NEW ROUTES TO ARYLATED AZABICYCLIC SYSTEMS FROM ENAMINONES, AND APPLICATIONS TO ALKALOID SYNTHESIS

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Degree of Doctor of Philosophy.

June 2008

Declaration

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

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13th day of June, 2008

Abstract

This thesis describes the application of enaminones towards the construction of azabicyclic systems. After a brief survey of indolizidine alkaloids bearing aromatic substituents an overview of the general strategies developed in laboratories at this University for the synthesis of alkaloids is given in Chapter 1. More specifically, the use of the Eschenmoser sulfide contraction for the construction of vinylogous amides is central to the work presented in this thesis.

Syntheses of nitrile containing indolizidine systems are described in chapter 2. Preliminary reactions towards this goal included the preparation of the vinylogous amide 3-{2-[(*E*)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}propanenitrile [157] by application of Eschenmoser's sulfide contraction reaction to the appropriate thiolactam 3-(2-thioxo-1-pyrrolidinyl)propanenitrile [168A]. In addition, the vinylogous amide was reduced to afford the key amino-ketone 3-[2-(2-oxo-2-phenylethyl)-1-pyrrolidinyl]propanenitrile [160]. Cyclization of this intermediate afforded the vinylogous amides *rel*-(7R,8aS)-7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179A] and *rel*-(7R,8aR)-7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179B] under specific reaction conditions. By altering the reaction conditions, an additional three products were isolated and characterized; a result that allowed for a step-by-step elucidation of the reaction mechanism for conversion of the amino-ketone 3-{2-[(*E*)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}propanenitrile [157] into the vinylogous amides *rel*-(7R,8aS)-7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179A] and *rel*-(7R,8aR)-7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179B]. In addition, approaches to sulfone-containing indolizidine systems were explored.

Approaches to the syntheses of the pyrrolidine 2-[1-(2-oxo-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [172A], a key precursor for the construction

of indolizidine systems as found in the alkaloid septicine are described in Chapter 3. In trying to achieve this strategy, we found that synthesis of the intermediate pyrrolidine 2-[1-(2-oxo-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [172A] proved to be non-trivial. Therefore the timing of reaction sequences and assembly of the *N*-alkyl chain was a necessary part of the strategy. A serendipitous discovery during this part of the research was the facile acid-induced cyclization of the vinylogous amides with an *N*-phenacyl group which lead to the formation of the pyrrolizine system.

Therefore, Chapter 4 describes some of the approaches that were attempted in constructing this class of nitrogen-containing compound. More specifically, we explored the ambident nucleophilicity and electrophilicity of vinylogous amides towards the construction of the pyrrolizine system. The chapter ends by extending this approach towards the potential synthesis of the lamellarin class of alkaloids by application of this novel cyclization strategy.

Acknowledgements

Personal acknowledgments

First and foremost, to my main supervisor, Professor J.P. Michael, for his guidance and wisdom in this project. Jo, I am forever grateful for all that you have done for me and you will never be forgotten.

In addition, I thank my co supervisor Professor W.A.L. van Otterlo for his valuable input with this project. Also, I had a great time discussing other projects with you and this has helped fuel my thirst for the subject.

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To all the researchers in the laboratories, I had a wonderful time interacting with you all and will miss you all dearly. Particular mention goes to Steve, Susan, Sameshnee and Stef as without you guys around I would have not had as much fun.

Finally, to my wife and life partner, Karin Morgans. It was my wife that suggested that I fulfill my ambitions of obtaining a PhD degree and without her emotional and financial support this would not have happened. Thank you Karin, I love you more than ever. Also, to my daughter Emma, whose cheerful disposition always puts a smile on my face whenever I am around her.

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The School of Chemistry and Education for the Teaching Assistantship bursaries, I thoroughly enjoyed my three years of lecturing.

I dedicate this thesis to:

My wife Karin Morgans

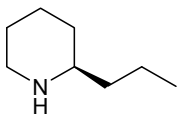
and to my daughter Emma Morgans

Contents

Chapter 1: Introduction, background and aims

1.1 Introduction

Alkaloids have been encountered in most orders of organisms from fungi to mammals, although most are found in the plant kingdom. They are structurally the most diverse class of secondary metabolites currently known. In the plant kingdom they range from the simple structures such as coniine [1] to complex structures such as strychnine [2]. In the animal kingdom, for example amphibians, complex structures such as the steroidal alkaloid batrachotoxin [3] have been isolated and characterized.



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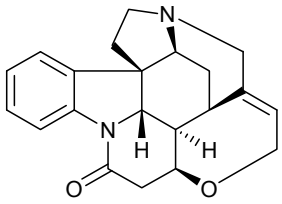

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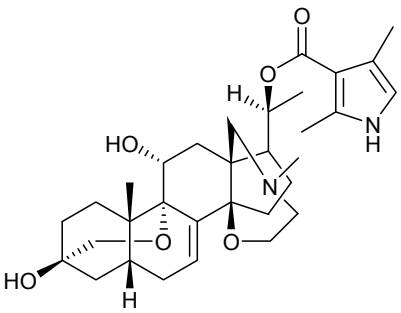

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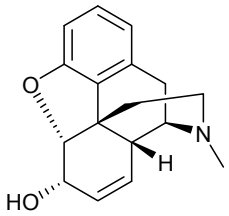

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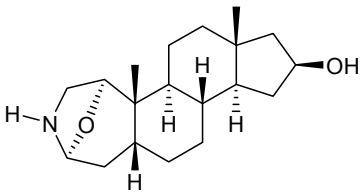


[5]

Many of the plant alkaloids seem to exhibit an allelochemical defence against herbivores, microorganisms and competing plants,[1] and it is this bioactivity that man has exploited which has, in part, led to the development of many of the modern pharmaceutical drugs as we know them today. One such drug is

codeine [4] which provides mild relief from pain for many people around the world every day.

Many attempts have been made to classify alkaloids. Bentley[2] was too general with: “natural product of a basic (*i.e*. alkaline) nature”. Ladenburg[3] suggested that “alkaloids were compounds derived from plants, with basic character, containing a nitrogen-based heterocyclic ring”. However, this definition excluded alkaloids found outside of the plant kingdom, for example the existence of the amphibian alkaloid samandarine [5] was established in 1866 when isolated from a European fire salamander.[4] A better definition was offered by Pelletier[5] who suggested that “an alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms”. Again, however, this definition is not perfect, since several acyclic amines and amides are generally classified as alkaloids. A more recent IUPAC definition of an alkaloid is a “… basic nitrogen containing compound (mostly heterocyclic) occurring mostly in the plant kingdom (but not excluding those from animal origin). Amino acids, peptides, nucleotides, nucleic acids, amino sugars and antibiotics are not normally regarded as alkaloids. By extension, certain neutral compounds biogenetically related to basic alkaloids are included.”[6] The vagueness of this definition should at least alert the reader to the large structural diversity of the alkaloids. In fact, this definition has at least attempted to embrace the classification of alkaloids by any one of the following means: biogenesis, structure, biological origin, and spectroscopic similarities.

A consideration of the basic carbon skeleton, for example, allows for the subdivision of alkaloids into groups with similar characteristics. One of these groups, alkaloids containing the 1-azabicyclo[4.3.0]nonane skeleton, is commonly known as the indolizidine alkaloids (Figure 1). And it is this class of alkaloid that we shall concentrate our efforts as it is most relevant to this Ph.D. thesis.

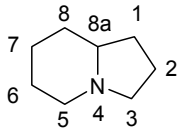


Figure 1: The indolizidine (1-azabicyclo[4.3.0]nonane) skeleton showing the conventional numbering system

This group of alkaloids is well represented in nature and a discussion confined to these alkaloids would be far too large an undertaking. Therefore, I am indebted to the work of the many people who have reviewed this class of alkaloid extensively. The indolizidine alkaloids and their syntheses are reviewed by Michael[7-16] and have been reviewed by others.[17-21]

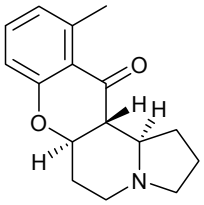
Indolizidine alkaloids are restricted to plants, some insects, amphibians (especially frogs), mammals, marine fauna, and a handful of micro-organism-derived alkaloids. For the purposes of this introduction, therefore, the reader will be taken on a brief survey of the bewildering richness, diversity and range of the indolizidine alkaloid natural product chemistry that forms the backdrop to this project. The examples given are by no means exhaustive, but merely a small selection of the complex array of the alkaloids found in this subclass of alkaloids.

1.2 Indolizidine alkaloids in Nature

1.2.1 Indolizidine alkaloids from plants

Although alkaloids are widely dispersed in the plant kingdom, they are not evenly distributed. By way of illustration, there are many examples of alkaloids in both the Leguminosae (lupin) and the Solanaceae (tomato, potato, tobacco) families, but they are almost absent in the gymnosperms (conifers), cryptograms (ferns and mosses), and monocotyledons (grasses).[22]

Alkaloids belonging to plants in the genus *Elaeocarpus* (family Elaeocarpaceae) have noteworthy structural diversity. A key feature of the *Elaeocarpus* alkaloids is that the nitrogen forms part of the indolizidine ring system. Furthermore, there are two basic structural types containing the indolizidine skeleton. There are those compounds in which the first (or A) ring is an aromatic or reduced aromatic ring, as exemplified by elaeocarpine [6]. Secondly, elaeokanine A [7], and elaeokanine C [8] represents those compounds which lack the first ring, but have a 4-carbon chain attached to the indolizidine unit. All of these compounds were the target of an early formal synthesis using the "Wits approach" developed in our laboratories, which is discussed in a later chapter section.[23, 24]



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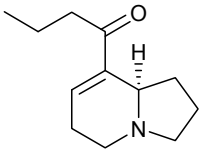

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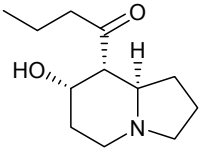
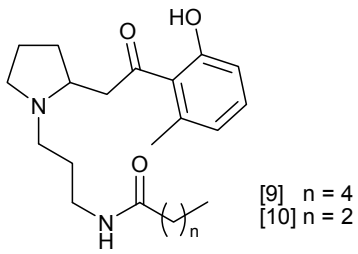


[8]

It should be noted that within this class of alkaloids exists the *Peripentadenia* alkaloids and they are considered *seco* derivatives of the indolizidine alkaloids given above. Representative examples are peripentadenine [9] and dinorperipentadenine [10], which were the targets of a successful Ph.D. project in these laboratories.[25] It should be mentioned that the Elaeocarpaceae family contains many other types of alkaloids, for example the substituted indole [11], but these will not be mentioned for reasons of brevity.



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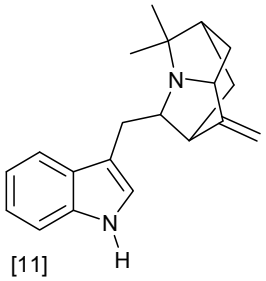
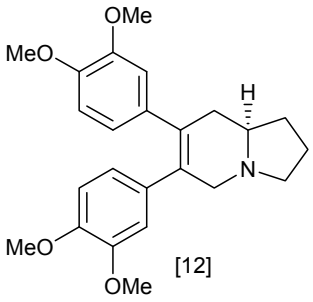


[11]

The earliest simple arylindolizidine alkaloid to be isolated is believed to be the diaryl-substituted septicine [12] in 1963, which was initially isolated from the tree *Ficus septic*a (Moraceae family), but subsequently found in another, quite different herb plant from the Asclepiadaceae (milkweed) family.[8, 26] This is one of many aryl indolizidines, including crepidamine [13] from the species *Dendrobium crepidatum* (family Orchidaceae) and ipalbidine [14] from the genus *Ipomoea* (family Convolvulaceae). Ipalbidine [14] was the target of an early formal synthesis using the "Wits approach" developed in our laboratories, which is discussed in a later chapter section.[27]



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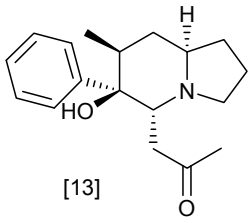

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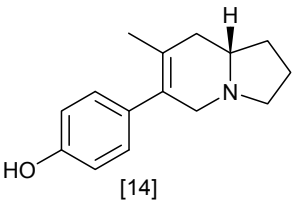
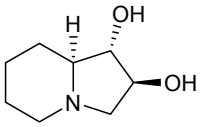


[14]

There also exists a class of hydroxylated indolizidine alkaloids. The high profile enjoyed by these alkaloids stems from their potent biological activity as inhibitors of glycosidases.[8] The alkaloid lentiginosine [15] is an example of a 1,2-dihydroxylated indolizidine alkaloid which was first isolated from the leaves of *Astragalus lentiginosus*.[28] The number of hydroxyl groups on the indolizidine framework is impressive, for example, the trihydroxylated alkaloid swainsonine [16], first isolated in 1973 from the fungus *Rhizoctonia*

leguminicola.[29] It has subsequently been found from plants belonging to the genera *Swainsona*, *Astragalus* and *Oxytropis* (family Leguminosae).[30] A polyhydroxylated version is castanospermine [17], which was originally isolated from seeds of the Australian legume *Castanospermum australe*.[31]



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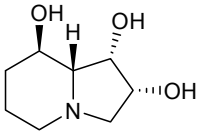

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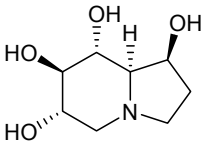
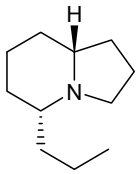


[17]

1.2.2 Indolizidine alkaloids from animals and insects

As mentioned earlier, the existence of the amphibian alkaloid samandarine [5] was established in 1866 when isolated from a European fire salamander. Subsequently, amphibians have proved to be a relatively rich source of alkaloids.[17] The amphibian alkaloids have proven to be remarkable in terms of both structure and biological activity. They include steroidal alkaloids, mono-, bi-, and tricyclic alkaloids, pyridines, indoles, imidazoles, morphine and guanidinium alkaloids, as well as several other miscellaneous alkaloids. The vast majority of the alkaloids have been isolated from skin extracts of the frogs of the family Dendrobatidae, of which the 5-monosubstituted indolizidine 167B [18] is an example. Interestingly, the 3,5-disubstituted indolizidine class within the amphibian alkaloids is not unique to amphibians as the 3,5-disubstituted indolizidine monomorine I [19] occurs in ants of the genera *Monomorium* and *Solenopsis*.[32] An example of the tricyclic class of alkaloids within the frog alkaloids is the alkaloid gephyrotoxin 287C [20].



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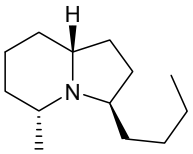

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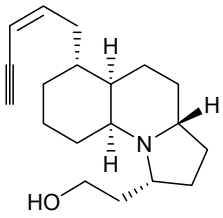

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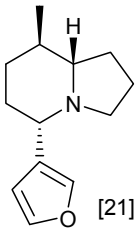
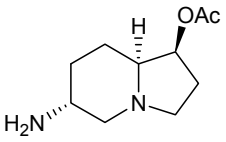


[21]

Other animals have structurally similar metabolites, in that the indolizidine skeleton is disubstituted, for example, the Nuphar indolizidine [21] which has been isolated from extracts of the scent glands of the Canadian beaver, *Castor fiber*.[33] The extracts are commercially valuable and its major use is as a fixative in perfumery.

1.2.3 Indolizidine alkaloids from fungal and microbial sources

Over the past two decades, a number of alkaloids have been isolated from the relatively unexplored areas of microorganisms. A number of simple indolizidine alkaloids from microorganisms have shown promising medicinal applications. Two of the most important examples to receive attention have been swainsonine [16] (which has also been found in higher order plants) and slaframine [22] isolated from the fungus *Rhizoctonia leguminicola*.[29] Slaframine [22] affects livestock, which develop 'slobber syndrome' when foraging on crops contaminated with the slaframine-producing fungus. Various species of *Streptomyces* have also been good sources of alkaloids, including the indolizidine alkaloid cyclizidine [23] isolated, among other sources, from *Streptomyces* NCIB 11649 and *Streptomyces* L-892.[34] A structurally related alkaloid indolizomycin [24] has also been isolated.[35]



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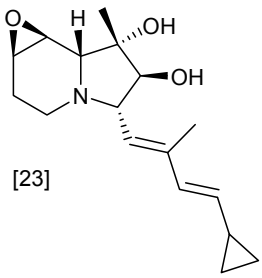

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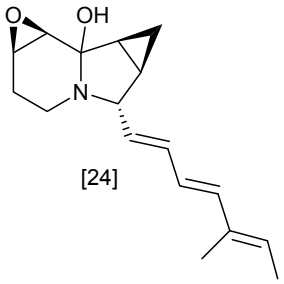
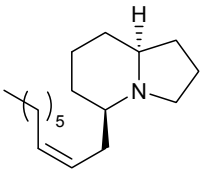


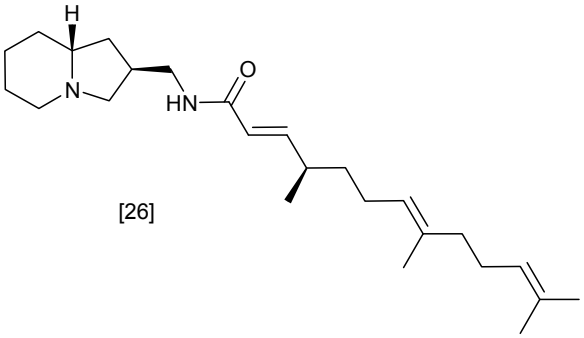
[24]

1.2.4 Indolizidine alkaloids from marine sources

A number of indolizidine alkaloids have been isolated from marine organisms, primarily from sponges, turnicates (sea-squirts), and nudibranchs. The discovery of antimicrobial activity of certain piclavines [25], of which only one is shown, isolated from the sea-squirt *Clavelina picta*, have prompted several syntheses of these alkaloids.[36] Much like the frog alkaloids, they are 5-monosubstituted alkaloids. Finally, another group of alkaloids worth mentioning for their historical significance is the stellettamides. These alkaloids were isolated from marine sponges belonging to the genus *Stelletta*, and stellettamide A [26] is credited as being the first simple indolizidine alkaloid to have been found in a marine organism.[37]



[25]



[26]

1.3 Arylated indolizidine alkaloids

In the following chapter sections, the two groups of alkaloids that have particular relevance to this project will be discussed. The first group is those that belong to the genus *Ipomoea*, pertaining to ipalbidine [14]. The second group is those from the Asclepiadaceae, Lauraceae, Leguminosae and Moraceae families, pertaining to septicine [12]. We have chosen these two compounds as they represent a class of *arylated* indolizidine alkaloids that we have an interest in. In each case, the alkaloids will be listed and the synthetic approaches towards them that have been used by previous workers in the field will be evaluated. This will be followed by a discussion of the "Wits approach" to alkaloid synthesis in these laboratories in developing a generalized route to alkaloid synthesis. Lastly, we will draw the themes of the chapter together by presenting the scope and aims of the project.

1.3.1 Occurrence and structural diversity of the arylated indolizidine alkaloids related to ipalbidine and septicine

The arylated indolizidine alkaloids from the genus *Ipomoea* are shown in Figure 2. Ipalbidine [14] is the aglycone of ipalbine [27], from which it is readily obtained, along with β-*D*-glucose, on hydrolysis in dilute acetic acid solution. Similarly, ipomine [28] when hydrolyzed with acetic acid gave ipalbidine [14], β-*D*-glucose, and p-coumaric acid. Isoipomine [29] which could not be separated from ipomine [28] was inferred to be the *cis*-*p*-coumaroyl isomer of ipomine [28] on the basis of ^{1}H NMR characterization. Furthermore, its existence stems possibly as a product of photoisomerization during isolation. The alkaloids methoxyipomine [30] and dimethoxyipomine [31] have been isolated from this genus. Interestingly, the alkaloid ipohardine [32], the aglycone of ipalbinium [33], has also been found in this genus and is one of a mere handful of naturally occurring indolizinium compounds.[38]

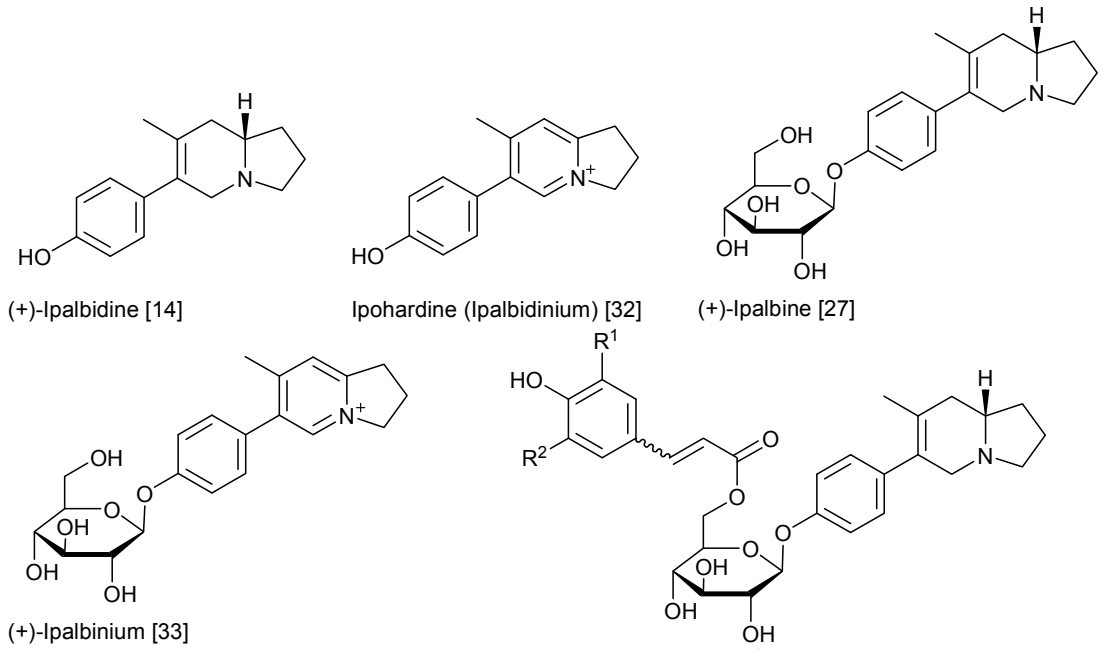
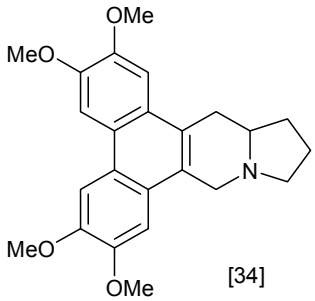


Figure 2: Arylated indolizidine alkaloids obtained from the genus Ipomoea

The arylated indolizidine alkaloid septicine [12] is a seco variant of the more populous phenanthroindolizidine class of alkaloids, of which tylophorine [34] and antofine [35] are commonly encountered examples.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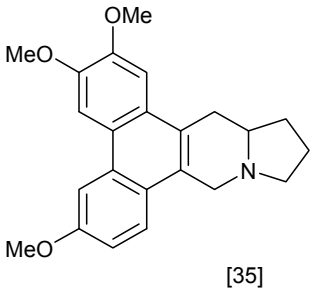
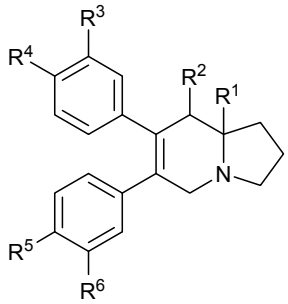

[35]

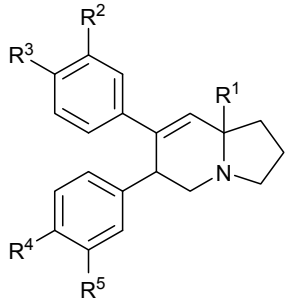
Therefore, a synthesis of septicine will constitute a formal synthesis of tylophorine as oxidative coupling with vanadium(V) oxyfluoride of the aryl units is known.[39] In addition, many of the compounds within the phenanthroindolizidine class have attracted synthetic interest owing to their

cytotoxicity towards cancer cells.[40-44] Our interest in septicine lies not with its biological activity but rather whether we can expand the range of natural products that have been generated through the “Wits approach” towards alkaloid synthesis (see section 1.4).

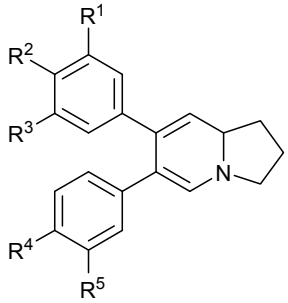
The secophenanthroindolizidine alkaloid class is relatively small and the structural diversity can be seen in the analogs of septicine which are given in Figure 3.



Septicine [12]: $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = R^6 = OMe$
Hispidine : $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = R^6 = OMe$
Secoantofine : $R^1 = R^2 = R^6 = H$, $R^3 = R^4 = R^5 = OMe$
6-*O*-Desmethyl secoantofine : $R^1 = R^2 = R^6 = H$, $R^3 = R^4 = OMe$, $R^5 = OH$
Phyllostemine : $R^1 = R^2 = R^6 = H$, $R^3 = R^5 = OH$, $R^4 = OMe$
Phyllosteminine [36]: $R^1 = R^6 = H$, $R^2 = R^5 = OH$, R^3-$R^4 = OCH_2O$
8a-Hydroxysepticine [40]: $R^1 = OH$, $R^2 = H$, $R^3 = R^4 = R^5 = R^6 = OMe$
Tylohirsuticine [37]: $R^1 = Me$, $R^2 = H$, $R^3 = OH$, $R^4 = R^5 = R^6 = OMe$
Tyloindicine B [38]: $R^1 = Me$, $R^2 = H$, $R^3 = OH$,$R^4 = OMe$, $R^5 = H$, $R^6 = OAc$



Tyloindicine F [41]: $R^1 = OH$, $R^2 = H$, $R^3 = R^4 = R^5 = OMe$
Tyloindicine G [42]: $R^1 = OH$, $R^2 = R^3 = R^4 = R^5 = OMe$
Tyloindicine H : $R^1 = H$, $R^2 = OH$, $R^3 = R^4 = R^5 = OMe$



Tyloindicine I : $R^1 = R^2 = R^3 = R^4 = R^5 = OMe$
Tyloindicine J [39]: $R^1 = OMe$, $R^2 = R^4 = OH$, $R^3 = H$, $R^5 = OAc$

Figure 3: Some arylated indolizidine alkaloids found in the Asclepiadaceae, Lauraceae, Leguminosae and Moraceae families

The first group shows the unsaturation at the usual $\Delta^{6,7}$-position while the last two groups, constituting most of the tyloindicines, are found in other positions. In addition, some other notable features include the 8-hydroxy position in phyllosteminine [36]; the angular methyl groups in tylohirsuticine [37] and tyloindicine B [38]; the acetoxy substituent in tyloindicine B and J [39], and the bridgehead hydroxy group in 8a-hydroxysepticine [40], tyloindicine F [41] and G [42].

1.3.2 Reported syntheses of ipalbidine and septicine

This section will include some of the synthetic approaches research groups have developed towards the construction of arylated indolizidine alkaloids related to ipalbidine and septicine. These compounds have been exceedingly popular targets for total synthesis; therefore it is not surprising that several common approaches have been developed. In this review we have chosen to classify the documented syntheses of these compounds on the basis of the mode of ring closure of the aryl-substituted ring (Figure 4). Disconnection G does not fit in this pattern but it makes use of some rather imaginative chemistry and deserves mention. It should be mentioned that this class of alkaloids has been exhaustively reviewed[8-16] and what will follow will be a brief survey of the crucial ring forming reactions.

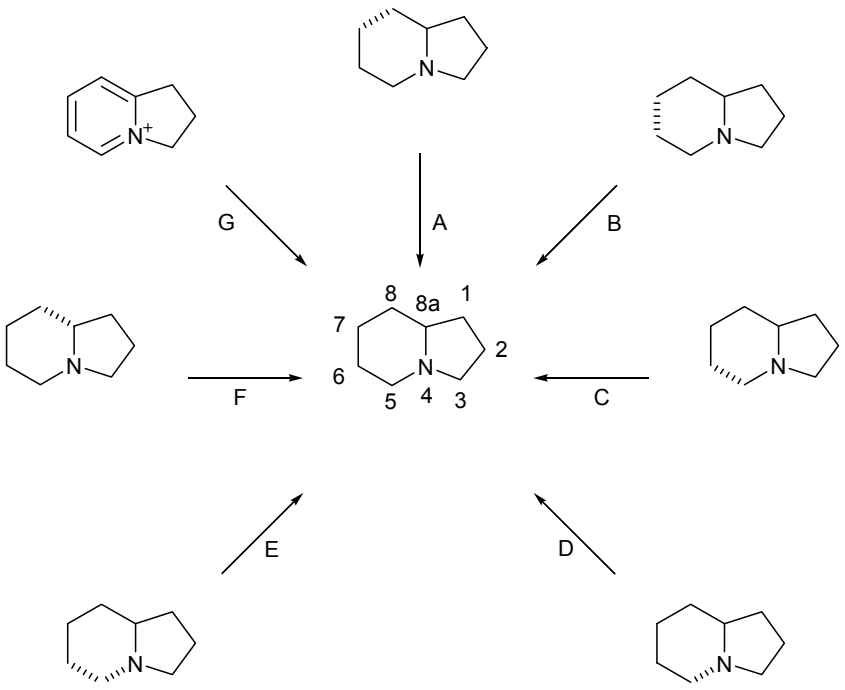
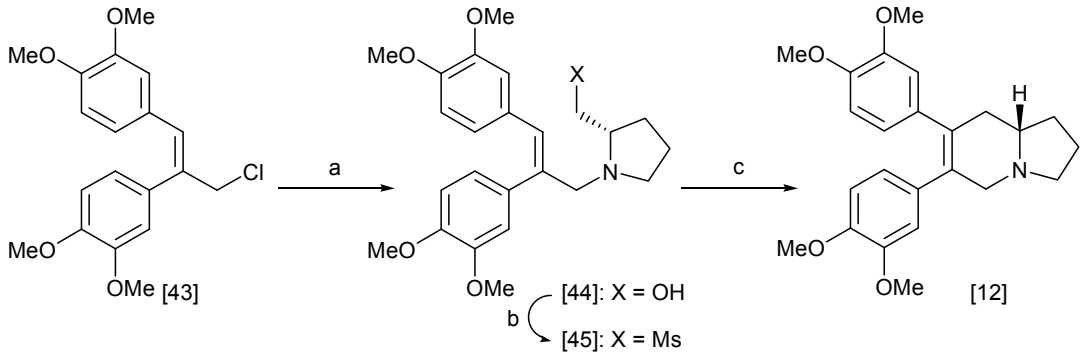


Figure 4: Disconnections to the indolizidine skeleton

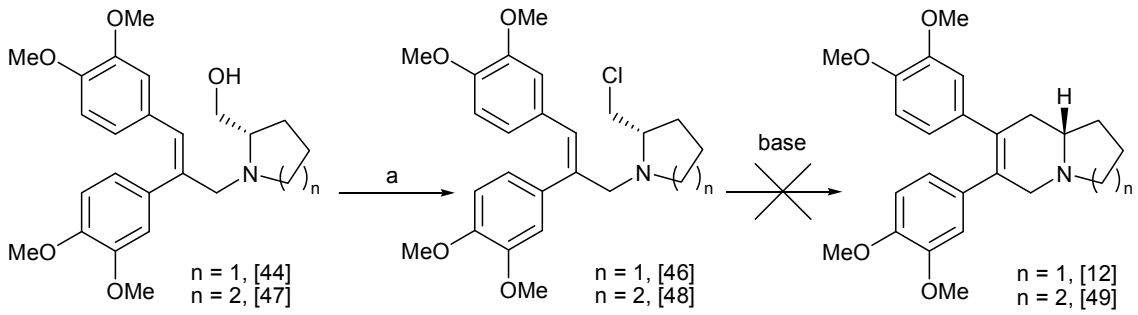
Disconnection A: The $C_7 – C_8$ annulation approach

This disconnection is largely historical in that it was allegedly the first route by which optically active septicine was made (Scheme 1).[45] Briefly, a three step synthesis produced the chloride [43], which was condensed with *L*-prolinol to give the alcohol [44]; a strategy which was to confer optical activity on the product. Reaction of this alcohol with methanesulfonyl chloride gave the mesylate [45] which underwent base-mediated cyclisation with sodium hydride to give septicine. However, this work has been somewhat discredited by Banwell and Sydnes,[46] who expected to use this final cyclisation protocol to prepare julandine [49] and septicine (Scheme 2).



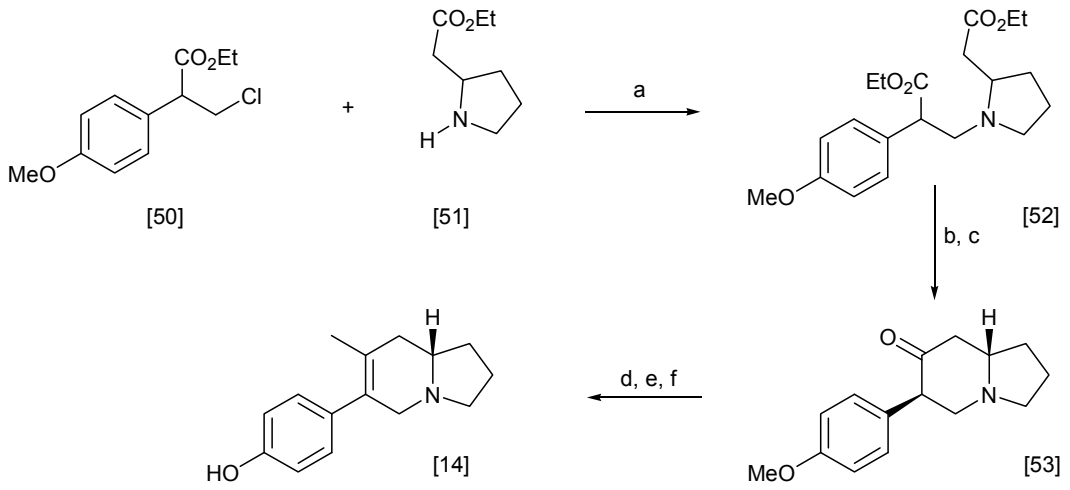
Scheme 1: Part of an alleged synthesis of (-)-septicine by Russel and Hunzicker.[45] Reagents: (a) *L*-Prolinol, DMF, pyridine; (b) MsCl, pyridine; (c) NaH, DMF.

For the julandine synthesis; in an entirely different manner, the alcohol [47] was prepared and attempts to mesylate this compound, in fact, produced the chloride [48] and not the expected mesylate. Attempts at cyclising this chloride under a variety of conditions met with failure. Concerned by this unexpected event, a reinvestigation was undertaken of the synthesis of septicine using the same alcohol precursor [44] as that of Russel and Hunzicker. Again, attempts to mesylate this compound produced the chloride [46]. Finally, attempts at cyclising the chloride failed to give any of the desired product.



Scheme 2: Part of a failed synthesis of septicine and julandine by Banwell and Sydnes.[46] Reagent: (a) MsCl, pyridine.

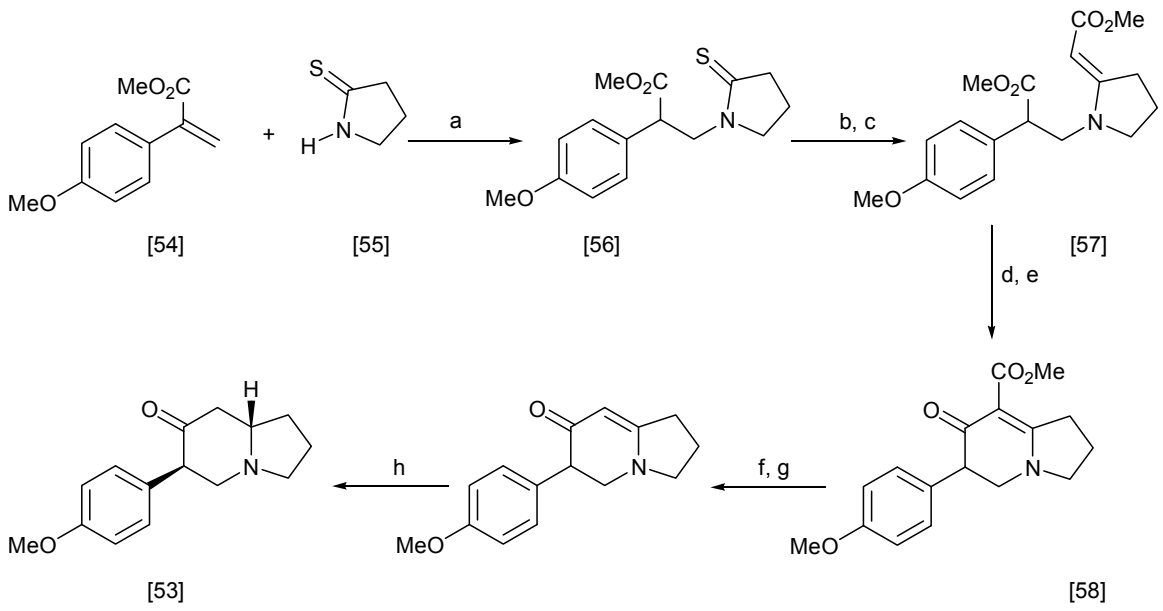
A generalized route to both ipalbidine and septicine has been reported by Govindachari and co-workers[47, 48] which makes use of the Dieckmann condensation to accomplish the pivotal ring closing reaction (Scheme 3). Briefly, a two step synthesis generated the appropriate phenethyl chloride [50] in 38% yield. It was then *N*-alkylated with the pyrrolidinylacetate [51] to afford the crucial diester [52] in an unsatisfactory 19% yield. Condensation followed by hydrolysis and decarboxylation gave the ketone [53] in a respectable 42% overall yield over the three steps. This ketone intermediate is the focal point of many formal syntheses of ipalbine, some of which will be mentioned later. Treatment with methyllithium then generated a carbinol which was dehydrated with sulphuric acid to give *O*-methylipalbidine in a moderate yield of 35% over the two steps. Demethylation of the derived methyl ether then gave ipalbidine; curiously, no yield was offered for this transformation.[47]



Scheme 3: Part of a synthesis of ipalbidine by Govindachari and co-workers.[47] Reagents: (a) K_2CO_3, toluene, Δ; (b) Ph_3CK, Et_2O - THF; (c) 2*M* HCl, Δ; (d) MeLi, Et_2O - THF, then 2*M* HCl; (e) H_2SO_4, H_2O, Δ; (f) $AlBr_3$, CS_2.

Ketone [53] was the focus of a formal synthesis of ipalbidine by Howard, Gerrans and Michael[27] (Scheme 4). A Michael addition of the acrylic ester [54] on to the nitrogen atom of pyrrolidine-2-thione [55] afforded the thione [56] in a yield of 82%. Eschenmoser sulfide contraction then afforded the vinylogous

urethane [57] in 74% yield. The saturated ester moiety was then converted into a mixed anhydride, and ring closure of which to afford [58] was effected by taking advantage of the enamine-like nucleophilicity of the vinylogous urethane. Product [58] was obtained in a yield of 77%. A series of hydrolysis, decarboxylation and reduction transformations completed the synthesis of ketone [53] in a yield of 72% over the three steps. This completed a formal synthesis of ipalbidine. The overall yield for the preparation of the ketone [53] from pyrrolidine-2-thione was 33% for the 8 steps of the synthesis. This is a notable achievement as it is an order of magnitude more efficient when compared to Govindachari and co-workers who prepared this intermediate in 3% over 5 steps!

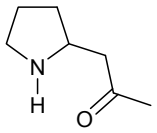


Scheme 4: Formal synthesis of ipalbidine by Howard, Gerrans and Michael.[27] Reagents: (a) NaOH (cat.), THF; (b) $BrCH_2CO_2Me$, THF; (c) Ph_3P, NEt_3, MeCN; (d) NaOH, H_2O, Δ; (e) $ClCO_2Me$, Bu_4NI (cat.), THF; (f) KOH, H_2O, Δ; (g) HCl, H_2O, Δ; (h) $LiAlH_4$, THF.

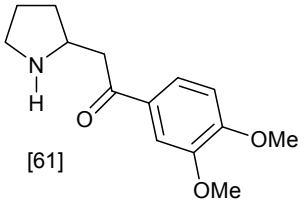
Disconnection B: The $C_6 - C_7$ annulation approach

It is believed that Δ^1-pyrroline [59] or biological equivalents are probably the first heterocyclic species in the biogenetic sequence of events, functioning as electrophiles for the attachment of side chains at their 2 positions.[7] Notable examples that conform to this hypothesis are the known natural products norhygrine [60] and ruspolinone [61].

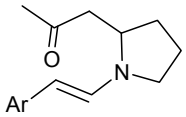
[59]



[60]

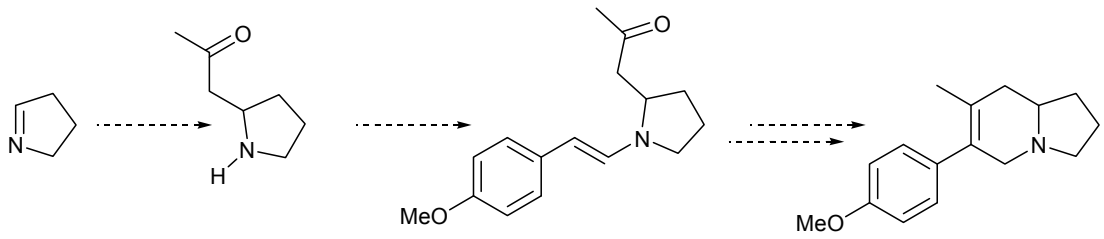


[61]



[62]

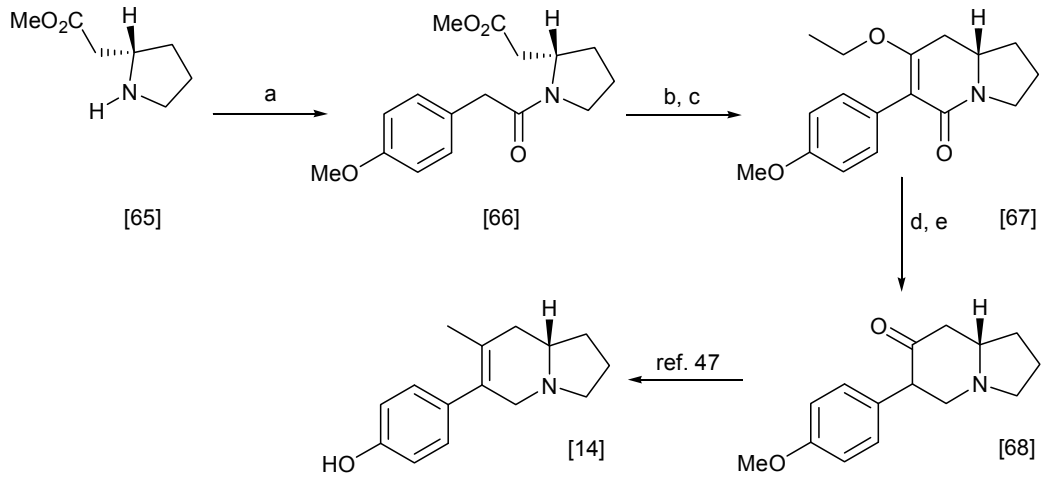
Herbert and co-workers[49] have fashioned syntheses of these two alkaloids by the oxidation of 1,4-diaminobutane with pea-seedling diamine oxidase in the presence of β-keto acids. Furthermore, these compounds could be elaborated into bicyclic alkaloids through the intermediacy of enamines [62] when condensed with suitably functionalized arylacetaldehydes.[50] For example, the synthesis of *O*-methylipalbidine [64] was achieved in an overall yield of 68% by this methodology. The synthesis commenced with preparation of norhygrine, by condensation of acetoacetic acid with Δ^1-pyrroline, generated from 1,4-diaminobutane by pea-seedling diamine oxidase. *N*-Alkylation with 4-methoxyphenylacetaldehyde gave the corresponding amino-ketone [63] with an alkyl carbonyl group. The amino-ketone was conveniently cyclised and dehydrated in methanol solution to give *O*-methylipalbidine (Scheme 5).



[59] [60] [63] [64]

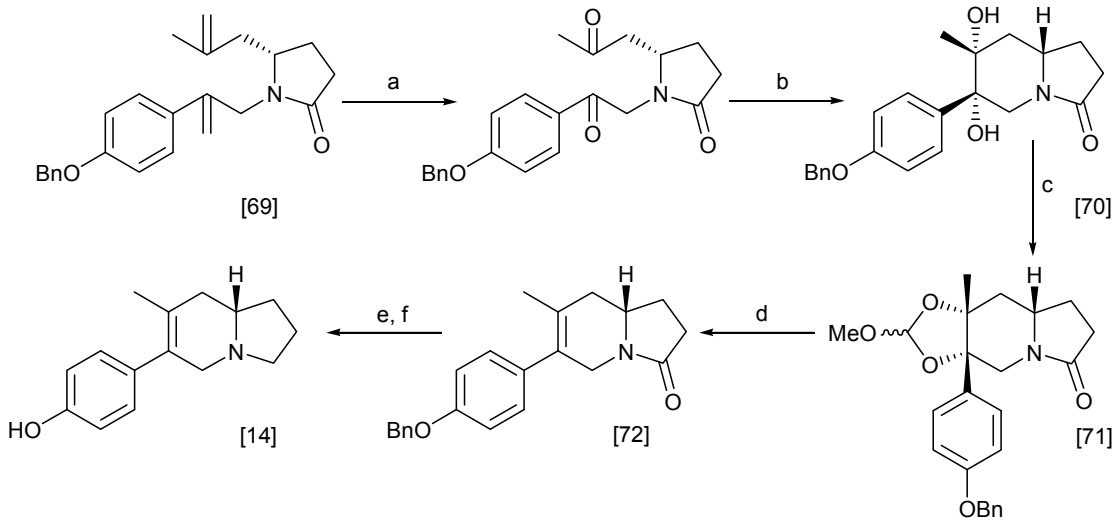
Scheme 5: Part of a biogenetically patterned synthesis of O-methylipalbidine by Herbert and co-workers[49]

Rather similar approaches have been devised which rely on base-induced intramolecular cyclisation of keto amides.[51-55] A radical-induced intramolecular cyclisation approach has also been disclosed.[56] Of the base-induced cyclisations of keto amides, Liu and co-workers[38, 57] deserve mention as theirs is the first enantioselective synthesis of (*S*)-(+)-ipalbidine [14]. The reaction sequence is summarized in Scheme 6. The pyrrolidinylacetic ester [65] was *N*-acylated with the appropriate acid chloride, as shown, to give the keto amide [66] in a yield of 96%. Intramolecular cyclisation was accomplished with sodium hydride and the resulting ketone was trapped as its enol ether [67]. The formation of the enol ether was a strategy that allowed for the reduction of the amide, the resulting ketone [68] from which was liberated after treatment with ethanolic HCl. The synthesis was then completed by following the same protocol as devised by Govindachari and co-workers.[47]



Scheme 6: Part of an enantioselective synthesis of ipalbidine by Liu and co-workers.[38] Reagents: (a) *p*-$MeOC_6H_4CH_2COCl$, K_2CO_3, MeCN; (b) NaH, THF; (c) $(EtO)_3CH$, HCl, EtOH; (d) AlH_3, THF; (e) HCl, H_2O.

Another approach using this disconnection strategy makes use of a McMurry coupling. Honda and co-workers[58] synthesized the chiral olefin [69] with a view of transforming it to the lactam [72] by way of a ring closing metathesis (Scheme 7). This failed regardless of whether they used the well-known Grubbs, Hoveyda or Schrock catalysts. Therefore, a new strategy using McMurry coupling was initiated. Ozonolysis of the olefin followed by McMurry coupling gave the *cis*-diol [70] as the major product, along with another minor diastereomer. The diol was transformed into the orthoformate [71] which, upon pyrolysis in refluxing acetic anhydride, liberated the lactam [72]. Conventional synthetic transformations then completed the synthesis of ipalbidine.

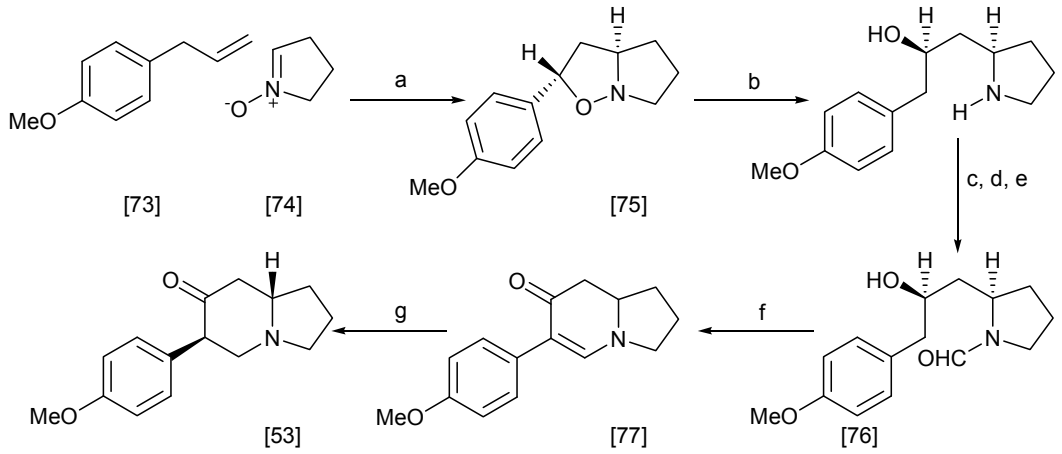


Scheme 7: Part of a synthesis of ipalbidine [14] by Honda and co-workers. [58]

Reagents: (a) O_3, MeOH, -78 °C, then Me_2S workup; (b) $TiCl_3(THF)_3$, Zn-Cu, DME, Δ; (c) $CH(OMe)_3$, PPTS, CH_2Cl_2; (d) Ac_2O, Δ; (e) $LiAlH_4$, THF; (f) H_2, 5% Pd/C, MeOH.

Disconnection C: The $C_5 – C_6$ annulation approach

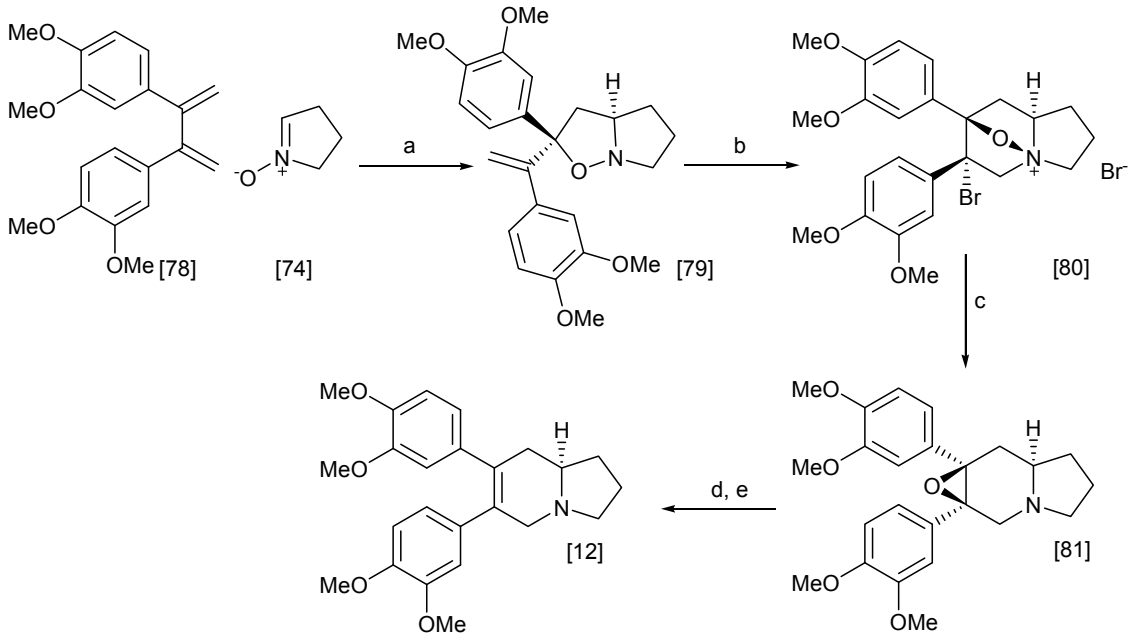
The interest in this disconnection is worthy of mention as it employs nitrone cycloaddition to create intermediates that can be *N*-acylated and cyclised (Scheme 8).This route may be exemplified by the formal synthesis of ipalbidine by Iiada and co-workers.[59, 60] The dipolarophile [73] was reacted with Δ^1-pyrroline *N*-oxide [74] to give isoxazolidine [75] as the sole product. Hydrogenation followed by several synthetic transformations led to the *N*-formyl product [76]. This *N*-acylated product was then cyclised under basic conditions to afford the vinylogous amide [77]. Selective reduction of the olefin led to the much synthesized ketone [53] and therefore completed the formal synthesis of ipalbidine.



Scheme 8: Formal synthesis of ipalbidine by Iida and co-workers.[59] Reagents: (a) Toluene, Δ; (b) H_2, 5% Pd-C, MeOH; (c) HCO_2H, toluene, Δ; (d) NH_3, MeOH;(e) Collins reagent, CH_2Cl_2; (f) $(^tBuO)_3Al$, xylene, Δ; (g) Li, NH_3, THF.

Disconnection D: The $C_4 – C_5$ annulation approach

This disconnection has also made use of the nitrone methodology, with one notable difference. Up to now we have seen examples that make use of "condensation" reactions for the ring annulations. Iwashita and co-workers[61], in fact, used an intramolecular addition reaction to set up the indolizidine framework (Scheme 9). The bisarylbutadiene [78] acted as the dipolarophile with Δ^1-pyrroline *N*-oxide [74] to give the isoxazolidine [79] as the major product. Treatment with bromine then afforded the salt [80] in good yield; presumably by attack of the lone-pair of electrons on the nitrogen onto the *in situ* generated halonium ion intermediate. Reduction with lithium aluminum hydride led to regeneration of [79] in 43% yield and also, more importantly, to the formation of the epoxide [81] in 24% yield. Removal of the epoxide, as shown, then afforded septicine [12] in 74% yield.

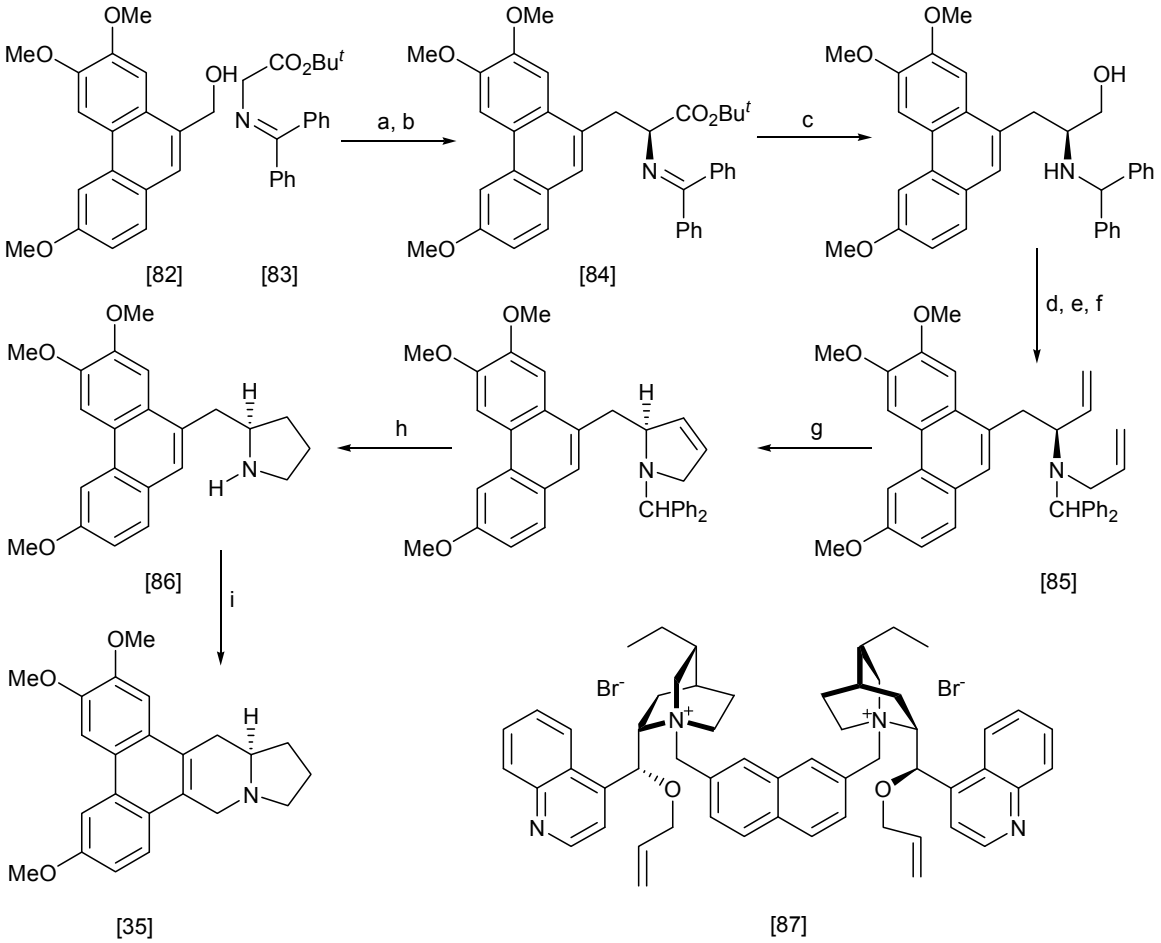


Scheme 9: Synthesis of septicine by Iwashita and co-workers.[61] Reagents: (a) Toluene, Δ; (b) Br_2, $CHCl_3$; (c) $LiAlH_4$, THF; (d) Me_3SiCl, $CHCl_3$; (e) Zn, HOAc-EtOH (1:10), Δ.

Disconnection E: The $N_4 – C_6$ annulation approach

Thus far we have used the numerous syntheses of ipalbidine and septicine to illustrate the various disconnection approaches in constructing the indolizidine skeleton. In this example we shall briefly show the ring annulation process from the enantioselective synthesis of antofine [35] by Kim and co-workers (Scheme 10).[62, 63] This route is somewhat different from other methodology in the construction of the indolizidine skeleton for three reasons. Firstly, it differs in that the phenanthrene core is already constructed. Most syntheses have first built the secophenanthroindolizidine analogue and then done an oxidative coupling reaction to build the phenanthrene core.[39, 64, 65] Secondly, chirality is induced through catalysis, and not from a "nature's pool" source (see discussion in Disconnection B). Lastly, both the five- and six-membered rings are constructed; in general the pyrrolidine ring or variations thereof, is the starting point of the synthesis.

Kim and co-workers developed two alternative but complementary routes for the synthesis of antofine [35], and only one will be shown here (Scheme 10). The bromide, generated from the known phenanthryl alcohol [82], was alkylated with the Schiff base [83] in the presence of the phase transfer catalyst [87] to afford the chiral imine [84] in good yield and enantioselectivity (97%, 96% ee). This reaction then obviously conferred optical activity onto the product. A series of transformations comprising a reduction, an oxidation, a Wittig olefination and an allylation afforded the diene [85]. The pyrrolidine [86] was constructed by way of a ring closing metathesis followed by simultaneous reduction of the olefin and protecting group. Therefore, the construction of the pyrrolidine core was completed. Annulation to give the indolizidine framework was completed by a Pictet-Spengler reaction with formaldehyde, thereby completing the synthesis of (–)-antofine. This final cyclisation reaction could arguably fall under disconnection C, however since the intermediate *N*-adduct was not isolated we have chosen to keep this disconnection as a class of its own.

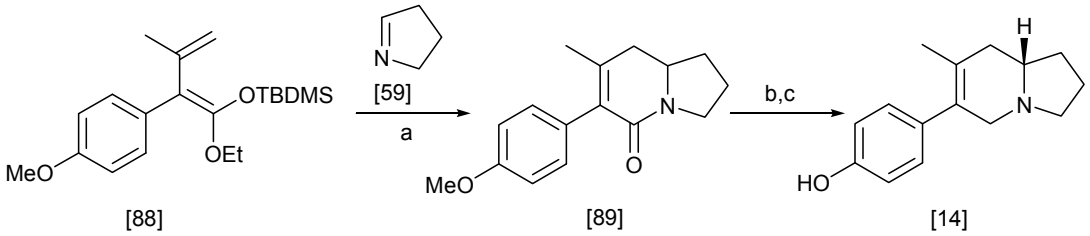


Scheme 10: Enantioselective synthesis of antofine [35] by Kim and co-workers.[62] Reagents: (a) CBr_4, PPh_3, MeCN; (b) [83], [87] (2 mol %), aq. NaOH (50%), toluene-$CHCl_3$; (c) $LiAlH_4$, THF; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (e) $Ph_3PMe^+I^-$, *n*-BuLi, TH;F (f) Allyl bromide, K_2CO_3, DMF; (g) Grubbs II, CH_2Cl_2; (h) H_2, 10% Pd/C, EtOH; (i) HCHO, HCl, EtOH, Δ in the dark.

Disconnection F: The C_8 – C_{8a} annulations approach

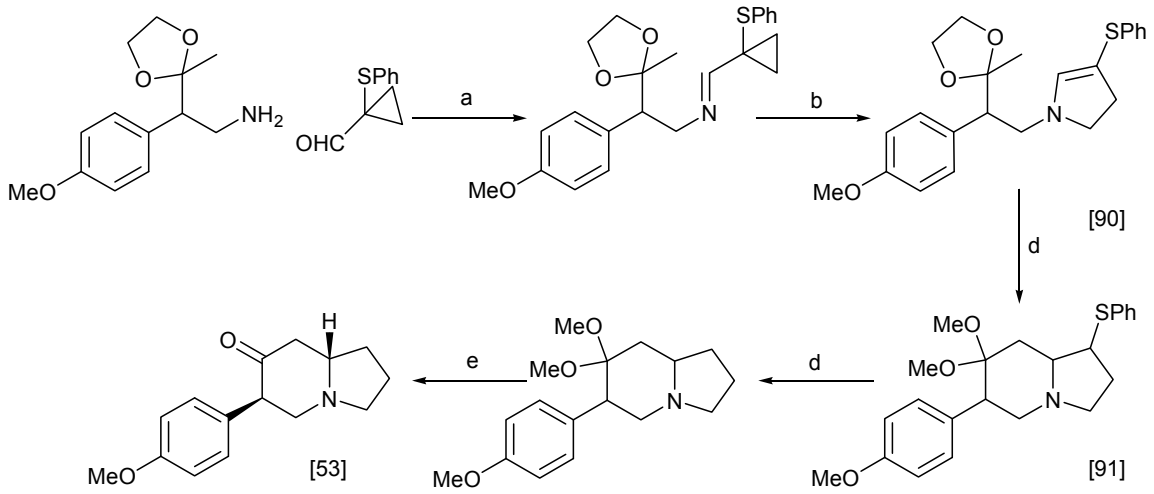
This disconnection strategy is one of the oldest routes to the synthesis of alkaloids.[66] Many of the syntheses in this group rely on the use of *N*-acyliminium ions,[67] although other strategies such as aldol and radical cyclisations exist. The *N*-acyliminium approach is worthy of mention since the α-carbonyl enhances the electrophilicity of the iminium ion, allowing for attack of suitably placed nucleophiles. One such approach was disclosed by Danishefsky and Vogel[68] in a short synthesis of racemic ipalbidine (Scheme

11). The synthesis centered on the acid-catalyzed cyclocondensation between the silyl ketene acetyl [88] and Δ^1-pyrroline [59] to give the indolizidine [89]. Standard synthetic transformations then completed the synthesis of ipalbidine.



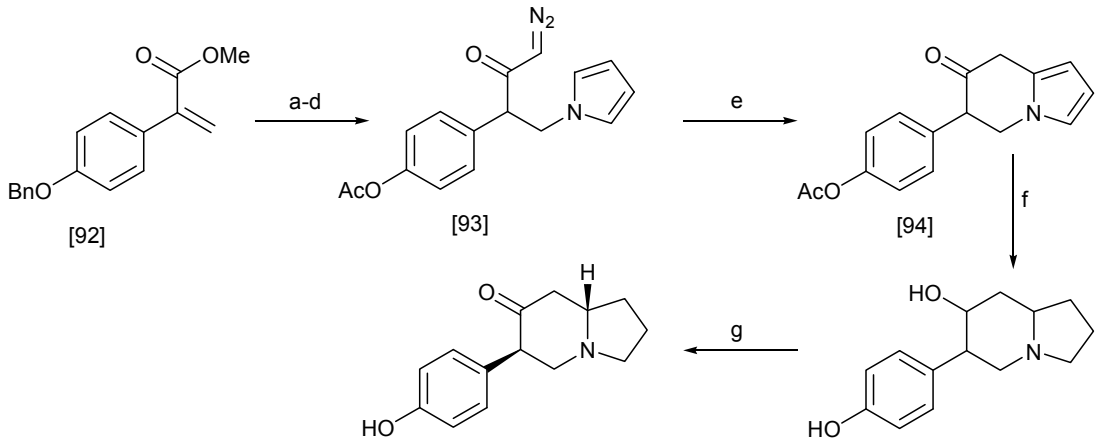
Scheme 11: Part of a synthesis of ipalbidine by Danishefsky and Vogel.[68] Reagents: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2; (b) $LiAlH_4$, $AlCl_3$; (c) BBr_3, CH_2Cl_2.

In a different yet complementary procedure, the cyclopropylimine-Δ^2-pyrroline rearrangement, a methodology developed by Stevens[69], has been applied to the synthesis of ipalbidine and septicine (Scheme 12).[70] The main interest in this synthesis lies in the rearrangement of cyclopropylimines to the phenylthio-stabilized Δ^2-pyrroline [90]. The disconnection-F annulation procedure is effectively accomplished by an intramolecular Mannich reaction to afford the indolizidine [91]. This is another example in which the pyrrolidine ring had to be constructed, before further elaboration into the indolizidine skeleton could be achieved.



Scheme 12: Formal synthesis of ipalbidine by Stevens and Luh.[70] Reagents: (a) Benzene, ∆; (b) NH_4Cl, xylene, ∆; (c) HCl, MeOH, $(MeO)_3CH$; (d) H_2, Raney Ni, EtOH; (e) 1*M* HCl, CH_2Cl_2.

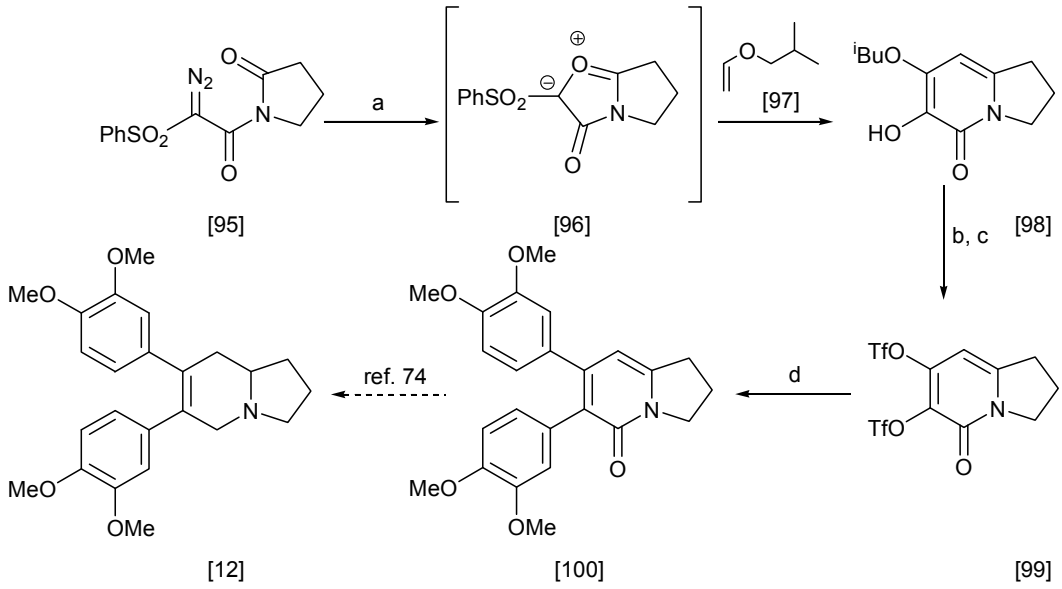
An approach using pyrrole as the template for further elaboration into the indolizidine skeleton also makes use of this disconnection strategy (Scheme 13). Jefford and co-workers[71] started with the conjugate addition between the acrylic ester [92] and pyrrole. A sequence of reduction, protection and homologation gave the diazoketone [93]. This intermediate then underwent smooth rhodium-induced intramolecular carbene cyclisation to afford the bicyclic adduct [94]. Reduction followed by oxidation then essentially completed the formal synthesis of ipalbine.



Scheme 13: Part of a synthesis of ipalbidine by Jefford and co-workers.[71] Reagents: (a) Pyrrole, $KOBu^t$, aq. DMSO; (b) H_2, Pd/C, EtOH; (c) *N*-methylmorpholine, AcCl, CH_2Cl_2; (d) $ClCO_2Bu^i$, *N*-methylmorpholine, Et_2O; (e) $Rh_2(OAc)_2$, CH_2Cl_2; (f) H_2, PtO_2, EtOAc; (g) CrO_3, H_2SO_4, Me_2CO.

Disconnection G: From aromatic precursors

The synthesis described here could be categorized in other disconnections; however we shall mention this disconnection as it showcases the imaginative use of short-lived 1,3-dipoles as partners in [3 + 2] cycloadditions by Padwa and co-workers[72, 73] for the synthesis of ipalbidine and septicine respectively. Using the septicine synthesis as an example (Scheme 14), we can see that this interesting transformation is used *en route* to the indolizidine skeleton by way of an aromatic precursor. When the diazo compound [95] was heated in the presence of a catalytic amount of rhodium(II) acetate, the resulting isomünchone intermediate [96] underwent a [3 + 2] dipolar cycloaddition with isobutyl vinyl ether [97] to afford the pyridone [98]. Conversion of this intermediate into the bistriflate [99] was followed by double arylation to afford the known intermediate [100]. This then constituted a formal synthesis as conditions have been described for conversion into septicine.[74]



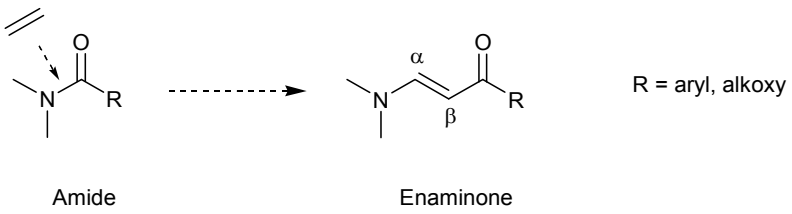
Scheme 14: Formal synthesis of septicine by Padwa and co-workers.[73]

Reagents: (a) $H_2C{=}CHOBu^i$, $Rh_2(OAc)_2$ (cat.), benzene, Δ; (b) BBr_3, CH_2Cl_2; (c) $PhN(Tf)_2$, Et_3N, CH_2Cl_2; (d) ArZnCl (from 4-bromoveratrole, ^tBuLi, THF, then $ZnCl_2$), $Pd(PPh_3)_4$, THF, rt to Δ.

1.4 The “WITS approach” to alkaloid synthesis

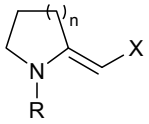
The synthesis of alkaloids in the Backeberg laboratories at the University of the Witwatersrand dates back over three decades, during which time eight M.Sc. students[75-82] and sixteen Ph.D. students[25, 83-98] have graduated from this programme.

The construction of the various alkaloids in these laboratories has largely been centered on the use of enaminones, especially vinylogous urethanes and amides. These are compounds in which a nitrogen atom is conjugated through a carbon-carbon double bond to an ester (vinylogous urethane) or a ketone (vinylogous amide) functional group. Enaminones may be viewed as amides into which a vinyl fragment has been interpolated (Scheme 15).[99]



Scheme 15: Explanation of the enaminone functional group

The compounds are thus β-acylated enamines. The research efforts of the Wits group have shown that the β-substituent is responsible for the alterations in the reactivity of the enaminone core, and to different extents. Most of the research has involved the synthesis of enaminones bearing electron-withdrawing groups, as β-substituents, of which the generalized structures are given in Figure 5. In the enaminones the Wits research group has used, the nitrogen atom is invariably tertiary and part of a pyrrolidine or piperidine ring, and has the carbon-carbon double bond exocyclic to the ring.



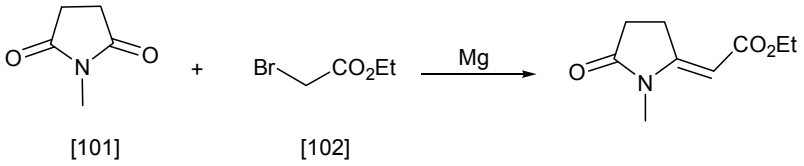
n = 1 or 2
R = H, alkyl, aryl, R' = alkyl, aryl

When:

X = COPh	vinylogous amide
X = CO_2R'	vinylogous urethane
X = $CONR'_2$	vinylogous urea
X = CN	vinylogous cyanamide
X = NO_2	vinylogous nitramine
X = SO_2R'	vinylogous sulfonamide

Figure 5: Enaminones bearing electron-withdrawing substituents

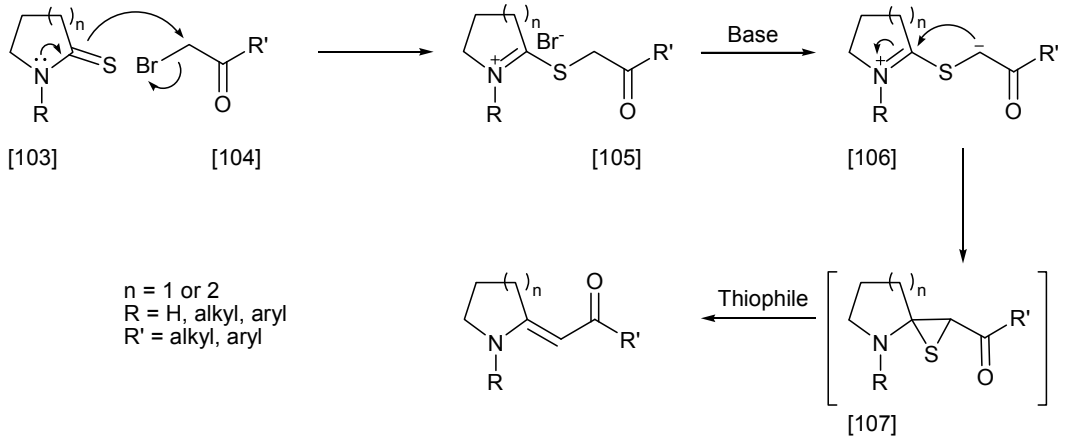
The earliest preparation of an exocyclic vinylogous urethane is by Lukeš[100] and dates from 1932. He utilized the Reformatsky reaction between *N*-methylsuccinimide [101] and ethyl bromoacetate [102], and the yield of the reaction was 68% (Scheme 16). This approach has largely been ignored and has been superseded by other approaches.[101-110]



[101] [102]

Scheme 16: Synthesis of an exocyclic vinylogous urethane by Lukeš[100]

The usual approach that this laboratory has taken for the synthesis of enaminones is one that uses the Eschenmoser sulfide contraction reaction (Scheme 17).[110]



[103] [104] [105] [106] [107]

Scheme 17: Postulated mechanism of the Eschenmoser sulfide contraction reaction

The required thiolactam [103] reacts with an appropriate α-halocarbonyl compound [104] (usually the halogen is bromine or iodine) to form the α-thioiminium salt [105]. Addition of an appropriate base (e.g. Et_3N, 1-methylpiperidine, ^tBuOK) then forms the anion [106] which undergoes spontaneous intramolecular cyclisation to the thiirane [107]. Extrusion of the sulfur is then carried out with an appropriate thiophile (e.g. PPh_3, $P(OEt)_3$, Hg(II) salts). In some cases expulsion of sulfur takes place spontaneously, or is affected by gentle heating. The true identity of the thiirane intermediate [107] is unknown; however there are literature precedents for spontaneous

elimination of sulfur from thiirane compounds[111, 112] suggesting that the intermediate shown is plausible.

The enaminone structure, although simple looking, contains a variety of interesting possible sites of reactivity. It may act as both a nucleophile and electrophile, and is therefore said to contain ambident reactivity (Figure 6).

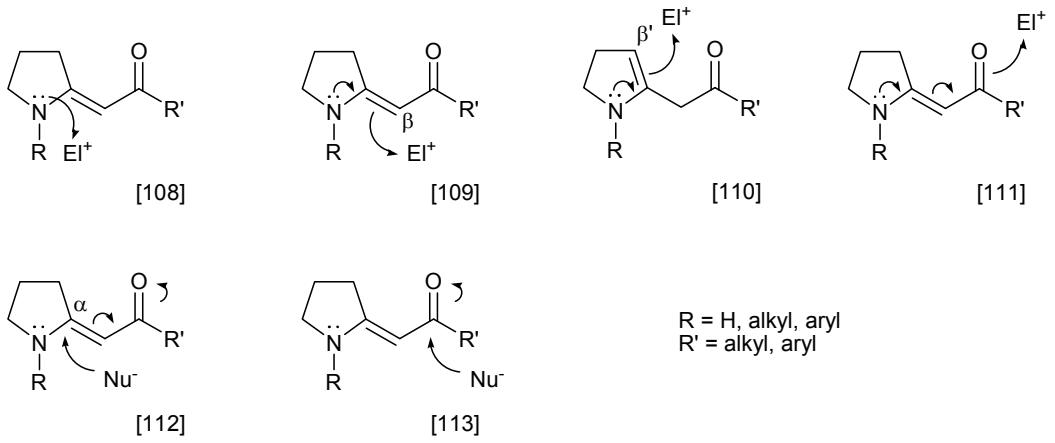


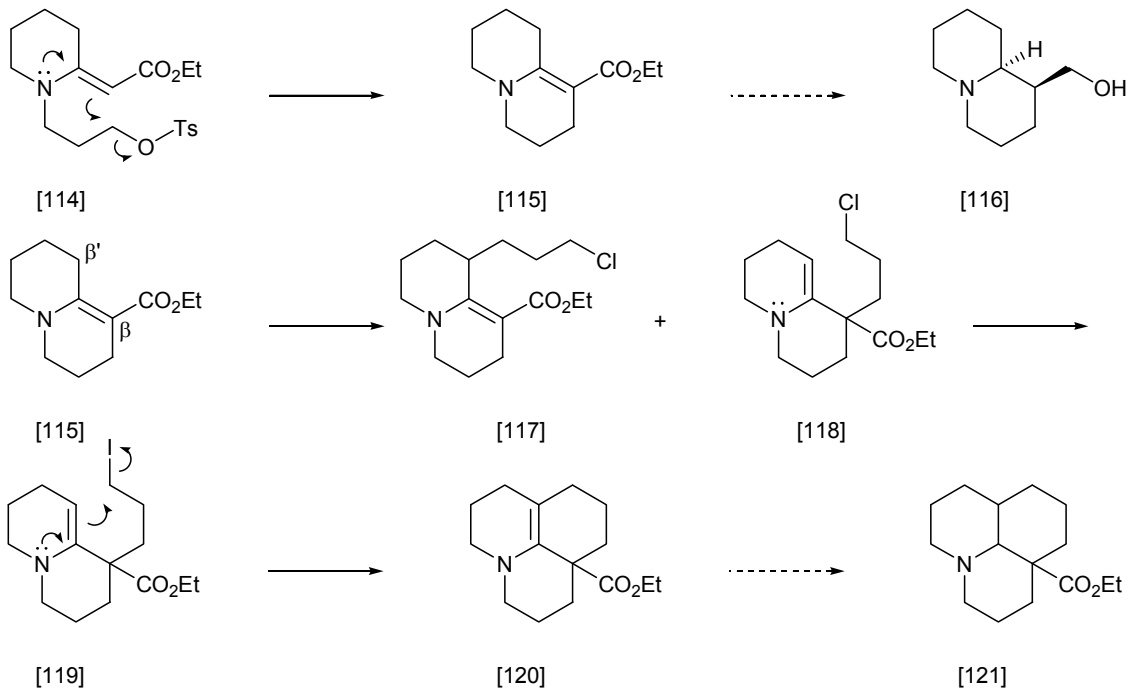
Figure 6: Reactive sites of the enaminone system

By incorporating a suitably placed electrophilic partner, the reaction may take place onto nitrogen [108], or the enamine β-carbon [109] of the enaminone. In addition, owing to the extended tautomeric delocalization of electron density, the β'-carbon [110] and oxygen [111] are additional sites of nucleophilicity. The enaminone can also act as the electrophilic partner. Therefore, nucleophilic attack can take place onto the α-carbon [112] of the enaminone or onto the carbonyl moiety [113].

By exploiting the ambident nucleophilicity and electrophilicity of enaminones, and using it combination with a plethora of other possible reactions, one can construct more complex ring structures. It is this philosophy that has been the thrust of the "Wits Approach" in constructing natural and unnatural alkaloids. What will follow are examples illustrating more clearly the ring annulation methodology that have been achieved in these laboratories over the years.

For clarity, these examples will only focus on the key annulation steps and will largely ignore the way the system was set up.

The first example illustrates an early attempt at the synthesis of lupinine [116] by Orlek[85, 113] and an interesting hydrojulolidine derivative [121] in our laboratories (Scheme 18).

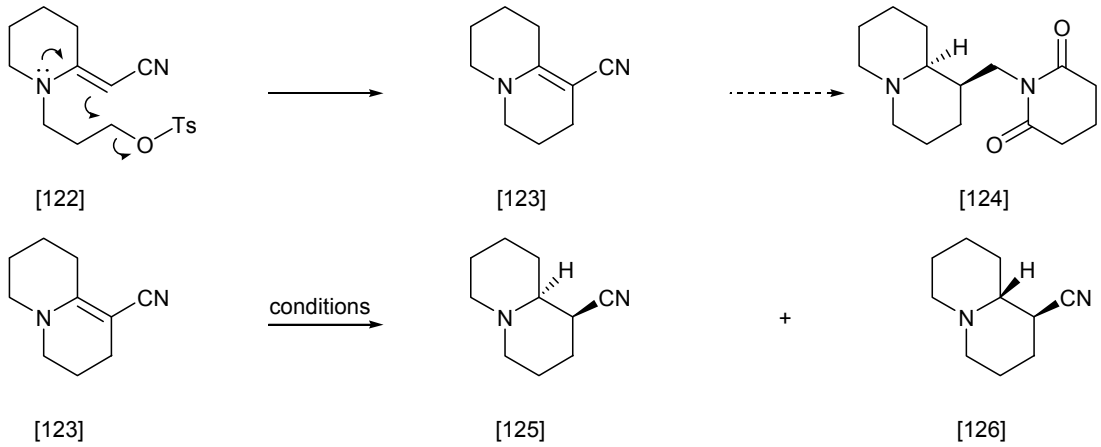


Scheme 18: Alkylative cyclisation to form lupinine and a functionalized hydrojulolidine derivative

Thus, the suitably placed toluenesulfonyl group [114] was displaced on warming in a solution of acetonitrile to give the unsaturated ester [115]. Reduction then gave lupinine, whose stereochemistry could not be conclusively elucidated at the time. However, the stereochemistry was confirmed 27 years later by Fat.[94, 114] Interestingly, when intermediate [115] was treated with *n*-butyllithium and 1-bromo-3-chloropropane, the products [117] and [118] were obtained, of which the latter was obtained as the major component. The preponderance of the β-substituted product was surprising in light of model studies carried out in this laboratory[115] and of published results.[116, 117] A Finkelstein reaction on this major product produced the iodide

[119] that underwent cyclisation on warming in a solution of acetonitrile to afford the tetrahydrojulolidine system [120]. Reduction then gave a stereoisomeric mixture of the hydrojulolidine derivative.

The second example is very similar, illustrating the same use of the tosyl leaving group in the alkylative cyclisation protocol. In this case the vinylogous cyanamide reacts in a very similar manner to generate the quinolizidine scaffold (Scheme 19).[76, 118]

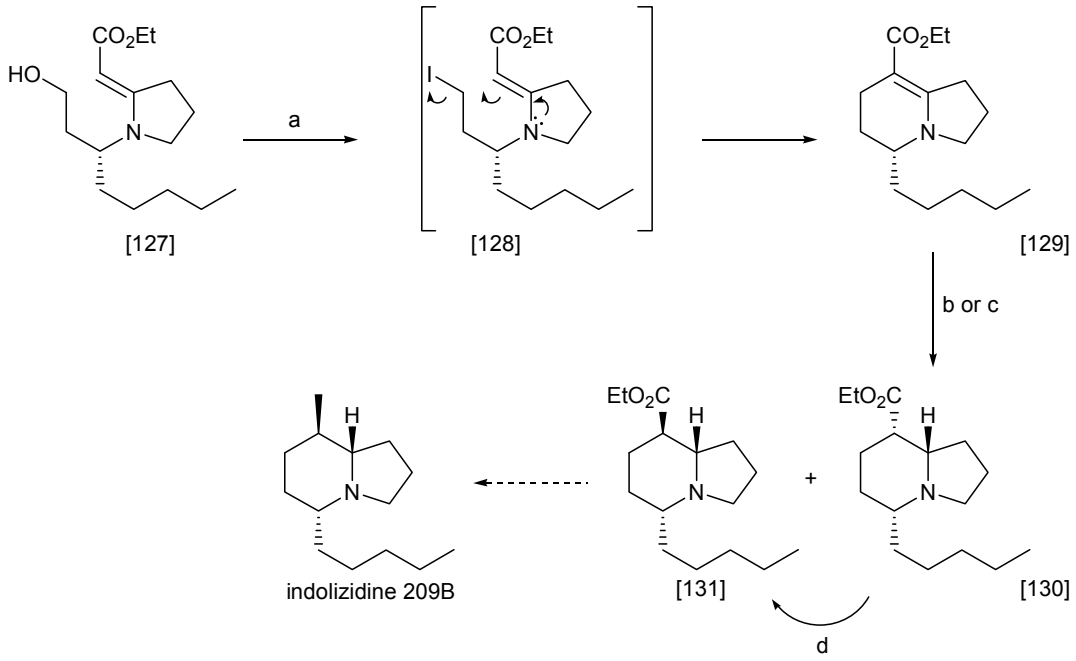


Scheme 19: Key cyclisation and intermediates in the synthesis of racemic lamprolobine

Therefore, on warming the tosyl derivative [122] in a solution of acetonitrile the bicyclic system [123] was formed. This was then elaborated further to give racemic lamprolobine [124]. It is worth mentioning at this time that stereoselective reduction of the double bond has been a key focus area in these laboratories. In this investigation, better selectivity was observed using catalytic hydrogenation with PtO_2 than with sodium cyanoborohydride. Thus, catalytic hydrogenation over platinum oxide under acidic conditions of the intermediate [123] afforded the expected *cis*-product [125] with a small quantity of the diastereomer [126], in a ratio of *ca*. 14:1 respectively. In contrast, reduction of the same intermediate [123] with sodium cyanoborohydride in ethanol at pH *ca*. 4 gave a more equal mixture (1:1.3) of the isomers. The isomers could be separated by chromatography, and this

allowed for the synthesis of the epimer of lamprolobine. This illustrates another central theme in our laboratories in that by exploiting the ambident electrophilicity of enaminones it can lead to divergence in a synthetic sequence, i.e. by controlling the reduction of the enaminones one can access diastereomers of both natural and unnatural products.

In the synthesis of two alkaloids (indolizidine 209B and 167B) found in the skin secretions of dendrobatid frogs, Gravestock[90, 119-122] used a similar methodology in an intramolecular cycloalkylation of a chiral enaminone (Scheme 20). In one such approach towards indolizidine 209B, the alcohol [127] was converted into the indolizidine [129] by way of an *in situ* generated iodide [128]. Again, selectivity was sought for the reduction of the indolizidine intermediate [128]. Therefore, reduction with sodium cyanoborohydride at pH 4 afforded [131] in a poor 36% yield. Hence, they turned to an alternative protocol using catalytic hydrogenation with PtO_2 in acetic acid. This more diastereoselective reduction yielded an 88:12 mixture of [130] and [131]. Although the wrong stereoisomer was obtained as the major product, the axial ester group of [130] was amenable to epimerization when the compound was heated with a catalytic quantity of sodium ethoxide in ethanol. Further elaboration then gave indolizidine 209B.

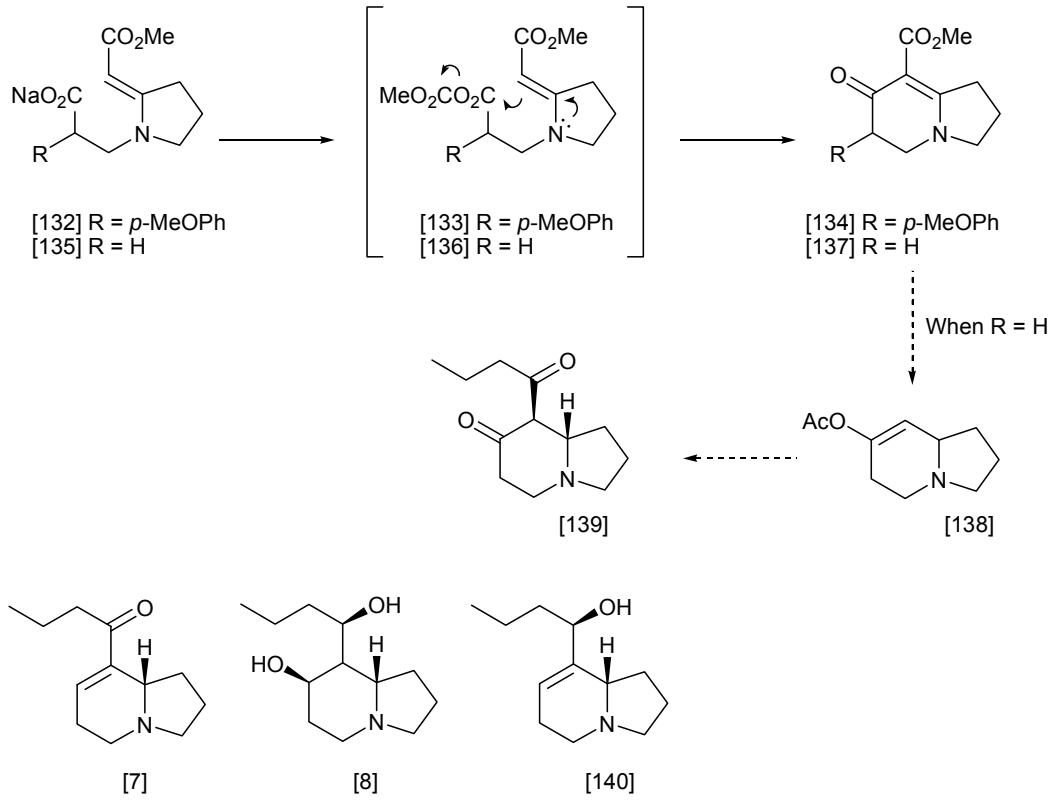


Scheme 20: Key cyclisation and intermediates in the enantioselective synthesis of indolizidine alkaloid 209B. Reagents: (a) I_2, imidazole, PPh_3, toluene, Δ; (b) $NaBH_3CN$, HCl (pH 4), EtOH; (c) H_2, PtO_2 (cat.), AcOH; (d) NaOEt (cat.), EtOH, Δ.

