ENAMINONE-BASED APPROACHES TO THE SYNTHESIS OF
ALKALOIDS POSSESSING THE PYRROLO[1,2-a]AZEPINE CORE

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Declaration

I declare that the work presented in this thesis was carried out solely by me under the supervision of Professor J.P. Michael and Professor C.B. de Koning. It is being submitted for the degree of doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

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27th day of February, 2018
Abstract

This thesis illustrates strides taken toward the construction of the pyrrolo[1,2-a]azepine 4 nucleus via enaminone chemistry developed in this University for creating pyrrolizidine 1, indolizidine 2 and quinolizidine 3 alkaloids. The pyrrolo[1,2-a]azepine 4 core is a fused pyrrolidine and azepine system found in lehmizidine, Stemona, Cephalotaxus alkaloids and other alkaloids. A concise background is given on the nature of enaminones, how they are accessed with strong emphasis on the Eschenmoser sulphide contraction reaction and their versatile reactivity, followed by literature review of this University background on synthesis of alkaloids containing 1, 2 and 3 nuclei. The aims and strategies presented are preceded by literature review of lehmizidine, Stemona, Cephalotaxus alkaloids and some reported synthesis.

A range of attempts and successes are reported in chapter 2 for making four-carbon chain length enaminones (via N-alkylation, condensation, thionation, Eschenmoser sulphide contraction and tandem acylation/Michael addition reactions) crucial in creating azepane onto pyrrolidine in an acylation or alkylation ring closing steps yielding lehmizidine like compounds (E)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 144 and (E)-ethyl 2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147. Vice versa, the synthesis of two carbon chain length N-alkyl vinylogous amides is demonstrated leading to the formation of pyrroles, ethyl 2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 222, ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 223 and ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 224 in Knoevenagel condensation reactions similar to those described by Garreth Morgans and Stefania Scalzullo in their PhD theses. The synthesis of 1-benzoylethyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 233 and 1-(4-methoxybenzoyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 235 in a double acylation reaction between NH vinylogous amides and oxalyl chloride is also demonstrated.

In chapter 3, the synthesis of vinylogous urethanes for making the Cephalotaxus core via N-alkylation, condensation, thionation, Eschenmoser sulphide contraction and tandem acylation/Michael addition reactions are described. A variety of attempts of the arylation reaction on
vinylogous urethanes are demonstrated leading to a comparison study to ascertain carbon chain length dependency of the step.

The synthesis of pyrido[1,2-a]azonine nucleus of Sessilifoliamide alkaloids, which are a subset of the Stemona alkaloids demonstrated in chapter 4 is in line with our fascination with bigger ringed alkaloids. The synthetic route is presented leading the formation of compounds 1-benzoyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 337, 3-methyl-1-(4-nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 338 and 1-(4-methoxybenzoyl)-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 339.
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DEDICATION

This Thesis is dedicated to my parents Lindiwe Kubheka and Jabulani Mthembu, Kubheka and Mthembu families.
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CHAPTER 1: INTRODUCTION

1.1 Background notes

The University of the Witwatersrand’s Organic Chemistry research team has for many years now researched and applied enaminone chemistry in their creation of bicyclic alkaloids. The versatile enaminone intermediates are at the core of our research owing to their unique patterns of reactivity.\textsuperscript{1,2,3,4} Previously, it has been established how enaminones can be used to synthesise alkaloids containing the pyrrolizidine 1, indolizidine 2 and quinolizidine 3 ring systems. Less attention had been paid to making bicyclic alkaloids containing the 1-azabicyclo[5.3.0]decane ring system, also known as the pyrrolo[1,2-a]azepine 4 ring system up to now. Alkaloids possessing this ring system are rare in nature, but have recently been the upcoming stars in the alkaloid business. The main purpose of this project is to exploit the already developed enaminone chemistry methodology towards the synthesis of lehmizidine alkaloids, Cephalotaxus alkaloids, Stemona alkaloids and related ring systems which are characterized by the pyrrolo[1,2-a]azepine nucleus 4, thus further expanding the scope of our work.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{enaminones.png}
\caption{Pyrrolizidine 1, indolizidine 2, quinolizidine 3 and pyrrolo[1,2-a]azepine 4}
\end{figure}

The discussion begins with a short survey of enaminones and their reactivity, followed by a Wits background on how alkaloids containing indolizidines 2 and quinolizidines 3 are synthesised. A brief account of lehmizidine, Stemona and Cephalotaxus alkaloids is then presented, as well as a short literature review on how other groups have gone about synthesising the pyrrolo[1,2-a]azepine 4 alkaloids. The specific aims and strategies to be followed in this project are then presented.
1.2 Enaminones

1.2.1 What are enaminones?

Enaminones are β-aminoenones in which the lone pair on nitrogen is in conjugation with the unsaturated system (Figure 2). The acyl group stabilises and modulates the reactivity of the enamine unit. The electron-withdrawing group (EWG) and sometimes the electron-donating group (EDG) may either influence or overwhelm the reactivity of the enaminone core. The kinds of enaminones this group has explored are not only those with a carbonyl substituent as the EWG (vinylogous amides, vinylogous urethanes, vinylogous ureas; (Figure 2) but also related systems with other EWGs (vinylogous cyanamides, vinylogous sulfonamides and vinylogous nitramines). In virtually all of our work, the nitrogen is part of a heterocyclic ring and the alkene part is exocyclic to the ring.

![Figure 2: Examples of enaminones and related systems.]

1.2.2 How are enaminones made?

There are many available methods for making the exocyclic enaminones needed for this project. One of the most common routes involves their synthesis from thiolactams. The thiolactams are prepared in a thionation reaction from lactams
made from primary amine and bifunctional reagents (e.g. 4-chlorobutanoyl chloride) or by a Michael addition reaction of secondary thiolactams (e.g. pyrrolidine-2-thione) to α, β-unsaturated acceptors (e.g. acrylate esters). The alkylidene substituent is either introduced in a Knoevenagel like condensation with a relatively acidic component (e.g. nitromethane) via methyl thioiminium salts, or in an Eschenmoser sulphide contraction reaction, with a loss of sulphur from the salt that results when thiolactams react with α-halocarbonyl compounds (Scheme 1).  

Scheme 1: General approach to enaminones.  

The Eschenmoser sulphide contraction reaction via alkylative precoupling is central to our reaction strategy achieving enaminones. Eschenmoser et al. elucidated the reaction mechanism, which involves the formation of the iminium or imine thioether, as a result of the nucleophilic attack of the thioamide on the alkyl halide, eliminating halide as leaving group. The base deprotonates the α-proton on the electron withdrawing group ($R^3$) resulting in formation of the episulphide. A thiophile then
scavenges the sulphur atom, collapsing the episulphide to an enaminone Scheme 2.\(^8,\)\(^11\)

\[
\begin{align*}
\text{Scheme 2: Eschenmoser sulphide contraction reaction mechanism via alkylative precoupling.}
\end{align*}
\]

An economical method for making exocyclic enaminones is a one step Michael addition-alkylation reaction, where amines are reacted with chloroalkynes in the presence of sodium iodide and potassium iodide Scheme 3.\(^9\) These reactions proceed with high efficiency.

\[
\begin{align*}
\text{Scheme 3: Michael addition-alkylation reaction.}
\end{align*}
\]

Thiolactams can also be converted into enaminones in a version of the Reformatsky reaction. This reaction involves the reaction between excess activated zinc and excess diethyl bromomalonate in the presence of catalytic iodine as the activator to form the zinc enolate in situ. The zinc enolate reacts with the carbonyl carbon of the thiolactam followed by elimination of the zinc-bromo-sulphur complex yielding an enaminone Scheme 4.\(^10\)
1.2.3 Versatile enaminone reactivity

Enaminones are able to react as both ambident nucleophiles and as ambident electrophiles. As nucleophiles, the enaminone’s expected nucleophilicity on the N (i, Figure 3) and C atoms (ii, Figure 3) is extended to the O atom of the carbonyl group (iii, Figure 3) through conjugation. Strong bases can deprotonate the carbon atom β to N atom or acid induced tautomerism to give further nucleophilicity (iv, Figure 3). As electrophiles, enaminones can participate in 1,2-addition and 1,4-addition (v, vi, Figure 3). The aim is to explore more of the nucleophilicity on carbon (ii, Figure 3) to access the 1-azabicyclo[5.3.0]decane core.
1.3 Wits background on synthesis of pyrrolizidines 1, indolizidines 2 and quinolizidines 3

1.3.1 Alkaloids containing the indolizidine 2 core

1.3.1.1 Acylation as key ring closing step

Michael et al.\(^2\) reported the synthesis of alkaloid 167B (±)-12 in eight steps with an overall yield of 7.2% based on pyrrolidine-2-thione 6. Their synthesis began with the Michael addition of pyrrolidine-2-thione 6 to the Michael acceptor 5 to yield ethyl 3-(2-thioxopyrrolidin-1-yl)hexanoate (±)-7 in moderate yield, which they could not improve (Scheme 5, a). They then took 3-(2-thioxopyrrolidin-1-yl)hexanoate (±)-7 through an Eschenmoser sulphide contraction reaction with ethyl 2-bromoacetate, resulting exclusively in the formation of (E)-ethyl 3-[2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]hexanoate (±)-8 in excellent yield (Scheme 5, b, c).

![Scheme 5](image)

Scheme 5: Reagents and conditions: (a) NaOH (cat.), THF, reflux; (b) BrCH₂CO₂Et, MeCN, rt; (c) PPh₃, NEt₃, MeCN, rt; (d) NaOH, H₂O, reflux; (e) Ac₂O, MeCN, rt; (f) MeCN, reflux.\(^2\)

Enaminone (±)-8 could form the basis for the desired acylative cyclisation on to the enaminone segment, but they had to convert compound (±)-8 into an anhydride (±)-
owing to inefficiency of the saturated ester as an acylating agent. This they did through a chemoselective hydrolysis of compound (±)-8 heating with sodium hydroxide under reflux in water. They then followed with the reaction of the resulting salt sodium (E):3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)hexanoate (±)-9 with acetic anhydride in situ at ambient temperature. The enaminone chemistry then took centre stage when heating under reflux resulted in a spontaneous ring formation via the reaction at the anhydride, yielding the ethyl 7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (±)-11 in excellent yield over three steps. The synthesis was completed by hydrolysis, decarboxylation of the ester and reduction of the remaining functional groups.2

1.3.1.2 Alkylation as key ring closing step

Michael et al.12 recently established the syntheses of naturally occurring indolizidine alkaloid (±)-tashiromine 22 and its unnatural epimer(±)-epitashiromine 21 through the use of enaminone chemistry, in the process also investigating the impact of various electron withdrawing groups on the alkylationative cyclisation and reduction steps.

They began synthesising lactam1-(3-hydroxypropyl)pyrrolidin-2-one 14 in 81% yield by reacting 3-aminopropan-1-ol with γ-butyrolactone in a sealed Carius tube at 250 °C (Scheme 6, a). Followed by protecting the alcohol group as an acetate in the presence of pyridine, achieving 3-(2-oxopyrrolidin-1-yl)propyl acetate 15 in 87% yield (Scheme 6, b). They then employed a Brillon procedure with phosphorus pentasulphide and aqueous sodium carbonate in tetrahydrofuran in thionating 15, achieving thiolactam3-(2-thioxopyrrolidin-1-yl)propyl acetate 16 in 90% yield (Scheme 6, c).13 Thiolactam 16 was reacted with various α-halocarbonyl compounds in an Eschenmoser sulphide contraction reaction, achieving enamiones 17 (i, ii, iv) in good yields between 85 – 95%, while enaminone 17 iii was achieved in 44% yield (Scheme 6; d, e).11 They then deacetylated the enamiones with potassium carbonate in methanol, achieving 18 (i – iv) in good yields between 82 – 89% (Scheme 6, f). The liberated enamiones were then cyclised by first treating them with imidazole and triphenylphosphine in acetonitrile-toluene at ambient temperature
followed by adding iodine while heating under reflux to yield bicyclic compounds 19 (ii – iv) in good yields 59 – 72%, except for bicyclic product 19 (i) with 27% yield. Owing to challenges in previous purification of bicyclic compounds 19 (i) and 19 (iv), they investigated the effect of cyclisation of the liberated enaminones 18 (iii, iv) by converting them to their corresponding tosylates (iii) 19% and (iv) 71% and reacting with sodium iodide.

\[ \text{Scheme 6: Reagents and conditions: (a) NH}_2(\text{CH}_2)\text{OH, 250 °C (sealed tube), 18 h, 81%; (b) A}_{\text{c}2}\text{O, pyridine, 0 °C, 10 min, then r.t., 18 h, 87%; (c) Na}_2\text{CO}_3, \text{P}_2\text{S}_5, \text{THF, 5 h, 90%; (d) BrCH}_2\text{R, CH}_3\text{CN, r.t., 24 h, (e) PPh}_3, \text{NEt}_3, \text{CH}_3\text{CN, 5 h, (i) 95%, (ii) 90%, (iii) 44%, (iv) 85; (f) K}_2\text{CO}_3, \text{MeOH, r.t., 3 h, (i) 82%, (ii) 85%, (iii) 89%, (vi) 83%; (g) Imidazole, PPh}_3, \text{I}_2, \text{CH}_3\text{CN-PhCH}_3, \text{reflux, 1 h; (i) 27%, (ii) 59%, (iii) 72%, (iv) 64%; (h) H}_2 (1 \text{ atm), Adams catalyst, AcOH, r.t., 24 h, (ii) 72% (dr 85:15), (iii) 85% (dr 92:8), (iv) 25% (dr 95:5);(i) LiAlH}_4, \text{EtO}_2, \text{3 h, 87% (dr 87:13).}^{12} \]

They went back to the original strategy and improved their purification procedure, having not succeeded in this regard even when they converted the intermediate to corresponding iodides in situ (Scheme 6, g). Catalytic hydrogenation of 19 (ii – iv) using Adams catalyst resulted in racemic mixtures of diastereomers, with major diastereomers resulting from cis addition of hydrogen, giving 20 (ii) 72% (dr 85:15), 20 (iii) 85% (dr 92:8), 20 (iv) 25% (dr 95:5) with indicated diastereomeric ratios (Scheme 6, h). Reduction of the racemic diastereomer mixture 20 (ii) with lithium
aluminium hydride in diethyl ether resulted in a mixture of pure(±)-tashiromine 22 and epimer(±)-epitashiromine 21 in 87% yield (dr 13:87), confirming the diasteomeric ratio of the precursor (Scheme 6, j).  

1.3.2 Alkaloids containing the quinolizidine 3 core

1.3.2.1 Alkylation as key ring closing step

The previous two syntheses illustrated the formation of an azabicyclic system by an intramolecular acylation and alkylation of enaminones. Michael’s team has also made quinolizidine systems by an intramolecular alkylation of an enaminone. They used six-membered vinylogous urethanes in the synthesis of (±)-lupinine 23 and (±)-epilupinine 32. This work also showed interesting differences in the behaviour of 5- and 6-membered vinylogous urethanes.

Their synthesis began with the Michael addition reaction of thiolactams 6 and 23 to tert-butyl acrylate or ethyl acrylate in dry tetrahydrofuran at 40 °C, giving N-alkyl-thiolactams 24a–d in excellent yield (Scheme 7, a). The N-alkyl-thiolactams 24a–d were converted into vinylogous urethanes 25a–d in good yields in a two-step Eschenmoser sulphide contraction reaction with ethyl bromoacetate in acetonitrile at room temperature and followed by triphenylphosphine and triethylamine in acetonitrile at room temperature (Scheme 7, b, c). Brown’s observation (“Reactions which involve the loss of an exo double bond will be favoured in the 6-ring as compared to the corresponding 5-ring derivative”) about the stability and reactivity of double bonds that are exocyclic or endocyclic to rings of varying size applied to their vinylogous urethanes. The loss of the exo double bond in their attempted reduction of the saturated ester of the vinylogous urethanes 25c and 25d resulted in compound 28, while their selective reduction of the saturated ester of the vinylogous urethanes 25a and 25b resulted in compound 26a (Scheme 7, d), which retained the exo double bond.

Michael and co-workers took their study further to investigate the lability of piperidinyldiene vinylogous urethanes towards conjugate reduction by using the
vinylogous cyanamide. They found that the reduction of vinylogous cyanamides 29a and 29b gave product 30 in good yields of 74% and 60% respectively, with no presence of over reduced product (Scheme 7, f). Compound 25d was best reduced with lithium aluminium hydride in a 4:1 ratio combination of solvents toluene and diethyl ether at 0 °C, yielding compound 26d (62%) and compound 28 (13%). Michael’s team converted the alcohol into a good leaving group by substituting it with iodine in the presence of triphenylphosphine and imidazole, making alkyl iodide, which formed in situ and immediately cyclised to give ethyl 3,4,6,7,8,9-hexahydro-2H-quinolizine-1-carboxylate 27 in 74% yield when the reactants were heated in a 2:1 mixture of toluene and acetonitrile. (±)-Lupinine 31 was achieved in two more steps and (±)-epilupinine 32 was made in three more steps from compound 27 in excellent yields.¹⁶

**Scheme 7:** Reagents and conditions: (a) CH₂CH₂CO₂R, NaOH or NaH, THF, 40 °C, 16 h; (b) BrCH₂CO₂Et, MeCN, rt, 16 h; (c) Ph₃P, NEt₃, MeCN, rt, 16 h; (d) LiAlH₄, THF, rt, 2 h; (e) Ph₃P, imidazole, I₂, toluene, 120 °C, 80 min; (f) LiAlH₄, THF, rt, 48 h.¹⁶
1.3.3 Alkaloids containing the pyrrolizidine 1 core

1.3.3.1 Arylation as key ring closing step

Michael et al.\textsuperscript{79} demonstrated a viable route towards the synthesis of arizidinomitosene target scaffold to Mitomycin A and related compounds. They illustrated an intramolecular Heck-type arylation coupling between an enaminone and brominated aryl group. Previously prepared 2-(benzyloxy)-6-bromo-4-methoxy-3-methylaniline 33 was reacted with ethylmagnesium chloride in tetrahydrofuran at $-50^\circ C$ to deprotonate the amine followed by addition of the lactone (3aR,6aR)-2,2-dimethyl-dihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one 34 and warming to room temperature, resulting in alcohol 35 (Scheme 8, a). The alcohol 35 was converted to a mesylate followed by treating with sodium hydride in a solvent mixture of N,N-dimethylformamide and tetrahydrofuran at room temperature, making lactam 36 in overall yield of 90\% from 34 as a 1:1 separable mixture of rotamers (Scheme 8, b, c). Lactam 36 was then thionated with Lawesson’s reagent heating under reflux in toluene to yield 73\% of thiolactam 37 as a mixture of rotamers (Scheme 8, d). The thiolactam was reacted with an organozinc reagent (in an Eschenmoser sulphide contraction reaction) heating under reflux in tetrahydrofuran to yield enaminone 38 in 87\% yields as a mixture of rotamers (Scheme 8, e). They perform the Heck-type transformation to ring close the enaminone, by heating enaminone 38 under reflux with palladium(II) acetate (0.3 eq), tri-o-tolyolphosphine, triethylamine in a 5:5:1 solvent solution of N,N-dimethylformamide, acetonitrile and water to yield 39 in 82\% yield (Scheme 8, f).
Using excess palladium(II) acetate debenzylated the aromatic alcohol and led to 40 in 90% yield (Scheme 8, g), while hydrogenation of 39 with Pd/C in ethanol achieved the same result giving 40 in 92% yield (Scheme 8, h). Their synthesis continued towards arizidinomitosene in steps described in the paper. The cycloarylation is the only successful method to date for the Wits conversion of enaminoines into the 5,5-azabicyclics.\textsuperscript{79}

\section*{1.4 A short survey of alkaloids containing the pyrrolo[1,2-a]azepine 4}

\subsection*{1.4.1 Lehmizidines}

Lehmizidine alkaloids originate from a group of Colombian dendrobatid frogs, principally Dendrobates lehmanni.\textsuperscript{7} Ten alkaloids 41 – 50 belonging to this group have been reported. Their structures were elucidated by mass spectral analysis. The mass spectrum of lehmizidines revealed the presence of a substituent at C-3, indicated by a base peak; and a methyl substituent at C-5, indicated by a small fragment. The substituent at C-3 was found to be a nine carbon liner chain with an alkene, alkyne and/or a ketone groups for some of the alkaloids. The relative
structural configuration of all lehmizidines is unknown, except for compound 41 (designated 275A) elucidated in 2001, which is shown with the relative configuration. Positions of the OH groups are also unknown. Unlike the frog lehmizidines with a methyl group, (3R)-3-pentyl-octahydro-1H-pyrrolo[1,2-a]azepine 50, isolated together with some indolizidine alkaloids from an ant Myrmicaria melanogaster from Brunei Darussalam in 2007, has a butyl side as the only substituent at C-3.14 No toxicity or biological activity data have been reported (Table 1).  

![Diagram of lehmizidine structure](image)

<table>
<thead>
<tr>
<th>Lehmizidines</th>
<th>R¹</th>
<th>R²</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>(CH₂)₇C≡CH</td>
<td>CH₃</td>
<td>H</td>
</tr>
<tr>
<td>42</td>
<td>(CH₂)₅CH=CHCH=CH₂</td>
<td>CH₃</td>
<td>H</td>
</tr>
<tr>
<td>43</td>
<td>(CH₂)₇CH=CH₂</td>
<td>CH₃</td>
<td>H</td>
</tr>
<tr>
<td>44</td>
<td>C₉H₁₃O (=O, C≡CH)</td>
<td>CH₃</td>
<td>H</td>
</tr>
<tr>
<td>45</td>
<td>(CH₂)₅CH=CHC≡CH</td>
<td>CH₃</td>
<td>OH</td>
</tr>
<tr>
<td>46</td>
<td>C₉H₁₅O</td>
<td>CH₃</td>
<td>H</td>
</tr>
<tr>
<td>47</td>
<td>(CH₂)₇C≡CH</td>
<td>CH₃</td>
<td>OH</td>
</tr>
<tr>
<td>48</td>
<td>C₉H₁₇O (=O)</td>
<td>CH₃</td>
<td>H</td>
</tr>
<tr>
<td>49</td>
<td>(CH₂)₇CH=CH₂</td>
<td>CH₃</td>
<td>OH</td>
</tr>
<tr>
<td>50</td>
<td>(CH₂)₃CH₃</td>
<td>H</td>
<td>–</td>
</tr>
</tbody>
</table>
The substituent $R^1$ in alkaloid 44 was not unambiguously identified by the authors. All they could say is that the nine-carbon chain has a ketone at an unspecified position, and a terminal alkyne group. The substituent has been amended to $C_6H_{12}(C=O)C≡CH$, [C=O position uncertain]

### 1.4.2 Stemona alkaloids

Stemona alkaloids are another group of alkaloids that contain the azabicyclic nucleus 4 of interest. They are found in the family Stemonaceae, which occurs from southern Asia and Malaysia to northern Australia. The pyrrolo[1,2-a]azepine 4 nucleus, also known as perhydroazaazulene and 4-azaazulene, is at the heart of most Stemona alkaloids (A, Figure 2). The Stemona alkaloids have been classified by Pilli and de Oliveira into five groups according to their structural features, namely stenine I, stemoamide II, tuberostemonine III, stemonamine IV and parvistemoline V (Figure 4).

Of interest to this project are alkaloids in which the azabicyclic system is not fused to any other carbocyclic rings at all. This leaves only members of the parvistemoline V family. The parvistemoline alkaloids are characterised by lack of the B-C ring fusion and a hexahydro-2,6-dimethyl-5-oxofuro[3,2-b]furan-3-yl moiety attached to C-9 in the pyrrolo[1,2-a]azepine nucleus. A few members of this group are parvistemoline 51, parvistemonine 52 and didehydroparvistemonine 53 (Figure 5).
The crude extracts of Stemonaceae species have been used in traditional oriental medicines in China and Japan as insecticides, vermifuges and in the treatment of respiratory diseases. They have also shown antitubercular and antitussive activities. Parvistemoline group has also been shown by Shinozaki and Ishida to depress glutamate-induced responses at similar concentrations to those of established glutamate inhibitors. This has been shown on the neuromuscular transmission in crayfish, which is considered a model for studying the mechanism of drug action in the mammalian central nervous system. A few other Stemona alkaloids have also been reported to show insect anti-feeding activity, but it seems that no other biological activity has been reported.\textsuperscript{15}

Recently Takeya et al. isolated two new alkaloids from the species Stemona sessilifolia. They named these alkaloids Sessilifoliamide K54 and L55 which have a unique pyrido[1,2-a]azonine nucleus. They elucidated their structure with extensive nuclear magnetic resonance spectroscopy characterisation. Their origin may be derived from tuberostemoninol-type alkaloids via the demonstrated biogenesis (\textbf{Scheme 9}).\textsuperscript{18}
1.4.3 Cephalotaxus alkaloids

The Cephalotaxus alkaloids belong to several species of the genus Cephalotaxus. There are six to twelve species and varieties depending on previous reports. Also known as Plum yews, these evergreen, coniferous trees or shrubs are widely distributed in southern and eastern Asia. Cephalotaxus alkaloids trees have been used in Japan for timber, fire wood, medicinal purposes due to anti-cancer alkaloids they generally contain and as illuminants in oil expressions. Owing to human pressure and low regeneration rate in the wild, some of these species have been considered endangered.16

The first representative of this family was cephalotaxine 56 from C. harringtonia var. drupacea described by Powell and co-workers as containing three five-membered rings, a seven-membered ring and an aromatic ring fused together in a unique way (Figure 7).17 Cephalotaxine esters such as 57, 58, 59 and 60 were found to have antileukemic and antitumor activity, leading the Chinese and the Americans to investigate them further in the 1970s. Currently, homoharringtonine 59 is sold alone or in drug combination in the treatment of chronic myeloid leukaemia (CML) or
refractor acute promyelocytic leukaemia, but is inactive against solid tumours. They also isolated 19 compounds containing the cephalotaxine 56 nucleus from various Cephalotaxus species (Figure 6).\textsuperscript{19}

![Chemical structures](image)

**Figure 6:** Cephalotaxus alkaloids esters and homoerythrina alkaloids.\textsuperscript{19,20}

Minor homoerythrina alkaloids 61 – 63 were isolated with cephalotaxine alkaloids. Their structure is tetracyclic in nature and they gave insight to the biosynthesis of Cephalotaxus alkaloids (Figure 6).\textsuperscript{20}

Recently, there have been discoveries of new Cephalotaxus alkaloids in a bid to find structurally and biologically interesting alkaloids. Takano et al. characterised four new oxygenated alkaloids; drupangtonine 64, 11\(\alpha\)-hydroxyhomodeoxyharringtonine 65, 11\(\beta\)-hydroxyhomodeoxyharringtonine 66, and 11\(\beta\)-hydroxydeoxyharringtonine 67, from C. harringtonia var. Drupacea (Figure 7). These compounds showed activity against P-388 leukaemia cells.\textsuperscript{21,22} In addition three more alkaloids, namely Nordeoxyharringtonine 69, homodeoxyharringtonine 70 and bishomodeoxyharringtonine 71 with side chain variants and differing levels of oxygenation were found to be active as well against the same cell line.\textsuperscript{26} Three more ester-type alkaloids neoharringtonine 68, homoneoharringtonine (R\(^1\) = H, R\(^2\) = Bn) and (3'S)-hydroxyneoharringtonine (R\(^1\) = OH, R\(^2\) = Ph), from C. harringtonia var. drupacea characterised by the presence of a phenyl or benzyl groups were also found to be active against P-388 cells.\textsuperscript{23} Kobayashi and co-workers reported more
new oxygenated alkaloids which were biologically active against human epidermoid carcinoma KB cells. Of interest was the first example of a Cephalotaxus glycoside, cephaledominine J 72 with a β-D-glucopyranose sugar moiety.24,25 They also reported five new heterodimers named bis-cephalezominines from C. harringtonia var. nana 73 - 78 (Figure 7). The cytotoxicity of these dimers was relatively weaker as compared to their monomeric forms.

**Figure 7:** Recent Cephalotaxus alkaloids.
1.5 Some reported synthesis of alkaloids containing the pyrrolo[1,2-a]azepine 4 nucleus

1.5.1 Lehmizidine alkaloids

Garraffo and co-workers have synthesised four diastereomers 79a – 79d from reductive amination of triketone 79 in a bid to determine the stereochemistry of alkaloid 275A (41) (Scheme 10). The central azabicyclic core was constructed in a single operation by a triple reductive amination of the triketone 80 with ammonium acetate and sodium cyanoborohydride.  

![Scheme 10](image)

**Scheme 10.** Frog skin alkaloid 275A (41) and four synthetic tetrahydro diastereomers (79a - 79d). Diastereomer 79c results from hydrogenation of 41. Lehmizidines from reductive amination of triketone 80. E and Z refer to the geometry of hydrogen atoms on the indicated sites relative to that at C-3.

Gas chromatography showed the third eluted component of the mixture of diastereomers to be identical in its Gas Chromatography retention time, Electron Ionisation Mass Spectrum and Chemical Ionisation (NH₃)-MS/MS, and Gas Chromatography–Fourier Transform Infrared Red spectrum with tetrahydro-41. So, they designed two efficient syntheses of the four diastereomers to determine the relative stereochemistry of 79c. They first made the 2,5-disubstituted pyrrolidines intermediates 82 (Scheme 11) by reductive amination of diketone 81 before
assembling the pyrrolo[1,2-a]azepine 4 core in a more controlled third reductive amination. This is a similar approach to the work they previously did to determine the stereochemistry of (6Z,10E)-4-methyl-6-n-propyl quinolizidine, which was detected in a Madagascan frog and also a Brazilian ant. The cis- and trans-pyrrolidine ketals 82a and 82b, prepared from 81, were cyclised by reductive amination after deprotection to give 79b and 79d as major products. When nearly pure 82a was treated in a similar manner, the major product was 79b. This proved not to be a good route for arriving at diastereomer 79c.

Another route that started from 2,7-disubstituted azepanes based on cyanoamine methodology was undertaken (Scheme 12). This method required the cyclisation of 84, a protected seven-carbon aldehyde, with an amine at C-6 to form cyanoazepane 85. To achieve this, ketoacetal 83 was easily made from commercial starting material using Ni0-mediated conjugate addition. The reductive amination of 83 in the presence of titanium isopropoxide resulted in aminoacetal 84. The deprotection of aminoacetal 84 in the presence of cyanide ion followed by treatment of cyanoazepane 85 with a Grignard reagent provided N-benzylazepane 88. Diastereomers 79a, 79b, 79c and 79d were achieved by the debenzylation of 88, which gave a 1:1 mixture of isomeric dioxanylazepanes 89a/89b, which were then deprotected in the presence of cyanide and treated with n-nonylmagnesium bromide.
When nearly pure cis azepane 89a was treated in a similar manner, the major products were 79b and 79d. The diastereomer 79c was obtained in sufficient quantity to establish that 41 had the 5Z,10E relative stereochemistry.

1.5.2 Stemona alkaloids

1.5.2.1 Synthesis of (±)-stemonamine

Yu-Ming Zao and co-workers have recently synthesized stemonamine 100a by the key tandem semipinacol rearrangement/Schmidt reaction and a Dieckmann condensation. Their synthesis began with a Grignard addition of (2-methylenebutyl)magnesium chloride to 2-(3-azidopropyl)cyclohex-2-enone 90 to form allylic alcohol 91 (Scheme 13, a). This alcohol 91 was epoxidised and protected to afford compound 92 in 66% overall yield (Scheme 13, b, c). Compound 92 was then subjected to the tandem semipinacol rearrangement/Schmidt reaction, in which it was treated with 2.2 equivalent of titanium tetrachloride in dichloromethane at −78 °C to 0 °C for 2 hours, resulting in amide 93 in 68% yield as a white solid (Scheme 13, d). Alcohol 93 was oxidized with pyridinium
chlorochromate giving ketone 94 (Scheme 13, e), which was ozonolysed and subjected to an aldol condensation that afforded 96 in 65% overall yield from 93 (Scheme 13, f, g). Ketone 95 was treated with lithium bis(trimethylsilyl)amide and Mander reagent (NCCO₂Me)⁴⁵ at −78 °C for 0.5 hours, and gave the acylation product 96 in 95% yield as a single diastereoisomer (Scheme 13, h). Under an atmosphere of oxygen with catalytic amounts of cerium(III) chloride heptahydrate, compound 96 was converted into 97a and its diastereoisomer 97b in a total yield of 92% (Scheme 13, i).⁴⁶,⁴⁷ The two epimers were separable by column chromatography on silica gel. They treated 97a with propionic anhydride, triethylamine, and 4-(dimethylamino)pyridine (cat.) in dry dichloromethane at room temperature, affording 98a in 95% isolated yield (Scheme 13, j).

Scheme 13: Reagents and conditions: (a) CH₃(CH₂)₃C(CH₂)₂CH₂MgBr, THF, 76%; (b) ¹BuOOH, VO(acac)₂, (c) TMSCI Imid., DMF, 66%; (d) TiCl₃, -78 °C to 0°C, 68%; (e) PCC, CH₂Cl₂, r.t., 85%; (f) O₂, CH₂Cl₂; (g) KO'Bu, ¹BuOH, 77%; (h) LHMDS, -78 °C, then HMPA, NCCO₂Me, 95%; (i) CeCl₃ · 7H₂O, O₂, ¹PrOH, r.t., 92%; (j) Et₃N, DMAP (cat.), Propionic anhydride, CH₂Cl₂, r.t., 95%; (k) KO'Bu, PhH, 18-crown-6, then Et₃N, Me₂SO₄, CH₂Cl₂, 44%; (l) Lawesson’s reagent, CH₂Cl₂; (m) Raney Ni, THF, 93%.⁴⁴

Compound 98a reacted with 18-crown-6 and potassium tert-butoxide in dry benzene at room temperature for 2 hours, followed by O-methylation, proceeded in moderate yield to afford 99a in a Dieckmann condensation to access the key tetronic acid ring system (Scheme 13, k). Lactam 99a was treated with Lawesson’s reagent, and
reduction of the resulting thiolactam using W-2 Raney nickel in THF gave the racemic stemonamine 100a in 93% yield over two steps (Scheme 13, I, m). The structure of the synthetic stemonamine 100a was confirmed by the X-ray crystallographic analysis of its hydrochloride dihydrate. Their attempts to continue the synthesis from 98b in a similar manner as in 98a failed, resulting in degradation of starting material. They synthesized stemonamine 100a for the first time in 13 steps from the known compound 90 in an overall yield of 3.7%, in a concise and efficient total synthesis featuring a tandem semipinacol rearrangement/Schmidt reaction and a Dieckmann condensation.48

1.5.3 Cephalotaxus alkaloids

Scheme 14 adapted from82 below summarises the activity in the first three decades of four decades, in which there had been intensive development and effort on the construction of the five-membered ring and access to a variety of Cephalotaxus alkaloids. This scheme shows key disconnection to make the pyrrolo[1,2-a]azepine 4 nucleus found in Cephalotaxine 56.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Synthesis determining steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinreb</td>
<td>1972</td>
<td>Made and used a Weinreb-Dolby enamine 102 made by eletrophilic cyclisation of the benzazepine ring from aldehyde 103 and through photolytic cyclisation of intermediate 104. This intermediate was used to form a vinylogous amide (crucial for ring-closing step) reacting with (ethyl carbonic) 2-oxopropanoic anhydride. 49, 50</td>
</tr>
<tr>
<td>Dolby</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semmelhack</td>
<td></td>
<td>Used 1-azaspiro[4.4]nonane 105 intermediate in intramolecular S_{RN}1 substitution of a benzyne ring. 51, 52, 53, 49</td>
</tr>
<tr>
<td>Hanaoka</td>
<td>1986</td>
<td>Made the ally vinyl ether 106 from a dicarbonyl compound made from aryl acylation. Claisen rearrangement was then used to install the quaternary carbon. 54</td>
</tr>
<tr>
<td>Fuchs</td>
<td>1988</td>
<td>Use [4+2] cycloaddition of a nitroso and a diene on intermediate 107 to introduce a quaternary nitrogen centre. 55, 56</td>
</tr>
<tr>
<td>Kuehne</td>
<td></td>
<td>Used intermediate 108 which oxidatively rearranged to 1-azaspiro[4.4]nonane, thus an electrophilic attack of the electron rich aromatic ring on cyclopently acetate was made possible to achieve the benzazepine ring. 57</td>
</tr>
<tr>
<td>Ikeda &amp; Ishibashi</td>
<td>1990</td>
<td>Used intermediate 109 in the Pummerer reaction. 58, 59, 60, 61, 62</td>
</tr>
<tr>
<td>Danishefsky</td>
<td></td>
<td>Used intramolecular carbenoid cyclisation on intermediate 112 to achieve Weinreb-Dolby enamine. 63</td>
</tr>
<tr>
<td>Mariano</td>
<td>1994</td>
<td>Used intermediate 110 in a quasi-biomimetrictrans annular cyclisation. The adjacent ketone on the cyclopentadiene was crucial for the reaction to be irreversible. 64, 65</td>
</tr>
</tbody>
</table>
The third decade is represented by Scheme 14 in which a few examples are highlighted, also showing key disconnections to making pyrrolo[1,2-a]azepine core.

Scheme 15: Recent key disconnections to making pyrrolo[1,2-a]azepine nucleus.
Table 3: Recent developments on construction of five-membered core of Cephalotaxus alkaloids

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Synthesis determining steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li</td>
<td>2003</td>
<td>Facile reductive rearrangement upon exposure of ketone to zinc dust in hot glacial acetic acid.\textsuperscript{67,68,69,70,71}</td>
</tr>
<tr>
<td>Ishibashi</td>
<td>2005</td>
<td>Cascade radical cyclisation in the presence of Bu\textsubscript{3}SnH and 1,10-azobiscyclohexanecarbonitrile (ACN) in boiling chlorobenzene.\textsuperscript{72,73,74}</td>
</tr>
<tr>
<td>Gin</td>
<td>2006</td>
<td>Rearrangement of compound heating in 1,2-dioxane, Cs\textsubscript{2}CO\textsubscript{3} followed by the [3 + 2] cycloaddition with phenyl vinyl sulfone after formation of a transient non stabilized azomethine ylide.\textsuperscript{75}</td>
</tr>
<tr>
<td>Li</td>
<td>2011</td>
<td>Spontaneous cyclisation of compound after zinc cleavage of N-Troc group.\textsuperscript{78}</td>
</tr>
</tbody>
</table>

1.5.3.1 Synthesis of Cephalotaxine 56

As already mentioned, Auerbach and Weinreb were the first to report a total synthesis of cephalotaxine in 1972.\textsuperscript{40,41} Their approach began with the conversion of acid 113 into its acid chloride derivative 114 (Scheme 16, a). The acid chloride 114 was then condensed with prolinol 115 resulting in the desired N-alkylated product and N,O-dialkylated products which were removed by selective hydrolysis of the ester (Scheme 16, b and c). The desired product was in the oxidized form, the aldehyde 116 which was required for cyclisation (Scheme 16, d). The cyclisation of 116 was achieved under acidic conditions to give 117 (Scheme 16, e). Compound 117 was then reduced to a labile compound 118 which was used immediately in the next alkylation reactions to form compounds 120 and 121 (Scheme 16, f, j, k). These did not yield to cyclisation to afford compounds 122 and 123. They alleviated the problem of ring closure by making vinylogous amide 119 from a reaction of 118 and a mixed anhydride prepared from pyruvic acid and ethyl chloroformate (Scheme 16, g). Compound 119 was successfully cyclised to demethylcephalotaxinone 124 using
magnesium methoxide in methanol (Scheme 16, h). Compound 124 was converted into cephalotaxinone 125 in high yield in a reaction with diazomethane, via an enol ether intermediate which conformed under equilibrating conditions of O-methylation (Scheme 16, i). The reduction of 125 with sodium borohydride gave cephalotaxine 56 in 4.5% overall yield. Compound 119 is of interest to us in our synthetic strategy of cephalotaxine 56. Compound 119 would be made in a Heck-type coupling reaction forming the seven-membered ring (See Scheme 25, e; section 1.6.2.4).

Scheme 16: Reagents and conditions: (a) SOCl₂; (b) CH₃CN, -20 °C, K₂CO₃; (c) K₂CO₃ (aq.), 82%; (d) DMSO, DCC, Cl₂CHCO₂H, 67%; (e) BF₃, CHCl₃, r.t.; (f) LiAlH₄, THF; (g) CH₃COCO₂CO₂Et; (h) Mg(OMe)₂, MeOH; (i) (MeO)₂C(CH₃)₂, p-TsOH; (j) propargyl bromide or methyl 4-bromo-3-methoxycrotonate; (k) Hg²⁺, H₂O⁺; (l) Sodium borohydride.⁴⁰,⁴¹
1.5.4 Miscellaneous alkaloids

1.5.4.1 Securinega alkaloids

The Securinega alkaloids are well known for their biological activities. These include acting as stimulants of the central nervous system\(^{32}\), having antimalarial and antibacterial activities\(^{33}\) and also acting as antitumor agents.\(^{35,34}\) There are a few examples on the construction of the concealed pyrrolo[1,2a]azepine 4 unit in a Securinega alkaloid by the Figueredo group.\(^{31}\) Their latest contribution was in the total synthesis of (−)-norsecurinine 136 where the crucial steps were a palladium-catalysed enantioselective imide alkylation, a vinylogous Mannich reaction, and a ring-closing metathesis process. In the midst of their synthesis they made the 1-azabicyclo[5.3.0]decane 4 core which was crucial for the success of their project.

Succinimide 126 and epoxide 127 were reacted under conditions (Scheme 17, a), and the alkylated product 128 was isolated in 91% yield and 87% enantiomeric excess (ee). The alcohol 128 was protected as the corresponding tert-butylidiphenylsilyl (TBDPS) ether 129, which crystallized from 2-propanol giving >98% ee and 81% yield from 126 (Scheme 17, b). Ether 129 was reduced with lithium triethylborohydride, leading to a mixture of the epimeric aminals 130 in 87% yield (Scheme 17, c). Triisopropylsiloxypyran 131 (which was previously prepared)\(^ {36}\) was reacted with 130 in the crucial vinylogous Mannich reaction which they found to work best under the illustrated conditions (Scheme 17, d), yielding a clean mixture of diastereomeric products 132 evident by NMR spectroscopic analysis. They were not able to separate this mixture by chromatography, but major isomer 132a crystallised from the mixture upon standing at room temperature overnight and was separated by filtration in 51% yield. They performed a ring closing metathesis (RCM) on the mixture 132, forming isomers 133a-d which confirmed the relative configuration of 132a-d (Figure 8, Scheme 17). Pure 133a was subjected to RCM reaction, leading to diene 133a isolated in >98% yield (Scheme 17, e). Lactam 133a was directly reduced with freshly prepared aluminium hydride\(^ {37,38}\) which allowed the isolation of 134 in 57% yield. Compound 134 was desilylated to the free alcohol 135 in good yield by reaction of 134 with an excess of triethylamine hydrofluoride in tetrahydrofuran at room temperature. The alcohol 135 was subjected
to conditions described by Jacobi et al., giving 136 in 60% yield. They accomplished their synthesis of (−)-norsecurinine 136 in nine steps and 11% overall yield.83

Scheme 17: Reagents and conditions: Enantioselective Synthesis of (−)-Norsecurinine(−)-136:
(a) (S,S)-137, 0.4% [h3-C6H5PdCl]2, NaHCO3, CH2Cl2, r.t.; (b) (i) TBDPSCI, imidazole, CH2Cl2 (ii) crystallization in 2-propanol; (c) LiBEt3H, THF, −78 °C; (d) 131, BF3·Et2O, Et2O, 0 °C; (e) 10% Grubbs II cat, CH2Cl2, r.t.; (f) 0.5 M AlH3, THF, 0 °C, 5 min; (g) Et3H, HF, THF, r.t.; (h) see ref. 39
Figure 8: Isomers from ring closing metathesis reaction.
1.6 Aims and strategy of this project

1.6.1 General aims

The main objective of this project is to attempt the construction of the pyrrolo[1,2-a]azepine (4) nucleus utilising enaminone chemistry. The intention is to construct a seven-membered ring onto a system that already contains a five-membered ring, thus making the enaminone unit a five-membered ring (n = 1). The choice of the R group is important since its length will guarantee the seven-membered ring size, based on the enaminone reactivity (Figure 3 (ii)). The alternative approach of building a five-membered ring on to a seven-membered ring enaminone-containing precursor is also a possibility, as will be described in the next Chapter.

![Figure 9: Enaminones](image)

The influence of the R group’s incorporation onto the enaminone unit is of interest (Figure 9), especially in relation to its effects as previously observed when making pyrrolizidine 1, indolizidines 2 and quinolizidines 3. Eschenmoser sulphide contraction reaction is employed to introduce the Z group and its choice is determined by good reactivity (previously observed) and ease of deprotection.

Enaminone chemistry would then take centre stage in construction of the five-membered ring by an intramolecular alkylation and intramolecular acylation of an enaminone (Scheme 18).
Lehmizidine alkaloids can then be accessed by either starting with already functionalised starting materials or functionalising at a later stage.

Second to the main objective is to access Cephalotaxus alkaloids via coupling reaction conditions forming the seven-membered ring. This work is well elaborated in our laboratories for indolizidine 2 alkaloids.\textsuperscript{79,80,81} The enaminoe unit will be built as described above for Lehmizidine alkaloids with the Z group ready to be functionalized further (Scheme 19). Note that in this case the cyclisation is by arylation instead of alkylation or acylation, which will be discussed further in Chapter 3.

**Scheme 18:** Enaminoe reactivity in alkylation and acylation reactions.

**Scheme 19:** Enaminoe reactivity in arylation reactions.
1.6.2 Specific aims

1.6.2.1 Lehmizidine alkaloids

The first aim of this project is to explore methodology that could in principle lead to the synthesis of lehmizidine alkaloid 50. This will employ the well established methodology within the Organic Chemistry group of the University of the Witwatersrand, in creating azabicyclic alkaloid systems via enaminone chemistry. If this can be achieved, the synthesis of the remaining lehmizidines could also be attempted. Although this would be a far more complex task, the methodology developed might be extended towards the synthesis of parvistemoline group members. The project begins with use of commercially cheap ingredients and use recently developed methods to convert them into suitable precursors for the cyclisation studies. Alternative disconnections towards pyrrolo[1,2-a]azepine 4 nucleus are shown in Scheme 20, with emphasis on alkylative and acylative ring closing mechanisms.

![Scheme 20](image)

R\(^1\) = EWG, R\(^2\) = alkyl, X = Br, Cl or H

**Scheme 20:** Alternative disconnections towards making pyrrolo[1,2-a]azepine core.
1.6.2.2 Strategy

The first strategy is an attempt on making the pyrrolo[1,2a]azepine 4 core, scaffold for lehmizidines and parvistemoline V. 4-Chlorobutanoyl chloride 138 can be reacted with ethyl 4-aminobutyrate hydrochloride in the presence of a base to yield ethyl 4-(4-chlorobutanamido)butanoate 139 (Scheme 21, a). Compound 139 can then be cyclised forming a five-membered ring in the presence of a strong base to form ethyl 4-(2-oxopyrrolidin-1-yl)butanoate 141 (Scheme 21, b). On the other hand compound 141 can be achieved by the N–alkylation of pyrrolidin-2-one 140 by ethyl 4-bromobutanoate in the presence of a strong base (Scheme 21, c). A thionation reaction on compound 141 using Lawesson's reagent or P₂S₅ should result in ethyl 4-(2-thioxopyrrolidin-1-yl)butanoate 142 (Scheme 21, d). The Eschenmoser sulphide contraction reaction of compound 142 would result in (E)-ethyl 4-[2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]butanoate 143 (Scheme 21, e). The seven-membered ring can now be made having accessed the all important enamine 143. Compound 143 can be cyclised acylatively to yield compound 144 (Scheme 21, f) or alkylatively to yield compound 147 (Scheme 21, g). At this point a goal of making the 1-azabicyclo[5.3.0]decane 4 core would be achieved. The hydrogenation of compounds 144 and 147 would result in compounds 145 and 148 respectively (Scheme 21, h). Decarboxylation of compound 145 (Scheme 21, i) followed by the reduction reaction of the ketone on compound 146 (Scheme 21, j) would lead to compound 4.
The key steps in accessing the lehmizidines 159 would be making the five-membered and seven-membered rings. The strategy assumes making the five-membered ring first, then later assembling the seven-membered ring. Ethyl 4-chloro-4-oxobutanoate 149 can be reacted with Grignard reagents marked R1CH2 under strict conditions to yield compounds 150 (Scheme 22, a). Compounds 150 can then be reacted with ethyl 4-aminobutyrate hydrochloride which is commercially available and ethyl 4-aminopentanoate (which can be synthesized from a reaction of commercially available 5-methylpyrrolidin-2-one with sodium ethoxide, to yield compounds 151 (Scheme 22, b). Compounds 151 would require a selective reduction of the enamine double bond in order to free the amide reactivity forming compounds 152 (Scheme 22, c). Compounds 152 can then be subjected to the same conditions to those already mentioned [Scheme 21, (d – j)] to yields lehmizidine alkaloids 159. The challenge from here on would be to synthesize these alkaloids enantioselectively.
The second aim of this project is to synthesise models for cephalotaxine 56. This will employ a recently developed methodology within the Organic Chemistry group of the University of the Witwatersrand, in creating azabicyclic alkaloid systems via a Heck-type coupling, linking an enaminone with a brominated aryl group. This intramolecular link has assisted in forming a five-membered ring (n = 0) in these alkaloids (Scheme 23). Now, this methodology will be extended towards making a seven-membered ring (n = 2). Also of interest is exploring alternatives with X = H because of the recent attention in the literature in the methods entailing to C-H activation.
**Scheme 23:** Heck type coupling.

1.6.2.4 **Strategy**

γ-Butyrolactone 13 will be reacted with homoveratrylamine 160 in an oven using a sealed tube reactor to yield lactam 1-(3,4-dimethoxyphenethyl)pyrrolidin-2-one 161 (Scheme 24, a). Lactam 161 will then be reacted with bromine in acetic acid to yield 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-one 162 (Scheme 24, b). Compound 162 will then be subjected to a thionation reaction using Lawesson’s reagent or $P_2S_5$ resulting in the formation of thiolactam 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidine-2-thione 163 (Scheme 24, c). Ethyl bromoacetate will be reacted with thiolactam 163 in the Eschenmoser sulphide contraction reaction resulting in enaminone (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 164 (Scheme 23, d). At this stage the Heck-type coupling reaction would be employed to create the seven-membered ring resulting in the target molecule 165 (Scheme 24, e). However, for comparison, studies in which the carbon chain between nitrogen and the aromatic ring is reduced by one or two methylene units in order to ascertain the relative ease of the cyclisation would be included. An investigation of aryl-containing pyrrolidones (without the aromatic halide) would be undertaken in order to see whether cyclisation by other C–H activation methods can be achieved.
If the cyclisation is successful, the synthesis (Scheme 24) can be extended to compound 119 (Scheme 25, e), which was an advanced intermediate in Weinreb’s synthesis of cephalotaxine 56.\textsuperscript{20,21} This will require the synthesis of the diketone-derived enaminone (E)-1-(1-(2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethyl)pyrrolidin-2-ylidene)butane-2,3-dione 169 (Scheme 25, d). The uniquely fused three five-membered rings, a seven-membered ring and an aromatic ring of cephalotaxine 56 will be created by Heck type coupling of enaminone 169 followed by Weinreb cyclisation (Scheme 25, f) as key steps. The first few reactions use similar reaction conditions as in Scheme 24, a, b, c, d with suitable modifications to some reagents, resulting in enaminone 169 where the Heck type coupling takes centre stage in creating the five-membered ring (Scheme 25, e). Making 119 will complete a formal synthesis of cephalotaxine 56 by converging with Weinreb’s route (f, g, h Scheme 25).
Scheme 25: Synthetic strategy towards Cephalotaxine 56.
CHAPTER 2: APPROACHES TOWARDS THE LEHMIZIDINE NUCLEUS

2.1 The lehmizidine core

(E)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 had to be synthesised before the strategies shown in the previous chapter could be carried out. Synthetic routes taken to achieve enaminone 143 are presented, followed by subsequent reactions towards the pyrrolo[1,2-a]azepine nucleus 4. Focus is placed on how reactions were performed, observations, discussions on the outcome of these reactions and elucidation of products through spectroscopic analysis.

2.2 Attempted synthesis of ethyl 4-(2-oxopyrrolidin-1-yl)butanoate 141

The synthesis of the pyrrolo[1,2-a]azepine nucleus 4 is essential for making lehmizidine alkaloids. The vinylogous urethane (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 takes centre stage for this synthesis, since it provides the five-membered ring onto which the seven-membered ring needs to be built on. The saturated ester group can be reduced to an alcohol group, converted into a better leaving group such as iodide, and the seven-membered ring formed by an alkylation reaction between the enaminone and alkyl halide group, resulting in (E)-ethyl 2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147 (Scheme 26, f). A similar cyclisation is achieved by hydrolysing the saturated ester to a carboxylic acid, converting the carboxylic acid into a carboxylic acid anhydride or halide, and the seven-membered ring is formed by an acylation reaction between the enamine and the activated carboxylic acid, resulting in (E)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 144 (Scheme 26, g).

A synthetic strategy was adopted that would involve the synthesis of the enaminone 143 from ethyl 4-(2-thioxopyrrolidin-1-yl)butanoate 142 in an Eschenmoser sulphide contraction reaction. The thiolactam would be prepared from a thionation reaction of ethyl 4-(2-oxopyrrolidin-1-yl)butanoate 141. This lactam would in turn be prepared
from an alkylation reaction of pyrrolidin-2-one and ethyl 4-bromobutyrate. Alternatively, the lactam ring could be prepared by acylation of ethyl 4-aminobutyrate with 4-chlorobutanoyl chloride, followed by cyclisation.

The synthesis of lactam ethyl 4-(2-oxopyrrolidin-1-yl)butanoate 141 utilising pyrrolidin-2-one 140 began with alkylation reactions. The deprotonation of pyrrolidin-2-one 140 by sodium hydride in N,N-dimethylformamide at 0 °C for half an hour proceeded with formation of its sodium salt, indicated by a white foam precipitate. Ethyl -4-bromobutyrate was then added into the sodium salt and reacted for 26 hours at room temperature followed by heating to 90 °C for 20 hours. Pyrrolidin-2-one (54%) and ethyl-4-bromobutyrate (26%) were recovered after purification from silica gel column chromatography, as shown by ¹H NMR spectroscopy (Table 4: entry 1). This indicated that the sodium salt of pyrrolidin-2-one did not react with ethyl -4-bromobutyrate both under ambient and high temperature conditions. Similarly, reacting pyrrolidin-2-one and ethyl -4-bromobutyrate at room temperature for 20 hours only afforded above starting materials (Table 4: entry 2). This further confirmed the reaction was a non-starter at ambient temperature.
The above conditions were clearly not suitable for the N-alkylation reaction, since it was possible that the bromide was not a good leaving group in the S\(_{N}\)2 reaction. Thus, the bromide was converted into an iodide in situ under Finkelstein reaction conditions and reacted with pyrrolidin-2-one. Ethyl 4-bromobutyrate, potassium carbonate, potassium iodide and pyrrolidin-2-one \textit{140} were heated under reflux in acetone for 5 hours. This resulted in recovery of brown ethyl 4-iodobutanoate and trace amount of pyrrolidin-2-one \textit{140} indicated by \(^1\)H NMR spectroscopy, revealing the chemical shift of triplet at \(\delta\) 3.53 ppm to triplet at \(\delta\) 2.91 ppm indicating the transformation from ClCH\(_2\) to ICH\(_2\) (Table 4: entry 3). This prompted the use of isolated ethyl 4-iodobutanoate in N-alkylation reaction with pyrrolidin-2-one. The sodium salt formed by reacting with sodium hydride in N,N-dimethylformamide at 0 °C for 10 min was reacted with ethyl 4-iodobutanoate at room temperature for 20 hours. One significant observation was the absence of the brown colour when ethyl 4-iodobutanoate was added into the sodium salt of pyrrolidin-2-one. Unidentified side products were recovered on purification (Table 4: entry 4). Pyrrolidin-2-one was then reacted with potassium tertiary butoxide at 0 °C in butanol making the potassium salt of pyrrolidin-2-one, followed by reacting it with ethyl 4-bromobutyrate at 35 °C for 20 hours. Changing the base to t-BuOK did not yield the desired product even when the potassium salt of pyrrolidin-2-one formed really well (Table 4: entry 5). With hindsight of the results in Section 2.3 where success was achieved in synthesising lactams \textit{170} and \textit{172} under N-alkylation reaction conditions, pyrrolidin-2-one \textit{140} was reacted with sodium hydride in tetrahydrofuran at room temperature for 30 minutes followed by release of heat and hydrogen gas indicative of the deprotonation of NH proton. Ethyl 4-bromobutyrate was added into the sodium salt of pyrrolidin-2-one and reacted at room temperature for 24 h resulting in the recovery of pyrrolidin-2-one \textit{140} and ethyl 4-bromobutyrate in 45% and 36% yield respectively (Table 4: entry 6).

