, the hygroscopic hydrochloride salt needed to be dried in vacuo at 100 °C before being used.

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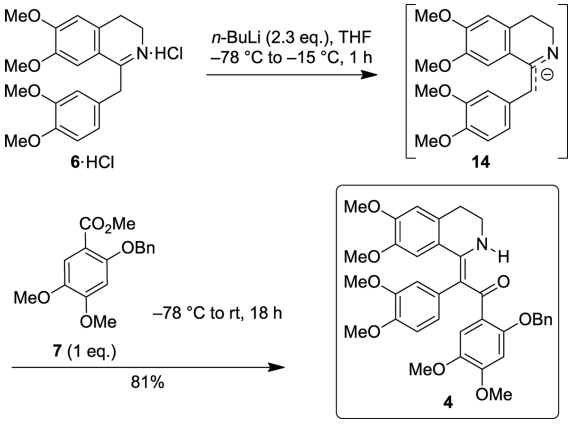
The deprotonation of the salt was then performed in tetrahydrofuran at −78 °C with *n*-butyllithium (2.3 equiv), the first equivalent of which neutralized the protonated base (Scheme 4). Formation of **14**, the putative aza-enolate of **6**,

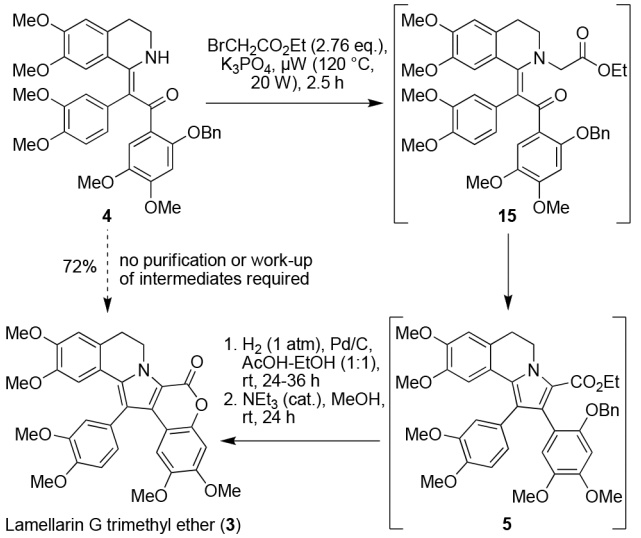
Scheme 4. Formation of the Key Enaminone Intermediate 4



was indicated by the development of a deep maroon-colored solution. Subsequent addition of the ester **7** and gradual warming of the reaction mixture to room temperature saw the color changing to yellow, which deepened overnight. The aqueous workup with neutralization of the excess base, extraction with ethyl acetate, and filtration of the extracts through a short plug of silica gel followed by removal of the solvent gave chromatographically and spectroscopically pure enaminone **4** as a bright yellow solid in 81% yield. That the product **4** exists as the enamine, rather than the imine, tautomer was indicated by the signal for the intramolecularly hydrogen-bonded N−H substituent in the ^{1}H NMR spectrum, which was located at 13.22 ppm. This intramolecular hydrogen bonding also implies that **4** is the (*Z*)-geometric isomer. The distinctive signal for the carbonyl group in the ^{13}C NMR spectrum was found at 192.2 ppm.

It was now the moment of truth for finding out whether enaminone **4** would indeed prove to be a suitable scaffold on which to construct the target's pyrrole ring. Although the ambident nucleophilicity of enaminones in general appears to favor the intermolecular reaction with alkylating agents (among other electrophiles) at the enamine carbon site rather than nitrogen,[25] we reasoned that steric hindrance at this site in our intermediate would deflect alkylation with ethyl bromoacetate toward nitrogen, presumably giving the *N*-alkyl compound **15** en route to the pyrrole-containing intermediate **5**. Encouraged by some preliminary results with related crowded enaminones,[26] we devised a set of reaction conditions for the heterocycle formation that entailed dissolving **3** in just enough ethyl bromoacetate (2−3 equiv) with anhydrous tripotassium phosphate as the base and irradiating the mixture under a low microwave power of only 20 W, as the inorganic salt is a highly effective absorber of microwave energy (Scheme 5). An internal temperature of 120 °C was reached within a few minutes, and heating was maintained for 2.5 h. At this stage, the bright yellow color of the enaminone had vanished, and both TLC and NMR spectroscopy indicated complete consumption of **3**. The NMR spectrum of the crude mixture also showed that some ethyl bromoacetate was still present along with contaminants arising from concomitant alkylation of the phosphate anion by ethyl bromoacetate (including

Scheme 5. Telescoped Final Steps in the Synthesis of Lamellarin G Trimethyl Ether (3)



triethyl 2,2′,2″-[phosphoryltris(oxy)]triacetate[27] and mono- and di-alkylated analogues). The entire mixture containing the putative intermediate **5** was transferred into a hydrogenation flask together with a catalytic amount of palladium on carbon (10%) under a balloon of hydrogen gas. The mixture was left to stir for 24−36 h until NMR showed no trace of the benzyl protecting group or of residual toxic ethyl bromoacetate, which was also destroyed during the hydrogenation. To telescope the final suite of reactions even further, the solvent was removed, and the residue was suspended in methanol containing a few drops of triethylamine to neutralize any remaining acetic acid, as well as to promote lactone formation. After overnight stirring at room temperature, lamellarin G trimethyl ether (**3**) had precipitated cleanly from the solution and could easily be filtered off, leaving all remaining contaminants in solution. The yield of **3** from enaminone **4** by this four-step tandem process was 72%. (This yield could be improved to 79% when triethylamine was replaced by DBU, but this base cannot be made easily from xylochemical precursors.) The ^{1}H NMR spectroscopic data obtained for lamellarin G trimethyl ether were within 0.03 ppm of those reported for the same compound in a recent publication,[6e] while the ^{13}C values were within 0.2 ppm.

CONCLUSIONS

The overall yields of lamellarin G trimethyl ether (**3**) based on homoveratric acid (**9**) and asaronic acid (**11**), both of which can in principle be derived from nonpetrochemical sources, are 56 and 66%, respectively, when triethylamine is used as the basic catalyst in the final step (61 and 73%, respectively, when nonxylochemical DBU is used as the base). The most efficient route to **3** hitherto reported results in a 69% overall yield based on 3,4-dimethoxyphenylacetonitrile.[6e] Our new route incorporates the novel use of enaminone **4** in the late-stage construction of the central pyrrole ring and telescopes this step into a tandem sequence of reactions that ultimately give the target product. The route employed is substantially green in that it eschews chlorinated solvents as well as chromatographic purification of intermediates, most of which could be obtained spectroscopically pure by crystallization or precipitation from the reaction medium. When solvents and certain

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other reagents (among them ethyl bromoacetate and *n*-butyllithium) are necessary for the reaction or purification, they can in principle be derived from xylochemically derived precursors such as methanol, ethanol, and butanol. The reaction conditions include only a single aqueous workup and one filtration through silica gel, and microwave heating in the absence of solvent is employed in two steps.

EXPERIMENTAL SECTION

Solvents were dried and purified, where necessary, by appropriate standard procedures. All other chemicals were purchased from commercial sources (Sigma-Aldrich, Alfa Aesar, Carbolution Chemicals, Acros Organics) and used as received unless mentioned otherwise. All reactions were performed under an inert atmosphere of argon in oven-dried glassware. Microwave heating was performed in capped vials of an appropriate size in a CEM Discover microwave reactor, and temperature was monitored by means of an external surface sensor. An oil bath was used for conventional heating. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker Avance III HD 300 spectrometer at frequencies of 300 and 75 MHz, respectively. Chemical shifts (δ) of ^{1}H signals are reported as parts per million (ppm) downfield from Me_4Si as an internal reference, while carbon resonances are referenced to the residual solvent signal. Deuterated solvents for NMR measurements were obtained from Deutereo and used as received. FT-IR spectra were recorded on a Tensor 27 spectrometer (Bruker) equipped with a diamond ATR unit. High-resolution masses (ESI) were recorded on a Q-ToF-Ultima 3 instrument (Waters) with a LockSpray interface and a suitable external calibrant. Thin-layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates (Merck). Compounds were visualized using UV light and/or by immersion in a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), 5% aqueous NaOH (5 mL), and water (300 mL) followed by heating.

***N*-(3,4-Dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-acetamide (10).** Method adapted from ref.[21] To 3,4-dimethoxyphenylacetic acid (homoveratric acid, **9**) (1.0 g, 5.1 mmol) in a microwave vial was added 3,4-dimethoxyphenethylamine (homoveratrylamine, **8**) (954 mg, 5.26 mmol). The vial was capped, and the mixture was heated in a microwave reactor (180 °C at 50 W power) for 1 h until an NMR spectrum of a sample showed complete formation of amide **10**. The residue in the vial was suspended in EtOAc (10 mL), and the resulting precipitated solid was filtered to provide amide **10** (1.757 g, 96%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.81 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 5.1 Hz, 1H), 6.70 (d, J = 6.3 Hz, 2H), 6.63 (d, J = 2.0 Hz, 1H), 6.53 (dd, J = 8.1, 2.0 Hz, 1H), 5.44 (br s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.84 (s, 6H), 3.49 (s, 2H), 3.48–3.40 (m, 2H), 2.69 (t, J = 6.9 Hz, 2H). The chemical shifts are within 0.01 ppm of those reported in the literature.[21]

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Hydrochloride (3,4-Dihydropapaverine Hydrochloride) (6·HCl). To a suspension of *N*-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide (**10**) (1.40 g, 3.9 mmol) in toluene (80 mL) was added $POCl_3$ (0.8 mL, ca. 1.31 g, ca. 8.5 mmol) dropwise at room temperature. The mixture was heated under reflux for 1 h under an inert atmosphere of Ar gas and then allowed to cool to room temperature. The cooled viscous precipitate of the crude imine HCl salt was triturated under toluene until it began to solidify as an off-white solid. [Note that this process was quite unpredictable but could be promoted by the addition of a seed crystal of the dry product, with the addition of diethyl ether, or simply by cooling the flask overnight in a freezer.] The solvent was reheated to its boiling point at which it was maintained for some minutes until the colorless solid had taken on a crystalline appearance. The suspension was filtered while still hot, washed with toluene (or diethyl ether for ease of drying), and immediately dried under vacuum to prevent adsorption of atmospheric water (hydrate detectable at 2.3 ppm by ^{1}H NMR). Thus obtained was the almost completely dry imine hydrochloride **6**·HCl as a fluffy white solid (1.53 g, quant.), m.p. 201–205 °C (lit., 106–115 °C;[28] 114–117 °C;[29] 186 °C[30]). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 14.20 (br s, 1H), 7.37 (s, 1H), 7.07 (d, J = 1.8 Hz, 1H), 6.89 (dd, J = 8.2, 1.8 Hz, 1H), 6.80 and 6.78 (superimposed s and d, J = 8.4 Hz, 2H), 4.48 (s, 2H), 3.99 (s, 3H), 3.95 (br s, 2H), 3.89 (s, 6H), 3.83 (s, 3H), 3.03 (t, J = 7.7 Hz, 2H). The chemical shifts are in broad agreement with those reported in the literature.[29]

2-Hydroxy-4,5-dimethoxybenzoic Acid (12). Method adapted from ref.[24] Anhydrous $AlCl_3$ (6.28 g, 47.1 mmol) was suspended in dry toluene (20 g) under an inert atmosphere of Ar gas. DMF (20 g, 273 mmol) was added dropwise at room temperature, which caused the evolution of heat and the solubilization of $AlCl_3$, presumably as a DMF chelate. 2,4,5-Trimethoxybenzoic acid (asaronic acid, **11**) (10.0 g, 47.1 mmol) was added, and the mixture was heated at 85 °C for 1.5 h. Once the mixture had cooled, concentrated HCl (35%, 5.89 g) was added dropwise, followed by water (17 mL). Heating at 75 °C for 1 h resulted in precipitation of a solid, which was collected by filtration, washed with water, and dried to provide **12** (8.76 g, 94%) as a colorless solid, m.p. 200–211 °C (lit.,[31] 210 °C decomp.). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 13.51 (v br s, 1H), 11.31 (v br s, 1H), 7.17 (s, 1H), 6.56 (s, 1H), 3.81 (s, 3H), 3.71 (s, 3H).

Methyl 2-Hydroxy-4,5-dimethoxybenzoate (13). A suspension of 2-hydroxy-4,5-dimethoxybenzoic acid (**12**) (5.0 g, 25.2 mmol) in MeOH (120 mL) containing sulfuric acid (95%; 5.2 g, 50.4 mmol, 2 equiv) was heated at reflux for 30 h, after which time NMR spectroscopy of a sample showed the reaction to be complete. Addition of an equal volume of water (120 mL) resulted in precipitation of a colorless solid, which was collected by filtration to provide the methyl ester **13** (5.34 g, quant.), m.p. 92–93 °C (lit.,[32] 94–94.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 10.73 (s, 1H), 7.19 (s, 1H), 6.47 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 170.3, 158.3, 155.7, 142.1, 110.3, 103.1, 100.2, 56.3, 56.2, 52.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{13}O_5$, 213.0757; found, 213.0760.

Methyl 2-Benzyloxy-4,5-dimethoxybenzoate (7). Benzyl bromide (4.70 g, 27.5 mmol, 1.1 equiv) was added to a suspension of methyl ester **13** (5.34 g, 25.2 mmol) and anhydrous K_2CO_3 (10.6 g, 76.7 mmol) in acetone (200 mL). The mixture was heated under reflux for 48 h, at which time the reaction was shown to be complete by TLC and NMR spectroscopy. The solids were removed by filtration and washed with acetone, and the combined organic phase was evaporated in vacuo to yield an oil. Dissolving in EtOAc (addition of cyclohexane was found to promote crystallization in some cases) led to the formation of **7** as white needles (7.47 g, 98%), m.p. 101–102 °C. IR (ATR, cm^{-1}) ν_{max}: 2988 (w), 2968 (w), 2902 (w), 1721 (s), 1518 (m), 1433 (m), 1382 (m), 1346 (m), 1248 (s), 1216 (s), 1199 (s), 1158 (s), 1077 (s), 1037 (m), 1014 (s), 813 (m), 750 (m), 699 (m). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.56–7.48 (m, 2H), 7.44 (s, 1H), 7.44–7.30 (m, 3H), 6.56 (s, 1H), 5.16 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 166.2, 154.4, 153.3, 143.2, 136.9, 128.5, 127.9, 127.2, 114.1, 111.9, 100.6, 72.6, 56.3, 56.0, 51.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{19}O_5$, 303.1227; found, 303.1235.

(*Z*)-1-[2-(Benzyloxy)-4,5-dimethoxyphenyl]-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-2-(3,4-dimethoxyphenyl)ethanone (Enaminone 4). The imine hydrochloride **6**·HCl (250 mg, 0.66 mmol) was heated to 100 °C under vacuum and with constant stirring for 1 h to remove traces of moisture. The reaction flask was then immediately flushed with dry Ar gas, and the solid was suspended in freshly distilled dry THF (5 mL). The mixture was cooled to −78 °C in an acetone/dry ice cooling bath after which *n*-butyllithium (1.6 M in hexanes; 0.95 mL, 1.52 mmol, 2.3 equiv) was added by a syringe. The mixture became homogeneous, and a deep maroon-red color developed. The solution was then warmed to −15 °C in a bath made by adding dry ice to a saturated brine solution until water ice had covered the dry ice pellets. The solution was left to stir for 1 h, after which time the red color had ceased to deepen. The solution was again cooled to −78 °C, and methyl 2-(benzyloxy)-4,5-dimethoxybenzoate (**7**) (201 mg, 0.66 mmol, 1 equiv) in freshly distilled dry THF (3 mL) was added dropwise such that the internal temperature remained constant. The

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solution's red color remained throughout the addition and began to fade slowly hereafter. Stirring was continued at −78 °C for 5 min after which the solution was allowed to reach room temperature. As the solution warmed, the deep red color changed to pale yellow, which intensified to a rich yellow color after 18 h. The residual base was neutralized with concentrated aq NH_4Cl solution. EtOAc (50 mL) was added to allow for a manageable volume at this small scale, and the organic phase was separated, washed with brine, dried (Na_2SO_4), and filtered through a short plug of silica gel, which was washed with additional EtOAc until all of the yellow eluents had been collected. After removal of the solvent, chromatographically pure enaminone **4** (328 mg, 81%) was obtained as a yellow solid, m.p. 89−90 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 13.22 (s, 1H), 7.42−7.25 (m, 8H), 6.65 (s, 1H), 6.58 (s, 1H), 6.54−6.47 (m, 2H), 6.43 (dd, J = 8.2, 1.9 Hz, 1H), 6.40 (s, 1H), 6.27 (s, 1H), 4.92 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.61−3.47 (m, 2H), 3.42 (s, 3H), 3.16 (s, 3H), 3.01−2.80 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 192.2, 158.7, 150.0, 148.7, 148.6, 148.2, 146.9, 146.0, 142.9, 138.0, 133.6, 132.1, 128.3, 127.5, 126.9, 126.1, 125.8, 121.4, 116.6, 114.1, 111.9, 110.4, 109.8, 107.1, 99.7, 71.9, 56.3, 55.85, 55.80, 55.77, 55.7, 55.1, 39.2, 28.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{36}H_{38}NO_8$, 612.2592; found, 612.2588.

Lamellarin G Trimethyl Ether (3). (a) Enaminone **4** (100 mg, 0.16 mmol) was dissolved in a minimum of ethyl bromoacetate (50 μL, ca. 75 mg, ca. 0.45 mmol, ca. 2.76 equiv) in a microwave vessel to which anhydrous K_3PO_4 (100 mg, 0.47 mmol) was added. The vessel was capped, and the bright yellow suspension was stirred gently while being heated to 120 °C in a microwave reactor (20 W power) for 2.5 h, at which stage the yellow color had disappeared, and an almost colorless supernatant solution had been formed. TLC showed that the enaminone (R_f, 0.4; EtOAc) had been replaced by a single brilliant blue fluorescent spot (R_f, 0.8; EtOAc), and signals for the enaminone were also absent from the NMR spectrum of the crude reaction mixture.

The entire contents of the microwave vial, including solids, were transferred to a hydrogenation flask with 50% glacial AcOH in EtOH (50 mL). The flask was briefly flushed with Ar gas before the addition of Pd/C (10%; 10% of the total mass of crude material; 17.5 mg). The suspension was stirred at room temperature under an atmosphere of H_2 (balloon pressure) until the reaction was shown to be complete by NMR spectroscopy (24−36 h). The solution was filtered through Celite, which was then rinsed with EtOAc (100 mL). The solvent was removed on a rotary evaporator to yield a pale amber oily residue. MeOH (20 mL) containing a few drops of NEt_3 was added, and the solution was left to stir at room temperature. Within 1−2 h, crystals of lamellarin G trimethyl ether (**3**) had begun to develop. After 24 h, the precipitated material was collected by filtration and rinsed with MeOH. After drying, lamellarin G trimethyl ether (**3**) (64 mg, 72%) was obtained as a white solid, m.p. 246−247 °C (lit., 235−236 °C;[6e] 233−234 °C;[6f] 238−239 °C;[6h] 239.1−240.7 °C[33]). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.14 (dd, J = 8.1, 1.8 Hz, 1H), 7.11−7.05 (m, 2H), 6.90 (s, 1H), 6.78 (s, 1H), 6.73 (s, 1H), 6.68 (s, 1H), 4.79 (sept, J = 6.6 Hz, 2H), 3.97 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.48 (s, 3H), 3.38 (s, 3H), 3.13 (t, J = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 155.5, 149.7, 149.0, 148.83, 148.75, 147.5, 146.1, 145.6, 136.0, 128.2, 128.0, 126.6, 123.6, 120.0, 114.8, 114.0, 113.7, 111.9, 111.0, 110.3, 108.7, 104.5, 100.5, 56.24, 56.17, 56.0, 55.9, 55.5, 55.2, 42.4, 28.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{31}H_{30}NO_8$, 544.1962; found, 544.1966.

(b) The above procedure was repeated with enaminone **4** (47.0 mg, 0.077 mmol), ethyl bromoacetate (50 μL, ca. 75 mg, ca. 0.45 mmol, ca. 2.76 equiv), and anhydrous K_3PO_4 (120 mg, 0.57 mmol). After hydrogenolysis of the benzyl ether and workup as described above, the crude reaction mixture was dissolved in toluene (20 mL) to which a drop of DBU was added. The mixture was heated to 80 °C for 40 min. The solvent was then removed on a rotary evaporator, and the residue was suspended in MeOH (10 mL). After a few minutes, crystals of **3** began to develop. These were collected by filtration and rinsed with MeOH. After drying, lamellarin G trimethyl ether (**3**) was obtained as a white solid (33 mg, 79%) (characterization as above).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01604.

^{1}H and ^{13}C NMR spectra (PDF)

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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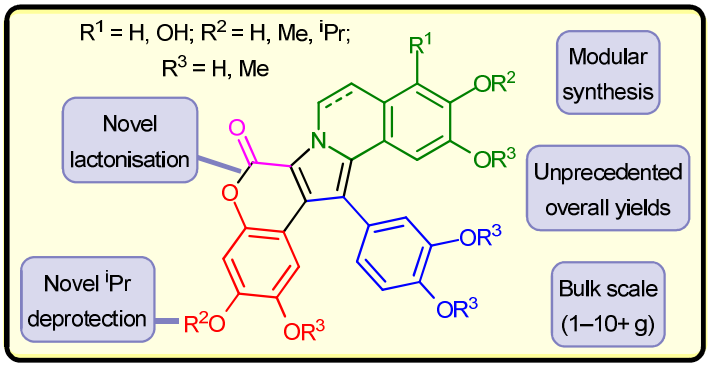
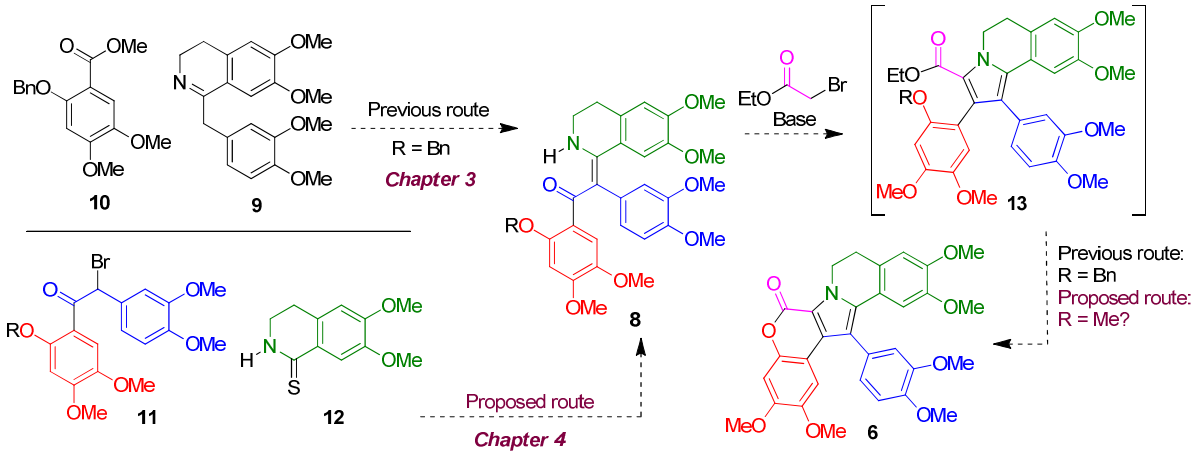
Chapter 4: Demethylative Lactonization Provides a Shortcut to High-Yielding Syntheses of Lamellarins



4.1 Foreword

The primary goal of this aspect of the project was to continue developing the Eschenmoser-sulphide contraction approach to enaminone synthesis, as described in *Section 2.2.2*. In this section, we describe the preparation of the indolizine-containing system **13** (R=Me, *Scheme 4.1*), using our [4 + 1] cycloaddition protocol. This compound is essentially a simplified methyl ether analogue of the indolizine **13** (R = Bn), which we had used as a precursor to lamellarin G trimethyl ether in the synthesis described in *Chapter 3*. During this phase of the project we had hoped to explore the viability of obtaining a selective demethylation of **13** (R = Me), to prepare lamellarin G trimethyl ether (**6**). In doing so, we would avoid the need for specific protection and deprotection strategies in the creation of ring F, by using what is essentially a methyl ether protecting group that comes preinstalled in the commercially available precursor to **11**. In the process, we succeeded in preparing the trimethyl ethers of lamellarins G and D, and lamellarins A4 and H, in the highest overall yields reported to date.

Scheme 4.1. Outline of previous and proposed routes to key enaminones **8** (R = Me), and further conversion into lamellarin G trimethyl ether (**6**).



The work pertaining to this chapter was performed at Wits, the main findings of which were published in 2020.[82] The corresponding paper is attached and serves as *Chapter 4* of this thesis.

4.2 Declaration

All experimental work reported within the attached publication was performed exclusively by me, without any contribution from other students. Every single experimental method detailed therein was performed by me alone. Furthermore, the initial drafts of the publication were also prepared by me.

4.3 Publication details

Title of paper: Demethylative Lactonization Provides a Shortcut to High-Yielding Syntheses of Lamellarins

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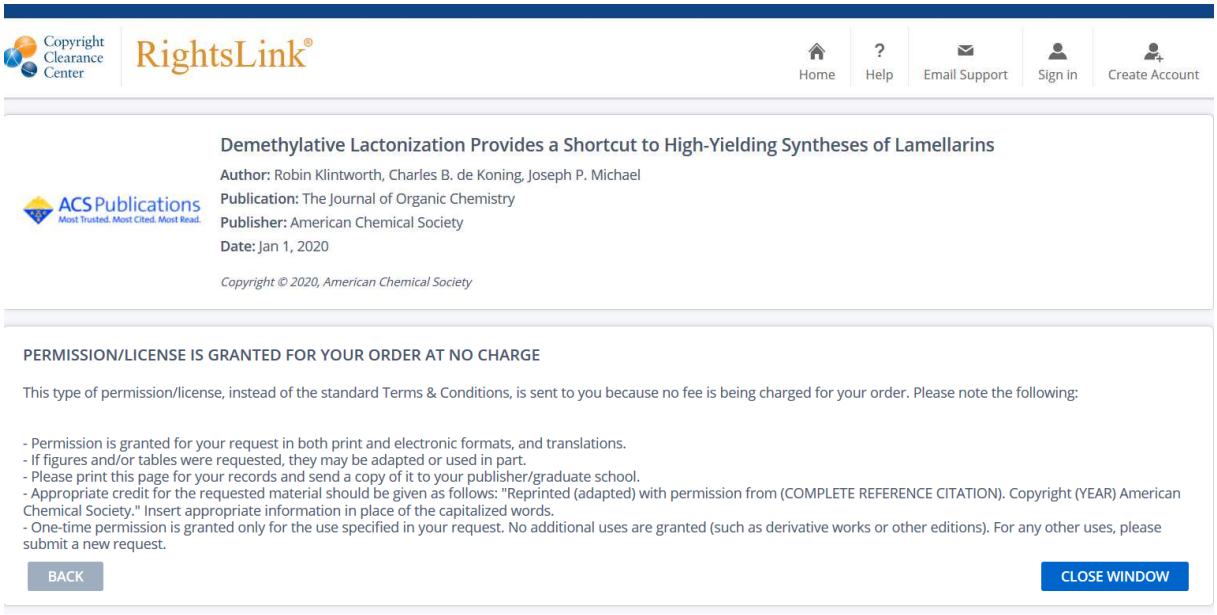

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Demethylative Lactonization Provides a Shortcut to High-Yielding Syntheses of Lamellarins

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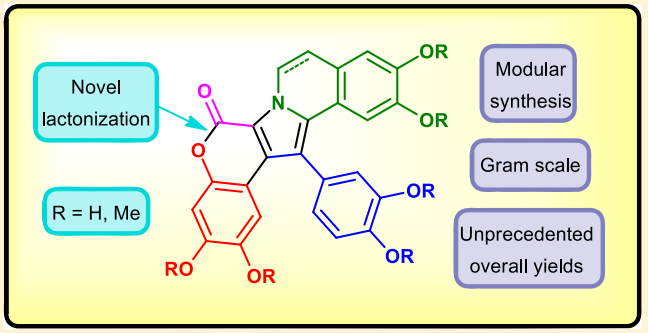
Supporting Information

ABSTRACT: Modular gram-scale syntheses of the trimethyl ethers of lamellarins G (**6**) and D (**7**) were achieved from readily accessible precursors in the highest overall yields reported to date (**6**, six steps, 82%; **7**, seven steps, 86%). A novel demethylative lactonization between an aryl methyl ether and a neighboring carboxylic acid was developed for creating the chromenone unit of the targets to avoid the need for additional protection and deprotection steps. The central pyrrole core was constructed in a late-stage [4 + 1] condensation between ethyl bromoacetate and an enaminone possessing the remaining components of the lamellarin skeleton. Exhaustive demethylation of both permethyl ethers **6** and **7** gave the polyphenolic natural lamellarins A4 (**3**) and H (**5**), respectively.



INTRODUCTION

Alkaloids are well represented among the astonishing diversity of natural products isolated from marine organisms.[1] The lamellarins, which occur in minor or trace amounts in a range of molluscs, sponges, and tunicates, form a particularly noteworthy family of nitrogen-containing marine metabolites.[2] These compounds and related natural products have attracted the attention of many research groups worldwide, and several useful reviews dedicated to their isolation, synthesis,[3] and remarkable biological activity[4] have been published.[5] Since the first members of the family were reported by Faulkner and co-workers in 1985,[6] more than 70 lamellarins and related alkaloids have been isolated to date.[7] The common structural feature of the lamellarins is a substituted pyrrole ring that, in the majority of typical cases, forms the core of a fused pentacyclic system, as shown in **1** (Figure 1, showing conventional lamellarin numbering[6]). These pentacyclic lamellarins are highly oxygenated and also bear an additional aryl substituent at C-1. Furthermore, the bond between C-5 and C-6 may be saturated, as in lamellarins G (**2**) and A4 (**3**) or unsaturated, as in lamellarins D (**4**) and H (**5**). The saturated and unsaturated modifications are representative of lamellarin classes variously designated as types 1a and 1b[2] or types I and II,[5b] respectively. The enduring interest in the lamellarins is principally due to their significant biological activity, especially the potency of certain members of the series as anticancer agents.[4,8]

We recently reported an efficient, comparatively green route to lamellarin G trimethyl ether (**6**) in which the key feature was the construction of the pyrrole ring in a [4 + 1] manner by reaction of ethyl bromoacetate with a sterically crowded enaminone possessing all of the remaining skeletal carbon atoms of the target (Scheme 1).[9] This [4 + 1] formation of the heterocyclic core at a late stage of the synthesis, uncommon in reported lamellarin syntheses,[10,11] has the advantage of giving a fully substituted pyrrole, thereby blocking the otherwise reactive pyrrole sites. We now report an alternative enaminone-based route that affords gram quantities of the trimethyl ethers of lamellarins G (**6**) and D (**7**) in the highest yields reported to date and with relatively little need for purification of intermediates. In this article, we also introduce a novel reaction: a simple and exceptionally efficient demethylative lactonization for the construction of ring D that avoids

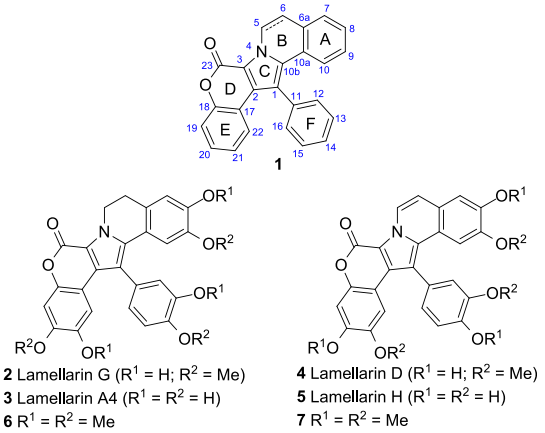


Figure 1. Lamellarin core **1** with conventional numbering;[6] natural and synthetic lamellarins **2**−**7**.

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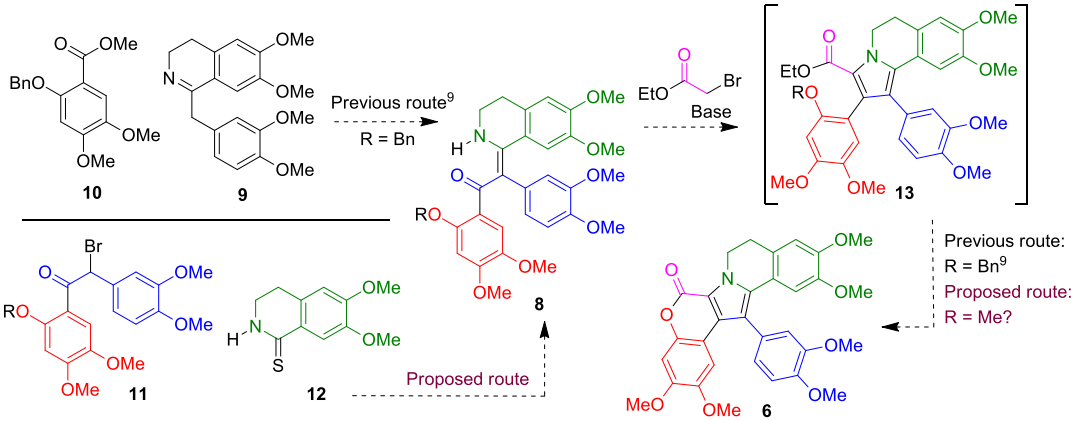
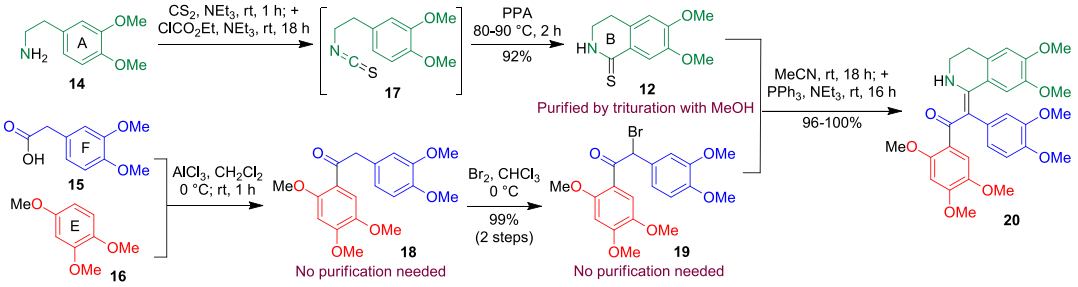
Scheme 1. Outline of Previous and Proposed Routes to Key Enaminone 8 and Further Conversion into Lamellarin G Trimethyl Ether (6)



Scheme 2. Synthesis of Key Enaminone 20



the protection−deprotection strategies common to many previously reported lamellarin syntheses.[3] The two naturally occurring polyphenolic lamellarins A4 (**3**) and H (**5**) were also obtained by exhaustive demethylation of (**6**) and (**7**), respectively.

RESULTS AND DISCUSSION

In our previous route to lamellarin G trimethyl ether (**6**), we constructed the pivotal enaminone **8** (R = Bn) by acylation of dihydropapaverine (**9**) with the benzyl-protected ester **10**[9] (Scheme 1, top). However, in view of our extensive experience in the synthesis and use of enaminones as intermediates en route to alkaloids and other nitrogen heterocycles,[12,13] we felt that the route to **6** and related lamellarins could benefit from a more versatile synthesis of **8** and analogues by using an Eschenmoser sulfide contraction[14,15] between α-bromoketones such as **11** and the dihydroisoquinolinethione **12** (Scheme 1, bottom). Furthermore, because microwave heating of **8** with ethyl bromoacetate and potassium phosphate, although very successful in our previous route, suffered from competing alkylation of the phosphate anion and the consequent contamination of the resulting 5,6-dihydropyrrolo[2,1-*a*]-isoquinoline intermediate **13** (R = Bn),[9] we believed that there was room for improvement in this step. Most pressing in our minds, however, was the need for improving the final step entailing lactonization of the intermediate **13** to form ring D. In our earlier approach, it was necessary to protect the phenol destined to become the ring oxygen because the trioxygenated ring E is otherwise susceptible to oxidative decomposition. We, like others before us,[16] chose to mask the phenol as benzyl ether; other workers have used allyl,[11a] isopropyl,[17] or methoxymethyl[18] ethers and even mesylate[19] as protecting groups. The undesirable consequence of these approaches is the need for additional protection and deprotection steps in the overall reaction sequence. In view of the widespread commercial availability of potential methoxy-containing aromatic precursors for ring E, we speculated that it might be possible to avoid these additional steps if lactonization could be effected simply from an aromatic methyl ether. Accomplishing the lactonization by intramolecular reaction of an anisole with an acyl moiety is unprecedented in lamellarin chemistry and constitutes a significant challenge in selectivity given the presence of methoxy substituents elsewhere in the targets. Our hopes in this regard were fueled by the chance finding of a small quantity of the lactone-containing product when preparing an acid chloride from intermediates akin to **13** (R = Me), as will be described below.