Besides using this nucleophilicity in cycloalkylation, the above reactivity has also been exploited in these laboratories in both cycloacylation and cycloarylation processes to form various products. Examples of the annulations being accomplished by an acylation of a vinylogous urethane can be found in the formal syntheses of ipalbidine [14] as well as the elaeokanine alkaloids (Scheme 21). Briefly, Michael[27, 84] was able to perform a spontaneous intramolecular cycloacylation of the vinylogous urethane [132] to prepare the 7-oxoindolizidine [134], by way of the highly electrophilic mixed anhydride [133]. Further elaboration of this intermediate then constituted a formal synthesis of ipalbidine (see page 16, and Scheme 4).

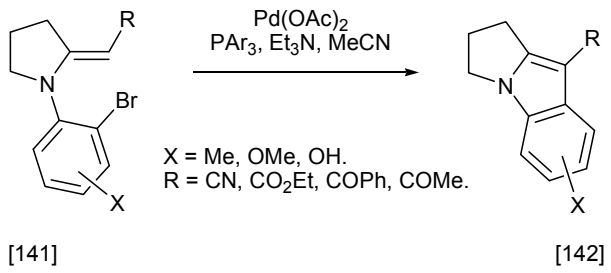
In an example of the importance of the 7-oxoindolizidine intermediate in natural product synthesis, Meerholz[24, 86] was able to analogously convert the intermediate [135] by intramolecular cycloacylation into the vinylogous urethane [137] by way of the mixed anhydride [136]. In addition, this vinylogous urethane through a series of synthetic steps was transformed to the regiospecific enolate [138], of which reaction with the appropriate acyl

cyanide afforded the diketone [139]. The general usefulness of this intermediate is apparent since it constituted the formal synthesis the elaeokanine alkaloids [7], [8] and [140].[123]



Scheme 21: Formation of a 7-oxoindolizidine intermediate by an acylative annulation

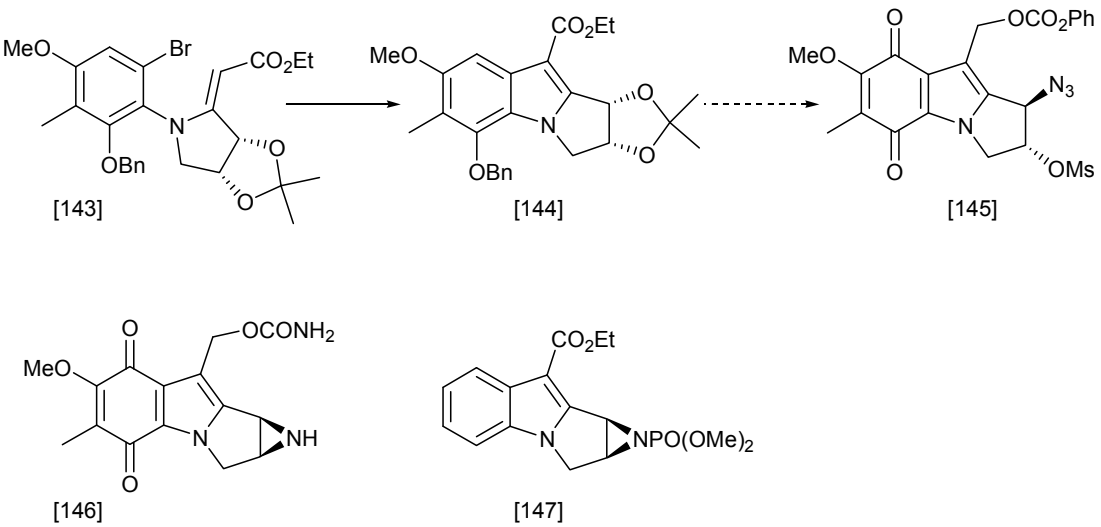
The work of Chang[89] and Wilson[77] gives several examples of the use of a cycloarylation onto the α-position of an enaminone (Scheme 22).[124] As precursors to the pyrrolo[1,2-*a*]indole derivatives [142], Chang and Wilson used a range of *N*-(2-bromoaryl) enaminones [141] using the well-known Heck reaction protocol. Chang's synthesis of these compounds constituted the first successful preparation of the pyrrolizidine ring system in these laboratories.



[141] [142]

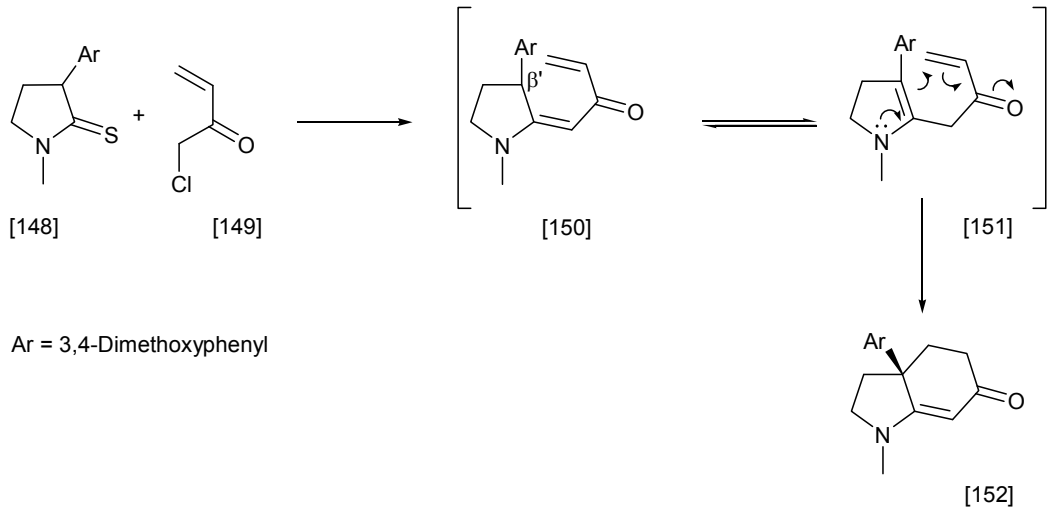
Scheme 22: Alkaloid synthesis using an intramolecular Heck cycloarylation

This methodology has been extended by Petersen[95, 125, 126] into the elegant asymmetric formal synthesis of 7-methoxyaziridinomitosene [146] (Scheme 23). Thus, cycloarylation of the vinylogous urethane [143] under Heck conditions afforded the pyrrolo[1,2-*a*]indole skeleton [144]. Further elaboration then afforded the azide [145] which constituted a formal synthesis of 7-methoxyaziridinomitosene.[127] It should be mentioned that the preliminary work in this field was done by Stanbury[91, 125] who prepared the model *N*-phosporylated aziridinomitosene analogue [147]. The synthesis of [146] was completed by a post-doctoral worker, Dr T.T. Mudzunga.[126]



Scheme 23: An elegant formal synthesis of 7-methoxyaziridinomitosene and analogues

Although the nucleophilicity of the β-position forms the bulk of the work in these laboratories, there are a few examples of synthetic intermediates which exploit the β'-position. We have already mentioned the serendipitous synthesis of a hydrojulolidine [121] derivative (see page 31). In a more directed approach Katz[87, 128-130] used the reactivity of the β'-position in a short synthesis of racemic Δ^7-mesembrenone [152] (Scheme 24). This work was later extended by Zwane [88, 129-131] Briefly, when the thione [148] was reacted with chloromethyl vinyl ketone [149] in refluxing nitromethane followed by the addition of the hindered base diisopropylethylamine at room temperature, the desired Δ^7-mesembrenone was obtained. The spontaneous ring closure of the putative vinylogous enamide intermediate [150] is remarkable, and presumably requires the participation of the endocyclic enamine tautomer [151] in order to accomplish so easy a ring closure.



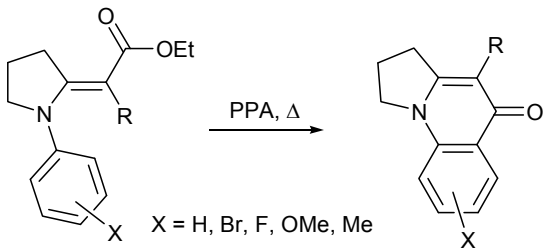
[148] [149] [150] [151] [152]

Ar = 3,4-Dimethoxyphenyl

Scheme 24: A short synthesis of racemic Δ^7-mesembrenone

The above examples illustrate the effective use of the nucleophilicity of the enaminone systems in these laboratories. The following examples make use of the ambident electrophilicity of enaminones.

In addition to the pyrrolo[1,2-*a*]indole nucleus, we have fashioned economical syntheses of the pyrrolo[1,2-*a*]quinolinone nucleus as well. The electrophilicity of the enaminone carbonyl moiety has been exploited during the synthesis of analogues of 4-quinolone antibacterial compounds (Scheme 25). Hosken[75] found that Conrad-Limpach cyclisations of suitably functionalized *N*-aryl vinylogous urethanes [153] gave the tricyclic 4-quinolinones [154]. Stanbury[91, 132] later extended this work by preparing tricyclic 4-quinolinones possessing the ethoxycarbonyl group [156] from the diester [155]. These ethoxycarbonyl compounds were subsequently hydrolyzed to give carboxylic acids, which are tricyclic analogues of the well-known quinolone antibiotics.

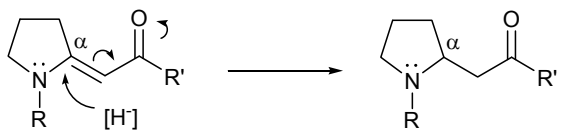


[153] R = H
[155] R = CO_2Et

[154] R = H
[156] R = CO_2Et

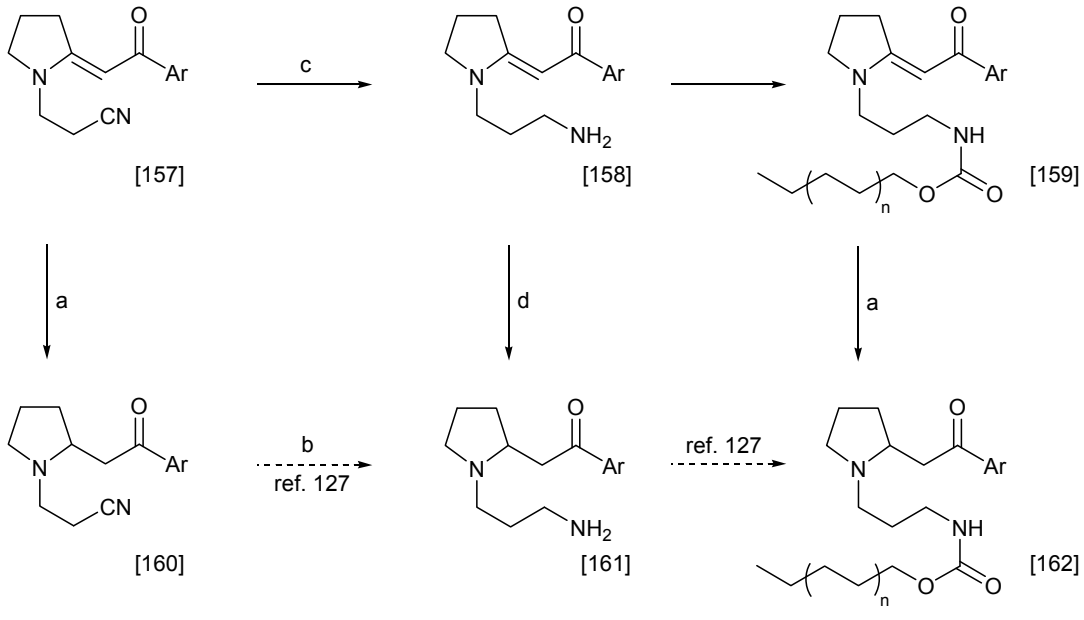
Scheme 25: Synthesis of pyrrolo[1,2-a]quinolinones by Conrad-Limpach cyclization

The final example illustrates a central theme in these laboratories. It is one in which we can exploit the electrophilicity of enaminones for purposes other than ring closure. We have already mentioned some examples of stereoselective reduction of the enaminone double bond; a reaction that formally represents an attack of a nucleophilic hydride at the electrophilic α-position of the enaminone (Scheme 26).



Scheme 26: Exploiting the electrophilic α-position of the enaminone for C=C bond reduction

In the syntheses of two of the *Peripentadenia* alkaloids, Parsons[25, 133] was able to show remarkable chemoselective reductions *en route* to the *O*-methylated alkaloid precursors of peripentadenine and dinorperipentadenine (Scheme 27). These sets of reactions showed the flexibility of the vinylogous amide system, in that judicious choice of reagents and reaction conditions allowed for the exploration of different routes to the same target by altering the timing of events. Thus, the vinylogous amide [157] could converge to the intermediate [161] by two different yet complementary routes. Firstly, the vinylogous amide could be reduced with lithium aluminum hydride to afford the intermediate tertiary amine [160], of which the nitrile moiety could be hydrogenated in the presence of catalytic PtO_2 to afford intermediate [161].[134] Secondly, chemoselective reduction, under dissolving metal conditions, of the nitrile moiety of the vinylogous amide [157] afforded the primary amine [158] which, upon reduction with sodium cyanoborohydride under acidic conditions, converged to the common intermediate [161]. In addition, the primary amine [158] could be functionalized to afford the vinylogous amides [159], reductions of which with lithium aluminum hydride afforded *O*-methylated [162] precursors of peripentadenine and dinorperipentadenine.



Ar = 2-MeO-6-Me-C_6H_3
n = 1, *O*-Methylperipentadenine.
n = 0, *O*-Methyldinorperipentadenine.

Scheme 27: Chemoselective reductions of some O-methylated Peripentadenia alkaloid intermediates.

Reagents: (a) $LiAlH_4$, THF; (b) H_2, PtO_2 (cat.), AcOH; (c) Ni/Al, NaOH, EtOH; (d) $NaBH_3CN$, HCl, MeOH.

As can be seen in this chapter section, the efforts we have invested in the chemistry of the pyrrolidines, indolizidines, quinolizidines, certain perhydroindole alkaloids as well as the pyrrolo[1,2-*a*]indole and the pyrrolo[1,2-*a*]quinolinone nucleus has allowed us to achieve the synthesis of many compounds. Perhaps, one disappointment has been the lack of success in preparing a range of bicyclic pyrrolizine ring systems by cyclising suitable exocyclic enaminones.[84] Should we be discouraged? This will be expanded upon in a later chapter.

1.5 The aims of the project

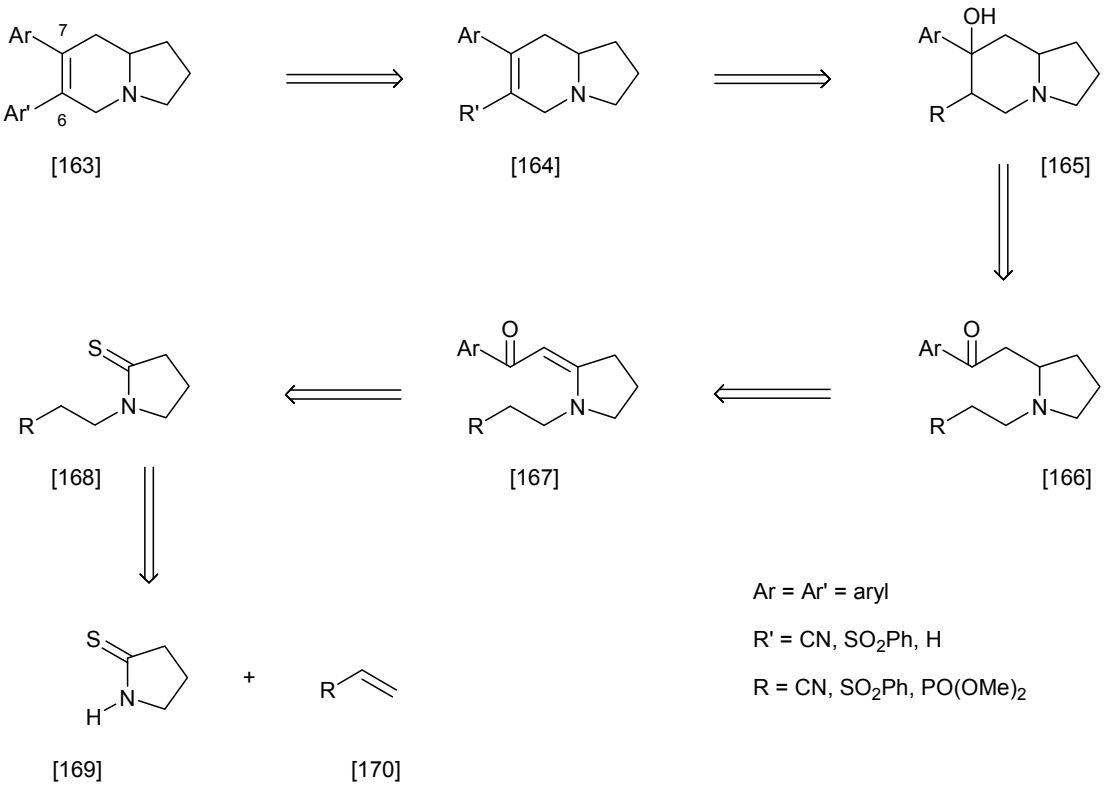
Having highlighted some of the work using the "Wits Approach" in the previous chapter section, and with a short review of the literature with regards to the synthesis of some of the secophenanthroindolizine alkaloids in the preceding chapter section, we can now clarify the aims of this project.

This project intended to develop further the synthetic utility of the Eschenmoser sulfide contraction as well as aspects of the "Wits approach" *en route* to the construction of the arylated indolizidine skeleton as found in the alkaloids ipalbidine [14] and septicine [12]. There are two ways in which we wished to do this, both of which rely on a disconnection B (see page 13) cyclisation strategy (bond formation between C_6 and C_7). The first approach was planned to explore a "condensation" strategy for the critical ring formation, and the second to explore the feasibility of a pinacol coupling strategy for the ring closure. In addition, this disconnection strategy has not been explored in these laboratories, and it was our wish to develop further this chemistry to add to our growing methodology in the construction of azabicyclic alkaloid compounds. Our intentions are illustrated in the subsequent subsections in 1.5.1 and 1.5.2.

1.5.1 Proposed strategy for the synthesis of arylated indolizidine alkaloids by way of a condensation strategy

In this strategy we wished to further what had been initiated in these laboratories many years ago through the Ph.D. work of Parsons[25] and the M.Sc. work of Brankin.[78] The initial stages of the strategy only contain one of the aryl rings as found in the secophenanthroindolizidine alkaloids; however we have plans for installing the second aryl ring at a late stage of the strategy. It should be mentioned that one such approach will only contain one aryl ring in the indolizidine skeleton (when R = CN), and hopefully the chemistry that will be developed will apply for the strategy for the implementation of the

second aryl ring when R = SO_2Ph and $PO(OMe)_2$. A retro-synthetic analysis is offered in Scheme 28.



Scheme 28: Retro-synthetic analysis for the "condensation" approach to arylated indolizidine alkaloids

An analysis of the generalized structure for the diaryl-phenanthroindolizidine alkaloid [163] reveals that the C_6 – C_7 bond can be suitably constructed by way of a condensation reaction. Functional group interconversion of Ar' to that of a nitrile, sulfone or of a hydrogen affords compounds of the generalized structure [164]. In a forward sense, when R' = H, we can install the additional aryl unit by way of the well known Heck reaction. Additionally, when R' = SO_2Ph we may make use of the nucleophilic addition of an aryl Grignard reagent onto the vinyl sulfone moieties. Obviously, when R = CN the reaction sequence terminates, however one of the project aims would have been fulfilled as this type of compound may be considered an analogue of the secophenanthroindolizidine type of alkaloids.

A second functional group interconversion affords compounds with the generalized structure [165] with the hydroxyl moiety at the C_7 position of the indolizidine skeleton. A further disconnection of this carbinol intermediate gives rise to the generalized pyrrolidines [166]. Therefore, in a forward sense we need to selectively derive an anion at the α-position of the nitrile, sulfone, or phosphonate which would then do an intramolecular attack onto the electrophilic carbonyl moiety to afford the intermediates [165]. It is at this point that R' = H [164] becomes obvious as both the sulfonyl and phosphonate groups are eliminated along with the hydroxyl group to create the double bond. In the case of the phosphonate moiety, Wittig-type elimination may occur *in situ* obviating the need to isolate the intermediate carbinol. For the sulfonyl case, a Julia-type olefination of the derived carbinol may occur by reductive elimination of the β-substituted sulfone.[135]

Functional group addition of the intermediates [166] affords the vinylogous amides [167] which can be disconnected to the thiones [168]. In a forward sense, an Eschenmoser sulfide contraction of the thiones will generate the vinylogous amides which can in turn be reduced to the pyrrolidines [166]. This methodology will realize another aim of this project in that we wish to extend the range of products that may be accessed by the Eschenmoser sulfide contraction reaction.

Lastly, the thiones [168] can be disconnected to pyrrolidine-2-thione [169] and the Michael acceptors [170]. The use of these Michael acceptors will realize another aim of this project as we wish to extend the scope of previous efforts in these laboratories, which have centered mainly on acrylates.[23, 27, 113, 114, 118-120]

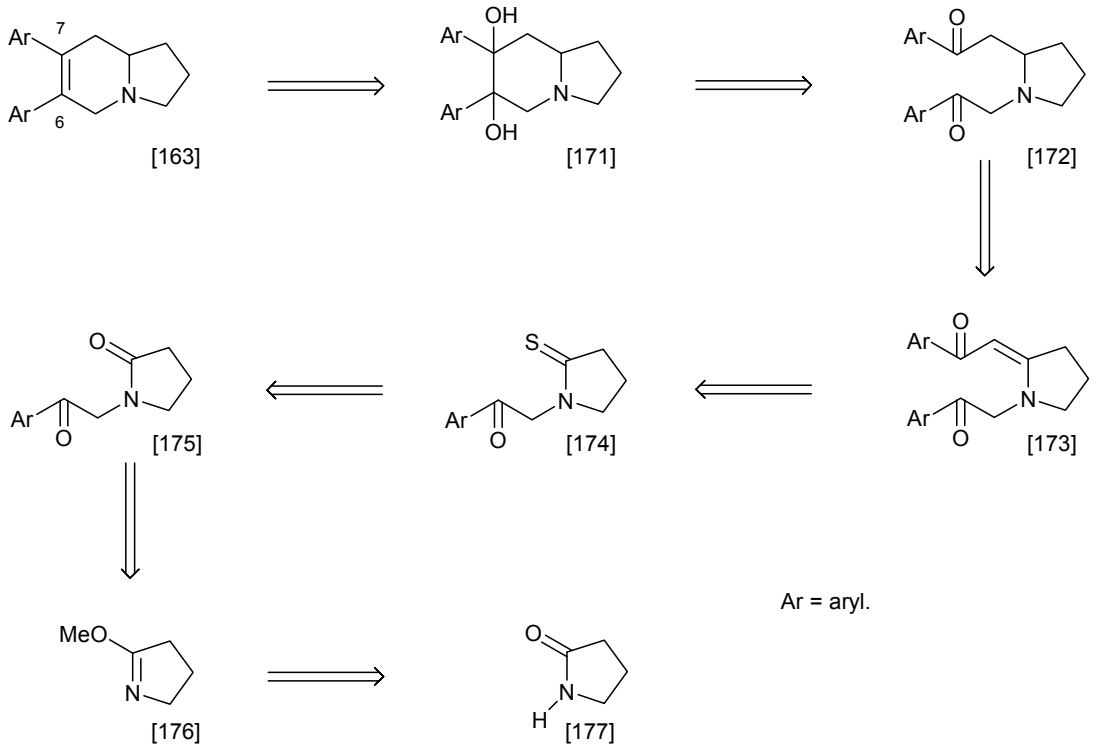
This route takes us into uncharted territory as we will not make use of the ambident electrophilicity or nucleophilicity of any of the derived enaminone intermediates to construct the bicyclic indolizidine skeleton. This is then an approach making this project somewhat unique at it moves away from the traditional "Wits approach". We shall reduce out the double bond of the enaminone (obviously by taking advantage of the electrophilicity of the α-position of the enaminone intermediates) and attempt to construct the

indolizidine skeleton by making use of “condensation” chemistry of the appropriately functionalized pyrrolidine intermediates. At this stage, it should be mentioned that aspects of the “condensation” protocol have been tackled by Parsons[25] and Brankin[78] but the results they obtained need further exploration. It is this exploration that will be discussed in chapter 2.

1.5.2 Proposed strategy for the synthesis of arylated indolizidine alkaloids by way of a pinacol coupling strategy

By constructing a suitably derived intermediate we can attempt radical cyclisation by way of a pinacol-coupling strategy; i.e. by coupling two suitably placed carbonyl moieties. This strategy will be discussed in chapter 3.

In this strategy we wished to further develop our strategy in developing routes to the arylated indolizidine skeleton. The initial stage of the above strategy makes use of one aryl unit with plans of installing the second aryl ring at a late stage of the strategy. In this strategy both the aryl units will be installed as early as possible before the pivotal construction of the indolizidine skeleton. A retro-synthetic analysis is given in Scheme 29.



Scheme 29: Retro-synthetic analysis for the pinacol coupling approach to arylated indolizidine alkaloids

An analysis of the generalized structure for the diaryl-phenanthroindolizidine alkaloid [163] reveals that the $C_6 – C_7$ bond can also be suitably constructed by way of a pinacol coupling reaction. Functional group addition gives rise to the diol [171] which can be disconnected to the pyrrolidine [172] containing the suitably placed carbonyl moieties. In a forward sense, pinacol coupling of the pyrrolidine intermediate using conditions as set out by Honda[58] (using a McMurry coupling strategy) should afford the diol, the olefin from which can be liberated through the intermediacy of an orthoformate.

Functional group addition of the pyrrolidine affords the enaminone [173] which can be disconnected to the thione [174]. In a forward sense, the transformations require an Eschenmoser sulfide contraction, followed by reduction of the derived enaminone to afford the pyrrolidine. Problems are expected at this stage as the question of chemoselectivity arises during the reduction stage of this synthetic sequence. It is likely that the carbonyl moiety

on the *N*-alkyl chain will be reduced as well; therefore an early protection of this carbonyl group may be sought.

Functional group interconversion of the thione gives the lactam [175], of which it may be disconnected to 5-methoxy-3,4-dihydro-2*H*-pyrrole [176] and a suitably functionalized phenacyl bromide, a reaction that has literature precedent.[136] Finally, the pyrrole may be accessed from pyrrolidin-2-one [177] by standard procedures.

I have already alluded to the construction of bicyclic pyrrolizine ring systems and this will be discussed in chapter 4 as this was an unexpected consequence of our exploration during the synthesis towards the arylated indolizidine alkaloids. The discussion of these compounds will conform to the traditional “Wits approach” as we shall make use of *both* the ambident nucleophilicity and electrophilicity of enaminones in constructing the bicyclic skeleton, a sequence that is unprecedented in these laboratories! In these laboratories we have constructed bicyclic systems by *exclusively* taking advantage of the ambident nucleophilicity of enaminones (e.g. in the directed approach towards the perhydroindoles, indolizidines and quinolizidine alkaloids). In the instances where we have constructed the pyrrolo[1,2-*a*]indoles and the pyrrolo[1,2-*a*]quinolinones we were *only* in the position to take advantage of the electrophilicity of enaminones for obvious reasons.

1.5.3 Summary of Aims

In brief the main aims of the project are:

- To extend the range of Michael acceptors which react with pyrrolidine-2-thione [169] at nitrogen.
- To demonstrate further the synthetic utility of enaminones in alkaloid synthesis by way of the Eschenmoser sulfide contraction;
- To extend the range of both arylated indolizidine and pyrrolidine alkaloids in these laboratories by developing a new route to the synthesis of the arylated indolizidine skeleton as found in the alkaloids ipalbidine [14] and septicine [12].

In the chapters that follow, the discussion will detail some model studies towards the synthesis of arylated indolizidine alkaloids along with studies towards the synthesis of septicine. In addition, some unexpected results that developed out of the main body of the research are discussed. Finally, the findings and achievements are summarized, future prospects are discussed, and conclusions are drawn.

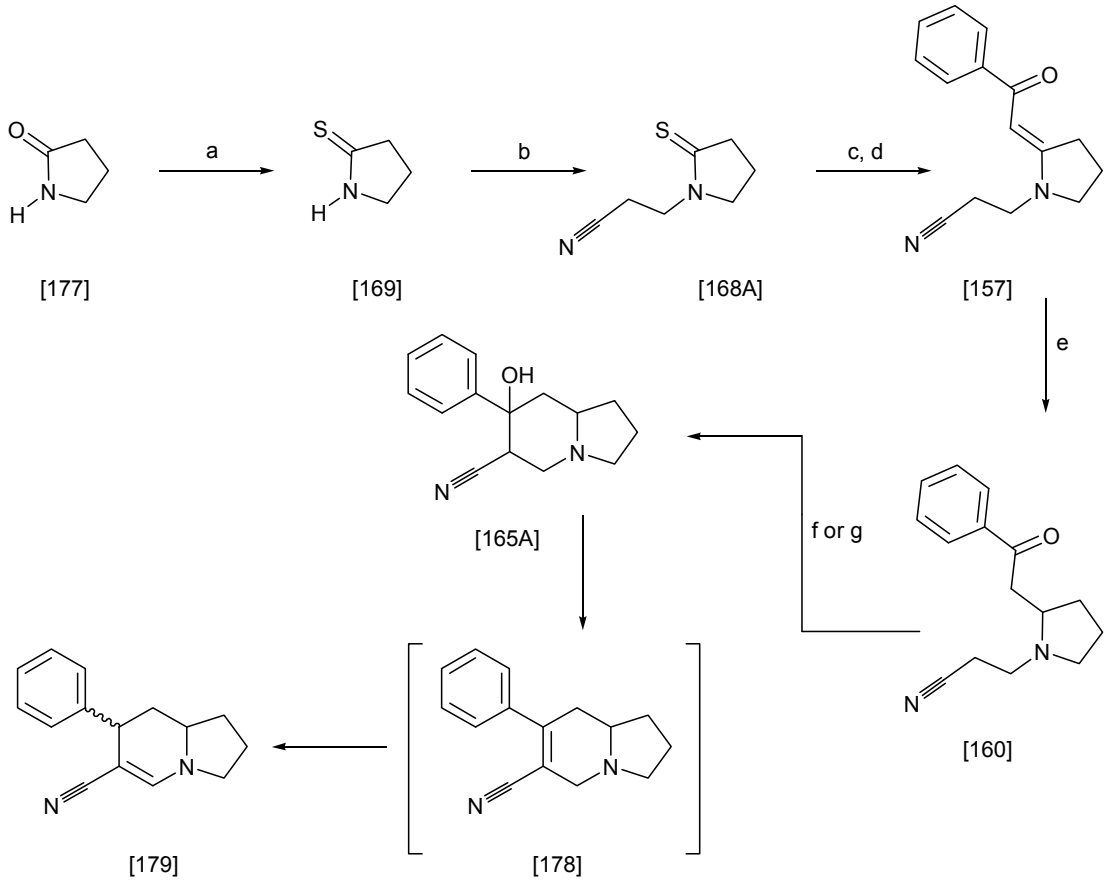
Chapter 2: Approaches to arylated indolizidine systems by way of a condensation strategy

2.1 Arylated indolizidine systems containing a nitrile functional group

2.1.1 Introduction

During the course of the synthesis of the *Peripentadenia* alkaloids, Parsons[25] was interested to see if he could cyclize the pyrrolidine intermediate [160] to form the indolizidine skeleton. The results he obtained were interesting (Scheme 30). Reaction of intermediate [160] with two equivalents of potassium tertiary butoxide in tetrahydrofuran at room temperature afforded the indolizidine [165A] in 75% yield as a possible mixture of diastereomers. When the same reaction was conducted at room temperature followed by heating under reflux, the indolizidine [179] was isolated as a mixture of diastereomers in 66% yield. Clearly, base-induced elimination from [160] took place, but instead of compound [178] being the product, a vinylogous cyanamide, was formed.

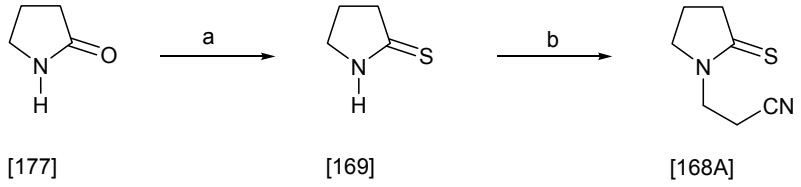
We decided to reinvestigate this set of reactions for several reasons. Firstly, the ^{1}H NMR spectral data was recorded on a 200 MHz spectrometer, and therefore Parsons was not able to estimate the diastereomer ratios of the products as severe overlap of signals was evident. As we have the services of a 400 MHz spectrometer we may be in a position to estimate the diastereomer ratios if there is sufficient separation of the signals. Secondly, attempts will be made to separate the diastereomers and characterize them fully. Thirdly, we wished to find reaction conditions that will allow for the isolation of intermediate [178] as its structure is obviously related to those found in the alkaloids ipalbidine and septicine. Finally, the chemistry learned during the course of this investigation may be applicable towards the synthesis of septicine. This is because we can replace the nitrile moiety by of a sulfone or a phosphonate moiety and attempt a ring-closure reaction.



Scheme 30: Synthesis of some arylated indolizidines by Parsons.[25] Reagents: (a) P_4S_{10}, Na_2CO_3, THF; (b) Acrylonitrile, NaOH (cat.), THF; (c) Phenacyl bromide, acetone; (d) PPh_3, Et_3N, MeCN; (e) $LiAlH_4$, THF, 0 ^oC; (f) ^tBuOK, THF, rt; (g) ^tBuOK, THF, Δ.

The following discussion details our approaches to this investigation. For the most part we duplicated the reaction conditions as shown in the scheme above; therefore discussions of most of the compounds will be necessarily brief as they have been characterized in these laboratories. We did achieve the goals that were set originally and, pleasingly, some interesting chemistry occurred along the way as well.

2.1.2 Preparation of thiolactam precursors



[177] [169] [168A]

Scheme 31: Thiolactam precursors. Reagents: (a) P_4S_{10}, Na_2CO_3, THF; (b) Acrylonitrile, NaOH (cat.), THF.

2-Pyrrolidinethione [169] was prepared according to Brillon's procedure.[137] This method uses a reagent made *in situ* by stirring together phosphorous pentasulfide and sodium carbonate in a 1:1 ratio in tetrahydrofuran. Thus, addition of 2-pyrrolidinone [177] to the above reagent followed by stirring for eighteen hours at room temperature afforded 2-pyrrolidinethione [169] in 85% yield. The product was obtained as a white solid and its melting point and spectroscopic data correspond closely with literature values.[137] Although there are numerous other thionation procedures,[138-142] Brillon's procedure is mild and generally gives thiolactams in high yields.

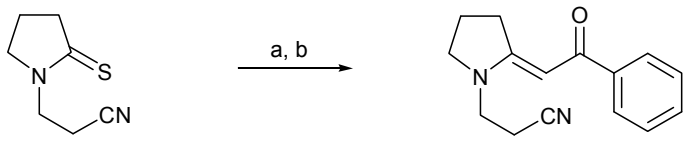
With the thiolactam in hand, the stage was set for the conjugate addition reaction (Scheme 31). Thus, compound [168A] was prepared in quantitative yield by the Michael reaction of 2-pyrrolidinethione [169] with acrylonitrile in the presence of a catalytic quantity of sodium hydroxide and a small quantity of water. The oil obtained after workup was pure enough to carry to subsequent reactions.

Traditionally, in these laboratories these types of reaction are carried out using undried tetrahydrofuran; however the addition of a small quantity of water ensures that the reaction goes to completion within a reasonable time-frame by helping to facilitate dissolution of the sodium hydroxide catalyst in the reaction medium.

The success of the reaction was evidenced from both the ^{13}C NMR and the FTIR spectra. The ^{13}C NMR spectrum showed a signal for the nitrile carbon

atom at 117.87 ppm which was corroborated by a weak absorption at 2249 cm^{-1} for the nitrile moiety in the FTIR spectrum. Other spectra were in agreement with those reported.[25]

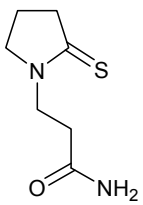
2.1.3 Preparation of vinylogous amide [157]



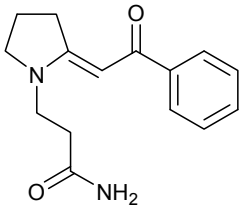
[168A] [157]

Scheme 32: Eschenmoser sulfide contraction. Reagents: (a) Phenacyl bromide, MeCN; (b) PPh_3, Et_3N, MeCN.

The preparation of the Eschenmoser sulfide contraction product [157] deserves some comment (Scheme 32). In the procedure of Parsons, the α-thioiminium salt was prepared in acetone from the thiolactam [168A] and phenacyl bromide by allowing the reaction mixture to stand in a fridge overnight. Once the reaction was deemed to be complete, the solvent was evaporated and acetonitrile was added to this salt and extrusion of the sulfur was facilitated by the addition of triphenylphosphine and triethylamine. Acid-base extraction followed by column chromatography afforded the desired compound in 71% yield, along with an 8% recovery of the unreacted thiolactam [168A]. Clearly, the reaction did not go to completion when allowed to stand unstirred in the fridge. In another preparation, [157] was obtained in 59% yield, 1% thiolactam was recovered, and amides [180] and [181], the products of the hydrolysis of the nitrile functional group, were isolated in yields of 2% and 6% respectively. The hydrolyzed products are not surprising in view of the aqueous workup.



[181]



[182]

In our preparation, the sulfide contraction was conducted in a one-pot procedure at room temperature. Salt formation and extrusion of the sulfur was carried out using acetonitrile as the solvent. The solvent was evaporated and the resulting gum was taken into ethyl acetate and washed thoroughly with water. The organic extract was then extracted into dilute hydrochloric acid and the product was liberated upon basification with a solution of concentrated aqueous ammonia. The resulting solid was extracted with ethyl acetate, thoroughly washed with water, dried and evaporated to afford the product in 86% yield without the need for chromatographic purification. This reaction could be done on an eight gram scale without any diminution of yield. Why we never saw any of the amides during the preparation of [157] remains a mystery as no special precautions were taken during the acid-base workup; in some instances the solution got very warm, necessitating the addition of ice to prevent entrained solvent from boiling too vigorously during the basification process.

The assignment of (*E)*-geometry, and more specifically the *trans-s-cis* structure, of this compound rests largely on the position of absorptions of the methylene protons at C-3 in the ring in the ^{1}H NMR spectrum. In secondary vinylogous amides of this type, where the Z-geometry (*cis-s-cis* structure) is greatly favoured by the resulting H-bonding, these protons absorb around 2.7 ppm.[110] In fact, it absorbs at 2.74 ppm (see discussion in 2.1.4 below). In the present case the absorption can be found at 3.40 ppm. It is only in the *trans-s-cis* isomers, where the methylene protons at C-3 fall into the deshielding zone of the carbonyl group that this shift is readily explainable.[143] The assignment of the *E*-geometry in compound [157] was further corroborated by obtaining a

crystal structure, confirming that we had indeed synthesized the *trans-s-cis* product as shown in the ORTEP diagram in Figure 7.

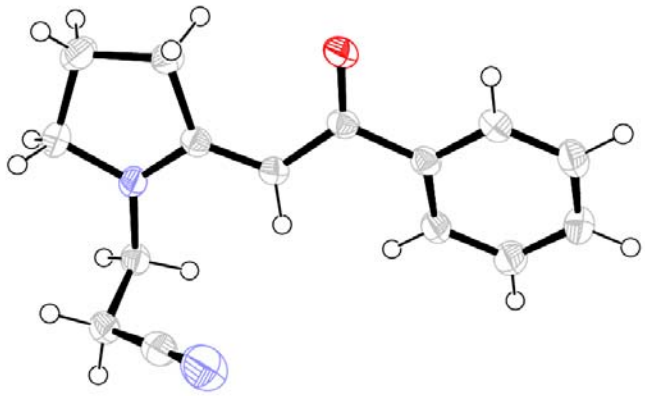
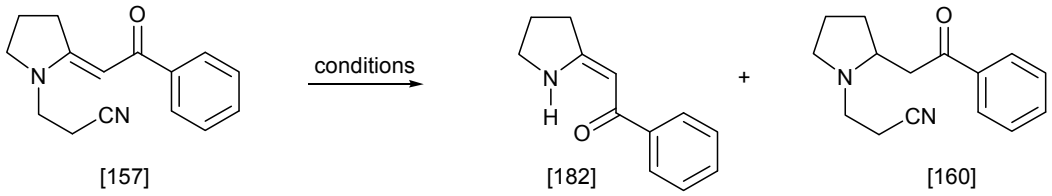


Figure 7: ORTEP diagram of vinylogous amide [157]. Thermal elipsoids are shown at the 50% probability level.

2.1.4 Reduction of vinylogous amide [157]

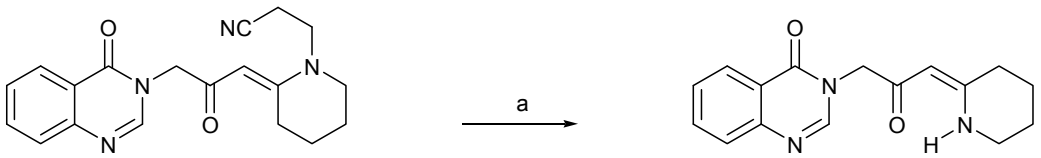


[157] [182] [160]

Scheme 33: Product distribution arising from lithium aluminium hydride redcution of [157]

The literature records[144] that the reduction of vinylogous amides to β-aminoketones is problematic, hydrogenolysis of the amino group and further reduction of the carbonyl group being frequently encountered. In our hands erratic results were obtained when attempts were made to reduce compound [157] to the β-aminoketone [160] (Scheme 33). In these laboratories the method of choice is the use of lithium aluminium hydride as the reductant as this gives more reliable results.[143] In the procedure of Parsons, reduction of

the double bond was achieved by stirring [157] for forty minutes with lithium aluminium hydride in tetrahydrofuran at 0 °C to afford the desired product [160] in 84% yield. If the same reaction was conducted at room temperature an almost 1:1 ratio of [160] and [182] is obtained. The loss of the cyanoethyl group is explained by the fact that a retro-Michael reaction is competing with the vinylogous amide reduction. In this case, the lithium aluminium hydride is acting as a base, rather than a nucleophile, by abstracting an acidic proton alpha to the nitrile group and causing a retro-Michael loss of the acrylonitrile to take place. It would then appear that the cyanoethyl group can act as an early protecting group for the synthesis of enaminones with *Z*-geometry as the synthesis of secondary vinylogous amides by way of the Eschenmoser sulfide contraction is problematic.[84] This was shown by Parsons who demonstrated that reaction of [157] with two equivalents of potassium tertiary butoxide in tetrahydrofuran at room temperature gave the enaminone [182] in 93% yield. This result has been extended by Pienaar[97] who prepared the key intermediate [183] in 85% yield *en route* to an analogue of the antimalarial alkaloid febrifugine (Scheme 34).



[183]

Scheme 34: The use of N-(2-cyanoethyl) as a protecting group of enaminones by Pienaar.[97] Reagent: (a) ^{t}BuOK, THF, rt, then acidic work-up.

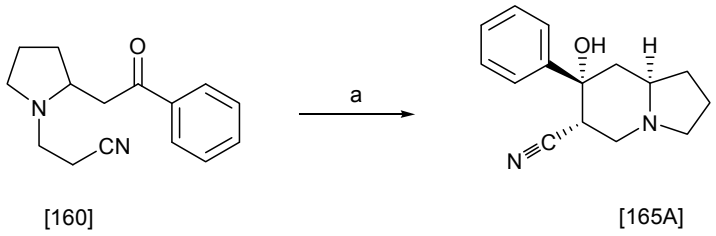
The identity of [182] was determined from its NMR spectra. The ^{1}H NMR spectrum was similar to that of [157], but lacked two triplets from the cyanoethyl chain, and a broad singlet, corresponding to the proton on nitrogen, had appeared at 10.28 ppm. The assignment of the *Z*-geometry is because the C-3 chemical shift had moved from the usual 3.3 – 3.4 ppm, seen in (*E)*-compounds as a result of deshielding through space by the

carbonyl group, to 2.74 ppm. As explained before, the driving force for the switch in geometry is probably the 6-membered hydrogen-bonded structure that is formed.

In our hands, reaction at 0 °C for forty minutes often resulted in an unidentifiable mixture being obtained. It is quite possible that a combination of any of the four reactions might be taking place: carbon-carbon double bond reduction, nitrile reduction, carbonyl reduction, and retro-Michael reaction. It would appear that the quality of the lithium aluminium hydride we had was superior to that of Parsons, in that it was exceedingly active. Therefore, it was imperative to cool the reaction to –10 °C and to work up the reaction within fifteen minutes to obtain the desired product in an 86% yield. At this temperature the retro-Michael product was also isolated in 3% yield. In addition, dilute reaction conditions with respect to the starting material (*ca.* 0.15 M) were required for optimal yields to be obtained.

The success of the reaction could be confirmed from the NMR spectra of the product. Of note was the disappearance of the C-2 carbon signal of [157] from 166.10 ppm and the appearance of a signal at 60.14 ppm for the C-2 carbon atom of [160]. In addition, the characteristic signal found for the enaminone C-8 carbon signal at 87.18 ppm had been replaced by a signal at 44.14 ppm, therefore suggesting the double bond had been successfully reduced. The characteristic vinyl peak in the ^{1}H NMR of [157] at 5.70 ppm had also disappeared, and the complex nature of all the signals in the ^{1}H NMR spectrum showed that the vinylogous amide system had been reduced, thus introducing a stereogenic centre.

2.1.5 Cyclization of β-aminoketone [160] to afford indolizidine [165A]



[160] [165A]

Scheme 35: Base mediated cyclization of pyrrolidine [160]. Reagent: (a) ^{t}BuOK, THF, rt.

With the β-aminoketone [160] in hand we were in a position to prepare the indolizidine skeleton (Scheme 35). Thus, reaction of [160] for three hours with two equivalents of potassium tertiary butoxide in tetrahydrofuran at room temperature afforded an orange gum containing the desired product [165A] in 80% yield after column chromatography. It appeared that we had a mixture of diastereomers present as evidenced by numerous small peaks in the ^{13}C NMR spectrum, owing to the fact that there were three stereogenic centres in the molecule, and thus possibly four racemic diastereomers present. However, one set of signals overwhelmingly dominated the other signals suggesting that one diastereomer was present in much higher concentration than the others. Slow recrystallization of this mixture afforded the major diastereomer in 58% yield. Attempts to furnish more products from the mother liquors resulted in decomposition to a black tar. Analysis of this tar showed many new signals in the ^{13}C NMR spectrum showing clearly that decomposition had occurred. This observation is in accord with Parsons who noted that compound [165A] tended to decompose on heating, which made recrystallization difficult. One then wonders whether the small signals seen in the original ^{13}C NMR spectrum are not in fact artifacts of decomposition of the indolizidine [165A] during isolation of the compound. However, the crystals obtained from the initial recrystallization were found to be exceptionally stable at room temperature and could be kept on the bench-top for several years without any noticeable change in colour or physical state.

In another similar preparation the product [165A] was obtained in 90% yield as a possible mixture of diastereomers, and rapid recrystallization of the gum in ethyl acetate – hexane mixtures at – 10 °C afforded the major diastereomer in 80% yield. These crystals tended to discolour and slowly decompose over time. The compounds, isolated by the above two different methods, appeared to be hydrates as a distinct signal for water could be found the ^{1}H NMR spectra in the region of 1.95 – 1.66 ppm. The coefficient of hydration was found to be slightly variable depending on the manner in which the compound was isolated (Figure 8).

Thus, slow recrystallization from ethyl acetate – hexane mixtures suggested a hydrate coefficient of 1 (Fig. 8A). It was this compound that was found to be very stable. However if recrystallization was induced rapidly, the hydration coefficient was found to be ½, and these crystals tended to discolour and slowly decompose over time (Fig. 8B). In addition, dissolving the solids from the rapid crystallization procedure in acetone and inducing crystallization by adding water to the mixture resulted in a solid with a hydration coefficient of 1 as well; and these crystals were also stable (Fig. 8C) .

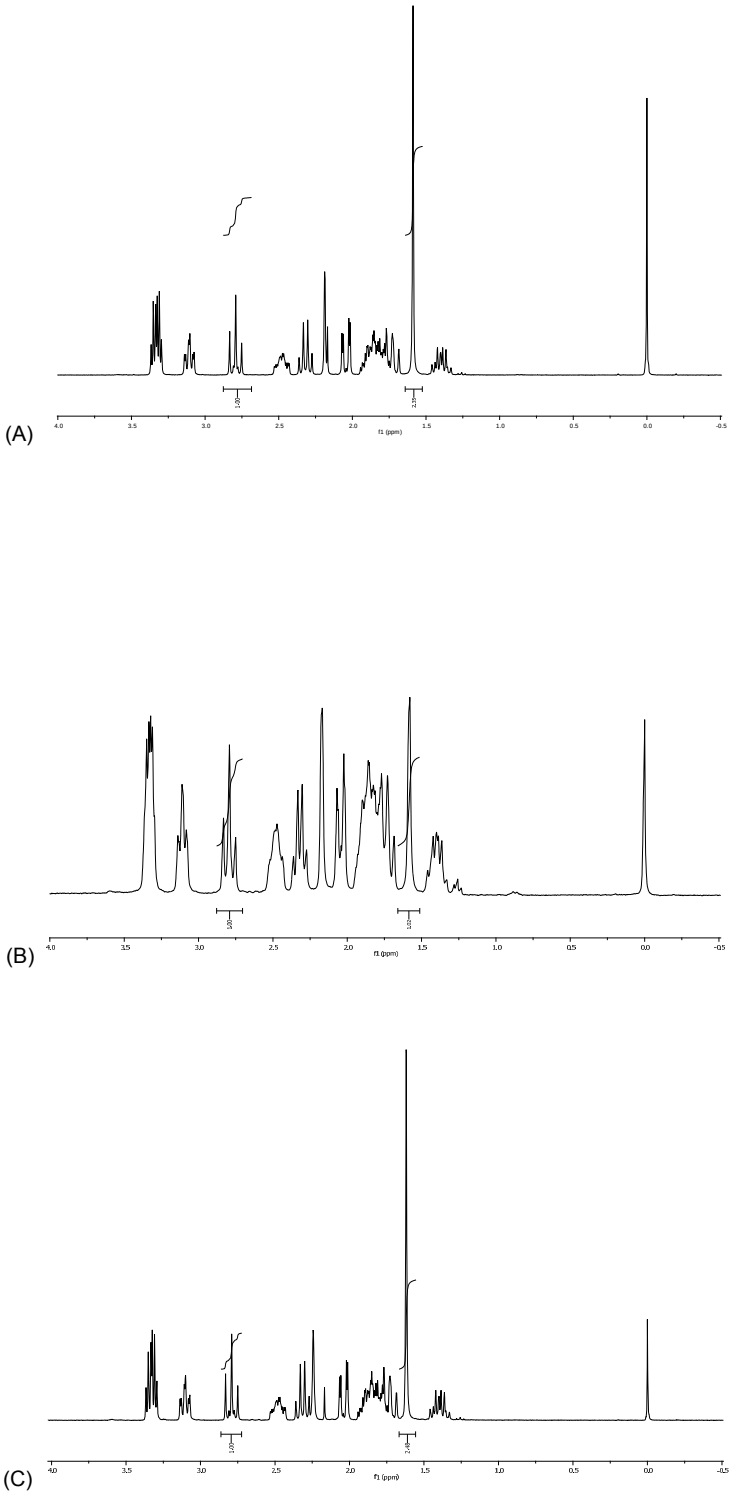


Figure 8: 300 MHz ^{1}H NMR spectra showing water of hydration of compound [165A]. All the spectra were recorded in $CDCl_3$. (A) Spectrum obtained from slow recrystallization of [165A]. (B) Spectrum obtained from rapid recrystallization of [165A]. (C) Spectrum obtained from recrystallization of the hemihydrate (as obtained in spectrum B) from aqueous acetone. The integration of the triplet signal at 2.79 ppm is for reference purposes only.

Regrettably, we were not able to elucidate the true coefficient of hydration by way of elemental analysis as the results we obtained were unreliable. Attempts to dehydrate the compound completely by sublimation or distillation resulted in decomposition of the starting material. These set of results seem to suggest that the product picked up the water during the work up in the first place. In addition, it would appear that during slow recrystallization, a fair amount of pre-organization is occurring during crystal growth between both the indolizidine and water molecules, thereby conferring stability to its lattice energy. In the case where crystallization is rapid, there appeared not to be as strong a stabilization of the lattice energy and slow decomposition of the indolizidine was occurring. Thus, an X-ray structure of the stable polymorph was done and is shown in the ORTEP diagram in Figure 9.

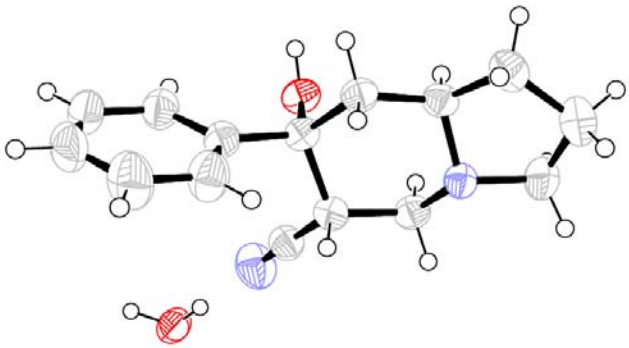


Figure 9: ORTEP diagram of indolizidine [165A] showing water of hydration. Thermal elipsoids are shown at the 50% probability level.

Interestingly, the water molecule had hydrogen-bonded to three different molecules and at different sites (Figure 9a). Thus, the oxygen atom of the water molecule was hydrogen-bonded to one molecule of [165A] at the hydroxyl terminus, one of the hydrogen atoms of the water molecule had hydrogen-bonded to a nitrile moiety of another molecule of [165A] and the other remaining hydrogen atom of the water molecule had hydrogen-bonded

to the tertiary amine of another molecule of [165A]. Another point of interest was the evidence of a *trans* fused ring structure.

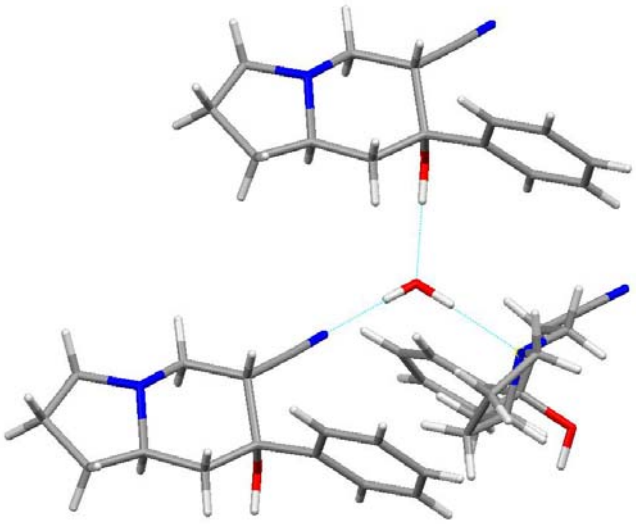
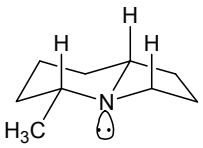


Figure 9a: MERCURY generated packing diagram showing the hydrogen bonding of water to three separate indolizidine [165A] molecules

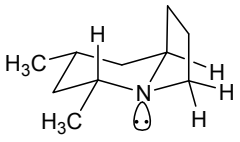
The crystal structure corroborated the NMR data obtained for this compound. The signals for the aromatic protons in the ^{1}H NMR spectrum of [165A] had coalesced into a narrow clump, evidence for the disappearance of the carbonyl group. The carbonyl carbon peak was absent from the spectrum while the nitrile carbon (C-9) was present in the ^{13}C NMR spectrum at 118.45 ppm. A quaternary carbon at 73.33 ppm indicated a carbon (C-7) atom bonded *inter alia* to a hydroxyl and phenyl group. The features of interest in the FTIR spectrum of [165A] were the sharp OH stretch at 3508 cm^{-1}, the nitrile stretch at 2246 cm^{-1}, and the lack of the carbonyl stretching vibration.

Another feature of interest is the presence of a Bohlmann band[145] for C-H stretching at 2826 cm^{-1} which implies *trans* ring fusion. Bohlmann bands refer to relatively strong C-H stretching bands in the range 2850 – 2700 cm^{-1} in the FTIR spectra of cyclic structures containing bridgehead nitrogen. It is common knowledge[146] that typical C-H stretching frequencies occur as two or three strong absorbances in the range 3000 – 2840 cm^{-1}. However, if two or more C-H bonds happen to be alpha to a nitrogen atom, and are orientated

antiparallel to the lone pair of electrons residing on the nitrogen atom as in indolizidine [184] (Figure 10), the stretching frequency of these bonds is lowered.[147]



[184]

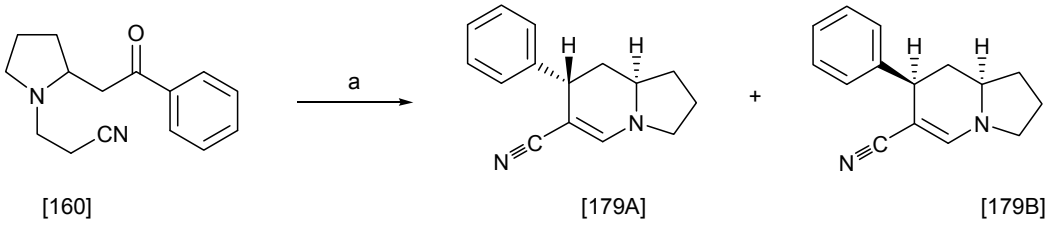


[185]

Figure 10: Trans- and cis-ring fusion in indolizidines. Bohlmann bands are strongest in the former.[147, 150]

This is rationalized by invoking delocalization of electron density from the nitrogen lone pair into the sigma antibonding orbitals of these C-H bonds.[148, 149] Such delocalization serves to weaken these C-H bonds and thus they stretch at a lower frequency. Bohlmann bands are thus only significant if the bicyclic system exhibits *trans* ring fusion. Indolizidine [185] exhibiting *cis* ring fusion completely lacks Bohlmann bands.[150] In addition, the *trans* ring fusion can be seen in the crystal structure where the bridgehead hydrogen is axially disposed relative to the lone pair of electrons on the nitrogen. Although the lone pair of electrons cannot be seen, it can be inferred by considering the general geometry around the nitrogen atom.

2.1.6 Cyclization of β-aminoketone [160] to afford indolizidines [179A] and [179B]



[160] [179A] [179B]

Scheme 36: Base mediated synthesis of vinylogous cyanamides [179]. Reagent: (a) ^{t}BuOK, THF, Δ.

With pyrrolidine [160] at hand we are in a position to prepare the vinylogous cyanamides [179A] and [179B] (Scheme 36). This route replicated that of Parsons. Therefore, reaction of pyrrolidine [160] with two equivalents of potassium tertiary butoxide in refluxing tetrahydrofuran for three hours afforded the vinylogous cyanamides [179A] and [179B] as a white solid in 88% yield after column chromatography. The diastereomer ratio could be determined by ^{1}H NMR spectroscopy recorded on a 300 MHz spectrometer, and was determined to be 3:1 in favour of [179A] (*vide infra*). Recrystallization of the solid afforded [179A] allowed for complete characterization of this compound. The solid was stable at room temperature and the melting point was determined at 120 – 122 °C.

The FTIR spectrum indicated a prominent Bohlmann band at 2870 cm^{-1} which implies a *trans* fusion of the bicyclic structure. Although the Bohlmann band lies outside the normal range of 2850-2700 cm^{-1}, they were well separated from the C-H stretches commonly found in this region, therefore allowing for the assignment of this band as a Bohlmann band. Another point of interest is the strong absorption at 2182 cm^{-1} for the nitrile group. Up until now the absorptions encountered have been weak in comparison. In addition, the absorption was somewhat lower than seen for the other nitrile containing compounds (typically, 2249 cm^{-1} for [168A], 2244 cm^{-1} for [157], 2248 cm^{-1} for [160] and 2246 cm^{-1} for [165A]). These features are consistent with the

findings of Jungmann[76] who has prepared vinylogous cyanamides by the sulfide contraction route (see section 1.4, page 33). Lastly, a strong absorption at 1614 cm^{-1} in the FTIR spectrum indicated the presence of the enamine double bond.

As the compound had two stereogenic centres, the ^{1}H NMR spectrum was complicated as a result of the diastereotopic nature of each proton. However, the spectrum obtained on the 400 MHz spectrometer separated most of the signals of which the following are examples. Points of interest in the ^{1}H NMR spectrum were the vinyl proton (H_5) at 7.19 ppm; and the corresponding signal for the vinyl carbon (C-5) in the ^{13}C NMR was found at lowest field at 145.26 ppm. In addition, the quaternary carbon C-6 of the double bond was found upfield at 74.10 ppm. Some additional diagnostic features in the ^{1}H NMR spectrum were the H_7 proton that appeared as a doublet of doublets (J = 2.0 and 5.3 Hz respectively) at 3.73 ppm. The corresponding coupling constants from the H_8 protons were found at the ddd multiplets at 2.06 ppm (J = 2.0 Hz) and 1.54 ppm (J = 5.3 Hz) respectively. Secondly, the H_8 protons exhibited a geminal coupling constant of 12.8 Hz. In addition, the H_8 proton at 2.06 ppm and 1.54 ppm exhibited coupling constants to H_{8a} (itself a complex multiplet found at 3.08 -2.99 ppm) of 3.5 and 11.7 Hz respectively. The H_3 protons can be found as a multiplet at 3.59-3.47 ppm and as a td multiplet at 3.33 ppm. Lastly, the H_1 protons can be found as ddd multiplet at 2.01 ppm and as a tdd multiplet at 1.45 ppm. In addition, geminal coupling constant was found to be 11.9 Hz. Finally, all of these assignments with respect to connectivity of the relevant protons were corroborated by two dimensional C-H and COSY NMR experiments.

The structure of the vinylogous cyanamide [179A] was corroborated by an X-ray structure and is shown in the ORTEP diagram in Figure 11. Again, the *trans* fusion of the ring was evident, along with the position of the double bond.

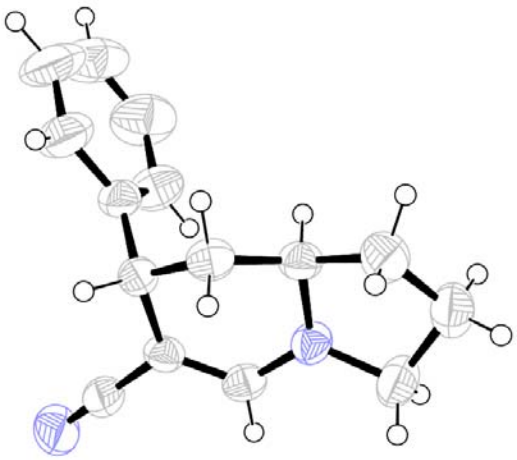
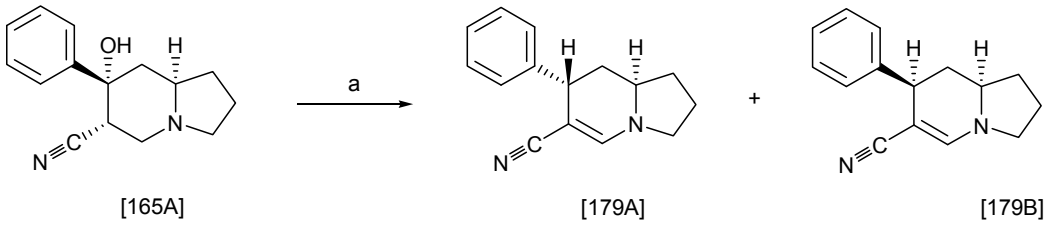


Figure 11: ORTEP diagram of vinylogous cyanamide [179A]. Thermal ellipsoids are shown at the 50% probability level.

2.1.7 Based-induced dehydration of indolizidine [165A]



[165A] [179A] [179B]

Scheme 37: Base mediated synthesis of vinylogous cyanamides [179]. Reagent: (a) ^{t}BuOK, THF, Δ.

Having repeated the experiments of Parsons in realizing the indolizidine [165A] and a diasteromerically pure vinylogous cyanamide [179A], we next attempted the base-induced dehydration of indolizidine [165A] (Scheme 37). At this point we should mention that we are trying a step-by-step elucidation of the mechanism. Therefore, does the indolizidine intermediate [165A] fall onto the reaction path? Thus, reaction of [165A] with two equivalents of potassium tertiary butoxide in refluxing tetrahydrofuran for four hours afforded the diastereomers [179A] and [179B] in an overall yield of 79% after flash chromatography. In this case, the use of flash chromatography gave partial

separation of the diastereomers. The vinylogous cyanamide [179A] eluted first in 51% yield, followed by a mixed fraction (14% yield), and finally the vinylogous cyanamide [179B] eluted in 14% yield. The diastereomer ratio was estimated by analysis of the ^{1}H NMR spectra of the three fractions, to be 3:1 as observed before. This then allowed for the characterization of the minor diastereomer [179B]. The cyanamide [179B] was a solid and its melting point was determined at 111–113 °C, which is different to that obtained for the major diastereomer. The solid was also relatively stable, although it rapidly turned brown on standing at room temperature. On prolonged storage at room temperature the compound collapsed to a black tar. Therefore, this experiment has shown that the indolizidine [165A] falls onto the reaction path.

The FTIR spectrum indicated a prominent Bohlmann band at 2869 cm^{-1} which again implies a *trans* fusion of the bicyclic structure. Another point of interest is the strong absorption at 2182 cm^{-1} for the nitrile group, and a strong absorption at 1608 cm^{-1} indicating the presence of the enaminone double bond.

Again, as the compound had two stereogenic centres, the ^{1}H NMR spectrum was complicated as a result of the diastereotopic nature of each proton. Diagnostic features of the vinylogous cyanamide [179B] can be found in the NMR spectra of this compound. The vinyl carbon atoms C-6 and C-5 can be found in the ^{13}C NMR at 145.33 ppm and 78.22 ppm respectively. The vinyl proton H_5 can be found as a doublet (J = 1.1 Hz) at 7.09 ppm in the ^{1}H NMR spectrum. This doublet implies ^{4}J coupling to proton H_7, which is in the acceptable range for vinylic coupling. This evidence was corroborated by observing a cross-peak in the two dimensional C-H correlation spectrum for these two protons. The rest of the data were similar to that of the other diastereomer and need no further discussion.

The structure of the minor diastereomer was corroborated by an X-ray structure and is shown in the ORTEP diagram in Figure 12. Again, the *trans* fusion of the ring was evident, along with the position of the double bond. In

addition, the relative disposition of the both the phenyl and the hydrogen atom on C-7 were opposite to that of the major diastereomer, confirming that we had indeed isolated a diastereomer of [179A].

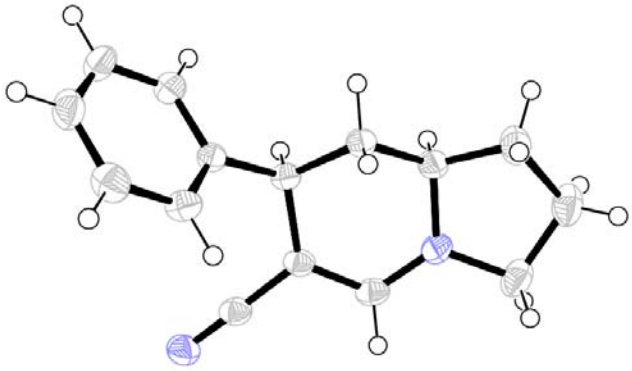
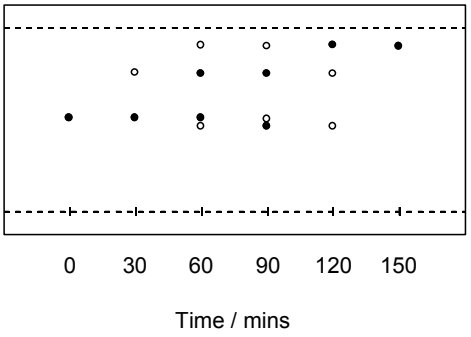


Figure 12: ORTEP diagram of vinylogous cyanamide [179B]. Thermal ellipsoids are shown at the 50% probability level.

2.1.8 Attempts to identify other reaction intermediates

In keeping with the idea that we are trying to elucidate the reaction mechanism for the transformation of pyrrolidine [160] into the vinylogous cyanamides [179], TLC monitoring of the reactions of the syntheses of the vinylogous cyanamides from either [160] or [165A], as described above, revealed two unknown intermediates that were detected at various time intervals and at different relative concentrations (Figure 13).



Key:

R_f (EtOAc): 0.90 - vinylogous cyanamides [179A] and [179B]

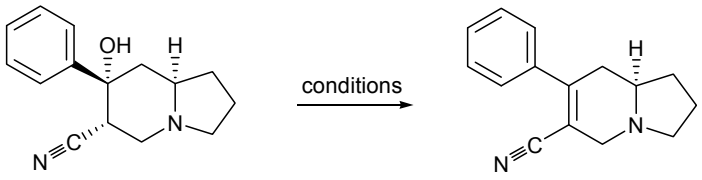
R_f (EtOAc): 0.75 - unknown intermediate

R_f (EtOAc): 0.51 - pyrrolidine [160] or indolizidine [165A]

R_f (EtOAc): 0.46 - unknown intermediate

Figure 13: Sketch of a TLC analysis reaction profile for the preparation of the vinylogous cyanamides. The hollow circles indicate relatively low intensity spots, and the bold circles indicate relatively higher intensity spots as viewed under UV lamp at 254 nm.

The first unknown intermediate formed reasonably rapidly and persisted during the course of the reaction, although its intensity, as judged by TLC, diminished during the course of the reaction. The other intermediate appeared to be a late stage intermediate *en route* to the vinylogous cyanamide products as the relative concentration, as adjudged by TLC analysis, only became apparent towards the latter half of the reaction progress (it was partly obscured by the starting materials due to the relatively close R_f values). It was also noted that this intermediate was consumed as rapidly as it was formed. Therefore, an investigation was undertaken to isolate these intermediates and to show that one of them should at least be the styrene [178], which we expect to be formed before isomerization to the final products. We reasoned that the first appearing unknown intermediate may in fact be a product of epimerization of indolizidine [165A], as the proton alpha to the nitrile moiety is acidic and therefore prone to epimerization under basic conditions.[151] Consequently we assumed the second more polar unknown intermediate may be the styrene [178] and therefore sought to isolate this compound.



[165A] [178]

Scheme 38: Synthesis of styrene [178] from indolizidine [165A]

The fact that this intermediate was consumed as rapidly as it formed presented some challenges in isolating this compound. In addition, the very close R_f value relative to the starting materials also complicated the isolation and purification of the compound. Therefore, we decided to repeat the experiment using the indolizidine [165A] as the starting material (Scheme 38). The reason for choosing indolizidine [165A] as the starting material of choice was that the pyrrolidine [160] had the same R_f value as indolizidine [165A] and would unnecessarily complicate the isolation of the unknown intermediate. It was decided to repeat the experiment as outlined in section 2.1.7 and arrest the reaction early when it appeared that a sufficient quantity of the intermediate had formed as judged by TLC analysis. Many reactions were attempted and regardless of whether the reactions were arrested after 30, 60, 90, and 120 minutes we could not isolate the intermediate in sufficiently quantity or pure form to unambiguously assign the compound as the styrene. It appeared that using TLC as a guide as to when to arrest the reaction was unreliable. A possible explanation for this failure to use TLC as a guide may stem from the fact that the relative intensity of the spots when visualized under UV irradiation at 254 nm was by no means an indication of the relative amounts of the various compounds within the reaction mixture as they may be absorbing the UV light to different extents. In these laboratories we also routinely make use of a basic potassium permanganate dip as a stain reagent to visualize TLC plates. In our case, dipping the TLC plates into this stain reagent was not of value as we were not able to judge the relative intensities of the resulting yellow spots after staining; they all appeared the same.

The majority of the experiments that had been attempted to isolate the unknown intermediate were conducted at *ca*. 0.10 M with respect to the starting material. We then wondered if dilution may assist us in preparing sufficient quantity of this product in pure form. In one such preparation, the indolizidine [165A] was stirred with two equivalents of potassium tertiary butoxide in tetrahydrofuran under very dilute (*ca.* 0.03 M) conditions for twenty-four hours with no discernible formation of the desired unknown intermediate; although traces of the other less polar intermediate could be detected, an observation that proved useful for its intended isolation. Therefore, the reaction was refluxed for an additional twenty-four hours. Work up and column chromatography finally afforded the styrene [178] as a yellow oil in 50% yield, therefore proving our initial assumption correct with regards to the identity of this intermediate. The oil was relatively unstable and rapidly turned black in colour on exposure to air.

As the styrene was the only isolable product and isolated in modest yield, this probably adds to the evidence as to the instability of the indolizidine [165A] when exposed to prolonged heating. A cautious observation can be inferred with respect as to the effect of dilution and prolonged heating. In addition to starting material decomposition we cannot discount the possibility of the existence of the hydrolysis of products of the *in situ* formed vinylogous cyanamides. This is so, as the indolizidine [165A] contained water and the water may have hydrolyzed the nitrile functional group to that of an amide under the basic conditions of the reaction. In addition, the styrene [178] may be the culprit as well, as deleterious decyanation reactions have been observed for these type of α,β-alkenenitriles.[152] Therefore, we may have totally missed these products during chromatography as they may have been very polar species. Regardless of these possibilities, what is more important is that the reaction had slowed sufficiently so as to isolate the styrene intermediate, when the experiment is performed under dilute conditions.

The FTIR spectrum indicated a strong series of prominent Bohlmann bands between 2700 and 2795 cm^{-1} which again implies a *trans* fusion of the bicyclic structure. Another point of interest is the strong absorption at 2210 cm^{-1} for the nitrile group, and a medium absorption at 1622 cm^{-1} indicating the

presence of the double bond. Other diagnostic features of this compound could be found in the NMR spectra. The C-6 and C-7 carbon signals of the double bond are found in the ^{13}C NMR spectrum at 106.53 ppm and 154.27 ppm respectively. A point of interest in the 1H NMR spectrum was the near collapse of the aromatic signals into a singlet at 7.42-7.29 ppm. In addition, the protons H_5 can be found as a doublet of doublets at 3.74 ppm and as a ddd multiplet at 3.06 ppm respectively. They exhibit geminal coupling of J = 15.8 Hz. The protons H_8 can be found as a dt multiplet at 2.71 ppm and as a dddd multiplet at 2.42 ppm respectively. These protons exhibit geminal coupling of J = 18.0 Hz. The dd and ddd multiplets observed for the H_5 protons can be readily explained as an interesting long range ^5J coupling to the H_8 protons. Therefore, the H_5 proton at 3.74 ppm shows coupling of ^5J = 2.6 Hz to the H_8 proton found at 2.42 ppm. This accounts for the doublet of doublets nature of this H_5 signal. In addition, the remaining H_5 proton at 3.06 ppm shows coupling of ^5J = 3.1 and 4.3 Hz to both of the H_8 protons at 2.71ppm and 2.42 ppm respectively. This evidence naturally was corroborated by a COSY experiment as shown in Figure 14.

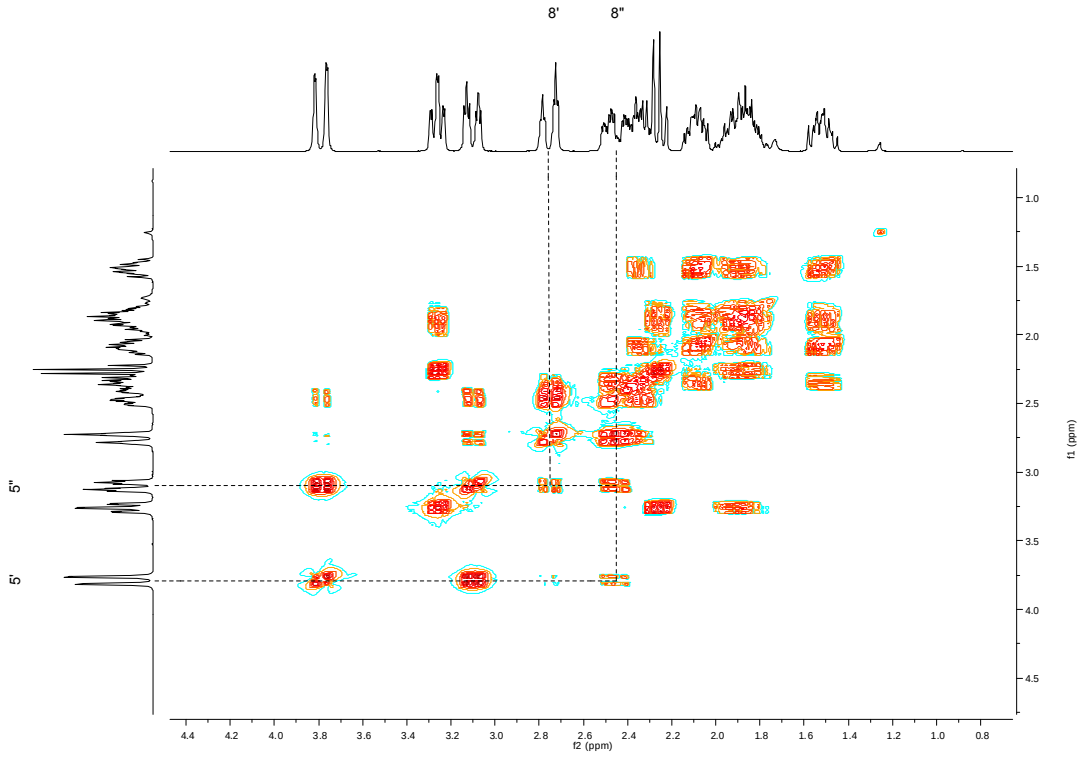


Figure 14: Cosy spectrum of styrene [178] showing ^5J coupling between H_5 and H_8

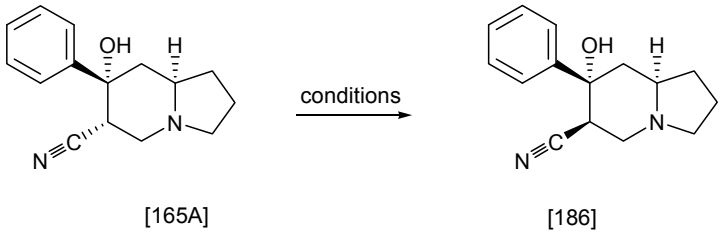
We next turned our attention to synthesizing the styrene by way of an acid-induced elimination. Attempted dehydration under Dean-Stark conditions failed, regardless of the acid source used. For example, a benzene solution of indolizidine [165A] was refluxed for twenty-four hours in the presence of catalytic *p*-toluenesulfonic acid or stoichiometric copper sulfate upon which returned the starting material unscathed. Reaction of the indolizidine [165A] in the presence of ethereal hydrochloric acid at room temperature also failed. In addition, reaction of the indolizidine [165A] with aqueous sulphuric acid also failed and returned starting material after work up. Finally, success was achieved by adding fifteen to twenty equivalents of concentrated sulphuric acid in one portion to a solution of indolizidine [165A] in dichloromethane at room temperature. The reaction got exceedingly warm, and therefore the reaction set-up required a fitted condenser to contain the refluxing dichloromethane. In addition, the reaction had to be neutralized within ninety seconds for the optimum yield of 50% to be achieved. This experiment was repeated three times and gave consistently a 50% yield. In one preparation the reaction was allowed to continue for twenty minutes under identical conditions and the isolated yield was 40%. The spectroscopic data for the styrene prepared in this manner agreed with those prepared earlier.

Having synthesized the styrene [178] by way of an acid-induced elimination of the indolizidine [165A], we next attempted an alternative elimination reaction by way of the mesylate in the hope of obtaining a higher yield. However, reaction of indolizidine [165A] with methanesulfonyl chloride in the presence of either pyridine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) met with failure. The failure of these reactions probably stems from the fact that the water of hydration that is associated with the indolizidine [165A] may have hydrolyzed the mesyl chloride before any reaction could take place.

With a sufficient quantity of styrene [178] in hand we next turned our attention to the isomerization of this compound to the vinylogous cyanamides. Therefore, reaction of the styrene [178] with two equivalents of potassium tertiary butoxide in refluxing tetrahydrofuran for five minutes afforded the vinylogous cyanamides in 74% yield, with the same diastereomer ratio as observed before. This rather quick reaction then accounts for the observation

that the styrene isomerizes rapidly, thereby consolidating the observation that it gets consumed as readily as it forms during the initial preparation of the vinylogous cyanamides from the indolizidine [165A] as judged by TLC analysis.

2.1.9 Epimerization of indolizidine [165A]



[165A] [186]

Scheme 39: Epimerization of indolizidine [165A]

The identity of the other less polar unknown intermediate was next investigated (Scheme 39). We assumed that this intermediate was the epimer of indolizidine [165A], as it appeared as the first intermediate *en route* to the synthesis of the vinylogous cyanamides from indolizidine [165A]. Gratifyingly, there exists a literature record[151] for epimerization of β-hydroxy nitriles, therefore reinforcing our initial assumption as to the identity of the intermediate. As we had trouble isolating sufficient quantity of styrene [178] from the refluxing tetrahydrofuran mixture of indolizidine [165A] under basic conditions, we decided not to use this method. As mentioned earlier, an attempted twenty-four hour room temperature reaction of indolizidine [165A] in tetrahydrofuran towards the isolation of the styrene [178] afforded only trace quantities of the suspected epimer, and it is this observation that we wished to develop further.

Thus, reaction of the indolizidine [165A] with two equivalents of potassium tertiary butoxide at room temperature for three to five days gave a spread of all the known products and in varying amounts; although the starting material was the most prominent product after column chromatography. This protocol

then necessitated repeated chromatography to isolate fractions enriched with the suspected epimer followed by resubmitting the crude starting material (as it was more often contaminated with the styrene) into several new reactions. Finally after several cycles, the fraction enriched with the suspected epimer was subjected to careful column chromatography in order to separate it from the vinylogous cyanamides as they had very close R_f values when 20% ethyl acetate/hexane was used as the eluent. Pleasingly, a small sample was obtained for comprehensive characterization and its identity was indeed revealed as the epimer [186].

The FTIR spectrum of the epimer [186] was very similar to that of the indolizidine [165A]. Notable differences are that the OH signal appeared as a new sharp absorption at 3472 cm^{-1} and the broad signal at 3192 cm^{-1} was absent. In addition, the nitrile group was found slightly lower as a weak absorption at 2248 cm^{-1}. The NMR spectra by all accounts were rather unremarkable relative to that of the indolizidine [165A], although slight differences in the positions of the signals were noted. The only other notable feature about this compound was the melting point, which was determined at 136 – 138 °C which differed to that of the indolizidine [165A] whose melting point was determined at 118 – 119 °C for the stable polymorph. Interestingly, the compound did not exist as a hydrate. In addition, a crystal structure was determined for this compound and is shown in the ORTEP diagram in Figure 15.

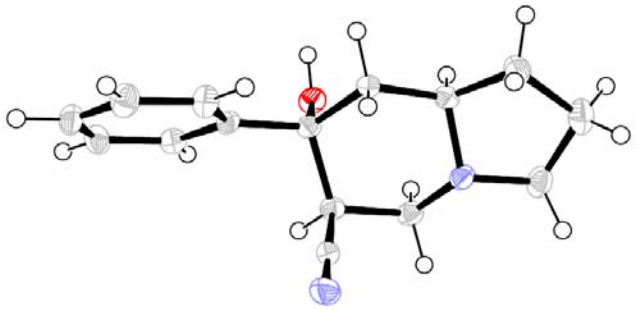


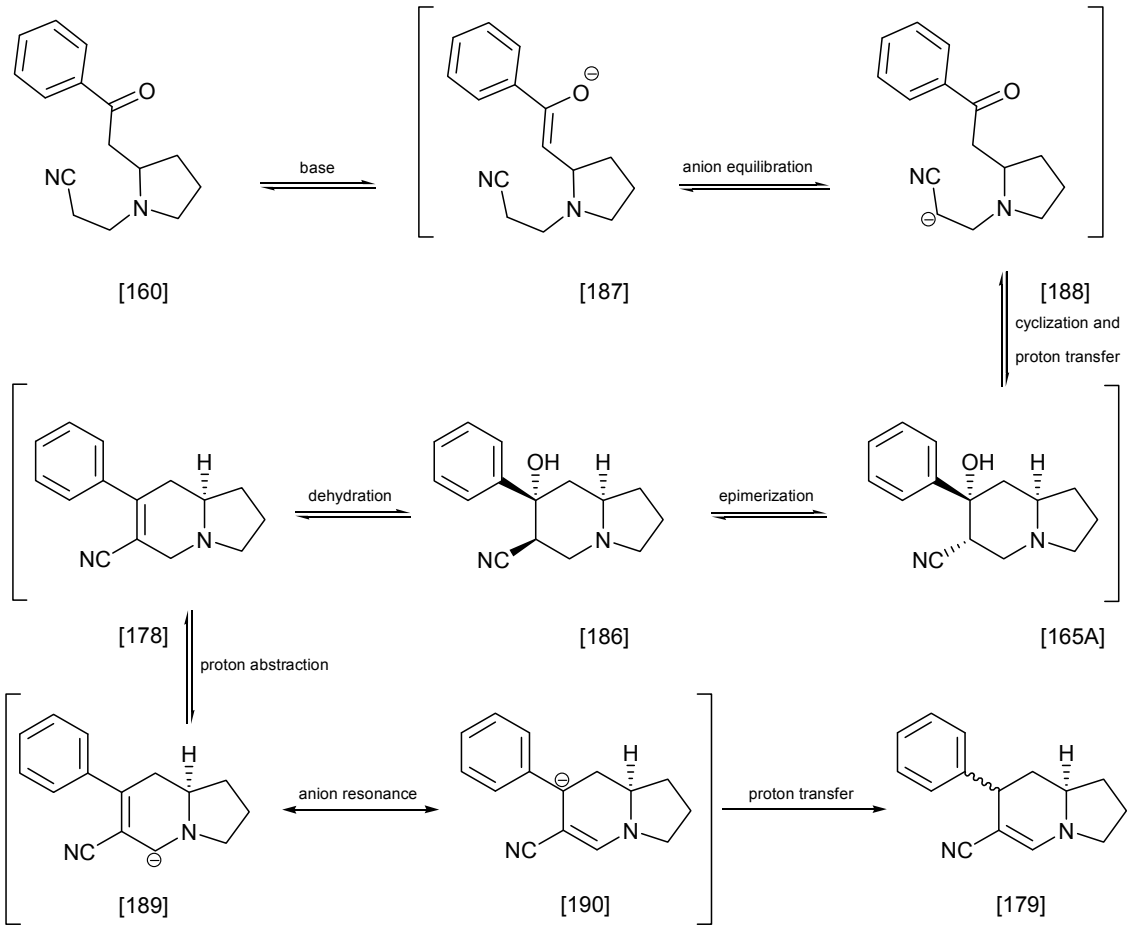
Figure 15: ORTEP diagram of indolizidine [186]. Thermal ellipsoids are shown at the 50% probability level.

As we had now confirmed the identity of this intermediate as the epimer [186] we next sought reaction conditions to improve its yield by reducing the number of equivalents of base used. Thus, reaction of the indolizidine [165A] with one equivalent of potassium tertiary butoxide, and maintaining the reaction at 40 – 50 °C for a period of forty-eight hours afforded the epimer [186] in 16% yield along with recovered starting material in 44% yield. The isolated yield could be improved upon by reaction of the indolizidine [165A] with ethanolic sodium ethoxide for four days to afford the epimer [186] in 33% yield along with quantitative recovery of starting material.

Finally, this investigation was brought to a close by reaction of the epimer [186] with two equivalents of potassium tertiary butoxide for two hours in refluxing tetrahydrofuran. This reaction afforded the vinylogous cyanamides in a modest yield of 56% after column chromatography.

2.1.10 Concluding remarks and comments

This investigation entailed the chemoselective condensation of a nitrile anion with a remote carbonyl group. In addition, careful monitoring and isolation of reaction intermediates have allowed for documentation of an unambiguous sequence of events occurring during the synthesis of the vinylogous cyanamides from either the pyrrolidine [160] or the indolizidine [165A]. The pK_a of acetophenone and acetonitrile are approximately 20 and 25 respectively, with the pK_a of acetonitrile being recently revised upward to approximately 30.[153] Remarkably, we encountered a chemoselective cyclization by way of a nitrile anion despite the presence of a more acidic carbonyl group (ΔpK_a = 6 – 11) favouring enolate formation and addition to the nitrile group. Thus, conceptually several competitive cyclisations exist with only one mode leading to the cyclic vinylogous cyanamides. Clearly, the cyclization's chemoselectivity depends on the relative basicity and electrophilicity of the ketone and nitrile groups with the latter being more critical. Despite a perception to the contrary, nitriles are poor electrophiles that often resist nucleophilic attack by organometallic reagents.[152] Ketones, by contrast, are excellent electrophiles that condense rapidly with a plethora of nucleophiles. Therefore, the combination of poor nitrile and high ketone electrophilicity favourably disposed the carbonyl-containing nitrile [160] towards nitrile anion cyclisation. Mechanistically, the formation of the vinylogous cyanamides [179] from the pyrrolidine [160] is shown in Scheme 40.



Scheme 40: Plausible reaction mechanisms en route to the diastereomers of the vinylogous cyanamides [179] from pyrrolidine [160]

Therefore, conversion to the cyclic styrene intermediate [178] implies a relatively efficient inter- or intramolecular proton transfer that converts the enolate [187] into the nitrile anion [188].[154] Diastereoselective cyclization and proton transfer from the *in situ* generated tertiary butanol affords the intermediate indolizidine [165A]. Epimerization then affords the intermediate [186]. Finally, dehydration furnishes the respective intermediate styrene [178]. Gratifyingly, these intermediates could be isolated and characterized.