It became apparent that formation of the sodium and potassium salts of pyrrolidin-2-one was not in question, but the reactivity of ethyl 4-bromobutyrate seemed to be the problem. It seems that the good results which were previously observed for N-alkylation with ethyl 2-chloroacetate and ethyl 3-chloropropanoate as alkylation agents are carbon-chain length dependent.\textsuperscript{84,85} As the carbon chain length increases, the reactivity decreases owing to reduced inductive effects between the carbonyl group and the halogen atom (Scheme 25: a, Table 4).
<table>
<thead>
<tr>
<th>No.</th>
<th>Reactants</th>
<th>Conditions</th>
<th>Solvents</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(i) NaH (1.2 eq), (ii) Ethyl 4-bromobutyrate (1.2 eq)</td>
<td>(i) 0.5 h at 0 °C, (ii) 26 hours at room temperature and 20 h at 90 °C</td>
<td>DMF</td>
<td>141 = 0%; 140 = 54%</td>
</tr>
<tr>
<td>2</td>
<td>(i) NaH (1.1 eq), (ii) Ethyl 4-bromobutyrate (1.1 eq)</td>
<td>(i) 0.5 h at 0 °C, (ii) 20 hours at room temperature</td>
<td>DMF</td>
<td>141 = 0%</td>
</tr>
<tr>
<td>3</td>
<td>Ethyl 4-bromobutyrate (1.1 eq), K$_2$CO$_3$ (1.1 eq), KI (1.1 eq),</td>
<td>5 h, heating under reflux</td>
<td>Acetone</td>
<td>141 = 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(i) NaH (1.22 eq), (ii) Ethyl 4-iodobutyrate (1.17 eq)</td>
<td>(i) 10 min at 0 °C, (ii) 20 hours at room temperature</td>
<td>DMF</td>
<td>141 = 0%</td>
</tr>
<tr>
<td>5</td>
<td>Ethyl 4-bromobutyrate (1 eq), t-BuOK (1 eq)</td>
<td>20 hours at 35 °C</td>
<td>BuOH</td>
<td>141 = 0%</td>
</tr>
<tr>
<td>6</td>
<td>(i) NaH (1.1 eq), (ii) Ethyl 4-bromobutyrate (1.1 eq)</td>
<td>(i) 0.5 h at room temperature, (ii) 24 hours at room temperature</td>
<td>THF</td>
<td>141 = 0%; 140 = 45%</td>
</tr>
</tbody>
</table>

A different approach towards the synthesis of ethyl 4-(2-oxopyrrolidin-1-yl)butanoate 141 was taken involving a C-acylation reaction and a ring closing intramolecular N-alkylation reaction. The intramolecular N-alkylation reaction of compound 139 was expected to be more efficient as compared to the previously discussed intermolecular N-alkylation reaction reactions of pyrrolidin-2-one. Ethyl 4-(4-chlorobutanamido)butanoate 139 was synthesised in an excellent 99% yield, using an acylation reaction between ethyl 4-aminobutyrte hydrochloride, 4-chlorobutryl chloride 138 and sodium hydrogen carbonate in dichloromethane at room temperature for 17 hours followed by heating under reflux for one hour (Scheme 25, b).
The IR spectrum of ethyl 4-(4-chlorobutanamido)butanoate 139 presented with peaks at $\nu_{\text{max}} = 3304 \text{ cm}^{-1}$ for the amide proton and $\nu_{\text{max}} = 1730, 1644 \text{ cm}^{-1}$ for the amide and the carboxylic ester carbonyl groups. The $^1$H NMR spectrum showed unresolved amide NH peak at $\delta 6.19 \text{ ppm}$ and the N-alkyl protons at $3.58 – 3.54 \text{ ppm}$, confirming the amide bond formation. The $^{13}$C NMR spectrum presented with the amide and ester carbonyl carbon peaks at $\delta 173.0$ and $171.8 \text{ ppm}$, respectively.

Having achieved the C-acylation reaction, it was now necessary to complete the cyclisation. Ethyl 4-(4-chlorobutanamido)butanoate 139 was reacted with potassium tertiary butoxide at 35 °C in butanol for 72 hours. The alkylation reaction failed to occur even though there was good anion formation as indicated by a colour change. Ethyl 4-(4-chlorobutanamido)butanoate 139 was recovered in 28% yield after reaction work up (Scheme 26, c).

2.3 N-Alkylation reactions of pyrrolidin-2-one with alkyl bromoacetates

The poor reactivity between pyrrolidin-2-one and ethyl 4-bromobutyrate encouraged the investigation of the reaction conditions employed on other related systems. To this effect the reaction conditions for pyrrolidin-2-one with ethyl 2-bromoacetate and tert-butyl 2-bromoacetate were examined, to which reaction conditions for ethyl 4-bromobutyrate with pyrrolidin-2-one was adapted. In two separate reactions under the same reaction conditions, pyrrolidin-2-one was reacted with sodium hydride in tetrahydrofuran at room temperature for half an hour. This was followed by the addition of ethyl 2-bromoacetate or tert-butyl 2-bromoacetate in tetrahydrofuran and left to stir at room temperature for 24 h. The alkylation reactions on pyrrolidin-2-one with ethyl 2-bromoacetate and tert-butyl 2-bromoacetate resulted in high yields of ethyl 2-(2-oxopyrrolidin-1-yl)acetate 170 (90%) and tert-butyl 2-(2-oxopyrrolidin-1-yl)acetate 172 (91%), respectively (Scheme 27, a). These results are in agreement with literature reported yields of 83% for 170 and slightly better than 60% for 172.84,86 The trick was to allow the deprotonation step to occur at room temperature, as opposed to a traditional 0 °C that controls the rapid release of heat.
The IR spectrum of ethyl 2-(2-oxopyrrolidin-1-yl)acetate 170 revealed a peak at $\nu_{\text{max}} = 1749$ cm$^{-1}$ for the amide and the ester carbonyl group. The $^1$H NMR spectrum confirmed the N-alkyl substituent with a singlet at $\delta 3.74$ ppm for the methylene group, while the quartet with $J = 7.1$ Hz and triplet with $J = 7.2$ Hz for the ethyl ester group were at $\delta 3.87$ ppm and $\delta 0.96$ ppm, respectively. The remaining pyrrolidinone ring $\alpha$, $\beta$, $\gamma$-protons triplet with $J = 8.1$ Hz, doublet of triplets with $J = 11.2$, $7.5$ Hz and triplet with $J = 7.1$ Hz of the amide were at $\delta 2.09$, $1.77$ and $3.19$ ppm respectively. The $^{13}$C NMR spectrum had peaks at $\delta 175.3$ and $168.4$ ppm for the amide and ethyl ester carbonyl carbons, respectively. The ethyl ester carbon peaks were at $\delta 60.9$, and $13.8$ ppm, while the methylene group carbon peak appeared at $\delta 47.4$. The remaining peaks at $\delta 30.0$, $17.7$ and $43.7$ ppm were for the pyrrolidinone ring $\alpha$, $\beta$, $\gamma$-carbons to the amide.

The IR spectrum of tert-butyl 2-(2-oxopyrrolidin-1-yl)acetate 172 had a peak at $\nu_{\text{max}} = 1765$ cm$^{-1}$ for the amide and butyl ester carbonyl groups. The $^1$H NMR spectrum revealed the N-alkyl substituent with a singlet at $\delta 3.96$ ppm for the methylene group, while the singlet for the tert-butyl protons was $\delta 1.47$ ppm. The pyrrolidine ring $\alpha$, $\beta$, $\gamma$-protons triplet with $J = 8.1$ Hz, multiplet and triplet with $J = 7.0$ Hz were at $\delta 2.42$, $2.15$ – $2.00$ and $3.49$ ppm, respectively. The $^{13}$C NMR spectrum showed peaks at $\delta$ 175.5, 167.7 and 81.9 ppm for the amide carbonyl, tert-butyl ester carbonyl and tert-butyl ester quaternary carbons respectively, while the tert-butyl ester methylene and methyl carbon peaks was at $\delta$ 47.6 and 27.9 ppm. The remaining peaks at $\delta$ 30.3, 17.9 and 44.6 ppm were for $\alpha$, $\beta$, $\gamma$-carbons to the amide of the pyrrolidine ring.
Lactams 2-(2-oxopyrrolidin-1-yl)acetate were thionated to compare success in thionation of ethyl 4-(2-oxopyrrolidin-1-yl)butanoate lactam 142. Ethyl 2-(2-oxopyrrolidin-1-yl)acetate or tert-butyl 2-(2-oxopyrrolidin-1-yl)acetate was reacted with phosphorus pentasulphide in dichloromethane at room temperature for 24 hours. The thionation reactions of these two N-(alkoxycarbonylmethyl)pyrrolidin-2-ones were also high yielding, leading to ethyl 2-(2-thioxopyrrolidin-1-yl)acetate 171 (97%) and tert-butyl 2-(2-thioxopyrrolidin-1-yl)acetate 173 (89%).

The IR spectrum of ethyl 2-(2-thioxopyrrolidin-1-yl)acetate 171 had a peak at $\nu_{\text{max}} = 1733$ cm$^{-1}$ for the ester carbonyl group. The $^1$H NMR spectrum of 171 had similar peaks to that of lactam 170 with a slight downfield shield shift in their chemical environments, owing to higher inductive effects from sulphur atom as compared to the oxygen atom (Table 5).

### Table 5: Selected $^1$H NMR spectroscopic signals of compounds 170 and 171

<table>
<thead>
<tr>
<th></th>
<th>NCH$_2$CO$_2$</th>
<th>CH$_2$CH$_3$</th>
<th>NCH$_2$CH$_2$</th>
<th>COCH$_2$CH$_2$</th>
<th>NCH$_2$CH$_2$</th>
<th>CH$_2$CH$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>170 / ppm</td>
<td>3.74</td>
<td>3.87</td>
<td>3.19</td>
<td>2.09</td>
<td>1.77</td>
<td>0.96</td>
</tr>
<tr>
<td>171 / ppm</td>
<td>4.56</td>
<td>4.22</td>
<td>3.85</td>
<td>3.06 (CSCH$_2$)</td>
<td>2.22 – 2.05</td>
<td>1.30</td>
</tr>
</tbody>
</table>

The $^{13}$C NMR spectrum of thiolactam 171 showed the absence of the amide carbonyl carbon peak, previously at $\delta$ 175.3 ppm and the presence of the thioamide carbonyl carbon peak at $\delta$ 203.5 ppm. The ethyl ester carbonyl peak was present at $\delta$ 167.0 ppm, confirming chemoselectivity of the thionation reaction towards the carboxylic amide. The remaining carbon peaks were similar to those of lactam 170 with a slight downfield chemical shift (Table 6).
Table 6: Selected $^{13}$C NMR spectroscopic signals of compounds 170 and 171

<table>
<thead>
<tr>
<th></th>
<th>NCH$_2$CO$_2$</th>
<th>NCH$_2$CH$_2$</th>
<th>COCH$_2$CH$_2$</th>
<th>NCH$_2$CH$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>170 / ppm</td>
<td>47.4</td>
<td>44.7</td>
<td>30.0</td>
<td>17.7</td>
</tr>
<tr>
<td>171 / ppm</td>
<td>55.5</td>
<td>49.0</td>
<td>44.3 (CSC$_2$)</td>
<td>19.7</td>
</tr>
</tbody>
</table>

The IR spectrum of tert-butyl 2-(2-thioxopyrrolidin-1-yl)acetate 173 had a peak at $\nu_{\text{max}} = 1747$ cm$^{-1}$ for the tert-butyl ester carbonyl group. The $^1$H NMR spectrum of thiolactam 173 was similar to that of lactam 172 with slight downfield chemical shift for some of the peaks due to electron withdrawing effect of the sulphur atom (Table 7).

Table 7: Selected $^1$H NMR spectroscopic signals of compounds 172 and 173

<table>
<thead>
<tr>
<th></th>
<th>NCH$_2$CO$_2$</th>
<th>NCH$_2$CH$_2$</th>
<th>COCH$_2$CH$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>172 / ppm</td>
<td>3.96</td>
<td>3.49</td>
<td>2.42</td>
</tr>
<tr>
<td>173 / ppm</td>
<td>4.44</td>
<td>3.83</td>
<td>3.05 (CSC$_2$)</td>
</tr>
</tbody>
</table>

The $^{13}$C NMR spectrum of thiolactam 173 revealed the absence of the amide carbonyl peak previously at $\delta$ 175.5 ppm and the presence of the thioamide carbonyl peak at $\delta$ 203.3 ppm. The tert-butyl ester carbonyl carbon peak was at $\delta$ 166.1 ppm, while the remaining peaks were similar to those of lactam 172 with a slight down field chemical shift (Table 8).
Table 8: Selected $^{13}$C NMR spectroscopic signals of compounds 172 and 173

<table>
<thead>
<tr>
<th></th>
<th>NCH$_2$CO$_2$</th>
<th>NCH$_2$CH$_2$</th>
<th>COCH$_2$CH$_2$</th>
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<tbody>
<tr>
<td>172 / ppm</td>
<td>47.6</td>
<td>44.6</td>
<td>30.3</td>
</tr>
<tr>
<td>173 / ppm</td>
<td>55.5</td>
<td>49.7</td>
<td>44.3 (CSCH$_2$)</td>
</tr>
</tbody>
</table>

2.4 Attempted synthesis of (E)-ethyl 4-(2-oxopyrrolidin-1-yl)but-2-enoate 174

The greater reactivity of the allyl halides with amides compared with alkyl halides encouraged the reaction of pyrrolidin-2-one with ethyl 4-bromocrotonate, aiming to achieve (E)-ethyl 4-(2-oxopyrrolidin-1-yl)but-2-enoate 174. The double bond of lactam 174 would then be hydrogenated with palladium on carbon as a catalyst to achieve ethyl 4-(2-oxopyrrolidin-1-yl)butanoate 141. The remaining steps from lactam 141 would be similar to those mentioned in Scheme 26 (d-g). Pyrrolidin-2-one 140 was reacted with sodium hydride in N,N-dimethylformamide at 0 ºC for 40 minutes after which the sodium salt formed followed by the drop-wise of addition of ethyl 4-bromocrotonate in N,N-dimethylformamide and reacting for 80 hours at room temperature (Scheme 28). The ethyl 4-bromocrotonate reacted with the sodium salt of pyrrolidin-2-one 140 giving a blue reaction mixture, which after 16 h had turned maroon. Work-up proved to be problematic with lots of foaming and no separation between aqueous and organic layers (Table 9, entry 1). The reaction (in entry 1) was repeated heating under reflux conditions for 22 hours instead of reacting at room temperature. Small amount of pyrrolidin-2-one 140 and polymeric tars were recovered after purification (Table 9, entry 2). Deprotonation of pyrrolidin-2-one 140 at room temperature would ensure complete salt formation and in addition to using tetrahydrofuran as solvent. Pyrrolidin-2-one 140 was reacted with sodium hydride in tetrahydrofuran at room temperature for 30 minutes after which the sodium salt formed followed by the drop-wise of addition of ethyl 4-bromocrotonate in tetrahydrofuran and reacting for 26 hours at room temperature. The reaction yielded small amounts of pyrrolidin-2-one 140 and polymeric tars (Table 9, entry 3). The
reaction (in entry 3) was repeated heating under reflux conditions for 20 hours instead of reacting at room temperature, but still recovered pyrrolidin-2-one 140 and polymeric tars (Table 9, entry 4). The expected N-alkylation reaction failed to occur. The polymeric tars may be a result of polymerisation or dimerisation of ethyl 4-bromocrotonate. The double bond in ethyl 4-bromocrotonate probably behaves more like a Michael acceptor as compared to the double bond of an allyl halide which allows direct nucleophilic attack on the allylic position in a $S_{N}2$ substitution reaction as will be seen in Section 2.19.

![Scheme 28](image)

**Scheme 28**: (a) Table 9. (b) Hydrogenation.

**Table 9: Intermolecular N-alkylation reactions of 2-pyrrolidinone with ethyl 4-bromocrotonate**

<table>
<thead>
<tr>
<th>No.</th>
<th>Reactants</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(i) NaH (1.2 eq), (ii) ethyl 4-bromocrotonate (1 eq)</td>
<td>(i) 40 minutes at 0 °C (ii) then 80 hours at room temperature</td>
<td>DMF</td>
<td>174 = 0%</td>
</tr>
<tr>
<td>2</td>
<td>(i) NaH (1.2 eq), (ii) ethyl 4-bromocrotonate (1 eq)</td>
<td>(i) 30 minutes at 0 °C (ii) then 22 hours heating under reflux</td>
<td>DMF</td>
<td>174 = 0%</td>
</tr>
<tr>
<td>3</td>
<td>(i) NaH (1.2 eq), (ii) ethyl 4-bromocrotonate (1 eq)</td>
<td>(i) 30 minutes at room temperature (ii) then 26 hours at room temperature</td>
<td>THF</td>
<td>174 = 0%</td>
</tr>
<tr>
<td>4</td>
<td>(i) NaH (1.2 eq), (ii) ethyl 4-bromocrotonate (1 eq)</td>
<td>(i) 30 minutes at room temperature (ii) then 20 hours heating under reflux.</td>
<td>THF</td>
<td>174 = 0%</td>
</tr>
</tbody>
</table>
The possibility that pyrrolidin-2-one 140 might react differently to other lactams was explored by reacting azepan-2-one 175 with sodium hydride in tetrahydrofuran at room temperature for 2 hours after which the salt precipitated. This was followed by drop-wise addition of ethyl 4-bromocrotonate in tetrahydrofuran, and the reaction was left to proceed at room temperature overnight (Scheme 29, a). This resulted in recovery of azepan-2-one 175 and polymeric tars after purification, showing similar results to those in Table 9.

2.5 Attempted synthesis of ethyl 4-(2-oxo-2H-pyrrol-1(5H)-yl)butanoate 178

Lactam 141 could be derived from lactam 178 in a hydrogenation reaction using palladium on carbon as catalyst and then following the synthetic strategy outlined in Scheme 25, d-g. The reactions of 2,5-dimethoxy-2,5-dihydrofuran 177 with primary amines in hydrochloric acid in water and acetonitrile have been reported to occur with low yields of unsaturated cyclised amides.87 Baussanne et al. found success with high yields in reactions of 2,5-dimethoxy-2,5-dihydrofuran 177 with substituted benzylamines in hydrochloric acid in water.88 Thus, 2,5-dimethoxy-2,5-dihydrofuran 177 was reacted with ethyl 4-aminobutyrate hydrochloride in 1M hydrochloric acid at room temperature for 6 hours with the mixture turning from yellow to maroon. The expected ethyl 4-(2-oxo-2H-pyrrol-1(5H)-yl)butanoate 178 was not recovered after purification, neither was 2,5-dimethoxy-2,5-dihydrofuran 177 nor ethyl 4-aminobutyrate, but maroon polymeric tars (Scheme 30, a). Could it be that the inductive effects on ethyl 4-aminobutyrate hydrochloride are unlike those found in
benzylamines! As an alternative for checking the procedure, ethyl 4-aminobutyrate was then substituted with homoveratrylamine 160 in line with Section 3.2 which requires synthesis of 1-(3,4-dimethoxyphenethyl)pyrrolidin-2-one which can be derived from hydrogenation of 1-(3,4-dimethoxyphenethyl)-1H-pyrrol-2(5H)-one 179. Thus, compound 177 was reacted with amine 160 in 1M hydrochloric acid at room temperature for 3.75 hours with the mixture turning from yellow to maroon. The reaction returned 53% of compound 177 and 85% of amine 160 (Scheme 30, b). The reaction conditions proved not suitable for our substrates possibly due to poor inductive effects between the nitrogen atom and aryl group in homoveratrylamine as compared to those in benzylamines.

![Scheme 30: Reagents and Conditions: (a) Ethyl 4-aminobutyrate.HCl (1 eq) or (b) homoveratrylamine (1 eq). 1M HCl, 3 - 6 h at r.t](image)

### 2.6 Synthesis of 1-(ω-hydroxyalkyl)pyrrolidin-2-ones with a twist

Commercially available 4-aminobutan-1-ol was decided upon in the quest to synthesise a four carbon chain lactam 180. The disadvantage was that 4-aminobutan-1-ol is expensive, supplied in small quantities and requires extra protection and deprotection steps towards desired enaminones. 4-Aminobutan-1-ol was chosen because it would have no competing intramolecular reactions, unlike ethyl 4-aminobutanoate which cyclised forming pyrrolidin-2-one 140.\(^{114}\) Dihydrofuran-2(3H)-one 13 was reacted with 4-aminobutan-1-ol neat in a microwave reactor at 150 W, 220 °C for 20 minutes resulting in 1-(4-hydroxybutyl)pyrrolidin-2-one 180 and 4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one 181 in 28% and 35% yields respectively. This was a setback because of the reaction’s lack of regioselectivity
towards the desired 1-(4-hydroxybutyl)pyrrolidin-2-one 180 and low yields (Scheme 31, a).

Scheme 31: Reagent and Conditions: (a) 4-amino-1-butanol (1 eq)/ 5-amino-1-pentanol (1 eq), 150 W, 220 °C, 20 min, 180 = 28%, 181 = 35%, 182 = 24%, 183 = 55%; (b) 3-Amino-1-propanol (0.91 eq), 150 W, 200 °C, 1.17 h, 184 = 88; (c) 4-amino-1-butanol (3 eq)/ 5-amino-1-pentanol (3 eq), [bmin]BF₄ (1 eq), 150 W, 220 °C, 35 min, 180 = 0%, 182 = 0%.

The IR spectrum of 1-(4-hydroxybutyl)pyrrolidin-2-one 180 had peaks at ν_max = 3441 and 1669 cm⁻¹ for the alcohol OH and amide groups respectively. The ¹H NMR spectrum had a singlet at δ 3.81 ppm for the OH proton. The butyl side chain was shown by two triplets with J = 5.9 Hz and J = 7.0 Hz at δ 3.63 and 3.30 ppm for the CH₂OH and NCH₂CH₂CH₂CH₂OH protons respectively. The pyrrolidinone ring’s presence was shown by two triplets at δ 3.41 and 2.39 ppm with J = 7.1 Hz and J = 8.2 Hz for the γ and α-protons of the amide respectively. The ¹³C NMR spectrum revealed the amide carbonyl carbon peak at δ 175.2 ppm while the butyl side chain’s major carbon peaks were at δ 61.7 and 42.2 ppm, corresponding to the CH₂OH and NCH₂CH₂CH₂CH₂OH carbon atoms. The major pyrrolidinone ring carbon peaks were at δ 47.1 and 29.6 ppm for the γ and α-carbons of the lactam. The ¹H and ¹³C NMR spectra had comparable peaks to those reported by Belanger et al. (Table 10).¹⁰⁰
Table 10: Comparison of $^1$H and $^{13}$C NMR spectroscopic data of lactam 180 to those of Belanger et al. 100

<table>
<thead>
<tr>
<th>$^1$H NMR ppm</th>
<th>$^1$H NMR (Lit.) ppm</th>
<th>$^{13}$C NMR ppm</th>
<th>$^{13}$C NMR (Lit.) ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.81 (s)</td>
<td>3.90 (s, OH)</td>
<td>175.2</td>
<td>175 (CON)</td>
</tr>
<tr>
<td>3.63 (t, $J = 5.9$ Hz)</td>
<td>3.42 (t, $J = 6.0$ Hz, CH$_2$OH)</td>
<td>61.7</td>
<td>61.5 (CH$_2$OH)</td>
</tr>
<tr>
<td>3.41 (t, 7.1 Hz)</td>
<td>3.22 (t, $J = 8.0$ Hz, NCH$_2$CH$_2$CH$_2$CO)</td>
<td>47.1</td>
<td>47.0 (NCH$_2$CH$_2$CH$_2$CO)</td>
</tr>
<tr>
<td>3.30 (t, 7.0 Hz)</td>
<td>3.11 (t, $J = 7.0$ Hz, NCH$_2$CH$_2$CH$_2$OH)</td>
<td>42.2</td>
<td>42.1 (NCH$_2$CH$_2$CH$_2$OH)</td>
</tr>
<tr>
<td>2.39 (t, 8.2 Hz)</td>
<td>2.19 (t, $J = 8.0$ Hz, NCH$_2$CH$_2$CH$_2$CO)</td>
<td>31.1</td>
<td>30.9 (NCH$_2$CH$_2$CH$_2$OH)</td>
</tr>
<tr>
<td>2.11 – 1.77 (m)</td>
<td>1.84 (q, $J = 8.0$ Hz, NCH$_2$CH$_2$CH$_2$CO)</td>
<td>29.6</td>
<td>29.5 (NCH$_2$CH$_2$CH$_2$CO)</td>
</tr>
<tr>
<td>1.71 – 1.47 (m)</td>
<td>1.47 (m, NCH$_2$CH$_2$CH$_2$CH$_2$OH)</td>
<td>23.6</td>
<td>23.6 (NCH$_2$CH$_2$CH$_2$OH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17.8</td>
<td>17.7 (NCH$_2$CH$_2$CH$_2$CO)</td>
</tr>
</tbody>
</table>

The IR spectrum of 4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one 181 had peaks at $\nu_{\text{max}} = 3420$ and 1667 cm$^{-1}$ for the alcohol OH and amide carbonyl groups respectively. The $^1$H NMR spectrum had no observable OH peak owing to proton exchange with the solvent MeOD. The pyrrolidinyl ring protons were shown by a triplet with $J = 6.4$ Hz at $\delta$ 3.46 for the four protons of NCH$_2$ and a multiplet at $\delta$ 1.45 ppm for the four protons of NCH$_2$CH$_2$. The butanone side chain protons were shown by the presence of a triplet with $J = 6.5$ Hz at $\delta$ 3.09 ppm for the γ-protons of the amide and by a triplet with $J = 7.6$ Hz at $\delta$ 2.16 ppm for the α-protons of the amide. The $^{13}$C NMR spectrum revealed the amide carbonyl carbon peak at $\delta$ 175.9 ppm while the butanone side chain major carbon peaks were at $\delta$ 40.2 and 33.7 ppm for the CH$_2$OH and COCH$_2$ protons correspondingly. The pyrrolidinyl ring peaks were at $\delta$ 62.6 and 62.3 ppm for the for two NCH$_2$ carbons, while the remaining peaks were at $\delta$ 29.9 and 26.9 ppm for two NCH$_2$CH$_2$ carbons. Some of the $^1$H and $^{13}$C NMR
spectra peaks for compound 181 were not comparable to those reported by Maulide et al. possibly owing to the different NMR machines used i.e. 300 MHz vs 500 MHz and the solvent used i.e. MeOD vs CDCl₃ for compound 181 and Maulide et al. data respectively (Table 11).

Table 11: Comparison of ¹H and ¹³C NMR spectroscopic data of lactam 181 to those of Maulide et al data¹⁷⁴

<table>
<thead>
<tr>
<th>¹H NMR (300MHz) ppm</th>
<th>¹H NMR (500 MHz) (Lit.) ppm</th>
<th>¹³C NMR ppm</th>
<th>¹³C NMR (Lit.) ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.09 (t, J = 6.5 Hz)</td>
<td>3.70 (t, J = 6.0 Hz, CH₂CH₂CH₂OH )</td>
<td>175.9</td>
<td>172.3 (C=O)</td>
</tr>
<tr>
<td>3.57 (bs, OH)</td>
<td></td>
<td>40.2</td>
<td>62.9(CH₂OH)</td>
</tr>
<tr>
<td>3.46 (t, J = 6.4 Hz)</td>
<td>3.40 – 3.50 (m, CH₂NCH₂)</td>
<td>62.6</td>
<td>46.8 (NCH₂)</td>
</tr>
<tr>
<td>2.16 (t, 7.6 Hz)</td>
<td>2.46 (t, J = 6.5 Hz, CH₂CO)</td>
<td>62.3</td>
<td>45.9(NCH₂)</td>
</tr>
<tr>
<td>1.77 – 1.62 (m)</td>
<td>1.97 (tt, J = 6.5, 6.0 Hz, CH₂CH₂CH₂OH)</td>
<td>33.7</td>
<td>32.8 (COCH₂)</td>
</tr>
<tr>
<td>1.45 (m)</td>
<td>1.83 – 2.00 (m, CH₂CH₂NCH₂CH₂)</td>
<td>31.0</td>
<td>27.2 (CH₂CH₂OH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29.9</td>
<td>26.1 (NCH₂CH₂)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26.9</td>
<td>24.4 (NCH₂CH₂)</td>
</tr>
</tbody>
</table>

This result (Scheme 31, a) prompted a probe into this phenomenon. Dihydrofuran-2(3H)-one 13 was then reacted with 5-amino-1-pentanol neat in a microwave reactor at 150 W, 220 °C for 20 minutes, resulting in the formation of the desired 1-(5-hydroxypentyl)pyrrolidin-2-one 182 and undesired 4-hydroxy-1-(piperidin-1-yl)butan-1-one 183 in 24% and 55% yields respectively (Scheme 31, a).

The IR spectrum of 1-(5-hydroxypentyl)pyrrolidin-2-ones 182 had peaks at ν_max = 3384 and 1701 cm⁻¹ for the alcohol OH and amide groups respectively. The ¹H NMR spectrum showed the pyrrolidinone ring’s presence by a triplet with J = 7.1 Hz at 3.40 ppm for the γ-protons of the lactam and a triplet with J = 8.1 Hz at δ 2.38 ppm.
for the α-protons of the lactam. The pentyl side chain’s presence was shown by a singlet at δ 3.75 ppm for the OH proton, a triplet with J = 6.5 Hz at δ 3.59 ppm for the CH₂OH protons and a triplet with J = 7.2 Hz at δ 3.27 ppm for the NCH₂CH₂CH₂CH₂CH₂OH protons. The ¹³C NMR spectrum showed a carbonyl peak at δ 175.1 ppm, while major pyrrolidinone ring peaks were at δ 47.1 and 31.0 ppm for the γ and α-carbons of the lactam respectively. The pentyl side chain major peaks were at δ 61.9 and 42.3 ppm for C₆H₂OH and NCH₂CH₂CH₂CH₂CH₂CH₂OH carbons respectively. The ¹H and ¹³C NMR spectra were comparable with the literature values from the article by Belanger et al. (Table 12).¹⁰⁰

Table 12: Comparison of ¹H and ¹³C NMR spectroscopic data of lactam 182 to those of Belanger et al. ¹⁰⁰

<table>
<thead>
<tr>
<th>¹H NMR ppm</th>
<th>¹H NMR (Lit.) ppm</th>
<th>¹³C NMR ppm</th>
<th>¹³C NMR (Lit.) ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.75 (s, OH)</td>
<td></td>
<td>175.1</td>
<td>175.0 (CON)</td>
</tr>
<tr>
<td>3.59 (t, J = 6.5 Hz)</td>
<td>3.64 (t, J = 6.5 Hz, CH₂OH)</td>
<td>61.9</td>
<td>61.6 (CH₂OH)</td>
</tr>
<tr>
<td>3.40 (t, J = 7.1 Hz)</td>
<td>3.37 (t, J = 7.0 Hz, NCH₂CH₂CH₂CO)</td>
<td>47.1</td>
<td>47.0 (NCH₂CH₂CH₂CO)</td>
</tr>
<tr>
<td>3.27 (t, J = 7.2 Hz)</td>
<td>3.29 (t, J = 7.0 Hz, NCH₂CH₂CH₂CH₂OH)</td>
<td>42.3</td>
<td>42.2 (NCH₂CH₂CH₂CH₂OH)</td>
</tr>
<tr>
<td>2.38 (t, J = 8.1 Hz)</td>
<td>2.39 (t, J = 7.0 Hz, COCH₂)</td>
<td>32.1</td>
<td>32.0 (NCH₂CH₂CH₂CH₂OH)</td>
</tr>
<tr>
<td>2.10 – 1.95 (m)</td>
<td>2.01 (qi, J = 7.0 Hz, NCH₂CH₂CH₂CO)</td>
<td>31.0</td>
<td>30.9 (COCH₂)</td>
</tr>
<tr>
<td>1.64 – 1.47 (m)</td>
<td>1.65 – 1.50 (m, NCH₂CH₂CH₂CH₂CH₂OH)</td>
<td>26.9</td>
<td>26.7 (NCH₂CH₂CH₂CH₂CH₂OH)</td>
</tr>
<tr>
<td>1.40 – 1.32 (m)</td>
<td>1.42 – 1.34 (m, NCH₂CH₂CH₂CH₂CH₂OH)</td>
<td>22.9</td>
<td>22.8 (NCH₂CH₂CH₂CH₂CH₂OH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17.7</td>
<td>17.6 (NCH₂CH₂CH₂CO)</td>
</tr>
</tbody>
</table>

The IR spectrum of 4-hydroxy-1-(piperidin-1-yl)butan-1-ones 183 had peaks at νₘₐₓ = 3513 and 1697 cm⁻¹ for the alcohol OH and amide carbonyl groups respectively. The
$^1$H NMR spectrum showed the piperidinyl ring’s presence by a triplet of doublets with $J = 6.4$ Hz at $\delta$ 3.57 ppm for the four NCH$_2$ protons and a multiplet at $\delta$ 1.64 – 1.46 ppm for the four NCH$_2$CH$_2$ protons. The butanone chain on nitrogen was shown by a triplet with $J = 6.9$ Hz at $\delta$ 3.18 ppm for $\gamma$-protons of the amide and a triplet with $J = 7.5$ Hz at $\delta$ 2.27 ppm for the $\alpha$-protons of the amide. The $^{13}$C NMR spectrum showed the amide carbonyl carbon peak at $\delta$ 175.8 ppm while the butanone’s major peaks were at $\delta$ 40.5 and 33.9 ppm for the $\gamma$ and $\alpha$ carbons of the amide respectively. The piperidinyl ring carbon peaks were at $\delta$ 62.9 and 62.4 ppm for the two NCH$_2$ carbons and peaks at $\delta$ 30.4 and 30.3 ppm for NCH$_2$CH$_2$ and NCH$_2$CH$_2$ carbons. Some of the $^1$H and $^{13}$C NMR spectra peaks for compound 183 were not comparable to those reported by Nolan et al. (Table 13).

Table 13: Comparison of $^1$H and $^{13}$C NMR spectroscopic data of lactam 183 to those of Nolan et al. $^{175}$

<table>
<thead>
<tr>
<th>$^1$H NMR ppm</th>
<th>$^1$H NMR (Lit.) ppm</th>
<th>$^{13}$C NMR ppm</th>
<th>$^{13}$C NMR (Lit.) ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.69 (br s, 2H)</td>
<td></td>
<td>175.8 (CO)</td>
<td>171.8</td>
</tr>
<tr>
<td>3.57 (td, $J = 6.4$ Hz, CH$_2$NCH$_2$)</td>
<td>3.58 – 3.54 (m, 2H)</td>
<td>62.9 (NCH$_2$)</td>
<td>62.9</td>
</tr>
<tr>
<td>3.18 (t, $J = 6.9$ Hz, CH$_2$OH)</td>
<td>3.43 – 3.40 (m, 2H)</td>
<td>62.4 (NCH$_2$)</td>
<td>46.8</td>
</tr>
<tr>
<td>2.27 (t, $J = 7.5$ Hz, COCH$_2$)</td>
<td>2.51 (t, $J = 6.5$ Hz, 2H)</td>
<td>40.5 (CH$_2$OH)</td>
<td>42.9</td>
</tr>
<tr>
<td>1.90 – 1.75 (m, CH$_2$CH$_2$OH)</td>
<td>1.96 – 1.83 (m, 2H)</td>
<td>33.9 (NCH$_2$CH$_2$)</td>
<td>31.1</td>
</tr>
<tr>
<td>1.64 – 1.46 (m, CH$_2$CH$_2$NCH$_2$CH$_2$)</td>
<td>1.66 – 1.42 (m, 8H)</td>
<td>33.4 (NCH$_2$CH$_2$)</td>
<td>27.6</td>
</tr>
<tr>
<td>1.46 – 1.32 (m, CH$_2$CH$_2$CH$_2$N)</td>
<td>30.3 (COCH$_2$)</td>
<td>26.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30.0 (CH$_2$CH$_2$OH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24.4 (NCH$_2$CH$_2$CH$_2$)</td>
<td>24.5</td>
</tr>
</tbody>
</table>
The reactions preferred a less strained cyclisation pathway, thus resulting in undesired 4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one 181 and 4-hydroxy-1-(piperidin-1-yl)butan-1-one 183 (Scheme 31). The amine attacks the carbonyl carbon of the lactone resulting in an acylation product which is an open chain. This is followed by 5-exo-Tet/ 6-exo-Tet cyclisation onto C-11 (Scheme 32) followed by a loss of a water molecule resulting in compounds 181 and 183 shown in Scheme 31. The reaction is not entirely chemoselective as seen from the yield but show that products resulting from less strained cyclisation are preferred. It was also noticed that the 6-exo-Tet mode was more preferred as compared to the 5-exo-Tet due to the fact that the resulting six-membered ring is less strained than the five-membered ring (Scheme 32).

![Scheme 32: Preferred 5-exo-Tet and 6-exo-Tet cyclisation.](image)

It was of interest as to how 3-amino-1-propanol would react with dihydrofuran-2(3H)-one 13 based on previous observations (Scheme 31, a). Dihydrofuran-2(3H)-one 13 was reacted with 3-amino-1-propanol neat in a microwave reactor at 150 W, 200 °C for 1.17 hours, resulting in 1-(3-hydroxypropyl)pyrrolidin-2-one 184 in excellent 88% yield. The 4-exo-Tet cyclisation from above proposed reaction mechanism was not preferred because of a high ring strain of a tetracyclic unit as compared to less a strained five-membered ring of compound 184. Two results showed less chemoselectivity towards the desired products with the four- and five-carbon chains, and also showed that the less strained six-membered ring was more preferred than the more strained five-membered ring of the undesired products 183 and 181 respectively.
The IR spectrum of 1-(3-Hydroxypropyl)pyrrolidin-2-one 184 revealed peaks at $\nu_{\text{max}} = 3449$ and $1632 \, \text{cm}^{-1}$ for the alcohol OH and the amide carbonyl groups in that order. The $^1$H NMR spectrum showed a multiplet at $\delta 4.23$ ppm for the OH proton and a multiplet at $\delta 3.24 - 2.90$ ppm for the NCH$_2$CH$_2$CH$_2$OH protons of the propyl side chain. The pyrrolidinone ring protons were represented by a multiplet at $\delta 3.24 - 2.90$ ppm for the $\gamma$-protons of the amide and a multiplet at $\delta 2.00$ ppm for the $\alpha$-protons of the amide. The $^{13}$C NMR spectrum showed the lactam carbonyl peak at $\delta 175.2$ ppm while the pyrrolidinone ring carbons were at $\delta 47.1$ and 29.6 ppm for the $\gamma$-carbon and $\alpha$-carbon of the lactam. The propyl side chain carbon peaks were at $\delta 61.2$ and 42.2 ppm for the CH$_2$OH and NCH$_2$CH$_2$CH$_2$OH carbons respectively.

Ionic liquids have been used for their negligible vapour pressure and polarity characteristics in reaction transformations of lactone to lactams instead of classical solvent reactions. Ionic liquids have been found to improve selectivity of reactions and promote conversion, hence high reaction yields. Larhed et al. reported a 92% yield of 1-(5-hydroxypentyl)pyrrolidin-2-one 182 from reaction of dihydrofuran-2(3H)-one 13 and 5-amino-1-pentanol in [bmim]BF$_4$ fewer than 35 minutes of microwave irradiation at 220 °C. Dihydrofuran-2(3H)-one 13 was then reacted with 4-amino-1-butanol or 5-amino-1-pentanol in [bmim]BF$_4$ ionic liquid in a microwave reactor at 150 W, 220 °C for 35 minutes, which resulted in no desired products being recovered and recovery of dihydrofuran-2(3H)-one 13 quantitatively.\(^{102}\)

### 2.7 Synthesis of 1,6-oxazecane-2,7-dione or its polymer

The condensation reactions of $\gamma$-butyrolactone 13 with primary amines in order to synthesise ethyl 4-(2-oxopyrrolidin-1-yl)butanoate 141 and its acid derivative 4-(2-oxopyrrolidin-1-yl)butanoic acid 185 were investigated. Ethyl 4-aminobutyrate HCl or 4-aminobutyric acid was reacted neat with $\gamma$-butyrolactone in a microwave reactor at 150 W, 220 °C for 10 to 20 minutes, resulting in 1,6-oxazecane 186a or its polymer 186b in 45% yield (Scheme 33, a). Although not a useful result, it showed that both
amines were reacting with γ-butyrolactone instead of each engaging in intramolecular reactions than would result in pyrrolidin-2-one 140.

![Scheme 33: Reagents and Conditions:](image)

The IR spectrum of 1,6-oxazecane-2,7-dione 186a or polymer 186b showed peaks at $\nu_{\text{max}}$ 3400 – 3200 and 1687 cm$^{-1}$ for the amide NH and the amide and ester carbonyl groups respectively. The $^1$H NMR spectrum revealed a triplet with $J = 7.1$ Hz at $\delta$ 4.08 ppm for the γ-protons of the amide group, a triplet with $J = 6.9$ Hz at $\delta$ 3.12 ppm for the γ-protons of the ester group and a broad singlet at $\delta$ 7.22 ppm for the amide NH proton, indicating formation of the ester and the amide groups. The remaining proton peaks present were accounted for, suggesting either compound 186a or 186b. The $^{13}$C NMR spectrum confirmed the presence of the amide and the ester group at $\delta$ 179.5 and 177.9 ppm correspondingly.

### 2.8 Condensation reactions of ethyl 4-oxooctanoate 188 with amines

The substituted five-membered ring is pivotal in achieving the synthesis of lehmizidine 50 which has a butyl side chain at position C-3. It would be synthetically efficient to begin with a butyl chain already in place at position C-3 rather than adding the substituent later on the synthetic route. This required making the five-membered ring with the butyl substituent in place in a condensation reaction of ethyl 4-oxooctanoate with ethyl 4-aminobutyrate hydrochloride, achieving (E)-ethyl 4-(2-butyldene-5-oxopyrrolidin-1-yl)butanoate 189, and by-passing the N-alkylation step.
The alkene would then be hydrogenated and the remainder of the synthetic steps towards compound 190 would be similar to Scheme 26, d-g. Ethyl 4-oxooctanoate 188 had to be synthesised to begin with and be in a position to carry out the synthetic strategy shown in Scheme 34. n-Butylmagnesium chloride was added drop-wise into a reaction mixture of commercially available ethyl 4-chloro-4-oxobutanoate 187 and catalytic amount of tris(acetylacetonato)iron(III) in tetrahydrofuran at −29 °C for a period of 9 minutes.⁶ The reaction was immediately quenched with dilute hydrochloric acid, followed by work up and purification, achieving ethyl 4-oxooctanoate 188 in 89% yield [Scheme 34, a (i)]. The reaction yield of ethyl 4-oxooctanoate 188 decreased to 59% when the reaction temperature was reduced to −78 °C on a similar reaction [Scheme 34, a (ii)]. This reaction owed its success to the presence of tris(acetylacetonato)iron(III) catalyst which promotes cross-coupling between the acyl chloride and the Grignard reagent, the short amount of time towards completion of the reaction and the −29 °C temperature. Lower reaction temperature was expected to increase the reaction yield of 188 by slowing down or eliminating competing reactions but hindered the progress of the reaction.

![Scheme 34](image)

**Scheme 34: Reagents and conditions:** (a) (i) Ethylmagnesium chloride (1 eq), Fe(acac)_3 (0.1 eq), TH-F, 9 min at −29 °C, 188 = 89%; (ii) Ethylmagnesium chloride (1 eq), Fe(acac)_3 (0.1 eq), TH-F, −78 °C, 188 = 59%; (c) Table 14.

The IR spectrum of ethyl 4-oxooctanoate 188 indicated the presence of the ester and ketone carbonyl of the groups with a peak at $\nu_{\text{max}} = 1754 \text{ cm}^{-1}$. The $^1$H NMR spectrum confirmed the exclusive C–C coupling between the acyl chloride and the Grignard reagent. A triplet with $J = 7.4$ Hz at $\delta 2.17$ ppm corresponded to the $\alpha$-protons for the ketone on the butyl side chain while another triplet with $J = 7.4$ Hz at $\delta 0.61$ ppm represented methyl protons on the butyl side chain. The triplet and quartet both with $J = 7.2$ Hz at $\delta 3.81$ and 0.94 ppm respectively, maintained the...
The tandem amination/acylation condensation reaction between ethyl 4-oxooctanoate 188 and ethyl 4-aminobutyrate hydrochloride could then be attempted. Ethyl 4-oxooctanoate was reacted with ethyl 4-aminobutyrate hydrochloride and 4Å molecular sieves heating under reflux in toluene for 21 hours. Ethyl 4-oxooctanoate 188 was recovered in 88% yield after purification (Scheme 34, b: Table 14, entry 1). In principle, the amination reaction should occur first followed by the acylation reaction and rearrangement of electrons giving the expected double bond. Surprisingly neither the amination nor the acylation reaction occurred but returned compound 188. Ethyl 4-aminobutyrate was possibly transformed to pyrrolidin-2-one (as shown in Scheme 35) which remained in the aqueous layer or itself remained in the aqueous layer. The amine hydrochloride salt could have rendered the amine less nucleophilic thus it needed to be neutralised.

The reaction was repeated, neutralising ethyl 4-aminobutyrate hydrochloride in situ with sodium hydrogen carbonate first followed by heating under reflux with ethyl 4-oxooctanoate 188 and excess acetic acid in toluene for 64 hours. Ethyl 4-oxooctanoate was recovered in 78% yield after purification (Scheme 34, b: Table 14, entry 2). The in situ neutralisation reaction of ethyl 4-aminobutyrate hydrochloride seemed to have not occurred under the above reaction conditions. Longer reaction time could not ensure desired success as well. Ethyl 4-aminobutyrate hydrochloride was then neutralised using sodium hydrogen carbonate in distilled water at room temperature. The free amine ethyl 4-aminobutyrate was isolated and reacted with ethyl 4-oxooctanoate and excess acetic acid, heating under reflux in toluene for 21 and 41 hours in two separate reaction, recovering ethyl 4-oxooctanoate in 61% and 65% respectively (Scheme 34, b: Table 14, entry 3). This further indicated a possibility of a competing intramolecular reaction preventing the desired reactivity. Perhaps the acid base reaction did not occur in situ due to the anhydrous reaction conditions; thus ethyl 4-oxooctanoate, ethyl 4-aminobutyrate hydrochloride, excess acetic acid, sodium hydrogen carbonate and water were heated under reflux for 45 hours (Scheme 34, b: Table 14, entry 4) resulting in 21% yield of ethyl 4-oxooctanoate after purification. The added water could have also assisted in shifting
the equilibrium of the reaction to the left in addition to the mystery as to why the desired reactivity was not observed. Changing the solvent to methanol had no effect on the success of the reaction. When ethyl 4-aminobutyrate was reacted with ethyl 4-oxooctanoate and excess acetic acid heating under reflux in methanol for 24 and 41 hours, ethyl 4-oxooctanoate was recovered in 95% yield (Scheme 34, b: Table 14, entry 5). It is likely that ethyl 4-aminobutyrate·HCl was reacting in an intramolecular condensation, reaction yielding pyrrolidin-2-one, which is hydrophilic and therefore lost during aqueous reaction work up, as proposed in Scheme 35.

\[
\text{Scheme 35: Proposed mechanism for pyrrolidin-2-one formation.}
\]

<table>
<thead>
<tr>
<th>No.</th>
<th>Reagents</th>
<th>Conditions</th>
<th>Solvents</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl 4-aminobutyrate·HCl (1 eq), 4Å molecular sieves</td>
<td>21 hours heating under reflux</td>
<td>Toluene</td>
<td>189 = 0%; 188 = 88%</td>
</tr>
<tr>
<td>2</td>
<td>Ethyl 4-aminobutyrate·HCl (1 eq), NaHCO₃ (1 eq), acetic acid (5 eq)</td>
<td>64 hours heating under reflux</td>
<td>Toluene</td>
<td>189 = 0%; 188 = 78%</td>
</tr>
<tr>
<td>3</td>
<td>Ethyl 4-aminobutyrate (1 eq), acetic acid (5 eq)</td>
<td>21–41 hours heating under reflux</td>
<td>Toluene, 188 = 61 – 65%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ethyl 4-aminobutyrate·HCl (1 eq), NaHCO₃ (1 eq), H₂O (1 eq), acetic acid (5 eq)</td>
<td>45 hours heating under reflux</td>
<td>Toluene</td>
<td>189 = 0%; 188 = 21%</td>
</tr>
<tr>
<td>5</td>
<td>Ethyl 4-aminobutyrate·HCl (1 eq), acetic acid (5 eq)</td>
<td>24 hours heating under reflux</td>
<td>Methanol</td>
<td>189 = 0%; 188 = 95%</td>
</tr>
</tbody>
</table>
This is contrary to the PhD work of Susan Winks, who was successful in synthesising (E)-ethyl 2-(2-butyldene-5-oxopyrrolidin-1-yl)hexanoate 191 in 87% yield from heating ethyl 4-oxooctanoate, ethyl 3-aminobutyrate and excess acetic acid under reflux in toluene for a minimum of 72 hours (Scheme 36, a). This further reveals that desired reactivity decreases with increasing carbon chain length of the amine (numbering carbon atoms between the nitrogen atom and the carbonyl carbon atom of the ester group).

![Scheme 36](image)

Scheme 36: Reagents and conditions: (a) Ethyl 3-aminobutyrate (0.5 eq), acetic acid (2.5), toluene, 72 h at reflux, 87%.

Ethyl 4-aminobutyrate was replaced with 4-aminobutyric acid in a condensation reaction with ethyl 4-oxooctanoate to avoid the possibility of competing intramolecular condensation of ethyl 4-aminobutyrate since the conditions are not conducive in the case of 4-aminobutyric acid. 4-Aminobutyric acid was reacted with ethyl 4-oxooctanoate and excess acetic acid heating under reflux in toluene for 50 hours, but ethyl 4-oxooctanoate 188 was recovered in 98% yield after purification (Scheme 37, a). 4-Aminobutyric acid’s amine might be a poor nucleophile reacting with ethyl 4-oxooctanoate because of strong hydrogen bonding between the amine and the carbonyl oxygen atom, or more likely, because of its zwitterionic nature. As an alternative to test this, reaction of homoveratrylamine with ethyl 4-oxooctanoate was attempted in order to eliminate the challenges of intramolecular condensation and poor nucleophilicity encountered. Homoveratrylamine was reacted with ethyl 4-oxooctanoate and excess acetic acid heating under reflux in toluene for 22 hours, giving (E)-1-(3,4-dimethoxyphenethyl)-5-butyldene.pyrrolidin-2-one 193 in 67% yield after purification (Scheme 37, b). This example shown that the condensation of ethyl 4-oxooctanoate was possible with a free amine. The better nucleophilicity of the nitrogen atom and lack of a competing electrophile was directly responsible for this good result.
The IR spectrum of (E)-1-(3,4-dimethoxyphenethyl)-5-butylidenepyrrrolidin-2-one 193 revealed peaks at $\nu_{\text{max}}$ 1751, 1588 and 1432 cm$^{-1}$ indicative for the carbonyl of the amide group, the phenyl ring and the alkene, respectively. The $^1$H NMR spectrum confirmed the presence of the enamide 193 by a triplet with $J = 7.5$ Hz at $\delta$ 4.70 ppm for the alkene proton, a doublet of doublets with $J = 8.9, 6.9$ Hz at $\delta$ 2.78 ppm for $\beta$-protons to the amide and a doublet of triplets with $J = 11.8, 5.8$ Hz at $\delta$ 2.00 ppm for the C=CHCH$_2$ protons. Also present were the methoxy groups’ singlets at $\delta$ 3.88 and 3.86 ppm and the methyl group triplet with $J = 7.3$ Hz for the butylidene side chain. This $^1$H NMR spectrum was comparable to literature values from Collado et al. 6.73 – 6.81 (m, 3H), 4.68 (t, $J = 7.9$ Hz, 1H), 3.84, 3.86 (2 x s, 3H), 2.73 – 2.79 (m, 2H), 1.98 (q, $J = 7.9$ Hz, 2H) and 0.92 (t, $J = 7.9$ Hz, 3H).$^{91}$

Another strategy for achieving the synthesis of (E)-ethyl 4-(2-butylidene-5-oxopyrrolidin-1-yI)butanoate 189 was considered. The ester group in ethyl 4-oxooctanoate was converted into an acid chloride in situ prior to reaction with ethyl 4-aminobutyrate hydrochloride. 4-Oxooctanoic acid 194 had to be made in a saponification reaction before this could happen. Ethyl 4-oxooctanoate 181 was reacted with potassium hydroxide in water for 2 hours at room temperature, giving 4-oxooctanoic acid 194 in 94% yield (Scheme 38, a). This transformation was confirmed by $^1$H NMR spectroscopy with the absence of the ethyl group and the presence of a carboxylic acid proton singlet at $\delta$ 11.12 ppm. The $^{13}$C NMR spectrum presented with a carboxylic acid carbonyl peak at $\delta$ 178.7 ppm which is more deshielded when compared with the peak of ester group at $\delta$ 171.9 ppm. The ketone carbonyl carbon peak was unaffected at $\delta$ 209.3 ppm.
4-Oxooctanoic acid 194 was heated in thionyl chloride under reflux for 2 hours, making 4-oxooctanoyl chloride in situ followed by addition of ethyl 4-aminobutyrate hydrochloride and excess acetic acid. This reaction mixture was heated under reflux for 42 hours, resulting in the formation of (E)-ethyl 4-(2-butylidene-5-oxopyrrolidin-1-yl)butanoate 189 in poor 36% yield (Scheme 38, b). The reaction occurred owing to chloride anion being a better leaving group as compared to the ethyl group. The poor yields are attributed to intramolecular condensation reaction of ethyl 4-aminobutyrate hydrochloride forming pyrrolidin-2-one. The enamide 189 formed was confirmed by $^1$H NMR spectroscopy, by a triplet with $J = 7.5$ Hz at $\delta 4.75$ ppm for the alkene proton, a triplet with $J = 7.1$ Hz at $\delta 3.51$ ppm for the $\gamma$-protons to the ester carbonyl group and a triplet with $J = 7.1$ Hz at $\delta 0.96$ ppm for the methyl of the butylidene chain. The ethyl ester group was still intact as shown by a quartet with $J = 7.1$ Hz at $\delta 4.14$ ppm and a triplet with $J = 7.1$ Hz at $\delta 1.28$ ppm. The $^{13}$C NMR spectrum supported the structure with the peaks at $\delta 175.6$ and 172.9 ppm for the amide and ester carbonyl carbons respectively, while the alkene peaks were at $\delta 138.9$ and 100.7 ppm.

Scheme 38: Reagents and conditions: (a) KOH (1 eq), H$_2$O, 2 h at r.t., 194 = 94%; (b) (i) SOCl$_2$ ( 1 eq), toluene, 2 h at reflux; (ii) Ethyl 4-aminobutyrate-HCl (1.2 eq), acetic acid (3 eq), toluene, 42 h at reflux, 189 = 36%.
2.9 Synthesis of (E)-5-butylidene-1-(4-hydroxybutyl)pyrrolidin-2-one 198 by condensation reaction

Ethyl 4-oxooctanoate was reacted neat with a variety of other amines in separate reactions, under microwave and classical conditions in attempts to make (E)-ethyl 4-(2-butylidene-5-oxopyrrolidin-1-yl)butanoate 195, (E)-4-(2-butylidene-5-oxopyrrolidin-1-yl)butanoic acid 196, (E)-5-butylidene-1-(4,4-diethoxybutyl)pyrrolidin-2-one 197 and (E)-1-(3,4-dimethoxyphenethyl)-5-butylidenepyrrrolidin-2-one 193 (Scheme 39 and Table 15, entries 1 – 4). Neat reactions increase the concentration of reactants thus ensuring better reaction outcomes. All of the above compounds have the required four carbon chain which would make possible the seven-membered ring at ring closing step. Compound 196 and 198 would have to be protected to avoid side reactions in the synthesis route, while compound 197 could be carried forward as a disguised aldehyde. Varying the reaction conditions was not sufficient to obtain targeted molecules except when (E)-5-butylidene-1-(4-hydroxybutyl)pyrrolidin-2-one 198 was synthesised in a poor 24% yield under classical reaction conditions by heating ethyl 4-oxooctanoate and 4-amino-1-butanol in excess acetic acid under reflux for 90 hours (Table 15, entry 7). The acetic acid was essential, protonating the ketone thus promoting the amination reaction. The other reactions gave back ethyl 4-oxooctanoate 188 and tars under microwave and classical reaction conditions as described in Table 15, entries 1 – 7 (i).