Our synthesis of the trimethyl ethers of lamellarins G (**6**) and D (**7**) as well as lamellarins A4 (**3**) and H (**5**) began with three cheap, readily available precursors: homoveratrylamine (**14**), homoveratric acid (**15**), and 1,2,4-trimethoxybenzene (**16**) (Scheme 2). Thiolactam **12** needed for the Eschenmoser sulfide contraction was obtained in two telescoped steps from homoveratrylamine (**14**) by adaptation of a reported method,[20] entailing formation of an intermediate isothiocyanate **17** by treatment of **14** with carbon disulfide and ethyl chloroformate, followed by cyclization with polyphosphoric acid at 80−90 °C. Trituration of the crude product with methanol afforded spectroscopically pure dihydroisoquinolinethione **12** in 92% yield. The brominated reaction partner was made in two steps: Friedel−Crafts acylation between homoveratroyl chloride (generated in situ from **15** with oxalyl chloride) and **16** was immediately followed by enolic bromination of the resulting deoxybenzoin **18** with molecular bromine in chloroform. No purification was required after

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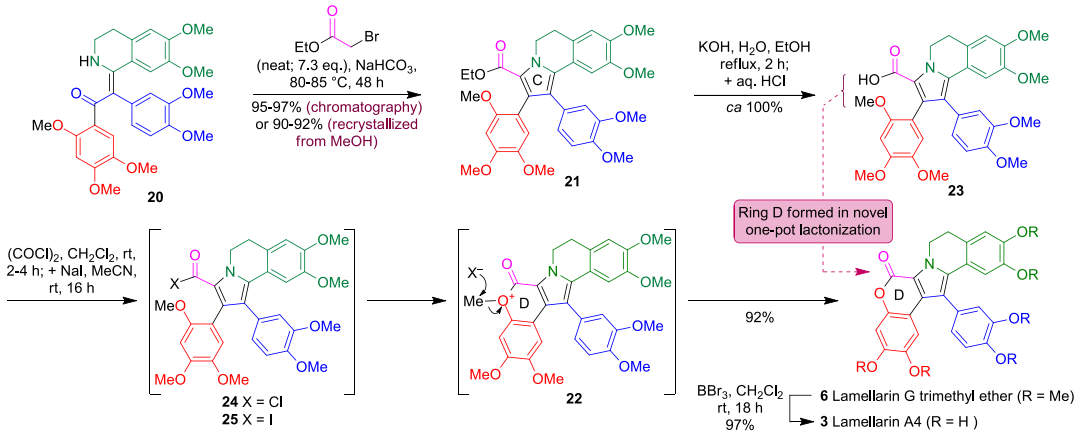
Scheme 3. Synthesis of Lamellarin G Trimethyl Ether (6) and Lamellarin A4 (3)



either step, and no bromination of the electron-rich aromatic rings was observed when the rate of bromine addition was carefully controlled. The bromoketone **19**, obtained in quantitative yield, was used without further purification in the subsequent Eschenmoser sulfide contraction step as it is unstable, especially on exposure to light. Simply mixing the two intermediates **12** and **19** (the latter in 5% molar excess) in acetonitrile allowed for the in situ formation of the thioiminium ether salt, from which the sulfur was extruded under standard Eschenmoser sulfide contraction conditions with triphenylphosphine and triethylamine. After chromatographic separation from the resulting phosphine sulfide, the heptamethoxylated enaminone **20** was obtained in consistent yields of 96−100%. The signal for the N−H substituent in the ^{1}H NMR spectrum, located far downfield at 13.24 ppm, indicated intramolecular hydrogen bonding with the carbonyl substituent of the enaminone (δ_C 192.1), thereby establishing that **20** is the (*Z*)-geometric isomer.

In our previous synthesis of lamellarin G trimethyl ether (**6**), we constructed the pyrrole ring C by microwave heating of the intermediate enaminone with excess ethyl bromoacetate and tripotassium phosphate.[9] We found that we could replace the phosphate by sodium bicarbonate, thereby avoiding the formation of alkylated phosphate byproducts. Thus, conventional heating of enaminone **20** in neat ethyl bromoacetate (1.5 mL/g of enaminone; 6−8 equiv) in the presence of the inorganic base at 80−85 °C for two days and subjecting the entire crude mixture to chromatography on silica gel provided the tricyclic product **21** in yields of 95−97% (Scheme 3). Alternatively, chromatography could be avoided entirely by recrystallizing the residue from methanol, which provided **21** in 90−92% yield. It was necessary to use the brominating agent as solvent because yields were adversely affected if concentrations were reduced when using other solvents.

At this stage, the critical lactonization needed to be optimized. As mentioned above, the chance discovery of small amounts of the lactone-containing product upon preparing the acid chloride from **21** suggested a completely new approach to the formation of ring D of the target alkaloids without the need for additional protecting groups. It seemed highly probable that the lactonization was facilitated by the proximity of the ortho-methoxy substituent on ring E to the acyl component on ring C, and that a selective halide-mediated demethylation then occurred via a cyclic intermediate such as **22**. Accordingly, hydrolysis of **21** with aqueous potassium hydroxide in an ethanol−water mixture gave a quantitative yield of carboxylic acid **23** (used without the need for further purification), from which the corresponding acid chloride **24** was prepared in situ by reaction with oxalyl chloride. We then attempted to improve the putative demethylative cyclization by adding the more nucleophilic iodide ion in the form of tetrabutylammonium iodide. While this accelerated the rate of the reaction, it still required high temperatures and long reaction times, with concomitant decomposition of the material being problematic and yields of lamellarin G trimethyl ether (**6**) never exceeding 60%. Eventually, we found that by adding sodium iodide in acetonitrile to the crude acid chloride, the lactonization could be forced to completion by way of what may possibly be a novel Finkelstein conversion of the acyl chloride **24** to the more reactive acyl iodide **25**, as evinced by the copious precipitation of sodium chloride. Not only was this reaction found to occur rapidly at room temperature but the isolated yields of the desired lamellarin derivative **6** were consistently above 90%, even when the reaction was performed on a multigram scale. As revealed by NMR spectroscopy, the product was remarkably pure directly after work-up, and there were no detectable byproducts. The overall yield of **6** based on homoveratrylamine (**14**) was 82%, which is the highest yield reported for this lamellarin derivative to date! The previous record was a 69% overall yield in seven linear steps from 3,4-dimethoxyphenylacetonitrile.[21]

Exhaustive O-demethylation of **6** with boron tribromide at room temperature, as reported by other workers,[22] provided the natural product lamellarin A4 (**3**) in 97% yield. It is worth noting that extensive NMR spectroscopic data for **3**, mentioned in passing as a metabolite of a didemnid ascidian and referred to as 5,6-dihydrolamellarin H, were reported as long ago as 1996.[23] However, the natural occurrence of the compound was overlooked in subsequent reviews of the lamellarins.[2−5] The name lamellarin A4 was assigned in later isolation from *Didemnum* sp.[24] Synthetic compound **3**, named as trisdesmethyl lamellarin G, was recently asserted not to have been previously reported.[22]

Lamellarin D trimethyl ether (**7**), the ring B-unsaturated equivalent of **6**, has previously been made from **6** by oxidation with 5,6-dichloro-2,3-dicyanobenzoquinone (DDQ).[16d] We have found that DDQ oxidation of intermediate **21** prior to lactonization provides the shortest reaction times and the highest yields, without any detectable byproducts being formed. In addition, the oxidation did not require heating, as

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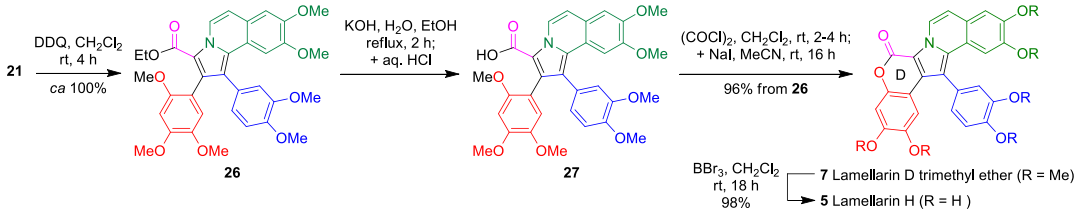
Scheme 4. Synthesis of Lamellarin D Trimethyl Ether (7) and Lamellarin H (5)



has been the case for conventional late-stage lamellarin oxidations. Thus, treating **21** with DDQ in dichloromethane at room temperature afforded the ring B-unsaturated analogue **26** as foam within 4 h (Scheme 4). Finally, application of our novel lactonization procedure after hydrolysis of **26** to the carboxylic acid **27** and in situ conversion into the acid chloride followed by treatment with sodium iodide in acetonitrile provided more than a gram of lamellarin D trimethyl ether (**7**) in yields consistently above 96%. Once again, no purification of the intermediates was required, and the final product could easily be purified by recrystallization. The overall yield of **7** based on homoveratrylamine (**14**) was 86%. This is the highest reported yield for lamellarin derivative **7** to date. To complete the reaction sequence, global demethylation of **7** with boron tribromide[18b,22,25] provided lamellarin H (**5**) in 98% yield.

CONCLUSIONS

In this article, we report efficient syntheses of two naturally occurring lamellarins (lamellarins A4 and H) and two synthetic lamellarin analogues (the trimethyl ethers of lamellarins D and G). Several features of our syntheses are particularly significant.

- The syntheses are both modular and operationally simple. All four compounds were made in six to eight steps from relatively cheap precursors (homoveratrylamine, homoveratric acid, 1,2,4-trimethoxybenzene, and ethyl bromoacetate). Furthermore, only a single chromatographic separation was required.
- We have discovered a novel late-stage method for making the alkaloids' chromenyl lactone ring by a demethylative cyclization between a methoxylated aromatic system and a nearby carboxylic acid situated on the pyrrole ring. This has the advantage of avoiding the need for additional protection and deprotection steps for the incipient phenol because a simple readily available anisole serves as the precursor.
- Although ours are not the shortest syntheses of lamellarins on record, the overall yields are outstanding and are, in fact, higher than any hitherto reported in the literature for any lamellarin,[3] let alone those we have chosen as examples (cf 82% for lamellarin G trimethyl ether, compared with a previously reported highest yield of 69%[20]). In addition, no other lamellarin synthesis reported in the periodicals literature to date has yielded gram quantities of the target products.

We believe that our new lactonization, in particular, represents a game-changing strategy in the quest for efficient and workable routes to pharmacologically valuable lamellarins. The methods reported in this article should, with suitable modifications, be readily applicable to the synthesis of virtually all known naturally occurring pentacyclic lamellarin alkaloids and should also provide a convenient route to numerous new synthetic derivatives.

EXPERIMENTAL SECTION

Solvents for reaction or chromatography were dried and purified, where necessary, by standard methods. All other chemicals and deuterated solvents were purchased from commercial sources (Merck, Sigma-Aldrich) and used as received. Merck silica gel (particle size 0.063−0.200 mm) was used for conventional silica gel chromatography and Merck silica gel (particle size 0.04−0.063 mm) for flash column chromatography. Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} plates, and compounds were visualized using UV light and/or by exposure to iodine vapor. All reactions were performed under an inert atmosphere of argon in oven-dried glassware. An oil bath was used for conventional heating. Melting points were recorded on a JM 626 melting-point apparatus with a microscope and a digital thermometer. Room temperature refers to ambient laboratory temperatures of 18−25 °C.

^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on Bruker Avance I 300 MHz, Avance III 400 MHz, and Avance III 500 MHz spectrometers at frequencies of 300, 400, and 500 MHz, respectively, for ^{1}H spectra and at frequencies of 75, 101, and 126 MHz, respectively, for ^{13}C spectra. Chemical shifts (δ) of ^{1}H and ^{13}C signals recorded in $CDCl_3$ solution are reported as parts per million (ppm) downfield from Me_4Si as the internal reference, while spectra recorded in DMSO-d_6 are referenced to the central peak of the solvent. High-resolution mass spectra were obtained on a Bruker Compact Q-TOF mass spectrometer. Samples were diluted to a concentration of approx. 10 ppm in MeOH and introduced by injection into a Dionex Ultimate 3000 UHPLC system. The ionization mode was electrospray positive with a capillary voltage of 4500 V and a desolvation temperature of 220 °C using N_2 gas at 9 L min^{-1}.

6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (12). (Method adapted from ref 20). NEt_3 (11.6 mL, ca. 83 mmol, 1 equiv) and CS_2 (7.5 mL, ca. 9.5 g, 125 mmol, 1.5 equiv) were added to a solution of 2-(3,4-dimethoxyphenyl)ethylamine (**14**) (15.0 g, 82.8 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then again cooled to 0 °C. Ethyl chloroformate (7.9 mL, ca. 9.0 g, ca. 83 mmol, 1 equiv) was added dropwise, which caused the immediate precipitation of triethylammonium chloride. After stirring at room temperature for 1 h, additional NEt_3 (11.6 mL, 1 equiv) was added and the reaction was left to stir overnight (18 h). Aqueous NaOH solution (10%, 100 mL) was added to maintain alkalinity during extraction; the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to provide 4-(2-isothiocyanatoethyl)-1,2-dimethoxybenzene (**17**) as oil that was used immediately without further purification. The crude isothiocyanate was dissolved in CH_2Cl_2 (10 mL) and added dropwise to stirring polyphosphoric acid (25 g), which was heated to 80−90 °C. The organic solvent evaporated on contact with the hot acid; the product began to precipitate immediately, and the mixture turned red. The reaction mixture was stirred for an additional 2 h. On cooling, water (300 mL) was added, which caused further precipitation of the product. Stirring was continued for 30 min, after which the product was filtered through a glass sinter and washed with additional water. The crude solid product was then triturated under boiling methanol (250 mL); after cooling, it was was filtered and dried to provide the pure product 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**12**) (17.0 g, 76.1 mmol, 92%); pale yellow powder, mp 231−232 °C (lit.,[20] 223

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°C). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.08 (s, 1H), 8.03 (br s, 1H, NH), 6.61 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.55 (td, J = 7.0, 3.4 Hz, 2H), 2.95 (t, J = 7.0 Hz, 2H). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 10.17 (br s, 1H, NH), 7.90 (s, 1H), 6.87 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.37 (td, J = 7.0, 3.3 Hz, overlapping with H_2O), 2.85 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6, δ): 191.2, 152.7, 147.5, 128.8, 125.6, 114.3, 110.4, 56.3, 55.0, 41.5, 27.1.

2-(3,4-Dimethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)-ethanone (18). Oxalyl chloride (4.8 mL, ca. 56 mmol) was added to an ice-cooled solution of 3,4-dimethoxyphenylacetic acid (**15**) (10.0 g, 51.0 mmol) in dry CH_2Cl_2 (150 mL), which caused the solution to turn a deep orange color. Addition of a few drops of dry dimethylformamide by a syringe resulted in the immediate formation of CO and CO_2 gas bubbles. The ice bath was removed, and the solution was left to stir until bubbling ceased (ca. 2 h). The solvent was removed by rotary evaporation, and the crude product was further dried under vacuum (ca. 0.1 Torr) to remove any residual oxalyl chloride. 3,4 Dimethoxyphenylacetyl chloride was obtained as orange oil and was used immediately without purification. This crude acid chloride was dissolved in dry CH_2Cl_2 (150 mL), to which was added a solution of 1,2,4-trimethoxybenzene (**16**) (8.56 g, 50.9 mmol, 1 equiv) in CH_2Cl_2 (50 mL). A little additional CH_2Cl_2 was used to ensure quantitative transfer. The stirred mixture was then cooled to 0 °C and anhydrous $AlCl_3$ (6.790 g, 50.9 mmol, 1 equiv) was added in portions, which caused the solution to turn into a deep brown-black color. The reaction mixture was allowed to warm to room temperature and stirred for 1 h before the addition of ice water (100 mL) followed by aqueous HCl solution (1 M) to hydrolyze any remaining aluminum adducts. The resulting clear phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent removed to provide **18** (17.61 g, 50.8 mmol, 99% based on acid **15**) as a pale purple solid. The material was spectroscopically pure and was used without further purification, although it could be recrystallized as a colorless crystalline solid from MeOH if required. mp 127−128 °C (lit.,[26] 121 °C). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.41 (s, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.80−6.71 (m, 2H), 6.50 (s, 1H), 4.25 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.86 and 3.85 (overlapping s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 197.6, 155.1, 153.9, 148.7, 147.7, 143.2, 128.3, 121.7, 118.8, 113.1, 112.9, 111.2, 96.4, 56.2, 56.1, 55.9, 55.8, 49.6. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{23}O_6^+$, 347.1489; found, 347.1490.

2-Bromo-2-(3,4-dimethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)ethanone (19). 2-(3,4-Dimethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)ethanone (**18**) (5.00 g, 14.4 mmol) was dissolved in $CHCl_3$ (100 mL), and the solution was cooled in an ice bath. An accurately prepared solution of Br_2 (2.30 g, 14.4 mmol, 1 equiv) in $CHCl_3$ (50 mL) was transferred to a dropping funnel, and one drop was added to the ketone solution. After 1 min, it was assumed that enough HBr had formed to catalyze enolic bromination. The remainder of the Br_2 solution was then added dropwise at 0 °C to the persistently amber solution of ketone at a rate of about 1−2 drops per second such that its red color was discharged immediately before the addition of the succeeding drop. Once addition was complete (ca. 1 h), saturated aqueous $NaHCO_3$ solution was added to quench the cold reaction mixture, which caused the color to clear considerably. The phases were separated, and the aqueous phase was further extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo to provide the bromoketone **19** (6.14 g, ca. 100%) as sticky foam. The material was used immediately as it proved susceptible to rapid decomposition, especially in the presence of light. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.44 (s, 1H), 7.11 (s, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.68 (s, 1H), 6.45 (s, 1H), 3.94 (s, 3H), 3.91 (s, 6H), 3.87 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, δ): 191.1, 154.74, 154.70, 149.5, 149.1, 143.6, 129.1, 122.0, 116.4, 113.7, 112.5, 110.7, 96.3, 56.33, 56.29, 56.16, 56.0, 55.9, 55.6. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{22}{}^{79}BrO_6^+$, 425.0594; found, 425.0532 (minor signal); [M − HBr]$^+$ calcd for $C_{19}H_{21}O_6^+$, 345.1333; found 345.1327 (major signal).

(*Z*)-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-2-(3,4-dimethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)-ethanone (20). 6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**12**) (5.98 g, 26.8 mmol) was added to a solution of the bromoketone **19** (12.0 g, 28.2 mmol, 1.05 equiv) in dry MeCN (150 mL), and the resulting solution was stirred at room temperature for 18 h to ensure complete salt formation, after which time Ph_3P (7.03 g, 26.8 mmol, 1 equiv) was added. The solution was stirred for 5 min until the phosphine had dissolved, after which NEt_3 (4.5 mL, ca. 32 mmol, 1.2 equiv) in MeCN (50 mL) was added at a rate of about 1 drop per second. The solution soon turned bright yellow, indicating the successful formation of the deeply colored enaminone. The reaction mixture was stirred at room temperature overnight. The solvent was then removed in vacuo, and the residue was purified by flash column chromatography (50−100% EtOAc in hexane). The yellow fractions containing the enaminone were combined and evaporated to give the desired product **20** as a bright yellow solid (14.3 g, 26.7 mmol, ca. 100%), mp 98−99 °C. [Note: yields of 96−100% were consistently obtained when the experiment was repeated several times on different scales.] ^{1}H NMR (300 MHz, $CDCl_3$, δ): 13.24 (br s, 1H), 6.64 (s, 1H), 6.60−6.51 (m, 3H), 6.46 (dd, J = 8.2, 1.7 Hz, 1H), 6.40 (s, 1H), 6.27 (s, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H), 3.60 (s, 3H), 3.55−3.40 and 3.54 (overlapping m and s, 5H), 3.15 (s, 3H), 3.03−2.74 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 192.1, 158.8, 150.1, 149.5, 149.1, 148.2, 146.9, 146.0, 142.4, 133.7, 132.1, 125.8, 125.0, 121.4, 116.5, 114.2, 112.2, 110.5, 109.9, 107.0, 96.9, 56.4, 56.2, 56.0, 55.81, 55.79, 55.1, 39.2, 28.8. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{30}H_{34}NO_8^+$, 536.2279; found, 536.2271.

Ethyl 1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (21). (a) The enaminone **20** (2.00 g, 3.73 mmol) was dissolved in ethyl bromoacetate (3.0 mL, ca. 4.53 g, ca. 27.1 mmol, ca. 7.3 equiv), to which was added solid $NaHCO_3$ (3.0 g, 35.7 mmol). The mixture was stirred under an atmosphere of argon gas at 80−85 °C for 48 h, after which the solution turned from bright yellow-orange to deep red and then to almost colorless. The total reaction mixture was loaded directly onto a column of flash silica gel (100 g) with a small quantity of CH_2Cl_2 to ensure quantitative transfer of soluble components. Chromatography was performed under slight positive pressure with increasing polarity of the eluant from 0−50% EtOAc in hexane to provide **21** (2.19 g, 3.62 mmol, 97%); characterization described below.

(b) The reaction was repeated with enaminone **20** (2.00 g, 3.73 mmol), ethyl bromoacetate (3.0 mL), and $NaHCO_3$ (3.0 g) as described in (a). Once the reaction was complete, the total reaction mixture was dissolved in enough CH_2Cl_2 to produce an easily filterable suspension of solids (ca. up to twice the volume of residual ethyl bromoacetate) and filtered. The solid residue was washed with additional CH_2Cl_2 until the filtrate was no longer colored. The solvent was removed in vacuo, and Et_2O (5 mL/g of starting enaminone) was added, followed by sufficient hexane (ca. 20 mL/g of starting enaminone) to induce a lasting turbidity. Soon, crystals began to develop, and after a few hours, they were collected by filtration, washed with hexane, and triturated under boiling MeOH. After cooling, the crystals were collected by filtration, washed with MeOH, and dried to give the dihydropyrrolo[2,1-*a*]isoquinoline **21** (2.07 g, 3.43 mmol, 92%) as a white solid, mp 94−96 °C (from MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.76 (s, 2H), 6.74−6.68 (m, 3H), 6.60 (s, 1H), 6.45 (s, 1H), 4.62 (br t, J = 5.5 Hz, 2H), 4.07 (q, J = 7.1 Hz, 2H), 3.87 (s, 6H), 3.83 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.56 (s, 3H), 3.35 (s, 3H), 3.06 (br t, J = 6.3 Hz, 2H), 0.98 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 162.3, 151.8, 148.8, 148.7, 148.3, 147.9, 147.5, 142.6, 131.2, 128.8, 128.6, 126.2, 123.4, 122.0, 121.4, 119.4, 117.0, 116.3, 114.3, 111.2, 111.0, 109.1, 97.6, 59.9, 56.7, 56.4, 56.24, 56.19, 56.1, 55.6, 43.2, 29.4, 14.3. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{34}H_{38}NO_9^+$, 604.2541; found, 604.2538.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic Acid (23). A solution of KOH (4.5 g, 80 mmol) in water (10

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mL) was added to the ethyl ester **21** (1.30 g, 2.15 mmol), followed by EtOH (100 mL) to ensure complete dissolution of the ester. The pale yellow solution was heated to reflux for 2 h, after which most of the EtOH was removed by rotary evaporation until the potassium carboxylate began to precipitate. The mixture was acidified with aqueous HCl (1 M), causing the free carboxylic acid to begin precipitating and turning the supernatant liquid bright yellow. The mixture was then extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts containing the dissolved carboxylic acid were washed with aqueous HCl (1 M, 100 mL) and brine (100 mL), dried over $MgSO_4$ and evaporated in vacuo to provide the carboxylic acid **23** (1.24 g, 2.15 mmol, 100%) as an off-white solid, mp 154−156 °C (from MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.96 (s, 1H, CO_2H, exchanges with D_2O), 6.92−6.86 (m, 2H), 6.84 (d, J = 6.6 Hz, 1H), 6.73 (s, 1H), 6.69 (s, 1H), 6.63 (s, 1H), 6.50 (s, 1H), 4.10 (t, J = 6.5 Hz, 2H), 3.87, 3.86 and 3.86 (3 × overlapping s, 9H), 3.69 (s, 3H), 3.63 (s, 3H), 3.51 (s, 3H), 3.39 (s, 3H), 3.06 (t, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ): 150.8, 148.8, 147.41, 147.36, 147.30, 146.7, 142.4, 130.1, 125.6, 124.0, 123.1, 122.5, 120.0, 119.33, 119.29, 116.0, 115.1, 114.1, 111.3, 111.1, 107.6, 97.7, 77.2, 56.2, 56.1, 56.0, 55.94, 55.88 (2 C), 55.3, 44.7, 29.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{32}H_{34}NO_9^+$, 576.2228; found, 576.2232 (minor signal); $[M - CO_2]^+$ calcd for $C_{31}H_{34}NO_7^+$, 532.2300; found, 532.2322 (major signal).

4-(3,4-Dimethoxyphenyl)-2,3,11,12-tetramethoxy-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one, Lamellarin G Trimethyl Ether (6). The carboxylic acid **23** (1.50 g, 2.61 mmol) was dissolved in dry CH_2Cl_2 (50 mL), and the solution was cooled to 0 °C under an atmosphere of argon. Oxalyl chloride (0.45 mL, ca. 5.2 mmol, 2 equiv) was added by syringe, causing the color to become deep orange. The stirred solution was warmed to room temperature, and reaction was judged to be complete by NMR spectroscopy after 4 h. The solvent was evaporated on a rotary evaporator, and the crude amber-colored acid chloride was dissolved in a solution of NaI (1.5 g, 10 mmol) in MeCN (50 mL). NaCl began to precipitate within 30 min. The suspension was stirred overnight, during which time a dense precipitate of NaCl and the desired lamellarin ether **6** was formed. The solvent was removed in vacuo and the residue was adsorbed onto silica gel (7.5 g) and washed through a pad of silica gel with EtOAc−hexane (1:1) (ca. 300 mL) until eluants no longer showed a bright blue fluorescent spot at 254 nm by TLC. The solvent was removed and MeOH (ca. 75 mL) was added. The suspension was heated to boiling and then allowed to cool to room temperature. The resulting solid was collected by filtration and dried to give lamellarin G trimethyl ether (**6**) (1.31 g, 2.40 mmol, 92%) as a colorless solid, mp 248−249 °C (lit., 235−236 °C;[21] 236−238 °C;[27] 238−239 °C[28]). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.13 (dd, J = 8.5, 2.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 1.5 Hz, 1H), 6.90 (s, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 6.67 (s, 1H), 4.79 (2 × quintet, J = 6.6 Hz, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.46 (s, 3H), 3.37 (s, 3H), 3.12 (t, J = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 155.5, 149.8, 149.0, 148.9, 148.8, 147.5, 146.1, 145.5, 135.9, 128.2, 128.0, 126.6, 123.6, 120.1, 114.8, 114.0, 113.8, 111.9, 111.0, 110.3, 108.7, 104.5, 100.5, 56.3, 56.2, 56.1, 55.9, 55.5, 55.2, 42.4, 28.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{31}H_{30}NO_8^+$, 544.1966; found, 544.1961. The ^{1}H chemical shifts observed for **6** are within 0.02 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.1 ppm[17a,22] (see Supporting Information, Table S1).

14-(3,4-Dihydroxyphenyl)-2,3,11,12-tetrahydroxy-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one, Lamellarin A4 (3). Neat BBr_3 (0.18 mL, ca. 10 equiv) was added to a stirring solution of lamellarin G trimethyl ether (**6**) (102 mg, 0.188 mmol) dissolved in CH_2Cl_2 (50 mL) at room temperature. The mixture was left to stir for 18 h, after which it was quenched with MeOH (1 mL), followed by water (100 mL). The solution was then extracted with EtOAc (4 × 100 mL) because the polyphenolic lamellarin is poorly soluble in chlorinated solvents. The combined organic phases were dried over $MgSO_4$, filtered, and solvent was partially removed on a rotary evaporator until solids began precipitating. Hexane (about half the volume of the remaining solvent) was added to complete the crystallization of the products, which were collected by filtration and dried to give lamellarin A4 (**3**) (84 mg, 0.183 mmol, 97%) as a white solid, mp >300 °C (lit.,[22] >300 °C). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.58 (s, 1H), 9.37 (s, 1H), 9.11 (s, 2H), 8.81 (s, 1H), 8.61 (s, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 6.70 and 6.69 (overlapping d and s, J = 2.0 Hz, 2H), 6.63 (dd, J = 8.0, 2.0 Hz, 1H), 6.53 (s, 1H), 6.47 (s, 1H), 4.60 (quintet, J ca. 6.8 Hz, 1H), 4.54 (quintet, J ca. 6.8 Hz, 1H), 2.95 (br t, J = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6, δ): 154.9, 146.5, 146.4, 146.3, 145.6, 145.1, 144.0, 142.4, 136.4, 127.9, 126.2, 125.8, 121.7, 118.9, 117.9, 117.2, 115.5, 115.1, 113.9, 112.6, 109.7, 109.3, 103.7, 42.4, 28.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{18}NO_8^+$, 460.1027; found, 460.1028. The ^{1}H chemical shifts observed for **3** are within 0.04 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.5 ppm[22,24] (see Supporting Information, Table S2).

Ethyl 1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (26). The saturated pyrrolo[2,1-*a*]isoquinoline **21** (1.50 g, 2.48 mmol) was dissolved in CH_2Cl_2 (100 mL), to which was added DDQ (0.70 g, 3.10 mmol, 1.25 equiv). The solution, which immediately turned to a muddy-brown color, was left to stir at room temperature for 4 h. Aqueous NaOH solution (2 M, 50 mL) was added, and the phases were separated. The aqueous phase was re-extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic fractions were washed with NaOH solution (2 M, 50 mL), water (50 mL), and brine (50 mL). After drying over $MgSO_4$, filtration, and evaporation in vacuo, spectroscopically homogeneous **26** (1.49 g, ca. 100%) was obtained as brownish foam, mp 95−98 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 9.32 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 7.02 (s, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.91 (dd, J = 8.2, 1.8 Hz, 1H), 6.87−6.83 and 6.85 (overlapping m and d, J = 8.0 Hz, 2H), 6.64 (br s, 1H), 6.46 (s, 1H), 4.14 (br q, J ca. 6 Hz, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H), 3.61 (br s, 3H), 3.45 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, δ): 162.1, 151.5, 149.2, 148.8, 148.7, 148.6, 147.9, 142.3, 131.9, 130.2, 128.8, 123.8, 123.7, 123.6, 119.8, 118.6, 116.7, 115.9, 114.7, 113.0, 111.9, 110.9, 107.1, 105.3, 97.2, 59.4, 56.5, 56.4, 56.1, 56.0, 55.9, 55.8, 55.3, 14.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{36}NO_9^+$, 602.2385; found, 602.2372.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylic Acid (27). Following the procedure described for the synthesis of carboxylic acid **23**, compound **27** (1.41 g, 2.46 mmol, 100%) was obtained from ethyl 1-(3,4-dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**26**) (1.48 g, 2.46 mmol) as a pale brown solid, mp 101−106 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.69 (d, J = 7.2 Hz, 1H), 7.54 (s, 1H, CO_2H; exchanges with D_2O), 7.19 (s, 1H), 7.00 and 6.98 (overlapping dd and s, J = 7.1, 1,8 Hz, 2H), 6.94−6.89 (m, 2H), 6.72 (s, 1H), 6.63 (d, J = 7.2 Hz, 1H), 6.52 (s, 1H), 3.93 (s, 3H), 3.89 and 3.88 (2 × s, 6H), 3.75 (s, 3H), 3.68 (s, 3H), 3.53 (s, 3H), 3.49 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 151.1, 148.9, 148.5, 147.9, 147.7, 147.6, 142.5, 130.5, 125.3, 124.0, 122.9, 121.8, 120.9, 115.6, 115.3, 114.8, 113.9, 111.3, 110.4, 107.9, 104.7, 97.8, 77.3, 56.4, 56.1, 56.04, 55.99, 55.90, 55.8, 55.3. HRMS (ESI) m/z: $[M - CO_2]^+$ calcd for $C_{31}H_{32}NO_7^+$, 530.2173; found, 530.2166.

14-(3,4-Dimethoxyphenyl)-2,3,11,12-tetramethoxy-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one, Lamellarin D Trimethyl Ether (7). Following the procedure described for the synthesis of lamellarin G trimethyl ether (**6**), lamellarin D trimethyl ether (**7**) (1.28 g, 2.36 mmol, 97%) was obtained from the carboxylic acid **27** (1.40 g, 2.44 mmol) as a colorless solid, mp 283−284 °C (lit.,[22,25a] 278−280 °C). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 9.18 (d, J = 7.3 Hz, 1H), 7.24 (dd, J = 8.0, 1.5 Hz, 1H), 7.19 (d, J = 1.5 Hz, 1H), 7.18−7.14 (m, 2H), 7.07 (s, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.87 (s, 1H), 6.74 (s, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.49 (s, 3H), 3.47 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, δ): 155.4, 150.1, 150.0, 149.6, 149.2, 149.1, 146.7, 145.5, 134.4, 129.3, 128.3, 124.8, 124.2, 123.3, 119.1, 114.5, 112.3, 112.0, 110.9, 109.9,

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107.8, 107.4, 105.3, 105.1, 100.5, 56.3, 56.2, 56.04, 55.97, 55.5, 55.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{31}H_{28}NO_8^+$, 542.1809; found, 542.1801. The ^1H chemical shifts observed for **7** are within 0.06 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.2 ppm[22,25c] (see Supporting Information, Table S3).

14-(3,4-Dihydroxyphenyl)-2,3,11,12-tetrahydroxy-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one, Lamellarin H (5). Following the procedure described for the synthesis of lamellarin A4 (**3**), lamellarin H (**5**) (42 mg, 0.0918 mmol, 98%) was obtained from lamellarin D trimethyl ether (**7**) (50 mg, 0.0923 mmol) as a white solid, mp >300 °C (lit.,[22] >300 °C). ^1H NMR (400 MHz, DMSO-d_6, δ): 10.04 (s, 1H), 9.81 (s, 1H), 9.47 (s, 1H), 9.26 and 9.25 (2 × s, 2H), 9.05 (d, J = 7.3 Hz, 1H), 8.96 (s, 1H), 7.21 and 7.19 (d, J = 6.0 Hz, and s, 2H), 7.06 (d, J = 7.6 Hz, 1H), 7.02 (s, 1H), 6.87 (s, 1H), 6.86 (d, J = 2.0 Hz, 1H), 6.78 (dd, J = 7.9, 2.0 Hz, 1H), 6.64 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6, δ): 154.9, 148.1, 147.3, 147.0, 146.7, 146.0, 145.7, 142.5, 134.4, 129.3, 125.9, 124.2, 121.9, 121.6, 118.6, 118.0, 117.5, 113.0, 111.87, 111.85, 110.1, 110.0, 109.3, 106.8, 103.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{16}NO_8^+$, 458.0870; found, 458.0865. The ^1H chemical shifts observed for **5** are within 0.07 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.5 ppm[22,25c] (see Supporting Information, Table S4).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b02983.

Tabulated comparisons of ^1H and ^{13}C NMR spectroscopic data for lamellarins **3**, **5**, **6**, and **7** with literature values and copies of ^1H and ^{13}C NMR spectra (PDF)

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Notes

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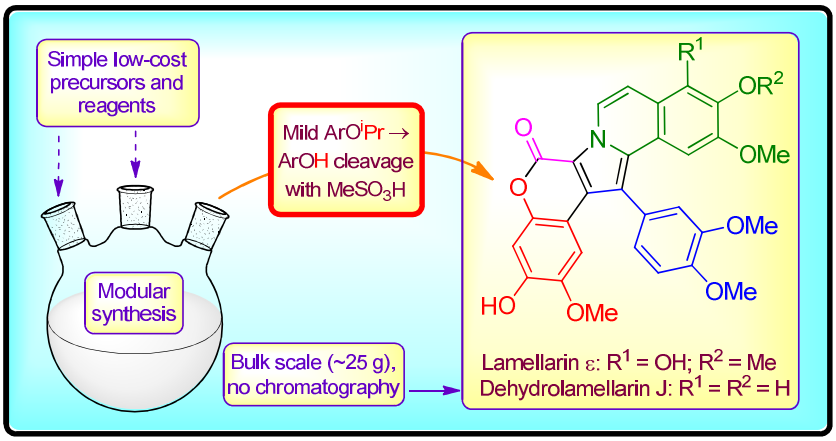
Chapter 5: Practical Decagram-Scale Synthesis of a Lamellarin Analogue and Deprotection of Lamellarin Isopropyl Ethers



5.1 Foreword

The primary goal of this project was to extend the synthetic strategy described in *Chapter 4* to the synthesis of a representative selection of the six lamellarins that are especially potent.[34–36,38] The trimethyl ether analogues we had previously prepared, discussed in *Chapter 3* and 4, are usually made as a proof of concept, but they are both unnatural and inactive.[35] The demethylated analogues lamellarin H and A4, the synthesis of which was described in *Chapter 4*, are natural products, but are not particularly interesting from a pharmaceutical perspective.[35] We set our sights on preparing lamellarin ε and dehydrolamellarin J, both of which are regarded as two of the most potent lamellarins ever tested, with each representing one of the two possible ring A structures that give rise to potent cytotoxicity (described in *Section 1.2.1*).[35] The synthetic strategy devised was fundamentally similar to that described in *Chapter 4*, featuring the Eschenmoser-sulphide contraction approach to enaminone synthesis, as well as our [4 + 1] cycloaddition and demethylative lactonization reactions. However, significant modifications to the synthesis of the enaminone precursors **13** and **14** (*Scheme 1* of attached publication) were needed, since protection of the obligatory phenols was required. In the process we developed a novel, mild deprotection of isopropyl protecting groups with methanesulphonic acid. We also succeeded in making over 25 g of dehydrolamellarin J, which is the largest quantity of any lamellarin prepared to date. The work pertaining to this chapter was performed at Wits, the main findings of which were published in 2020.[83] The corresponding paper is attached and serves as *Chapter 5* of this thesis.

5.2 Declaration

All experimental work reported within the attached publication was performed exclusively by me, without any contribution from other students. Every single experimental method detailed therein was performed by me alone. Furthermore, the initial drafts of the publication were also prepared by me.

5.3 Publication details

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Lamellarin Synthesis

Practical Decagram-Scale Synthesis of a Lamellarin Analogue and Deprotection of Lamellarin Isopropyl Ethers

Robin Klintworth,[a] Charles B. de Koning,[a] and Joseph P. Michael*[a]

Abstract: Modular syntheses of naturally occurring lamellarin ε (**5**) and the synthetic analogue dehydrolamellarin J (**6**), both of them promising lead candidates for anticancer activity, were accomplished in high overall yields. Key steps in these routes are a late-stage installation of the central pyrrole core by [4 + 1] cyclocondensation between ethyl bromoacetate and an enaminone possessing the remaining components of the lamellarin skeleton; and our recently revealed demethylative lactonization for building the chromenone components. Additionally, a mild and nearly quantitative new method for cleaving isopropyl-protected phenols at room temperature with the comparatively green reagent methanesulfonic acid has been developed. The feasibility of exploiting the simplicity and efficiency of the new reactions on a multi-gram scale was demonstrated by preparing over 25 g of dehydrolamellarin J, one of the most cytotoxic anticancer agents in the lamellarin family, without the need for chromatographic purification of intermediates.