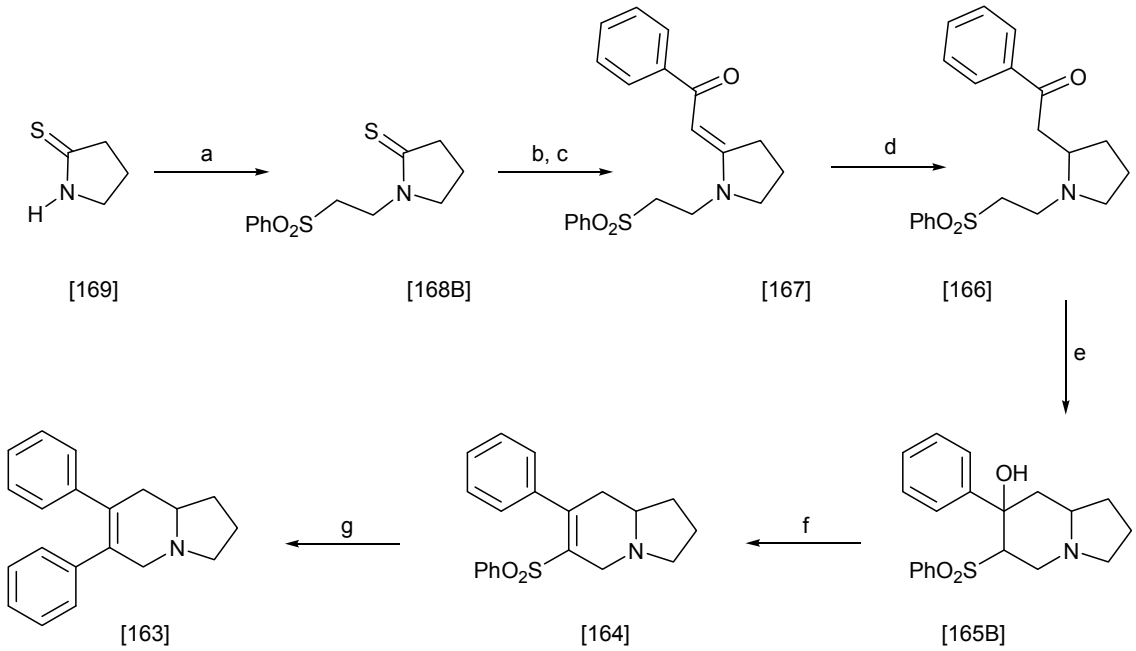
Base-promoted isomerizations, as has been shown repeatedly, are regarded as occurring through a carbanion generated by a base.[155, 156] Thus, isomerization of intermediate [178] probably occurs through the resonating carbanions [189] and [190]. Since the alkenes are not held as carbanions in the presence of the tert-butoxide, but rather isomerize by way of the

carbanion, the isomerization produces the thermodynamically most stable alkene. Therefore, proton transfer completes the cascade of events to afford the thermodynamic more stable vinylogous cyanamides [179]. In addition, for the observed vinylogous cyanamide products to be formed there must be better π-orbital overlap than in the alternative product. This is because the two electron-rich groups conjugated through the double bond are orientated in a *trans*, rather than a *cis* geometry. In addition, nitrogen is more electron rich than the phenyl group, and therefore a better π-donor.

2.2 Arylated indolizidine systems containing a sulfone moiety

2.2.1 Introduction

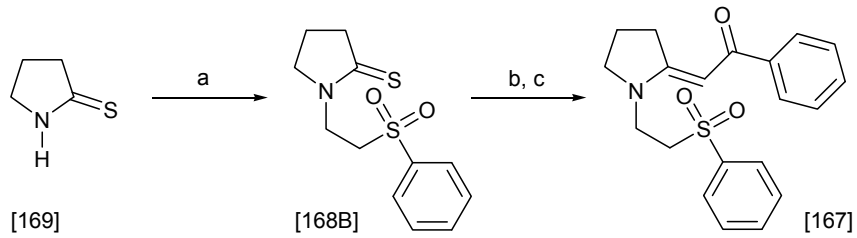
The main objective of this phase of the project is to transfer the methodology developed above, relating to intramolecular cyclisations, to new systems. This will allow access to the indolizidine skeleton as found the alkaloids ipalbidine [14] and septicine [12]. The synthesis of the alkaloid septicine is intended, and we hoped to develop a general methodology for gaining access to the unsaturated bicyclic skeleton. In addition, we planned to extend the range of Michael acceptors that can add to 2-pyrrolidinethione at nitrogen. Again the synthesis and reactions of vinylogous amides form the core of the approach to the desired alkaloids. Aspects of this work have been tackled by Brankin[78] and therefore most of the compounds have been satisfactorily characterized in these laboratories. Before an actual undertaking of the synthesis of septicine was to commence, we decided to do a model study as outlined in the envisaged route shown in Scheme 41.



Scheme 41: Envisaged model study towards the synthesis of a diarylated indolzidine. Reagents: (a) Phenyl vinyl sulfone, NaOH (cat.), wet THF, rt; (b) Phenacyl bromide, MeCN, rt; (c) PPh_3, Et_3N, rt; (d) $LiAlH_4$, THF, 0 ^oC; (e) ^tBuOK, THF, rt; (f) ^tBuOK, THF, rt or Δ; (g) PhMgBr, $Ni(acac)_2$, THF, rt.

The success of the project ultimately relies upon the crucial cyclization of the pyrrolidine [166] into the indolizidine [165B]. This then can allow for olefination affording the styrene [164], under basic conditions. Lastly, the indolizidine [163] in which the second aryl unit has been installed can be accomplished by way of a nickel-catalyzed substitution reaction with an aryl Grignard reagent.

2.2.2 Preparation of vinylogous amide [167]



Scheme 42: Preparation of the Eschenmoser sulfide contraction product [167]. Reagents: (a) Phenyl vinyl sulfone, NaOH (cat.), wet THF, rt; (b) Phenacyl bromide, MeCN, rt; (c) PPh_3, Et_3N, rt;

Compound [168B] was prepared by the Michael reaction of 2-pyrrolidinethione [169] with phenyl vinyl sulfone in tetrahydrofuran in the presence of a catalytic quantity of sodium hydroxide (Scheme 42). In this instance the need for the addition of water to solubilize the catalyst is unnecessary as the reaction is consistently completed within twenty-four hours. Workup and chromatography afforded the product as a white solid and in quantitative yield.

The appearance of the aromatic signals at 7.97 – 7.90 ppm and 7.73 – 7.65 ppm in the ^1H NMR spectrum indicated the presence of the phenylsulfonyl group. Further evidence of the Michael product was provided by the FTIR spectrum. The prominent N-H stretch observed at 3157 cm^{-1} for the secondary thiolactam [169] was absent in the tertiary Michael product.

With the thione in hand, the Eschenmoser sulfide contraction was conducted in a one-pot procedure at room temperature. As previously mentioned, salt formation and extrusion of the sulfur was carried out using acetonitrile as the solvent. The solvent was evaporated and the resulting gum was taken into ethyl acetate and washed thoroughly with water. The organic extract was then extracted into dilute hydrochloric acid and the product was liberated upon basification with a solution of concentrated aqueous ammonia. The resulting solid was extracted with dichloromethane, thoroughly washed with water, dried and evaporated to afford the product in 91% yield without the need for chromatographic purification.

The ^{1}H NMR spectrum showed the distinguishing vinyl proton H_{12}, at 5.58 ppm, while the vinyl carbon signal C-12 appeared at 87.00 ppm in the ^{13}C NMR spectrum. Interestingly, long range coupling of ^{4}J = 1.2 Hz of the vinyl proton H_{12} to one of the protons H_3 can be detected in the ^{1}H NMR spectrum. Again, the assignment of *E*-geometry of this compound rests largely on the position of absorptions of the methylene protons at C-3 in the ring in the ^{1}H NMR spectrum. In the present case the absorption can be found at 3.29 ppm which is similar to that of the vinylogous amide [157] where it was found at 3.40 ppm. The assignment of the (*E)*-geometry in compound [167] was further corroborated by obtaining a crystal structure, confirming that we had indeed synthesized the *trans-s-cis* product as shown in the ORTEP diagram in Figure 16.

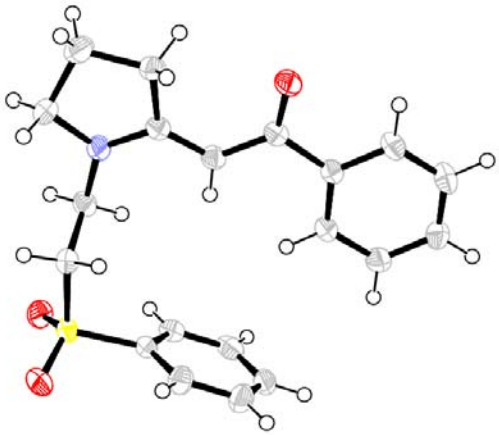
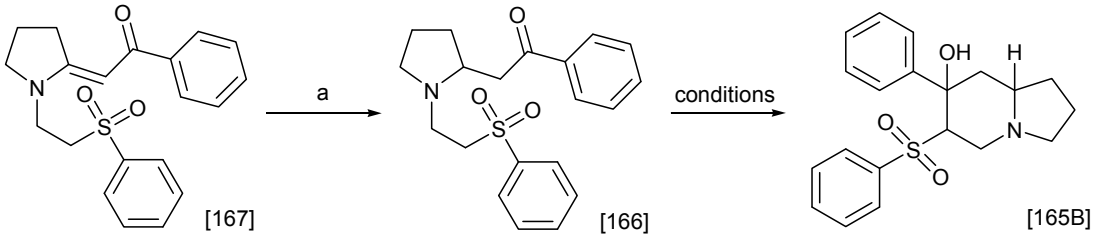


Figure 16: ORTEP diagram of vinylogous amide [167]. Thermal ellipsoids are shown at the 50% probability level.

Finally, the FTIR spectrum of the vinylogous amide contained two absorption bands indicative of the enaminone system, i.e. a C=O stretch at 1624 cm^{-1} and a C=C stretch at 1597 cm^{-1} respectively. In addition the HRMS gave a molecular ion peak at *m/z* = 355.1263 confirming the formula $C_{20}H_{21}NO_3S$ ($C_{20}H_{21}NO_3S$ requires 355.1242).

2.2.3 Preparation and attempts at cyclization of β-aminoketone [166] to afford indolizidine [165B]

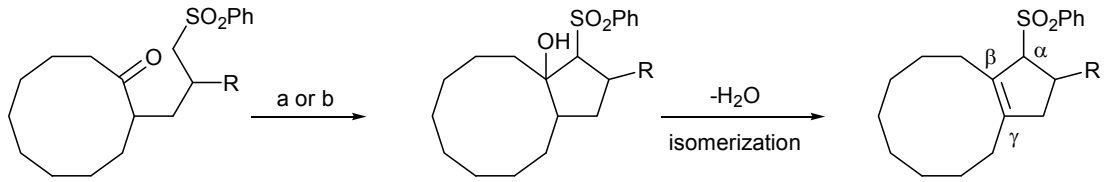


Scheme 43: Attempted preparation of indolizidine [165B]. Reagent: (a) $LiAlH_4$, THF, 0 ^{o}C.

The carbon-carbon double bond of the vinylogous amide [167] was reduced using lithium aluminium hydride (Scheme 43). Thus, the pyrrolidine [166] was prepared by treating the vinylogous amide [167] with lithium aluminium hydride in tetrahydrofuran at 0 °C for five minutes. Work up and chromatography afforded the product as a thick oil in 95% yield. The absence of the vinyl proton singlet at 5.58 ppm and the increased complexity of all the signals in the ^{1}H NMR spectrum indicated that a new stereogenic centre had been introduced into the compound. In addition, the FTIR spectrum showed an absorption for the carbonyl group at 1676 cm^{-1} which is at a higher wavenumber than that of the carbonyl group for the vinylogous amide [167].

With the pyrrolidine [166] intermediate in hand we are in a position to attempt an intramolecular cyclization for the synthesis of the indolizidine compound [165B]. An outline of reported intramolecular cyclisations of sulfonyl ketones precedes the discussion of the attempted preparation of the indolizidine [165B]. These examples at first appear unrelated to our intended strategy. However, they all include formation of an α-sulfonyl anion followed by intramolecular nucleophilic attack at a remote carbonyl moiety. The methodology employed is the feature of interest, rather than the products synthesized.

Fehr[157] described the intramolecular condensation of sulfonyl ketones [191] or [192] to give the β-hydroxy sulfones [193] or [194] (Scheme 44). Of note is the use of potassium hydroxide and potassium tertiary butoxide as the base and the isomerization to the β,γ-alkene [195], a feature common to sulfonyl-containing compounds.[158]



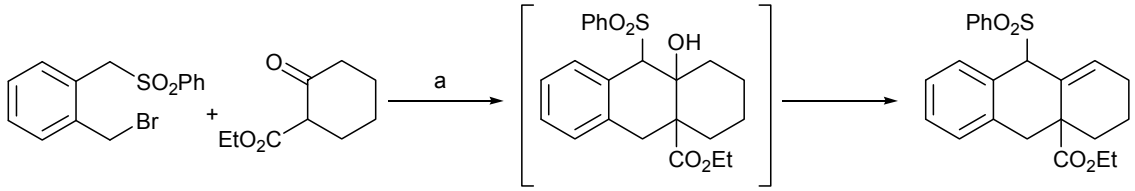
[191] R = H
[192] R = CH_3

[193] R = H
[194] R = CH_3

[195]

Scheme 44: Intramolecular condensation and isomerization as reported by Fehr.[157] Reagents: (a) ^{t}BuOK (1.5 eq.), toluene, 50 ^{o}C, 1h *or* KOH (7 eq.), toluene, Δ, 30 min; (b) ^{t}BuOK (2.5 eq.), toluene, Δ, 1 h *or* KOH (6.5 eq.), toluene, DMSO (2.8 eq.), Δ, 15 h.

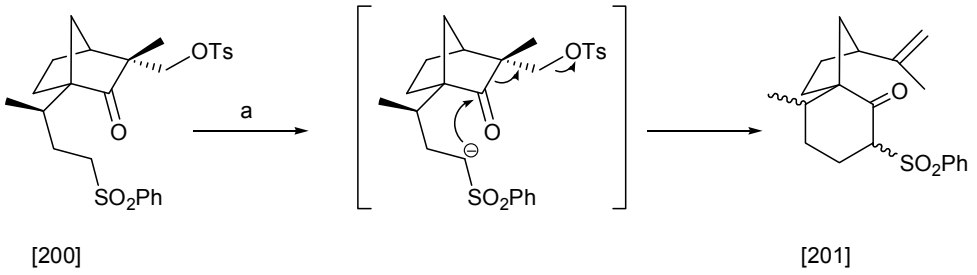
Ghera and co-workers[159] found that bromosulfone [196] reacted with the ester [197] in two consecutive steps, by preferential attack of the sulfonyl carbanion on the carbonyl group to give the β,γ-alkene [199], by way of the sulfone intermediate [198] (Scheme 45).



[196] [197] [198] [199]

Scheme 45: Formation of the α,γ-alkene by Ghera and co-workers.[159] Reagent: (a) NaH, THF/DMSO.

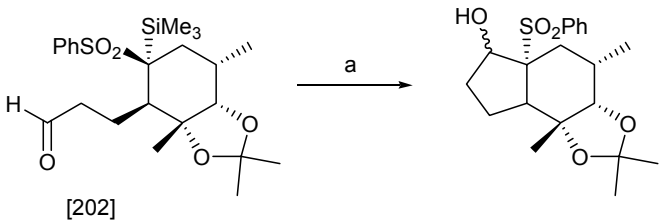
Chass and co-workers[160] prepared the spiro[4.5] decane [201] from the fragmentation of [200] as shown in Scheme 46.



[200] [201]

Scheme 46: Fragmentation reaction by Chass and co-workers.[160] Reagent: (a) NaH, DMSO.

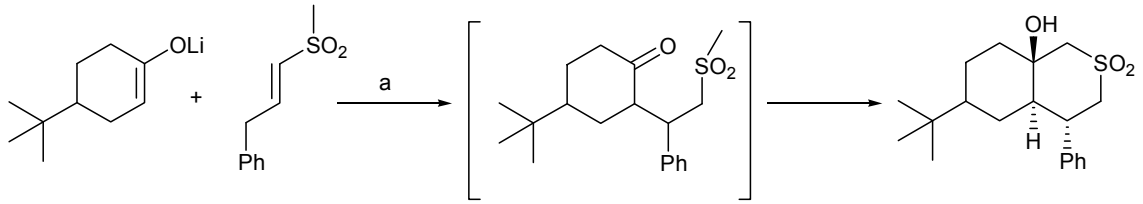
An imaginative generation of an α-sulfonyl carbanion was disclosed by Anderson and co-workers[161] who formed the α-silyl sulfone [202], by Michael addition to a vinyl sulfone. Fluoride was used to regenerate the α-sulfonyl carbanion, thereby enabling an intramolecular aldol-type reaction to occur (Scheme 47).



[202]

Scheme 47: Use of an α-silyl sulfone by Anderson and co-workers.[161] Reagent: (a) TBAF, THF, 4 Å sieves.

Finally, Takaki and co-workers[162] developed a useful method of utilizing vinyl sulfones (specifically methyl styryl sulfones [204]) for the preparation of thiane dioxides in good yields. The ketone enolates [203] add to the vinyl sulfone, followed by an intramolecular ketone sulfonyl condensation that leads to the sulfone [205] (Scheme 48).



[203] [204] [205]

Scheme 48: An example of a preparation of a thiane sulfone by Takaki and co-workers.[162] Reagent: (a) LDA, DMF.

In the current project attempts were made to prepare the indolizidine [165B] from the pyrrolidine [166] with at least one equivalent of base to create the α-sulfonyl anion and therefore induce cyclization. A number of different bases were tried. Table 1 summarizes the reaction details obtained by Brankin[78] and Table 2 summarizes the details in this work along with the outcome of the various reactions.

Table 1: Reaction details for the attempted preparation of [165B] from [166] by Brankin[78]

Expt. No.	Base	Eq. Base	Solvent	Temp. / °C	Time / h	Recovered Material
1	NaOEt	10.90	EtOH	Reflux	1.5	[166] 57%
2	^{t}BuOK	2.01	THF	Reflux	16.3	–
3	^{t}BuOK	2.19	THF	25	5.0	[166] 0.8%
4[a]	^{t}BuOK	2.33	THF	25 Reflux	45.0 21.5	[182] 51% –
5	^{n}BuLi	1.55	THF	25	5.5	[166] 14%
6	^{n}BuLi	2.33	THF	Reflux	114.5	[166] 15%

[a] Starting material was contaminated with vinylogous amide [167]. This indicates that the penylsulfonylethyl group can also act as a temporary protecting group for nitrogen.

Table 2: Reaction details for the attempted preparation of [165B] from [166] in this work

Expt. No.	Base	Eq. Base	Solvent	Additive	Temp. / °C	Time / h	Recovered Material
1	^{t}BuOK	2.04	THF	–	23	16	–
2	^{t}BuOK	2.00	Toluene	–	23	4	[166] 100%
3	^{t}BuOK	1.49	Toluene	–	Reflux	0.12	–
4	KOH	7.28	Toluene	–	Reflux	20	–
5[a]	^{t}BuOK	2.00	THF/ ^{t}BuOH	–	23	18	–
6[a]	^{t}BuOK	10.00	THF / ^{t}BuOH	–	23	18	–
7[a]	^{t}BuOK	10.00	THF / ^{t}BuOH	–	23	3	[165B] 6%
8[b]	LDA	2.00	THF	Benzyl bromide	-10	2	–
9[c]	^{n}BuLi	2.00	THF	Acetic anhydride	-78	2	–

[a] The ratio of tetrahydrofuran and ^{t}BuOH was 1:1.

[b] Benzyl bromide was added drop-wise after 30 minutes of reaction.

[c] Acetic anhydride was added over 2 hours by way of a syringe pump.

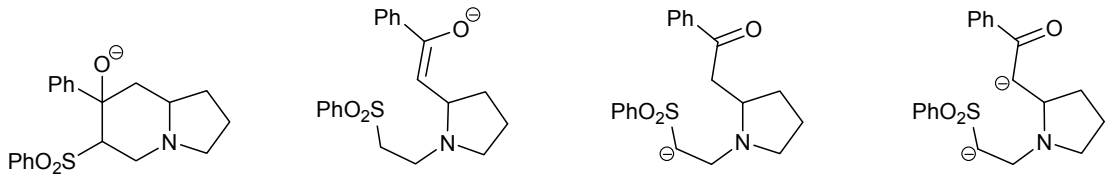
A consideration of the work shown in both tables indicates that chemoselective generation of an α-sulfonyl anion failed regardless of the reaction conditions employed as either starting material or decomposition products were encountered. On one solitary occasion, the desired product was obtained in 6% yield (entry 7, Table 2); tragically we lost this material when attempting to prepare a suitable crystal for x-ray analysis, and therefore only a partial characterization is offered in the experimental section of this thesis. In addition, we could never duplicate this result under identical reaction conditions to furnish more material. However, the result indicated that perhaps low temperatures and trapping of the intermediate tetrahedral alkoxide may promote cyclisation to occur to some extent. Thus additional experiments were attempted to trap the intermediate alkoxide by way of benzylation and acetylation (entries 8 and 9, Table 2) and were met with failure.

The signals for the aromatic protons in the ^{1}H NMR spectrum of [165B] had coalesced into a narrower clump, evidence for the disappearance of the carbonyl group. In addition, no carbonyl peak was found in the ^{13}C NMR spectrum. A quaternary carbon at 74.00 ppm indicated a carbon (C-7) atom bonded *inter alia* to a hydroxyl and phenyl group. As the compound has three stereogenic centres, the ^{1}H NMR spectrum was complicated as a result of the diastereotopic nature of each proton providing further evidence that the compound had been prepared, albeit in poor yield.

The formation of olefins from sulfones and carbonyl compounds, known as the Julia olefination, is one of the most powerful tools of modern organic chemistry.[163] This widely used method suffers from several drawbacks. One of them is the relatively high stability of the sulfonyl anion which limits its reactivity. For example, if an additional electron-withdrawing substituent is present on the anion-bearing carbon, the anion becomes so stable that it does not add even to activated aldehydes.[164] Moreover, in the case of the reaction of nonstabilized sulfones with some aldehydes and ketones, the position of the equilibrium between the starting carbonyl compound and the sulfone anion is shifted towards the starting materials. The desired adduct (tertiary alkoxide) is therefore present in the reaction mixture as the minor component. Trapping this intermediate *in situ* with several electrophiles, such as benzoyl chloride, mesyl chloride, or acetic anhydride, amongst others, is a common trick employed to shift the equilibrium towards products.

In our case, we seem to have encountered these problems. Firstly, the existence of several anionic species may exist in equilibrium and to different extents (Figure 17). The enolate anion [207] may have converged to the stable sulfonyl anion [207]; however the lack of product formed suggested the preponderant existence of this stable sulfonyl anion [208] relative to the tertiary alkoxide [206]. In spite of trapping experiments conducted (entry 8 and 9, Table 2) we were not able to isolate any identifiable products. This suggests that the generated sulfonyl anion is so stable that it does not add to the carbonyl to any extent in the first place. Lastly, the sulfone group is known to allow multiple deprotonation to form a range of polyanions[165] and we

cannot exclude the possible formation of the dianion [209], as most of the reactions were done in the presence of two equivalents of base. It is this species that may have ultimately destroyed our starting material by facilitating decomposition, possibly by way of a polymerization mechanism amongst others.



[206] [207] [208] [209]

Figure 17: Possible range of anions formed in the attempted cyclization of pyrrolidine [166]

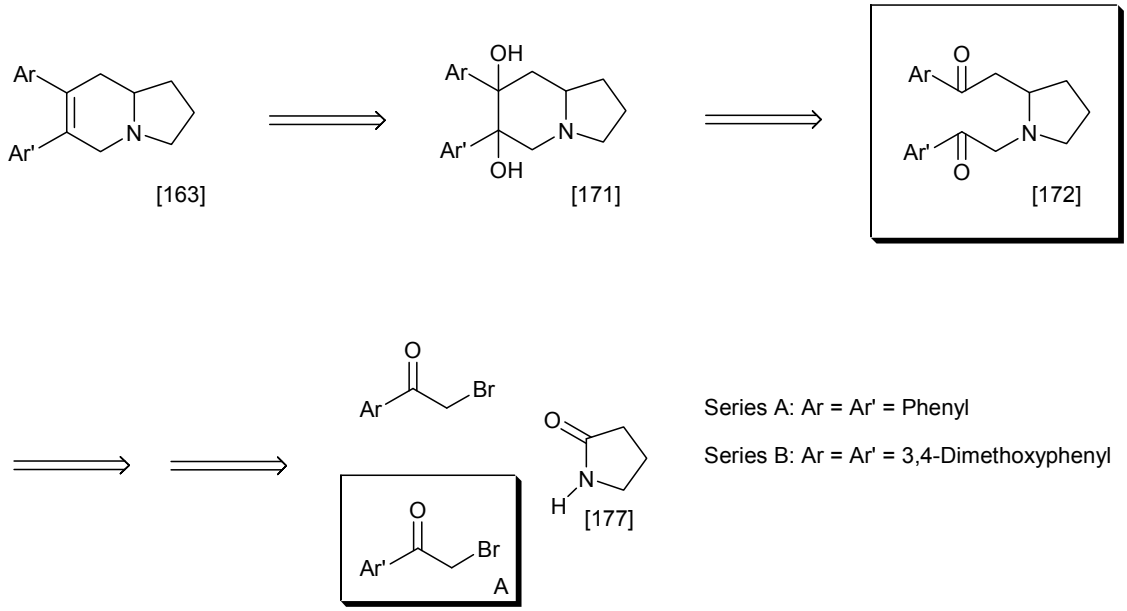
Therefore, a new strategy is required to overcome these problems. Perhaps the use of a sulfoxide is required. The use of a sulfoxide as a sulfone equivalent in the Julia olefination has been introduced by several workers. [166-168] As an advantage, the carbanion generated alpha to the sulfoxide group is less stabilized than in the case of the corresponding sulfone; and the addition reaction, leading to the formation of the C-C bond, is favoured. We did not follow this route in view of investigations to be described in subsequent chapters. However it may overcome some of the problems associated with ring closure encountered in this model study towards the diaryl-containing indolizidine alkaloids.

Lastly, the Julia reaction resembles the Wittig reaction in that the α-hetero substituted carbanion and a carbonyl compound are combined, followed by vicinal elimination of two functional groups to give a double bond. The two reactions are therefore both connective and regiospecific, but produce the same results. The main difference between the two reactions is the subsequent manipulations needed in the Julia procedure to afford the olefin, whereas the Wittig elimination occurs *in situ*. Although the use of the Wittig reaction was alluded to in the aims of this project in chapter 1 as a possible

preparation of indolizidine systems, we did not explore this conceptually attractive alternative in view of investigations to be described in subsequent chapters.

Chapter 3: Approaches to the synthesis of precursors for pinacol coupling

This section will deal with the methodological studies towards the arylated indolizidine alkaloids as found in septicine. This methodology differs from that in Chapter 2 in that both the aryl units will be installed prior to the pivotal ring closure reaction. The envisaged method of ring closure will approximate that of Honda[58] (see page 20) who disclosed an efficient synthesis of ipalbidine by way of a low-valent titanium pinacol coupling strategy – the so-called McMurry coupling reaction. A reminder of the basic strategy is shown in disconnection form in Scheme 49. Therefore, the key dicarbonyl compound [172] was the initial focus of this work, as it is this precursor on which we wish to perform the McMurry coupling reaction to afford the diaryl-indolizidine using the procedure of Honda.

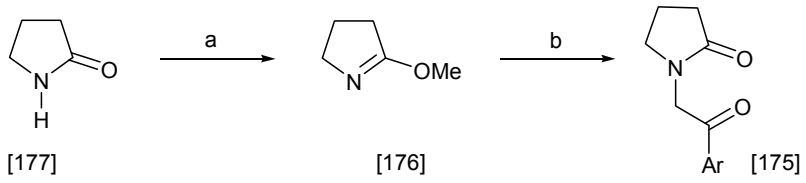


Scheme 49: Basic strategy for the synthesis of the key pyrrolidine intermediate [172]

In trying to achieve this original strategy, we found that synthesis of the intermediate pyrrolidine [172] proved to be non-trivial. Therefore, several alternatives were explored in which the bromide (shown in Box A) was modified in an attempt to circumvent the problems associated with the synthesis of intermediate [172]. Therefore the timing of reaction sequences and assembly of the *N*-alkyl chain as shown in compound [172] was a necessary part of the strategy. In the following section, the variations we tried to explore will be presented along with the original strategy.

3.1 Approaches to compound [172] by way of an *N*-phenacyl strategy

3.1.1 Preparation of *N*-phenacyl lactams [175]



[177] [176] [175]

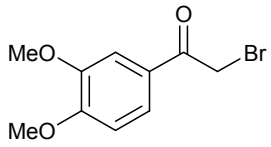
Series A: Ar = Phenyl

Series B: Ar = 3,4-Dimethoxyphenyl

Scheme 50: Reagents: (a) Dimethyl sulfate, ∆; (b) Phenacyl bromide (Series A) or 3,4-dimethoxyphenacyl bromide (Series B), DMF, ∆.

The preparation of intermediate [172] was a two-prong thrust. Firstly, a model study with no substitution on the aromatic units was considered. In addition the requisite methoxylation patterns on the aromatic units were investigated, as required for septicine [12] itself. The initial strategy employed for the preparation of the *N*-(2-aryl-2-oxoethyl)lactams was one that was disclosed by Fuji and co-workers.[136] The synthetic route employed involves the conversion of the lactam [177] into lactim ether [176] followed by *N*-alkylation with appropriately substituted phenacyl bromides (Scheme 50). Thus, reaction of

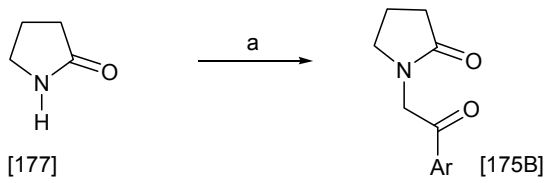
2-pyrrolidinone [177] with dimethyl sulfate at 60 °C afforded the lactim ether in 75% yield as a volatile oil with a characteristic odor. Diagnostic spectroscopic evidence of this compound was found in the FTIR as an absorbance for the C=N functional group at 1654 cm^{-1}.



[210]

Our first attempt at the *N*-alkylation of the lactim ether involved the use of the known 3,4-dimethoxyphenacyl bromide [210], as this bromide contains the requisite functional groups contained in the alkaloid septicine. The bromide is not commercially available and was prepared according to a known literature procedure.[169] Of the many methods available for α-bromination of acetophenones, the use of *N*-bromosuccinimide and *p*-toluenesulfonic acid appeared attractive because the starting materials are readily available and easy to handle. Thus, treatment of 3,4-dimethoxyacetophenone with *N*-bromosuccinimide and excess *p*-toluenesulfonic acid in acetonitrile by heating at reflux for 2 hours afforded the desired 3,4-dimethoxyphenacyl bromide [210] in 80% yield after recrystallization from hot methanol. The data obtained for this compound agreed with those in the literature.[170] In particular, the chemical shift of the methylene functional group was easily identified at 4.41 ppm in the ^{1}H NMR spectrum. With the bromide in hand, alkylation of the lactim ether with a solution of 3,4-dimethoxyphenacyl bromide in dimethylformamide for eighteen hours and at 60 °C afforded the *N*-substituted lactam [175B] in 91% yield (literature yield 87%[136]). Of note was the new position of the methylene group alpha to both nitrogen and the carbonyl functional group which was found at 4.73 ppm in the ^{1}H NMR spectrum. Similarly, reaction of the lactim ether with the commercially available phenacyl bromide afforded the *N*-substituted lactam [175A] in 80% yield (literature yield 87%[136]). The spectroscopic data also agreed with the literature[136] and the position of the methylene group alpha to both nitrogen and the carbonyl functional group was found at 4.68 ppm in the ^{1}H NMR spectrum.

3.1.2 Attempted direct preparation of lactam [175B] from 2-pyrrolidinone



Series B: Ar = 3,4-Dimethoxyphenyl

Scheme 51: Potential one-step synthesis of lactam [175B]. Reagents: (a) 3,4-Dimethoxyphenacyl bromide, NaH, DMF, rt.

We wondered if the preparation of the *N*-phenacyl lactams [175] could be achieved directly from 2-pyrrolidinone [177] as this would cut the number of synthetic steps in half (Scheme 51). An examination of the structures of the *N*-substituted pyrrolidinones suggested that they could be prepared by alkylation of 2-pyrrolidinone and an appropriately substituted phenacyl bromide. It seemed reasonable that the sodium salt of 2-pyrrolidinone should condense with the appropriate phenacyl bromide to afford the lactam. A search of the literature revealed a few precedents involving reaction with various phenethyl halides[171-173], although they indicated that this type of *N*-alkylation requires drastic conditions (e.g. K metal, Cu powder and refluxing toluene) and the yield of the desired product was usually low (8–22%) owing to competitive *E*2 elimination reaction of the starting phenethyl bromides to form the corresponding styrene derivative. We were interested to see if we could expand on this procedure by way of the phenacyl bromides rather than the phenethyl bromides.

Our first attempt at this reaction involved the use of 3,4-dimethoxyphenacyl bromide. Therefore, reaction of the bromide with the sodium salt of 2-pyrrolidinone, prepared by treating a solution of 2-pyrrolidinone in dimethylformamide with sodium hydride, afforded an orange solid after workup. Column chromatography afforded no characterizable product from

this solid. It was noted that a precipitate remained on the base-line of the silica-gel column, although we were unable to flush it off the column with neat methanol. Suspecting that this unknown solid may be of some interest in that it may cast light on for the failure of the synthesis of the desired product, the experiment was repeated.

Therefore, the orange solid obtained after the workup was washed several times with ethyl acetate to afford a sufficiently clean sample of a white solid that was analyzed by NMR and FTIR spectroscopy. The identity of the solid was determined as the known *trans*-1,2,3-tris(3,4-dimethoxy-benzoyl)-cyclopropane [211] (Figure 18). The ^{1}H NMR spectrum was surprisingly simple in that a high degree of symmetry was noted due to the lack of signals present. The aromatic signals when counted accounted for nine protons. The spectrum showed a triplet signal at 4.17 ppm integrating for one proton. Three sets of signals, each integrating for six protons were found in the range 3.97 – 3.87 ppm. Finally, a doublet signal integrating for two protons was found at 3.69 ppm. The integration of the triplet and doublet signal, in addition to the presence of three, rather than two sets of proton signals for the methoxy groups of [211], support the *trans* configuration assigned. In addition the FTIR spectrum showed an absorbance at 1656 cm^{-1} which is close to that found in the literature[174] (1660 cm^{-1}). In an entirely different experiment, yet still in the presence of 2-pyrrolidinone and in the presence of potassium carbonate as the base, the cyclopropane was isolated in 51% yield, with no other characterizable product formed.

We concluded that the phenacyl bromide had trimerized to afford the cyclopropane. Moreover, the strongly basic lactam anion had caused deprotonation of the phenacyl bromide which then entered into a cascade of events that lead to the cyclopropane. In other words, the lactam anion failed to act as a nucleophile but rather as a base at ambient temperature. For such a stereospecific reaction to have occurred the intermediate olefin [212] must have formed by initial dimerization and concomitant dehalogenation under the basic conditions employed. Finally, a third equivalent of the bromide anion participated in conjugate addition to [212], resulting in intermediate [213] *en route* to the final cyclization to allow for the observed *trans* configuration.

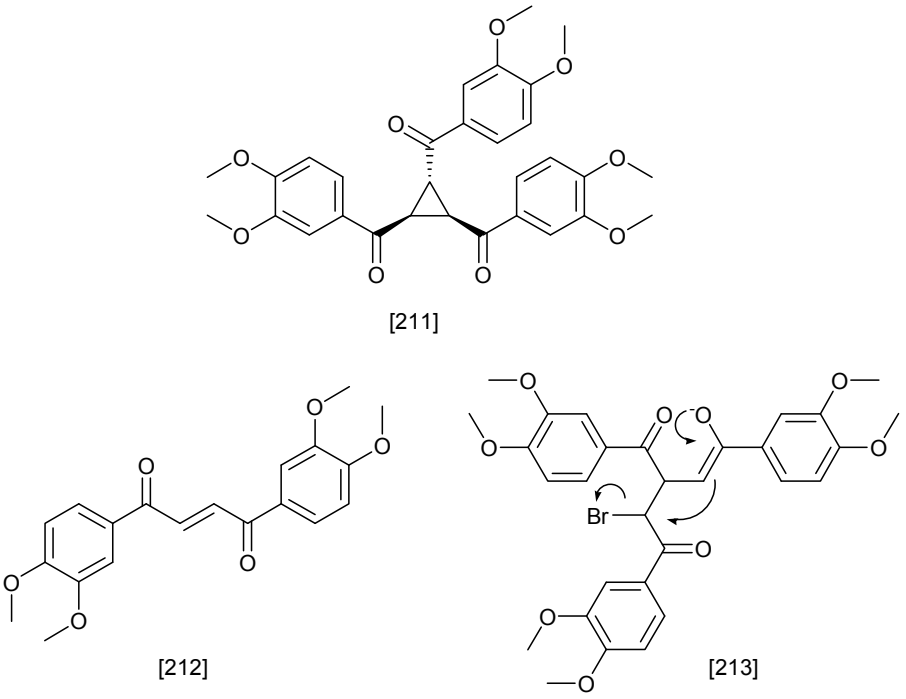
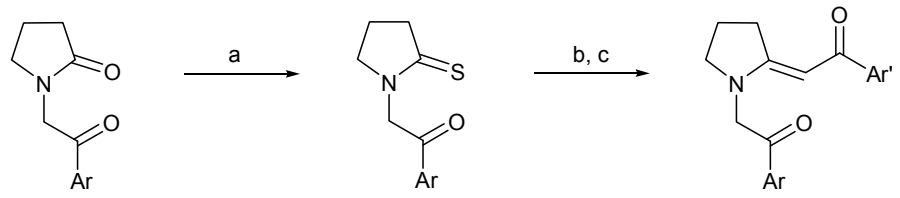


Figure 18: Formation of cyclopropane [211] and possible reaction intermediates

We did not pursue this interesting reaction further as it was not the focus of our investigation.

3.1.3 Towards the sulfide contraction products [173]



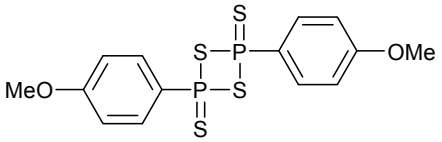
[175] [174] [173]

Series A: Ar = Ar' = Phenyl

Series B: Ar = Ar' = 3,4-Dimethoxyphenyl

Scheme 52. Reagents: (a) P_4S_{10}, HMDO, CH_2Cl_2, rt (Series A) or Lawesson's reagent, toluene, Δ (Series B); (b) Phenacyl bromide (Series A) or 3,4-Dimethoxyphenacyl bromide (Series B), MeCN; (c) $P(OEt)_3$, Et_3N, MeCN.

With the two *N*-phenacyl lactams [175A] and [175B] in hand, we were in a position to thionate the compounds and do the sulfide contraction on the intermediate thiolactams (Scheme 52). The traditional procedure used in these laboratories for converting a carbonyl group into a thionyl group is to use the Brillon reagent, which is generated *in situ* by the addition of equimolar quantities of phosphorus pentasulfide and sodium carbonate in tetrahydrofuran at room temperature. This procedure is impractical and expensive for the large-scale synthesis of thiolactams, owing to the copious amounts of tetrahydrofuran required. In addition, recovery and purification of the solvent by repeated distillation affords an odoriferous liquid which is not suitable for use in similar thionation reactions.[96] This thesis is replete with many thionation reactions and an alternative was sought to avoid the use of expensive tetrahydrofuran. Therefore, the thionation procedure employed was one that uses Lawesson's reagent [214] in toluene at elevated temperatures (typically 80 °C).



[214]

Lawesson's reagent is commercially available and expensive. However it can conveniently be prepared in large quantity from readily available phosphorus pentasulfide and anisole. The disadvantages of using this method are the high cost of the reagent, the requirement for anhydrous reaction conditions (the reagent is hygroscopic) and purification difficulties during the isolation of products from phosphorus-containing by-products.

A cheaper alternative to the above two methods is a new thionation method disclosed by Curphey.[175] The method employs the use of phosphorus pentasulfide in conjunction with hexamethyldisiloxane (HMDO), in solvents such as acetonitrile, toluene, xylene or dichloromethane. Generally the yields are comparable when comparing this thionation procedure to that of Brillon or Lawesson. Phosphorus-containing by-products are easily removed, either by mild alkaline hydrolysis, or by filtering through a short silica-gel column (20 g SiO_2 / mmol P_4S_{10}). The mechanism by which the hexamethyldisiloxane enhances the thionating ability of phosphorus pentasulfide is still uncertain. After much experimentation by the various researchers in these laboratories, this method has been optimized and found to be as good as or better for the preparation of a variety thiolactam from lactam precursors. Therefore, the Curphey procedure is now the method of choice for thionation of lactams owing to low solvent loading and ease of purification. Typically the use of the cheaper solvent dichloromethane is employed. In addition, hexamethyldisiloxane is relatively inexpensive. Before this group became aware of this procedure, the author of this work had prepared Lawesson's reagent on an 80 g scale and therefore chose to use this reagent for the preparation of most of the thiolactams so as not to waste this expensive reagent. Pleasingly, purification of the desired products in most cases was non-problematic, and the yields obtained were good to excellent.

In the one and only instance, the thionation procedure of Curphey was used for the preparation of a thiolactam. In addition, as the reaction was conducted on a large scale, the protocol involving initial purification through a short silica-gel column to remove the phosphorus-containing by-products was used as recommended by Curphey. Thus, reaction of [175A] with phosphorus pentasulfide and hexamethyldisiloxane in dichloromethane for 18 hours afforded an orange gum that was passed through a silica-gel column with a copious amount of ethyl acetate. The resulting thick oil was re-chromatographed through another silica-gel column using 40% ethyl acetate in hexane as the eluent to afford the thiolactam in 80% yield as a white solid. This isolation procedure in effect resulted in a double chromatographic purification step, which is a waste of time, solvent and silica-gel. As mentioned earlier, for large scale reactions, the workers in these laboratories have subsequently optimized this procedure to include only one chromatographic purification step.

The use of freshly prepared Lawesson's reagent was used for the preparation of the thioamide [174B] from the corresponding lactam [175B]. Thus, reaction of the lactam [175B] with Lawesson's reagent in toluene at 80 °C afforded the desired thioamide [174B] in 72% yield as a pale yellow solid after a single column chromatographic purification

A good indication of the thionyl carbon is provided in the ^{13}C NMR spectrum which showed up at in the sparsely populated δ = 200 ppm range, as a typically small signal (Table 3). The remaining NMR spectral signals are largely unchanged with respect to those of the starting material, with the exception of the signals adjacent to the thiocarbonyl group, which tended to shift to lower field strengths ($\Delta\delta_H$ (H_3) = ~ 0.7 ppm for the ^1H signal and $\Delta\delta_C$ (C-3) = ~ 14 ppm for the ^{13}C signal).

Table 3: Selected ^{1}H and ^{13}C NMR spectral data for lactams [175] and thiolactams [174]

Compound		Protons H_3 δ_H / ppm	Carbon C-2 δ_C / ppm	Carbon C-3 δ_C / ppm
Lactam	175A	2.47	175.66	30.28
Thiolactam	174A	3.14	203.53	44.26
Lactam	175B	2.47	175.60	30.43
Thiolactam	174B	3.13	203.26	44.30

Of note in the FTIR spectra for the two thiolactams was the absence of the amide carbonyl absorbance at around 1680 – 1700 cm^{-1}. In addition, the FTIR spectra indicated the presence of the thiocarbonyl band at 1127 cm^{-1} for compound [174A] and 1124 cm^{-1} for compound [174B] respectively.

With the thiolactams in hand, the one-pot Eschenmoser sulfide contraction reaction was next attempted. The reaction proved non-trivial to execute. Thus, thiolactam [174A] and phenacyl bromide in acetonitrile were stirred for twenty-four hours at room temperature to effect complete salt formation. The success of the salt formation was highly dependent on concentration effects. Dilute reaction conditions (less than 0.15*M* relative to the thiolactam) often resulted in incomplete reaction and decomposition of starting materials as evidenced by TLC analysis. Generally, the reactions were carried out around 0.5*M* to 1.0*M* concentration relative to the thiolactams. In addition, an excess of the bromide is desirable to effect completion of reaction. In this manner, salt formation would occur with the minimum of decomposition. Extrusion of the sulfur was carried out with drop-wise addition of a solution of triethyl phosphite and triethylamine in acetonitrile to the salt. After 2 hours, a TLC analysis indicated a mess by virtue of 6 spots present. Column chromatography of the resulting gum afforded the vinylogous amide [173A] in a disappointing 44% yield as a yellow solid. The product was suspected, at the time, to be decomposing during the extrusion step of the Eschenmoser sulfide contraction as well as the chromatographic purification step. This suspicion

turned out to be false, and will be elaborated upon in Chapter 4. Similarly, reaction of compound [174B] with 3,4-dimethoxyphenacyl bromide under the same Eschenmoser sulfide contraction conditions afforded the vinylogous amide [173B] in a more acceptable 78% yield after careful column chromatography. Again, the reason for this careful isolation will be advanced in Chapter 4.

Many of these and other "vinylogous amide" compounds have been synthesized in these laboratories and their identification was easily achieved by comparison of spectral data with those obtained previously. Three common features are apparent. Firstly, the disappearance of the thione signals in the ^{13}C NMR spectra, and to a lesser extent in the FTIR spectra, is evident. Secondly, the appearance of a vinyl hydrogen signal appearing in the unique $\delta = 4 – 6$ ppm range, as a singlet, of the ^{1}H NMR spectra is easily identifiable. In this instance the vinyl signal for compound [173A] was found at 5.57 ppm, and that of compound [173B] was found at 5.60 ppm. Lastly, the corresponding vinyl carbon signals can be found in the $\delta = 70 – 90$ ppm range in the ^{13}C NMR spectra. In this instance the corresponding vinyl carbon signal for compound [173A] was found at 86.95 ppm, and that of compound [173B] was found at 86.42 ppm.

Again, the assignment of the (*E)*-geometry in compound [173A] was further corroborated by obtaining a crystal structure, confirming that we had indeed synthesized the *trans-s-cis* product as shown in the ORTEP diagram in Figure 19.

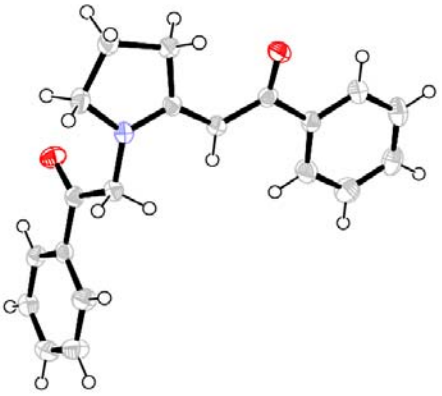
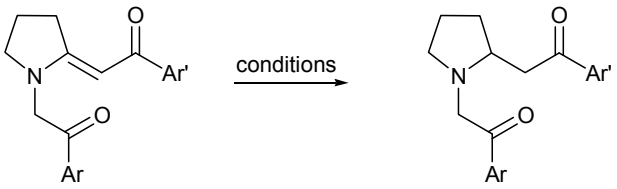


Figure 19: ORTEP diagram of vinylogous amide [173A]. Thermal ellipsoids are shown at the 50% probability level

3.1.4 Attempted hydrogenation of vinylogous amide [173B] over Adams catalyst



[173B] [172B]

Series B: Ar = Ar' = 3,4-Dimethoxyphenyl

Scheme 53: Attempted reduction of vinylogous amide [173B] under a variety of conditions

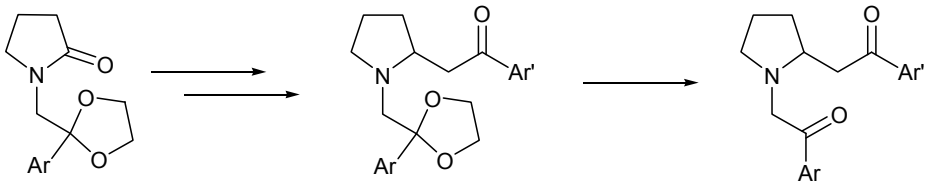
With the vinylogous amide [173B] in hand we next attempted the chemoselective reduction of the enaminone system (Scheme 53). However, we were concerned that chemoselective reduction of the vinylogous amide [173B] might be problematic as a remote carbonyl functional group is present in the compound. The usual practice in these laboratories is to reduce vinylogous amides with lithium aluminium hydride as it gives more reliable

results than those of catalytic hydrogenation. However this reductant will not be compatible with the vinylogous amide in question as concomitant reduction of the remote carbonyl group will occur. Therefore the use of Adams catalyst (PtO_2) under acidic and non-acidic conditions was explored for the chemoselective reduction of the vinylogous amides, as it has been used *en route* to the preparation of a number of alkaloids in these laboratories. However, reduction of vinylogous amides by catalytic methods is often problematic, with hydrogenolysis of the amino group and further reduction of the carbonyl group being frequently encountered.[25, 84] Therefore, we may reduce out the remote carbonyl group as well.

Not discouraged, the vinylogous amide [173B] was added to a stirring solution of a catalytic amount of Adams catalyst in degassed methanol and hydrogenated at five atmosphere of pressure for forty-eight hours. Analysis of the crude material by ^1H NMR showed no reaction had occurred. This failed result at least stressed the importance of using acidic conditions for the preparation of β-aminoketones from enaminones as it is assumed to occur through an iminium ion species. Thus, vinylogous amide [173B] was added to a stirring solution of a catalytic amount of Adams catalyst in degassed glacial acetic acid and hydrogenated at five atmosphere of pressure for three hours. A reaction did occur but the resulting product was unexpected. The result of this reaction will be discussed in Chapter 4. Finally, an alternative hydrogenation procedure was attempted: one that entails transfer hydrogenation. Thus, transfer hydrogenation by way of hydrazine hydrate and a suspension of Raney nickel in methanol failed to give a reaction after forty-eight hours had elapsed.

These sets of results were disappointing as we did not realize our intended strategy towards the synthesis of pyrrolidine [172] by way of the vinylogous amides [173]. We did not attempt the reduction of the vinylogous amide [173A] in light of the above results and therefore sought an alternative route for the formation of the crucial intermediates [172]. In fact, three such routes were explored and they are presented below.

3.2 Alternative route 1: Ketal protection strategy



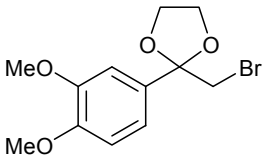
Series A: Ar = Ar' = Phenyl

Series B: Ar = Ar' = 3,4-Dimethoxyphenyl

Scheme 54: An envisaged strategy to pyrrolidines [172] by way of a ketal protection strategy

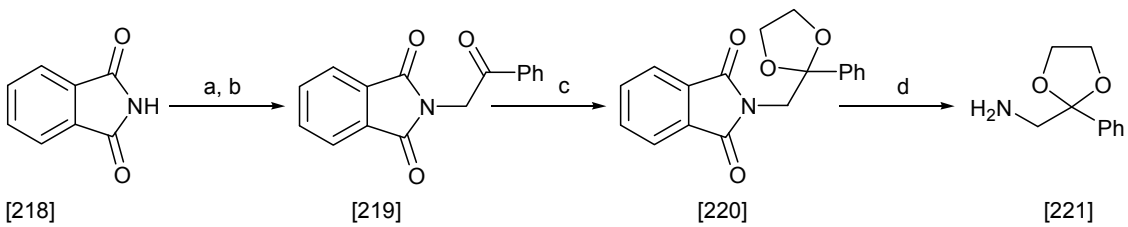
One such route entails the protection of the remote carbonyl functional group early in the synthetic sequence (Scheme 54). The most useful protective groups are the acyclic and cyclic acetals or ketals. The protective group is introduced by treating the carbonyl compound in the presence of acid with an alcohol or a diol. Cyclic and acyclic acetals and ketals are stable to aqueous and non-aqueous bases, to nucleophiles including organometallic reagents, and to hydride reduction. In addition, the acetals and ketals are readily cleaved by acidic hydrolysis. Therefore, the strategy was to protect the remote carbonyl as a cyclic ketal [215] and to carry this compound through to the reduction step. Finally, acidic hydrolysis will be attempted to afford the pivotal intermediate [172]. Although, IUPAC no longer uses the term “ketal”, we have retained it to indicate compounds formed from ketones.

3.2.1 Approaches to the preparation of ketal lactams [215]



[217]

The 1,3-dioxolane group is probably the most widely used carbonyl protective group, and we chose this group for the existing strategy. A possible route to ketal [215B] is the condensation of the lactim ether [176] with the ketalized bromide [217]. However, Fujii and co-workers[136] failed to get the *N*-substituted lactam [215B] under a variety of conditions. The failure is probably due to the steric bulk of the ketalized bromide at the benzylic position.[176] Therefore, It seemed logical to start the ketalization strategy from the readily prepared lactams [175]. Thus, lactam [175A] was added to a stirring solution of ethylene glycol in dry benzene containing a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was refluxed under Dean-Stark conditions for 16 hours. Conventional work-up followed by column chromatography afforded recovered starting material in 93% yield. It appeared that the *p*-toluenesulfonic acid was not an efficient catalyst for promoting the ketalization of the lactam [175A]. In addition, a higher boiling solvent may be required to effect the reaction. Therefore, the use of sulfuric acid as the catalyst and a higher boiling solvent such as toluene was investigated. Thus, the lactam [175A] was refluxed under Dean-Stark conditions for 16 hours, in the presence of a solution of a catalytic amount of sulfuric acid, ethylene glycol and dry toluene. The black reaction mixture was worked up and chromatographed to afford recovered starting material in 50% yield. This disappointing set of results then forced us to consider another strategy.



[218] [219] [220] [221]

Scheme 55. Reagents: (a) KOH, EtOH, Δ; (b) Phenacyl bromide, DMF; (c) Ethylene glycol, p-TsOH, benzene, Δ; (d) Hydrazine, EtOH, Δ.

A synthesis of the primary amine [221] was now the focus of our attention (Scheme 55). The reasoning for this approach will become apparent in the following section. Pleasingly, a search of the literature[177] revealed that this amine has been prepared by the well-known Gabriel synthesis.[178, 179] The Gabriel synthesis is a chemical reaction that transforms primary alkyl halides into primary amines using potassium phthalimide. Typically, potassium phthalimide reacts with a primary alkyl halide to form an *N*-alkylphthalimide. Upon work-up by acidic hydrolysis the primary amine is liberated as the amine salt. Alternatively, the work-up may be by way of the Ing-Manske[180] procedure, involving reaction with aqueous or ethanolic hydrazine at reflux. This produces a precipitate of phthalalhydrazide along with the primary amine.

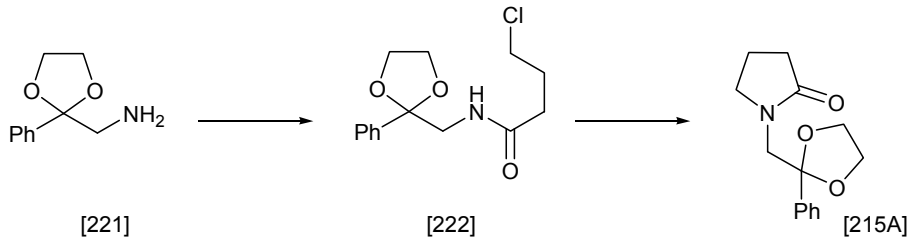
Thus, phthalimide [218] was refluxed in ethanol in the presence of potassium hydroxide to afford the potassium phthalimide in quantitative yield after filtration and drying under vacuum. The salt was amenable to storage at room temperature provided it was kept in a well-sealed desiccator. Alkylation of potassium phthalimide with phenacyl bromide in warm dimethylformamide afforded the *N*-alkylphthalimide [219] as a white solid in quantitative yield after an aqueous work-up. The solid was identified by its melting point which corresponded with that found in the literature (165 – 167 °C; lit.,[181] 165 – 167 °C). In addition, the signal for the ketone carbonyl carbon at 190.91 ppm was noted in the ^{13}C NMR spectrum.

With the imide [219] in hand, ketalization was next attempted. Thus, the imide [219] was transformed into the ketal [220] by treatment with ethylene glycol in the presence of *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of the water formed. The reaction took thirteen days to reach completion; a reaction time not too dissimilar from that of the literature which *only* took ten days! This reaction deserves some comment. During, a second preparation of this compound, a small aliquot of the reaction mixture was taken at several time intervals and analyzed by ^{1}H NMR spectroscopy. After seven days, 44% conversion was noted, and on day eleven, 38% conversion was noted. Therefore, a stoichiometric amount of *p*-toluenesulfonic acid was added to the reaction mixture and within twenty-four hours the reaction was completed. Therefore, this indicates that the reaction can be effected in a

shorter time by using excess acid rather than a sub-stoichiometric amount of acid. This was a useful result and its application will be discussed later.

The success of the reaction could be determined from the NMR spectra of the product [220]. Diagnostic features in the ^{13}C NMR spectrum were the disappearance of the carbonyl carbon signal and the appearance of a small signal at 108.68 ppm for the corresponding ketal quaternary carbon atom. In addition, the appearance of the ethylene moiety of the ketal was noted as a new signal at 64.80 ppm. The corresponding proton signals of this moiety can be found in the ^{1}H NMR spectrum as two distinct sets of complex multiplets between 4.03 – 3.88 ppm and 3.86 – 3.77 ppm respectively. In addition, the melting point corresponded well with the literature value [142 – 143 °C (ethanol); lit.,[177] 145 °C (ethanol)].

Finally, the ketal [220] was readily converted into primary amine [221] in 98% yield, as an oil, by use of hydrazine hydrate according to the previously mentioned Ing-Manske procedure. The ^{1}H and ^{13}C NMR spectra showed a marked simplicity of the signals in the aromatic regions, attesting to the removal of the phthalimide moiety. In addition, the appearance of a broad singlet at 1.39 ppm integrating for two protons in the ^{1}H NMR spectrum implies the presence of the primary amine functional group. Further evidence of the amine functional group was corroborated in the FTIR as an absorbance found at 3409 cm^{-1}.



Scheme 56: Reagents (a) 4-Chlorobutanoyl chloride, Na_2CO_3, CH_2Cl_2; (b) NaOMe, MeOH, rt.

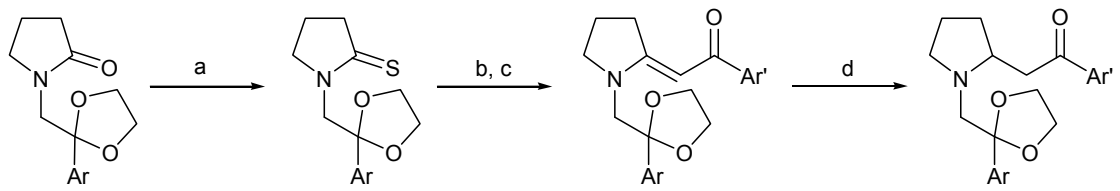
With amine [221] in hand, the next step was to incorporate it into lactam [215A] (Scheme 56). The strategy we envisaged was one that involves the conversion of the amino ketal [221] by way of the chloroamide [222] into the ketal lactam [215A] (Scheme 56).[182] In these laboratories, this two-stage procedure has been used *en route* to the synthesis of the amphibian alkaloid (–)-indolizidine 209B[119], and analogues[183] as well as variously substituted *N*-aryl lactams,[184] amongst others.

Thus, conversion of the amino ketal [221] by way of the chloroamide into ketal lactam [215A] was achieved by a two-stage procedure involving sequential treatment with 4-chlorobutanoyl chloride and sodium carbonate in dry dichloromethane, followed by cyclization of the intermediate with a methanolic solution of sodium methoxide. In this manner, the yield of the two-step reaction was 74%. Evidence for the reaction could be inferred from the NMR spectra. The ^{1}H NMR spectrum contained the characteristic sets of multiplets associated with a pyrrolidine ring, with one of the multiplets more down-field than the other two. In addition, the ^{13}C NMR spectrum indicated the presence of a new lactam carbonyl signal at 175.34 ppm.

The protection of lactams [175] with ethylene glycol was revisited. As mentioned earlier, we were not able to prepare the ketal lactam [215A] by way of the acid catalyzed ketalization of lactam [175A] with ethylene glycol. In the methodology employed 0.1 equivalents of acid with respect to the lactam was used. However, with the observation that excess acid effectively catalyzes the ketalization of imide [220] in a short period of time, we attempted a modification of the original catalytic procedure to that of one that employs

excess acid. As we had copious amounts of the ketal lactam [215A] in hand the reaction was attempted with the lactam [175B] only. Thus, the lactam [175B] was transformed into the ketal [215B] by treatment with ethylene glycol in the presence of excess *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of the water formed. The yield of the product was 80%, although it was contaminated with a trace amount of the starting lactam. Diagnostic features in the ^{13}C NMR spectrum were the disappearance of the carbonyl carbon signal and the appearance of a small signal at 108.95 ppm for the corresponding ketal quaternary carbon atom. In addition, the appearance of the ethylene functional group of the ketal was noted as a new signal at 64.30 ppm. The corresponding proton signals of this functional group can be found in the ^{1}H NMR spectrum as two distinct sets of complex multiplets between 4.08 – 3.99 ppm and 3.86 – 3.79 ppm respectively.

3.2.2 Preparation and reduction of the vinylogous amides [224]



[215] [223] [224] [216]

Series A: Ar = Ar' = Phenyl

Series B: Ar = Ar' = 3,4-Dimethoxyphenyl

Scheme 57. Reagents: (a) Lawesson's reagent, toluene, Δ; (b) Phenacyl bromide (Series A) or 3,4-Dimethoxy-phenacyl bromide (Series B), MeCN; (c) $P(OEt)_3$, Et_3N, MeCN; (d) $LiAlH_4$, THF, 0 ^{o}C (Series A) or -10 ^{o}C (Series B).

The lactam [215A] was successfully thionated with Lawesson's reagent in refluxing toluene to give the thiolactam [223A] in 71% yield (Scheme 57). Reaction of thiolactam [223A] with phenacyl bromide followed by treatment with triphenylphosphine and triethylamine in acetonitrile afforded the vinylogous amide [224A] in 82% yield. Finally, reduction of vinylogous amide

[224A] with lithium aluminium hydride in tetrahydrofuran at 0 °C for ten minutes afforded the pyrrolidine [216A] in 98% yield.

A similar protocol to that described above allowed for the preparation of pyrrolidine [216B]. Thus, the lactam [215B] was thionated with Lawesson's reagent in toluene at 80 °C to give the thiolactam [223B] in an un-optimized 45% yield. The low yield may be attributed to an incomplete reaction occurring. In addition, although TLC analysis of the crude reaction mixture prior to column chromatography suggested the presence of some starting material, the lactam could not be purified from the phosphorus-containing by-products of the reaction.

A one-pot two-stage Eschenmoser sulfide contraction of the thiolactam [223B] was effected by reaction with 3,4-dimethoxyphenacyl bromide in acetonitrile followed by treatment with triphenylphosphine and triethylamine in acetonitrile. Work-up followed by column chromatography afforded the vinylogous amide [224B] in 70% yield. Finally, reduction of the vinylogous amide [224B] with lithium aluminium hydride in tetrahydrofuran at –10 °C for five minutes afforded the pyrrolidine [216B] in 97% yield.

The characterization data of the compounds [223], [224] and [216] indicate clearly that the desired compounds were obtained. The most important data are summarized in Table 4. Again, a good indication of the thionyl carbon (C-2) is provided in the ^{13}C NMR spectrum which showed up at in the sparsely populated δ = 200 ppm range, as a typically small signal. The remaining NMR signals are largely unchanged with respect to those of the starting material, with the exception of the signals adjacent to the thiocarbonyl group, which tended to shift to lower fields [$\Delta\delta_H$ (H_3) = 0.65 – 0.67 ppm for the ^1H signals and $\Delta\delta_C$ (C-3) = 11.1 – 11.2 ppm for the ^{13}C signals]. Another exception noted was the methylene signal for the protected *N*-(2-aryl-2-oxo)lactam moiety which tended to shift to a low field strength as well [$\Delta\delta_H$ (H_6) = 0.58 – 0.60 ppm for the ^1H NMR signals]. The corresponding shift of C-6 in the ^{13}C NMR was not significant. Of note in the FTIR spectra for the two thiolactams was the absence of the amide carbonyl absorbance at around 1660 – 1700 cm^{-1}.

Four common features are apparent for the vinylogous amides [224]. Firstly, the disappearance of the thione signals in the ^{13}C NMR spectra is evident. Secondly, the appearance of the quaternary C-2 carbon of the olefin is found down-field [δ_C (C-2) = 167.99 ppm for [224A] and δ_C (C-2) = 167.41 ppm for [224B] respectively] in the ^{13}C NMR spectra. Thirdly, the appearance of a vinyl hydrogen signal [δ_H (H_{14}) = 5.83 ppm for [224A] and δ_H (H_{18}) = 5.95 ppm for [224B] respectively] appearing in the δ = 4 – 6 ppm range of the ^{1}H NMR spectra is easily identifiable. Lastly, the corresponding vinyl carbon signals [δ_C (C-14) = 87.63 ppm for [224A] and δ_C (C-18) = 87.02 ppm for [224B] respectively] can be found in the δ = 70 – 90 ppm range in the ^{13}C NMR spectra. Of note in the FTIR spectra for the two vinylogous amides was the presence of the conjugated carbonyl absorbance at around 1620 – 1600 cm^{-1}.

Table 4: Important NMR and FTIR spectroscopic evidence for the preparation of compounds [223], [224] and [216]

Compound	δ_H (H_3) / ppm (multiplicity)	δ_H (H_6) / ppm (multiplicity)	δ_H (H_{14}) / ppm (multiplicity)	δ_C (C-2) ppm	δ_C (C-3) ppm	δ_C (C-6) ppm	δ_C (C-14) ppm	IR (*v*/cm-1): Amide C=O	IR (*v*/cm^{-1}): Ketone C=O
215A*	2.27 (t)	3.67 (s)	–	175.43	30.56	49.55	–	1665	–
223A	2.94 (t)	4.25 (s)	–	203.42	44.63	53.86	–	–	–
224A	3.24 (t)	3.58 (s)	5.83 (s)	167.99	33.43	54.58	87.63	–	1625
216A[#]	2.00 (dd) and 1.44 – 1.27 (m)	3.09 (d) and 2.83 (d)	3.13 – 2.98 (m) and 2.65 (dd)	61.28	30.95	62.43	44.42	–	1677
Compound	**δ_H (H_3) / ppm (multiplicity)**	**δ_H (H_6) / ppm (multiplicity)**	**δ_H (H_{18}) / ppm (multiplicity)**	**δ_C (C-2) ppm**	**δ_C (C-3) ppm**	**δ_C (C-6) ppm**	**δ_C (C-18) ppm**	**IR (*v*/cm-1): Amide C=O**	**IR (*v*/cm^{-1}): Ketone C=O**
215B*	2.27 (t)	3.66 (s)	–	174.88	30.23	49.08	–	1660	–
223B	2.91 (t)	4.26 (s)	–	202.78	44.28	53.43	–	–	–
224B	3.31 (t)	3.58 (s)	5.95 (s)	167.41	33.19	54.36	87.02	–	1620
216B	2.07–1.90 (m) and 1.38 (ddt)	3.09 (d) and 2.82 (d)	3.03 (dd) and 2.69 (dd)	61.44	30.75	62.28	43.73	–	1671

* Included for references purposes to make comparisons easy to follow

[#] The expected double doublet signal for H_{14} is obscured under a complex multiplet found in the indicated range.

Finally, the success of the reduction of the vinylogous amides [224] can be attributed to the noticeable absence of the vinyl protons amongst others. Furthermore, a stereogenic centre results at C-2 of the pyrrolidine ring, which causes increased proton-proton coupling and a more complex spectrum. The diastereotopic protons (H_{14} and H_{18}) appear as two doublet signals in the ^1H NMR with characteristic geminal coupling constants [J = 16.4 Hz and 15.9 Hz for [216A] and [216B] respectively]. In addition the protons H_6 appear as two doublet signals in the ^1H NMR with geminal coupling constants of J = 14.0 Hz for [216A] and [216B] respectively. The associated carbon signal (C-6) was found noticeably down-field at δ_C (C-6) = 62.43 ppm for [216A] and δ_C (C-6) = 62.28 ppm for [216B] respectively. Of note in the FTIR spectra for the two pyrrolidines was the presence of the carbonyl absorbance at around 1670 – 1680 cm^{-1}.

3.2.3 Deprotection of ketalized pyrrolidines [216]

With the protected pyrrolidines in hand, the deprotection of the ketal moiety was investigated and the results are summarized in Table 5. The reaction conditions employed were those that have found success in unrelated systems.[185-189] Thus, reactions conducted at room temperature afforded near quantitative recovery of starting material (entries 1–2) when a catalytic amount of acid was used. Attempts at persuading the reaction to occur at elevated temperature also failed; although the percentage recovery of starting material was lower (entry 3). We next tried a reaction that made use of excess acid and at higher temperature and this resulted in a low 35% recovery of starting material after work-up and chromatography (entry 4).

Table 5: Deprotection attempts on [216A] and [216B]

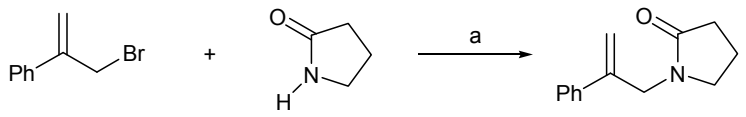
Entry	Compound	Reaction conditions (solvent, reagent, temperature, time)	Result (% recovery)	Adapted from the following references
1	216A	8:1 EtOH/H_2O, conc. HCl (cat.), rt, 18 h	99	184
2	216A	AcOH, conc. H_2SO_4 (cat.), rt, 18 h	99	185
3	216A	10:1 Acetone/H_2O, *p*-TsOH (cat.), 60 °C, 18 h	95	186
4	216A*	2M HCl, 80 °C, 24 h	35	187
5	216B	Aqueous borax buffer pH 8, CAN (cat.), 60 °C, 30 min	100	188

* The aqueous acid is both the solvent and reagent.

No other characterizable product was identified during column chromatography. In one attempt, under oxidizing conditions, and in the presence of a basic buffer, no reaction occurred (entry 5). The results lead us to conclude that the ketal was stable to both acid hydrolysis at ambient temperature and oxidation under basic conditions. In addition, acid-induced hydrolysis at elevated temperature results in decomposition of starting material. The failure of this strategy at such a late stage was extremely disappointing. We were forced to consider a completely different approach: one in which the desired carbonyl group in the *N*-substituent was unmasked by ozonolysis of a suitable styrene precursor, as will now be described.

3.3 Alternative route 2: Ozonolysis of a remote aromatic styrene

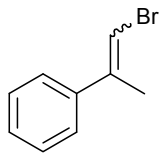
3.3.1 Approaches to *N*-(2-phenylallyl) lactam [226]



[225] [177] [226]

Scheme 57. Reagent (a) NaH, DMF, rt.

As has been described in the preceding sections, the synthesis of compound [172] was proving non-trivial, therefore a new variation of the *N*-alkylation of a bromide onto the 2-pyrrolidinone was investigated (Scheme 57). One such approach made use of the allyl bromide [225]. One of the most common approaches for the synthesis of allyl halides is the direct halogenations of alkenes. *N*-Bromosuccinimide (NBS) has been used extensively in allylic bromination, while *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS) have been used to a lesser extent. [190, 191] Generally, these halogenations proceed by a radical mechanism in the presence of radical initiators such as azobis(isobutyronitrile) (AIBN) or benzoyl peroxide which is promoted either by light or heat. Consequently, these reactions sometimes become complicated and give a mixture of products. Under these reaction conditions, vinylic halogenations also take place (for example compound [227]). No selectivity between allylic and vinylic bromide has been observed. In addition, initiation of the reaction is often erratic.[192, 193]



[227]

We first investigated the bromination of α-methylstyrene with *N*-bromosuccinimide without initiator at a bath temperature of 160 °C, which produced only a trace amount of the allyl bromide [225], whereas the same reaction in the presence of a catalytic amount of benzoyl peroxide under the typical protocol for radical bromination gave the desired product in 23% yield after 6 hours (Table 6, entries 1 and 2). The use of azobis(isobutyronitrile) (AIBN) also gave trace amounts of product (entry 3). Suspecting the bath temperature was too low, we raised it to 200 °C, although this is not recommended as *N*-bromosuccinimide decomposes at its melting point of 175 – 178 °C). Thus, reaction of α-methylstyrene with *N*-bromosuccinimide in the presence of a combination of both radical initiators afforded the desired product in 48% yield (entry 4). Since, excess α-methylstyrene was used, initial purification was done by distillation. The crude material was then further purified by column chromatography. It should be mentioned that we did not attempt to isolate the vinyl bromide [227] as it often decomposed during distillation. Interestingly, microwave irradiation for 10 minutes, in the absence of initiator, afforded the desired product in an un-optimized yield of 41%, although severe decomposition of the starting materials was noted. Clearly, the use of microwave irradiation merits further investigation as the reaction time is fast and gives a comparable yield of product. As the compound is known, we need not discuss the spectroscopic data other than to say that they were in agreement with those found in the literature.[194]

Table 6: Results obtained in this work of the allylic bromination of α-methyl-styrene with NBS

Entry	Catalyst (mol %)	Time / h	Yield of [225][a] (%)
1[b]	None	3	trace
2[b]	$(PhCO_2)_2$ (3.00)	6	23
3[b]	AIBN (0.03)	6	trace
4[c]	$(PhCO_2)_2$ (0.05) + AIBN (0.004)	1.5	48
5[d]	None	0.1	41

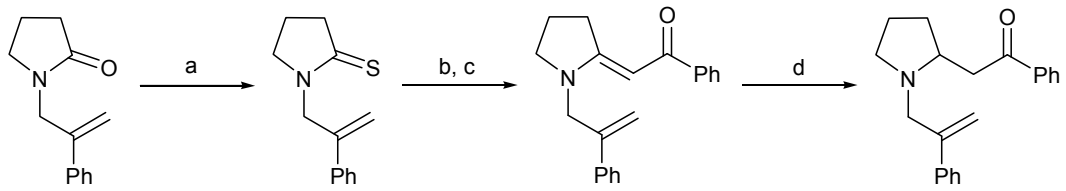
[a] Isolated yield. [b] Reaction was carried out under reflux in CCl_4; reaction bath temperature 160 °C. [c] Reaction was carried out under reflux in CCl_4; reaction bath temperature 200 °C. [d] Microwave irradiation; 160 °C, 150 W power.

With the allyl bromide in hand, we were in a position to prepare the styrene-containing lactam [226]. Thus, alkylation of the sodium salt of 2-pyrrolidinone with the allyl bromide [225] in dimethylformamide at 60 °C for three hours afforded the styrene lactam [226] in 94% yield as a yellow oil. Spectroscopic evidence for the reaction can be inferred from both the NMR and FTIR spectra. Evidence for the reaction was the lack of the amide proton signal for 2-pyrrolidinone in both the FTIR and ^{1}H NMR spectra. In addition, the ^{1}H NMR spectrum showed clearly the presence of an aromatic group at 7.49 – 7.23 ppm. Other notable signals were the two sets of singlets found at 5.51 ppm and 5.19 ppm for the alkene terminal protons. The corresponding C-8 signal was found at 114.72 ppm in the ^{13}C NMR spectrum. Lastly, a singlet integrating for two protons at 4.35 ppm was assigned as the methylene protons (H_6) alpha to both nitrogen and the styrene functional group.

Another approach to the styrene lactam considered was the Wittig olefination of lactam [175A]. Thus, the lactam [175A] in tetrahydrofuran was added to the Wittig ylide (prepared from methyltriphenylphosphonium bromide and *n*-butyllithium in tetrahydrofuran at –10 °C) to afford the styrene lactam in a 48%

yield. The spectral data matched those found previously. Although not optimized, this one-step procedure at least negates the need for the preparation of the allyl bromide (which is prepared in low yields), and therefore shortens the number of synthetic steps towards the synthesis of the crucial pyrrolidine intermediate [172A].

3.3.2 Preparation and reduction of the vinylogous amide [229]



[226] [228] [229] [230]

Scheme 58. Reagents: (a) Lawesson's reagent, toluene, Δ; (b) Phenacyl bromide, MeCN; (c) $P(OEt)_3$, Et_3N, MeCN; (d) $LiAlH_4$, THF, 0 ^oC.

The styrene lactam [226] was successfully thionated with Lawesson's reagent in toluene at 60 °C for fifteen hours to give the thiolactam [228] in 84% yield (Scheme 58). Eschenmoser sulfide contraction was effected by treatment with phenacyl bromide and then by treatment with triphenylphosphine and triethylamine in acetonitrile to afford the vinylogous amide [229] in 91% yield. Finally, reduction of vinylogous amide with lithium aluminium hydride in tetrahydrofuran at 0 °C for thirty minutes afforded the pyrrolidine [230] in 86% yield.

The characterization data of the compounds [228] – [230] indicate clearly that the desired compounds were obtained. The most important data are summarized in Table 7 and Table 8.

The trends in Table 7 and Table 8 were similar to those found for the ketals in Table 4. Namely, the thionyl carbon atom was easily identified at 201.62 ppm in the ^{13}C NMR spectrum. In addition, the signals adjacent to the thiocarbonyl,

also tended to shift to lower field strengths [$\Delta\delta_H$ (H_3) = 0.66 ppm for the ^1H NMR signal and $\Delta\delta_C$ (C-3) = 13.89 ppm for the ^{13}C NMR signal]. Another similarity noted was the signal for the methylene protons alpha to both nitrogen and the styrene functional group which tended to shift to a low field strength as well [$\Delta\delta_H$ (H_6) = 0.51 ppm for the ^1H signal]. The corresponding shift in the ^{13}C NMR was also noticeable [$\Delta\delta_c$ (C-6) = 7.26 ppm]. Of note in the FTIR spectra for the thiolactam was the absence of the amide carbonyl absorbance at around 1660 – 1700 cm^{-1}.

Table 7: Important ^1H NMR spectroscopic evidence for the preparation of compounds [228] through to [230]

Compound	**δ_H (H_3) / ppm (multiplicity)**	**δ_H (H_6) / ppm (multiplicity)**	**δ_H (H_8) / ppm (multiplicity)**	**δ_H (H_{13}) / ppm (multiplicity)**
226*	2.31 (t)	4.35 (s)	5.51 (s) and 5.19 (s)	–
228	2.97 (t)	4.86 (s)	5.58 (s) and 5.24 (s)	–
229	3.42 (t)	4.31 (s)	5.52 (s) and 5.41 (s)	5.83 (s)
230	2.09 (ddd) and 1.47 (ddt)	3.84 (d) and 3.23 (d)	5.40 (s) and 5.28 (s)	3.34 (dd) and 2.92 dd)

* Included for references purposes to make comparisons easy to follow

Table 8: Important ^{13}C NMR spectroscopic evidence for the preparation of compounds [228] through to [230]

Compound	δ_C (C-2) / ppm	δ_C (C-3) / ppm	δ_C (C-6) / ppm	δ_C (C-8) / ppm	δ_C (C-13) / ppm
226*	174.61	30.77	46.26	114.72	–
228	201.62	44.66	53.50	115.64	–
229	167.22	33.70	52.61	113.99	87.08
230	60.86	31.39	59.31	114.75	44.19

* Included for references purposes to make comparisons easy to follow

Similarly, common features are apparent for the vinylogous amide [229]. Firstly, the disappearance of the thione signals in the ^{13}C NMR spectra is evident. Secondly, the appearance of the quaternary C-2 carbon of the olefin is found down-field [δ_C (C-2) = 167.22 ppm in the ^{13}C NMR spectrum]. Thirdly, the appearance of a vinyl hydrogen signal [δ_H (H_{14}) = 5.83 ppm] in the ^{1}H NMR spectrum is easily identifiable. Lastly, the corresponding vinyl carbon signal [δ_C (C-13) = 87.08 ppm] can be found in the characteristic δ = 70 – 90 ppm range in the ^{13}C NMR spectrum. Of note in the FTIR spectra for the vinylogous amides was the presence of the conjugated carbonyl absorbance at around 1611 cm^{-1}

Finally, the success of the reduction of the vinylogous amide [229] can be seen from the characteristic absence of the vinyl proton, amongst others. In addition, the stereogenic centre at C-2 of the pyrrolidine ring results in a more complex spectrum due to the diastereotopic nature of the protons. The diastereotopic protons (H_{13}), alpha to both the ketone and the pyrrolidine ring appear as two doublet signals in the ^{1}H NMR with characteristic geminal coupling constants (J = 16.0 Hz). In addition the protons H_6 appear as two doublet signals in the ^{1}H NMR with geminal coupling constants of J = 13.5 Hz.

The associated carbon signal (C-6) was found not as noticeably down-field at δ_C (C-6) = 59.31 ppm relative to those of the ketals. Of note in the FTIR spectra for the pyrrolidine was the presence of the un-conjugated carbonyl absorbance at around 1679 cm^{-1} which is at a higher wavenumber than that found for the enaminone carbonyl functional group.

Another obvious diagnostic characteristic of this set of compounds is the presence of the styrene olefin. Interestingly, the terminal olefin C-8 signals in the ^{13}C NMR spectra was little changed as were the corresponding H_8 signals in the ^{1}H NMR spectra.

Finally, the assignment of the (*E*)-geometry in compound [229] was further corroborated by obtaining a crystal structure, confirming that we had indeed synthesized the *trans-s-cis* product as shown in the ORTEP diagram in Figure 20.

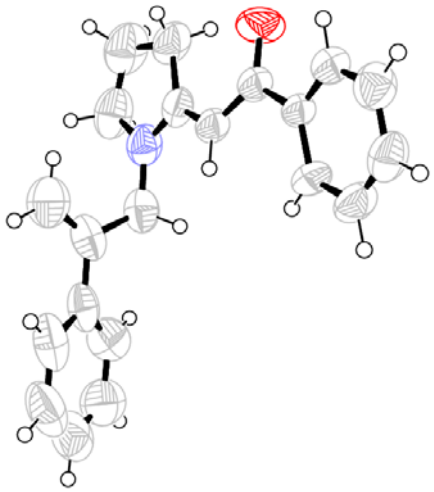
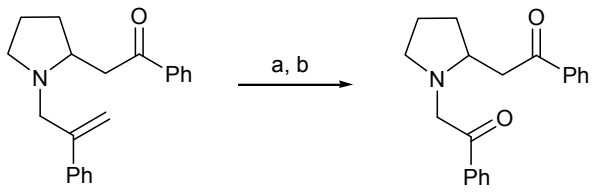


Figure 20: ORTEP diagram of vinylogous amide [229]. Thermal ellipsoids are shown at the 50% probability level.

3.3.3 Ozonolysis of the *N*-(2-phenylallyl) pyrrolidine [230]



[230] [172A]

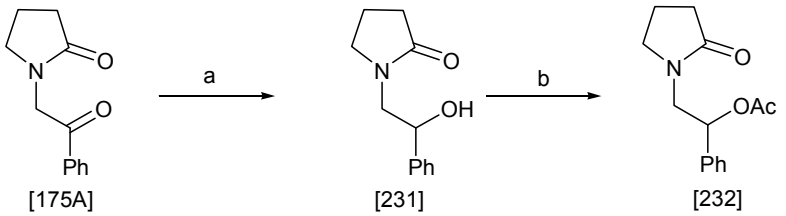
Scheme 59. Reagents (a) Acetyl chloride, MeOH; (b) O_3, -78 ^{o}C, then Me_2S.

With the pyrrolidine [230] in hand the ozonolysis of the terminal olefin was next attempted (Scheme 59). Thus, the olefin was added to an acidic solution of methanol and then cooled to – 78 °C. Ozone was passed through the methanolic solution until a blue colour persisted, at which point oxygen was passed through the solution to remove excess ozone. Reduction of the molozonide intermediate was accomplished by stirring the solution in the presence of dimethyl sulfide for eighteen hours at room temperature. Basic work-up followed by column chromatography afforded an uncharacterizable red oil that suggested a trace amount of product was present as analyzed by ^{13}C NMR spectroscopy. In this instance, the presence of two carbonyl signals can be found at 199.44 ppm and 197.20 ppm respectively.

This result was as equally disappointing as those for the ketal strategy in that the intermediate [172A] was not realized. Therefore, another oxidation strategy was attempted; one that involved oxidation of a secondary alcohol.

3.4 Alternative route 3: Oxidation of a remote secondary alcohol

3.4.1 Reduction and acetylation of lactam [175A]

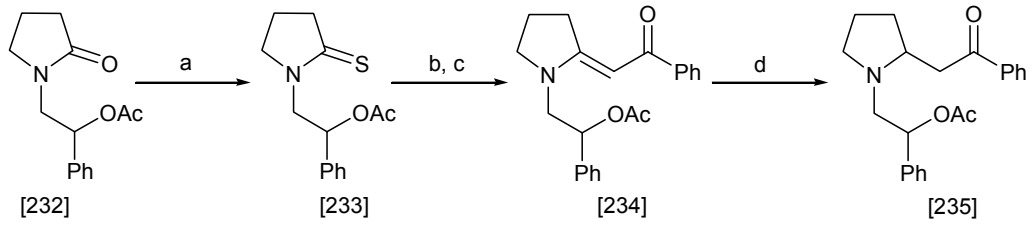


[175A] [231] [232]

Scheme 60. Reagents: (a) $NaBH_4$, EtOH, rt; (b) Ac_2O, pyridine, rt.

In this final alternative strategy, reduction of the lactam [175A] followed by acetylation was considered (Scheme 60). It was felt necessary to protect the ensuing secondary alcohol as we were concerned that it may have an adverse affect in a later thionation reaction using Lawesson's reagent. Therefore, following a literature procedure[136], reduction of the remote ketone of lactam [175A] with ethanolic $NaBH_4$ at room temperature for 18 hours afforded the secondary alcohol [231] in an excellent yield of 92% after column chromatography. The FTIR spectrum showed a broad absorbance at 3214 cm^{-1} and an absence of the ketone moiety of the starting material. In addition, the ^1H NMR spectroscopic data agreed with those in the literature. The alcohol was acetylated with acetic anhydride in the presence of pyridine as base to afford the ester [232] in 90% yield as a yellow oil. Diagnostic features of this compound could be found in the FTIR and NMR spectra respectively. In the FTIR spectrum, the disappearance of the secondary alcohol absorbance was replaced with an ester carbonyl absorbance found at 1737 cm^{-1}. The ester functional group was apparent in the ^{13}C NMR spectrum as a signal for the carbonyl group is found at 170.11 ppm. In addition, the methyl group of the acetate is found as a signal at 21.55 ppm. Lastly, a singlet, integrating for three protons for the methyl group, is found at 2.09 ppm in the ^1H NMR spectrum.

3.4.2 Preparation and reduction of the vinylogous amide [234]



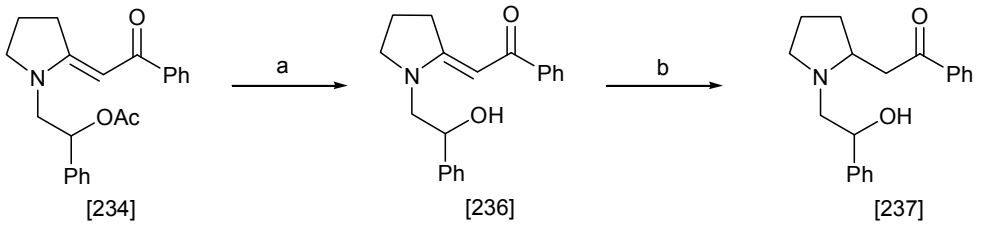
[232] [233] [234] [235]

Scheme 61. Rreagents: (a) Lawesson's reagent, toluene, Δ; (b) Phenacyl bromide, MeCN; (c) $P(OEt)_3$, Et_3N, MeCN; (d) H_2, PtO_2 (cat.), AcOH.

The lactam [232] was successfully thionated with Lawesson's reagent in toluene at 80 °C for eighteen hours to give the thiolactam [233] in 90% yield as a yellow oil (Scheme 61). Reaction of the thiolactam with phenacyl bromide in acetonitrile followed by treatment with triphenylphosphine and triethylamine in acetonitrile afforded the vinylogous amide [234] in 91% yield as a solid.

Obviously, lithium aluminium hydride reduction will not be compatible with this vinylogous amides as concomitant reduction of the remote ester functional group will occur. Therefore the use of Adams catalyst (PtO_2) was explored for the chemoselective reduction of the vinylogous amide, as it has been used for the preparation of a number of alkaloids in these laboratories. The choice of catalyst may seem strange at first; however in these laboratories, the use of Adams catalyst for the reduction of vinylogous urethanes gives little or no evidence of over-reduction of the ester moiety. This implies that the ester is not prone to reduction in the presence of Adams catalyst. Therefore, we were cautiously optimistic that the reduction of the vinylogous amide can be accomplished with chemoselectivity and that the presence of the remote ester functional group will remain unscathed during the course of the reaction. Thus, atmospheric hydrogenation of vinylogous amide [234] with a catalytic amount Adams catalyst (PtO_2) in glacial acetic acid afforded an oil that could not be characterized by spectroscopic means. In fact over 221 signals were

found in the ^{13}C NMR spectrum! Clearly, our reservations were confirmed as to the efficacy of the use of Adams catalyst in the presence of a remote ester functional group. Therefore, we chose to deprotect the acetyl protecting group and re-attempt the reaction on the resulting secondary alcohol (Scheme 62).



[234] [236] [237]

Scheme 62. Rreagents: (a) K_2CO_3, MeOH, rt; (b) H_2, PtO_2 (cat.), AcOH.

The acetyl protecting group of the vinylogous amide [234] was effortlessly deprotected by stirring with potassium carbonate in dry methanol for eighteen hours. Work-up followed by rapid crystallization afforded the secondary alcohol [236] in quantitative yield. Thereafter, atmospheric hydrogenation of vinylogous amide [236] with a catalytic amount of Adams catalyst (PtO_2) in glacial acetic acid afforded an approximately 1:2 diastereomeric mixture of the desired pyrrolidine [237] in 87% yield as an orange oil. The presence of the unequal amounts of the diastereomers was surprising. Catalytic metallic reductants are expected to give almost 100% *cis* reduction due to the activation of the metal surface with hydrogen and subsequent adsorption of the substrate. This state results in the nearly simultaneous delivery of hydrogen atoms to the same face of the C=C bond. It would appear that the remote secondary alcohol, which contains a stereogenic centre, was probably interacting with the catalyst and therefore exerting stereo bias during the course of the reduction.

Excluding the compound [235], the characterization data of the compounds [233] – [237] indicate clearly that the desired compounds were obtained. The most important data is summarized in Table 9 and Table 10 respectively.