Scheme 39: Reagents and Conditions: (a) Table 13.
Table 15: Ethyl 4-oxooctanoate 188 microwave and classical condensation reactions with various amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl 4-aminobutyrate·HCl (1 eq)</td>
<td>50 W, 150 °C, 80 min</td>
<td>195 = 0%</td>
</tr>
<tr>
<td>2</td>
<td>4-Aminobutyraldehyde diethyl acetal (1 eq)</td>
<td>(i) 60 W, 148 °C, 10 min, (ii) 70 W, 181 °C, 20 min, (iii) 150 W, 215 °C, 20 min</td>
<td>197 = 0%</td>
</tr>
<tr>
<td>3</td>
<td>Homoveratrylamine (1 eq)</td>
<td>150 W, 220 °C, 35 min</td>
<td>193 = 0%</td>
</tr>
<tr>
<td>4</td>
<td>4-Aminobutyric acid (1 eq)</td>
<td>150 W, 220 °C, 40 min</td>
<td>196 = 0%</td>
</tr>
<tr>
<td>5</td>
<td>Ethyl 4-aminobutyrate·HCl (1 eq), acetic acid (5 eq)</td>
<td>(i) 100 W, stage 1: 60 °C, 15 min; stage 2: 80 °C, 15 min; stage 3: 100 °C, 15 min; stage 4: 110 °C, 15 min, 45 min and 30 min. (ii) Heating under reflux, 90 h</td>
<td>195 = 0%</td>
</tr>
<tr>
<td>6</td>
<td>4-Aminobutyraldehyde diethyl acetal (1 eq), acetic acid (5 eq)</td>
<td>(i) Same as in entry 5</td>
<td>197 = 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(ii) Same as in entry 5</td>
<td>197 = 0%</td>
</tr>
<tr>
<td>7</td>
<td>4-Amino-1-butanol (1 eq), acetic acid (5 eq)</td>
<td>(i) Same as in entry 5, 0%</td>
<td>198 = 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(ii) Same as in entry 5, 24%</td>
<td>198 = 24%</td>
</tr>
</tbody>
</table>

(E)-5-Butylidene-1-(4-hydroxybutyl)pyrrolidin-2-one’s 198 IR spectrum had peaks at $\nu_{\text{max}} = 3386, 1711$ and 1465 cm$^{-1}$ for the alcohol, amide and alkene groups. The $^1$H NMR spectrum showed the hydroxybutyl side chain by a triplet with $J = 5.9$ Hz at $\delta$ 4.08 ppm for the (OCH$_2$) protons and a triplet with $J = 6.6$ Hz at $\delta$ 3.49 ppm for the (NCH$_2$) protons. The butylidene side chain was indicated by a doublet of doublet of doublet with $J = 7.4, 4.8, 2.2$ Hz at $\delta$ 4.65 ppm for the vinyl proton and a triplet with $J$
= 7.3 Hz $\delta$ 0.92 ppm for methyl protons. The pyrrolidinone ring was shown by a doublet of triplets with $J = 7.2, 2.7$ Hz at $\delta$ 2.48 ppm for the $\alpha$-protons of the amide and a doublet of doublets with $J = 14.1, 6.0$ Hz at $\delta$ 2.61 ppm for the $\beta$-protons of the amide. The $^{13}$C NMR spectrum showed peaks at $\delta$ 175.5, 139.1 and 100.6 ppm for the amide carbonyl, alkene quaternary and vinyl carbons respectively. The peaks at $\delta$ 64.0 and 13.7 ppm were for (CH$_2$OH) and methyl carbons.

2.10 Attempted synthesis of N-substituted 5-butylpyrrolidin-2-ones via microwave reaction conditions

Commercially available 5-butyl-dihydrofuran-2(3H)-one 200 was suitable for our synthetic strategy towards lehmizidine 50 with the butyl side chain already in place. Lactone 200 was to be converted into lactams with a four carbon chain substituent, which would cyclise into a seven-membered ring once the enaminone was in place. 5-Butyl-dihydrofuran-2(3H)-one 200 was reacted with ethyl 4-aminobutyrate.HCl, 4-amino-1-butanol, 4-aminobutyraldehydediethyl acetal or 4-aminobutyric acid neat in a microwave reactor at 150 W, 220 °C for between 0.17 – 1.75 hours, but this returned 5-butyl-dihydrofuran-2(3H)-one 200 in between 50 – 70% yield and tars (Scheme 40, Table 16, 1 – 5). This clearly indicated that the reaction between the amines and lactone 200 never occurred but the amines decomposed under the conditions. In addition to the returned tars and starting material, reactions with 4-aminobutyric acid and 4-aminobutyrate hydrochloride yielded pyrrolidin-2-one 140. For comparison, 5-butyl-dihydrofuran-2(3H)-one 200 was also reacted with 4-methoxyaniline neat in a microwave reactor at 150 W, 220 °C for 50 minutes, resulting in no desired product. This revealed that 5-butyl-dihydrofuran-2(3H)-one 200 reacts differently as compared to dihydrofuran-2(3H)-one 13, which undergoes acylation reaction with an amine resulting in a secondary amide and a primary alcohol followed by a $S_N2$ reaction between the secondary amide and primary alcohol in the presence of water as the catalyst forming five-membered ring lactams (see Section 2.19).
Table 16: Microwave reactions of 5-butyl-dihydrofuran-2(3H)-one 200 with various amines 114

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl 4-aminobutyrate.HCl (1 eq)</td>
<td>100 – 150 W, 220 °C, 25 min</td>
<td>201 = 0%</td>
</tr>
<tr>
<td>2</td>
<td>4-Methoxyaniline (1 eq)</td>
<td>150 W, 280 °C, 50 min</td>
<td>201 = 0%</td>
</tr>
<tr>
<td>3</td>
<td>4-Amino-1-butanol (1 eq)</td>
<td>150 W, 220 °C, 1.75 h</td>
<td>201 = 0%</td>
</tr>
<tr>
<td>4</td>
<td>4-Aminobutyraldehyde diethyl acetal (1 eq)</td>
<td>150 W, 220 °C, 10 min</td>
<td>201 = 0%</td>
</tr>
<tr>
<td>5</td>
<td>4-Aminobutyric acid (1 eq)</td>
<td>150 W, 220 °C, 25 min</td>
<td>201 = 0%</td>
</tr>
</tbody>
</table>

In principle, the metathesis reaction between ethyl acrylate and the allyl chain would convert the 3-carbon allyl chain into the desired 4-carbon chain ester at the terminus. 5-Butylidihydrofuran-2(3H)-one 200 was then reacted with neat allylamine in a microwave reactor at 100 W, 60 °C for 1 hour with the aim to synthesise 1-allyl-5-butyldihydrofuran-2-one 203. Since the reaction was not complete, the conditions were changed to 150 W, 100 °C for 0.5 hours, but this resulted in formation of N-allyl-4-hydroxyoctanamide 202 in a good yield of 69% [Scheme 41, a (i)]. Harsher reaction condition were employed, reacting 5-butylidihydrofuran-2(3H)-one 200 with allylamine neat in a Carius tube at 220 °C for 60 hours, but this still returned N-allyl-4-hydroxyoctanamide 202 in an excellent 88% yield [Scheme 41, a (ii)]. The water
produced in the acylation reaction was alone not enough to catalyse the $\text{SN}_1$ reaction between the secondary amide and the secondary alcohol. Thus silica was used as an acid catalyst to promote ring cyclisation by reacting 5-butylidihydrofuran-2(3H)-one 200 with allylamine neat in a Carius tube for 25 hours but only obtained N-allyl-4-hydroxyoctanamide 202 in a quantitative yield [Scheme 41, a (iii)]. Obviously, while acylation of the amine by the lactone took place, the desired thermally-induced cyclisation failed.

Several reaction conditions were applied to cyclise N-allyl-4-hydroxyoctanamide 202 by first reacting with tosyl chloride in the presence of pyridine at room temperature for 24 hours to convert the alcohol into a better leaving group, but without success, returning tars [Scheme 41, b (i)]. Sodium hydride was employed to deprotonate the more acidic NH proton of compound 202 aiming to eliminate secondary alcohol group which would result in cyclisation to 1-allyl-5-butylpyrrolidin-2-one 203, thus N-allyl-4-hydroxyoctanamide 202 was reacted with sodium hydride in tetrahydrofuran at room temperature, but returned compound 202 in 65% yield [Scheme 41, b (ii)]. Converting the secondary alcohol of N-allyl-4-hydroxyoctanamide 202 into a mesylate, by reacting with methanesulphonyl chloride in dichloromethane at room temperature for 4 days followed by heating N-allyl-4-hydroxyoctanamide 202 under reflux with methanesulphonyl chloride in toluene overnight resulted in tars [Scheme 41, b (iii, iv)].

![Scheme 41: Reagents and Conditions](image)

(a) (i) Allyl amine (1 equiv), 1 drop HCl, neat, (150 W, 60 min at 60 °C) or (100 W, 30 min at 100 °C), 202 = 69%; (ii) Allyl amine (1 equiv), neat, over weekend at 220 °C in an oven, 202 = 88%; (iii) Allyl amine (1 equiv), silica, neat, 25 h at 220 °C in an oven, 202 = 100%; (c) (i) TsCl (1 equiv), pyridine, 24 h at r.t., 203 = 0%, (ii) NaH (1 equiv), THF, r.t., overnight, 203 = 0%, (iii) Methanesulphonyl chloride (1 equiv), TEA (1 equiv), DCM, r.t., 4 days, 203 = 0%, (iv) Methanesulphonyl chloride (1 equiv), TEA (1 equiv), toluene, reflux, overnight, 203 = 0%.
The IR spectrum of N-allyl-4-hydroxyoctanamide 202 had peaks at $\nu_{\text{max}} = 3540$, 3420, 1734 and 1643 cm$^{-1}$ for the alcohol, amide NH, amide carbonyl and alkene groups in that order. The $^1$H NMR spectrum revealed a broad singlet at $\delta$ 6.96 and a singlet at $\delta$ 4.06 ppm for the amide NH and the alcohol OH. The OH proton is deshielded owing to hydrogen bonding. The allyl group proton peaks were at $\delta$ 5.75 ppm as a doublet of triplets of doublets with $J = 15.8$, 10.8, 5.5 Hz for the vinyl alkene proton, at $\delta$ 5.07 ppm as a doublet of doublets of doublets with $J = 13.7$, 11.6, 1.4 Hz for the terminal alkene protons and at 3.76 ppm as a multiplet for the NCH$_2$ protons. The structure of the molecule was confirmed by a multiplet at $\delta$ 3.52 ppm for the $\gamma$-proton of the amide, the triplet with $J = 7.0$ Hz at $\delta$ 2.32 ppm for the $\alpha$-protons of the amide, and a triplet with $J = 7.0$ Hz at $\delta$ 0.83 ppm for the methyl protons. The $^{13}$C NMR spectrum revealed carbon peaks at $\delta$ 174.1, 134.2, 116.0 and 41.9 ppm for the amide carbonyl and the allyl groups correspondingly. The peak at $\delta$ 71.0 ppm was for the $\gamma$-carbon of the amide. The remaining carbon peaks observed confirmed the structure. The HRMS found [M+H]$^+$ 200.1654 for a molecular formula C$_{11}$H$_{22}$NO$_2$ with a calculated exact mass of 200.1645.

### 2.11 N-Alkylation reactions of azepan-2-one

As part of the aims and strategies, the pyrrolo[1,2-a]azepine 4 nucleus was to be synthesised by constructing the five-membered ring onto an enaminone system containing an already formed seven-membered ring. This is disadvantageous since similar work done for indolizidines 2 and quinolizidines 3 in our research group has not been successful, so this approach could be a challenge. The expected 5-exo-trig cyclisation is permissible by Baldwin’s rules where for acylative ring closure the bond to be broken will be between the carbonyl carbon of a carboxylic anhydride and its oxygen atom.$^{115}$ The favoured path to transition state is a 109° angle on approach by the nucleophilic $\alpha$-carbon of the unsaturated ester group towards electrophilic carbonyl carbon of a carboxylic anhydride as demonstrated by the intermediate acid anhydride in Scheme 42, f. The expected 5-exo-tet is also permissible by Baldwin’s rules where the breaking bond will be between the carbon and the halogen for the
alkylative ring closure. The favoured path to transition state in a 180° angle on approach by the nucleophilic α-carbon of the unsaturated ester group towards the electrophilic carbon bonded to a halogen as shown by the intermediate iodide in

**Scheme 42.**

The plan was to synthesise lactams in an N-alkylation reaction of azepan-2-one 175 with ethyl bromoacetate or tert-butyl bromoacetate. This would then be followed by the C-alkylation reaction of both lactams with butyl bromide on the α-carbon of the ester to yield diversified lactams, followed by their thionation reactions in phosphorus pentasulphide resulting in formation of their respective thiolactams. The thiolactams would then undergo an Eschenmoser sulphide contraction reaction with ethyl bromoacetate, transforming them into the respective vinlogous urethanes. The product containing the tert-butyl ester would then be hydrolysed to a carboxylic acid in situ using trifluoroacetic acid, followed by converting the acid into a carboxylic anhydride and acylative ring closure onto the vinlogous urethane. Alternatively, the product containing the ethyl ester would be reduced by lithium aluminium hydride, the resulting alcohol then being converted to an iodide in situ prior to alkylative ring closure onto the vinlogous urethane.

**Scheme 42: Reagents and conditions:** (a) (i) NaH (1 eq), THF, 0°C - 5 min at r.t., (ii) Ethyl bromoacetate or tert-Butyl bromoacetate (1 eq), THF, 20 - 22 h at r.t., 204 = 55%; 205 = 97%; (b) (i) LCA (1.2 eq), 204, THF, 15 min at -78°C, (ii) Butyl bromide, THF, -78°C to r.t. for 22 h, 206 = 0%; (c)(i) LCA (1.2 eq), 204, THF, 30 min at r.t., (ii) Icoethane, THF, r.t. for 22 h, 207 = 0%; (d) (i) F₂S₅ (0.5 eq), LCM, 5 days at r.t., 208 = 28%; 209 = 35%; (ii) F₂S₅ (0.5 eq), LCM, 20 h at r.t., 208 = 93%; 209 = 97%; (e) (i) Ethyl bromoacetate (1 eq), MeCH₂, 9 h at r.t., (ii) TEA (1 eq), TFF (1 eq), MeCH₂, 24 h at r.t.; (f) Acalytive ring closure; (g) Reduction with hydrazines; (h) Alkylative ring closure.
The N-alkyl substituent would have to be a two carbon chain in order to achieve five-membered ring cyclisation later on in the synthesis. Azepan-2-one 175 was reacted with sodium hydride in tetrahydrofuran at room temperature for 10 – 15 min, followed by the addition of ethyl bromoacetate or tert-butyl bromoacetate and reacted at room temperature for 20 – 22 h, achieving ethyl 2-(2-oxoazepan-1-yl)acetate 204 and tert-butyl 2-(2-oxoazepan-1-yl)acetate 205 in 95% and 97% yields respectively (Scheme 42, a). The above results are in agreement with yields reported in section 2.3 where N-alkylated five-membered ring lactams were synthesised.

The IR spectrum of ethyl 2-(2-oxoazepan-1-yl)acetate 204 showed peaks at $\nu_{\text{max}} = 1721 \text{ cm}^{-1}$ for the lactam and the ester carbonyl group. The $^1$H NMR spectrum for ethyl 2-(2-oxoazepan-1-yl)acetate 204 included a multiplet at $\delta 4.18$ ppm for the $\alpha$-protons to the ester carbonyl and methylene of the ester ethyl group and a triplet at $\delta 1.28$ ppm with $J = 7.1$ Hz for the methyl on the ethyl ester group, indicating the newly formed N-C bond and the presence of the ethyl ester group. The $^{13}$C NMR spectrum further confirmed the structure with the carbonyl carbons of the lactam group and ester groups giving signals at $\delta 176.2$ and 169.7 ppm, respectively. The newly formed N-CH$_2$ substituent was shown by the peak at $\delta 51.2$ ppm and the ester group carbons were at $\delta 61.0$ and 14.1 ppm.

The IR spectrum of tert-butyl 2-(2-oxoazepan-1-yl)acetate 205 showed peaks at $\nu_{\text{max}} = 1732 \text{ cm}^{-1}$ for the amide and the ester carbonyl group. The $^1$H NMR spectrum for tert-butyl 2-(2-oxoazepan-1-yl)acetate presented with a singlet at $\delta 4.05$ ppm for the newly formed N-CH$_2$ bond. The tertiary butyl ester group was shown by a singlet at $\delta 1.47$ ppm. The $^{13}$C NMR presented with the carbonyl carbons of the lactam, and ester groups peaks at $\delta 176.1$ and 168.8 ppm respectively and a tert butyl quartenary carbon peak at $\delta 81.5$ ppm. The newly formed N-CH$_2$ bond was shown by the peak at $\delta 51.1$ ppm and the tertiary butyl ester group methyl carbons were at $\delta 28.0$ ppm.

The butyl substituent needed to be added at $\alpha$-carbon to the ester of lactams 204 and 205, which is characteristic of lehmizidine 50. Ethyl 2-(2-oxoazepan-1-yl)acetate 204 was reacted with n-butyllithium or lithium diisopropylamide at $-78 \degree C$ in tetrahydrofuran for 0.5 – 1 h followed by addition of n-butyl bromide and the reaction was left to stir at room temperature for 22 hours (Scheme 42, b). The butyllithium
reaction returned ethyl 2-(2-oxoazepan-1-yl)acetate 204 in 54% yield while the lithium diisopropylamide reaction also returned compound 204 in 40% yield. The base was expected to deprotonate α-proton to the ester group followed by the S_N2 alkylation reaction between the lithium enolate and the haloalkane. The lithium enolate proved to either not form owing to steric hindrance between lithium diisopropylamide and the α-carbon of the ester; or unfavourable electronic effects due to the electron rich nitrogen atom. Another deprotonation could have occurred on the lactam’s α-protons but no product evidence was available. The bromide was substituted with an iodide to observe what a good leaving group might do to the success of the reaction. Ethyl 2-(2-oxoazepan-1-yl)acetate 204 was reacted with lithium diisopropylamide at −78 °C in tetrahydrofuran for 30 minutes followed by addition of iodoethane and the reaction was left to stir at room temperature for 22 hours, recovering polymeric tars (Scheme 4, c). Marcin et al. performed a similar reaction using allyl bromide as the alkylation agent and ethyl 2-(2-oxoazepan-1yl)acetate 204 as the substrate. They reacted compound 204 with n-butyl lithium at −78 °C in tetrahydrofuran for 10 minutes followed by addition of allyl bromide, warmed to room temperature in 2 hours and recovered (E)-ethyl 2-(2-ethoxy-2-oxoethyldiene)pyrrolidin-1-yl)pent-4-enoate in 24 % yield.

After failing to attach the butyl substituent, attention shifted to thionation reactions of lactams 204 and 205. Ethyl 2-(2-oxoazepan-1-yl)acetate 204 or tert-butyl 2-(2-oxoazepan-1-yl)acetate 205 were reacted with phosphorus pentasulphide in dichloromethane at room temperature for 5 days, resulting in ethyl 2-(2-thioxoazepan-1-yl)acetate 208 and tert-butyl 2-(2-thioxoazepan-1-yl)acetate 209 in 28% and 35% yields respectively [Scheme 42, d(i)]. There were insoluble by-products that were recovered which may account for the huge mass loss. Reducing the reaction time from 5 days to 20 hours under the same reaction conditions proved successful, giving ethyl 2-(2-thioxoazepan-1-yl)acetate 208 and tert-butyl 2-(2-thioxoazepan-1-yl)acetate 209 in 93% and 97% yields respectively [Scheme 42, d(ii)]. Longer reaction times decompose the above reaction mixtures while shorter reaction times ensured high yields of products and the reaction was selective in reacting only with the tertiary amide.
The IR spectra of ethyl 2-(2-thioxoazepan-1-yl)acetate 208 and tert-butyl 2-(2-thioxoazepan-1-yl)acetate 209 showed peaks at $\nu_{\text{max}} = 1739$ and 1741 cm$^{-1}$, respectively. The $^1$H NMR spectrum for ethyl 2-(2-thioxoazepan-1-yl)acetate 208 showed a more resolved singlet at $\delta$ 4.61 ppm for the $\alpha$-protons to the ester carbonyl group of the ester, a quartet and a triplet with $J = 7.1$ Hz at $\delta$ 4.07 and 1.14 ppm for the ethyl ester moiety. The multiplet peak for the $\alpha$-protons of the thiocarbonyl was at $\delta$ 3.03 ppm, demonstrating the molecule is intact. The $^{13}$C NMR spectrum revealed the absence of the lactam carbonyl peak at $\delta$ 176.2 ppm and the presence of the thiocarbonyl peak at $\delta$ 208.0 ppm. The ester carbonyl carbon peak shifted upfield to $\delta$ 167.7 ppm from $\delta$ 169.7 ppm of the lactam’s carbonyl carbon, owing to the presence of a more electron rich sulphur atom. HRMS found [M+H]$^+$ 216.1063 which is representative of C$_{10}$H$_{18}$NO$_2$S$^+$ with the calculated exact mass of 216.1053.

The $^1$H NMR spectrum of tert-butyl 2-(2-thioxoazepan-1-yl)acetate 209 presented with two singlets at $\delta$ 4.63 and 1.48 ppm for the $\alpha$-protons to the ester carbonyl group of the ester and methyl protons of the tert-butyl ester moiety. The singlet for the $\alpha$-protons of the ester carbonyl was at $\delta$ 4.63 ppm and the multiplet for the $\alpha$-protons of the thiocarbonyl was at $\delta$ 3.17 ppm, demonstrating the molecule is intact. The $^{13}$C NMR spectrum revealed the absence of the lactam carbonyl carbon peak at $\delta$ 176.1 ppm and the presence of the thiocarbonyl carbon peak at $\delta$ 207.9 ppm. The ester carbonyl carbon peak shifted upfield to $\delta$ 166.6 ppm from $\delta$ 168.8 ppm of the lactams ester carbonyl carbon and the quaternary carbon of the tertiary butyl ester shifted downfield to $\delta$ 82.0 ppm from $\delta$ 81.5 ppm of the lactam’s tertiary butyl ester quaternary carbon.

The Eschenmoser sulphide contraction reactions using ethyl bromoacetate became a crucial step in making the key enaminones in this sequence of reactions. Ethyl 2-(2-thioxoazepan-1-yl)acetate 208 or tert-butyl 2-(2-thioxoazepan-1-yl)acetate 209 was reacted with ethyl bromoacetate in acetonitrile at room temperature for 19 hours, followed by addition of triethylamine and triphenylphosphine in acetonitrile and reacted at room temperature for 24 hours (Scheme 42, e). Longer reaction times were necessary to induce salt formations, which were indicated by a milky colour change and a spot on a TLC plate with $R_f = 0.00$ eluting with 30% ethyl acetate: hexane mixture. In addition, on the same plate, spots at $R_f = 0.42$ and 0.48
were also observed which were for thiolactams 208 and 209 respectively. The sulphide extrusion step resulted in no desired vinylogous urethane 210 and 211 being formed, but returned lactams 204 and 205 in 26% and 32% respectively, perhaps due to the salts’ destruction by adventitious moisture in the nitrogen line owing to longer periods of time leading to the hydrolysis of the salt. Alternatively, the reaction may be intrinsically unfavourable due to the α-protons of the saturated ester being more acidic than the α-protons of the saturated ester in the iminium thioether (see Scheme 2) resulting in unfavourable reactions. Successes in the past were only observed when various phenacyl bromides were used, not bromoesters.\textsuperscript{94,95} The aim to form the five-membered ring using acylating and alkylating reaction conditions to demonstrate an alternative way to achieve the pyrrolo[1,2-a]azepine 4 nucleus could therefore not be attempted because the necessary precursors could not be synthesised [Scheme 42 (f, g, h)].

2.12 N-alkyl vinylogous amides from ethyl 2-(2-thiooxazepan-1-yl)acetate

The Eschenmoser sulphide contraction reaction with phenacyl bromide, para-nitrophenacyl bromide and para-methoxyphenacyl bromide was decided upon to test the hypothesis that phenacyl bromides were better than bromoesters in salt formation and sulphide contraction. The N-alkyl vinylogous amides were synthesised successfully for the first time compared to failed attempts on the N-alkyl vinylogous urethanes. These reactions owe their success to the more acidic α-protons of the phenacyl bromides as compared to less acidic α-protons of the bromoesters, therefore making the former more likely to be deprotonated under Eschenmoser conditions which is necessary to form the thiirane intermediate (see Eschenmoser mechanism in Chapter 1, Scheme 2). Ethyl 2-(2-thiooxazepan-1-yl)acetate 208 was reacted with each of the three phenacyl bromides in acetonitrile at room temperature for 0.67 – 2 hours, followed by the addition of triethylamine and triethyl phosphite in acetonitrile and reacted at room temperature overnight to achieve (E)-ethyl 2-(2-(2-oxo-2-phenylethylidene)azepan-1-yl)acetate 215 and (E)-ethyl 2-(2-(2-(4-nitrophenyl)-2-oxoethylidene)azepan-1-yl)acetate 216 in yields of 83% and 86%,
respectively (Scheme 43). The yield of (E)-ethyl 2-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)azepan-1-yl)acetate 217, however, was much poorer at 22%, probably because the electron-donating p-methoxy substituent reduces the acidity of the methylene position thus reducing the success of the Eschenmoser sulphide contraction reaction.

![Scheme 43: Reagents and conditions: (a) (i) Phenacyl bromide/para-nitrophenacyl bromide/para-methoxyphenacyl bromide (1 eq), MeCN, 0.67 - 2 h at r.t., (ii) TEA (1 eq), TEP (1 eq), MeCN, overnight at r.t., 215 = 83%, 216 = 86%, 217 = 22%.

The IR spectrum of (E)-ethyl 2-(2-(2-oxo-2-phenylethylidene)azepan-1-yl)acetate 215 had peaks at $\nu_{\text{max}} = 1709$ and 1599 cm$^{-1}$ for the ketone and ester carbonyl and alkene groups respectively. The $^1$H NMR spectrum showed a doublet of doublets with $J = 7.8, 1.7$ Hz at $\delta 7.81$ ppm for the two aromatic protons closer to the carbonyl group, a multiplet at $\delta 7.37$ ppm for the remaining three aromatic protons and a singlet at $\delta 5.47$ ppm for the vinyl proton, confirming the newly formed double bond. The singlet for the $\alpha$-protons to the ester carbonyl group was at $\delta 4.07$ ppm which is shielded as compared to the $\alpha$-protons of the ester carbonyl group in thioamide 208 at $\delta = 4.61$ ppm. The multiplet at $\delta 3.50$ ppm was for the (CH$_2$C=CH) protons, which is a slight chemical shift from a multiplet at $\delta 3.03$ ppm for the $\alpha$-protons of the thiocarbonyl in thiolactam 208, suggesting an entgegen geometry for the vinylogous amide 215. The other proton chemical shifts in the molecule remained relatively unchanged. The $^{13}$C NMR spectrum revealed absence of the thiocarbonyl carbon peak at $\delta 208.0$ ppm for the thioamide 208 and presence of peaks at $\delta 188.4$, 169.2 and 92.7 ppm for the ketone carbonyl, quaternary alkene and vinyl carbons respectively. The ester $\alpha$-carbon peak was at $\delta 55.6$ ppm, upfield from $\delta 58.6$ ppm of ester $\alpha$-carbon peak of thiolactam 208. The aromatic carbon peaks were at $\delta 142.6$, 130.5, 128.0, 127.3 ppm, while other carbon chemical shifts in the molecule
remained relatively unchanged. The HRMS found \([M+H_2O+H]^+\) equal to 320.1867 for a monohydrated molecule of molecular formula \(C_{18}H_{26}NO_4^+\) with an exact calculated mass of 320.1856.

The assigned \(E\) geometry of the above vinylogous amide, as well as other enaminones reported in this thesis, requires comment. This geometry, and more specifically a trans-s-cis conformation, could be inferred from the through-space anisotropic deshielding by the carbonyl group of the pyrrolidine ring’s 3-H hydrogens, which are in the region of \(\delta 3.5\) ppm. The same hydrogens in enaminones with the \(Z\) configuration have signals around \(\delta 2.5\) ppm.\(^{179}\) While proving the geometry by means of NOE NMR spectroscopic experiments would have confirmed the assignments, some of such interactions could never be definitively observed. However, the organic chemistry group at Wits has obtained several X-ray crystal structures of related enaminones over the years, and these support the assignments of geometry based on the through-space deshielding.

The melting point of (\(E\))-ethyl 2-(2-(2-(4-nitrophenyl)-2-oxoethylidene)azepan-1-yl)acetate 216 was 119 – 121 °C. Its IR spectrum showed peaks at \(\nu_{\max} = 1698, 1603, 1525\) and 1347 cm\(^{-1}\) for the ester and ketone carbonyl and alkene groups respectively. The \(^1\)H NMR spectrum revealed a doublet at \(\delta 8.23\) ppm with \(J = 8.9\) Hz for the two aromatic protons closer to the nitro group, a doublet with \(J = 8.9\) Hz at \(\delta 7.91\) ppm for the two aromatic protons closer to the carbonyl group and a singlet at \(\delta 5.40\) ppm for the vinyl proton. The singlet for the \(\alpha\)-protons to the ester carbonyl group was at \(\delta 4.11\) ppm which is slightly shielded as compared to the \(\alpha\)-protons of the ester carbonyl group in thioamide 208 at \(\delta 4.61\) ppm. The multiplet at \(\delta 3.53\) ppm was for the (\(CH_2C=CH\)) protons, which is a slight chemical shift from a multiplet at \(\delta 3.03\) ppm for the \(\alpha\)-protons of the thiocarbonyl in thiolactam 208, suggesting an entgegen geometry for the vinylogous amide 216. The other protons chemical shifts in the molecule remained relatively unchanged. The \(^13\)C NMR spectrum revealed the absence of the thiocarbonyl carbon peak at \(\delta 208.0\) ppm for the thioamide 208 and presence of peaks at \(\delta 185.8, 171.0\) and 92.4 ppm for the ketone carbonyl, quaternary alkene and vinyl carbons respectively. The ester \(\alpha\)-carbon peak was at \(\delta 55.7\) ppm, upfield from \(\delta 58.6\) ppm of ester \(\alpha\)-carbon peak of thiolactam 208.
aromatic carbon peaks were at δ 148.8, 148.2, 128.2, 123.3 ppm, while other carbon chemical shifts in the molecule remained relatively unchanged. The HRMS found [M+H]⁺ equal to 347.1614 for a molecule of molecular formula C₁₈H₂₅N₂O₅⁺ with an exact calculated mass of 347.1601.

The IR spectrum of (E)-ethyl 2-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)azepan-1-yl)acetate 217 had peaks at \( \nu_{\text{max}} = 1756, 1520 \) and 1468 cm⁻¹ for the ester and ketone carbonyl and alkene groups in that order. The ¹H NMR revealed a doublet with \( J = 8.9 \) Hz at δ 7.81 ppm for the two aromatic protons closer to the carbonyl group, a doublet with \( J = 8.9 \) Hz at δ 6.88 ppm for the two aromatic protons closer to the methoxy group, a singlet at δ 5.48 ppm for the vinyl proton and a singlet at δ 3.84 ppm for the methyl protons on the methoxy group. The singlet for the \( \alpha \)-protons to the ester carbonyl group was at δ 4.07 ppm which is slightly shielded as compared to the \( \alpha \)-protons of the ester carbonyl group in thioamide 208 at δ = 4.61 ppm. The multiplet at δ 3.53 – 3.42 ppm was for the (CH₂C=CH) protons, which is a slight chemical shift from a multiplet at δ 3.03 ppm for the \( \alpha \)-protons of the thiocarbonyl in thiolactam 208, suggesting an entgegen geometry for the vinylogous amide 217. The other protons chemical shifts in the molecule remained relatively unchanged. The ¹³C NMR spectrum showed the absence of the thiocarbonyl carbon peak at δ 208.0 ppm for the thioamide 208 and presence peaks at δ 187.6, 169.3, 92.6 and 55.3 ppm for the ketone carbonyl, the quaternary alkene, vinyl and methoxy group carbons respectively. The ester \( \alpha \)-carbon peak was at δ 55.7 ppm upfield from δ 58.6 ppm of ester \( \alpha \)-carbon peak of thiolactam 208. The aromatic carbon peaks were at δ 161.7, 135.2, 129.4, 113.2 ppm, while other carbon chemical shifts in the molecule remained relatively unchanged. The HRMS found [M+H₂O⁺H]⁺ equal to 350.1969 for a monohydrate molecule of molecular formula C₁₉H₂₈NO₅⁺ with an exact mass of 350.1962.

The p-OMe is an electron donating group that enriches the aromatic ring with electron density, such that long range proton coupling becomes possible (i.e. meta and para coupling) in a unsymmetric system leading to a set of distinct doublets that contain satellites which may also be second order effects, hence the observed multiplets. p-OMe conjugates to less strongly to the aromatic ring as compared to p-
NO₂, which may lead to more pronounced second order effects on p-OMe as compared to the p-NO₂. The p-NO₂ is an electron withdrawing group that decreases the electron density of the aromatic ring such that second order coupling is less pronounced since it is symmetrical, hence a set of distinct doublets are observed. This phenomenon was seen on all the p-OMe containing compounds.

2.13 Pyrrolo[1,2-a]azepine nucleus from Knoevenagel condensation reactions of N-alkyl vinylogous amides

This part of the project was inspired by the PhD research of Garreth Morgans and Stefania Scalzullo, 94,95 who studied pyrrole formation as part of the synthesis of lamellarin alkaloids. They found the transformation of vinylogous amides to pyrroles occurred under acidic conditions. Their first strategy involved the reaction of vinylogous amide 218 in acetic acid at 40 °C for 24 hours, which produced the pyrrolizine 219 in 59% yield (Scheme 44, a). The second strategy involved adsorbing the vinylogous amide 218 onto 10 equivalents of silica-gel and heating at 90 °C for 2 hours, which gave pyrrolizine 219 in 72% yield (Scheme 44, b). The third strategy was heating the vinylogous amide 220 with silica-gel in xylene under microwave conditions (150 W, 180 °C, 30 min) resulting in pyrrolizine 221 in 73% yield (Scheme 44, c).

![Scheme 44](image)

Scheme 44: Reagents and conditions: (a) EtOAc, 40 °C, 24 h, 219 = 59%; (b) SiO₂, 90 °C, 2 h, 219 = 72%; (c) SiO₂, xylene, 150W, 180 °C, 30 min, 221 = 73%.
For the present project, the Knoevenagel condensation reactions of the vinylogous amides 215, 216 and 217 in various solvents under microwave conditions were undertaken. Reacting vinylogous amide 216 with ten equivalents of silica-gel in toluene in a microwave reactor with 150 W at 110 °C for 1 hour resulted in decomposed tars being recovered. Vinylogous amide 216 in toluene was reacted in the absence of silica-gel in a microwave reactor with 100 W at 110 °C for 10 minute and at 150 °C for 40 minutes, resulting in tars. However, pyrrole 223 was recovered in 63% yield from vinylogous amide 216 when the solvent was changed from toluene to N,N-dimethylformamide and in the absence of silica-gel. This reaction was done in a microwave reactor with 150 W at 150 °C for 10 minutes, and 180 °C for 30 minutes. It is worth nothing that shorter reaction times of vinylogous amides 215 and 216 in N,N-dimethylformamide in a microwave reactor with 150 W at 180 °C for 20 minutes resulted in lower yields for pyrroles 222 and 223 of 36% and 19% respectively. Acetonitrile was also not a suitable solvent for reacting vinylogous amide 215 in a microwave reactor with 150 W at 82 – 150 °C for 1 hour 10 minutes, resulting in recovery of tars. Vinylogous amides 215, 216 and 217 were then reacted in N,N-dimethylacetamide in a microwave reactor with 150 W and stepped temperatures 150 °C for 10 minutes, 165 °C for 10 minutes and 180 °C for 40 minutes, which resulted in the isolation of pyrroles ethyl 2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 222, ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 223 and ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 224 in yields of 27 – 51%, 62 – 90% and 1.58% respectively (Scheme 45, a). Shorter reaction times in the case of vinylogous amide 216 in a microwave reactor at 150 W (150 °C for 10 minutes, 165 °C for 10 minutes and 180 °C for 20 minutes) resulted in 27% and 53% yields of pyrrole 223 and vinylogous amide 216 respectively. The reaction of vinylogous amide 216 under classical condition, heating under reflux in N,N-dimethylacetamide at 180 °C for 7 hours, resulted in pyrrole 223 in 54% yield.
The IR spectrum of ethyl 2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 222 had peaks at $\nu_{\text{max}} = 1683, 1471$ and 1434 cm$^{-1}$ for the ester carbonyl and alkene groups. The $^1$H NMR spectrum revealed overlap of the aromatic proton peaks at $\delta 7.44 - 7.17$ ppm and a downfield shift of the vinyl proton singlet from $\delta 5.47$ ppm to $\delta 5.93$ ppm, now representing the pyrrole proton in the newly formed ring. The ethyl carboxylate side chain’s quartet and triplet proton both with $J = 7.1$ Hz were at $\delta 4.07$ and 1.00 ppm, revealing the absence of $\alpha$-protons to the ester carbonyl at $\delta 4.07$ ppm of the vinylogous amide 215. The $^{13}$C NMR spectrum revealed the absence of the ketone carbonyl and ester $\alpha$-carbon peaks at $\delta 188.4$ and 55.6 ppm respectively from vinylogous amide 215 and the presence of pyrrole quaternary carbon peaks at $\delta 118.3$ ppm (CH$_2$C=CH) and 137.3 ppm (C$\text{CO}_2$) respectively. The vinyl carbon peak which was at $\delta 92.7$ ppm for vinylogous amide 215 shifted downfield to $\delta 109$ ppm for the pyrrole carbon peak (CH$_2$C=CH). The alkene quaternary carbon which was at $\delta 169.2$ ppm for vinylogous amide 215 shifted upfield to $\delta 142.3$ ppm for the pyrrole quaternary carbon. The aromatic carbon peaks were at $\delta 132.69, 129.53, 127.35$ and 126.25 ppm, while the ethyl carboxylate side chain peaks were at $\delta 162.23, 59.67$ and 13.74 ppm for the ester carbonyl and ethyl carbons. The HRMS found [M+H]$^+$ equal to 284.1652 for a molecular formula C$_{18}$H$_{22}$NO$_2$ with a calculated exact mass of 284.1645.

The IR spectrum of ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 223 had peaks at $\nu_{\text{max}} = 1692, 1598$ and 1517 cm$^{-1}$ for the ester carbonyl and alkene groups respectively. The $^1$H NMR spectrum revealed two
doublet both with $J = 8.8$ Hz at $\delta 8.17$ and $7.50$ ppm for the two aromatic protons adjacent to the nitro group and two aromatic protons adjacent to the pyrrole ring respectively. The new pyrrole ring proton singlet was at $\delta 5.96$ ppm which a slight chemical field downshift from $\delta 5.40$ ppm of the then vinyl proton singlet of vinylogous amide 216. The ethyl carboxylate side chains quartet and triplet proton both with $J = 7.1$ Hz were at $\delta 4.12$ and 1.05 ppm, revealing the absence of $\alpha$-protons to the ester carbonyl at $\delta 4.11$ ppm of the vinylogous amide 216. The $^{13}$C NMR spectrum revealed the absence of the ketone carbonyl and ester $\alpha$-carbon peaks at $\delta 185.8$ and $55.7$ ppm respectively from vinylogous amide 216 and the presence of pyrrole quaternary carbon peaks at $\delta 130.0$ ppm (CH$_2$C=CHC) and $118.7$ ppm (CCO$_2$) respectively. The vinyl carbon peak which was at $\delta 92.4$ ppm for vinylogous amide 216 shifted downfield to $\delta 109.4$ ppm for the pyrrole carbon peak (CH$_2$C=CH). The alkene quaternary carbon which was at $\delta 171.0$ ppm for vinylogous amide 216 shifted upfield to $\delta 142.8$ ppm for the pyrrole quaternary carbon. The aromatic carbon peaks were at $\delta 146.3$, 144.5, 130.2, and 122.7 ppm, while the ethyl carboxylate side chain peaks were at $\delta 161.6$, 60.0 and 13.8 ppm for the ester carbonyl and ethyl carbons. The HRMS found [M+H]$^+$ equal to 329.1506 for a molecule of molecular formula C$_{18}$H$_{21}$N$_2$O$_4$ with an exact calculated mass of 329.1496.

The IR spectrum of ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 224 had peaks at $\nu_{\text{max}} = 1774$, 1580, 1469 cm$^{-1}$ for the ester carbonyl and alkene groups respectively. The $^1$H NMR spectrum revealed two doublets with unresolved fine coupling, both with $J = 8.6$ Hz at $\delta 7.29$ ppm and 6.87 ppm respectively for the two aromatic protons adjacent to the pyrrole ring, two aromatic protons adjacent to the methoxy group respectively, while the methoxy group singlet was at $\delta 3.83$ ppm. The new pyrrole ring proton singlet was at $\delta 5.90$ ppm which is a slight chemical field downshift from $\delta 5.48$ ppm of the then vinyl proton singlet of vinylogous amide 217. The ethyl carboxylate side chains quartet and triplet proton peaks both with $J = 7.1$ Hz were at $\delta 4.10$ and 1.06 ppm, revealing the absence of $\alpha$-protons to the ester carbonyl at $\delta 4.11$ ppm of the vinylogous amide 217. The $^{13}$C NMR spectrum revealed the absence of the ketone carbonyl and ester $\alpha$-carbon peaks at $\delta 187.6$ and $55.7$ ppm respectively from vinylogous amide 217.
and the presence of pyrrole quaternary carbon peaks at δ 132.4 ppm (CH$_2$C=CHC) and 129.8 ppm (CCO$_2$) respectively. The vinyl carbon peak which was at δ 92.6 ppm for vinylogous amide 217 shifted downfield to δ 109.6 ppm for the pyrrole carbon peak (CH$_2$C=CH). The alkene quaternary carbon which was at δ 169.3 ppm for vinylogous amide 217 shifted upfield to δ 142.4 ppm for the pyrrole quaternary carbon. The aromatic carbon peaks were at δ 158.3, 130.6, 118.2 and 112.8 ppm, while the ethyl carboxylate side chain peaks were at δ 162.3, 59.6 and 13.9 ppm for the ester carbonyl and ethyl carbons. HRMS found [M+H]$^+$ equal to 314.1758 for a molecule of molecular formula C$_{19}$H$_{24}$NO$_3$ with an exact calculated mass with of 314.1751.

The Knoevenagel condensation reaction’s proposed mechanism is in Scheme 46. The N,N-dimethylacetamide might be basic enough to deprotonate the α-proton of the ester leading to an enolate anion under the above described conditions Scheme 45. The enolate anion then reacted in a favoured 5-exo-trig cyclisation with the carbonyl carbon of the unsaturated ketone forming the five-membered ring. However, the entgegen geometry is less desired for the cyclisation. The E to Z equilibration must take place at the temperature at which the reaction is done before cyclisation can occur. This is a 1,2 addition (v) of a nucleophile to an enamino-nes reactivity described in section 1.2.3. The dehydration of a water molecule resulted in aromatisation of the five-membered ring making the pyrrolizidine core. An electron donating R group decreases the electrophilicity of the ketone’s carbonyl carbon while an electron withdrawing R group increases the electrophilicity of the ketone’s carbonyl carbon, hence higher yields were observed when R = NO$_2$ and low yields were observed when R = OMe, while moderate yields were observed for R = H. In addition, the nature of the reaction not allowing for the removal of water may have forced an equilibrium limiting the dehydration step. This mechanism is different from acid-promoted mechanisms proposed by Morgans and Scalzullo.\textsuperscript{94,95}
2.14 LiAlH₄ reduction of ethyl 2-(aryl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylates

The position of the ethoxycarbonyl side chains at C-3 in products 222 and 223 provided an opportunity for transformation of the ester into the butyl chain found in lehmizidine 50. The ethoxycarbonyl substituent is at the same position as the butyl chain on the pyrrolo[1,2-a]azepine nucleus. A strategy was devised that would employ the reduction of the ester with lithium aluminium hydride to the alcohol 225 and 226, followed by its protection as a tosylate 227 and finally displacing the tosylate with propylmagnesium bromide in a Grignard reaction, forming a four carbon chain compound 228. Ethyl 2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 222 or ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 223 were reacted with lithium aluminium hydride from 0 °C to room temperature for between 6 – 12 hours, achieving (2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-3-yl)methanol 225 and (2-(4-aminophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-3-yl)methanol 226 in excellent yields of
94% and 61% respectively (Scheme 46, a). Compound 226 was of no further use in tosylation reaction as competing deprotonation between amine and alcohol would result in undesired products. Thus (2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-3-yl)methanol 225 was then reacted with triethylamine and catalytic 4-dimethylaminopyridine in dichloromethane at room temperature for 1 hour followed by the addition of 4-toluenesulphonyl chloride and left to react for 48 hours. The reaction returned decomposed material after purification (Scheme 47, b).

The IR spectrum of (2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-3-yl)methanol 225 had peaks at \( \nu_{max} = 3340 \) and 1443 cm\(^{-1}\) for the alcohol OH and alkene groups respectively. The \(^1\)H NMR spectrum revealed the absence of the ethyl carboxylate peaks which were at \( \delta = 4.07 \) and 1.00 ppm and the presence of a singlet at \( \delta = 4.62 \) ppm for the methanol side chain’s (CH\(_2\)) protons and a doublet at \( \delta = 3.50 \) ppm with \( J = 4.9 \) Hz for the OH proton. The aromatic multiplet was at \( \delta = 7.43 \) – 7.15 ppm, while the pyrrole proton singlet was at \( \delta = 5.98 \) ppm. The remainder of the peaks remained relatively unchanged, confirming the structure.

The IR spectrum of (2-(4-aminophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-3-yl)methanol 226 had peaks at \( \nu_{max} = 3450 \) and 1484 cm\(^{-1}\) for the alcohol OH and the alkene groups respectively. The \(^1\)H NMR spectrum revealed the absence of ethyl carboxylate side chain proton peaks at \( \delta = 4.12 \) and 1.05 ppm and the presence of a triplet with \( J = 4.6 \) Hz at \( \delta = 5.14 \) ppm for the alcohol proton and a doublet with \( J = 3.9 \) Hz at \( \delta = 4.48 \) ppm for the methanol CH\(_2\) protons. The spectrum showed two doublets with \( J = 8.4 \) and 8.3 Hz respectively at \( \delta = 7.87 \) and 7.59 ppm for the two aromatic protons adjacent to the pyrrole ring and for the two aromatic protons adjacent to the amine group respectively. The pyrrole ring singlet was at \( \delta = 6.05 \) ppm. The \(^13\)C NMR
spectrum revealed the loss of the ethyl carboxylate carbon peaks which were at δ 161.6, 60.0 and 13.8 ppm and the presence of the methanol side chain carbon peak which was at δ 52.7 ppm. The azepinyl ring, the pyrrole ring and aromatic ring carbon peaks were all present, demonstrating the molecule is as predicted.

2.15 Synthesis of 1-(4-aroyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-diones containing the pyrrolo[1,2-a]azepine nucleus

NH vinylogous amides showed great potential for the construction of the pyrrolo[1,2-a]azepine (4) nucleus. The synthesis route had fewer steps and a five-membered ring forms onto an already existing seven-membered ring at the same time. It was not clear whether the reaction would occur first on the nitrogen or α-carbon of the unsaturated ester, but it should not matter as long as both happened. ε-Caprolactam 175 was reacted with phosphorus pentasulphide and hexamethyldisiloxane in dichloromethane at room temperature for 24 hours, resulting in azepane-2-thione 229 in excellent 89 – 95% yield (Scheme 48, a). Azepane-2-thione 229 then was reacted with phenacyl bromide, para-nitrophenacyl bromide or para-methoxyphenacyl bromide in an Eschenmoser sulphide contraction reaction in acetonitrile at room temperature for 5 minutes, after which the salt precipitated. Triethylamine and triphenylphosphine in acetonitrile were then added to the salt and left to react for 24 hours at room temperature, achieving (Z)-2-(azepan-2-ylidene)-1-phenylethanone 230, (Z)-2-(azepan-2-ylidene)-1-(4-nitrophenyl)ethanone 231 and (Z)-2-(azepan-2-ylidene)-1-(4-methoxyphenyl)ethanone 232 in 93%, 86% and 83 – 95% in excellent yields respectively (Scheme 48, b). Yields improved to 100% and 89% respectively for NH-vinylogous amides 230 and 231 when triethyl phosphite was used in the sulphur extrusion step instead of triphenylphosphine, while there was a drop in reaction yield to 46% observed for NH-vinylogous amide 232 (Scheme 48, c). The less bulky triethyl phosphite suffers less steric hindrance in the sulphur extrusion stage as compared to the more bulky triphenylphosphine hence the improved yields. It remains a mystery as to why this was not the case for enaminone 232.
The melting point of azepane-2-thione 229 was 103 – 104 °C. The IR spectrum indicated the presence of the NH by an absorbance peak at \( v_{\text{max}} = 3426 \text{ cm}^{-1} \). The \(^1H\) NMR spectrum had a singlet at \( \delta 9.56 \text{ ppm} \) for the thioamide’s NH proton. A doublet of doublets with \( J = 10.1, 5.9 \text{ Hz} \) was observed at \( \delta 3.88 \text{ ppm} \) for the \( \varepsilon \)-protons to the thiocarbonyl group, while a multiplet at \( \delta 3.04 – 2.90 \text{ ppm} \) represented \( \alpha \)-protons of the thiocarbonyl group. The remaining proton peaks were observed, confirming the structure. The \(^{13}C\) NMR spectrum revealed the presence of a thiocarbonyl carbon peak at \( \delta 209.4 \text{ ppm} \) with the remaining five carbon peaks also well represented. The spectra matched those reported.\(^{116}\)

The melting point of (Z)-2-(azepan-2-ylidene)-1-phenylethanone 230 was 75 – 76 °C. Its IR spectrum revealed peaks at \( v_{\text{max}} = 3400 – 3200, 1740, 1586 \text{ and } 1546 – 1436 \text{ cm}^{-1} \) for the NH of the secondary enamine, carbonyl of the ketone, alkene and phenyl, respectively. The \(^1H\) NMR spectrum revealed two singlets at \( \delta 11.55 \text{ and } 5.67 \text{ ppm} \) for the secondary enamine and the vinyl proton correspondingly. The secondary enamine proton peak was greatly deshielded as compare to the thioamide’s NH proton which was at \( \delta 8.84 \text{ ppm} \). The delocalised electron system of the enaminone and the strong hydrogen bonding between N and O atoms had influence on the environmental shift of the NH proton, thus strongly deshielding the
N-H proton. The chemical shift of the CH\textsubscript{2} protons in the ring next to the enamine at δ 2.55 – 2.37 ppm were not deshielded through-space by ketone carbonyl as compared with previous N-substituted (E)-analogues, in which their peak generally appeared at δ 3.50 ppm, suggest the Z isomer. The multiplet peaks at δ 7.86 and 7.39 ppm were for the two aromatic protons adjacent to the ketone and the three remaining aromatic protons respectively. The azepanylidene ring peaks were also observed confirming the Z isomer. The 13\textsuperscript{C} NMR spectrum showed the alkene quaternary carbon and vinyl carbon peaks at δ 171.4 and 91.0 ppm confirming the newly formed double bond between the azepanylidene ring and phenylethanone side chain, while the thioamide 213 carbonyl carbon which was at δ 210.7 ppm disappeared. The ketone carbonyl and the aromatic ring carbon peaks were at δ 188.2, 140.7, 130.4, 128.1 and 126.9 ppm. The HRMS found [M+H]\textsuperscript{+} 216.1393 matching molecular formula C\textsubscript{14}H\textsubscript{18}NO\textsuperscript{+} with an exact calculated mass 216.1383. The spectra were comparable to those reported by Petterson et al.\textsuperscript{13}

The melting point of (Z)-2-(azepan-2-ylidene)-1-(4-nitrophenyl)ethanone 231 had a melting point of 143 – 144 °C. The IR spectrum showed peaks at ν\textsubscript{max} = 3400 – 3200, 1736, 1589 and 1474 cm\textsuperscript{-1} suggestive for the secondary amine N-H, carbonyl of the ketone, alkene and aromatic alkene respectively. The 1\textsuperscript{H} NMR spectrum revealed two singlets at δ 11.69 and 5.67 ppm for the secondary enamine and the vinyl protons respectively. The presence of the nitrophenyl was indicative by the two doublets both with J = 8.9 Hz at δ 8.24 and 7.98 ppm for the two aromatic protons adjacent the nitro group and two aromatic protons adjacent the ketone carbonyl group respectively. The 13\textsuperscript{C} NMR spectrum showed the alkene quaternary carbon and vinyl carbon peaks at δ 172.8 and 91.7 ppm confirming the newly formed double bond between the azepanylidene ring and phenylethanone side chain. The ketone carbonyl and the aromatic ring carbon peaks were at δ 185.0, 146.2, 127.8, and 123.5 ppm. The HRMS found [M+H]\textsuperscript{+} 261.1240 which is representative of C\textsubscript{14}H\textsubscript{17}N\textsubscript{2}O\textsubscript{3}\textsuperscript{+} with an exact calculated mass of 261.1234. The melting point of (Z)-2-(azepan-2-ylidene)-1-(4-methoxyphenyl)ethanone 232 was 151 – 152 °C. The IR spectrum exposed peaks at ν\textsubscript{max} = 3400 – 3200, 1744, 1577 and 1444 cm\textsuperscript{-1} for the presence of the secondary amine NH, carbonyl of the ketone, alkene and phenyl, respectively. The 1\textsuperscript{H} NMR spectrum revealed two singlets at δ
11.47 and 5.64 ppm for the secondary enamine and the vinyl protons respectively. The presence of the methoxyphenyl was indicative by the two doublets both with $J = 8.9$ Hz, with unresolved fine coupling at $\delta$ 7.85 ppm and 6.90 ppm for the two aromatic protons adjacent the ketone carbonyl group and two aromatic protons adjacent the methoxy group respectively. The $^{13}$C NMR spectrum showed the alkene quaternary carbon and vinyl carbon peaks at $\delta$ 170.4 and 90.0 ppm confirming the newly formed double bond between the azepanylidene ring and phenylethanone side chain. The ketone carbonyl and the aromatic ring carbon peaks were at $\delta$ 186.9, 161.2, 133.0, 128.3, and 113.0 ppm, while the methoxy carbon peak was at $\delta$ 54.9 ppm. The HRMS established $[\text{M+H}]^+$ 246.1506 equivalent to molecular formula $\text{C}_{15}\text{H}_{20}\text{NO}_2^+$ with exact calculated mass of 246.1489.

NH vinylogous amides were reacted with oxalyl chloride in double acylation reaction involving nucleophilic enaminone reactivity from both carbon and nitrogen atoms. This resulted in formation of the pyrrolo[1,2-a]azepine 4 nucleus. A solution of NH vinylogous amides 230, 231 and 232 in tetrahydrofuran was added dropwise into a solution of oxalyl chloride in tetrahydrofuran at room temperature. This was done to minimise formation of dimers and polymers and to encourage intramolecular acylation reactions. The reaction was left for between 7 and 22 hours at room temperature resulting in the formation of 1-benzoyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 233 in a poor 16% yield and 1-(4-methoxybenzoyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 235 in a good 58% yield respectively (Scheme 48, d). The reaction of NH vinylogous amide 231 resulted in tars that could not be identified. Success for this reaction probably depends on the intermolecular acylation reaction to occur initially at the vinyl carbon atom. The cis geometric isomeric nature of the NH vinylogous amides may hinder the nitrogen atom from reacting first and allow more exposed vinyl carbon to react first under mild conditions. If the nitrogen reacts first, the formed amide locks up the nitrogen lone pair and diminishes its participation in extended vinylogy and because of the bifunctional nature of oxalyl chloride, other intermolecular reactions might lead to the formation of polymers and tars. Secondly, the success of the reaction may also depend on the type of electron donating or withdrawing group. The para-methoxy group on vinylogous amide 232 donates electrons to the carbonyl carbon of the ketone, making its $\alpha$-carbon slightly nucleophilic when compared to the $\alpha$-carbon of
ketone in vinylogous amide 230, which has a proton para to the ketone. The para-nitro group’s ability to withdraw electrons renders the α-carbon of vinylogous amides 215 less nucleophilic, hence no desired product was observed in its case.

The IR spectrum of 1-benzoyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 233 had major peaks at $\nu_{\text{max}} = 1719, 1544$ and 1460 cm$^{-1}$ indicative of the carbonyl, alkene and aromatic groups. The $^1$H NMR spectrum showed the absence of peaks for the secondary enamine singlet and vinyl proton singlet which were at δ 11.55 and 5.67 ppm. The two multiplets at δ 8.18 – 8.09 and 7.49 ppm were for the two aromatic protons adjacent the ketone group and the three remaining aromatic protons respectively. The remaining seven-membered ring proton peaks confirmed the structure of the molecule.

The IR spectrum of 1-(4-methoxybenzoyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 235 had major peaks at $\nu_{\text{max}} = 1744, 1566$ and 1447 cm$^{-1}$ representatives for the ketones, alkene and aromatic groups. The $^1$H NMR revealed the absence of the secondary enamine singlet and vinyl proton singlet which were at δ 11.47 and 5.64 ppm. The two doublets both with $J = 8.9$ Hz, with unresolved fine coupling at δ 7.72 ppm and 6.92 ppm respectively, were for the two aromatic protons adjacent the ketone group and the two aromatic protons adjacent the methoxy group respectively, while the methoxy singlet was at δ 3.86 ppm. The remaining seven-membered ring proton peaks confirmed the structure of the molecule. The $^{13}$C NMR spectrum revealed the absence of the vinyl carbon δ 90.0 ppm and the emergence of a new alkene quaternary carbon peak down-field δ 110.2 ppm. Two new carbonyl carbon peaks appeared at δ 185.0 and 179.2 ppm for the unsaturated ketone and amide respectively. The quaternary alkene carbon peak α to the nitrogen atom was at δ 156.6 ppm, while the benzylic ketone peak was at δ 186.8 ppm. The remaining aromatic and seven-membered ring carbon peaks present confirmed the structure of the molecule.
2.16 Attempted synthesis of (Z)-ethyl 2-(azepan-2-ylidene)acetate 236 and (Z)-ethyl 2-(pyrrolidin-2-ylidene)acetate 237 in an Eschenmoser sulphide contraction reaction

In view of the success in forming N-H vinylogous amides, attempts to form the corresponding N-H vinylogous urethanes from azepane-2-thione 229 and ethyl bromoacetate were made. However, the five-membered ring NH vinylogous urethane 236 could never be synthesised. Ethyl bromoacetate was added to a solution of azepane-2-thione 229 in acetonitrile and left to react at room temperature for 0.5 - 6 hours, after which the salt precipitated. This was followed by addition of a solution of triethylamine and triphenylphosphine in acetonitrile and left to react for 22 – 24 hours at room temperature, which resulted in the resulted in tars after purification (Scheme 49; Table 17, entry 1). Alternatively, ethyl bromoacetate was added to a solution of azepane-2-thione 229 in acetonitrile and left to react at room temperature for 5 – 20 hours, after which the salt precipitated. This was followed by addition of a solution of potassium tertiary butoxide and triphenylphosphine in acetonitrile and heating under reflux for 20 – 72 hours which resulted in the resulted in azepane-2-thione 229 and tars after purification (Scheme 49; Table 17, entry 2). Finally, tert-butyl bromoacetate was added to a solution of azepane-2-thione 229 in acetonitrile and left to react at room temperature for 20 hours, after which the salt precipitated and followed by addition of a solution of potassium tertiary butoxide and triphenylphosphine in acetonitrile and heating under reflux for 72 hours which resulted in the isolation of tars after purification (Scheme 49; Table 17, entry 3). The complications arose from difficulties in the sulphur extrusion step, possibly due to the strength of a base that can induce sulphur extrusion. Longer reaction times were sometimes necessary to encourage the salt to precipitate. A more robust base, tert-BuOK, was used instead of mild triethylamine but resulted in no desired product.