Introduction

Lamellarins occupy a prominent position among the numerous plant- and animal-derived natural products possessing the pyrrolo[2,1-*a*]isoquinoline ring system.[1] These marine metabolites have been isolated from sponges, molluscs and ascidians, and almost 60 of them are extensively oxygenated pentacyclic compounds in which an additional 2*H*-chromen-2-one unit is fused to the pyrrole ring, which also carries a pendent aryl substituent at C-1 (Figure 1, conventional lamellarin numbering shown).[2,3] The intense interest in the synthesis[4] and properties of these alkaloids, the first examples of which were reported more than 30 years ago,[5] is chiefly due to their impressive biological activity, aspects of which have been comprehensively covered in a recent review that also summarizes the numerous published syntheses of natural lamellarins and some synthetic analogues,[2] as well as in other important reviews.[6,7] Bioactivity manifested by these compounds includes anti-HIV-1-integrase activity, cardiovascular and immunomodulatory effects, antioxidant and antibacterial properties and, most notably, antiproliferative activity against some cancer cell lines.[6]

One of the most striking properties of several anticancer lamellarins is their ability to reverse resistance to currently available chemotherapeutic drugs, even in multi-drug resistant cancer cell lines and at sub-cytotoxic doses.[6,8] The modes of action displayed by the most active natural and synthetic lamellarins, particularly lamellarin D (**1**), include the inhibition of nuclear and mitochondrial topoisomerase I (in some cases at the nanomolar level) as well as a number of protein kinases; and modification of mitochondrial function.[6] The ability of **1**, for instance, to bypass the nucleus and promote mitochondrial apoptosis, although by an as-yet unknown mechanism, appears to be unprecedented for chemotherapeutics in general,[9] and offers an exciting new target in the treatment of multi-drug resistant cancers.[10]

Structure–activity relationship studies for those lamellarins that display the greatest cytotoxicity towards cancer cells indicate that the oxidation pattern of aromatic rings A and E and a

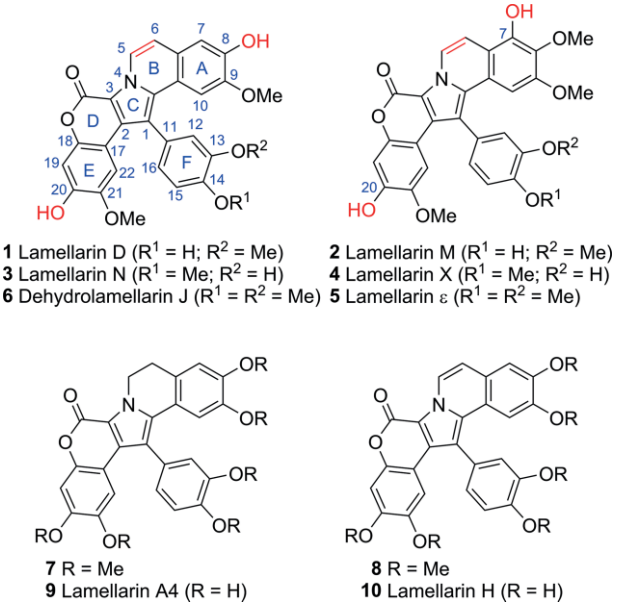

Figure 1. Natural and synthetic lamellarins **1**–**10**. Components in red in structures **1**–**6** are regarded as essential for biological activity.

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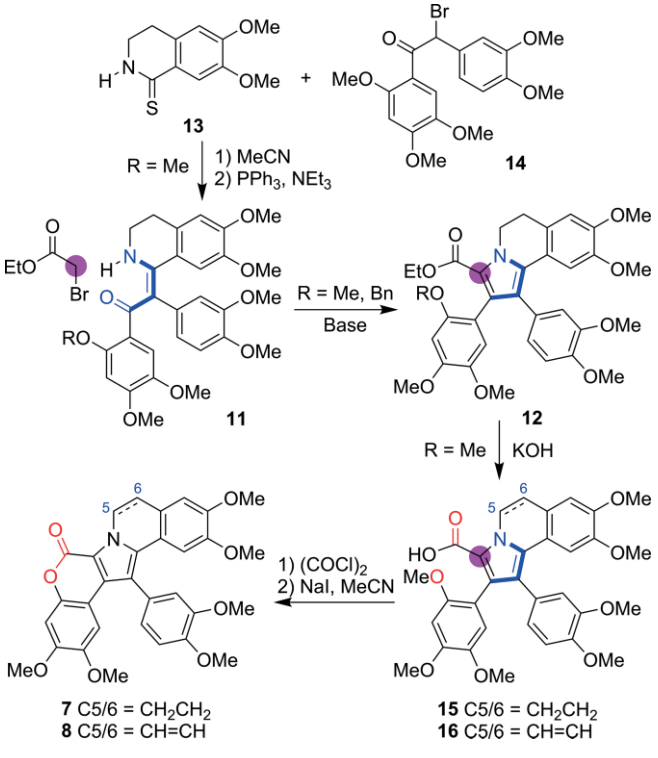
C-5/C-6 double bond are crucial for activity, while ring F is amenable to change.[11,12] In general, potent cytotoxicity is associated with a hydroxy substituent at either C-7 or C-8, while the phenol at C-20 is indispensable. Although hydroxylation of ring F has also been considered important for bioactivity,[13] alkaloids and analogues with no hydroxylation in this ring retain potency.[11] Among the most effective cytotoxins are lamellarins D (**1**), M (**2**), N (**3**), X (**4**), ε (**5**), and a synthetic analogue, dehydrolamellarin J (**6**).[11]

Two recent publications from our research group dealing with the modular synthesis of several lamellarins and analogues included a number of innovative features. The first of these articles showcased an efficient, relatively "green", route to lamellarin G trimethyl ether (**7**), the crux of which was the formation of the central pyrrole ring by a [4 + 1] cyclocondensation between ethyl bromoacetate and a sterically crowded enaminone **11** (R = Bn) possessing all of the remaining skeletal carbon atoms of the target, thereby giving a 1,2-diaryl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline **12** (Scheme 1, **11** → **12**).[14] The second article contained an improved method for constructing the enaminone **11** (R = Me) by Eschenmoser sulfide contraction[15,16] between the dihydroisoquinolinethione **13** and the α-bromoketone **14** (Scheme 1, **13** + **14** → **11**); more significantly, we devised a method for introducing the chromen-2-one unit by an unprecedented intramolecular demethylative lactonization of carboxylic acids **15** and **16** containing a neighboring aryl methyl ether (Scheme 1, **15** → **7** and **16** → **8**).[17] This route also provided the first gram-scale syntheses of **7**, lamellarin D trimethyl ether (**8**), lamellarin A4 (**9**) and lamellarin H (**10**) in the highest overall yields reported to date, and with relatively little need for purification of intermediates. As indicated in the introductory paragraph, although the lamellarins contain a myriad of substitution patterns, only a select few impart highly potent cytotoxicity.



Scheme 1. The key enaminone, pyrrole and lactone formation steps in our previous syntheses of lamellarin G trimethyl ether (**7**) and lamellarin D trimethyl ether (**8**).[14,17]

In the present article we have focused our efforts on developing a practical and flexible method for the synthesis of lamellarins that meet the crucial structural requirements for pharmacophoric efficacy.[11] We now report applications of our novel synthetic approaches to the synthesis of the naturally-occurring lamellarin ε (**5**)[18] and the synthetic compound dehydrolamellarin J (**6**),[19] which were chosen as representatives of the different ring A and E substitution patterns found in the most cytotoxic analogues. However, the free phenolic substituents in these targets needed to be protected throughout the reaction sequences. For reasons to be made clear subsequently, we selected isopropyl as the protecting group. Fortuitously, it also provided an opportunity for developing and disclosing a new and significantly improved procedure for the cleavage of aryl isopropyl ethers. In addition, we reveal procedural adaptations for scaling up the synthesis of **6**, which has permitted the manufacture of more than 25 g of this compound – the largest quantity of any lamellarin ever made – without the need for chromatographic purification of intermediates.

Results and Discussion

For our proposed syntheses of lamellarin ε (**5**) and dehydrolamellarin J (**6**), our previously reported strategy for making the permethyl ethers **7** and **8** needed to be modified, since protection of the obligatory phenols could not be avoided. While the key steps so successfully employed in our previous route[17] (Eschenmoser sulfide contraction, pyrrole formation and demethylative lactonization) remained the same, the changes required were in the precursors for rings A and E, where protection of the incipient phenols was necessary. Benzyl and especially isopropyl ethers feature prominently in routes to these rings by other workers.[2–4] Our strategy for making the 3,4-dihydroisoquinolinethione precursors for the sulfide contraction entailed treating appropriately substituted phenylethylamines with carbon disulfide and ethyl chloroformate to give isothiocyanate intermediates, cyclization of which under acidic conditions was expected to yield the desired thiones.[20] Initial experiments ruled out the use of benzyl ethers as protecting groups, since they were invariably cleaved under acidic cyclization conditions, giving mixtures of uncharacterizable products in some of which the benzyl substituents appeared to have migrated to other sites in the compounds. Such intramolecular and intermolecular migration in aryl benzyl ethers under acidic conditions is certainly precedented.[21] The alternative selection of isopropyl is not without potential problems since acid-induced migration in isopropyl aryl ethers, though rare, is not unknown.[22] However, our choice of isopropyl turned out to be fortunate, since not only was it remarkably stable under optimized conditions for isoquinolinethione formation (see below), but it also led to the discovery of a novel method for its removal at the end of the synthetic route.

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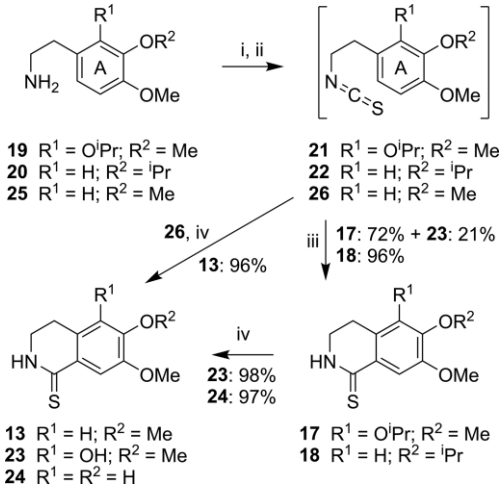
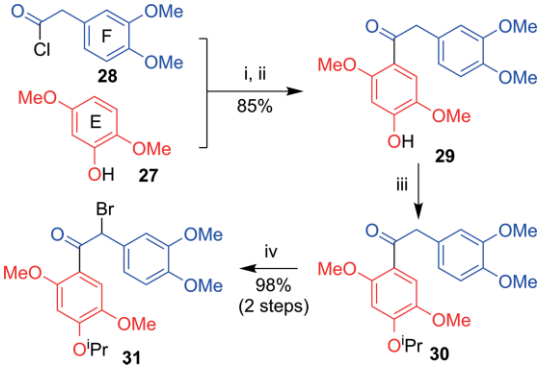
Our route to the requisite isopropyl-protected isoquinolinethiones **17** and **18** is shown in Scheme 2. Both isopropyl-protected phenylethylamines **19**[23] and **20**,[24] the requisite building blocks for lamellarins **5** and **6**, are known compounds, and were readily made according to the reported procedures by Henry reaction of the corresponding aldehydes with nitromethane, followed by reduction of the resulting nitrostyrenes with lithium aluminum hydride. Conversion of these amines into the corresponding isothiocyanate intermediates **21** and **22** with carbon disulfide followed by reaction with ethyl chloroformate was straightforward. These intermediates were used immediately in the next step without purification. Unfortunately, attempted cyclization of **22** to the thione **18** with polyphosphoric acid at 80–90 °C,[25] the method we previously used for making the 3,4-dimethoxy analogue,[17] failed because the isopropyl protecting groups did not survive the reaction conditions even though the desired cyclization appeared to have taken place. Other acidic reagents (neat methanesulfonic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, aluminum trichloride, boron trifluoride) also led to some cyclization, but with concomitant loss of the protecting group and, in some cases, with the formation of significant amounts of by-products. No reaction of the isothiocyanates was found with camphorsulfonic acid, *p*-toluenesulfonic acid or acetic acid. To our gratification, however, the use of *dilute* methanesulfonic acid in dichloromethane at ambient temperature brought about the desired reactions. Under these conditions, products **17** and **18**, both of which retained the protecting group, were isolated in yields of 72 % and 96 %, respectively, on a multi-gram scale after purification by column chromatography. In the case of **17**, however, the reaction required 18 hours for completion, and some of the isopropyl protecting group was also lost, giving the free phenol analogue **23** (21 %). This fortuitous discovery suggested that the use of methanesulfonic acid might be fine-tuned to effect not only what appears to be a novel procedure for cyclizing isothiocyanates to isoquinolinethiones, but also for cleaving aryl isopropyl ethers to the parent phenols, since we hypothesized that **23** was probably formed owing to the extended reaction time. Indeed, treating **17** with neat methanesulfonic acid caused clean deprotection to **23** in 98 % isolated yield within 30 minutes at room temperature without destroying the thiocarbonyl group. Similar treatment of thione **18** also brought about clean and nearly quantitative formation of phenol **24** (97 %). Thus in the course of these investigations we appear to have discovered two new reactions mediated by methanesulfonic acid: cyclization of isothiocyanates to isoquinolinethiones, and mild deprotection of aryl isopropyl ethers. We are currently exploring further applications of these reactions; in the meantime, we can report that conversion of homoveratrylamine (**25**) into the corresponding thione **13** proceeds in 96 % yield when the intermediate isothiocyanate **26** is treated with neat methanesulfonic acid at ambient temperature. We had previously accomplished this transformation in 92 % overall yield under more vigorous conditions with polyphosphoric acid at 80–90 °C.[17]

For both target compounds **5** and **6**, the precursor of ring E was 2,5-dimethoxyphenol (**27**) which, though commercially available, was conveniently prepared by Baeyer–Villiger oxidation of 2,5-dimethoxybenzaldehyde.[26] Initial in situ ester formation between homoveratroyl chloride (**28**) and **27** followed by *para*-Fries rearrangement[27] proceeded satisfactorily with 1 % phosphorus pentoxide in methanesulfonic acid (a diluted version of Eaton's reagent[28]), giving essentially pure deoxybenzoin product **29** in 85 % yield after trituration with diethyl ether (Scheme 3). This appears to be a novel reagent for the rearrangement. Interestingly, decomposition occurred with Eaton's reagent itself (7.7 % P_2O_5), while lower yields (50–60 %) were obtained if phosphorus pentoxide was omitted. The oxide seems to be necessary to remove traces of moisture in the solvent, which otherwise cause some hydrolysis of the acyl species. Protection of the phenol was effected with isopropyl bromide in *N*,*N*-dimethylformamide at 60 °C. The choice of solvent for the O-isopropylation was found to be crucial; in less polar solvents such as acetone or acetonitrile, it appeared that alkylation of the benzoin enolate on carbon was a competing reaction. The protected intermediate **30**, obtained in approximately 98 % yield, was immediately treated with molecular bromine in



Scheme 2. Conversion of arylethylamines into 3,4-dihydroisoquinoline-2-thiones. Reagents and conditions: (i) CS_2, NEt_3, 0°, then r.t., 1 h; (ii) add $ClCO_2Et$, NEt_3, r.t., overnight; (iii) dilute $MeSO_3H$ in CH_2Cl_2, r.t., 18 h (for **17**) or 4 h (for **18**); (iv) neat $MeSO_3H$, r.t., 0.5 h.



Scheme 3. Synthesis of isopropyl-protected bromodeoxybenzoin **31**. Reagents and conditions: (i) **27** + **28**, CH_2Cl_2, r.t., then evaporate solvent; (ii) P_2O_5 (1 %) in $MeSO_3H$, r.t., overnight; (iii) Me_2CHBr (3.5 equiv.), DMF, K_2CO_3, 60 °C, 2 h; (iv) Br_2 (1 equiv.), $CHCl_3$, 0 °C.

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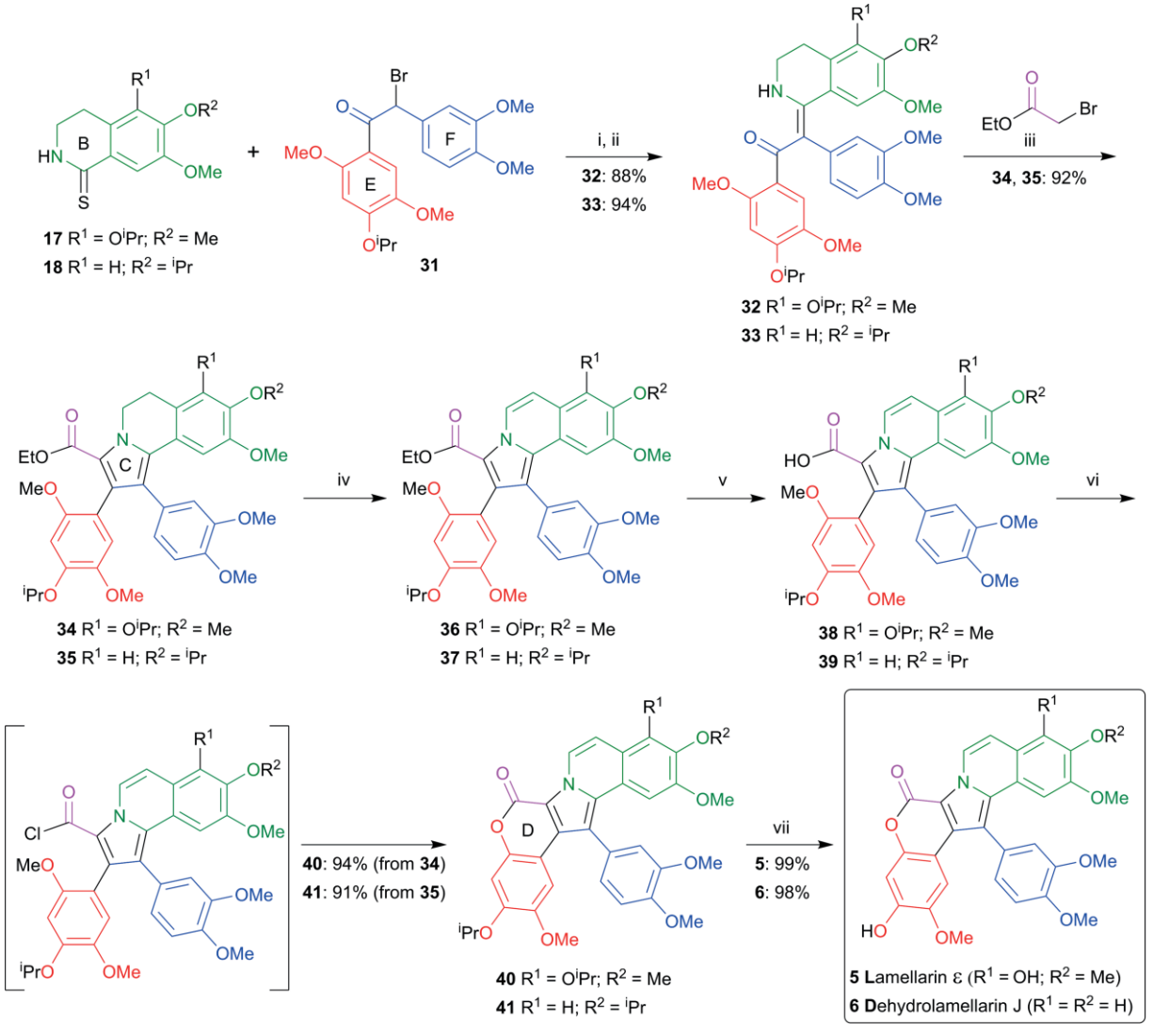
chloroform at 0 °C to afford the α-bromoketone **31** in almost quantitative yield. The reaction was found to take place with no detectable bromination of the aromatic rings under these conditions. However, compound **31** decomposed quite rapidly and did not survive storage; it needed to be prepared fresh before its use in the sulfide contraction step.

Sulfide contraction of the isopropyl protected thiolactams **17** and **18** with the bromoketone **31** proceeded uneventfully even on a multi-gram scale, and afforded enaminones **32** and **33** in yields of 88 % and 94 %, respectively, after chromatography (Scheme 4). The ensuing [4 + 1] cyclisation with ethyl bromoacetate gave the pyrrolo[2,1-*a*]isoquinolines **34** and **35**, both in 92 % yield, after chromatographic separation from excess ethyl bromoacetate. Oxidation of ring B in these two intermediate with DDQ to give the unsaturated intermediates **36** and **37** was followed by ester hydrolysis to the corresponding carboxylic acids **38** and **39**. Application of our new demethylative lactonization protocol[17] thereafter provided the isopropyl-protected lamellarin scaffolds **40** and **41** in yields of 94 % and 91 %, respectively over the three steps from the pyrrole-containing intermediates **34** and **35**. Purification of the intermediates in the intermediate steps was unnecessary, since the final isopropylated products could be separated from inorganic and other by-products by filtration through a short pad of silica gel followed by trituration with hot methanol.

The deprotection of isopropyl ethers in rings A and E, a standard transformation in published syntheses of lamellarins, has usually been accomplished with boron trichloride[2–4] or, occasionally, with aluminum trichloride.[23,29] For example, a patented procedure for deprotecting the isopropylated intermediate **41** with aluminum trichloride gave only a 26 % yield of dehydrolamellarin J (**6**).[30] On the other hand, boron trichloride is toxic, expensive and awkward to handle, although reported yields of the liberated phenols have generally been in excess of 90 %. However, our accidental finding of methanesulfonic acid-mediated isopropyl ether cleavage without migration of the iso-



Scheme 4. Completion of the syntheses of lamellarin ε (**5**) and dihydrolamellarin J (**6**). Reagents and conditions: (i) **17/18** + **31**, MeCN, r.t., 16 h; (ii) add PPh_3 (1 equiv.), NEt_3 (1.2 equiv.) in MeCN, r.t., 16 h; (iii) EtO_2CCH_2Br (neat; 6–8 equiv.), $NaHCO_3$, 80–85 °C, 48 h; (iv) DDQ, CH_2Cl_2, r.t., 18 h (for **36**) or 4 h (for **37**); (v) KOH, H_2O, EtOH, reflux; (vi) $(COCl)_2$ (2 equiv.), 0 °C, then r.t., 2–4 h; (vii) add NaI, MeCN, r.t., 16 h; (viii) $MeSO_3H$ (neat), r.t., 30 min.

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propyl group to the electron-rich aryl rings during the synthesis of isoquinolinethiones, as reported above, provided a perfect opportunity for testing this novel procedure on the two lamellarin precursors **40** and **41**. We found to our delight that treating these protected lamellarins with neat methanesulfonic acid at room temperature for only 30 minutes led to complete deprotection even when performed without exclusion of air, and gave almost quantitative yields of pure lamellarin ε (**5**) and dehydrolamellarin J (**6**) after precipitation of the desired products merely upon addition of water to the reaction mixture. Furthermore, we were able to characterize isopropyl methanesulfonate as a by-product of the reaction, indicating that the putative isopropyl cation is effectively trapped by methanesulfonate – a surprising finding for such a relatively non-nucleophilic anion. Since methanesulfonic acid is regarded as a green and sustainable solvent,[31] its use thus provides a cheap, simple, safe, relatively eco-friendly and scalable alternative to the toxic and less desirable Lewis acids conventionally used for deprotecting aryl isopropyl ethers. The overall yield of lamellarin ε (**5**) from the substituted phenylethylamine **19** by our route was 55 % over seven steps, while the overall yield of dehydrolamellarin J (**6**) from amine **20** was 75 %. It is worth mentioning that the efficient removal of isopropyl substituents from *N*-isopropylamides with methanesulfonic acid has been reported, although a temperature of 90 °C was required for the cleavage, and reaction times varied from 2 to 72 hours.[32]

Our success with these relatively short, high-yielding modular syntheses of lamellarins suggested that we should be able to increase the scale even further in order to obtain multi-gram quantities of these valuable compounds. As proof of concept, we chose to prepare at least 25 g of the highly bioactive lamellarin analogue dehydrolamellarin J (**6**), the cytotoxicity of which towards various cancer cell lines is similar to (and in some cases exceeds) that of lamellarin D (**1**),[11] usually regarded as the front runner in the field.[6] The sequence of reactions from the phenylethylamine **20** to the target **6** was essentially as shown in Scheme 2, Scheme 3, and Scheme 4, but with the important difference that we were able to avoid chromatographic purification of the intermediates without materially affecting the yields. Thus the dihydroisoquinolinethione **18**, made from **20** in 81 % yield on a 30 g scale, was purified by recrystallization from methyl *tert*-butyl ether. From this point on, reactions were carried out in duplicate in order to assess the reproducibility of the transformations. The enaminone **33**, made in two batches of more than 30 g each, was purified via its hydrochloride salt, neutralization of which afforded the desired product in 90–92 % yield. The pivotal pyrrole formation with ethyl bromoacetate proceeded well to give two 27 g batches of intermediate **35** (76–77 %), purification of which was accomplished by precipitation from suitable solvents followed by trituration with methanol. Oxidation of ring B with DDQ on two batches of over 20 g each gave almost quantitative yields of the unsaturated analogue **37**.

Of greatest interest was whether our novel demethylative lactonization procedure would work well on a large scale. The conversion of **37** into the substituted lamellarin **41** proceeded beyond expectations: the intermediate carboxylic acid **39** (13 g and 22 g), made by hydrolyzing **37** (14 g and 23 g) with potassium hydroxide in water, underwent the oxalyl chloride/sodium iodide-mediated cyclization to give the desired product **41** in 99 % and 96 % yields after recrystallization from methanol. The final cleavage of the isopropyl protecting groups was done on batches of *ca* 10 g and 20 g, and afforded dehydrolamellarin J (**6**) (10 g, 96 %; and 16.5 g, 97 %) simply by precipitating the product from the reaction mixture with water. In this way we achieved our target of making over 25 g of the exceptionally potent lamellarin derivative **6** without chromatography of the intermediates – a quantity that, to the best of our knowledge, exceeds even that in which simpler inactive model compounds such as **7** and **8** have previously been made. The overall average yield of dehydrolamellarin J (**6**) from thiolactam **18** on this large scale was 63 % over six steps.

Conclusion

In this article we report the total syntheses of the potent cytotoxins lamellarin ε (**5**) and dehydrolamellarin J (**6**) using our previously reported methods for installing the pyrrole core[14] and the 2-chromenone component.[17] In addition, we demonstrate novel uses for the relatively cheap and "green" reagent[31] methanesulfonic acid, including cyclization of (2-isothiocyanatoethyl)benzenes to 3,4-dihydroisoquinoline-1(2*H*)-thiones; a role in a Fries rearrangement; and, most usefully, the rapid deprotection of isopropyl aryl ethers at ambient temperature. A scaled-up synthesis of dehydrolamellarin J (**6**) produced batches of 10 g and 20 g without chromatographic purification of intermediates while still maintaining excellent efficiency and affordability. We have thereby prepared the largest quantities of this compound (or, indeed, of any lamellarin reported in the periodical literature) to date. Our procedures should lend themselves to the convenient and procedurally simple synthesis of other pentacyclic lamellarins as well as numerous new synthetic derivatives.

Experimental Section

General Remarks: Chemicals and deuterated solvents were purchased from commercial sources (Merck, Sigma-Aldrich) and used as received. Merck silica gel (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography, and Merck silica gel (particle size 0.04–0.063 mm) for flash column chromatography. Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} plates, and compounds were visualized using UV light and/or by exposure to iodine vapour. Solvents for reaction or chromatography were dried and purified, where necessary, by standard methods. All reactions were performed under an inert atmosphere of argon in oven-dried glassware. Room temperature refers to ambient laboratory temperatures of 18–25 °C. Melting points were recorded on a JM 626 melting-point apparatus with microscope and a digital thermometer. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on Bruker Avance I 300 MHz, Avance III 400 MHz and Avance III 500 MHz spectrometers at frequencies of 300 MHz, 400 MHz and 500 MHz, respectively, for ^{1}H spectra; and at frequencies of 75 MHz, 101 and 126 MHz, respectively, for ^{13}C spectra. Chemical shifts (δ) of ^{1}H signals recorded in $CDCl_3$ solution are reported as parts per million (ppm) downfield from Me_4Si as internal reference, while

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spectra recorded in [D_6]DMSO are referenced to the central peak of the solvent (2.50 ppm). Chemical shifts (δ) of ^{13}C signals are referenced to the central peaks of $CDCl_3$ (77.16 ppm) or [D_6]DMSO (39.52 ppm). High resolution mass spectra were obtained on a Bruker Compact Q-TOF mass spectrometer in electrospray positive ionization mode.

General Procedure for Preparing 3,4-Dihydroisoquinolinethiones 13, 17, 18, 23: NEt_3 (1.00 mmol, 1 equiv.) and CS_2 (1.50 mmol, 1.5 equiv.) were added to a solution of the phenylethylamine (1.00 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under an atmosphere of Ar. The reaction mixture was stirred at room temperature for 1 h, then again cooled to 0 °C. Ethyl chloroformate (1.00 mmol, 1 equiv.) was added dropwise, which caused the immediate precipitation of triethylammonium chloride. After stirring at room temperature for 1 h, additional NEt_3 (1.00 mmol, 1 equiv.) was added and the reaction was left to stir overnight. Aqueous NaOH solution (10 %, 10 mL) was added to maintain alkalinity during extraction, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated to provide the isothiocyanate intermediates as oils, which were used immediately without further purification. Methanesulfonic acid (0. 28 mL, *ca* 4.3 equiv.) was added dropwise with stirring to a solution of the isothiocyanate (1 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The solution was warmed to room temperature and stirred until an NMR spectrum of the mixture indicated that the reaction was complete. The reaction was then quenched with saturated aqueous $NaHCO_3$ solution and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), at which point the extracts were no longer yellow. The combined organic phases were dried with $MgSO_4$, filtered, and the solvent was removed to provide an oily residue, which was purified by chromatography on silica gel (40 % EtOAc in hexane) to provide the thiolactams as yellow solids, which were further purified if necessary as described below.

6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (13): Prepared from homoveratrylamine (**25**) (5.00 g, 27.3 mmol) via the isothiocyanate intermediate **26** according to the general procedure, but using neat $MeSO_3H$ (25 mL) for the cyclization. The reaction time for thiolactam formation was 0.5 h. After addition of water (100 mL), collection of the resulting solid by filtration, washing with MeOH (100 mL) and drying, thione **13** (5.90 g, 26.4 mmol, 96 %) was obtained as a spectroscopically homogeneous cream-colored crystalline solid, m.p. 221–222 °C (lit.[20a] 223 °C); spectroscopic details are as described previously.[17]

5-Isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (17) and 5-Hydroxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (23): Prepared from 2-(2-isopropoxy-3,4-dimethoxyphenyl)ethylamine (**19**)[23] (7.07 g, 29.5 mmol) via the isothiocyanate intermediate **21** according to the general procedure. The reaction time for thiolactam formation was 18 h. A by-product, isopropyl methanesulfonate, co-eluted with **17**, but was removed by triturating the crude solid with Et_2O/hexane (1:1), and collecting the desired thione **17** (6.00 g, 72 %) by filtration. Some deprotected phenol **23** (1.50 g, 6.27 mmol, 21 %) was obtained from later fractions after chromatography. **5-Isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (17):** spectroscopically homogeneous yellow crystalline solid, R_f = 0.40 (hexane/EtOAc, 3:2); m.p. 114–116 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.36 (br s, 1H), 7.94 (s, 1H), 4.52 (septet, *J* = 6.2 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.47 (td, *J* = 6.9, 3.4 Hz, 2H), 2.95 (t, *J* = 6.9 Hz, 2H), 1.27 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 193.0, 151.8, 147.0, 146.5, 127.8, 122.3, 110.7, 75.6, 60.6, 56.1, 41.7, 22.6 (2 × C), 21.8. HRMS (ESI) Found: $[M + H]^+$, 282.1160; $C_{14}H_{20}NO_3S^+$ requires 282.1158. **5-Hydroxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (23):** pale yellow solid, m.p. 214–215 °C; ^1H NMR (500 MHz, [D_6]DMSO) δ 10.29 (br s, 1H), 9.22 (s, 1H), 7.57 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.32 (td, *J* = 7.0, 3.5 Hz, 2H, partly obscured by water), 2.75 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, [D_6]DMSO) δ = 191.1, 150.6, 146.0, 139.7, 127.9, 115.7, 106.1, 60.3, 55.7, 40.8, 20.4.

6-Isopropoxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (18): Prepared from 2-(4-isopropoxy-3-methoxyphenyl)ethylamine (**20**)[24b] (3.01 g, 14.4 mmol) via the isothiocyanate intermediate **22** according to the general procedure. The reaction time for thiolactam formation was 4 h. After chromatographic purification, thione **18** (3.47 g, 96 %) was obtained as a spectroscopically homogeneous yellow crystalline solid, R_f = 0.35 (hexane/EtOAc, 3:2); m.p. 120–121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.34 (t, *J* = 3.3 Hz, 1H, NH), 8.00 (s, 1H), 6.57 (s, 1H), 4.57 (septet, *J* = 6.1 Hz, 1H), 3.86 (s, 3H), 3.52 (td, *J* = 7.0, 3.3 Hz, 2H), 2.84 (t, *J* = 7.0 Hz, 2H), 1.32 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 192.3, 151.3, 148.5, 127.8, 125.1, 114.7, 111.9, 71.2, 56.0, 41.6, 27.3, 21.8 (2 × C). HRMS (ESI) Found: $[M + H]^+$, 252.1051; $C_{13}H_{18}NO_2S^+$ requires 252.1053.

Alternative Route to 5-Hydroxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (23): 5-Isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**17**) (123 mg, 0.44 mmol) was stirred at room temperature in neat methanesulfonic acid (0.60 mL) for 30 min. Addition of ice-cold water induced precipitation of the product, which was collected by filtration. The filter paper was extracted with warm MeOH (100 mL), which was evaporated to give thione **23** (102 mg, 0.43 mmol, 98 %); characterization as described above.

6-Hydroxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (24): 6-Isopropoxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**18**) (1.00 g, 3.98 mmol) was stirred at room temperature in neat methanesulfonic acid (5.0 mL) for 30 min. The precipitate resulting from addition of ice-cold water was collected by filtration, washed with water and dried to yield thione **24** (809 mg, 3.87 mmol, 97 %). ^1H NMR (300 MHz, [D_6]DMSO) δ 10.08 (t, *J* = 3.3 Hz, 1H, NH), 9.89 (s, 1H), 7.90 (s, 1H), 6.64 (s, 1H), 3.79 (s, 3H), 3.33 (td, *J* = 6.9, 3.3 Hz, 2H), 2.76 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, [D_6]DMSO) δ = 190.8, 150.8, 146.2, 128.7, 124.3, 114.8, 113.6, 55.7, 41.0, 26.5.

2-(3,4-Dimethoxyphenyl)-1-(4-hydroxy-2,5-dimethoxyphenyl)-ethanone (29): Oxalyl chloride (2.4 mL, *ca* 28 mmol) was added to an ice-cooled solution of 3,4-dimethoxyphenylacetic acid (5.0 g, 25.5 mmol) in dry CH_2Cl_2 (75 mL) under Ar, which caused the solution to turn a deep orange color. Addition of a few drops of dry DMF by syringe resulted in the immediate formation of CO and CO_2 gas bubbles. The ice bath was removed and the solution was left to stir until bubbling ceased (*ca* 2 h). The solvent was removed by rotary evaporation, and the crude product was further dried under vacuum (*ca* 0.1 Torr) to remove any residual oxalyl chloride. 3,4-Dimethoxyphenylacetyl chloride (**28**), obtained as an orange oil, was used immediately without purification. 2,5-Dimethoxyphenol (**27**)[26] (3.92 g, 25.4 mmol, 1 equiv.) in dry CH_2Cl_2 (10 mL) was then added to the crude acid chloride **28** using additional dry CH_2Cl_2 (*ca* 5 mL) to ensure quantitative transfer. The solvent was removed in vacuo, and the reaction vessel was flushed with Ar. A dilute solution of P_2O_5 in methanesulfonic acid (1 %; 20 mL; prepared at least a day in advance to allow for complete formation of the active species) was added to the well-mixed residue at room temperature. HCl gas was immediately produced, and the solution turned dark brown. This was left to stir overnight at room temperature, after which time ice water (250 mL) was added. The solution was then neutralized by adding solid $NaHCO_3$ with vigorous stirring until

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bubbling ceased and the dark color lightened to pale amber. Extraction with CH_2Cl_2 (3 × 100 mL) followed by drying of the combined organic extracts over $MgSO_4$, filtration and removal of solvent gave a thick amber oil to which Et_2O (150 mL) was added with swirling. Crystals immediately started to precipitate. These were collected by filtration, washed with hexane and dried to yield the substituted deoxybenzoin **29** (7.19 g, 21.6 mmol, 85 % based on 3,4-dimethoxyphenylacetic acid) as a cream colored solid, m.p. 152–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.84–6.72 (m, 3H), 6.57 (s, 1H), 6.24 (s, 1H), 4.24 (s, 2H), 3.86 (s, 3H), 3.85 and 3.84 (2 × s, 6H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.7, 155.6, 151.3, 148.8, 147.7, 140.8, 128.4, 121.9, 118.7, 113.0, 112.9, 111.2, 99.2, 56.4, 56.0, 55.94, 55.86, 49.6. HRMS (ESI) Found: $[M + H]^+$, 333.1338; $C_{18}H_{21}O_6^+$ requires 333.1333. *Note:* The compound could be used in the subsequent reaction without further purification. However, it can be recrystallized from MeOH if required although at least 24 h are necessary for complete crystallization, and repeated recrystallization of material obtained from the mother liquors from MeOH/H_2O is necessary in order to obtain comparable yields.

2-(3,4-Dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)ethanone (30): 2-Bromopropane (5 mL, *ca* 53 mmol) and K_2CO_3 (8.29 g, 60 mmol) were added to a solution of 2-(3,4-dimethoxyphenyl)-1-(4-hydroxy-2,5-dimethoxyphenyl)ethanone (**29**) (5.00 g, 15.0 mmol) in DMF (50 mL). The mixture was heated at 60 °C for 2 h until TLC showed that the reaction was complete. Water (800 mL) was added, and the mixture was extracted with EtOAc (100 mL). The organic phase was washed successively with water (3 × 500 mL) and brine (100 mL), dried with $MgSO_4$, filtered and the solvents evaporated in vacuo to provide the isopropylated deoxybenzoin **30** (5.52 g, 14.7 mmol, 98 %) as an amber oil that was sufficiently pure for subsequent use. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.80–6.77 (m, 1H), 6.76 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.51 (s, 1H), 4.65 (septet, *J* = 6.1 Hz, 1H), 4.25 (s, 2H), 3.90 (s, 3H), 3.86 (s, 6H), 3.82 (s, 3H), 1.41 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 197.6, 154.9, 152.4, 148.7, 147.6, 144.2, 128.3, 121.7, 119.0, 113.8, 112.9, 111.1, 99.6, 71.7, 56.3, 56.1, 55.9, 55.8, 49.6, 22.0 (2 × C). HRMS (ESI) Found: $[M + H]^+$, 375.1812; $C_{21}H_{27}O_6^+$ requires 375.1802.