Table 9: Important ^{1}H NMR spectroscopic evidence for the preparation of compounds [233] through to [237]

Compound	**δ_H (H_3) / ppm (multiplicity)**	**δ_H (H_6) / ppm (multiplicity)**	**δ_H (OH) / ppm (multiplicity)**	**δ_H (H_{12}) / ppm (multiplicity)**
232*	2.33 (t)	3.85 (dd) and 3.43 (dd)	–	–
233	3.00 (t)	4.22 (dd) and 3.98 (dd)	–	–
234	3.35 (t)	3.86 (dd) and 3.45 (dd)	–	5.97 (s)
236	3.38 (dt)	3.62 (dd) and 3.49 (dd)	3.06 (s)	5.83 (s)
237	2.24 – 2.06 (m) and 1.60 – 1.43 (m)	2.77 – 2.65 (m) and 2.52 (dd)	3.89 (br s)	3.27 (dd) and 3.07 – 2.88 (m)

* Included for references purposes to make comparisons easy to follow

Table 10: Important ^{13}C NMR spectroscopic evidence for the preparation of compounds [232] through to [237]

Compound	**δ_C (C-2) / ppm**	**δ_C (C-3) / ppm**	**δ_C (C-6) / ppm**	**δ_C (C-7) / ppm**	**δ_C (C-12) / ppm**
232*	175.42	30.68	48.03	73.07	–
233	202.84	44.79	56.14	72.63	–
234	167.14	33.40	51.69	71.91	86.87
236	167.82	33.97	54.59	71.07	86.79
237 major	60.64	31.21	62.95	70.42	44.17
237 minor	61.09	31.10	63.10	71.18	43.86

* Included for references purposes to make comparisons easy to follow

Again the trends are similar to those obtained for the analogous ketals and styrenes. Namely, the thionyl carbon atom was easily identified at 201.62 ppm in the ^{13}C NMR spectrum. In addition, the signals adjacent to the thiocarbonyl, also tended to shift to lower field strengths ($\Delta\delta_H$ (H_3) = 0.67 ppm for the ^1H NMR signal and $\Delta\delta_C$ (C-3) = 44.79 ppm for the ^{13}C NMR signal). An obvious difference was noted for the H_6 signals of the methylene group alpha to both nitrogen and the benzylic secondary alcohol functional group which appeared as two sets of double doublets because of the introduced stereogenic centre at C-7. However, the trend for the H_6 protons of the thiolactam [233] relative to the lactam [232] was similar in that they tended to shift to a low field strength as well ($\Delta\delta_H$ (H_6) = 0.55 – 0.37 ppm for the ^1H NMR signal). The corresponding shift in the ^{13}C NMR was also noticeable [$\Delta\delta_c$ (C-6) = 8.11 ppm]. Of note in the FTIR spectra for the thiolactam was the absence of the amide carbonyl absorbance at around 1671 cm^{-1}.

Similarly, common features are apparent for the vinylogous amides [234] and [236]. Firstly, the disappearance of the thione signals in the ^{13}C NMR spectra is evident. Secondly, the appearance of the quaternary C-2 carbon of the olefin is found down-field δ_C (C-2) = 167.14 ppm and 167.82 ppm for [234] and [236] respectively in the ^{13}C NMR spectrum. Thirdly, the appearance of a vinyl hydrogen signal δ_H (H_{12}) = 5.97 ppm for [234] and 5.83 ppm for [236] respectively in the ^{1}H NMR spectrum is easily identifiable. Lastly, the corresponding vinyl carbon signal (δ_C (C-12) = 86.97 ppm for [234] and 86.79 ppm for [236] respectively can be found in the usual characteristic region of the ^{13}C NMR spectrum. Of note in the FTIR spectra for the vinylogous amides was the presence of the conjugated carbonyl absorbance at around 1590 – 1620 cm^{-1}.

Finally, the success of the reduction of the vinylogous amide [236] is apparent from the more complex spectrum obtained because of the diastereotopic nature of the protons. The diastereotopic protons (H_{12}), alpha to both the ketone and the pyrrolidine ring appear as two distinct multiplet signals in the ^{1}H NMR spectrum. In addition, one of the sets shows similar geminal coupling (J = 13.3 Hz) to those found for the ketals and the styrene compounds. In addition the protons H_6 appear as two distinct multiplet signals in the ^{1}H NMR. Again, one of the multiplet sets exhibit similar geminal coupling (J = 13.5 Hz) to those already encountered for the ketals and styrene compounds. The associated carbon signal (C-6) was similarly found as down-field at δ_C (C-6) = 62.95 ppm and 63.10 ppm for the major and minor diastereomers respectively when compared to those of the ketals. Of note in the FTIR spectra for the pyrrolidine was the presence of the carbonyl absorbance at around 1682 cm^{-1} which is at a higher wavenumber than that found for the enaminone carbonyl functional groups.

An obvious diagnostic characteristic of this set of compounds is the presence of the signals in the δ_C = 70 – 74 ppm region of the ^{13}C NMR spectra which accounts for the carbon (C-7) attached to either an ester or an alcohol. They remained little affected during the various transformations.

3.4.3 Oxidation approaches to pyrrolidine [172A]

With the secondary alcohol in hand we are in a position to oxidize the compound by several methods. The results are summarized in Table 11. The first method employed made use of the well-known Swern oxidation and a variation thereof.[195] As can be seen in the table, no reaction occurred (entry 1 and 2). Attempted oxidation mediated by $Pd(OAc)_2$ also failed (entry 3).[196] In addition, the use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[197] and an *in situ* generated 2-iodoxybenzoic acid[198] resulted in decomposition. An unmistakable odor of benzaldehyde was noted and this suggested fragmentation of the starting material to give trace amounts of benzaldehyde (entries 4 and 5).

The use of Jones reagent under acidic conditions afforded the desired compound [172A] in 93% crude yield as an orange oil (entry 6). However, the oil rapidly darkened to red within minutes of isolation and within an hour it had decomposed. In addition, attempts to purify the crude reaction mixture by column chromatography resulted in decomposition as well. On one occasion, ^{1}H and ^{13}C NMR spectra were obtained from the crude reaction mixture within 10 minutes of isolation, and these are shown in Figures 21 and 22 respectively.

Table 11: Results of oxidation of pyrrolidine [237]

Entry	Reaction conditions (compound [237] in solvent, reagent, temperature, time)	Results and comments
1	1st stage: CH_2Cl_2, DMSO and oxalyl chloride, –78 °C, 15 minutes. 2nd stage: Add [237] in CH_2Cl_2 and allow to stir for 15 minutes. 3rd stage: Add Et_3N and allow warming to room temperature over 2 hours.	Quantitative recovery of [237] with trace [172A] detected.
2	[237] in DMSO* then add P_4O_{10}, room temperature, 18 hours.	96% recovery of [237].
3	[237] in THF; $Pd(OAc)_2$, molecular sieves, Et_3N, O_2; room temperature, 17 hours.	83% recovery of [237].
4	[237] in CH_2Cl_2, DDQ, room temperature, 24 hours.	Decomposition and an odor of benzaldehyde noted.
5	[237] in 2:1 MeCN/H_2O, 2-iodobenzoic acid and oxone, 70 °C, 5 hours.	Decomposition and an odor of benzaldehyde noted.
6	[237] in AcOH, add Jones reagent drop-wise, room temperature, 15 minutes.	93% crude [172A] that rapidly decomposes when isolated.
7	[237] in CH_2Cl_2, MnO_2, room temperature, 24 hours.	Quantitative recovery of [237].
8	[237] in $CHCl_3$, CrO_2 (Magtrieve™), room temperature, 24 hours.	Decomposition and an odor of benzaldehyde noted.

* DMSO is both the solvent and reagent.

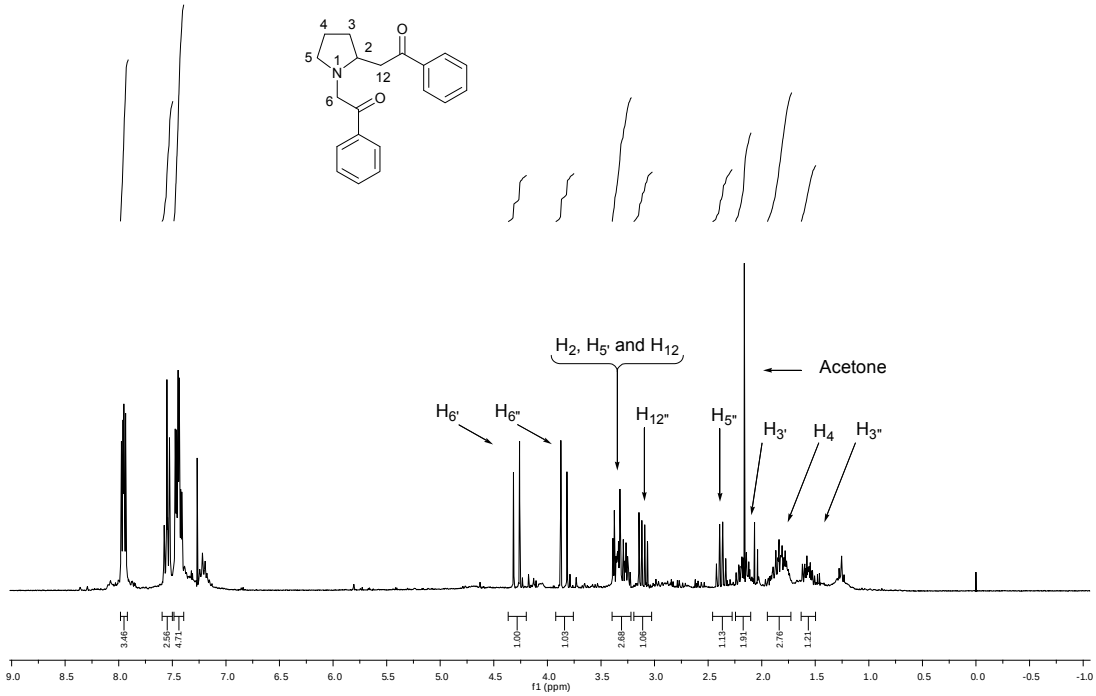


FIGURE 21: 300 MHz ^{1}H NMR spectrum of crude pyrrolidine [172A]

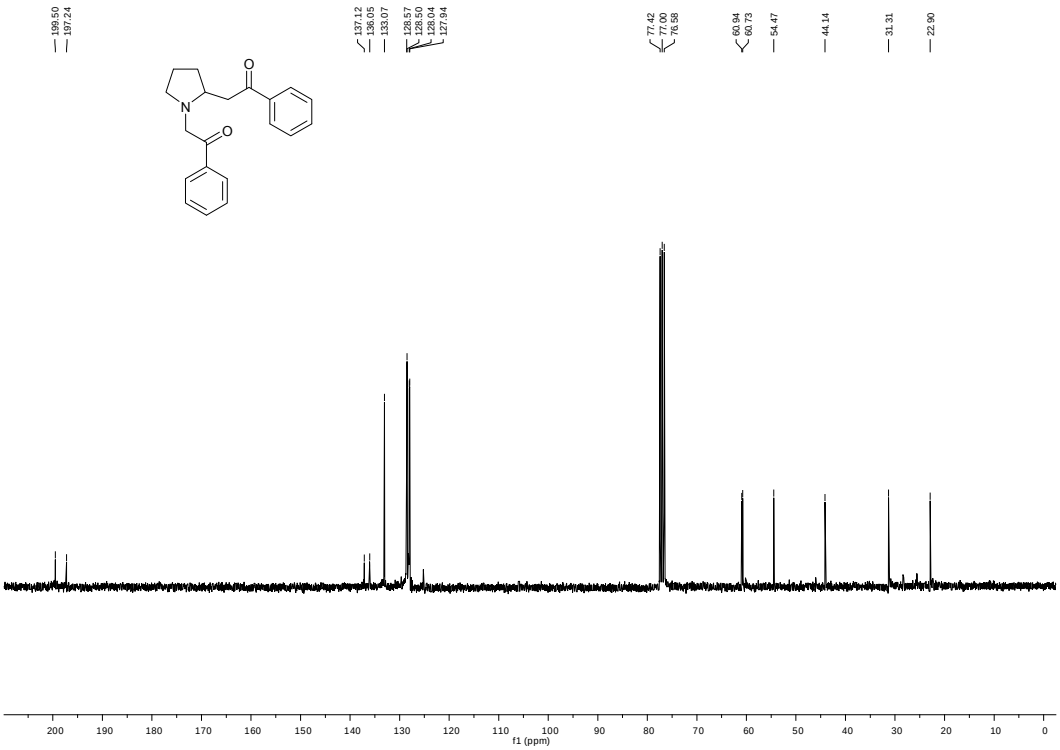
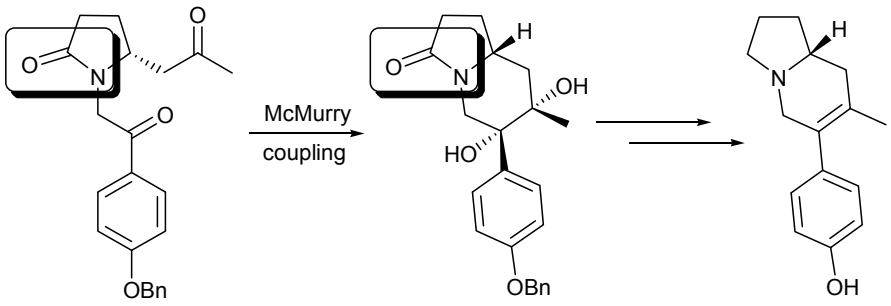


FIGURE 22: 75 MHz ^{13}C NMR spectrum of crude pyrrolidine [172A]

The spectra were surprisingly good for a crude reaction mixture. The McMurry procedure as disclosed by Honda[58] is a technical and time-consuming procedure to effect and therefore we sought a simpler procedure to attempt the pinacol reaction to test the efficacy of the reaction. Thus the procedure of Zhao and co-workers[199] was attempted. Therefore, pyrrolidine [172A] was dissolved in bromobenzene and sodium metal was added to the reaction mixture. Stirring was continued for eighteen hours under an atmosphere of nitrogen followed by workup. However, the oil obtained could not be characterized by spectroscopic means. This result then ties in with the results in Table 11 (more specifically entries 4 and 5) wherein the reagents probably start the oxidation process by way of a single electron process. To further clarify this we attempted two additional oxidation reactions. Thus, an attempted oxidation by the heterogeneous metal oxide manganese(II) oxide (MnO_2) and Magtrieve™ (CrO_2).[200] resulted in fragmentation and decomposition as well (entries 7 and 8). These two results and the results obtained in entry 4 and 5 in the above table, as well as the failed pinacol coupling reaction, forced us to bring this part of the project to a close. The reagents employed (entries 4, 5, 7 and 8) are those that probably start the oxidation process by way of a single electron transfer (SET) mechanism. In addition, fragmentation also occurred as evidenced by the trace amounts of benzaldehyde noted. Since the pinacol coupling reaction occurs through a single electron transfer mechanism we could not foresee any reasonable attempt to synthesize the indolizidine [171] from pyrrolidine [172A].

In addition, an analysis of the intermediate [238] used by Honda and co-workers[58] *en route* to the synthesis of ipalbidine [14] suggests that the amide functional group is crucial for the stability of both the reactant and for the product (Scheme 63). In addition, it allows for single electron transfer (SET) to occur without destruction of the starting material. It should be mentioned that the amide functional group of intermediate [238] was not installed to negate any potential stability problems during the course of the synthesis of ipalbidine, but was as a consequence of the initial chiral starting material employed.



[238] [70] [14]

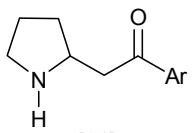
Scheme 63: Part of a synthesis of ipalbidine [14] by Honda and co-workers.[58] The boxes highlight the importance of the amide functional group. This group confers stability on the starting material and during the pinacol coupling reaction.

The final nail in the coffin for this route came about from a cursory examination of the literature. The literature revealed that although cyclic pyrrolidines and piperidines have been synthesized from acyclic dicarbonyl compounds by pinacol coupling reactions, the nitrogen was always protected as an amide[201, 202] or as a sulfonamide.[203] In addition, indolizidinones[204, 205] have been prepared from cyclic imides, where the nitrogen may be viewed as protected.

3.4.4 Concluding remarks

The dicarbonyl-containing pyrrolidine [172] proved to be a Trojan horse. At first glance the intermediate appeared both reasonable and useful for the intended synthesis of diarylated containing indolizidine scaffolds by way of a pinacol coupling reaction. However, the pyrrolidines [172] could not be prepared or isolated by the various methodologies employed. In addition, although partial spectroscopic evidence of pyrrolidine [172A] was obtained on one occasion it proved to be highly unstable. Therefore, unwittingly we were tricked by this compound and therefore failed to realize the goals of this project. A remarkable finding during this investigation was the stability of the related series of pyrrolidines. Thus, the ketals [216], the styrene [230] and

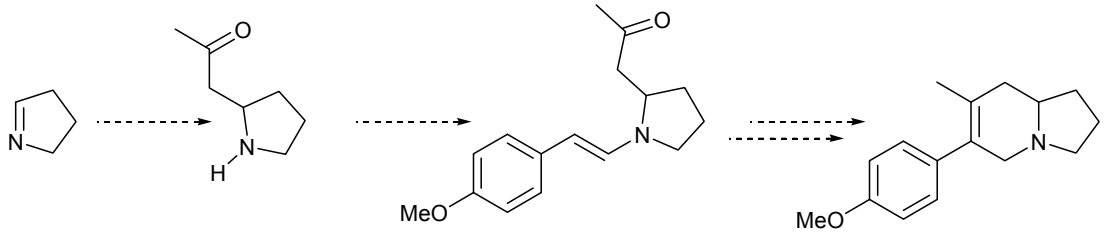
finally the secondary alcohol [237] were stable, yet the ketone [172A] was not. This could not have been predicted. Nonetheless, we were able to demonstrate further the synthetic utility of enaminones in pyrrolidine synthesis by way of the Eschenmoser sulfide contraction.



[61]

Ar = 3,4-Dimethoxypenyl

Furthermore, an aspect of this failed methodology needs comment. The synthesis of the secondary alcohol [237] may be useful in extending the work of Herbert and co-workers.[49, 50] Scheme 5 is reproduced here for ease of reference. Briefly, Herbert and co-workers have fashioned syntheses of norhygrine [60] and ruspolinone [61] by the oxidation of 1,4-diaminobutane with pea-seedling diamine oxidase in the presence of β-keto acids. Furthermore, these compounds could be elaborated into bicyclic alkaloids such as *O*-methylipalbidine [64] through the intermediacy of enamines [63] when condensed with suitably functionalized arylacetaldehydes. In addition, the amino-ketone conveniently cyclised and dehydrated in methanol solution. Finally reduction with sodium borohydride in methanol affords *O*-methylipalbidine.

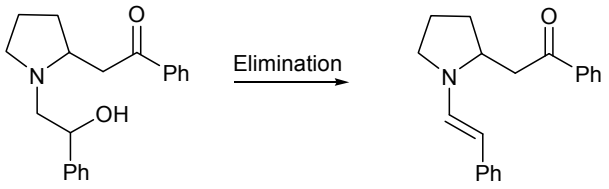


[59] [60] [63] [64]

Scheme 5: Part of a biogenetically patterned synthesis of O-methylipalbidine by Herbert and co-workers[49]

An analysis of the secondary alcohol shows that the enamine [239] may be synthesized by way of a base- or acid-induced elimination reaction and therefore may be the basis a new synthesis towards the

secophenanthroindolizidine alkaloids (Scheme 64). This route will not be as efficient as the biogenetic route adopted by Herbert and co-workers, however it will add to the body of work in these laboratories with regard to the synthetic utility of enaminones in alkaloid synthesis.



[237] [239]

Scheme 65: Possible new route to keto-enamine [239]

A final comment from the ever-quotable Thomas Edison offered this view on failure seems appropriate in light of the work disclosed in this chapter section of this thesis.

"I have not failed 700 times. I have not failed once. I have succeeded in proving that those 700 ways will not work. When I have eliminated the ways that will not work, I will find the way that will work."

From "Edison: The Man And His Work" by George S. Bryan, 1926.

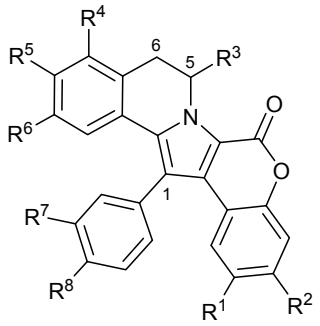
Perhaps the new route will work, but that is a story for another day. More importantly, we did not explore this route in light of work to be discussed in the following chapter.

Chapter 4: A model study towards the synthesis of the lamellarin alkaloids

4.1 Introduction

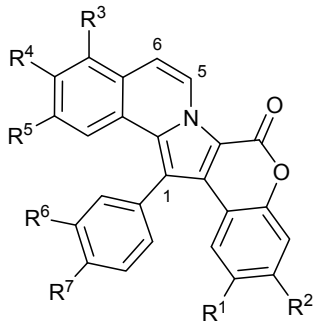
The lamellarins are a growing family of marine natural products and more than thirty have been characterized since the first isolation by Faulkner and co-workers in 1985.[206] The original source of the lamellarin alkaloids was from molluscs of the family Lamellariidae. However since molluscs are described as specific predators of colonial ascidians, it was speculated[206] that the lamellarin alkaloids found in molluscs had most likely been sequestered from a colonial ascidian food source. In addition, the presence of lamellarins in molluscs, turnicates and sponges gives rise to speculations about the role of symbiotic organisms associated with the invertebrates.[207]

The structures of all the pentacyclic lamellarins are shown in Figures 23 and 24. The basic structural variation seen is the hydroxy and methoxy substitution of the aryl rings, and the presence or absence of a $\Delta^{5,6}$ alkene or a C-5 carbinolamine. In some cases, the hydroxy groups are sulfated or acetylated. There is one more interesting structural feature of these natural products–the restricted rotation of the aryl ring at C-1. As a result of the restricted rotation, the lamellarins can exist as atropisomers and thus can exist in two enantiomeric forms. Interestingly, only one lamellarin, lamellarin S, has been isolated in optically active form, suggesting a high barrier to rotation. The biosynthesis of these metabolites is presumed to originate from two, three or more tyrosine and/or DOPA units[208] although specific studies have not been conducted.



Saturated	**R^1**	**R^2**	**R^3**	**R^4**	**R^5**	**R^6**	**R^7**	**R^8**
A	OMe	OH	OH	OMe	OMe	OMe	OMe	OH
C	OMe	OH	H	OMe	OMe	OMe	OMe	OH
E	OMe	OH	H	OH	OMe	OMe	OH	OMe
F	OMe	OH	H	OH	OMe	OMe	OMe	OMe
G	OH	OMe	H	H	OH	OMe	OH	OMe
I	OMe	OH	H	OMe	OMe	OMe	OMe	OMe
I acetate	OMe	OAc	H	OMe	OMe	OMe	OMe	OMe
J	OMe	OH	H	H	OH	OMe	OMe	OMe
K	OMe	OH	H	OH	OMe	OMe	OMe	OH
K triacetate	OMe	OAc	H	OAc	OMe	OMe	OMe	OAc
L	OMe	OH	H	H	OH	OMe	OH	OMe
L triacetate	OMe	OH	H	H	OAc	OMe	OAc	OMe
S	OH	OH	H	H	OH	OMe	OH	OH
T	OMe	OH	H	OMe	OMe	OMe	OH	OMe
T sulfate	OMe	OSO_3Na	H	OMe	OMe	OMe	OMe	OH
U	OMe	OH	H	H	OMe	OMe	OH	OMe
U sulfate	OMe	OSO_3Na	H	H	OMe	OMe	OH	OMe
V	OMe	OH	OH	OMe	OMe	OMe	OH	OMe
V sulfate	OMe	OSO_3Na	OH	OMe	OMe	OMe	OH	OMe
Y sulfate	OMe	OSO_3Na	H	H	OMe	OH	OH	OMe
Z	OH	OMe	H	H	OH	OMe	OH	OH
β	OH	OH	H	H	OH	OH	OH	OMe

Figure 23: Structure of saturated pentacyclic lamellarins



Unsaturated	**R^1**	**R^2**	**R^3**	**R^4**	**R^5**	**R^6**	**R^7**
B	OMe	OH	OMe	OMe	OMe	OMe	OH
D	OMe	OH	H	OMe	OH	OMe	OH
H	OH	OH	H	OH	OH	OH	OH
M	OMe	OH	OH	OMe	OMe	OMe	OH
N	OMe	OH	H	OMe	OMe	OH	OMe
W	OMe	OH	OMe	OMe	OMe	OH	OMe
X	OMe	OH	OH	OMe	OMe	OH	OMe
α	OMe	OSO_3Na	OMe	OMe	OMe	OH	OMe

Figure 24: Structures of unsaturated pentacyclic lamellarins

In addition to the pentacyclic structures, there exists a less populous group of lamellarin alkaloids in which the pyrroles is not fused to another aromatic ring and are known as pyrrole derivatives. The structures of lamellarin pyrrole derivatives are shown in Figure 25.

While for the pyrrole derived lamellarins and related compounds no biological activity has been described, several pentacyclic lamellarins show important cytotoxic activities.[206, 209-216] Thus, the wide range of biological activities and the interesting pentacyclic ring system with the pyrrole core of the lamellarins have attracted considerable interest from the synthetic community. From a synthetic point of view the lamellarins are synthesized by two main strategies: (i) by pyrrole formation as the key step of the synthesis and (ii) by transformation of a pre-existing pyrrole derivative through cross-coupling

reactions. Most of these strategies have been reviewed.[217-220] Therefore, what will follow is a short review of the pyrrole formation strategy as this applies most to what we envisage as a possible new route to the lamellarin scaffold.

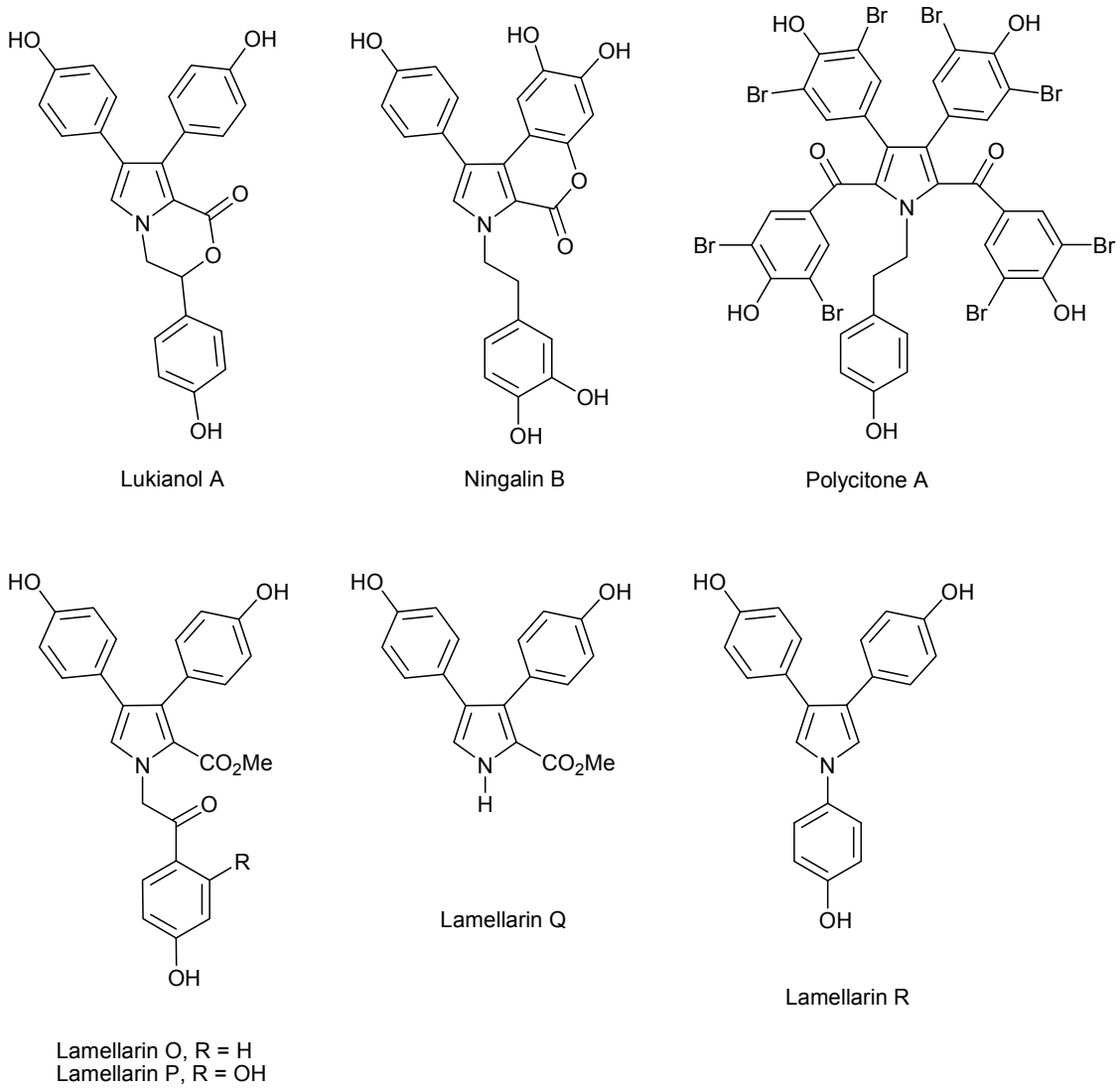
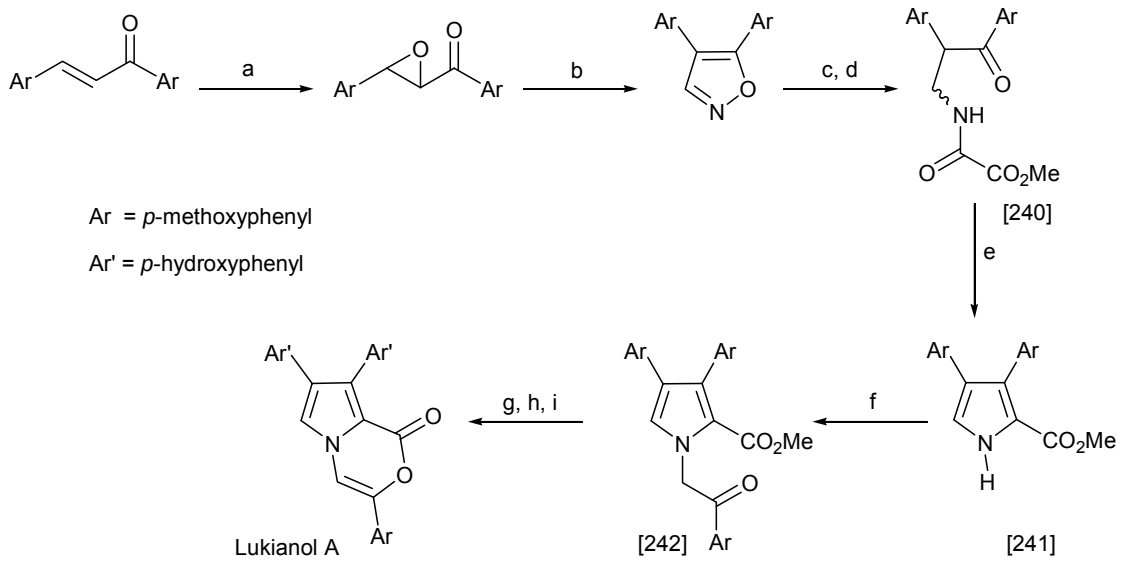


Figure 25: Structures of lamellarin pyrrole derivatives and of related natural products

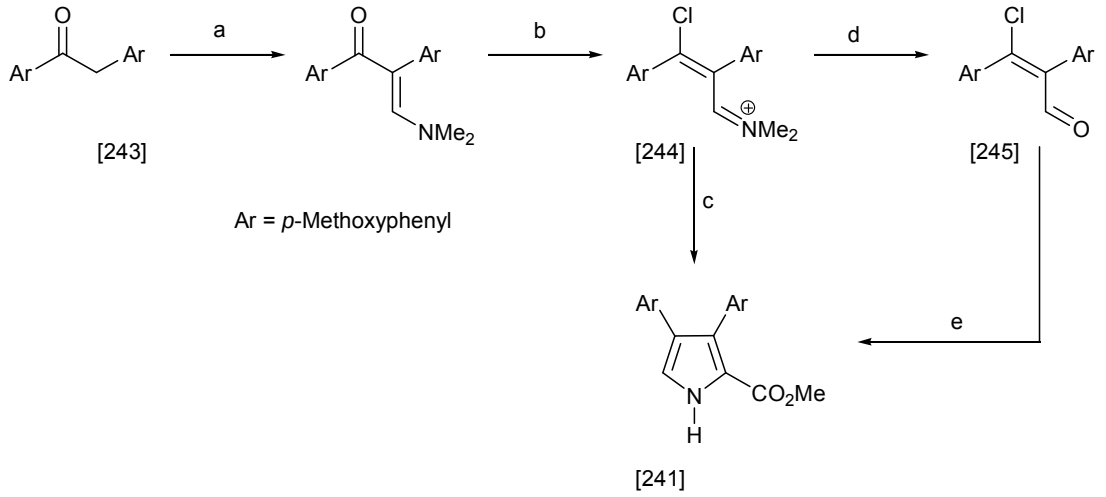
Fürstner and co-workers[221] reported the first synthesis of a lamellarin – lamellarin O dimethyl ether [242], along with a related alkaloid, lukianol A (Scheme 66). The key feature of the synthesis is the titanium-mediated cyclization of the amido-enone [240] to form the substituted pyrrole [241], also

known as the Fürstner intermediate. Further elaboration afforded the lamellarin O [242] analogue and the related alkaloid lukianol A.



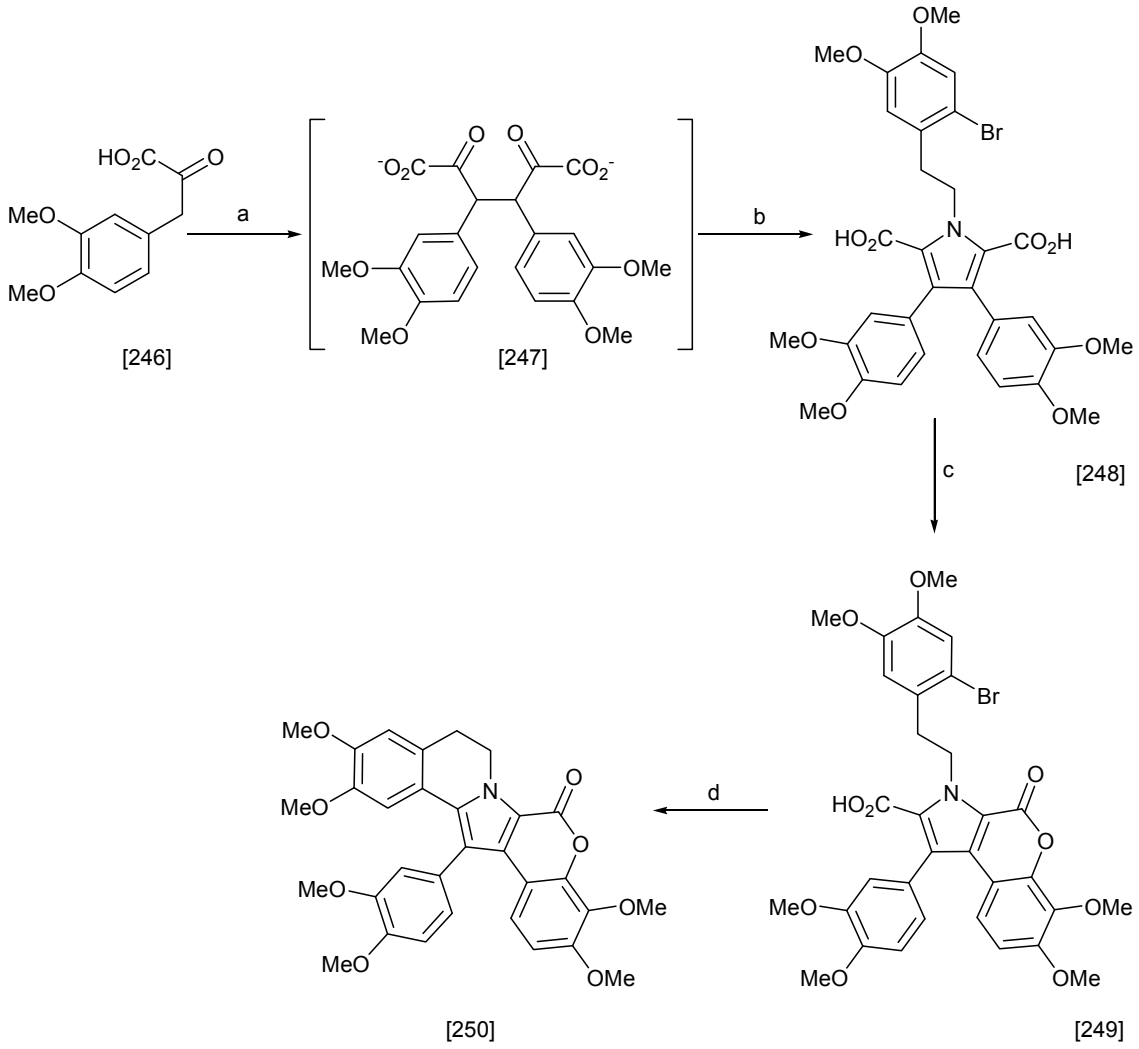
Scheme 66: Fürstner's synthesis of Lamellarin O dimethyl ether [242] and Lukianol A.[221] Reagents: (a) H_2O_2, NaOH; (b) $BF_3.Et_2O$ then $NH_2OH.HCl$, pyridine, EtOH; (c) H_2, Pd/C; (d) $ClOCCO_2Me$, pyridine, THF; (e) Ti/C, THF; (f) *p*-Methoxyphenacyl bromide, K_2CO_3; (g) ^tBuOK, H_2O; (h) Ac_2O, NaOAc; (i) BBr_3.

Another variation on the preparation of the pyrrole derivatives of the lamellarin family of natural products is the iminium ion chemistry developed by Gupton and co-workers.[222] Their formal synthesis of lamellarin O dimethyl ether and lukianol A intersects with the Fürstner intermediate [241] in just three steps from commercially available ketone [243] (Scheme 67). Thus, reaction of the chloropropeniminium salt [244] under basic conditions afforded the intermediate [241] in 77% yield. In addition, reaction of the β-chloroenal [245] under neutral conditions afforded the intermediate [241] in 82% yield. A similar approach has been disclosed by Kim and co-workers.[223]



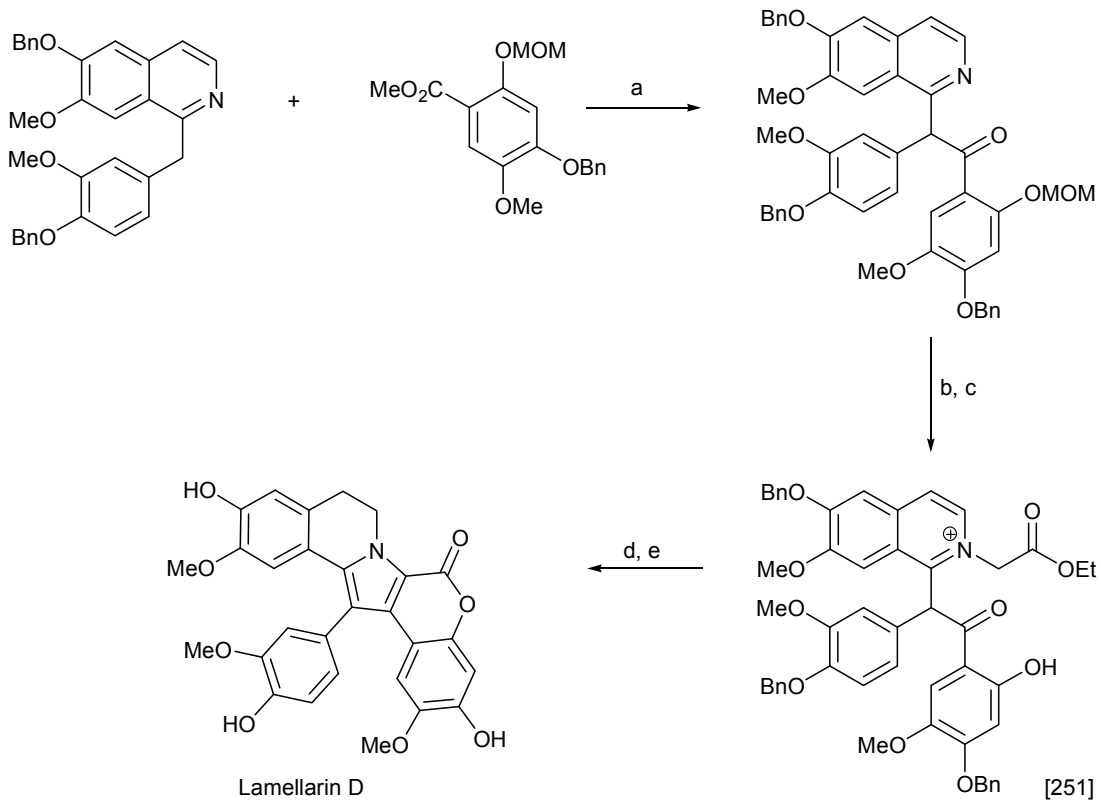
Scheme 67: Gupton's short synthesis of a Lamellarin O precursor.[222] Reagents: (a) $(MeO)_2CHNMe_2$; (b) $POCl_3$; (c) Methyl glycinate hydrochloride, NaH, DMF; (d) H_2O; (e) Methyl glycinate hydrochloride, DMF.

Following on from their previous work on the biomimetic synthesis of marine natural products, Steglich and co-workers[224, 225] have envisioned that the lamellarin compounds could be derived from 3,4-diarylpyrrole dicarboxylic acids [247] by two consecutive oxidation reactions (Scheme 68) . The first entails oxidative coupling of two acids [246] to afford compound [248], and the second a lactone formation between an aryl ring and a carboxylic acid (as in [248]) to afford the intermediate [249]. Further elaboration then afforded lamellarin G trimethyl ether [250].



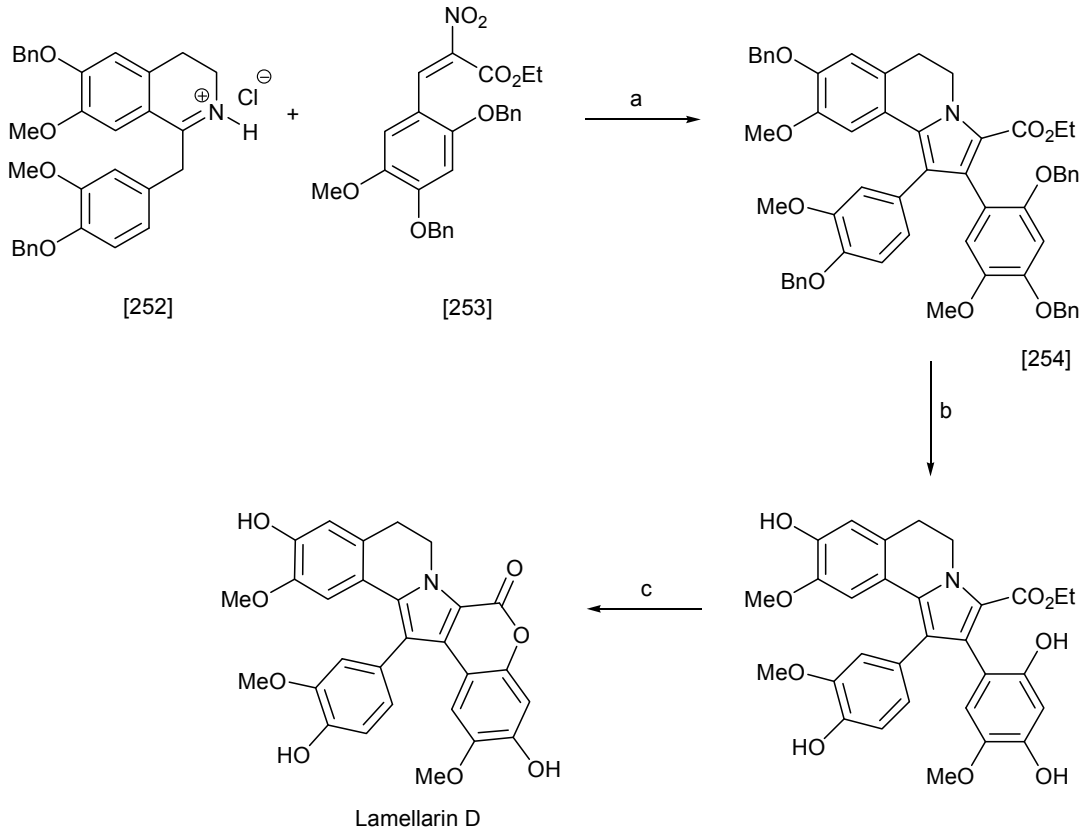
Scheme 68: Steglich's biomimetic synthesis of Lamellarin G trimethyl ether [250].[224] Reagents: (a) *n*-BuLi then I_2; (b) 2-Bromo-4,5-dimethoxyphenethylamine, molecular sieves; (c) $Pb(OAc)_4$; (d) $Pd(OAc)_2$, PPh_3, Et_3N, MeCN.

Ishibashi and co-workers[226] have approached the synthesis of the lamellarin alkaloids by way of an *N*-ylide-mediated pyrrole formation of a quaternary ammonium salt such as [251], followed by lactonization (Scheme 69). Hydrogenation of the benzyl protecting groups then liberated the known alkaloid lamellarin D. Ruchirawat and co-workers[227, 228] have fashioned syntheses of lamellarin alkaloids in a similar manner.



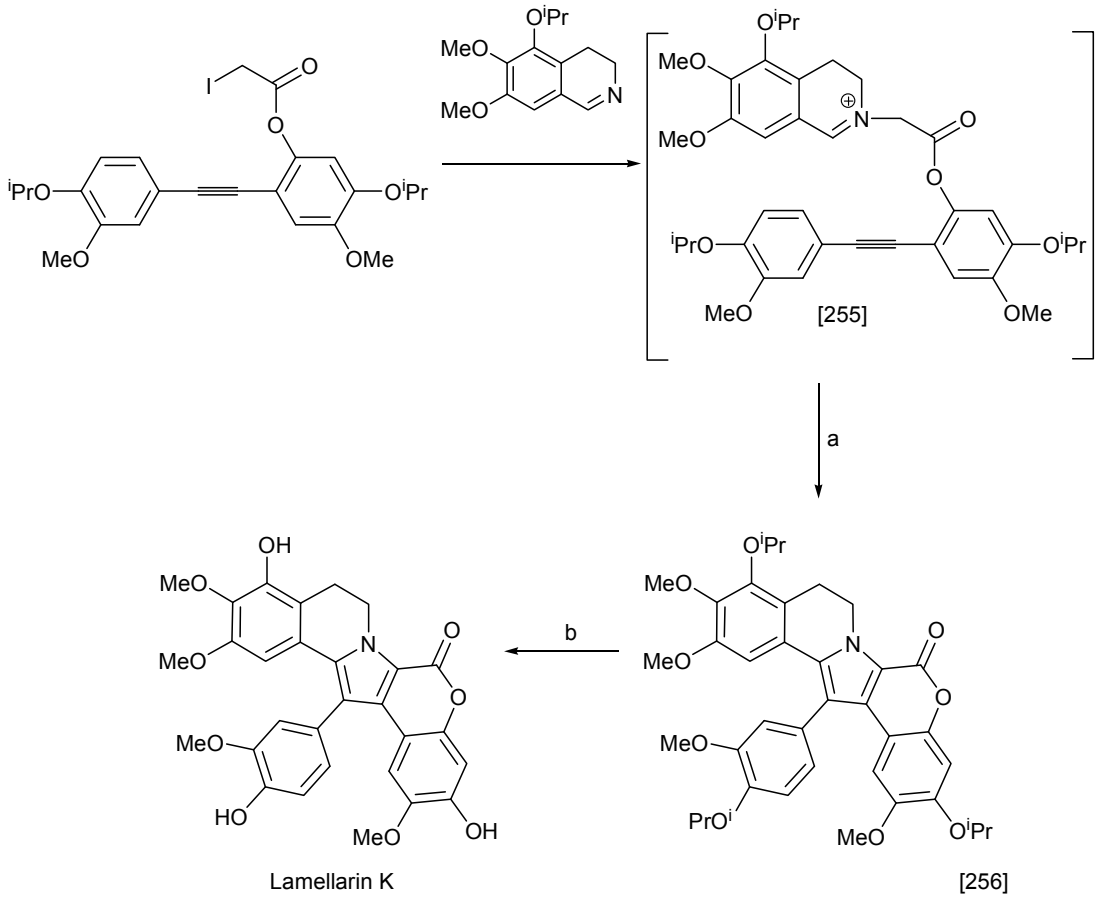
Scheme 69: Ishibashi's synthesis of Lamellarin D.[226] Reagents: (a) LDA, THF; (b) Ethyl 2-bromoacetate, THF; (c) HCl (cat.), MeOH; (d) Et_3N, CH_2Cl_2; (e) H_2, Pd/C, EtOAc.

Since imines, which exist in equilibrium with their enamines, have been shown to react with β-nitrostyrene to give the corresponding pyrroles[229], Ruchirawat has reported a new condensation pathway making use of this strategy (Scheme 70).[230] Thus, reaction of 3,4-dihydropapaverine hydrochloride [252] with the highly activated ester-containing nitrostyrene [253] afforded the pyrrole [254], which was further elaborated to afford lamellarin D.



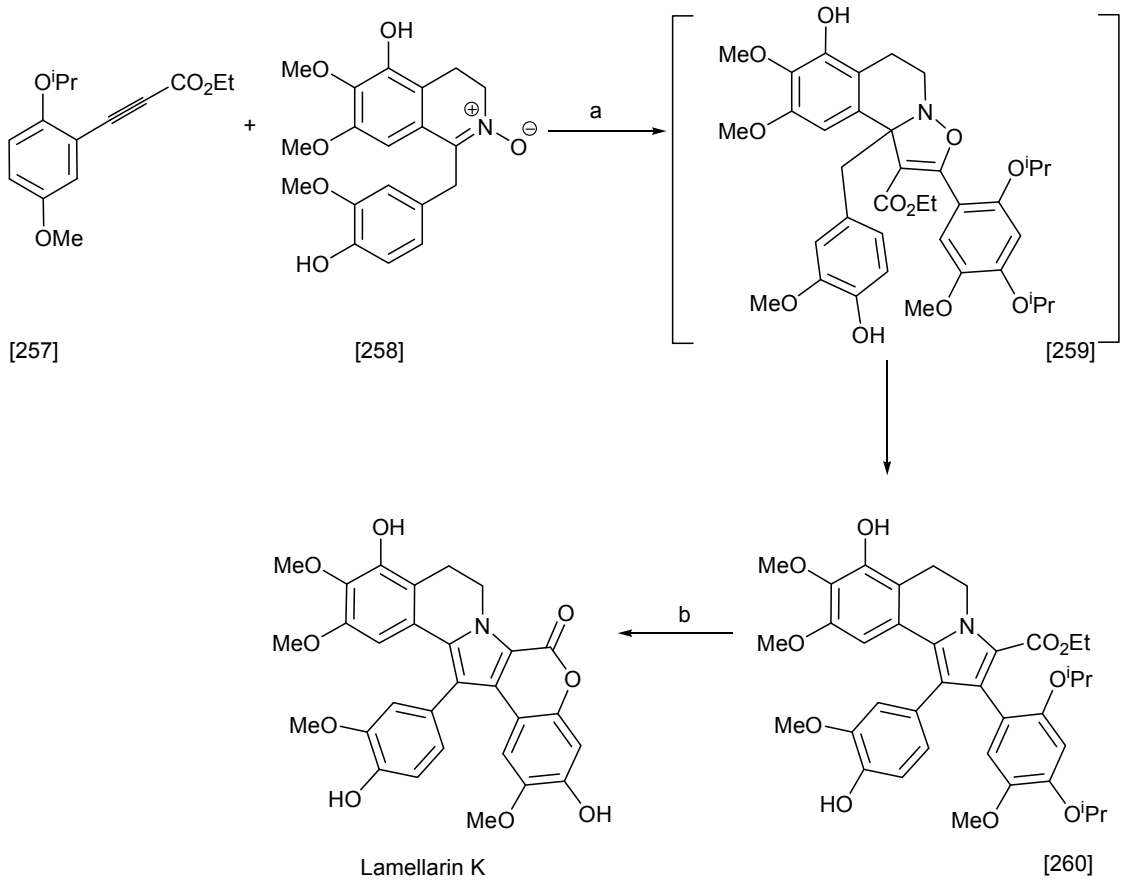
Scheme 70: Ruchirawat's synthesis of Lamellarin D.[230] Reagents: (a) $NaHCO_3$, MeCN, Δ; (b) H_2, Pd/C, EtOAc; (c) NaH, THF.

Banwell and co-workers[231] developed an intramolecular 1,3-dipolar cycloaddition synthesis of lamellarins (Scheme 71). The key step was the formation of the ammonium salt intermediate [255] which was immediately subjected to treatment with Hunig's base, effecting cyclization to give lamellarin K triisopropyl ether [256]. Deprotection with aluminium trichloride then afforded lamellarin K. Faulkner and co-workers[232] has adapted the Banwell strategy to synthesize the analogues of saturated lamellarin α. In addition, Álverez and co-workers[233, 234] have adapted the Banwell synthesis to the solid-phase and have prepared a number of lamellarin alkaloids, including lamellarin U and L.



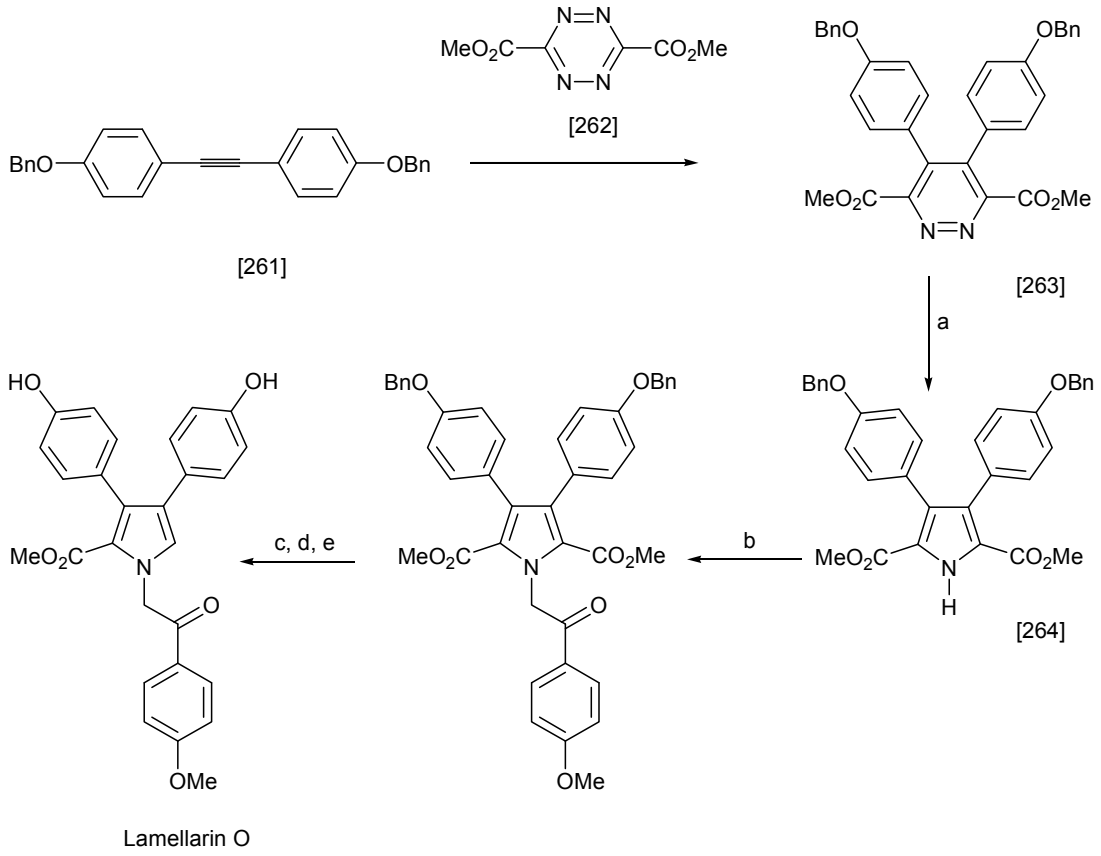
Scheme 71: Banwell's cycloaddition pathway to Lamellarin K.[231] Reagents: (a) Hunig's base; (b) $AlCl_3$, CH_2Cl_2.

In a related approach, Guitián and co-workers[235] employed a 1,3-dipolar cycloaddition between an alkyne [257] and a dihydroisoquinoline *N*-oxide [258] (Scheme 72). The key cycloaddition step was achieved by heating a mixture of the alkyne and the *N*-oxide at 120 °C in a sealed tube. The isoxazoline intermediate [259] rearranged to give the pyrrole [260]. Further elaboration afforded lamellarin K.



Scheme 72: Guitián's cycloaddition pathway to Lamellarin K.[235] Reagents: (a) 120 ^{o}C; (b) $AlCl_3$, CH_2Cl_2.

Finally, Boger and co-workers[236] employed an approach that utilizes an aza Diels-Alder reaction between an alkyne [261] and a tetrazine-dicarboxylate [262] to furnish the 1,2-diazine core [263] (Scheme 73). Zinc mediated reductive contraction of the 1,2-diazine intermediate afforded the pyrrole [264]. Further elaboration afforded lamellarin O.



Scheme 73: Boger's synthesis of Lamellarin O.[236] Reagents: (a) Zn, AcOH; (b) *p*-Methoxyphenacyl bromide, K_2CO_3; (c) LiOH; (d) TFA; (e) H_2, Pd/C.

This brief review has covered some of the important strategies that the synthetic community has developed in constructing the pyrrole moiety of the lamellarin framework. What will follow in the next sections is our potential approach to constructing the lamellarin framework by way of some chemistry that was initially discovered for the pyrrolizine class of compounds. It is envisaged that the chemistry disclosed may in fact be applicable towards the synthesis of the lamellarin alkaloids.

4.2 Exploiting the ambident nucleophilicity of vinylogous amides

A pyrrolizine is a bicyclic heterocycle consisting of a pyrrole ring fused to that of pyrrolidine (Figure 26).

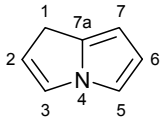
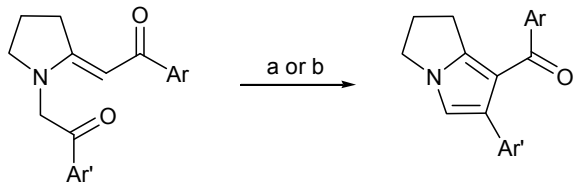


Figure 26: Structure of 1*H*-pyrrolizine showing the conventional numbering system

It is this class of heterocycle that will form the basis of the results and discussion of this section. What will follow is the serendipitous discovery of the pyrrolizine system from vinylogous amides. In the next section, we will discuss the results obtained from systems that exploit the ambident nucleophilicity of enaminones. In addition, the last section will discuss progress towards the lamellarin alkaloids.

4.2.1 Preparation of 6,7-substituted pyrrolizine systems

As mentioned in chapter 3, the attempted hydrogenation of the vinylogous amide [173B] with Adams catalyst, under acidic conditions, for seven hours resulted in an unexpected product (Scheme 74). The product was characterized as the pyrrolizine [265B] and was isolated in 83% yield. Diagnostic features of this compound could be found by spectroscopic means. The pyrrolidine core was found intact by way of the characteristic triplet, triplet and quintet signals for the H_2, H_1 and H_3 signals at 4.03 ppm, 2.97 ppm and 2.52 ppm respectively in the ^{1}H NMR spectrum.



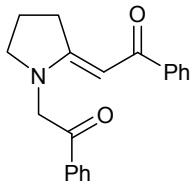
[173B] [265B]

Series B: Ar = Ar' = 3,4-Dimethoxyphenyl

Scheme 74: Formation of pyrrolizine [265B]. Reagents: (a) H_2, PtO_2 (cat.), AcOH / MeOH, rt; (b) AcOH / MeOH, rt.

In addition to the absence of the vinyl proton of the starting material, a new vinyl signal was found down-field at 6.73 ppm in the ^{1}H NMR spectrum of the product. The corresponding vinyl carbon atom was found at 113.37 ppm in the ^{13}C NMR spectrum. The C-7 carbon atom was readily identifiable as a small signal found at 114.26 ppm in the ^{13}C NMR spectrum. In addition, the presence of sixteen signals in the range δ 109 – 151 ppm accounts for all of the aromatic protons. The FTIR spectrum showed an absorbance at 1704 cm^{-1} which implies the presence of a ketone functional group. This ketone functional group was corroborated by a single small signal at 191.23 ppm in the ^{13}C NMR spectrum. Finally, the HRMS spectrum showed a molecular ion at 407.1733 which was in agreement with the expected molecular formula ($C_{24}H_{25}NO_5$ requires 407.1733).

In order to exclude the role of the Adams catalyst in the pyrrole formation, a control experiment was conducted with the absence of both the hydrogen gas and the Adams catalyst and this experiment resulted in the quantitative formation of the pyrrolizine [265B] after twenty-four hours of stirring at room temperature. This experiment then proved that the catalyst did not play a role in the formation of the pyrrole, and that it was the protic solvent, acetic acid, that caused the eventual aromatization of the enaminone.

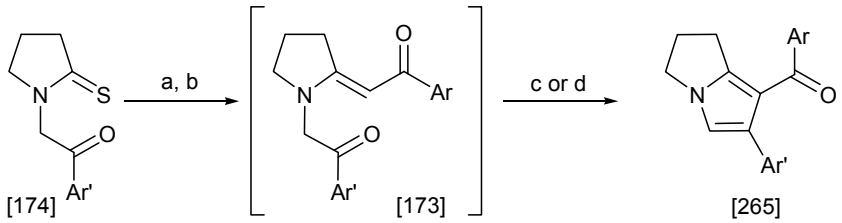


[173A]

This experiment then made us realize that the poor yields associated with the formation of the vinylogous amide [173A] from the thiolactam by way of the Eschenmoser sulfide contraction reaction was as a result of pyrrole formation during column chromatography as the silica-gel used is slightly acidic.

As a test of this hypothesis, a two-dimensional TLC analysis was attempted. The vinylogous amide [173A] was spotted on the TLC plate and developed in 50% EtOAc/hexane as the solvent. Two spots of equal intensity were evident [R_f (50% EtOAc/hexane): 0.49 for the vinylogous amide and R_f (50% EtOAc/hexane): 0.60 for the pyrrolizine respectively]. The plate was allowed to dry and then developed in the second dimension using the same solvent system as before. In this instance, only one spot at R_f = 0.60 was observed. The results indicated that the vinylogous amide [173A] substantially converted to the pyrrolizine on prolonged contact with silica-gel. In addition, this silica-gel reaction was not initially picked up as the pyrrole eluted with the by-products of the Eschenmoser sulfide contraction reaction.

The ease with which the vinylogous amide aromatized during column chromatography suggested that the product could be made directly from the crude reaction mixture of the Eschenmoser sulfide contraction reaction. Therefore, two strategies were considered for the synthesis of the pyrrolizine system (Scheme 75).



Series A: Ar = Ar' = Phenyl

Series C: Ar = Phenyl, Ar' = 3,4-Dimethoxyphenyl

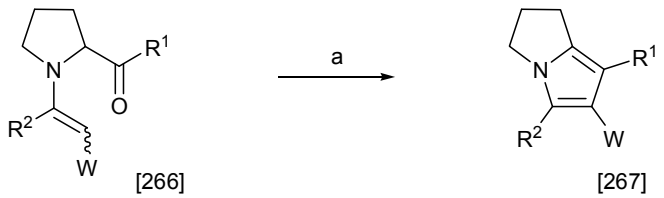
Scheme 75: Formation of pyrrolizines [265]. Reagents: (a) Phenacyl iodide, MeCN; (b) $P(OEt)_3$, Et_3N, MeCN; (c) AcOH, 40 ^oC; (d) SiO_2, 90^oC.

The first strategy involved stirring the crude vinylogous amide from the Eschenmoser sulfide contraction reaction with acetic acid at 40 °C for twenty-four hours. Thus for Series A, a work-up followed by column chromatography afforded the pyrrolizine [265A] in 59% yield. In the second strategy, the crude reaction mixture from the Eschenmoser sulfide contraction reaction was adsorbed onto silica-gel and heated at 90 °C for two hours. Work-up and column chromatography afforded the pyrrolizine [265A] in an improved yield of 72%.

Diagnostic features of this compound were very similar to that of pyrrolizine [265B]. Thus, the vinyl signal was found down-field at 6.69 ppm in the ^1H NMR spectrum of the product. The corresponding vinyl carbon atom was found at 114.19 ppm in the ^{13}C NMR spectrum as was the C-7 carbon atom at 114.28 ppm. In addition, the presence of twelve signals in the range δ 114 – 146 ppm accounts for all of the aromatic protons. The FTIR spectrum showed an absorbance at 1709 cm^{-1} which implies the presence of a ketone functional group. Again, this functional group was corroborated by a single small signal at 191.18 ppm in the ^{13}C NMR spectrum. Finally, the HRMS spectrum showed a molecular ion at 287.1305 which was in agreement with the expected molecular formula ($C_{20}H_{17}NO$ requires 287.1310).

In Series C, the method using silica-gel as the acid source was only considered as it gave the better yield in the Series A reaction sequence. Thus, the crude Eschenmoser sulfide contraction product [173C] was subjected to heating with silica-gel to afford the pyrrolizine [265C] in 66% yield after purification by column chromatography. Again, the pyrrolidine core was found intact by way of the characteristic triplet, triplet, multiplet signals for the H_2, H_1 and H_3 signals at 4.01 ppm, 2.87 ppm and 2.57 – 2.42 ppm respectively in the ^{1}H NMR spectrum. Although the vinyl signal was obscured in the aromatic region of the ^{1}H NMR spectrum of the product, the corresponding vinyl carbon atom was found at 113.75 ppm in the ^{13}C NMR spectrum. In addition, the diagnostic C-7 carbon atom was readily identifiable as a small signal found at 114.27 ppm in the ^{13}C NMR spectrum. The FTIR spectrum showed an absorbance at 1709 cm^{-1} which implies the presence of a ketone functional group. This ketone functional group was corroborated by a single small signal at 192.31 ppm in the ^{13}C NMR spectrum. Finally, the HRMS spectrum showed a molecular ion at 347.1518 which was in agreement with the expected molecular formula ($C_{22}H_{21}NO_3$ requires 347.1521).

A search of the literature revealed a similar observation with regards to the ease of cyclization of enaminone precursors. Thus, González-Ortega and co-workers reported the facile cyclization of a variety of β-functionalized enamines [266] attached directly to nitrogen to afford the pyrrolizines [267] when heated in the presence of silica-gel (Scheme 76).[237]



[266] [267]

Series A: R^1 = Me, R^2 = Me, W = CN

Series B: R^1 = C≡ CBu, R^2 = Me, W = COPh

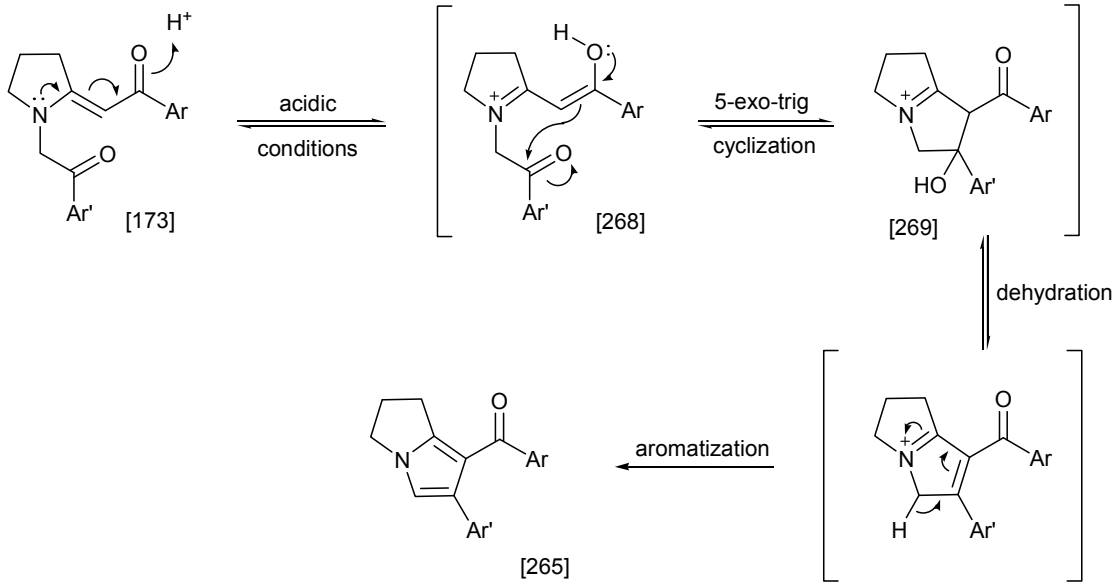
Series C: R^1 = C≡ CPh, R^2 = H, W = CO_2Et

Series D: R^1 = C≡ CH, R^2 = W = CO_2CMe=CH

Scheme 76: Examples of pyrrolizine systems synthesized by González-Ortega and co-workers.[237] Reagent: (a) SiO_2, toluene, ∆.

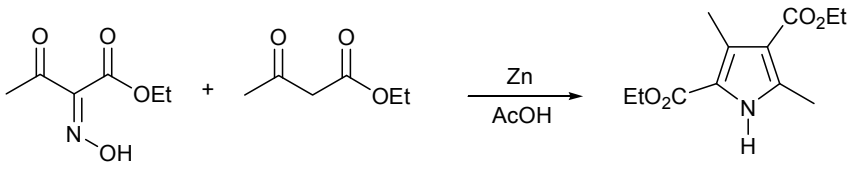
Therefore, although our method of pyrrole formation is not entirely unique, it is novel as we have made pyrrolizine systems with β-functionalized enaminones in which the double bond is exocyclic to the ring, that is, part of an alkylidene system. Nonetheless, the products that we have synthesized by way of this cyclization protocol have led to new and novel compounds. In addition, we wished to extend this methodology towards the synthesis of the lamellarin alkaloids.

To conclude this chapter section, Scheme 77 shows a plausible reaction mechanism for the formation of the pyrrolizine systems. Thus, under the acidic conditions employed (AcOH or SiO_2) protonation to intermediate [268] occurred. In addition, a consideration of Baldwin's rules[238] led us to believe that the favorable five exo-trig cyclisation as opposed to the disfavored five endo-trig cyclisation occurred to afford the intermediate [269]. Loss of a molecule of water followed by aromatization then completes the formation of the pyrrolizine [265].



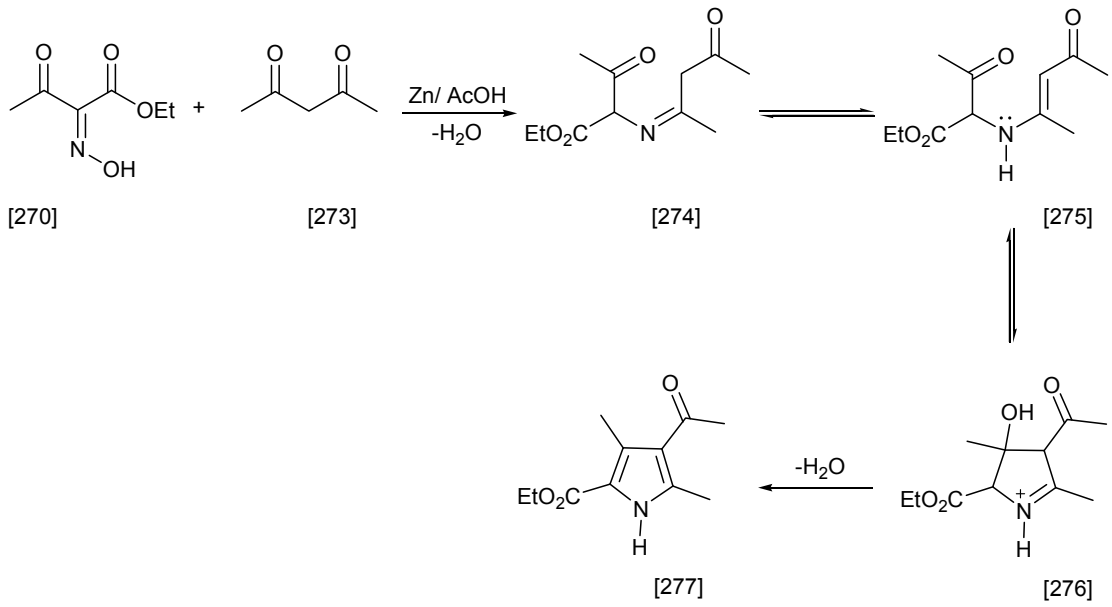
Scheme 77: Proposed mechanism for cyclisation

A literature search led us to believe that this cyclization is a variation of the Knorr pyrrole synthesis. Discovered more than a 120 years ago, the Knorr and Paal-Knorr pyrrole syntheses are similar intermolecular condensations of amines with carbonyl compounds to give pyrroles. Knorr discovered that treatment of ethyl α-oximinoacetoacetate [270] and ethyl acetoacetate [271] with zinc and acetic acid affords the tetra-substituted pyrrole [272] (Scheme 78).[239, 240] Extensive modifications of this reaction over the past 100 years have elevated the Knorr pyrrole synthesis to one of exceptional generality and versatility.



Scheme 78: Discovery of a pyrrole synthesis by Knorr[239, 240]

In addition, Paal and Knorr independently discovered the straightforward reaction of primary amines (or ammonia) with 1,4-diketones to give pyrroles following loss of water.[241, 242] Like the Knorr pyrrole synthesis, the Paal-Knorr method is a powerful and widely used method of constructing pyrroles (*vide infra*). Similarly, the Hantzsch pyrrole synthesis is the chemical reaction of β-ketoesters with ammonia (or primary amines) and α-haloketones to give substituted pyrroles.[243] The mechanism of the original Knorr pyrrole synthesis entails *in situ* reduction of the oxime moiety to an amine (Scheme 79). The amine then condenses with the second carbonyl compound [273] to form the imine [274]. Tautomerization affords [275] which cyclizes to form the intermediate [276]. Finally, loss of a second molecule of water affords the pyrrole [277].[244]

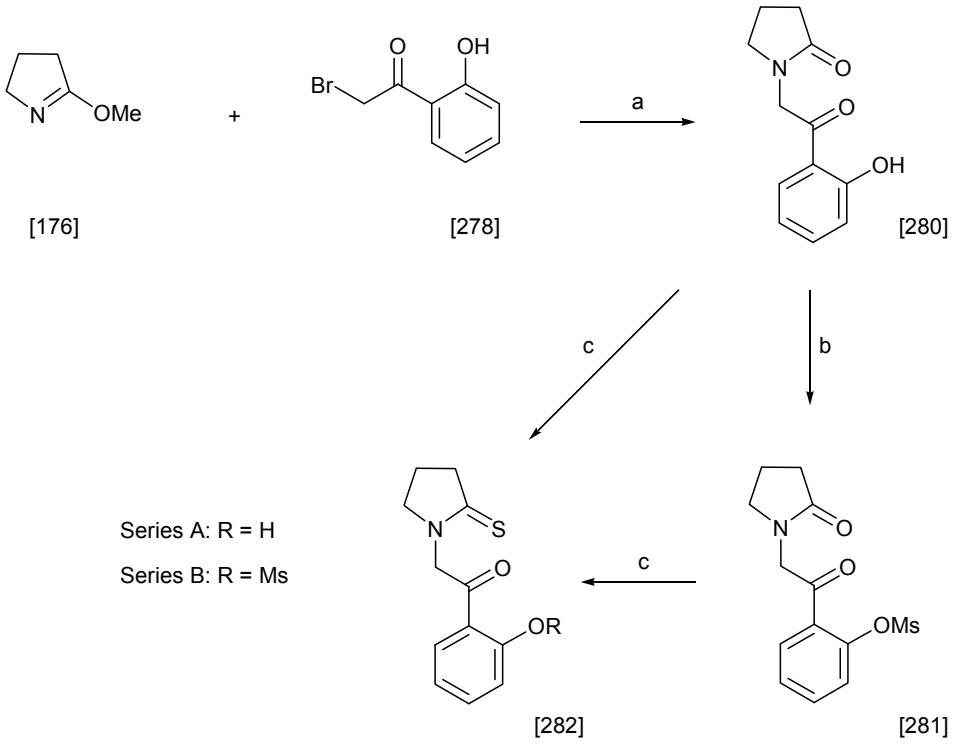


Scheme 79: General mechanism of the Knorr pyrrole synthesis

Thus a consideration of intermediates [173] and [269] in Scheme 77 and of the intermediates [275] and [276] in Scheme 79, suggests that the acid-induced cyclization of the vinylogous amides is indeed a variation of the Knorr pyrrole synthesis.

4.2.2 Preparation of thiolactam precursors containing an additional functional group on the aromatic ring

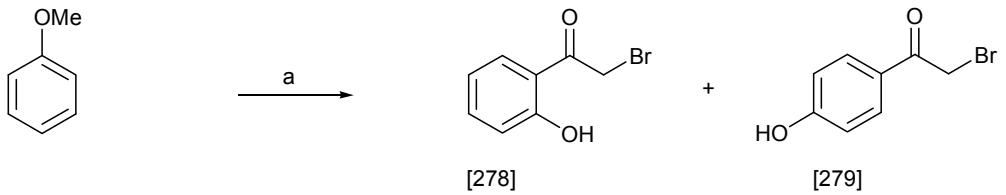
In addition to the pyrrolizine systems described above, we investigated systems in which an *ortho* substituent was present on the aromatic ring that is tethered to the nitrogen atom. Therefore, two additional thiolactam precursors were synthesized (Scheme 80).



Scheme 80: Synthesis of thioamides [282]. Reagents: (a) DMF, 60 ^{o}C; (b) NaH, THF then MsCl; (c) Lawesson's reagent, toluene, 80 ^{o}C.

The preparation of the bromide [278] followed the route disclosed in a patent.[245] The method entailed the Friedel-Craft acylation of anisole with 2-bromoacetyl chloride in the presence of aluminium trichloride which gives both the *ortho*- and *para*-substituted phenacyl bromides. Thus, reaction of anisole with 2-bromoacetyl chloride in hot tetrachloroethane and in the presence of

aluminium trichloride afforded the phenacyl bromides [278] and [279] in 81% yield overall (Scheme 81).



[278] [279]

Scheme 81: Preparation of a phenacyl bromides. Reagents: (a) 2-Bromoacetyl chloride, $AlCl_3$, $Cl_2CHCHCl_2$, Δ.

Column chromatography of the mixture afforded the *para*-substituted phenacyl bromide [279] in 34% yield as a brown solid. Further elution of the column afforded the desired *ortho*-substituted phenacyl bromide [278] in 47% yield. The melting point obtained was 42 – 43 °C which corresponded reasonably well with the literature value of 40 °C.[246] Diagnostic features of the desired product could be obtained from the NMR spectra. Thus, the absence of the methoxy group of the starting material was noted and the appearance of a signal down-field at 11.73 ppm for a phenol group in the ^1H NMR spectrum was also noted. In addition, a singlet signal integrating for two protons at 4.45 ppm in the ^1H NMR spectrum of the product attests to the presence of a methylene group bonded to both a bromine atom and a carbonyl group. In addition, the ^{13}C NMR spectrum displayed a signal at 29.96 ppm for the corresponding carbon atom as well as a carbonyl signal at 196.95 ppm.

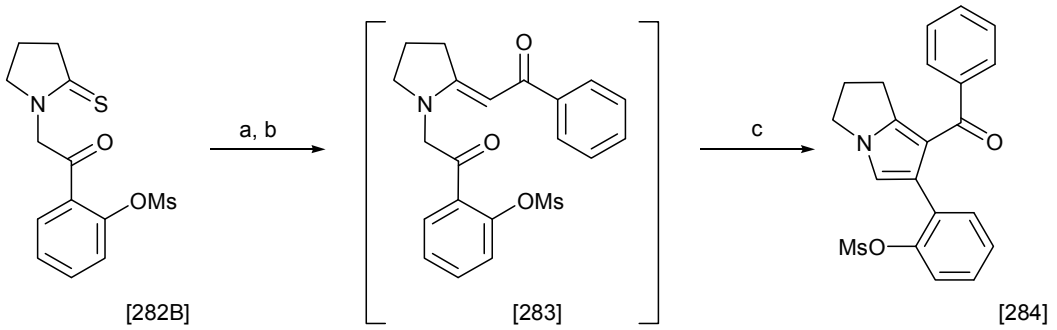
Subsequent reaction of the bromide with the imino ether [176] afforded the lactam [280] in a modest 57% yield (Scheme 80). The low yield may have been as a result of an acid-base reaction between the weakly acidic aromatic phenol and the weakly basic imino ether. The pyrrolidine core was easily identified by way of the characteristic triplet, triplet, multiplet signals for the H_5, H_3 and H_4 signals at 3.51 ppm, 2.49 ppm and 2.21 – 2.05 ppm respectively in the ^1H NMR spectrum. In addition, the appearance of a new signal at 175.78 ppm in the ^{13}C NMR spectrum was assigned as the amide carbonyl of the

lactam, and this was corroborated in the FTIR spectrum as a new absorbance found at 1646 cm^{-1}.

In series B, the lactam was protected as the mesylate by reaction with methanesulfonyl chloride in the presence of sodium hydride as the base to afford the lactam [281] in an unoptimized yield of 49%. Diagnostic features of this compound were the appearance of a new methyl signal found at 3.29 ppm in the ^{1}H NMR spectrum as well as the disappearance of the hydroxyl group of the phenol of the starting material. In addition, a new signal at 38.37 ppm in the ^{13}C NMR spectrum of the product was assigned as the methyl group of the mesylate protecting group. Finally, thionation of this lactam with Lawesson's reagent in hot toluene afforded the thiolactam [282B] in 78% yield. Diagnostic evidence of this reaction was the disappearance of the amide carbonyl functional group and the appearance of a new signal at 203.53 ppm for the thionyl functional group in the ^{13}C NMR spectrum.

Similarly for series A, reaction of the lactam [280] with Lawesson's reagent in hot toluene afforded the thiolactam [282A] in 67% yield. Again, the diagnostic evidence for this reaction was the down-field signal of 204.02 ppm for the thionyl carbon atom in the ^{13}C NMR spectrum. In addition, the HRMS spectrum showed a molecular ion at 235.0663 which is in agreement with the expected molecular formula of the product ($C_{12}H_{13}NO_2S$ requires 235.0667).

With the thiolactams in hand, we were in a position to attempt the "one-pot" synthesis of the pyrrolizine system by way of an Eschenmoser sulfide contraction reaction followed by aromatization of the crude vinylogous amides. The first attempt is illustrated in Scheme 82.

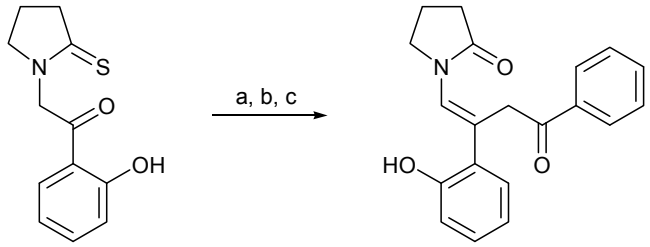


Scheme 82: Synthesis of pyrrolizine [284]. Reagents: (a) Phenacyl iodide, MeCN; (b) $P(OEt)_3$, Et_3N, MeCN; (c) AcOH, MeOH, 45 ^oC.

Thus, reaction of the thiolactam [282B] with phenacyl iodide followed by extrusion of the sulfur with triethyl phosphite, as the thiophile, afforded crude vinylogous amide [283] as an orange gum after an aqueous work-up. The crude reaction mixture was then dissolved in acetic acid and methanol and allowed to stir for 18 hours at 45 °C. Work-up followed by chromatography afforded the desired pyrrolizine [284] in 58% yield over the two steps. Again, the product had spectral features similar to the other previously prepared pyrrolizines. Of note, was the appearance of one carbonyl signal in the ^{13}C NMR spectrum which was found at 191.83 ppm. This carbonyl moiety was corroborated in the FTIR spectrum as an absorbance found at 1709 cm^{-1}. In addition, the mesyl protection group remained unscathed during the course of the reaction as the appearance of the methyl signal in the ^1H NMR spectrum was readily identifiable at 2.84 ppm, also the corresponding carbon signal was identified at 37.52 ppm in the ^{13}C NMR spectrum.

The same protocol was attempted for the unprotected phenol [282A] as illustrated in Scheme 83. Instead of subjecting the crude vinylogous amide to the cyclization step, we sought to isolate this intermediate. Thus, reaction of the thiolactam [282A] with excess phenacyl iodide in refluxing diethyl ether for forty-eight hours effected complete salt formation. The solvent was evaporated and replaced with dry acetonitrile. Eschenmoser sulfide contraction was effected with triphenylphosphine as the thiophile in the presence of triethylamine as the base. Work-up followed by column

chromatography afforded a material that contained several products as evidenced by a TLC analysis. In addition analysis of this material by ^{1}H NMR spectroscopy was not possible owing to the complex nature of all the signals present. Therefore, the material was subjected to the acid-induced cyclization step, as we suspected that one of the products was at least the expected pyrrolizine. However, reaction of this mixture of products with silica-gel as the acid source in refluxing toluene unexpectedly afforded the pyrrolidine [285] as the sole identifiable product in a low 27% yield.



[282A] [285]

Scheme 83: An unexpected synthesis of pyrrolidine [285]. Reagents: (a) Phenacyl iodide, Et_2O, Δ; (b) PPh_3, Et_3N, MeCN; (c) SiO_2, toluene, Δ.

The ^{13}C NMR spectrum showed a signal at 200.73 ppm for the carbonyl carbon atom. This was corroborated by an absorbance found at 1692 cm^{-1} in the FTIR spectrum. In addition, the conjugated olefin functional group was readily assignable in the ^{13}C NMR spectrum. The C-6 carbon of the olefin (alpha to the nitrogen) was observed at 116.72 ppm and the C-7 carbon of the olefin was observed as a small signal at 110.20 ppm respectively. In the ^{1}H NMR spectrum, the singlet signal found at 4.10 ppm was assigned as the H_8 protons alpha to the olefin moiety of the compound. Finally, a crystal was grown that was suitable for X-ray analysis and pleasingly confirmed the identity of the product as shown in the ORTEP diagram in Figure 27.

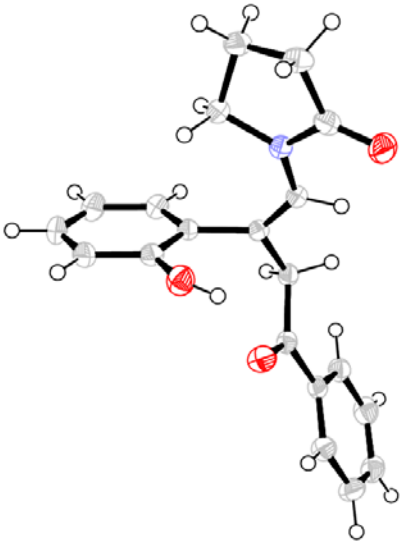
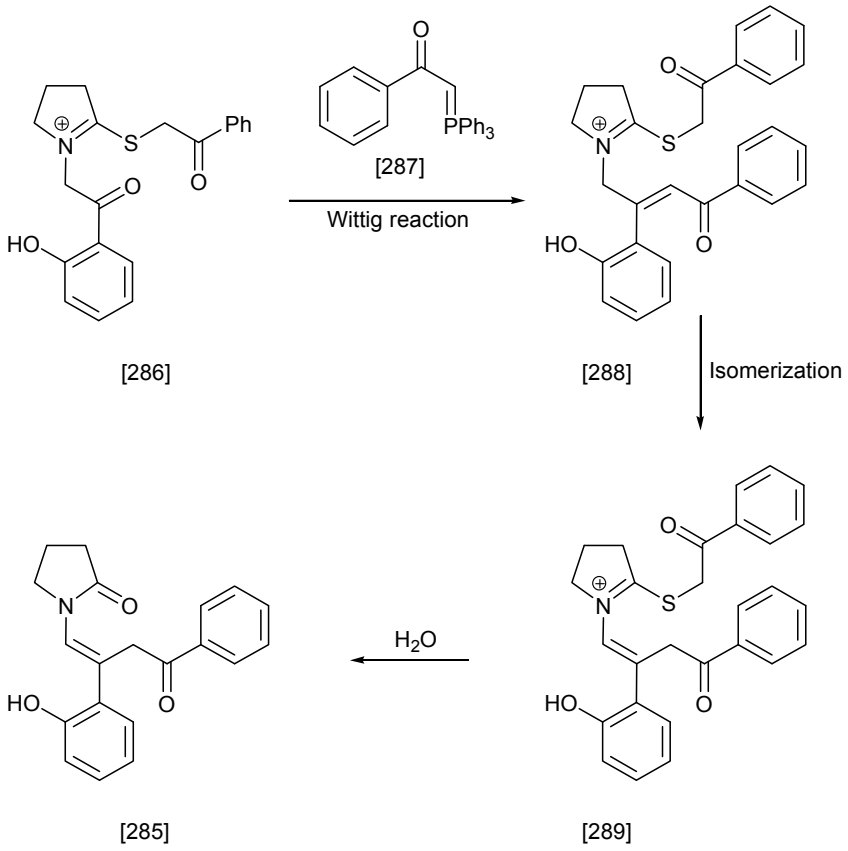


Figure 27: ORTEP diagram of pyrrolidine [285]. Thermal ellipsoids are shown at the 50% probability level.

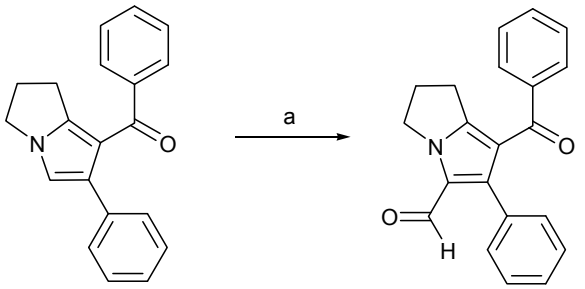
The manner in which this product formed is speculative. However, we can at least consider the formation of the ylide [287] during the extrusion step of the sulfide contraction reaction (Scheme 84) as excess phenacyl iodide and triphenylphosphine was initially used. This ylide then may have done a Wittig reaction with the remote carbonyl of compound [286] to afford intermediate [288]; and in the presence of the excess base isomerization to intermediate [289] may have occurred. It is through this reaction that we may readily explain the presence of the acetophenone moiety at the benzylic position of the substituted phenol. In addition, this must all have occurred before the thioiminium salt had a chance to enter into the Eschenmoser sulfide contraction reaction. Finally, work-up then hydrolyzed the salt to afford the observed product. In addition, the product was finally isolated after refluxing with silica-gel in toluene which presumably decomposed the other impurities that allowed for isolation of the pyrrolidine, albeit in low yield.