![Diagram](image-url)
Table 17: Eschenmoser sulphide contraction reactions of thiolactam 229 with ethyl bromoacetate

<table>
<thead>
<tr>
<th>No.</th>
<th>Reactants</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(i) Ethyl bromoacetate (1 eq), (ii) Triethylamine (1 eq), triphenylphosphine (1 eq)</td>
<td>(i) 0.5 – 6 hours at room temperature, (ii) 22 – 24 hours at room temperature</td>
<td>MeCN</td>
<td>236 = 0%</td>
</tr>
<tr>
<td>2</td>
<td>(i) Ethyl bromoacetate (1 eq), (ii) tert-BuOK (1 eq), triphenylphosphine (1 eq)</td>
<td>(i) 5 – 20 hours at room temperature, (ii) 20 - 72 hours heating under reflux</td>
<td>MeCN</td>
<td>236 = 0%</td>
</tr>
<tr>
<td>3</td>
<td>(i) tert-Butyl bromoacetate (1 eq), (ii) tert-BuOK (1 eq), triphenylphosphine (1 eq)</td>
<td>(i) 20 hours at room temperature, (ii) 72 hours heating under reflux</td>
<td>MeCN</td>
<td>236 = 0%</td>
</tr>
</tbody>
</table>

On the contrary, the attempted synthesis of NH vinylogous urethane (Z)-ethyl 2-(pyrrolidin-2-ylidene)acetate 237, by reacting thiolactam 6 (synthesised in section 2.17) with ethyl bromoacetate in acetonitrile at room temperature for 21 hours followed by addition of a solution of triethylamine and triphenylphosphine in acetonitrile and left overnight at room temperature to induce sulphur extrusion resulted in the synthesis of ethyl 2-(4,5-dihydro-3H-pyrrol-2-yl)acetate 238 in 78% yield after purification (Scheme 50, a). The reaction probably proceeded via an in situ formation of (E)/(Z)-ethyl 2-(pyrrolidin-2-ylidene)acetate followed by a 1,3 NH hydride migration, resulting in an imine.
The IR spectrum of ethyl 2-(4,5-dihydro-3H-pyrrol-2-yl)acetate 238 showed peaks at $\nu_{\text{max}} = 1721, 1422 \text{ cm}^{-1}$ for the ester carbonyl and alkene groups in that order. The $^1$H NMR spectrum revealed a singlet at $\delta$ 3.86 ppm, a quartet peak with $J = 7.1$ Hz at $\delta$ 4.01 ppm and a triplet with $J = 7.1$Hz at $\delta$ 1.09 ppm for the $\alpha$-protons of the ethyl ester and ethyl protons of the ester. The pyrrolyl ring had a triplet with $J = 7.2$ Hz at $\delta$ 3.63 ppm, a triplet with $J = 8.2$ Hz at $\delta$ 2.44 ppm and a multiplet at $\delta$ 1.91 – 1.76 ppm for the C-5, C-3 and C-4 protons respectively. The $^{13}$C NMR spectrum revealed imine quaternary carbon peak at $\delta$ 168.9 ppm and ester $\alpha$-carbon peak at $\delta$ 61.4 ppm confirming the newly formed C-C and imine bond. The ethyl ester carbon peaks were at $\delta$ 170.1, 60.5 and 14.0 ppm for the ester carbonyl carbon and the ethyl carbons in that order. The pyrrolyl ring carbon peaks were at 37.9, 32.8 and 23.7 ppm for C-5, C-3 and C-4 respectively.

This finding is very strange indeed since there is no literature report of this transformation. It is worth noting the difference between the spectra of ethyl 2-(4,5-dihydro-3H-pyrrol-2-yl)acetate 238 and (Z)-ethyl 2-(pyrrolidin-2-ylidene)acetate 237 where the latter had peaks at 7.93, 4.52 and 76.2 ppm of which the former lacks, instead had peaks at 3.68, 61.4 and 37.9 ppm. Imine 238 lacks the vinyl and secondary amine protons as suggested by spectra data and has two $\alpha$-protons next to the ester compared to one vinyl proton in NH vinylogous urethane 237. In addition, carbon peak at position C-5 is less deshielded on imine 238 as compared to its counterpart on NH vinylogous urethane 237, Table 18.
Table 18: Comparison of the $^1$H and $^{13}$C NMR spectra of compounds 238 and 237

<table>
<thead>
<tr>
<th>238 $^1$H NMR (300 MHz)/ppm</th>
<th>237 $^1$H NMR (250 MHz)/ppm$^{15}$</th>
<th>237 $^1$H NMR (500 MHz)/ppm$^{14}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.93 (br, s, 1H)</td>
<td>7.90 (br, s, 1H, NH)</td>
<td></td>
</tr>
<tr>
<td>3.68 (s, 2H,CH$_2$CO$_2$)</td>
<td>4.52 (s, 1H)</td>
<td>4.52 (s, 1H, C=CH)</td>
</tr>
<tr>
<td>4.01 (q, J = 7.1 Hz, 2H,</td>
<td>4.12 (q, J = 7.1 Hz, 2H)</td>
<td>4.09 (q, J = 7.1 Hz, 2H, OCH$_2$CH$_3$)</td>
</tr>
<tr>
<td>CH$_2$CH$_3$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.63 (t, J = 7.2 Hz, 2H,</td>
<td>3.52 (t, J = 6.9 Hz, 2H)</td>
<td>3.50 (t, J = 6.9 Hz, 2H, NCH$_2$)</td>
</tr>
<tr>
<td>NCH$_2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.44 (t, J = 8.2 Hz, 2H,</td>
<td>2.58 (t, J = 7.7 Hz, 2H)</td>
<td>2.57 (t, J = 7.7 Hz, 2H, CH$_2$C=CH)</td>
</tr>
<tr>
<td>C=CH$_2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.91 – 1.76 (m, 2H, NHCH$_2$CH$_2$)</td>
<td>1.97 (tt, J = 7.3, 7.3 Hz, 2H)</td>
<td>1.96 (tt, J = 7.3, 7.3 Hz, 2H, NCH$_2$CH$_2$)</td>
</tr>
<tr>
<td>1.09 (t, J = 7.1 Hz, 3H, O CH$_2$CH$_3$)</td>
<td>1.24 (t, J = 7.1 Hz, 3H)</td>
<td>1.24 (t, J = 7.1 Hz, 3H, OCH$_2$CH$_3$)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>238 $^{13}$C NMR (75 MHz)/ppm</th>
<th>237 $^{13}$C NMR (63 MHz)/ppm</th>
<th>237 $^{13}$C NMR (125 MHz)/ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>170.1 (C=O)</td>
<td>170.3</td>
<td>170.8 (C=O)</td>
</tr>
<tr>
<td>168.9 (N=C)</td>
<td>166.1</td>
<td>166.4 (C=CH)</td>
</tr>
<tr>
<td>61.4 (CH$_2$CO$_2$)</td>
<td>76.2</td>
<td>76.6 (C=CH)</td>
</tr>
<tr>
<td>60.5 (OCH$_2$CH$_3$)</td>
<td>58.0</td>
<td>58.4 (OCH$_2$CH$_3$)</td>
</tr>
<tr>
<td>37.9 (NCH$_2$)</td>
<td>46.7</td>
<td>47.0 (NCH$_2$)</td>
</tr>
<tr>
<td>32.8 (N=CCH$_2$CH$_2$)</td>
<td>31.9</td>
<td>32.2 (CH$_2$C=CH)</td>
</tr>
<tr>
<td>23.7 (NCH$_2$CH$_2$)</td>
<td>21.7</td>
<td>22.0 (NCH$_2$CH$_2$)</td>
</tr>
<tr>
<td>14.0 (OCH$_2$CH$_3$)</td>
<td>14.4</td>
<td>14.7 (OCH$_2$CH$_3$)</td>
</tr>
</tbody>
</table>
2.17 Attempted synthesis of para-substituted (E)-9-benzoyl-2,3,6,7-tetrahydro-1H-pyrrolo[1,2-a]azepine-5,8-diones

In view of the success in appending oxalyl chloride to seven-membered ring vinylogous amide, could the reverse be achieved, joining succinoyl chloride onto a five-membered ring? The difference between the succinoyl chloride approach and the oxalyl chloride approach is that forming a seven-membered ring is generally less favoured as compared to making a five-membered ring. The similarities are that the double acylation is expected to occur in order to form the seven-membered ring as was observed in the oxalyl approach. Pyrrolidin-2-one 140 was reacted with phosphorus pentasulphide and hexamethyldisiloxane in dichloromethane at room temperature for 7 days resulting in pyrrolidine-2-thione 6 in excellent 94% yield (Scheme 51, a). Pyrrolidine-2-thione 6 then was reacted with phenacyl bromide, para-nitrophenacyl bromide or para-methoxyphenacyl bromide in an Eschenmoser sulphide contraction reaction in acetonitrile at room temperature for 5 minutes, after which the salt precipitated. Triethylamine and triphenylphosphine in acetonitrile were then added to the salt and left to react for 24 hours at room temperature, achieving (Z)-1-phenyl-2-(pyrrolidin-2-ylidene)ethanone 239, (Z)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone 240 and (Z)-1-(4-methoxyphenyl)-2-(pyrrolidin-2-ylidene)ethanone 241 in 40%, 95% and 47% yields respectively (Scheme 51, b). Replacing triphenylphosphine with triethyl phosphite in the sulphur extrusion step improved yields of vinylogous amides 239, 240 and 241 to 100%, 100% and 88% respectively (Scheme 51, c). A solution of vinylogous amides 239, 240 or 241 in tetrahydrofuran was added dropwise into a solution of succinoyl chloride in tetrahydrofuran at room temperature followed by heating the resulting reaction mixture under reflux for 22 hours. The reaction proceeded with solution turning murky at room temperature with possible production of hydrochloric acid. Unfortunately, the reactions returned tars after purification with no starting material being retained. It was possible that the intermediates polymerised owing to the difficulty of forming a seven-membered ring where intermolecular reactions were favoured.
The melting point of pyrrolidin-2-thione 6 was 103 – 105 °C. The IR spectrum indicated the presence of the NH by an absorbance peak at $\nu_{\text{max}} = 3134$ cm$^{-1}$. The $^1$H NMR spectrum had a singlet at $\delta = 8.59$ ppm for the thioamides NH proton. A triplet peak with $J = 7.2$ Hz was observed at $\delta = 3.67$ ppm for the $\varepsilon$-protons to the thiocarbonyl group, while a triplet peak with $J = 7.9$ Hz was at $\delta = 2.92$ ppm represented $\alpha$-protons of the thiocarbonyl group. The remaining proton peak was observed, confirming the structure. The $^{13}$C NMR spectrum revealed the presence of a thiocarbonyl carbon peak at $\delta = 206.0$ ppm with the remaining three carbon peaks also well represented. The spectra matched to those reported.  

The melting point of (Z)-1-phenyl-2-(pyrrolidin-2-ylidene)ethanone 239 was 105 – 106 °C. The IR spectrum revealed peaks for the amine NH, carbonyl, alkene and aromatic groups at $\nu_{\text{max}} = 3400 – 3200, 1741, 1588$ and 1436 cm$^{-1}$ respectively. The $^1$H NMR spectrum confirmed the synthesis of the enaminone by two singlet at $\delta = 10.28$ and 5.81 ppm for the secondary enamine and the vinyl protons in that order. The aromatic multiplets were at $\delta = 7.98 – 7.78$ and 7.49 – 7.32 ppm for the two protons adjacent the ketone and the remaining three protons respectively. The triplet with $J = 7.8$ Hz at $\delta = 2.75$ ppm was for the $\gamma$-protons of the enaminone unit. Their chemical position suggests the Z isomer for vinlyllogous amide 239 since they are not deshielded through space by the ketone. The remainder of the peaks confirmed the

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**Scheme 51:** Reagents and Conditions: (a) $\text{F}_2\text{SSF}$ (0.5 eq), HMDS (1.5 eq), $\text{CF}_2\text{Cl}_2$, 7 days at r.t., 6 = 94%; (b) (i) Phenacyl bromide para-nitrophenacyl bromide para-methoxyphenacyl bromide (1.1 eq), MeCN, 22 h at r.t., (ii) TEA (1.2 eq), TEP (1.2 eq), MeCN, 24 h at r.t., 239 = 47%, 240 = 55%, 241 = 40%; (c) (i) Phenacyl bromide para-nitrophenacyl bromide para-methoxyphenacyl bromide (1.2 eq), MeCN, 22 h at r.t., (ii) TEA (1.2 eq), TEP (1.2 eq), MeCN, 2 days at r.t., 239 = 77% 100%, 240 = 80 – 100%, 241 = 88%; (c) Succinyl chloride (1 eq), THF, 22 h at refl., 242 = 0%, 243 = 0%, 244 = 0%.
structure. The $^{13}\text{C}$ NMR spectrum revealed the absence of thiocarbonyl carbon peak at $\delta$ 206.0 ppm for thioamide 6 and presence of quaternary alkene carbon peak at $\delta$ 158.4 ppm. The ketone carbonyl carbon came in at $\delta$188.14 ppm while the vinyl carbon was at $\delta$ 86.53 ppm. The aromatic group carbon peaks were at $\delta$ 149.0, 130.4, 128.2 and 127.0 ppm, while the pyrrolidinylidene ring carbon peaks were at $\delta$ 47.7, 30.9 and 21.4 ppm confirming the structure of the molecule. The HRMS found [M+H]$^+$ 188.1084 suggestive of a molecule with a molecular formula C$_{12}$H$_{14}$NO$^+$ with exact calculated mass of 188.1070. The spectra were comparable to those reported by Pettersson et al.\textsuperscript{96}

The melting point of (Z)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone 240 was 174 – 175 °C. The IR spectrum had peaks at $\nu_{\max} = 3279, 1737, 1599, 1538$ and 1476 cm$^{-1}$ revealing the presence of the amine NH, carbonyl of ketone, alkene and aromatic nitro groups in that order. The $^1\text{H}$ NMR spectrum’s significant two singlet peaks were at $\delta$ 10.45 and 5.80 ppm for the amine and vinyl protons respectively. The nitro aromatic group had two doublets, both with $J = 8.8$ Hz, at $\delta$ 8.24 and 8.00 ppm for the two protons adjacent the nitro group and the two protons adjacent the ketone group in that order. The pyrrolidinylidene ring had a doublet of doublet with $J = 7.7, 7.3$ Hz at $\delta$ 4.11 ppm for the $\alpha$-protons of the enaminone unit, a triplet with $J = 7.1$ Hz at $\delta$ 3.72 ppm for the $\gamma$-protons of the enaminone unit and a doublet of doublet with $J = 14.8, 7.5$ Hz at $\delta$ 2.11 ppm for the $\beta$-protons of the enaminone unit which confirmed the structure of the molecule. The pyrrolidinylidene ring $\alpha$ and $\gamma$-protons to the enaminone unit were greatly deshielded owing to the electron withdrawing nitro group para to the ketone group and there was no observable through space interaction between pyrrolidinylinene ring $\alpha$-protons and the ortho protons of the aromatic ring in the nOe spectrum, hence the vinylogous amide 240 was a Z isomer. Deshielding through space would only affect $\gamma$-protons to the enaminone unit if vinylogous amide 240 was an E isomer to which was not the case. The $^{13}\text{C}$ NMR revealed the newly formed quaternary alkene carbon at $\delta$ 170.6 ppm, replacing thioamide carbonyl carbon which was at $\delta$ 206.0 ppm for thioamide 6. The ketone and vinyl carbon peaks were at $\delta$ 190.2 and $\delta$ 87.0 ppm correspondingly confirming the formation of the enaminone unit. The nitro aromatic carbon peaks were at $\delta$ 150.9, 148.6, 127.9 and 123.5 ppm, while the pyrrolidinylidene ring carbon peaks were at $\delta$ 48.0, 33.1 and 30.9 ppm. The HRMS established [M+H]$^+$ 233.0928
indicative for a molecule with molecular formula $\text{C}_{12}\text{H}_{13}\text{N}_{2}\text{O}_{3}^+$ with an exact calculated mass of 233.0921.

The melting point of (Z)-1-(4-methoxyphenyl)-2-(pyrrolidin-2-ylidene)ethanone 241 was 125 – 126 °C. The IR spectrum showed peaks at $v_{\text{max}} = 3400 - 3200, 1734,1576$ and 1434 cm$^{-1}$ representative of the amine NH, ketone carbonyl, alkene and aromatic alkene groups respectively. The $^1\text{H}$ NMR spectrum revealed at $\delta$ 10.17 and 5.77 ppm for secondary amine and vinyl protons respectively confirming the formation of the carbon-carbon double bond. The aromatic protons doublets both with $J = 8.9$ Hz, with unresolved fine coupling were at $\delta$ 7.86 ppm and 6.90 ppm respectively for the two aromatic protons adjacent the ketone group and the two aromatic protons adjacent the methoxy group respectively, while the methoxy protons singlet was at $\delta$ 3.84 ppm. The triplet with $J = 7.8$ Hz at $\delta$ 2.73 ppm was for the $\gamma$-protons of the enaminone unit suggestive of the Z isomer. The $^{13}\text{C}$ NMR spectrum had peaks at $\delta$ 170.9 and 85.9 for the quaternary alkene and vinyl carbons indicative for the newly formed C=C bond. The ketone peak was at $\delta$ 192.4 ppm and aromatic carbons were at $\delta$ 163.8, 130.9, 128.7 and 113.8 ppm, while the methoxy carbon peak was at $\delta$ 60.6 ppm. The remaining peaks at $\delta$ 55.5, 38.3 and 23.8 ppm were for the pyrrolinylidene ring carbons confirming the structure of the molecule. The HRMS shown [M+H]$^+$ 218.1190 suggestive of a molecule with molecular formula $\text{C}_{13}\text{H}_{16}\text{NO}_2^+$ with an exact calculated mass of 218.1176.

Succinoyl chloride and (Z)-1-(4-methoxyphenyl)-2-(pyrrolidin-2-ylidene)ethanone 241 were heated under reflux in tetrahydrofuran with the aim of constructing the seven-membered ring onto a system that already contains the five-membered ring. The reaction was conducted in two stages after which tars were initially formed with no desired product in sight (Scheme 51, d). The first stage was a reaction between the two starting materials under mild conditions and isolation of the intermediate product. In the second stage, the isolated intermediate was reacted further in an acylative ring closing step. (Z)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone 240 was added dropwise into a solution of succinoyl chloride in tetrahydrofuran at room temperature followed by heating under reflux for 2 hours after which the reaction was left at room temperature overnight. The resulting residue was purified by column chromatography without prior aqueous workup, giving intermediate (E)-4-(2-(2-(4-
nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoyl chloride 245 in a poor 25% yield. A large quantity of compound 245 was hydrolysed to carboxylic acid 246 during silica gel chromatography hence poor yields. The carboxylic acid 246 was not isolated at this stage due to the non-polar (ethyl acetate: hexane) eluent used. This result showed that the acylation at nitrogen must be the first step in the reaction, however the second acylation at the carbon was not favoured under reaction condition (Scheme 52, a). Succinoyl chloride was added into a solution of (Z)-1-(4-methoxyphenyl)-2-(pyrrolidin-2-ylidene)ethanone 241 in tetrahydrofuran at room temperature and reacted for 24 hours, achieving (E)-4-(2-(4-methoxyphenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoic acid 246 in 40% yield after workup and purification by column chromatography (Scheme 52, b). This further confirmed that acylation at nitrogen was the first step suggesting that the nitrogen atom was more nucleophilic when compared to the carbon atom.

The IR spectrum of (E)-4-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoic acid 245 had peaks at ν_max = 1766, 1624 and 1458 cm⁻¹ for the acid chloride, amide, ketone and alkene groups in that order. The ¹H NMR spectrum showed the absence of a broad singlet peak at δ 10.45 ppm from vinylogous amide 240 spectrum representing the secondary enamine proton and the presence of a singlet at δ 2.72 representing α,β-protons of the amide, while the vinyl proton singlet peak was at δ 6.27 ppm. The aromatic and pyrrolidinyl ring proton peaks were also observed confirming the structure. The ¹³C NMR spectrum revealed peaks at δ
178.3, 177.2, 37.1 and 28.2 ppm for the amide carbonyl carbon, the acid chloride carbonyl carbon and the β and α carbons of the amide in that order. The ketone carbonyl, the quaternary alkene carbon and vinyl carbon peaks were at δ 198.8, 177.2 and 97.6 ppm respectively. The remaining pyrrolidinyl ring and aromatic carbons elucidated the structure of the molecule.

The IR spectrum of (E)-4-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoic acid 246 had major peaks at ν<sub>max</sub> = 3401, 1696, 1622, 1443 cm<sup>-1</sup> representing the carboxylic acid OH, carbonyl groups, alkene and aromatic groups in that order. The <sup>1</sup>H NMR spectrum revealed the absence of the enamine proton peak previously at δ 10.17 ppm, indicative of reaction at nitrogen. The presence of a peak at δ 11.44 ppm confirmed the carboxylic acid proton, while the multiplet peaks at δ 1.75 – 1.64 ppm were for the α and β-proton of the amide. The vinyl proton singlet peak was at δ 5.63 ppm while the methoxy singlet peak was at δ 3.81 ppm. The aromatic and pyrrolidinyl ring protons peaks were also observed, confirming the structure of the molecule is as predicted. The <sup>13</sup>C NMR spectrum revealed the carbonyl carbon peaks for the newly formed amide and carboxylic acid both at δ 171.0 ppm, while the ketone carbonyl carbon peak was at δ 187.3 ppm and the quaternary alkene carbon was at δ 170.8 ppm. The vinyl carbon was at δ 90.4 ppm validating that the reaction occurred on the nitrogen atom, while the methoxy carbon peak was at δ 55.3 ppm. The remaining aromatic carbon and pyrrolidinyl ring carbon peaks accounted for the structure of the molecule.

Could the cyclisation be induced by first activating the carboxylic acid as a mixed anhydride? The carboxylic acid 246 was heated under reflux with potassium carbonate, acetic anhydride in tetrahydrofuran for 24 hours; however carboxylic acid 246 was recovered in 80% yield after reaction workup and column chromatography (Scheme 52, c). The problem might be that the lone pair on the nitrogen atom is locked in the amide group, thus limiting its ability to participate in the enaminone’s reactivity.
2.18 Various attempts towards the synthesis of the pyrrolo[1,2-a]azepine nucleus

(Z)-1-(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone was reacted with 4-chlorobutyryl chloride with the aim to construct a seven-membered ring onto a system that already contains the five-membered ring, because it appeared that acylation of N-H vinylogous amides takes place on nitrogen. Vinylogous amide 240 and 4-chlorobutyryl chloride were heated under reflux in tetrahydrofuran for 20 hours, resulting in the formation of (E)-4-chloro-1-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)butan-1-one 247 in a good 74% yield (Scheme 53, a). The reaction proceeded with nucleophilic nitrogen lone pair attack on the carboxylic acid chloride group, proving once more that the nitrogen atom is more nucleophilic than the enamine carbon atom. However, the nitrogen lone pair was no longer available for extending nucleophilicity to the carbon atom alpha to the ketone as mentioned previously. A more useful product would have been (E)-6-chloro-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)hexane-1,3-dione, where the enamine nucleophilicity of nitrogen would have been explored in an N-alkylation reaction with the terminal haloalkane. The chloride was transformed to an iodide in situ which would have the iodide as a good leaving group to allow a much better chance of cyclisation. Vinylogous amide 240 and 4-chlorobutyryl chloride were heated under reflux in tetrahydrofuran for 19 hours resulting in the formation of (E)-4-chloro-1-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)butan-1-one 247 in situ as indicated by thin layer chromatography, followed by removal of tetrahydrofuran in vacuo. Sodium iodide, potassium carbonate and acetonitrile were added and the reaction mixture was heated under reflux for 20 hours, but it returned (E)-4-chloro-1-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)butan-1-one 247 in 86% yield (Scheme 53, b). Not only did compound 247 fail to cyclise but it also failed to exchange the chloride with the iodide.
The IR spectrum of (E)-4-chloro-1-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)butan-1-one 240 had peaks at $\nu_{\text{max}} = 1697, 1587, 1543$ and 1488 cm$^{-1}$ for the amide, ketone, aromatic alkene and alkene groups. The $^1$H NMR spectrum revealed the absence of the secondary enamine broad singlet peaks at $\delta$ 10.45 ppm for vinylogous amide 240 and the presence of triplet peak with $J = 6.0$ Hz at $\delta$ 3.71 ppm and a triplet peak with $J = 6.8$ Hz at $\delta$ 2.73 ppm for the $\gamma$ and $\alpha$-protons of the amide respectively. The vinyl singlet was more deshielded at $\delta$ 8.23 ppm as compared to that of vinylogous amide 240 which was at $\delta$ 5.80 ppm owing to the enaminone-amide system. The molecule had an entgegen geometry as shown by a through space interaction between $\gamma$-protons of the ketone (a triplet of doublets with $J = 7.8, 1.6$ Hz at $\delta$ 3.37 ppm showing long range coupling to the vinyl proton) and the ortho protons of the aromatic ring (a doublet with $J = 8.9$ Hz at $\delta$ 8.08 ppm) as shown by the NOE spectrum. The aromatic and pyrrolidinyl ring proton peaks were observed, confirming the structure of the molecule. The $^{13}$C NMR spectrum presented with peaks at $\delta$ 172.7, 44.3 and 34.1 ppm for the amide carbonyl, the $\gamma$ and $\beta$-carbons of the amide respectively. The vinyl carbon peak was at $\delta$ 103.0 ppm while the ketone carbonyl carbon was at $\delta$ 189.6 ppm. The remaining aromatic and pyrrolidinyl ring carbon peaks were observed, demonstrating the molecule is intact. The vinyl proton and carbon peak’s chemical shifts indicate the break in extended vinylogy.

In a further different attempt, (Z)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone 240 was reacted with ethyl4-chloro-4-oxobutyrate (the half-ester, half-acid chloride of succinic acid) under two separate reaction conditions. Vinylogous amide 240 and ethyl4-chloro-4-oxobutyrate were heated under reflux in tetrahydrofuran for 18 hours.
achieving (E)-ethyl 4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoate 249 in an excellent 90% yield after purification (Scheme 54, a). A poor 48% yield of compound 249 was recovered when the reaction was heated under reflux for 1 hour and left to stir at room temperature overnight.

It would be beneficial to selectively reduce the amide to a tertiary amine in order to regain the enaminone activity of the molecule. To this, (E)-ethyl 4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoate 249 was reacted with 1M borane in tetrahydrofuran at room temperature overnight. Unfortunately, starting material was returned in 50% yield (Scheme 54, b).

The melting point of (E)-ethyl 4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoate 249 was 118 – 119 °C. The IR spectrum showed peaks at νmax = 1745 and 1532 cm⁻¹ for the amide, ester, ketone carbonyl and alkene groups. The ¹H NMR spectrum revealed the absence of the NH proton and the presence of a quartet and triplet both with J = 7.1 Hz at δ 4.19 and 1.29 ppm for the ethyl ester side chain. The vinyl proton peak shifted down field to δ 8.21 ppm confirming the reaction to occur at the nitrogen. The aromatic and pyrrolidinyl ring proton peaks were also accounted for. The ¹³C NMR spectrum revealed peaks at δ 172.6 and 172.2 ppm for the amide and ester carbonyl carbons. The vinyl carbon peak shifted down field to δ 103.1 ppm, while the quaternary alkene carbon peak was at δ 160.3 ppm a significant shift from δ 170.6 ppm in compound 240's ¹³C NMR spectrum. The conversion of the secondary amine in the enaminone system to a tertiary amide pulls the electron density towards the amide thus shielding the quaternary alkene. The ketone carbonyl carbon appeared at δ 189.7 ppm. The
remaining aromatic and pyrrolidinyl ring carbon peaks confirmed the structure of the molecule. The HRMS found [M+ H2O+H]+ 379.1510 for a monohydrated molecule of molecular formula C18H23N2O7 with an exact calculated mass of 379.1500.

Often a six-membered ring has been grafted onto enaminones, so it seemed logical to see whether malonyl chloride could be used in place of oxalyl and succinoyl chloride. Malonyl chloride was heated under reflux with vinylogous amides 230, 231, 239 or 240 for 23 hours resulting in no desired cyclised products 251, 252, 257 or 258, but only returning tars. In summary, oxalyl chloride, malonyl chloride and succinoyl chloride were reacted with vinylogous amides in Scheme 55. The reactions generally proceeded with a milky colour change and a precipitate, indicating the amide formation. Most reaction returned unused vinylogous amides in small amounts, as well as tars after work up and purification. Previous results suggested a loss of the free acid derivatives of the uncyclised acid chloride intermediates during work up and purification steps.

Scheme 55: Reagents and Conditions: (a) (i) Oxalyl chloride (1 eq)/ (ii) malonyl chloride (1 eq)/ succinyl chloride (1eq), THF, 18 h at r.t., 23 h at reflux, 233 = 16%, 234 = 0%, 251 = 0%, 252 = 0%, 253 = 0%, 254 = 0%; (b) (i) Oxalyl chloride (1 eq)/ (ii) malonyl chloride (1 eq)/ (iii) succinyl chloride (1 eq), THF, 18 h at r.t., 23 h at reflux, 242 = 0%, 243 = 0%, 255 = 0%, 256 = 0%, 257 = 0%, 258 = 0%.
2.19 Synthesis of ethyl 1-allyl-6-oxo-2,3,3a,4,5,6-hexahydro-1H-indole-7-carboxylate 264

The strategy was to form the seven-membered ring via a ring closing metathesis onto a system that already contains a five-membered ring in order to achieve pyrrolo[1,2-a]azepine 4 nucleus. This required setting up the advanced enaminone such that it would have two side chains with terminal alkenes. The metathesis reaction required the synthesis of advanced enaminones (E)-ethyl 2-(1-allylpyrrolidin-2-ylidene)pent-4-enoate 262 and (E)-ethyl 2-(1-allylpyrrolidin-2-ylidene)-3-oxopent-4-enoate 263 as precursors. Advanced enaminones 262 and 263 would be synthesised from enaminone (E)-ethyl 2-(1-allylpyrrolidin-2-ylidene)acetate 261 in an alkylation reaction with allyl bromide and acylation reaction with acryloyl chloride respectively. The enaminone 261 would come from an Eschenmoser sulphide contraction reaction of thioamide 1-allylpyrrolidine-2-thione 260 with ethyl bromoacetate. The thioamide 260 would be synthesised from lactam 1-allylpyrrolidin-2-one 259 in a thionation reaction with phosphorus pentasulphide.

1-Allylpyrrolidin-2-one 259 was synthesised using three different methods. In the first method, allylamine and γ-butyrolactone were reacted neat in a microwave reactor at 150 W, 220 °C for 20 minutes, producing 1-allylpyrrolidin-2-one 259 in 79% yield after purification [Scheme 56, a (i)]. Allylamine’s ability to react efficiently with γ-butyrolactone is due to the absence of other electrophiles that could react with the secondary amide formed as was seen in Scheme 31. This method was quick and efficient, but was only possible on a small scale based on the microwave model; hence traditional methods had to be considered. In the second method, allylamine and γ-butyrolactone were reacted neat in a Carius tube in an oven at 220 °C overnight, giving 1-allylpyrrolidin-2-one 259 in 88% yield after purification [Scheme 56, a (ii)]. The high yields are in agreement with 78% for lactam 259 reported by Kulig et al.\textsuperscript{177} when allylamine and γ-butyrolactone were reacted neat at 200 °C in an autoclave. In the third method, pyrrolidin-2-one 140 was deprotonated with sodium hydride at room temperature for 30 minutes, followed by the addition of allyl bromide and left to react at room temperature for 24 hours. This gave 1-allylpyrrolidin-2-one 259 in 91% yield after purification (Scheme 56, b). The yield of lactam 259 falls
short of the quantitative yields reported by Tokunaga et al. using a similar N-alkylation method.\textsuperscript{178}

\[ \text{Scheme 56: Reagents and Conditions: (a) (i) Allyl amine (1 eq), neat, 150 W, 30 min at } 220 ^\circ \text{C, } 259 = 79\%; (ii) Allyl amine (1 eq), neat, overnight at } 220 ^\circ \text{C, } 259 = 88\%; (b) (i) NaH (1 eq), THF, 0.5 h at r.t.; (ii) Allyl bromide (1 eq), 24 h at r.t., } 259 = 91\%; (c) P\textsubscript{2}S\textsubscript{5} (0.5 eq), DCM, 24 h at r.t., } 260 = 71 - 78\%; (d) (i) Ethyl bromoacetate (1 eq), MeCN, r.t., 18 h (ii) Triethylamine (1.1 eq), triethylphosphite (1.1 eq), MeCN, r.t., 5 h, } 261 = 70 - 83\%; (e) Allyl bromide (1 eq), THF, 16 h at reflux, } 262 = 0\%; (f) Acryloyl chloride (1 eq), THF, 10 min at r.t., } 263 = 0\%, } 264 = 79\%; (g) Metathesis. \]

The IR spectrum of 1-allylpyrrolidin-2-one 259 had peaks at } \nu_{\text{max}} = 1691 \text{ and } 1640 \text{ cm}^{-1}, \text{ representative of the amide carbonyl and the alkene groups. The } ^1\text{H NMR spectrum confirmed the formation of a tertiary amide by a doublet with } J = 6.0 \text{ Hz at } \delta 3.50 \text{ ppm for the (NCH}_2\text{CH) protons, a double of doublet of triplets with } J = 17.0, 9.9, 6.0 \text{ Hz at } \delta 5.35 \text{ ppm for the (NCH}_2\text{CH) protons and a doublet of doublets with } J = 11.1, 6.2 \text{ Hz at } \delta 4.81 \text{ ppm for the (CH=CH}_2\text{) protons of the allyl side chain, which did not give the expected doublet of doublets of doublets system due to poor resolution. The pyrrolidinone ring protons were represented by a triplet with } J = 7.1 \text{ Hz at } \delta 2.99 \text{ ppm for the } \gamma\text{-protons of the amide and a triplet with } J = 8.1 \text{ Hz at } \delta 2.00 \text{ ppm for the } \alpha\text{-protons of the amide. The } ^{13}\text{C NMR spectrum showed the amide carbon peak at } \delta 174.3 \text{ ppm and the alkene carbon peaks at } \delta 132.2 \text{ and } \delta 117.2 \text{ ppm for (CH=CH}_2\text{) and (CH=CH}_2\text{) respectively. The } ^1\text{H NMR of lactam 259 obtained from a 300 MHz NMR in CDCl}_3 \text{ was similar to literature values reported by Tokunaga et al. obtained from a 400 MHz NMR in CDCl}_3 \text{ with a difference of } \delta 0.39 \text{ ppm in chemical shift of signals (Table 19).} \]
Lactam 259 was reacted with phosphorus pentasulphide in dichloromethane at room temperature for 24 hours, achieving 1-allylpiprilidine-2-thione 260 in good yield between 71 – 78% after purification (Scheme 56, c). This result was in line with good results observed in Scheme 27.

The IR spectrum of 1-allylpiprilidine-2-thione 260 revealed the absence of the amide carbonyl peak while maintaining a peak at $\nu_{\text{max}} = 1624 \text{ cm}^{-1}$ for the alkene group. The $^1$H NMR spectrum showed a downfield shift of the allyl side chain proton peaks to $\delta$ 4.39, 5.81 and 5.33 – 5.20 ppm when compared to those from lactam 259 at $\delta$ 3.50, 5.35 and 4.81 ppm respectively owing to the presence of a more electronegative sulphur atom as compared to oxygen atom. The pyrrolidinone ring proton peaks were also deshielded at $\delta$ 3.78 – 3.67 and 3.02 ppm as compared to those from lactam 259 at $\delta$ 2.99 and 2.00 ppm respectively. The $^{13}$C NMR spectrum revealed the absence of the amide carbonyl carbon peak at $\delta$ 174.3 ppm and the presence of the thioamide carbonyl carbon peak at $\delta$ 201.1 ppm. The HRMS found [M+H]$^+$ 142.0693 representative of a molecular formula C$_7$H$_{12}$NS$^+$ with an exact calculated mass of 142.0685.

The thiolactam 260 was then reacted with ethyl bromoacetate in an Eschenmoser sulphide contraction reaction at room temperature for 18 hours after which the salt precipitated, followed by the addition of triethylamine and triethyl phosphite for the extrusion step at room temperature and reacted for 5 hours resulting in (E)-ethyl 2-
(1-allylpyrrolidin-2-ylidene)acetate 261 in good yields between 70 – 83% (Scheme 55, d).

The IR spectrum of (E)-ethyl 2-(1-allylpyrrolidin-2-ylidene)acetate 261 revealed peaks at $\nu_{\text{max}} = 1666$ and $1514 \text{ cm}^{-1}$ for the ester carbonyl and the alkene groups respectively. The $^1$H NMR spectrum showed a singlet at $\delta 4.52$ ppm for the vinyl proton, a quartet and triplet both with $J = 7.1$ Hz at $\delta 4.05$ and 1.23 ppm for the ethyl ester side chain. The allyl group and pyrrolidinylidene ring proton peaks were also accounted for, confirming the structure of the molecule. The $^{13}$C NMR spectrum revealed the absence of the thioamide carbonyl peak $\delta 201.1$ and the presence of the quaternary alkene carbon peak at $\delta 164.4$ ppm. The unsaturated ethyl ester carbon peaks were at $\delta 169.1$, 77.9, 57.8 and 14.5 ppm for the ester carbonyl, the vinyl carbon and ethyl side chain carbons respectively. The allyl group and pyrrolidinylidene ring carbon peaks were accounted for confirming the structure of the molecule. The HRMS found $[\text{M+H}]^+$ 196.1341 for molecular formula $\text{C}_{11}\text{H}_{18}\text{NO}_2^+$ with exact calculated mass of 196.1332.

Enaminone 261 was reacted with allyl bromide heating under reflux in tetrahydrofuran for 16 hours, but the desired (E)-ethyl 2-(1-allylpyrrolidin-2-ylidene)pent-4-enoate 262 was not formed. This product, would have been cyclised in metathesis reaction with a Grubbs catalyst to form (6Z,9E)-ethyl 2,3,5,8-tetrahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147 (Scheme 56, e, g). Enaminone 261 was then reacted with acryloyl chloride in tetrahydrofuran at room temperature for 10 minutes, resulting in synthesis of ethyl 1-allyl-6-oxo-2,3,3a,4,5,6-hexahydro-1H-indole-7-carboxylate 264 in good yield of 79%, instead of the desired (E)-ethyl 2-(1-allylpyrrolidin-2-ylidene)-3-oxopent-4-enoate 263 (Scheme 56, e). It is speculated that (E)-ethy 2-(1-allylpyrrolidin-2-ylidene)-3-oxopent-4-enoate 263 which would have been used in a ring closing metathesis reaction to form (6Z,9E)-ethyl 8-oxo-2,3,5,8-tetrahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 144, forms as an intermediate in situ which quickly cyclises to oxoindolecarboxylate 264 under acidic conditions.

The proposed mechanism for the cyclisation is shown below (Scheme 57). The vinylogous urethane 261 is acylated by acryloyl chloride at the enamine carbon owing to nucleophilicity extended from the nitrogen atom resulting in a chloro-
iminium salt which rearranges as shown. The chloride anion then extracts the α-proton of the keto-ester resulting in the formation of (Z)-ethyl 2-(1-allylpyrrolidin-2-ylidene)-3-oxopent-4-enoate 263 and hydrochloric acid. The chloride anion remove the α-proton of the enaminone unit resulting in (E)-2-(1-allyl-4,5-dihydro-1H-pyrrol-2-yl)-1-ethoxy-1-hydroxypenta-1,4-dien-3-one. The enamine then reacts in a Michael addition with the vinyl ketone resulting in formation of a six-membered ring. A loss of a proton results in formation of compound 264.

![Scheme 57: Proposed cyclisation mechanism.](image)

The IR spectrum of 1-allyl-6-oxo-2,3,3a,4,5,6-hexahydro-1H-indole-7-carboxylate 264 showed peaks at $\nu_{\text{max}} = 1732$ and 1645 cm$^{-1}$ for the unsaturated ketone, ester and alkene groups. The $^1$H NMR spectrum revealed that the five-membered and six-membered rings protons were represented by a triplet with $J = 10.0$ Hz at $\delta 3.58$ ppm for the $\varepsilon$-protons of the ketone group, a multiplet at $\delta 3.47$ ppm for the $\gamma$-protons of the ketone, a multiplet at $\delta 2.90 – 2.69$ ppm for the $\delta$-protons of the ketone and two multiplets at $\delta 2.57 – 2.36$ and 2.32 – 2.02 ppm for the $\alpha$ and $\beta$-protons of the ketone. The doublet of doublet of doubles with $J = 22.4, 10.8, 5.6$ Hz at $\delta 5.78$ ppm, and the two multiplets at $\delta 5.27 – 5.16$ and 3.94 – 3.75 ppm were for the allyl group. The ester group presented with a proton multiplet was at $\delta 4.27 – 4.15$ ppm and a
triplet with $J = 7.1$ Hz at $\delta 1.29$ ppm. The $^{13}$C NMR revealed carbon peaks at $\delta$ 190.6, 169.6, 61.7, 14.1, 163.2, 110.3, 132.5, 117.9 and 49.3 ppm for the ketone, ester carbonyl and ethyl side chain, quaternary alkenes and allyl groups respectively. The remaining peaks at $\delta$ 32.9, 26.3, 38.6, 24.0 and 51.4 ppm were for $\alpha$, $\beta$, $\gamma$, $\delta$ and $\varepsilon$-carbons of the ketone respectively on the six-membered and five-membered rings.

The above result in Scheme 56 were subsequently investigated with vinylogous amides in order to see whether better results could be obtained leading to the metathesis reaction. The vinylogous amides (E)-2-(1-allylpyrrolidin-2-ylidene)-1-phenylethanone 267, (E)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-nitrophenyl)ethanone 268 and (E)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-methoxyphenyl)ethanone 269 were synthesised in an Eschenmoser sulphide contraction reaction in excellent yields of 93%, 78% and 93% respectively by reacting phenacyl bromide, para-nitrophenacyl bromide or para-methoxyphenacyl bromide with 1-allylpyrrolidine-2-thione 260 in acetonitrile at room temperature for 1 – 2 hours followed by addition of a solution of triethylamine and triethyl phosphite in acetonitrile and reacting at room temperature overnight (Scheme 58, a).

![Scheme 58: Reagents and Conditions: (a) (i) Phenacyl bromide (1 eq) / para-nitrophenacyl bromide (1 eq)/ para-methoxyphenacylethionyl bromide (1 eq), MeCN, 1 h - 2 h at r.t. (ii) Triethyl amine (1.1 eq), triethylphosphite (1.1 eq), MeCN, overnight at r.t., 267 = 93%, 268 = 78%, 269 = 93%; (b) Acryloyl chloride (1 eq), THF, overnight at r.t.](image)

The IR spectrum of (E)-2-(1-allylpyrrolidin-2-ylidene)-1-phenylethanone 267 had peaks at $\nu_{\text{max}} = 1743, 1582$ and 1432 cm$^{-1}$ for the ketone and alkene groups respectively. The $^1$H NMR spectrum showed the phenyl proton peaks with two multiplets at $\delta$ 7.93 – 7.77 and 7.48 – 7.31 ppm for the two protons adjacent the
ketone and the remaining three protons respectively, while the vinyl singlet was at δ 5.75 ppm, confirming the formation of the vinylogous amide. The allyl group and pyrrolidine ring peaks were observed demonstrating the molecule is intact. The $^{13}$C NMR spectrum indicated the absence of the thioamide’s carbonyl carbon peak at δ 201.1 ppm and the presence of the quaternary alkene carbon peak at δ 167.1 ppm. The presence of the ketone and the vinyl carbon peaks at δ 187.8 and 86.8 ppm respectively confirmed the success of the reaction. The allyl and pyrrolidine ring carbon peaks were present confirming the structure of the molecule. The HRMS found [M+H]$^+$ 228.1390 for molecular formula C$_{15}$H$_{18}$NO$^+$ with an exact calculated mass of 228.1383.

The melting point of (E)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-nitrophenyl)ethanone 268 was 129 – 130 °C. The IR spectrum showed peaks at $\nu_{\text{max}} = 1745, 1585$ and 1402 cm$^{-1}$ for the ketone and alkene groups in that order. The $^1$H NMR spectrum showed the phenyl proton peaks with two doublets both with $J = 8.9$ Hz, with unresolved fine coupling at δ 8.23 ppm and 7.97 ppm respectively for the two protons adjacent the nitro group and the two protons adjacent the ketone respectively, while the vinyl singlet proton peak was at δ 5.69 ppm confirming the formation of the vinylogous amide. The allyl group and pyrrolidine ring peaks were observed demonstrating the molecule is intact. The $^{13}$C NMR spectrum again showed the absence of the thioamide carbonyl carbon peak at δ 201.1 ppm and the presence of the quaternary alkene carbon peak at δ 168.5 ppm. The presence of the ketone and the vinyl carbon peaks at δ 185.1 and 86.8 ppm respectively confirmed the success of the reaction. The allyl and pyrrolidine ring carbon peaks were present confirming the structure of the molecule. The HRMS found [M+H]$^+$ 272.1241 for molecular formula C$_{15}$H$_{17}$N$_2$O$_3$ with exact calculated mass of 273.1234.

The IR spectrum of (E)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-methoxyphenyl)ethanone 269 IR spectrum had peaks at $\nu_{\text{max}} = 1743, 1571$ and 1423 cm$^{-1}$ for the ketone carbonyl and alkene groups respectively. The $^1$H NMR spectrum showed the aryl proton peaks by two doublets both with $J = 8.9$ Hz, with unresolved fine coupling at δ 7.86 ppm and 6.88 ppm respectively for the two protons adjacent the ketone and the two protons adjacent the methoxy group respectively, while the vinyl singlet and
methoxy singlets were at δ 5.73 and 3.82 ppm, confirming the formation of the vinylogous amide. The allyl group and pyrrolidine ring peaks were observed demonstrating the molecule is intact. The $^{13}$C NMR spectrum showed the absence of the thioamide carbonyl carbon peak at δ 201.1 ppm and the presence of the quaternary alkene carbon peak at δ 166.6 ppm. The presence of the ketone and the vinyl carbon peaks at δ 186.8 and 86.3 ppm respectively confirmed the success of the reaction. The allyl and pyrrolidine ring carbon peaks were present confirming the structure of the molecule. The HRMS found [M+H]$^+$ 258.1499 for a molecular formula C$_{16}$H$_{20}$NO$_2$ with an exact calculated mass of 258.1489.

The vinylogous amides 267, 268 or 269 reacted with acryloyl chloride in tetrahydrofuran at room temperature overnight, but resulted in low yields of products that could not be purified enough to elucidate their structures. Perhaps longer reaction time and the acid environment were not suitable for preserving the product. The results from LRMS spectra of reaction mixtures of (E)-2-(1-allylpyrrolidin-2-ylidene)-1-phenylethanone 267 and (E)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-methoxyphenyl)ethanone 269 (found [M+H]$^+$ = 282.3 and [M+H]$^+$ = 312.3 for molecular formulas C$_{18}$H$_{20}$NO$_2$ and C$_{19}$H$_{22}$NO$_3$ with a nominal mass of 282.1 and 312.2 respectively) indicating the formation of the hydroindoles 1-allyl-7-benzoyl-1,2,3,3a,4,5-hexahydroindol-6-one 273 and 1-allyl-7-(4-methoxybenzoyl)-1,2,3,3a,4,5-hexahydroindol-6-one 275 on the basis of the other reaction with acryloyl chloride.

2.20 Synthesis of (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281

4-Iodobutyl benzoate 277 was chosen as an alternative in tackling our challenge of attaching a protected four carbon side chain to the nitrogen of pyrrolidin-2-one 140, the number four is the holy grail to pyrrolo[1,2-a]azepine nucleus 4. 4-Iodobutyl benzoate 277 was expected to be a better alkylating agent as compared to bromoalkanes previously used and is a disguised 4-iodobutanol-1-ol where the alcohol group would be essential later in alkylative ring closing step. Belanger et al.
synthesised 1-(4-hydroxybutyl)pyrrolidin-2-one 180 in overall 78% yield over two steps by first making 4-(2-oxopyrrolidin-1-yl)butyl benzoate 278 in a N-alkylation reaction between 2-pyrrrolidinone 140 and 4-iodobutyl benzoate 277 followed by saponification of the benzoyl ester. The strategy followed previously described routes where 4-(2-oxopyrrolidin-1-yl)butyl benzoate 278 should result from N-alkylation reaction between lactam 140 and 4-iodobutyl benzoate 277. The lactam 278 would then be thionated with Lawesson’s reagent making 4-(2-thioxopyrrolidin-1-yl)butyl benzoate 279. Thiolactam 279 would be reacted with ethyl bromoacetate in an Eschenmoser sulphide contraction reaction to yield (E)-4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butyl benzoate 280. Vinylogous urethane 280 would then be deprotected, releasing the free alcohol (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281. The free alcohol 281 could then be cyclised in an alkylation reaction where a transformation that converts OH to iodide in situ would result in (E)-ethyl 2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147.

![Chemical Structure](attachment:image.png)

**Scheme 59:** Reagents and Conditions: (a) Tetrahydrofuran (1 eq), NaI (1 eq), MeCN, r.t., overnight, 277 = 66%; (b) 2-pyrrrolidinone 140 (0.83 eq), potassium bis(trimethylsilyl)amide (1.2 eq), THF, overnight at 0 °C - r.t., 278 = 75%; (c) Lawessons reagent (1 eq), DCM, 32 h at r.t., 279 = 90%; (d) (i) Ethyl bromoacetate (1 eq), MeCN, 16 h at r.t. (ii) TEA (1.2 eq), TEP (1.2 eq), MeCN, 12h at r.t., 280 = 48%; (e) KOH (1.1 eq), MeOH/H2O (20:1), 1.5 h at r.t., 281 = 89%.

Alternatively, an acylation reaction could be used where alcohol 281 would be oxidised to a carboxylic acid and the carboxylic acid derivative would be converted into a mixed anhydride in situ that should cyclise, achieving (E)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 144. 4-Iodobutyl benzoate was made according to a reported procedure from a solution of benzoyl
chloride, tetrahydrofuran and sodium iodide in acetonitrile, which was kept overnight at room temperature, achieving product 277 in good 66% yield (Scheme 59, a).99

The IR spectrum of 4-iodobutyl benzoate 277 had peaks at $\nu_{\text{max}} = 1721$ and 1495 cm$^{-1}$ for the ester carbonyl and benzyl aromatic groups. The $^1$H NMR spectrum revealed three multiplets at $\delta$ 8.13 – 7.98, 7.63 – 7.49 and 7.42 ppm for the two protons ortho to the ester group, the para proton and the two meta protons respectively. The four-carbon chain was represented by two significant peaks, a triplet with $J = 6.1$ Hz at $\delta$ 4.32 ppm for the OCH$_2$ protons and a triplet with $J = 6.7$ Hz at $\delta$ 3.23 ppm for the ICH$_2$ protons. The $^{13}$C NMR revealed carbon peaks at $\delta$ 166.5, 133.0, 130.1, 129.6 and 128.4 ppm for the ketone carbonyl and phenyl ring. The butyl side chain’s significant peaks were at $\delta$ 63.9 and 6.3 ppm for the OCH$_2$ and ICH$_2$ carbons. NMR spectra were identical to literature values reported by Belanger et al. and Kang et al. (Table 20).100,101

<table>
<thead>
<tr>
<th>$^1$H NMR/ ppm</th>
<th>$^1$H NMR (Lit.)/ ppm</th>
<th>$^{13}$C NMR/ ppm</th>
<th>$^{13}$C NMR (Lit.)/ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.13 – 7.42 (m)</td>
<td>8.05 – 7.40 (m, aromatic)</td>
<td>166.5</td>
<td>166.4 (CO$_2$)</td>
</tr>
<tr>
<td>4.32 (t, $J = 6.1$ Hz)</td>
<td>4.33 (t, $J = 6.0$ Hz, OCH$_2$)</td>
<td>133.0</td>
<td>132.8 para-carbon</td>
</tr>
<tr>
<td>3.23 (t, $J = 6.7$ Hz)</td>
<td>3.24 (t, $J = 6.0$ Hz, ICH$_2$)</td>
<td>130.1</td>
<td>130.0 (CH$_2$(CO$_2$)CH)</td>
</tr>
<tr>
<td>2.06 – 1.78 (m)</td>
<td>1.99 – 1.85 (m, ICH$_2$CH$_2$CH$_2$)</td>
<td>129.6</td>
<td>129.4 ortho-carbons</td>
</tr>
<tr>
<td></td>
<td></td>
<td>128.4</td>
<td>128.2 meta-carbons</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63.9</td>
<td>63.6 (OCH$_2$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30.1</td>
<td>29.9 (ICH$_2$CH$_2$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29.7</td>
<td>29.5 (OCH$_2$CH$_2$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.3</td>
<td>6.0 (ICH$_2$)</td>
</tr>
</tbody>
</table>
This alkyl halide 277 was then used in an N-alkylation reaction with 2-pyrrolidinone 140. Potassium bis(trimethylsilyl)amide reacted with pyrrolidin-2-one 140 in tetrahydrofuran at 0 °C for 1 hour followed by addition of 4-iodobutyl benzoate 277 and left to react at room temperature overnight achieving 4-(2-oxopyrrolidin-1-yl)butyl benzoate 278 in good 75% yield (Scheme 59, b). So at last a four carbon chain N-alkyl lactam was made after many previous failed attempts (see sections 2.2, 2.4, 2.5, 2.6 and 2.7). The success of the reaction could be attributed the use of potassium bis(trimethylsilyl)amide as a base and the highly reactive nature of 4-iodobutyl benzoate 277. Potassium bis(trimethylsilyl)amide could not be trialled in the reactions in sections 2.2 and 2.4 owing to time constraints as this was a late discovery in the project.

The IR spectrum of 4-(2-oxopyrrolidin-1-yl)butyl benzoate 278 contained peaks at \( \nu_{\text{max}} = 1698 \) and 1505 cm\(^{-1}\) for the amide and ester carbonyl and aromatic alkene groups. The \(^1\)H NMR spectrum revealed success of the reaction with oxopyrrolidinyldiene ring multiplet at \( \delta 3.26 – 3.20 \) ppm for the \( \gamma \)-protons of the lactam and a triplet with \( J = 8.1 \) Hz at \( \delta 2.23 \) ppm for the \( \alpha \)-protons of the lactam. The benzoate ester was represented by a doublet with \( J = 7.2 \) Hz at \( \delta 7.92 \) ppm for the ortho-protons, a triplet with \( J = 7.4 \) Hz at \( 7.43 \) ppm for the para-proton and a triplet with \( J = 7.6 \) Hz at \( 7.32 \) ppm for meta protons. The butyl chain was shown by a triplet peak with \( J = 6.2 \) Hz at \( \delta 4.22 \) ppm for \( \text{CO}_2\text{CH}_2 \) protons and a multiplet at \( \delta 3.26 – 3.20 \) ppm for the \( \text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2 \) protons. The \(^{13}\)C NMR spectrum revealed peaks at \( \delta 173.3 \) and 164.8 ppm for the amide and the ester carbonyl carbons. The aromatic carbon peaks were at \( \delta 131.4, 128.8, 128.0 \) and 126.9 ppm. The significant butyl chain peaks were at \( \delta 62.9 \) and 40.5 ppm for \( \text{CO}_2\text{CH}_2 \) and \( \text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2 \) carbons. The oxopyrrolidinyldiene ring’s significant peaks were at \( \delta 45.5 \) and, 29.5 ppm for the \( \gamma \)-carbon and \( \alpha \)-carbon of the lactam respectively.

4-(2-Oxopyrrolidin-1-yl)butyl benzoate 278 was then thionated in dichloromethane at room temperature for 32 hours with the aid of Lawesson’s reagent to give 4-(2-thioxopyrrolidin-1-yl)butyl benzoate 279 in excellent 90% yield (Scheme 59, c). The reaction conditions were mild, enabling Lawesson’s reagent to chemoselectivity react with the tertiary amide.
The IR spectrum of 4-(2-thioxopyrrolidin-1-yl)butyl benzoate 279 had minor changes compared with lactam 278, with peaks at $\nu_{\text{max}} = 1722$ and 1488 cm$^{-1}$ for the ester carbonyl and the aromatic alkene groups. The $^1$H and $^{13}$C NMR showed a slight downfield chemical shift on all peaks detailed in Table 16 due to the stronger inductive effects of the sulphur atom as compared to the oxygen. The $^{13}$C NMR spectrum revealed the absence of the lactam carbonyl carbon peak at $\delta$ 173.3 ppm and presence of thioamide carbonyl carbon peak at $\delta$ 201.0 ppm.