2-Bromo-2-(3,4-dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)ethanone (31): The deoxybenzoin **30** (4.02 g, 107.4 mmol) was dissolved in $CHCl_3$ (200 mL) and the solution was cooled in an ice bath. An accurately prepared solution of Br_2 (110 mmol, 1 equiv.) in $CHCl_3$ (100 mL) was transferred to a dropping funnel, and one drop was added to the ketone solution. After 1 min it was assumed that enough HBr had formed to catalyse enolic bromination. The remainder of the Br_2 solution was then added dropwise to the persistently amber solution of ketone at a rate of about 1–2 drops per second such that its red color was discharged immediately before the addition of the succeeding drop. Once addition was complete, saturated aqueous $NaHCO_3$ solution was added to quench the cold reaction mixture, which caused the color to clear considerably. The phases were separated, and the aqueous phase was further extracted with $CHCl_3$ (2 × 150 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvents evaporated in vacuo to provide the bromoketone **31** (4.84 g, *ca* 99 %) as a greenish gel. This product was used immediately as it proved susceptible to rapid decomposition, especially in the presence of light. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 7.02 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.69 (s, 1H), 6.46 (s, 1H), 4.64 (septet, *J* = 6.1 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 1.42 and 1.41 (2 × overlapping d, *J* = 6.1 and 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.0, 154.7, 153.4, 149.5, 149.1, 144.6, 129.2, 122.0, 116.4, 114.4, 112.5, 110.8, 99.2, 71.4, 56.4, 56.3, 56.0, 55.9, 55.7, 22.0 (2 × C). HRMS (ESI) Found: $[M + H]^+$, 453.0912; $C_{21}H_{26}{}^{79}BrO_6^+$ requires 453.0907.

General Method for the Synthesis of Enaminones 32 and 33 by Eschenmoser Sulfide Contraction: Immediately after synthesis as described above, the bromoketone **31** (1.05 mmol) was dissolved in dry MeCN (30 mL), to which was added the relevant dihydroisoquinoline-1(2*H*)-thione (1 mmol). The mixture was stirred for 18 h at room temperature to ensure complete salt formation, after which time Ph_3P (1 equiv.) was added. The solution was stirred for 5 min until the phosphine had dissolved, after which NEt_3 (1.2 equiv.) in MeCN (10 mL) was added at a rate of about 1 drop per second. The solution soon turned bright yellow, indicating the successful formation of the deeply colored enaminone. Once the reaction mixture had been stirred at room temperature overnight, the solvent was removed and the residue was purified by flash column chromatography (50–100 % EtOAc in hexane). The yellow fractions containing the enaminone were combined and evaporated to give the desired products as bright yellow solids that were purified by careful column chromatography on silica gel. [*Note*: Replacing PPh_3 by the relatively volatile $P(OMe)_3$ simplified the purification of the enaminones because both it and the corresponding sulfide can be removed by co-evaporation with ethanol, followed by acid–base extractive purification. However, the yields of enaminone were consistently lower (78–82 %)].

(*Z*)-2-(3,4-Dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)-2-(5-isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)ethanone (32): This product (7.00 g) partially contaminated with an inseparable quantity of Ph_3PS was obtained from 5-isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**17**) (3.200 g, 113.7 mmol) by the general procedure. The purity of **32** was estimated as 90 % by NMR spectroscopy against DMF added as internal reference, indicating an approximate yield of 88 %. The compound could be used in the subsequent cyclization without detriment, after which the contaminant was readily removed by chromatography or recrystallization. Bright yellow solid, R_f = 0.50 (EtOAc); m.p. 74–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.23 (br t, *J* = 3.7 Hz, 1H), 6.59–6.48 (m, 3H), 6.45 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.30 (s, 1H), 6.26 (s, 1H), 4.47 and 4.42 (2 × overlapping septets, *J* = 6.1 and 6.1 Hz, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H), 3.52 (s, 3H), 3.44 (s, 2H), 3.12 (s, 3H), 2.92 (br s, 2H), 1.29 (d, *J* = 6.0 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.4, 158.9, 150.2, 149.5, 148.1, 147.12 (2 × C), 147.09, 146.9, 144.2, 143.8, 133.7, 126.3, 126.0, 125.6, 124.3, 116.6, 113.0, 111.0, 110.4, 107.2, 102.0, 75.6, 72.1, 60.5, 56.5, 56.1, 55.8, 55.7, 55.1, 39.1, 22.5 (2 × C), 22.0 (2 × C). HRMS (ESI) Found: $[M + H]^+$, 622.3027; $C_{35}H_{44}NO_9^+$ requires 622.3011.

(*Z*)-2-(3,4-Dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)-2-(6-isopropoxy-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)ethanone (33): This product (2.91 g, 49.2 mmol, 94 %) was obtained from 6-isopropoxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**18**) (1.32 g, 52.5 mmol) by the general procedure. Bright yellow solid, R_f = 0.40 (EtOAc); m.p. 89–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.24 (br s, 1H), 6.62 (s, 1H), 6.58–6.52 (m, 2H), 6.50 (s, 1H), 6.46 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.41 (s, 1H), 6.30 (s, 1H), 4.57 (septet, *J* = 6.1 Hz, 1H), 4.42 (septet, *J* = 6.1 Hz, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 3.58 (s, 3H), 3.53 (s, 3H), 3.60–3.40 (br m, 2H), 3.11 (s, 3H), 2.95–2.80 (br m, 2H), 1.37 (d, *J* = 6.1 Hz, 6H), 1.29 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.1, 158.9, 149.4, 148.6, 148.2, 147.1, 146.94, 146.91, 144.2, 133.7, 131.8, 126.1, 125.7, 121.2, 116.6, 114.7, 113.0, 112.7, 110.5, 106.9, 102.0, 72.1, 71.0, 56.5, 56.1, 55.80, 55.75, 55.2, 39.2, 28.8, 22.04 (2 × C), 22.00 (2 × C). HRMS (ESI) Found: $[M + H]^+$, 592.2908; $C_{34}H_{42}NO_8^+$ requires 592.2905.

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General Procedure for Formation of Pyrroles 34 and 35 from Enaminones 32 and 33: The enaminone (1.00 g, 1.6–1.8 mmol) was dissolved in ethyl bromoacetate (1.5 mL; *ca* 2.26 g, *ca* 13.5 mmol, *ca* 6–8 equiv; some CH_2Cl_2 can be used to ensure homogeneity, as it evaporates over the course of the reaction), to which was added $NaHCO_3$ (1.50 g, 179 mmol). The mixture was stirred under an atmosphere of argon gas at 80–85 °C for 48 h, after which time the solution had gone from bright yellow-orange to deep red and then to an almost colorless state. The total crude product was dissolved in a small quantity of CH_2Cl_2 and loaded onto a column of flash silica gel. Gradient elution with 0–50 % EtOAc/hexane mixtures provided the pyrrole-fused products. (Alternatively, the product was dissolved in CH_2Cl_2 and filtered to remove insoluble material. After evaporation of the solvent, the residue was dissolved in Et_2O (5 mL gram^{-1} of starting enaminone), and hexane was added to induce a lasting turbidity. Soon crystals began to develop, and after a few hours these were collected by filtration, washed with hexane and triturated under boiling MeOH. After cooling, the crystals were collected by filtration, washed with MeOH and dried. Additional product could be obtained by further treatment of the mother liquors.

Ethyl 1-(3,4-Dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo-[2,1-*a*]isoquinoline-3-carboxylate (34): Compound **34** (1.762 g, *ca* 92 %) was obtained from (*Z*)-2-(3,4-dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)-2-(5-isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)ethanone (**32**) (2.00 g, *ca* 90 % pure) according to the general procedure after purification by chromatography. Alternatively, **34** (3.10 g, *ca* 80 %) was obtained from **32** (3.90, *ca* 90 % pure) after recrystallization from MeOH. White solid, R_f = 0.30 (hexane/EtOAc, 3:2); m.p. 72–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.80 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 1.8 Hz, 1H), 6.57 (s, 2H), 6.47 (s, 1H), 4.65–4.40 (m, 4H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 6H), 3.64 (s, 3H), 3.61 (s, 3H), 3.55 (s, 3H), 3.33 (s, 3H), 3.09 (br t, *J* = 6.7 Hz, 2H), 1.34 and 1.32 (2 × overlapping d, *J* = 6.1 and 6.2 Hz, 12H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.9, 151.5, 151.4, 148.4, 148.1, 147.5, 146.4, 144.1, 141.5, 130.6, 128.4, 128.2, 123.9, 123.2, 122.2, 120.4, 119.3, 117.8, 116.7, 114.0, 110.8, 104.9, 102.4, 75.5, 72.1, 60.5, 59.6, 56.5, 56.3, 55.9, 55.7, 55.2, 42.7, 23.0, 22.7 (2 × C), 22.1 (2 × C), 13.8. HRMS (ESI) Found: $[M + H]^+$, 690.3252; $C_{39}H_{48}NO_{10}^+$ requires 690.3273.

Ethyl 1-(3,4-Dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (35): Compound **35** (2.35 g, 3.56 mmol, 92 %) was obtained from (*Z*)-2-(3,4-dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxy-phenyl)-2-(6-isopropoxy-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)ethanone (**33**) (2.27 g, 3.84 mmol) according to the general procedure as a colorless gel that gradually solidified after purification by chromatography; R_f = 0.30 (hexane/EtOAc, 3:2); m,p. 160–161 °C (from MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.78 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.76–6.71 (m, 3H), 6.69 (d, *J* = 1.8 Hz, 1H), 6.57 (s, 1H), 6.47 (s, 1H), 4.61 (br t, *J ca* 7.5 Hz, 2H), 4.51 (septet, *J* = 6.0 Hz, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 3.62 (s, 3H), 3.61 (s, 3H), 3.54 (s, 3H), 3.33 (s, 3H), 3.03 (t, *J* = 6.6 Hz, 2H), 1.37 (d, *J* = 6.0 Hz, 6H), 1.33 (d, *J* = 6.0 Hz, 6H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.0, 151.5, 148.4 (2 × C), 147.5, 146.4, 146.3, 144.1, 131.0, 128.4, 128.3, 125.7, 123.1, 121.5, 121.3, 119.0, 118.0, 116.8, 114.7, 114.0, 110.8, 109.3, 102.5, 72.1, 71.4, 59.6, 56.5, 56.3, 55.9, 55.7, 55.3, 42.8, 29.0, 22.1 (4 × C), 13.8. HRMS (ESI) Found: $[M + H]^+$, 660.3147; $C_{38}H_{46}NO_9^+$ requires 660.3167.

General Procedure for DDQ Oxidation of Ethyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-3-carboxylates 34 and 35: The 5,6-dihydropyrrolo[2,1-*a*]isoquinoline (1 mmol) was dissolved in CH_2Cl_2 (100 mL), to which was added DDQ (1.25 mmol). The solution, which immediately turned a muddy-brown color, was left to stir at room temperature for the specified time. Aqueous NaOH solution (2 M, 50 mL) was added, and the phases were separated. The aqueous phase was re-extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic fractions were washed with NaOH solution (2 M, 50 mL), water (50 mL) and brine. After drying over $MgSO_4$, filtration, evaporation in vacuo, the spectroscopically homogeneous products were obtained as foams in quantitative yields.

Ethyl 1-(3,4-Dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (36): Compound **36** (1.98 g, 28.8 mmol, 99 %) was obtained from ethyl 1-(3,4-dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**34**) (2.00 g, 29.0 mmol) according to the general procedure as a brownish solid foam, m.p. 85–86 °C; reaction time 18 h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.05 (s, 1H), 6.95–6.73 (m, 3H), 6.61 (s, 1H), 6.48 (s, 1H), 4.70 (septet, *J* = 6.2 Hz, 1H), 4.50 (septet, *J* = 6.1 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.71 (s, 3H), 3.64 (s, 3H), 3.58 (s, 3H), 3.42 (s, 3H), 1.34 (d, *J* = 6.0 Hz, 12H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.1, 152.8, 151.5, 148.6, 147.9, 146.6, 146.1, 144.1, 141.5, 131.8, 129.6, 128.8, 123.8, 122.9, 121.9, 119.6, 119.4, 117.8, 116.7, 114.7, 113.4, 110.8 (br), 107.2, 102.3 (br), 101.3, 76.1, 72.1, 60.7, 59.5, 56.6, 56.3, 56.0, 55.8, 55.3, 22.72, 22.70, 22.1 (br, 2 × C), 13.8. HRMS (ESI) Found: $[M + H]^+$, 688.3116; $C_{39}H_{46}NO_{10}^+$ requires 688.3116.

Ethyl 1-(3,4-Dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxypyrrolo[2,1-a]isoquinoline-3-carboxylate (37): Compound **37** (796 mg, 1.21 mmol, 100 %), was obtained from ethyl 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxy-5,6-dihydropyrrolo-[2,1-*a*]isoquinoline-3-carboxylate (**35**) (800 mg, 1.21 mmol) according to the general procedure as a brownish gel that gradually solidified; m.p. 96–100 °C; reaction time 4 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (d, *J* = 7.5 Hz, 1H), 7.26 (s, 1H), 7.04 (s, 1H), 6.92 and 6.91–6.87 (overlapping d and m, *J* = 7.5 Hz, 2H), 6.86–6.80 (m, 2H), 6.62 (s, 1H), 6.48 (s, 1H), 4.66 (septet, *J* = 6.1 Hz, 1H), 4.51 (septet, *J* = 6.1 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 3.57 (br s, 3H), 3.43 (s, 3H), 1.42 (d, *J* = 6.1 Hz, 6H), 1.35 (d, *J* = 6.1 Hz, 6H), 0.97 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.2, 151.5, 149.8, 148.5, 147.8, 147.4, 146.6, 144.1, 131.9, 130.2, 128.8, 123.8, 123.5 (2 × C), 119.7, 118.5, 117.9, 116.7, 114.6, 112.9, 111.9, 110.5, 105.6, 102.3, 72.1, 71.1, 59.4, 56.6, 56.3, 56.0, 55.7, 55.3, 22.1 (br, 2 × C), 22.0 (2 × C), 13.8. HRMS (ESI) Found: $[M + H]^+$, 658.3005; $C_{38}H_{44}NO_9^+$ requires 658.3011.

General Procedure for Hydrolysis of Esters 36 and 37: A solution of KOH (4.5 g, 80 mmol) in water (10 mL) was added to the ethyl pyrrolo[2,1-*a*]isoquinoline-3-carboxylates (1.00 mmol), followed by EtOH (100 mL) to ensure complete dissolution of the ester. The pale yellow solution was heated to reflux for 2 h, after which most of the EtOH was removed by rotary evaporation until the potassium carboxylate salt began to precipitate. The mixture was acidified with aqueous HCl (1 M), causing the free carboxylic acid to begin precipitating and turning the supernatant liquid bright yellow. The mixture was then extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts containing the dissolved carboxylic acid were washed with aqueous HCl (1 M; 100 mL) and brine (100 mL), dried with $MgSO_4$ and the solvents evaporated in vacuo to provide quantitative yields of spectroscopically pure carboxylic acids. The high-resolution mass spectra showed minor or no signals for the molecular ions, but ions for

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the decarboxylated products were apparent. However, the presence of the carboxylic acid was apparent in the ^{1}H (D_2O-exchangeable proton in the range δ 7.0–7.6) and ^{13}C NMR (C=O *ca* 150 ppm) spectra.

1-(3,4-Dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylic Acid (38): The acid **38** (1.50 g, 2.27 mmol, *ca* 100 %) was obtained according to the general procedure from ethyl 1-(3,4-dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**36**) (1.57 g, 2.28 mmol) as a pale brown solid, m.p. 76–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.4 Hz, 1H), 7.54 (s, 1H, CO_2H, exchanges with D_2O), 7.04 (d, *J* = 7.2 Hz, 1H), 7.02–6.95 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.70 (s, 1H), 6.53 (s, 1H), 4.67 (septet, *J* = 6.2 Hz, 1H), 4.50 (septet, *J* = 6.1 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H), 3.48 (s, 3H), 3.45 (s, 3H), 1.35 and 1.34 (2 × superimposed d, *J* = 6.4 and 6.0 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.6, 151.0, 148.9, 147.7, 146.5, 146.0, 144.1, 140.1, 130.5, 124.8, 124.0 (2 × C), 123.1, 122.9, 122.3, 117.9, 116.6, 116.5, 116.1, 114.9, 114.4, 111.3, 105.7, 102.6, 100.5, 75.9, 72.0, 60.6, 56.3, 56.1, 55.9 (2 × C), 55.3, 22.7 (2 × C), 22.2 (2 × C). HRMS (ESI) Found: $[M - CO_2]^+$, 616.2908; $C_{36}H_{42}NO_8^+$ requires 616.2905.

1-(3,4-Dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylic Acid (39): The acid **39** (1.43 g, 2.27 mmol, 100 %) was obtained according to the general procedure from ethyl 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**37**) (1.49 g, 2.27 mmol) as an off-white crystalline solid, m.p. 182–184 °C (from MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.2 Hz, 1H), 7.54 (s, 1H, CO_2H, exchanges with D_2O), 7.20 (s, 1H), 6.99 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 6.95 (s, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.71 (s, 1H), 6.61 (d, *J* = 1.8 Hz, 1H), 6.53 (s, 1H), 4.59 (septet, *J* = 6.1 Hz, 1H), 4.50 (septet, *J* = 6.1 Hz, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 3.64 (s, 3H), 3.49 (s, 3H), 3.45 (s, 3H), 1.39 (d, *J* = 6.1 Hz, 6H), 1.35 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 151.0, 149.8, 148.9, 147.6, 145.9, 145.8, 144.1, 130.6, 125.3, 124.0 (2 × C), 122.83, 122.76, 121.7, 121.1, 116.6, 116.0, 115.7, 114.8, 114.0, 112.1, 111.3, 110.4, 105.0, 102.5, 72.0, 71.2, 56.3, 56.08, 56.07, 55.9, 55.3, 22.2 (2 × C), 22.1 (2 × C). HRMS (ESI) Found: $[M - CO_2]^+$, 586.2834; $C_{35}H_{40}NO_7^+$ requires 586.2799.

Conversion of Pyrrolo[2,1-*a*]isoquinoline-3-carboxylic Acids 38 and 39 into Lamellarin Isopropyl Ethers 40 and 41 via Acid Chlorides: The carboxylic acid (1.00 mmol) was dissolved in dry CH_2Cl_2 (100 mL), and the solution was cooled to 0 °C under an atmosphere of argon. Oxalyl chloride (2 equiv.) was added by syringe, causing the color to become deep orange. The stirred solution was warmed to room temperature, and reaction was judged to be complete by NMR spectroscopy after 2–4 h. The solvent was evaporated on a rotary evaporator, and the crude amber-colored acid chloride was dissolved in a solution of NaI in MeCN (1 g in 100 mL; 80 mL). NaCl began to precipitate within 30 min. The suspension was stirred overnight, during which time a dense precipitate of NaCl and desired lamellarin ether was formed. The solvent was removed in vacuo and the residue was adsorbed onto silica gel (*ca* 5 g/g of starting material) and washed through a pad of silica gel with EtOAc/hexane (1:1) (*ca* 20 mL/g) until eluents no longer showed a bright blue fluorescent spot at 254 nm by TLC. The solvent was removed and MeOH (50 mL g^{-1}) was added. The suspension was heated to boiling, then cooled to room temperature. The resulting solids, consisting of spectroscopically homogeneous lamellarin ethers, were collected by filtration. Solutions of the products fluoresce bright purple in direct sunlight.

14-(3,4-Dimethoxyphenyl)-3,10-diisopropoxy-2,11,12-trimethoxy-6*H*-chromeno[4′,3′:4,5] pyrrolo[2,1-*a*]isoquinolin-6-one (40): The lamellarin ether **40** (1.04 g, 1.66 mmol, 94 %) was obtained according to the general procedure from 1-(3,4-dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxy-phenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (**38**) (1.16 g, 1.76 mmol); pale pink solid, m.p. 183–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 13.6 Hz, 2H), 6.71 (s, 1H), 4.72 (septet, *J* = 6.1 Hz, 1H), 4.58 (septet, *J* = 6.1 Hz, 1H), 4.00 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.45 and 3.44 (overlapping s, 6H), 1.41 (d, *J* = 6.1 Hz, 6H), 1.37 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.6, 153.3, 149.9, 149.1, 147.9, 146.62, 146.58, 146.5, 142.5, 133.8, 129.3, 128.4, 124.1, 122.6, 121.3, 120.8, 114.4, 112.0, 111.8, 109.9, 108.2, 107.8, 105.5, 103.5, 101.4, 76.4, 71.5, 60.7, 56.3, 56.2, 55.5, 55.2, 22.7 (2 × C), 21.85, 21.83. HRMS (ESI) Found: $[M + H]^+$, 628.2546; $C_{36}H_{38}NO_9^+$ requires 628.2541.

14-(3,4-Dimethoxyphenyl)-3,11-diisopropoxy-2,12-dimethoxy-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (41): Lamellarin ether **41** (1.23 g, 2.06 mmol, 91 %) was obtained according to the general procedure from 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxypyrrolo-[2,1-*a*]isoquinoline-3-carboxylic acid (**39**) (1.43 g, 2.27 mmol); pale pink solid, m.p. 207–209 °C (lit.[33] 208–209 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 7.3 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.17–7.10 (m, 4H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.97 (s, 1H), 6.74 (s, 1H), 4.70 (septet, *J* = 6.1 Hz, 1H), 4.58 (septet, *J* = 6.1 Hz, 1H), 4.00 (s, 3H), 3.88 (s, 3H), 3.45 (s, 3H), 3.44 (s, 3H), 1.44 (d, *J* = 6.0 Hz, 6H), 1.41 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.6, 150.2, 149.9, 149.0, 148.5, 147.9, 146.7, 146.6, 134.4, 129.5, 128.4, 124.8, 124.2, 123.2, 119.0, 114.5, 112.4, 112.0, 110.9, 110.5, 110.0, 107.9, 105.7, 105.6, 103.5, 71.5, 71.2, 56.3, 56.2, 55.5, 55.2, 21.91, 21.89, 21.85, 21.83. HRMS (ESI) Found: $[M + H]^+$, 598.2437; $C_{35}H_{36}NO_8^+$ requires 598.2435. The ^{1}H chemical shifts observed for **47** are within 0.02 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.1 ppm.[33]

Deprotection of Lamellarin Isopropyl Ethers 40 and 41: To the isopropyl-protected lamellarins (1 g) was added methanesulfonic acid (10 mL) at room temperature. The flask was then swirled to ensure complete dissolution of the solid precursor and the color immediately turned bright yellow. After allowing the solution to stand at room temperature for 30 min, water (100 mL) was added and the precipitated solids were collected by filtration, washed with water and dried under vacuum to provide off-white solids of high purity. For quantitative transfer of residual solids from the filtration head and paper, hot EtOAc was used, followed by evaporation. (The phenolic lamellarins are only sparingly soluble in most cold solvents. Solutions exhibit a bright purple fluorescence in direct sunlight).

Lamellarin ε, 14-(3,4-Dimethoxyphenyl)-3,10-dihydroxy-2,11,12-trimethoxy-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (5): Cyclization of 14-(3,4-dimethoxy-phenyl)-3,10-diisopropoxy-2,11,12-trimethoxy-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]-isoquinolin-6-one (**40**) (1.10 g, 1.75 mmol) according to the general procedure afforded lamellarin ε (**5**) as a white amorphous solid (944 mg, 1.74 mmol, 99 %), m.p. 261–262 °C (lit.[18] 271–275 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.20 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 6.99 (s, 1H), 6.79 (s, 1H), 6.67 (s, 1H), 6.21 (s, 1H), 5.78 (s, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.50 (s, 3H), 3.45 (s, 3H); ^{1}H NMR (500 MHz, [D_6]DMSO) δ 9.86 (br s, 2H), 8.96 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.22 and 7.21 (overlapping

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d, J = 8.0 Hz, and d, J = 2.0 Hz, 2H), 7.11 (dd, J = 8.0, 2.0 Hz, 1H), 6.86 (s, 1H), 6.72 (s, 1H), 6.62 (s, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.35 (s, *ca* 6H, obscured by H_2O); ^{13}C NMR (126 MHz, [D_6]DMSO) δ = 154.7, 153.3, 150.1, 149.3, 148.2, 146.6, 146.0, 144.9, 136.1, 133.6, 129.1, 127.6, 123.9, 121.2, 121.1, 115.1, 114.9, 113.2, 112.0, 108.4, 107.8, 107.2, 105.8, 104.0, 97.5, 60.8, 56.3, 56.2, 55.3, 54.9. HRMS (ESI) Found: $[M + H]^+$, 544.1606; $C_{30}H_{26}NO_9^+$ requires 544.1602. The ^1H chemical shifts observed for **5** are within 0.03 ppm of previously reported values (other than for OH signals), while the ^{13}C chemical shifts are within 0.5 ppm[18,19] (Table 1, Supporting Information, page S2).

Dehydrolamellarin J, 14-(3,4-Dimethoxyphenyl)-3,11-dihydroxy-2,12-dimethoxy-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one, (6): Cyclization of 14-(3,4-dimethoxyphenyl)-3,10-diisopropoxy-2,11,12-trimethoxy-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (**41**) (199 mg, 0.333 mmol) according to the general procedure afforded dehydrolamellarin J (**6**) (168 mg, 0.327 mmol, 98 %) as an amorphous white solid, m.p. >300 °C (decomp.) (lit.[33] 280–295 °C (decomp.); ^1H NMR (500 MHz, [D_6]DMSO) δ 9.95 (br s, 1H), 9.84 (br s, 1H), 9.00 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.21 and 7.20 (overlapping d, J = 2.5 and 7.5 Hz, 2H), 7.19 (s, 1H), 7.14 (dd, J = 8.0, 2.0 Hz, 1H), 7.08 (s, 1H), 6.87 (s, 1H), 6.67 (s, 1H), 3.87 (s, 3H), 3.7 (s, 3H), 3.37 and 3.36 (overlapping s, 6H); ^{13}C NMR (75 MHz, DMSO) δ = 154.3, 149.9, 149.0, 148.6, 148.3, 147.9, 146.3, 144.6, 134.0, 128.9, 127.3, 124.7, 123.7, 122.0, 117.5, 114.7, 113.0, 112.4, 111.5, 110.5, 108.3, 106.5, 105.6, 105.3, 103.8, 56.0, 55.9, 55.1, 54.5. HRMS (ESI) Found: $[M + H]^+$, 514.1492; $C_{29}H_{24}NO_8^+$ requires 514.1496. The ^1H chemical shifts observed for **10** are within 0.3 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.1 ppm[30,33] (Table 2, Supporting Information, page S3).

Large Scale Synthesis of Dehydrolamellarin J (6) from 2-(4-Isopropoxy-3-methoxyphenyl)ethylamine (20): The average overall yield of dehydrolamellarin J (**6**) over six steps from the readily prepared 6-isopropoxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**18**) on a large scale was 63 %. There was no need for chromatographic purification of intermediates, all of which could be used in subsequent steps after purification by precipitation or recrystallization. The individual stages, with modification of the procedures described above, are outlined below, and stages 2–7 were performed in duplicate as a check on reproducibility.

Stage 1: 6-Isopropoxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (18): The procedure reported above was successfully scaled up with 2-(4-isopropoxy-3-methoxyphenyl)ethylamine (**20**) (32.23 g, 149 mmol) to give the thiolactam **18** (30.52 g, 81 %) after recrystallization from methyl *tert*-butyl ether without the need for column chromatography; characterization as described above.

Stage 2: (Z)-2-(3,4-Dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)-2-(6-isopropoxy-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)ethanone (33): (i) Immediately after its synthesis as described above, 2-bromo-2-(3,4-dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxy-phenyl)ethanone (**31**) (27.2 g, 60 mmol) was dissolved in dry MeCN (250 mL), to which was added the thiolactam **18** (14.8 g, 58.9 mmol). The mixture was stirred for 18 h at room temperature to ensure complete salt formation, after which time Ph_3P (60 mmol) was added. The solution was stirred for 5 min until the phosphine had dissolved, after which NEt_3 (70 mmol) in MeCN (100 mL) was added at a rate of about 1 drop per second. The solution soon turned bright yellow and was left to stir at room temperature overnight. The solvent was removed and the residue was suspended in Et_2O (1 L) and left to stand in the freezer overnight to ensure complete precipitation of the triphenylphosphine sulfide under a clear supernatant liquid. The solids were filtered and washed with Et_2O (100 mL). A solution of concentrated aqueous HCl (32 %; 10 mL, *ca* 100 mmol) in *i*-PrOH (50 mL) was added dropwise to the clear, by now reddish, Et_2O extract with stirring. The HCl salt of the desired enaminone immediately began precipitating from solution as a solid which subsequently formed a thick gel. After standing for 1 h the supernatant Et_2O was decanted and the semisolid residue was washed with Et_2O (2 × 200 mL). Upon addition of saturated aqueous $NaHCO_3$ solution (500 mL) to the semisolid, the liberated enaminone was formed as a bright yellow solid. The desired product was extracted from the solids with Et_2O (2 × 200 mL), and the combined extracts were washed with saturated aqueous $NaHCO_3$ solution (200 mL) and brine (200 mL), dried with Na_2SO_4, filtered and the solvents evaporated in vacuo. The enaminone **33** (32.1 g, 54.3 mmol, 92 %) was obtained as a spectroscopically homogeneous yellow solid characterization as described above. (ii) Repeating the large scale reaction with isoquinolinethione **18** (14.7 g, 58.5 mmol) and bromoketone **31** (27.9 g, 61.5 mmol) yielded enaminone **33** (31.0 g, 52.4 mmol, 90 %).

Stage 3: Ethyl 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxy-5,6-dihydropyrrolo-[2,1-*a*]isoquinoline-3-carboxylate (35): (i) The preceding enaminone **33** (32.0 g, 54.1 mmol) was dissolved in ethyl bromoacetate (60 mL. *ca* 90 g, *ca* 539 mmol) to which was added solid $NaHCO_3$ (70 g, 833 mmol). The mixture was stirred under an atmosphere of argon gas at 80–85 °C for 18 h, and then at 95 °C for an additional 2 h, at which point the reaction was complete. CH_2Cl_2 (100 mL) was added, and the suspension was filtered and washed with CH_2Cl_2 until the filtrate was clear. The solvent was evaporated in vacuo, and Et_2O (100 mL) and hexane (500 mL) were added to the residue. Crystals of **35** soon began to form. The mixture was left standing overnight at room temperature to ensure complete precipitation of solids. The supernatant liquid was then decanted, and the remaining material was washed with methyl *tert*-butyl ether (MTBE; 2 × 150 mL) and then triturated under MeOH (300 mL). The product was filtered, washed with MeOH (2 × 150 mL) and dried to provide **35** as a pale yellow solid (22.9 g). The Et_2O/hexane supernatant liquid was allowed to evaporate in a beaker overnight, and the semicrystalline residue was triturated under MTBE (200 mL) and allowed to stand for a few hours before being filtered, washed with additional MTBE (2 × 100 mL), triturated under MeOH (100 mL), filtered and dried to provide another batch of **35** (4.10 g). Total yield: 27.0 g (40.9 mmol, 76 %); characterization as described above. (ii) Repeating the large scale reaction with enaminone **33** (31.0 g, 52.4 mmol) yielded **35** (26.6 g, 40.3 mmol, 77 %).

Stage 4: Ethyl 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (37): (i) The pyrrolo[2,1-*a*]isoquinoline **35** (25.9 g, 39.3 mmol) was dissolved in CH_2Cl_2 (250 mL), to which was added DDQ (13.0 g, 57.3 mmol). The solution, which immediately turned a muddy brown color, was left to stir at room temperature for 2 h. Aqueous NaOH solution (10 %, 250 mL) was added, and the biphasic mixture was left to stir for 1 h before separation of the very dark phases. The aqueous phase was re-extracted with CH_2Cl_2 (3 × 300 mL), at which point the extracts were almost colorless and no longer fluoresced bright blue under 254 nm UV irradiation when spotted on a TLC plate. The combined organic extracts were washed with brine (250 mL) and dried with $MgSO_4$, filtered and the solvents evaporated in vacuo to give the ring B-unsaturated pyrrolo[2,1-*a*]isoquinoline **37** as a brown solid (25.7 g, 39.1 mmol, 99 %); characterization as described above. The product was used in the next step without further purification. (ii) Repeating the large scale reaction with the pyrrolo[2,1-*a*]isoquinoline **35** (20.0 g, 30.3 mmol) yielded the ring-B unsaturated product **37** (19.8 g, 30.1 mmol, 99 %).

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Stage 5: 1-(3,4-Dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (39): (i) KOH (45 g, 803 mmol) and water (100 mL) were added to the preceding ethyl pyrrolo[2,1-*a*]isoquinoline-3-carboxylate **37** (23.0 g, 35.0 mmol), followed by EtOH (400 mL). The suspension was heated to reflux, and after about 30 min had become homogeneous. Reflux was maintained for 2 h, after which most of the EtOH was removed by rotary evaporation until the potassium carboxylate began to precipitate. The mixture was acidified with aqueous HCl (1 M), causing the free carboxylic acid to begin precipitating and turning the supernatant liquid bright yellow. The mixture was then extracted with CH_2Cl_2 (3 × 150 mL). The combined extracts containing the dissolved carboxylic acid were washed with aqueous HCl (1 M; 250 mL) and brine (100 mL), dried with $MgSO_4$ and the solvents evaporated in vacuo to provide the carboxylic acid **39** as a brown solid that could not be dried completely (22.4 g, 35.6 mmol). It was used in the next step without further purification. (ii) Repeating the large scale reaction with the ester **37** (14.4 g, 21.9 mmol) yielded carboxylic acid **39** (13.1 g, 20.8 mmol, 95 %).

Stage 6: 14-(3,4-Dimethoxyphenyl)-3,11-diisopropoxy-2,12-dimethoxy-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (41): (i) The above carboxylic acid **39** (13.0 g, *ca* 20.6 mmol) was dissolved in dry CH_2Cl_2 (200 mL), and the solution was cooled to 0 °C under an atmosphere of argon. Oxalyl chloride (4 mL, *ca* 5.92 g, *ca* 2.25 equiv.) was added by syringe, causing the color to become deep orange. The stirred solution was warmed to room temperature, and reaction was judged to be complete by NMR spectroscopy after 4 h. The solvent was evaporated on a rotary evaporator, and then dried under high vacuum to yield a brownish solid residue. To this was added a solution of NaI (18 g, 120 mmol) in MeCN (250 mL) at room temperature. NaCl began to precipitate after 30 min, and the evolution of a gas was noted. The suspension was stirred overnight, during which time a dense precipitate of NaCl and desired lamellarin ether had formed. The solvent was removed in vacuo and MeOH (250 mL) was added to the residue. The solvent was heated to boiling with stirring; upon cooling the desired protected lamellarin **41** crystallized. This was filtered and washed with MeOH (2 × 100 mL). Although it was spectroscopically pure by NMR analysis, the residual greenish color was removed by dissolving the compound in a minimum of CH_2Cl_2 (100 mL), to which was added MeOH (250 mL). Crystals of purified **41** began to form. After 30 min a portion of the solvent (largely CH_2Cl_2; *ca* 150 mL) was removed by rotary evaporation, and more MeOH (150 mL) was added. After several hours at room temperature, no further crystallization was evident. The solids were collected by filtration and dried to provide the lamellarin derivative **41** compound as a pale yellow solid (12.2 g, 20.4 mmol, 99 %). (ii) The lactonization was repeated with carboxylic acid **39** (22.0 g, 34.9 mmol) and oxalyl chloride (5 mL, *ca* 2.8 equiv.) in CH_2Cl_2 (200 mL) as described above. After evaporation of the solvent, a solution of NaI (18 g, 120 mmol) in MeCN (250 mL) was added, and the suspension was stirred overnight at room temperature. The subsequent work-up was improved by adding water (150 mL) to dissolve the inorganic salts. The suspension was briefly stirred before being filtered through a sintered glass disc. The solid obtained was washed with MeOH (in which the desired product is insoluble) until the filtrate was clear. After drying the substituted lamellarin **41** was obtained as a pale pink solid (19.8 g, 33.1 mmol, 95 %).

Stage 7: Dehydrolamellarin J (6): (i) Methanesulfonic acid (150 mL) was added to the isopropyl protected lamellarin **41** (12.2 g, 20.4 mmol) at room temperature, and the mixture was stirred to ensure complete dissolution of the solid. The color immediately turned bright fluorescent yellow. After standing at room temperature for 30 min at room temperature, ice water (300 mL) was added to precipitate the product as a fine powder, the collection of which by filtration through a sintered glass disc proved to be very slow. The isolated product was washed with H_2O and dried under vacuum to provide dehydrolamellarin J (**6**) (10.1 g, 19.7 mmol, 96 %) as a pale grey amorphous solid; characterization as described above. (ii) The deprotection step was repeated with the isopropyl protected lamellarin **41** (19.8 g, 33.1 mmol) and methanesulfonic acid (150 mL) at room temperature. The suspension was stirred to ensure complete dissolution of the solid (*ca* 30 min), after which the solution was allowed to stir for a further 30 min. In an improved work-up procedure, water (600 mL) was added to precipitate the product as a fine yellow powder. After 20 min, the mixture was heated to 70 °C, which improved its flow upon filtration through a sintered glass disc. The solid paste thus obtained was washed with hot water (3 × 200 mL at *ca* 80–90 °C) and then dried under vacuum to provide dehydrolamellarin J (**6**) (16.5 g, 32.1 mmol, 97 %).

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Keywords: Enaminones · Isopropyl ether cleavage · Lamellarins · Methanesulfonic acid · Total synthesis

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Chapter 6: Conclusions and Future Work

6.1 Summary and conclusions

In *Chapter 2*, *Section 2.1*, a methodological investigation into the cyclization of pyrrolidinyl enaminones to pyrrolizines is described. We were able to show that the method developed by Morgans and Scalzullo,[75,77] which makes use of silica gel as a heterogeneous acid catalyst, reliably provides 2,3-dihydro-1*H*-pyrrolizine-5-carboxylates in good to excellent yields from various *N*-(ethoxycarbonylmethyl)pyrrolidine-containing enaminones. The reaction tolerates a diverse array of aryl substituents, giving pyrrolizines connected via a biaryl axis to the aryl substituents. Heterocyclic-substituted enaminones proved particularly good substrates for the reaction and provided bis(hetero)aryl structures, for which there are very few preparative methods. The main limitations to the methodology were shown to be aryl groups with labile substituents on the *ortho*-aryl position, in which cases the reactions were severely impaired and often did not yield any isolatable material.

Then, in *Section 2.2.2*, the development of an analogous process applied to six-membered enaminones, to provide 2,3-dihydro-1*H*-indolizine-5-carboxylates, is described. We showed that for *N*-(ethoxycarbonylmethyl)piperidine-containing enaminones, the thermodynamic favorability of double bond migration from the exocyclic to endocyclic position, as explained using Brown's hypothesis, imparts increased nucleophilicity of the enamine carbon towards the ester electrophile, as well as towards protons of the acid catalyst. Using the protic solvent ethanol, we were able to facilitate these reactions selectively, though silica gel did appear to increase the reaction rate. This reaction was also proven to be limited to aryl systems without a labile electrophilic substituent at the 2'-aryl position.