Scheme 84: A possible reaction mechanism for the formation of pyrrolidine [285]

4.2.3 Preparation of 5,6,7-trisubstituted pyrrolizine systems

The lamellarin alkaloids contain a pyrrole moiety that is fully substituted; therefore we investigated the preparation of pyrrolizine systems that are also fully substituted. The first reaction that we attempted made use of the Vilsmeier-Haack[247] formylation in an attempt to introduce a formyl group at the 5-position of the pyrrolizine [265A] chemoselectively (Scheme 85).



[265A] [290]

Scheme 85: Formylation of pyrrolizine [265A]. Reagent: (a) DMF, $POCl_3$, CH_2Cl_2 then H_2O work-up.

Thus, reaction of the pyrrolizine [265A] in the presence of dimethylformamide and phosphorus oxychloride in dichloromethane as the solvent afforded the formyl adduct in a modest 45% yield as a brown solid. The chemoselective reaction was inferred from the ^{1}H NMR spectrum by the absence of the aromatic vinyl proton of the pyrrole moiety and the presence of the aldehyde functional group by way of a signal found at 9.42 ppm for the aldehyde proton. In addition, the corresponding carbon signal for the aldehyde functional group was found at 180.11 ppm in the ^{13}C NMR spectrum. Lastly, the HRMS spectrum showed a molecular ion at 315.1278 which is in close agreement with the expected molecular formula ($C_{21}H_{17}NO_2$ requires 315.1259). Finally, as the product was a solid an x-ray analysis corroborated the structure of the product as shown in the ORTEP diagram in Figure 28.

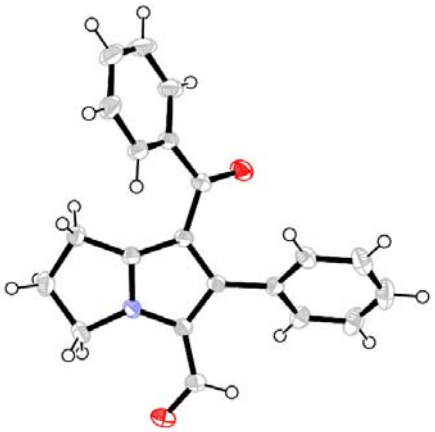
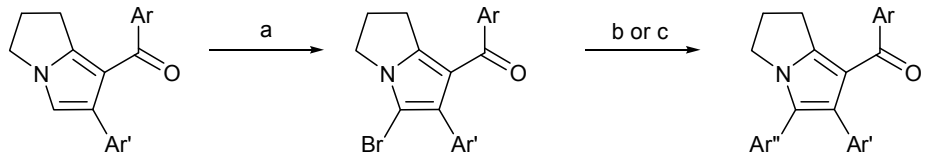


Figure 28: ORTEP diagram of pyrrolizine [290]. Thermal ellipsoids are shown at the 50% probability level.

Therefore, with the reaction having occurred chemoselectively at the C-5 position, we then embarked on a strategy to functionalize the pyrrolizine system by way of a Suzuki-Miyaura coupling reaction sequence.[248] The Suzuki reaction is the organic reaction of an aryl- or vinyl-boronic acid with an aryl or vinyl halide catalyzed by a palladium(0) complex. It is widely used to synthesize poly-olefins, styrenes, and substituted biphenyls, amongst others. Thus, the strategy for the installation of an aryl group at the C-5 position of the pyrrolizine system is outlined in Scheme 86.



[265] [291] [292]

Series A: Ar = Ar' = Ar'' = Phenyl

Series B: Ar = Ar' = Phenyl, Ar'' = 3,4-Dimethoxyphenyl

Series C: Ar = Phenyl, Ar' = Ar'' = 3,4-Dimethoxyphenyl

Scheme 86: Bromination and Suzuki-Miyaura coupling reaction sequence. Reagent: (a) NBS, THF; (b) Phenylboronic acid, $Pd(PPh_3)_4$ (cat.), Na_2CO_3, EtOH, H_2O, DME, Δ; (c) 3,4-Dimethoxyphenylboronic acid, $Pd(PPh_3)_4$ (cat.), Na_2CO_3, EtOH, H_2O, DME, Δ.

Thus, bromination of pyrrolizine [265A] with *N*-bromosuccinimide in tetrahydrofuran for twenty minutes afforded the bromide [291A] in 54% yield after column chromatographic purification. The low yield may be attributed to decomposition of the bromide during column chromatography as a red band suddenly appeared during the course of the chromatographic purification; the colour may be indicative of dehalogenation. In addition, the solid rapidly turned black within several hours of standing at room temperature. Therefore, the bromide was used without delay into the next subsequent reaction. On one occasion, ^1H and ^{13}C NMR spectroscopy was performed on the bromide and although the compound was in a state of decomposition it was clear that bromination had occurred as we were able to notice the absence of the vinyl proton in the ^1H NMR spectrum and the corresponding vinyl carbon atom in the ^{13}C NMR spectrum of the starting material. In addition, a new small signal at 97.09 ppm was assigned as the carbon atom attached to the bromine atom.

Bromination of pyrrolizine [265C] under identical conditions afforded the bromide [291C] in 78% yield after a rapid flash chromatographic purification. This bromide was also found to be unstable and turned black within hours of isolation. Accordingly, the bromide was used without delay. A diagnostic signal found in the ^{13}C NMR spectrum, which also showed an advanced state

of decomposition, was found at 96.79 ppm for the C-5 carbon atom which is similar to that found for pyrrolizine [291A].

With the bromides in hand we then attempted the Suzuki-Miyaura coupling reaction. Thus, reaction of bromide [291A] with phenylboronic acid in the presence of a catalytic amount of $Pd(PPh_3)_4$ and sodium carbonate as the base, for eighteen hours at reflux afforded the desired pyrrolizine [292A] in 73% yield after chromatographic purification. The ^1H NMR spectrum of the product showed a complex set of signals for the aromatic protons between 7.61 – 7.02 ppm. More importantly, the integration was found to be fifteen which matched the expected number of protons in this region of the spectrum for the product. In addition, the signal attributed to the C-5 carbon atom of the starting bromide was absent and replaced by a new small signal found at 127.04 in the ^{13}C NMR spectrum. In addition, the HRMS spectrum showed a molecular ion at 363.1617 which is in agreement with the expected molecular formula ($C_{26}H_{21}NO$ requires 363.1623).

Similarly, reaction of the bromide [291A] with 3,4-dimethoxyphenylboronic acid under identical conditions afforded the pyrrolizine [292B] in 87% yield after chromatographic purification. Although the aromatic protons were observed as a complex set of signals in the ^1H NMR spectrum they integrated for the expected number of thirteen protons. In addition, the two methoxy groups were readily identifiable as singlets found at 3.85 ppm and 3.51 ppm respectively in the ^1H NMR spectrum. The ^{13}C NMR spectrum implied the presence of the methyl groups of the methoxy moiety as signals found at 55.66 ppm and 55.37 ppm respectively. Again, the HRMS spectrum showed a molecular ion at 423.1828 which is in close agreement for the expected molecular formula ($C_{28}H_{25}NO_3$ requires 423.1834).

Finally, a one hour reaction of the bromide [291C] with 3,4-dimethoxyphenylboronic acid under the Suzuki-Miyaura conditions described above afforded the pyrrolizine [292C] in 87% yield after chromatographic purification. It should be mentioned that the short reaction time was by default as the reaction had turned black within this time. We initially suspected that the catalyst had been poisoned by air, resulting in the palladium black

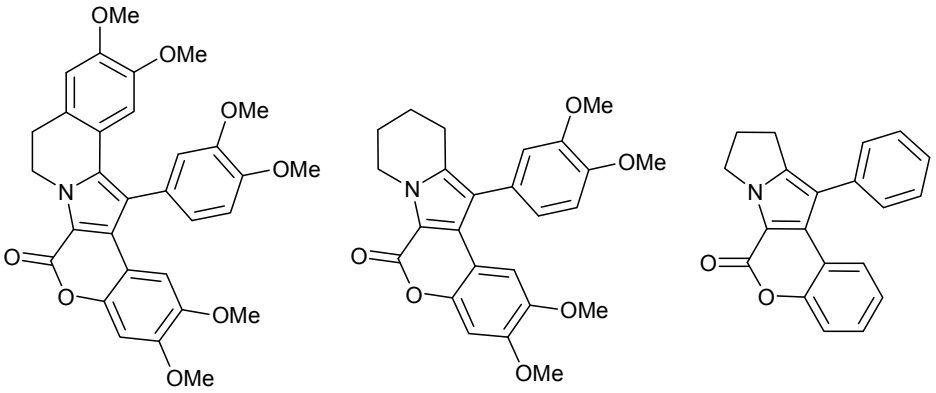
crashing out of solution. Surprisingly, upon work-up and chromatography we had actually synthesized the desired product and not isolated starting material. Diagnostic evidence of the reaction was found in the ^{1}H NMR spectrum by the presence of four singlets for the methoxy groups at 3.86 ppm, 3.76 ppm, 3.59 ppm and 3.57 ppm respectively. In addition, the ^{13}C NMR spectrum implied the presence of the methyl signals of the methoxy moiety at 55.63 ppm, 55.61 ppm, 55.46 ppm and 55.41 ppm respectively. Finally, the HRMS spectrum gave a molecular ion at 483.2009 which is in agreement with the expected molecular formula ($C_{30}H_{29}NO_5$ requires 483.2046).

In conclusion, the synthesis of 6,7-substituted pyrrolizine systems was found to be achievable by cyclization of the vinylogous amides under acidic conditions. The formation of the pyrrole was found by analogy to be a variation of the Knorr pyrrole synthesis. In addition, the reaction occurred by way of exploiting the ambident nucleophilicity of the vinylogous amide systems. Pleasingly, the pyrrolizine systems could be further elaborated to give 5,6,7-substituted systems in which the C-5 position was amenable to aryl functionalization by way of the Suzuki-Miyaura reaction conditions from the corresponding bromides. This work was important in that we were able to explore and get a feel for the chemistry that may be amenable towards a model system towards the lamellarin framework. In the next section we shall discuss progress towards this model system by exploiting the ambident electrophilicity of vinylogous amides.

4.3 Exploiting the ambident electrophilicity of vinylogous amides

4.3.1 Introduction

In this chapter section we will discuss some results that exploit the ambident electrophilicity of vinylogous amides and their potential in constructing the lamellarin scaffold. A consideration of the scaffold shown in lamellarin G trimethyl ether suggests a simplified analogue by way of the indolizine [293] (Figure 29) which contains all the features of the lamellarin alkaloids excepting for the isoquinoline aromatic moiety. In light of the results to be discussed we felt we could access this simplified analogue by exploiting the ambident electrophilicity of vinylogous amides. Before this undertaking was attempted we wished to further extend the results obtained, to date, for pyrrolizine systems by preparing the pyrrolizine [294], therefore the preparation of the pyrrolizine [294] was to serve as a model system for the intended synthesis of the indolizine [293] system. The pyrrolizine [294] at first seems an unlikely model substrate for the eventual synthesis of the lamellarin alkaloids, however the formation of the central pyrrole ring as well as the presence of the coumarin part of the molecule is analogous to that found in the lamellarin alkaloids. Moreover, the way we are to set up the pyrrole ring is far removed to that disclosed in the literature as we are to prepare this ring by way of a variation of the Knorr pyrrole synthesis. In addition, the lamellarin alkaloids are reasonably complex structures and we felt that the chemistry learned here can be extended to the indolizine system which, in principle, can be extended to the lamellarin system. Therefore, this chapter section will discuss progress towards the synthesis of the pyrrolizine system [294].



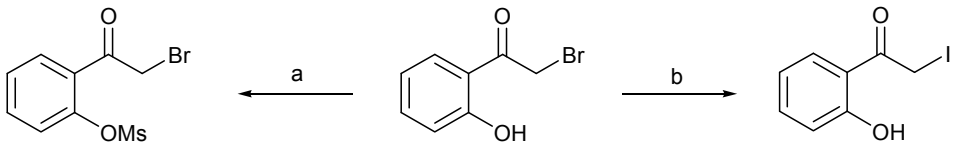
Lamellarin G trimethyl ether [250] [293] [294]

Figure 29: Lamellarin G trimethyl ether [250] shown alongside with a tetrahydro-6H-chromeno[4,3-b]indolizin-6-one [293] and a more simplified dihydrochromeno[4,3-b]pyrrolizin-6(8H)-one [294]

4.3.2 Preparation of functionalized phenacyl iodides

As we are to use a variety of functionalized phenacyl bromides and iodides in this section of the project, more specifically phenacyl halides that contain functional groups on C-2 of the aromatic ring, it is prudent to group them in one section.

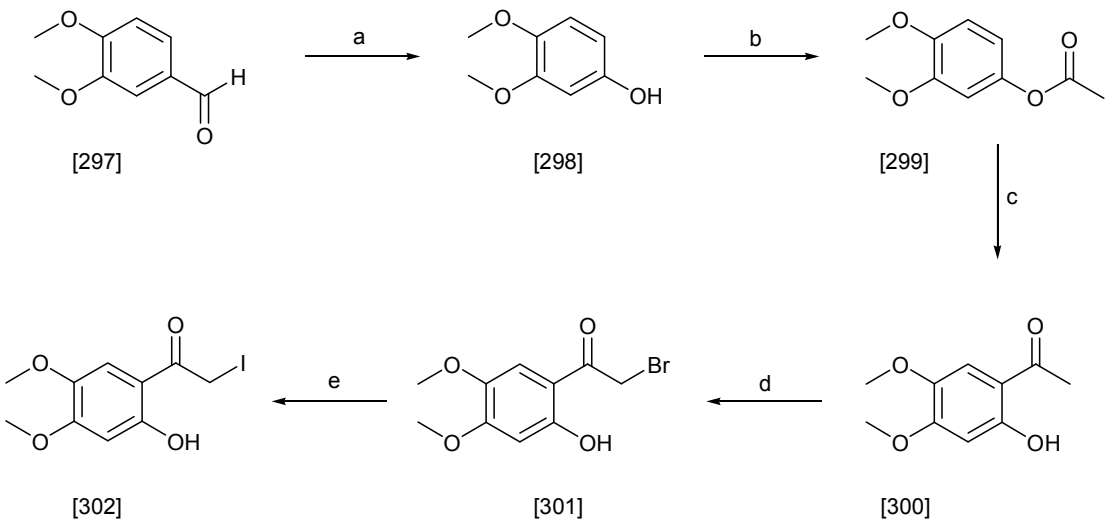
It was necessary to prepare the iodide [296] (Scheme 87), as the subsequent sulfide contraction reactions (section 4.3.3) could not be persuaded to go to completion with the corresponding bromide. Thus, the previously prepared bromide [278] was subjected to a Finkelstein reaction to prepare the corresponding phenacyl iodide. Reaction of the bromide [278] with sodium iodide in acetone afforded the iodide [296] in 88% yield after a rapid flash chromatography purification as a yellow solid. The product was generally prepared immediately prior to use as it tended to decompose on standing at room temperature. The solid was identified by way of a melting point analysis which was determined at 62 – 63 °C which is in close agreement with the literature value of 65 °C.[245]



[295] [278] [296]

Scheme 87: Preparation of phenacyl halides from bromide [278]. Reagents: (a) Methanesulfonyl chloride, Et_3N, THF; (b) NaI, acetone.

In addition to the phenacyl bromides with a free phenol substituent, we sought phenacyl bromides with the phenol group protected. In this regard, the use of a mesyl protecting was sought. The choice of a mesyl protecting group may seem strange at first. However, the aromatic mesylate is stable to the acidic conditions used for nitration of an aromatic ring (HNO_3/AcOH),[249] and to the high temperatures (200 – 250 °C) of an Ullman reaction.[250] Therefore, we expected this protective group to survive the acidic conditions and high temperatures of the various transformations that we envisaged to carry out. Thus, reaction of the bromide [278] with methanesulfonyl chloride in the presence of triethylamine at 0 °C in tetrahydrofuran furnished the expected product [295] in 92% yield as an oil. The ^{1}H NMR indicated the presence of a new singlet integrating for three protons at 3.17 ppm. In addition, the absence of the phenol signal was noted. Further evidence of the success of the reaction can be found in the HRMS where the molecular ion of 291.9400 was determined ($C_9H_9{}^{79}BrO_4S$ requires 291.9405).

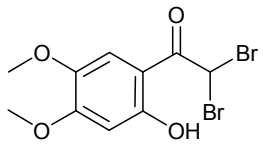


Scheme 88: Preparation of a phenacyl iodide [302]. Reagents: (a) H_2O_2, H_2SO_4 (cat.), MeOH; (b) Ac_2O, pyridine (c) $BF_3.Et_2O$, Δ; (d) $CuBr_2$, EtOAc/$CHCl_3$, Δ; (e) NaI, acetone.

In addition, it was necessary to prepare the iodide [302] as the substitution pattern closely resembles those found in lamellarin G trimethyl ether [250] (Scheme 88). Although the phenol [298] is commercially available it is expensive, therefore the route started from the inexpensive veratraldehyde [297]. Thus, Baeyer-Villiger reaction of [297] with hydrogen peroxide in acidic methanol afforded the phenol [298] in 75% yield. Pleasingly, the yield was somewhat better than the 60% yield obtained from that reported in the literature.[251] The melting point was determined at 78 – 80 °C (lit.[252] 79 – 82 °C). In addition, the absence of the aldehyde functional group was noted in the relevant ^1H and ^{13}C NMR spectra. The phenol was immediately acylated with acetic anhydride in the presence of pyridine as the base to afforded the ester [299] in 93% crude yield, as an oil, after a conventional work-up. The product was not characterized but subjected to a Fries rearrangement with a Lewis acid. To our delight, the acid-promoted rearrangement was found to proceed effectively by treating the ester [299] with neat boron triflouride etherate (5 equiv.) at reflux for five hours, which led to the formation of the acetophenone [300] in 92% yield. Diagnostic features of the ^1H NMR spectrum for the product were the two aromatic singlets at 7.06 ppm and 6.45 ppm respectively, a sequence that corroborates the expected substitution pattern of the desired product. The appearance of a sharp singlet at the down-

field region of the spectrum at 12.64 ppm for the hydrogen-bonded phenol proton was noted. In addition, the appearance of an additional signal integrating for three protons at 2.56 ppm in the ^{1}H NMR spectrum was readily assigned as the methyl group belonging to the newly installed acetyl unit. The ^{13}C NMR spectrum showed an absence of an ester carbonyl carbon atom and was replaced with that of an aromatic ketone with the carbonyl carbon found at 201.96 ppm. This evidence was corroborated by the appearance of an absorbance at 1630 cm $^{-1}$ in the FTIR spectrum. Finally, in addition to the methoxy signals, the appearance of an additional methyl group was observed at 26.27 ppm in the ^{13}C NMR spectrum.

Bromination was effected with copper(II) bromide according to a known literature procedure.[246] Thus, reaction of acetophenone [300] with copper(II) bromide in boiling chloroform/ethyl acetate afforded the bromide [301] in 57% yield after a single recrystallization. It should be mentioned that the product was always slightly contaminated with starting material and the dibromide [303]. It was found not feasible to carry out multiple recrystallizations as severe losses in yield occurred in each crystallization step. Nonetheless, the impurities did not have an effect on subsequent reactions.



[303]

The ^{1}H NMR showed the absence of the acetyl group and the appearance of a new signal at 4.35 ppm integrating for two protons of the methylene group. Two aromatic signals were found at 7.06 ppm and 6.48 ppm which attests to the fact that no nuclear bromination occurred. In addition, the ^{13}C NMR spectrum showed a new signal at 29.83 ppm for the new methylene group. Lastly, the HRMS showed a molecular ion at 273.9835 which is in agreement with the expected molecular formula ($C_{10}H_{11}{}^{79}BrO_4$ requires 273.9841).

Finally, reaction of the bromide [301] with sodium iodide in acetone afforded the iodide [302] in 98% yield after chromatographic purification. The ^{1}H NMR spectrum was very similar to that of the bromide [301] and therefore gave no clear cut evidence of the success of the reaction. The success of the reaction, however, could be ascertained from the ^{13}C NMR spectrum. The signal found at the very upfield region at 0.61 ppm was inferred to be the carbon atom

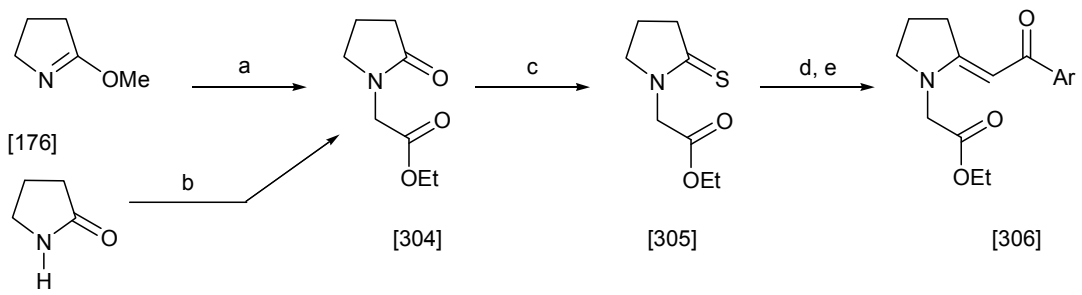
attached to the iodide which was clearly different from that of the bromide as described above.

Thus, with these new bromides and iodides in hand were now in a position to proceed with the Eschenmoser sulfide contraction reactions of the requisite thiolactam precursor.

4.3.3 Preparation of a series of vinylogous amides

The vinylogous amide of interest is one that contains an ethoxycarbonyl methyl attached to nitrogen (Scheme 89). Thus, construction of this molecule can be readily accessed by way of the Eschenmoser sulfide contraction reaction starting from either the imino ether or from 2-pyrrolidinone.

Thus, the first route entailed the preparation of the lactam [304] by way of the imino ether [176]. Therefore, reaction of excess imino ether with ethyl 2-bromoacetate in dimethylformamide at 80 °C for seventeen hours afforded the lactam in a modest 49% yield after chromatographic purification. An improved procedure involved reaction of 2-pyrrolidinone with sodium hydride in tetrahydrofuran which formed a gelatinous reaction mixture. Addition of ethyl 2-bromoacetate to this reaction mixture followed by stirring for an additional eighteen hours afforded the lactam in near quantitative yield after a work-up and chromatographic purification.



Series A: Ar = Phenyl

Series B: Ar = 2-Hyrdroxyphenyl

Series C: Ar = 2-[(Methylsulfonyl)oxy]phenyl

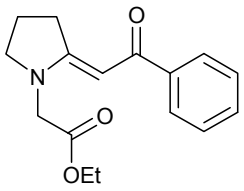
Series D: Ar = 2-Hydroxy-4,5-dimethoxyphenyl

Scheme 89: Preparation of a series of vinylogous amides. Reagents: (a) Ethyl 2-bromoacetate, DMF, 80 ^{o}C; (b) NaH, THF, ethyl 2-bromoacetate; (c) Lawesson's reagent, toluene, 80 ^{o}C; (d) Series A: Phenacyl iodide, MeCN; Series B: 2-Hydroxyphenacyl iodide, MeCN; Series C: 2-[(Methylsulfonyl)oxy]phenacyl bromide, MeCN; Series D: 2-Hydroxy-4,5-dimethoxyphenacyl iodide, MeCN; (e) PPh_3, Et_3N, MeCN.

Diagnostic evidence for the success of the reaction can be found in the relevant NMR spectra. Thus, the typical quartet and triplet signal for the ethyl ester were found at 4.19 ppm and 1.28 ppm respectively. In addition, the methylene group alpha to both the nitrogen and the carbonyl ester functional group was readily identified as a singlet at 4.05 ppm. The presence of the ester carbonyl carbon atom was found at 168.62 ppm in the ^{13}C NMR spectrum. In addition, the FTIR spectrum corroborated the presence of the carbonyl ester functional group with an absorbance found at 1742 cm^{-1}.

Thionation of the lactam [304] with Lawesson's reagent in hot toluene afforded the thiolactam [305] in 88% yield after two chromatographic purifications. In this instance the known purification difficulties associated with the use of Lawesson's reagent became apparent in that the phosphorus-containing by-products of the reaction co-eluted with the product during the first chromatographic purification, therefore necessitating a second

chromatographic purification. Diagnostic evidence in the FTIR spectrum was the absence of the amide carbonyl absorbance and the appearance of a strong absorbance at 1196 cm^{-1} for the thione functional group. The ^{13}C NMR spectrum corroborated this finding with an absence of the amide carbonyl noted and the appearance of a new signal at 203.78 ppm. In addition, the characteristic down-field shift ($\Delta\delta \sim 0.65$) of the protons alpha to the thione group at 3.08 ppm was noted relative to the starting lactam (2.43 ppm) in the ^{1}H NMR spectrum.



[306A]

With the thiolactam [305] in hand we were in a position to investigate the preparation of a number of vinylogous amides. Eschenmoser sulfide contraction with phenacyl bromide failed to afford preparative yields of the desired product as salt formation failed to occur to any extent. Therefore, the use of phenacyl iodide was investigated. Thus, alkylation of thiolactam [305] on sulfur with phenacyl iodide for one hour followed by Eschenmoser sulfide contraction upon treatment with triphenylphosphine and triethylamine in acetonitrile afforded the vinylogous amide [306A] in 96% yield after chromatographic purification. The feature of interest in the ^{1}H NMR spectrum was the appearance of the aromatic protons in the range 7.84 – 7.34 ppm and the appearance of the characteristic vinyl signal at 5.66 ppm. In addition, the corresponding vinyl carbon was found at 87.00 ppm in the ^{13}C NMR spectrum. The FTIR spectrum implied the presence of the carbonyl ketone with an absorbance found at 1735 cm^{-1}, and this evidence was corroborated with the appearance of the signal at 187.95 ppm in the corresponding ^{13}C NMR spectrum. As we have mentioned in previous chapters the evidence of the (*E*)-geometry may be readily observed in the ^{1}H NMR spectrum. Thus, the protons on C-3 were found as a triplet signal down-field at 3.42 pm which is readily explained by the protons falling into the through space deshielding zone of the proximal carbonyl group. This evidence was corroborated by an x-ray structure and the ORTEP diagram is shown in figure 30.

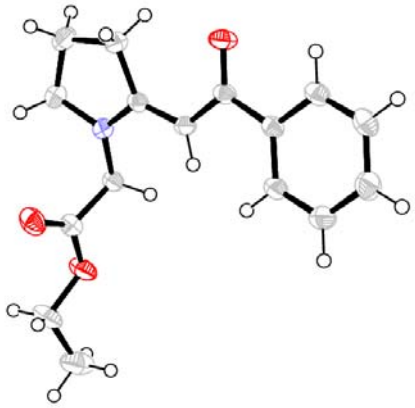
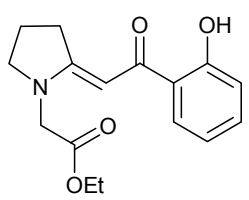


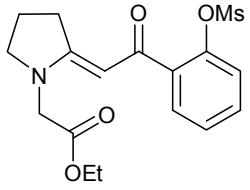
Figure 30: ORTEP diagram of vinylogous amide [306A]. Thermal ellipsoids are shown at the 50% probability level

The preparation of the vinylogous amide [306A] was trivial when compared to the preparation of the rest of the vinylogous amides shown in Scheme 89. For example, it was found necessary to use concentrated reaction conditions (0.5*M* – 1.1*M* relative to the thiolactam [305]) and a large excess of the phenacyl iodides (1.5 – 2.0 equivalents) to effect complete salt formation. Excepting for one occasion, it was necessary to use the iodides and not the bromides to effect complete salt formation. In addition, the large excess of the phenacyl halides was necessary because dehalogenation often occurred during the salt formation step as evidenced by the recovery of the corresponding acetophenones during column chromatographic purification of some of the crude reaction mixtures. In addition, a short reaction time for some of the sulfur extrusion steps was necessary to obtain high yields. Usually, the phase of the reaction that involves extrusion of the sulfur can be accomplished by stirring overnight without affecting the yield of the reaction. However, after much experimentation, four to five hours of reaction time was deemed optimal for good yields to be obtained.



[306B]

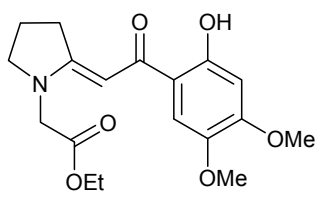
Thus, reaction of the thiolactam [305] with 2-hydroxyphenacyl bromide [278] under the Eschenmoser contraction reaction conditions failed to afford a product. However, reaction of the thiolactam [305] with 1.5 equivalents of 2-hydroxyphenacyl iodide [296] afforded a slow, yet complete, salt formation within eighteen hours. Extrusion of the sulfur with triphenylphosphine and triethylamine at 0 °C followed by work-up after four hours of reaction afforded the vinylogous amide [306B] in an excellent 96% yield after a single column chromatographic purification. The feature of interest in the ^{1}H NMR spectrum was the appearance of the aromatic protons in the range 7.08 – 6.42 ppm as well as the appearance of the hydrogen-bonded phenol proton down-field at 13.99 ppm. The appearance of the characteristic vinyl signal at 5.53 ppm was also noted in the ^{1}H NMR spectrum along with the characteristic C-3 protons found at 3.40 ppm which allowed for assignment of the (*E*)-geometry. In addition, the corresponding vinyl carbon was found at 85.11 ppm in the ^{13}C NMR spectrum. The FTIR spectrum indicated the presence of the carbonyl ketone with an absorbance found at 1734 cm^{-1}, and this evidence was corroborated with the appearance of the ketone carbonyl carbon signal at 191.38 ppm in the corresponding ^{13}C NMR spectrum. Finally, the HRMS spectrum indicated a molecular ion at 289.1309 which is in agreement with the expected molecular formula ($C_{16}H_{19}NO_4$ requires 289.1314).



[306C]

Interestingly, the Eschenmoser sulfide contraction reaction of bromide [295] with the thiolactam [305] produced the vinylogous amide [306C] in 86% yield; although 1.5 equivalent of the bromide was necessary to force complete salt formation in the initial stages of the reaction. The NMR spectral features were similar to those found for the vinylogous amide [306B] with the obvious absence of the phenol protons noticed. This signal had been replaced with the methyl protons of the mesyl protecting group as a singlet at 3.09 ppm. In addition, the characteristic vinyl proton had shifted slightly up-field to 5.42 ppm. The corresponding vinyl carbon atom was found more down-field at 91.31 ppm in the ^{13}C NMR

spectrum as well. The (*E*)-geometry of the vinylogous amide was implied in the ^{1}H NMR spectrum as the protons on C-3 were found as a triplet signal down-field at 3.38 ppm.



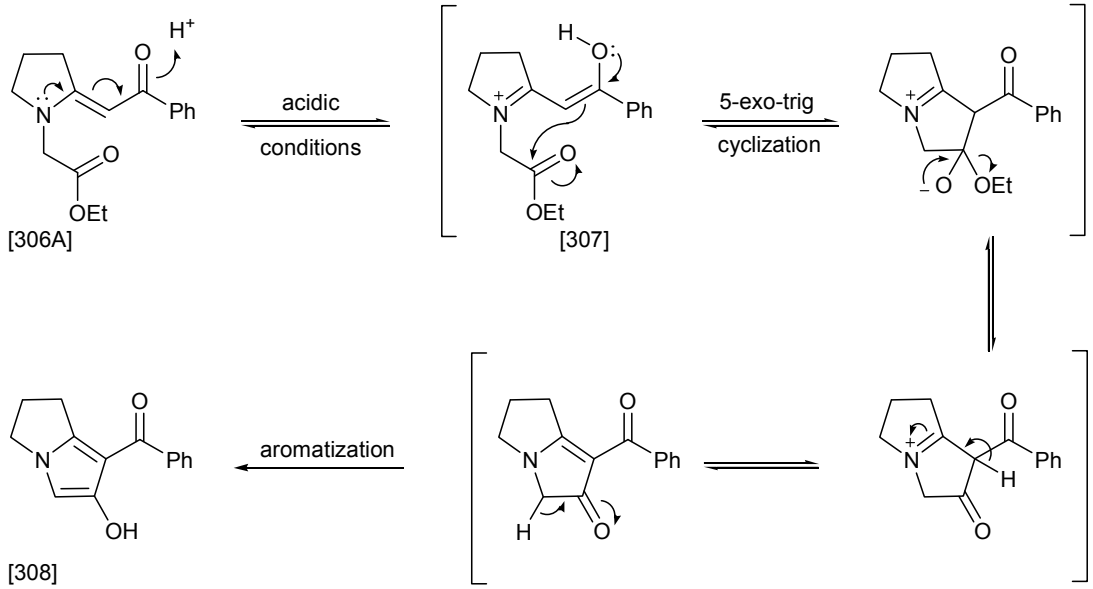
[306D]

The last reaction in this series involved reaction of the thiolactam [305] with the iodide [302]. When both the salt formation and the extrusion step were allowed to occur for eighteen hours each a number of products was isolated. Firstly, the acetophenone [300] was isolated in 39% recovered yield. In addition, the thiolactam [305] was recovered in 21% yield along with the desired vinylogous amide [306D] in 35% yield. The isolation of the acetophenone indicated that dehalogenation had occurred, probably during the salt formation step. To test this hypothesis, salt formation between the thiolactam [305] and 1.5 equivalents of the iodide [302] was allowed to occur for five hours only. Pleasingly, the reaction was complete, although substantial acetophenone [300] was present as evidenced by TLC analysis. Completion of the reaction by addition of triphenylphosphine and triethylamine then afforded the desired product [306D] in an excellent 90% yield. The presence of the hydrogen-bonded phenol proton was found very down-field at 14.29 ppm in the ^{1}H NMR spectrum. In addition, two sets of singlets in the aromatic region at 7.08 ppm and 6.42 ppm accounted for the aromatic protons in the ^{1}H NMR spectrum as did the set of two singlets at 3.87 ppm and 3.83 ppm account for the methoxy protons. The ever characteristic vinyl proton of the enaminone moiety was found at 5.53 ppm in the ^{1}H NMR spectrum and the corresponding vinyl carbon atom was found at 85.11 ppm in the ^{13}C NMR spectrum. In addition, the HRMS spectrum showed a molecular ion at 349.1520 which is in agreement with the expected molecular formula ($C_{18}H_{23}NO_6$ requires 349.1525). Once again, The (*E*)-geometry of the vinylogous amide was readily implied in the ^{1}H NMR spectrum as the protons on C-3 were found as a triplet signal down-field at 3.38 ppm.

Pleasingly, the vinylogous amides were eventually synthesized in high yields. In addition, at no stage did we detect the formation of pyrrolizine systems during chromatographic purification; a result that suggests that the formation of such systems may need forcing conditions.

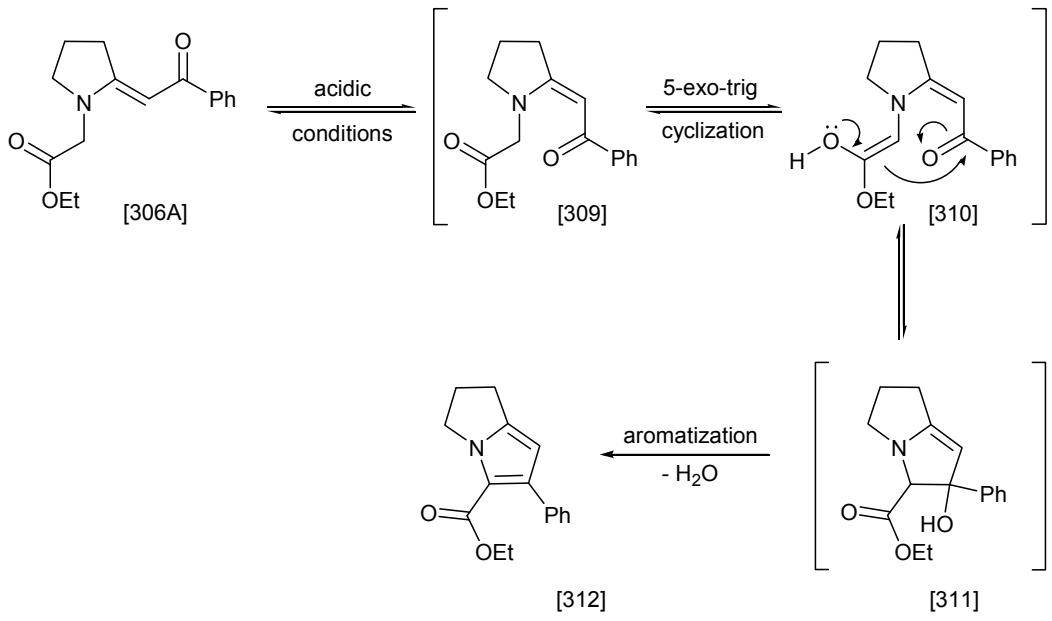
4.3.4 Cyclization of vinylogous amides [306]

The cyclization of the vinylogous amides was a natural extension of the work disclosed in section 4.2. The initial aim was to extend the range of compounds that could be produced by taking advantage of the ambident nucleophilicity of enaminones as outlined in Scheme 90. Thus, using vinylogous amide [306A] as an example, we assumed that the reaction would proceed under acidic conditions to afford intermediate [307], which would immediately cyclize and enter into an aromatization cascade to afford the pyrrolizine [308]. In this manner, we wished to synthesize a range of pyrrolizine systems with an hydroxyl group at the 6-position of the molecule.



Scheme 90: Expected formation of pyrrolizine [308] by way of the ambident nucleophilicity of the vinylogous amide

However, reaction of the vinylogous amide [306A] with ten equivalents of flash silica-gel in refluxing toluene for eighteen hours afforded the pyrrolizine [312] in 76% yield (Scheme 91). Fascinatingly the reactivity of the system was reversed compared to the expected outcome: the vinylogous amide appeared to have reacted as an electrophile rather than a nucleophile! For this to have happened, isomerization of the (*E*)-alkene to the (*Z*)-system [309] must occur under the acidic conditions, probably by way of an intermediate analogous to [307] in Scheme 90. The methylene group adjacent to the ester then acts as a nucleophile, perhaps through the enol form [310], to complete 1,2-addition to the vinylogous amide to afford the intermediate carbinol [311]. Loss of water then completes aromatization to afford the pyrrolizine [312]

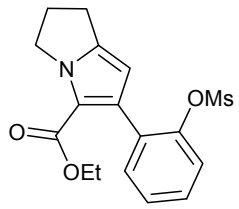


Scheme 91: Plausible mechanism for the formation of pyrrolizine [312]

Evidence for the success of the reaction was found in the NMR spectra. Thus, the typical quartet, triplet signals of the ethyl ester were found at 4.17 ppm and 1.17 ppm in the ^{1}H NMR spectrum. In addition to the absence of the ketone signal of the starting material being noted the ester carbonyl carbon was readily identifiable at 161.36 ppm in the ^{13}C NMR spectrum. This

evidence was corroborated by an absorbance found at 1682 cm^{-1} in the FTIR spectrum. Interestingly, the vinyl proton of the starting material was replaced with a vinyl signal at a slightly down-field position of 5.95 ppm for the product in the ^{1}H NMR spectrum. The associated vinyl carbon atom was found at 103.47 ppm in the ^{13}C NMR spectrum.

An observation worth mentioning is the use of flash silica-gel. When the cyclization reaction of the vinylogous amide [306A] was attempted with ten equivalents of normal silica-gel in refluxing toluene for twenty-four hours the product profile was in favour of the starting material. Therefore, the higher surface area of the flash silica-gel was an added advantage to effect the requisite cyclization reaction. We did not repeat this reaction with the protic solvent, acetic acid. However, the use of acetic acid is discussed for the preparation of pyrrolizine [313].



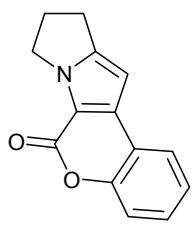
[313]

The preparation of the pyrrolizine [313] containing an *ortho*-mesylate substituent was not trivial as it transpired that long reaction times led to decomposition of the starting material as well as the product. For example, the reaction of the vinylogous amide [306C] with ten equivalents of flash silica-gel in refluxing toluene for eighteen hours afforded a complex reaction mixture product. In addition, a low mass return was obtained. Analysis of the crude material by ^{1}H NMR spectroscopy suggested the formation of the desired product in trace quantities amongst the complex set of signals. Therefore, it appeared that the long reaction time was leading to decomposition products. Therefore, we replaced the solvent by the higher boiling *o*-xylene and investigated whether a higher temperature and a shorter reaction time would deliver a product in preparative yield. Thus, reaction of the vinylogous amide [306C] with ten equivalents of flash silica-gel in refluxing *o*-xylene for five hours afforded the desired product [313] in a modest 53% yield. In an effort to improve the yield, the same reaction was subjected to microwave irradiation (300W, 200 °C) in a sealed tube for three minutes which afforded the desired product [313] in 53% yield. Although the reaction time

was short, the use of a higher reaction temperature conferred no added advantage.

We next turned our attention to the use of the protic solvent, acetic acid. Thus, reaction of the vinylogous amide [306C] in refluxing acetic acid for 48 hours (admittedly a weekend reaction) afforded the pyrrolizine [313] in 38% yield. This was a good result as we felt that this reaction could be optimized by way of microwave irradiation. After much experimentation with respect to reaction temperatures, power settings and reaction times we were able to optimize the yield of the reaction. Thus, microwave irradiation (50W, 120 °C) of the vinylogous amide [306C] in acetic acid for one hour afforded the pyrrolizine [313] in an optimized 65% yield. The spectroscopic data of this compound were similar to those of the pyrrolizine [312]. Of note was the vinyl proton of the product found at 5.98 ppm in the ^{1}H NMR spectrum. The corresponding vinyl carbon atom was found at 104.03 ppm in the ^{13}C NMR spectrum. The obvious difference was the presence of the methyl signal of the mesyl group which was found at 2.68 ppm in the ^{1}H NMR spectrum. In addition, the HRMS spectrum showed a molecular ion at 349.0979 which is in agreement with the expected molecular formula ($C_{17}H_{23}NO_5S$ requires 349.0984).

The use of protecting groups in a synthetic strategy is not desirable as it adds two extra steps into the synthesis. The first extra step is putting on the protecting group and the second extra step involves removing the protecting group. Thus, with this in mind we investigated whether we could form the central pyrrole core as well as the coumarin part of the molecule in a one-pot synthesis. We reasoned that this may be feasible under the acid conditions employed in that the ester of the resulting pyrrolizine may be partial to attack from the proximal phenol by way of an acid-mediated lactonization.

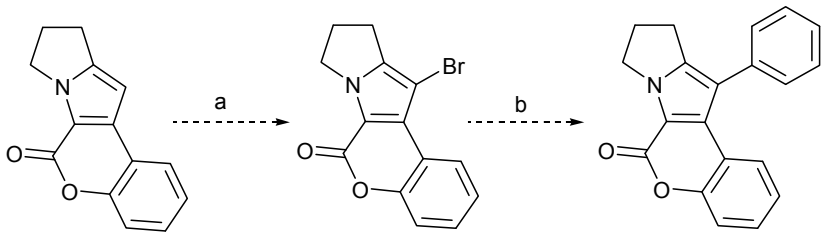


[314]

Thus, reaction of the vinylogous amide [306B] with ten equivalents of flash silica-gel in refluxing toluene for eighteen hours afforded the 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one [314] in 23% yield. Similarly, reaction of the vinylogous amide [306B] with ten equivalents of flash silica-gel in refluxing *o*-xylene for 4 hours afforded the desired product [314] in 36%

yield. Diagnostic evidence for the success of the reaction was found in the ^{1}H NMR spectrum. Thus, the characteristic quartet and triplet signals of the ethyl ester were absent. The ^{13}C NMR spectrum also lacked the corresponding signals for the ethyl ester functional group. In addition, s signal found at 154.93 ppm was readily assigned to the carbonyl carbon atom in the ^{13}C NMR spectrum. Finally, a molecular ion was found at 225.0784 in the HRMS spectrum which is in agreement with the expected molecular formula ($C_{14}H_{11}NO_2$ requires 225.0790).

This fantastic result met one of the aims of this project in that both the central pyrrole core and the coumarin part of the lamellarin alkaloid, in principle, can be achieved in a one pot reaction. Regrettably, owing to time constraints this reaction was not optimized. For the same reasons, the one-pot cyclization-lactonization strategy of the vinylogous amide [306D] was not attempted. Therefore, future work for the completion of the target molecule [294] by way of this novel strategy is shown in Scheme 92.



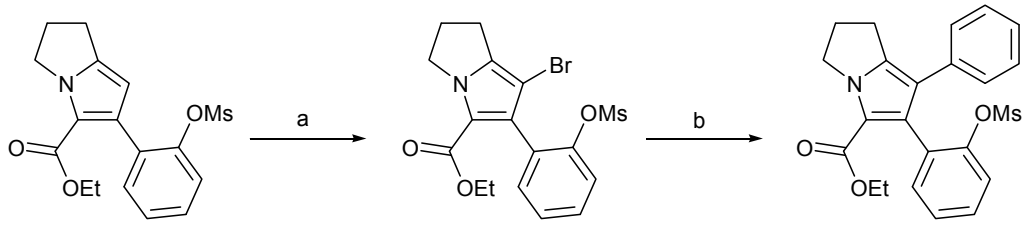
[314] [315] [294]

Scheme 92: A proposed completion of model compound [294]. Reagents: (a) NBS, THF; (b) Phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, EtOH, DME, H_2O, Δ.

Thus, bromination should afford the intermediate bromide [315] which can be subjected to a Suzuki-Miyaura coupling reaction to afford the target model compound.

4.3.5 Bromination and Suzuki-Miyaura reaction of pyrrolizine [313]

In continuing with our pursuit towards the model compound [294], we envisaged a strategy that installs an additional aryl ring on the C-7 of the target compound. Therefore, we investigated the bromination and Suzuki-Miyaura coupling reaction strategy (Scheme 93).



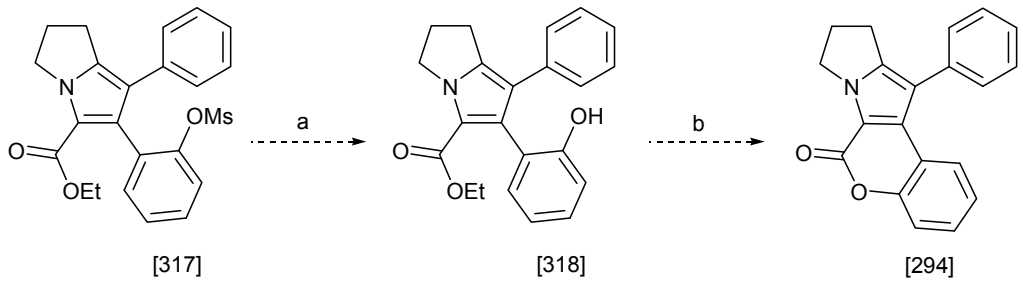
[313] [316] [317]

Scheme 93: Synthesis of a highly functionalized pyrrolizine [317. Reagents: (a) NBS, DMF; (b) Phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME, EtOH, H_2O, Δ.

Thus, reaction of the pyrrolizine [313] with *N*-bromosuccinimide in dimethylformamide afforded the bromide [316] in 90% yield after column chromatographic purification. The bromide was reasonably stable provided it was stored in a fridge if not in use. Diagnostic evidence of the reaction was the absence of the vinyl proton of the starting material in the ^1H NMR spectrum. In addition, the vinyl C-7 carbon atom of the starting material had moved up-field to 91.40 ppm for the C-7 carbon atom of the product in the ^{13}C NMR spectrum. In addition, the HRMS spectrum showed a molecular ion at 427.0083 which is in agreement with the expected molecular formula ($C_{17}H_{18}{}^{79}BrNO_5S$ requires 427.0089). Finally, Suzuki-Miyaura coupling between the bromide [316] and phenylboronic acid mediated by catalytic $Pd(PPh_3)_4$ afforded the pyrrolizine [317] in an unoptimized 50% yield. Diagnostic evidence of the reaction was the presence of aromatic signals integrating for nine protons in the aromatic region of the ^1H NMR spectrum. In addition, the ^{13}C NMR spectrum indicated an extra 4 sets of aromatic signals for the addition of the newly installed aryl unit. In addition, the C-7 carbon

atom had shifted down-field to 117.47 ppm in the ^{13}C NMR spectrum. Finally, the HRMS spectrum showed a molecular ion at 425.1294 which is in agreement with the expected molecular formula ($C_{23}H_{23}NO_5S$ requires 425.1297).

Regrettably owing to time constraints we were not able to complete the synthesis of the desired model compound. The basic strategy for the completion of the model compound was to follow that disclosed by Ruchirawat[227] and co-workers. Thus, the mesylate functional group was to be deprotected by way of refluxing ethanolic potassium hydroxide followed by base-induced lactonization of the phenol intermediate [318] to afford the target compound [294] (Scheme 94).



[317] [318] [294]

Scheme 94: A proposed strategy for the completion of model compound [294. Reagents: (a) KOH, EtOH, Δ; (b) NaH, THF.

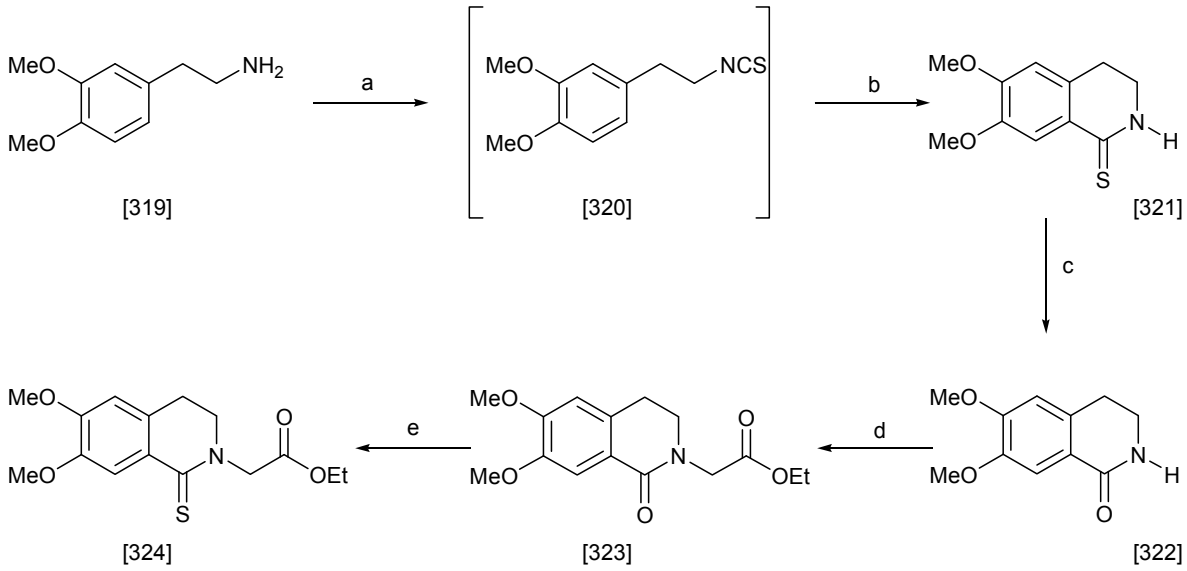
4.4 Towards the synthesis of the lamellarin framework

4.4.1 Introduction

As time constraints brought a premature end to our efforts towards the synthesis of the model pyrrolizine compound we proceeded to start our envisaged synthesis of the lamellarin alkaloid framework. The work is by no means complete; however the foundations have been laid for a future generation of post-graduate students to complete the work. Thus, this chapter section will discuss some of the attempts in constructing the isoquinolinyl acetate scaffold. In addition, some results will be discussed with regards to the preparation of some vinylogous amides from isoquinolinethiones.

4.4.2 A route to thioamide [324]

The synthesis began with the preparation of the Eschenmoser sulfide contraction precursor [324] as shown in Scheme 95. The preparation of the isoquinolinone [321] followed that of a literature procedure.[253] Thus, the β-phenethyl isothiocyanate [320] was prepared by treatment of the phenethylamine [319] with carbon disulfide and triethylamine in dichloromethane followed by treatment with ethyl chloroformate. The product was not isolated but subjected to a cyclization reaction upon treatment with polyphosphoric acid at 70 – 80 °C for ninety minutes to afford the thioamide [321] in 94% yield over the two steps.

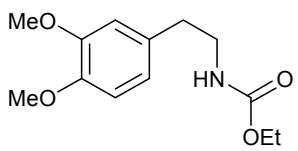


Scheme 95: Synthesis of compound [324]. Reagents: (a) (i) CS_2, Et_3N, CH_2Cl_2, 0 ^oC; then (ii) Ethyl chloroformate, Et_3N; (b) PPA, 70 - 80 ^oC; (c) KOH, H_2O, H_2O_2, MeOH; (d) NaH, THF, then ethyl 2-bromoacetate; (e) Lawesson's reagent, toluene, 80 ^oC.

Diagnostic evidence for the success of the reaction was the presence of the singlet signal for the thioamide NH found at 8.59 ppm in the ^1H NMR spectrum. This evidence was corroborated in the FTIR spectrum by the appearance of a broad absorbance centered at 3216 cm^{-1}. In addition, the FTIR spectrum showed an absorbance for the thione group at 1132 cm^{-1}, and this evidence was corroborated by the appearance of a signal at 193.20 ppm in the ^{13}C NMR spectrum. Treatment of the thioamide [321] with hydrogen peroxide in a basic solution of methanol for four hours at 0 °C, followed by an acidic workup afforded the isoquinolinone [322] in 90% yield. The ^1H NMR spectrum was very similar to that of the thioamide [321] excepting for the shift of the amide proton which was found upfield at 7.54 ppm. Clear evidence of the success of the reaction was found in the ^{13}C NMR spectrum. Thus, the absence of the thione carbon was noted and replaced with an amide carbonyl carbon atom found at 166.68 ppm in the ^{13}C NMR spectrum. In addition, the melting point was determined at 172 – 174 °C which is in close agreement with that found in the literature[254] (174 – 176 °C).

Treatment of the isoquinolinone [322] with sodium hydride in tetrahydrofuran at 0°C for thirty minutes followed by addition of ethyl 2-bromoacetate afforded the intermediate [323] in 98% yield after workup and chromatographic purification. Diagnostic evidence for the success of the reaction was the appearance of the characteristic quartet, triplet signals of the ethyl ester group found at 4.22 ppm and 1.29 ppm in the ^{1}H NMR spectrum. In addition, a singlet signal found at 4.31 ppm was readily assigned as the methylene group alpha to both nitrogen and the carbonyl ester functional group. In addition, the ^{13}C NMR spectrum exhibited a new signal at 169.33 ppm which was assigned the ester carbonyl carbon atom. This finding was corroborated by an absorbance in the FTIR spectrum found at 1736 cm^{-1}. Finally, the HRMS spectrum showed a molecular ion at 293.1258 which is in agreement with the expected molecular formula ($C_{15}H_{19}NO_5$ requires 293.1263).

Finally, thionation of isoquinolinone [323] with Lawesson's reagent in hot toluene for four hours afforded the thioamide [324] in 66% yield after a single chromatographic purification. The ^{1}H NMR spectrum was very similar to the isoquinolinone [323] excepting for the aromatic H_8 which had shifted downfield to 8.13 ppm, presumably due to shielding from the proximal thione group. Moreover, the success of the reaction was clear from examination of the ^{13}C NMR spectrum. Thus, in addition to the absence of the amide carbonyl carbon atom of the starting material the appearance of a signal at 192.92 ppm was readily assigned to the newly introduced thione functional group of the product in the ^{13}C NMR spectrum. In addition, the FTIR spectrum of the product showed an absence of the amide functional group. The final piece of evidence for the success of the reaction was the molecular ion found at 309.1027 in the HRMS spectrum which is in agreement with the expected molecular formula ($C_{15}H_{19}NO_4S$ requires 309.1035).



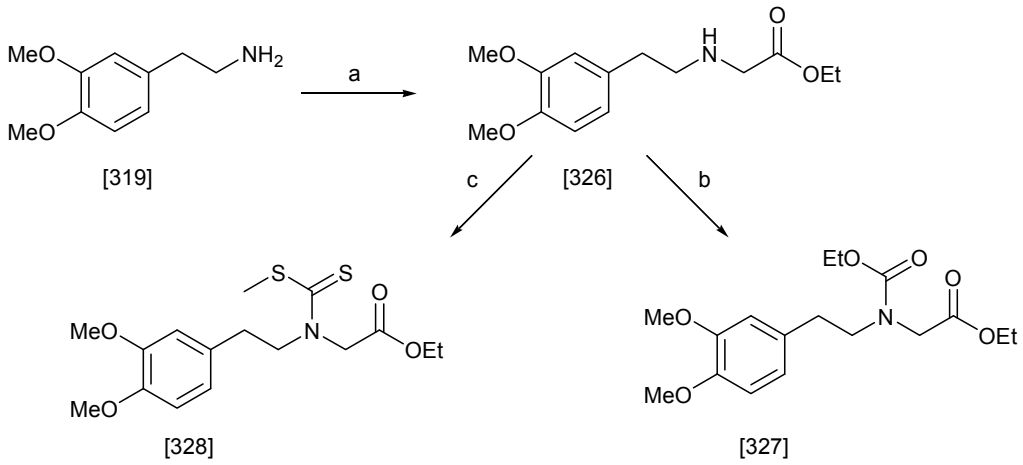
[325]

The route taken, as shown in Scheme 95, for the synthesis of the isoquinolinone [322] deserves some comment. The synthesis of the isoquinolinone [322] was achieved in 83% overall yield starting from the phenethylamine [319]. In addition, the literature method we followed reported an overall 50% yield of the isoquinolinone [322] starting from the β-phenethyl isothiocyanate [320]. Therefore, we substantially improved upon this known method for the preparation of the isoquinolinone [322]. A more direct route is from the urethane [325], which is prepared in near quantitative yield from phenethylamine [319] and ethyl chloroformate. Thus, a Bischler-Napieralski cyclization of the urethane with phosphorus oxychloride and a catalytic amount of phosphorus pentoxide in refluxing xylene affords the isoquinolinone [322] in a modest 45% yield as reported by Sharma and co-workers.[255] Therefore, the route chosen is justified in light of the yields obtained by ourselves and those obtained by Sharma and co-workers.

4.4.3 Attempts at a more expedient route to the intermediates [323] and [324]

The route chosen for the synthesis of the two intermediates [323] and [324] was re-explored. In keeping with the theme of a Bischler-Napieralski cyclization, we attempted the synthesis of cyclization precursors as shown in Scheme 96. Thus, reaction of the phenethylamine [319] with ethyl 2-bromoacetate in the presence of triethylamine in dry chloroform afforded the ester [326] in 61% yield as the only isolable product after a chromatographic purification. The FTIR spectrum showed a broad signal centered around 3333 cm^{-1} for the amine proton. In addition, the ester carbonyl functional group was found as an absorbance at 1736 cm^{-1}. The ^{1}H and ^{13}C NMR spectra supported these findings. Thus, the amine proton was found as a broad signal at 1.62 ppm in the ^{1}H NMR spectrum. In addition, the characteristic quartet, triplet signal of the ethyl ester moiety was found at 4.17 ppm and 1.26 ppm in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum implied the presence of the

carbonyl ester carbon atom with a signal at 172.27 ppm. Finally, the HRMS spectrum showed a molecular ion at 267.1465 which is in agreement with the expected molecular formula ($C_{14}H_{21}NO_4$ requires 267.1471).



Scheme 96: Synthesis of potential Bischler-Napieralski precursors. Reagents: (a) (i) Ethyl 2-bromoacetate, Et_3N, CH_3Cl; (b) Ethyl chloroformate, Et_3N, CH_2Cl_2, 0 ^oC; (c) (i) NaH, THF then CS_2, 0 ^oC; (ii) MeI.

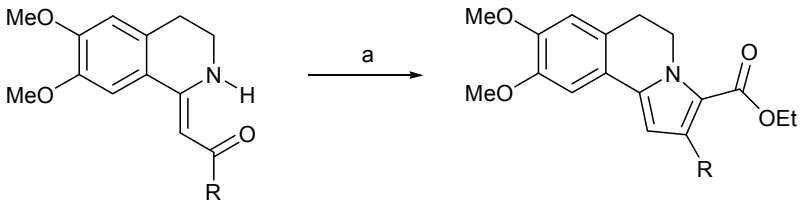
Reaction of the ester [326] with ethyl chloroformate in the presence of triethylamine in dichloromethane at 0 °C afforded the carbamate [327] in quantitative yield after a conventional chromatographic purification. The FTIR spectrum showed an absence of the amine proton and a new absorbance found at 1698 cm^{-1} was inferred as the carbamate carbonyl moiety. The ^1H spectrum showed the presence of a new set of characteristic quartet, triplet signals of the ethyl ester moiety of the installed carbamate group as signals at 4.15 ppm and 1.23 ppm. In addition, most of the signals in the ^{13}C NMR spectrum had doubled up in nearly equal proportions. This may be as a result of restricted rotation around the *N*-carbamate bond giving rise to conformational isomers. However, the signal pair found at 156.49 ppm and 155.89 ppm was readily assigned as the carbamate carbonyl carbon atom in the ^{13}C NMR spectrum. The HRMS spectrum showed a molecular ion at 339.1676 which is agreement with the expected molecular formula ($C_{17}H_{25}NO_6$ requires 339.1682).

As an exploratory reaction, the carbamate [327] was reacted with polyphosphoric acid at room temperature for sixteen hours to test whether the ester functional group would survive the acidic conditions of this reaction. Disappointingly, no characterizable product could be isolated after workup of the reaction. Therefore, this potential route towards the synthesis of the intermediate [323] by way of the Bischler-Napieralski cyclization was abandoned.

Finally, reaction of the ester [326] with sodium hydride at 0 °C in tetrahydrofuran followed by sequential addition of carbon disulfide and methyl iodide afforded the thiocarbamate [328] in 67% yield as an odoriferous oil. Surprisingly, no doubling of the peaks in the ^{13}C NMR spectrum was evident and the features of note were the thione carbon atom signal at 199.71 ppm as well as the new methyl signal at 20.01 ppm of the thiocarbamate group of the product. In addition to noting the absence of the amine proton of the starting material in the ^{1}H NMR spectrum a new methyl signal at 2.66 ppm of the thiocarbamate functional group was readily identifiable of the product. However, reaction of the thiocarbamate [328] with polyphosphoric acid at room temperature afforded a product that could not be characterized. Hence, this potential route towards the synthesis of the intermediate [324] by way of the Bischler-Napieralski cyclization was abandoned.

4.4.4 Proof of concept synthesis of the central pyrrole core of the lamellarin framework

The preparation of the thioamide allowed for a potential divergence in our intended approach towards the lamellarin alkaloids. Junjappa and co-workers disclosed a route to the pyrrolo[2,1-*a*] isoquinoline framework by way of vinylogous amides (Scheme 97).[256]



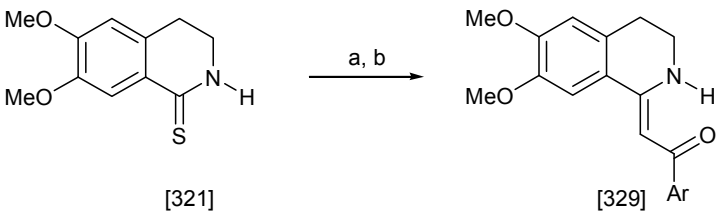
[329] [330]

Series A: R = Ph

Series B: R = Me

Scheme 97: Synthesis of lamellarin framework by Junjappa and co-workers.[256] Reagent: (a) Ethyl 2-bromoacetate, DMF, Δ.

The vinylogous amides were prepared by Bischler-Napieralski type of cyclization of newly synthesized ketene N,S-acetals derived from 2,4-dimethoxyphenethylamine and polarized ketene dithioacetals.[257] Thus, reaction of the vinylogous amides [329] with ethyl 2-bromoacetate in refluxing dimethylformamide afforded the isoquinoline carboxylates [330] in 70% (series A) and 66% (series B) yield respectively. Junjappa and co-workers did not extend this result to the eventual synthesis of the lamellarin alkaloids. Thus, with the thioamide [321] prepared earlier we felt we could access the vinylogous amides under standard Eschenmoser sulfide contraction conditions and perhaps extend the work of Junjappa and co-workers towards the lamellarin alkaloids (Scheme 98).



[321] [329]

Series A: Ar = Phenyl

Series C: Ar = 2-Hydroxy-3,4-dimethoxyphenyl

Series D: Ar = 3,4-Dimethoxyphenyl

Scheme 98: Synthesis of vinylogous amides. Reagent: (a) For Series A: Phenacyl bromide, MeCN; For Series C: 2-Hydroxy-3,4-dimethoxyphenacyl bromide, MeCN; For Series D: 3,4-Dimethoxyphenacyl bromide, MeCN; (b) PPh_3, Et_3N, MeCN.

Thus reaction of the thioamide [321] with phenacyl bromide under Eschenmoser sulfide contraction conditions afforded the corresponding vinylogous amide [329B] in a good 86% yield. Diagnostic evidence for the success of the reaction was the disappearance of the thione group in the ^{13}C NMR spectrum of the starting material. Of note was the downfield signal at 158.61 ppm which was assigned as the C-1 carbon in the ^{13}C NMR spectrum. In addition, the vinyl carbon of the product was readily assigned as the signal at 86.34 ppm. The corresponding vinyl proton was found at 6.20 ppm in the ^{1}H NMR spectrum.

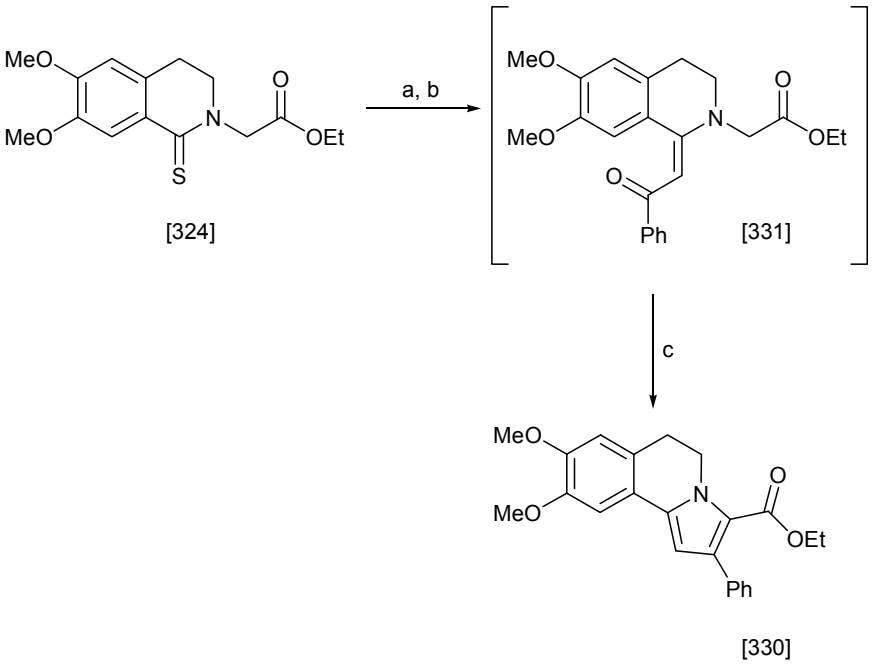
Similarly, reaction of the thioamide [321] with 2-hydroxy-3,4-dimethoxyphenacyl bromide [301] under Eschenmoser sulfide contraction conditions afforded the vinylogous amide [329C] in 73% yield. Again, the thione unit was absent in the ^{13}C NMR spectrum. Again, the downfield signal at 159.01 ppm was assigned as the C-1 carbon in the ^{13}C NMR spectrum. In addition, the vinyl carbon atom was assigned as the signal found at 84.57 ppm as was the ketone functional group at 189.65 ppm in the ^{13}C NMR spectrum. The FTIR spectrum implied the presence of the ketone with an absorbance at 1604 cm^{-1}. The ^{1}H NMR spectrum showed two downfield signals at 13.80 ppm and 11.22 ppm which were assigned as the phenol proton and the amide proton respectively. In addition, the characteristic vinyl proton was assigned as the signal found at 6.03 ppm.

Finally, reaction of thioamide [321] with 3,4-dimethoxyphenacyl bromide [210] under the same Eschenmoser sulfide contraction conditions afforded the vinylogous amide [329D] in 81% yield. The thione functional group of the starting material was absent in the ^{13}C NMR spectrum. The downfield signal at 158.21 ppm was assigned as the C-1 carbon in the ^{13}C NMR spectrum as was the ketone functional group at 187.43 ppm. In addition, the vinyl carbon atom was assigned as the signal found at 85.80 ppm in the ^{13}C NMR spectrum as was the corresponding vinyl proton assigned at 6.19 ppm in the ^{1}H NMR spectrum.

Therefore the scene was set to repeat the cyclisation reaction of vinylogous amide [329A] with ethyl 2-bromoacetate as disclosed by Junjappa and co-workers. Unfortunately, reaction of the vinylogous amide [329A] with ethyl 2-bromoacetate in refluxing dimethylformamide for seven hours afforded complete decomposition of the starting material. This reaction was repeated several times and under different reaction conditions (for example shorter reaction times, and cooler reaction temperatures) and yet we could not replicate the results obtained by Junjappa and co-workers. Similarly, we were not able to cyclize the vinylogous amide [329D] under identical reaction conditions. In addition, complete decomposition of the starting occurred as well. This was very disappointing, and we decided to abandon this route.

We next turned our attention to our original strategy. Owing to time constraints only one attempt was made to extend the methodology of preparing the central pyrrole core of the lamellarin framework.

Thus, alkylation of thioamide [324] on sulfur with phenacyl iodide for four hours followed by Eschenmoser sulfide contraction upon treatment with triphenylphosphine and triethylamine in acetonitrile afforded the crude vinylogous amide [331] as an orange gum after a chromatographic purification (Scheme 99).



Scheme 99: Formation of the central pyrrole core of the lamellarin framework. Reagents: (a) Phenacyl iodide, MeCN; (b) PPh_3, Et_3N, MeCN; (c) SiO_2, toluene , Δ.

The product was heavily contaminated with phosphorus-containing by-products as evidenced by extra peaks in the aromatic region of the ^1H NMR spectrum. Of note in the spectrum was the presence a broad signal for the vinyl proton at 6.02 ppm which is in the characteristic region expected for vinylogous amides. The product was not fully characterized but submitted into the next subsequent reaction. Thus, reaction of the crude vinylogous amide [331] with ten equivalents of flash silica-gel in refluxing toluene for two hours afforded the putative isoquinoline carboxylate [330] in a poor 5% yield over the two steps. The characterization data for this compound were limited to NMR spectroscopic data as we only had a small quantity of the material. Unfortunately, the NMR spectral data showed discrepancies with those reported by Junjappa and co-workers for compound [330][256] (Tables 12 and 13).

Table 12: Comparison of selected ^{1}H NMR data obtained for compound [330] prepared in this project with published values (ppm)

entry	**This work** **(300 MHz, $CDCl_3$)**	**Junjappa and co-workers[256]** **(400 MHz, $CDCl_3$)**
1	6.48 (s, 1H)	5.52 (s, 1H)
2	4.63 (t, *J* = 6.8, 2H)	3.93 (t, *J* = 6.6, 2H)
3	4.14 (q, *J* = 7.1, 2H)	4.05 (q, *J* = 7.1, 2H)
4	3.92 (s, 6H)	3.88 (s, 3H), 3.71 (s, 3H)
5	3.06 (t, *J* = 6.8, 2H)	2.97 (t, *J* = 6.6, 2H)
6	1.07 (t, *J* = 7.1, 3H)	1.41 (t, *J* = 7.1, 3H)

Table 13: Comparison of ^{13}C NMR spectral data obtained for compound [330] prepared in this project with published values (ppm)

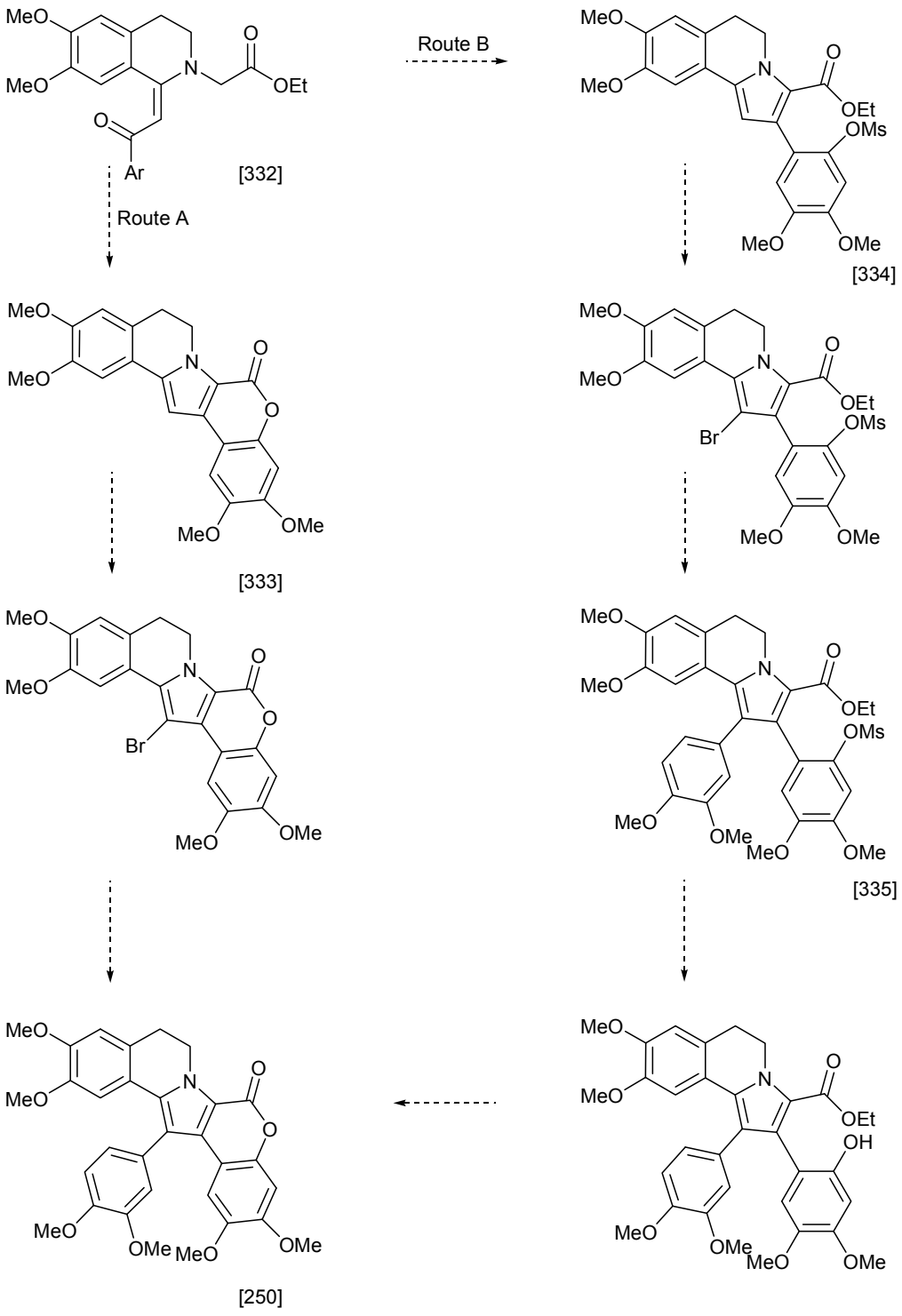
entry	This work (75 MHz, $CDCl_3$)	Junjappa and co-workers[256] (100 MHz, $CDCl_3$)
1	161.87	192.4
2	148.81	147.9
3	148.29	147.4
4	136.92	145.2
5	134.90	140.9
6	134.49	131.2
7	129.57	129.5
8	127.38	127.9
9	126.58	126.2
10	124.77	125.1
11	120.76	121.2
12	118.20	116.5
13	110.96	110.9
14	106.85	110.6
15	105.88	89.1
16	59.75	66.4
17	56.07	55.9
18	56.01	55.9
19	42.81	38.9
20	28.65	28.8
21	13.81	14.7

Of note in the ^{1}H NMR spectrum of Junjappa and co-workers was the assignment of the vinyl proton (Table 12, entry 1) of compound [330] which is at Δδ = ~1 ppm upfield than our assignment. For analogous compounds (for example compounds [312] and [313]) we have assigned this signal at or above δ = 6 ppm. In addition, the methyl group of the ester functional group is significantly different. In the ^{13}C NMR spectra, there are other obvious differences, especially for the carbonyl carbon of the ester, as well as for the signals in entries 4–6, 12, 14, 15 and 16 in Table 13. Our assignment (entry 15) for the unsubstituted pyrrole carbon atom of compound [330] (δ = 105.88 ppm) was consistent with the assignments for the related pyrrolizine [312] (δ = 103.47 ppm) and for pyrrolizine [313] (δ = 104.03 ppm), but not with the assignment of δ = 89.1 ppm offered by Junjappa and co-workers, which is closer to the characteristic δ = 70 – 90 ppm of enaminones. Could Junjappa and co-workers have, in fact, isolated the vinylogous amide [331]? Their mass spectral and microanalytical data agree with their reported structure of [330], but since we have shown that cyclisation to pyrroles is easy, perhaps their product could have dehydrated under the analytical conditions. The more prudent explanation is that we did not succeed in making [330], and that we have isolated an interesting but unidentified product. Time constraints prevented us from synthesizing a clean sample of the vinylogous amide [331], and obviously the work needs to be repeated in order to solve this puzzle and clarify the discrepancy between our work and that of Junjappa

4.4.5 Conclusion and future prospects

The potential synthesis of the lamellarin alkaloids arose from the discovery of the ambident electrophilicity of the vinylogous amide [306A] which gave rise to incorporation of an ester substituent at the C-5 position of the pyrrolizine system on an aryl substituent at C-6. In addition, the model pyrrolizine system had shown that a one-pot cyclization-lactonization strategy to afford the pyrrolizine [314] installs the central pyrrole core as well as a coumarin moiety, as found in the lamellarin alkaloids. As mentioned previously, bromination

followed by Suzuki-Miyaura coupling should, in principle, should afford the requisite appendages found around the pyrrole unit of the lamellarin alkaloid. In addition, a route towards the Eschenmoser precursor, isoquinoline-2-thione acetate [324], was achieved in good yield. Therefore, Eschenmoser sulfide contraction of this precursor with a variety of phenacyl halides (more specifically those containing a hydroxy or protected hydroxy functional group at the two position of the aryl unit) followed by acid-induced cyclization may afford a range of isoquinoline carboxylates as exemplified in Scheme 100. Thus, for route A we envisage immediate formation of the central pyrrole core along with the coumarin part of the molecule to afford [333]. This could then be followed by a typical Suzuki-Miyaura coupling strategy to form lamellarin G trimethyl ether [250]. Alternatively, if the one-pot pyrrole formation and subsequent formation of the coumarin part of the molecule as shown in route A is problematic then route B may be considered. Thus, the central pyrrole core may be generated to afford the mesyl protected intermediate [334]. We envisage a standard Suzuki-Miyaura coupling reaction to afford the intermediate [335] which contains the necessary aryl substituents. The last synthetic steps in the sequences that we envisage are deprotection of the mesylate followed by lactonization to afford lamellarin G trimethyl ether [250].

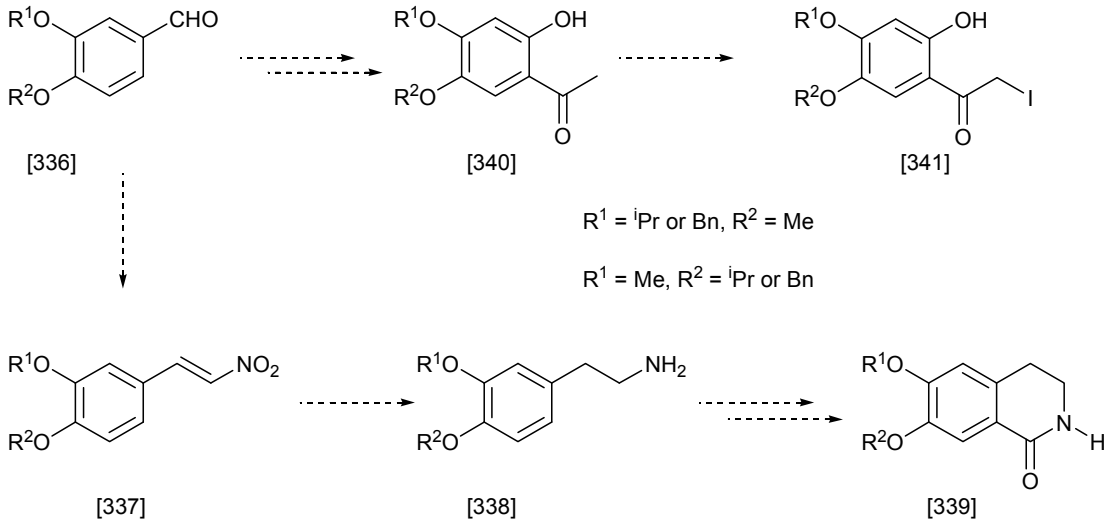


For route A: Ar = 2-Hydroxy-3,4-dimethoxyphenyl

For route B: Ar = 2-[(Methylsulfonyl)oxo]-3,4-dimethoxyphenyl

Scheme 100: Proposed routes to lamellarin G trimethyl ether [250]

In addition, we feel that the route envisaged, as disclosed in Scheme 100, is amenable to variations with regards to various substitution patterns found in the natural lamellarin alkaloids, more specifically, the OH groups which most of the lamellarin alkaloids have (Scheme 101).



Scheme 101: Potential syntheses of protected phenacyl iodides [341] and isoquinolinones [339] from a common benzaldehyde building block

Structural analysis of some of the natural lamellarin alkaloids show that the dihydroisoquinoline moiety may be constructed from the suitably protected common benzaldehyde derivatives [336]. Thus, the synthesis of the protected isoquinolinones [339] are amenable by way of an Henry condensation to give [337], followed by reduction to give the phenethylamines [338], and finally a Bischler-Napieralski cyclization sequence to afford isoquinolinones [339] as reported by Ruchirawat and co-workers.[258] In addition, the phenacyl iodides [341] may be accessed from the same protected benzaldehyde derivatives by way of a Baeyer-Villiger oxidation and Fries rearrangement to give intermediates [340]. Finally, and a bromination-iodination sequence should give the iodides [341] as we have disclosed in section 4.3.2. In this manner construction of a number of the naturally occurring lamellarin alkaloids may be possible after removal of the relevant protective groups. Finally, another variation in the strategy is possible at the C-1 position of the lamellarin

alkaloids. The Suzuki-Miyaura coupling reaction makes use of both aryl boronic acids and aryl bromides, therefore variation at C-1 may be achieved by making use of the plethora of commercially available boronic acids.

This part of the project has been left hanging at a very exciting stage. We have demonstrated that the construction of the pyrrole core of the lamellarin system can be achieved by way of a variation of the Knorr pyrrole synthesis; although much optimization of the reaction conditions is needed. Our data for the putative lamellarin precursor [330] need to be checked in view of the discrepancy with the data offered by Junjappa and co-workers. Thus, future work necessarily must be undertaken to clarify whether, in fact, the intermediate we obtained is in fact [330] or another, as yet unidentified, product. Lastly, the groundwork has been laid for a future generation of post-graduate students to complete the potential synthesis towards the lamellarin alkaloids.

Chapter 5: Experimental pertaining to Chapter 2

5.1 General procedures

5.1.1 Purification of solvents

Solvents used for chromatographic purposes were distilled before use by means of conventional distillation procedures. Unless otherwise stated, solvents used for reaction purposes were dried over an appropriate drying agent and then distilled under nitrogen gas. Tetrahydrofuran and diethyl ether were distilled from sodium wire using benzophenone as an indicator. Toluene was distilled from sodium lumps. Dichloromethane, dimethylformamide and acetonitrile were distilled from calcium hydride. Pyridine was distilled from potassium hydroxide.

5.1.2 Chromatography

Separation of compounds by column chromatography was performed using Merck silica-gel (particle size 0.063–0.200 mm). Separation of compounds by flash column chromatography was performed using Merck silica-gel (particle size 0.04–0.063 mm). Thin layer chromatography was performed using Merck silica-gel 60 F_{254} coated on aluminium sheets. Compounds on the TLC plates were either viewed under UV light or by dipping the plates into a basic $KMnO_4$ staining solution.

5.1.3 Spectroscopic and physical data

^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AVANCE 300 spectrometer or on a Bruker DRX-400 spectrometer at the frequency indicated. DEPT, C-H correlated and COSY spectra were run on some samples to enable more complete assignments of signals. *J* values are given in Hz.

Infra-red spectra were recorded on Bruker Vector-22 Fourier Transform spectrometer or on a Bruker Tensor 27 Fourier Transform spectrometer.

Melting points were measured using a Reichart micro hot stage apparatus and are uncorrected.

High-resolution mass spectra were recorded either on a VG70 MS (Mass spectrum CC Pyramid data system) or on a VG70 SEQ (VG 11-205J or Marc II data system) or on a DFS High Resolution Magnetic Sector mass spectrometers

Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_{α} radiation (50kV, 30mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the programme SAINT+. The crystal structure was solved by direct methods using SHELXTL. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F2 using SHELXTL. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL and PLATON.

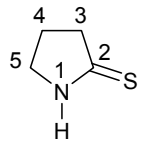
5.1.4 Other general procedures

All reactions, unless otherwise stated, were carried out under Argon and the reaction vessels were dried either in an oven or flame-dried whilst under vacuum.

Evaporation of solvent from chromatographic purification refers to removal of solvent using a rotary evaporator followed by removal of trace amounts of solvent using a high vacuum pump at *ca*. 0.5 mmHg

5.2 Experimental work pertaining to indolizidine systems containing a nitrile functional group

5.2.1 Synthesis of 2-pyrrolidinethione [169]



[169]

This compound was prepared by a known procedure.[137] P_4S_{10} (13.550 g, 30.48 mmol) was added to dry THF (125 cm^3) and stirred under an atmosphere of N_2. Na_2CO_3 (6.460 g, 60.95 mmol) was added portion-wise over a period of 30 minutes and stirring was continued until all the solids had dissolved. 2-Pyrrolidinone (5.190 g, 60.98 mmol) in dry THF (25 cm^3) was added drop-wise and stirring was continued for 24 hours. Aqueous Na_3PO_4 (10% m/v, 100 cm^3) and EtOAc/hexane (1:1, 120 cm^3) was added in that order and vigorous stirring was continued for 10 minutes. The organic phase was separated and the aqueous phase was extracted with additional EtOAc/hexane (1:1, 4 × 100 cm^3). The organic extracts were combined and dried over Na_2SO_4, filtered and evaporated to afford a pale yellow solid. The solid was taken up into toluene (50 cm^3) and heated until most of the solids had dissolved. The hot solution was rapidly vacuum-filtered through a pad of Celite (previously warmed in an oven) and allowed to cool to room temperature. The crystals

were filtered and air-dried to afford 2-pyrrolidinethione [169] (5.250 g, 51.89 mmol, 85% yield) as a white solid.

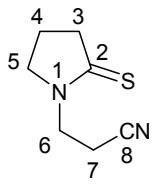
M.p: 108 – 110 °C (toluene), [lit.,[137] 109 – 110 °C].

IR (ν/cm^{-1}): 3157 (br s, NH stretch), 3050, 2976 and 2885 (m, C-H stretch), 1663 (m), 1593 (s, N-C=S), 1418 (m), 1294 (s), 1115 (m, C=S).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H, NH), 3.67 (t, J = 7.2, 2H, H_5), 2.92 (t, J = 7.9, 2H, H_3), 2.36 – 2.09 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 206.34 (C-2), 49.59 (C-5), 43.09 (C-3), 23.10 (C-4).

5.2.2 Synthesis of 3-(2-thioxo-1-pyrrolidinyl)propanenitrile [168A]



[168A]

This compound was prepared by a known procedure.[133] 2-Pyrrolidinethione [169] (3.000 g, 29.65 mmol) was added to a solution of acrylonitrile (2.35 cm^3, 1.904 g, 35.58 mmol), NaOH (0.100 g, 2.50 mmol) and water (one drop delivered by a Pasteur pipette) in THF (100 cm^3). After 18 hours of stirring under an atmosphere of nitrogen, the solvent was evaporated to give a yellow oil. The oil was taken up into CH_2Cl_2 (50 cm^3) and washed with H_2O (3 × 25 cm^3) and brine (25 cm^3). The organic phase was dried over $MgSO_4$, filtered and evaporated to give 3-(2-thioxo-1-pyrrolidinyl)propanenitrile [168A] (4.573 g, 29.65 mmol, quantitative yield) as a pale yellow oil. The oil was pure enough to carry through to subsequent reactions.

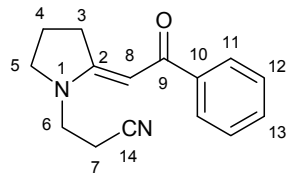
R_f (2:1 benzene/EtOAc): 0.59

IR (ν/cm^{-1}): 2240 (w, C≡N), 1510 (s, N-C=S), 1125 (m, C=S).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (t, J = 6.4, 2H, H_6), 3.94 (t, J = 7.3, 2H, H_5), 3.05 (t, J = 7.9, 2H, H_3), 2.88 (t, J = 6.4, 2H, H_7), 2.21 – 2.08 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.98 (C-2), 117.87 (C-8), 56.36 (C-5), 44.62 (C-3), 43.85 (C-6), 19.97 (C-4), 14.65 (C-7).

5.2.3 Synthesis of 3-{2-[(*E*)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}propanenitrile [157]



[157]

This compound was prepared by a known procedure.[133] Phenacyl bromide (8.208 g, 41.24 mmol) was added to a solution of 3-(2-thioxo-1-pyrrolidinyl)propanenitrile [168A] (6.000 g, 38.90 mmol) in dry acetonitrile (50 cm^3) and stirred under an atmosphere of N_2 for 24 hours. A solution of $P(OEt)_3$ (tech. grade 94%, 7.50 cm^3, 7.264 g, 41.24 mmol) and Et_3N (5.95 cm^3, 4.330 g, 42.79 mmol) in dry acetonitrile (20 cm^3) was added drop-wise over 5 minutes and stirring was continued for an additional 17 hours. The solvent was evaporated and the residue was taken up into EtOAc (200 cm^3) and washed with H_2O (2 × 100 cm^3). The organic phase was extracted with 2M HCl (1 × 200 cm^3, 2 × 50 cm^3) and the aqueous HCl extracts were combined and back-extracted with EtOAc (100 cm^3). The aqueous HCl extract was basified with 25% ammonia solution (pH 10) and extracted with EtOAc (4 × 50 cm^3). The combined organic extracts were washed with additional H_2O (4 × 50 cm^3), dried over $MgSO_4$, filtered and finally evaporated to give 3-{2-[(*E*)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}-propanenitrile [157] (8.007 g, 33.32 mmol, 86% yield) as an orange solid.