Table 21: $^1$H and $^{13}$C NMR spectroscopic data for lactam 278 and thiolactam 279

<table>
<thead>
<tr>
<th>278 $^1$H NMR/ ppm</th>
<th>279 $^1$H NMR/ ppm</th>
<th>278 $^{13}$C NMR/ ppm</th>
<th>279 $^{13}$C NMR/ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.92 (d, J = 7.2 Hz)</td>
<td>8.04 (d, J = 7.4 Hz, CHC(CO$_2$)CH)</td>
<td>173.3 (NCO)</td>
<td>201.0 (NCS)</td>
</tr>
<tr>
<td>7.43 (t, J = 7.3 Hz)</td>
<td>7.56 (t, J = 7.4 Hz, CHCHCH)</td>
<td>164.8</td>
<td>166.6 (CO$_2$)</td>
</tr>
<tr>
<td>7.32 (t, J = 7.6 Hz)</td>
<td>7.44 (t, J = 7.6 Hz, CHCHCH)</td>
<td>131.4</td>
<td>133.0 (CHCHCH)</td>
</tr>
<tr>
<td>4.22 (t, J = 6.2 Hz)</td>
<td>4.38 – 4.34 (m, OCH$_2$)</td>
<td>128.8</td>
<td>130.1 (CHC(CO$_2$)CH)</td>
</tr>
<tr>
<td>3.26 – 3.20 (m)</td>
<td>3.80 – 3.88 (m, NCH$_2$CH$_2$CH$_2$CH$_2$O)</td>
<td>128.0</td>
<td>129.5 (CHC(CO$_2$)CH)</td>
</tr>
<tr>
<td>3.26 – 3.20 (m)</td>
<td>3.73 (t, J = 6.8 Hz, NCH$_2$CH$_2$CH$_2$CS)</td>
<td>126.9</td>
<td>128.4 (CHCHCH)</td>
</tr>
<tr>
<td>2.23 (t, J = 8.2 Hz)</td>
<td>3.03 (t, J = 7.9 Hz, CSCH$_2$)</td>
<td>62.9</td>
<td>64.4 (CO$_2$CH$_2$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45.5</td>
<td>54.7 (NCH$_2$CH$_2$CH$_2$CS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40.5</td>
<td>47.5 (NCH$_2$CH$_2$CH$_2$CH$_2$O)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29.5</td>
<td>45.0 (CSCH$_2$)</td>
</tr>
</tbody>
</table>
The Eschenmoser sulphide contraction of thiolactam 279 with ethyl bromoacetate gave (E)-4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butyl benzoate 280 in poor 48% yield. Thiolactam 279 was reacted with ethyl bromoacetate in acetonitrile at room temperature for 16 hours after which the salt had precipitated. A solution of triethylamine and triphenylphosphine in acetonitrile was then added and reacted for 12 hours at room temperature. The poor yield may be attributed to longer hours need for salt formation where some of the salt may have hydrolysed due to adventitious moisture (Scheme 59, d).

The IR spectrum of (E)-4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butyl benzoate 280 showed peaks at $\nu_{\text{max}} = 1728, 1567$ and 1514 cm$^{-1}$ for the ester carbonyl, alkene and aromatic groups. The $^1$H NMR spectrum revealed a singlet at $\delta$ 4.55 ppm for the vinyl proton and a quartet and a triplet, both with $J = 7.1$ Hz at $\delta$ 4.09 ppm and 1.24 ppm for ethyl groups indicating the presence of the unsaturated ester group hence the success of the reaction. The aromatic, butyl side chain and pyrrolidinyl ring proton peaks were also observed, confirming the structure of the molecule.

(E)-4-(2-(2-Ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butyl benzoate 280 was subjected to saponification reaction using potassium hydroxide in a 20:1 solution of methanol and water at room temperature for 1.5 hours to achieve (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281 in excellent 89% yield (Scheme 59, e). For the first time a suitable precursor for cyclisation was made. The biggest challenge was to improve the yields of the Eschenmoser sulphide contraction reaction in order to carry enough material after saponification. The route was abandoned in view of lack of time, too little material was obtained to continue with the scheme and because this work came right at the end of the project. However, this approach is definitely worth pursuing since it solved the stumbling block which was making a four-carbon chain substituent on nitrogen. The cyclisation story continues in section 2.21 where another method was used to make vinylogous urethane 281.

The IR spectrum of (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281 showed peaks at $\nu_{\text{max}} = 3401, 1657$ and 1577 cm$^{-1}$ for the alcohol, ester carbonyl and alkene groups. The $^1$H NMR spectrum revealed the absence of the aromatic protons and the presence of a broad singlet at $\delta$ 4.26 ppm for the alcohol proton,
while the triplet with \( J = 6.1 \) Hz at \( \delta \) 3.61 ppm was for the \( \text{CH}_2\text{OH} \) protons. The unsaturated ester’s presence was shown by a singlet at \( \delta \) 4.47 ppm for the vinyl proton and a quartet and triplet, both with \( J = 7.1 \) Hz at \( \delta \) 4.03 and 1.20 ppm for the ethyl ester side chain, showing the chemoselectivity of the reaction. The \(^{13}\text{C} \) NMR spectrum revealed the loss of the benzoyl ester group with absence of its carbon peaks. The unsaturated ethoxycarbonylmethylene group’s carbon peaks were at \( \delta 169.8, 165.1, 77.3, 58.3 \) and 14.7 ppm for the ester carbonyl, quaternary alkene, vinyl and ethyl groups. The butyl side chain’s significant peak was at \( \delta \) 62.0 ppm for the \( \text{CH}_2\text{OH} \) carbon.

### 2.21 Synthesis of chloroalkyne esters and amides

A new strategy involving a \( \text{SN}_2/\text{Michael} \) addition reaction for synthesising enaminones was adopted from Zhu and Ma in the interest of saving time and improving yields for continuity.\(^{103,104,105}\) This strategy involves a reaction between \( \omega \)-halo-\( \alpha,\beta \)-alkynoates and amines, resulting in formation of desired enaminones in a single operation. A variety of \( \omega \)-chloro-\( \alpha,\beta \)-alkynoates 283, 285 and 286 were prepared in good to excellent yields between 64 – 99%, except for ethyl 9-chloro-4-oxonon-5-ynoate 284 achieved in poor 28% yield possibly due to a reaction between the alkyne enolate and the ester. The above products were achieved by reacting 5-chloropent-1-yn with butyllithium in tetrahydrofuran at \(-78^\circ\text{C}\) to \(-20^\circ\text{C}\) for 20 minutes followed by addition of benzoyl chloride, ethyl 4-chloro-4-oxobutanoate (1 eq), ethyl chloroformate or cyclopropanecarbonyl chloride at \(-20^\circ\text{C}\) and reacting for 20 hours at room temperature (Scheme 60, a).\(^{106,107}\) Of interest was ethyl 6-chlorohex-2-ynoate 285 which would give the much desired vinylogous urethanes when condensed with appropriate amines.
The IR spectrum of ethyl 6-chlorohex-2-ynoate 285 had peaks at $\nu_{\text{max}} = 2238$ and 1714 cm$^{-1}$ for the alkyne and ester carbonyl groups. The $^1$H NMR spectrum revealed the ethyl side chain protons by a quartet and a triplet, both with $J = 7.1$ Hz at $\delta$ 4.22 and 1.31 ppm. The chlorohexyne chain’s major peaks were a triplet with $J = 6.2$ Hz at $\delta$ 3.66 ppm for the $\varepsilon$-protons of the ester, and a triplet with $J = 6.9$ Hz at $\delta$ 2.55 ppm for the $\gamma$-protons of the ester. The $^{13}$C NMR spectrum showed peaks at $\delta$ 153.5, 87.0 and 73.9 ppm for the ester carbonyl and the $\beta$ and $\alpha$ alkyne quaternary carbons of the ester respectively. The haloalkane carbon peak at 43.2 ppm confirmed the structure.

The IR spectrum of 6-chloro-1-phenylhex-2-yn-1-one 283 had peaks at $\nu_{\text{max}} = 2962, 2202, 1640, 1597$ and 1579 cm$^{-1}$ for the ketone, alkyne and alkene groups respectively. The $^1$H NMR spectrum showed a multiplet at $\delta$ 8.20 – 8.10 ppm for the ortho-protons and a multiplet at $\delta$ 7.72 – 7.44 ppm for the meta and para-protons of the phenyl group. The chlorohexyn side chain major peaks were a triplet with $J = 6.2$ Hz at $\delta$ 3.72 ppm for the $\varepsilon$-protons of the ketone and a triplet with $J = 6.9$ Hz at $\delta$ 2.73 ppm for the $\delta$-protons of the ketone. The $^{13}$C NMR spectrum revealed the phenyl carbon peaks at $\delta$ 136.8, 134.1, 129.6, 128.6 ppm, while the ketone peak at $\delta$ 178.0 ppm. The alkyne carbon peaks were at $\delta$ 94.1 and 80.3 ppm for the $\beta$ and $\alpha$ alkyne quaternary carbons of the ketone respectively, while the haloalkane carbon peak was at $\delta$ 43.4 ppm illuminated the structure. The NMR spectra agreed with the literature values from Wang et al. (Table 22)$^{108}$
<table>
<thead>
<tr>
<th>H NMR/ ppm</th>
<th>H NMR (Lit.)/ ppm</th>
<th>13C NMR/ ppm</th>
<th>13C NMR (Lit.)/ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.20 – 8.10 (m)</td>
<td>8.12 (m, CHC(CO)CH)</td>
<td>177.98</td>
<td>178.1 (CO)</td>
</tr>
<tr>
<td>7.72 – 7.44 (m)</td>
<td>7.60 - 7.48 (m, CHCHCH)</td>
<td>136.76</td>
<td>136.8 (CHC(CO)CH)</td>
</tr>
<tr>
<td>3.72 (t, J = 6.2 Hz)</td>
<td>3.71 (t, J = 6.2 Hz, CH2Cl)</td>
<td>134.07</td>
<td>134.2 (CHCHCH)</td>
</tr>
<tr>
<td>2.73 (t, J = 6.9 Hz)</td>
<td>2.72 (t, J = 6.9 Hz, CH2CH2Cl)</td>
<td>129.57</td>
<td>129.7 (CHCHCH)</td>
</tr>
<tr>
<td>2.20 – 2.07 (m)</td>
<td>2.13 (m, CH2C≡C)</td>
<td>128.58</td>
<td>128.7 (CHC(CO)CH)</td>
</tr>
</tbody>
</table>

The IR spectrum of 6-chloro-1-cyclopropylhex-2-yn-1-one 286 revealed νmax = 2218 and 1651 cm⁻¹ for alkyne and ketone carbonyl groups. The 1H NMR spectrum showed the presence of cyclopropyl ring by a multiplet at δ 2.11 – 1.96 ppm for the α-protons of the ketone and a multiplet at δ 1.29 – 1.15, 1.10 – 0.98 ppm for the β-protons of the ketone. The chlorohexyne side chain’s major peaks were a triplet with J = 6.2 Hz at δ 3.65 ppm for the ε-protons of the ketone and a triplet with J =6.9 Hz at δ 2.57 ppm for the δ-protons of the ketone. The 13C NMR spectrum revealed peaks at δ 24.4 and 10.9 ppm for α and β-carbons of the ketone on the cyclopropyl ring, while the ketone peak was at δ 188.3 ppm. The alkyne carbon peaks were at δ 91.4 and 79.6 ppm for the β and α-carbons of the amide on the chlorohexyne chain, while the haloalkane carbon peak was at δ 43.3 ppm. The NMR spectra agreed with the literature values from Wang et al. (Table 23).

Table 22: ¹H and ¹³C NMR spectroscopic data literature comparison for 6-chloro-1-phenylhex-2-yn-1-one 283

The IR spectrum of 6-chloro-1-cyclopropylhex-2-yn-1-one 286 revealed νmax = 2218 and 1651 cm⁻¹ for alkyne and ketone carbonyl groups. The ¹H NMR spectrum showed the presence of cyclopropyl ring by a multiplet at δ 2.11 – 1.96 ppm for the α-protons of the ketone and a multiplet at δ 1.29 – 1.15, 1.10 – 0.98 ppm for the β-protons of the ketone. The chlorohexyne side chain’s major peaks were a triplet with J = 6.2 Hz at δ 3.65 ppm for the ε-protons of the ketone and a triplet with J =6.9 Hz at δ 2.57 ppm for the δ-protons of the ketone. The ¹³C NMR spectrum revealed peaks at δ 24.4 and 10.9 ppm for α and β-carbons of the ketone on the cyclopropyl ring, while the ketone peak was at δ 188.3 ppm. The alkyne carbon peaks were at δ 91.4 and 79.6 ppm for the β and α-carbons of the amide on the chlorohexyne chain, while the haloalkane carbon peak was at δ 43.3 ppm. The NMR spectra agreed with the literature values from Wang et al. (Table 23).}

The IR spectrum of 6-chloro-1-cyclopropylhex-2-yn-1-one 286 revealed νmax = 2218 and 1651 cm⁻¹ for alkyne and ketone carbonyl groups. The ¹H NMR spectrum showed the presence of cyclopropyl ring by a multiplet at δ 2.11 – 1.96 ppm for the α-protons of the ketone and a multiplet at δ 1.29 – 1.15, 1.10 – 0.98 ppm for the β-protons of the ketone. The chlorohexyne side chain’s major peaks were a triplet with J = 6.2 Hz at δ 3.65 ppm for the ε-protons of the ketone and a triplet with J =6.9 Hz at δ 2.57 ppm for the δ-protons of the ketone. The ¹³C NMR spectrum revealed peaks at δ 24.4 and 10.9 ppm for α and β-carbons of the ketone on the cyclopropyl ring, while the ketone peak was at δ 188.3 ppm. The alkyne carbon peaks were at δ 91.4 and 79.6 ppm for the β and α-carbons of the amide on the chlorohexyne chain, while the haloalkane carbon peak was at δ 43.3 ppm. The NMR spectra agreed with the literature values from Wang et al. (Table 23).
Table 23: $^1$H and $^{13}$C literature NMR spectroscopic data comparison for 6-chloro-1-cyclopropylhex-2-yn-1-one 286

<table>
<thead>
<tr>
<th>$^1$H NMR/ ppm</th>
<th>$^1$H NMR (Lit.)/ ppm</th>
<th>$^{13}$C NMR/ ppm</th>
<th>$^{13}$C NMR (Lit.)/ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.65 (t, $J = 6.2$ Hz)</td>
<td>3.62 (t, $J = 6.2$ Hz, CH$_2$Cl)</td>
<td>188.3</td>
<td>188.4 (CO)</td>
</tr>
<tr>
<td>2.57 (t, $J = 6.9$ Hz)</td>
<td>2.54 (t, $J = 6.9$ Hz, CH$_2$CH$_2$Cl)</td>
<td>91.4</td>
<td>91.4 (CH$_2$CΞC)</td>
</tr>
<tr>
<td>2.11 – 1.96 (m)</td>
<td>2.00 (m, CH$_2$CΞC, COCH)</td>
<td>79.6</td>
<td>79.6 (CH$_2$CΞC)</td>
</tr>
<tr>
<td>1.29 – 1.15 (m)</td>
<td>1.18 (m, COCH(CH$_2$CH$_2$))</td>
<td>43.3</td>
<td>43.4 (CH$_2$Cl)</td>
</tr>
<tr>
<td>1.10 – 0.98 (m)</td>
<td>1.00 (m, COCH(CH$_2$CH$_2$))</td>
<td>30.4</td>
<td>30.5 (CH$_2$CH$_2$Cl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24.4</td>
<td>24.5 (COCH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.3</td>
<td>16.4 (CH$_2$CΞC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.9</td>
<td>11 (COCH(CH$_2$CH$_2$))</td>
</tr>
</tbody>
</table>

The IR spectrum of ethyl 9-chloro-4-oxonon-5-ynoate 284 had peaks at $\nu_{\text{max}} = 2239$ and 1723 cm$^{-1}$ for the alkyne, ketone and ester carbonyl groups respectively. The $^1$H NMR spectrum revealed a quartet and triplet, both with $J = 7.1$ Hz at $\delta$ 4.15 and 1.26 ppm for the ethyl side chain, while a triplet with $J = 6.7$ Hz at $\delta$ 2.89 ppm for the $\beta$-protons of the ester and a triplet peak with $J = 6.6$ Hz at $\delta$ 2.63 ppm for the $\alpha$-protons of the ester. The chloropropyl side chain major peaks were a triplet with $J = 6.2$ Hz at $\delta$ 3.65 ppm for the $\varepsilon$-protons of the ketone and triplet with $J = 6.9$ Hz at $\delta$ 2.59 ppm for the $\gamma$-protons of the ketone.

2.21.1 Synthesis of enaminones from ethyl 6-chlorohex-2-ynoate 285

The enaminones were synthesised successfully from the reaction of ethyl 6-chlorohex-2-ynoate 285 with 3-amino-1-propanol, 4-amino-1-butanol or ethyl 4-aminobutyrate hydrochloride by heating the above ingredients under reflux in acetonitrile with sodium iodide and potassium carbonate in the presence of 4Å activated molecular sieves for between 18 – 48 hours, achieving (E)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate 288, (E)-ethyl 2-(1-(4-
hydroxybutyl)pyrrolidin-2-ylidene)acetate 281 and (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 in good yields of 81%, 70% and 74% respectively (Scheme 61: a, b, f). Ethyl 6-chlorohex-2-ynoate 285 was also converted into ethyl 6-iodohex-2-ynoate 287 in a Finkelstein reaction by heating with sodium iodide under reflux in acetone overnight, achieving a good 77% yield (Scheme 61, d.) A better conversion of 6-iodohex-2-ynoate 287 into enaminones was expected in its reaction with amines since the reaction commences with better leaving group at inception. 6-Iodohex-2-ynoate 287 was reacted with 4-amino-1-butanol or ethyl 4-aminobutyrate hydrochloride, sodium iodide, caesium carbonate and 4Å activated molecular sieves in acetonitrile for 22 hours, achieving (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281 and (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 in moderate yields of 58% and 59% respectively (Scheme 61: c, e). The yields of enaminones prepared using ethyl 6-chlorohex-2-ynoate 285 were slightly higher than those prepared from ethyl 6-iodohex-2-ynoate 287 because there was a noticeable decomposition of the 6-iodohex-2-ynoate.

![Scheme 61](image)

Scheme 61: Reagents and Conditions: (a) 3-Amino-1-propanol (1 eq), K₂CO₃ (2 eq), NaI (2 eq), 4Å molecular sieves, MeCN, 24 h at reflux, 288 = 81%; (b) 4-Amino-1-butanol (1 eq), K₂CO₃ (2 eq), NaI (2 eq), 4Å molecular sieves, MeCN, 48 h at reflux, 281 = 70%; (c) 4-Amino-1-butanol (0.83 eq), Cs₂CO₃ (2 eq), NaI (2 eq), 4Å molecular sieves, MeCN, 22 h at reflux, 281 = 58%; (d) NaI (5 eq), acetone, overnight at reflux, 287 = 77%; (e) ethyl-4-aminobutyrate hydrochloride (0.34 eq), Cs₂CO₃ (2 eq), NaI (2 eq), 4Å molecular sieves, MeCN, 22 h at reflux, 143 = 59%; (f) ethyl-4-aminobutyrate hydrochloride (1 eq), K₂CO₃ (3 eq), NaI (2 eq), 4Å molecular sieves, MeCN, 18 h at reflux, 143 = 74%.

The IR spectrum of ethyl 6-iodohex-2-ynoate 287 had peaks at ν_max = 2238 and 1708 cm⁻¹ for the alkyne and the ester carbonyl groups. The 1H NMR revealed the
ethyl side chain protons by quartet and triplet, both with $J = 7.1$ Hz at $\delta$ 4.22 and 1.31 ppm respectively. The iodoxyne side chain was shown by two triplets with $J = 6.2$ and 6.7 Hz at $\delta$ 3.66 and 3.29 ppm respectively for the $\epsilon$-protons of the ester and two triplets with $J = 7.0$ and 6.9 Hz at $\delta$ 2.55 and 2.51 ppm for the $\gamma$-protons of the ester. The $^{13}$C NMR spectrum showed peaks at $\delta$ 153.5, 87.0, and 86.7 ppm for the ethyl ester carbonyl carbon and $\beta$ and $\alpha$-carbons of the ethyl ester respectively, while the haloalkane carbon peak was at $\delta$ 4.35 ppm. The $^1$H NMR spectrum was similar to literature reported values by Pier et al. (Table 24). 

Table 24: $^1$H NMR spectroscopic data literature comparison for ethyl 6-iodohex-2-ynoate 287

<table>
<thead>
<tr>
<th>$^1$H NMR/ ppm</th>
<th>$^1$H NMR (Lit.)/ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.22 (q, $J = 7.1$ Hz)</td>
<td>4.17 (q, $J = 8$ Hz, CH$_2$CH$_3$)</td>
</tr>
<tr>
<td>3.66, 3.29 (t, $J = 6.2$ Hz); (t, $J = 6.7$ Hz)</td>
<td>3.24 (t, $J = 8$ Hz, CH$_2$I)</td>
</tr>
<tr>
<td>2.55, 2.51 (t, $J = 7.0$ Hz); (t, $J = 6.9$ Hz)</td>
<td>2.45 (t, $J = 8$ Hz, CH$_2$C≡C)</td>
</tr>
<tr>
<td>2.14 – 1.98 (m)</td>
<td>2.02 (m, CH$_2$CH$_2$I)</td>
</tr>
<tr>
<td>1.31 (t, $J = 7.1$ Hz)</td>
<td>1.26 (t, $J = 8$ Hz, CH$_2$CH$_3$)</td>
</tr>
</tbody>
</table>

The IR spectrum of (E)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate 288 had peaks $\nu_{max} = 3420$, 1726, 1658 and 1577 cm$^{-1}$ representing the alcohol OH, ester carbonyl and alkene groups. The $^1$H NMR spectrum revealed singlet at $\delta$ 4.55 ppm for the vinyl proton, a quartet and a triplet, both with $J = 7.1$ Hz at $\delta$ 4.08 and 1.25 ppm respectively for the ethyl side chain protons. The propanol side chain presented with a singlet at $\delta$ 2.32 ppm for the OH proton, a triplet with $J = 6.0$ Hz at $\delta$ 3.67 ppm for CH$_2$OH protons and a triplet with $J = 7.1$ Hz for NCH$_2$CH$_2$CH$_2$OH protons. The pyrrolidinyl ring was shown by a triplet with $J = 7.2$ Hz at $\delta$ 3.31 ppm for the $\gamma$-protons of the enaminone and a triplet with $J = 7.4$ Hz at $\delta$ 3.15 ppm for the $\alpha$-protons of the enaminone. The $^{13}$C NMR spectrum showed peaks at $\delta$ 169.7, 60.0 and 14.7 ppm for the ester carbonyl and ethyl side chain carbons respectively, while the vinyl carbon peak was at $\delta$ 77.4 ppm. The propanol side chain carbon peaks were at $\delta$ 58.3 and 52.8 ppm for the CH$_2$OH and NCH$_2$CH$_2$CH$_2$OH protons respectively. The pyrrolidinyl ring carbons were at $\delta$ 165.1 ppm for the alkene
quaternary, at δ 43.1 and 29.0 ppm for the γ and α-carbons of the enaminone respectively.

The IR spectrum of (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 had peaks at ν_{max} = 1729 and 1587 cm\(^{-1}\) for the ester carbonyl and alkene groups. The \(^1\)H NMR showed a singlet at δ 4.53 ppm for the vinyl proton and a quartet with J = 7.1 Hz at δ 4.11 ppm and multiplet at δ 1.26 ppm for the ethyl side chain of the unsaturated ester. The butanoate ester proton peaks were presented by a quartet with J = 7.1 Hz at δ 4.11 ppm and a multiplet at δ 1.26 ppm for the ethyl side chain of the saturated ester, a triplet with J = 7.1 Hz at δ 3.38 ppm for the γ-protons of the saturated ester and a triplet with J = 7.3 Hz at δ 2.32 ppm for the α-protons of the saturated ester. The pyrrolidinyl ring protons were shown by a multiplet at δ 3.23 – 3.13 ppm for the γ and α-protons of the enaminone. The \(^{13}\)C NMR spectrum showed peaks at δ 169.5, 60.6, 14.7, and 77.3, ppm for the ester carbonyl carbon, the ethyl side chain carbons and the vinyl carbons. The butanoate ester carbons were represented by peaks at δ 58.2 and 14.2 ppm for the ethyl side chain of the saturated ester and γ and α-carbons of the saturated ester at δ 52.6 and 31.4 ppm respectively. The pyrrolidinyl ring was shown by peaks at δ 169.5, 45.4 and 32.6 ppm for the quaternary alkene carbons, α and γ-carbons of the enaminone. The HRMS found [M+H]\(^+\) 270.1707 for molecular formula C\(_{14}\)H\(_{24}\)NO\(_4\) with an exact calculated mass of 270.1700.

2.21.2 C-Acylation reaction of (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate

It was then time to perform acylation cyclisation reaction to achieve (E)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 144 having successfully synthesised (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143. The acylation reaction required a mixed anhydride in order to succeed, which could be formed in situ by first converting the saturated ester into a carboxylic acid and followed by acylating it with acetic anhydride. The mixed anhydride is a better leaving group from an attack of the enaminone that uses its ambident nucleophilicity. (E)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-
yl)butanoate 143 was reacted with excess potassium hydroxide (18 equivalents) heating under reflux in methanol for 0.5 hours, followed by the addition of potassium carbonate and acetic anhydride and the reaction mixture was heated under reflux for 18 hours, resulting in (E)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 144 in poor 5% yield (Scheme 62, a). Similar reaction conditions had worked previously in synthesis of quinolizidine type alkaloids by Howard et al. within our research group.27 Was the carboxylic acid formed efficiently? Did it react to form an acid anhydride, which is the desired intermediate for acylative ring closing mechanism? Was the high equivalence of the KOH hydrolysing even the unsaturated ester? What happens to the rest of the starting material? The carboxylic acid 291 was synthesised and isolated in order to answer some of the questions. (E)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 was reacted with potassium hydroxide in a solvent mixture of tetrahydrofuran and water at room temperature overnight, achieving (E)-4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoic acid 289 quantitatively (Scheme 62, b.) The carboxylic acid was then reacted with potassium carbonate and acetic anhydride heating under reflux in acetonitrile for 18 hours, returning 29% of the acid with no desired product 144 in sight (Scheme 62, c). The suspicion was that most of the carboxylic acid was converted to a mixed anhydride but could not cyclise under the above described conditions. The mixed anhydride was then hydrolysed during the basic reaction work up followed by its loss in aqueous layer.

![Scheme 62: Reagents and Conditions: (a)(i) \textsuperscript{1}N KCF (18 eq), MeCH\textsubscript{3}, 30 min at reflux, (ii) K\textsubscript{2}CO\textsubscript{3} (2 eq), acetic anhydride (5 eq), MeCN, \textsuperscript{1}8 h at reflux, 144 \textsuperscript{2}5\% (b) KCF (1.2 eq), THF: H\textsubscript{2}O (3:2), overnight at r.t., 289 \textsuperscript{2}10\% (c) K\textsubscript{2}CO\textsubscript{3} (2 eq), acetic anhydride (5 eq), MeCN, \textsuperscript{1}41 h at reflux, 144 \textsuperscript{2}0\%.](image-url)
The IR spectrum of (E)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate had peaks at $\nu_{\text{max}} = 1738$ and 1622 cm$^{-1}$ for the ketone, ester carbonyl and alkene groups in that order. The $^1$H NMR spectrum showed a quartet and a triplet, both with $J = 7.1$ Hz at $\delta$ 4.22 and 1.30 ppm respectively for the ethyl ester side chain protons. The pyrrolidinyl ring protons were shown by a two multiplets at $\delta$ 3.50 – 3.39 and 2.74 – 2.62 ppm for the $\gamma$ and $\alpha$-protons of the enaminone. The triplets with $J = 7.1$ Hz and $J = 7.8$ Hz at $\delta$ 3.65 and 3.02 ppm respectively were for the $\gamma$ and $\alpha$-protons of the ketone finally elucidating the molecular structure. The $^{13}$C NMR showed the quaternary peaks at $\delta$ 196.2, 168.9, 168.9 and 103.0 ppm for the ketone carbonyl, ester carbonyl, and alkene $\beta$ and $\alpha$-carbons respectively. This revealed the loss of the saturated ester carbonyl and vinyl carbons. The pyrrolidinyl ring carbon peaks were at $\delta$ 50.9 and 35.5 ppm for the $\gamma$ and $\alpha$-carbons of the enaminone, while the ethyl side chain carbons were at $\delta$ 60.3 and 14.3 ppm. The remaining peaks at $\delta$ 57.3 and 42.7 ppm for the $\gamma$ and $\alpha$ of the ketone confirmed structure of the molecule.

The IR spectrum of (E)-4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoic acid had peaks at $\nu_{\text{max}} = 3600 – 3200$, 1695 and 1588 cm$^{-1}$ for the carboxylic acid OH, carboxylic acid and ester carbonyl and alkene groups respectively. The $^1$H NMR spectrum revealed the absence of the saturated esters ethyl side chain proton peaks and maintained unsaturated esters singlet at $\delta$ 4.54 ppm for the vinyl proton, a quartet and triplet, both with $J = 7.1$ Hz at $\delta$ 4.09 and 1.25 ppm for the unsaturated esters ethyl side chain, while the pyrrolidinyl ring presented with a multiplet at $\delta$ 3.27 – 3.19 and a triplet with $J = 7.8$ Hz at $\delta$ 3.15 ppm for the $\gamma$ and $\alpha$-protons of the enaminone. The singlet peak at $\delta$ 6.06 ppm was for the carboxylic acid OH proton, while the triplet with $J = 7.1$ Hz at $\delta$ 3.38 ppm and the triplet with $J = 7.3$ Hz at $\delta$ 2.38 ppm were for the $\gamma$ and $\alpha$-protons of the carboxylic acid.

The molarity of methanolic KOH was lowered to 0.3 molar trying to answer above questions. (E)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate was reacted with excess potassium hydroxide (5 equivalents) heating under reflux in methanol for 0.5 hours, followed by the addition of potassium carbonate and acetic anhydride and the reaction mixture was heated under reflux for 18 hours resulting in
(E)-methyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 290 and 4-((E)-2-(1-ethoxy-6-((E)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)-1,3-dioxohexan-2-ylidene)pyrrolidin-1-yl)butanoic acid 291 in 5% and 4% yields respectively (Scheme 63, a). This result gave a picture of competing reaction in our reaction pot which could account for very poor yields of our desired product 144 and heavy losses in mass of unreacted starting material 143.

The IR spectrum of (E)-methyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoates 290 had peaks at $\nu_{\text{max}} = 1732$ and 1660 cm$^{-1}$ for the ester carbonyl and alkene groups respectively. The $^1$H NMR spectrum showed absence of the saturated ester ethyl protons and presence of the methyl butanoate ester side chain protons by a singlet at $\delta$ 3.69 ppm for the methyl protons, a triplet with $J = 7.1$ Hz at $\delta$ 3.37 ppm for the $\gamma$-protons of the methyl ester and a triplet $J = 7.3$ Hz at $\delta$ 2.33 ppm for the $\alpha$-protons of the methyl ester. The pyrrolidinyl ring proton peaks were shown by a multiplet at $\delta$ 3.24 – 3.12 ppm for the $\gamma$-protons of the enaminone and a multiplet at $\delta$ 2.01 – 1.84 ppm for the $\alpha$-protons of the enaminone. The unsaturated ethyl ester side chain presence was shown by a singlet at $\delta$ 4.52 ppm for the vinyl proton, a quartet and triplet both with $J = 7.1$ Hz at $\delta$ 4.09 and 1.25 ppm for the ethyl side chain protons. The $^{13}$C NMR spectrum showed the unsaturated ethoxycarbonylmethylene side chain by peaks at $\delta$ 171.7, 78.0, 58.2 and 14.7 ppm for the ester carbonyl, the vinyl and the ethyl side chain carbons respectively. The pyrrolidinyl ring peaks were at $\delta$ 165.0, 45.5 and 32.7 ppm for the alkene quaternary carbon, $\gamma$-carbon of the enaminone and $\alpha$-carbon of the enaminone. The methyl butanoate side chain peaks were at $\delta$ 173.3, 52.6, 51.7 and 31.2 ppm for the

**Scheme 63:** Reagents and Conditions: (a) 0.3 M KOH (5 eq), MeOH, 1 h, (ii) K$_2$CO$_3$ (2 eq), acetic anhydride (1 eq), MeCN, 25.5 h heating under reflux, 290 = 5%, 291 = 4%
saturated ester carbonyl, the γ-carbon of the methyl ester, methyl group and α-carbon of the methyl ester.

The IR spectrum of 4-((E)-2-(1-ethoxy-6-((E)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)-1,3-dioxohexan-2-ylidene)pyrrolidin-1-yl)butanoic acid had peaks at \( \nu_{\text{max}} = 3340, 1711, 1582 \text{ cm}^{-1} \) for the carboxylic acid OH, the carboxylic acid, ester and ketone carbonyl and alkene groups respectively. The \(^1\)H NMR showed two singlet peaks at \( \delta = 8.43 \) and \( \delta = 4.53 \) for the \( \text{CO}_2\text{H} \) and vinyl protons in that order. The quartet with \( J = 7.0 \text{ Hz} \) at \( \delta = 4.21 \text{ ppm} \) and a triplet with \( J = 7.1 \text{ Hz} \) at \( \delta = 1.27 \text{ ppm} \) were for the \( \text{C}=\text{C}(\text{CO})\text{CO}_2\text{H} \) and vinyl protons of the ester, while the quartet with \( J = 7.1 \text{ Hz} \) at \( \delta = 4.08 \text{ ppm} \) and a triplet with \( J = 7.1 \text{ Hz} \) at \( \delta = 1.27 \text{ ppm} \) were for the \( \text{C}=\text{HCO}_2\text{H} \) and \( \text{C}=\text{HCO}_2\text{H} \) protons of the ester. The triplet with \( J = 7.0 \text{ Hz} \) at \( \delta = 3.38 \text{ ppm} \) and the triplet with \( J = 7.7 \text{ Hz} \) at \( \delta = 3.14 \text{ ppm} \) were for the \( \text{CH}=\text{CCH}_2\text{CH}=\text{C} \) and \( \text{CH}=\text{CCH}_2\text{CH}=\text{C} \) protons of the pyrrolidinyl ring, while the multiplet at \( \delta = 3.26–3.18 \text{ ppm} \) and a triplet with \( J = 7.8 \text{ Hz} \) at \( \delta = 3.03 \text{ ppm} \) were for the \( \text{C}=\text{CCH}_2\text{CH}=\text{C} \) and \( \text{C}=\text{CCH}_2\text{CH}=\text{C} \) protons of the pyrrolidinyl ring. The triplet with \( J = 7.1 \text{ Hz} \) at \( \delta = 3.68 \text{ ppm} \) and a triplet with \( J = 6.7 \text{ Hz} \) at \( \delta = 2.68 \text{ ppm} \) were for the \( \text{NCH}_2\text{CH}_2\text{CH}_2\text{COC}=\text{C} \) and \( \text{NCH}_2\text{CH}_2\text{CH}_2\text{COC}=\text{C} \) protons of the butanoyl link. The multiplet at \( \delta = 3.52–3.43 \text{ ppm} \) and triplet with \( J = 7.2 \text{ Hz} \) at \( \delta = 2.33 \text{ ppm} \) were for the \( \text{NCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \) and \( \text{NCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \) of the butanoyl chain. The \(^{13}\)C NMR spectrum showed peaks at \( \delta = 196.5, 169.7, 168.8, 165.1, 102.7 \text{ and } 77.8 \text{ ppm} \) for the ketone, ester \( \text{CO}_2\text{CH}=\text{C} \), \( \text{CO}_2\text{C}=\text{C} \) and carboxylic acid \( \text{CO}_2\text{OH} \) carbonyl carbons, alkene quaternary \( \text{CO}_2\text{CH}=\text{C} \), \( \text{CO}_2\text{C}=\text{C} \), \( \text{CO}_2\text{C}=\text{C} \) and vinyl \( \text{CO}_2\text{CH}=\text{C} \) carbons respectively. The remaining peaks at \( \delta = 60.3, 58.4, 57.4, 52.7, 50.9, 45.6, 42.4, 35.7, 32.7, 31.7, 26.8, 21.6, 21.1, 14.8 \text{ and } 14.3 \text{ ppm} \) confirmed the structure of the compound.

2.21.3 C-Alkylation reactions of (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate

It was time to try the alkylation cyclisation, having managed to obtain enaminone in excellent yield. This in situ transformation involves the formation of a diiodo(triphenyl)phosphorane which is attacked by alcohol resulting in a
phosphorane complex and the loss of hydrogen iodide. The complex is then attacked by iodide anion, replacing the oxygen atom resulting in (E)-ethyl 2-(1-(4-iodobutyl)pyrrolidin-2-ylidene)acetate 292, hydrogen iodide and triphenylphosphine oxide. Compound 292 then undergoes enaminone chemistry where nucleophilicity is extended from the nitrogen atom to the α-carbon of the ester and engages in $\text{S}_\text{N}2$ alkylation with haloalkane, cyclising to form (E)-ethyl 2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147. The alkylation reactions of (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281 by heating imidazole, iodine and triphenylphosphine under reflux in toluene for 2 hours proceeded with much difficulty to make (E)-ethyl 2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147 in a low 9% yield. The reaction employed conditions shown in Scheme 64 a, making (E)-ethyl 2-(1-(4-iodobutyl)pyrrolidin-2-ylidene)acetate 292 in situ followed by C-alkylation reaction, resulting in the formation of the seven-membered ring. Perhaps the low yield was due to not giving the reaction enough time. The reaction (in Scheme 64, a) was repeated, increasing the amount of time to between 18 hours and 4 days only to return tars and no desired product (Scheme 64, b; and Table 25, entries 1-3). Substituting triphenylphosphine with tri-o-tolylphosphine followed by heating under reflux in acetonitrile overnight yielded tars (Scheme 64, b; and Table 25, entry 4). (E)-Ethyl 2-(1-(4-iodobutyl)pyrrolidin-2-ylidene)acetate 292 was isolated in excellent 85% yield when vinylogous urethane 281 was heated under reflux in toluene with imidazole, iodine and triphenylphosphine for 3.75 hours (Scheme 64, c). However, cyclisation was achieved by heating compound 292 under reflux with Na$_2$HPO$_4$ in N,N-dimethylformamide for 3 hours affording (E)-ethyl 2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147 in low 25% yield (Scheme 64, d). Heating compound 292 under reflux with DBU in acetonitrile for 14 hours resulted in tars (Scheme 64, e). In view of the above result, vinylogous urethane 281 was reacted with Na$_2$HPO$_4$, iodine and triphenylphosphine heating under reflux in N,N-dimethylformamide for 3 hours, but only produced tars (Scheme 64, b; and Table 25, entry 5).
The IR spectrum of (E)-ethyl 2-(1-(4-iodobutyl)pyrrolidin-2-ylidene)acetate 292 had peaks at $\nu_{\text{max}} = 1736$ and 1631 cm$^{-1}$ for the ester carbonyl and alkene groups respectively. The $^1$H NMR spectrum revealed a singlet at $\delta = 4.51$ ppm for the vinyl proton, a quartet and a triplet, both with $J = 7.1$ Hz at $\delta = 4.09$ and 1.24 ppm respectively for the ethyl side chain protons. The butyl side chain peaks were shown by a triplet with $J = 7.1$ Hz at $\delta = 3.38$ ppm for NCH$_2$CH$_2$CH$_2$CH$_2$I protons and a multiplet at $\delta = 3.22 - 3.13$ ppm for CH$_3$I protons, where a noticeable upfield chemical shift in conversion of $\delta = 3.61$ CH$_2$OH ppm to CH$_2$I. The pyrrolidinyl ring was
represented by a multiplet at δ 3.22 – 3.13 ppm for the γ and α-protons of the enaminone. The $^{13}$C NMR spectrum showed peaks at δ 169.5 and 77.7 ppm for the ester carbonyl and vinyl carbons. The pyrrolidinyl ring carbon peaks were at δ 164.9, 52.5 and 32.7 ppm for the quaternary alkene carbon, the γ and α-carbons of the enaminone. The iodobutyl side chain peaks were at δ 45.2 for the NCH$_2$CH$_2$CH$_2$CH$_2$I carbon and at δ 5.9 ppm for CH$_2$I carbon, which is a sizeable upfield chemical shift from δ 62.0 ppm of CH$_2$OH carbon.

The IR spectrum of (E)-ethyl 2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147 had peaks at $\nu_{\text{max}}$ = 1714 and 1543 cm$^{-1}$ for the ester carbonyl and alkene groups in that order. The $^1$H NMR spectrum revealed the absence of the vinyl and CH$_2$I proton peaks which were at δ 4.51 and 5.9 ppm respectively. A quartet and a triplet both with $J$ = 7.1 Hz at δ 4.10 and 1.26 ppm respectively were for the 13-H and 14-H protons of the ethyl ester side chain. The pyrrolidinyl ring was shown by a triplet with $J$ = 6.5 Hz at δ 3.28 ppm for the 3-H protons and a triplet with $J$ = 7.6 Hz at δ 2.99 ppm for the 1-H protons. The triplet with $J$ = 6.5 Hz at δ 3.28 ppm for the 5-H protons and a multiplet at δ 2.61 – 2.57 ppm for the 8-H protons elucidated the structure of the molecule. The $^{13}$C NMR spectrum showed the absence of peaks at 77.7 and 5.87 ppm for C=CH and CH$_2$I respectively and the manifestation of peaks at 94.5 and 25.7 ppm for the C-9 and C-8 carbons respectively owing to the newly formed C-C bond. The ethyl ester peaks were at δ 170.2, 58.9 and 14.7 ppm for the C-10, C-13 and C-14 carbons respectively. The pyrrolidinyl ring presented with peaks at 165.7, 56.2 and 35.2 ppm for the C-9a, C-3 and C-1 carbons respectively, while the peak at δ 49.9 ppm was for C-5 carbon on the seven-membered ring. The NMR spectra did not agree with those reported in literature by Kim et al (Table 26).$^{111}$ Their $^1$H NMR spectrum had the right number of protons but their chemical shifts were not in accord with some of those from our spectrum. Noticeably were the missing two carbons from their $^{13}$C NMR spectrum, possibly overlapping signals but were not mentioned. Their C-5 chemical shift was more characteristic of an ester carbonyl carbon rather than enaminone quaternary carbon. Their C-6 chemical shift was off the range of being a quaternary enaminone carbon.
Table 26: Comparison of the $^1$H and $^{13}$C NMR spectra of compound 147 with literature values from Kim et al.\textsuperscript{111}

<table>
<thead>
<tr>
<th>$^1$H NMR/ ppm</th>
<th>$^1$H NMR (Lit.)/ ppm</th>
<th>$^{13}$C NMR/ ppm</th>
<th>$^{13}$C NMR (Lit.)/ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.10 (q, $J$ = 7.1 Hz, 13-H)</td>
<td>4.17 (q, $J$ = 7.1 Hz, 2H)</td>
<td>170.2 (C-10)</td>
<td>177.6</td>
</tr>
<tr>
<td>3.28 (m, 3-H)</td>
<td>3.86 – 3.81 (m, 2H)</td>
<td>165.7 (C-9a)</td>
<td>174.7</td>
</tr>
<tr>
<td>3.28 (m, 5-H)</td>
<td>2.53 – 2.46 (m, 2H)</td>
<td>94.5 (C-9)</td>
<td>60.9</td>
</tr>
<tr>
<td>2.99 (t, $J$ = 7.6 Hz, 1-H)</td>
<td>2.27 – 2.17 (m, 2H)</td>
<td>58.9 (C13)</td>
<td>60.5</td>
</tr>
<tr>
<td>2.61 – 2.57 (m, 8-H)</td>
<td>2.15 – 2.04 (m, 2H)</td>
<td>56.2 (C-3)</td>
<td>58.5</td>
</tr>
<tr>
<td>1.86 (m, C-2)</td>
<td>1.89 (tt, $J$ = 7.7, 7.7 Hz, 2H)</td>
<td>49.9 (C-5)</td>
<td>34.8</td>
</tr>
<tr>
<td>1.83 – 1.76 (m), 1.73 (m, C-6, C-7)</td>
<td>1.75 – 1.62 (m, 4H)</td>
<td>35.2 (C-1)</td>
<td>34.4</td>
</tr>
<tr>
<td>1.26 (t, $J$ = 7.1 Hz), 14-H)</td>
<td>1.25 (t, $J$ = 7.1 Hz, 3H)</td>
<td>27.6 (C-6)</td>
<td></td>
</tr>
<tr>
<td>26.0 (C-7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.7 (C-8)</td>
<td></td>
<td>24.9</td>
<td></td>
</tr>
<tr>
<td>22.3 (C-2)</td>
<td></td>
<td>23.1</td>
<td></td>
</tr>
<tr>
<td>14.7 (C-14)</td>
<td></td>
<td>14.1</td>
<td></td>
</tr>
</tbody>
</table>

In contrast, (E)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate 288 was reacted with imidazole, triphenylphosphate and iodine heating under reflux in toluene for 18 hours and met with success, achieving ethyl 1,2,3,5,6,7-hexahydroindolizine-8-carboxylate 293 in a moderate 57% yield (Scheme 65, a). This is not surprising, since Riley et al. has carried out the same reaction previously where (E)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate 288 was reacted with imidazole, triphenylphosphate and iodine heating under reflux in acetonitrile for 1 hour, producing ethyl 1,2,3,5,6,7-hexahydroindolizine-8-carboxylate 293 in a moderate 59% yield.\textsuperscript{12,113}
The IR spectrum of (E)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate 293 had peaks at $\nu_{\text{max}} = 1666$ and $1586$ cm$^{-1}$ for the ester carbonyl and alkene groups respectively. The $^{1}H$ NMR spectrum revealed the absence of the peaks at $\delta = 4.55$, 3.67 and 2.32 ppm for the vinyl, $\text{CH}_2\text{OH}$ and alcohol protons. The ethyl ester side chain was shown by a quartet and a triplet both with $J = 7.1$ Hz at $\delta = 4.11$ and 1.25 ppm for the 12-H and 13-H protons respectively. The pyrrolidinyl rings presence was shown by a triplet with $J = 7.0$ Hz at $\delta = 3.28$ and a triplet with $J = 7.8$ Hz at $\delta = 3.05$ ppm for the 3-H and 1-H protons. The piperidinyl ring presented with a multiplet at $\delta = 3.17 – 3.12$ and a triplet with $J = 6.3$ Hz at $\delta = 2.35$ ppm for 5-H and 7-H protons. The $^{13}C$ NMR spectrum revealed peaks at 168.9, 58.4 and 14.8 ppm for C-9, C12 and C-13 carbons of the ethyl ester side chain. The pyrrolidinyl ring peaks at $\delta = 159.2$, 45.0 and 32.7 ppm were for the C-8a, C-3 and C-1 carbons. The piperidinyl ring peaks at $\delta = 87.5$, 53.0 and 21.4 ppm were for C-8, C-5 and C-7 carbons. The NMR spectra were in agreement with those reported in literature by Kim et al see Table 27.$^{111}$
Table 27: Comparison of the $^1$H and $^{13}$C NMR spectra of compound 293 with literature values from Kim et al.\textsuperscript{111}

<table>
<thead>
<tr>
<th>$^1$H NMR ppm</th>
<th>$^1$H NMR (Lit.) ppm</th>
<th>$^{13}$C NMR ppm</th>
<th>$^{13}$C NMR (Lit.) ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.11 (q, $J$ = 7.1 Hz)</td>
<td>4.06 (t, $J$ = 7.1 Hz, 12-H)</td>
<td>168.9</td>
<td>168.8 (C-9)</td>
</tr>
<tr>
<td>3.28 (t, $J$ = 7.0 Hz)</td>
<td>3.24 (t, $J$ = 7.1 Hz, 3-H)</td>
<td>159.2</td>
<td>159.2 (C-8a)</td>
</tr>
<tr>
<td>3.17 – 3.12 (m)</td>
<td>3.11 (t, $J$ = 5.7 Hz, 5-H)</td>
<td>87.5</td>
<td>87.45 (C-8)</td>
</tr>
<tr>
<td>3.05 (t, $J$ = 7.8 Hz)</td>
<td>3.01 (t, $J$ = 7.6 Hz, 1-H)</td>
<td>58.4</td>
<td>58.4 (C-12)</td>
</tr>
<tr>
<td>2.35 (t, $J$ = 6.3 Hz)</td>
<td>2.31 (t, $J$ = 6.3 Hz, 7-H)</td>
<td>53.0</td>
<td>52.9 (C-5)</td>
</tr>
<tr>
<td>1.96 – 1.87 (m), 1.87 – 1.79 (m)</td>
<td>1.74 – 1.93 (m, 6-H, 2-H)</td>
<td>45.0</td>
<td>45.0 (C-3)</td>
</tr>
<tr>
<td>1.25 (t, $J$ = 7.1 Hz)</td>
<td>1.21 (t, $J$ = 7.1 Hz, 13-H)</td>
<td>32.7</td>
<td>32.7 (C-1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.6</td>
<td>21.6 (C-6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.4</td>
<td>21.4 (C-7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.0</td>
<td>21.0 (C-2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.8</td>
<td>14.8 (C-13)</td>
</tr>
</tbody>
</table>

### 2.22 Summary, Conclusion and Future prospects

The N-alkylation reactions between γ-butyrolactam 140, ethyl 4-bromobutyrate and ethyl 4-bromocrotonate in the presence of sodium hydride were unsuccessful in making lactams 141 and 174 which have a desired four carbon chain length needed to create a seven-membered ring at the penultimate step. Successful synthesis of lactams 170 and 172 suggested that the shorter chain length (two carbons) was accompanied by stronger inductive effects between the carbonyl group and halogenated carbon atom which facilitated the substitution reaction. The resonance effects of C=C bond in ethyl 4-bromocrotonate did not mimic those of allyl bromide, as seen by successful N-alkylation with 140, leading to 1-allylpyrrolidin-2-one 259. A four carbon chain lactam, 4-(2-oxopyrrolidin-1-yl)butyl benzoate 278, was successfully synthesised when 140 was reacted with 4-iodobutyl benzoate 277 using potassium bis(trimethylsilyl)amide as base. Lactam 278 was transformed into vinylogous urethane (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate
via a thionation, Eschenmoser sulphide contraction and saponification reaction, but the latter gave poor yield, forcing abandonment of the route.

The condensation reactions of γ-butyrolactone 13 with a variety of amines led to unwanted but fascinating results. The desired 1-(4-hydroxybutyl)pyrrolidin-2-one 180 was synthesised in poor yields alongside undesired 4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one 181 in a reaction of 13 with 4-aminobutan-1-ol. It was found that 5-aminopentan-1-ol reacted similarly with 13, giving desired 1-(5-hydroxypentyl)pyrrolidin-2-one 182 in poor yields and undesired 4-hydroxy-1-(piperidin-1-yl)butan-1-one 183 in moderate yield. 3-Aminopropan-1-ol gave only the desired 1-(3-hydroxypropyl)pyrrolidin-2-one 184 in high yields. Poor regioselectivity towards compound 180 led to abandoning the route, in which primary alcohol protection was to follow. More complications arose when 1,6-oxazecane-2,7-dione 186a or its polymer 186b was realised in a reaction of ethyl 4-aminobutyrate hydrochloride or 4-aminobutyric acid with 13, showing poor regioselectivity towards the desired products.

On the quest to introduce the butyl side chain of lehmizidine alkaloids, ethyl 4-oxooctanoate 188 reacted poorly with a variety of amines. Successes were observed with homoveratrylamine under classical conditions and 4-amino-1-butanol, resulting in the formation of (E)-1-(3,4-dimethoxyphenethyl)-5-butylidenepyrrolidin-2-one 193 and (E)-5-butylidene-1-(4-hydroxybutyl)pyrrolidin-2-one 198 respectively, but they could not be taken forwards owing to incompatibility and poor yields. A more compatible intermediate was finally synthesised from 188, first by converting it into a carboxylic acid and secondly transforming it into a carboxylic acid chloride in situ which reacted with ethyl 4-aminobutyrate hydrochloride to give (E)-ethyl 4-(2-butylidene-5-oxopyrrolidin-1-yl)butanoate 189 in poor yield.

Focus was placed onto reactions of 5-butyl-dihydrofuran-2(3H)-one 200 with amines in a microwave reactor, in line with achieving the butyl side chain of lehmizidines. None of the four-carbon chain amines were able to react with lactone 200, but allylamine could manage to ring open the lactone, leading to N-allyl-4-hydroxyoctanamide 202. A number of attempts to ring close 202 were taken but yielded no desired 1-allyl-5-butylpyrrolidin-2-one 203.
Synthesis of the vinylogous urethanes (E)-ethyl 2-(2-(2-ethoxy-2-oxoethyldiene)azepan-1-yl)acetate 210 and (E)-tert-butyl 2-(2-(2-ethoxy-2-oxoethyldiene)azepan-1-yl)acetate 211 was unsuccessful from thiolactams ethyl 2-(2-thiooxazepan-1-yl)acetate 208 and tert-butyl 2-(2-thiooxazepan-1-yl)acetate 209 respectively in the Eschenmoser sulphide contraction reaction with ethyl bromoacetate. Difficulties were experienced in the salt formation stage, where the salt never precipitated and required longer reaction times, which could have let adventitious moisture into the reaction vessel. This hindered exploring possibilities of building a five-membered ring onto a seven-membered ring via acylation and/or alkylation mechanisms. However, success was achieved in accessing vinylogous amides (E)-ethyl 2-(2-(2-oxo-2-phenylethylidene)azepan-1-yl)acetate 215, (E)-ethyl 2-(2-(2-(4-nitrophenyl)-2-oxoethyldiene)azepan-1-yl)acetate 216 and (E)-ethyl 2-(2-(2-(4-methoxyphenyl)-2-oxoethyldiene)azepan-1-yl)acetate 217 from the Eschenmoser sulphide contraction reaction of 208 with phenacyl bromides. The vinylogous amides 215, 216 and 217 were transformed in Knoevenagel condensation reactions into pyrroles ethyl 2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 222, ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 223 and ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 224, which contained the pyrrolo[1,2-a]azepine nuclei.

NH vinylogous amides (Z)-2-(azepan-2-ylidene)-1-phenylethanone 230, (Z)-2-(azepan-2-ylidene)-1-(4-nitrophenyl)ethanone 231 and (Z)-2-(azepan-2-ylidene)-1-(4-methoxyphenyl)ethanone 232 were synthesised successfully in the Eschenmoser sulphide contraction of thiolactam azepane-2-thione 229 with phenacyl bromides. The two carbon chain unit was introduced via a double acylation reaction of the NH vinylogous amides with oxalyl chloride, leading to 1-benzoyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 233 and 1-(4-methoxybenzoyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 235, but failed to make 1-(4-nitrobenzoyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 234. Similarly, the NH vinylogous amides (Z)-1-phenyl-2-(pyrrolidin-2-ylidene)ethanone 239, (Z)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone 240 and (Z)-1-(4-methoxyphenyl)-2-(pyrrolidin-2-ylidene)ethanone 241 were synthesised from thiolactam pyrrolidine-2-thione 6. Attempts to introduce a four-carbon chain via double acylation reaction with
succinoyl chloride (as previously described) proved ineffective, only resulting in N-acylation products in which the enaminone electron system was localised by the amide, thus it could not react further to form the seven-membered ring.

Enaminone 261 was successfully synthesised in the Eschenmoser sulphide contraction of thiolactam 260 with ethyl bromoacetate. Compound 261 was reacted with acryloyl chloride to create carbon chain length that would give rise to a seven-membered ring when Wittig reaction was applied, but an unexpected 1-allyl-6-oxo-2,3,3a,4,5,6-hexahydro-1H-indole-7-carboxylate 264 was formed, leading to abandonment of the route. This demonstrated the enaminone reactivity shown in section 1.2.3 (Figure 3, iv).

Vinylogous urethanes (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281 and (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 were obtained in moderate yields in an S_N_2/Michael addition reaction between amines and ethyl 6-chlorohex-2-ynoate 285. The alkylation and acylation reactions of 281 and 143 gave (E)-ethyl 2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147 and (E)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 144 in poor yields respectively. More research is recommended to find the suitable alkylation and acylating reaction conditions for compounds 281 and 143. A suggestion is to react 285 with 4-chlorobutan-1-amine hydrochloride 294, which may lead to the formation of 147 (Scheme 66).

![Scheme 66: Proposed transformation towards compound 147](image-url)
3.1 Cephalotaxus core

Studies towards Cephalotaxus alkaloids core required a synthesis of its derivatives in order to assess reaction reactivity along the route’s pipeline. It was essential to initially use homoveratrylamine instead of homopiperonylamine owing to their great price difference. In addition, good reactivity has been observed in similar systems owing to the electron donating effects of the methoxy groups when the starting materials were 3,4-dimethoxylaniline 312 and 3,4-dimethoxybenzylamine 313. Strides taken towards the synthesis of the Cephalotaxus core are presented, while results are discussed and detailed spectral analysis of the obtained products is presented.