In *Section 2.3,* our preliminary investigations into the applicability of this methodology to the synthesis of the lamellarin alkaloid precursors are described. We confirmed the results obtained by Scalzullo and Morgans, which indicate mixed pyrrole cyclization pathways occur for lamellarin related isoquinoline-containing enaminones. The development of a new synthetic route is then described, which ultimately led to the invention of a novel [4 + 1] cycloaddition reaction between secondary sterically crowded enaminones and ethyl bromoacetate, providing pyrrolo[1,2-*a*]isoquinolines in excellent yields.

Chapter 3 describes the successful application of our [4 + 1] cycloaddition reaction to the synthesis of lamellarin G trimethyl ether using precursors, reagents and solvents that can all be derived from xylochemical sources. This synthesis was thus comparatively "green". This work also includes the development of a novel route to the lamellarin enaminones, using an aza-enolate acylation reaction, the findings of which were published in the *Journal of Organic Chemistry* in 2019.[81]

Chapter 4 describes the development of a novel demethylative lactonization reaction. This reaction was reported, in combination with the Eschenmoser-sulphide contraction approach to lamellarin enaminone synthesis in a 2020 publication, also in the *Journal of Organic Chemistry*.[82] Here, we applied our methodology to the preparation of lamellarin G trimethyl ether, lamellarin D trimethyl ether, lamellarin H and lamellarin A4, all in the highest yields ever reported for each. This work served as the first ever reported synthesis of a lamellarin analogue at the gram-scale.

In *Chapter 5,* the extension of our methodology to the synthesis of the potent lamellarins ε and dehydrolamellarin J is described. We also describe the application of the green reagent methanesulphonic acid in three separate reactions, with particular emphasis on its use as a novel reagent for the deprotection of isopropyl aryl ethers. The culmination of this work was published in the *European Journal of Organic Chemistry* in 2020.[83] Herein, we present the highest yielding syntheses of these alkaloids to date, and this was the first-ever reported syntheses of active lamellarins at the gram-scale. The synthesis of dehydrolamellarin J was then adapted to successfully prepare 25 g of this alkaloid, without any chromatography being required.

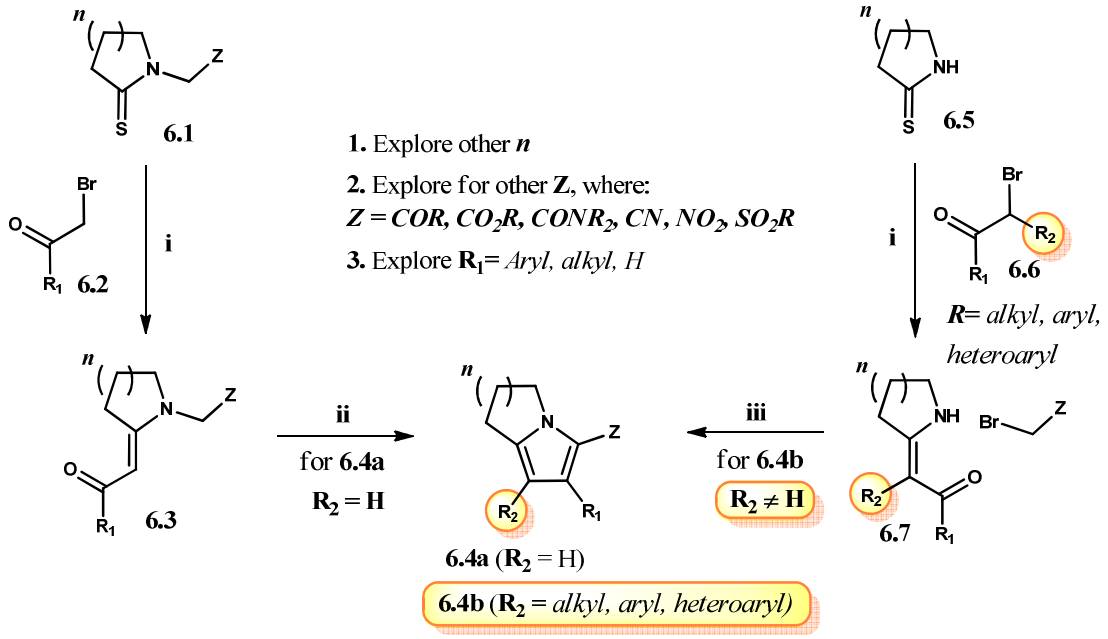
6.2 Future work

6.2.1 Cyclization of enaminones to pyrroles

Our initial studies into the cyclization of enaminones to pyrroles, which was described in *Chapter 2*, resulted in the development of three different cyclization strategies, which can be used to obtain either tetra-substituted bicyclic pyrroles **6.4a** (*Figure 6.1*), where n = 1 or n = 2, or penta-substituted bicyclic pyrroles **6.4b** (only explored for n = 2). Each of these methodologies deserves further investigations into the scope of their applicability to different ring sizes, as well as to the inclusion of different nitrogen-methylene substituents (Z), such as

amide, nitrile, nitro or sulphonyl. These alternative functional groups would offer interesting possibilities for further elaboration. Considering the stark reactivity difference noted between five- and six-membered ring systems, it would be interesting to investigate the applicability of these methods to alternative ring sized analogues. In this respect, a former PhD student, Siyanda Mthembu,[115] carried out a preliminary investigation with an azepane-derived enaminone; results were promising but inconclusive, and a more thorough investigation is warranted. Extension of the methodology beyond acyl-aryl enaminones (**6.3** or **6.7**), where R_1 = Ar, to R_1 = alkyl or heteroalkyl, would also be worth exploring. Our preliminary investigations (*Section 2.1.4*) into these analogues suggested a different, or modified, synthetic strategy for the enaminones would be needed.

Figure 6.1. Modifications of enaminones to expand scope of cyclization methodologies.



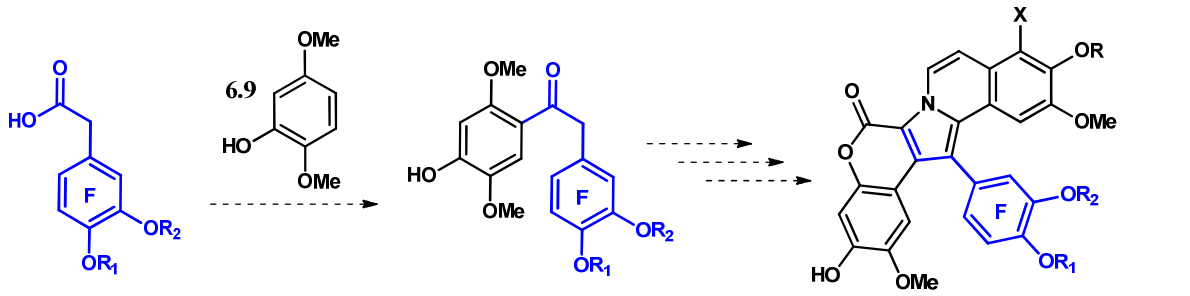
Reagents and conditions: i. Eschenmoser sulphide contraction; ii. see *Section 2.1-2.3*; iii. see *Section 2.3*

6.2.2 Lamellarins and related analogues

The most pertinent contribution to the field of lamellarin synthesis would undoubtedly be the extension of our methodology to the natural lamellarins with differing ring F substituents other than the 3,4-dimethoxyphenyl pattern of lamellarin ε and dehydrolamellarin J. The four remaining uniquely potent members of the lamellarin family possess either a 3-hydroxy-4-methoxy or a 3-methoxy-4-hydroxy substitution pattern on ring F, giving lamellarins D and N (**6.11a**) (*Scheme 6.2*), or lamellarins M and X (**6.11b**), respectively (See *Figure 1.5, Section*

1.2). Extending our methodology to these lamellarins should be relatively straightforward. Starting from the appropriately oxygenated phenylacetic acids **6.8a** or **6.8b**, a Friedel-Crafts or Fries type acylation with the same phenol precursor **6.9** should provide the corresponding deoxybenzoin ketones **6.10a** or **6.10b**. Thereafter, the synthesis should be identical to that described in *Chapter 5*. If successful, we would be the first group to have developed the synthesis of all of the six most potent lamellarins, accounting for every single natural substitution found in the pharmacologically active members of the series.

Scheme 6.2. Extension of Chapter 5 methodology to other potent natural lamellarins with different ring F substitutions.



6.8a: R_1 =H; R_2 = Me
6.8b: R_1 = Me; R_2 = H

6.10a: R_1 =H; R_2 = Me
6.10b: R_1 = Me; R_2 = H

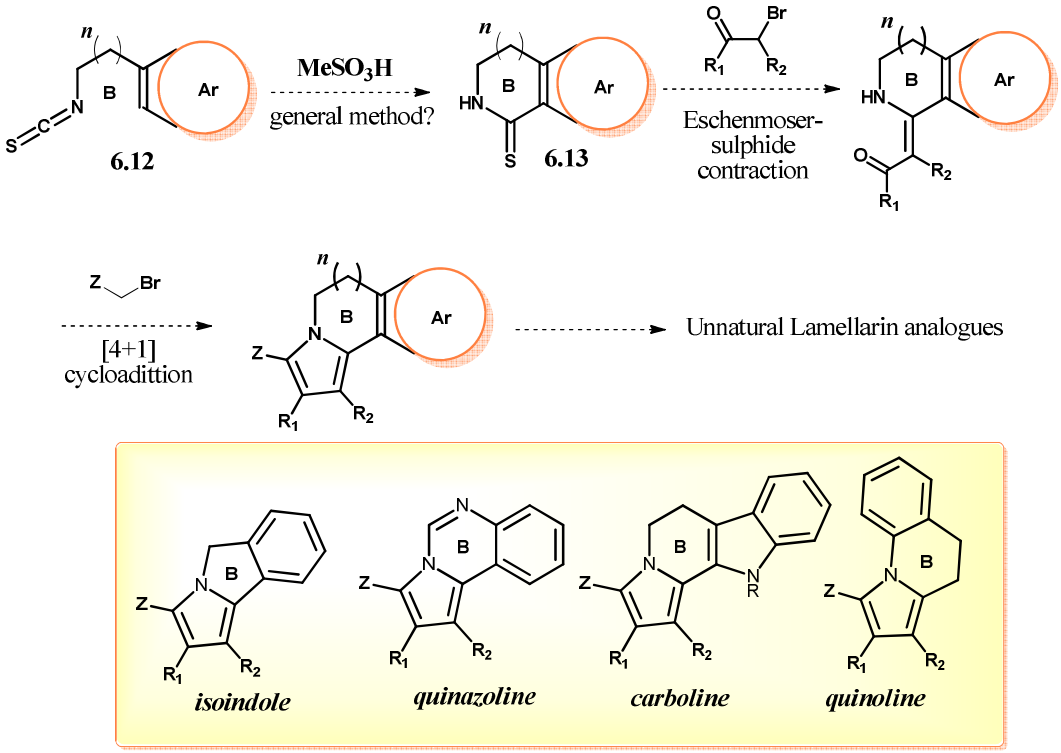
6.11a: R_1 =H; R_2 = Me (Lamellarins D or N)
6.11b: R_1 = Me; R_2 = H (Lamellarins M or X)

Furthermore, since ring F is most amenable to modifications with retention of activity (See *Figure 1.5, Section 1.2*), investigating the structure-activity relationship for unnatural substituents or substitution patterns on this ring would provide the greatest possibility of improving the pharmacodynamic properties of the lamellarins, for use as potential chemotherapeutics. Ring F is thus the primary modification site, which could be used to moderate the potency, lipophilicity and solubility properties of synthetic lamellarin analogues. This would be relatively simple using our method, because ring F is derived from phenylacetic acid precursors (*Scheme 6.2*), which are widely available and easy to prepare, generally at a low cost. All other ring precursors would remain the same. Some of the most easily prepared lamellarin analogues would also be some of the most medicinally relevant. Halogenated ring F analogs could offer improved lipophilicity, as well as the potential for late stage coupling reactions to form a myriad of structural analogs at a late stage. Nitriles preinstalled on ring F could be hydrolyzed to provide hydrophilic carboxylates, and nitro groups can be reduced to provide anilines, which can be protonated to form a variety of hydrophilic salt forms. Furthermore, other heterocycles such as thiophene, furan, benzofuran and even indoles could be prepared from available arylacetic acid precursors. Late stage oxidations of certain oxygenated ring F analogues could provide quinones, which could have

interesting effects on DNA damage during intercalation. Similarly, other alkylating agents, such as methylene halides, could be easily installed on this ring at a late stage, which could alter or improve cytotoxicity by alkylating DNA during intercalation.

Another interesting series of lamellarin modifications to explore would be the extension of our methodology beyond the isoquinoline ring system (rings A and B; See *Figure 1.5, Section 1.2*), to other unnatural variations. Pertinent examples include the five membered isoindoline, the indolic beta carboline, quinazoline, and various other potential analogs (*Scheme 6.3*). This could also serve as a methodological study on the scope of our novel isoquinolinethione cyclization using methanesulphonic acid, described in *Chapter 5,* for the preparation of the required thiones **6.13**, where appropriate.

Scheme 6.3. Expanding the scope of our methodology to other heterocyclic systems.

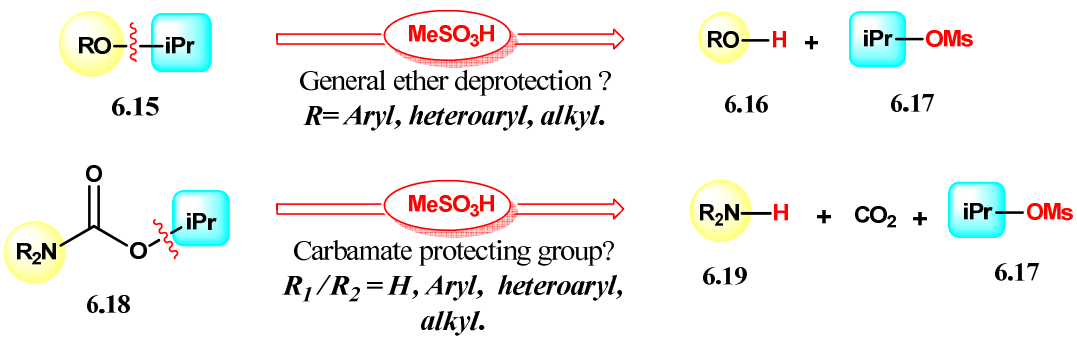


6.2.3 Expanding the scope of novel methanesulphonic acid-mediated reactions

The use of methanesulphonic acid (MsOH) to easily and efficiently deprotect lamellarin isopropyl ethers was perhaps one of the most groundbreaking discoveries of this project. As was discussed in *Chapter 5*, traditional methods to facilitate this deprotection make use of toxic, expensive and difficult to handle Lewis acids such as aluminium chloride ($AlCl_3$) and especially boron trichloride (BCl_3). Further investigating the scope of this reaction applied to

other, non-lamellarin isopropyl protected substrates such as **6.15** (*Scheme 6.4*) could serve as a significant contribution to organic synthesis at large. The extension of this methodology to include isopropyl carbamates **6.18** would also be potentially useful as an alternative to the expensive and relatively labile *tert*-butoxycarbonyl (BOC) protecting group for amines and other nitrogen containing heterocycles.[116] BOC protections are ubiquitous, especially for amines and nitrogenous heterocycles, but require the use of di-*tert*-butyl dicarbonate (BOC anhydride), because the chloride cannot be efficiently prepared or stored.[116] BOC-anhydride is relatively expensive and is a less efficient acylating agent than the corresponding carbonate chlorides. Being a relatively high molecular weight anhydride it is also not atom economical, requiring two effective equivalents of *tert*-butyl precursor for its preparation.[109] Investigating the potential applicability of MsOH to the deprotection of the analogous isopropyl carbonates/carbamates could offer an exceptionally useful alternative to the BOC protecting group. This potential protecting group could be easily installed using isopropyl chloroformate, which is considerably cheaper than BOC-anhydride, and should be easier to install. Following conventional nomenclature, an equally catchy abbreviation POC (for isopropoxycarbonyl) would be fitting. It is worth mentioning that there is even some literature precedent for this idea, where the cleavage of N-isopropyl substituents on amides with MsOH has been reported, though a completely different cleavage mechanism was put forth by the authors.[117] The deprotection of BOC carbonates/carbamates usually involves treatment with trifluoroacetic acid in chlorinated solvents.[116] MsOH is a relatively cheap and benign reagent which is biodegradable.[118] The resultant isopropyl methanesulphonate product **6.17** (see *Chapter 5*) should be easily hydrolysable after the addition of water during work-up, providing waste material that is non-toxic and easy to dispose of, especially on an industrial scale.

Scheme 6.4. Expanding the scope of the isopropyl-ether deprotection methodology using MsOH.



Chapter 7: Experimental methods pertaining to unpublished work

7.1 General methods

7.1.1 Purification of solvents and reagents

Column chromatography was performed exclusively (unless stated otherwise) using mixtures of ethyl acetate and hexane, which were distilled before use by means of conventional distillation procedures. All 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 containing benzophenone as an indicator, under an inert atmosphere, when needed.
- Toluene was pre-dried over sodium wire, and distilled therefrom under an inert atmosphere.
- Acetonitrile (MeCN), dichloromethane (DCM), chloroform, methanol (MeOH) were distilled from calcium hydride under an inert atmosphere.
- *N*,*N*-Dimethylformamide (DMF) was distilled from, and stored over, 4 Å molecular sieves.
- Ethanol (absolute, 98%) and xylene (mixture of isomers, 99%) were used as purchased, without further purification.

7.1.2 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 approximately 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 typically adjusted to afford an R_f of 0.2-0.3 for the desired compound (using TLC). The appropriate amount of silica gel was measured out and 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, or was loaded directly onto the silica surface by dissolving in a minimum of dichloromethane (DCM). The adsorbed product was

covered with acid-washed sand and 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, ceric ammonium sulphate and iodine), where additional identification was required.

7.1.3 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.
- Hydrogen (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance-300 spectrometer, with the proton frequency at 300.13 MHz and the carbon frequency at 75.47 MHz; or a Bruker Avance III 400 MHz, at 400MHz (proton frequency) and 101MHz (carbon frequency); or on a Bruker Avance III 500 spectrometer, at 500.13 MHz (proton frequency) and at 125.75 MHz (carbon frequency). 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 programs 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), p (pentet), m (multiplet).
- High resolution mass spectra (ESI/EI) were recorded on a Waters Synapt G2 instrument. 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*).

7.1.4 Additional general procedures and techniques

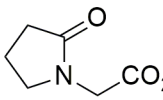
All reactions were performed under an inert argon atmosphere using a standard manifold line connected to a vacuum pump. The argon was passed through self-indicating silica gel. Reaction vessels were initially oven dried and subsequently dried further by heating while under vacuum, after which time they were allowed to cool to room temperature and flushed with dry argon gas. 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.

7.1.5 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.

7.2 Preparation of *N*-alkylated thiolactams

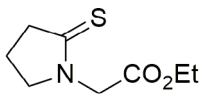
7.2.1 Ethyl 2-(2-oxo-1-pyrrolidinyl)acetate (**2.2**)



To a stirring solution of sodium hydride (60% dispersion in oil, 2.81 g, 70.1 mmol) in tetrahydrofuran (100 cm^3) under an inert atmosphere of argon gas was added 2-pyrrolidinone (5.00 g, 58.5 mmol) in tetrahydrofuran (50 cm^3) dropwise over 20 minutes. The residual material in the dropping funnel was then rinsed into the reaction flask using additional tetrahydrofuran (20 cm^3). Stirring was continued at room temperature for an additional 2 hours. Ethyl 2-bromoacetate (11.7 g, 8.1 cm^3, 70.2 mmol) in tetrahydrofuran (50 cm^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 16 hours. Water (100 cm^3) was

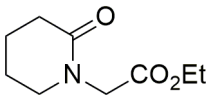
then cautiously added to the mixture until bubbling ceased and all solids dissolved. The mixture was then extracted into ethyl acetate (100 cm^3). The organic phase was separated and the aqueous phase was re-extracted twice with ethyl acetate (2 × 50 cm^3). The combined organic fractions were then washed 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* (**2.2**) (7.76 g, 27.8 mmol, 77%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 2H), 3.42 (t, *J* = 7.0 Hz, 2H), 2.36 (t, *J* = 8.1 Hz, 2H), 2.02 (p, *J* = 7.6 Hz, 2H), 1.22 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.62, 168.64, 61.25, 47.67, 44.06, 30.28, 17.92, 14.12. The spectroscopic data reported agreed with previously reported values.[119]

7.2.2 Ethyl 2-(2-thioxo-1-pyrrolidinyl) acetate (**2.3**)



To a solution of ethyl 2-(2-oxo-1-pyrrolidinyl)acetate (**2.2**) (5.00 g, 29 mmol) in toluene (1000 cm^3) was added Lawesson's reagent (7.00 g, 17.5 mmol). The mixture was brought to 80 °C and allowed to stir under an inert atmosphere of argon gas for 18 hours, after which time reaction was deemed complete by TLC. The solvent was evaporated *in vacuo* and the crude residue was adsorbed onto silica gel (ca. 50 g) and purified by flash column chromatography (20-30% ethyl acetate in hexane) to provide *ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate* (**2.3**) (4.70 g, 25 mmol, 88%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 1H), 3.76 (t, *J* = 7.3 Hz, 1H), 3.01 (t, *J* = 7.9 Hz, 1H), 2.06 (p, *J* = 7.8 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.86, 167.18, 61.69, 55.49, 49.05, 44.30, 19.74, 14.13. The spectroscopic data below were in agreement with the previously reported values.[74,77]

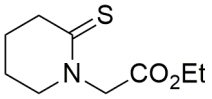
7.2.3 Ethyl 2-(2-oxopiperidin-1-yl)acetate (**2.21**)



To an ice-cooled solution of sodium hydride (60% dispersion in oil, 2.65 g, 65.9 mmol) in tetrahydrofuran (50 cm^3) under an inert atmosphere of argon gas was added 2-piperidinone (4.00 g, 41.1 mmol) in tetrahydrofuran (50 cm^3) dropwise over 20 minutes. The residual material in the dropping funnel was then rinsed into the reaction flask using additional tetrahydrofuran (20 cm^3). The emulsion was warmed to room temperature and refluxed for 2 hours. On cooling to room temperature, and then again to 0°C, ethyl 2-bromoacetate (6.0 cm^3, ca. 8.94 g, 53.5 mmol) was added to the stirring emulsion which immediately turned yellow and began to homogenize. After an additional 16

hours of stirring at room temperature water (100 cm^3) was cautiously added to the reaction mixture until the solids dissolved and two clear phases were observed. 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 until solids began to precipitate. Then hexane (100 cm^3) was added and the resultant suspension was heated until boiling and triturated. After cooling, the solids were collected by filtration, washed with additional hexane, and dried to provide *ethyl 2-(2-oxopiperidin-1-yl)acetate* (**2.21**) (6.90 g, 37 mmol, 90%) as a white solid. M.p.: 75–76 °C (Lit.[120] 70–71 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.1 Hz, 2H,), 4.10 (s, 2H), 3.35 (t, *J* = 5.9 Hz, 2H), 2.42 (t, *J* = 6.9 Hz, 2H, 3H), 1.85 (dt, *J* = 5.8, 2.7 Hz, 4H), 1.27 (t, *J* = 7.2 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.01, 169.05, 61.11, 49.11, 48.61, 32.16, 23.23, 21.40, 14.12. The spectroscopic data below were in agreement with the previously reported values.[120]

7.2.4 Ethyl 2-(2-thioxopiperidin-1-yl)acetate (**2.22**)



To a solution of ethyl 2-(2-oxopiperidin-1-yl)acetate (**2.21**) (3.53 g, 30.0 mmol) in toluene (150 cm^3) was added Lawesson's reagent (7.24 g, 17.9 mmol), and the mixture was heated at 80 °C for 18 hours. On cooling, the solvent was removed under reduced pressure to afford the crude a red residue which was adsorbed onto silica gel (ca. 50 g) and purified by flash column chromatography (20-30% ethyl acetate in hexane) to provide *ethyl 2-(2-thioxopiperidin-1-yl)acetate* (**2.22**) (3.45 g, 27 mmol, 90%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.02 (t, *J* = 6.4 Hz, 2H), 1.96 (tdd, *J* = 9.5, 6.1, 3.8 Hz, 2H), 1.80 (dtd, *J* = 8.7, 6.2, 3.9 Hz, 2H,), 1.31(t, *J* = 7.1 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.61, 167.11, 61.11, 55.99, 52.42, 41.32, 22.78, 20.50, 14.00. The spectroscopic data below were in agreement with the previously reported values.[74,77]

7.3 General method for the preparation of enaminones

7.3.1 Preparation of α-bromoketones

The following α-bromoketones used in the Eschenmoser sulphide contraction reaction were prepared by bromination of the corresponding methyl ketones by reported methods:

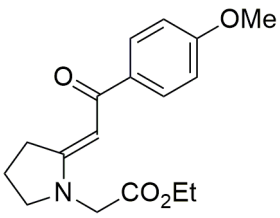
- **j:** 2-bromo-1-(**1-naphthyl**)ethanone.[99]
- **k:** 2-bromo-1-**styryl**ethanone.[98]
- **m:** 2-bromo-1-(**2-iodophenyl**)ethanone.[96]
- **n:** 2-bromo-1-(**2-bromo-3,4-dimethoxyphenyl**)ethanone.[97]
- **o:** 2-bromo-1-(**2-bromophenyl**)ethanone.[96]
- **p:** 2-bromo-1-(**2-chlorophenyl**)ethanone.[96]
- **s:** 2-bromo-1-(**2-furyl**)ethanone.[95]
- **t:** 2-bromo-1-(**2-thiophenyl**)ethanone.[94]
- **u:** 2-bromo-1-(**2-benzofuryl**)ethanone.[93]
- **v:** 2-bromo-1-(**1-tosyl-1*H*-indol-3-yl**)ethanone.[92]
- **x:** 2-bromo-1-(**3,4-dimethoxyphenyl**)ethanone.[121]
- **y:** 1-bromo-(**3,3-dimethylbutan**)-2-one.[122]
- **z:** 2-bromo-1-(**2-hydroxyphenyl**)ethanone.[123]

All other α-bromoketones were obtained from Sigma-Aldrich.

7.3.2 Preparation of enaminones **2.10a-z** and **2.23a-c** by Eschenmoser sulphide contraction

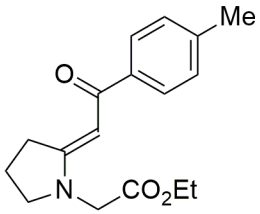
To solution of ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate (**2.3**) or ethyl 2-(2-thioxopiperidin-1-yl)acetate (**2.22**) (1.0 mmol) in anhydrous acetronitrile (2 cm^3) was added the bromo-ketone (1.2 mmol, 1.2 eq.). The reaction mixture was stirred at room temperature overnight. To a dropping funnel was added triethyl phosphite (1.2 mmol, 1.2 eq.) or triphenylphosphine (1.2 mmol, 1.2 eq.) (see *Table 2.2*) and triethylamine (1.2 mmol, 1.2 eq.), in acetonitrile (5 cm^3), dropwise, over 15 minutes. The reaction was then left for a further 18 hours. The solvent was removed and the crude extract was purified by flash column chromatography (40% ethyl acetate in hexane) to afford the corresponding (*E*)-*ethyl 2-[2-(2-aryl-2-oxoethylidene)pyrrolidin-1-yl]acetates* (**2.10**) or (*E*)-*ethyl 2-[2-(2-aryl-2-oxoethylidene)piperidin-1-yl]acetates* (**2.23**). The following compounds were obtained by this method.

(E)-Ethyl 2-{2-[2-(4-methoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10a**):



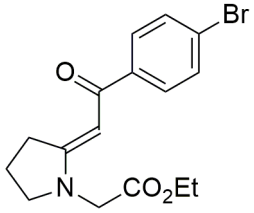
Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(4-methoxyphenyl)ethanone (0.319 g, 1.61 mmol, 1.2 eq.), with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.). Provided enaminone **2.10a** (0.340 g, 1.12 mmol, 84%) as a colourless solid. M.p.: 81-83 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.64 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.04 (s, 2H), 3.82 (s, 3H), 3.54 (t, *J* = 7.2 Hz, 2H), 3.40 (t, *J* = 7.8 Hz, 2H), 2.05 (p, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.17, 168.27, 166.88, 161.77, 134.35, 129.28, 113.33, 86.93, 61.69, 55.42, 53.74, 48.34, 33.45, 21.37, 14.34. HRMS (ESI): Found $[M + H]^+$ = 304.1543, $C_{17}H_{22}NO_4^+$ requires 304.1549.

(E)-Ethyl 2-{2-[2-oxo-2-(4-tolylphenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10b**): Prepared



from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(4-tolyl)ethanone (0.343 g, 1.61 mmol, 1.2 eq.), with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10b** (0.315 g, 1.11 mmol, 82%) as a colourless solid. M.p.: 95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 5.65 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.04 (s, 2H), 3.54 (t, *J* = 7.2 Hz, 2H), 3.40 (t, *J* = 7.8 Hz, 2H), 2.36 (s, 3H), 2.05 (p, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.91, 168.15, 167.02, 140.85, 138.98, 128.78, 127.37, 87.14, 61.61, 53.68, 48.23, 33.43, 21.45, 21.28, 14.27. HRMS (ESI): Found $[M + H]^+$ = 288.1606, $C_{17}H_{22}NO_3^+$ requires 288.1600.

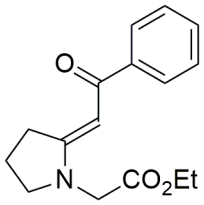
(E)-Ethyl 2-{2-[2-oxo-2-(4-bromophenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10c**): Prepared



from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(4-bromophenyl)ethanone (0.448 g, 1.61 mmol, 1.2 eq.), with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10c** (0.437 g, 1.24 mmol, 93%) as a colourless solid. M.p.: 122-123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 5.52 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 2H), 3.51 (t, *J* = 7.3 Hz, 2H), 3.34 (t, *J* = 7.8 Hz, 2H), 2.01 (p, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.83, 168.00,

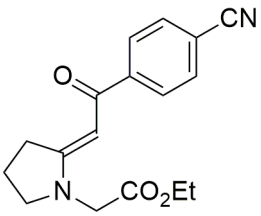
167.92, 140.56, 131.36, 129.07, 125.24, 86.89, 61.84, 53.96, 48.35, 33.69, 21.28, 14.36. HRMS (ESI): Found $[M + H]^+ = 352.0543$, $C_{16}H_{19}BrNO_2^+$ requires 352.0548.

(E)-Ethyl 2-{2-[2-oxo-2-(phenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10d = 2.4**): Prepared



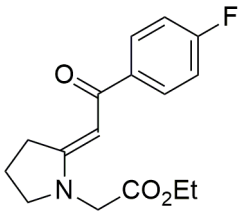
from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-phenylethanone (0.319 g, 1.61 mmol, 1.2 eq.) (0.448 g, 1.61 mmol, 1.2 eq.), with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10d** (0.335 g, 1.22 mmol, 92%) as a colourless solid. M.p.: 82-83 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.38–7.27 (m, 3H), 5.59 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 2H), 3.49 (t, *J* = 7.2 Hz, 2H), 3.35 (t, *J* = 7.8 Hz, 2H), 2.00 (p, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.24, 168.15, 167.38, 141.77, 130.64, 128.16, 127.36, 87.28, 77.16, 61.73, 53.78, 48.26, 33.53, 21.30, 14.31. Spectroscopic data were in agreement with previously reported values.[74,77]

(E)-Ethyl 2-{2-[2-oxo-2-(4-cyanophenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10e**): Prepared



from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 4-(2-bromoacetyl)benzonitrile (0.360 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.). Provided enaminone **2.10e** as a colourless solid, M.p.: 116 °C; (0.368 g, 1.23 mmol, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 5.58 (s, 1H), 4.07 (s, 2H), 3.61 (t, *J* = 7.3 Hz, 2H), 3.43 (t, *J* = 7.7 Hz, 2H), 2.11 (p, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.92, 168.89, 167.73, 145.58, 132.17, 127.91, 118.81, 113.85, 87.05, 61.96, 54.19, 48.37, 33.92, 21.16, 14.36. HRMS (ESI): Found $[M + H]^+ = 299.1389$, $C_{17}H_{19}N_2O_3^+$ requires 299.1396.

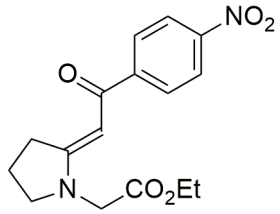
(E)-Ethyl 2-{2-[2-oxo-2-(4-fluorophenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10f**): Prepared



from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(4-fluorophenyl)ethanone (0.349 g, 1.61 mmol, 1.2 eq.) with triphenylphosphine as thiophile (0.420 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10f** (0.350 g, 1.21 mmol, 90 %) as a colourless solid. M.p.: 80-81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.73 (m, 2H), 7.14–6.79 (m, 2H), 5.61 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.05 (s, 2H), 3.56 (t, *J* = 7.3 Hz, 2H), 3.41 (t, *J* = 7.5 Hz, 2H), 2.07

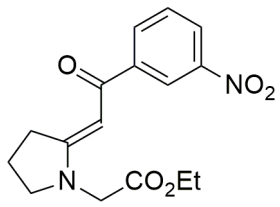
(p, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.58, 168.0, 167.5 167.75 (d, *J* = 250.1 Hz), 137.90 (d, *J* = 3.0 Hz), 129.49 (d, *J* = 8.7 Hz), 114.88 (d, *J* = 21.5 Hz). 86.77, 61.65, 53.73, 48.20, 33.46, 21.18, 14.22. HRMS (ESI): Found $[M + H]^+$ = 292.1383, $C_{16}H_{19}FNO_3^+$ requires 292.1343.

(E)-Ethyl 2-{2-[2-oxo-2-(4-nitrophenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10g**): Prepared



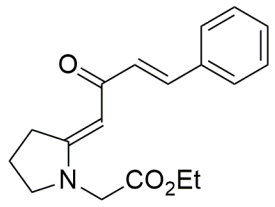
from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(4-nitrophenyl)ethanone (0.392 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10g** (0.424 g, 1.33 mmol, *c.a* 100%) as a yellow solid. M.p.: 136-138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 8.9 Hz, 2H), 5.53 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.03 (s, 2H), 3.55 (t, *J* = 7.3 Hz, 2H), 3.37 (t, *J* = 7.8 Hz, 2H), 2.05 (p, *J* = 7.4 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 185.46, 168.89, 167.53, 148.84, 147.19, 128.12, 123.37, 87.10, 61.83, 54.07, 48.22, 33.81, 20.99, 14.21. HRMS (ESI): Found $[M + H]^+$ = 319.1287, $C_{16}H_{19}N_2O_5^+$ requires 319.1294.

(E)-Ethyl 2-{2-[2-oxo-2-(3-nitrophenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10i**): Prepared



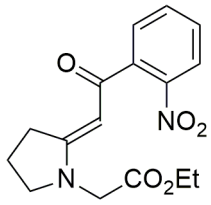
from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(3-nitrophenyl)ethanone (0.392 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10i** (0.420 g, 1.32 mmol, 99%) as a yellow solid. M.p.: 126-127 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, *J* = 2.1 Hz, 1H), 8.34–8.08 (m, 2H), 7.57 (t, *J* = 7.9 Hz, 1H), 5.64 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.13 (s, 2H), 3.63 (t, *J* = 7.3 Hz, 2H), 3.45 (t, *J* = 7.8 Hz, 2H), 2.12 (p, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.77, 168.82, 167.63, 148.11, 143.30, 133.22, 129.18, 124.92, 122.09, 86.39, 61.84, 54.02, 48.17, 33.78, 21.02, 14.21. HRMS (ESI): Found $[M + H]^+$ = 319.1281, $C_{16}H_{19}N_2O_5^+$ requires 319.1288.

(E)-Ethyl 2-{2-[2-oxo-2-(styryl)ethylidene]pyrrolidin-1-yl}acetate (**2.10k**): Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), (*E*)-1-bromo-4-phenylbut-3-en-2-one[98] (0.362 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10k** (0.351 g, 1.17 mmol, 88%) as a pale brown solid. M.p.: 90-94 °C. ^{1}H NMR (300 MHz,



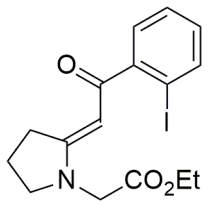
$CDCl_3$) δ 7.59–7.41 (m, 3H), 7.32 (q, *J* = 7.5, 6.9 Hz, 3H), 6.75 (d, *J* = 15.8 Hz, 1H), 5.15 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 2H), 3.52 (t, *J* = 7.3 Hz, 2H), 3.39 (t, *J* = 7.8 Hz, 2H), 2.04 (p, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.61, 167.93, 167.00, 137.75, 135.97, 129.82, 128.98, 128.63, 127.78, 91.45, 61.61, 53.62, 48.02, 33.41, 21.15, 14.21. ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.98, 168.07, 167.91, 156.52, 155.07, 128.26, 126.23, 123.21, 122.47, 112.00, 108.32, 87.00, 77.16, 61.82, 53.87, 48.25, 33.78, 21.22, 14.34. HRMS (ESI): Found $[M + H]^+$ = 300.1587, $C_{18}H_{22}NO_3^+$ requires 300.1594.

(E)-Ethyl 2-{2-[2-oxo-2-(2-nitrophenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10l**)**:** Prepared



from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(2-nitrophenyl)ethanone (0.392 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10l** (0.370 g, 1.18 mmol, 88%) as an orange gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91–7.81 (m, 1H), 7.58 (td, *J* = 7.4, 0.9 Hz, 1H), 7.51–7.38 (m, 2H), 5.13 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 2H), 3.58 (t, *J* = 7.3 Hz, 2H), 3.38 (t, *J* = 7.8 Hz, 2H), 2.09 (dt, *J* = 13.9, 7.0 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.17, 167.79, 167.57, 147.44, 140.13, 132.76, 129.10, 128.57, 123.88, 89.10, 61.75, 53.89, 48.07, 33.55, 20.99, 14.15. HRMS (ESI): Found $[M + H]^+$ = 319.1313, $C_{16}H_{19}N_2O_5^+$ requires 319.1294.