R_f (EtOAc): 0.44

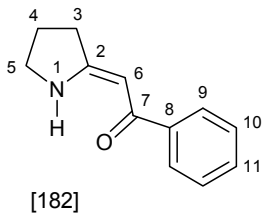
M.p: 124 – 125 °C (MeOH), [lit.,[133] 124.5 – 125.5 °C (benzene/hexane)].

IR (v/cm^{-1}): 3061 (w, aromatic C-H stretch), 2960, 2930 and 2882 (m, C-H stretch), 2244 (w, C≡N stretch), 1624 (s, C=O), 1597 (s, C=C stretch), 1577 (s), 1539 (s), 1480 (s), 1300 (s), 1218 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 6.5, 2H, H_{11}), 7.50 – 7.33 (m, 3H, H_{12} and H_{13}), 5.70 (s, 1H, H_8), 3.66 (t, J = 6.6, 2H, H_6), 3.58 (t, J = 7.2, 2H, H_5), 3.40 (t, J = 7.7, 2H, H_3), 2.69 (t, J = 6.6, 2H, H_7), 2.06 (quintet, J = 7.5, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 188.17 (C-9), 166.10 (C-2), 141.48 (C-10), 130.69 (C-13), 128.12 (C-12), 127.19 (C-11), 117.51 (C-14), 87.18 (C-8), 53.24 (C-5), 42.40 (C-6), 33.52 (C-3), 21.14 (C-4), 14.90 (C-7).

5.2.4 Synthesis of (*Z*)-1-phenyl-2-(2-pyrrolidinylidene)-1-ethanone [182] and 3-[2-(2-oxo-2-phenylethyl)-1-pyrrolidinyl]propanenitrile [160]



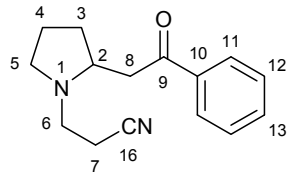
[182]

These compounds were prepared by a known procedure.[133] 3-{2-[(*E*)-2-Oxo-2-phenylethylidene]-1-pyrro-lidinyl}propanenitrile [157] (5.000 g, 20.81 mmol) in THF (150 cm^3) was cooled to –10 °C and stirred under an atmosphere of Ar for 10 minutes. $LiAlH_4$ (95%, 0.7897, 20.81 mmol) was added in one portion and stirring was continued for 15 minutes. EtOAc (20 cm^3) was added followed by H_2O (3 cm^3). Once the solution went white Na_2SO_4 was added and stirring was continued for 20 minutes. The reaction mixture was filtered through a pad of Celite and the pad was rinsed with EtOAc (4 × 50 cm^3). Evaporation of the solvents afforded a yellow oil that was flash chromatographed (70% EtOAc/hexane) to afford the known compound (*Z*)-1-phenyl-2-(2-pyrrolidinylidene)-1-ethanone [182] (0.100 g, 0.61 mmol, 3% yield) as a colourless solid.

M.p: 114 – 116 °C (acetone), [lit.,[25] 115.5 – 117.5 °C(benzene/hexane)].

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (br s, 1H, NH), 7.92 – 7.82 (m, 2H, H_9), 7.44 – 7.34 (m, 3H, H_{10} and H_{11}), 5.81 (s, 1H, H_6), 3.65 (t, *J* = 7.0, 2H, H_5), 2.74 (t, *J* = 7.8, 2H, H_3), 2.12 – 1.96 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 188.03 (C-7), 169.15 (C-2), 140.33 (C-8), 130.68 (C-11), 128.09 (C-10), 126.95 (C-9), 86.47 (C-6), 47.67 (C-5), 32.83 (C-3), 21.36 (C-4).



[160]

Further elution of the column afforded 3-[2-(2-oxo-2-phenylethyl)-1-pyrrolidinyl]propanenitrile [160] (4.321 g, 17.83 mmol, 86% yield) as a yellow oil.

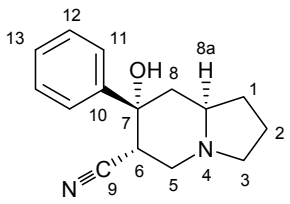
R_f (EtOAc): 0.51

IR (*v*/cm^{-1}): 3060 (w, aromatic C-H stretch), 2963 (m), 2813 (m), 2248 (w, C≡N stretch), 1682 (s, C=O) 1597 (m), 1580 (m), 1449 (m), 1210 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.4, 2H, H_{11}), 7.57 (t, *J* = 7.3, 1H, H_{13}), 7.47 (t, *J* = 7.6, 2H, H_{12}), 3.26 (dd, *J* = 4.2, 16.4, 1H, $H_{8'}$), 3.19 – 3.09 (m, 2H, $H_{5'}$ and H_2), 3.07 (dt, *J* = 7.7, 12.4, 1H, $H_{6'}$), 3.01 (dd, *J* = 8.1, 16.4, 1H, $H_{8''}$), 2.60 (ddd, *J* = 5.8, 6.6, 12.3, 1H, $H_{6''}$), 2.49 (dd, *J* = 6.2, 7.8, 2H, H_7), 2.29 (q, *J* = 8.6, 1H, $H_{5''}$), 2.12 (ddt, *J* = 7.4, 8.9, 12.7, 1H, $H_{3'}$), 1.89 – 1.72 (m, 2H, H_4), 1.50 (dddd, *J* = 5.7, 6.6, 8.7, 12.5, 1H, $H_{3''}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.28 (C-9), 137.08 (C-10), 133.17 (C-13), 128.62 (C-12), 128.04 (C-11), 118.87 (C-14), 60.14 (C-2), 53.34 (C-5), 49.83 (C-6), 44.14 (C-8), 31.36 (C-3), 22.77 (C-4), 17.66 (C-7).

5.2.5 Synthesis of the hydrates of *rel*-(6R,7R,8aR)-7-hydroxy-7-phenyloctahydroindolizine-6-carbonitrile [165A]



rel-[165A]

This compound was prepared by a known procedure.[133] ^{t}BuOK (3.626 g, 32.31 mmol) was added to a solution of 3-[2-(2-oxo-2-phenylethyl)-1-pyrrolidinyl]propane-nitrile [160] (3.845 g, 15.87 mmol) in dry THF (100 cm^3) and stirred under N_2 at room temperature for 3 hours. The solvent was evaporated and the residue partitioned between brine (100 cm^3) and EtOAc (200 cm^3) and stirred for 15 minutes. The organic extracts were separated and rewashed with additional brine (4 × 100 cm^3) and then dried over Na_2SO4, filtered and evaporated to afford an orange oil. Column chromatography (60% EtOAc/hexane) afforded impure product as an orange solid (3.065 g). Slow recrystallization from hot 30% EtOAc/hexane afforded *rel*-(6*R*,7*R*,8a*R*)-7-hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hydrate [165A] (2.234 g, 8.58 mmol, 54% yield) as a colorless solid. Attempts to furnish more products from the mother liquors resulted in decomposition to a black tar. The product was isolated as a hydrate, and attempts to remove the water by recrystallization from dry solvents, sublimation (80 °C, 5 mmHg) or distillation (160 °C, 5 mmHg) failed. In addition, attempts to elucidate the coefficient of hydration by way of elemental analysis failed.

Similarly, ^{t}BuOK (2.415 g, 21.52 mmol) was added to a solution of 3-[2-(2-oxo-2-phenylethyl)-1-pyrrolidinyl]propane-nitrile [160] (2.370 g, 9.78 mmol) in dry THF (50 cm^3) and stirred under N_2 at room temperature for 3 hours. Workup and chromatography as described above afforded an orange solid (2.147 g). Rapid recrystallization from chilled (–10 °C) EtOAc/hexane mixtures afforded *rel*-(6*R*,7*R*,8a*R*)-7-hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hemihydrate [165A] (1.717 g, 6.83 mmol, 70% yield). The hemihydrate can be converted to the hydrate by recrystallization from aqueous acetone.

R_f (EtOAc): 0.51

M.p: hydrate: 118 – 119 °C (30% EtOAc/hexane), [lit.,[25] 101 – 105 °C (EtOAc)]

IR (ν/cm^{-1}): 3508 (s, H-bonded OH), 3192 (br, m, OH), 2946 (s), 2874 (s), 2826 (s), 2256 (w, C≡N stretch), 1447 (m), 1383 (m), 1343 (m), 1217 (s).

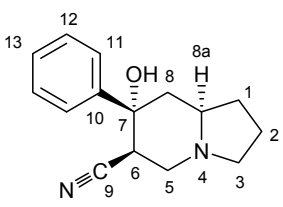
^{1}H NMR (400 MHz, CDCl3) δ 7.50 (d, J = 7.5, 2H, H_{11}), 7.41 (t, J = 7.6, 2H, H_{12}), 7.33 (t, J = 7.2, 1H, H_{13}), 3.37 – 3.27 (m, 2H, $H_{5'}$ and H_6), 3.10 (td, J = 2.6, 8.6, 1H, $H_{3'}$), 2.79 (t, J = 12.7, 1H, $H_{5''}$), 2.48 (tdd, J = 2.8, 6.0, 10.9, 1H, H_{8a}), 2.39 (br s, 1H, OH), 2.31 (q, J = 8.9, 1H, $H_{3''}$), 2.03 (dd, J = 2.7, 13.8, 1H, $H_{8'}$), 1.95 – 1.66 (m, 5H, $H_{1'}$, H_2, $H_{8''}$ and ½H_2O), 1.39 (qd, J = 6.8, 11.1, 1H, $H_{1''}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.55 (C-10), 128.81 (C-12), 128.05 (C-13), 124.35 (C-11), 118.45 (C-9), 73.33 (C-7), 58.50 (C-8a), 53.05 (C-3), 50.58 (C-5), 44.21 (C-8), 40.16 (C-6), 29.89 (C-1), 21.22 (C-2).

HRMS: Found M^+ = 242.1412, $C_{15}H_{18}N_2O$ requires 242.1419

5.2.6 Synthesis of *rel*-(6R,7S,8aS)-7-hydroxy-7-phenyloctahydro-6-indolizinecarbonitrile [186]

Method 1:



rel-[186]

^{t}BuOK (0.277 g, 2.47 mmol) was added to a solution of *rel*-(6*R*,7*R*,8a*R*)-7-hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hydrate [165A] (0.536 g, 2.06 mmol) in dry THF (25 cm^3) and stirred under argon for 21 hours. The temperature was then increased and maintained at 40-50 °C for an additional 48 hours. The solvent was evaporated and the residue was taken into EtOAc (25 cm^3) and washed with H_2O (10 cm^3) and brine (10 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to afford an orange gum. Flash chromatography (50%

EtOAc/hexane) afforded *rel*-(6*R*,7*S*,8a*S*)-7-hydroxy-7-phenyloctahydro-6-indolizinecarbonitrile [186] (0.079 g, 0.33 mmol, 16% yield) as a solid. Further elution of the column afforded recovered starting material as a hydrate (0.237 g, 44% mass recovery).

Method 2:

rel-(6*R*,7*R*,8a*R*)-7-Hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hemi-hydrate [165A] (0.251 g, 1.00 mmol) was added to a solution of sodium (0.028 g, 1.20 mmol) in absolute ethanol (5 cm^3) and stirred at room temperature for 4 days under Argon. H_2O (15 cm^3) was added and the aqueous reaction mixture was extracted with CH_2Cl_2 (3 × 15 cm^3). The organic extracts were dried over Na_2SO_4, filtered and evaporated to give an orange gum. Flash chromatography (50% EtOAc/hexane) afforded *rel*-(6*R*,7*S*,8a*S*)-7-hydroxy-7-phenyloctahydro-6-indolizinecarbonitrile [186] (0.083 g, 0.34 mmol, 34% yield). Further elution of the column afforded quantitative return of unreacted starting material as the hydrate (0.172 g).

R_f (EtOAc): 0.75

M.p: 136 – 138 °C

IR (ν/cm^{-1}): 3472 (s, H-bonded OH), 2843 and 2826 (s, Bohlmann band), 2248 (w, C≡N stretch), 1665 (m), 1493 (s), 1336 (s), 1045 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.7, 2H, H_{11}), 7.41 (t, J = 7.5, 2H, H_{12}), 7.38 – 7.31 (m, 1H, H_{13}), 3.19 (dd, J = 2.2, 11.3, 1H, $H_{5'}$), 3.13 (td, J = 2.5, 8.6, 1H, $H_{3'}$), 2.98 (dd, J = 2.4, 4.9, 1H, H_6), 2.81 (dd, J = 3.0, 11.3, 1H, $H_{5''}$), 2.47 (tdd, J = 2.3, 5.7, 10.7, 1H, H_{8a}), 2.34 (dd, J = 11.1, 13.3, 1H, $H_{8'}$), 2.27 (q, J = 8.6, 1H, $H_{3''}$), 2.01 (dt, J = 2.3, 13.4, 2H, OH and $H_{8''}$), 1.98 – 1.85 (m, 2H, $H_{1'}$ and $H_{2'}$), 1.82 – 1.68 (m, 1H, $H_{2''}$), 1.64 – 1.51 (m, 1H, $H_{1''}$).

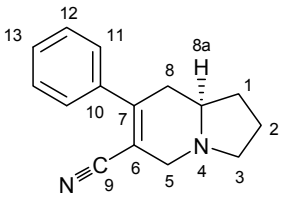
^{13}C NMR (75 MHz, $CDCl_3$) δ 144.28 (C-10), 128.69 (C-11), 128.53 (C-13), 125.34 (C-12), 119.97 (C-9), 73.04 (C-7), 58.31(C-8a), 53.00 (C-3), 50.14 (C-5), 41.02 (C-6), 38.97 (C-8), 30.32 (C-1), 21.27 (C-2).

HRMS: Found M^+ = 242.1421, $C_{15}H_{18}N_2O$ requires 242.1419

5.2.7 Synthesis of 7-phenyl-1,2,3,5,8,8a-hexahydro-6-indolizinecarbonitrile [178]

Acidic conditions:

Method 1:



[178]

rel-(6*R*,7*R*,8a*R*)-7-Hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hydrate [165A] (0.299 g, 1.15 mmol) was added to CH_2Cl_2 (20 cm^3) and stirred under N_2 until dissolved. Concentrated H_2SO_4 (2.030 g, 1.10 cm^3, 20.70 mmol) was added in one portion and stirring was continued for 90 seconds. At this time, Na_2CO_3 (5.00 g) was cautiously added to the red reaction mixture. The reaction mixture was filtered and the filter pad was washed with CH_2Cl_2 (20 cm^3). Evaporation afforded a red oil that was subjected to column chromatography (80% EtOAc/hexane) to afford 7-phenyl-1,2,3,5,8,8a-hexahydro-6-indolizinecarbonitrile [178] (0.130 g, 0.58 mmol, 50% yield) as a yellow oil. The oil rapidly turned black on standing in air.

R_f (EtOAc): 0.46

IR (ν/cm^{-1}): 2967 (s, C-H stretch), 2877, 2795 (Bohlmann bands), 2210 (s, C≡N stretch), 1622 (w, C=C stretch), 1444 (s), 1416 (s), 1314(s), 1033 (m).

1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 5H, H_{11}, H_{12} and H_{13}), 3.74 (dd, J = 2.6, 15.8, 1H, $H_{5'}$), 3.22 (td, J = 2.6, 8.6, 1H, $H_{3'}$), 3.06 (ddd, J = 3.1, 4.2,

15.8, 1H, $H_{5'}$), 2.71 (dt, *J* = 3.2, 18.0, 1H, $H_{8'}$), 2.42 (dddd, *J* = 2.5, 4.4, 10.0, 18.0, 1H, $H_{8''}$), 2.30 (tdd, *J* = 3.5, 6.6, 9.9, 1H, H_{8a}), 2.22 (q, *J* = 9.0, 1H, $H_{3''}$), 2.05 (dddd, *J* = 4.2, 6.7, 9.8, 12.4, 1H, $H_{1'}$), 1.95 – 1.71 (m, 2H, H_2), 1.47 (dddd, *J* = 6.5, 9.3, 11.1, 12.4, 1H, $H_{1''}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.27 (C-7), 138.63 (C-10), 129.16 (C-13), 128.66 (C-11), 127.08 (C-12), 118.03 (C-9), 106.53 (C-6), 59.23 (C-8a), 53.71 (C-5), 53.67 (C-3), 37.95 (C-8), 30.47 (C-1), 21.33 (C-2).

HRMS: Found M^+ = 224.1299, $C_{15}H_{16}N_2$ requires 224.1314

Method 2:

rel-(6*R*,7*R*,8a*R*)-7-Hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hydrate [165A] (0.166 g, 0.64 mmol) was added to CH_2Cl_2 (25 cm^3) and stirred under N_2 until dissolved. Concentrated H_2SO_4 (0.50 cm^3, 9.38 mmol) was added in one portion and stirring was continued for 20 minutes. At this time, Na_2CO_3 (5.00 g) was cautiously added to the red reaction mixture. The reaction mixture was filtered and the filter pad was washed with CH_2Cl_2 (20 cm^3). Evaporation afforded a red oil that was subjected to column chromatography (80% EtOAc/hexane) to afford 7-phenyl-1,2,3,5,8,8a-hexahydroindolizine-6-carbonitrile [178] (0.062 g, 0.28 mmol, 44% yield) as a yellow oil. The oil rapidly turned black on standing in air. The spectroscopic data matched those given above.

Basic conditions:

Method 1:

rel-(6*R*,7*R*,8a*R*)-7-Hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hydrate [165A] (0.084 g, 0.32 mmol) was added to a solution of ^{t}BuOK (0.078 g, 0.69 mmol) in dry THF (25 cm^3) and stirred under N_2 at room temperature for 24 hours. As no discernible reaction was occurring, the reaction was refluxed for 24 hours. The solvent was evaporated and the residue was taken up into

CH_2Cl_2 (50 cm^3) and washed with H_2O (20 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Column chromatography (80% EtOAc/hexane) afforded 7-phenyl-1,2,3,5,8,8a-hexahydro-6-indolizinecarbonitrile [178] (0.039 g, 0.18 mmol, 56% yield) as a yellow oil. The oil rapidly turned black on exposure to air. The spectroscopic data matched those given above.

Method 2:

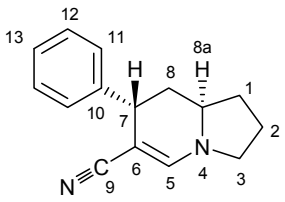
rel-(6*R*,7*R*,8a*R*)-7-Hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hydrate [165A] (0.138 g, 0.57 mmol) was added to a solution of pyridine (155 µL, 0.152 g, 1.88 mmol) in CH_2Cl_2 (20 cm^3) and stirred under N_2 until dissolved. Methanesulfonyl chloride (53 µL, 0.078 g, 0.68 mmol) was added and stirring was continued for 40 hours. The reaction mixture was washed with H_2O (20 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford a brown tar. The tar could not be characterized by ^1H NMR spectroscopy.

Method 3:

rel-(6*R*,7*R*,8a*R*)-7-Hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hydrate [165A] (0.073 g, 0.30 mmol) was added to a solution of DBU (140 µL, 0.138 g, 0.90 mmol) in CH_2Cl_2 (10 cm^3) and stirred under N_2 until dissolved. Methanesulfonyl chloride (25 µL, 0.038 g, 0.33 mmol) was added and stirring was continued for 24 hours. The reaction mixture was washed with H_2O (20 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford starting material (0.070 g, 96% recovery).

5.2.8 Synthesis of *rel*-(7R,8aS)-7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179A] and *rel*-(7R,8aR)-7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179B].

From 3-[2-(2-oxo-2-phenylethyl)-1-pyrrolidinyl]propanenitrile [160]:



rel-[179A]

^{t}BuOK (0.745 g, 6.64 mmol) was added to a solution of 3-[2-(2-oxo-2-phenylethyl)pyrrolidin-1-yl]propanenitrile [160] (0.805 g, 3.32 mmol) in dry THF (15 cm^3) and stirred under N_2 at reflux temperature for 3 hours. The solvent was evaporated and taken up into brine (50 cm^3) and extracted with EtOAc (3 × 50 cm^3). The organic extracts were then dried over MgSO4, filtered and evaporated to afford an orange oil that solidified on standing. Column chromatography (20% EtOAc/hexane) afforded 7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile (0.656 g, 2.92 mmol, 88% yield) as a white solid. ^{1}H NMR suggested the presence of diastereomers in a 3:1 ratio of [179A] and [179B] (*vida infra*). Recrystallization from EtOAc/hexane mixtures afforded *rel*-(7*R*,8a*S*)-7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179A] as a white solid.

Characterization data for compound [179A]:

R_f (20% EtOAc/hexane): 0.21

M.p: 120 – 122 °C (EtOAc/hexane mixtures), [lit.,[133] 121 – 125 °C (EtOAc)].

IR (v/cm^{-1}): 2968 (w, C-H stretch), 2870 (Bohlmann band), 2182 (m, C≡N stretch), 1614 (s, C=C stretch), 1408 (m), 1355 (m), 1082 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J = 7.5, 2H, H_{11}), 7.25 – 7.20 (m, 3H, H_{12} and H_{13}), 7.19 (s, 1H, H_5), 3.73 (dd, J = 2.0, 5.3, 1H, H_7), 3.59 – 3.47 (m, 1H, $H_{3'}$), 3.33 (td, J = 6.9, 9.8, 1H, $H_{3''}$), 3.08 – 2.99 (m, 1H, H_{8a}), 2.06 (ddd, J = 2.0, 3.5, 12.8, 1H, $H_{8'}$), 2.01 (ddd, J = 2.1, 6.3, 12.1, 1H, $H_{1'}$), 1.98 – 1.88 (m,

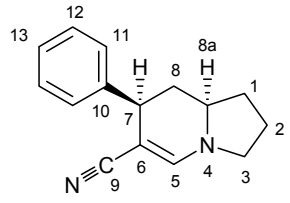
1H, $H_{2'}$), 1.88 – 1.73 (m, 1H, $H_{2''}$), 1.54 (ddd, *J* = 5.3, 11.7, 12.8, 1H, $H_{8''}$), 1.45 (tdd, *J* = 7.0, 9.8, 11.7, 1H, $H_{1''}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.26 (C-5), 144.24 (C-10), 128.36 (C-12), 127.80 (C-11), 126.52 (C-13), 123.44 (C-9), 74.10 (C-6), 51.61 (C-8a), 50.21 (C-3), 39.43 (C-7), 34.86 (C-8), 31.89 (C-1), 23.74 (C-2).

HRMS: Found M^+ = 224.1326, $C_{15}H_{16}N_2$ requires 224.1314

From *rel*-(6R,7R,8aR)-7-hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hydrate [165A]:

rel-(6*R*,7*R*,8a*R*)-7-Hydroxy-7-phenyloctahydroindolizine-6-carbonitrile hydrate [165A] (0.502 g, 1.93 mmol) was added to a solution of ^tBuOK (0.542g, 2.33 mmol) in dry THF (25 cm^3) and stirred under N_2 at reflux temperature for 4 hours. The solvent was evaporated and the residue was taken up into EtOAc (50 cm^3) and washed with H_2O (20 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to afford an orange gum. Partial separation of the diastereoisomers was achieved by flash chromatography (20% EtOAc/hexane). The first eluting fraction afforded *rel*-(7*R*,8a*S*)-7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179A] (0.236 g, 1.05 mmol, 54% yield) as a white solid, a mixed fraction (0.068 g, 16% yield), and finally *rel*-(7*R*,8a*R*)-7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179B] (0.063 g, 0.28 mmol, 15% yield) as a brown solid that darkened to black on standing in air. Therefore the combined yield for the diastereoisomers was 85% (0.367 g, 1.64 mmol).



rel-[179B]

Characterization data for compound [179B]:

R_f (20% EtOAc/hexane): 0.16

M.p: 111 – 113 °C (EtOAc/hexane mixtures)

IR (v/cm^{-1}): 3027 and 2945 (w, C-H stretch), 2869 (Bohlmann band), 2182 (s, C≡N stretch), 1608 (s, C=C stretch), 1408 (m), 1329 (m), 1066 (m).

1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H, H_{11}), 7.28 – 7.19 (m, 3H, H_{12} and H_{13}), 7.09 (d, J = 1.1, 1H, H_5), 3.64 (ddd, J = 1.1, 5.2, 11.5, 1H, H_7), 3.55 – 3.44 (m, 2H, H_{8a} and $H_{3'}$), 3.31 (td, J = 7.0, 9.8, 1H, $H_{3''}$), 2.26 (ddd, J = 3.2, 5.2, 12.9, 1H, $H_{8'}$), 2.15 (dtd, J = 2.2, 6.3, 8.5, 1H, $H_{1'}$), 1.98 (dtt, J = 2.4, 7.1, 11.9, 1H, $H_{2'}$), 1.94 – 1.80 (m, 1H, $H_{2''}$), 1.49 (tdd, J = 7.4, 9.9, 11.9, 1H, $H_{1''}$), 1.41 (dt, J = 11.4, 13.0, 1H, $H_{8''}$).

^{13}C NMR (75 MHz, CDCl3) δ 145.33 (C-5), 142.31(C-10), 128.60 (C-12), 127.50 (C-11), 126.99 (C-13), 122.68 (C-9), 78.22 (C-6), 56.61(C-8a), 49.81 (C-3), 40.56 (C-7), 38.07 (C-8), 32.23 (C-1), 23.98 (C-2).

HRMS: Found M^+ = 224.1305, $C_{15}H_{16}N_2$ requires 224.1314

From *rel*-(6R,7S,8aS)-7-hydroxy-7-phenyloctahydro-6-indolizinecarbonitrile [186]:

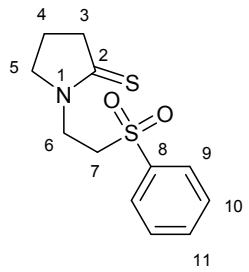
^{t}BuOK (0.0.84 g, 0.75 mmol) was added to a solution of *rel*-(6*R*,7*S*,8a*S*)-7-hydroxy-7-phenyloctahydro-6-indolizinecarbonitrile [186] (0.083 g, 0.34 mmol) in dry THF (5 cm^3) and stirred at reflux for 3 hours under argon. The reaction mixture was poured into a saturated solution of NH_4Cl (15 cm^3) and extracted with EtOAc (3 × 15 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Column chromatography (50% EtOAc/hexane) afforded a 3:1 diastereomer ratio of 7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179] (0.042 g, 0.19 mmol, 56% yield) as a brown solid.

From 7-phenyl-1,2,3,5,8,8a-hexahydro-6-indolizinecarbonitrile [178]:

7-Phenyl-1,2,3,5,8,8a-hexahydro-6-indolizinecarbonitrile [178] (0.053 g, 0.24 mmol) was added to a solution of ^{t}BuOK (0.074g, 0.66 mmol) in dry THF (5 cm^3) and stirred under N_2 at reflux temperature for 5 minutes. The solvent was evaporated and the residue was taken up into EtOAc (20 cm^3) and washed with H_2O (20 cm^3) and brine (20 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to afford an orange gum. Column chromatography (20% EtOAc/hexane) afforded a 3:1 diastereomer ratio of 7-phenyl-1,2,3,7,8,8a-hexahydro-6-indolizinecarbonitrile [179] (0.039 g, 0.18 mmol, 74 % yield) as a cream solid.

5.3 Experimental work pertaining to Chapter 2: Towards indolizidine systems containing a sulfone functional group

5.3.1 Synthesis of 1-[2-(phenylsulfonyl)ethyl]-2-pyrrolidinethione [168B]



[168B]

This compound was prepared by a known procedure.[78] 2-Pyrrolidinethione [169] (1.500 g, 14.83 mmol) was added to a stirring solution of phenyl vinyl sulfone (2.545 g, 15.13 mmol) in undried THF (40 cm^3) under N_2. NaOH (*ca.* 10 mg) was added and stirring was continued for 24 hours. The solvent was evaporated and H_2O (40 cm^3) was added followed by extraction with CH_2Cl_2 (2 × 50 cm^3). The organic extracts were dried over Na_2SO_4, filtered and evaporated to afford a white solid. Column chromatography (EtOAc) afforded 1-[2-(phenylsulfonyl)ethyl]-2-pyrrolidinethione [168B] (4.000 g, 14.83 mmol, 100% yield) as a white solid.

R_f (EtOAc): 0.70

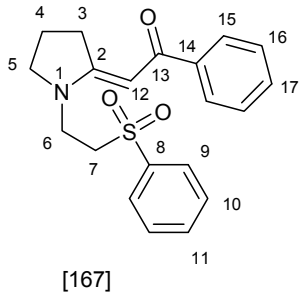
M.p: 91 – 92 °C (1:1 benzene/hexane), [lit.,[78] 95 – 96 °C (1:1 benzene/hexane)]

IR (ν/cm^{-1}): 3059 (w, C-H stretch), 2970 (m, C-H stretch), 1583 (w), 1509 (s), 1448 (m), 1293 (s), 1247 (m), 1152 (s).

1H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 2H, H_9), 7.73 – 7.65 (m, 1H, H_{11}), 7.64 – 7.56 (m, 2H, H_{10}), 4.12 (t, J = 6.4, 2H, H_6), 3.89 (t, J = 7.3, 2H, H_5), 3.59 (t, J = 6.4, 2H, H_7), 2.95 (t, J = 7.9, 2H, H_3), 2.11 – 1.99 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.58 (C-2), 139.00 (C-8), 134.07 (C-11), 129.44 (C-10), 127.75 (C-9), 56.33 (C-5), 51.90 (C-7), 44.63 (C-3), 41.74 (C-6), 19.98 (C-4).

5.3.2 Synthesis of (*E*)-1-phenyl-2-{1-[2-(phenylsulfonyl)ethyl]-2-pyrrolidinylidene}-1-ethanone [167]



[167]

This compound was prepared by a known procedure.[78] 1-[2-(Phenylsulfonyl)ethyl]-2-pyrrolidinethione [168B] (4.000 g, 14.83 mmol) was added to a stirring solution of phenacyl bromide (3.103 g, 15.59 mmol) in dry MeCN (50 cm^3) under N_2. After 30 hours, a solution of $P(OEt)_3$ (94% pure, 2.765 g, 15.64 mmol) and Et_3N (2.20 cm^3, 1.584 g, 15.65 mmol) in dry MeCN (15 cm^3) was added drop-wise to the above reaction mixture at 0 °C. Stirring was continued for an additional 18 hours. The solvent was evaporated and the residue was taken into CH_2Cl_2 (200 cm^3) and washed with H_2O (3 × 50 cm^3). The organic phase was extracted with 5M HCl (10 × 100 cm^3). The acidic aqueous phase was back-extracted with CH_2Cl_2 (2 × 25 cm^3) and then basified with concentrated ammonia solution (pH 10). The solid was filtered and taken into CH_2Cl_2 (100 cm^3) and dried over $MgSO_4$, filtered and evaporated to afford (*E*)-1-phenyl-2-{1-[2-(phenylsulfonyl)ethyl]-2-pyrro-

lidinylidene}-1-ethanone [167] (4.800 g, 13.50 mmol, 91% yield) as a cream coloured solid.

R_f (EtOAc): 0.41

M.p: 150 – 151 °C (methanol), [lit.,[78] 151 – 151.5 °C (EtOAc)]

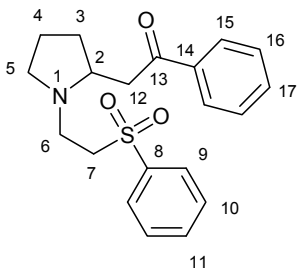
IR (ν/cm^{-1}): 3061 (w, C-H stretch), 2951 (w, C-H stretch), 1624 (m, C=O stretch), 1596 (m, C=C stretch), 1539 (s), 1298 (s), 1222 (s), 1152 (s).

1H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H, H_9), 7.82 – 7.74 (m, 2H, H_{15}), 7.69 (t, J = 7.4, 1H, H_{11}), 7.58 (t, J = 7.5, 2H,H_{10}), 7.49 – 7.34 (m, 3H, H_{16} and H_{17}), 5.58 (br t, J = 1.2, 1H, H_{12}), 3.79 (t, J = 7.1, 2H, H_6), 3.48 – 3.36 (m, 4H, H_5 and H_7), 3.29 (t, J = 7.7, 2H, H_3), 1.93 (quintet, J = 7.5, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.78 (C-13), 166.06 (C-2), 141.29 (C-14), 138.87 (C-8), 134.16 (C-11), 130.65 (C-17), 129.53 (C-10), 128.09 (C-16), 127.77 (C-9), 127.21 (C-15), 87.00 (C-12), 52.76 (C-5), 51.59 (C-7), 40.06 (C-6), 33.44 (C-3), 20.92 (C-4).

HRMS: Found M^+ = 355.1263, $C_{20}H_{21}NO_3S$ requires 355.1242

5.3.3 *Synthesis of 1-phenyl-2-{1-[2-(phenylsulfonyl)ethyl]-2-pyrrolidinyl}-1-ethanone [166]*



[166]

This compound was prepared by a known procedure.[78] (*E*)-1-Phenyl-2-{1-[2-(phenylsulfonyl)-ethyl]-2-pyrrolidinylidene}-1-ethanone [167] (3.350 g, 9.42 mmol) was added to dry THF (100 cm^3) and stirred at 0 °C under N_2. $LiAlH_4$ (95% pure, 0.394 g, 9.89 mmol) was added in one portion and stirring was continued for 5 minutes. H_2O (1.00 cm^3) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was dried

over $MgSO_4$ and filtered through a pad of Celite. The Celite pad was rinsed with EtOAc (25 cm^3). The combined organic extracts were evaporated to afford a yellow oil. Column chromatography (EtOAc) afforded 1-phenyl-2-{1-[2-(phenylsulfonyl)ethyl]-2-pyrrolidinyl}-1-ethanone [166] (3.209 g, 8.98 mmol, 95% yield) as a thick yellow oil.

R_f (EtOAc): 0.54

IR (ν/cm^{-1}): 3057 and 2953 (w, C-H stretch), 2816 (w), 1676 (s, C=O stretch), 1597 (w), 1581 (w), 1445 (m), 1306 (s), 1296 (s), 1146 (s).

1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2, 4H, H_9 and H_{15}), 7.68 – 7.59 (m, 1H, H_{11}), 7.59 – 7.43 (m, 5H, H_{10}, H_{16} and H_{17}), 3.30 (q, J = 7.4, 2H, $H_{12'}$), 3.28 – 3.16 (m, 2H, $H_{6'}$ and H_7), 2.99 (ddd, J = 3.7, 7.4, 14.3, 1H, H_2), 2.94 – 2.82 (m, 2H, $H_{5'}$ and $H_{12''}$), 2.71 – 2.59 (m, 1H, $H_{6''}$), 2.22 – 1.97 (m, 2H, $H_{3'}$ and $H_{5''}$), 1.73 – 1.56 (m, 2H, H_4), 1.48 – 1.32 (m, 1H, $H_{3''}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.09 (C-13), 139.65 (C-14), 136.99 (C-8), 133.58 (C-11), 133.13 (C-17), 129.09 (C-10), 128.58 (C-16), 128.00 (C-9), 127.94 (C-15), 60.00 (C-2), 54.60 (C-7), 52.98 (C-5), 47.06 (C-6), 43.51 (C-12), 31.17 (C-3), 22.41 (C-4).

HRMS: Found M^+ = 357.1389, $C_{20}H_{23}NO_3S$ requires 357.1399

5.3.4 Attempted synthesis of 7-phenyl-6-(phenylsulfonyl)octahydro-7-indolizinol [165B]

Method 1:

1-Phenyl-2-{1-[2-(phenylsulfonyl)ethyl]pyrrolidin-2-yl}ethanone [166] (0.912 g, 2.55 mmol) was added to a stirring solution of ^{t}BuOK (0.613 g, 5.19 mmol) in dry THF (50 cm^3) under N_2. After 16 hours the solvent was evaporated and the residue was taken into EtOAc (50 cm^3) and washed with brine (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford an orange oil. Column chromatography (70% EtOAc/hexane) afforded an oil (0.102 g) that could not be characterized by ^{1}H NMR spectroscopy.

Method 2:

1-Phenyl-2-{1-[2-(phenylsulfonyl)ethyl]pyrrolidin-2-yl}ethanone [166] (0.112 g, 0.31 mmol) was added to a stirring solution of ^{t}BuOK (0.070 g, 0.62 mmol) in dry toluene (5 cm^3) under N_2. After 3 hours additional ^{t}BuOK (0.035 g, 0.31 mmol) was added. After an additional hour of stirring the solvent was evaporated and the residue was taken into H_2O and extracted with EtOAc (3 × 15 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford starting material (0.110 g, quantitative recovery).

Method 3:

1-Phenyl-2-{1-[2-(phenylsulfonyl)ethyl]pyrrolidin-2-yl}ethanone [166] (0.316 g, 0.88 mmol) was added to a stirring solution of ^{t}BuOK (0.148 g, 1.32 mmol) in dry toluene (15 cm^3) and brought to reflux under N_2. After 5 minutes the solution became homogeneous and 2 minutes later a white powder crashed out of solution. The reaction was cooled and the solvent was evaporated to give a red oil. The residue was taken into H_2O (50 cm^3) and extracted with Et_2O (3 × 50 cm^3). The organic extract was dried over $MgSO_4$, filtered and

evaporated to afford a red oil that that could not be characterized by ^{1}H NMR spectroscopy.

Method 4:

1-Phenyl-2-{1-[2-(phenylsulfonyl)ethyl]pyrrolidin-2-yl}ethanone [166] (0.346 g, 0.97 mmol) was added to a stirring solution of KOH (0.396 g, 7.06 mmol) in dry toluene (10 cm^3) and brought to reflux under N_2. After 20 hours of reflux TLC analysis showed complete decomposition (6 spots), therefore no purification was attempted.

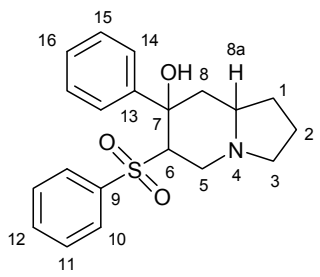
Method 5:

1-Phenyl-2-{1-[2-(phenylsulfonyl)ethyl]pyrrolidin-2-yl}ethanone [166] (0.171 g, 0.48 mmol) was added to a stirring solution of $^{t}BuOK$ (0.113 g, 0.96 mmol) in dry THF/ $^{t}BuOH$ (1:1, 20 cm^3) under N_2. After 18 hours the solvent was evaporated and the residue was taken into EtOAc (50 cm^3) and washed with brine (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange oil. Column chromatography (70% EtOAc/hexane) afforded an oil (0.006 g) that could not be characterized by ^{1}H NMR spectroscopy.

Method 6:

1-Phenyl-2-{1-[2-(phenylsulfonyl)ethyl]pyrrolidin-2-yl}ethanone [166] (0.180 g, 0.50 mmol) was added to a stirring solution of $^{t}BuOK$ (0.501 g, 5.00 mmol) in dry THF/ $^{t}BuOH$ (1:1, 20 cm^3) under N_2. After 18 hours the solvent was evaporated and the residue was taken into EtOAc (50 cm^3) and washed with brine (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford an orange oil. Column chromatography (70% EtOAc/hexane) afforded an oil (0.007 g) that could not be characterized by ^{1}H NMR spectroscopy.

Method 7:



[165B]

1-Phenyl-2-{1-[2-(phenylsulfonyl)ethyl]pyrrolidin-2-yl}ethanone [166] (0.232 g, 0.65 mmol) was added to a stirring solution of ^{t}BuOK (0.728 g, 6.50 mmol) in dry THF/ ^{t}BuOH (1:1, 20 cm^3) under N_2. After 3 hours the reaction was quenched with a saturated solution of NH_4Cl (40 cm^3). The reaction mixture was extracted with CH_2Cl_2 (3 × 50 cm^3). The organic extracts were dried over $MgSO_4$, filtered and evaporated to give an orange oil. Column chromatography (EtOAc) afforded an oily solid (0.085 g). Recrystallization from EtOAc/ hexane mixtures afforded 7-phenyl-6-(phenylsulfonyl)octahydro-7-indolizinol [165B] as a white solid (0.015 g, 0.04 mmol, 6% yield). Attempts to get an X-ray quality crystal resulted in loss of material, therefore only a partial characterization is presented below.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 6.88 (m, 10H), 4.82 (d, *J* = 2.9, 1H, OH), 4.13 (d, *J* = 7.9, 1H, H_6), 3.77 (dd, *J* = 4.1, 11.0, 1H, $H_{5'}$), 3.20 (t, *J* = 8.4, 1H, $H_{3'}$), 3.04 (t, *J* = 11.5, 1H, $H_{5''}$), 2.72 – 2.54 (m, 1H, H_{8a}), 2.44 (q, *J* = 8.9, 1H, $H_{3''}$), 1.94 (dd, *J* = 2.7, 13.7, 1H, $H_{8'}$), 1.91 – 1.75 (m, 3H, $H_{1'}$ and H_2), 1.55 (ddd, *J* = 2.8, 11.3, 13.8, 1H, $H_{8''}$), 1.44 – 1.23 (m, 1H, $H_{1''}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.95 (C-13), 140.33 (C-9), 132.73, 128.64, 128.01, 127.32, 127.03, 124.87, 74.00 (C-7), 67.52 (C-6), 58.59 (C-8a), 53.46 (C-3), 47.07 (C-8), 46.97 (C-5), 29.49 (C-1), 21.31 (C-2).

5.3.5 Attempts to trap the intermediate alkoxide anion of compound [165B]

Method 1:

1-Phenyl-2-{1-[2-(phenylsulfonyl)ethyl]pyrrolidin-2-yl}ethanone [166] (0.572 g, 1.60 mmol) was added drop-wise to a stirring solution of 2 equivalents of LDA [prepared by the addition of 1.6 M *n*-BuLi (2.00 cm^3, 3.20 mmol) to diisopropylamine (0.324 g, 0.45 cm^3, 3.20 mmol at -10 °C] in dry THF (10 cm^3) at –10 °C under N_2. After 30 minutes benzyl bromide (0.274 g, 0.19 cm^3, 1.60 mmol) in dry THF (10 cm^3) was added drop-wise to the reaction mixture. The reaction mixture was stirred for an additional 2 hours at -10 °C and then allowed to stir at room temperature 16 hours. The reaction was quenched with a saturated solution of NH_4Cl (20 cm^3) and extracted with CH_2Cl_2 (3 × 20 cm^3). The organic extracts were dried over $MgSO_4$, filtered and evaporated to afford red oil. Column chromatography (EtOAc) afforded an oil (0.351 g) that could not be characterized by ^1H NMR spectroscopy.

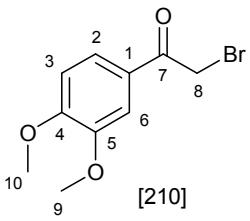
Method 2:

1-Phenyl-2-{1-[2-(phenylsulfonyl)ethyl]pyrrolidin-2-yl}ethanone [166] (0.304 g, 0.85 mmol) was added to dry THF (25 cm^3) and cooled with stirring to –78°C under Ar. 1.6 M *n*-BuLi (1.00 cm^3, 1.60 mmol) was added and stirring was continued for 20 minutes. Ac_2O (96 µL, 1.02 mmol) was added over 2 hours by way of a syringe pump and stirring was continued for an additional 1 hour. The solution was allowed to warm to room temperature and stirring was continued for an additional five days. H_2O (2 cm^3) was added and the solvent was evaporated and taken into EtOAc (25 cm^3), dried over $MgSO_4$, filtered and evaporated to afford a red oil that suggested decomposition of starting material as judged by TLC analysis.

Chapter 6: Experimental pertaining to Chapter 3

6.1 Experimental procedures for the *N*-phenacyl strategy

6.1.1 Synthesis of 2-bromo-1-(3,4-dimethoxyphenyl)-1-ethanone [210]



[210]

This compound was prepared by a known procedure.[169] 3,4-Dimethoxyacetophenone (5.000 g, 27.75 mmol) was added to a stirring solution of *p*-TsOH (7.919 g, 41.63 mmol) in dry MeCN (500 cm^3) at 50 °C under N_2. NBS (4.989 g, 28.03 mmol) in dry MeCN (100 cm^3) was added drop-wise over 30 minutes. The reaction was then allowed to reflux for 2 hours. The reaction was cooled to room temperature and the solvent was evaporated to afford a red tar. The tar was taken up into CH_2Cl_2 (100 cm^3) and washed with H_2O (3 × 100 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a red oil. MeOH (25 cm^3) was added and warmed to *ca*. 60 °C and then allowed to crystallize. The solids were filtered and rinsed with ice-cold MeOH (10 cm^3) to afford 2-bromo-1-(3,4-dimethoxyphenyl)ethanone [210] (1st crop: 5.000 g, 19.23 mmol, 69.3% yield) as a white solid. Treatment of the mother liquors afforded a second crop of 2-bromo-1-(3,4-dimethoxyphenyl)-1-ethanone [210] (0.750 g, 2.89 mmol, 10.4% yield). Therefore the total yield of 2-bromo-1-(3,4-dimethoxyphenyl)-1-ethanone [210] was 5.750 g (22.12 mmol, 80% yield).

M.p: 83 – 84 °C (MeOH), [lit.,[170] 90 – 91 °C (EtOAc)]

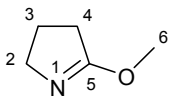
IR (ν/cm^{-1}): 2940 (w), 2843 (w), 1678 (m, C=O stretch), 1584 (m), 1512 (s), 1278 (s, C-O stretch), 1016 (s), 867 (m), 796 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, J = 1.9, 8.4, 1H, H_2), 7.54 (d, J = 1.8, 1H, H_6), 6.91 (d, J = 8.4, 1H, H_3), 4.41 (s, 2H, H_8), 3.96 (s, 3H, H_9*), 3.94 (s, 3H, H_{10}*).

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.85 (C-7), 153.80 (C-4), 149.07 (C-3), 126.81 (C-1), 123.69 (C-6), 110.59 (C-5), 109.93 (C-2), 55.98 (C-9*), 55.84 (C-10*), 30.42 (C-8).

Assignments denoted by * are interchangeable.

6.1.2 Synthesis of 5-methoxy-3,4-dihydro-2H-pyrrole [176]



[176]

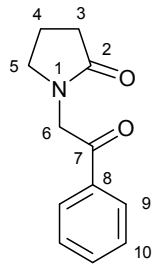
2-Pyrrolidinone (71.79 g, 0.84 mol) was added in one portion to a stirring solution of dimethyl sulfate (106.40 g, 0.84 mol) under N_2. After approximately 5 minutes the temperature rose to 60 °C. The reaction was stirred until room temperature had been attained (approximately 2 hours) at which point the reaction mixture was stirred at 60 °C for 18 hours. The reaction mixture was allowed to cool to room temperature and then carefully poured into an aqueous solution of K_2CO_3 (prepared from K_2CO_3 (232.00 g, 1.68 mol) in 500 cm^3 H_2O). After 30 minutes of stirring the solution was transferred to a separating funnel and extracted with Et_2O (2 × 100 cm^3, 3 × 50 cm^3). The organic extracts were dried over $MgSO_4$, filtered and rotary evaporated (bath temperature 20 °C) to give an orange oil. Vacuum distillation (52-55 °C, 20 mmHg) afforded 5-methoxy-3,4-dihydro-2*H*-pyrrole [176] (62.00 g, 0.63 mol, 75% yield) as a colourless oil.

IR (ν/cm^{-1}): 1654 (C=N).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H, H_6), 3.67 (t, J = 6.5, 2H, H_2), 2.45 (t, J = 8.4, 2H, H_4), 2.11 – 1.96 (m, 2H, H_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.72 (C-5), 55.18 (C-6), 54.82 (C-6), 30.71 (C-4), 23.21 (C-3).

6.1.3 Synthesis of 1-(2-oxo-2-phenylethyl)-2-pyrrolidinone [175A]



[175A]

This compound was prepared by a known procedure.[136] 5-Methoxy-3,4-dihydro-2*H*-pyrrole [176] (6.000 g, 60.53 mmol) was added to phenacyl bromide (8.000 g, 40.19 mmol) under N_2. The solution was heated at 60 °C for 20 hours. The residue was taken up into EtOAc (100 cm^3) and washed with 2M NaOH (3 × 100 cm^3), H_2O (100 cm^3) and brine (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford a red oil. Column chromatography (EtOAc) afforded 1-(2-oxo-2-phenylethyl)-2-pyrrolidinone [175A] (6.492 g, 31.94 mmol, 80% yield) as a white solid.

R_f (EtOAc): 0.29

M.p: 69 – 71 °C, [lit.,[136] 70 – 71 °C]

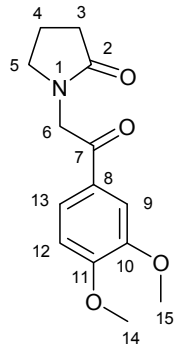
IR (ν/cm^{-1}): 3062 and 2917 (w, C-H stretch), 1698 (s, ketone C=O stretch), 1681 (s, amide C=O stretch), 1597 (w), 1580 (w), 1385 (w), 1290 (m), 1228 (m), 1075 (w).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.91 (m, 2H, H_9), 7.65 – 7.55 (m, 1H, H_{11}), 7.48 (t, J = 7.5, 2H, H_{10}), 4.73 (s, 2H, H_6), 3.50 (t, J = 7.1, 2H, H_5), 2.47 (t, J = 8.1, 2H, H_3), 2.20 – 2.02 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 193.70, (C-7), 175.66 (C-2), 134.80 (C-8), 133.65 (C-11), 128.69 (C-9), 127.87 (C-10), 48.95 (C-6), 47.76 (C-5), 30.28 (C-3), 17.94 (4).

HRMS: Found M^+ = 203.0915, $C_{12}H_{13}NO_2$ requires 203.0946

6.1.4 Synthesis of 1-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]-2-pyrrolidinone [175B]



[175B]

This compound was prepared by a known procedure.[136] 5-Methoxy-3,4-dihydro-2*H*-pyrrole [176] (1.190 g, 12.00 mmol) was added to a stirring solution of 2-bromo-1-(3,4-dimethoxyphenyl)ethanone [210] (2.591 g, 10.00 mmol) in dry DMF (5 cm^3) under N_2. The solution was heated at 80 °C for 4 hours and then the solvent was evaporated to afford a red oil. Column chromatography (10% MeOH/EtOAc) afforded 1-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]-2-pyrrolidinone [175B] (2.397 g, 9.10 mmol, 91% yield) as a yellow gum.

R_f (10% MeOH/EtOAc): 0.44

IR (ν/cm^{-1}): 3085, 2955 and 2928 (w, C-H stretch), 2841 (w), 1686 (s, ketone C=O stretch), 1670 (s, amide C=O stretch), 1587 (m), 1516 (m), 1261 (s), 1152 9s), 1018 (s).

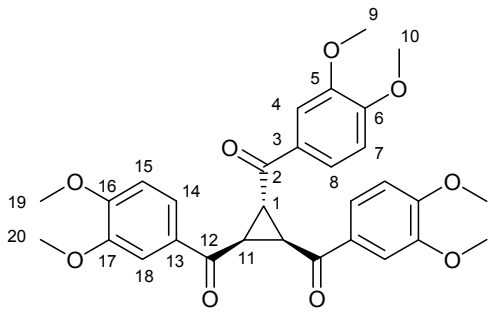
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 2.0, 8.4, 1H, H_{13}), 7.52 (d, *J* = 1.9, 1H, H_9), 6.91 (d, *J* = 8.4, 1H, H_{12}), 4.68 (s, 2H, H_6), 3.96 (s, 3H, H_{14}*), 3.93 (s, 3H, H_{15}*), 3.49 (t, *J* = 7.1, 2H, H_5), 2.47 (t, *J* = 8.1, 2H, H_3), 2.16 – 2.05 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.53 (C-7), 175.60 (C-2), 153.80 (C-11), 149.16 (C-10), 128.06 (C-8), 122.72 (C-13), 110.20 (C-12), 110.18 (C-9), 56.09 (C-14*), 56.00 (C-15*), 48.74 (C-6), 47.83 (C-5), 30.43 (C-3), 18.02 9C-4).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 263.1130, $C_{14}H_{17}NO_4$ requires 263.1158

6.1.5 Synthesis of [2,3-bis(3,4-dimethoxybenzoyl)cyclopropyl](3,4-dimeth-oxy-phenyl)methanone [211]



[211]

TBAB (7.570 g, 23.48 mmol) and K_2CO_3 (8.113 g, 58.70 mmol) was added to a solution of 2-pyrrolidinone (0.500 g, 5.87 mmol) in dry MeCN (30 cm^3). 2-Bromo-1-(3,4-dimethoxyphenyl)-1-ethanone [210] (2.000 g, 7.72 mmol) was added and the solution was vigorously stirred for 24 hours under an atmosphere of N_2. The heterogeneous reaction mixture was filtered and the filter pad was washed with EtOAc (50 cm^3). The filtrate was taken up into additional EtOAc (150 cm^3) and washed with H_2O (3 × 50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a red crystalline mass. The solid was washed repeatedly with a minimum volume of EtOAc to afford an amorphous powder of [2,3-bis(3,4-dimethoxybenzoyl)cyclopropyl](3,4-dimethoxy-phenyl)-methanone [211] (0.700 g, 1.31 mmol, 51% yield).

M.p: 200 – 201 °C, [lit.,[174] 200 – 202 °C]

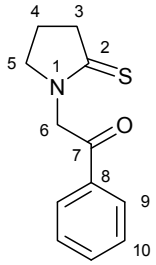
IR (ν/cm^{-1}): 2938 (w, C-H stretch), 2841 (w), 1656 (s, C=O), 1584 (s), 1512 (s), 1260 (s, C-O stretch), 1242 (s), 1144 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, J = 1.9, 8.4, 1H, H_8), 7.72 (dd, J = 1.9, 8.4, 2H, H_{14}), 7.67 (d, J = 1.9, 1H, H_4), 7.52 (d, J = 1.9, 2H, H_{18}), 6.96 (d, J = 8.5, 1H, H_7), 6.86 (d, J = 8.4, 2H, H_{15}), 4.17 (t, J = 5.6, 1H, H_1), 3.97 (broad s, 6H, H_9 and H_{10}), 3.92 (s, 6H, H_{19}*), 3.87 (s, 6H, H_{20}*), 3.69 (d, J = 5.6, 2H, H_{11}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.56 (C-2), 191.70 (C-12), 154.01 (C-6), 153.63 (C-16), 149.14 (C-5), 149.04 (C-17), 129.91(C-13), 129.73 (C-3), 124.04 (C-8), 123.36 (C-14), 110.34 (C-7), 110.27 (C-4 and C-15), 110.02 (C-18), 56.13 (C-9*), 56.05 (C-19$^{\#}$), 56.04 (C-10*), 55.88 (C-20$^{\#}$), 35.79 (C-11), 30.16 (C-1).

Assignments denoted by * and $^{\#}$ are interchangeable.

6.1.6 Synthesis of 1-phenyl-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [174A]



[174A]

This compound was prepared by a known thionation procedure.[175] P_4S_{10} (3.337 g, 7.51 mmol) was added to a stirring solution of 1-(2-oxo-2-phenylethyl)-2-pyrrolidinone [175A] (8.000 g, 39.36 mmol) in dry CH_2Cl_2 under N_2. HMDO (15.00 cm^3, 11.46 g, 70.58 mmol) in dry CH_2Cl_2 (50 cm^3) was added and stirring was continued for 18 hours. EtOAc (50 cm^3) was added and the reaction mixture was filtered through a pad of SiO_2 (150 g, 20 g SiO_2 / mmol P_4S_{10}) with EtOAc (1000 cm^3). The filtrate was evaporated to give a yellow gum. Column chromatography (40% EtOAc/hexane) afforded 1-phenyl-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [174A] (6.866 g, 31.31 mmol, 80% yield) as a white solid.

R_f (50% EtOAc/hexane): 0.49

M.p: 64 – 65 °C

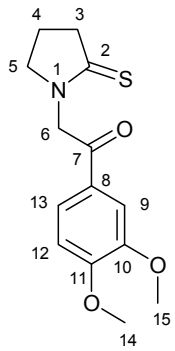
IR (ν/cm^{-1}): 3053, 2965 and 2899 (w, C-H stretch), 1689 (s, C=O stretch), 1597 (m), 1581 (w), 1461 (s), 1230 (s), 1218 (s), 1127 (s, C=S), 1076 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 7.3, 2H, H_9), 7.63 (t, J = 7.4, 1H, H_{10}), 7.50 (t, J = 7.6, 2H, H_{11}), 5.29 (s, 2H, H_6), 3.85 (t, J = 7.3, 2H, H_5), 3.14 (t, J = 7.9, 2H, H_3), 2.17 (p, J = 7.7, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.53 (C-2), 192.14 (C-7), 134.86 (C-8), 133.99 (C-11), 128.89 (C-9), 128.04 (C-10), 55.64 (C-5), 53.98 (C-6), 44.26 (C-3), 19.79 (C-4).

HRMS: Found M^+ = 219.0716, $C_{12}H_{13}NOS$ requires 219.0718

6.1.7 Synthesis of 1-(3,4-dimethoxyphenyl)-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [174B]



[174B]

1-[2-(3,4-Dimethoxyphenyl)-2-oxoethyl]-2-pyrrolidinone [2] (0.495 g, 1.88 mmol) was added to a stirring solution of Lawesson's reagent (0.421 g, 1.04 mmol) in dry toluene (10 cm^3) under N_2. The reaction was heated at 80 °C for 30 minutes and then allowed to cool to room temperature. Evaporation of the solvent gave a yellow gum. Column chromatography (50% EtOAc/hexane) afforded 1-(3,4-dimethoxyphenyl)-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [174B] (0.377 g, 1.35 mmol, 72% yield) as a pale yellow solid.

R_f (50% EtOAc/hexane): 0.26

M.p: 97 – 98 °C

IR (ν/cm^{-1}): 2942 and 2903 (w, C-H stretch), 1679 (s, C=O stretch), 1597 (m), 1587 (m), 1510 (s), 1258 (s), 1237 (s), 1144 (s), 1124 (s, C=S), 1060 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, J = 2.0, 8.4, 1H, H_{13}), 7.54 (d, J = 1.9, 1H, H_9), 6.92 (d, J = 8.4, 1H, H_{12}), 5.23 (s, 2H, H_6), 3.96 (s, 3H, H_{14}*), 3.94 (s, 3H, H_{15}*), 3.83 (t, J = 7.3, 2H, H_5), 3.13 (t, J = 7.9, 2H, H_3), 2.21 – 2.09 (m, 2H, H_4).

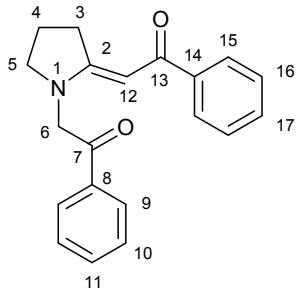
^{13}C NMR (75 MHz, $CDCl_3$) δ 203.26 (C-2), 190.82 (C-7), 154.05 (C-11), 149.25 (C-10), 127.99 (C-8), 122.82 (C-13), 110.25 (C-12), 110.17 (C-9),

56.14 (C-14*), 56.07 (C-15*), 55.58 (C-5), 53.67 (C-6), 44.30 (C-3), 19.76 (C-4).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 279.0948, $C_{14}H_{17}NO_3S$ requires 279.0929

6.1.8 Synthesis of 2-{2-[(*E*)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}-1-phenyl-1-ethanone [173A]



[173A]

1-Phenyl-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [174A] (0.658 g, 3.00 mmol) was added to a stirring solution of phenacyl bromide (0.597 g, 3.00 mmol) in dry MeCN (5 cm^3) under N_2. After 24 hours, $P(OEt)_3$ (0.57 cm^3, 0.548 g, 3.30 mmol) and Et_3N (0.47 cm^3, 0.334 g, 3.30 mmol) were added respectively. After 30 minutes the reaction was poured into H_2O (25 cm^3) and extracted with CH_2Cl_2 (20 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Column chromatography (50% EtOAc/hexane) afforded (2-{2-[(*E*)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}-1-phenyl-1-ethanone [173A] (0.400 g, 1.31 mmol, 44% yield) as a yellow solid.

R_f (50% EtOAc/hexane): 0.49

M.p: 102 – 104 °C (acetone)

IR (ν/cm^{-1}): 3074 and 2962 (w, C-H stretch), 2886 (w), 1686 (m, ketone C=O stretch), 1609 (m, C=O stretch), 1594 (m), 1477 (br s), 1215 (s, C-O stretch), 1019 (m), 759 (s).

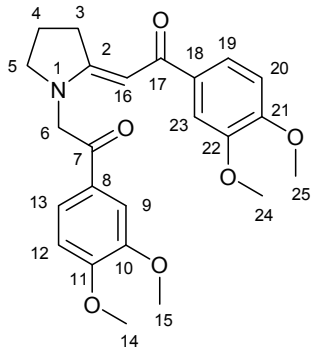
1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.1, 2H, H_9), 7.76 (d, J = 6.6, 2H, H_{15}), 7.66 (t, J = 7.4, 1H, H_{11}), 7.54 (t, J = 7.6, 2H, H_{10}), 7.41 – 7.28 (m, 3H,

H_{16} and H_{17}), 5.57 (s, 1H, H_{12}), 4.77 (s, 2H, H_6), 3.56 (t, J = 7.3, 2H, H_5), 3.50 (t, J = 7.8, 2H, H_3), 2.13 (p, J = 7.5, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.36 (C-7 and C-13), 167.72 (C-2), 141.86 (C-14), 134.86 (C-8), 134.11 (C-11), 130.33 (C-17), 129.04 (C-15), 127.95 (C-16), 127.89 (C-9), 127.20 (C-10), 86.95 (C-12), 53.75 (C-5), 52.55 (C-6), 33.54 (C-3), 21.21 (C-4).

HRMS: Found M^+ = 305.1390, $C_{20}H_{19}NO_2$ requires 305.1416

6.1.9 Synthesis of 1-(3,4-dimethoxyphenyl)-2-{2-[(*E*)-2-(3,4-dimethoxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}-1-ethanone [173B]



[173B]

1-(3,4-Dimethoxyphenyl)-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [174B] (0.200 g, 0.72 mmol) was added to a stirring solution of 2-bromo-1-(3,4-dimethoxyphenyl)ethanone [210] (0.197 g, 0.76 mmol) in dry MeCN (5 cm^3) under N_2. After 2 hours the reaction mixture was heated at 50 °C for 48 hours. The reaction was allowed to cool to room temperature. $P(OEt)_3$ (0.14 cm^3, 0.131 g, 0.79 mmol) and Et_3N (0.11 cm^3, 0.080 g, 0.79 mmol) was added respectively. After 2 hours of additional stirring the reaction mixture was poured into EtOAc (50 cm^3) and washed with H_2O (2 × 25 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a yellow oil. Column chromatography (EtOAc) afforded 1-(3,4-dimethoxyphenyl)-2-{2-[(*E*)-2-(3,4-dimethoxyphenyl)-2-oxoethylidene]-1-pyrro-lidinyl}-1-ethanone [4173B] (0.240 g, 0.56 mmol, 78% yield) as a yellow gum.

R_f (EtOAc): 0.20

IR (v/cm^{-1}): 2937 (w, C-H stretch), 2837 (w), 1703 (m, ketone C=O stretch), 1610 (m, C=O stretch), 1582 (m), 1511 (s), 1261 (s, C-O stretch), 1018 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, J = 2.0, 8.4, 1H, H_{13}), 7.54 (d, J = 1.9, 1H, H_9), 7.48 (d, J = 1.9, 1H, H_{23}), 7.32 (dd, J = 1.9, 8.4, 1H, H_{19}), 6.94 (d, J = 8.4, 1H, H_{12}), 6.76 (d, J = 8.4, 1H, H_{20}), 5.60 (s, 1H, H_{16}), 4.72 (s, 2H, H_6), 3.98 (s, 3H, H_{14}*), 3.94 (s, 3H, H_{15}*), 3.87 (s, 3H, $H_{24}^{\#}$), 3.86 (s, 3H, $H_{25}^{\#}$), 3.55 (t, J = 7.2, 2H, H_5), 3.49 (t, J = 7.8, 2H, H_3), 2.19 – 2.06 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.15 (C-7), 186.85 (C-17), 167.29 (C-2), 154.13 (C-11), 151.06 (C-21), 149.46 (C-10), 148.60 (C-22), 134.75 (C-18), 128.09 (C-8), 122.38 (C-13), 120.36 (C-19), 110.44 (C-20), 110.23 (C-12), 110.05 (C-9), 109.76 (C-23), 86.42 (C-16), 56.18 (C-14*), 56.04 (C-15*), 55.88 (C-24$^{\#}$), 55.78 (C-25$^{\#}$), 53.71 (C-5), 52.18 (C-6), 33.45 (C-3), 21.25 (C-4).

Assignments denoted by * and $^{\#}$ are interchangeable.

HRMS: Found M^+ = 425.1818, $C_{24}H_{27}NO_6$ requires 425.1838

6.1.10 Attempted hydrogenation of compound [173B] under neutral conditions

1-(3,4-Dimethoxyphenyl)-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [174B] (0.103 g, 0.24 mmol) was added to a stirring solution of $PtO_2.\times H_20$ (0.003 g, 0.02 mmol) in degassed MeOH (5 cm^3) and hydrogenated at 5 atmosphere of pressure for 48 hours. The reaction mixture was filtered through a pad of Celite. The Celite pad was washed with additional MeOH (20 cm^3) and the combined solvents were evaporated. Analysis of the crude material (*ca.* 0.102 g) by ^{1}H NMR showed no reaction had occurred.

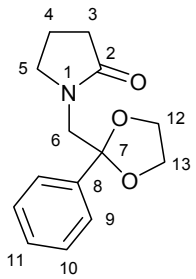
Similarly:

1-(3,4-Dimethoxyphenyl)-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [174B] (0.102 g, 0.24 mmol) was added to MeOH (10 cm^3) and stirred under N_2. Hydrazine hydrate (60 µL, 0.060 g, 1.20 mmol) was added followed by a suspension of Raney Nickel (enough to coat the poles of the magnetic stir bar). The reaction mixture was heated at 65 °C and stirred for an additional 18 hours. TLC analysis showed no reaction had occurred. The experiment was then abandoned without recovering the starting material.

6.2 Experimental procedures for the ketal protection strategy

6.2.1 Attempted synthesis of 1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinone [215A] from compound [175A]

Method 1:



[215A]

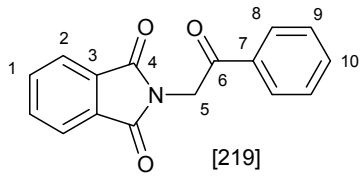
1-(2-Oxo-2-phenylethyl)-2-pyrrolidinone [175A] (0.893 g, 4.40 mmol) was added to a stirring solution of *p*-TsOH (0.084 g, 0.44 mmol) and ethylene glycol (0.60 cm^3, 0.655 g, 10.56 mmol) in dry benzene (50 cm^3). The reaction mixture was refluxed under Dean-Stark conditions for 16 hours. The reaction mixture was evaporated and taken up into CH_2Cl_2 (30 cm^3) and washed with H_2O (25 cm^3) and brine (25 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford starting material (0.834 g, 93% recovery).

Method 2:

1-(2-Oxo-2-phenylethyl)pyrrolidin-2-one [175A] (0.834 g, 4.09 mmol) was added to a stirring solution of concentrated H_2SO_4 (0.50 cm^3) and ethylene glycol (1.00 cm^3, 1.110 g, 17.88 mmol) in dry toluene (100 cm^3). The reaction mixture was refluxed under Dean-Stark conditions for 16 hours. The black reaction mixture was cooled and $NaHCO_3$ (*ca*. 1.00 g) was added to neutralize the solution. CH_2Cl_2 (200 cm^3) was added the solution was washed with H_2O (100 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange oil. Column chromatography (EtOAc) afforded starting material (0.414 g, 50% recovery) as an orange oil.

6.2.2 Synthesis of 2-(2-oxo-2-phenylethyl)-1H-isoindole-1,3(2H)-dione [219]

Phthalimide (4.414 g, 30.00 mmol) was added to a stirring solution of KOH (3.367 g, 60.00 mmol) in EtOH (100 cm^3) and refluxed for 3 hours. The salt was filtered and rinsed with additional EtOH (200 cm^3) and then dried under vacuum to afford potassium phthalimide (5.550 g, 30.00 mmol) as a white solid. The solid was kept in a desiccator until required.



[219]

Potassium phthalimide (2.037 g, 11.00 mmol) was added to a stirring solution of phenacyl bromide (1.991 g, 10.00 mmol) in dry DMF (30 cm^3) under N_2. The reaction mixture was heated at 90 °C for 18 hours. The reaction mixture was poured into H_2O (300 cm^3) and extracted with CH_2Cl_2 (4 × 50 cm^3). The organic extract was additionally washed with an aqueous solution of 3% NaOH (100 cm^3) and H_2O (100 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford 2-(2-oxo-2-phenylethyl)-1*H*-isoindole-1,3(2*H*)-dione [219] (2.650 g, 9.99 mmol, quantitative yield) as a white solid.

M.p: 165 – 167 °C, [lit.,[181] 165 – 167 °C].

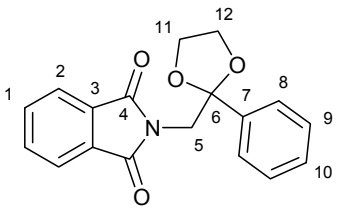
IR (ν/cm^{-1}): 3044, 2974 and 2938 (w, C-H stretch), 1770 (w), 1697 (br s, C=O stretch), 1469 (m), 1450 (m), 1423 (s), 1226 (m), 1109 (m).

^{1}H NMR (300 MHz, CDCl3) δ 8.01 (d, J = 7.6, 2H, H_2), 7.95 – 7.83 (m, 2H, H_8), 7.83 – 7.69 (m, 2H, H_1), 7.63 (t, J = 7.3, 1H, H_{10}), 7.51 (t, J = 7.6, 2H, H_9), 5.13 (s, 2H, H_5).

^{13}C NMR (75 MHz, CDCl3) δ 190.91 (C-6), 167.83 (C-4), 134.37 (C-7), 134.08 (C-1), 133.99 (C-10), 132.19 (C-3), 128.85 (C-8), 128.09 (C-9), 123.49 (C-2), 44.16 (C-5).

The spectroscopic data are in agreement with those found in the literature.[259]

6.2.3 Synthesis of 2-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-1H-isoindole-1,3(2H)-dione [220]



[220]

This compound was prepared by a known procedure.[177] 2-(2-Oxo-2-phenylethyl)-1*H*-isoindole-1,3(2*H*)-dione [219] (3.341 g, 12.59 mmol) was added to a stirring solution of *p*-TsOH (0.155 g, 0.82 mmol) and ethylene glycol (3.50 cm^3, 3.907 g, 62.95 mmol) in dry benzene (100 cm^3). The reaction mixture was refluxed under Dean-Stark conditions for 2 days when additional ethylene glycol (3.50 cm^3, 3.907 g, 62.95 mmol) and PTSA (0.465 g, 2.45 mmol) was added. After an additional 10 days the reaction mixture was poured into H_2O (100 cm^3) and extracted with CH_2Cl_2 (2 × 100 cm^3). The organic phase was washed with 1M NaOH (2 × 100 cm^3), H_2O (100 cm^3) and brine (50 cm^3). The organic extract was dried over $MgSO_4$ and evaporated to afford 2-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione [220] (3.535 g, 11.43 mmol, 91% yield) as a white solid.

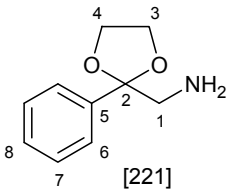
M.p: 142 – 143 °C (ethanol), [lit.,[177] 145 °C (ethanol)].

IR (ν/cm^{-1}): 3057, 2941 and 2885 (w, C-H stretch), 1774 (m), 1709 (br s), 1467 (w), 1448 (w), 1420 (m), 1389 (s), 1004 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.80 (m, 2H, H_2), 7.78 – 7.67 (m, 2H, H_1), 7.65 – 7.53 (m, 2H, H_8), 7.42 – 7.29 (m, 3H, H_9 and H_{10}), 4.08 (s, 2H, H_5), 4.03 – 3.88 (m, 2H, $H_{11'}$ and $H_{12'}$), 3.86 – 3.70 (m, 2H, $H_{11''}$ and $H_{12''}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.77 (C-4), 139.80 (C-7), 133.84 (C-1), 132.01 (C-3), 128.60 (C-10), 128.24 (C-8), 126.05 (C-9), 123.34 (C-2), 108.68 (C-6), 64.80 (C-11 and C-12), 44.25 (C-5).

6.2.4 Synthesis of (2-phenyl-1,3-dioxolan-2-yl)methylamine [221]



[221]

This compound was prepared by a known procedure.[177] 2-[(2-Phenyl-1,3-dioxolan-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione [220] (1.700 g, 5.50 mmol) was added to a stirring solution of 80% hydrazine hydrate (3.20 cm^3, 3.304 g, 55.00 mmol) in EtOH (100 cm^3) under N_2. The reaction mixture was refluxed for 30 hours, cooled to room temperature and filtered to remove the phthalalhydrazide by-product. The solvent was evaporated to give an oily white solid. The residue was taken up into an aqueous solution of 30% NaOH (50 cm^3) and extracted with Et_2O (4 × 50 cm^3). The organic extract was dried over NaOH pellets overnight, filtered and evaporated to give (2-phenyl-1,3-dioxolan-2-yl)methylamine [221] (0.963 g, 5.40 mmol, 98% yield) as a murky yellow oil. This compound was used immediately upon preparation.

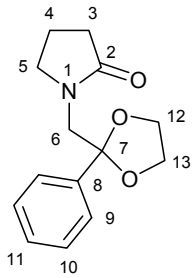
IR (ν/cm^{-1}): 3409 (br w), 2983 and 2881 (w, C-H stretch), 1631 (m), 1566 (m), 1469 (s), 1376 (s), 1049 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.41 (m, 2H, H_6), 7.40 – 7.27 (m, 3H, H_7 and H_8), 4.14 – 3.99 (m, 2H, $H_{3'}$ and $H_{4'}$), 3.92 – 3.76 (m, 2H, $H_{3''}$ and $H_{4''}$), 2.92 (s, 2H, H_1), 1.39 (br s, 2H, NH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.12 (C-5), 128.15 (C-7), 128.11 (C-8), 125.83 (C-6), 109.90 (C-2), 64.99 (C-3 and C-4), 50.19 (C-1).

6.2.5 Synthesis of 1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinone [215A]

(2-Phenyl-1,3-dioxolan-2-yl)methylamine [221] (0.895 g, 5.02 mmol) was added to a solution of Na_2CO_3 (0.638 g, 6.02 mmol) and 4-chlorobutanoyl chloride (0.68 cm^3, 0.849 g, 6.02 mmol) in dry CH_2Cl_2 (25 cm^3) at 0 °C under N_2. The reaction mixture was gradually warmed to room temperature and then allowed to stir for an additional 48 hours. The reaction mixture was filtered through a pad of Celite and the Celite pad was washed with additional CH_2Cl_2 (20 cm^3). Evaporation of the solvent gave a crude sample of 4-chloro-*N*-[(2-phenyl-1,3-dioxolan-2-yl)methyl]butanamide [222] as a yellow semi-solid that was immediately used into the next reaction.



[215A]

To a flame dried flask was added dry MeOH (60 cm^3) followed by Na (0.254 g, 11.04 mmol) and the mixture was stirred under N_2 until complete dissolution of Na had occurred. Crude 4-chloro-*N*-[(2-phenyl-1,3-dioxolan-2-yl)methyl]butanamide [222] in dry MeOH (15 cm^3) was added drop-wise and stirring was continued for 24 hours. The solvent was evaporated and a saturated solution of NH_4Cl (50 cm^3) was added followed by an aqueous solution of 2M NaOH (50 cm^3). The aqueous solution was extracted with CH_2Cl_2 (2 × 30 cm^3), dried over $MgSO_4$, filtered and evaporated to give a yellow oil. Column chromatography (50%

EtOAc/hexane to 100% EtOAc) afforded 1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinone [215A] (0.924 g, 3.73 mmol, 74% yield) as a yellow oil.

The R_f could not be determined as a staining reagent could not be found for this compound. Therefore, gradient elution was the method employed for chromatographic purification. The idea was to remove less polar impurities first (colour was an indicator in this instance) and then to isolate the product by evaporating individual fractions. If an oil was present, they were pooled with other fractions that also contained an oil. Fortunately, the fractions collected were pure.

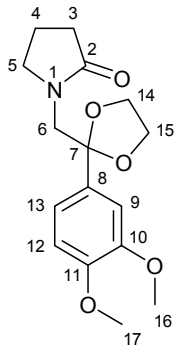
IR(ν/cm^{-1}): 2961, 2932 and 2897 (C-H stretch), 1665 (br s, C=O stretch), 1466 (m), 1450 (m), 1424 (m), 1410 (m), 1225 (br s), 1027 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 7.7, 2H, H_9), 7.40 – 7.28 (m, 3H, H_{10} and H_{11}), 4.12 – 3.96 (m, 2H, $H_{12'}$ and $H_{13'}$), 3.89 – 3.73 (m, 2H, $H_{12''}$ and $H_{13''}$), 3.67 (s, 2H, H_6), 3.44 (t, J = 6.9, 2H, H_5), 2.27 (t, J = 8.0, 2H, H_3), 2.00 – 1.83 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.34 (C-2), 140.05 (C-8), 128.41 (C-11), 128.11 (C-10), 125.87 (C-9), 109.35 (C-7), 64.65 (C-12 and C-13), 49.55 (C-6), 48.76 (C-5), 30.56 (C-3), 18.37 (C-4).

HRMS: Found M^{+1} = 248.1280, $C_{14}H_{18}NO_3$ requires 248.1282

6.2.6 Synthesis of 1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]methyl}-pyrrolidin-2-one [215B]


[215B]

1-[2-(3,4-Dimethoxyphenyl)-2-oxoethyl]pyrrolidin-2-one [175B] (0.914, 3.47 mmol) was added to a stirring solution of *p*-TsOH (0.991 g, 5.21 mmol) and ethylene glycol (1.94 cm^3, 2.154 g, 34.70 mmol) in dry toluene (50 cm^3). The reaction was refluxed under Dean-Stark conditions for 24 hours. The reaction mixture was allowed to cool to room temperature and then H_2O (100 cm^3) and $NaHCO_3$ (1.00 g) were added. After stirring for 20 minutes, the reaction mixture was extracted with CH_2Cl_2 (100 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a red gum. Column chromatography (5% MeOH/EtOAc) afforded 1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]methyl}pyrrolidin-2-one [215B] (0.853 g, 2.78 mmol, 80% yield) as an orange gum.

IR (ν/cm^{-1}): 2937 (w, CH stretch), 2848 (w) 1660 (s, lactam C=O), 1586 (m), 1516 (s), 1262 (s, C-O stretch), 1151 (m), 1132 (m), 1033 (m).

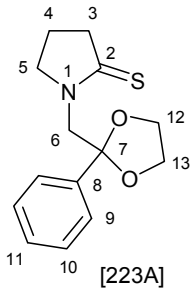
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 2.0, 8.2, 1H, H_9), 7.03 (d, *J* = 2.0, 1H, H_9), 6.84 (d, *J* = 8.2, 1H, H_{12}), 4.08 – 3.99 (m, 2H, $H_{14'}$ and $H_{15'}$), 3.89 (s, 3H, H_{16}*), 3.87 (s, 3H, H_{17}*), 3.86 – 3.79 (m, 2H, $H_{14''}$ and $H_{15''}$), 3.66 (s, 2H, H_6), 3.45 (t, *J* = 7.0, 2H, H_5), 2.27 (t, *J* = 8.0, 2H, H_3), 1.99 – 1.82 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.88 (C-2), 148.63 (C-11), 148.30 (C-10), 132.34 (C-8), 117.92 (C-13), 110.26 (C-12), 108.95 (C-70, 108.83 (C-9), 64.30 (C-14 and C-15), 55.59 (C-16*), 55.46 (C-17*), 49.08 (C-6), 48.35 (C-5), 30.23 (C-3), 18.01 (C-4).

Assignments denoted by * are interchangeable.

HRMS: found M^+ = 307.1404, $C_{16}H_{21}NO_5$ requires 307.1420

6.2.7 Synthesis of 1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinethione [223A]



[223A]

1-[(2-Phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinone [215A] (3.278 g, 13.26 mmol) was added to a stirring solution of Lawesson's reagent (3.220 g, 7.96 mmol) in dry CH_2Cl_2 (75 cm^3) under N_2. The reaction mixture was refluxed for 18 hours. The solvent was evaporated to give an orange gum. Column chromatography (30% EtOAc/hexane to 50% EtOAc/hexane) afforded 1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidine-thione [223A] (2.490 g, 9.46 mmol, 71% yield) as a white solid.

R_f (20% EtOAc/hexane): 0.15

M.p: 81 – 82 °C

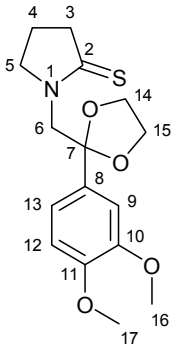
IR(ν/cm^{-1}): 2979 and 2926 (w, C-H stretch), 2888 (w), 1504 (s), 1452 (w), 1439 (w), 1272 (s, C-O stretch), 1225 (br s), 1175 (s, C=S stretch), 1057 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.47 (m, 2H, H_9), 7.42 – 7.28 (m, 3H, H_{10} and H_{11}), 4.25 (s, 2H, H_6), 4.15 – 3.96 (m, 2H, $H_{12'}$ and $H_{13'}$), 3.90 – 3.77 (m, 2H, $H_{12''}$ and $H_{13''}$), 3.79 (t, J = 7.3, 2H, H_5), 2.94 (t, J = 7.8, 2H, H_3), 2.04 – 1.85 (m, 2H, H_4).

^{13}C NMR (75 MHz, CDCl3) δ 203.42 (C-2), 139.56 (C-8), 128.66 (C-11), 128.21 (C-10), 125.90 (C-9), 109.09 (C-7), 64.59 (C-12 and C-13), 55.92 (C-5), 53.86 (C-6), 44.63 (C-3), 20.11 (C-4).

HRMS: Found M^+ = 263.0999, $C_{14}H_{17}NO_2S$ requires 263.0980

6.2.8 Synthesis of 1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]methyl}-2-pyrrolidinethione [223B]



[223B]

1-{[2-(3,4-Dimethoxyphenyl)-1,3-dioxolan-2-yl]methyl}pyrrolidin-2-one [215B] (0.688 g, 2.24 mmol) was added to a stirring solution of Lawesson's reagent (0.542 g, 1.34 mmol) in dry toluene (20 cm^3) under N_2. The reaction mixture was heated at 80 °C for 18 hours. The solvent was evaporated to give an orange gum. Column chromatography (30% EtOAc/hexane) afforded 1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]methyl}-2-pyrrolidinethione (0.326 g, 1.01 mmol, 45% yield) as a yellow gum.

IR (v/cm^{-1}): 2932 and 2879 (w, C-H stretch), 2830 (w), 1601 (m), 1590 (m), 1265 (s, C-O stretch), 1133 (s, C=S stretch), 1119 (s), 1031 (s).

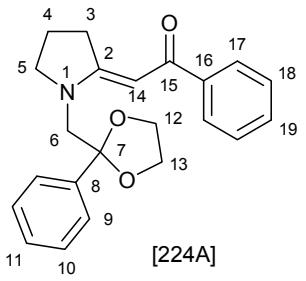
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (m, 2H, H_9 and H_{13}), 6.83 (d, J = 8.8, 1H, H_{12}), 4.26 (s, 2H, H_6), 4.10 – 4.02 (m, 2H, $H_{14'}$ and $H_{15'}$), 3.90 (s, 3H, H_{16}*), 3.87 (s, 3H, H_{17}*), 3.89 – 3.81 (obscured m, 2H, $H_{14''}$ and $H_{15''}$), 3.77 (t, J = 7.2, 2H, H_5), 2.91 (t, J = 7.8, 2H, H_3), 1.93 (p, J = 7.6, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.78 (C-2), 148.86 (C-10), 148.38 (C-11), 131.69 (C-8), 117.82 (C-13), 110.19 (C-12), 109.02 (C-9), 108.66 (C-7), 64.29 (C-14 and C-15), 55.66 (C-16*), 55.51 (C-17*), 55.40 (C-5), 53.43 (C-6), 44.28 (C-3), 19.74 (C-4).

Assignments denoted by * are interchangeable.

HRMS: found M^+ = 323.1184, $C_{16}H_{21}NO_4S$ requires 323.1191

6.2.9 Synthesis of (*E*)-1-phenyl-2-{1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinylidene}-1-ethanone [224A]



[224A]

1-[(2-Phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidine-thione [223A] (2.490 g, 9.46 mmol) was added to a stirring solution of phenacyl bromide (1.921 g, 9.65 mmol) in dry MeCN (25 cm^3) under N_2. After 18 hours TLC analysis indicated the reaction had not gone to completion, therefore the solution was heated at 50 °C for 1 hour and then allowed to stir at room temperature for an additional 18 hours. At this point another quantity of phenacyl bromide (0.100 g, 0.50 mmol) was added and stirring was continued for an additional 24 hours. Again, TLC analysis indicated an incomplete reaction, therefore the solvent was evaporated to approximately 10 cm^3 and the reaction mixture was allowed to stir at room temperature for another 16 hours. A solution of $P(OEt)_3$ (1.70 cm^3, 1.650 g, 9.93 mmol) and Et_3N (1.60 cm^3, 1.149 g, 11.35 mmol) in dry MeCN (50 cm^3) was added drop-wise over 5 minutes to the white suspension and stirring was continued for an additional 24 hours. The solvent was evaporated and the residue was taken up into EtOAc (100 cm^3) and washed with H_2O (4 × 100 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange gum. Column chromatography (40% EtOAc/hexane to 100% EtOAc) afforded (*E*)-1-phenyl-2-{1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinylidene}-1-ethanone [224A] (2.722 g, 7.79 mmol, 82% yield) as a pale-yellow solid.

R_f (40% EtOAc/hexane): 0.20

M.p: 86 – 88 °C (EtOAc/hexane mixtures)

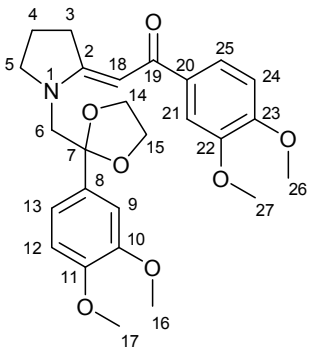
IR (ν/cm^{-1}): 2963 (m, C-H stretch), 2899 (w), 1625 (m, C=O stretch), 1577 (m), 1533 (s), 1472 (s), 1338 (m), 1304 (m), 1263 (s, C-O stretch), 1044 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.66 (m, 2H, H_{17}), 7.44 (d, *J* = 7.5, 2H, H_9), 7.39 – 7.13 (m, 6H, H_{10}, H_{11}, H_{18} and H_{19}), 5.83 (s, 1H, H_{14}), 4.03 – 3.88 (m, 2H, $H_{12'}$ and $H_{13'}$), 3.87 – 3.66 (m, 2H, $H_{12''}$ and $H_{13''}$), 3.58 (s, 2H, H_6), 3.35 (t, *J* = 7.1, 2H, H_5), 3.24 (t, *J* = 7.7, 2H, H_3), 1.84 (p, *J* = 7.3, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.99 (C-15), 167.99 (C-2), 142.12 (C-16), 140.09 (C-8), 130.16 (C-19), 128.65 (C-11), 128.33 (C-10), 127.89 (C-9), 127.30 (C-18), 125.73 (C-17), 109.72 (C-7), 87.63 (C-14), 64.91 (C-12 and C-13), 55.08 (C-5), 54.58 (C-6), 33.43 (C-3), 21.46 (C-4).

HRMS: Found M^+ = 349.1672, $C_{22}H_{23}NO_3$ requires 349.1678

6.2.10 Synthesis of (*E*)-1-(3,4-dimethoxyphenyl)-2-(1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]methyl}-2-pyrrolidinylidene)-1-ethanone [224B]



[224B]

1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]-methyl}-2-pyrrolidinethione [223B] (0.173 g, 0.53 mmol) was added to a stirring solution of 2-bromo-1-(3,4-dimethoxyphenyl)-1-ethanone [210] (0.143 g, 0.55 mmol) in dry MeCN (5 cm^3) under N_2. After 18 hours, a solution of $P(OEt)_3$ (100 µL, 0.096 g, 0.58mmol) and Et_3N (80 µL, 0.059 g, 0.58 mmol) in dry MeCN (2 cm^3) was added and stirring was continued for an additional 2 hours. The solvent was evaporated and taken into CH_2Cl_2 (30 cm^3) and washed with H_2O (2 × 50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a yellow gum. Column chromatography (EtOAc) afforded (*E*)-1-(3,4-dimethoxyphenyl)-2-(1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]-methyl}-2-pyrrolidinylidene)-1-ethanone [224B] (0.173 g, 0.37 mmol, 70% yield) as a yellow gum.

R_f (EtOAc): 0.19

IR (ν/cm^{-1}): 2961 (m, C-H stretch), 2899 (w), 1615 (m, C=O stretch), 1576 (m), 1527 (s), 1468 (s), 1339 (m), 1300 (m), 1258 (s, C-O stretch), 1044 (m).

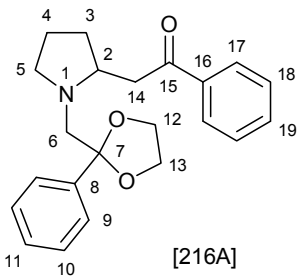
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 1.4, 1H, H_{21}), 7.42 (dd, J = 1.4, 8.3, 1H, H_{25}), 7.07 (dd, J = 1.7, 8.2, 1H, H_{13}), 7.02 (d, J = 1.5, 1H, H_9), 6.86 (d, J = 8.3, 2H, H_{24}), 6.85 (d, J = 8.2, 1H, H_{12}), 5.95 (s, 1H, H_{18}), 4.09 - 4.02 (m, 2H, $H_{14'}$ and $H_{15'}$), 3.94 (s, 3H, H_{26}*), 3.92 (s, 3H, $H_{16}$$^{\#}$), 3.89-3.82 (obscured m, 2H, $H_{14''}$ and $H_{15''}$), 3.87 (s, 3H, H_{27}*), 3.84 (s, 3H, $H_{17}$$^{\#}$), 3.66 (s, 2H, H_6), 3.38 (t, J = 7.2, 2H, H_5), 3.31 (t, J = 7.7, 2H, H_3), 1.90 (p, J = 7.5, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.68 (C-19), 167.41 (C-2), 150.79 (C-23), 149.11 (C-22), 148.74 (C-10), 148.41 (C-11), 134.96 (C-20), 132.48 (C-8), 120.30 (C-25), 118.08 (C-13), 110.75 (C-24), 110.32 (C-21), 109.70 (C-12), 109.50 (C-7), 108.86 (C-9), 87.02 (C-18), 64.73 (C-14 and C-15), 55.81 (C-16*), 55.76 (C-17*), 55.73 (C-26*), 55.64 (C-27*), 55.11 (C-5), 54.36 (C-6), 33.19 (C-3), 21.39 (C-4).