3.2 Attempted synthesis of compounds 165 and 301

Our strategy towards the Cephalotaxus core depended on the Heck reaction to bring about arylation ring closure. For this a synthesis of vinylogous urethanes and amides which contained a two-carbon chain between the nitrogen atom and the brominated aryl group was needed. This would allow the creation of a seven-membered ring via intramolecular arylation reaction. The strategy entails initial condensation between γ-butyrolactone 13 and homoveratrylamine 160 to make 1-(3,4-dimethoxyphenethyl)pyrrolidin-2-one 161 (Scheme 6). Lactam 161 could then be brominated with bromine in the presence of acetic acid giving brominated lactam 162. Brominated lactam 162 could be thionated with phosphorus pentasulphide leading to the thiolactam 163. Vinylogous urethanes 164 and vinylogous amide 299 could then be synthesised from the Eschenmoser sulphide contraction reaction of thiolactam 163 with various α-halocarbonyl compounds. The Heck reaction would be applied to couple the aryl bromide with vinyl carbon atoms resulting in ethyl 8,9-dimethoxy-2,3,5,6-tetrahydro-1H-benzo[d]pyrrolo[1,2-a]azepine-11-carboxylate 165 and ethyl 2-(8,9-dimethoxy-
2,3,5,6-tetrahydro-1H-benzo[d]pyrrolo[1,2-a]azepin-11-yl)-2-oxoacetate \textsuperscript{301}.\textsuperscript{79,80} In this Heck reaction, it is assumed that oxidative addition of palladium(0) to the aromatic bromide precedes nucleophilic attack by the enaminone onto the aromatic ring. This leads to syn addition of Pd and Ar to the C=C bond. The subsequent β-hydride elimination of Pd probably occurs with ring hydrogen at C-3 to give a pyrroline, which then tautomerises to give more stable enaminone.

Homoveratrylamine and butyrolactone were reacted neat in a microwave reactor at 150 W, 220 °C for between 1 and 1.33 hours, making 1-(3,4-dimethoxyphenethyl)pyrrolidin-2-one \textsuperscript{161} in excellent 90% yield (\textbf{Scheme 67}, a). The resulting lactam \textsuperscript{161} was brominated exclusively at C-4 by liquid bromine in acetic acid for 1 hour at room temperature, achieving 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-one \textsuperscript{162} in an excellent 96% yield (\textbf{Scheme 67}, b). The brominated lactam \textsuperscript{162} was reacted with P\textsubscript{2}S\textsubscript{5} in dichloromethane at room temperature for 17 hours in a thionation reaction, replacing the carbonyl group with the thionyl group to give 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidine-2-thione \textsuperscript{163} in excellent 98% yield (\textbf{Scheme 67}, c). The brominated thiolactam \textsuperscript{163} was then transformed to enaminone (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate \textsuperscript{164} in an Eschenmoser sulphide contraction reaction in excellent 80% yield by reacting with ethyl bromoacetate in acetonitrile at room temperature for 24 hours; after the salt had precipitated, this was followed by addition of a solution of triethylamine and triphenylphosphine and left to react at room temperature for 20 hours (\textbf{Scheme 67}, d).
Alternatively, commercially available ethyl bromopyruvate was reacted with thiolactam 163 in acetonitrile at room temperature for 3 hours, and after the salt had precipitated this was followed by the addition of a solution of triethylamine and triphenylphosphine in acetonitrile and reacted for 20 hours at room temperature to give (E)-ethyl 3-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)-2-oxopropanoate 299 in 84% yield (Scheme 67, e).

1-(3,4-Dimethoxyphenethyl)pyrrolidin-2-one 161 had a melting point of 58 – 59 °C. The IR spectrum revealed peaks at \( \nu_{\text{max}} = 1689 \) and 1451 cm\(^{-1} \) for the amide carbonyl and aromatic functional groups. The \(^1\)H NMR spectrum showed multiplets at \( \delta = 6.84 - 6.72 \) ppm for the aromatic protons, a singlet at \( \delta = 3.87 \) ppm for the two methoxy groups protons and two multiplets at \( \delta = 3.56 - 3.47 \) and 2.84 – 2.75 ppm for the NCH\(_2\)CH\(_2\)-Ar and NCH\(_2\)CH\(_2\)-Ar protons of the 3,4-dimethoxyphenethyl side chain. The pyrrolidinone ring was shown by a triplet peak with \( J = 7.0 \) Hz at \( \delta = 3.27 \) ppm for the \( \gamma \)-protons of the lactam and a triplet with \( J = 8.1 \) Hz at 2.36 ppm for \( \alpha \)-protons of the lactam protons. The \(^{13}\)C NMR spectrum revealed peaks at \( \delta = 148.9, 147.6, 131.3, 120.6, 111.9 \) and 111.3 ppm for C-3, C-4, C-1, C-6, C-5 and C-2 carbons, while the two methoxy carbon peaks were at \( \delta = 55.9 \) ppm and the ethyl side chain peaks were at \( \delta = 47.7 \) and 33.3 ppm for the NCH\(_2\)CH\(_2\)-Ar and NCH\(_2\)CH\(_2\)-Ar
The pyrrolidinone ring carbon peaks at δ 175.0, 44.1 and 31.0 ppm were for the carbonyl, γ and α-carbons of the lactam.

The IR spectrum of 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-one 162 had peaks at $\nu_{\text{max}} = 1689$ and 1586 cm$^{-1}$ for the amide and the aromatic groups respectively. The $^1$H NMR revealed the reduction of the number of aromatic protons from three to two, shown by two singlet peaks at δ 7.00 and 6.79 ppm for 3-H and 6-H respectively, proving that bromine was attached adjacent to the carbon chain. The $^{13}$C NMR spectrum showed an up field chemical shift of the corresponding aromatic carbon C-2, which had shifted from δ 120.6 ppm to δ 114.0 ppm owing to the electron donating effect of the bromine atom.

The IR spectrum of 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidine-2-thione 163 had a peak at $\nu_{\text{max}} = 1591$ and 1123 cm$^{-1}$ for the aromatic and sulphur carbonyl groups. The $^1$H NMR spectrum revealed a slight downfield chemical shift for all peaks due to the electron withdrawing abilities of the sulphur atom, a triplet with $J = 7.4$ Hz at δ 3.95 ppm for NCH$_2$CH$_2$-Ar and a triplet with $J = 7.2$ Hz at δ 3.08 ppm for NCH$_2$CH$_2$-Ar. The pyrrolidinethione ring was shown by a triplet with $J = 7.2$ Hz at δ 3.75 ppm for the γ-protons of the thiolactam and a triplet with $J = 8.0$ Hz at δ 3.00 ppm for the α-protons of the thiolactam. The $^{13}$C NMR spectrum showed a peak at δ 201.0 ppm for the thioacarbonyl carbon, revealing the absence of lactam carbonyl peak at δ 174.9 ppm in the spectrum of 162. The pyrroldinethione ring peaks shifted downfield to δ 55.7 and 44.9 ppm respectively for the γ and α-carbons of the thiolactam.

The IR spectrum of (E)-ethyl 2-((1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 164 had peaks at $\nu_{\text{max}} = 1678$ and 1585 cm$^{-1}$ for the ester and alkene groups respectively. The $^1$H NMR revealed a singlet at δ 4.65 ppm for the vinyl proton, a quartet and a triplet both with $J = 7.1$ Hz at δ 4.11 and 1.29 ppm for the ethyl side chain protons, confirming the success of the Eschenmoser sulphide contraction reaction. The triplet with $J = 7.5$ Hz at δ 3.15 ppm for the enaminone α-protons was suggestive of the E geometry since the protons were de-shielded through space by the ester oxygen atom. The $^{13}$C NMR spectrum revealed the absence of the thiocarbonyl carbon peak at δ 201.0 ppm and the presence of the alkene quaternary carbon peak at δ 164.5 ppm. The ethoxycarbonylmethylene side
chain peaks were at δ 169.4, 77.9, 58.2 and 14.7 ppm for the ester carbonyl, the vinyl and the ethyl side chain carbons respectively.

The IR spectrum of (E)-ethyl 3-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)-2-oxopropanoate 299 had peaks at ν_{max} = 1702, 1685 and 1556 cm⁻¹ representing the ketone, ester, vinyl and aromatic alkene groups. The ¹H NMR spectrum revealed a singlet at δ 5.94 ppm for the vinyl proton, quartet and triplet both with J = 7.1 Hz at δ 4.28 and 1.35 ppm respectively for the ethyl side chain protons. The triplet with J = 7.8 Hz at δ 3.29 ppm for the enaminone α-protons was suggestive of the E geometry since the protons were deshielded through space by the ester oxygen atom. The ¹³C NMR spectrum revealed the absence of the thiocarbonyl carbon peak at δ 201.0 ppm and the presence of the quaternary alkene carbon peak at δ 171.0 ppm, while the ethyl 2-oxopropanoate side chain peaks were at δ 175.8, 165.9, 86.3, 61.9 and 14.1 ppm for the ketone carbonyl, ester carbonyl, vinyl and the ethyl side chain carbons respectively.

The Heck coupling reactions was attempted on both (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 164 and (E)-ethyl 3-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)-2-oxopropanoate 299 (Scheme 67, f). Compounds 164 and 299 were both reacted (in separate reactions) with catalytic amount of palladium acetate, tri-o-tolylphosphine as the activating ligand and triethylamine as a base heating under reflux in a solvent mixture of N,N-dimethylformamide, acetonitrile and water overnight according to a method previously optimised for similar reactions.⁷⁹ The results were a recovery of the enaminones 164 and 299 in 88% and 29% yield respectively and some tars. This is an indication that the reactions probably never went past the oxidative addition stage where the activate palladium(0) adds across the carbon halide bond. However, this may also suggest that the palladium(0) catalyst never formed in the first place. The precedent is that compound 38 was arylated forming compound 39 as shown in Scheme 8, section 1.3.3.1 under the same above Heck coupling reaction conditions. Perhaps, the methyl substituent with less electron donating ability in compound 38 promotes the oxidative addition of palladium(0) across the carbon halide bond as compared to the methoxy group substituent with more electron donating ability in compounds 165 and 299, which disfavours the oxidative addition of palladium(0). In addition, compound 39’s formation may be favoured since a five-membered ring is
formed compared to seven-membered ring that would be formed had compounds 165 and 301 been synthesised.

### 3.3 Alternative attempts to synthesise compound 165

A direct coupling reaction between the vinyl and the aryl groups was attempted, having been inspired by alkene to aryl coupling methods.\(^{139,140}\) The coupling in the first of these reported methods relied on the use of palladium acetate as the catalyst and a co-catalyst to regenerate the palladium acetate catalyst at the end of the cycle. The second method reported the synthesis of various carbazoles in a one pot N-arylation and coupling between aryl triflates and aniline in the presence of palladium acetate and acetic acid, with oxygen as the oxidant. The enaminone (as an electron-rich nucleophile) would be able to mimic the role of the electron-rich aromatic nucleophile in the second method, as well as in some alternative methods to be described below.

Compound 161 (prepared as described previously) was transformed into 1-(3,4-dimethoxyphenyl)pyrrolidine-2-thione 302 in moderated yields between 51 – 77\% using phosphorus pentasulphide as the thionating agent in dichloromethane at room temperature overnight (Scheme 68, b). Loss in yield may be due to the tars formed at the bottom of the round bottom flask which were insoluble in dichloromethane. (E)-Ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 was then achieved in yields between 35 – 60\% in an Eschenmoser sulphide contraction reaction of 302 with ethyl bromoacetate in acetonitrile at room temperature overnight after which the salt had precipitated. The reaction was completed by the addition of a solution of triethylamine and triphenylphosphine in acetonitrile and left to react at room temperature overnight to induce sulphur extrusion. A lower equivalence of triphenylphosphine and triethylamine plus leaving the Eschenmoser salt formation step for longer hours ensured higher yields (Scheme 68, c, d). The enaminone 303 was then subjected to a number of coupling reactions utilising reagents in Scheme 68, e.
Wurtz et al. demonstrated an efficient synthesis of indoles from anilines by a palladium-catalysed intramolecular oxidative coupling. They used palladium(II) acetate as the catalyst, copper(II) acetate as the oxidant to reoxidise Pd\(^0\) complexes to Pd\(^{II}\) and potassium carbonate as the base in N,N-dimethylformamide. The optimal conditions for para-substituted anilines were reacting at 140 °C.\(^{138,138}\) (E)-Ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 was reacted under these conditions for 18 h, returning 86% of compound 303 after purification (Table 28, entry 1). Vinylogous urethane 303 was not a suitable substrate for this transformation under the above reaction conditions. The reason maybe that compound 303 had a tertiary amine while anilines had secondary amine where the NH proton was crucial in reaction mechanism.

Fujiwara et al. reported the arylation of arenes with olefins by palladium(II) acetate in acetic acid in the presence of air for a few minutes to several hours resulting in high yields of arylated products.\(^{143}\) The co-catalyst was therefore changed from copper(II) acetate to oxygen gas by heating (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 under reflux with palladium(II) acetate in acetic acid while bubbling oxygen gas for 1 hour. This also returned compound 303 in high 80% yield (Table 28, entry 2).\(^{140}\)
Scheme 68: Reagents and Conditions: (a) (i) Dicyclohexylcarbodiimide (1 eq)  and 2-(3,4-dimethoxypyridine)ethylenediamine (1 eq), reflux, 150 °C, 1 h, (b) 1,3-Dimethylimidazolidin-2-one (1 eq), reflux, 150 °C, 1 h, (c) Cu(OAc)₂, K₂CO₃, 80 °C, 10 h, (d) Cu(OAc)₂, 150 °C, 10 h, (e) Cu(OAc)₂, 80 °C, 10 h, (f) Cu(OAc)₂, 150 °C, 10 h, (g) Cu(OAc)₂, 80 °C, 10 h, (h) Cu(OAc)₂, 150 °C, 10 h, (i) Cu(OAc)₂, 80 °C, 10 h, (j) Cu(OAc)₂, 150 °C, 10 h, (k) Cu(OAc)₂, 80 °C, 10 h, (l) Cu(OAc)₂, 150 °C, 10 h, (m) Cu(OAc)₂, 80 °C, 10 h, (n) Cu(OAc)₂, 150 °C, 10 h, (o) Cu(OAc)₂, 80 °C, 10 h, (p) Cu(OAc)₂, 150 °C, 10 h, (q) Cu(OAc)₂, 80 °C, 10 h, (r) Cu(OAc)₂, 150 °C, 10 h, (s) Cu(OAc)₂, 80 °C, 10 h, (t) Cu(OAc)₂, 150 °C, 10 h, (u) Cu(OAc)₂, 80 °C, 10 h, (v) Cu(OAc)₂, 150 °C, 10 h, (w) Cu(OAc)₂, 80 °C, 10 h, (x) Cu(OAc)₂, 150 °C, 10 h, (y) Cu(OAc)₂, 80 °C, 10 h, (z) Cu(OAc)₂, 150 °C, 10 h.

Table 28: Various coupling reactions of compound 303

<table>
<thead>
<tr>
<th>No.</th>
<th>Reagents</th>
<th>Conditions</th>
<th>Solvents</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>(0.1 eq) Pd(OAc)₂, (3 eq) Cu(OAc)₂, (3 eq) K₂CO₃</td>
<td>140 °C, 18 h</td>
<td>DMF</td>
<td>165 = 0%; 303 = 86%</td>
</tr>
<tr>
<td>2.</td>
<td>(0.1 eq) Pd(OAc)₂, bubbling O₂ gas</td>
<td>Reflux, 1 h</td>
<td>Acetic acid</td>
<td>165 = 0%; 303 = 86%</td>
</tr>
<tr>
<td>3.</td>
<td>(0.1 eq) Pd(OAc)₂, bubbling O₂ gas</td>
<td>100 °C, 1 h</td>
<td>DMF</td>
<td>165 = 0%; 303 = 86%</td>
</tr>
<tr>
<td>4.</td>
<td>(0.4 eq) Pd(OAc)₂, (1.6 eq) P(o-tolyl)₃, (10.6 eq) TEA</td>
<td>55 °C, 22 h</td>
<td>DMF, MeCN, H₂O</td>
<td>165 = 0%; 303 = 79%</td>
</tr>
<tr>
<td>5.</td>
<td>(10 eq) FeCl₃</td>
<td>r.t.</td>
<td>DCM</td>
<td>165 = 0%; 303 = 93%</td>
</tr>
</tbody>
</table>

Changing the solvent from acetic acid to N,N-dimethylformamide had no benefit for the reaction. (E)-Ethyl 2-(1-(3,4-dimethoxypyridin-2-ylidene)acryloyl)acetate 303 was reacted with palladium(II) acetate in N,N-dimethylformamide while bubbling oxygen gas at 100 °C for 1 hour, but this returned 86% of compound 303 after...
purification (Table 28, entry 3). In another attempt, (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 was reacted with tri-o-tolylphosphine and triethylamine in a mixture of acetonitrile, N,N-dimethylformamide and water as solvents at 55 °C for 22 hours, returning 79% of compound 303 (Table 28, entry 4).

Iron(III) chloride has been used as a mild oxidising agent in oxidative carbon-carbon coupling reactions between arenes. Arenes were reacted with iron(III) chloride in dichloromethane at room temperature for 3 hours, resulting in desired products.123,124 The iron(III) chloride could oxidise the aromatic ring of compound 303 followed by a nucleophilic carbon attack from the enaminone system, coupling the vinyl to the aromatic carbon (C-4). (E)-Ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 was reacted with iron(III) chloride in dichloromethane at room temperature for 23 hours, resulting in the return of compound 303 in 93% yield (Table 28, entry 5).

The IR spectrum of 1-(3,4-dimethoxyphenethyl)pyrrolidine-2-thione 302 revealed the absence of the amide carbonyl peak and had a peak at \( \nu_{\text{max}} = 1456 \text{ cm}^{-1} \) for the aromatic group. The \(^1\)H NMR spectrum revealed a downfield chemical shift of proton peaks due to stronger electron withdrawing sulphur atom as compared to the oxygen atom, while ring and methoxy proton peaks were not affected by the change. The comparison changes are listed in Table 26. The \(^{13}\)C NMR spectrum revealed the absence of the amide carbonyl carbon peak at \( \delta = 175.0 \text{ ppm} \) and the presence of the thiocarbonyl carbon peak at \( \delta = 200.6 \text{ ppm} \). The remainder of the carbon peaks showed a slight downfield chemical shift at seen from Table 29.
Table 29: Comparison of the $^1$H and $^{13}$C NMR spectra of lactam 161 and thiolactam 302

<table>
<thead>
<tr>
<th>161 $^1$H NMR /ppm</th>
<th>302 $^1$H NMR /ppm</th>
<th>161 $^{13}$C NMR /ppm</th>
<th>302 $^{13}$C NMR /ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.56 – 3.47 (m)</td>
<td>3.95 (t, $J = 7.4$ Hz, NCH$_2$CH$_2$Ar)</td>
<td>47.7</td>
<td>55.6 (NCH$_2$CH$_2$Ar)</td>
</tr>
<tr>
<td>3.27 (t, $J = 7.0$ Hz)</td>
<td>3.52 (t, $J = 7.3$ Hz, $\gamma$-protons)</td>
<td>44.1</td>
<td>49.4 ($\gamma$-carbon)</td>
</tr>
<tr>
<td>2.36 (t, $J = 8.1$ Hz)</td>
<td>3.05 – 2.87 (m, $\alpha$-protons)</td>
<td>33.3</td>
<td>44.9 (NCH$_2$CH$_2$Ar)</td>
</tr>
<tr>
<td>2.84 – 2.75 (m)</td>
<td>3.05 – 2.87 (m, NCH$_2$CH$_2$Ar)</td>
<td>31.0</td>
<td>31.7 ($\alpha$-carbon)</td>
</tr>
</tbody>
</table>

The melting point of (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2ylidene)acetate 303 was 108 – 109 °C. The IR spectrum revealed peaks at $\nu_{\text{max}} = 1668$ and 1585 cm$^{-1}$ for the ester carbonyl and the vinyl groups. The $^1$H NMR spectrum revealed new peaks, a singlet at $\delta = 4.61$ ppm for the vinyl peak and a triplet and a quartet, both with $J = 7.1$ Hz at $\delta = 4.11$ and 1.27 ppm respectively, for the ethyl side chain, confirming the formation of the unsaturated ester. The reduced electron withdrawing effect from the unsaturated ester produced an upfield chemical shift of the peaks, as shown in Table 30.

Table 30: Comparison of the $^1$H NMR spectra of thiolactam 302 and vinylogous urethane 303

<table>
<thead>
<tr>
<th>302 $^1$H NMR /ppm</th>
<th>303 $^1$H NMR /ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.92</td>
<td>3.39 (t, $J = 7.3$ Hz, NCH$_2$CH$_2$Ar)</td>
</tr>
<tr>
<td>3.52</td>
<td>3.16 (m, $\varepsilon$-protons)</td>
</tr>
<tr>
<td>3.05 – 2.87</td>
<td>2.80 (t, $J = 7.3$ Hz, $\gamma$-protons)</td>
</tr>
<tr>
<td>3.05 – 2.87</td>
<td>3.16 (m, NCH$_2$CH$_2$Ar)</td>
</tr>
</tbody>
</table>
Compound 303 had an E geometry as indicated by the through-space deshielding of γ-protons of the unsaturated ester. The $^{13}$C NMR spectrum revealed the absence of the thiocarbonyl peak at δ 200.6 ppm and the presence of peaks at δ 169.5, 164.5, 77.6, 58.2 and 14.8 ppm for the ester carbonyl, the quaternary alkene, vinyl and ethyl side chain carbons respectively. The remainder of the carbon peaks remained relatively unchanged except for the CH$_2$Ar peak which shifted up field to 32.7 ppm from 44.9 ppm. The HRMS spectrum found [M+H]$^+$ 320.1853 for a molecular formula C$_{18}$H$_{26}$NO$_4$ with an exact calculated mass of 320.1856.

Attempts were made to form five-membered and six-membered rings since forming a seven-membered ring was a challenge under the oxidative coupling reaction conditions. Compounds 304 (with no CH$_2$ link between nitrogen atom and aryl group) and 307 (with one CH$_2$ link between nitrogen atom and aryl group) would make these transformations possible. Thus (E)-ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 304 (synthesised in section 3.4; see below) was heated under reflux (80 °C) with palladium(II) acetate in acetic acid under oxygen atmosphere (balloon) for 1 hour resulting in formation of an unexpected ethyl 2-(1-(3,4-dimethoxyphenyl)-1H-pyrrol-2-yl)acetate 305 in 14% yield and decomposed tars (Scheme 69, a). The reaction gave the desired ethyl 6,7-dimethoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate 306 in 14% yield and decomposed tars when the reaction temperature was reduced to 55 °C. Further attempts to improve the yields were unsuccessful.

![Scheme 69: Reagents and Conditions: (a) Pd(OAc)$_2$ (0.1 eq), O$_2$ balloon, acetic acid, 1 h at reflux (80°C), 305 = 14%; (b) Pd(OAc)$_2$ (0.1 eq), O$_2$ balloon, acetic acid, 1 h at 55 °C, 305 = 14%.

The IR spectrum of ethyl 2-(1-(3,4-dimethoxyphenyl)-1H-pyrrol-2-yl)acetate 305 had peaks at $\nu_{max} = 1730$ and 1435 cm$^{-1}$ for the ester carbonyl and aromatic groups. The
$^1$H NMR spectrum revealed the absence of the vinyl peak which was at $\delta$ 4.65 ppm in 306's $^1$H NMR spectrum and the presence of a singlet at $\delta$ 3.56 ppm for $\alpha$-protons of the ethyl ester. The pyrrole ring was represented by a multiplet at $\delta$ 6.80 – 6.75 ppm for the $\varepsilon$-proton and a multiplet at $\delta$ 6.31 – 6.14 ppm for the $\gamma$ and $\delta$-protons of the ethyl ester revealing the absence of the pyrrolidinyl ring proton peaks which were at $\delta$ 3.63, 3.23 and 2.02 ppm of 304's $^1$H NMR spectrum. The $^{13}$C NMR spectrum revealed the absence of the vinyl and quaternary carbon peaks which were at $\delta$ 80.7 and 164.8 ppm in 304's $^1$H NMR spectrum and the presence of pyrrol peaks at $\delta$ 125.8, 122.7, 110.4 and 109.3 ppm for the $\beta$, $\varepsilon$, $\gamma$ and $\delta$ carbons of the ethyl ester respectively. The $\alpha$-carbon peak to the ester group registered at $\delta$ 32.7 ppm. The HRMS found [M+H]$^+$ equal to 290.1319 for a molecule with a molecular formula C$_{16}$H$_{20}$NO$_4^+$ with an exact calculated mass of 290.1387.

The IR spectrum of ethyl 6,7-dimethoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate 306 showed peaks at $\nu_{\text{max}}$ = 1678 and 1579 – 1427 cm$^{-1}$ for the ester carbonyl and aromatic groups. The $^1$H NMR spectrum revealed the absence of the vinyl singlet at $\delta$ 4.65 ppm in 304's $^1$H NMR spectrum. The aromatic peaks resolved to two singlets at $\delta$ 7.63 and 6.75 ppm for 8-H and 5-H protons, from three proton peaks previously observed in 304's $^1$H NMR spectrum. The $^{13}$C NMR spectrum revealed the absence of the vinyl carbon peak at $\delta$ 80.7 ppm in 306's $^1$H NMR spectrum and the presence of a quaternary alkene carbon peak at $\delta$ 99.0 ppm for C-6. The newly formed quaternary aromatic carbon peak C-9 was at $\delta$ 124.1 ppm, a downfield shift from $\delta$ 117.5 ppm in 304's $^{13}$C NMR spectrum due to added electron delocalisation by the ester group. The aromatic carbon peaks C-8 and C-5 shifted up field to $\delta$ 103 and 93.5 ppm respectively from 111.6 and 109.0 ppm in 304's $^{13}$C NMR spectrum. The remainder of the quaternary and pyrrolidinylidene ring carbon peaks slightly shifted up field except for $\delta$-carbon peak which shifted downfield. The HRMS found [M+H]$^+$ equal to 290.1389 for a molecule with molecule formula C$_{16}$H$_{20}$NO$_4^+$ and exact calculated mass of 290.1387.

(E)-Ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307 (synthesised in section 3.4; see below) was also reacted with palladium(II) acetate to observed whether it would give the desired products 308 (E)-ethyl 2-(1-(3,4-
dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307 was heated under reflux (80 °C) with palladium(II) acetate in acetic acid under oxygen atmosphere for 24 hours resulting in unidentified by-products (Scheme 70, a). The reaction of compound 307 returned tars and 18% of starting material when the temperature was reduced to 50 °C (Scheme 70, b).

![Scheme 70: Reagents and Conditions: (a) Fc(CAC)₂ (C₁.₁ eq), C₂ ballor, acetic acid, 1 - 24 h at reflux, 308 = 0%; (b) Fc(CAC)₂ (C₁.₁ eq), C₂ ballor, acetic acid, 4 h at 50 °C, 308 = 0%.](image)

The coupling reactions for compounds 303 and 307 in Scheme 64 and Scheme 66 respectively may have failed due to difficulties in creating six-membered and seven-membered rings as compared to making five-membered rings via arylation, even though the synthesis of compound 306 was demonstrated in significantly poor yields. The lack of CH₂ link between the nitrogen atom and the aryl group on 306 influences the electronics of the aryl group. The nitrogen atom together with OMe (C-3) activate C-6 on the aryl group making it more nucleophilic as compared to C-6 from compounds 307 and 303 which have carbon linkers between the nitrogen atom and aryl group.

### 3.4 Attempted synthesis of compounds 165, 306 and 308

The following reactions were done in comparison to each other. The coupling reactions were of interest, to see whether they would differ from reaction to reaction in terms of results when forming a five-membered ring versus forming a six-membered ring versus forming a seven-membered ring. Thiolactams 1-(3,4-
dimethoxyphenyl)pyrrolidine-2-thione 309, 1-(3,4-dimethoxybenzyl)pyrrolidine-2-thione 310 and 1-(3,4-dimethoxyphenethyl)pyrrolidine-2-thione 302 were synthesized in excellent yields of 88%, 77% and 86% respectively over two steps. The first step was the reaction of γ-butyrolactone 13 with 3,4-dimethoxylaniline, 3,4-dimethoxybenzylamine or homoveratrylamine neat in a microwave reactor at 150 W, 220 ºC for 1 hour to yield the desired corresponding lactams, which were not characterized, but reacted further after reaction work up (Scheme 71, a [i]). The second step involved the thionation of the lactams using phosphorus pentasulphide in dichloromethane at room temperature for 18 hours to achieve the thiolactams 309, 310 and 302 respectively (Scheme 71, a [ii]).

![Scheme 71: Reagents and Condition:](image)

The IR spectrum of 309 had peaks at $\nu_{\text{max}} = 1509$ cm$^{-1}$ for the aromatic ring. The $^1$H NMR spectrum showed a doublet with $J = 2.2$ Hz at δ 7.18 ppm for the 2-H proton, a doublet of doublets with $J = 8.6, 2.2$ Hz at δ 6.97 ppm for the 6-H proton, a doublet with $J = 8.6$ Hz at δ 6.92 ppm for the 5-H proton and a singlet at δ 3.91 ppm for the methoxy protons, all representative of the aromatic ring. The pyrrolidinethione ring protons was shown by a triplet with $J = 7.2$ Hz at 4.12 ppm for the γ-protons and a triplet with $J = 7.9$ Hz at 3.25 ppm for the α-protons of the thiolactam. The $^{13}$C NMR spectrum revealed the thiocarbonyl peak at δ 202.5 ppm, while the remainder of
pyrrolidinethione ring’s presence was shown by peaks at δ 59.1 and 46.3 ppm for the γ and α-carbons of the thiolactam respectively. The aromatic ring was shown by peaks at δ 149.0, 148.3, 133.6, 116.9, 111.0 and 108.9 ppm for C-4, C-3, C-1, C-5, C-6 and C-2 respectively, while the methoxy carbon peaks were at δ 56.1 and 56.0 ppm.

The IR spectrum of 310 showed a peak at $\nu_{\text{max}} = 1514$ cm$^{-1}$ for the aromatic alkene. The $^1$H NMR spectrum a doublet with $J = 1.7$ Hz at δ 6.95 ppm for the 2-H proton, a doublet of doublet with $J = 8.2, 1.7$ Hz at δ 6.87 ppm for the 6-H proton, a doublet with $J = 8.1$ Hz at δ 6.82 ppm for 5-H proton and two singlets at δ 3.88 and 3.87 ppm for the methoxy protons, all representative of the aromatic ring. The benzyl protons were represented by a singlet at δ 4.92 ppm. The pyrrolidinethione ring was shown by a triplet with $J = 7.2$ Hz at 3.59 ppm for the γ-protons and a triplet with $J = 7.9$ Hz at 3.09 ppm for the α-protons. The $^{13}$C NMR spectrum revealed the thiocarbonyl carbon peak at δ 201.3 ppm, while the remainder of pyrrolidinethione rings presence was shown by peaks at δ 53.9 and 45.0 ppm for the γ and α-carbons of the thiolactam respectively. The benzyl carbon peak was at δ 51.4 ppm. The aromatic ring was shown by peaks at δ 149.2, 148.9, 127.8, 120.9, 111.6 and 111.0 ppm for C-3, C-4, C-1, C-6, C-2 and C-5 respectively, while the methoxy carbon peaks were at δ 56.0 and 55.9 ppm. The spectra for compound 302 were discussed in section 3.3.

The thiolactams 309, 310 and 302 were then subjected to the Eschenmoser sulphide contraction reaction with ethyl bromoacetate in acetonitrile at room temperature for 3 hours, followed by the addition of a solution of triethylamine and triphenylphosphine in acetonitrile and left to react at room temperature for 20 hours. The respective vinylogous urethanes (E)-ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 304 and (E)-ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307 were obtained in excellent 87% and 84% yields respectively, but (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 was achieved in 60% yield (Scheme 71, b).
The IR spectrum of 304 showed peaks at $\nu_{\text{max}} = 1671, 1577, 1505 \text{ and } 1450 \text{ cm}^{-1}$ for the ester carbonyl, the vinyl and aromatic alkene groups respectively. The $^1$H NMR spectrum revealed the presence of the unsaturated ester by singlet at $\delta$ 4.72 ppm for the vinyl proton and a quartet and a triplet both with $J = 7.1 \text{ Hz}$ at $\delta$ 4.06 and 1.21 ppm respectively for the ethyl side chain. The pyrrolidinylidene ring was shown by a triplet with $J = 7.0 \text{ Hz}$ at $\delta$ 3.69 ppm for $\epsilon$-protons and a triplet with $J = 7.8 \text{ Hz}$ at $\delta$ 3.31 ppm for the $\gamma$-protons of the unsaturated ethyl ester. The chemical shift of $\gamma$-protons suggested deshielding of the protons through space, hence the E geometry. The aromatic alkene proton peaks were similar to those described in 309 $^1$H NMR spectrum. The $^{13}$C NMR spectrum revealed the absence of the thioamide carbonyl peak which was at $\delta$ 202.5 ppm of 309's $^{13}$C NMR spectrum and the presence of the ester carbonyl carbon peak at $\delta$ 169.5 ppm, the quaternary alkene carbon peak at $\delta$ 164.9 ppm and the vinyl carbon peak at $\delta$ 80.7 ppm. The pyrrolidinylidene ring carbon peaks shifted up field to $\delta$ 55.1 and 32.5 ppm for $\epsilon$ and $\gamma$-carbon of the unsaturated ethyl ester respectively, from $\delta$ 55.1 and 56.0 ppm in that order owing to lesser inductive effects from the unsaturated alkene as compared to the sulphur atom.

The IR spectrum of 307 showed peaks at $\nu_{\text{max}} = 1743$ and 1524 cm$^{-1}$ for the ester carbonyl and aromatic alkene groups. The $^1$H NMR spectrum revealed the presence of the unsaturated ester group by a triplet and a quartet, both with $J = 7.1 \text{ Hz}$ at $\delta$ 4.07 and 1.22 ppm respectively for the ethyl side chain protons and a singlet at $\delta$ 4.69 ppm for the vinyl proton, indicating the success of the Eschenmoser sulphide contraction reaction. The molecule had E geometry as indicated by deshielded $\gamma$-protons of the unsaturated ethyl ester at $\delta$ 3.21 ppm with $J = 7.8 \text{ Hz}$ by the ester carbonyl oxygen atom through space. The $^{13}$C NMR spectrum revealed the absence of the thiolactam carbonyl carbon peak at $\delta$ 201.3 ppm on 310's $^{13}$C NMR spectrum and the presence of the alkene quaternary carbon peak at $\delta$ 165.2 ppm confirming the thioamide to alkene transformation. The ester carbonyl and vinyl carbon peaks at $\delta$ 169.6 and 78.2 ppm respectively confirmed the presence of the unsaturated ester. The $\gamma$-carbon became more shielded with the introduction of the unsaturated ester group appearing at $\delta$ 32.7 ppm from $\delta$ 45.0 ppm on the 310's $^{13}$C NMR spectrum.
The vinylogous urethanes were then subjected to palladium-catalyzed oxidative coupling reactions. A mixture of 303, palladium(II) acetate, copper(II) acetate monohydrate was reacted in ethanol for 10 minutes at room temperature. It was then heated under reflux under oxygen atmosphere in a balloon for 28 hours. The TLC indicated the presence of a new spot (which was never recovered after column chromatography) as well as a spot for 303 at 21 hours. Compound 303 was returned in 68% yield after purification without the desired compound 300 (Scheme 71, c). Giving the reaction more time would perhaps improve chances of success. In light of this compound 304 was reacted with, palladium(II) acetate, copper(II) acetate monohydrate in ethanol for 10 minutes at room temperature followed by heating under reflux in oxygen atmosphere (in a balloon) for 42 hours, but this returned 67% of compound 304 after purification (Scheme 71, c). Similarly, reacting 307, palladium(II) acetate, copper(II) acetate monohydrate in ethanol for 10 minutes at room temperature followed by heating under reflux in oxygen atmosphere (in a balloon) for 42 hours, returned 84% of compound 307 after purification (Scheme 71, c).

The coupling reaction conditions from Wurtz et al.\textsuperscript{138} previously employed on enaminone 303 resulting in no desired product 165 were also applied to enaminones 304 and 307 to assess reactivity of enaminones differing in carbon chain length between the nitrogen atom and the aryl group. Compounds 304 and 307 were reacted in separate reactions with palladium(II) acetate, copper(II) acetate and potassium carbonate in N,N-dimethylformamide at 140 °C for 18 hours returning compounds 304 and 307 in 88% and 90% yields respectively. These results are similar to those obtained for compound 303 in section 3.3, Table 28: entry 1 where compound 303 was returned in 86% yield. It is apparent that the reactions never made the oxidative cleavage step as indicated by high yields of starting materials.

### 3.5 Attempted arylation of compounds 165, 304 and 307 via vanadium(V) oxytrifluoride oxidative coupling reaction

The oxidative coupling reactions between aryl groups using vanadium(V) oxytrifluoride are well reported on the literature.\textsuperscript{125,126} Su et al. and Pettit et al.
reported using vanadium(V) oxytrifluoride in the presence of trifluoroacetic acid and trifluoroacetic anhydride in dichloromethane for intramolecular coupling of para-substituted aryl groups at \(-15^\circ\text{C}\), leading to good and poor yields for their desired products respectively. Of interest was to see whether an enaminone’s vinyl group could be coupled with an aryl group using vanadium(V) oxytrifluoride. A solution of (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 in dichloromethane was added to a reaction mixture of vanadium(V) oxytrifluoride and trifluoroacetic anhydride in a 2:1 solvent mixture of dichloromethane and trifluoroacetic acid at \(-15^\circ\text{C}\) and left to react for 2.5 hours, giving what appeared to be (E)-(2-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)ethyl)-4,5-dimethoxyphenyl)(oxo)vanadium(V) fluoride 311 in 42% yield (Scheme 72, a).

\[
\begin{align*}
311 & \quad \overset{\text{a}}{\longrightarrow} \quad 303 \\
311 & = (E)-(2-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)ethyl)-4,5-dimethoxyphenyl)(oxo)vanadium(V) fluoride
\end{align*}
\]

Scheme 72: Reagents and Conditions: (a) VOF\(_{3}\) (3 eq), TFA: DCM (2:1), TFAA, 2.5 h at -15°C. 311 = 42%.

The IR spectrum of vanadium intermediate 311 had peaks at \(\nu_{\text{max}} = 1702\) and 1590 cm\(^{-1}\) for the ester carbonyl and aromatic alkene groups. The \(^1\)H NMR spectrum showed two singlets at \(\delta 6.78\) and 6.69 ppm for the 3-H and 6-H protons respectively, revealing the absence of the proton formally at position 2-H of the aromatic ring. The remainder of the spectrum’s peaks were similar to those of compound 303 but with slightly changed chemical shifts and unique splitting patterns as seen in the Table 31 below. The less deshielded nature of \(\gamma\)-protons of the unsaturated ethyl ester in 311 as compared to the same protons in 303 may indicate split attention from the olefinic \(=\text{CH}\) hydrogen bonding with the vanadium group (Table 31).
Table 31: Comparison of $^1$H NMR spectra of compounds 311 and 303

<table>
<thead>
<tr>
<th>311 $^1$H NMR /ppm</th>
<th>303 $^1$H NMR /ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.38 (s, vinyl proton)</td>
<td>4.61 (s)</td>
</tr>
<tr>
<td>4.08 (q, $J = 7.1$ Hz, CH$_2$CH$_3$ )</td>
<td>4.11 (q, $J = 7.1$ Hz)</td>
</tr>
<tr>
<td>3.94, 3.87 (2×s, methoxy protons)</td>
<td>3.87 (s)</td>
</tr>
<tr>
<td>3.17 (t, $J = 7.7$ Hz, NCH$_2$CH$_2$-Ar)</td>
<td>3.39 (t, $J = 7.3$ Hz)</td>
</tr>
<tr>
<td>3.06 (ddd, $J = 15.8$, 8.4, 2.4 Hz, $\varepsilon$-protons, NCH$_2$CH$_2$-Ar)</td>
<td>3.16 (m)</td>
</tr>
<tr>
<td>2.59 (dtd, $J = 20.9$, 13.5, 7.7 Hz, $\gamma$-protons)</td>
<td>2.80 (t, $J = 7.3$ Hz)</td>
</tr>
<tr>
<td>1.83 (p, $J = 7.5$ Hz, $\delta$-protons)</td>
<td>1.83 (m)</td>
</tr>
<tr>
<td>1.25 (t, $J = 7.1$ Hz, CH$_2$CH$_3$)</td>
<td>1.27 (t, $J = 7.1$ Hz)</td>
</tr>
</tbody>
</table>

The $^{13}$C NMR spectrum contained a deshielded chemical shift of carbon atom C-2 from $\delta$ 120.7 ppm in compound 303 to $\delta$ 128.8 ppm. This was as a direct result of electron-withdrawing effects of the vanadyl group. It would appear that the vanadyl group had stronger inductive effects as indicated by the de-shielding of NCH$_2$CH$_2$-Ar and NCH$_2$CH$_2$-Ar carbons, since their chemical environments shifted downfield to $\delta$ 52.1 and 47.3 ppm from $\delta$ 48.1 and 32.7 ppm respectively for compound 303. The remainder of the carbon chemical shifts were similar to those in compound 303 (see Table 32).

Table 32: Comparison of the $^{13}$C NMR spectra of compounds 311 and 303

<table>
<thead>
<tr>
<th>311 $^{13}$C NMR /ppm</th>
<th>303 $^{13}$C NMR /ppm</th>
<th>311 $^{13}$C NMR /ppm</th>
<th>303 $^{13}$C NMR /ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>148.4 (Ar C-5)</td>
<td>149.0</td>
<td>77.7 ($\alpha$-carbon)</td>
<td>77.6</td>
</tr>
<tr>
<td>147.4 (Ar C-4)</td>
<td>147.7</td>
<td>52.7 ($\varepsilon$-carbon)</td>
<td>48.1</td>
</tr>
<tr>
<td>132.6 (Ar C-1)</td>
<td>131.4</td>
<td>52.6 (NCH$_2$CH$_2$-Ar)</td>
<td>53.2</td>
</tr>
<tr>
<td>128.8 (Ar C-2)</td>
<td>120.7</td>
<td>47.3 (NCH$_2$CH$_2$-Ar)</td>
<td>32.7</td>
</tr>
<tr>
<td>113.4 (Ar C-3)</td>
<td>111.9</td>
<td>32.6 ($\gamma$-carbon)</td>
<td>31.7</td>
</tr>
<tr>
<td>112.5 (Ar C-6)</td>
<td>111.4</td>
<td>20.9 ($\delta$-carbon)</td>
<td>21.1</td>
</tr>
</tbody>
</table>
The reaction conditions were slightly modified to observe whether the synthesis of desired compound 165 could be achieved. A solution of compound 303 and trifluoroacetic anhydride in dichloromethane was added drop wise to a solution of vanadium(V) oxytrifluoride and trifluoroacetic acid in dichloromethane and ethyl acetate at \(-5\) °C over a period of 3 minutes and allowed to react at ambient temperature overnight, resulting in no desired product 165 after purification. The reaction mixture returned compound 303 and what appeared to be (E)-(1-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)-2-ethoxy-2-oxoethyl)(oxo)vanadium(V) fluoride 312 in 2.7% and 13% respectively (Scheme 73, a).

![Scheme 73: Reagents and Conditions: (e) VOF\(_2\) (2 eq), TFAA (1.3 eq), TFA (2.6 eq), LCM: EtOAc (4:1), overnight at \(-5\) °C to r.t., 312 = 13%, 303 = 2.7%]

The IR spectrum of vanadium(V) intermediate 312 had peaks at \(\nu_{\text{max}} = 1735\) and \(1588\) cm\(^{-1}\) for the ester carbonyl and aromatic groups respectively. The \(^1\text{H}\) NMR revealed that compound 312 had no vinyl peak present which would have been at \(\delta 4.61\) ppm in 303's \(^1\text{H}\) NMR spectrum and maintained the presence of the three aromatic peaks, a doublet with \(J = 7.9\) Hz at \(\delta 6.81\) ppm for 5-H and a multiplet at \(\delta 6.74 - 6.65\) ppm for 2-H and 6-H protons. The remainder of the peaks were similar to those found in 303's \(^1\text{H}\) NMR spectrum. The \(^{13}\text{C}\) NMR revealed that \(\alpha\)-carbon of the unsaturated ethyl ester was at \(\delta 95.0\) ppm which is significantly downfield from \(\delta 77.6\) ppm in 303's \(^{13}\text{C}\) NMR spectrum, indicating that the carbon is attached to an electron withdrawing group like the vanadium(V) difluoride. The remainder of the carbon peaks were similar to those found in 303's \(^{13}\text{C}\) NMR spectrum.

The vanadium(V) oxytrifluoride reaction was extended to compounds 304 and 307 to assess whether a desired result could be obtained. A solution of (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 304 or (E)-ethyl 2-(1-(3,4-
dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307 in dichloromethane in separate reactions was added to a reaction mixture of vanadium(v) oxytrifluoride and trifluoroacetic anhydride in a 2:1 solvent mixture of dichloromethane and trifluoroacetic acid at −15 °C and left to react for 2.5 hours, but resulted in tars, with no desired compounds 308 and 309 after purification (Scheme 74, a).

Compounds 304 and 307 were then reacted under the reaction conditions in Scheme 74, b. Separate solutions of compounds 304 and 307 and trifluoroacetic anhydride in dichloromethane were added drop wise to a solution of vanadium(V) oxytrifluoride and trifluoroacetic acid in dichloromethane and ethyl acetate over a period of three minutes at −5 °C and the reaction was left to warm up to room temperature overnight. Both reactions did not produced desired results after purification but returned starting compounds 304 and 307.

(E)-Ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 was exposed to ultra violet light in order to initiate a photo radical reaction in which the vinyl group would react with the aromatic group. A solution of compound 303 in dichloromethane was exposed to a UV lamp under 256 nm wavelengths for 16 hours. No desired compound 165 was recovered after purification but returned 46%
- 99% of compound 303. A new spot was observed on thin layer chromatography plate which was later not observed during purification (Scheme 75, a [i]). A solution of compound 303 in acetonitrile was exposed to a UV lamp with 650 W, 120 V for 20 hours, resulting in 25% recovery of compound 303. Similarly, a different spot to that of compound 303 was apparent on a thin layer chromatography plate but could not be isolated during purification (Scheme 75, a [ii]).

![Scheme 75: Reagents and Conditions: (a)(i) UV lamp (256 nm), DCM, 6 h, 165 = C%; (ii) UV lamp (650 W, 120 V), MeCN, 2 h, 165 = C%.](image)

### 3.7 PIDA and PIFA oxidative coupling reactions of compounds 303, 304 and 307

A combination of a Michael addition with an alkylation reaction was employed to make enaminones (also see section 2.21.1). This reaction made enaminones in one step ensuring high yields and saved production time as compared to previously employed routes. Previously synthesised ethyl 6-chlorohex-2-ynoate 285 was heated under reflux with 3,4-dimethoxyaniline 313 in acetonitrile in the presence of sodium iodide, potassium carbonate and 4Å molecular sieves for 20 hours and resulting in (E)-ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 304 in 43% yield after purification. Increasing the reaction time to 43 hours improved the yield of compound 304 to 73%. Similarly, 3,4-dimethoxybenzylamine 314 was heated under reflux with 6-chlorohex-2-ynoate 285, potassium carbonate and sodium iodide in acetonitrile for 21 hours, achieving (E)-ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307 in 62% yield, which was improved to 86% by heating under reflux for 24 hours. On the other hand, the reaction leading to (E)-ethyl 2-(1-(3,4-
dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 was high yielding at 21 hours heating under reflux. Homoveratrylamine 160 was reacted with 285, potassium carbonate and sodium iodide heating under reflux in acetonitrile, achieving (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 in 78% and 89% yield when heating time was 21 and 24 hours respectively (Scheme 76, a).

\[
\begin{align*}
\text{Scheme 76: Reagents and Conditions:} & \quad (a) \text{3,4-Dimethoxyaniline 313 (1 eq), 3,4-dimethoxybenzylamine 314 (2 eq) or homoveratrylamine 294 (1 eq), NaI (2 eq), K}_{2} \text{C} \text{C}_{2} (2 \text{ eq}), \text{ 4Å molecular sieve, MeCN, } 2^\circ \text{ - 43 h at reflux, 304 = 43 - 73%, 307 = 62 - 86%, 303 = 78 - 89%;} \quad (b) \text{PIDA (1.3 eq), DCE, 3 h at } 60^\circ \text{C, 306 = C%, 308 = C%, 165 = 0%; (c) FIPA (1.3 eq), DCM, 22 h at r.t., 306 = 0%, 308 = C%, 165 = C%.}
\end{align*}
\]

Phenyliodine(III) diacetate (PIDA) mediated oxidative carbon-carbon formation reaction conditions developed by Zhao et al. for novel synthesis of indoles from N-aryl enamines were decided upon. Zhao and Zheng et al. found that adding a solution of PIDA (1.3 equivalents) in dichloroethane to a solution of 3-phenylaminoacrylonitrile derivatives in dichloroethane and reacting at 60 °C for 2 hours were optimal conditions for indole synthesis (Scheme 77).\(^{127,128,129}\)

\[
\begin{align*}
\text{Scheme 77: (a) PIDA (1.3 eq), DCE, 2 h at 60 °C, 33 - 91%}
\end{align*}
\]
Following this precedent, enaminones were reacted with PIDA under the optimal reaction conditions. A solution of phenyliodine(III) diacetate in dichloroethane was added drop wise to a solution of (E)-ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 304 in dichloroethane at 60 °C and left to react for 3 hours. The TLC plate revealed reduction in concentration of compound 304 after 2 hours of reaction time, and two unidentified by-products were recovered after purification with no sign of desired cyclised product or starting material. (E)-Ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307 was then reacted with PIDA. A solution of PIDA in dichloroethane was added drop wise to a solution of compound 307 in dichloroethane at 60 °C and and left to react for 3 hours, similarly achieving an unidentified by-product after purification (Scheme 76, b). A similar result was observed in the reactions of (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 with PIDA, where a solution of PIDA in dichloroethane was added dropwise to a solution of compound 303 in dichloroethane at 60 °C and reacted for 3 hours resulting in an unidentified product (Scheme 76, b).

A more potent hypervalent oxidant was then used, phenyliodine(III) bis(trifluoroacetate) (PIFA) to assist the conversion of compounds 304, 307 and 303 to desired products. A solution of PIFA in dichloromethane was added drop wise into a solution of (E)-ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 304 in dichloromethane at room temperature and reacted for 22 hours resulting in unidentified by-products (Scheme 76, c). Reacting PIFA with (E)-ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307 and (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 under reaction conditions in Scheme 76, c, similarly afforded unidentified by-products.

The absence of a NH proton on enaminones could have led to the reaction’s failure, since the proton plays an important role on the elimination of first acetic acid molecule. A complex salt could have formed in the case of enaminones which could not react any further and be lost during reaction work up (Scheme 78).
3.8 Attempted synthesis of compounds 165, 308, 321 and 322 via Heck-type, Herrmann-Beller catalyst and Bu$_3$SnH coupling methods

The mixed Michael addition/alkylation reaction was extended to making 2-bromo-4,5-dimethoxy enaminones. There was reasonably confidence of forming a five-membered ring in a Heck-type reaction because this type of cyclisation was previously achieved with similar systems.$^{81,80}$ However, six-membered and seven-membered rings had not been previously made in this way, hence it was necessary to observe if there was an intrinsic problem with this approach. In a similar reaction Michael et al.$^{79}$ heated vinylogous urethane (E)-ethyl 2-((3aS,6aR)-5-(2-(benzyl ox)-6-bromo-4-methoxy-3-methylphenyl)-2,2-dimethyl-dihydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-4(5H)-ylidene)acetate 38 with palladium acetate, tris(o-tolyl)phosphine and triethylamine under reflux in mixture of acetonitrile, N,N-dimethylformamide and water for 4 hours giving (–)-ethyl(3aR,10bS)-6-benzyloxy-8-methoxy-2,2,7-trimethyl-3a,10b-dihydro-4H-[1,3]dioxolo-[4',5':3,4]pyrrolo[1,2-a]indole-10-carboxylate 39 in 82% yield (Scheme 79, a).
The brominated arylamines were prepared by bromination reaction of relevant amines. A solution of bromine in acetic acid was added drop wise into solutions of 3,4-dimethoxyaniline 313, 3,4-dimethoxybenzylamine 314 or homoveratrylamine 294 in acetic acid over a period of 2 hours at room temperature, which resulted in 2-bromo-4,5-dimethoxybenzylamine hydrobromide 318 and 2-bromo-4,5-dimethoxyphenethylamine hydrobromide 319 in 89% and 93% yields respectively after purification, while no 2-bromo-4,5-dimethoxyaniline hydrobromide 317 was recovered (Scheme 80, a). The reaction with 3,4-dimethoxyaniline 313 returned an unidentified by-product. Another way of arriving at (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate was to brominate previously prepared (E)-ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 304 with hydrobromic acid and potassium bromate. A solution of hydrobromic acid in acetic acid was added drop wise over a period of 10 minutes into a solution of compound 304 and potassium bromate in acetic acid cooled in a water bath. The reaction turned maroon and was left to stir for 30 minutes, after which it was quenched with ice forming a precipitate which was then purified by column chromatography. This returned compound 304 in 77% yield with no desired (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate in sight.

The IR spectrum of 318 revealed the amine an aromatic group peaks at \( \nu_{\text{max}} = 3111 \) and 1478 cm\(^{-1} \) respectively. The \(^1\)H NMR spectrum had two single peaks at \( \delta = 7.06 \) and 6.92 ppm for the 3-H and 5-H protons of the aromatic ring indicative that the bromine atom replaced the hydrogen atom at C-2 of the aryl group.
The IR spectrum of 319 showed peaks at $\nu_{\text{max}} = 3114$ and 1509 – 1439 cm$^{-1}$ for the amine and aromatic groups respectively. The $^1$H NMR spectrum revealed two singlet peaks at $\delta$ 7.00 and 6.82 ppm for the 3-H and 5-H protons of the aromatic ring.

The brominated amines were then reacted with ethyl 6-chlorohex-2-ynoate 285 to achieve the desired enamines. In separate reaction, 318 and 319 were reacted with compound 285, sodium iodide, potassium carbonate and 4Å molecular sieves while heating under reflux in acetonitrile for 17 – 24 hours. This afforded (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 320 and (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 164 in 83% and 88% yields respectively after purification (Scheme 80, b).

![Scheme 80: Reagents and Conditions: (a) Br$_2$ (* ec), acetic acid, 2 h at r.t., 317 = 0%, 318 = 89%, 319 = 93%; (b) Ethyl 6-chlorohex-2-ynoate (1 eq), NaI (2 eq), K$_2$CO$_3$ (3 eq), 4Å molecular sieves, MeCN, reflux over night. 320 = 83%, 164 = 88%; (c) Fe(18C6)$_2$ (0.4 eq), F(6-iodopyridine)$_2$ (*1.6 eq), TEA (*1.6 eq), DMF/MeCN:H$_2$C (5:5:1), 22 h at reflux. 308 = 0%, 165 = 0%; (d) Fehrmann-Eisler catalyst (0.01 ec), NaOAc, DMA, 17 h at 135 °C, 308 = 0%, 165 = 0%; (e) Li$_3$SrH (2 ec), AIE (1.5 ec), benzene, 5 h at reflux. 321 = 0%, 322 = 0%.](image)

The melting point of 320 was 108 – 109 °C. The IR spectrum had peaks at $\nu_{\text{max}} = 1683$ and 1589 cm$^{-1}$ for the ester carbonyl, alkene and aromatic groups in that order. The $^1$H NMR spectrum revealed presence of the vinyl proton by a singlet at $\delta$ 4.63 ppm indicative of the formation of the carbon-carbon double bond from the Michael addition reaction and a triplet with $J = 7.0$ Hz at $\delta$ 3.33 ppm for the $\varepsilon$-protons confirming the alkylative reaction. The remainder of the molecule was confirmed by quartet and a triplet both with $J = 7.1$ Hz at $\delta$ 4.09 and 1.24 ppm respectively for the ethyl chain of the ester and the two singlets at $\delta$ 7.03 and 6.60 ppm for the 3-H and
6-H on the aromatic ring respectively. The $^{13}$C NMR spectrum showed the presence of the vinyl and quaternary alkene carbons by peaks at $\delta$ 165.1 and 79.0 ppm respectively. The ester carbonyl carbon was at $\delta$ 169.5 ppm while the aromatic carbon peaks were at 149.1, 148.8, 126.8, 115.8, 113.4 and 111.3 ppm for the C-5, C-4, C-1, C-2, C-6 and C-3. The HRMS found [M+H]$^+$ equal to 384.0811 for molecular formula C$_{17}$H$_{23}$BrNO$_4$ with exact calculated mass of 384.0805.

(E)-Ethyl 2-(1-(2-bromo-4,5-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 320 and (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 164 were heated under reflux in separate reaction with palladium acetate, tris(o-tolyl)phosphine, triethylamine in a mixture of acetonitrile/ N,N-dimethylformamide and water for 22 hour resulting in unidentified by-products and recovery of compounds 320 and 164 in 75% and 85% yields respectively (Scheme 80, c).

Herrmann et al. reported an efficient synthesis of Heck vinylation products from styrene and aryl bromides using a phosphapalladacycle 325 as a catalyst achieving high yields which were exclusively trans-products. The phosphapalladacycle 325 catalyst, now commonly known as the Herrmann-Beller catalyst, was freshly prepared. They reacted styrene, aryl bromides, trans-di(µ-acetato)-bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) in N,N-dimethylacetamide/ N,N-dimethylformamide at 130 °C for 6 hours.$^{132,133,134,135}$

Tietze et al. synthesised 3,5,6,8,9,14b-hexahydro-4H-cyclopenta[a][1,3]dioxolo[4,5-h]-pyrrolo[2,1-b][3]-benzazepine 324 (the five-membered core of cephalotaxine 56) in 81% yield enantioselectively, via a Heck reaction of 1-[2-(6-bromo-benzo[1,3]dioxol-5-yl)-ethyl]-1-aza-spiro[non-6-ene 323 with palladacycle 325 (synthesised from palladium acetate and tris(o-tolyl)phosphine) under conditions described by Herrmann and Beller.$^{135}$ In their reaction, a mixture containing acetonitrile, N,N-dimethylformamide, water, tetra-n-butyrammonium acetate and the above two reagents was stirred for 7 hours at 120 °C (Scheme 81, a).$^{131}$
In view of these results, it was worthwhile to change from palladium(II) acetate to the Herrmann-Beller catalyst. However, when (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 320 and (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 164 were treated with trans-di(µ-acetato)-bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) 325 in N,N-dimethylacetamide at 130 °C for 17 hours, only unidentified by-products as well as 40% and 37% of compounds 320 and 164 were obtained respectively (Scheme 80, d).