(E)-Ethyl 2-{2-[2-oxo-2-(2-iodophenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10m**): Prepared



from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(2-iodo)ethanone[96] (0.377 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10m** (0.497 g, 1.25 mmol, 93%) as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 4.3 Hz, 2H), 6.99 (dt, *J* = 7.9, 4.5 Hz, 1H), 5.16 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 2H), 3.56 (t, *J* = 7.3 Hz, 2H), 3.33 (t, *J* = 7.3 Hz, 2H), 2.06 (p, *J* = 7.4 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.29, 167.67, 167.16, 148.87, 139.50, 129.69, 127.78, 127.63, 92.39, 90.29, 61.57, 53.71, 47.85, 33.37, 20.95, 14.17. HRMS (ESI): Found $[M + H]^+$ = 400.0411, $C_{16}H_{19}INO_3^+$ requires 400.0404.

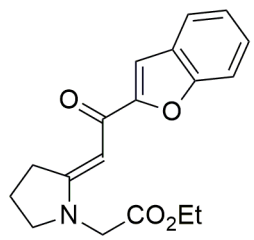
(E)-Ethyl 2-{2-[2-oxo-2-(2-bromo-4,5-dimethoxyphenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10n**): Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(2-bromo-4,5-dimethoxyphenyl)ethanone[97] (0.544 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10n** (0.512 g, 1.24 mmol, 93% yield) as a cream coloured solid. M.p.: 66-69 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.99 (s, 1H), 5.35 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.02 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.57 (t, *J* = 7.3 Hz, 2H), 3.37 (t, *J* = 7.7 Hz, 2H), 2.09 (p, *J* = 7.5 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 189.08, 167.89, 166.72, 149.9, 148.15, 137.5, 115.69, 112.16, 109.80, 91.51, 61.66, 56.23, 56.05, 53.71, 47.96, 33.42, 21.15, 14.20. HRMS (ESI): Found $[M + H]^+$ = 352.0560, $C_{16}H_{19}BrNO_3^+$ requires 352.0543.

(E)-Ethyl 2-{2-[2-oxo-2-(2-chlorophenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10p**): Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(2-chlorophenyl)ethanone[96] (0.357 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10p** (0.378 g, 1.23 mmol, 92%) as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 5.8, 3.5 Hz, 1H), 7.37–7.29 (m, 1H), 7.30–7.18 (m, 2H), 5.27 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 2H), 3.56 (t, *J* = 7.3 Hz, 2H), 3.37 (t, *J* = 7.8 Hz, 2H), 2.07 (p, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.91, 167.76, 167.02, 143.26, 130.43, 129.87, 129.61, 128.87, 126.55, 91.38, 61.64, 53.72, 47.95, 33.45, 21.08, 14.15. HRMS (ESI): Found $[M + H]^+$ = 308.1052, $C_{16}H_{19}ClNO_3^+$ requires 308.1048.

(E)-Ethyl 2-{2-[2-oxo-2-(furan-2-yl)ethylidene]pyrrolidin-1-yl}acetate (**2.10s**): Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(furan-2-yl)ethanone[95] (0.304 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10s** (0.329 g, 1.25 mmol, 93% yield) as a cream coloured solid. M.p.: 82-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.93 (dd, *J* = 3.4, 0.9 Hz, 1H), 6.37 (dd, *J* = 3.4, 1.7 Hz, 1H), 5.57 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 2H), 3.48 (t, *J* = 7.3 Hz, 2H), 3.33 (t, *J* = 7.8 Hz, 2H), 1.99 (p, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 177.20,

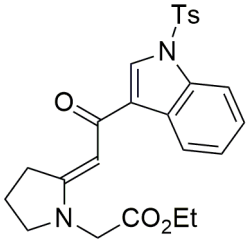
167.96, 167.18, 155.65, 143.54, 112.50, 111.72, 86.24, 61.63, 53.59, 48.05, 33.40, 21.17, 14.21. HRMS (ESI): Found $[M + H]^+ = 264.1232$, $C_{14}H_{18}NO_4^+$ requires 264.1236.

(E)-Ethyl 2-{2-[2-oxo-2-(benzofuran-3-yl)ethylidene]pyrrolidin-1-yl}acetate (**2.10u**):



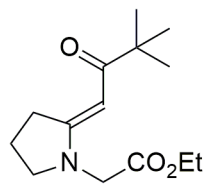
Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 1-(benzofuran-3-yl)-2-bromoethanone[93] (0.384 g, 1.61 mmol, 1.2 eq.) with triphenylphosphine as thiophile (0.420 g, 1.6 mmol, 1.2 eq.) triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10u** (0.389 g, 1.25 mmol, 93% yield) as a cream coloured solid. M.p.: 90-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.45–7.32 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 5.83 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.11 (s, 2H), 3.56 (t, *J* = 7.3 Hz, 2H), 3.45 (t, *J* = 7.8 Hz, 2H), 2.07 (p, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 177.88, 168.02, 167.82, 156.36, 154.94, 128.13, 126.13, 123.10, 122.38, 111.90, 108.25, 86.85, 61.75, 53.79, 48.13, 33.69, 21.11, 14.25**.** HRMS (ESI): Found $[M + H]^+ = 314.1401$, $C_{18}H_{20}NO_4^+$ requires 314.1387.

(E)-Ethyl 2-{2-[2-oxo-2-(1-tosyl-1H-indol-3-yl)ethylidene]pyrrolidin-1-yl}acetate (**2.10v**):



Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(1-tosyl-1*H*-indol-3-yl)ethanone[92] (0.631 g, 1.61 mmol, 1.2 eq.) with triphenylphosphine as thiophile (0.420 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10v** (0.548 g, 1.18 mmol, 88%) as a cream coloured solid. M.p.: 143-146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38–8.20 (m, 1H), 8.01 (s, 1H), 7.97–7.85 (m, 1H), 7.85–7.66 (m, 2H), 7.38–7.08 (m, 4H), 5.54 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.08 (s, 2H), 3.54 (t, *J* = 7.2 Hz, 2H), 3.42 (t, *J* = 7.7 Hz, 2H), 2.31 (s, 3H), 2.06 (p, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.68, 168.04, 166.42, 145.32, 135.12, 134.94, 129.98, 128.94, 127.91, 126.93, 124.97, 124.91, 124.01, 123.08, 113.07, 88.44, 61.67, 53.52, 48.09, 33.45, 21.53, 21.24, 14.25. HRMS (ESI): Found $[M + H]^+ = 467.1656$, $C_{25}H_{26}N_2O_5S^+$ requires 467.1635.

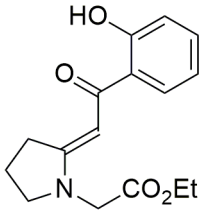
(E)-Ethyl 2-{2-[2-oxo-2-(tert-butyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10y**): Prepared from



the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(*tert*-butyl)ethanone (0.288 g, 1.61 mmol, 1.2 eq.) with triphenylphosphine as thiophile (0.420 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.*

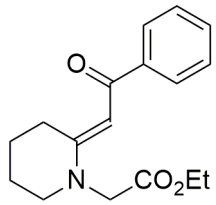
0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10y** (0.192 g, 0.817 mmol, 61%) as a colourless oil. ^{1}H NMR (300 MHz, CDCl3) δ 5.18 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 2H), 3.50 (t, *J* = 7.2 Hz, 2H), 3.25 (t, *J* = 7.8 Hz, 2H), 2.01 (p, *J* = 7.5 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.46, 168.70, 166.20, 86.18, 61.76, 53.69, 48.50, 42.80, 33.32, 28.14, 21.63, 14.59. HRMS (ESI): Found $[M + H]^+$ = 254.1767, $C_{14}H_{24}NO_3^+$ requires 254.1751.

(E)-Ethyl 2-{2-[2-oxo-2-(2-hydroxyphenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10z**):



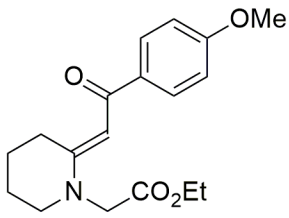
Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(2-hydroxy)ethanone (0.346 g, 1.61 mmol, 1.2 eq.) with triphenylphosphine as thiophile (0.420 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10z** (0.344 g, 1.19 mmol, 89%) as a colourless solid. M.p.: 90-91 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.02 (s, 1H), 7.63 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.38–7.23 (m, 1H), 6.91 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.84–6.73 (m, 1H), 5.70 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.08 (s, 2H), 3.59 (t, *J* = 7.3 Hz, 2H), 3.41 (t, *J* = 7.8 Hz, 2H), 2.08 (p, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 191.40, 168.38, 167.68, 162.78, 133.49, 127.95, 121.25, 118.17, 117.83, 85.52, 61.78, 53.99, 48.25, 33.82, 20.95, 14.21. Spectroscopic data were in agreement with previously reported values.[74,77]

(E)-Ethyl 2-{2-[2-oxo-2-(phenyl)ethylidene]piperidin-1-yl}acetate (**2.23a**): Prepared from the



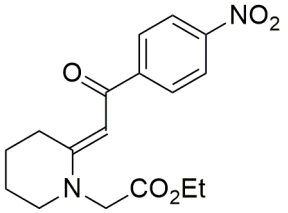
thiolactam **2.22** (0.250 g, 1.24 mmol, 1.0 eq.), 2-bromo-1-phenylethanone (0.297 g, 1.49 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.21 ml, *ca.* 0.15 g, 1.5 mmol, 1.2 eq.) provided enaminone **2.23a** (0.317 g, 1.11 mmol, 89%) as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.45–7.24 (m, 3H), 5.55 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 2H), 3.39 (t, *J* = 6.1 Hz, 2H), 3.32 (t, *J* = 6.5 Hz, 2H), 1.82 (p, *J* = 6.0 Hz, 2H), 1.70 (p, *J* = 6.3 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.63, 168.54, 164.45, 142.59, 130.23, 127.93, 127.10, 91.23, 61.40, 54.26, 51.80, 28.11, 22.97, 19.29, 14.18. HRMS (ESI): Found $[M + H]^+$ = 288.1608, $C_{17}H_{22}NO_3^+$ requires 288.1594 Spectroscopic data were in agreement with previously reported values.[74,77]

(E)-Ethyl 2-{2-[2-oxo-2-(4-methoxyphenyl)ethylidene]piperidin-1-yl}acetate (**2.23b**):



Prepared from the thiolactam **2.22** (0.250 g, 1.24 mmol, 1.0 eq.), 2-bromo-1-(4-methoxyphenyl)ethanone (0.341 g, 1.49 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.21 ml, *ca.* 0.15 g, 1.5 mmol, 1.2 eq.) provided enaminone **2.23b** (0.343 g, 1.11 mmol, 87%) as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.56 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 2H), 3.83 (s, 3H), 3.44 (t, *J* = 6.1 Hz, 2H), 3.32 (t, *J* = 6.5 Hz, 2H), 1.87 (p, *J* = 6.1 Hz, 2H), 1.73 (p, *J* = 6.4 Hz, 2H), 1.31 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.66, 168.72, 163.76, 161.42, 135.12, 128.97, 113.07, 90.97, 61.35, 55.21, 54.30, 51.77, 27.98, 23.06, 19.40, 14.20. HRMS (ESI): Found $[M + H]^+$ = 318.1716, $C_{18}H_{24}NO_4^+$ requires 318.1700.

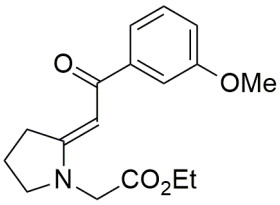
(E)-Ethyl 2-{2-[2-oxo-2-(4-nitrophenyl)ethylidene]piperidin-1-yl}acetate (**2.23c**): Prepared



from the thiolactam **2.22** (0.250 g, 1.24 mmol, 1.0 eq.), 2-bromo-1-(4-nitrophenyl)ethanone (0.364 g, 1.49 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.21 ml, *ca.* 0.15 g, 1.5 mmol, 1.2 eq.). Provided enaminone **2.23c** (0.355 g, 1.11 mmol, 87%) as a yellow solid. M.p.: 120-122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 5.51 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.05 (s, 2H), 3.50 (t, *J* = 6.1 Hz, 2H), 3.35 (t, *J* = 6.4 Hz, 2H), 1.91 (p, *J* = 5.8 Hz, 2H), 1.77 (p, *J* = 6.3 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 185.01, 168.18, 166.32, 148.65, 148.32, 128.03, 123.33, 91.03, 61.76, 54.48, 52.19, 28.49, 22.87, 19.10, 14.28. HRMS (ESI): Found $[M + H]^+$ = 333.1458, $C_{17}H_{21}N_2O_5^+$ requires 333.1445

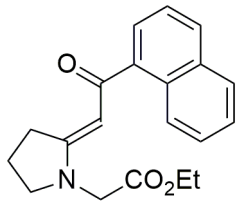
The following enaminones were obtained, after attempted chromatographic separation, as a mixture with phosphine-derived by-products(s). In some cases the mixtures could not be unambiguously characterized. They were used in the subsequent cyclization reactions without further purification.

(E)-Ethyl 2-{2-[2-oxo-2-(3-methoxyphenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10h**): Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 1-(3-methoxyphenyl)-2-bromoethanone (0.319 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.)



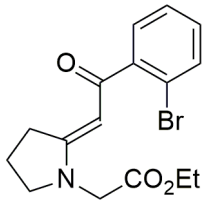
provided enaminone **2.10h** contaminated with by-product(s), as a brown oil (0.450 g), which was used without further purification. Discernible signals are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.35 (m, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 6.97 (ddd, *J* = 8.1, 2.6, 0.9 Hz, 1H), 5.56 (s, 1H), 4.24–4.15 (m, 2H), 3.98 (s, 2H), 3.83 (s, 3H), 3.52 (t, *J* = 7.2 Hz, 2H), 3.37 (t, *J* = 7.8 Hz, 2H), 2.07 (p, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H). Found $[M + H]^+$ = 304.1549, $C_{17}H_{22}NO_4^+$ requires 304.1543.

(E)-Ethyl 2-{2-[2-oxo-2-(naphthylen-1-yl)ethylidene]pyrrolidin-1-yl}acetate (**2.10j**):



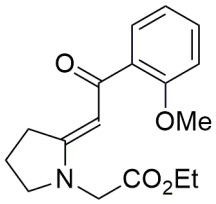
Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 1-(naphthylen-1-yl)-2-bromoethanone[99] (0.399 g, 1.61 mmol, 1.2 eq.) with triphenylphosphine as thiophile (0.420 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10j** contaminated with by-product(s), as a brown oil (0.470 g), which was used without further purification. Discernible signals are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47–8.22 (m, 1H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.58 (d, *J* = 7.0 Hz, 1H), 7.52–7.37 (m, 3H), 5.41 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 2H), 3.58–3.49 (m, 2H), 3.44 (t, *J* = 7.8 Hz, 2H), 2.13–2.00 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). HRMS (ESI): Found $[M + H]^+$ = 324.1610, $C_{20}H_{22}NO_3^+$ requires 324.1594.

(E)-Ethyl 2-{2-[2-oxo-2-(2-bromophenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10o**)**:**



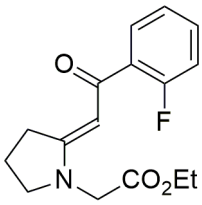
Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 1-(2-bromophenyl)-2-bromoethanone[96] (0.447 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10o** contaminated with phosphite-derived by-product(s), as a brown oil (0.480 g). Discernible signals are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.23 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.10 (td, *J* = 7.6, 1.9 Hz, 1H), 5.16 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 2H), 3.50 (t, *J* = 7.3 Hz, 2H), 3.29 (t, *J* = 7.7 Hz, 2H), 2.01 (p, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H). HRMS (ESI): Found $[M + H]^+$ = 352.0543, $C_{16}H_{19}BrNO_2^+$ requires 352.0548.

(E)-Ethyl 2-{2-[2-oxo-2-(2-methoxyphenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10q**): Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(2-methoxyphenyl)ethanone (0.367 g, 1.61 mmol, 1.2 eq.) with triphenylphosphine as thiophile



(0.420 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10q** contaminated with by-product(s), as an amber oil (0.456 g), which was used without further purification. Discernible signals are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.31 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 6.98–6.89 (m, 2H), 5.56 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 2H), 3.83 (s, 3H), 3.52 (t, *J* = 7.2 Hz, 2H), 3.37 (t, *J* = 7.8 Hz, 2H), 2.04 (p, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 188.87, 168.08, 166.08, 156.92, 133.11, 130.54, 129.58, 120.45, 111.52, 92.33, 61.41, 55.66, 53.46, 48.03, 33.42, 21.26, 14.18. HRMS (ESI): Found $[M + H]^+$ = 304.1543, $C_{17}H_{22}NO_4^+$ requires 304.1549.

(E)-Ethyl 2-{2-[2-oxo-2-(2-fluorophenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10r**): Prepared



from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(2-fluorophenyl)ethanone (0.349 g, 1.61 mmol, 1.2 eq.) with triphenylphosphine as thiophile (0.420 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10r** contaminated with by-product(s), as an amber oil (0.440 g), which was used without further purification. The sample could not be unambiguously characterized. HRMS (ESI): Found $[M + H]^+$ = 292.1367, $C_{16}H_{19}FNO_3^+$ requires 292.1343.

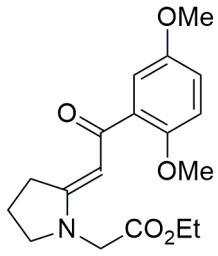
(E)-Ethyl 2-{2-[2-oxo-2-(thiophen-2-yl)ethylidene]pyrrolidin-1-yl}acetate (**2.10t**): Prepared



from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(thiophen-2-yl)ethanone[94] (0.330 g, 1.61 mmol, 1.2 eq.) with triphenylphosphine as thiophile (0.420 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10t**, contaminated with a phosphine derived by-product, as an amber oil (0.440 g), which was used without further purification. This sample could not be unambiguously characterized. However, a small analytical sample, obtained after a similar attempted synthesis of the target enaminone using triethyl phosphite as thiophile, could be recrystallized from cold diethyl ether, providing a low yield of pure material. Characterization data for this sample are as follows: M.p.: 78-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.93 (dd, *J* = 3.4, 0.9 Hz, 1H), 6.37 (dd, *J* = 3.4, 1.7 Hz, 1H), 5.57 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 2H), 3.48 (t, *J* = 7.3 Hz, 2H), 3.33 (t, *J* = 7.8 Hz, 2H), 1.99 (p, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.30, 167.93, 166.94, 148.80, 129.74, 127.55, 127.48,

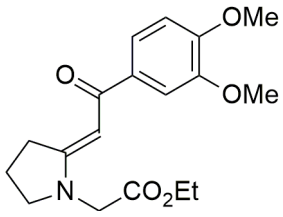
86.59, 61.55, 53.65, 48.08, 33.34, 21.10, 14.19 . HRMS (ESI): Found $[M + H]^+$ = 280.1013, $C_{14}H_{18}NO_3S^+$ requires 280.1002.

(E)-Ethyl 2-{2-[2-oxo-2-(2,5-dimethoxyphenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10w**):



Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(2,5-dimethoxyphenyl)ethanone (0.417 g, 1.61 mmol, 1.2 eq.) with triphenylphosphine as thiophile (0.420 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.) provided enaminone **2.10w**, contaminated with a phosphine derived by-product, as an amber oil (0.432 g). Discernible signals are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 2.6 Hz, 1H), 6.89–6.83 (m, 2H), 5.64 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.54 (t, *J* = 7.3 Hz, 2H), 3.39 (t, *J* = 7.6 Hz, 2H), 2.08 (p, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 188.19, 168.07, 166.37, 153.60, 151.37, 133.5, 116.74, 114.12, 113.53, 92.21, 61.48, 56.66, 55.78, 53.51, 48.06, 33.51, 21.27, 14.19. HRMS (ESI): Found $[M + H]^+$ = 334.1674, $C_{14}H_{18}NO_4^+$ requires 334.1649.

(E)-Ethyl 2-{2-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]pyrrolidin-1-yl}acetate (**2.10x**):

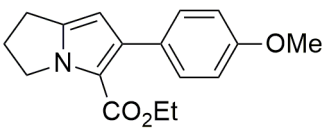


Prepared from the thiolactam **2.3** (0.250 g, 1.34 mmol, 1.0 eq.), 2-bromo-1-(3,4-dimethoxyphenyl)ethanone[121] (0.417 g, 1.61 mmol, 1.2 eq.) with triethyl phosphite as thiophile (0.28 cm^3, *ca.* 0.27 g, 1.6 mmol, 1.2 eq.), triethylamine as base (0.23 ml, *ca.* 0.16 g, 1.6 mmol, 1.2 eq.). Provided enaminone **2.10w**, contaminated with a phosphite derived by-product, as an amber oil (0.445 g). Discernible signals are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 8.4, 2.0 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 5.67 (s, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.06 (s, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.56 (t, *J* = 7.2 Hz, 2H), 3.42 (t, *J* = 7.8 Hz, 2H), 2.09 (p, *J* = 7.5 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 186.95, 168.32, 166.79, 151.24, 148.71, 134.61, 120.51, 110.45, 109.87, 86.73, 61.57, 55.94, 53.63, 48.25, 33.33, 21.28, 14.24. HRMS (ESI): Found $[M + H]^+$ = 334.1642, $C_{18}H_{24}NO_5^+$ requires 334.1649.

7.4 General method for the formation of ethyl 6-aryl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylates 2.11a–z

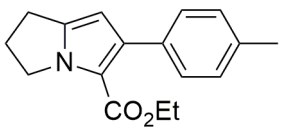
To a sealed microwave tube was added the enaminones, (*E*)-ethyl 2-[2-(2-aryl-2-oxoethylidene)pyrrolidin-1-yl]acetates (**2.10**) dissolved in xylene (5 cm^3/mmol). Flash silica gel (5 times mass of starting material) was added to the solution and the mixture was then irradiated under microwave conditions (150 W, 180 °C) for the stipulated time (see *Table 2.2*) while maintaining moderate stirring. The reaction mixture was then transferred to a suitable flask by washing with dichloromethane to ensure quantitative transfer of solvent and solids and the solvent was evaporated *in vacuo* and dried under vacuum to provide the material adsorbed onto silica (more silica was added as needed to provide a free-flowing, easy to handle material). This residue was then purified by column chromatography with ethyl acetate–hexane mixtures to provide the corresponding *6-aryl-2,3-dihydro-1H-pyrrolizine-5-carboxylates* **2.11**. The following products were prepared and characterized.

Ethyl 6-(4-methoxyphenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11a**): The product



was obtained according to the general method from (*E*)-ethyl 2-{2-[2-(4-methoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10a**) (0.101 g, 0.33 mmol), providing **2.11a** (0.091 g, 0.32 mmol, 96%) as a white crystalline solid. M.p.: 71-72 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.92 (s, 1H), 4.31 (t, *J* = 7.2Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.49 (p, *J* = 7.4 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.38, 158.50, 142.28, 137.24, 130.71, 129.13, 114.15, 112.90, 103.38, 59.48, 55.23, 48.91, 26.72, 24.50, 14.25. HRMS (ESI): Found $[M + H]^+$ = 286.1441, $C_{17}H_{20}NO_3^+$ requires 286.1438 .

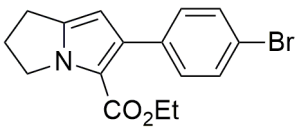
Ethyl 6-(p-tolyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11b**): The product was



obtained according to the general method from (*E*)-ethyl 2-{2-[2-(*p*-tolylphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10b**) (0.100 g, 0.35 mmol), providing **2.11b** (0.084 g, 0.31 mmol, 90%) as a white crystalline solid. M.p.: 73-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 5.94 (s, 1H), 4.32 (dd, *J* = 7.8, 6.6 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.52 (p, *J* = 7.7 Hz, 2H), 2.37 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.37, 142.24, 137.47, 136.18, 133.67, 129.50, 128.15, 114.25,

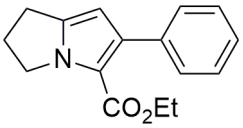
103.46, 59.49, 48.87, 26.75, 24.49, 21.21, 14.22. HRMS (ESI): Found $[M + H]^+$ = 270.1508, $C_{17}H_{20}NO_2^+$ requires 270.1489 .

Ethyl 6-(4-bromophenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11c**): The product was



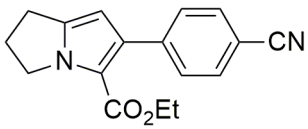
obtained according to the general method from (*E*)-ethyl 2-{2-[2-(*p*-bromophenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10c**) (0.100 g, 0.28 mmol), providing **2.11c** (0.092 g, 0.28 mmol, 97%) as an amber oil**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.92 (s, 1H), 4.31 (t, *J* = 7.2 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.50 (p, *J* = 7.4 Hz, 2H), 1.18 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.17, 142.45, 135.99, 135.60, 131.30, 130.50, 120.61, 114.33, 103.38, 59.66, 48.94, 26.75, 24.47, 14.21. HRMS (ESI): Found $[M + H]^+$ = 334.0429, $C_{16}H_{17}BrNO_2^+$ requires 334.0437.

Ethyl 6-phenyl-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11d** = **2.8**): The product was



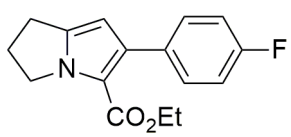
obtained according to the general method from (*E*)-ethyl 2-{2-[2-(phenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10d**) (0.100 g, 0.369 mmol), providing **2.11d** (0.0869 g, 0.340 mmol, 93%) as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.38–7.24 (m, 3H), 5.95 (s, 1H), 4.33 (t, *J* = 7.2 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.49 (p, *J* = 7.2 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.37, 142.29, 137.38, 136.67, 129.64, 127.38, 126.55, 114.32, 103.50, 59.52, 48.83, 26.76, 24.48, 14.13. Spectroscopic data were in agreement with previously reported values.[77]

Ethyl 6-(4-cyanophenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11e**): The product was



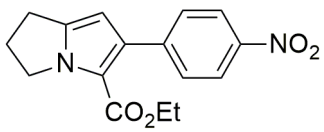
obtained according to the general method from (*E*)-ethyl 2-{2-[2-(cyanophenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10e**) (0.100 g, 0.335 mmol), providing **2.11e** (0.086 g, 0.308 mmol, 92%) as a white solid. M.p.: 83-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 5.96 (s, 1H), 4.34 (t, *J* = 7.2 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.53 (p, *J* = 7.5 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 160.92, 142.70, 141.58, 135.13, 131.26, 130.30, 119.35, 114.68, 109.97, 103.49, 59.87, 49.06, 26.78, 24.47, 14.17. HRMS (ESI): Found $[M + H]^+$ = 281.1291, $C_{17}H_{17}N_2O_2^+$ requires 281.1285.

Ethyl 6-(4-fluorophenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11f**): The product was



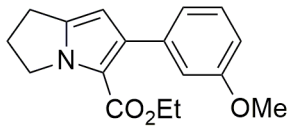
obtained according to the general method from (*E*)-ethyl 2-{2-[2-(*p*-fluorophenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10f**) (0.100 g, 0.343 mmol), providing **2.11f** (0.092 g, 0.336 mmol, 98%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.38 (m, 2H), 7.14–6.85 (m, 2H), 5.91 (s, 1H), 4.32 (t, *J* = 7.2 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.49 (p, *J* = 7.4 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.52 (d, *J* = 243.5 Hz), 161.25, 142.35, 136.35, 132.67 (d, *J* = 3.3 Hz), 131.17 (d, *J* = 7.9 Hz), 114.21 (d, *J* = 21.4 Hz), 103.49, 59.57, 48.92, 26.75, 24.48, 14.18. HRMS (ESI): Found $[M + H]^+$ = 274.1265, $C_{16}H_{17}FNO_2^+$ requires 274.1252.

Ethyl 6-(4-nitrophenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11g**): The product was



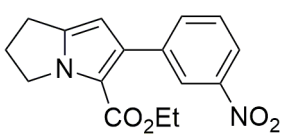
obtained according to the general method from (*E*)-ethyl 2-{2-[2-(*p*-nitro)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10g**) (0.100 g, 0.314 mmol), providing **2.11g** (0.074 g, 0.245 mmol, 78%) as a bright yellow solid. M.p.: 75 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.9 Hz, 2H), 7.62 (d, *J* = 8.9 Hz, 2H), 6.00 (s, 1H), 4.35 (t, *J* = 7.2 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.54 (p, *J* = 7.4 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 160.86, 146.40, 143.64, 142.78, 134.60, 130.32, 122.77, 114.82, 103.62, 59.95, 49.12, 26.78, 24.46, 14.21. HRMS (ESI): Found $[M + H]^+$ = 301.1178, $C_{16}H_{17}N_2O_4^+$ requires 301.1183 .

Ethyl 6-(3-methoxyphenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11h**): The product



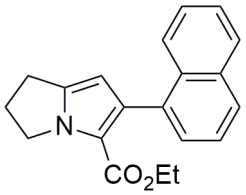
was obtained according to the general method from a portion of the above impure sample of (*E*)-ethyl 2-{2-[2-(3-methoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10h**) (0.150 g,), providing **2.11h** (0.127 g, 0.362 mmol, 81% based on thiolactam **2.3**) as colourless gel. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.20 (m, 1H), 7.12–6.94 (m, 2H), 6.83 (dd, *J* = 8.3, 2.6 Hz, 1H), 5.96 (s, 1H), 4.33 (t, *J* = 7.2 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.51 (p, *J* = 7.4 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 161.36, 158.84, 142.22, 138.03, 137.08, 128.29, 122.29, 115.31, 114.43, 112.24, 103.50, 59.53, 55.19, 48.83, 26.78, 24.48, 14.15. HRMS (ESI): Found $[M + H]^+$ = 286.1440, $C_{17}H_{20}NO_3^+$ requires 286.1438 .

Ethyl 6-(3-nitrophenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11i**): The product was



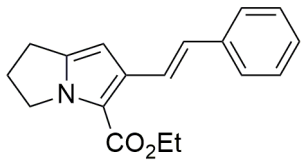
obtained according to the general method from (*E*)-ethyl 2-{2-[2-(*m*-nitro)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10i**) (0.100 g, 0.314 mmol), providing **2.11i** (0.073 g, 0.244 mmol, 78%) as a bright yellow solid. M.p.: 109–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.2 Hz, 1H), 8.12 (dd, *J* = 8.1, 2.7 Hz, 1H), 7.81 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 6.00 (s, 1H), 4.34 (t, *J* = 7.2 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.54 (p, *J* = 7.4 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 160.91, 147.66, 142.74, 138.33, 135.75, 134.31, 128.19, 124.65, 121.31, 114.65, 103.48, 59.86, 49.02, 26.75, 24.45, 14.07. HRMS (ESI): Found $[M + H]^+$ = 301.1177, $C_{16}H_{17}N_2O_4^+$ requires 301.1183 .

Ethyl 6-(naphthalen-1-yl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11j**): The product



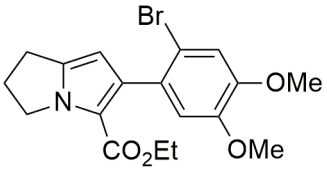
was obtained according to the general method from a portion of the above impure sample of (*E*)-ethyl 2-{2-[2-(naphthalen-1-yl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10j**) (0.150 g), providing **2.11j** (0.106 g, 0.347 mmol, 83% based on thiolactam **2.3**) as an off-white solid. M.p.: 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.71 (m, 3H), 7.50–7.30 (m, 4H), 5.99 (s, 1H), 4.39 (br q, *J* = 8.0 Hz, 2H), 3.83 (q, *J* = 7.1 Hz, 2H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.55 (p, *J* = 7.3 Hz, 2H), 0.57 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.39, 142.34, 135.44, 134.57, 133.31, 132.81, 127.83, 127.17, 126.99, 126.65, 125.30, 125.22, 124.92, 116.17, 104.56, 59.15, 48.47, 26.93, 24.57, 13.31. HRMS (ESI): Found $[M + H]^+$ = 306.1492, $C_{20}H_{20}NO_2^+$ requires 306.1489.

(E)-Ethyl 6-(styryl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11k**): The product was



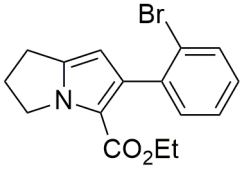
obtained according to the general method from (*E*)-ethyl 2-{2-[2-(styryl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10k**) (0.100 g, 0.334 mmol), providing **2.11k** (0.077 g, 0.274 mmol, 82%) as a white gel. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 16.4 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.25–7.07 (m, 1H), 6.91 (d, *J* = 16.4 Hz, 1H), 6.24 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.24 (t, *J* = 7.2 Hz, 2H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.45 (p, *J* = 7.4 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.51, 143.19, 138.14, 134.17, 128.54, 128.00, 126.98, 126.25, 122.68, 115.71, 98.14, 59.74, 48.58, 26.72, 24.30, 14.56. HRMS (ESI): Found $[M + H]^+$ = 282.1492, $C_{18}H_{20}NO_2^+$ requires 282.1489.

Ethyl 6-(2-bromo-4,5-dimethoxyphenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11n**):



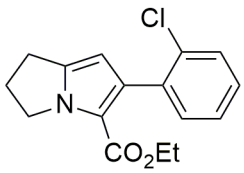
The product was obtained according to the general method from (*E*)-ethyl 2-{2-[2-(2-bromo-4,5-dimethoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10n**) (0.100 g, 0.254 mmol), providing **2.11n** (0.034 g, 0.087 mmol, 34%) as a brown gel. The reaction mixture had turned a dark brown colour, indicating significant concomitant decomposition had occurred, even though it had still not reached completion by TLC analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.83 (s, 1H), 5.89 (s, 1H), 4.40–4.28 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.53 (p, *J* = 7.4 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 161.24, 148.51, 147.67, 141.98, 135.22, 130.66, 115.79, 115.14, 114.73, 114.47, 103.80, 59.60, 56.34, 56.14, 48.65, 26.95, 24.70, 14.23. HRMS (ESI): Found $[M + H]^+$ = 394.0626, $C_{18}H_{21}BrNO_4^+$ requires 394.0648.

Ethyl 6-(2-bromophenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11o**): The product was



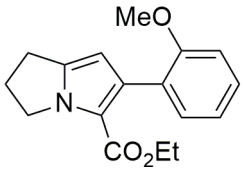
obtained according to the general method, from a portion of the above impure sample of (*E*)-ethyl 2-{2-[2-(2-bromophenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10o**) (0.150 g), providing **2.11o** (0.064 g, 0.193 mmol, 46% based on thiolactam **2.3**) as colourless gel. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.7 Hz, 1H), 7.32–7.11 (m, 2H), 7.12–6.95 (m, 1H), 5.79 (s, 1H), 4.25 (t, *J* = 7.2 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.44 (p, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.11, 141.95, 138.48, 135.14, 132.01, 131.70, 128.13, 126.43, 124.40, 115.53, 103.45, 59.46, 48.42, 26.85, 24.56, 13.87. HRMS (ESI): Found $[M + H]^+$ = 334.0437, $C_{16}H_{17}BrNO_2^+$ requires 334.0437.

Ethyl 6-(2-chlorophenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11p**): The product was

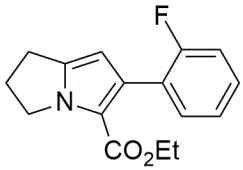


obtained according to the general method from (*E*)-ethyl 2-{2-[2-(2-chloro)-2-oxoethylidene]pyrrolidin-1-yl}acetate **(2.10p)** (0.100 g, 0.325 mmol), providing **2.11p** (0.087 g, 0.30 mmol, 92%) as a white gel. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.36 (m, 1H), 7.33–7.26 (m, 1H), 7.26–7.17 (m, 2H), 5.90 (s, 1H), 4.34 (t, *J* = 7.2 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.53 (p, *J* = 7.4 Hz, 2H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.15, 142.04, 136.34, 133.83, 133.25, 131.82, 128.88, 127.94, 125.81, 115.67, 103.52, 59.48, 48.45, 26.83, 24.54, 13.85. HRMS (ESI): Found $[M + H]^+$ = 290.0941, $C_{16}H_{17}ClNO_2^+$ requires 290.0942.

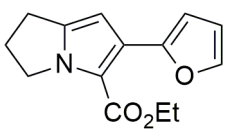
Ethyl 6-(2-methoxyphenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11q**): The product was obtained according to the general method from a portion of the above impure sample of (*E*)-ethyl 2-{2-[2-(2-methoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10q**) (0.150 g), providing **2.11q** (0.103 g, 0.361 mmol, 82% based on thiolactam **2.3**) as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.20 (m, 2H), 7.00–6.79 (m, 2H), 5.92 (s, 1H), 4.31 (t, *J* = 7.2 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.49 (p, *J* = 7.3 Hz, 2H), 1.05 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.48, 156.93, 141.96, 132.29, 131.48, 128.05, 126.23, 119.82, 115.64, 110.25, 103.73, 59.25, 55.46, 48.48, 26.80, 24.57, 14.05. HRMS (ESI): Found $[M + H]^+$ = 286.1440, $C_{17}H_{20}NO_3^+$ requires 286.1438 .



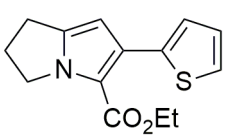
Ethyl 6-(2-fluorophenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11r**)**:** The product was obtained according to the general method from a portion of the above impure sample of (*E*)-ethyl 2-{2-[2-(2-fluorophenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10r**) (0.150 g), providing **2.11r** (0.124 g, 0.456 mmol, *ca.* 100% based on thiolactam **2.3**) as a pale pink solid. M.p.: 71-72 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (td, *J* = 7.5, 1.8 Hz, 1H), 7.30–7.20 (m, 1H), 7.16–6.93 (m, 2H), 5.94 (s, 1H), 4.32 (t, *J* = 7.2 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.49 (p, *J* = 7.3 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160,04 (d, *J* = 244.6 Hz), 161.18, 142.29, 131.85 (d, *J* = 3.3 Hz), 129.31, 128.39 (d, *J* = 8.2 Hz), 124.94 (d, *J* = 15.6 Hz), 123.19 (d, *J* = 3.6 Hz), 115.69, 115.00 (d, *J* = 22.8 Hz), 103.68 (d, *J* = 1.0 Hz), 59.56, 48.63, 26.84, 24.52, 13.96. HRMS (ESI): Found $[M + H]^+$ = 274.1265, $C_{16}H_{17}FNO_2^+$ requires 274.1238.