Assignments denoted by * and $^{\#}$ are interchangeable.

HRMS: Found M^+ = 469.2110, $C_{26}H_{31}NO_7$ requires 469.2098

6.2.11 Synthesis of 1-phenyl-2-{1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrro-lidinyl}-1-ethanone [216A]



[216A]

(*E*)-1-Phenyl-2-{1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrro-lidinylidene}-1-ethanone [224A] (0.204 g, 0.58 mmol) was added to dry THF (5 cm^3) and cooled to 0 °C with stirring under N_2. $LiAlH_4$ (95% purity, 0.023 g, 0.58 mmol) was added in one portion. After 10 minutes, EtOAc (1 cm^3) was added followed by H_2O (1 cm^3). The reaction mixture was filtered through a small SiO_2 pad and the pad was washed with 60% EtOAc/hexane. Evaporation of the solvents afforded 1-

phenyl-2-{1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinyl}-1-ethanone [216A] (0.200 g, 0.57 mmol, 98% yield) as a yellow gum.

R_f (60% EtOAc/hexane): 0.50

IR (ν/cm^{-1}): 2950 (w, C-H stretch), 2887 (w), 1677 (br m, C=O stretch), 1597 (w), 1578 (w), 1538 (w), 1477 (m), 1278 (br s, C-O stretch), 1025 (s).

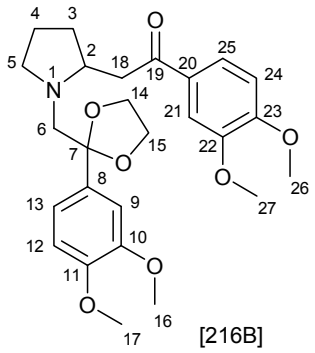
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.5, 2H, H_{17}), 7.59 – 7.28 (m, 8H, H_9, H_{10}, H_{11}, H_{18} and H_{19}), 4.19 – 3.93 (m, 2H, $H_{12'}$ and $H_{13'}$), 3.88 – 3.72 (m, 2H, $H_{12''}$ and $H_{13''}$), 3.23 – 3.13 (m, 1H, $H_{5'}$), 3.13 – 2.98 (m, 2H, H_2 and $H_{14'}$), 3.09 (d, J = 13.9, 1H, $H_{6'}$), 2.83 (d, J = 14.0, 1H, $H_{6''}$), 2.65 (dd, J = 9.1, 16.4, 1H, $H_{14''}$), 2.39 (q, J = 8.4, 1H, $H_{5''}$), 2.00 (ddd, J = 7.5, 12.5, 16.1, 1H, $H_{3'}$), 1.81 – 1.60 (m, 2H, H_4), 1.44 – 1.27 (m, 1H, $H_{3''}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.89 (C-15), 141.90 (C-16), 137.27 (C-8), 132.83 (C-11 and C-19), 128.43 (C-10), 128.07 (C-9), 127.78 (C-18), 126.24 (C-17), 110.08 (C-7), 64.76 (C-12*), 64.42 (C-13*), 62.43 (C-6), 61.28 (C-2), 55.61 (C-5), 44.42 (C-14), 30.95 (C-3), 23.42 (C-4).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 351.1861, $C_{22}H_{25}NO_3$ requires 351.1834

6.2.12 Synthesis of 1-(3,4-dimethoxyphenyl)-2-(1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]methyl}-2-pyrrolidinyl)-1-ethanone [216B]



[216B]

(*E*)-1-(3,4-Dimethoxyphenyl)-2-(1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]-methyl}-2-pyrrolidinylidene)-1-ethanone [224B] (0.173 g, 0.37 mmol) was added to dry THF (20 cm^3) and cooled to -10 °C with stirring under N_2. $LiAlH_4$ (95% pure, 0.015 g, 0.39 mmol) was added and stirring was continued for an additional 30 minutes. The cooling bath was removed and stirring was continued for an additional 5 minutes at room temperature. EtOAc (2.00 cm^3) was added followed by H_2O (0.50 cm^3). Additional EtOAc (20 cm^3) was added and the reaction mixture was dried over $MgSO_4$, filtered and evaporated to give an orange gum. The gum was filtered through a Pasteur pipette silica gel column (EtOAc) to afford 1-(3,4-dimethoxyphenyl)-2-(1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]-methyl}-2-pyrrolidinyl)-1-ethanone [216B] (0.170 g, 0.36 mmol, 97% yield) as an orange gum.

IR (ν/cm^{-1}): 2964, 2891 and 2862 (w, C-H stretch), 1671 (s, C=O stretch), 1586 (m), 1513 (s), 1257 (s, C-O stretch), 1238 (s), 1128 (s), 1020 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.42 (m, 2H, H_{21} and H_{25}), 7.09 – 6.98 (m, 2H, H_9 and H_{13}), 6.88 (d, J = 8.9, 1H, H_{24}), 6.82 (d, J = 8.9, 1H, H_{12}), 4.14 – 4.00 (m, 2H, $H_{14'}$ and $H_{15'}$), 3.94 (s, 3H, H_{26}*), 3.92 (s, 3H, H_{27}*), 3.88 (s, 3H, H_{16}*), 3.87 (s, 3H, H_{17}*), 3.86 – 3.77 (m, 2H, $H_{14''}$ and $H_{15''}$), 3.23 – 3.14 (m, 1H, $H_{5'}$), 3.13 – 3.04 (obscured m, 1H, H_2), 3.09 (d, J = 14.0, 1H, $H_{6'}$), 3.03 (dd, J = 2.8, 15.9, 1H, $H_{18'}$), 2.82 (d, J = 14.0, 1H, $H_{6''}$), 2.69 (dd, J = 9.1, 15.9, 1H, $H_{18''}$), 2.38 (q, J = 8.3, 1H, $H_{5''}$), 2.07 – 1.90 (m, 1H, $H_{3'}$), 1.82 – 1.60 (m, 2H, H_4), 1.38 (ddt, J = 6.1, 8.1, 12.5, 1H, $H_{3''}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 198.25 (C-19), 152.97 (C-23), 148.79 (C-22), 148.48 (C-10), 148.28 (C-11), 134.38 (C-20), 130.45 (C-8), 122.65 (C-25),

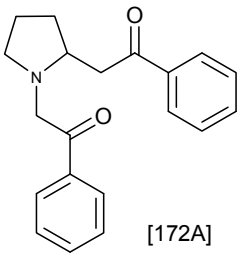
118.36 (C-18), 110.27 (C-24), 109.89 (C-21), 109.81 (C-12), 109.77 (C-7), 109.53 (C-9), 64.55 (C-14*), 64.25 (C-15*), 62.28 (C-6), 61.44 (C-2), 55.88 (C-16#), 55.76 (C-17# and C-26#), 55.69 (C-27#), 55.46 (C-5), 43.73 (C-18), 30.75 (C-3), 23.26 (C-4).

Assignments denoted by * and # are interchangeable.

HRMS: found M^+ = 471.2250, $C_{26}H_{33}NO_7$ requires 471.2257

6.2.14 Attempted synthesis of 2-[1-(2-oxo-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [172A]

Method 1:



[172A]

Adapted by modification of a known literature procedure.[185] 1-Phenyl-2-{1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinyl}-1-ethanone [216A] (0.156 g, 0.44 mmol) was added to a stirring solution of EtOH (4.00 cm^3) containing concentrated HCl (3 drops) and H_2O (0.50 cm^3) under N_2. After 5 minutes the solution became milky and stirring was continued for an additional 18 hours at room temperature. The reaction mixture was poured into H_2O (10 cm^3) and basified with an aqueous solution of 1M NaOH (10 cm^3) and then extracted with CH_2Cl_2 (3 × 10 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford starting material (0.154 g, 99% recovery) as an orange gum.

Method 2:

Adapted by modification of a known literature procedure.[186] 1-Phenyl-2-{1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinyl}-1-ethanone [216A] (0.154 g, 0.44 mmol) was added to a stirring solution of AcOH (4.00 cm^3) containing concentrated H_2SO_4 (5 drops) under N_2. After 18 hours at room temperature, the reaction mixture was poured into H_2O (10 cm^3) and basified with an

aqueous solution of 1M NaOH (10 cm^3) and then extracted with CH_2Cl_2 (2 × 10 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford starting material (0.152 g, 99% recovery) as an orange oil.

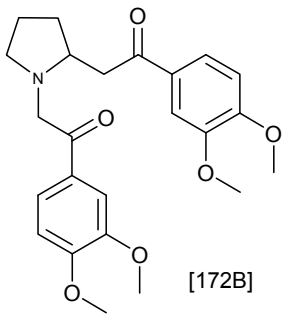
Method 3:

Adapted by modification of a known literature procedure.[187] 1-Phenyl-2-{1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinyl}-1-ethanone [216A] (0.152 g, 0.44 mmol) was added to a stirring solution of acetone (5.00 cm^3) containing *p*-TsOH (0.008 g, 0.04 mmol) and H_2O (1.00 cm^3) under N_2. The reaction mixture was heated at reflux for 18 hours. The reaction mixture was poured into H_2O (10 cm^3) and basified with an aqueous solution of 1M NaOH (10 cm^3) and then extracted with CH_2Cl_2 (3 × 10 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford starting material (0.148 g, 95% recovery) as a dark red gum.

Method 4:

Adapted by modification of a known literature procedure.[188] 1-Phenyl-2-{1-[(2-phenyl-1,3-dioxolan-2-yl)methyl]-2-pyrrolidinyl}-1-ethanone [216A] (0.140 g, 0.40 mmol) was added to a stirring aqueous solution of 2M HCl (4 cm^3) and heated at 80 °C for 24 hours under N_2. The reaction mixture was poured into H_2O (10 cm^3) and basified with an aqueous solution of 1M NaOH (10 cm^3) and then extracted with CH_2Cl_2 (3 × 10 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford starting material (0.049 g, 35% recovery).

6.2.15 Attempted synthesis of 1-(3,4-dimethoxyphenyl)-2-{1-[2-(3,4-dimeth-oxyphenyl)-2-oxoethyl]-2-pyrrolidinyl}-1-ethanone [172B]



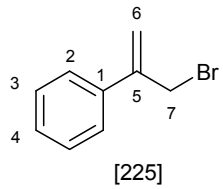
[172B]

The experimental procedure was adapted from a literature procedure.[189] 1-(3,4-Dimethoxyphenyl)-2-(1-{[2-(3,4-dimethoxyphenyl)-1,3-dioxolan-2-yl]-methyl}-2-pyrro-lidinyl)-1-ethanone [216B] (0.040 g, 0.09 mmol) was added to a stirring solution of aqueous borate–HCl buffer (pH 8.00, 1.00 cm^3) in MeCN (1.00 cm^3) under N_2. CAN (0.002 g, 0.003 mmol) was added and the reaction mixture was heated at 60 °C for 30 minutes. TLC analysis showed no apparent reaction had occurred. The reaction was abandoned.

6.2 Experimental procedures for the *N*-(2-phenylallyl) strategy

6.3.1 Synthesis of [1-(bromomethyl)vinyl]benzene [225]

Under thermal conditions:



[225]

This synthesis of this compound was a modification of a literature procedure.[190] α-Methylstyrene (18.20 g, 154.00 mmol) was added to a solution of NBS (20.00 g, 112.37 mmol) and AIBN (10 mg) in CCl_4 (20 cm^3) under N_2. The reaction mixture was slowly heated to *ca*. 200 °C. Rapid effervescence of the solution was noted at 90 °C. As no discernable reaction was occurring at this temperature benzoyl peroxide (20 mg) was added. After 90 minutes a very vigorous and exothermic reaction occurred. The reaction mixture was allowed to cool to room temperature over 2 hours. Ice-cold pentane (100 cm^3) was added to precipitate most of the succinimide by-product. The solution was filtered and evaporated (atmospheric pressure and a bath temperature of 50

°C) to remove most of the pentane. At this stage, more solids precipitated which were filtered. Finally, the solvents were removed to afford a red oil. Vacuum distillation (13 mmHg) afforded a fore-run of α-methylstyrene (72-76 °C) and an impure fraction of [1-(bromomethyl)vinyl]benzene [225] (126-132 °C). The crude product was further purified by column chromatography (hexane) to afford [1-(bromomethyl)vinyl]benzene [225] (10.63 g, 53.95 mmol, 48% yield) as a yellow oil. The oil is a lachrymator and was used immediately upon isolation.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.43 (m, 2H, H_2), 7.42 – 7.31 (m, 3H, H_3 and H_4), 5.55 (s, 1H, $H_{6'}$), 5.49 (s, 1H, $H_{6''}$), 4.38 (s, 2H, H_7).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.28 (C-5), 137.61 (C-1), 128.49 (C-3), 128.25 (C-4), 126.09 (C-2), 117.17 (C-6), 34.17 (C-7).

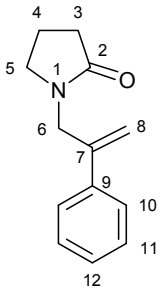
Other spectroscopic data agreed with the literature.[194]

Under microwave irradiation conditions:

α-Methylstyrene (5.88 g, 49.75 mmol) was added to NBS (6.12 g, 34.39 mmol) in a round bottom flask attached to a reflux condenser. The reaction was subjected to micro-wave irradiation (150W, 160 °C) for 10 minutes. The black gum was filtered through a short pad of silica (hexane) to afford [1-(bromomethyl)vinyl]benzene [225] (2.77 g, 14.06 mmol, 41% yield) as a pale yellow oil. The spectroscopic data matched those given above.

6.3.2 Synthesis of 1-(2-phenyl-2-propenyl)-2-pyrrolidinone [226]

From 2-pyrrolidinone:



[226]

NaH (60% dispersion in oil, 0.960 g, 24.00 mmol) was added to a stirring solution of 2-pyrrolidinone (1.702 g, 20.00 mmol) in dry DMF (50 cm^3) under argon. The solution was warmed to 60 °C and stirred for a further 1 hour. The solution was cooled to 0 °C and [1-(bromomethyl)vinyl]benzene [225] (4.730 g, 24.00 mmol) in dry DMF (10 cm^3) was added drop-wise. The reaction mixture was allowed to warm to room temperature and then heated at 60 °C for 3 hours. The solvent was evaporated and the residue was taken up into EtOAc (100 cm^3) and washed with H_2O (4 × 50 cm^3) and brine (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a yellow oil. Column chromatography (80% EtOAc/hexane) afforded 1-(2-phenyl-2-propenyl)-2-pyrrolidinone [226] (3.783 g, 18.80 mmol, 94% yield) as a pale-yellow oil.

R_f (80% EtOAc/hexane): 0.25

IR (ν/cm^{-1}): 3030 and 2917 (w, C-H stretch), 1658 (br s), 1576 (m), 1494 (m), 1463 (m), 1446 (m), 1310 (m), 1286 (m), 1070 9m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H, H_{10}), 7.37 – 7.23 (m, 3H, H_{11} and H_{12}), 5.51 (s, 1H, $H_{8'}$), 5.19 (d, J = 0.9, 1H, $H_{8''}$), 4.35 (s, 2H, H_6), 3.21 (t, J = 7.1, 2H, H_5), 2.31 (t, J = 8.1, 2H, H_3), 1.96 – 1.77 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.61 (C-2), 142.93 (C-7), 137.81 (C-9), 128.30 (C-11), 127.89 (C-12), 125.92 (C-10), 114.72 (C-8), 46.29 (C-5*), 46.26 (C-6*), 30.77 (C-3), 17.57 (C-4).

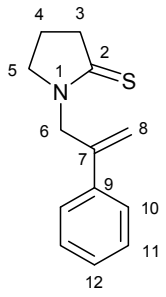
Note: assignments denoted by * are interchangeable.

HRMS: Found M^+ = 201.1152, $C_{13}H_{15}NO$ requires 211.1154

By Wittig olefination of compound [175A]:

Methyltriphenylphosphonium bromide (1.072 g, 3.00 mmol) in dry THF (20 cm^3) was stirred and cooled to –10 °C under argon. ^{n}BuLi (1.6M, 1.84 cm^3, 2.95 mmol) was added and stirring was continued for 10 minutes at –10 °C. The cooling bath was removed and stirring was continued at room temperature for 1 hour. The reaction mixture was re-cooled to –10 °C and 1-(2-oxo-2-phenylethyl)-2-pyrrolidinone [175A] (0.500 g, 2.46 mmol) in THF (5.00 cm^3) was added drop-wise. Stirring at –10 °C for 30 minutes was followed by stirring at room temperature for 40 hours. H_2O (50 cm^3) was added followed by extraction with EtOAc (150 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a red oil. Column chromatography (80% EtOAc/hexane) afforded 1-(2-phenyl-2-propenyl)-2-pyrrolidinone [226] (0.222 g, 1.18 mmol, 48% yield) as a yellow oil. The spectroscopic data matched those reported above.

6.3.4 Synthesis of 1-(2-phenyl-2-propenyl)-2-pyrrolidinethione [228]



[228]

1-(2-phenyl-2-propenyl)-2-pyrrolidinone [226] (3.000 g, 14.91 mmol) was added to a stirring solution of Lawesson's reagent (3.135 g, 7.75 mmol) in dry toluene (50 cm^3) under Ar. The reaction mixture was warmed to 60 °C and stirred for a further 15 hours. Evaporation of the solvent gave a yellow gum. Column chromatography (20% EtOAc/hexane) afforded 1-(2-phenylprop-2-en-1-yl)pyrrolidine-2-thione [228] (2.727 g, 12.55 mmol, 84% yield) as a pale-yellow oil.

R_f (20% EtOAc/hexane): 0.23

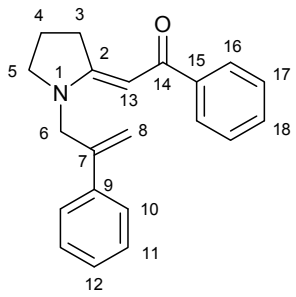
IR (ν/cm^{-1}): 3055 and 2916 (w, C-H stretch), 1599 (w), 1574 (w), 1496 (br s), 1464 (m), 1448 (m), 1235 (m), 1119 (m, C=S stretch), 1028 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.41 (m, 2H, H_{10}), 7.39 – 7.24 (m, 3H, H_{11} and H_{12}), 5.58 (s, 1H, $H_{8'}$), 5.24 (s, 1H, $H_{8''}$), 4.86 (s, 2H, H_6), 3.53 (t, J = 7.3, 2H, H_5), 2.97 (t, J = 7.9, 2H, H_3), 1.99 – 1.79 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 201.62 (C-2), 141.79 (C-7), 137.27 (C-9), 128.41 (C-11), 128.17 (C-12), 125.88 (C-10), 115.64 (C-8), 53.50 (C-6), 51.43 (C-5), 44.66 (C-3), 19.31 (C-4).

HRMS: Found M^+ = 217.0923, $C_{13}H_{15}NS$ requires 217.0925

6.3.5 Synthesis of (*E*)-1-phenyl-2-[1-(2-phenyl-2-propenyl)-2-pyrrolidin-ylidene]-1-ethanone [229]



[229]

1-(2-phenylprop-2-en-1-yl)pyrrolidine-2-thione [228] (4.266 g, 19.63 mmol) was added to a stirring solution of 2-bromo-1-phenylethanone (4.298 g, 21.59 mmol) in dry MeCN (20 cm^3) under Ar. The gum that formed was briefly warmed to homogenize the solution, thereafter stirring was continued at room temperature for 3 hours. A solution of PPh_3 (5.663, 21.59 mmol) and Et_3N (3.31 cm^3, 2.384 g, 23.56 mmol) in dry MeCN (20 cm^3) was added drop-wise and stirring was continued for 18 hours. The solvent was evaporated and the residue was taken up into EtOAc (200 cm^3) and washed with H_2O (3 × 100 cm^3) and brine (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange gum. Column chromatography (40% EtOAc/hexane) afforded (*E*)-1-phenyl-2-[1-(2-phenyl-2-propenyl)-2-pyrrolidin-ylidene]-1-ethanone [229] (5.419 g, 17.86 mmol, 91% yield) as a yellow solid.

R_f (40% EtOAc/hexane): 0.30

M.p: 62 – 63 °C

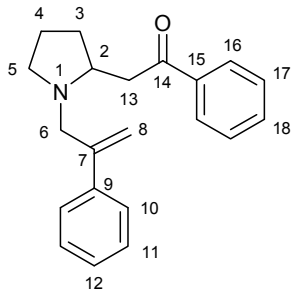
IR (ν/cm^{-1}): 2888 (w), 1611 (m, C=O stretch), 1596 (m), 1575 (m), 1530 (br s), 1469 (s), 1289 (m), 1086 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.5, 2H, H_{10} and H_{16}), 7.47 – 7.27 (m, 8H, H_{11}, H_{12}, H_{16}, H_{17} and H_{18}), 5.83 (s, 1H, H_{13}), 5.52 (s, 1H, $H_{8'}$), 5.14 (s, 1H, $H_{8''}$), 4.31 (s, 2H, H_6), 3.43 (t, J = 7.7, 2H, H_5), 3.42 (t, J = 7.1, 2H, H_3) 2.09 – 1.88 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.93 (C-14), 167.22 (C-2), 141.96 (C-7), 140.82 (C-9), 138.55 (C-15), 130.30 (C-18), 128.60 (C-11), 128.22 (C-12), 127.99 (C-16), 127.21 (C-17), 125.90 (C-10), 113.99 (C-8), 87.08 (C-13), 52.61 (C-6), 50.52 (C-5), 33.70 (C-3), 21.03 (C-4).

HRMS: Found M^+ = 303.1618, $C_{21}H_{21}NO$ requires 303.1623

6.3.6 Synthesis of 1-phenyl-2-[1-(2-phenyl-2-propenyl)-2-pyrrolidinyl]-1-ethanone [230]



[230]

(*E*)-1-phenyl-2-[1-(2-phenyl-2-propenyl)-2-pyrrolidinylidene]-1-ethanone [229] (1.368 g, 4.51 mmol) was added to dry THF (50 cm^3) and stirred at 0 °C under Ar. $LiAlH_4$ (95%, 0.189 g, 4.74 mmol) was added and stirring was continued for 30 minutes. The reaction was carefully quenched with H_2O (2 cm^3) and the solvent was evaporated. The residue was taken up into EtOAc (100 cm^3) and washed with H_2O (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a yellow oil. Column chromatography (20% EtOAc/hexane) afforded 1-phenyl-2-[1-(2-phenyl-2-propenyl)-2-pyrrolidinyl]-1-ethanone [230] (1.183 g, 3.87 mmol, 86% yield) as a pale-yellow oil.

R_f (20% EtOAc/hexane): 0.27

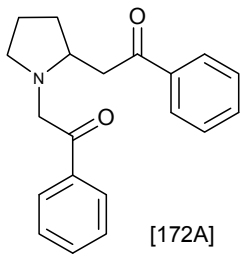
IR (ν/cm^{-1}): 3057 and 2951 (w, C-H stretch), 1679 (br s), 1597 (m), 1578 (m), 1447 (m), 1210 (m), 1000 (br m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 7.4, 2H, H_{16}), 7.60 – 7.38 (m, 5H, H_{10}, H_{11}, and H_{18}), 7.37 – 7.20 (m, 3H, H_{12} and H_{17}), 5.40 (s, 1H, $H_{8'}$), 5.28 (s, 1H, $H_{8''}$), 3.84 (d, J = 13.5, 1H, $H_{6'}$), 3.34 (dd, J = 3.7, 16.0, 1H, $H_{13'}$), 3.23 (d, J = 13.5, 1H, $H_{6''}$), 3.15 – 2.98 (m, 2H, H_2 and $H_{5'}$), 2.92 (dd, J = 8.8, 16.0, 1H, $H_{13'}$), 2.23 (q, J = 8.7, 1H, $H_{5''}$), 2.09 (ddd, J = 7.9, 12.8, 16.0, 1H, $H_{3'}$), 1.78 – 1.61 (m, 2H, H_4), 1.47 (ddt, J = 6.4, 8.5, 12.9, 1H, $H_{3''}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.78 (C-14), 145.95 (C-7), 140.45 (C-9), 137.31 (C-15), 132.94 (C-18), 128.53 (C-11), 128.13 (C-16), 128.09 (C-17), 127.43 (C-12), 126.25 (C-10), 114.75 (C-8), 60.86 (C-2), 59.31 (C-6), 53.89 (C-5), 44.19 (C-13), 31.39 (C-3), 22.53 (C-4).

HRMS: Found M^+ = 305.1792, $C_{21}H_{23}NO$ requires 305.1780

6.3.7 Attempted synthesis of 2-[1-(2-oxo-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [172A]



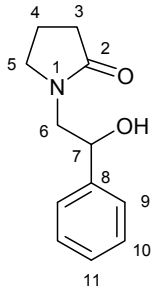
[172A]

Acetyl chloride (1.10 cm^3, 1.198 g, 15.26 mmol) was cautiously added to MeOH (50 cm^3) and stirred for 1 hour under Ar. 1-Phenyl-2-[1-(2-phenyl-2-propenyl)-2-pyrrolidinyl]-1-ethanone [230] (0.666 g, 2.18 mmol) was added to the above solution and cooled to –78 °C. The reaction mixture was ozonolyzed until the solution became blue. The reaction mixture was purged with O_2 for 5 minutes and then treated with Me_2S (0.32 cm^3, 0.271 g, 8.72 mmol). After stirring at room temperature for 18 hours the reaction was carefully quenched with a saturated solution of Na_2CO_3. Evaporation of most of the solvent gave an aqueous solution that was taken into EtOAc (100 cm^3) and washed with H_2O (2 × 50 cm^3) and brine (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an

orange oil (0.725 g). Column chromatography (20% MeOH/EtOAc) gave a red oil that could not be characterized by ^{1}H NMR spectroscopy.

6.3 Experimental procedures for the oxidation of a remote secondary alcohol strategy

6.4.1 Synthesis of 1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinone [231]



[231]

This compound was synthesized according to a known literature procedure.[136] 1-(2-Oxo-2-phenylethyl)-2-pyrrolidinone [175A] (11.00 g, 54.12 mmol) was added to EtOH (75 cm^3) and cooled to –10 °C with stirring under N_2. $NaBH_4$ (2.047 g, 54.12 mmol) was added in several portions to the reaction mixture. The reaction was allowed to warm to room temperature and then stirred for an additional 18 hours. A saturated solution of NH_4Cl (25 cm^3) was cautiously added followed by H_2O (25 cm^3). The aqueous solution was extracted with EtOAc (200 cm^3, 2 × 50 cm^3). The organic extracts were dried over $MgSO_4$, filtered and evaporated to give a yellow sludge. Solidification was induced by triturating with 20% EtOAc/hexane. The solid was filtered and dried under vacuum to afford 1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinone [231] (10.24 g, 49.89 mmol, 92% yield) as a white solid.

R_f (EtOAc): 0.29 with streaking

M.p: 116 – 117 °C (50% EtOAc/hexane), [lit.,[136] 117 – 118 °C (50% EtOAc/hexane)]

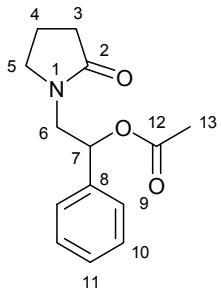
IR (ν/cm^{-1}): 3214 (br, m, OH), 2981, 2959 and 2910 (w, C-H stretch), 1645 (s, lactam C=O), 1491 (m), 1419 (m), 1279 (m), 1241 (m), 1062 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.22 (m, 5H, H_9, H_{10} and H_{11}), 4.95 (q, *J* = 5.3, 1H, H_7), 4.17 (d, *J* = 4.5, 1H, OH), 3.52 (d, *J* = 5.5, 2H, H_6), 3.32 (ddd, *J* = 6.5, 7.7, 9.6, 1H, $H_{5'}$), 3.20 (ddd, *J* = 6.2, 7.8, 9.6, 1H, $H_{5''}$), 2.37 (t, *J* = 8.1, 2H, H_3), 2.02 – 1.88 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.09 (C-2), 142.00 (C-8), 128.38 (C-10), 127.64 (C-11), 125.72 (C-9), 73.15 (C-7), 51.90 (C-6), 49.46 (C-5), 30.79 (C-3), 18.35 (C-4).

HRMS: Found M^+ = 205.1116, $C_{12}H_{15}NO_2$ requires 205.1103

6.4.2 Synthesis of 2-(2-oxo-1-pyrrolidinyl)-1-phenylethyl acetate [232]



[232]

1-(2-Hydroxy-2-phenylethyl)-2-pyrrolidinone [231] (10.24 g, 49.89 mmol) was dissolved in CH_2Cl_2 (100 cm^3) and cooled to 0 °C under N_2. Pyridine (4.85 cm^3, 4.736 g, 59.87 mmol) was added and stirring was continued for 2 minutes. Acetic anhydride (5.65 cm^3, 6.112 g, 59.87 mmol) was added drop-wise over 10 minutes. After 2 hours DMAP (0.201 g, 1.65 mmol) was added and stirring was continued at room temperature for 20 hours. The reaction mixture was washed with a saturated solution of NH_4Cl (50 cm^3), 0.5M HCl (2 × 50 cm^3), H_2O (50 cm^3) and brine (2 × 50 cm^3) successively. The organic extract was dried over $MgSO_4$, filtered and evaporated to afford 2-(2-oxo-1-pyrrolidinyl)-1-phenylethyl acetate [232] (11.86 g, 47.96 mmol, 96% yield) as a yellow oil.

R_f (EtOAc): 0.41

IR (ν/cm^{-1}): 2991, 2972, 2931 and 2907(w, C-H stretch), 1737 (s, ester C=O), 1671 (s, lactam C=O), 1492 (m), 1377 (m), 1350 (m), 1219 (s), 1020 (s).

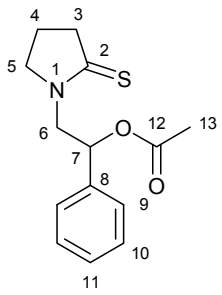
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H, H_9, H_{10} and H_{11}), 5.97 (dd, *J* = 4.1, 8.8, 1H, H_7), 3.85 (dd, *J* = 8.8, 14.3, 1H, $H_{6'}$), 3.47-3.37 (m, 1H, $H_{5'}$),

3.43 (dd, J = 4.0, 14.2, 2H, $H_{6"}$), 3.32 (dt, J = 7.0, 9.3, 1H, $H_{5"}$), 2.33 (t, J = 8.1, 2H, H_3), 2.09 (s, 3H, H_{13}), 2.03 – 1.90 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.42 (C-2), 170.11 (C-12), 137.64 (C-8), 128.61 (C-10), 128.46 (C-11), 126.53 (C-90, 73.07 (C-7), 48.03 (C-6), 47.81 (C-5), 30.68 (C-3), 21.15 (C-13), 18.19 (C-4).

HRMS: Found M^+ = 247.1208, $C_{14}H_{17}NO_3$ requires 247.1208

6.4.3 Synthesis of 1-phenyl-2-(2-thioxo-1-pyrrolidinyl)ethyl acetate [233]



[233]

2-(2-Oxo-1-pyrrolidinyl)-1-phenylethyl acetate [232] (3.766 g, 15.23 mmol) was added to a stirring solution of Lawesson's reagent (3.203 g, 7.92 mmol) in dry toluene (50 cm^3) under N_2. The reaction mixture was heated at 80 °C for 18 hours. The solvent was evaporated to give a yellow gum. Column chromatography (30% EtOAc/hexane) afforded 1-phenyl-2-(2-thioxo-1-pyrrolidinyl)ethyl acetate [233] (3.608 g, 13.70 mmol, 90% yield) as a yellow oil.

R_f (30% EtOAc/hexane): 0.18

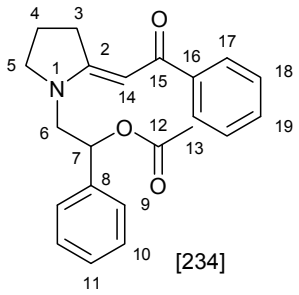
IR (ν/cm^{-1}): 3033, 2929 and 2886 (w, C-H stretch) 1740 (s, ester C=O stretch), 1503 (s, N-C=S stretch), 1452 (m), 1276 (m), 1229 (s, C-O stretch), 1122 (s, C=S stretch), 1043 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.28 (m, 5H, H_9, H_{10} and H_{11}), 6.21 (dd, J = 4.0, 9.0, 1H, H_7), 4.22 (dd, J = 9.1, 13.8, 1H, $H_{6'}$), 3.98 (dd, J = 4.0, 13.8, 1H, $H_{6"}$), 3.76 – 3.60 (m, 2H, H_5), 3.00 (t, J = 7.8, 2H, H_3), 2.10 (s, 3H, H_{13}), 2.07 – 1.91 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.84 (C-2), 169.87 (C-12), 137.40 (C-8), 128.70 (C-10), 128.60 (C-11), 126.29 (C-9), 72.63 (C-7), 56.14 (C-6), 52.91 (C-5), 44.79 (C-3), 21.21 (C-4), 20.07 (C-13).

HRMS: Found M^+ = 263.0971, $C_{14}H_{17}NO_2S$ requires 263.0980

6.4.4 Synthesis of 2-{2-[(E)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}-1-phenylethyl acetate [234]



[234]

1-Phenyl-2-(2-thioxo-1-pyrrolidinyl)ethyl acetate [233] (3.530 g, 13.40 mmol) was added to a stirring solution of phenacyl bromide (2.934 g, 14.74 mmol) in dry MeCN (10 cm^3) under N_2. Salt completion took place within 5 hours. A solution of $P(OEt)_3$ (2.41 cm^3, 2.338 g, 14.07 mmol) and Et_3N (1.98 cm^3, 1.424 g, 14.07 mmol) in dry MeCN (10 cm^3) was added drop-wise. Stirring was continued for 18 hours. The solvent was evaporated and the residue was taken up into EtOAc (100 cm^3) and washed with H_2O (4 × 50 cm^3) and brine (25 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange gum. Column chromatography (50% EtOAc/hexane) afforded an orange oil. EtOAc (25 cm^3) was added and the crude product was stirred at 0 °C for 1 hour. Hexane (75 cm^3) was then added and stirring was continued for an additional 1 hour. The solid was filtered and dried under vacuum to afford 2-{2-[(*E*)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}-1-phenylethyl acetate [234] (4.245 g, 12.15 mmol, 91% yield) as a white solid.

R_f (50% EtOAc/hexane): 0.29

M.p: 74 – 76 °C

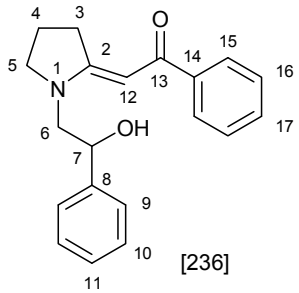
IR (ν/cm^{-1}): 2945 and 2869 (w, C-H stretch), 1733 (m, ester C=O stretch), 1620 (m, enaminone C=O stretch), 1608 (m, C=C stretch), 1578 (m), 1531 (s), 1173 (s), 1020 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.88 (m, 2H, H_{17}), 7.44 – 7.28 (m, 8H, H_9, H_{10}, H_{11}, H_{18} and H_{19}), 6.09 (dd, J = 5.6, 7.6, 1H, H_7), 5.97 (s, 1H, H_{14}), 3.86 (dd, J = 7.6, 14.4, 1H, $H_{6'}$), 3.45 (dd, J = 5.7, 14.5, 1H, $H_{6''}$), 3.35 (t, J = 7.7, 2H, H_3), 3.27 (dt, J = 7.3, 9.9, 1H, $H_{5'}$), 3.16 (ddd, J = 6.4, 7.8, 9.8, 1H, $H_{5''}$), 2.06 (s, 3H, H_{13}), 1.96 – 1.78 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.51 (C-15), 169.74 (C-12), 167.14 (C-2), 141.59 (C-8), 137.39 (C-16), 130.24 (C-19), 128.64 (C-10), 128.59 (C-11), 127.89 (C-9), 127.06 (C-17), 126.25 (C-18), 86.87 (C-14), 71.91 (C-7), 53.47 (C-5), 51.69 (C-6), 33.40 (C-3), 21.05 (C-4), 20.94 (C-13).

HRMS: Found M^+ = 349.1685, $C_{22}H_{23}NO_3$ requires 349.1678

6.4.5 Synthesis of (*E*)-2-[1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinylidene]-1-phenyl-1-ethanone [236]



[236]

2-{2-[(*E*)-2-Oxo-2-phenylethylidene]-1-pyrrolidinyl}-1-phenylethyl acetate [234] (1.000 g, 2.86 mmol) was added to a stirring solution of K_2CO_3 (0.415 g, 3.00 mmol) in dry MeOH (25 cm^3) under N_2. After 18 hours the solvent was evaporated and the residue was taken up into EtOAc (50 cm^3) and washed with H_2O (2 × 30 cm^3) and brine (25 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange glass. Et_2O was added and vigorously stirred for 5 minutes to induce precipitation of a white solid. The solvent was evaporated to afford 2-[1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinylidene]-1-

phenyl-1-ethanone [236] (0.874 g, 2.84 mmol, 99% yield) as a white amorphous powder.

M.p: 75 – 77 °C

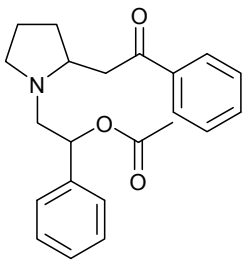
IR (ν/cm^{-1}): 3189 (br, m, OH), 2961, 2921 and 2885 (w, C-H stretch), 1595 (m, enaminone C=O stretch), 1575 (m), 1529 (s), 1221 (s), 1027 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 6.0, 2H, H_{15}), 7.49 – 7.29 (m, 8H, H_9, H_{10}, H_{11}, H_{16}, H_{17}), 5.83 (s, 1H, H_{12}), 5.12 (dd, J = 4.6, 8.1, 1H, H_7), 3.62 (dd, J = 8.1, 14.4, 1H, $H_{6'}$), 3.56 – 3.49 (m, 1H, $H_{5'}$), 3.49 (dd, J = 4.7, 14.4, 1H, $H_{6''}$), 3.38 (td, J = 3.9, 7.8, 2H, H_3), 3.25 (ddd, J = 6.0, 8.1, 10.0, 1H, $H_{5''}$), 3.06 (s, 1H, OH), 2.00 – 1.78 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.59 (C-13), 167.82 (C-2), 141.93 (C-8), 141.87 (C-14), 130.39 (C-17), 128.72 (C-11), 128.18 (C-10), 128.08 (C-90, 127.21 (C-150, 125.78 (C-16), 86.79 (C-12), 71.07 (C-7), 54.70 (C-5), 54.59 (C-6), 33.97 (C-3), 21.04 (C-4).

HRMS: Found M^{+1} = 308.1644, $C_{20}H_{22}NO_2$ requires 308.1651

6.4.6 Attempted synthesis of 2-[2-(2-oxo-2-phenylethyl)-1-pyrrolidinyl]-1-phenylethyl acetate [235]

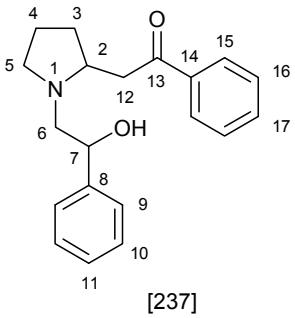


[235]

2-{2-[(*E*)-2-Oxo-2-phenylethylidene]-1-pyrrolidinyl}-1-phenylethyl acetate [234] (0.855 g, 2.56 mmol) was added to a stirring solution of degassed AcOH (50 cm^3) containing PtO_2.×H_2O (0.116 g, 0.51 mmol). The solution was hydrogenated at atmospheric pressure for 24 hours. The solution was filtered through a pad of Celite and the Celite pad was washed with additional AcOH (50 cm^3). The solvent was evaporated and the residue was taken up into EtOAc (50 cm^3) and washed with H_2O (50 cm^3), a saturated solution of Na_2CO_3 (50 cm^3) and

finally with more H_2O (2 × 25 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange gum (0.762 g). Analysis of the crude product could not be assessed by $^1H/^{13}C$ NMR spectroscopy because of the complexity and number of signals present.

6.4.7 Synthesis of 2-[1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [237]



[237]

2-[1-(2-Hydroxy-2-phenylethyl)-2-pyrrolidinylidene]-1-phenyl-1-ethanone [236] (1.573 g, 5.12 mmol) was added to a stirring solution of degassed AcOH (30 cm^3) containing $PtO_2.\times H_2O$ (0.059 g, 0.26 mmol). The reaction was hydrogenated at atmospheric pressure for 22 hours. The solution was filtered through a pad of Celite and the Celite pad was washed with additional AcOH (50 cm^3). The solvent was evaporated and the residue was taken up into EtOAc (50 cm^3) and washed with H_2O (50 cm^3), a saturated solution of Na_2CO_3 (50 cm^3) and finally with more H_2O (2 × 25 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange gum. Column chromatography (2½% MeOH/EtOAc) afforded *ca.* 1:2 diastereomeric mixture of 2-[1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [237] (1.376 g, 4.45 mol, 87% yield) as an orange gum.

R_f (10% MeOH/EtOAc) 0.39

IR (ν/cm^{-1}): 3403 (br, w, OH), 3061, 3029 and 2930 (m, C-H stretch), 1682 (s, C=O stretch), 1597 (w), 1580 (w), 1408 (s), 1205 (s, C-O stretch), 1060 (m).

The ^1H NMR spectrum was very complicated, therefore characterization is offered for the major diastereomer only.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.89 (m, 2H, H_{15}), 7.57 (t, *J* = 7.3, 1H, H_{17}), 7.47 (t, *J* = 7.5, 2H, H_{16}), 7.41 – 7.21 (m, 5H, H_9, H_{10} and H_{11}), 4.70 (dd, *J* = 3.1, 10.8, 1H, H_7), 4.29 – 3.49 (br s, 1H, OH), 3.46 – 3.22 (m, 1H, $H_{5'}$), 3.27 (dd, *J* = 4.0, 13.3, 1H, $H_{12'}$), 3.15 (ddd, *J* = 4.0, 7.6, 15.2, 1H, H_2), 3.07 – 2.88 (m, 2H, $H_{12''}$), 2.77 – 2.65 (m, 1H, $H_{6'}$), 2.52 (dd, *J* = 3.1, 12.1, 1H, $H_{6''}$), 2.35 (q, *J* = 8.6, 1H, $H_{5''}$), 2.24 – 2.06 (m, 1H, $H_{3'}$), 1.91 – 1.71 (m, 2H, H_4), 1.60 – 1.43 (m, 1H, $H_{3''}$).

Major diastereomer:

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.23 (C-13), 142.04 (C-8), 137.18 (C-14), 133.16 (C-17), 128.64 (C-15), 128.31 (C-10), 128.09 (C-16), 127.50 (C-11), 127.3, 125.85 (C-9), 70.42 (C-7), 62.95 (C-6), 60.64 (C-2), 53.20 (C-5), 44.17 (C-12), 31.21 (C-3), 22.89 (C-4).

Minor diastereomer:

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.34 (C-13), 142.88 (C-8), 137.15 (C-14), 133.16 (C-17), 128.64 (C-15), 128.28 (C-10), 128.09 (C-16), 127.31 (C-11), 125.70 (C-9), 71.18 (C-7), 63.10 (C-6), 61.09 (C-2), 55.04 (C-5), 43.86 (C-12), 31.10 (C-3), 23.29 (C-4).

HRMS: Found M^{+1} = 310.1800, $C_{20}H_{24}NO_2$ requires 310.1807

6.4.8 Attempted synthesis of 2-[1-(2-oxo-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [172A].

Attempted Swern oxidations:

Method 1:

DMSO (192 µL, 0.211 g, 2.70 mmol) was added to a stirring solution of oxalyl chloride (104 µL, 0.151 g, 1.19 mmol) in CH_2Cl_2 (5 cm^3) at -78 °C under N_2. A solution of 2-[1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [7] (0.333 g, 1.08 mmol) in CH_2Cl_2 (5 cm^3) was added drop-wise over 5

minutes. Stirring was continued for an additional 15 minutes. Et_3N (0.76 cm^3, 0.546 g, 5.40 mmol) was added and the solution was allowed to warm to room temperature. The reaction mixture was poured into H_2O (20 cm^3) and extracted with CH_2Cl_2 (2 × 20 cm^3). The organic extracts were dried over $MgSO_4$, filtered and evaporated to give a yellow oil (0.340 g). The crude material was examined by ^1H NMR and was found to be starting material containing trace amounts of the desired product.

Method 2:

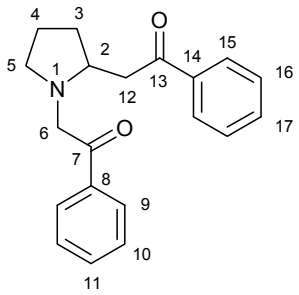
The experimental procedure was adapted from a literature procedure.[195] 2-[1-(2-Hydroxy-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [7] (0.100 g, 0.32 mol) was added to a flame dried flask. DMSO (1.00 cm^3) was added and stirring was commenced under Ar. P_4O_{10} (0.033 g, 0.12 mmol) was added and stirring was continued for 18 hours. H_2O (20 cm^3) and Et_2O (15 cm^3) were added successively and the reaction mixture was then carefully neutralized with Na_2CO_3. The organic extract was dried over $MgSO_4$, filtered and evaporated to afford starting material (0.096 g, 96% recovery) as a yellow oil.

Method 3:

The experimental procedure was adapted from a literature procedure.[196] Activated molecular sieves (crushed, 0.200 g) and $Pd(OAc)_2$ (0.011 g, 0.05 mmol) was added to a dry flask. A solution of Et_3N (42μL, 0.030 g, 0.30 mmol) in dry THF (3 cm^3) was added and the flask was evacuated and back-filled with O_2 several times. Stirring was continued for 30 minutes under O_2. A solution of 2-[1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [7] (0.309 g, 1.00 mmol) in THF (3 cm^3) was added and stirring was continued for 17 hours. The reaction was placed directly on a silica plug and eluted with Et_2O. Evaporation of the solvents afforded starting material (0.258 g, 83% recovery) as a yellow oil.

Method 4:

Jones reagent was cautiously prepared from CrO_3 (0.681 g, 6.81 mmol)), H_2O (2.00 cm^3) and H_2SO_4 (0.58 cm^3) to afford an orange solution.



2-[1-(2-Hydroxy-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [237] (2.141 g, 6.81 mmol) was dissolved in AcOH (10 cm^3) and stirred under N_2 for 5 minutes. Jones reagent (2.00 cm^3) was added drop-wise over a period of 2 minutes, and stirring was continued for an additional 15 minutes at room temperature. The solvent was evaporated to give a blue/green sludge. EtOAc (25 cm^3) was added followed by H_2O (25 cm^3) and the reaction mixture was vigorously stirred. $NaHCO_3$ was added until effervescence ceased. Additional EtOAc (50 cm^3) and H_2O (50 cm^3) was added and the organic extract was separated. The aqueous phase was re-extracted with EtOAc (50 cm^3 and the pooled organic extracts were dried over $MgSO_4$, filtered and evaporated to afford crude 2-[1-(2-oxo-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [172A] (1.941 g) as an orange oil that rapidly darkened to red. The sample decomposed within an hour of isolation.

The following data could be extracted from the ^1H NMR of the crude material.

^1H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.92 (m, 4H, H_9 and H_{15}), 7.60 – 7.50 (m, 2H, H_{11} and H_{17}), 7.48 – 7.39 (m, 4H, H_{10} and H_{16}), 4.29 (d, *J* = 17.2, 1H, $H_{6'}$), 3.85 (d, *J* = 17.2, 1H, $H_{6''}$), 3.40 – 3.22 (m, 3H, H_2, $H_{5'}$ and $H_{12'}$), 3.11 (dd, *J* = 7.6, 15.9, 1H, $H_{12''}$), 2.38 (dd, *J* = 8.6, 17.2, 1H, $H_{5''}$), 2.26 – 1.98 (m, 1H, $H_{3'}$), 1.98 – 1.69 (m, 2H, H_4), 1.69 – 1.38 (m, 1H, $H_{3''}$)

^{13}C NMR (75 MHz, CDCl3) δ 199.50 (C-13), 197.24 (C-7), 137.12 (C-14), 136.05 (C-8), 133.07 (C-11 and C-17), 128.57 (C-15*), 128.50 (C-9*), 128.04 (C-16$^{\#}$), 127.94 (C-10$^{\#}$), 60.94 (C-6), 60.73 (C-2), 54.47 (C-5), 44.14 (C-12), 31.31 (C-3), 22.90 (C-4).

Assignments denoted by * and $^{\#}$ are interchangeable.

Miscellaneous oxidation attempts:

Method 1:

The experimental procedure was adapted from a literature procedure.[197] DDQ (0.341 g, 1.50 mmol) was added to a solution of 2-[1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [237] (0.314 g, 1.01 mmol) in CH_2Cl_2 (20 cm^3) and stirred for 24 hours under N_2. The solvent was decanted from the solids and added to EtOAc (100 cm^3). The dark brown extract was washed with H_2O (8 × 50 cm^3) and brine (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a black tar. An odour of benzaldehyde was noted.

Method 2:

MnO_2 (0.617 g, 7.10 mmol) was added to a solution of 2-[1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [237] (0.219 g, 0.71 mmol) in CH_2Cl_2 (20 cm^3) and stirred for 24 hours under N_2. The reaction mixture was filtered through a pad of Celite and the Celite pad was washed with additional CH_2Cl_2 (50 cm^3). Evaporation of the solvent afforded starting material (0.219 g) as a yellow oil.

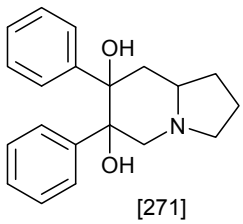
Method 3:

The experimental procedure was adapted from a literature procedure.[260] 2-Iodobenzoic acid (0.036 g, 0.14 mmol) and oxone (0.300 g, 0.48 mmol) were added to a solution of 2-[1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [237] (0.147 g, 0.48 mol) in 2:1 MeCN/H_2O (9.00 cm^3) under N_2. The reaction mixture was heated at 70 °C for 5 hours under N_2. H_2O (20 cm^3) and CH_2Cl_2 (30 cm^3) were added and the organic phase was separated and washed with a saturated solution of $NaHCO_3$ (20 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to afford an orange oil (0.065 g) that could not be characterized by ^1H NMR. An odour of benzaldehyde was noted.

Method 4:

Magtrieve (0.478 g, 4.80 mmol) was added to a solution of 2-[1-(2-hydroxy-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [237] (0.099 g, 0.32 mmol) in CH_3Cl (20 cm^3) and stirred for 24 hours under N_2. The reaction mixture was filtered through a pad of Celite and the Celite pad was washed with CH_2Cl_2 (50 cm^3). Evaporation of the solvent afforded impure starting material (0.060 g) as a yellow oil. An odour of benzaldehyde was noted.

6.4.9 Attempted synthesis of 6,7-diphenyloctahydro-6,7-indolizinediol [171]



[271]

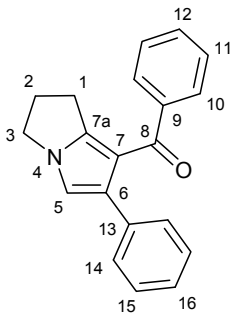
The experimental procedure was adapted from a literature procedure.[199] Crude 2-[1-(2-oxo-2-phenylethyl)-2-pyrrolidinyl]-1-phenyl-1-ethanone [172A] (1.810 g) was added to bromobenzene (2.00 cm^3) and stirred under N_2. Sodium metal (0.176 g, 7.66 mmol) was added and stirring was continued for 18 hours. The solvent was evaporated and the residue was added to H_2O (5 cm^3) and extracted into EtOAc (20 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a red oil. The oil could not be characterized by spectroscopic means.

Chapter 7: Experimental pertaining to Chapter 4

7.1 Preparation of 6,7-substituted pyrrolizine systems

7.1.1 Synthesis of phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone [265A]

Method 1:



[265A]

2-{2-[(*E*)-2-Oxo-2-phenylethylidene]-1-pyrrolidinyl}-1-phenyl-1-ethanone [173A] (0.214 g, 0.70 mmol) was added to a solution of AcOH (5 cm^3) containing EtOH (2 cm^3) and stirred under N_2 for 24 hours. The solvent was evaporated and the gum was extracted with EtOAc (25 cm^3). The organic extract was washed with a saturated solution of $NaHCO_3$ (2 × 25 cm^3) and H_2O (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Column chromatography (50% EtOAc/hexane) afforded phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone [265A] (0.187 g, 0.64 mmol, 93% yield) as a pale-yellow gum.

R_f (50% EtOAc/hexane): 0.60

IR (ν/cm^{-1}): 3058, 3029, 2964 (w, C-H stretch), 1709 (m, C=O stretch), 1630 (s), 1578 (m), 1371 (m), 1317 (m), 1272 (m), 1026 (w), 908 (s), 728 (s), 696 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, 2H, H_{10}), 7.33 (t, J = 7.3, 1H, H_{12}), 7.26 – 7.17 (m, 4H, H_{11} and H_{14}), 7.18 – 7.03 (m, 3H, H_{15} and H_{16}), 6.69 (s, 1H, H_5), 3.96 (t, J = 7.2, 2H, H_3), 2.79 (t, J = 7.4, 2H, H_1), 2.43 (p, J = 7.3, 2H, H_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.18 (C-8), 145.40 (C-7a), 140.07 (C-13), 135.42 (C-9), 130.99 (C-12), 130.92 (C-6), 129.00 (C-10), 128.50 (C-11), 127.68 (C-15), 127.59 (C-14), 125.71 (C-16), 114.28 (C-7), 114.19 (C-5), 46.87 (C-3), 26.76 (C-2), 26.17 (C-1).

HRMS: Found M^+ = 287.1305, $C_{20}H_{17}NO$ requires 287.1310

Method 2:

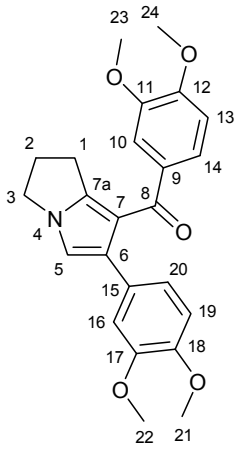
1-Phenyl-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [175A] (2.487 g, 11.34 mmol) was added to MeCN (20 cm^3) and stirred under Argon. Phenacyl iodide (3.071 g, 12.48 mmol) was added and stirring was continued 4 hours at which time salt formation was complete. The deep-red reaction mixture was cooled to –10 °C. A solution of $P(OEt)_3$ (2.074 g, 2.14 cm^3, 12.48 mmol) and Et_3N (2.296 g, 3.19 cm^3, 22.68 mmol) in dry MeCN (20 cm^3) was added drop-wise over 5 minutes. The reaction mixture was warmed to room temperature and allowed to stir for an additional 16 hours. The solvent was evaporated and CH_2Cl_2 (200 cm^3) was added. The organic extract was washed with H_2O (2 × 50 cm^3) and brine (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange gum. The gum was dissolved into AcOH (50 cm^3) and MeOH (50 cm^3) was added to facilitate dissolution of the gum. The reaction mixture was stirred for 24 hours at 40 °C. The solvents were evaporated and the gum was extracted with EtOAc (50 cm^3) and washed with a saturated solution of $NaHCO_3$ (50 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a brown gum. Column chromatography (30% EtOAc/hexane) afforded phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone [265A] (1.923 g, 6.69 mmol, 59% yield) as an orange gum. The spectroscopic data matched those given above.

Method 3:

1-Phenyl-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [175A] (3.347 g, 15.26 mmol) was added to Et_2O (25 cm^3) and stirred under Argon. Phenacyl iodide (5.631 g, 22.89 mmol) was added and the reaction mixture was refluxed under Argon for 18 hours. The solvent was decanted and the yellow solid was rinsed with dry Et_2O (3 × 25 cm^3) to remove excess phenacyl iodide. MeCN (25 cm^3) was added and the heterogeneous solution was stirred under Argon. A solution of PPh_3 (4.404 g, 16.79 mmol) and Et_3N (3.088 g, 4.29 cm^3, 30.52 mmol) in MeCN (25 cm^3) was added drop-wise and stirring was continued for 18 hours. The solvent was evaporated and the orange gum was extracted into EtOAc (100 cm^3). The organic extract was washed with H_2O (50 cm^3) and brine (2 × 50 cm^3). The organic extract was dried over Na_2SO_4 and filtered. Silica-gel (30 g) was added and the reaction mixture was heated (90 °C) on a rotary evaporator, slowly distilling the solvent. When a free-flowing powder was obtained stirring was continued for an additional 2 hours. The silica-gel was poured into a glass-sintered filter funnel and washed with acetone (200 cm^3). The organic extract was evaporated to give an orange gum. Column chromatography (30% EtOAc/hexane) afforded phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone [265A] (3.013 g, 10.94 mmol, 72% yield) as a yellow gum. The spectroscopic data matched those given above.

7.1.2 Synthesis of (3,4-dimethoxyphenyl)[6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl]methanone [265B]

Method 1:



[265B]

1-(3,4-Dimethoxyphenyl)-2-{2-[(*E*)-2-(3,4-dimethoxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}-1-ethanone [173B] (0.435 g, 1.02 mmol) was added to degassed solution of AcOH (6 cm^3) containing MeOH (2 cm^3) and PtO_2 (0.013 g, 0.10 mmol). The solution was hydrogenated at atmospheric pressure for 7 hours. The reaction mixture was filtered through a Celite pad and the pad was rinsed with additional AcOH (15 cm^3). The solvent was evaporated to give a brown gum. The gum was extracted into CH_2Cl_2 (20 cm^3) and washed with a saturated solution of $NaHCO_3$ (3 × 20 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange gum. Column chromatography (5% MeOH/ EtOAc) afforded (3,4-dimethoxyphenyl)[6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl]methanone [265B] (0.347 g, 0.85 mmol, 83% yield) as a yellow gum.

R_f (10% MeOH/EtOAc): 0.66

IR (ν/cm^{-1}): 2937 (w, C-H stretch), 2866 (w), 1704 (m, C=O stretch), 1651 (m), 1515 (s), 1267 (s, C-O stretch), 1021 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, J = 1.9, 8.3, 1H, H_{14}), 7.27 (d, J = 1.5, 1H, H_{10}), 6.84 (dd, J = 1.9, 8.2, 1H, H_{20}), 6.73 (s, 1H, H_5), 6.72 – 6.67 (m, 3H, H_{13}, H_{16} and H_{19}), 4.03 (t, J = 7.2, 2H, H_3), 3.86 (s, 3H, H_{21}*), 3.81 (s, 3H, H_{22}*), 3.74 (s, 3H, H_{23}*), 3.65 (s, 3H, H_{24}*), 2.97 (t, J = 7.4, 2H, H_1), 2.52 (p, J = 7.3, 2H, H_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.23 (C-8), 151.94 (C-12), 148.31 (C-17), 148.15 (C-11), 147.37 (C-18), 145.02 (C-7a), 132.49 (C-15), 130.35 (C-9),

128.79 (C-6), 123.81 (C-10), 120.11 (C-20), 114.26 (C-7), 113.37 (C-5), 112.68 (C-19), 112.36 (C-13), 110.96 (C-10), 109.69 (C-16), 55.87 (C-21*), 55.84 (C-22*), 55.74 (C-23*), 55.59 (C-24*), 46.95 (C-3), 26.87 (C-1), 26.03 (C-2).

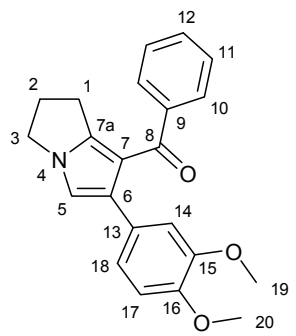
Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 407.1733, $C_{24}H_{25}NO_5$ requires 407.1733

Method 2:

1-(3,4-Dimethoxyphenyl)-2-{2-[(*E*)-2-(3,4-dimethoxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}-1-ethanone [173B] (0.049 g, 0.12 mmol) was added to degassed solution of AcOH (2 cm^3) containing MeOH (1 cm^3). The reaction mixture was stirred under Argon for 18 hours. The reaction mixture was filtered through a Celite pad and the pad was rinsed with additional AcOH (15 cm^3). The solvent was evaporated to give a brown gum. The gum was extracted into CH_2Cl_2 (20 cm^3) and washed with a saturated solution of $NaHCO_3$ (3 × 20 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give an orange gum. Column chromatography (5% MeOH/ EtOAc) afforded (3,4-dimethoxyphenyl)[6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl]me-thanone [265B] (0.049 g, 0.12 mmol, quantitative yield) as a yellow gum. The spectroscopic data matched those reported above.

7.1.3 Synthesis of [6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone [265C]



[265C]

1-(3,4-Dimethoxyphenyl)-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [174B] (0.645 g, 2.31 mmol) was added to MeCN (1.00 cm^3) and stirred under Argon. Phenacyl iodide (1.137 g, 4.62 mmol) was added and the reaction mixture was stirred for 4 hours. The reaction mixture was cooled to 0°C and a solution of PPh_3 (1.212 g, 4.62 mmol) and Et_3N (0.468 g, 0.65 cm^3, 4.62 mmol) in MeCN (5 cm^3) was added drop-wise. Stirring was continued for 18 hours at room temperature. The solvent was evaporated and the residue was extracted with EtOAc (50 cm^3) and washed with H_2O (25 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4 and filtered. Silica-gel (8 g) was added and the reaction mixture was heated (90 °C) on a rotary evaporator, slowly distilling the solvent. When a free-flowing powder was obtained stirring was continued for an additional 1 hour. The silica-gel was poured into a glass-sintered filter funnel and washed with acetone (100 cm^3). The organic extract was evaporated to give an orange gum. Column chromatography (40% EtOAc/hexane) afforded [6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone [265C] (0.527 g, 1.52 mmol, 66% yield) as an orange gum.

R_f (40% EtOAc/hexane): 0.29

IR (ν/cm^{-1}): 3058, 2936 (w, C-H stretch), 2835 (w), 1704 (m, C=O stretch), 1627 (s), 1597 (s), 1447 (s), 1248 (s, C-O stretch), 1023 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 7.4, 2H, H_{10}), 7.33 (t, J = 7.1, 1H, H_{12}), 7.21 (t, J = 7.5, 2H, H_{11}), 6.84 (dd, J = 2.0, 8.2, 1H, H_{18}), 6.75 – 6.65 (m, 3H, H_5, H_{14} and H_{17}), 4.01 (t, J = 7.1, 2H, H_3), 3.81 (s, 3H, H_{19}*), 3.67 (s, 3H, H_{20}*), 2.87 (t, J = 7.3, 2H, H_1), 2.57 – 2.42 (m, 2H, H_2).

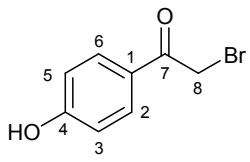
^{13}C NMR (75 MHz, $CDCl_3$) δ 192.31 (C-8), 148.06 (C-15), 147.27 (C-16), 145.67 (C-7a), 140.11 (C-9), 131.08 (C-12), 130.64 (C-13), 129.01 (C-10), 128.48 (C-6), 127.60 (C-11), 120.39 (C-18), 114.27 (C-7), 113.75 (C-5), 112.60 (C-17), 110.78 (C-14), 55.77 (C-19*), 55.53 (C-20*), 46.92 (C-3), 26.75 (C-1), 26.25 (C-2).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 347.1518, $C_{22}H_{21}NO_3$ requires 347.1521

7.2 Preparation of additional thiolactam precursors and cyclization to 6,7-substituted pyrrolizine systems

7.2.1 Synthesis of 2-bromo-1-(2-hydroxyphenyl)-1-ethanone [278] and 2-bromo-1-(4-hydroxyphenyl)-1-ethanone [279]



[279]

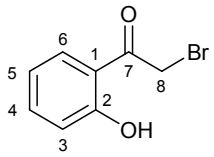
These compounds were prepared by a known literature procedure.[245] $AlCl_3$ (40.00 g, 300.00 mmol) was added to 1,1,2,2-tetrachloroethane (100 cm^3) and the reaction mixture was cooled to 0 °C. Anisole (21.63 g, 200 mmol) was added followed by 2-bromoacetyl chloride (31.38 g, 200 mmol). The solution was initially stirred at 0 °C for 10 minutes and then allowed to warm to room temperature. The reaction mixture was slowly heated to 100 °C and allowed to stir for 6 hours at that temperature. The reaction mixture was poured into water (500 cm^3) and stirred for 30 minutes. The heterogeneous solution was extracted with EtOAc (200 cm^3) and washed with additional H_2O (100 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give a brown solid. Flash chromatography (10% EtOAc/hexane to 40% EtOAc/hexane) afforded 2-bromo-1-(4-hydroxyphenyl)-1-ethanone [279] (14.70 g, 68.36 mmol, 34% yield) as a brown solid.

M.p: 126 – 128 °C [lit.,[245] 124 – 126 °C]

^{1}H NMR (300 MHz, $CDCl_3$ + 5 drops d_6-DMSO) δ 10.09 (s, 1H, OH), 7.86 (d, *J* = 8.7, 2H, H_2 and H_6), 6.89 (d, *J* = 8.7, 2H, H_3 and H_5), 4.47 (s, 2H, H_8).

^{13}C NMR (75 MHz, $CDCl_3$ + 5 drops d_6-DMSO) δ 188.75 (C-7), 162.09 (C-4), 130.47 (C-2 and C-6), 124.51 (C-1), 114.76 (C-3 and C-5), 30.65 (C-8).

Other spectroscopic data agreed with the literature



[278]

Further elution of the column afforded 2-bromo-1-(2-hydroxyphenyl)-1-ethanone [278] (20.00 g, 93.00 mmol, 47% yield) as a white solid that turned orange on standing at room temperature.

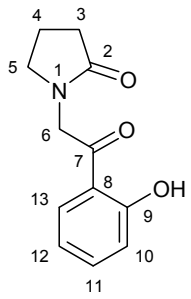
M.p. : 42 – 43 °C, [lit.,[246] 40 °C]

IR (ν/cm^{-1}): 3109 (br w, OH stretch), 3008 and 2948 (w, C-H stretch), 1644 (s, C=O stretch), 1614 (s), 1574 (s), 1484 (s), 1223 (s), 992 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.73 (s, 1H, OH), 7.75 (dd, *J* = 1.7, 8.4, 1H, H_6), 7.52 (ddd, *J* = 1.7, 7.2, 8.4, 1H, H_4), 7.02 (dd, *J* = 1.2, 8.5, 1H, H_3), 6.94 (ddd, *J* = 1.2, 7.2, 8.4, 1H, H_5), 4.45 (s, 2H, H_8).

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.95 (C-7), 163.12 (C-2), 137.40 (C-4), 130.29 (C-6), 119.25 (C-5), 118.87 (C-3), 116.97 (C-1), 29.96 (C-8).

7.2.2 Synthesis of 1-[2-(2-hydroxyphenyl)-2-oxoethyl]-2-pyrrolidinone [280]



[280]

2-Bromo-1-(2-hydroxyphenyl)-1-ethanone [278] (6.000 g, 27.90 mmol) was added to a solution of 5-methoxy-3,4-dihydro-2*H*-pyrrole [176] (4.150 g, 41.85 mmol) in dry DMF (25 cm^3) and heated at 60 °C for 18 hours under Argon. The solvent was evaporated and the residue was extracted with EtOAc (100 cm^3) and washed with H_2O (2 × 50 cm^3) and brine (2 × 50 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give a red oil. Column chromatography (80% EtOAc/hexane) afforded 1-[2-(2-hydroxyphenyl)-2-oxoethyl]-2-pyrrolidinone [280] (3.510 g, 16.01 mmol, 57% yield) as a pink solid. The solid turned white on standing in air.

R_f (80% EtOAc/hexane): 0.30

M.p: 78 – 79 °C

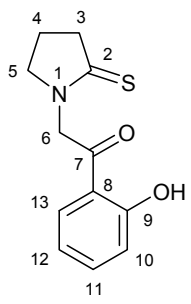
IR (*v*/cm-1): 2945, 2863 (br w, C-H stretch), 1675 (m, ketone C=O stretch), 1646 (s, amide C=O stretch), 1598 (s), 1457 (s), 1227 (m, C-O stretch), 1161 (m), 1026 (m), 764 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.76 (s, 1H, OH), 7.75 (dd, *J* = 1.2, 8.0, 1H, H_{13}), 7.55 – 7.43 (m, 1H, H_{11}), 7.00 (d, *J* = 8.4, 1H, H_{10}), 6.92 (t, *J* = 7.6, 1H, H_{12}), 4.76 (s, 2H, H_6), 3.51 (t, *J* = 7.0, 2H, H_5), 2.49 (t, *J* = 8.1, 2H, H_3), 2.21 – 2.05 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.24 (C-7), 175.78 (C-2), 162.29 (C-9), 136.89 (C-11), 129.04 (C-13), 119.21 (C-12), 118.59 (C-10), 117.84 (C-8), 48.41 (C-6), 47.89 (C-5), 30.23 (C-3), 18.04 (C-4).

HRMS: Found M^+ = 219.0891, $C_{12}H_{13}NO_3$ requires 219.0895

7.2.3 Synthesis of 1-(2-hydroxyphenyl)-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [282A]



[282A]

1-[2-(2-Hydroxyphenyl)-2-oxoethyl]-2-pyrrolidinone [280] (0.517 g, 2.36 mmol) was added to a solution of Lawesson's reagent (0.485 g, 1.20 mmol) in dry toluene and heated at 80 °C for 4 hours under Argon. Evaporation of the solvent afforded an orange gum. Flash chromatography (30% EtOAc/hexane) afforded 1-(2-hydroxyphenyl)-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [282A] (0.368 g, 1.57 mmol, 67% yield) as a yellow solid.

R_f (30% EtOAc/hexane): 0.26

M.p: 85 – 86 °C (Sublimation noted at 75 °C)

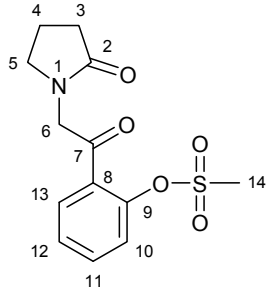
IR (ν/cm^{-1}): 3053 (br w, OH), 2982, 2943, 2912 (w, C-H stretch), 1643 (s, C=O stretch), 1615 (m), 1576 (m), 1511 (s), 1236 (s), 1198 (s), 1155 (s, C=S stretch), 1020 (m), 756 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.66 (s, 1H, OH), 7.78 (dd, J = 1.4, 8.1, 1H, H_{13}), 7.59 – 7.48 (m, 1H, H_{11}), 7.07 – 6.89 (m, 2H, H_{10} and H_{12}), 5.32 (s, 2H, H_6), 3.85 (t, J = 7.3, 2H, H_5), 3.16 (t, J = 7.9, 2H, H_3), 2.28 – 2.10 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 204.02 (C-2), 197.37 (C-7), 162.35 (C-9), 137.21 (C-11), 128.98 (C-13), 119.39 (C-12), 118.77 (C-10), 117.87 (C-8), 55.71 (C-6), 53.23 (C-5), 44.18 (C-3), 19.82 (C-4).

HRMS: Found M^+ = 235.0663, $C_{12}H_{13}NO_2S$ requires 235.0667

7.2.4 Synthesis of 2-[2-(2-oxo-1-pyrrolidinyl)acetyl]phenyl methanesulfonate [281]



[281]

1-[2-(2-Hydroxyphenyl)-2-oxoethyl]-2-pyrrolidinone [280] (1.033 g, 4.71 mmol), was added to dry THF (25 cm^3) and stirred under Argon. NaH (60% dispersion in oil, 0.226 g, 5.65 mmol) was added and stirring was continued for 30 minutes. Methanesulfonyl chloride (0.647 g, 0.44 cm^3, 5.65 mmol) was added and stirring was continued for 35 minutes. H_2O (1 cm^3) was added and stirring was continued for 5 minutes. The solvent was evaporated and the residue was extracted with EtOAc (25 cm^3) and washed with H_2O (25 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Flash chromatography (EtOAc) afforded 2-[2-(2-oxo-1-pyrrolidinyl)acetyl]phenyl methanesulfonate [281] (0.687 g, 2.31 mmol, 49% yield) as an orange gum.

R_f (EtOAc): 0.30

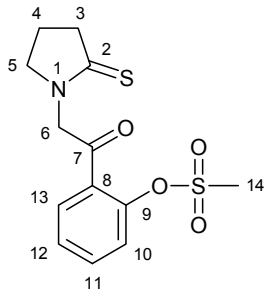
IR (ν/cm^{-1}): 2938 (w, C-H stretch), 1670 (br m, C=O stretch), 1604 (m), 1291 (s), 1198 (m), 1157 (s), 971 (m), 862 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, J = 1.6, 7.7, 1H, H_{13}), 7.63 – 7.55 (m, 1H, H_{11}), 7.50 – 7.41 (m, 2H, H_{10} and H_{11}), 4.63 (s, 2H, H_6), 3.52 (t, J = 7.0, 2H, H_5), 3.29 (s, 3H, H_{14}), 2.46 (t, J = 8.1, 2H, H_3), 2.16 – 2.05 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.84 (C-7), 175.80 (C-2), 146.05 (C-9), 133.61 (C-11), 130.88 (C-8), 129.95 (C-13), 127.52 (C-12), 123.76 (C-10), 51.71 (C-6), 47.86 (C-5), 38.30 (C-14), 30.26 (C-3), 18.09 (C-4).

HRMS: Found M^+ = 297.0666, $C_{13}H_{15}NO_4S$ requires 297.0671

7.2.5 Synthesis of 2-[2-(2-thioxo-1-pyrrolidinyl)acetyl]phenyl methanesulfonate [282B]



[282B]

2-[2-(2-Oxo-1-pyrrolidinyl)acetyl]phenyl methanesulfonate [281] (1.330 g, 4.47 mmol) was added to dry toluene (50 cm^3) and stirred under Argon. Lawesson's reagent (0.938 g, 2.32 mmol) was added and the reaction mixture was heated at 80 °C for 18 hours. The solvent was evaporated to give an orange gum. Column chromatography (40% EtOAc/hexane) afforded 2-[2-(2-thioxo-1-pyrrolidinyl)acetyl]phenyl methanesulfonate [282B] (1.094 g, 3.49 mmol, 78% yield) as an orange gum.

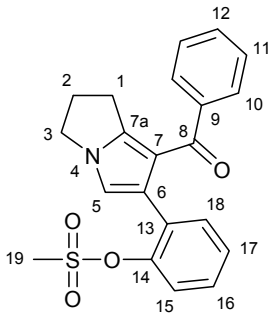
R_f (40% EtOAc/hexane): 0.26

IR (ν/cm^{-1}): 2994, 2956, 2919 (w, C-H stretch), 1689 (m, C=O stretch), 1672 (w), 1603 (m), 1572 (m), 1297 (s), 1170 (s), 1155 (s, C=S stretch), 1059 (m), 860 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, J = 1.5, 7.6, 1H, H_{13}), 7.65 – 7.57 (m, 1H, H_{11}), 7.46 (t, J = 7.4, 2H, H_{10} and H_{11}), 5.16 (s, 2H, H_6), 3.87 (t, J = 7.3, 2H, H_5), 3.29 (s, 3H, H_{14}), 3.11 (t, J = 7.9, 2H, H_3), 2.23 – 2.09 (m, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.53 (C-2), 192.56 (C-7), 146.07 (C-9), 133.81 (C-11), 130.76 (C-8), 130.21 (C-13), 127.57 (C-12), 123.54 (C-10), 56.53 (C-6), 55.67 (C-5), 44.07 (C-3), 38.37 (C-14), 19.79 (C-4).

7.2.6 Synthesis of 2-(7-benzoyl-2,3-dihydro-1*H*-pyrrolizin-6-yl)phenyl methanesulfonate [284]



[284]

2-[2-(2-Thioxo-1-pyrrolidinyl)acetyl]phenyl methanesulfonate [282B] (1.047 g, 3.34 mmol) was added to dry MeCN (10 cm^3) and stirred under Argon. Phenacyl iodide (0.846 g, 3.44 mmol) was added and stirring was continued for 18 hours. A solution of $P(OEt)_3$ (0.610 g, 0.63 cm^3, 3.67 mmol) and Et_3N (0.676 g, 0.94 cm^3, 6.68 mmol) in MeCN (10 cm^3) was added drop-wise and stirring was continued for 18 hours. The solvent was evaporated and the residue was extracted with EtOAc (50 cm^3) and washed with H_2O (3 × 50 cm^3) and brine (50 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. The gum was added to a solution of AcOH (25 cm^3) in MeOH (25 cm^3) and heated at 45 °C for 18 hours. The solvent was evaporated and the residue was extracted with EtOAc (50 cm^3) and washed successively with a saturated solution of $NaHCO_3$ (50 cm^3), H_2O (2 × 50 cm^3) and brine (50 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Column chromatography (50% EtOAc/hexane) afforded 2-(7-benzoyl-2,3-dihydro-1*H*-pyrrolizin-6-yl)phenyl methanesulfonate [284] (0.731 g, 1.92 mmol, 58% yield) as a brown gum.

R_f (60% EtOAc/hexane): 0.50

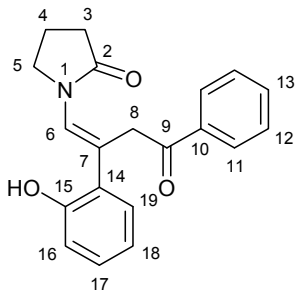
IR (ν/cm^{-1}): 2961, 2921 (w, C-H stretch), 1709 (m, C=O stretch), 1623 (m), 1356 (s), 1157 (s), 1031 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 7.2, 2H, H_{10}), 7.39 (t, J = 7.3, 1H, H_{18}), 7.34 – 7.24 (m, 3H, H_{11} and H_{12}), 7.24 – 7.14 (m, 3H, H_{15}, H_{16} and H_{17}), 6.80 (s, 1H, H_5), 4.04 (t, J = 7.1, 2H, H_3), 2.84 (s, 3H, H_{19}), 2.77 (t, J = 7.3, 2H, H_1), 2.48 (p, J = 7.2, 2H, H_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.83 (C-8), 146.24 (C-14), 144.53 (C-7a), 139.72 (C-9), 131.63 (C-12), 131.29 (C-16), 129.47 (C-13), 128.97 (C-10), 127.76 (C-11), 127.70 (C-18), 126.97 (C-17), 124.38 (C-6), 122.54 (C-15), 115.97 (C-5), 115.26 (C-7), 47.07 (C-3), 37.52 (C-19), 26.92 (C-1), 26.17 (C-2).

Found: $[M + Na]^+$ = 404.0924, $C_{21}H_{19}NNaO_4S$ requires 404.0932

7.2.7 Synthesis of 1-[(*E*)-2-(2-hydroxyphenyl)-4-oxo-4-phenyl-1-butenyl]-2-pyrrolidinone [285]



[285]

1-(2-hydroxyphenyl)-2-(2-thioxo-1-pyrrolidinyl)-1-ethanone [282A] (0.850 g, 3.61 mmol) was added to dry Et_2O (25 cm^3) and stirred under Argon. A solution of phenacyl iodide (1.334 g, 5.42 mmol) in Et_2O (25 cm^3) was added and the reaction mixture was refluxed for 48 hours. A solution of PPh_3 (1.516 g, 5.78 mmol) and Et_3N (0.731 g, 1.01 cm^3, 7.22 mmol) in dry MeCN (25 cm^3) was added drop-wise and stirring was continued for 4 hours. The solvents were evaporated and the residue was extracted with EtOAc (50 cm^3) and washed with H_2O (50 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give a red gum. Flash chromatography (40% EtOAc/hexane to 60% EtOAc/hexane) afforded impure enaminone as an orange powder. The powder was dissolved in toluene (25 cm^3) containing silica-gel (2.73 g) and refluxed under Dean-Stark conditions for 90 minutes. The reaction mixture was filtered through a glass sintered funnel and the silica-gel was rinsed with acetone (3 × 10 cm^3). The organic extract was evaporated to give an orange gum. Flash chromatography (40% EtOAc/hexane) afforded impure 1-[(*E*)-2-(2-hydroxyphenyl)-4-oxo-4-phenyl-1-butenyl]-2-pyrrolidinone [285] (0.317 g, 0.99 mmol, 27% yield) as an orange gum.

R_f (40% EtOAc/hexane): 0.50

IR (v/cm^{-1}): 3333 (w br, OH), 2979, 2981 (w, C-H stretch), 1692 (s, C=O stretch), 1675 (s), 1658 (s), 1598 (m), 1574 (m), 1488 (m), 1120 (s), 744 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (br s, 1H, OH), 7.93 (d, J = 7.3, 2H, H_{11}), 7.55 (t, J = 7.4, 1H, H_{13}), 7.42 (t, J = 7.6, 2H, H_{12}), 7.22 – 7.14 (m, 1H, H_{17}), 7.03 (dd, J = 1.5, 7.6, 1H, H_{19}), 7.00 (s, 1H, H_6), 6.92 (d, J = 7.6, 1H, H_{16}), 6.88 – 6.79 (m, 1H, H_{18}), 4.10 (s, 2H, H_8), 3.08 (br s, 2H, H_5), 2.33 (t, J = 8.2, 2H, H_3), 1.80 (p, J = 7.6, 2H, H_4).

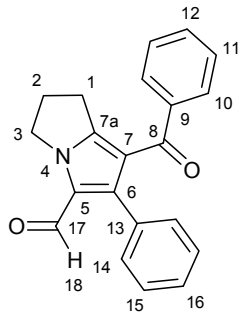
^{13}C NMR (75 MHz, $CDCl_3$) δ 200.73 (C-9), 174.87 (C-2), 154.45 (C-15), 135.51 (C-10), 133.80 (C-13), 130.16 (C-17), 129.42 (C-19), 128.55 (C-11), 128.18 (C-12), 126.70 (C-18), 126.13 (C-14), 119.70 (C-16), 116.72 (C-6), 110.20 (C-7), 48.12 (C-5), 45.87 (C-8), 30.00 (C-3), 17.99 (C-4).

LRMS: m/z (%): 303 (100), 248 (10), 246 (56), 232 (52), 220 (24), 176 (6), 115 (4).

Found: $[M + Na]^+$ = 344.1262, $C_{20}H_{19}NNaO_3$ requires 344.1263

7.3 Preparation of 5,6,7-substituted pyrrolizine systems

7.3.1 Synthesis of 7-benzoyl-6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carb-aldehyde [290]



[290]

Phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone [265A] (1.923 g, 6.69 mmol) was added to a solution of DMF (0.616 g, 0.66 cm^3, 8.43 mmol) in CH_2Cl_2 (10 cm^3) and stirred under N_2. $POCl_3$ (1.293 g, 0.78 cm^3, 8.43 mmol) was cautiously added by way of a syringe and stirring was continued for an additional 1 hour. Crushed ice was added and stirring was continued for 5 minutes. The deep-red solution was neutralized with a saturated solution of $NaHCO_3$. The

reaction mixture was extracted with EtOAc (50 cm^3) and passed through a short silica-gel pad to remove most of the red colour. The silica-gel pad was rinsed with additional EtOAc (100 cm^3) and the combined organic extract was evaporated to give a brown gum. Column chromatography (40% EtOAc/hexane) afforded 7-benzoyl-6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carbaldehyde [290] (0.948 g, 3.01 mmol, 45% yield) as a brown gum. The gum was crystallized by slow evaporation from CH_2Cl_2/hexane mixtures to afford a brown solid.

R_f (40% EtOAc/hexane): 0.50

M.p: 97 – 98 °C (CH_2Cl_2/hexane)

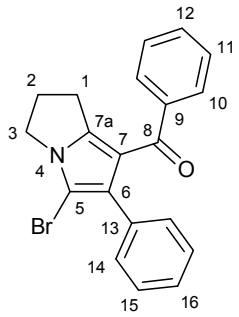
IR (ν/cm^{-1}): 3057, 3026, 2965 (w, C-H stretch), 2832 (w), 1643 (s, C=O stretch), 1598 (m), 1579 (m), 1464 (s), 1276 (m), 1218 (m, C-O stretch), 1032 (w), 970 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H, H_{18}), 7.52 (d, J = 7.4, 2H, H_{10}), 7.28 (t, J = 7.4, 1H, H_{12}), 7.24 – 7.07 (m, 7H, H_{11}, H_{14}, H_{15} and H_{16}), 4.39 (t, J = 7.2, 2H, H_3), 2.95 (t, J = 7.6, 2H, H_1), 2.60 – 2.44 (m, 2H, H_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.61 (C-8), 180.11 (C-17), 150.39 (C-7a), 141.28 (C-13), 138.62 (C-9), 131.91 (C-6), 131.32 (C-12), 130.37 (C-10), 128.70 (C-15), 127.56 (C-11), 127.45 (C-14), 127.34 (C-5), 125.27 (C-16), 116.25 (C-7), 48.38 (C-3), 26.07 (C-2), 25.47 (C-1).

HRMS: Found M^+ = 315.1278, $C_{21}H_{17}NO_2$ requires 315.1259

7.3.2 Synthesis of (5-bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)-methanone [291A]



[291A]

Phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone [265A] (1.377 g, 5.00 mmol) was added to dry THF (25 cm^3) and stirred under Argon. NBS (0.979 g, 5.50 mmol) was added and stirring was continued for 20 minutes. the solvent was evaporated and the residue was extracted with EtOAc (50 cm^3) and washed with H_2O (2 × 50 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Flash chromatography (10% EtOAc/hexane to 20% EtOAc/hexane) afforded (5-bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone [291A] (0.952 g, 2.69 mmol, 54% yield) as a cream solid which was used immediately into the next set of reactions as it tended to decompose rapidly upon isolation. The low yield may be attributed to decomposition of the product during the course of chromatography. In addition, the NMR data indicated the product was in a state of decomposition as evidenced by numerous extraneous peaks in the spectra.

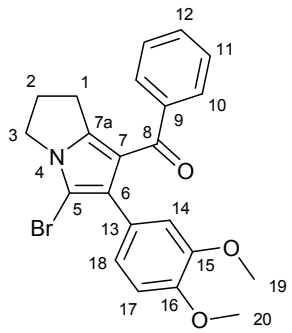
The following data could be extracted from the impure product.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2, 2H, H_{10}), 7.32 (t, *J* = 7.3, 1H, H_{12}), 7.27 – 7.06 (m, 7H, H_{11}, H_{14}, H_{15} and H_{16}), 4.02 (t, *J* = 7.2, 2H, H_3), 2.94 (t, *J* = 7.4, 2H, H_1), 2.50 (p, *J* = 7.3, 2H, H_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.33 (C-8), 144.42 (C-7a), 139.42 (C-13), 133.92 (C-9), 131.21 (C-12), 129.85(C-10), 129.00 (C-15), 127.64 (C-11 and C-14), 126.39 (C-16), 116.24 (C-6), 112.84 (C-7), 97.09 (C-5), 47.08 (C-3), 27.22 (C-1), 25.81 (C-2).

HRMS: Found M^+ = 365.0410, $C_{20}H_{16}{}^{79}BrNO$ requires 365.0415

7.3.3 Synthesis of [5-bromo-6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone [291C]



[291C]

NBS (0.269 g, 1.51 mmol) was added to a solution of [6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone [265C] (0.499 g, 1.44 mmol) in dry THF (25 cm^3) and stirred at 0 °C for 1 hour under Argon. The solvent was evaporated and the residue was extracted with EtOAc (25 cm^3) and washed with H_2O (25 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give a red gum. Flash chromatography (30% EtOAc/hexane) afforded [5-bromo-6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone [291C] (0.483 g, 1.13 mmol, 78% yield) as a yellow foam. The foam turned black within several hours of isolation. The product was used immediately into the next set of reactions as it tended to decompose rapidly upon isolation.

The following data could be extracted from the impure product.

R_f (40% EtOAc/hexane): 0.41

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.3, 2H, H_{10}), 7.38 – 7.28 (m, 1H, H_{12}), 7.24 – 7.13 (m, 2H, H_{11}), 6.83 (dd, *J* = 1.6, 8.2, 1H, H_{18}), 6.72 (d, *J* = 8.3, 1H, H_{17}), 6.67 (d, *J* = 1.3, 1H, H_{14}), 4.03 (t, *J* = 7.2, 2H, H_3), 3.82 (s, 3H, H_{19}*), 3.71 (s, 3H, H_{20}*), 2.99 (t, *J* = 7.5, 2H, H_1), 2.51 (p, *J* = 7.3, 2H, H_2).

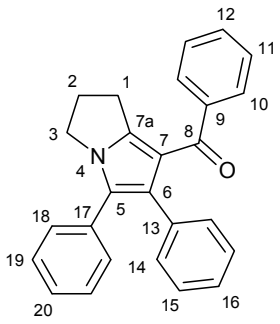
^{13}C NMR (75 MHz, $CDCl_3$) δ 191.48 (C-8), 148.01 (C-15), 147.55 (C-16), 144.52 (C-7a), 139.42 (C-9), 131.28 (C-12), 128.93 (C-10), 127.93 (C-13), 127.60 (C-11), 126.64 (C-6), 122.20 (C-18), 116.15 (C-7), 113.43 (C-17), 110.54 (C-14), 96.79 (C-5), 55.73 (C-19*), 55.61 (C-20*), 47.10 (C-3), 27.21 (C-1), 25.74 (C-2).

Assignments denoted by * are interchangeable.

A molecular ion could not be obtained by HRMS as the sample had decomposed. A LRMS was obtained on a partially decomposed sample.

LRMS: *m/z* (%): 426 (24), 410 (5), 386 (10), 372 (9), 346 (100), 330 (27), 105 (83), 77 (19).

7.3.4 Synthesis of (5,6-diphenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)-methanone [292A]



[292A]

(5-Bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone [291A] (0.350 g, 0.99 mmol) was added to a round bottom flask containing phenylboronic acid (0.183 g, 1.50 mmol), $Pd(PPh_3)_4$ (0.116 g, 0.10 mmol) and Na_2CO_3 (1.060 g, 10.00 mmol). The flask was evacuated and back-filled with Argon several times to remove O_2. H_2O (5 cm^3), EtOH (5 cm^3) and DME (5 cm^3) was thoroughly degassed and added to the solids under a positive pressure of argon. The heterogeneous mixture was stirred at room temperature for 10 minutes and then allowed to reflux for 18 hours. After cooling to room temperature, H_2O (25 cm^3) was added to the black reaction mixture followed by CH_2Cl_2 (50 cm^3) and stirring was continued for 5 minutes. The organic phase was separated and the aqueous phase was re-extracted with additional CH_2Cl_2 (2 × 50 cm^3). The combined organic extract was dried over Na_2SO_4, filtered and evaporated to give a brown oil. Flash chromatography (10% EtOAc/hexane) afforded (5,6-diphenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone [292A] (0.260 g, 0.72 mmol, 73% yield) as a pale-yellow fluffy solid.