3.9 Attempted tributyltin hydride mediated coupling of enamionines 320 and 164

In a paper titled “A study of aryl radical cyclisation in enaminone esters”, Dominguez et al. demonstrated N-benzyl and N-phenethyl enaminone esters cyclised giving 5-exo and 6-exo products when treated with tributyltin hydride in benzene as a solvent and azobis(isobutyronitrile) as the radical initiator. In addition de-brominated enaminone esters were recovered in each case. However, the N-phenyl enaminone esters did not cyclise, but afforded the de-brominated enaminone esters. They also established that the endo and 4-exo cyclisations were unfavourable because of significant electron distortions of the conjugated system of enaminones in the transition state (Scheme 82).
A solution of tributyltin hydride and azobis(isobutyronitrile) in benzene was added dropwise over a period of 3 hours into solutions of (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 320 or (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 164 heating under reflux, which were for an additional 3 hours heating under reflux. The desired products ethyl 2-(8,9-dimethoxy-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-a]isoindol-9b-yl)acetate 321 or ethyl 2-(9,10-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-10b-yl)acetate 322 were not obtained after purification (see section 3.8; Scheme 80, e). Instead, the debrominated enaminones (E)-ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307 and (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 were recovered in 79 – 87% and 95% respectively.

3.10 Reactions of vinylogous urethanes and amides with benzyne

Ramtohul et al. reported carbon arylation of β-enaminone esters and ketones with arynes formed from ortho-silyl aryltriflates in the presence of cesium fluoride using acetonitrile as the solvent resulting in substituted aromatic β-enamino compounds in moderate to excellent yields (Scheme 83).136
As a trial experiment to see which kinds of enaminoones would react with arynes, (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 was treated with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate 326 and cesium fluoride in acetonitrile at 25 °C for 50 hours. (E)-Ethyl 4-(2-(2-ethoxy-2-oxo-1-phenylethylidene)pyrrolidin-1-yl)butanoate 327 and compound 143 were isolated in 39% and 58% yields respectively after purification (Scheme 84, a). The reaction was not complete at 24 hours as was shown by the TLC and similarly at 50 hours. The temperature was raised in order to accelerate the reaction rate. 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate 326 in acetonitrile was added dropwise into a reaction mixture of (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 and cesium fluoride and the reaction mixture was left heating under reflux for 18 hours, leading to compounds 327 and 143 in 31% and 76% respectively after purification (Scheme 84, b). It was apparent that the reaction rate was not influenced by heating under reflux only as compound 327 yields decreased from 39% to 31% in the previous reaction.

Ramtohul et al. later reported "The synthesis of polycyclic indoles and pyrroloindole heterocycles via the annulation of indole- and pyrrole-2-carboxylate esters with
arynes where the indoles, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate and anhydrous tetramethylammonium fluoride (TMAF) were reacted at room temperature for 1 – 2 hours, yielding desired products in good yields (Scheme 85).

Scheme 85: Reagents and Conditions: (a) TMAF (2.27 eq), THF, 1 - 2 h at r.t., 53 - 90%.25

Cesium fluoride was replaced with a solution of tetra-n-butylammonium fluoride (TBAF) in tetrahydrofuran as a fluoride anion source to improve reaction yields. tetra-n-Butylammonium fluoride was added drop wise over 30 minutes into a solution of compound 143 and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate in tetrahydrofuran at 65 °C. The reaction was then heated under reflux for 20 hours resulting in compounds 327 and 143 in 27% and 70% yields respectively after purification. TBAF perhaps added to the complications with the reaction yield of compound 327 further decreasing to 27%. Mild reaction conditions were suitable as seen from decreasing reaction yields with increasing temperature. CsF was the better fluoride source when compared to TBAF based on yields of compound 327 obtained even though the yields were low. It became apparent that compound 143 was less nucleophilic reacting with generated benzynes (see successes in Scheme 86).

The IR spectrum of 327 showed peaks at $\nu_{\text{max}} = 1734$ and 1454 cm$^{-1}$ for the ester carbonyl, alkene and aromatic groups. The $^1$H NMR spectrum revealed the absence of the vinyl proton peak at $\delta$ 4.53 ppm in 143's $^1$H NMR spectrum and the presence of a multiplet at $\delta$ 7.35 – 7.12 ppm for the aromatic group. The $^{13}$C NMR spectrum revealed the absence of the vinyl carbon peak at $\delta$ 77.3 ppm in 143's $^{13}$C NMR spectrum and the presence of quaternary carbon peak at $\delta$ 96.1 ppm for the $\alpha$-carbon of the unsaturated ester. The aromatic carbon peaks appeared at $\delta$ 139.1, 132.0, 127.7 and 126.0 ppm.
Since the above reactions were partially successful, additional vinylogous amides and urethanes were chosen to react with benzyne generated from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate 326 to assess the reaction conditions. Reagent 326 was added drop wise into a solution of (Z)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone 240 and cesium fluoride at 60 °C and the reaction was left to heat under reflux for 23 hours affording (Z)-1-(4-nitrophenyl)-2-phenyl-2-(pyrrolidin-2-ylidene)ethanone 328 in 79% yield (Scheme 86, a). It was interesting to observe that the reaction preferred nucleophilicity on the carbon atom instead of the nitrogen atom, demonstrating the versatile reactivity of enamiones.

The IR spectrum of 328 had peaks at $\nu_{\text{max}} = 3400 – 3200, 1742, 1567, 1541$ and 1480 cm$^{-1}$ for the amine NH, alkene and aromatic groups respectively. The $^1$H NMR spectrum revealed the absence of the vinyl singlet at $\delta 5.80$ ppm in compounds 240’s $^1$H NMR spectrum and revealed the presence of the phenyl ring with multiplets at $\delta 7.16$ and 7.02 ppm for (ortho and para protons) and meta protons. The NH singlet appeared at $\delta 11.19$ ppm confirming that no reaction occurred at the nitrogen atom and the chemical shift suggested the structure’s geometry as the hydrogen-bonded Z isomer. The $^{13}$C NMR spectrum revealed the loss of the vinyl carbon peak at $\delta 87.0$ ppm in 240’s spectrum and the emergence of a quaternary alkene carbon peak (α-carbon of the ketone) at $\delta 105.4$ ppm. There were eight aromatic carbon peaks representative of the structure.

Compound 326 was added drop wise into a solution of (E)-ethyl 2-(2-(2-(4-nitrophenyl)-2-oxoethylidene)azepan-1-yl)acetate 216 and cesium fluoride in
acetonitrile and left heating under reflux for 18 hours resulting in unidentified by-products after purification (Scheme 87, a).

![Scheme 87: Reagents and Conditions: (a) 326 (1.5), CsF (2 eq.), MeCN, reflux, 329 = 0%.

Compound 326 was added drop wise into a solution of (E)-ethyl 2-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)ethanoate 330 and cesium fluoride and left heating under reflux for 6 hours affording unidentified by-products after purification (Scheme 88, a).

![Scheme 88: Reagents and Conditions: (a) 326 (+1.5), CsF (2 eq.), MeCN, reflux, 331 = 0%.

The nucleophilic nature α-carbons of the saturated esters in compounds 216 and 330 may have led to complications in the reaction. The highly acidic α-protons of the saturated esters in compounds 216 and 330 may be deprotonated in the presence of CsOTf leading to competing nucleophilic reactions for the benzyne. The less acidic α-protons of the saturated ester in compound 327 were not deprotonated as observed by return of large quantities of compound 327 (see Scheme 84). The absence of the highly acidic α-protons of the saturated ester in compound 240 and high yields of compound 328 suggested that the desired compound can be achieved without complications of competing reaction (Scheme 86).
3.11 Summary, Conclusion and Future Prospects

The highly effective condensation reactions between amines 160, 313, 314, 318 and 319 and γ-butyrolactone 13 made it possible to achieve desired lactams of varying carbon chain lengths, with emphasis to lactams 161 and 303 which have a two carbon chain length between the nitrogen and the aryl group, which is necessary for formation of a seven-membered ring on the arylation step. The enaminones were accessed in high yields via the Eschenmoser sulphide contraction reaction of thiolactams, which were prepared in a thionation reaction of lactams. The enaminones were also efficiently synthesised by a Michael/alkylation reaction between amines and 6-chlorohex-2-ynoate 285, making use of fewer steps, thus ensuring high yields and saving time.

The enaminones were subjected to a number of oxidative olefin/aryl coupling reaction but to no avail, except when compounds 305 and 306 were formed by palladium(II) acetate coupling reaction in acetic acid at moderate temperatures. Other interesting results were formation of the vanadium intermediates 311 and 312 when vanadium(V) oxytrifluoride was applied to vinylogous urethane 303. These were positive results because enaminone reactivity leading to these products was observed even though the yields were low, where starting material and tars were observed in other cases. Other positive results came from in situ reactions of enaminones with arynes leading to vinyl/aryl coupling.

The ambident nucleophilicity of vinylogous urethanes 164, 303, 304, 307 and 320's ambident nucleophilicity was insufficient for the coupling reactions. Complications could have occurred when the oxidative addition for the vinylogous urethanes never materialised, leading to the recovery if intact vinylogous urethanes. This could have been due to a weaker ethyl ester as an electron withdrawing group. The electron donating groups on the aromatic rings could have also factored into the complications. The β-H elimination step may have not occurred for cases where tars were recovered.

Studies have to be undertaken in order to ascertain how vinylogous amides, vinylogous cyanamides, vinylogous sulphonamides, vinylogous ureas and
vinylogous nitramines would behave in the coupling methods that the vinylogous urethanes underwent or failed to undergo. Varying the aromatic substituents would also assist in understanding the electron distribution patterns and their importance in arylation coupling step. Perfecting the creation of the five-membered and six-membered rings on the arylation step should be our main focus in order to transfer the wealth of knowledge to making the seven-membered ring.

An opportunity of exploring aryne reactivity on our systems is at hand, where the enaminone unit would attack the aryne leading to formation of desired products and by-products (Scheme 89). Substituted derivatives of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate 326 could also be made, which would be used to create five-membered, six-membered and seven-membered rings when the alkene and aryl group are coupled.

![Scheme 89: Proposed reaction strategy towards compounds 165, 306 and 308.](image-url)
CHAPTER 4: APPROACHES TOWARDS SESSILIFOLIAMIDE NUCLEUS

4.1 Synthesis of the pyrido[1,2-a]azonine nucleus

An opportunity of making the pyrido[1,2-a]azonine nucleus based on work previously done in our laboratories\textsuperscript{144} presented itself as a side issue in this project. The pyrido[1,2-a]azonine nucleus contains a nine-membered and six-membered fused units system that can be used a scaffold in creating Sessilifoliamide alkaloids, which are a subset of the Stemona alkaloids (see Scheme 9 in chapter 1). The nine-membered lactam azonan-2-one 332, had to be synthesised from cyclooctanone 331 in a Schmidt reaction.\textsuperscript{146} Sodium azide was added portion wise into a solution of 331 in concentrated hydrochloric acid placed in an ice bath. The reaction was left to stir for 4 hours at room temperature, giving 332 in 98% excellent yield after purification (Scheme 90, a).

Azonan-2-one 332 had a melting point of 75 – 76 °C. The IR spectrum had peaks at $v_{\text{max}} = 3301$ and $1651$ cm$^{-1}$ for the lactam NH and the amide’s carbonyl group respectively. The $^1$H NMR spectrum showed a singlet at $\delta 6.36$ ppm for the NH proton, while a multiplet at $\delta 3.36$ ppm and a triplet with $J = 6.35$ Hz at $\delta 2.43$ ppm represented the $\alpha$ and $\eta$-protons of the lactam respectively. The $^{13}$C NMR spectrum revealed the presence of the lactam’s carbonyl carbon at $\delta 178.1$ ppm.

Forming the six-membered ring onto the nine-membered ring required a combination of a tandem Michael addition/acylation reactions between NH vinylogous amides and methacrylic anhydride. The NH vinylogous amides had to be synthesised from thiolactam 333 in an Eschenmoser sulphide contraction\textsuperscript{122} reaction. Thiolactam 333 was made from lactam 332 in a thionation reaction.\textsuperscript{147} Lactam 332 was reacted with phosphorus pentasulphide and hexamethyldisiloxane in dichloromethane at room temperature for 20 hours, resulting in excellent 81% yield of azonane-2-thione 333 (Scheme 90, b).

The melting point of azonane-2-thione 333 was 72 – 75 °C. The IR spectrum still indicated the presence of the NH proton at $v_{\text{max}} = 3407$ cm$^{-1}$. The $^1$H NMR spectrum
revealed a downfield chemical shift of NH singlet to δ 8.30 ppm and slight downfield chemical shift of the α and η-protons multiplets to δ 3.51 and 2.92 ppm respectively as a result of stronger inductive effect from sulphur atom when compared to oxygen atom. The 13C NMR spectrum revealed the absence of the lactam carbonyl carbon peak which was at δ 178.1 ppm in 332's spectrum and the presence of the thiolactam's thiocarbonyl peak at δ 209.5 ppm.

![Scheme 90](image)

**Scheme 90:** Reagents and Conditions: (a) Sodium azide (1.54 eq), HCl (conc), 4 h at 0 - r.t., 332 = 98%; (b) P2S5 (0.5 eq), HMDSO (1.5 eq), DCM, 20 h at r.t., 333 = 81%; (c) (i) Phenacyl bromide, para-nitrophenacyl bromide or para-methoxyphenacyl bromide (1.1 eq), MeCN, 30 min, 2 min, 5 sec at r.t. (ii) TEP (1.1 eq), TEA (1.1 eq), MeCN, 2 days at r.t., 334 = 70%, 335 = 100%, 336 = 91%; (d) Methacrylic anhydride (1 eq) (neat), 150 W, 60 min at 150 °C, 337 = 95%, 338 = 90%, 339 = 87%; (e) H2 gas, Pd/C (0.05 eq), MeOH, 20 h at r.t., 340 = 30%; (f) Triphenylsilane (1 eq), TFA (1 eq), 1,2 dichloroethane, 23 h at reflux, 341 = 40%.

The NH vinylogous amides could then be synthesised in an Eschenmoser sulphide contraction reaction between the 333 and phenacyl bromides. In separate reactions; phenacyl bromide, para-nitrophenacyl bromide and para-methoxyphenacyl bromide were added to a solution of 333 in acetonitrile at room temperature followed by the salt precipitation after 30 minutes, 2 minutes and 5 seconds in that order. A solution
of triethyl phosphite and triethylamine in acetonitrile was then added to each reaction to induce sulphur extrusion, resulting in the formation of \((Z)-2-(azonan-2-ylidene)-1\)-phenylethanone \(334\), \((Z)-2-(azonan-2-ylidene)-1-(4-nitrophenyl)ethanone \(335\) and \((Z)-2-(azonan-2-ylidene)-1-(4-methoxyphenyl)ethanone \(336\) in 70%, 100% and 91% yields respectively (Scheme 90, c). The para-nitro electron withdrawing group presented with excellent results because it increases the acidity of the \(\alpha\)-protons of the ketone in the sulphur extrusion stage.

The IR spectrum of \((Z)-2-(azonan-2-ylidene)-1\)-phenylethanone \(334\) had peaks at \(\nu_{\text{max}} = \) above 3000, 1739, 1586 and 1474 cm\(^{-1}\) for the enaminone NH, ketone carbonyl, vinyl and aromatic groups respectively. The \(^1\)H NMR spectrum showed two singlets at \(\delta 11.77\) and 5.63 ppm for the enaminone NH and vinyl protons, indicating that the Eschenmoser sulphide contraction reaction was a success. The much deshielded NH signal strongly suggests intramolecular hydrogen bonding to the carbonyl group, implying that the compound has Z geometry. The two multiplets at \(\delta 7.88\) and 7.38 ppm were for the ortho and meta/para aromatic protons respectively. Compound \(334\) had Z geometry as indicated by a multiplet upfield at \(\delta 2.43\) ppm for the \(\gamma\)-protons of the ketone, showing the lack of space deshielding from the oxygen atom. The \(^{13}\)C NMR spectrum showed peaks \(\delta 187.4, 171.3\) and 91.0 ppm for the ketone’s carbonyl, quaternary alkene and vinyl carbon peaks respectively. It also presented with aromatic peaks at \(\delta 140.6, 130.3, 128.1, 126.8\) ppm. The HRMS found [M+H]\(^+\) equal to 244.1711 for molecular formula \(\text{C}_{16}\text{H}_{22}\text{NO}\)\(^+\) with exact calculated mass of 244.1696.

The melting point of \((Z)-2-(azonan-2-ylidene)-1-(4-nitrophenyl)ethanone \(335\) was 121 – 122 °C. The IR spectrum showed peaks at \(\nu_{\text{max}} = \) above 3000, 1739, 1586, 1555 and 1474 cm\(^{-1}\) for the enaminone NH, ketone carbonyl, vinyl and aromatic groups respectively. The \(^1\)H NMR spectrum showed two singlets at \(\delta 12.02\) and 6.18 – 4.65 ppm for the enaminone’s NH and vinyl protons respectively. The vinyl singlet was unusually broad when compared to \(334\)’s vinyl singlet. There were two doublets with \(J = 8.25\) and 8.02 Hz at \(\delta 8.26\) and 8.03 ppm respectively for the meta and ortho aromatic protons respectively. The molecule had Z geometry, shown by an upfield multiplet peak at \(\delta 2.51\) ppm for the \(\gamma\)-protons of the ketone, and the highly deshielded NH signal. The \(^{13}\)C NMR spectrum showed peaks at \(\delta 184.3, 172.9\) and
90.9 ppm representing the ketone carbonyl, quaternary alkene and vinyl carbons. The aromatic carbon peaks were at δ 148.8, 146.1, 127.8 and 123.4 ppm. The HRMS found [M+H]^+ equal to 289.1556 for a molecular formula C_{16}H_{21}N_{2}O_{3}^+ with exact calculated mass of 289.1547.

The IR spectrum of (Z)-2-(azonan-2-ylidene)-1-(4-methoxyphenyl)ethanone 336 had peaks at ν_{max} = above 3000, 1742, 1577 and 1484 cm^{-1} for the enaminone NH, ketone carbonyl, vinyl and aromatic groups respectively. The ^1H NMR spectrum showed two singlets at δ 11.67 and 5.60 ppm for the enaminone NH and the vinyl protons respectively. Both doublets at δ 7.86 and 6.90 ppm with J = 8.9 Hz were for the ortho and meta aromatic protons respectively, while the methoxy singlet was at δ 3.84 ppm. The molecule had Z geometry as shown by a multiplet upfield position at δ 2.50 – 2.33 ppm. The ^13C NMR spectrum revealed peaks at δ 186.8, 170.7, 161.5 and 90.5 ppm for the ketone carbonyl, quaternary alkene, para-aromatic and vinyl carbons respectively. The remaining aromatic peaks were at δ 133.3, 128.6 and 113.3 ppm. The HRMS found [M+H]^+ equal to 274.1807 for a molecular formula C_{17}H_{24}NO_{2}^+ with an exact calculated mass of 274.1802.

The synthesis of the pyrido[1,2-a]azonine nucleus proceeded in a regioselective tandem N-acylation/Michael addition reaction after having made the NH vinylogous amides. Vinylogous amides 334, 335 and 336 were reacted neat with methacrylic anhydride in a microwave reactor at 150 W, 150 °C for 1 hour, resulting in excellent 95%, 90% and 87% yields of racemic mixtures of 1-benzoyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 337, 3-methyl-1-(4-nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 338 and 1-(4-methoxybenzoyl)-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 339 respectively (Scheme 90, d).

The IR spectrum of 337 had peaks at ν_{max} = 1701, 1575 and 1465 cm^{-1} for the ketone and amide carbonyl, alkene and aromatic groups in that order. The ^1H NMR spectrum revealed the absence of enaminone NH and vinyl singlets which were at δ 11.77 and 5.63 ppm of 334’s spectrum and the presence of a multiplet at δ 2.50 ppm and doublet with J = 6.0 Hz at δ 1.15 ppm for the α-proton of the amide and the methyl protons, indicating the formation of the six-membered ring. The ^13C NMR spectrum revealed the absence of the vinyl carbon peak at δ 91.0 ppm of 334’s
spectrum and the presence of quaternary alkene carbon peak at δ 116.6 ppm for the α-carbon of the ketone. The amide carbonyl carbon peak was δ 173.5 ppm confirming that the isomer that had formed only contained one ketone group. The HRMS found [M+H]^+ equal to 312.1970 for a molecular formula C_{20}H_{26}NO_{2}^+ with exact calculated mass of 312.1958.

The melting point of 338 was 104 – 105 °C. The IR spectrum had peaks at \( \nu_{\text{max}} = 1670, 1598 \) and 1452 cm\(^{-1}\) for the ketone and amide carbonyl, alkene and aromatic groups. The \(^1\)H NMR spectrum revealed the absence of enaminone NH and vinyl singlets which were at δ 12.02 and 6.18 – 4.65 ppm of 335’s spectrum and the presence of a multiplet at δ 2.51 ppm and doublet with \( J = 6.0 \) Hz at δ 1.19 ppm for the α-proton of the amide and the methyl protons, indicating the formation of the six-membered ring. The \(^{13}\)C NMR spectrum revealed the absence of the vinyl carbon peak at δ 90.9 ppm of 335’s spectrum and the presence of quaternary alkene carbon peak at δ 114.8 ppm for the α-carbon of the ketone. The amide carbonyl carbon peak was δ 173.3 ppm confirming that the isomer that had formed only contained one ketone group. The HRMS found [M+H]^+ equal to 357.1814 for a molecular formula C_{20}H_{25}N_{2}O_{4}^+ with exact calculated mass of 357.1809.

The IR spectrum of 339 had peaks at \( \nu_{\text{max}} = 1720 \) and 1548 cm\(^{-1}\) for the ketone and amide carbonyl, alkene and aromatic groups. The \(^1\)H NMR spectrum revealed the absence of enaminone NH and vinyl singlets which were at δ 11.67 and 5.60 ppm of 336’s spectrum and the presence of a multiplet at δ 2.73 ppm and doublet with \( J = 6.7 \) Hz at δ 1.21 ppm for the α-proton of the amide and the methyl protons, indicating the formation of six-membered ring. The \(^{13}\)C NMR spectrum revealed the absence of the vinyl carbon peak at δ 90.5 ppm of 336’s spectrum and the presence of quaternary alkene carbon peak at δ 113.8 ppm for the α-carbon of the ketone. The amide carbonyl carbon peak was δ 173.5 ppm confirming that the isomer that had formed only contained one ketone group. The HRMS found [M+H]^+ equal to 342.2072 for a molecular formula C_{21}H_{28}NO_{3}^+ with exact calculated mass of 342.2064.

After successfully making the pyrido[1,2-a]azonine nucleus, the additional aroyl group had served its purpose and become redundant for further synthesis of relevant alkaloids. Therefore, it needed to be removed in a way that would preserve the OH
group which forms part of the final structure 342, as found in the sessilifoliamides themselves. This could probably be done by a Baeyer Villiger reaction, but in that case it becomes necessary to reduce the enaminone’s C=C bond first. The Baeyer Villiger products would then be hydrolysed, leading to 1-hydroxy-3-methyl-decahydropyrido[1,2-a]azonin-2(1H)-one 342 (Scheme 91).

A reaction mixture containing 337 and palladium on carbon in methanol was stirred under hydrogen atmosphere (balloon) at room temperature for 20 hours. This resulted in 31% yield of 1-benzyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 340 after purification (Scheme 90, e). So, instead of the desired C=C reduction, the benzylic ketone was reduced instead. This was not a useful product to take through the Baeyer Villiger oxidation reaction but was in line with observations reported previously by Riedl et al.

The IR spectrum of 340 had peaks at $\nu_{\text{max}} = 1648$, 1520, and 1450 cm$^{-1}$ for the amide carbonyl, alkene and aromatic groups. The $^1$H NMR spectrum revealed the presence of a doublet with $J = 34.4$ Hz at $\delta 3.69$ ppm for the benzylic protons. The $^{13}$C NMR spectrum showed the absence of the ketone carbonyl carbon peak at $\delta 196.7$ ppm of 337’s spectrum, followed by an upfield chemical shift of the $\delta$-carbon peak to $\delta 137.9$ ppm owing to the replacement of the ketone carbonyl carbon by CH$_2$. The amide carbonyl carbon peak and the $\gamma$-carbon peak of the amide were at $\delta 173.1$ and 114.9 ppm, indicating that only the ketone carbonyl carbon was reduced.
Molinski et al. reported a selective reduction of 2-aryl-1-N-carboalkoxyenamines to 2-arylethylamine carbamates in high yield by triethylsilane-trifluoroacetic acid complex, where a hydride adds on C-1 followed by a proton capture at C-2 from trifluoroacetic acid (Scheme 92).\textsuperscript{150}

\[
\begin{array}{c}
\text{Et}_3\text{SiH, TFA, -10 °C} \\
\end{array}
\]

\textbf{Scheme 92:} Et\textsubscript{3}SiH-TFA reduction of 2-aryl-1-N-carboalkoxyenamines

As an alternative, compound 338 was heated under reflux with triphenylsilane in the presence of trifluoroacetic acid in 1,2-dichloroethane for 23 hours, resulting in 40% combined yield of two diastereomers of 3-methyl-1-(4-nitrobenzoyl)-decahydropyrido[1,2-a]azonin-4(1H)-one 341 (Scheme 90, f). The reaction was chemoselective for the enaminone’s C=C bond and affected neither the ketone nor the nitro groups under these conditions.

The IR spectrum of 341 had peaks at $\nu_{\text{max}} = 1710$ and 1480 for the ketone and amide carbonyl, and aromatic groups. The $^1$H NMR spectrum revealed the presence of a multiplet at $\delta$ 4.08 – 3.99 ppm for the $\delta$-proton of the amide and a doublet of doublet of doublets with $J = 10.5$, 7.6, 5.3 Hz for the $\alpha$-proton of the ketone, confirming the selective reduction of the alkene in the enaminone system. The methyl protons were presented by a doublet with $J = 6.8$ H at $\delta$ 1.23 ppm indicating that there were diastereomers. The $^{13}$C NMR spectrum revealed the absence of quaternary alkene carbon peaks at $\delta$ 154.7 and 114.8 ppm of 338’s spectrum and the presence of peaks at $\delta$ 60.3 and 45.9 ppm for the $\delta$-carbon of the amide and for the $\alpha$-carbon of the ketone respectively.
4.2 Conclusion

The pyrido[1,2-a]azonine nucleus was synthesised but could not be functionalised to 342 by Baeyer Villiger oxidation and hydrolysis reactions owing to time constraints. It is essential that the synthesis of 342 is completed in the near future with chromatographic resolution of mixtures of diastereomers, and perhaps even enzymatic resolution of the racemates in order to achieve derivatives of Sessilifoliamide K (54) and L (55).
CHAPTER 5: EXPERIMENTAL

5.1 General experimental methods

Glassware was washed and dried in an oven at 110 °C for moisture sensitive reactions. Reactions were done either under nitrogen atmosphere, in vessels open to atmospheric pressure, in sealed tubes in a microwave reactor, and oven reactor as indicated for individual experiments. Solvents used in reactions were dried by distillation prior to use for moisture sensitive reactions. Tetrahydrofuran (THF) (stored over oven-activated 4Å molecular sieves) and toluene were distilled under nitrogen atmosphere from sodium, while using benzophenone as an indicator for the former. Acetonitrile (MeCN), dichloromethane DCM and N, N-dimethylformamide (DMF) were distilled under nitrogen from calcium hydride. High grade purity solvents were not pre-dried for reactions. Reaction work up generally involved quenching the reaction mixture with water, followed by adjusting the pH to pH~8 or as specified, extracting the aqueous layer with a suitable solvent and concentrating the organic layer with a brine wash. The organic layers were dried over magnesium sulphate; volatiles were removed in vacuo using a rotary evaporator and samples were prepared for purification.

Thin layer chromatography was performed on aluminium-backed AlugramSil G/UV$_{254}$ plates pre-coated with 0.25 mm silica gel 60 and separation patterns were visualized using ultraviolet light, potassium permanganate, vanillin developing reagent or iodine vapour. Samples were purified by column chromatography on silica gel (Merck, 60-230). Some samples were added as oils on silica gel and other samples were pre-dried onto silica in preparation for column chromatography and eluted with a predetermined distilled solvent mixture system that best separated compounds over retention time. Pure compounds were recovered after removing volatiles in vacuo followed by concentrating with an oil vacuum pump. Melting points were measured uncorrected on Stuart melting point SMP10 apparatus.
Compounds were analyzed using Infrared Spectroscopy (IR) on a Bruker Tensor 27 FTIR spectrometer with a diamond ATR attachment, revealing functional groups present indicated by absorptions on the cm\(^{-1}\) scale. Compounds were analyzed on a Bruker WM-300 instrument at 300 MHz for proton (\(^1\)H) NMR and at 75 MHz for carbon (\(^{13}\)C) NMR spectra, or a Bruker WM-500 instrument at 500 MHz for proton (\(^1\)H) NMR and at 126 MHz for carbon (\(^{13}\)C) NMR spectra. Samples were prepared using deuteriated chloroform, MeOH, DMSO or water, doped with tetramethylsilane (TMS) as an internal standard. Chemical shifts (\(\delta\)) are reported in parts per million (ppm) relative to TMS. The multiplicity is abbreviated as follows: d = doublet, m = multiplet, q = quartet, t = triplet and s = singlet. HRMS results were obtained from a Waters Synapt G2 with conditions: ESI probe injected into a stream of MeCN, ESI positive, cone voltage 15V.

5.2 Experimental Section for Chapter 2

Synthesis of ethyl 4-(4-chlorobutanamido)butanoate 139

To a two necked round bottom flask equipped with a reflux condenser under nitrogen atmosphere was added ethyl 4-aminobutyrate hydrochloride (1.124 g, 6.705 mmol, 1 eq), 4-chlorobutyl chloride 138 (0.91 mL, 8.046 mmol, 1.2 eq), NaHCO\(_3\) (1.368 g, 16.09 mmol, 2.4 eq) in DCM (25 mL). The reaction mixture was left to stir a room temperature for 17 h. The resulting reaction mixture was then heated under reflux for 1 h. A saturated solution of NaHCO\(_3\) was added to the reaction mixture after cooling, and the reaction mixture was extracted with DCM (5 x 20 mL). The resulting organic layer was dried over MgSO\(_4\) and the solvent evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20 – 50% EtOAc: Hex mixture to yield ethyl 4-(4-chlorobutanamido)butanoate 139 (1.567 g, 99%) as an oil; \(R_i\) 0.69 (EtOAc: Hex, 1:0); \(v_{\text{max}}/\text{cm}^{-1}\) 3304 (m, br, N-H), 2938 (w, C-H), 1730, 1644 (s, C=O), 1175 (s, C-O) and
1030 (m, C-N); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.19 (s, 1H), 4.12 – 4.07 (m, 2H), 3.58 – 3.54 (m, 2H), 3.26 – 3.25 (m, 2H), 2.34 – 2.30 (t, J = 5.4 Hz, 4H), 2.08 – 2.05 (m, 2H), 1.82 – 1.78 (m, 2H), 1.24 – 1.20 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.0, 171.8, 60.1, 44.2, 38.4, 34.2, 31.5, 27.9, 24.3, 14.0.

**Synthesis of ethyl 2-(2-oxopyrrolidin-1-yl)acetate 170**$^{162,163}$

![Chemical structure](image)

NaH 60% in oil (0.395 g, 16.45 mmol, 1.4 eq) was washed with Hex (3 × 5 mL) in a two necked round bottom flask under nitrogen atmosphere. Clean NaH was then dried under high vacuum. Pyrrolidin-2-one 140 (1.00 g, 11.8 mmol, 1 eq) in dry DCM (5 mL) was added to the two necked round bottom flask all at once. The reaction mixture was left to stir at room temperature for 20 minutes after which the sodium salt had precipitated. Ethyl 2-bromoacetate (1.55 mL, 14.10 mmol, 1.2 eq) in DCM (20 mL) was added all at once and the reaction mixture was left to stir at room temperature for 2 h. The reaction mixture was dissolved in water in a separating funnel and the organic was extracted with diethyl ether (3 × 40 mL). The resulting organic layer was dried over MgSO$_4$ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20 – 40% EtOAc: Hex to yield ethyl 2-(2-oxopyrrolidin-1-yl)acetate 170 (1.257 g, 62%) as an oil; $\nu_{\text{max}}$/cm$^{-1}$ 2950 (w, C-H), 1749 (s, C=O), 1186 (s, C-O) and 1034 (s, C-N); $^1$H NMR (300 MHz, CDCl$_3$) δ 3.87 (q, J = 7.1 Hz, 2H), 3.74 (s, 2H), 3.19 (t, J = 7.1 Hz, 2H), 2.09 (t, J = 8.1 Hz, 2H), 1.77 (dt, J = 11.2, 7.5 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.3, 168.4, 60.9, 47.4, 43.7, 30.0, 17.7, 13.8.

(ii) NaH 60% in oil (0.338 g, 14.10 mmol, 1.2 eq) was washed with Hex (3 × 5 mL) in a two necked round bottom flask under nitrogen atmosphere. Clean NaH was then dried under high vacuum. Pyrrolidin-2-one 140 (1.00 g, 11.75 mmol, 1 eq) in dry THF (5 mL) was added to the two necked round bottom flask all at once. The reaction mixture was left to stir at room temperature for 10 minutes after which the sodium salt had precipitated. Ethyl 2-bromoacetate (1.43 mL, 12.93 mmol, 1.1 eq) in THF (20 mL) was added all at once and the reaction mixture was left to stir at room temperature for 24 h. 1 M HCl was added to the reaction mixture adjusting the pH to
pH~5 and the organic was extracted with diethyl ether (3 × 40 mL). The resulting organic layer was dried over MgSO$_4$ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20 – 40% EtOAc: Hex to yield ethyl 2-(2-oxopyrrolidin-1-yl)acetate $\textit{170}$ (1.828 g, 91%) as oil; The analytical data was as shown above.

**Synthesis of tert-butyl 2-(2-oxopyrrolidin-1-yl)acetate $\textit{172}$**

![Chemical Structure](image)

\[\text{NaH 60\% in oil (0.395 g, 16.45 mmol, 1.4 eq) was washed with hexane (3 × 5 m) in a two necked round bottom flask under nitrogen atmosphere. Clean NaH was then dried under high vacuum. Pyrrolidin-2-one $\textit{140}$ (1.00 g, 11.75 mmol, 1 eq) in dry DCM (5 mL) was added to the two necked round bottom flask all at once. The reaction mixture was left to stir at room temperature for 20 minutes after which the sodium salt had precipitated. tert-Butyl 2-bromoacetate (2.08 mL, 14.10 mmol, 1.2 eq) in DCM (20 mL) was added all at once and the reaction mixture was left to stir at room temperature for 2 h. The reaction mixture was dissolved in water in a separating funnel and the organic layer was extracted with diethyl ether (3 × 40 mL). The resulting residue was purified by silica gel column chromatography eluting with 20 – 40% EtOAc: Hex to yield tert-butyl 2-(2-oxopyrrolidin-1-yl)acetate $\textit{172}$ (1.047 g, 48%) as a low melting solid; $\nu_{\max}$/cm$^{-1}$ 2997 (w, C-H), 1765 (s, C=O), 1170 (s, C-O) and 1011 (s, C-N); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.96 (s, 2H), 3.49 (t, $J = 7.0$ Hz, 2H), 2.42 (t, $J = 8.1$ Hz, 2H), 2.15 – 2.00 (m, 2H), 1.47 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.5, 167.7, 81.9, 47.6, 44.6, 30.3, 27.9, 17.9.]

(ii) NaH 60% in oil (0.338 g, 14.10 mmol, 1.2 eq) was washed with hexane (3 × 5 mL) in a two necked round bottom flask under nitrogen atmosphere. Clean NaH was then dried under high vacuum. Pyrrolidin-2-one $\textit{140}$ (1.00 g, 11.8 mmol, 1 eq) in dry THF (5 mL) was added to the two necked round bottom flask all at once. The reaction mixture was left to stir at room temperature for 10 minutes after which the sodium salt had precipitated. tert-Butyl 2-bromoacetate (1.91 mL, 12.93 mmol, 1.2 eq) in THF (20 mL) was added all at once and the reaction mixture was left to stir at
room temperature for 24 h. 1 M HCl was added to the reaction mixture adjusting the pH to pH~5 and the organic was extracted with diethyl ether (3 × 40 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20 – 40% EtOAc: Hex to yield tert-butyl 2-(2-oxopyrrolidin-1-yl)acetate 172 (2.0116 g, 90%) as a low melting solid; Analytical data was as shown above.

**Synthesis of ethyl 2-(2-thioxopyrrolidin-1-yl)acetate 171**

![](image)

Ethyl 2-(2-oxopyrrolidin-1-yl)acetate 170 (0.400 g, 2.34 mmol, 1 eq) and of P₂S₅ (0.240 g, 1.08 mmol, 1 eq) were reacted in DCM (50 mL) at room temperature for 20 h under nitrogen atmosphere. A saturated solution of K₂CO₃ was poured onto the reaction mixture and the organic layer was extracted with dichloromethane (3 × 20 mL). The resulting organic layer was then dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield ethyl 2-(2-thioxopyrrolidin-1-yl)acetate 171 (0.425 g, 97%) as an oil; Rf 0.29 (EtOAc: Hex, 3:7); ν<sub>max</sub>/cm⁻¹ 2954 (w, C-H), 1733 (s, C=O), 1131 (m, C-N) and 1034 (m, C-O); ¹H NMR (300 MHz, CDCl₃) δ 4.56 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.85 (t, J = 7.3 Hz, 2H), 3.06 (t, J = 7.9 Hz, 2H), 2.22 – 2.05 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 203.5, 167.0, 61.5, 55.5, 49.0, 44.3, 19.7, 14.1.

**Synthesis of tert-butyl 2-(2-thioxopyrrolidin-1-yl)acetate 173**

![](image)

tert-Butyl 2-(2-oxopyrrolidin-1-yl)acetate 172 (0.400 g, 2.01 mmol, 1 eq) and of P₂S₅ (0.206 g, 0.925 mmol, 1 eq) were reacted in DCM (50 mL) at room temperature for 20 h under nitrogen atmosphere. A saturated solution of K₂CO₃ was poured onto the reaction mixture and the organic layer was extracted with DCM (3 × 20 mL). The resulting organic layer was then dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography
eluting with 30% EtOAc: Hex to yield tert-butyl 2-(2-thioxopyrrolidin-1-yl)acetate 173 (0.385 g, 89%) as an oil; R_f 0.38 (EtOAc: Hex, 3:7); $\nu_{\text{max}}$/cm$^{-1}$ 2998 (w, C-H), 1747 (s, C=O), 1135 (m, C-N) and 1044 (m, C-O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.44 (s, 2H), 3.83 (t, $J$ = 7.3 Hz, 2H), 3.05 (t, $J$ = 7.9 Hz, 2H), 2.12 (dt, $J$ = 15.3, 7.8 Hz, 2H), 1.48 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 203.3, 166.1, 82.5, 55.5, 49.7, 44.3, 28.0, 19.7.

**Synthesis of 1-(4-hydroxybutyl)pyrrolidin-2-one 180 and 4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one 181**

Dihydrofuran-2(3H)-one 13 (0.483 g, 5.61 mmol, 1 eq) and 4-aminobutan-1-ol (0.500 g, 5.61 mmol, 1 eq) was reacted neat in a sealed tube reactor under microwave conditions: 150 W, 220 °C, 20 min. The resulting reaction mixture was cooled, dissolved in water and extracted with diethyl ether ($3 \times 10$ mL). The resulting organic layer was dried over MgSO$_4$ and then evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with 20% MeOH: EtOAc to yield 1-(4-hydroxybutyl)pyrrolidin-2-one 180 (0.247 g, 28%) as oil, and 4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one 181 (0.313 g, 35%) as oil.

1-(4-Hydroxybutyl)pyrrolidin-2-one 180: R_f 0.26 (MeOH: EtOAc, 1:4); $\nu_{\text{max}}$/cm$^{-1}$ 3441 (s, br, O-H), 2922 (w, C-H), 1669 (s, C=O), 1100 (m, C-O) and 1065 (m, C-N); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.81 (s, 1H), 3.63 (t, $J$ = 5.9 Hz, 2H), 3.41 (t, $J$ = 7.1 Hz, 2H), 3.30 (t, $J$ = 7.0 Hz, 2H), 2.39 (t, $J$ = 8.2 Hz, 2H), 2.11 – 1.77 (m, 2H), 1.71 – 1.47 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.2, 61.7, 47.1, 42.2, 31.1, 29.6, 23.6, 17.8.

4-Hydroxy-1-(pyrrolidin-1-yl)butan-1-one 181: (R_f 0.18 (MeOH: EtOAc, 1:4); $\nu_{\text{max}}$/cm$^{-1}$ 3420 (s, br, O-H), 2934 (w, C-H), 1667 (s, C=O), 1130 (m, C-O) and 1095 (m, C-N); $^1$H NMR (300 MHz, MeOD) $\delta$ 3.46 (t, $J$ = 6.4 Hz, 4H), 3.09 (t,
J = 6.5 Hz, 2H), 2.16 (t, J = 7.6 Hz, 2H), 1.77 – 1.62 (m, 2H), 1.45 (m, 4H); \(^{13}\)C NMR (75 MHz, MeOD) \(\delta\) 175.9, 62.6, 62.3, 40.2, 33.7, 31.0, 29.9, 26.9.

**Synthesis of 1-(5-hydroxypentyl)pyrrolidin-2-one 182 and 4-hydroxy-1-(piperidin-1-yl)butan-1-one 183**

Dihydrofuran-2(3H)-one 13 (0.834 g, 9.69 mmol, 1 eq) and 5-aminopentan-1-ol (1.00 g, 9.96 mmol, 1 eq) was reacted neat in a sealed tube reactor under microwave conditions: 150 W, 220 °C, 20 min. The resulting reaction mixture was cooled, dissolved in water and extracted with diethyl ether (3 × 10 mL). The resulting organic layer was dried over MgSO\(_4\) and then evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10% MeOH: EtOAc to yield 1-(5-hydroxypentyl)pyrrolidin-2-one 182 (0.405 g, 24%) as an oil, and 4-hydroxy-1-(piperidin-1-yl)butan-1-one 183 (0.905 g, 55%) as oil.

1-(5-Hydroxypentyl)pyrrolidin-2-one 182: \(R_f\) 0.37 (MeOH: EtOAc, 1:4); \(\nu_{\text{max/cm}^{-1}}\) 3384 (s, br, O-H), 2929 (w, C-H), 2918 (s, C=O), 1259 (m, C-O) and 1129 (m, C-N); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.75 (s, 1H), 3.59 (t, \(J = 6.5\) Hz, 2H), 3.40 (t, \(J = 7.1\) Hz, 2H), 3.27 (t, \(J = 7.2\) Hz, 2H), 2.38 (t, \(J = 8.1\) Hz, 2H), 2.10 – 1.95 (m, 2H), 1.64 – 1.47 (m, 4H), 1.40 – 1.32 (m, 2H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 175.1, 61.9, 47.1, 42.3, 32.1, 31.0, 26.9, 22.9, 17.7. The data agree with those reported previously for the compound.

4-Hydroxy-1-(piperidin-1-yl)butan-1-one 183: \(R_f\) 0.27 (MeOH: EtOAc, 1:4); \(\nu_{\text{max/cm}^{-1}}\) 3513 (s, br, O-H), 2968 (w, C-H), 1697 (s, C=O), 1230 (m, C-O) and 1140 (m, C-N); \(^1\)H NMR (300 MHz, MeOD) \(\delta\) 3.57 (td, \(J = 6.4, 3.5\) Hz, 4H), 3.18 (t, \(J = 6.9\) Hz, 2H), 2.27 (t, \(J = 7.5\) Hz, 2H), 1.90 – 1.75 (m, 2H), 1.64 – 1.46 (m, 4H), 1.46 – 1.32 (m, 2H) ppm; \(^{13}\)C NMR (75 MHz, MeOD) \(\delta\) 175.8, 62.9, 62.4, 40.5, 33.9, 33.4, 30.3, 30.0, 24.4.
Synthesis of 1-(3-hydroxypropyl)pyrrolidin-2-one 184

Dihydrofuran-2(3H)-one \(13\) (1.296 g, 15.05 mmol, 1.1 eq) and 3-aminopropan-1-ol (1.028 g, 13.68 mmol, 1 eq) were irradiated in a microwave reactor under these conditions (150 W, 200 \(^\circ\)C, 1 h, 10 min). The resulting reaction mixture was then cooled, dissolved in water and extracted with diethyl ether (3 \(\times\) 10 mL). The resulting organic layer was dried over \(\text{MgSO}_4\) and then evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with 10% EtOAc: Hex to yield 1-(3-hydroxypropyl)pyrrolidin-2-one \(184\) (1.959 g, 88%) as an oil; \(\nu_{\text{max}}/\text{cm}^{-1}\) 3449 (s, br, O-H), 2940 (w, C-H), 1632 (s, C=O), 1187 (s, C-O) and 1050 (s, C-N); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.23 (m, 1H), 3.24 – 2.90 (m, 6H), 2.00 (m, 2H), 1.68 (m, 2H), 1.36 (m, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 175.2, 61.2, 47.1, 42.2, 31.0, 29.6, 17.8. The data agree with those previously reported for the compound.\(^{165}\)

Synthesis of 1,6-oxazecane-2,7-dione 186a/186b

Dihydrofuran-2(3H)-one \(13\) (0.203 g, 2.40 mmol, 1.2 eq) and ethyl 4-aminobutyrate hydrochloride (0.335 g, 2.00 mmol, 1 eq) was reacted neat in a sealed tube reactor under microwave conditions: 150 W, 220 \(^\circ\)C, 10 min. The reaction mixture was cooled down to room temperature. The residue was purified by silica gel column chromatography eluting with 10 – 30% EtOAc: Hex to yield 1,6-oxazecane-2,7-dione \(186a/186b\) (0.342 g, 100%) as an oil; \(\nu_{\text{max}}/\text{cm}^{-1}\) 3400 – 3200 (s, br, N-H), 2967 (w, C-H) 1687 (s, C=O), 1122 (m, C-O) and 1043 (m, C-N); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.22 (s, 2H), 4.08 (t, \(J = 7.1\) Hz, 2H), 3.12 (t, \(J = 6.9\) Hz, 2H), 2.25 – 2.22 (m, 2H), 2.11 – 1.94 (m, 4H) and 1.91 – 1.73 (m, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 179.5, 177.9, 68.5, 42.3, 30.0, 27.6, 21.9, 20.5.

Dihydrofuran-2(3H)-one \(13\) (0.172 g, 2.0 mmol, 1 eq) and 4-aminobutyric acid (0.206 g, 2.0 mmol, 1 eq) was reacted neat in a sealed tube reactor under microwave
conditions: 2 x [100 W, 200 °C, 10 min]. The reaction mixture was cooled down to room temperature. The resulting residue was purified by silica gel column chromatography eluting with 10 – 30% EtOAc: Hex to yield 1,6-oxazecane-2,7-dione 186a/186b (0.341 g, 100%) as oil; The analytical data was as above.

**Ethyl 4-oxooctanoate 188**

Conditions (i): Ethyl 4-chloro-4-oxobutanoate (5.00 mL, 35 mmol, 1 eq) and Fe(acac)₃ (0.371 g, 1.05 mmol, 0.03 eq) were added to an oven-dried two necked round bottom flask containing dry THF (50 mL) under nitrogen atmosphere, equipped with a dropping funnel containing prepared n-butylmagnesium bromide (20 mL, 1.75 M, 35 mmol, 1 eq) in THF (50 mL). The reaction mixture in the round bottom flask was cooled to –35 °C (in a xylene liquid nitrogen bath) followed by the drop-wise addition of the contents in the dropping funnel over a period of 20 minutes while stirring. 10%(v/v) HCl was then added to quench the reaction mixture. The reaction mixture was then extracted with EtOAc (3× 50 mL), the combined extracts were then washed with saturated NaHCO₃ solution, distilled water and dried over MgSO₄. The extract was evaporated in vacuo and the resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex mixture to yield ethyl 4-oxooctanoate 188 (3.33 g, 51%) as an oil; Rᶠ 0.45 (EtOAc: Hex, 1:5); νₘₐₓ/cm⁻¹ 2991 (w, C-H), 1754 (s, C=O), 1241 (s, C-O); ¹H NMR (300 MHz, CDCl₃) δ 4.13 (q, J = 7.1 Hz, 2H), 2.72 (t, J = 6.3 Hz, 2H), 2.64 – 2.53 (m, 2H), 2.45 (t, J = 7.4 Hz, 2H), 1.67 – 1.50 (m, 2H), 1.40 – 1.20 (m, 5H), 0.91 (t, J = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 209.2, 172.9, 60.6, 42.5, 37.1, 28.0, 25.9, 22.3, 14.2, 13.8.

Conditions (iii): Ethyl 4-chloro-4-oxobutanoate (5.00 mL, 35 mmol, 1 eq), Fe(acac)₃ (0.371 g, 1.05 mmol, 0.03 eq) were added to an oven dried two necked round bottom flask containing dried THF (50 mL) under nitrogen atmosphere, equipped with a dropping funnel containing butylmagnesium chloride (20 mL, 1.6 M, 35 mmol, 1 eq) in THF (50 mL). The reaction mixture in the round bottom flask was cooled to –29 °C (in a xylene liquid nitrogen bath) followed by the drop-wise addition of the contents in the dropping funnel over a period of 9 minutes while stirring. The resulting reaction mixture was worked up as above. The resulting residue was purified by silica gel
column chromatography eluting with 2% to 5% EtOAc: Hex mixture to yield ethyl 4-oxooctanoate 188 (5.80 g, 89%) as oil. The analytical data is as shown above.

Conditions (iv): Ethyl 4-chloro-4-oxobutanoate (5.00 mL, 35 mmol, 1 eq) and Fe(acac)$_3$ (0.371 g, 1.05 mmol, 0.03 eq) were added to an oven dried two necked round bottom flask containing dried THF (50 mL), equipped with a dropping funnel containing butylmagnesium chloride (20 mL, 1.6 M, 35 mmol, 1 eq) in THF (50 mL). The reaction mixture in the round bottom flask was cooled to –78 °C (in an acetone liquid nitrogen bath) followed by the drop-wise addition of the contents in the dropping funnel over a period of 9 minutes while stirring. The resulting reaction mixture was worked up as above. The resulting residue was purified by silica gel column chromatography eluting with 2% to 5% EtOAc: Hex mixture to yield ethyl 4-oxooctanoate 188 (3.85 g, 59%) as oil. The analytical data is as shown above.

**Synthesis of (E)-1-(3,4-dimethoxyphenethyl)-5-butylidenepyrrolidin-2-one 193**

![Chemical structure](image)

Ethyl 4-oxooctanoate 188 (0.123 g, 0.731 mmol, 1 eq), homoveratrylamine 160 (0.146 g, 0.804 mmol, 1.1 eq), acetic acid (0.220 g, 3.66 mmol, 5 eq) and 4 Å molecular sieves were heated under reflux in toluene (45 mL) under nitrogen atmosphere for 45 h. The resulting reaction mixture was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield (E)-1-(3,4-dimethoxyphenethyl)-5-butylidenepyrrolidin-2-one 193 (0.148 g, 67%) as an oil; $R_f$ 0.20 (EtOAc: Hex, 3:7); $v_{max}$ /cm$^{-1}$ 2985 (w, C-H), 1751 (s, C=O), 1588 (m, aromatic, C=C), 1432 (m, C=C), 1132 (m, C-N) and 1023 (s, C-O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.85 – 6.70 (m, 3H), 4.70 (t, $J$ = 7.5 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.66 (dd, $J$ = 9.0, 6.9 Hz, 2H), 2.78 (dd, $J$ = 8.9, 6.9 Hz, 2H), 2.67 – 2.55 (m, 2H), 2.46 (dd, $J$ = 9.7, 5.3 Hz, 2H), 2.00 (dt, $J$ = 11.8, 5.8 Hz, 2H), 1.49 – 1.34 (m, 2H), 0.93 (t, $J$ = 7.3 Hz, 3H).
Synthesis of 4-oxooctanoic acid 194

![4-Oxooctanoic acid](image)

Ethyl 4-oxooctanoate 188 (0.500 g, 2.68 mmol, 1) was reacted with KOH (0.451 g, 8.04 mmol, 3 eq) in distilled water (30 mL) in an open vessel for 2 h. 1M HCl was added to the reaction mixture to adjust pH to pH~5. The organic layer was extracted with EtOAc (3 × 20 mL). The resulting organic layer was then dried over MgSO₄ and evaporated in vacuo to yield 4-oxooctanoic acid 194 (0.399 g, 94%) as a solid; ν_max/cm⁻¹ 3400 (m, br, O-H), 2999 (w, C-H) and 1766 (s, C=O); ^1H NMR (300 MHz, CDCl₃) δ 11.12 (s, 1H), 2.65 (t, J = 6.5 Hz, 2H), 2.54 (dd, J = 9.7, 3.8 Hz, 2H), 2.38 (t, J = 7.4 Hz, 2H), 1.49 (dt, J = 15.3, 7.5 Hz, 2H), 1.24 (dq, J = 14.5, 7.3 Hz, 2H), 0.82 (t, J = 7.3 Hz, 3H); ^13C NMR (75 MHz, CDCl₃) δ 209.3, 178.7, 42.3, 36.7, 27.7, 25.8, 22.2, 13.7.

Synthesis of (E)-ethyl 4-(2-butylidene-5-oxopyrrolidin-1-yl)butanoate 189

![4-Oxooctanoic acid](image)

4-Oxooctanoic acid 194 (1.50 g, 9.48 mmol, 1 eq) and SOCl₂ (1.13 g, 9.48 mmol, 1 eq) in toluene (20 mL) was heated under reflux for 3.5 h under nitrogen atmosphere. Ethyl 4-aminobutyrate hydrochloride (2.38 g, 14.22 mmol, 1.5 eq) and K₂CO₃ (3.94 g, 28.44 mmol, 3 eq) were added to the reaction mixture and left heating under reflux for 12.5 h. Water was added to the reaction mixture followed by acetic acid adjusting the pH the pH~8. The resulting reaction mixture was then extracted with ethyl acetate (3 × 50 mL). The collected extracts were washed with water (100 mL) and brine (100 mL). The organic layer was dried over MgSO₄, evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5 – 30% EtOAc: Hex to yield (E)-ethyl 4-(2-butylidene-5-oxopyrrolidin-1-yl)butanoate 189 (0.4806 g, 20%) as a brown oil; R_f 0.22 (EtOAc: Hex, 1:1); ν_max/cm⁻¹ 2987 (w, C-H), 1720 (s, C=O), 1468 (m, C=C) and 1127 (m, C-
O); $^1$H NMR (300 MHz, CDCl$_3$) δ 4.72 (t, $J = 7.5$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.56 – 3.45 (m, 2H), 2.67 – 2.56 (m, 2H), 2.53 – 2.43 (m, 2H), 2.33 (t, $J = 7.4$ Hz, 2H), 1.99 (dd, $J = 14.6, 7.4$ Hz, 2H), 1.93 – 1.81 (m, 2H), 1.41 (dq, $J = 14.5, 7.3$ Hz, 2H), 1.26 (t, $J = 7.1$ Hz, 3H), 0.97 – 0.86 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.5, 173.0, 139.0, 100.7, 60.5, 39.0, 31.6, 28.9, 28.8, 23.3, 21.9, 21.4, 14.2, 13.7; HRMS (ESI): m/z [M+H]$^+$ found 254.1733, calcd for C$_{14}$H$_{24}$NO$_3$ $^+$ 254.1751.

4-Oxooctanoic acid 194 (0.369 g, 2.33 mmol, 1 eq) and thionyl chloride (0.17 mL, 2.33 mmol, 1 eq) were heated under reflux in toluene (30 mL) under nitrogen atmosphere in a two neck-round bottom flask equipped with condenser for 2 h. Ethyl 4-aminobutyrate hydrochloride (0.469 g, 2.80 mmol, 1.2 eq) and acetic acid (0.67 mL, 11.7 mmol, 5 eq) were added into the resulting reaction mixture and heated under reflux for 42 h. The resulting reaction mixture was evaporated in vacuo. The resulting residue was dissolved in water and extracted with DCM (3 × 30 mL). The resulting organic layer was dried over MgSO$_4$ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10 – 30% EtOAc: Hex to yield (E)-ethyl 4-(2-butylidene-5-oxopyrrolidin-1-yl)butanoate 189 (0.214 g, 36%) as an oil; R$_f$ 0.25 (EtOAc: Hex, 3:7); $\nu_{\text{max}}$/cm$^{-1}$ 2993 (w, C-H), 1692 (s, C=O), 1401 (m, C=C), 1112 (m, C-N) and 1066 (m, C-O); $^1$H NMR (300 MHz, CDCl$_3$) δ 4.75 (t, $J = 6.2$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.51 (t, $J = 7.1$ Hz, 2H), 2.65 – 2.61 (m, 2H), 2.58 – 2.51 (m, 2H), 2.45 (t, $J = 7.3$ Hz, 2H), 2.03 – 1.98 (m, 2H), 1.94 – 1.91 (m, 2H), 1.47 – 1.43 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.96 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.6, 172.9, 138.9, 100.7, 60.3, 38.9, 31.4, 28.8, 28.7, 23.2, 21.8, 21.3, 13.9, 13.2.