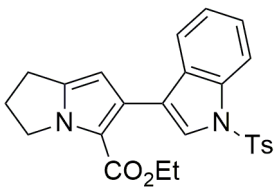
Ethyl 6-(furan-2-yl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11s**): The product was obtained according to the general method from (*E*)-ethyl 2-{2-[2-(furan-2-yl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10s**) (0.100 g, 0.380 mmol), providing **2.11s** (0.093 g, 0.379 mmol, *ca.* 100%) as white crystalline solid. M.p.: 93 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.05 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.44 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.29 (s, 1H), 4.32 and 4.30 (overlapping q, *J* = 7.2 Hz, and t, *J* = 7.2 Hz, 4H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.48 (p, *J* = 7.5 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 4H).^{13}C NMR (101 MHz, $CDCl_3$) δ 160.87, 149.69, 142.54, 140.80, 126.47, 113.55, 111.29, 108.71, 101.13, 59.81, 49.21, 26.72, 24.40, 14.47. HRMS (ESI): Found $[M + Na]^+$ = 268.0964, $C_{14}H_{16}NaNO_3^+$ requires 268.0944.



Ethyl 6-(thiophen-2-yl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11t**): The product was obtained according to the general method from a portion of the above impure sample of (*E*)-ethyl 2-{2-[2-(thiophen-2-yl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10t**) (0.150 g), providing **2.11t** (0.118 g, 0.451 mmol, 99% based on thiolactam **2.3**) as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 3.8 Hz, 1H), 7.23 (d, *J* = 5.3 Hz, 1H), 7.06–6.93 (m, 1H), 6.08 (s, 1H), 4.41–4.13 (m, 4H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.47 (p, *J* = 7.4 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.06, 142.33, 137.94, 129.13, 126.73, 126.59, 124.41, 114.39, 103.72, 59.79, 49.20, 26.66, 24.44, 14.35. HRMS (ESI): Found $[M + H]^+$ = 262.0896, $C_{14}H_{16}NO_2S^+$ requires 262.0896 .

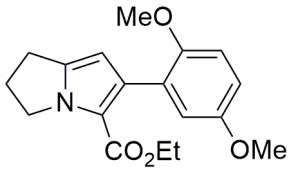


Ethyl 6-(benzofuran-3-yl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11u**): The product was obtained according to the general method from (*E*)-ethyl 2-{2-[2-(benzofuran-3-yl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10u**) (0.100 g, 31.9 mmol), providing **2.11u** (0.090 g, 0.305 mmol, 96%) as a white solid. M.p.: 106-107 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (apparent d, *J* = 8.5 Hz, 1H), 7.52 (s, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.26–7.13 (m, 2H), 6.47 (s, 1H), 4.32 (dq, *J* = 14.9, 7.2 Hz, 4H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.44 (p, *J* = 7.4 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 160.61, 154.02, 151.62, 142.49, 129.73, 125.79, 123.62, 122.36, 120.85, 114.68, 110.55, 104.95, 101.96, 77.42, 77.00, 76.58, 59.94, 49.37, 26.60, 24.27, 14.39. HRMS (ESI): Found $[M + H]^+$ = 296.1295, $C_{18}H_{18}NO_3^+$ requires 296.1281.



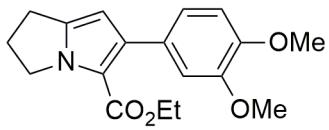
Ethyl 6-(1-tosyl-1H-indol-3-yl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11v**): The product was obtained according to the general method from (*E*)-ethyl 2-{2-[2-(1-tosyl-1*H*-indol-3-yl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10v**) (0.100 g, 0.214 mmol), providing **2.11v** (0.088 g, 0.196 mmol, 92 %) as a white gel. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.72 (s, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.40–6.97 (m, 4H), 6.05 (s, 1H), 4.35 (t, *J* = 7.2 Hz, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.51 (p, *J* = 7.3 Hz, 2H), 2.30 (s, 3H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.23, 144.64, 142.64, 135.48, 134.83, 131.15, 129.72, 126.84, 125.99, 124.86, 124.24, 123.00, 121.04, 118.53, 115.48, 113.53, 103.71, 59.56, 48.82, 26.82, 24.53, 21.48, 13.69. HRMS (ESI): Found $[M + H]^+$ = 449.1539, $C_{25}H_{25}N_2O_4S^+$ requires 449.1530.

Ethyl 6-(2,5-dimethoxyphenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11w**): The



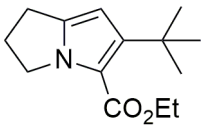
product was obtained according to the general method from a portion of the above impure sample of (*E*)-ethyl 2-{2-[2-(2,5-dimethoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10w**) (0.100 g), providing **2.11w** (0.087 g, 0.276 mmol, 82% based on thiolactam **2.3**) as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, *J* = 2.6 Hz, 1H), 6.83–6.78 (m, 2H), 5.92 (s, 1H), 4.31 (t, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.50 (p, *J* = 7.4 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.43, 152.94, 151.34, 141.95, 132.02, 127.16, 117.37, 115.68, 112.67, 111.28, 103.66, 59.30, 56.11, 55.70, 48.47, 26.81, 24.56, 14.07. HRMS (ESI): Found $[M + H]^+$ = 316.1542, $C_{18}H_{22}NO_4^+$ requires 316.1543.

Ethyl 6-(3,4-dimethoxyphenyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11x**): The



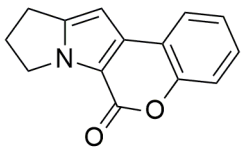
product was obtained according to the general method from a portion of the above impure sample of (*E*)-ethyl 2-{2-[2-(3,4-dimethoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10x**) (0.124 g), providing **2.11x** (0.105 g, 0.333 mmol, 90% based on thiolactam **2.3**) as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–6.98 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.95 (s, 1H), 4.33 (t, *J* = 7.2 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.51 (p, *J* = 7.4 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 4H).^{13}C NMR (101 MHz, $CDCl_3$) δ 161.34, 147.98, 147.94, 142.25, 137.25, 129.50, 121.89, 114.27, 113.42, 110.47, 103.46, 59.48, 55.91, 55.83, 48.93, 26.74, 24.50, 14.32. HRMS (ESI): Found $[M + H]^+$ = 316.1542, $C_{18}H_{22}NO_4^+$ requires 316.1543.

Ethyl 6-(tert-butyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylate (**2.11y**): The product was



obtained according to the general method from (*E*)-ethyl 2-{2-[2-(*tert*-butyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10y**) (0.0752 g, 0.394 mmol, providing **2.11y** (0.105 g, 0.320 mmol, 81%) as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1H), 4.29 and 4.26 (superimposed q, *J* = 7.2 Hz, and br t, *J* = 7.2 Hz, 4H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.42 (p, *J* = 7.4 Hz, 2H), 1.39 and 1.36 (superimposed s and t, *J* = 7.2 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.44, 148.45, 141.14, 114.87, 101.01, 59.82, 50.23, 32.79, 30.80, 26.74, 24.92, 14.79. HRMS (ESI): Found $[M + H]^+$ = 236.1640, $C_{14}H_{22}NO_2^+$ requires 236.1645.

9,10-Dihydrochromeno[4,3-b]pyrrolizin-6(8H)-one (**2.16**): The product was obtained

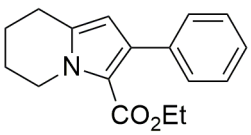


according to the general method from (*E*)-ethyl 2-{2-[2-(2-hydroxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**2.10z**) (0.100 g, 0.346 mmol), providing **2.16** (0.067 g, 0.298 mmol, 86%) as a white solid. M.p.: 233-234 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.47–7.09 (m, 3H), 6.33 (s, 1H), 4.38 (t, *J* = 7.2 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 2.62 (p, *J* = 7.3 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 155.04, 151.40, 148.85, 134.01, 127.40, 123.91, 122.85, 118.67, 117.24, 112.81, 94.47, 46.92, 27.45, 24.71. Spectroscopic data were in agreement with previously reported values.[124]

7.5 General method for the formation of ethyl 2-aryl-5,6,7,8-tetrahydroindolizine-3-carboxylates 2.26a–c

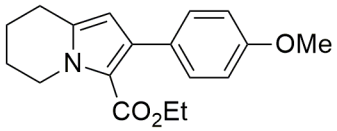
To a sealed microwave tube was added the enaminone **2.23** dissolved in absolute ethanol (5 cm^3/mmol). Flash silica gel (5 times mass of starting material) was added to the solution and the mixture was then irradiated under microwave conditions (50 W, 100 °C) for the stipulated time (see *Table 2.3, page 58)* while maintaining moderate stirring. The reaction mixture was then transferred to a suitable flash by washing with ethanol to ensure quantitative transfer of solvent and solids and the solvent was evaporated *in vacuo* and dried under vacuum to provide the material adsorbed onto silica (more silica was added as needed to provide a free-flowing, easy to handle material). This residue was then purified by column chromatography to provide the corresponding *ethyl 2-aryl-5,6,7,8-tetrahydroindolizine-3-carboxylates* **2.21**. The following three compounds were prepared and characterized.

Ethyl 2-(phenyl)-5,6,7,8-tetrahydroindolizine-3-carboxylate (**2.26a**): The product was



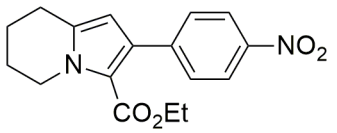
obtained according to the general method from (*E*)-ethyl 2-[2-(2-oxo-2-phenylethylidene)piperidin-1-yl]acetate (**2.23a**) (0.100 g, 0.348 mmol), providing **2.26a** (0.077 g, 0.286 mmol, 82 %) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.21 (m, 5H), 5.92 (s, 1H), 4.35 (t, *J* = 6.1 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.82 (t, *J* = 6.3 Hz, 2H), 2.03–1.93 (m, 2H), 1.88–1.77 (m, 2H), 1.03 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.77, 137.28, 135.66, 133.75, 129.58, 127.29, 126.33, 117.32, 108.71, 59.38, 45.96, 23.93, 23.63, 20.09, 13.86. HRMS (ESI): Found $[M + H]^+$ = 270.1483, $C_{17}H_{20}NO_2^+$ requires 270.1489.

Ethyl 2-(4-methoxyphenyl)-5,6,7,8-tetrahydroindolizine-3-carboxylate (**2.26b**): The product



was obtained according to the general method from (*E*)-ethyl 2{(2-[2-oxo-2-(4-methoxyphenyl)-ethylidene]piperidin-1-yl}acetate (**2.23b**) (0.100 g, 0.315 mmol), providing **2.26b** (0.698 g, 0.233 mmol, 74%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.81 (s, 1H), 4.26 (t, *J* = 6.1 Hz, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 2.74 (d, *J* = 6.4 Hz, 2H), 1.96–1.83 (m, 2H), 1.79–1.68 (m, 2H), 1.01 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.80, 158.36, 135.67, 133.49, 130.63, 129.64, 117.18, 112.79, 108.71, 59.35, 55.25, 46.00, 23.93, 23.65, 20.09, 14.03. HRMS (ESI): Found $[M + H]^+$ = 300.1587, $C_{18}H_{22}NO_3^+$ requires 300.1594.

Ethyl 2-(4-nitrophenyl)-5,6,7,8-tetrahydroindolizine-3-carboxylate (**2.26c**): The product was

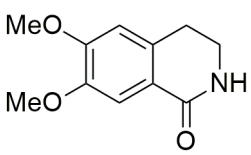


obtained according to the general method from (*E*)-ethyl 2-{2-[2-oxo-2-(4-nitrophenyl)-ethylidene]piperidin-1-yl}acetate (**2.23c**) (0.100 g, 0.283 mmol), providing **2.26c** (0.061 g, 0.195 mmol, 69%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.9 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 5.87 (s, 1H), 4.29 (t, *J* = 6.1 Hz, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 2.76 (t, *J* = 6.3 Hz, 2H), 2.02–1.82 (m, 2H), 1.83–1.64 (m, 2H), 1.00 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.16, 146.36, 144.48, 136.20, 131.13, 130.30, 122.63, 117.68, 108.67, 59.75, 46.20, 23.88, 23.50, 19.92, 13.97. HRMS (ESI): Found $[M + H]^+$ = 315.1341, $C_{17}H_{19}N_2O_4^+$ requires 315.1339.

7.6 Experimental methods pertaining to *Chapter 2, Section 2.3*

Experimental methods pertaining to the preparation of 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2H)-thione (**2.34**) are described in the publications included in *Chapters 4* and *5*. Those pertaining to the preparation of ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (**2.37**) are given below:

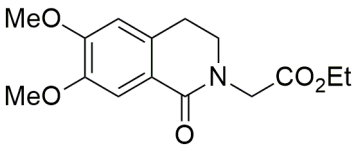
7.6.1 Preparation of 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (**2.35**).[125]



Potassium hydroxide (3.08 g, 53.2 mmol) was dissolved in water (15 cm^3) and swirled until homogenous and cooled to room temperature. This solution was then added to methanol (60 cm^3) and stirred at room temperature for 10 minutes. The reaction vessel was then cooled to 0ºC and hydrogen

peroxide (100 vols, 40 cm^3) was slowly added to the stirring mixture. 6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**2.34**) (4.75 g, 21.3 mmol) was then added portion-wise by spatula over a period of 20 minutes whilst maintaining vigorous stirring of the reaction mixture, which was then left to stir at 0ºC for 3 hours and was immediately filtered through a plug of Celite® and washed with methanol until all of the yellow colour had eluted from the filter cake. 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 (**2.35**) (3.07 g, 14.8 mmol, 70%) was isolated as a white crystalline solid. M.p.: 165–167 °C (Lit.[125] 174–177 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 1H), 6.89 (s, 1H), 6.68 (s, 1H), 3.56 (td, *J* = 6.7, 2.8 Hz, 2H), 2.92 (t, *J* = 6.7 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 166.66, 152.16, 148.03, 132.70, 121.45, 110.15, 109.61, 56.12, 56.05, 40.42, 27.99. Spectroscopic data were in agreement with previously reported values.[125,126]

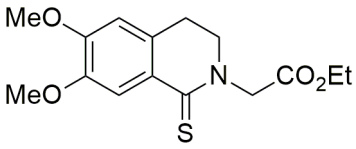
7.6.2 Preparation of ethyl 2-(6,7-dimethoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (**2.36**).[74,77]



6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (**2.35**) (4.00 g, 19.3 mmol) was dissolved in tetrahydrofuran (120 cm^3) by applying gentle heating with vigorous stirring. Then, the solution was cooled to 0 °C under an inert atmosphere of argon gas and 60% sodium hydride in paraffin oil (1.16 g, 28.99 mmol) was slowly added portion-wise. The reaction mixture was then heated to reflux for 2 hours and then again cooled to 0 ºC, before adding ethyl 2-bromoacetate (3.88 g, 2.6 cm^3, 23.16 mmol). The reaction mixture was warmed to room temperature and allowed to stir for 20 hours. The reaction mixture was then carefully quenched with water (100 cm^3) and the solution became clear. The solvent was evaporated and the crude residue was extracted into dichloromethane (2 × 100 cm^3), washed with water (100 cm^3) and brine (100 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 (**2.36**) (4.23 g, 14.2

mmol, 73%) as white crystals. M.p.: 88–90 °C (Lit.[77] 85–90 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 6.65 (s, 1H), 4.31 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 6H), 3.65 (t, *J* = 6.7 Hz, 2H), 2.99 (t, *J* = 6.7 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 166.66, 152.16, 148.03, 132.70, 121.45, 110.15, 109.61, 56.12, 56.05, 40.42, 27.99. Spectroscopic data were in agreement with previously reported values.[74,77].

7.6.3 Preparation of ethyl 2-(6,7-dimethoxy-1-thioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (**2.37**).[74,77]



To a solution of ethyl 2-(6,7-dimethoxy-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (**2.36**) (3.06 g, 10.4 mmol) in toluene (80 cm^3), under an inert atmosphere of argon gas, was added Lawesson's reagent (2.58 g, 6.23 mmol). The reaction was heated to reflux and stirred for 18 hours, after which time it had turned a deep blood-red colour. 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 (**2.37**) (2.40 g, 7.8 mmol, 75%) as a yellow solid, which could be seen eluting from the column as an obvious yellow band. M.p.: 122–125 °C (Lit.[77] 125–126 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 6.58 (s, 1H), 4.96 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.77 (t, *J* = 6.8 Hz, 2H), 3.00 (t, *J* = 6.7 Hz, 2H), 1.31 (t, *J* = 7.7 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 193.10, 167.95, 152.30, 147.64, 126.95, 126.77, 115.37, 108.59, 61.54, 57.34, 56.12, 56.09, 50.48, 27.49, 14.20. Spectroscopic data were in agreement with previously reported values.[74,77]

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Appendix: NMR Spectra of Lamellarins

Table A1. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for lamellarin G trimethyl ether with reported values 158

^{1}H and ^{13}C NMR spectra of lamellarin G trimethyl ether 159

Table A2. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for lamellarin A4 with reported values 160

^{1}H and ^{13}C NMR spectra of lamellarin A4 161

Table A3. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for lamellarin D trimethyl ether with reported values 162

^{1}H and ^{13}C NMR spectra of lamellarin G trimethyl ether 163

Table A4. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for lamellarin H with reported values 164

^{1}H and ^{13}C NMR spectra of lamellarin H 165

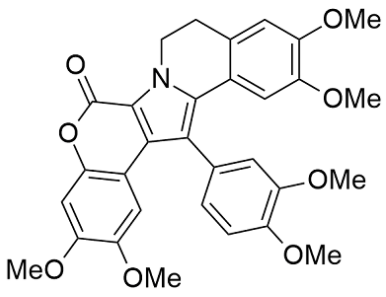
Table A5. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for lamellarin ε with reported values 166

^{1}H and ^{13}C NMR spectra of lamellarin ε 167

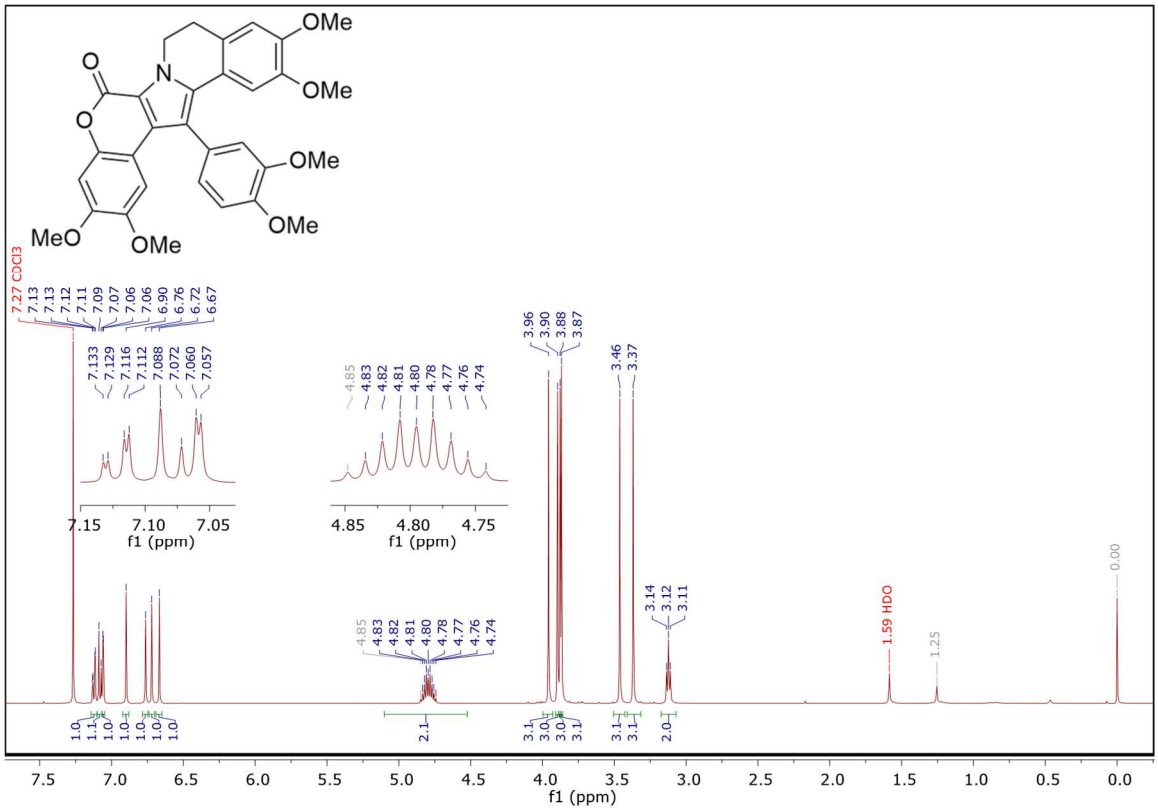
Table A6. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for dehydrolamellarin J with reported values 169

^{1}H and ^{13}C NMR spectra of dehydrolamellarin J 170

Table A1. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for lamellarin G trimethyl ether with reported values

^{1}H NMR DATA				**^{13}C NMR DATA**		
This work	Kumar *et al.*[1]	Colligs *et al.*[2]		This work	Kumar *et al.*[1]	Colligs *et al.*[2]
500 MHz	400 MHz	400 MHz		126 MHz	100 MHz	100 MHz
$CDCl_3$	$CDCl_3$	$CDCl_3$		$CDCl_3$	$CDCl_3$	$CDCl_3$
7.13 (dd, *J* = 8.5, 2.0 Hz, 1H)	7.11 (d, *J* = 8.2 Hz, 1H)	7.11 (dd, *J* = 8.1, 1.8 Hz, 1H)		155.5	155.6	155.5
7.08 (d, *J* = 8.0 Hz, 1H)	7.07 (d, *J* = 8 Hz, 1H)	7.07 (d, *J* = 8.1 Hz, 1H)		149.8	149.7	149.7
7.06 (d, *J*= 1.5 Hz, 1H)	7.04 (d, *J* = 2 Hz, 1H)	7.05 (d, *J* = 1.8 Hz, 1H)		149.0	149.0	149.0
6.90 (s, 1H)	6.90 (s, 1H)	6.90 (s, 1H)		148.9	148.84	148.8
6.76 (s, 1H)	6.76 (s, 1H)	6.78 (s, 1H)		148.8	148.81	148.8
6.72 (s, 1H)	6.71 (s, 1H)	6.71 (s, 1H)		147.5	147.5	147.5
6.67 (s, 1H)	6.66 (s, 1H)	6.66 (s, 1H)		146.1	146.1	146.1
4.79 (d × quintet, *J* = 6.6 Hz, 2H)	4.86-4.7 (m, 2H)	4.85-4.73 (m, 2H)		145.5	145.5	145.5
3.96 (s, 3H)	3.95 (s, 3H)	3.95 (s, 3H)		135.9	136.0	135.9
3.90 (s, 3H)	3.89 (s, 3H)	3.89 (s, 3H)		128.2	128.2	128.2
3.88 (s, 3H)	3.88 (s, 3H)	3.87 (s, 3H)		128.0	128.0	128.0
3.87 (s, 3H)	3.86 (s, 3H)	3.86 (s, 3H)		126.6	126.6	126.6
3.46 (s, 3H)	3.45 (s, 3H)	3.45 (s, 3H)		123.6	123.6	123.6
3.37 (s, 3H)	3.36 (s, 3H)	3.36 (s, 3H)		120.1	120.0	120.0
3.12 (t, *J* = 6.6 Hz, 2H)	3.12 (t, *J* = 7.2 Hz, 2H)	3.12 (m, 2H)		114.8	114.8	114.7
				114.0	114.0	114.0
				113.8	113.8	113.7
				111.9	111.8	111.9
				111.0	111.0	111.0
				110.3	110.3	110.3
				108.7	108.6	108.7
				104.5	104.5	104.5
				100.5	100.5	100.5
				56.3	56.24	56.2
				56.2	56.16	56.1
				56.1	56.1	56.0
				55.9	55.9	55.9
				55.5	55.5	55.4
				55.2	55.2	55.2
				42.4	42.4	42.4
				28.7	28.7	28.7

^{1}H NMR spectrum of lamellarin G trimethyl ether (500 MHz, $CDCl_3$)



^{13}C NMR spectrum of lamellarin G trimethyl ether (126 MHz, $CDCl_3$)

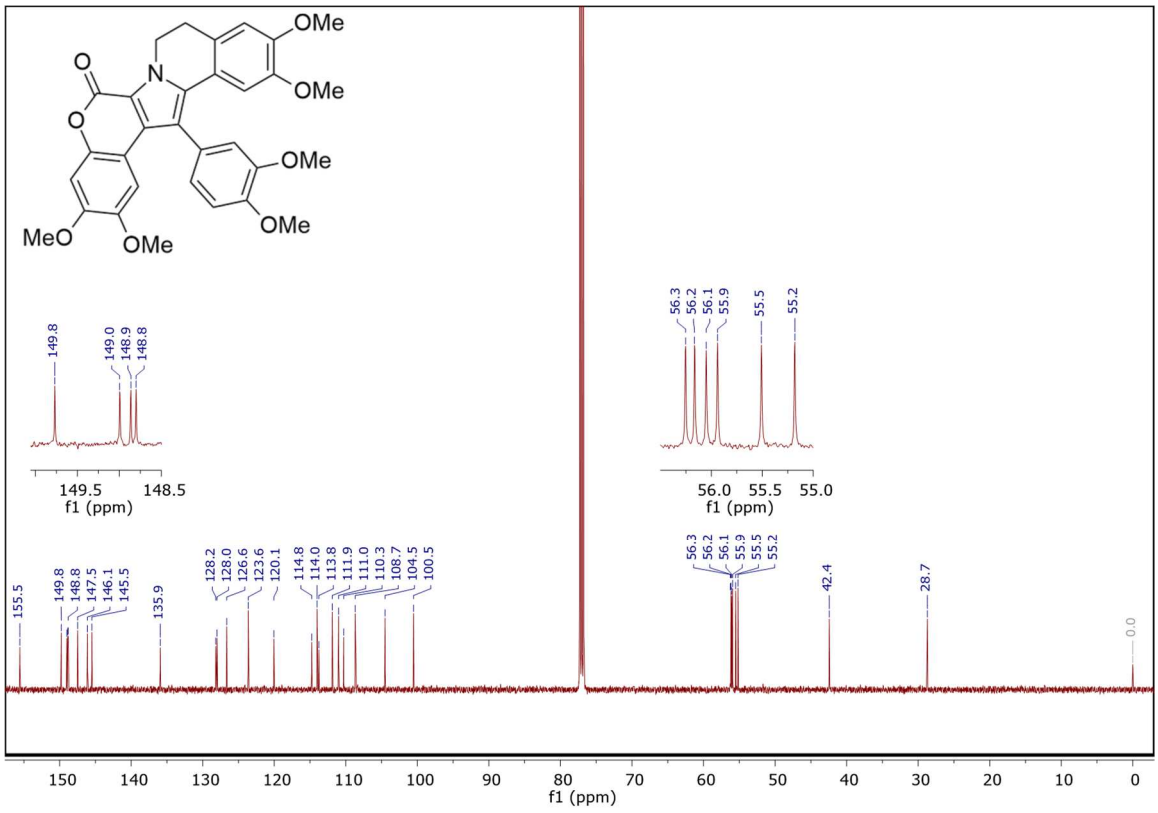
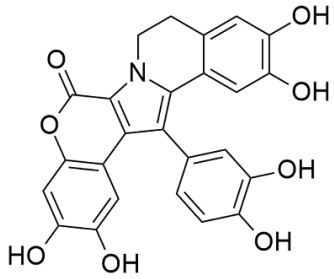
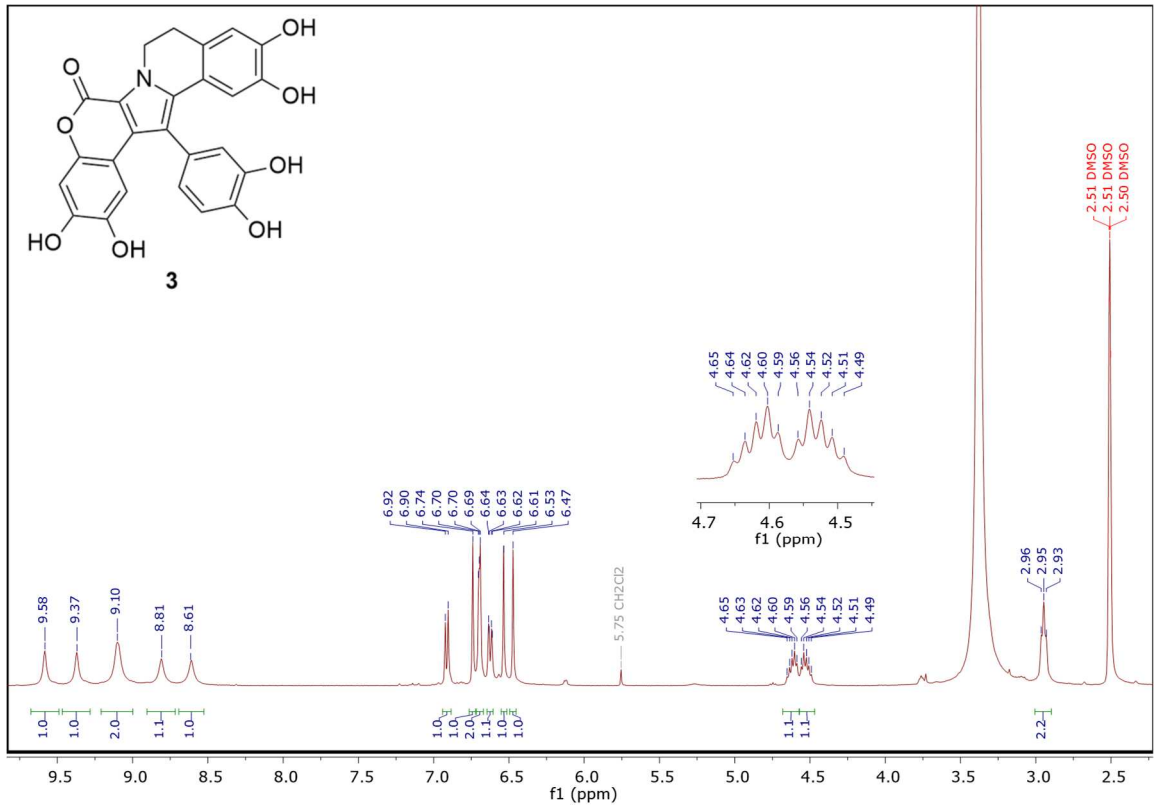


Table A2. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for lamellarin A4 with reported values

^{1}H NMR DATA				**^{13}C NMR DATA**		
This work	Kumar *et al.*[1]	Plisson *et al.*[3]		This work	Kumar *et al.*[1]	Plisson *et al.*[3]
400 MHz	400 MHz	600 MHz		101 MHz	100 MHz	125 MHz
DMSO-d_6	DMSO-d_6	DMSO-d_6		DMSO-d_6	DMSO-d_6	DMSO-d_6
9.58 (s, 1H)	9.55 (s, 1H)	9.58 (s, 1H)		154.9	154.9	154.4
9.37 (s, 1H)	9.37 (s, 1H)	9.37 (s, 1H)		146.5	146.5	146.0
9.11 (s, 2H)	9.10 (s, 2H)	9.10 (s, 1H)		146.4	146.4	145.9
		9.08 (s, 1H)		146.3	146.3	145.8
8.81 (s, 1H)	8.82 (s, 1H)	8.81 (s, 1H)		145.6	145.6	145.1
8.61 (s, 1H)	8.63 (s, 1H),	8.61 (s, 1H)		145.1	145.1	144.6
6.91 (d, J = 8.0 Hz, 1H)	6.87 (d, J = 8 Hz, 2H)	6.90 (d, 1H)		144.0	144.0	143.5
6.74 (s, 1H)	6.72 (s, 1H),	6.73 (s, 1H)		142.4	142.2	141.9
6.70 (d, J = 2.0 Hz, 1H)	6.67 (d, J = 2 Hz, 1H)	6.69 (d, 1H)		136.4	136.4	135.9
6.69 (s, 1H)	6.66 (s, 1H)	6.68 (s, 1H)		127.9	127.9	127.5
6.63 (dd, J = 8.0, 2.0 Hz, 1H)	6.59 (dd, J = 8, 1.6 Hz, 1H)	6.61 (d, 1H)		126.2	126.2	125.7
6.53 (s, 1H)	6.50 (s, 1H)	6.53 (s, 1H)		125.8	125.8	125.4
6.47 (s, 1H)	6.44 (s, 1H)	6.46 (s, 1H)		121.7	121.17	121.2
4.60 and 4.54 (2 × quintets, J *ca* 6.8 Hz, 2H)	4.63–4.47 (m, 2H)	4.60, 4.52 (2 × m, 2H)		119.0	118.9	118.5
2.95 (br t, J = 6.8 Hz, 2H)	2.92 (t, J = 6.4 Hz, 2H)	2.93 (t?, 2H)		117.9	117.9	117.4
				117.2	117.2	116.7
				115.5	115.5	115.0
				115.1	115.1	114.6
				113.9	113.8	113.4
				112.6	112.6	112.1
				109.7	109.7	109.2
				109.3	109.3	108.8
				103.7	103.6	103.2
				42.7	42.4	42.0
				28.3	28.3	27.8

^{1}H NMR spectrum of lamellarin A4 (400 MHz, DMSO-d_6)



^{13}C{^{1}H} NMR spectrum of lamellarin A4 (101 MHz, DMSO-d_6)

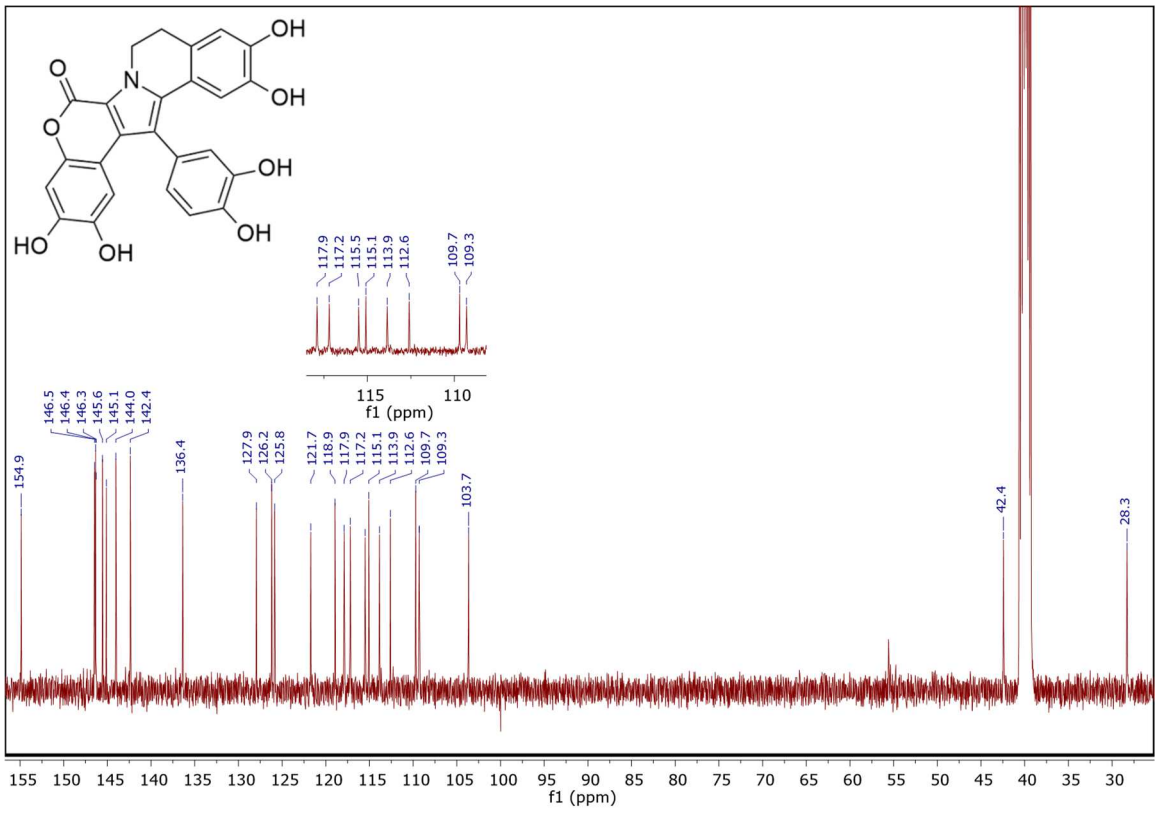
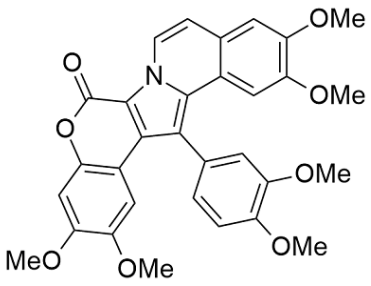
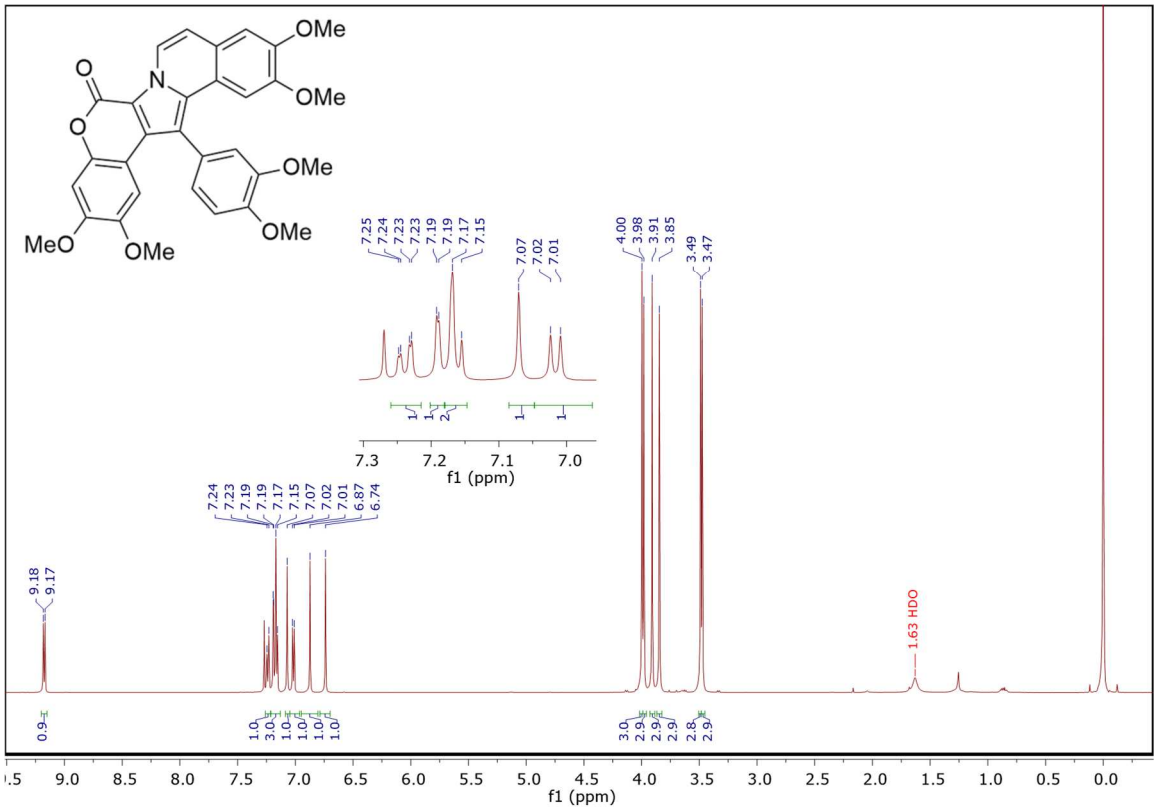