R_f (10% EtOAc/hexane): 0.20

M.p: 105 – 108 °C (sweating noted at 102 °C).

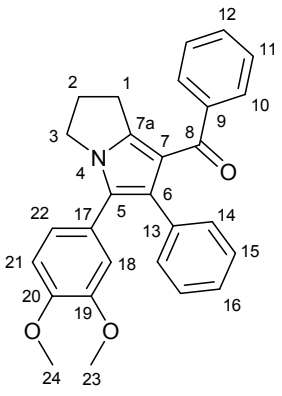
IR (ν/cm^{-1}): 3057 and 2964 (w, C-H stretch), 1631 (s, C=O stretch), 1597 (m), 1470 (m), 1369 (m), 1278 (m), 1050 (m)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 7.1, 2H, H_{10}), 7.41 – 7.10 (m, 8H), 7.02 (br s, 5H), 4.02 (t, J = 6.7, 2H, H_3), 2.94 (t, J = 7.0, 2H, H_1), 2.56 – 2.38 (m, 2H, H_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.51 (C-8), 144.44 (C-7a), 140.12 (C-13), 135.16 (C-9), 131.84 (C-17), 130.90 (C-12), 130.65 (C-10), 129.39 (C-15), 129.01 (C-11), 128.22 (C-19), 127.53 (C-14), 127.44 (C-18), 127.04 (C-5), 126.93 (C-20), 126.83 (C-6), 125.65 (C-16), 115.59 (C-7), 46.76 (C-3), 26.54 (C-1), 26.37 (C-2).

HRMS: Found M^+ = 363.1617, $C_{26}H_{21}NO$ requires 363.1623

7.3.5 Synthesis of [5-(3,4-dimethoxyphenyl)-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone [292B]



[292B]

(5-Bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone [291A] (0.425 g, 1.20 mmol) was added to a round bottom flask containing 3,4-dimethoxyphenylboronic acid (0.328 g, 1.80 mmol), $Pd(PPh_3)_4$ (0.139 g, 0.12 mmol) and Na_2CO_3 (1.272 g, 12.00 mmol). The flask was evacuated and back-filled with Argon several times to remove O_2. H_2O (10 cm^3), EtOH (10 cm^3) and DME (10 cm^3) was thoroughly degassed and added to the solids under a positive pressure of Argon. The heterogeneous mixture was stirred at room temperature for 10 minutes and then allowed to reflux for 18 hours. After cooling to room temperature, H_2O (25 cm^3) was added to the black reaction

mixture followed by CH_2Cl_2 (50 cm^3) and stirring was continued for 5 minutes. The organic phase was separated and the aqueous phase was re-extracted with additional CH_2Cl_2 (2 × 50 cm^3). The combined organic extract was dried over Na_2SO_4, filtered and evaporated to give a brown oil. Flash chromatography (10% EtOAc/hexane) afforded [5-(3,4-dimethoxyphenyl)-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone [292B] (0.427 g, 1.04 mmol, 87% yield) as a yellow foam.

R_f (20% EtOAc/hexane): 0.12

M.p: 59 – 60 °C

IR (ν/cm^{-1}): 3054 and 2934 (w, C-H stretch), 1633 (s, C=O stretch), 1597 (m), 1443 (s), 1204 (s), 1038 (s), 956 (s).

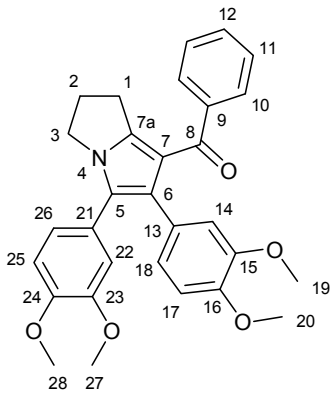
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 7.1, 2H, H_{10}), 7.40 – 7.14 (m, 3H), 7.14 – 6.94 (m, 5H), 6.82 (s, 2H, H_{21} and H_{22}), 6.55 (s, 1H, H_{18}), 4.04 (t, J = 6.5, 2H, H_3), 3.85 (s, 3H, H_{23}*), 3.51 (s, 3H, H_{24}*), 2.92 (t, J = 6.9, 2H, H_1), 2.59 – 2.36 (m, 2H, H_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.34 (C-8), 148.27 (C-19*), 147.88 (C-20*), 144.16 (C-7a), 140.16 (C-13), 135.43 (C-9), 130.80 (C-12), 130.63 (C-10), 128.88 (C-15), 127.48 (C-11), 127.44 (C-14), 126.74 (C-5), 126.56 (C-6), 125.57 (C-16), 124.32 (C-17), 121.06 (C-22), 115.42 (C-7), 113.05 (C-21), 110.74 (C-18), 55.66 (C-23$^{\#}$), 55.37 (C-24$^{\#}$), 46.75 (C-3), 26.49 (C-1), 26.32 (C-2).

Assignments denoted by * and $^{\#}$ are interchangeable.

HRMS: Found M^+ = 423.1828, $C_{28}H_{25}NO_3$ requires 423.1834

7.3.6 Synthesis of [5,6-bis(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone [292C]



[292C]

[5-Bromo-6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone [291C] (0.200 g, 0.47 mmol) was added to a round bottom flask containing 3,4-dimethoxyphenylboronic acid (0.130 g, 0.71 mmol), $Pd(PPh_3)_4$ (0.055 g, 0.05 mmol) and Na_2CO_3 (0.498 g, 4.70 mmol). The flask was evacuated and back-filled with Argon several times to remove O_2. H_2O (10 cm^3), EtOH (10 cm^3) and DME (10 cm^3) was thoroughly degassed and added to the solids under a positive pressure of Argon. The heterogeneous mixture was stirred at room temperature for 10 minutes and then allowed to reflux for 1 hour. After cooling to room temperature, H_2O (25 cm^3) was added to the black reaction mixture followed by CH_2Cl_2 (50 cm^3) and stirring was continued for 5 minutes. The organic phase was separated and the aqueous phase was re-extracted with additional CH_2Cl_2 (2 × 50 cm^3). The combined organic extract was dried over Na_2SO_4, filtered and evaporated to give a brown oil. Flash chromatography (10% EtOAc/hexane) afforded [5,6-bis(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone [292C] (0.181 g, 0.37 mmol, 79% yield) as a thick yellow gum.

R_f (40% EtOAc/hexane): 0.24

IR (ν/cm^{-1}): 2935 (w, C-H stretch), 2834 (w), 1699 (w, C=O stretch), 1516 (s), 1496 (m), 1237 (s, C-O stretch), 1137 (s), 1022 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 7.5, 2H, H_{10}), 7.32 (t, J = 7.4, 1H, H_{12}), 7.20 (t, J = 7.5, 2H, H_{11}), 6.82 (s, 2H, H_{14} and H_{22}), 6.66 – 6.53 (m, 4H, H_{17}, H_{18}, H_{25} and H_{26}), 4.04 (t, J = 7.0, 2H, H_3), 3.86 (s, 3H, H_{19}*), 3.76 (s, 3H, H_{20}*), 3.59 (s, 3H, $H_{27}$$^{\#}$), 3.57 (s, 3H, $H_{28}$$^{\#}$), 2.95 (t, J = 7.3, 2H, H_1), 2.49 (p, J = 7.2, 2H, H_2).

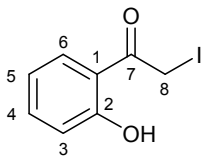
^{13}C NMR (75 MHz, $CDCl_3$) δ 192.39 (C-8), 148.27 (C-15), 147.87 (C-16), 147.76 (C-23), 146.90 (C-24), 144.22 (C-7a), 140.15 (C-9), 130.80 (C-12), 128.77 (C-10), 128.05 (C-13), 127.41 (C-11), 126.53 (C-6), 126.05 (C-5), 124.42 (C-21), 122.94 (C-26), 121.29 (C-18), 115.27 (C-7), 114.19 (C-25), 112.86 (C-17), 110.74 (C-14), 110.49 (C-22), 55.63 (C-19*), 55.61 (C-20*), 55.46 (C-27*), 55.41 (C-28*), 46.67 (C-3), 26.38 (C-1), 26.29 (C-2).

Assignments denoted by * and # are interchangeable.

HRMS: Found M^+ = 483.2009, $C_{30}H_{29}NO_5$ requires 483.2046

7.4 Preparation of functionalized phenacyl halides

7.4.1 Synthesis of 1-(2-hydroxyphenyl)-2-iodo-1-ethanone [296]



[296]

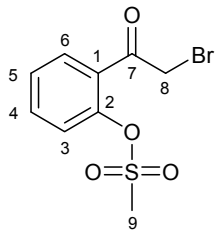
2-Bromo-1-(2-hydroxyphenyl)-1-ethanone [278] (2.150 g, 10.00 mmol) was added to a solution of NaI (1.649 g, 11.00 mmol, 1.10 equivalents) in acetone (25 cm^3) and stirred at room temperature for 2 hours under an atmosphere of Argon. The solvent was evaporated and the residue was taken up into EtOAc (50 cm^3) and washed with water (2 × 25 cm^3) and brine (25 cm^3). The organic phase was dried over Na_2SO_4, filtered and evaporated to give a red oil. Rapid flash chromatography (10% EtOAc/hexane) afforded 1-(2-hydroxyphenyl)-2-iodo-1-ethanone [296] (2.300 g, 8.78 mmol, 88% yield) as a yellow solid. The compound was used immediately upon preparation.

R_f (10% EtOAc/hexane): 0.20

M.p: 62 – 63 °C [lit.[245] 65 °C (methanol)]

IR (ν/cm^{-1}): 2958, 2928, 2854 (m, C-H stretch), 1741 (m, C=O stretch), 1696 (s), 1670 (s), 1260 (s), 1219 (s), 1034 (s), 978 (s), 956 (s).

7.4.2 Synthesis of 2-(2-bromoacetyl)phenyl methanesulfonate [295]



[295]

2-Bromo-1-(2-hydroxyphenyl)-1-ethanone [278] (4.301 g, 20.00 mmol) was added to dry THF (25 cm^3) and cooled to –10 °C under Argon. Et_3N (2.024 g, 2.81 cm^3, 20.00 mmol) was added and stirring was continued for 5 minutes. A solution of MsCl (2.291 g, 1.55 cm^3, 20.00 mmol) in dry THF (25 cm^3) was added drop-wise to the solution. After 1hour of stirring at room temperature the reaction mixture was filtered through a pad of Celite. The Celite pad was rinsed with additional THF (25 cm^3). The combined organic extracts were evaporated to afford an orange oil. Rapid flash chromatography (30% EtOAc/hexane) afforded 2-(2-bromoacetyl)phenyl methanesulfonate [295] (5.417 g, 18.48 mmol, 92% yield) as a pale yellow oil.

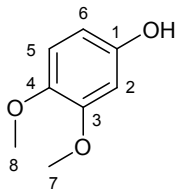
IR (ν/cm^{-1}): 3033 and 2939 (w, C-H stretch), 1693 (m, C=O stretch), 1601 (m), 1350 (s), 1156 (s), 968 (s), 857 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, J = 1.7, 7.7, 1H), 7.56 – 7.47 (m, 1H), 7.41 – 7.28 (m, 2H), 4.39 (s, 2H), 3.17 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.33 (C-7), 146.28 (C-2), 134.00 (C-4), 130.61 (C-6), 129.95 (C-1), 127.47 (C-5), 123.63 (C-3), 38.38 (C-9), 34.10 (C-8).

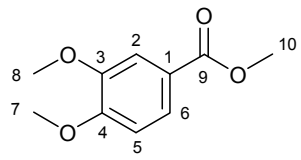
HRMS: Found M^+ = 291.9400, $C_9H_9{}^{79}Br\ O_4S$ requires 291.9405

7.4.3 Synthesis of 3,4-dimethoxyphenol [298]



[298]

3,4-Dimethoxyphenol [298] was prepared by a modification of a literature procedure.[251] Veratraldehyde (50.00 g, 300.90 mmol) was added to MeOH (560 cm^3) and cooled to –15 °C under Argon with stirring. H_2O_2 (100 vol., 44.00 cm^3, 385.15 mmol) was added followed immediately by concentrated H_2SO_4 (3.00 cm^3). Stirring was continued at –15 °C for 1 hour and the reaction mixture was allowed to warm to –5 °C and stirred at that temperature for an additional 1 hour. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and then stirred for an additional 18 hours at that temperature. Activated charcoal (1.00 g) was added and stirring was continued for 1 hour. The reaction mixture was filtered through a pad of neutral alumina and the filter pad was washed with additional MeOH (2 × 100 cm^3). The reaction mixture was evaporated to remove most of the MeOH and the aqueous emulsion was extracted with EtOAc (500 cm^3). The organic extract was washed with H_2O (5 × 200 cm^3) and brine (3 × 200 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give a red tar. Careful column chromatography (30% EtOAc/hexane) afforded methyl 3,4-dimethoxybenzoate (2.338 g, 11.92 mmol, 4% yield) as a white solid.



R_f (30% EtOAc/hexane): 0.50

M.p: 56 – 59 °C

IR (ν/cm^{-1}): 2958, 2934 (w, C-H stretch), 2840 (w), 1716 (s, C=O stretch), 1594 (s), 1513 (s), 1227 (w, C-O stretch), 1105 (s), 1034 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4, 1H, H_6), 7.54 (s, 1H, H_2), 6.88 (d, J = 8.4, 1H, H_5), 3.93 (s, 6H, H_7 and H_8), 3.89 (s, 3H, H_{10}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.64 (C-9), 152.72 (C-4), 148.36 (C-3), 123.35 (C-6), 122.41 (C-1), 111.70 (C-2), 110.03 (C-5), 55.75 (C-7 and C-8), 51.76 (C-10).

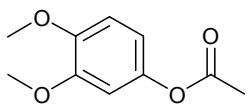
HRMS: Found M^+ = 196.0730, $C_{10}H_{12}O_4$ requires 196.0736

Further elution of the column afforded 3,4-dimethoxyphenol (34.81 g, 225.80 mmol, 75% yield) as a cream solid.

M.p: 78 – 80 °C (lit.,[252] 79 – 82 °C)

Other spectroscopic data matched those in the literature.[261]

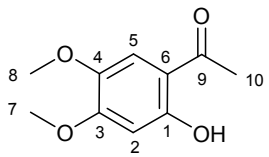
7.4.4 Synthesis of 3,4-dimethoxyphenyl acetate [299]



[299]

3,4-Dimethoxyphenol [298] (20.00 g, 129.74 mmol) was added to a solution of pyridine (29.40 g, 30.00 cm^3, 371.68 mmol) in Ac_2O (32.40 g, 30.00 cm^3, 316.75 mmol) and stirred under Argon at 0 °C for 1hour. The cooling bath was removed and stirring was continued for 18 hours. The solvent was evaporated and the residue was extracted with EtOAc (100 cm^3). The organic extract was washed with 2M HCl (5 × 100 cm^3), H_2O (2 × 100 cm^3) and finally with brine (1 × 100 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to afford 3,4-dimethoxyphenyl acetate [299] (23.76 g, 121.10 mmol, 93% yield) as an orange oil. The oil was used immediately into the next reaction.

7.4.5 Synthesis of 1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [300]



[300]

$BF_3.OEt_2$ (110.00 g, *ca.* 96 cm^3, 774.72 mmol) that had been previously chilled to 0 °C was added to 3,4-dimethoxyphenyl acetate [299] (38.00 g, 193.68 mmol) and the reaction mixture was stirred at 0°C under Argon for 10 minutes. The purple reaction mixture was slowly warmed to 110 °C over 2 hours and then left to reflux for 4 hours. The brown heterogeneous reaction mixture was cooled to room temperature and then cautiously quenched with H_2O (200 cm^3). The solid was filtered through a glass sintered funnel under vacuum and the filter-cake was washed with additional H_2O (*ca*. 1000 cm^3) until the washings were no longer coloured. The green solid was transferred to a beaker containing MeOH (100 cm^3) and vigorously stirred while refluxing open to the air. The green solution was allowed to evaporate until solids started crashing out of the solution. At this point the heat source was removed and stirring was continued for 1 hour at room temperature. Finally, the beaker was immersed into a cooling bath (–60 °C) and stirred for an additional 20 minutes. The solids were rapidly filtered under suction and washed with very cold (– 60 °C) MeOH until the washings became clear (5 × 25 cm^3). The solids were transferred to a round bottom flask and dried under vacuum to afford 1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [300] (35.00 g, 178.39 mmol, 92% yield) as a light-brown crystalline solid.

R_f (40% EtOAc/hexane): 0.53

M.p: 74 – 75 °C (acetone)

IR (ν/cm^{-1}): 3011, 2969 (w, C-H stretch), 2844 (w), 1630 (s, C=O stretch), 1579 (w), 1507 (s), 1259 (s), 1236 (s, C-O stretch), 1202 (s), 1158 (s), 1032 (s).

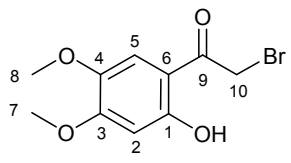
1H NMR (300 MHz, $CDCl_3$) δ 12.64 (s, 1H, OH), 7.06 (s, 1H, H_5), 6.45 (s, 1H, H_2), 3.91 (s, 3H, H_7*), 3.87 (s, 3H, H_8*), 2.56 (s, 3H, H_{10}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 201.96 (C-9), 160.05 (C-1), 156.76 (C-3), 141.83 (C-4), 111.68 (C-5), 111.65 (C-6), 100.48 (C-2), 56.63 (C-7*), 56.08 (C-8*), 26.27 (C-10).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 196.0730, $C_{10}H_{12}O_4$ requires 196.0736

7.4.6 Synthesis of 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [301] and 2,2-dibromo-1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [303]



[301]

1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [300] (9.810 g, 50.00 mmol) in $CHCl_3$ (50 cm^3) was added rapidly to a solution of $CuBr_2$ (24.569 g, 110.00 mmol) in refluxing EtOAc (50 cm^3). Reflux was continued for 3 days until the black $CuBr_2$ had turned into white CuBr powder. After the solution had cooled to room temperature, it was filtered through a pad of Celite and the pad was rinsed with additional EtOAc (200 cm^3). Evaporation of the solvent gave a black solid that was dissolved into EtOAc (50cm^3) and filtered through a pad of SiO_2. The pad was washed with additional EtOAc (200 cm^3). Rotary evaporation afforded an orange solid which was taken up into MeOH (50 cm^3) and heated until most of the solids had dissolved.

The solution was allowed to stand at room temperature overnight and the solids were separated by decanting the mother liquor. The solids were rinsed with cold MeOH (2 × 25 cm^3) and hexane (3× 25 cm^3) and the washings added to the original mother liquor. The solids were taken up into EtOH (75 cm^3) and refluxed until the solids had dissolved. The mixture was concentrated to approximately 25 cm^3 and allowed to stand at room temperature for 5 hours. The solvent was decanted and the solids were washed with cold EtOH (2 × 25 cm^3). The solid was vacuumed dried to afford 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [301] (7.800 g, 28.35

mmol, 57% yield) as a yellow powder that contained trace quantities of starting material and 2,2-dibromo-1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [303].

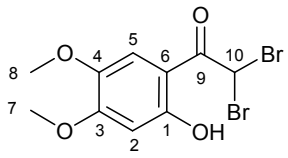
IR (ν/cm^{-1}): 3005, 2948 (C-H stretch), 1618 (s, C=O stretch), 1509 (s), 1240 (s, C-O stretch), 1198 (s), 1188 (s), 1155 (s), 1032 (m), 841 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.18 (s, 1H, OH), 7.06 (s, 1H, H), 6.48 (s, 1H), 4.35 (s, 2H), 3.94 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.59 (C-9), 161.40 (C-1), 157.72 (C-3), 142.16 (C-4), 110.69 (C-5), 108.98 (C-6), 100.76 (C-2), 56.57 (C-7*), 56.27 (C-8*), 29.83 (C-10).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 273.9835, $C_{10}H_{11}{}^{79}BrO_4$ requires 273.9841



[303]

The mother liquors were again added to the previously pooled mother liquors and evaporated to afford a yellow solid. Flash chromatography (20% EtOAc/hexane) afforded 2,2-dibromo-1-(2-hydroxy-4,5-dimethoxy-phenyl)-1-ethanone [303] (2.800 g, 7.91 mmol, 16% yield) as a yellow solid.

M.p: 70 – 71 °C

IR (ν/cm^{-1}): 3087, 2994, 2942 (w, C-H stretch), 1675 (s, C=O stretch), 1585 (s), 1335 (s), 1269 (s), 1232 (s, C-O stretch), 1206 (s), 1153 (s), 1029 (m), 964 (s), 740 (s), 704 (s).

^{1}H NMR (300 MHz, CDCl3) δ 11.92 (s, 1H, OH), 7.23 (s, 1H, H_5), 6.63 (s, 1H, H_{10}), 6.50 (s, 1H, H_2), 3.95 (s, 3H, H_7*), 3.89 (s, 3H, H_8*).

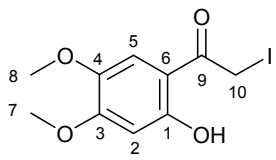
^{13}C NMR (75 MHz, CDCl3) δ 188.71 (C-9), 162.58 (C-1), 158.31 (C-3), 142.02 (C-4), 110.13 (C-5), 105.50 (C-6), 100.94 (C-2), 56.48 (C-7*), 56.36 (C-8*), 38.58 (C-10).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 351.8941, $C_{10}H_{10}{}^{79}Br_2O_4$ requires 351.8946

Further elution afforded an inseparable mixture (0.942 g) of starting material and 2-bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [301] in a ratio of 1: 0.38 respectively.

7.4.7 Synthesis of 1-(2-hydroxy-4,5-dimethoxyphenyl)-2-iodo-1-ethanone [302]



[302]

2-Bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [301] (4.127 g, 15.00 mmol) was added to a solution of NaI (2.548 g, 17.00 mmol) in acetone (30 cm^3) and stirred under Argon for 3 hours. The reaction mixture was filtered through a pad of Celite and the pad was rinsed with additional acetone. Evaporation of the solvent gave a red solid. Rapid flash chromatography (30% EtOAc/hexane) afforded 1-(2-hydroxy-4,5-dimethoxyphenyl)-2-iodo-1-ethanone [302] (4.753 g, 14.76 mmol, 98% yield) as a yellow solid.

M.p: 82 – 84 °C (sweating noted from 72 °C)

IR (ν/cm^{-1}): 3018, 2957, 2930 (w, C-H stretch), 2848 (w), 1631 (m, C=O stretch), 1597 (m), 1581 (m), 1274 (m), 1226 (s, C-O stretch), 1167 (s), 1147 (s), 1030 (m), 868 (s), 757 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.29 (s, 1H, OH), 7.04 (s, 1H, H_5), 6.47 (s, 1H, H_2), 4.28 (s, 2H, H_{10}), 3.93 (s, 3H, H_7*), 3.88 (s, 3H, H_8*).

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.31 (C-9), 161.39 (C-1), 157.60 (C-3), 142.01 (C-4), 110.96 (C-5), 108.49 (C-6), 100.88 (C-2), 56.59 (C-7*), 56.29 (C-8*), 0.61 (C-10).

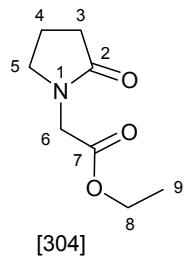
Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 321.9700, $C_{10}H_{11}IO_4$ requires 321.9702

7.5 Preparation of vinylogous amides that contain an ethoxycarbonyl methyl attached to nitrogen

7.5.1 Synthesis of ethyl 2-(2-oxo-1-pyrrolidinyl)acetate [304]

Method 1:



[304]

5-Methoxy-3,4-dihydro-2*H*-pyrrole [176] (2.974 g, 30.00 mmol) was added to dry DMF (10 cm^3) and warmed to 80 °C under Argon. A solution of ethyl 2-bromoacetate (3.340 g, 2.23 cm^3, 20.00 mmol) in dry DMF (10 cm^3) was added drop-wise and stirring was continued for 17 hours. The solvent was evaporated and the residue was extracted with EtOAc (100 cm^3) and washed with H_2O (3 × 50 cm^3) and brine (25 cm^3). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a yellow oil. Column chromatography (50% EtOAc/hexane) afforded ethyl 2-(2-oxo-1-pyrrolidinyl)acetate [304] (1.570 g, 9.17 mmol, 46% yield) as a yellow oil.

R_f (50% EtOAc/hexane): 0.23

IR (v/cm^{-1}): 2982, 2938 (w, C-H stretch), 1742 (m, ester C=O stretch), 1679 (s, amide C=O stretch), 1257 (m, C-O stretch), 1190 (s), 1023 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, J = 7.1, 2H, H_8), 4.05 (s, 2H, H_6), 3.49 (t, J = 7.1, 2H, H_5), 2.43 (t, J = 8.1, 2H, H_3), 2.15 – 2.00 (m, 2H, H_4), 1.28 (t, J = 7.1, 3H, H_9).

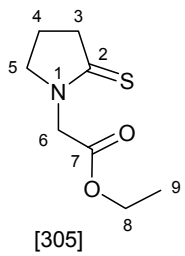
^{13}C NMR (75 MHz, $CDCl_3$) δ 175.54 (C-2), 168.62 (C-7), 61.20 (C-8), 47.62 (C-6), 44.04 (C-5), 30.24 (C-3), 17.90 (C-4), 14.09 (C-9).

HRMS: Found M^+ = 171.0889, $C_6H_{11}NO_3$ requires 171.0895

Method 2:

NaH (65% dispersion in oil, 2.400 g, 60.00 mmol) was added to dry THF (150 cm^3) and stirred under Argon for 10 minutes. A solution of 2-pyrrolidinone (4.256 g, 50.00 mmol) in dry THF (50 cm^3) was added drop-wise over 45 minutes and stirring was continued for 2 hours at room temperature. A solution of ethyl 2-bromoacetate (10.021 g, 6.64 cm^3, 60.00 mmol) in dry THF (50 cm^3) was added drop-wise to the gelatinous reaction mixture over 20 minutes and stirring was continued for 18 hours. H_2O (25 cm^3) was cautiously added and the solvent was evaporated. The aqueous residue was extracted with EtOAc (100 cm^3) and washed with H_2O (50 cm^3) and brine (50 cm^3). The organic extract was dried over Na_2SO4, filtered and evaporated to give a colourless oil. Flash chromatography (EtOAc) afforded ethyl 2-(2-oxo-1-pyrrolidinyl)acetate [304] (8.540 g, 49.88 mmol, 99% yield) as a colourless oil. The spectroscopic data agreed with those reported above.

7.5.2 Synthesis of ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate [305]



[305]

Lawesson's reagent (3.846 g, 9.51 mmol) was added to a solution of 2-(2-oxo-1-pyrrolidinyl)acetate [304] (2.960 g, 17.29 mmol) in dry toluene (50 cm^3) and heated at 80 °C for 18 hours under Argon. The solvent was evaporated to give an orange gum. Column chromatography (40% EtOAc/hexane) afforded an impure product that was contaminated with phosphorous-containing by-products. Recolumning (40% EtOAc/hexane) afforded ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate [305] (2.838 g, 15.16 mmol, 88% yield) as a yellow oil.

R_f (20% EtOAc/hexane): 0.26

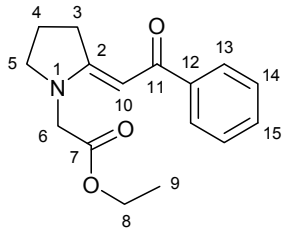
IR (ν/cm^{-1}): 2979, 2919, 2882 (w, C-H stretch), 1738 (m, ketone C=O stretch), 1688 (w), 1643 (w), 1504 (m), 1328 (m), 1224 (m, C-O stretch), 1196 (s, C=S stretch), 1129 (m), 1021 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (s, 2H, H_6), 4.23 (q, J = 7.1, 2H, H_8), 3.83 (t, J = 7.3, 2H, H_5), 3.08 (t, J = 7.9, 2H, H_3), 2.21 – 2.05 (m, 2H, H_4), 1.30 (t, J = 7.1, 3H, H_9).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.78 (C-2), 167.07 (C-7), 61.57 (C-8), 55.40 (C-6), 48.98 (C-5), 44.26 (C-3), 19.71 (C-4), 14.10 (C-9).

HRMS: Found M^+ = 187.0672, $C_8H_{13}NO_2S$ requires 187.0667

7.5.3 Synthesis of 2-{2-[(*E*)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}acetate [306A]



[306A]

2-(2-Thioxo-1-pyrrolidinyl)acetate [305] (0.468 g, 2.50 mmol) was dissolved in MeCN (2 cm^3) and was stirred at 0 °C under Argon. Phenacyl iodide (0.923 g, 3.75 mmol) was added and stirring was continued for 10 minutes. The cooling bath was removed and stirring was continued at room temperature for an additional 1 hour. A solution of PPh_3 (1.115 g, 4.25 mmol) and Et_3N (0.506 g, 0.70 cm^3, 5.00 mmol) in MeCN (10 cm^3) was added drop-wise and stirring was continued for 18 hours. The solvent was evaporated and the residue was extracted with EtOAc (50 cm^3) and washed with H_2O (2 × 25 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give a red gum. Flash chromatography (40% EtOAc/hexane) afforded ethyl 2-{2-[(*E*)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}acetate [306A] (0.659 g, 2.41 mmol, 96% yield) as a yellow oil. The oil eventually solidified upon standing at room temperature.

R_f (40% EtOAc/hexane): 0.16

M.p: 55 – 57 °C

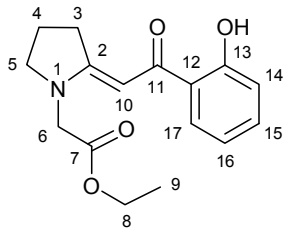
IR (ν/cm^{-1}): 2984, 2940, 2882 (C-H stretch), 1735 (m, ketone C=O stretch), 1714 (m, ester C=O stretch), 1598 (m, C=C stretch), 1479 (s), 1276 (s, C-O stretch), 1184 (s), 1158 (s), 1040 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6, 2H, H_{13}), 7.43 – 7.34 (m, 3H, H_{14} and H_{15}), 5.66 (s, 1H, H_{10}), 4.23 (q, J = 7.1, 2H, H_8), 4.05 (s, 2H, H_6), 3.55 (t, J = 7.2, 2H, H_5), 3.42 (t, J = 7.7, 2H, H_3), 2.06 (p, J = 7.4, 2H, H_4), 1.28 (t, J = 7.1, 3H, H_9).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.95 (C-11), 167.89 (C-7), 167.15 (C-2), 141.54 (C-12), 130.39 (C-15), 127.91 (C-13), 127.10 (C-14), 87.00 (C-10), 61.48 (C-8), 53.53 (C-6), 47.99 (C-5), 33.30 (C-3), 21.05 (C-4), 14.08 (C-9).

HRMS: Found M^+ = 273.1362, $C_{16}H_{19}NO_3$ requires 273.1365

7.5.4 Synthesis of 2-{2-[(*E*)-2-(2-hydroxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}acetate [306B]



[306B]

Ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate [305] (1.170 g, 6.25 mmol) was dissolved in MeCN (5 cm^3) and stirred under Argon. 1-(2-Hydroxyphenyl)-2-iodo-1-ethanone [296] (2.456 g, 9.37 mmol) was added and stirring was continued for 18 hours. The reaction mixture was cooled to 0 °C and a solution of PPh_3 (2.788 g, 10.63 mmol) and Et_3N (1.440 g, 2.00 cm^3, 14.23 mmol) in MeCN (20 cm^3) was added drop-wise and stirring was continued for 10 minutes. The cooling bath was removed and stirring was continued for 4 hours at room temperature. The solvent was evaporated and the residue was extracted with EtOAc (50 cm^3) and washed with H_2O (25 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give a red gum. Flash chromatography (30% EtOAc/hexane) afforded ethyl 2-{2-[(*E*)-2-(2-hydroxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}-acetate [306B] (1.740 g, 6.01 mmol, 96% yield) as a yellow solid.

R_f (30% EtOAc/hexane): 0.26

M.p: 65 – 66 °C

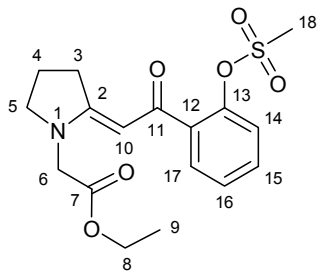
IR (ν/cm^{-1}): 2982, 2965, 2935, 2876 (w, C-H stretch), 1734 (m, C=O stretch), 1613 (m, C=C stretch), 1600 (m), 1540 (s), 1488 (s), 1284 (m), 1223 (s, C-O stretch), 1095 (s), 751 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 13.99 (s, 1H, OH), 7.62 (d, *J* = 7.0, 1H, H_{17}), 7.39 – 7.22 (m, 1H, H_{15}), 6.90 (d, *J* = 7.9, 1H, H_{16}), 6.78 (t, *J* = 7.1, 1H, H_{14}), 5.69 (s, 1H, H_{10}), 4.25 (q, *J* = 6.9, 2H, H_8), 4.07 (s, 2H, H_6), 3.58 (t, *J* = 7.1, 2H, H_5), 3.40 (t, *J* = 7.3, 2H, H_3), 2.15 – 1.99 (m, 2H, H_4), 1.30 (t, *J* = 7.0, 3H, H_9).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.38 (C-11), 168.31 (C-7), 167.63 (C-2), 162.74 (C-13), 133.45 (C-15), 127.90 (C-17), 121.21 (C-12), 118.14 (C-16), 117.77 (C-14), 85.49 (C-10), 61.74 (C-8), 53.94 (C-6), 48.21 (C-5), 33.76 (C-3), 20.92 (C-4), 14.17 (C-9).

HRMS: Found M^+ = 289.1309, $C_{16}H_{19}NO_4$ requires 289.1314

7.5.5 Synthesis of 2-[2-((*E*)-2-{2-[(methylsulfonyl)oxy]phenyl}-2-oxoethylidene)-1-pyrrolidinyl]acetate [306C]



[306C]

Ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate [305] (1.873 g, 10.00 mmol) was dissolved in MeCN (10 cm^3) and stirred under Argon. 2-(2-Bromoacetyl)phenyl methanesulfonate [295] (4.397 g, 15.00 mmol) was added and stirring was continued for 18 hours. the reaction mixture was cooled to 0°C and a solution of PPh_3 (4.328 g, 16.50 mmol) and Et_3N (2.024 g, 2.81 cm^3, 20.00 mmol) in MeCN (25 cm^3) was added drop-wise. The cooling bath was removed and stirring was continued for 6 hours at room temperature. The solvent was evaporated and the residue was extracted with EtOAc (100 cm^3) and washed with H_2O (50 cm^3) and brine (50 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Flash chromatography (60% EtOAc/hexane) afforded ethyl 2-[2-((*E*)-2-{2-[(methylsulfonyl)oxy]phenyl}-2-oxoethylidene)-1-pyrrolidinyl]acetate [306C] (3.143 g, 8.55 mmol, 86% yield) as an orange gum.

R_f (60% EtOAc/hexane): 0.18

IR (ν/cm^{-1}): 2981 and 2935 (w, C-H stretch), 2877 (w), 1740 (m, ester C=O stretch), 1624 (m, amide C=O stretch), 1601 (m), 1573 (m), 1478 (s), 1302 (m), 1262 (m, C-O stretch), 1118 (s), 1027 (m).

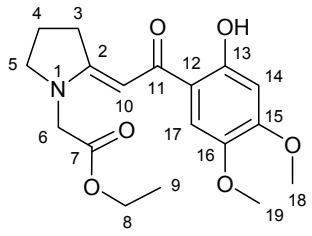
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J = 1.4, 7.4, 1H, H_{17}), 7.44 – 7.29 (m, 3H, H_{14}, H_{15} and H_{16}), 5.42 (s, 1H, H_{10}), 4.25 (q, J = 7.1, 2H, H_8), 4.02 (s, 2H, H_6), 3.57 (t, J = 7.3, 2H, H_5), 3.38 (t, J = 7.8, 2H, H_3), 3.09 (s, 3H, H_{18}), 2.10 (p, J = 7.6, 2H, H_4), 1.29 (t, J = 7.1, 3H, H_9).

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.63 (C-11), 167.58 (C-7), 167.54(C-2), 145.89 (C-13), 137.16 (C-12), 130.51 (C-15), 129.74 (C-17), 127.21 (C-16), 123.46 (C-14), 91.31 (C-10), 61.81 (C-8), 53.74 (C-6), 47.77 (C-5), 37.54 (C-18), 33.68 (C-3), 20.96 (C-4), 14.10 (C-9).

HRMS: Found M^+ = 367.1083, $C_{17}H_{21}NO_6S$ requires 367.1090

7.5.6 Synthesis of ethyl 2-{2-[(*E*)-2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxo-ethylidene]-1-pyrrolidinyl}acetate [306D]

Method 1:



[306D]

Ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate [305] (0.337 g, 1.80 mmol) was dissolved in MeCN (2 cm^3) and stirred under Argon. 1-(2-Hydroxy-4,5-dimethoxyphenyl)-2-iodo-1-ethanone [302] (0.6442 g, 2.00 mmol) was added and stirring was continued for 5 hours. Additional 1-(2-hydroxy-4,5-dimethoxyphenyl)-2-iodo-1-ethanone [302] (0.040 g, 0.12 mmol) was added and stirring was continued for 20 hours. Again, additional 1-(2-hydroxy-4,5-dimethoxyphenyl)-2-iodo-1-ethanone [302] (0.050 g, 0.16 mmol) was added and stirring was continued for 20 hours. A solution of PPh_3 (0.656 g, 2.50 mmol) and Et_3N (0.729 g, 1.01 cm^3, 7.20 mmol) in MeCN (5 cm^3) was added

drop-wise and stirring was continued for 18 hours. The solvent was evaporated and the red residue was extracted with EtOAc (100 cm^3) and washed with a saturated solution of NH_4Cl (2 × 50 cm^3) and brine (50 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated. Flash chromatography (30% EtOAc/hexane) afforded 1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [300] (0.174 g, 0.89 mmol, 39% yield from starting iodide) as the first eluting fraction. The spectroscopic data matched those previously reported. Further elution of the column afforded ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate [305] (0.071 g, 0.38 mmol, 21% recovery). Finally, the last eluting fraction afforded ethyl 2-{2-[(*E*)-2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}acetate [306D] (0.219 g, 0.63 mmol, 35% yield).

R_f (40% EtOAc/hexane): 0.24

M.p: 79 – 80 °C

IR (ν/cm^{-1}): 2979, 2959, 2934 (w, C-H stretch), 1725 (m, C=O stretch), 1586 (m, C=C stretch), 1571 (m), 1541 (s), 1517 (s), 1093 (s), 1022 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 14.29 (s, 1H, OH), 7.08 (s, 1H, H_{17}), 6.42 (s, 1H, H_{14}), 5.53 (s, 1H, H_{10}), 4.23 (q, *J* = 7.1, 2H, H_8), 4.07 (s, 2H, H_6), 3.87 (s, 3H, H_{18}*), 3.83 (s, 3H, H_{19}*), 3.57 (t, *J* = 7.3, 2H, H_5), 3.38 (t, *J* = 7.8, 2H, H_3), 2.06 (quintet, *J* = 7.6, 2H, H_4), 1.28 (t, *J* = 7.1, 3H, H_9).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.19 (C-11), 167.71 (C-7), 167.31 (C-2), 159.65 (C-3), 154.41 (C-15), 140.81 (C-16), 112.52 (C-12), 111.23 (C-17), 100.69 (C-14), 85.11 (C-10), 61.50 (C-8), 56.93 (C-18*), 55.67 (C-19*), 53.73 (C-6), 48.20 (C-5), 33.44 (C-3), 20.88 (C-4), 14.05 (C-9).

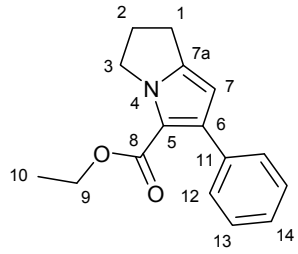
HRMS: Found M^+ = 349.1520, $C_{18}H_{23}NO_6$ requires 349.1525

Method 2:

Ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate [305] (0.411 g, 2.19 mmol) was dissolved in MeCN (2 cm^3) and stirred under Argon at 0 °C. 1-(2-Hydroxy-4,5-dimethoxyphenyl)-2-iodo-1-ethanone [302] (1.009 g, 3.13 mmol) was added and stirring was continued for 5 hours at room temperature. A solution of PPh_3 (0.863 g, 3.29 mmol) and Et_3N (0.720 g, 1.00 cm^3, 7.12 mmol) in MeCN (5 cm^3) was added drop-wise and stirring was continued for 12 hours. The solvent was evaporated and the red residue was extracted with EtOAc (50 cm^3) and washed with H_2O (25 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give a yellow oil. Flash chromatography (40% EtOAc/hexane) afforded ethyl 2-{2-[(*E*)-2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}acetate [306D] (0.687 g, 1.97 mmol, 90% yield). The spectroscopic data matched those reported above.

7.6 Preparation of 5,6-substituted pyrrolizines

7.6.1 Synthesis of ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate [312]



[312]

Ethyl 2-{2-[(*E*)-2-oxo-2-phenylethylidene]-1-pyrrolidinyl}acetate [306A] (0.245 g, 0.90 mmol) was added to a solution of dry toluene (10 cm^3) containing flash silica-gel (2.40 g) and stirred under Argon. The reaction mixture was refluxed for 18 hours. The reaction mixture was filtered through a sintered glass funnel and the silica-gel was washed with acetone (3 × 10 cm^3). The organic extract was evaporated to give a brown oil. Flash chromatography (10% EtOAc/hexane) afforded ethyl 6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate [312] (0.173 g, 0.68 mmol, 76% yield) as a colourless oil.

R_f (10% EtOAc/hexane); 0.29

IR (ν/cm^{-1}): 2979, 2902 (C-H stretch), 1682 (s, C=O stretch), 1603 (w), 1281 (m), (1246 (s, C-O stretch), 1177 (m), 1095 (s), 1037 (m), 758 (s), 696 (s).

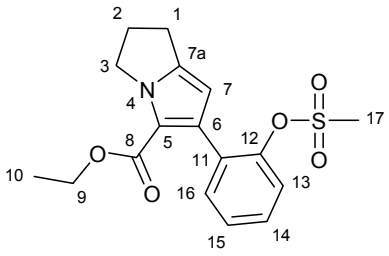
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 7.0, 2H, H_{12}), 7.38 – 7.21 (m, 3H, H_{13} and H_{14}), 5.95 (s, 1H, H_7), 4.33 (t, J = 7.2, 2H, H_3), 4.17 (q, J = 7.1, 2H, H_9), 2.88 (t, J = 7.5, 2H, H_1), 2.58 – 2.40 (m, 2H, H_2), 1.17 (t, J = 7.1, 3H, H_{10}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.36 (C-8), 142.28 (C-7a), 137.33 (C-11), 136.61 (C-6), 129.61 (C-13), 127.37 (C-12), 126.54 (C-14), 114.27 (C-5), 103.47 (C-7), 59.51 (C-9), 48.80 (C-3), 26.73 (C-1), 24.46 (C-2), 14.10 (C-10).

HRMS: Found M^+ = 255.1254, $C_{16}H_{17}NO_2$ requires 255.1259

7.6.2 Synthesis of ethyl 6-{2-[(methylsulfonyl)oxy]phenyl}-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate [313]

Method 1:



[313]

2-[2-((*E*)-2-{2-[(Methylsulfonyl)oxy]phenyl}-2-oxo-ethylidene)-1-pyrrolidinyl]acetate [306C] (1.008 g, 2.74 mmol) was added to a solution of *o*-xylene (25 cm^3) containing flash silica-gel (10.00 g) and stirred at reflux for 5 hours under an Argon atmosphere. The reaction mixture was filtered through a pad of Celite and the pad was rinsed with acetone (3 × 20 cm^3). The organic extract was evaporated to give a brown gum. Flash chromatography (40% EtOAc/hexane) afforded ethyl 6-{2-[(methylsulfonyl)oxy]phenyl}-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate [313] [(0.502 g, 1.44 mmol, 53% yield) as an orange gum.

R_f (40% EtOAc/hexane): 0.47

IR (ν/cm^{-1}): 2979 (w, C-H stretch), 1683 (m, C=O stretch), 1542 (m), 1270 (s, C-O stretch), 1162 (s), 1030 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 4H, H_{13}, H_{14}, H_{15} and H_{16}), 5.98 (s, 1H, H_7), 4.40 – 4.26 (m, 2H, H_3), 4.11 (q, J = 7.1, 2H, H_9), 2.90 (t, J = 7.5, 2H, H_1), 2.68 (s, 3H, H_{17}), 2.61 – 2.47 (m, 2H, H_2), 1.07 (t, J = 7.1, 3H, H_{10}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.99 (C-8), 147.01 (C-12), 142.31 (C-7a), 132.36 (C-14), 130.36 (C-11), 130.10 (C-6), 128.33 (C-16), 126.52 (C-15), 122.76 (C-13), 115.67 (C-5), 104.03 (C-7), 59.71 (C-9), 48.53 (C-3), 37.31 (C-17), 26.82 (C-1), 24.45 (C-2), 13.89 (C-10).

HRMS: Found M^+ = 349.0979, $C_{17}H_{23}NO_5S$ requires 349.0984

Method 2:

2-[2-((*E*)-2-{2-[(Methylsulfonyl)oxy]phenyl}-2-oxo-ethylidene)-1-pyrrolidinyl]-acetate [306C] (0.120 g, 0.33 mmol) was added to a solution of *o*-xylene (3 cm^3) containing flash silica-gel (1.20 g) in a microwave tube. The tube was sealed and subjected to microwave irradiation (300 W, 200 °C) for 3 minutes. The reaction mixture was filtered through a pad of Celite and the pad was rinsed with acetone (3 × 10 cm^3). The organic extract was evaporated to give a brown gum. Flash chromatography (40% EtOAc/hexane) afforded ethyl 6-{2-[(methylsulfonyl)oxy]phenyl}-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate [313] (0.060 g, 0.17 mmol, 52% yield) as an orange gum. The spectroscopic data matched those reported above.

Method 3:

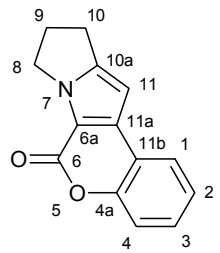
2-[2-((*E*)-2-{2-[(Methylsulfonyl)oxy]phenyl}-2-oxo-ethylidene)-1-pyrrolidinyl]-acetate [306C] (0.094 g, 0.26 mmol) was added to glacial AcOH (10 cm^3) and refluxed for 48 hours under an atmosphere of Argon. The solvent was evaporated to give a brown gum. Flash chromatography (40% EtOAc/hexane) afforded ethyl 6-{2-[(methylsulfonyl)oxy]phenyl}-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate [313] (0.034 g, 0.01 mmol, 38% yield) as a colourless gum. The spectroscopic data matched those reported above.

Method 4:

2-[2-((*E*)-2-{2-[(Methylsulfonyl)oxy]phenyl}-2-oxo-ethylidene)-1-pyrrolidinyl]-acetate [306C] (0.714 g, 1.94 mmol) was added to a solution of glacial AcOH (3 cm^3) in a microwave tube. The tube was sealed and subjected to microwave irradiation (50 W, 120 °C) for 1 hour. The solvent was evaporated to give a brown gum. Flash chromatography (30% EtOAc/hexane) afforded ethyl 6-{2-[(methylsulfonyl)oxy]phenyl}-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate [313] (0.440 g, 1.26 mmol, 65% yield) as an orange gum. The spectroscopic data matched those reported above.

7.6.3 Synthesis of 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one [314]

Method 1:



[314]

Ethyl 2-{2-[(*E*)-2-(2-hydroxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}acetate [306B] (0.294 g, 1.02 mmol) was added to a solution of toluene (10 cm^3) containing flash silica-gel (3.00 g) and stirred under Argon. The reaction mixture was refluxed for 18 hours, cooled and filtered. The silica-gel was washed with additional acetone (3 × 10 cm^3). The solvent was evaporated to give a brown gum. Flash

chromatography (20% EtOAc/hexane) afforded 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one [314] (0.052 g, 0.23 mmol, 23% yield) as a white solid.

R_f (30% EtOAc/hexane): 0.35

M.p: 145 – 146 °C (sublimation noted from 102 °C through to 136 °C)

IR (ν/cm^{-1}): 2987 and 2959 (C-H stretch), 1695 (s, C=O stretch), 1616 (m), 1442 (m), 1201 (s, C-O stretch), 1081 (s), 979 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 7.4, 1H, H_1), 7.43 – 7.14 (m, 3H, H_2, H_3 and H_4), 6.29 (s, 1H, H_{11}), 4.34 (t, J = 7.1, 2H, H_8), 2.95 (t, J = 7.4, 2H, H_{10}), 2.68 – 2.47 (m, 2H, H_9).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.93 (C-6), 151.31 (C-4a), 148.79 (C-10a), 133.91 (C-11b), 127.31 (C-3), 123.83 (C-1), 122.78 (C-2), 118.59 (C-11a), 117.13 (C-4), 112.69 (C-6a), 94.39 (C-11), 46.83 (C-8), 27.35 (C-10), 24.62 (C-9).

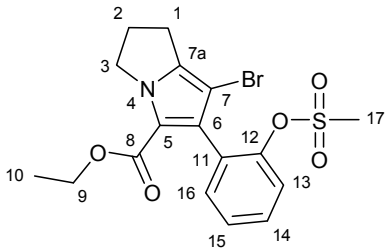
HRMS: Found M^+ = 225.0784, $C_{14}H_{11}NO_2$ requires 225.0790

Method 2:

Ethyl 2-{2-[(*E*)-2-(2-hydroxyphenyl)-2-oxoethylidene]-1-pyrrolidinyl}acetate [306B] (0.479 g, 1.65 mmol) was added to a solution of *o*-xylene (10 cm^3) containing flash silica-gel (5.00 g) and stirred under Argon. The reaction mixture was refluxed for 4 hours, cooled and filtered. The silica-gel was washed with additional acetone (3 × 10 cm^3). The solvent was evaporated to give a brown gum. Flash chromatography (20% EtOAc/hexane) afforded 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one [314] (0.135 g, 0.60 mmol, 36% yield) as a white solid. The spectroscopic data matched those above.

7.7 Preparation of additional 5,6,7-substituted pyrrolizine systems

7.7.1 Synthesis of ethyl 7-bromo-6-{2-[(methylsulfonyl)oxy]phenyl}-2,3-dihydro-1*H*-pyrrolizine-5-carboxy-late [316]



[316]

6-{2-[(Methylsulfonyl)oxy]phenyl}-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate [313] (0.290 g, 0.83 mmol) was added to dry DMF (5 cm^3) and stirred under Argon. NBS (0.178 g, 1.00 mmol) was added and stirring was continued for 20 hours. The solvent was evaporated and the residue was extracted with CH_2Cl_2 (20 cm^3) and washed with H_2O (10 cm^3) and brine (10 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Flash chromatography (30% EtOAc/hexane) afforded ethyl 7-bromo-6-{2-[(methylsulfonyl)oxy]phenyl}-2,3-dihydro-1*H*-pyrrolizine-5-carboxy-late [316] (0.320 g, 0.75 mmol, 90% yield) as an orange gum.

R_f (30% EtOAc/hexane): 0.35

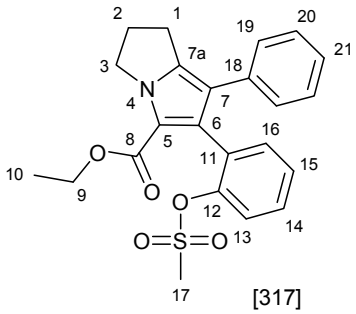
IR (ν/cm^{-1}): 3029 and 2984 (w, C-H stretch), 1689 (s, C=O stretch), 1518 (m), 1360 (s), 1276 (m, C-O stretch), 1158 (s), 1036 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.28 (m, 4H, H_{13}, H_{14}, H_{15} and H_{16}), 4.48 (dt, J = 7.1, 12.4, 1H, $H_{5'}$), 4.34 (dt, J = 7.4, 12.1, 1H, $H_{5''}$), 4.19 – 3.95 (m, 2H, H_9), 2.89 (t, J = 7.8, 2H, H_1), 2.72 (s, 3H, H_{17}), 2.57 (quintet, J = 7.4, 2H, H_2), 1.01 (t, J = 7.1, 3H, H_{10}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.11 (C-8), 147.64 (C-12), 141.16 (C-7a), 132.63 (C-14), 129.10 (C-16), 128.28 (C-11), 127.92 (C-6), 126.53 (C-15), 122.49 (C-13), 116.84 (C-5), 91.40 (C-7), 59.99 (C-9), 49.79 (C-3), 37.13 (C-17), 26.08 (C-1), 24.19 (C-2), 13.72 (C-10).

HRMS: Found M^+ = 427.0083, $C_{17}H_{18}{}^{79}BrNO_5S$ requires 427.0089

7.7.2 Synthesis of ethyl 6-{2-[(methylsulfonyl)oxy]phenyl}-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxy-late [317]



[317]

Ethyl 7-bromo-6-{2-[(methylsulfonyl)oxy]phenyl}-2,3-dihydro-1*H*-pyrrolizine-5-carboxy-late [316] (0.199 g, 0.46 mmol was added to a round bottom flask containing phenylboronic acid (0.112 g, 0.92 mmol), $Pd(PPh_3)_4$ (0.053 g, 0.10 mmol) and Na_2CO_3 (0.488 g, 4.60 mmol). The flask was evacuated and back-filled with Argon several times to remove O_2. H_2O (5 cm^3), EtOH (5 cm^3) and DME (5 cm^3) was thoroughly degassed and added to the solids under a positive pressure of Argon. The heterogeneous mixture was stirred at room temperature for 10 minutes and then allowed to reflux for 18 hours. After cooling to room temperature, H_2O (25 cm^3) was added to the black reaction mixture followed by CH_2Cl_2 (50 cm^3) and stirring was continued for 5 minutes. The organic phase was separated and the aqueous phase was re-extracted with additional CH_2Cl_2 (2 × 50 cm^3). The combined organic extract was dried over Na_2SO_4, filtered and evaporated to give a black oil. Flash chromatography (30% EtOAc/hexane) afforded ethyl 6-{2-[(methylsulfonyl)oxy]phenyl}-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxy-late [317] (0.098 g, 0.23 mmol, 50% yield) as a solid. The product was slightly contaminated with ethyl 6-{2-[(methylsulfonyl)oxy]phenyl}-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate [313].

R_f (40% EtOAc/hexane): 0.47

IR (ν/cm^{-1}): 2969 and 2932 (w, C-H stretch), 1681 (s, C=O stretch), 1604 (w), 1544 (m), 1297 (s, C-O stretch), 1134 (s), 1081 (m).

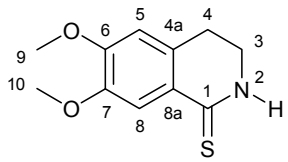
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.00 (m, 9H, H_{13}, H_{14}, H_{15}, H_{16}, H_{19}, H_{20} and H_{21}), 4.52 – 4.27 (m, 2H, H_3), 4.18 – 4.00 (m, 2H, H_9), 3.05 (t, J = 7.5, 2H, H_1), 2.65 (s, 3H, H_{17}), 2.60 – 2.52 (m, 2H, H_2), 1.02 (t, J = 7.1, 3H, H_{10}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.05 (C-8), 147.67 (C-12), 140.63 (C-7a), 134.54 (C-18), 133.24 (C-14), 129.19 (C-11), 128.49 (C-21), 128.22 (C-20), 127.86 (C-19), 126.98 (C-6), 126.28 (C-16), 125.66 (C-15), 122.11 (C-13), 117.47 (C-7), 116.36 (C-5), 59.73 (C-9), 48.70 (C-3), 37.62 (C-17), 26.50 (C-1), 25.03 (C-2), 13.78 (C-10).

HRMS: Found M^+ = 425.1291, $C_{23}H_{23}NO_5S$ requires 425.1297

7.8 Preparation of isoquinolinethiones

7.8.1 Synthesis of 6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinethione [321]



[321]

The preparation of this compound was adapted from a literature procedure.[253] 3,4-Dimethoxyphenethylamine (18.124 g, 100.00 mmol) was added to a solution of Et_3N (10.119 g, 14.10 cm^3, 100.00 mmol) in dry CH_2Cl_2 (15 cm^3) and stirred at 0°C under Argon. A solution of CS_2 (7.614 g, 6.00 cm^3, 100.00 mmol) in dry CH_2Cl_2 (15 cm^3) was added drop-wise over a period of 15 minutes. After the addition was complete the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was re-cooled to 0 °C and ethyl chloroformate (10.850 g, 100.00 mmol) was added drop-wise over a period of 15 minutes. Again, after addition was complete the reaction mixture was stirred at room temperature for 1 hour. Et_3N (10.119 g, 14.10 cm^3, 100.00 mmol) was added and the reaction mixture

was stirred for an additional 2 hours before being refluxed for 30 minutes. The reaction mixture was poured into water (200 cm^3) and made alkaline with 2M NaOH solution. The reaction mixture was extracted with dichloromethane (3 × 100 cm^3), dried over Na_2SO_4, filtered and finally evaporated to afford crude 4-(2-isothiocyanatoethyl)-1,2-dimethoxybenzene [320] (23.36 g, 105% of theoretical yield). This crude mixture was used directly into the next reaction.

Polyphosphoric acid (115 g) was added to crude 4-(2-isothiocyanatoethyl)-1,2-dimethoxybenzene [320] (23.36 g) and the mixture was heated at 70-80 °C for 90 minutes. The red mixture was poured into water (300 cm^3) and stirred for 30 minutes. The solid was vacuum-filtered through a glass sintered funnel and washed with additional water (500 cm^3). The solids were rinsed into a flask with copious amounts of acetone (*ca*. 1500 cm^3) and the solvent was allowed to evaporate overnight. The damp residue was extracted into MeOH (200 cm^3) and brought to reflux for 10 minutes along with vigorous stirring. The stirring heterogeneous solution was allowed to cool to room temperature before being finally cooled to -10 °C. After 20 minutes of stirring, the solids were vacuum-filtered through a glass sintered funnel and washed with additional cold MeOH until the washings were clear. Finally, the solid was washed with hexane (100 cm^3) and dried under vacuum to afford 6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinethione [321] (21.00 g, 58.22 mmol, 94% yield over 2 steps) as a pink solid.

M.p: 210 – 212 °C [lit.,[255] 213 – 214 °C (CH_2Cl_2/hexane)].

IR (ν/cm^{-1}): 3216 (m br, NH), 2994, 2939 (w, C-H stretch), 2829 (w), 1605 (m), 1581 (m), 1529 (s), 1509 (s), 1273 (s), 1250 (s, C-O stretch), 1181 (m), 1132 (m, C=S stretch), 1050 (s), 866 (s).

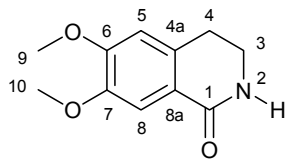
^{1}H NMR (300 MHz, CDCl3) δ 8.59 (s, 1H, NH), 8.08 (s, 1H, H_8), 6.62 (s, 1H, H_5), 3.97 (s, 3H, H_9*), 3.94 (s, 3H, H_{10}*), 3.54 (td, J = 3.4, 6.9, 2H, H_3), 2.95 (t, J = 6.9, 2H, H_4).

^{13}C NMR (75 MHz, CDCl3) δ 193.20 (C-1), 152.92 (C-6), 147.84 (C-7), 127.83 (C-4a), 125.37 (C-8a), 114.41 (C-8), 109.11 (C-5), 56.12 (C-9*), 56.09 (C-10*), 41.88 (C-3), 27.57 (C-4).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 223.0661, $C_{11}H_{13}NO_2S$ requires 233.0667

7.8.2 Synthesis of 6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinone [322]



[322]

The preparation of this compound was adapted from a literature procedure.[253] KOH (4.080 g, 72.71 mmol) was dissolved in H_2O (10 cm^3) and allowed to cool to room temperature. Once cooled, the solution was added to MeOH (60 cm^3) and stirred at 0 °C for 10 minutes. H_2O_2 (100 vols, 20 cm^3) was added to give a cloudy solution. 6,7-Dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinethione [321] (6.518 g, 29.19 mmol) was added over 20 minutes and stirring was continued for 4 hours at 0 °C (Note: internal temperature rose to 30 °C during the course of the reaction). The heterogeneous solution was filtered through a pad of Celite and the pad was rinsed with MeOH (2 × 25 cm^3). The filtrate was evaporated to remove most of the MeOH. CH_2Cl_2 (50 cm^3) and H_2O (50 cm^3) was added to the aqueous residue. The extract was cautiously acidified with concentrated HCl and the organic phase was separated. The aqueous layer was re-extracted with CH_2Cl_2 (2 × 50 cm^3). The combined organic extract was dried over Na_2SO_4, filtered and evaporated to afford 6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinone [322] (5.444 g, 26.27 mmol, 90% yield) as a white solid.

M.p: 170 – 172 °C [lit.,[254] 175 °C (EtOAc)].

IR (ν/cm^{-1}): 3188 (w br, NH), 2968, 2952 (w, C-H stretch), 2866 (w), 1655 (s, C=O stretch), 1602 (s), 1510 (s), 1480 (s), 1257 (s), 1237 (s, C-O stretch), 1050 (s), 805 (s).

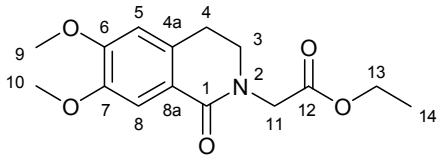
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 1H, H_8), 7.54 (br s, 1H, NH), 6.69 (s, 1H, H_5), 3.94 (s, 3H, H_9*), 3.93 (s, 3H, H_{10}*), 3.57 (td, J = 2.6, 6.7, 2H, H_3), 2.92 (t, J = 6.7, 2H, H4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.68 (C-1), 151.85 (C-6), 147.71 (C-7), 132.54 (C-4a), 121.21 (C-8a), 109.77 (C-5), 109.38 (C-8), 55.87 (C-9*), 55.81 (C-10*), 40.09 (C-3), 27.69 (C-4).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 207.0890, $C_{11}H_{13}NO_3$ requires 207.0895

7.8.3 Synthesis of ethyl 2-[6,7-dimethoxy-1-oxo-3,4-dihydro-2(1*H*)-isoquinolinyl]acetate [323]



[323]

6,7-Dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinone [322] (2.072 g, 10.00 mmol) was added to dry THF (25 cm^3) and stirred at 0 °C under Argon. NaH (60% dispersion in oil, 0.480 g, 12.00 mmol) was added and stirring was continued for 30 minutes. The cooling bath was removed and the reaction mixture was refluxed for 6 hours to effect complete salt formation. After cooling to 0 °C, ethyl 2-bromoacetate (2.004 g, 1.34 cm^3, 12.00 mmol) was added and stirring was continued for 10 minutes. The cooling bath was removed and stirring was continued for 18 hours at room temperature. H_2O (1 cm^3) was added and stirring was continued for 5 minutes. The solvent was evaporated and the residue was extracted with CH_2Cl_2 (50 cm^3) and washed with H_2O (50 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and

evaporated to give an orange gum. Flash chromatography (60% EtOAc/hexane) afforded ethyl 2-[6,7-dimethoxy-1-oxo-3,4-dihydro-2(1*H*)-isoquinolinyl]acetate [323] (2.886 g, 9.84 mmol, 98% yield) as an orange gum.

R_f (60% EtOAc/hexane): 0.29

IR (ν/cm^{-1}): 2996, 2967, 2935 (w, C-H stretch), 2828 (w), 1736 (m, ester C=O stretch), 1646 (m, amide C=O stretch), 1606 (m), 1519 (m), 1280 (s, C-O stretch), 1195 (s), 1116 (s), 1025 (s).

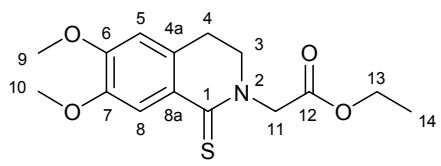
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H, H_8), 6.65 (s, 1H, H_5), 4.31 (s, 2H, H_{11}), 4.22 (q, J = 7.1, 2H, H_{13}), 3.92 (s, 3H, H_9*), 3.92 (s, 3H, H_{10}*), 3.65 (t, J = 6.7, 2H, H_3), 2.99 (t, J = 6.6, 2H, H_4), 1.29 (t, J = 7.2, 3H, H_{14}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.33 (C-12), 164.98 (C-1), 151.92 (C-6), 147.85 (C-7), 132.10 (C-4a), 121.26 (C-8a), 110.53 (C-5), 109.22 (C-8), 61.13 (C-13), 55.98 (C-9*), 55.95 (C-10*), 49.17 (C-11), 47.59 (C-3), 27.59 (C-4), 14.12 (C-14).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 293.1258, $C_{15}H_{19}NO_5$ requires 293.1263

7.8.4 Synthesis of ethyl 2-[6,7-dimethoxy-1-thioxo-3,4-dihydro-2(1*H*)-isoquinolinyl]acetate [324]



[324]

Ethyl 2-[6,7-dimethoxy-1-oxo-3,4-dihydro-2(1*H*)-isoquinolinyl]acetate [323] (2.158 g, 7.36 mmol) was added to dry toluene (25 cm^3) and stirred under Argon. Lawesson's reagent (1.638 g, 4.05 mmol) was added and the reaction mixture was heated at 80 °C for 4 hours. the solvent was evaporated to give a green residue. Flash chromatography (40% EtOAc/hexane) afforded ethyl 2-[6,7-dimethoxy-

1-thioxo-3,4-dihydro-2(1*H*)-isoquinolinyl]acetate [324] (1.507 g, 4.87 mmol, 66% yield) as a yellow solid.

R_f (40% EtOAc/hexane): 0.26

M.p: 89 – 90 °C

IR (ν/cm^{-1}): 2976, 2934 and 2906 (w, C-H stretch), 2832 (w), 1745 (s, C=O stretch), 1603 (m), 1578 (m), 1497 (s), 1258 (m, C-O stretch), 177 (s, C=S stretch), 1028 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 6.58 (s, 1H), 4.95 (s, 2H), 4.24 (q, *J* = 7.1, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.76 (t, *J* = 6.7, 2H), 2.99 (t, *J* = 6.7, 2H), 1.30 (t, *J* = 7.1, 3H).

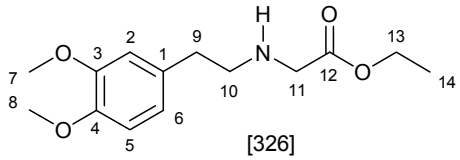
^{13}C NMR (75 MHz, $CDCl_3$) δ 192.92 (C-1), 167.82 (C-12), 152.16 (C-6), 147.48 (C-7), 126.89 (C-4a), 126.60 (C-8a), 115.18 (C-8), 108.49 (C-5), 61.41 (C-13), 57.23 (C-4), 56.02 (C-9*), 55.97 (C-10*), 50.37 (C-3), 27.34 (C-4), 14.10 (C-14).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 309.1027, $C_{15}H_{19}NO_4S$ requires 309.1035

7.9 Attempts to a more expedient route to compounds [323] and [324]

7.9.1 Synthesis of ethyl 2-[(3,4-dimethoxyphenethyl)amino]acetate [326]



[326]

3,4-Dimethoxyphenethylamine (3.691 g, 20.36 mmol) was added to a solution of dry $CHCl_3$ (25 cm^3) containing Et_3N (2.064 g, 2.88 cm^3, 20.40 mmol) and stirred under Argon. A solution of ethyl 2-bromoacetate (3.407 g, 2.26 cm^3, 20.40

mmol) in dry $CHCl_3$ (25 cm^3) was added drop-wise and stirring was continued for 48 hours. The reaction mixture was poured into H_2O (50 cm^3) and the organic phase was separated and washed with brine (50 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Column chromatography (EtOAc) afforded ethyl 2-[(3,4-dimethoxyphenethyl)amino]acetate [326] (3.307 g, 12.37 mmol, 61% yield) as an orange oil.

R_f (EtOAc): 0.32 (with streaking)

IR (ν/cm^{-1}): 3333 (br w, NH), 2938 (w, C-H stretch), 2837 (w), 1736 (m, C=O stretch), 1466 (s), 1262 (s), 1236 (s, C-O stretch), 1141 (s), 1027 (s).

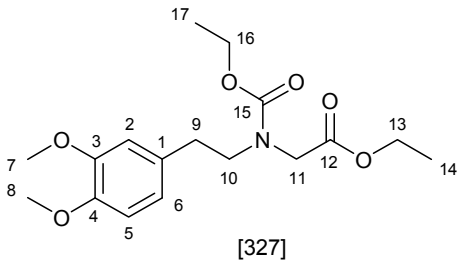
^1H NMR (300 MHz, $CDCl_3$) δ 6.83 – 6.72 (m, 3H, H_2, H_5 and H_6), 4.17 (q, J = 7.1, 2H, H_{13}), 3.87 (s, 3H, H_7*), 3.85 (s, 3H, H_8*), 3.41 (s, 2H, H_{11}), 2.88 (dd, J = 3.9, 10.8, 2H, H_{10}), 2.76 (dd, J = 3.9, 10.7, 2H, H_9), 1.62 (br s, 1H, NH), 1.26 (t, J = 7.1, 3H, H_{14}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.27 (C-12), 148.89 (C-3), 147.45 (C-4), 132.23 (C-1), 120.49 (C-6), 111.94 (C-5), 111.33 (C-2), 60.62 (C-13), 55.87 (C-7*), 55.78 (C-8*), 50.91 (C-11), 50.76 (C-10), 35.98 (C-9), 14.16 (C-14).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 267.1465, $C_{14}H_{21}NO_4$ requires 267.1471

7.9.2 Synthesis of ethyl 2-[(3,4-dimethoxyphenethyl)(ethoxycarbonyl)-amino]acetate [327]



[327]

Ethyl 2-[(3,4-dimethoxyphenethyl)amino]-acetate [326] (1.000 g, 3.74 mmol), and Et_3N (0.416 g, 0.58 cm^3, 4.11 mmol) were added to dry CH_2Cl_2 (20 cm^3) and cooled to 0 °C under Argon. Ethyl chloroformate (0.446 g, 0.39 cm^3, 4.11 mmol) was added drop-wise and stirring was continued for an additional 20 hours at room temperature. The organic phase was washed with water (25 cm^3), and brine (20 cm^3). The organic phase was dried over Na_2SO_4, filtered and evaporated to give a yellow oil. Flash chromatography (40% EtOAc/hexane) afforded ethyl 2-[(3,4-dimethoxyphenethyl)(ethoxycarbonyl)amino]acetate [327] (1.268 g, 3.74 mmol, 100% yield) as a thick yellow oil.

R_f(40% EtOAc/hexane): 0.38

IR (ν/cm^{-1}): 2983, 2939 (w, C-H stretch), 2838 (w), 1750 (m, ester C=O stretch), 1698 (s, amide C=O stretch), 1610 (w), 1593 (w), 1517 (s), 1261 (s), 1236 (s, C-O stretch), 1028 (s).

^{1}H NMR (300 MHz, CDCl3) δ 6.84 – 6.65 (m, 3H, H_2, H_5 and H_6), 4.18 (q, J = 7.2, 2H, H_{13}*), 4.15 (q, J = 7.2, 2H, H_{14}*), 3.89 (s, 1H, part of H_{11}), 3.87 (s, 3H, $H_7^{\#}$), 3.86 (s, 3H, $H_8^{\#}$), 3.83 (s, 1H, part of H_{11}), 3.52 (m, 2H, H_{10}), 2.80 (m, 2H, H_9)), 1.26 (t, J = 7.1, 3H, $H_{14}^{\$}$), 1.23 (t, J = 7.3, 3H, $H_{17}^{\$}$).

Doubling of most signals was observed in the ^{13}C NMR:

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.80 and 169.77 (C-12), 156.49 and 155.89 (C-15), 148.92 and 148.91 (C-3), 147.62 and 147.53 (C-2), 131.49 (C-1), 120.66 and 120.63 (C-6), 111.99 (C-5), 111.34 and 111.29 (C-2), 61.64 and 61.50 (C-16), 61.02 (C-13), 55.85 (C-7*), 55.81 (C-8*), 50.74 and 50.08 (C-

10), 49.50 and 49.49 (C-11), 34.59 and 34.06 (C-9), 14.53 (C-14), 14.12 and 14.10 (C-17).

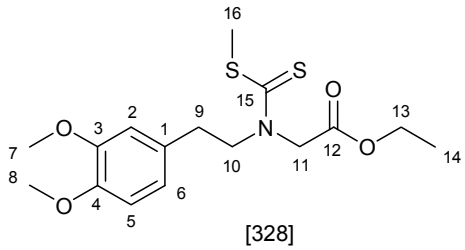
Assignments denoted by * or # and $ are interchangeable.

HRMS: Found M^+ = 339.1676, $C_{17}H_{25}NO_6$ requires 339.1682

7.9.3 Attempted preparation of ethyl 2-[6,7-dimethoxy-1-oxo-3,4-dihydro-2(1*H*)-isoquinolinyl]acetate [323]

Ethyl 2-[(3,4-dimethoxyphenethyl)(ethoxycarbonyl)amino]acetate [327] (1.268 g, 3.74 mmol) was dissolved into PPA (5 cm^3) and stirred at room temperature for 16 hours. H_2O (25 cm^3) was added and the reaction mixture was extracted with CH_2Cl_2 (50 cm^3). The organic extract was washed with H_2O (20 cm^3) and brine (20 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an oil that could not be characterized by spectroscopic means.

7.9.4 Synthesis of ethyl 2-{(3,4-dimethoxyphenethyl)[(methylsulfanyl)-carbothioyl]amino}acetate [328]



[328]

Ethyl 2-[(3,4-dimethoxyphenethyl)amino]-acetate [326] (0.507 g, 1.89 mmol) was added to dry THF and stirred under Argon. NaH (60 % dispersion in oil, 0.080 g, 1.98 mmol) was added and stirring was continued for 20 minutes. The reaction mixture was cooled to 0 °C and CS_2 (0,151 g, 0.12 cm^3, 1.98 mmol) was added. The cooling bath was removed and stirring was continued for 20 minutes at room temperature. The reaction mixture was re-cooled to 0 °C and MeI (0.281 g, 0.13 cm^3, 1.98 mmol) was added. After 5 minutes the cooling bath was removed and stirring was continued for an additional 3 hours. Water (0.50 cm^3) was added followed by

Na_2SO_4. The reaction mixture was filtered and evaporated to give a yellow oil. Flash chromatography (40% EtOAc/hexane) afforded ethyl 2-{(3,4-dimethoxy-phenethyl)[(methylsulfanyl)carbothioyl]amino}acetate [328] (0.455 g, 1.27 mmol, 67% yield) as an odoriferous thick yellow oil.

R_f (40% EtOAc/hexane): 0.26

IR (ν/cm^{-1}): 2934 (w, C-H stretch), 2834 (w), 1742 (m, C=O stretch), 1607 (w), 1591 (w), 1514 (s), 1318 (s), 1260 (s), 1235 (s, C-O stretch), 1153 (s, C=S stretch), 1025 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 – 6.66 (m, 3H, H_2, H_5 and H_6), 4.54 (s, 2H, H_{11}), 4.18 (q, J = 7.1, 2H, H_{13}), 4.01 (t, J = 7.6, 1H, H_{10}), 3.86 (s, 3H, H_7*), 3.85 (s, 3H, H_8*), 3.00 (t, J = 7.5, 2H, H_9), 2.66 (s, 3H, H_{16}), 1.26 (t, J = 7.1, 3H, H_{14}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.71 (C-15), 167.27 (C-12), 148.80 (C-3), 147.64 (C-4), 129.88 (C-1), 120.44 (C-6), 111.71 (C-5), 111.26 (C-2), 60.99 (C-13), 56.56 (C-11), 55.60 (C-10), 55.57 (C-7*), 55.45 (C-8*), 32.87 (C-9), 20.01 (C-16), 13.80 (C-14).

Assignments denoted by * are interchangeable.

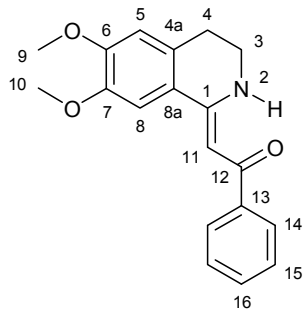
HRMS: Found M^+ = 357.1065, $C_{16}H_{23}NO_4S_2$ requires 357.1068

7.9.5 Attempted preparation of ethyl 2-[6,7-dimethoxy-1-thioxo-3,4-dihydro-2(1*H*)-iso-quinolinyl]acetate [324]

Ethyl 2-{(3,4-dimethoxy-phenethyl)[(methylsulfanyl)carbothioyl]amino}acetate [328] (0.455 g, 1.27 mmol) was dissolved into PPA (5 cm^3) and stirred at room temperature for 16 hours. H_2O (25 cm^3) was added and the reaction mixture was extracted with CH_2Cl_2 (50 cm^3). The organic extract was washed with H_2O (20 cm^3) and brine (20 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an oil that could not be characterized by spectroscopic means.

7.10 Preparation of vinylogous amides

7.10.1 Synthesis of (*Z*)-2-[6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinoliny-lidene]-1-phenyl-1-ethanone [329A]



[329A]

6,7-Dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinethione [321] (0.936 g, 4.19 mmol) was added to dry MeCN (20 cm^3) and stirred under Argon. Phenacyl bromide (0.917 g, 4.61 mmol) was added and stirring was continued for 30 minutes. A solution of PPh_3 (1.209 g, 4.61 mmol) and Et_3N (0.848 g, 1.18 cm^3, 8.38 mmol) in dry MeCN (20 cm^3) was added drop-wise and stirring was continued for 45 minutes. The solvent was evaporated and the residue was extracted with CH_2Cl_2 (50 cm^3) and washed with H_2O (50 cm^3) and brine (50 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Flash chromatography (50% EtOAc/hexane) afforded (*Z*)-2-[6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinylidene]-1-phenyl-1-ethanone [329A] (1.115 g, 3.61 mmol, 86% yield) as a yellow solid.

R_f (50% EtOAc/hexane): 0.36

M.p: 130 – 133 °C [lit.,[262] 135 – 136 (hexane/$CHCl_3$)]

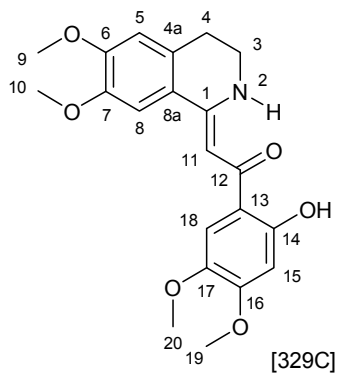
IR (ν/cm^{-1}): 2996 and 2929 (w, C-H stretch), 2829 (w), 1602 (m, C=O stretch), 1584 (m), 1504 (s), 1260 (s, C-O stretch), 1065 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.82 (s, 1H, NH), 7.98 – 7.88 (m, 2H, H_{14}), 7.49 – 7.40 (m, 3H, H_{15} and H_{16}), 7.25 (s, 1H, H_8), 6.72 (s, 1H, H_5), 6.20 (s, 1H, H_{11}), 3.96 (s, 3H, H_9*), 3.94 (s, 3H, H_{10}*), 3.60 – 3.47 (m, 2H, H_3), 2.90 (t, J = 6.5, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 188.40 (C-12), 158.61 (C-1), 151.69 (C-6), 147.95 (C-7), 141.21 (C-13), 130.59 (C-4a), 130.34 (C-16), 128.18 (C-14), 126.82 (C-15), 121.35 (C-8a), 110.73 (C-5), 108.49 (C-8), 86.34 (C-11), 56.25 (C-9*), 56.00 (C-10*), 38.68 (C-3), 27.97 (C-4).

Assignments denoted by * are interchangeable.

7.10.2 Synthesis of (*Z*)-2-[6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinoliny-lidene]-1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [329C]



[329C]

6,7-Dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinethione [321] (0.420 g, 1.88 mmol) was added to dry MeCN (10 cm^3) and stirred under Argon. 2-Bromo-1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [301] (0.541 g, 1.97 mmol) was added and stirring was continued for 18 hours. A solution of PPh_3 (0.543 g, 2.07 mmol) and Et_3N (0.381 g, 0.53 cm^3, 3.76 mmol) in dry MeCN (10 cm^3) was added drop-wise and stirring was continued for 2 hours. The solvent was evaporated and the residue was extracted with CH_2Cl_2 (50 cm^3) and washed with H_2O (25 cm^3) and brine (2 × 25 cm^3). Evaporation of the solvent afforded a red gum. The gum was taken up into 2M HCl (50 cm^3) and stirred in the presence of EtOAc (50 cm^3) at 60 °C for 45

minutes. The aqueous phase was separated and back-extracted with Et_2O (2 × 50 cm^3). The aqueous phase was carefully neutralized with concentrated ammonia solution (pH 7) and then the solids were filtered and washed with water (200 cm^3). The solids were taken up into dichloromethane (50 cm^3), dried over Na_2SO_4, filtered and evaporated to give (*Z*)-2-[6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinylidene]-1-(2-hydroxy-4,5-dimethoxyphenyl)-1-ethanone [329C] (0.532 g, 1.38 mmol, 73% yield) as a yellow solid.

R_f (40% EtOAc/hexane): 0.20

M.p: 143 – 144 °C

IR (ν/cm^{-1}): 2945 (w, C-H stretch), 2836 (w), 1604 (m, C=O stretch), 1588 (m, C=C stretch), 1562 (m), 1502 (s), 1276 (m), 1249 (s, C-O stretch), 1206 (s), 1036 (s).

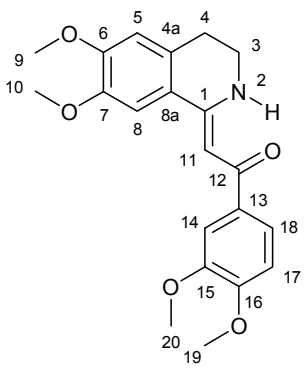
^{1}H NMR (300 MHz, $CDCl_3$) δ 13.80 (s, 1H, OH), 11.22 (s, 1H, NH), 7.25 (s, 1H, H_{18}), 7.19 (s, 1H, H_8), 6.73 (s, 1H, H_5), 6.46 (s, 1H, H_{15}), 6.03 (s, 1H, H_{11}), 3.97 (s, 3H, H_9*), 3.95 (s, 3H, H_{10}*), 3.89 (s, 3H, H_{19}*), 3.88 (s, 3H, H_{20}*), 3.62 – 3.47 (m, 2H, H_3), 2.90 (t, J = 6.5, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.65 (C-12), 159.01 (C-1), 158.61 (C-16), 154.47 (C-14), 152.01 (C-6), 148.09 (C-7), 141.29 (C-17), 130.79 (C-4a), 121.39 (C-8a), 112.50 (C-13), 111.21 (C-18), 110.86 (C-5), 109.04 (C-8), 101.07 (C-15), 84.57 (C-11), 57.41 (C-9*), 56.42 (C-10*), 56.06 (C-19*), 55.87 (C-20*), 38.85 (C-3), 27.99 (C-4).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 385.1519, $C_{21}H_{23}NO_6$ requires 385.1525

7.10.3 Synthesis of (*Z*)-2-[6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinoliny-lidene]-1-(3,4-dimethoxyphenyl)-1-ethanone [329D]



[329D]

6,7-Dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinethione [321] (1.000 g, 4.48 mmol) was added to a solution of MeCN (15 cm^3) containing 2-bromo-1-(3,4-dimethoxyphenyl)-1-ethanone [210] (1.218 g, 4.70 mmol) and stirred for 2 hours under Argon. A solution of PPh_3 (1.293 g, 4.93 mmol) and Et_3N (0.499 g, 0.69 cm^3, 4.93 mmol) in dry MeCN (20 cm^3) was added drop-wise and stirring was continued for an additional 3 hours. The solvent was evaporated and the residue was extracted with dichloromethane (50 cm^3) and washed with H_2O (2 × 50 cm^3). The organic extract was extracted with 2M HCl (50 cm^3). The acidic aqueous phase was back-extracted with Et_2O (2 × 25 cm^3) and then basified with concentrated ammonia solution. The solid was extracted with dichloromethane (3 × 50 cm^3), dried over Na_2SO_4, filtered and evaporated to afford a red solid. Flash chromatography (EtOAc) afforded (*Z*)-2-[6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinylidene]-1-(3,4-dimethoxy-phenyl)-1-ethanone [329D] (1.332 g, 3.61 mmol, 81% yield) as a red solid.

R_f (EtOAc): 0.30

M.p: 100 – 102 °C

IR (ν/cm^{-1}): 2939 (w, C-H stretch), 2836 (w), 1590 (m, C=O stretch), 1561 (m), 1498 (s), 1463 (m), 1219 (s, C-O stretch), 1169 (m), 1025 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.73 (s, 1H, NH), 7.54 (dd, *J* = 1.8, 8.4, 1H, H_{18}), 7.27 (s, 1H, H_{14}), 7.26 (s, 1H, H_8), 6.90 (d, *J* = 8.3, 1H, H_{17}), 6.72 (s, 1H, H_5), 6.19 (s, 1H, H_{11}), 3.97 (s, 3H, H_9*), 3.96 (s, 3H, H_{10}*), 3.94 (s, 3H, H_{19}*), 3.94 (s, 3H, H_{20}*), 3.53 (td, *J* = 3.2, 6.6, 2H, H_3), 2.90 (t, *J* = 6.6, 2H, H_4).

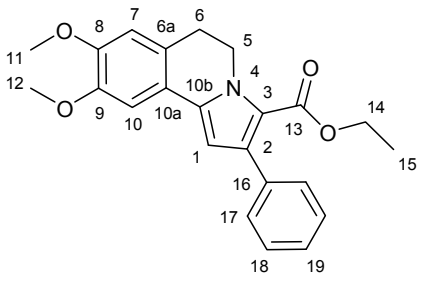
^{13}C NMR (75 MHz, $CDCl_3$) δ 187.43 (C-12), 158.21 (C-1), 151.62 (C-16), 151.04 (C-15), 148.74 (C-6), 147.91 (C-7), 134.14 (C-4a), 130.59 (C-13), 121.47 (C-8a), 119.93 (C-14), 110.74 (C-17), 110.03 (C-18), 109.90 (C-5), 108.54 (C-8), 85.80 (C-11), 56.26 (C-9*), 55.98 (C-10*), 55.92 (C-19*), 55.90 (C-20*), 38.65 (C-3), 28.03 (C-4).

Assignments denoted by * are interchangeable.

HRMS: Found M^+ = 369.1523, $C_{21}H_{23}NO_5$ requires 369.1576

7.11 Proof of concept synthesis of the lamellarin framework

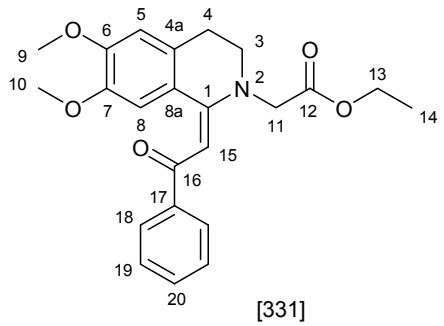
7.11.1 Synthesis of ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate [330A]



[330A]

Ethyl 2-[6,7-dimethoxy-1-thioxo-3,4-dihydro-2(1*H*)-isoquinolinyl]acetate [324] (0.239 g, 0.77 mmol) was added to dry MeCN (2 cm^3) and stirred under Argon. Phenacyl iodide (0.379 g, 1.54 mmol) was added and stirring was continued for 4 hours. The reaction mixture was cooled to 0 °C and a solution of PPh_3 (0.425 g, 1.62 mmol) and Et_3N (0.216 g, 0.30 cm^3, 2.13 mmol) in dry MeCN (5 cm^3) was added drop-wise. The cooling bath was removed and stirring was continued for 18 hours. The solvent was evaporated and the residue was extracted with EtOAc (50 cm^3) and washed with H_2O (25 cm^3) and brine (25 cm^3). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum. Flash chromatography (60% EtOAc/hexane) afforded crude ethyl 2-[6,7-dimethoxy-1-[(*E*)-2-oxo-2-phenylethylidene]-3,4-dihydro-2(1*H*)-isoquinolinyl]acetate [331] (0.300 g) as an orange gum that was heavily contaminated with phosphorous-containing by-products.

The following peaks were discernable by ^{1}H NMR spectroscopy of the crude product.



[331]

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 1H, H_5), 6.02 (br s, 1H, H_{15}), 4.54 (br s, 2H, H_{11}), 4.19 (q, *J* = 7.1, 2H, H_{13}), 3.88 (s, 3H, H_9*), 3.83 (s, 3H, H_{10}*), 3.60 – 3.43 (m, 2H, H_3), 3.03 – 2.88 (m, 2H, H_4), 1.23 (t, *J* = 7.1, 3H, H_{14}).

Assignments denoted by * are interchangeable.

The orange gum [331] (0.300 g) was added to a solution of dry toluene (10 cm^3) containing flash silica-gel (3.30 g) and refluxed for 2 hours under Argon. The silica-gel was filtered through a glass sintered funnel and the silica-gel was rinsed with acetone (3 × 10 cm^3). The solvents were evaporated to afford a red gum. Flash chromatography (30% EtOAc/hexane) afforded ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate [330] (0.015 g, 0.04 mmol, 5% yield).

R_f (30% EtOAc/hexane): 0.26

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.6, 2H, H_{17}), 7.41 – 7.28 (m, 3H, H_{18} and H_{19}), 7.07 (s, 1H, H_{10}), 6.76 (s, 1H, H_7), 6.48 (s, 1H, H_1), 4.63 (t, *J* = 6.8, 2H, H_5), 4.14 (q, *J* = 7.1, 2H, H_{14}), 3.92 (s, 6H, H_{11} and H_{12}), 3.06 (t, *J* = 6.8, 2H, H_6), 1.07 (t, *J* = 7.1, 3H, H_{15}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.87 (C-13), 148.81 (C-8), 148.29 (C-9), 136.92 (C-10b), 134.90 (C-16), 134.49 (C-6a), 129.57 (C-18), 127.38 (C-17), 126.58 (C-19), 124.77 (C-10a), 120.76 (C-2), 118.20 (C-3), 110.96 (C-7), 106.85 (C-10), 105.88 (C-1), 59.75 (C-14), 56.07 (C-11*), 56.01 (C-12*), 42.81 (C-5), 28.65 (C-6), 13.81 (C-15).

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