Table A3. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for lamellarin D trimethyl ether with reported values

^{1}H NMR DATA				**^{13}C NMR DATA**		
This work	Kumar *et al.*[1]	Dialer *et al.*[4]		This work	Kumar *et al.*[1]	Dialer *et al.*[4]
500 MHz	400 MHz	400 MHz		126 MHz	100 MHz	100 MHz
$CDCl_3$	$CDCl_3$	$CDCl_3$		$CDCl_3$	$CDCl_3$	$CDCl_3$
9.18 (d, *J* = 7.3 Hz, 1H)	9.26 (d, *J* = 7.6 Hz, 1H)	9.20 (d, *J* = 7.3 Hz, 1H)		155.4	155.5	155.6
7.24 (dd, *J* = 8.0, 1.5 Hz, 1H)	7.25 (dd, *J* = 8, 1.6 Hz, 1H)	7.23 (dd, *J* = 8.1, 1.9 Hz, 1H)		150.1	150.2	150.3
7.19 (d, *J* = 1.5 Hz, 1H)	7.19-7.17 (m, 3H)	7.17 (d, *J* = 1.9 Hz, 1H)		150.0	149.9	150.0
7.18-7.14 (m, 2H)		7.164 (s, 1H)		149.6	149.6	149.7
		7.162 (d, *J* = 8.1 Hz, 1H)		149.2	149.2	149.3
7.07 (s, 1H)	7.12 (s, 1H)	7.08 (s, 1H)		149.1	149.1	149.2
7.02 (d, *J* = 7.3 Hz, 1H)	7.08 (d, *J* = 7.6 Hz, 1H)	7.03 (d, *J* = 7.3 Hz, 1H)		146.7	146.8	146.8
6.87 (s, 1H)	6.97 (s, 1H)	6.90 (s, 1H)		145.5	145.6	145.7
6.74 (s, 1H)	6.76 (s, 1H)	6.73 (s, 1H)		134.4	134.5	134.5
4.00 (s, 3H)	4.02 (s, 3H)	3.99 (s, 3H)		129.3	129.5	129.5
3.98 (s, 3H)	4.01 (s, 3H)	3.98 (s, 3H)		128.3	128.2	128.4
3.91 (s, 3H)	3.92 (s, 3H)	3.89 (s, 3H)		124.8	124.9	125.0
3.85 (s, 3H)	3.90 (s, 3H)	3.87 (s, 3H)		124.2	124.1	124.3
3.49 (s, 3H)	3.49 (s, 3H)	3.48 (s, 3H)		123.3	123.4	123.4
3.47 (s, 3H)	3.48 (s, 3H)	3.47 (s, 3H)		119.1	119.1	119.2
				114.5	114.4	114.6
				112.3	112.4	112.5
				112.0	112.0	112.1
				110.9	111.0	111.1
				109.9	109.9	110.0
				107.8	107.9	108.0
				107.4	107.4	107.5
				105.3	105.3	105.4
				105.1	105.1	105.2
				100.5	100.6	100.7
				56.3	56.3	56.4
				56.2	56.2	56.3
				56.04	56.1	56.2
				55.97	56.0	56.1
				55.5	55.35	55.6
				55.2	55.2	55.4

^{1}H NMR spectrum of lamellarin D trimethyl ether (500 MHz, $CDCl_3$)



^{13}C{^{1}H} NMR spectrum of lamellarin D trimethyl ether (126 MHz, $CDCl_3$)

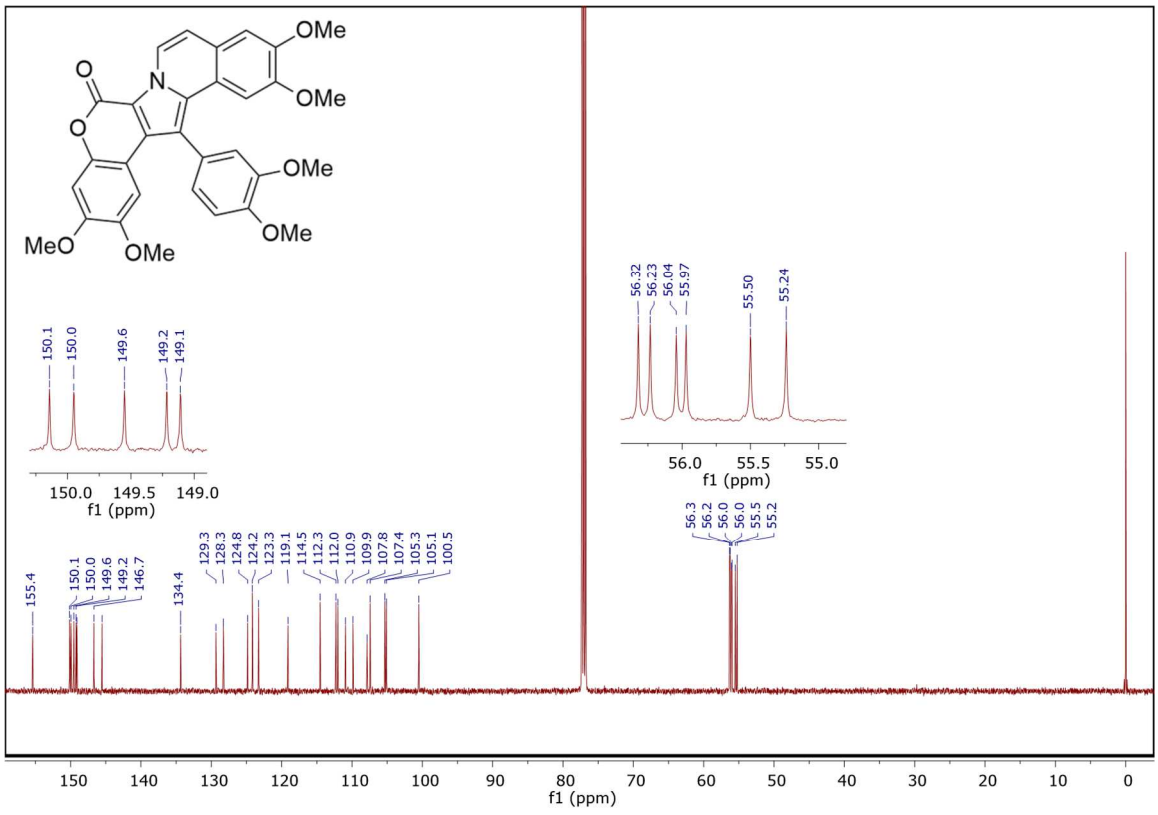
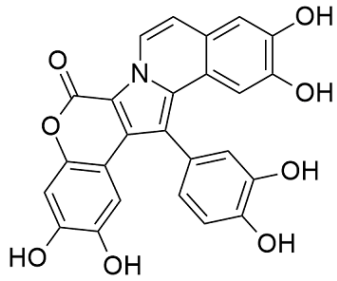
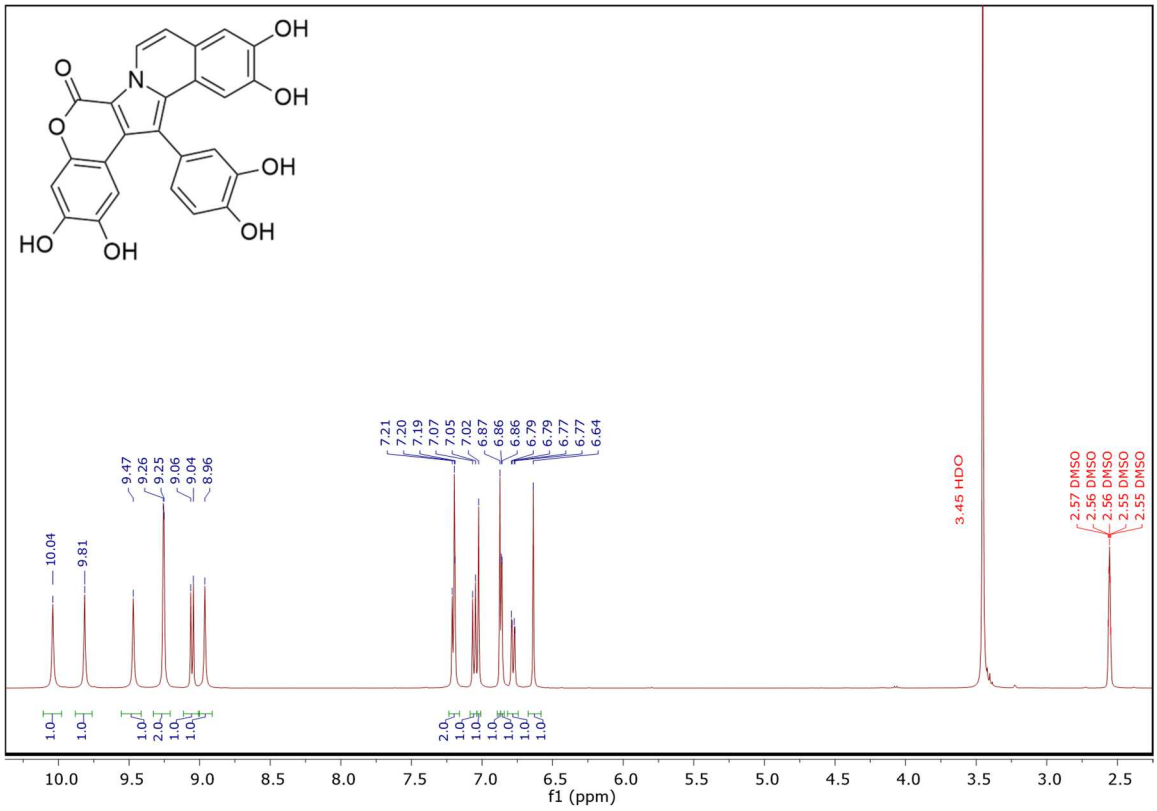


Table A4. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for lamellarin H with reported values

^{1}H NMR DATA				**^{13}C NMR DATA**		
This work	Kumar *et al.*[1]	Dialer *et al.*[4]		This work	Kumar *et al.*[1]	Dialer *et al.*[4]
400 MHz	400 MHz	400 MHz		101 MHz	100 MHz	100 MHz
DMSO-d_6	DMSO-d_6	DMSO-d_6		DMSO-d_6	DMSO-d_6	DMSO-d_6
10.04 (s, 1H)	10.00 (s, 1H)	9.99 (br s, 1H)		154.9	155.0	154.5
9.81 (s, 1H)	9.77 (s, 1H)	9.76 (br s, 1H)		148.1	148.1	147.7
9.47 (s, 1H)	9.43 (s, 1H)	9.42 (br s, 1H)		147.3	147.3	146.8
9.26 (s, 1H)	9.22 (s, 1H)	9.20 (br s, 2H)		147.0	147.0	146.6
9.25 (s, 1H)	9.21 (s, 1H)			146.7	146.7	146.2
9.05 (d, *J* = 7.3 Hz, 1H)	8.99 (d, *J* = 7.6 Hz, 1H)	8.99 (d, *J* = 7.3 Hz, 1H)		146.0	146.0	145.5
8.96 (s, 1H)	8.92 (s, 1H)	8.91 (br s, 1H)		145.7	145.7	145.3
7.21 (d, *J* = 6.0 Hz, 1H)	7.15 (d, *J* = 8 Hz, 1H)	7.14 (d, *J* = 7.3 Hz, 1H)		142.5	142.6	142.1
7.19 (s, 1H)	7.14 (s, 1H)	7.13 (s, 1H)		134.4	134.4	133.9
7.06 (d, *J* = 7.6 Hz, 1H)	6.99 (d, *J* = 8 Hz, 1H)	6.99 (d, *J* = 8.0 Hz, 1H)		129.3	129.3	128.9
7.02 (s, 1H)	6.96 (s, 1H)	6.95 (s, 1H)		125.9	125.9	125.4
6.87 (s, 1H)	6.83 (s, 1H)	6.81 (s, 1H)		124.2	124.2	123.8
6.86 (d, *J* = 2.0Hz, 1H)	6.79 (d, *J* = 2 Hz, 1H)	6.79 (d, *J* = 2.0 Hz, 1H)		121.9	121.9	121.4
6.78 (dd, *J* = 7.9, 2.0 Hz, 1H)	6.71 (dd, *J* = 8.0, 2.0 Hz, 1H)	6.71 (dd, *J* = 8.0, 2.0 Hz, 1H)		121.6	121.6	121.2
6.64 (s, 1H)	6.57 (s, 1H)	6.57 (s, 1H)		118.6	118.6	118.1
				118.0	118.0	117.6
				117.5	117.5	117.0
				113.0	113.0	112.6
				111.87	111.9	111.41
				111.85	111.9	111.39
				110.1	110.1	109.62
				110.0	110.0	109.56
				109.3	109.2	108.8
				106.8	106.8	106.3
				103.8	103.8	103.3

^{1}H NMR spectrum of lamellarin H (400 MHz, DMSO-*d*$_6$)



^{13}C{^{1}H} NMR spectrum of lamellarin H (101 MHz, DMSO-*d*$_6$)

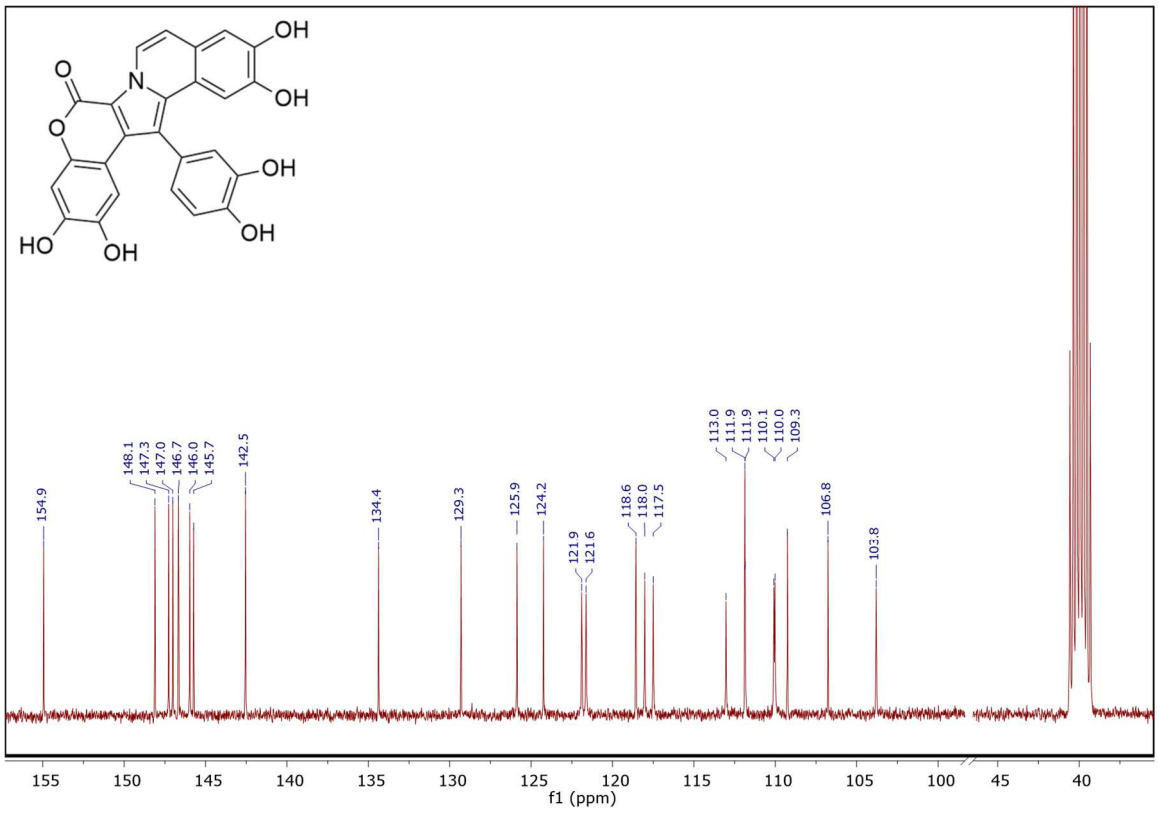
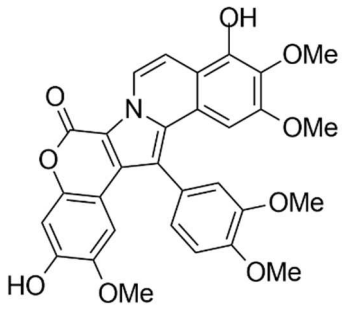
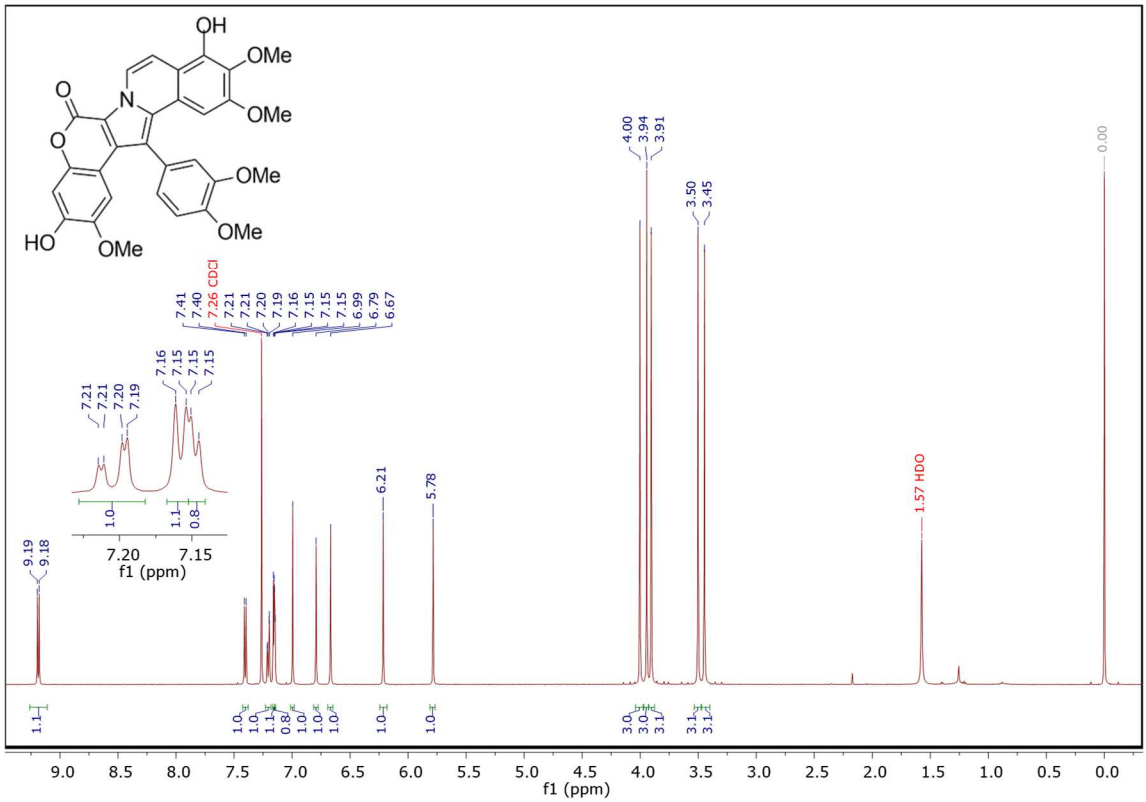


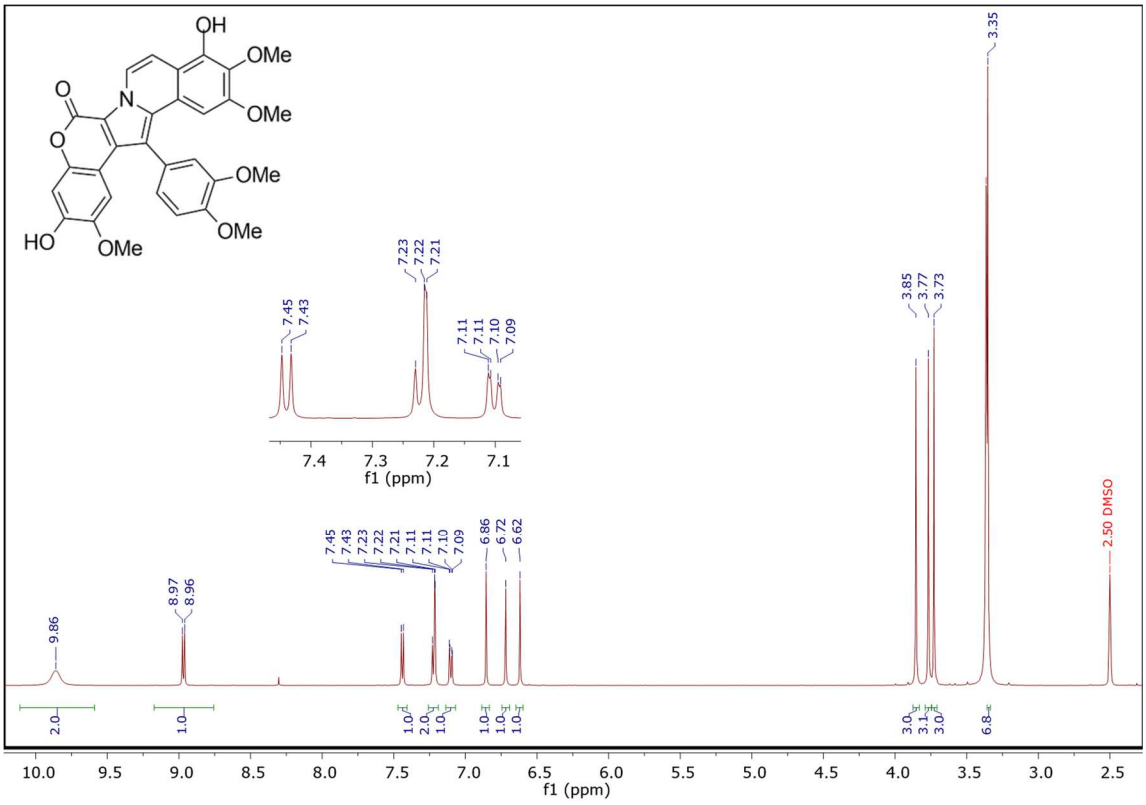
Table A5. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for lamellarin ε with reported values

^{1}H NMR DATA					**^{13}C NMR DATA**	
This work	Krishnaiah *et al.*[5]	This work	Ploypradith *et al.*[6]		This work	Ploypradith *et al.*[6]
500 MHz	400 MHz	500 MHz	200 MHz		126 MHz	50 MHz
$CDCl_3$	$CDCl_3$	DMSO-d_6	DMSO-d_6		DMSO-d_6	DMSO-d_6
9.19 (d, *J* = 7.5 Hz, 1H)	9.20 (d, *J* = 7.5 Hz, 1H)	9.86 (br s, 2H)	9.94 (br s, 1H)		154.7	154.8
7.40 (d, *J* = 7.5 Hz, 1H),	7.42 (d, *J* = 7.5 Hz, 1H)		9.90 (br s, 1H)		153.3	153.3
7.20 (dd, *J* = 8.1, 1.8 Hz, 1H)	7.20 (dd, *J* = 8.1, 1.8 Hz, 1H)	8.96 (d, *J* = 7.5 Hz, 1H)	8.99 (d, *J* = 7.6 Hz, 1H)		150.1	150.4
7.16 (d, *J* = 8.1 Hz, 1H)	7.15 (d, *J* = 8.1 Hz), 1H)	7.44 (d, *J* = 7.5 Hz, 1H)	7.45 (d, *J* = 7.6 Hz, 1H)		149.3	149.6
7.15 (d, *J* = 1.8 Hz, 1H),	7.14 (d, *J* = 1.8 Hz, 1H)	7.22 (d, *J* = 8.0 Hz, 1H)	7.25 (d, *J* = 8.0 Hz, 1H)		148.2	148.3
6.99 (s, 1H)	7.01 (s, 1H)	7.21 (d, *J* = 2.0 Hz, 1H)	7.20 (s, 1H)		146.6	146.7
6.79 (s, 1H)	6.79 (s, 1H)	7.11 (dd, *J*- 8.0, 2.0 Hz, 1H)	7.12 (d, *J* = 8.0 Hz, 1H),		146.0	146.1
6.67 (s, 1H)	6.67 (s, 1H)	6.86 (s, 1H)	6.86 (s, 1H)		144.9	145.1
6.21 (s, 1H)	6.23 (br s, 1H)	6.72 (s, 1H)	6.72 (s, 1H)		136.1	136.4
5.78 (s, 1H)	5.80 (br s, 1H)	6.62 (s, 1H)	6.62 (s, 1H)		133.6	133.7
4.00 (s, 3H)	4.00 (s, 3H)	3.85 (s, 3H)	3.85 (s, 3H)		129.1	129.2
3.94 (s, 3H),	3.94 (s, 3H)	3.77 (s, 3H)	3.75 (s, 3H)		127.6	127.8
3.91 (s, 3H)	3.90 (s, 3H)	3.73 (s, 3H)	3.71 (s, 3H)		123.9	124.1
3.50 (s, 3H)	3.50 (s, 3H)	3.35 (s, 6H)	3.37 (s, 6H)		121.2	121.4
3.45 (s, 3H)	3.44 (s, 3H)				121.1	121.2
					115.1	115.3
					114.9	
					113.2	113.7
					112.0	112.2
					108.4	108.6
					107.8	107.9
					107.2	107.4
					105.8	106.2
					104.0	104.2
					97.5	97.8
					60.8	60.9
					56.3	56.5
					56.2	56.4
					55.3	55.5
					54.9	55.1

^{1}H NMR spectrum of lamellarin ε (500 MHz, $CDCl_3$)



^{1}H NMR spectrum of lamellarin ε (500 MHz, DMSO-d_6)



^{13}C NMR spectrum of lamellarin ε (126 MHz, DMSO-d_6)

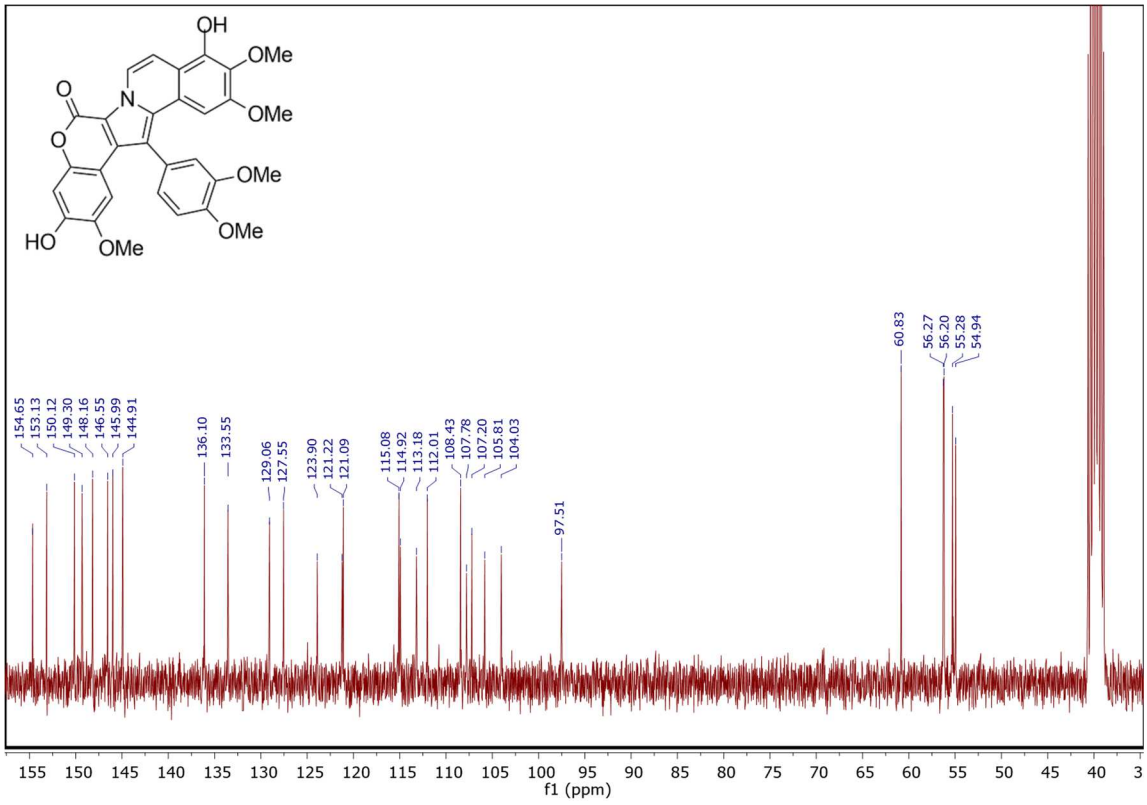
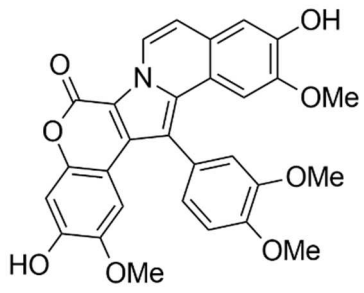
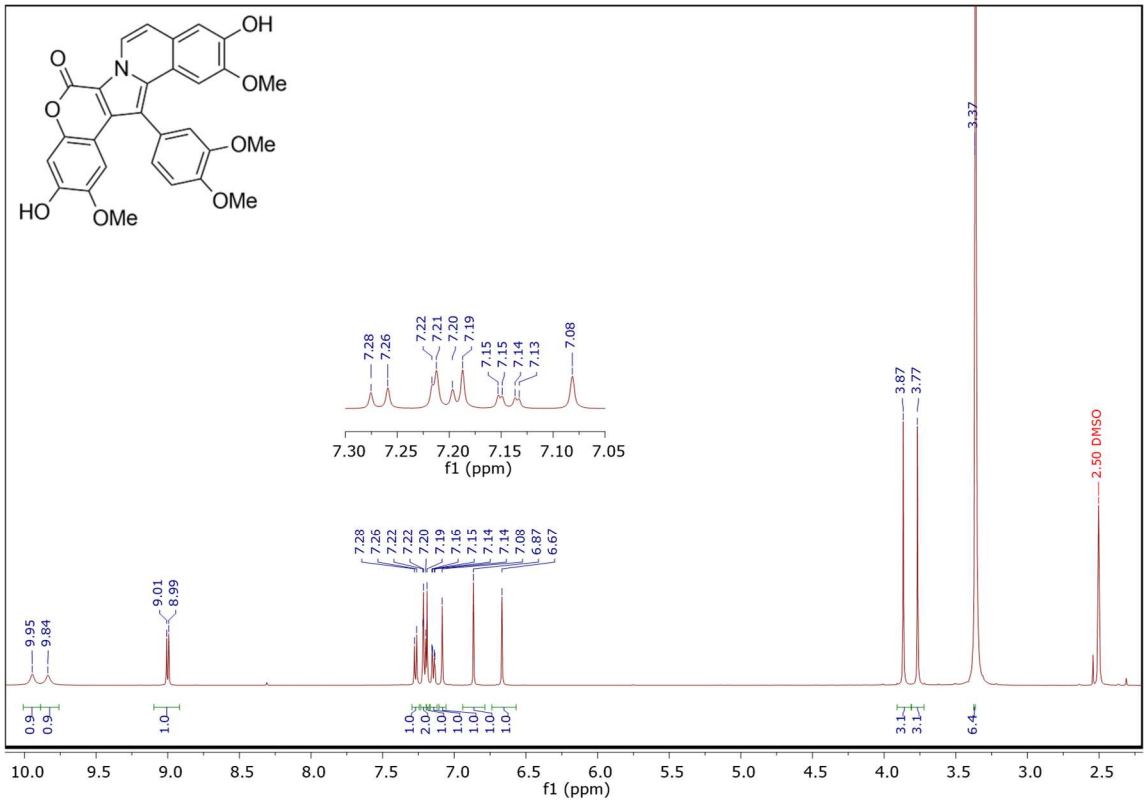


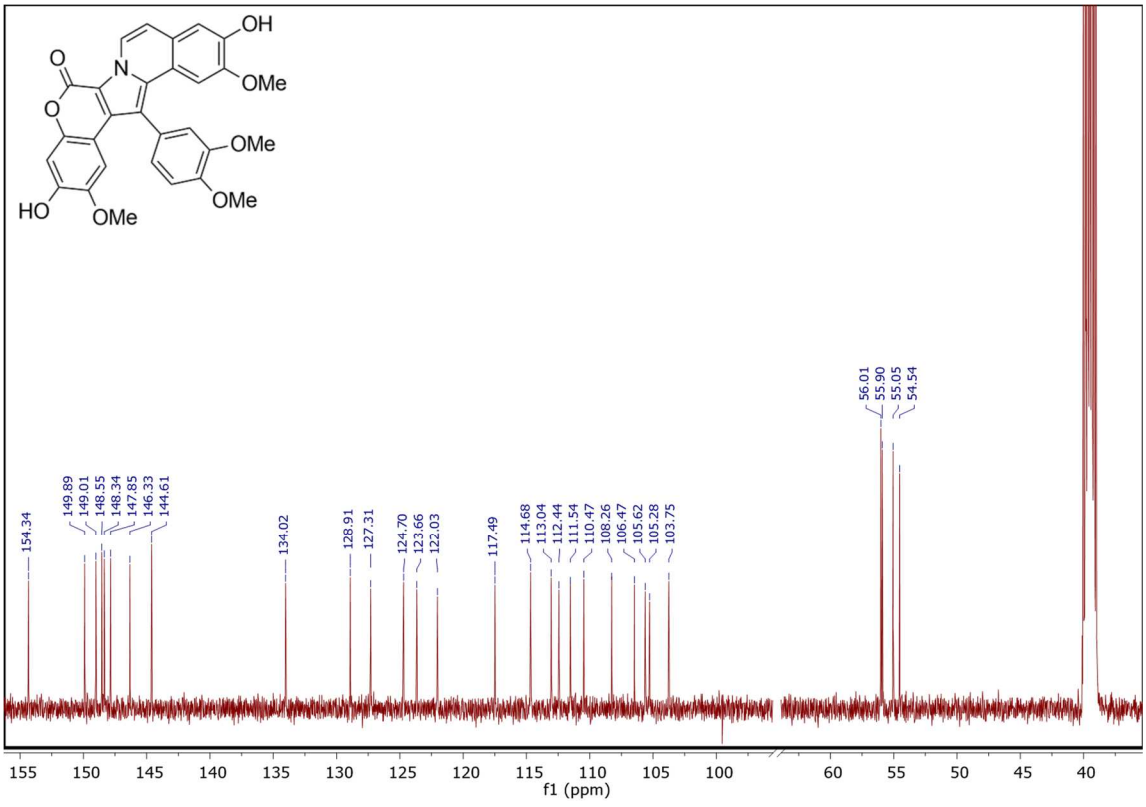
Table A6. Comparison of ^{1}H and ^{13}C NMR spectroscopic data for dehydrolamellarin J with reported values

^{1}H NMR DATA				**^{13}C NMR DATA**		
This work	Ohta *et al.*[7]	Bailly *et al.*[8]		This work	Ohta *et al.*[7]	Bailly *et al.*[8]
500 MHz	400 MHz	500 MHz		126 MHz	100 MHz	125 MHz
DMSO-d_6	DMSO-d_6	DMSO-d_6		DMSO-d_6	DMSO-d_6	DMSO-d_6
9.95 (s, 1H)	9.93 (br s, 1H)	9.97 (s, 1H)		154.3	154.2	154.3
9.84 (s, 1H)	9.84 (br s, 1H)	9.86 (s, 1H)		149.9	149.8	149.9
9.00 (d, J = 7.5 Hz, 1H)	9.02 (d, J = 7.4 Hz, 1H)	9.02 (d, J = 7.4 Hz, 1H)		149.0	148.9	149.0
7.27 (d, J = 8.0 Hz, 1H)	7.29 (d, J = 8.1 Hz, 1H)	7.29 (d, J = 8.2 Hz, 1H)		148.5	148.6	148.5
7.21 (d, J = 2.5 Hz, 1H) overlap	7.22 (d, J = 1.9 Hz, 1H)	7.23 (d, J = 7.4 Hz, 1H)		148.3	148.3	148.3
7.20 (d, J = 7.5 Hz, 1H)	7.22 (d, J = 7.4 Hz, 1H)	7.21 (d, J = 2.5 Hz, 1H)		147.8	147.9	147.8
7.19 (s, 1H)	7.20 (s, 1H)	7.20 (s, 1H)		146.3	146.2	146.3
7.14 (dd, J = 8.0, 2.0 Hz, 1H)	7.16 (dd, J = 8.1, 1.9 Hz, 1H),	7.16 (dd, J = 8.2, 2.5 Hz, 1H)		144.6	144.5	144.6
7.08 (s, 1H)	7.09 (s, 1H)	7.09 (s, 1H)		134.0	133.9	134.0
6.87 (s, 1H)	6.88 (s, 1H)	6.87 (s, 1H)		128.9	128.8	128.9
6.67 (s, 1H)	6.68 (s, 1H)	6.67 (s, 1H)		127.3	127.2	127.3
3.87 (s, 3H	3.87 (s, 3H)	3.86 (s, 3H)		124.7	124.6	124.7
3.77 (s, 3H)	3.77 (s, 3H)	3.76 (s, 3H)		123.7	123.6	123.6
3.37 and 3.36 (6H)	3.37 (s, 3H)	3.36 (s, 3H)		122.0	121.9	122.0
	3.36 (s, 3H)	3.35 (s, 3H)		117.5	117.4	117.4
				114.7	114.6	114.6
				113.0	113.0	113.1
				112.4	112.3	112.4
				111.5	111.4	111.5
				110.5	110.4	110.4
				108.3	108.2	108.2
				106.5	106.4	106.4
				105.6	105.6	105.6
				105.3	105.2	105.3
				103.8	103.7	103.7
				56.0	55.9	56.0
				55.9	55.8	55.8
				55.0	55.0	55.0
				54.5	54.4	54.5

^{1}H NMR spectrum of dehydrolamellarin J (500 MHz, DMSO-d_6)



^{13}C NMR spectrum of dehydrolamellarin J (126 MHz, DMSO-d_6)



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