**Synthesis of (E)-5-butylidene-1-(4-hydroxybutyl)pyrrolidin-2-one 198**

![Chemical structure of 198](image)

Ethyl 4-oxooctanoate 188 (1.34 g, 7.21 mmol, 1 eq), 4-amino-1-butanol (0.643 g, 7.21 mmol, 1 eq) and acetic acid (2.17 g, 3.6 mmol, 5 eq) were heated under reflux in toluene (20 mL) under nitrogen atmosphere for 90 h. Saturated NaHCO$_3$ was added to the cooled reaction mixture and was extracted with
DCM (3 × 30 mL). The organic solvent was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10, 20, 33, 40% EtOAc: Hex to yield (E)-5-butylidene-1-(4-hydroxybutyl)pyrrolidin-2-one 198 (0.3595 g, 24%) as an oil; Rf 0.41 (EtOAc: Hex, 1:3); v_max /cm⁻¹ 3386 (m, br, OH), 2982 (w, C-H), 1711 (s, C=O), 1465 (m, C=C), 1123 (m, C-N) and 1034 (s, C-O); ¹H NMR (300 MHz, CDCl₃) δ 4.65 (ddd, J = 7.4, 4.8, 2.2 Hz, 1H), 4.08 (t, J = 5.9 Hz, 2H), 3.49 (t, J = 6.6 Hz, 2H), 2.61 (dd, J = 14.1, 6.0 Hz, 2H), 2.48 (dt, J = 7.2, 2.7 Hz, 2H), 2.03 – 1.93 (m, 2H), 1.71 – 1.52 (m, 4H), 1.41 (dq, J = 14.5, 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 139.1, 100.6, 64.0, 39.3, 28.9, 28.8, 26.2, 23.3, 21.4, 13.7.

**Synthesis of N-allyl-4-hydroxyoctanamide 202**

5-Butyl-dihydrofuran-2(3H)-one 200 (0.800 g, 5.63 mmol, 1 eq) and allylamine (0.321 g, 5.63 mmol, 1 eq) and HCl (10 drops) were irradiated neat in a microwave reactor under these conditions (Stage 1: 100 w, 60 °C, 1 h; Stage 2: 150 w, 100°C, 0.5 h). The resulting reaction mixture was cooled, dissolved in water and extracted with diethyl ether (3 × 5 mL). The resulting organic layer was dried over MgSO₄ and then evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 40% EtOAc: Hex to yield N-allyl-4-hydroxyoctanamide 202 (0.769 g, 69%) as an oil; Rf 0.13 (EtOAc: Hex, 2:3); v_max /cm⁻¹ 3540 (s, br, O-H), 3420 (s, br, N-H), 2927 (w, C-H), 1734 (m, C=O), 1643 (m, C=C), 1137 (s, C-O) and 1027 (s, C-N); ¹H NMR (300 MHz, CDCl₃) δ 6.96 (s, 1H), 5.75 (dtd, J = 15.8, 10.6, 5.5 Hz, 1H), 5.07 (dd, J = 13.7, 11.6, 1.4 Hz, 2H), 4.06 (s, 1H), 3.76 (m, 2H), 3.52 (m, 1H), 2.32 (t, J = 7.0 Hz, 2H), 1.78 (dt, J = 10.4, 7.3, 3.0 Hz, 1H), 1.67 – 1.49 (m, 1H), 1.48 – 1.13 (m, 6H), 0.83 (t, J = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 174.1, 134.2, 116.0, 71.0, 41.9, 37.2, 33.0, 32.8, 27.9, 22.7, 14.0; HRMS (ESI): m/z [M+H]⁺ found 200.1654, calcd for C₁₁H₂₂NO₂⁺ 200.1645.
**Synthesis of ethyl 2-(2-oxoazepan-1-yl)acetate 204**

\[ \begin{align*} \text{C} & \quad \text{N} \\ & \quad \text{C} \end{align*} \]

Na\textsubscript{H} 60\% in oil (2.121 g, 53.01 mmol, 1 eq) was washed with Hex (3 x 10 mL) in a two necked round bottom flask under nitrogen atmosphere. Clean Na\textsubscript{H} was then dried under high vacuum. Azepan-2-one 175 (6.00 g, 53.0 mmol, 1 eq) in dry THF (30 mL) was added to the two necked round bottom flask all at once. The reaction mixture was left to stir at room temperature for 0.5 h after which the sodium salt had precipitated. Ethyl 2-bromoacetate (5.88 mL, 53.0 mmol, 1 eq) in THF (30 mL) was added all at once and the reaction mixture was left to stir at room temperature overnight. The reaction mixture was dissolved in water in a separating funnel and the organic layer was extracted with diethyl ether (3 x 40 mL). The resulting residue was purified by silica gel column chromatography eluting with 20 – 50\% EtOAc: Hex to yield (E)-ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 204 (0.833 g, 73\%) as a solid; R\textsubscript{f} 0.47 (EtOAc: Hex, 3:2); \nu\textsubscript{max}/cm\textsuperscript{-1} 2937 (w, C-H), 1721 (s, C=O), 1232 (s, C-O) and 1045 (s, C-N); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 4.18 (m, 4H), 3.42 (m, 2H), 2.62 – 2.53 (m, 2H), 1.74 (m, 6H), 1.28 (t, J = 7.1, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta 176.2, 169.7, 61.0, 51.2, 50.4, 36.9, 29.9, 28.0, 23.2, 14.1.

**Synthesis of tert-butyl 2-(2-oxoazepan-1-yl)acetate 205**

\[ \begin{align*} \text{O} & \quad \text{N} \\ & \quad \text{O} \end{align*} \]

Na\textsubscript{H} 60\% in oil (0.254 g, 10.60 mmol, 1.2 eq) was washed with Hex (3 x 5 mL) in a two necked round bottom flask under nitrogen atmosphere. Clean Na\textsubscript{H} was then dried under high vacuum. Azepan-2-one 175 (1.00 g, 8.84 mmol, 1 eq) in dry THF (20 mL) was added to the two necked round bottom flask all at once. The reaction mixture was left to stir at room temperature for 10 minutes after which the sodium salt had precipitated. tert-Butyl 2-bromoacetate (1.57 mL, 10.60 mmol,
1.2 eq) in THF (20 mL) was added all at once and the reaction mixture was left to stir at room temperature for 22 h. The reaction mixture was dissolved in water in a separating funnel and the organic was extracted with diethyl ether (3 × 40 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20 – 50% EtOAc: Hex to yield tert-butyl 2-(2-oxoazepan-1-yl)acetate 205 (1.940 g, 97%) as a solid; Rf 0.43 (EtOAc: Hex, 3:2); νmax/cm⁻¹ 2940 (w, C-H), 1732 (s, C=O), 1221 (s, C-O) and 1015 (s, C-N); ¹H NMR (300 MHz, CDCl₃) δ 4.05 (s, 2H), 3.40 (m, 2H), 2.64 – 2.51 (m, 2H), 1.74 (s, 6H), 1.47 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 176.1, 168.8, 81.5, 51.1, 36.9, 29.9, 28.0, 28.0, 23.2.

**Synthesis of ethyl 2-(2-thioxoazepan-1-yl)acetate 208¹⁴⁷**

![Image](image-url)

Ethyl 2-(2-oxoazepan-1-yl)acetate 204 (9.50 g, 47.7 mmol, 1 eq), P₂S₅ (5.299 g, 23.84 mmol, 0.5 eq) and hexamethyldisiloxane (11.612 g, 71.51 mmol, 1.5 eq) were stirred in DCM (500 mL) at room temperature for 24 h under nitrogen atmosphere. A saturated solution of NaHCO₃ was poured onto the reaction mixture and the organic layer was extracted with DCM (3 × 50 mL). The resulting organic layer was then dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20% ethyl acetate: hexane to yield ethyl 2-(2-thioxoazepan-1-yl)acetate 208 (10.3 g, 82%) as an oil; Rf 0.62 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 2928 (w, C-H), 1739 (s, C=O), 1185 (s, C-O) and 1118 (s, C-N); ¹H NMR (300 MHz, CDCl₃) δ 4.61 (s, 2H), 4.07 (q, J = 7.1, 2H), 3.60 (m, 2H), 3.03 (m, 2H), 1.63 (m, 6H), 1.14 (t, J = 7.1, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 208.6, 167.7, 61.4, 58.6, 55.9, 46.7, 29.2, 26.5, 24.6, 14.1; HRMS (ESI): m/z [M+H]⁺ found 216.1063, calcd for C₁₀H₁₈NO₂S⁺ 216.1053.
Synthesis of tert-butyl 2-(2-thiooxazepan-1-yl)acetate 209

![Chemical Structure](image)

tert-Butyl 2-(2-oxoazepan-1-yl)acetate 205 (1.00 g, 4.40 mmol, 1 eq), P$_2$S$_5$ (0.450 g, 2.024 mmol, 0.46 eq) were stirred in DCM (40 mL) at room temperature for 5 days under nitrogen atmosphere. A saturated solution of K$_2$CO$_3$ was poured onto the reaction mixture and the organic layer was extracted with DCM (3 × 30 mL). The resulting organic layer was then dried over MgSO$_4$ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20% EtOAc: Hex to yield tert-butyl 2-(2-thiooxazepan-1-yl)acetate 209 (0.378 g, 35%) as an oil; R$_f$ 0.53 (EtOAc: Hex, 1:1); $\nu_{\text{max}}$/cm$^{-1}$ 2995 (w, C-H), 1741 (s, C=O), 1176 (s, C-O) and 1127 (s, C-N); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.63 (s, 2H), 3.75 (d, $J$ = 5.4 Hz, 2H), 3.17 (d, $J$ = 6.1 Hz, 2H), 1.78 (s, 6H), 1.48 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 207.9, 166.6, 82.0, 59.5, 56.0, 46.7, 29.2, 28.0, 26.4, 24.5.

Synthesis of (E)-ethyl 2-(2-oxo-2-phenylethylidene)azepan-1-yl)acetate 215

![Chemical Structure](image)

Phenacyl bromide (0.490 g, 2.46 mmol, 1 eq) was added to a solution of ethyl 2-(2-thiooxazepan-1-yl)acetate 208 (0.500 g, 2.46 mmol, 1 eq) in dry MeCN (10.00 mL). The resulting solution was stirred at room temperature for 2 h under nitrogen atmosphere, after which the S-alkylation was complete shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (0.56 mL, 2.46 mmol, 1 eq) and triethylamine (0.25 mL, 2.46 mmol, 1eq) in MeCN (20 ml) to induce sulphur extrusion, left to stir at room temperature overnight. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5 – 30% EtOAc: Hex to yield to (E)-ethyl 2-(2-oxo-2-phenylethylidene)azepan-1-yl)acetate 215 (0.592 g, 83%) as an oil; R$_f$ 0.50 (EtOAc: Hex, 1:1); $\nu_{\text{max}}$/cm$^{-1}$ 2932 (w, C-H),
1709 (s, C=O), 1599 (s, C=C), 1265 (s, C-O) and 1223 (s, C-N); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.81 (dd, $J = 7.8, 1.7, 2$H), 7.37 (m, 3H), 5.47 (s, 1H), 4.23 (q, $J = 7.1$, 2H), 4.07 (s, 2H), 3.56 (m, 2H), 3.50 (m, 2H), 1.73 (m, 6H), 1.28 (t, $J = 7.1$, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 188.4, 169.2, 169.0, 142.6, 130.5, 128.0, 127.3, 92.7, 61.5, 55.6, 54.7, 29.5, 27.8, 27.8, 25.5, 14.2; HRMS (ESI): m/z [M+H$_2$O+H]$^+$ found 320.1867, calcd for C$_{18}$H$_{26}$NO$_4$+ 320.1856.

**Synthesis of (E)-ethyl 2-(2-(2-(4-nitrophenyl)-2-oxoethylidene)azepan-1-yl)acetate 216$^{151,161}$**

$\text{C}_2\text{N}$

p-Nitrophenacyl bromide (0.600 g, 2.46 mmol, 1 eq) was added to a solution of ethyl 2-(2-thioxoazepan-1-yl)acetate 208 (0.500g, 2.46 mmol, 1 eq) in dry MeCN (10.00 mL). The resulting solution was stirred at room temperature for 2 h under nitrogen atmosphere, after which the S-alkylation was complete shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (0.56 mL, 2.46 mmol, 1 eq) and triethylamine (0.25 mL, 2.46 mmol, 1 eq) in MeCN (20 mL) to induce sulphur extrusion, left to stir at room temperature over night. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5 – 30% EtOAc: Hex to yield (E)-ethyl 2-(2-(4-nitrophenyl)-2-oxoethylidene)azepan-1-yl)acetate 216 (0.711 g, 86%) as a solid; melting point = 119 – 121 °C; $R_f$ 0.55 (EtOAc: Hex, 1:1); $\nu_{max}$/cm$^{-1}$ 2935 (w, C=H), 1698 (m, C=O), 1603 (m, C=C), 1525 (s, aromatic, N-O), 1347 (s, aromatic, C=C) 1105 (w, C-O) and 1014 (s, N-O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.23 (d, $J = 8.9$, 2H), 7.91 (d, $J = 8.9$, 2H), 7.41 (d, $J = 8.9$, 2H), 5.40 (s, 1H), 4.27 (q, $J = 7.1$, 2H), 4.11 (s, 2H), 3.62 (m, 2H), 3.53 (m, 2H), 1.77 (m, 6H), 1.31 (t, $J = 7.1$, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 185.8, 171.0, 168.6, 148.8, 148.2, 128.2, 123.3, 92.4, 61.7, 55.7, 55.1, 29.5, 28.0, 27.5, 25.2, 14.3; HRMS (ESI): m/z [M+H]$^+$ found 347.1614, calcd for C$_{18}$H$_{23}$N$_2$O$_4^+$ 347.1601.
Synthesis of (E)-ethyl 2-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)azepan-1-syl)acetate 217\textsuperscript{151,161}

2-Bromo-1-(4-methoxyphenyl)ethanone (0.532 g, 2.32 mmol, 1 eq) was added to a solution of ethyl 2-(2-thioxoazepan-1-yl)acetate 208 (0.500 g, 2.32 mmol, 1 eq) in dry MeCN (5.00 mL). The resulting solution was stirred at room temperature for 40 min, after which the S-alkylation was complete as shown by the base-line spot on the TLC. This was then followed by the addition of triethylphosphite (0.462 g, 2.78 mmol, 1.2 eq) and triethylamine (0.281 g, 2.78 mmol, 1.2 eq) in acetonitrile (15 mL) to induce sulphur extrusion, left to stir at room temperature over night. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5 – 30% EtOAc: Hex to yield (E)-ethyl 2-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)azepan-1-yl)acetate 217 (0.166 g, 22%) as an oil; R\textsubscript{f} 0.44 (EtOAc: Hex, 1:1); \(v_{\text{max}}/\text{cm}^{-1}\) 2990 (w, C-H), 1756 (m, C=O), 1520 (m, C=C), 1468 (m, aromatic, C=C) and 1220 (m, C-O); \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.81 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 6.88 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 5.48 (s, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.07 (s, 2H), 3.84 (s, 3H), 3.57 (m, 2H), 3.53 – 3.42 (m, 2H), 1.74 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 187.6, 169.3, 168.5, 161.7, 135.2, 129.4, 113.2, 92.6, 61.5, 55.7, 55.3, 54.7, 29.6, 28.0, 27.9, 25.7, 14.3; HRMS (ESI): m/z [M+H\textsubscript{2}O+H]\textsuperscript{+} found 350.1969, calcd for C\textsubscript{19}H\textsubscript{28}NO\textsubscript{5}\textsuperscript{+} 350.9162.
Synthesis of ethyl 2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 222

(E)-Ethyl 2-(2-(2-oxo-2-phenylethylidene)azepan-1-yl)acetate 215 (0.699 g, 2.22 mmol, 1 eq) in DMA (2 mL) was irradiated in a microwave reactor under these conditions (Stage 1: 150 W, 150 °C, 10 min; Stage 2: 150 W, 165 °C, 10 min; Stage 3: 150 W, 180 °C, 40 min). The resulting reaction mixture was cooled, dissolved in water and extracted with diethyl ether (3 × 5 ml). The resulting organic layer was dried over MgSO₄ and then evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10% EtOAc: Hex to yield ethyl 2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 222 (0.319 g, 51%) as an oil; Rf 0.83 (EtOAc: Hex, 1:1); vmax/cm⁻¹ 2927 (w, C-H), 1683 (s, C=O), 1471, 1434 (m, C=C), 1183 (s, C-O) and 1122 (s, C-N); ¹H NMR (300 MHz, CDCl₃) δ 7.44 – 7.17 (m, 5H), 5.93 (s, 1H), 4.52 (s, 2H), 4.07 (q, J = 7.1 Hz, 2H), 2.87 – 2.66 (m, 2H), 1.97 – 1.59 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 162.2, 142.3, 137.3, 132.7, 129.5, 127.5, 126.3, 118.3, 109.6, 59.7, 46.5, 31.0, 28.9, 28.1, 27.4, 13.7; HRMS (ESI): m/z [M+H]⁺ found 284.1652, calcd for C₁₈H₂₂NO₂⁺ 284.1645.

Synthesis of ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 223

(E)-Ethyl 2-(2-(4-nitrophenyl)-2-oxoethylidene)azepan-1-yl)acetate 216 (0.599 g, 1.73 mmol, 1 eq) in DMA (2 mL) was irradiated in a microwave reactor...
under these conditions (Stage 1: 150 W, 150 °C, 10 min; Stage 2: 150 W, 165 °C, 10 min; Stage 3: 150 W, 180 °C, 40 min). The resulting reaction mixture was cooled, dissolved in water and extracted with diethyl ether (3 ×5 mL). The resulting organic layer was dried over MgSO₄ and then evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10% EtOAc: Hex to yield ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 223 (0.509 g, 90%) as an oil; Rf 0.81 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 2930 (w, C-H), 1692 (m, C=O), 1598 (m, C=N), 1517 (m, aromatic, C=C) and 1345 (s, C-O); ¹H NMR (300 MHz, CDCl₃) δ 8.17 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 5.96 (s, 1H), 4.55 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.86 – 2.69 (m, 2H), 1.95 – 1.59 (m, 6H), 1.05 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 161.6, 146.3, 144.5, 142.8, 130.2, 130.0, 122.7, 118.7, 109.4, 60.0, 46.7, 30.8, 28.7, 28.0, 27.3, 13.8; HRMS (ESI): m/z [M+H]+ found 329.1506, calcd for C₁₈H₂₁N₂O₄⁺ 329.1496.

Synthesis of ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 224

(E)-Ethyl 2-(2-(4-methoxyphenyl)-2-oxoethylidene)azepan-1-ylacetate 217 (20.1 mg, 6.67×10⁻² mmol, 1 eq) in DMA (2 ml) was irradiated in a microwave reactor under these conditions (Stage 1: 150 W, 150 °C, 10 min; Stage 2: 150 W, 165 °C, 10 min; Stage 3: 150 W, 180 °C, 10 min). The resulting reaction mixture was then cooled, dissolved in water and extracted with diethyl ether (3 × 5 mL). The resulting organic layer was dried over MgSO₄ and then evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10% EtOAc: Hex to yield ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 224 (0.0003 g, 1.58%) as an oil; Rf 0.79 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 2891 (w, C-H), 1774 (m, C=O), 1580, 1469 (m, aromatic, C=C) and 1122 (m, C-O); ¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, J = 8.6 Hz,
with unresolved fine coupling, 2H), 6.87 (m, d, J = 8.6 Hz, with unresolved fine coupling, 2H), 5.90 (s, 1H), 4.51 (s, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.77 – 2.72 (m, 2H), 1.85 – 1.75 (m, 4H), 1.69 (dt, J = 10.5, 5.3 Hz, 2H), 1.06 (t, J = 7.1 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 162.3, 158.3, 142.4, 132.4, 130.6, 129.8, 118.2, 112.8, 109.6, 59.6, 55.3, 46.5, 31.0, 28.9, 28.1, 27.4, 13.9; HRMS (ESI): m/z [M+H]+ found 314.1758, calcd for C19H24NO3+ 314.1751.

**Synthesis of (2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-3-yl)methanol 225**

To a solution of ethyl 2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 222 (0.100 g, 0.353 mmol, 1 eq) in THF (10 mL) at 0 °C was added LiAlH4 (0.013 g, 0.353 mmol, 1 eq). The reaction mixture was left to stir at room temperature for 12 h. The reaction mixture was adsorbed onto silica and was purified by silica gel column chromatography eluting with 30 – 50% EtOAc: Hex to yield (2-phenyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-3-yl)methanol 225 (0.084 g, 94%) as an oil; Rf 0.59 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 3340 (s, br, O-H), 2927 (w, C-H), 1709 (s, C=C), 1443 (m, aromatic, C=C), 1265 (s, C-O) and 1221 (s, C-N); 1H NMR (300 MHz, CDCl3) δ 7.43 –7.15 (m, 5H), 5.98 (s, 1H), 4.62 (s, 2H), 4.11 – 3.96 (m, 2H), 3.50 (d, J = 4.9 Hz, 1H), 2.81 – 2.66 (m, 2H), 1.92 – 1.69 (m, 6H).
Synthesis of (2-(4-aminophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-3-yl)methanol 226

To a solution of ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylate 223 (0.100 g, 0.353 mmol, 1 eq) in THF (10 mL) at 0 °C was added LiAlH₄ (0.013 g, 0.353 mmol, 1 eq). The reaction mixture was left to stir at room temperature for 6 h. The reaction mixture was adsorbed onto silica and was purified by silica gel column chromatography eluting with 30 – 50% EtOAc:Hex to yield (2-(4-aminophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-3-yl)methanol 226 (0.051 g, 61%) as an oil; Rᶠ 0.49 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 3450 (s, br, O-H), 3330 (s, br, N-H), 2921 (w, C-H), 1484 (s, C=C, aromatic), 1203 (m, C=O), 1130 (m, C-N) and 1017 (m, N-O); ¹H NMR (300 MHz, DMSO-d₆) δ 7.87 (d, J = 8.4 Hz, 2H), 7.71 – 7.53 (d, J = 8.3 Hz, 2H), 6.05 (s, 1H), 5.14 (t, J = 4.6 Hz, 1H), 4.48 (d, J = 3.9 Hz, 2H), 4.04 (m, 2H), 2.66 (m, 2H), 1.88 – 1.46 (m, 6H); ¹³C NMR (126 MHz, DMSO) δ 149.6, 140.0, 136.0, 128.5, 128.0, 122.7, 120.5, 104.9, 52.7, 45.2, 30.3, 29.1, 27.9, 27.4.

Azepane-2-thione 229

Azepan-2-one 175 (5.00 g, 44.2 mmol, 1 eq) and P₂S₅ (6.527 g, 22.09 mmol, 1 eq) were stirred in DCM (150 mL) at room temperature for 17 h under nitrogen atmosphere. A saturated solution of NaHCO₃ was poured into the reaction mixture and the organic layer was extracted with DCM (3 × 50 mL). The resulting organic layer was then dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc:Hex to yield azepane-2-thione 229 (2.30 g, 40%) as a solid; melting point = 103 –
104 °C; Rf 0.42 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 3423 (m, br, N-H), 2936 (w, C-H); ¹H NMR (300 MHz, CDCl₃) δ 8.84 (s, 1H), 3.38 (dd, J = 5.6, J = 9.7, 2H), 2.99 (m, 2H) and 1.81 – 1.71 (m, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 210.7, 47.4, 45.2, 30.6, 28.4, 24.8.

To a 250 mL two necked round bottom flask containing DCM (150 mL) equipped with a nitrogen line was added ε-caprolactam 175 (5.00 g, 44.2 mmol, 1 eq), HMDSO (10.761 g, 66.27 mmol, 1.5 eq) and P₂S₅ (4.517 g, 20.32 mmol, 0.46 eq), which were reacted at room temperature for 24 h. A saturated solution of NaHCO₃ was poured onto the reaction mixture and the organic layer was extracted with DCM (3 × 50 mL). The resulting organic layer was then dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield azepane-2-thione 229 (5.083 g, 89%) as a solid. The analytical data is as above.

**Synthesis of (Z)-2-(azepan-2-ylidene)-1-phenylethanone 230**¹⁵¹,¹⁶¹

![Structural formula](image)

2-Bromo-1-phenylethanone (1.11 g, 5.57 mmol, 1.2 eq) was added to a solution of azepane-2-thione 229 (0.600 g, 4.64 mmol, 1 eq) in dry MeCN (5 mL). The resulting solution was stirred at room temperature 1 minute, after which the completion of S-alkylation was shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (0.96 mL, 5.57 mmol, 1.2 eq) and triethylamine (0.78 mL, 5.57 mmol, 1.2 eq) in MeCN (35 mL) and left stirring at room temperature for 2 days to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield (Z)-2-(azepan-2-ylidene)-1-phenylethanone 230 (0.995 g, 100%) as a solid; melting point = 75 – 76 °C; Rf 0.66 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 3400 – 3200 (s, br, N-H), 2925 (w, C-H), 1740 (m, C=O), 1586 (m, C=C) and 1546 - 1436 (m, aromatic, C=C); ¹H NMR (300
MHz, CDCl$_3$) δ 11.55 (s, 1H), 7.86 (m, 2H), 7.39 (m, 3H), 5.67 (s, 1H), 3.42 (dd, $J$ = 10.0, 5.8 Hz, 2H), 2.55 – 2.37 (m, 2H), 1.91 – 1.52 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 188.2, 171.4, 140.7, 130.4, 128.1, 126.9, 91.0, 44.4, 35.4, 30.6, 29.3, 25.9; HRMS (ESI): m/z [M+H]$^+$ found 216.1393, calcd for C$_{14}$H$_{15}$NO$^+$ 216.1383.

**Synthesis of (Z)-2-(azepan-2-ylidene)-1-(4-nitrophenyl)ethanone 231$^{151,161}$**

2-Bromo-1-(4-nitrophenyl)ethanone (1.36 g, 5.57 mmol, 1.2 eq) was added to a solution of azepane-2-thione 229 (0.600 g, 4.64 mmol, 1 eq) in dry MeCN (5 mL). The resulting solution was stirred at room temperature 30 seconds, after which the S-alkylation was complete as shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (0.96 mL, 5.57 mmol, 1.2 eq) and triethylamine (0.78 mL, 5.57 mmol, 1.2 eq) in MeCN (35 mL) and left stirring at room temperature for 2 days to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield (Z)-2-(azepan-2-ylidene)-1-(4-nitrophenyl)ethanone 231 (1.083 g, 90%) as a solid; melting point = 143 – 144 °C; R$_f$ 0.27 (EtOAc: Hex, 1:1); $\nu$$_{\text{max}}$/cm$^{-1}$ 3400 – 3200 (m, N-H), 2926 (w, C-H), 1736 (m, C=O), 1589 (m, C=C), 1546 (s, aromatic, N-O), 1474 (m, aromatic, C=C) and 1336 (s, aromatic, C-N); $^1$H NMR (300 MHz, CDCl$_3$) δ 11.69 (s, 1H), 8.24 (d, J = 8.9 Hz, 2H), 7.98 (d, J = 8.9 Hz, 2H), 5.67 (s, 1H), 3.61 – 3.35 (m, 2H), 2.62 – 2.40 (m, 2H), 1.73 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 185.0, 172.8, 153.8, 146.2, 127.8, 123.5, 91.7, 44.7, 35.4, 30.6, 29.0, 25.6; HRMS (ESI): m/z [M+H]$^+$ found 261.1240, calcd for C$_{14}$H$_{17}$N$_2$O$_3^+$ 261.1234.
Synthesis of (Z)-2-(azepan-2-ylidene)-1-(4-methoxyphenyl)ethanone 232

2-Bromo-1-(4-methoxyphenyl)ethanone (2.23 g, 9.75 mmol, 1.2 eq) was added to a solution of azepane-2-thione 229 (1.05 g, 8.12 mmol, 1 eq) in dry MeCN (12 mL). The resulting solution was stirred at room temperature for 2 minutes, after which the S-alkylation was complete shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (1.67 mL, 9.75 mmol, 1.2 eq) and triethyl amine (1.36 mL, 9.75 mmol, 1.2 eq) in MeCN (35 mL) and left stirring at room temperature for 2 days to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to (Z)-2-(azepan-2-ylidene)-1-(4-methoxyphenyl)ethanone 232 (0.913 g, 46%) as a solid; melting point = 151 – 152 °C; R_f 0.55 (EtOAc: Hex, 1:1); ν_max/cm⁻¹ 3400 – 3200 (s, br, N-H), 2966 (w, C-H), 1744 (m, C=O), 1577 (m, C=C), 1444 (m, aromatic, C=C) and 1150 (m, C-O); ¹H NMR (300 MHz, CDCl₃) δ 11.47 (s, 1H), 7.85 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 6.90 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 5.64 (s, 1H), 3.84 (s, 3H), 3.41 (dd, J = 9.9, 5.8 Hz, 2H), 2.48 – 2.40 (m, 2H), 1.68 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 186.9, 170.4, 161.2, 133.0, 128.3, 113.0, 90.0, 54.9, 44.0, 35.0, 30.2, 29.1, 25.6; HRMS (ESI): m/z [M+H]+ found 246.1506, calcd for C₁₅H₂₀NO₂⁺ 246.1489.
Synthesis of 1-benzoyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 233

(Z)-2-(Azep-2-ylidene)-1-phenylethanone 230 (100 mg, 0.464 mmol, 1 eq) dissolved in dry THF (5 mL) was added drop-wise to a two necked round bottom flask containing a solution of oxalyl chloride (0.040 mL, 0.464 mmol, 1 eq) in THF (5 mL) under nitrogen atmosphere. The reaction mixture was left to stir at room temperature for a period of 18 h. The reaction mixture was then heated to 60 °C for 23 h. Saturated NaHCO₃ (5 mL) was added to the reaction mixture and extracted with DCM (35 mL). The resulting extracts were dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20% EtOAc: Hex to yield 1-benzoyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 233 (0.020 g, 16%) as an oil; Rf 0.28 (EtOAc: Hex, 2:3); νmax/cm⁻¹ 2984 (w, C-H), 1719 (m, C=O), 1544 (m, C=C) and 1460 (m, aromatic, C=C); ¹H NMR (300 MHz, CDCl₃) δ 8.18 – 8.09 (m, 2H), 7.49 (m, 3H), 3.85 (m, 2H), 2.85 (t, J = 5.9 Hz, 2H), 2.10 – 1.93 (m, 6H).

Synthesis of 1-(4-methoxybenzoyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 235

(Z)-2-(Azep-2-ylidene)-1-(4-methoxyphenyl)ethanone 232 (200 mg, 0.819 mmol, 1.1 eq) dissolved in dry THF (5 mL) was added drop-wise to a two necked round bottom flask containing a solution of oxalyl chloride (0.08 mL, 0.901 mmol, 1 eq) in THF (5 mL) under nitrogen atmosphere. The reaction mixture was then heated under reflux for a period of 18 h. Volatiles were removed in vacuo. Saturated NaHCO₃ (5 mL) was added to the residue and extracted with DCM (3 × 5 mL). The resulting extracts were dried over MgSO₄ and evaporated in vacuo. The
resulting residue was purified by silica gel column chromatography eluting with 20% EtOAc: Hex to yield 1-(4-methoxybenzoyl)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione 235 (0.142 g, 58%) as an oil; Rf 0.28 (EtOAc: Hex, 1:1); $\nu_{\text{max}}$/cm$^{-1}$ 2935 (w, C=H), 1744 (m, C=O), 1566 (m, C=C) and 1447 (m, aromatic, C=C); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.73 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 6.92 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 3.86 (s, 3H), 3.17 (m, 2H), 2.49 – 2.47 (m, 2H), 1.87 – 1.73 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 186.8, 185.0, 179.2, 163.8, 156.6, 132.1, 130.6, 113.5, 110.2, 55.5, 41.4, 30.0, 28.6, 28.3, 26.1.

Pyrrolidine-2-thione 6

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\text{Pyrrolidin-2-one 140 (5.00 g, 58.7 mmol, 1 eq) and P}_2\text{S}_5 (6.527 g, 29.37 mmol, 1 eq) were stirred in DCM (150 mL) at room temperature for 17 h under nitrogen atmosphere. A saturated solution of NaHCO}_3\text{ was poured into the reaction mixture and the organic layer was extracted with DCM (3 x 50 mL). The resulting organic layer was then dried over MgSO}_4\text{ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield pyrrolidine-2-thione 6 (2.26 g, 38%) as a solid; melting point = 103 – 105 \degree C; Rf 0.33 (EtOAc: Hex, 1:1); $\nu_{\text{max}}$/cm$^{-1}$ 3135 (w, br, N-H), 2947 (w, C=H); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.59 (s, 1H), 3.67 (t, J = 7.2, 2H), 3.92 (t, J = 7.9, 2H), 2.23 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 206.0, 49.7, 43.3, 23.0.}

To a 250 mL two necked round bottom flask containing DCM (80 mL) equipped with a nitrogen line was added γ-butyrolactam 140 (5.00 g, 70.4 mmol, 1 eq), HMDSO (14.31 g, 88.11 mmol, 1.5 eq) and P$_2$S$_5$ (4.517 g, 20.32 mmol, 0.46 eq), which were reacted at room temperature for 7 days. A saturated solution of NaHCO$_3$ was poured onto the reaction mixture and the organic layer was extracted with DCM (3 x 50 mL). The resulting organic layer was then dried over MgSO$_4$ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield pyrrolidin-2-thione 6 (6.698 g, 94%) as a solid. The analytical data is as above.
**Synthesis of ethyl 2-(4,5-dihydro-3H-pyrrol-2-yl)acetate 238**

![Chemical structure](image)

Ethyl bromoacetate (1.074 g, 6.432 mmol, 1.2 eq) was added to a solution of pyrrolidine-2-thione 6 (0.542 g, 5.36 mmol, 1eq) in dry MeCN (1.00 mL). The resulting solution was stirred at room temperature for 21 h under nitrogen atmosphere, after which the S-alkylation was complete as shown by the precipitation of the thioiminium salt. This was then followed by the addition of triphenylphosphine (1.546 g, 5.896 mmol, 1.1 eq) and triethylamine (0.78 mL, 5.896 mmol, 1.1eq) in MeCN (20 mL) and left stirring at room temperature for overnight to induce sulphur extrusion. The reaction mixture was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield ethyl 2-(4,5-dihydro-3H-pyrrol-2-yl)acetate 238 (0.653 g, 78%) as an oil; Rr 0.36 (EtOAc: Hex, 3:7); νmax /cm⁻¹: 2898 (w, C-H), 1721 (s, C=O), 1422 (m, C=C), 1145 (m, C-N) and 1132 (s, C-O); ¹H NMR (300 MHz, CDCl₃) δ 4.01 (q, J = 7.1 Hz, 2H), 3.68 (s, 2H), 3.63 (t, J = 7.2 Hz, 2H), 2.44 (t, J = 8.2 Hz, 2H), 1.91 – 1.76 (m, 2H), 1.09 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.1, 168.9, 61.4, 60.5, 37.9, 32.8, 23.7, 14.0.

**Synthesis of (Z)-1-phenyl-2-(pyrrolidin-2-ylidene)ethanone 239**

![Chemical structure](image)

2-Bromo-1-phenylethanone (1.42 g, 7.12 mmol, 1.2 eq) was added to a solution of pyrrolidine-2-thione 6 (0.600 g, 5.93 mmol, 1 eq) in dry MeCN (5 mL). The resulting solution was stirred at room temperature 30 seconds, after which the S-alkylation was complete shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (0.99 mL, 7.12 mmol, 1.2 eq) and triethylamine (1.22 mL, 7.12 mmol, 1.2 eq) in MeCN (35 mL) and left stirring at room
temperature for 2 days to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield (Z)-1-phenyl-2-(pyrrolidin-2-ylidene)ethanone 239 (0.859 g, 77%) as a solid; melting point = 105 – 106 °C; Rf 0.42 (EtOAc: Hex, 1:1); $\nu_{\text{max}}/\text{cm}^{-1}$ 3400 – 3200 (s, br, N-H), 2927 (w, C-H), 1741 (m, C=O), 1588 (m, C=C) and 1436 (m, aromatic, C=C); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.28 (s, 1H), 7.98 – 7.78 (m, 2H), 7.49 – 7.32 (m, 3H), 5.81 (s, 1H), 3.66 (t, $J$ = 7.0 Hz, 2H), 2.75 (t, $J$ = 7.8 Hz, 2H), 2.06 (dt, $J$ = 15.1, 7.5 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 188.1, 158.4, 149.0, 130.4, 128.2, 127.0, 86.5, 47.7, 30.9, 21.4; HRMS (ESI): m/z [M+H]$^+$ found 188.1084, calcd for C$_{12}$H$_{14}$NO$^+$ 188.1070.

**Synthesis of (Z)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone 240**

2-Bromo-1-(4-nitrophenyl)ethanone (1.74 g, 7.12 mmol, 1.2 eq) was added to a solution of pyrrolidine-2-thione 6 (0.600 g, 5.93 mmol, 1 eq) in dry MeCN (5 mL). The resulting solution was stirred at room temperature 30 seconds, after which the S-alkylation was complete shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (0.99 mL, 7.12 mmol, 1.2 eq) and triethylamine (1.22 mL, 7.12 mmol, 1.2 eq) in MeCN (35 mL) and left stirring at room temperature for 2 days to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield (Z)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone 240 (1.38 g, 100%) as a solid; melting point = 174 – 175 °C; Rf 0.25 (EtOAc: Hex, 1:1); $\nu_{\text{max}}/\text{cm}^{-1}$ 3279 (m, N-H), 2894 (w, C-H), 1737 (s, C=O), 1599 (m, C=C), 1538 (s, aromatic, N-O), 1476 (m, aromatic, C=C), and 1330 (s, aromatic, C-N); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.45 (s, 1H), 8.24 (d, $J$ = 8.8 Hz, 2H), 8.00 (d, $J$ = 8.8 Hz, 2H), 5.80 (s, 1H), 4.11 (dd, $J$ = 7.7, 7.3 Hz, 2H), 3.72 (t, $J$ = 7.1 Hz, 2H), 2.11 (dd, $J$ = 14.8, 7.5 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$, 188.1, 158.4, 149.0, 130.4, 128.2, 127.0, 86.5, 47.7, 30.9, 21.4; HRMS (ESI): m/z [M+H]$^+$ found 188.1084, calcd for C$_{12}$H$_{14}$NO$^+$ 188.1070.
CDCl₃) δ 190.2, 170.6, 150.9, 148.6, 127.9, 123.5, 87.0, 48.0, 33.1, 30.9; HRMS (ESI): m/z [M+H]+ found 233.0928, calcd for C₁₂H₁₃N₂O₃⁺ 233.0921.

Synthesis of (Z)-1-(4-methoxyphenyl)-2-(pyrrolidin-2-ylidene)ethanone 241

2-Bromo-1-(4-methoxyphenyl)ethanone (2.80 g, 12.2 mmol, 1.2 eq) was added to a solution of pyrrolidine-2-thione 6 (1.03 g, 10.2 mmol, 1 eq) in dry MeCN (12 mL). The resulting solution was stirred at room temperature for 2 minutes, after which the S-alkylation was complete shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (1.22 mL, 12.2 mmol, 1.2 eq) and triethylamine (1.69 mL, 12.2 mmol, 1.2 eq) in MeCN (35 mL) and left stirring at room temperature for 2 days to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield (Z)-1-(4-methoxyphenyl)-2-(pyrrolidin-2-ylidene)ethanone 241 (1.97 g, 88%) as a solid; melting point = 125 – 126 °C; Rf 0.31 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 3400 – 3200 (s, br, N-H), 2956 (w, C-H), 1734 (m, C=O), 1576 (m, C=C), 1434 (m, aromatic, C=C) and 1145 (m, C-O); ¹H NMR (300 MHz, CDCl₃) δ 10.17 (s, 1H), 7.86 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 6.90 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 5.77 (s, 1H), 3.84 (s, 3H), 3.64 (t, J = 7.0 Hz, 2H), 2.73 (t, J = 7.8 Hz, 2H), 2.11 – 1.96 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 192.4, 170.9, 163.8, 130.9, 128.7, 113.8, 85.9, 60.6, 55.5, 38.3, 23.8; HRMS (ESI): m/z [M+H]+ found 218.1190, calcd for C₁₃H₁₆NO₂⁺ 218.1176.
Synthesis of \((E)-4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoyl chloride\) 245

\[
\text{(Z)-1-\text{(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethenone 240}}
\]

(0.500 g, 2.15 mmol, 1 eq) and succinoyl dichloride (0.28 mL, 2.58 mmol, 1.2) were heated under reflux in THF (20 mL) for 2 h and left to stirring at room temperature overnight under nitrogen atmosphere. The solvent was removed in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 70% EtOAc: Hex to yield \((E)-4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoyl chloride\) 245 (0.148 g, 25%) as an oil; \(R_f\) 0.41 (EtOAc: Hex, 7:3); \(\nu_{\text{max}}/\text{cm}^{-1}\) 2968 (w, C-H), 1766 (s, C=O), 1624 (m, C=C), 1512 (s, N-O, aromatic), 1458 (m, C=C, aromatic), 1117 (s, C-O) and 1043 (m, C-N); \(^1\text{H NMR\ (300 MHz, CDCl}_3\)} \(\delta\) 8.30 (d, \(J = 8.7\) Hz, 2H), 8.04 (d, \(J = 8.7\) Hz, 2H), 6.27 (s, 1H), 3.62 (t, \(J = 7.0\) Hz, 2H), 2.72 (s, 4H), 2.55 (t, \(J = 7.2\) Hz, 2H), 2.01 (p, \(J = 7.1\) Hz, 2H); \(^{13}\text{C NMR\ (75 MHz, CDCl}_3\)} \(\delta\) 198.2, 178.3, 177.2, 177.2, 149.8, 140.1, 127.9, 123.8, 97.6, 38.2, 37.1, 28.2, 28.2, 23.0.

Synthesis of \((E)-4-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)pyrrolidin-1-yl)butanoic acid\) 246

\[
\text{(Z)-1-\text{(4-Methoxyphenyl)-2-(pyrrolidin-2-ylidene)ethanone 241}}
\]

(0.320 g, 1.47 mmol, 1 eq) and succinyl dichloride (0.21 mL, 1.88 mmol, 1.28 eq) were stirred at room temperature in THF (10 mL) for 24 h under nitrogen atmosphere. The solvent was removed in vacuo. The resulting residue was dissolved in a saturated NaHCO\(_3\) solution and extracted with DCM (3 \times 30 mL). The resulting organic layer was dried over MgSO\(_4\) and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10 – 30% EtOAc: Hex to yield \((E)-4-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)pyrrolidin-1-\)}
yl)butanoic acid \(246\) (0.349 g, 40%) as an oil; R\(_f\) 0.67 (EtOAc: Hex, 7:3); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3401 (m, br, O-H), 2993 (w, C-H), 1696 (s, C=O), 1622 (m, C=C), 1443 (m, C=C, aromatic), 1120 (s, C-O) and 1054 (m, C-N); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 11.44 (s, 1H), 7.84 (d, \(J = 8.7\) Hz, 2H), 6.89 (d, \(J = 8.7\) Hz, 2H), 5.63 (s, 1H), 3.81 (s, 3H), 3.43 – 3.38 (m, 2H), 2.45 – 2.42 (m, 2H), 1.75 – 1.64 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 187.3, 171.0, 170.8, 161.5, 133.2, 133.2, 128.7, 113.3, 90.4, 55.3, 44.4, 35.4, 30.6, 29.4, 25.9.

**Synthesis of (E)-4-chloro-1-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)butan-1-one 247**

\[
\begin{align*}
\text{O}_2\text{N} &\quad \text{O} \\
\text{(Z)}-1-(4\text{-Nitrophenyl})-2-(\text{pyrrolidin-2-ylidene})\text{ethanone} \\
\text{Cl}
\end{align*}
\]

240 (0.098 g, 0.422 mmol, 1 eq) and 4-chlorobutanoyl chloride (0.073 g, 0.516 mmol, 1.22 eq) were reacted in THF (10 ml), heating under reflux at 45 °C under nitrogen atmosphere for 20 h. Saturated NaHCO\(_3\) solution was added to the cooled reaction mixture and it was then extracted with DCM (3 × 15 mL). The resulting organic layer was dried on MgSO\(_4\) and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield (E)-4-chloro-1-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)butan-1-one \(247\) (0.104 g, 74%) as a solid; R\(_f\) 0.22 (EtOAc: Hex, 3:7); \(\nu_{\text{max}}/\text{cm}^{-1}\) 2983 (w, C-H), 1697 (s, C=O), 1587 (m, aromatic, C=C), 1543 (s, aromatic, N-O), 1488 (m, C=C), and 1128 (s, aromatic, C-N); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.27 (d, \(J = 8.9\) Hz, 2H), 8.23 (s, 1H), 8.08 (d, \(J = 8.9\) Hz, 2H), 3.88 (t, \(J = 7.2\) Hz, 2H), 3.71 (t, \(J = 6.0\) Hz, 2H), 3.37 (td, \(J = 7.8, 1.6\) Hz, 2H), 2.73 (t, \(J = 6.8\) Hz, 2H), 2.28 – 2.16 (m, 2H), 2.09 (p, \(J = 7.5\) Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 189.6, 172.7, 160.3, 149.6, 145.0, 128.9, 123.6, 103.0, 50.0, 44.3, 34.1, 32.7, 26.9, 21.6.
Synthesis of (E)-ethyl 4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoate 249

(i) (Z)-1-(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethenone 240 (0.500 g, 2.15 mmol, 1 eq) and ethyl 4-chloro-4-oxobutanoate (0.36 mL, 2.37 mmol, 1.1) were heated under reflux in THF (20 mL) for 1 h and left to stirring at room temperature 24 h under nitrogen atmosphere. The solvent was removed in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 70% EtOAc: Hex to yield (E)-ethyl 4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoate 249 (0.371 g, 48%) as a solid; melting point = 118 – 119 °C; Rf 0.24 (EtOAc: Hex, 7:3); νmax/cm⁻¹ 2931 (w, C-H), 1745 (m, C=O), 1532 (m, C=C, aromatic), 1345 (s, aromatic, N-O) and 1206 (m, C-O); ¹H NMR (300 MHz, CDCl₃) δ 8.27 (d, J = 8.9 Hz, 2H), 8.21 (s, 1H), 8.08 (d, J = 8.9 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.90 (t, J = 7.2 Hz, 2H), 3.36 (td, J = 7.8, 1.7 Hz, 2H), 2.88 – 2.78 (m, 2H), 2.78 – 2.69 (m, 2H), 2.15 – 2.01 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 189.7, 172.6, 172.2, 160.3, 149.6, 145.0, 129.0, 123.6, 103.1, 61.0, 50.0, 32.7, 32.3, 28.7, 21.7, 14.2; HRMS (ESI): m/z [M+H₂O+H]^+ found 379.1510, calcd for C₁₈H₂₃N₂O₇+ 379.15.

(ii) (Z)-1-(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethenone 240 (0.151 g, 0.650 mmol, 1 eq) and ethyl 4-chloro-4-oxobutanoate (0.11 mL, 0.780 mmol, 1.2 eq) were heated under reflux in THF (12 mL) for 18 h under nitrogen atmosphere. The solvent was removed in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 70% EtOAc: Hex to yield (E)-ethyl 4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoate 249 (0.211 g, 90%) as a solid; The analytical data is shown above.
Synthesis of 1-allylpyrrolidin-2-one 259

Dihydrofuran-2(3H)-one 13 (1.334 g, 15.49 mmol, 1 eq) and allylamine (1.734 g, 30.36 mmol, 1.96 eq) were irradiated in a microwave reactor under these conditions (150 W, 220 °C, 30 min). The resulting reaction mixture was then cooled, dissolved in water and extracted with EtOAc (3 x 20 mL). The resulting organic layer was dried over MgSO₄ and then evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with 20% EtOAc: Hex to yield 1-allylpyrrolidin-2-one 259 (1.541 g, 79%) as an oil; Rₜ 0.43 (EtOAc: Hex, 1:0); ν̴ max/cm⁻¹ 2928 (w, C-H) 1691 (s, C=O), 1640 (s, C=C), 1231 (m, C-O) and 1114 (m, C-N); ¹H NMR (300 MHz, CDCl₃) δ 5.35 (ddt, J = 17.0, 9.9, 6.0 Hz, 1H), 4.81 (dd, J = 11.1, 6.2 Hz, 2H), 3.50 (d, J = 6.0 Hz, 2H), 2.99 (t, J = 7.1 Hz, 2H), 2.00 (t, J = 8.1 Hz, 2H), 1.73 – 1.56 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 174.3, 132.2, 117.2, 111.4, 46.4, 44.7, 30.6, 17.4. The data agree with those previously reported for the compound.

NaH 60% in oil (0.338 g, 14.11 mmol, 1.2 eq) was washed with Hex (3 x 5 mL) in a two necked round bottom flask under nitrogen atmosphere. Clean NaH was then dried under high vacuum. Pyrrolidin-2-one 140 (1.00 g, 11.75 mmol, 1 eq) in dry THF (5 mL) was added to the two necked round bottom flask all at once. The reaction mixture was left to stir at room temperature for 10 minutes after which the sodium salt had precipitated. Allyl bromide (1.12 mL, 12.93 mmol, 1.2 eq) in THF (20 mL) was added all at once and the reaction mixture was left to stir at room temperature for 24 h. The reaction mixture was dissolved in water in a separating funnel, adjusted the pH to pH~5 with 1M HCl and the organic was extracted with diethyl ether (3 x 40 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20 – 40% EtOAc: Hex to yield 1-allylpyrrolidin-2-one 259 (1.471 g, 91%) as a low melting solid. The analytical data is as above.
**Synthesis of 1-allylpyrrolidine-2-thione 260**

1-Allylpyrrolidin-2-one 259 (1.419 g, 10.05 mmol, 1 eq) and P₂S₅ (2.234 g, 10.05 mmol, 1 eq) were stirred in DCM (350 mL) at room temperature for 24 h under nitrogen atmosphere. A saturated solution of NaHCO₃ was poured into the reaction mixture and the organic layer was extracted with DCM (3 × 80 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 40% EtOAc: Hex to yield 1-allylpyrrolidine-2-thione 260 (1.420 g, 78%) as an oil; Rᵣ 0.50 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 2900 (w, C-H), 1624 (s, C=C), and 1131 (m, C-N); ¹H NMR (300 MHz, CDCl₃) δ 5.81 (ddt, J = 17.4, 9.8, 6.1 Hz, 1H), 5.33 – 5.20 (m, 2H), 4.39 (d, J = 6.1 Hz, 2H), 3.78 – 3.67 (m, 2H), 3.02 (t, J = 7.9 Hz, 2H), 2.15 – 2.01 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 201.1, 130.5, 119.1, 54.4, 50.4, 45.0, 19.6; HRMS (ESI): m/z [M+H]⁺ found 142.0693, calcd for C₇H₁₂NS⁺ 142.0685.

Dihydrofuran-2(3H)-one 13 (15.00 g, 174.2 mmol, 1 eq) and allylamine (10.00 g, 175.1 mmol, 1.01 eq) were heated at 220 ºC in a sealed tube oven for 1 day. The resulting reaction mixture was dissolved in water (100 mL), adjusted to pH~ 8 using NaHCO₃ and extracted with EtOAc (3 × 100 mL). The resulting organic layer was dried over MgSO₄, evaporated in vacuo to yield crude 1-allylpyrrolidin-2-one which was used in the next reaction without further purification. Crude 1-allylpyrrolidin-2-one was dissolved in DCM (250 mL) followed by the addition of P₂S₅ (38.72 g, 174.2 mmol, 1 eq), and hexamethyldisiloxane (42.43 g, 261.3 mmol, 1.5 eq). The resulting solution was stirred at room temperature overnight. A saturated solution of NaHCO₃ was poured onto the reaction mixture and the organic layer was extracted with DCM (3 × 100 mL). The resulting organic layer was then dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography with 10% EtOAc: Hex to yield 1-allylpyrrolidine-2-thione 260 (16.217 g, 66%) as oil. The analytical data is as above.
Synthesis of (E)-ethyl 2-(1-allylpyrrolidin-2-ylidene)acetate 261

Ethyl 2-bromoacetate (4.99 mL, 45.17 mmol, 1.1 eq) was added to a solution of 1-allylpyrrolidine-2-thione 260 (5.800 g, 41.06 mmol, 1 eq) in dry MeCN (10.00 mL). The resulting solution was stirred at room temperature overnight under nitrogen atmosphere, after which the S-alkylation was complete shown by the precipitation of the thioiminium salt. This was followed by the addition of triethylphosphite (8.96 mL, 49.27 mmol, 1.1 eq) and triethylamine (6.61 mL, 49.27 mmol, 1.1 eq) in MeCN (100 mL) and left stirring at room temperature for overnight to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10% EtOAc: Hex to yield (E)-ethyl 2-(1-allylpyrrolidin-2-ylidene)acetate 261 (5.588 g, 70%) as an oil; Rf 0.53 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 2935 (w, C-H), 1666 (s, C=O), 1514 (s, C=C), 1154 (s, C-O) and 1026 (s, C-N); ¹H NMR (300 MHz, CDCl₃) δ 5.84–5.66 (m, 1H), 5.22–5.08 (m, 2H), 4.52 (s, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.77 (d, J = 5.4 Hz, 2H), 3.37 (t, J = 7.6 Hz, 2H), 3.15 (t, J = 7.6 Hz, 2H), 2.03–1.88 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.1, 164.4, 130.8, 117.0, 77.9, 57.8, 52.0, 48.5, 32.4, 20.8, 14.5; HRMS (ESI): m/z [M+H]⁺ found 196.1341, calcd for C₁₁H₁₈NO₂⁺ 196.1332.

Synthesis of ethyl 1-allyl-6-oxo-2,3,3a,4,5,6-hexahydro-1H-indole-7-carboxylate 264

(E)-Ethyl 2-(1-allylpyrrolidin-2-ylidine)acetate 261 (0.513 g, 2.627 mmol, 1 eq) and acryloyl chloride (0.238 g, 2.627 mmol, 1 eq) were stirred in THF (50 mL) at room temperature for 10 min under nitrogen atmosphere. The resulting reaction mixture was evaporated in vacuo. The resulting residue was dissolved in water and extracted with EtOAc (3 × 10 mL). The combined organic extracts were
dried over MgSO₄ and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with 10% EtOAc: Hex to yield ethyl 1-allyl-6-oxo-2,3,3a,4,5,6-hexahydro-1H-indole-7-carboxylate 264 (0.405 g, 24%) as an oil; Rf 0.44 (EtOAc: Hex, 7:3); νmax/cm⁻¹ 2926 (w, C-H), 1732 (s, C=O), 1645 (m, C=C), 1213 (s, C-O) and 1120 (m, C-N); ¹H NMR (300 MHz, CDCl₃) δ 5.78 (ddd, J = 22.4, 10.8, 5.6 Hz, 1H), 5.27 – 5.16 (m, 2H), 4.27 – 4.15 (m, 2H), 3.94 – 3.75 (m, 2H), 3.58 (t, J = 10.0 Hz, 2H), 3.47 (m, 1H), 2.90 – 2.69 (m, 2H), 2.57 – 2.36 (m, 2H), 2.32 – 2.02 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 190.6, 169.6, 163.2, 132.5, 117.9, 110.3, 61.7, 51.4, 49.3, 38.6, 32.9, 26.3, 24.0, 14.1; HRMS (ESI): m/z [M+H]+ found 250.0885, calcd for C₁₄H₁₂NO₃⁺ 250.1438.

Synthesis of (E)-2-(1-allylpyrrolidin-2-ylidine)-1-phenylethanone 267¹⁵¹,¹⁶¹

2-Bromo-1-phenylethanone (1.55 g, 7.79 mmol, 1.1 eq) was added to a solution of 1-allylpyrrolidine-2-thione 260 (1.00 g, 7.08 mmol, 1 eq) in dry MeCN (3.00 mL). The resulting solution was stirred at room temperature for 1 h, after which the S-alkylation was complete as shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (1.33 mL, 7.99 mmol, 1.1 eq) and triethylamine (1.09 mL, 7.79 mmol, 1.1 eq) in MeCN (80 mL) and left stirring at room temperature overnight to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was dissolved in EtOAc and saturated NaHCO₃ solution. The resulting mixture was then extracted with ethyl acetate (3 × 30 mL) and the resulting organic layer washed with brine. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10, 20, 30, 40% EtOAc: Hex to yield (E)-2-(1-allylpyrrolidin-2-ylidine)-1-phenylethanone 267 (1.7041 g, 93%) as an oil; Rf 0.30 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 2889 (w, C-H), 1743 (s, C=O), 1582 (m, aromatic, C=C), 1432(m, C=C) and 1212 (s, C-O); ¹H NMR (300 MHz, CDCl₃) δ 7.93 – 7.77 (m, 2H), 7.48 – 7.31 (m, 3H), 5.87 – 5.76 (m, 1H), 5.75 (s, 1H), 5.33 – 5.09 (m, 2H), 3.92 (d, J = 5.3 Hz, 2H), 3.55 – 3.33 (m, 4H), 2.14 – 1.94 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 187.8, 167.1, 142.0, 130.6 – 130.5 (m), 130.3, 128.0, 127.2 (t, J = 4.7
Hz), 117.7 (dd, J = 4.8, 2.5 Hz), 86.8, 52.6, 49.1, 33.8, 20.9; HRMS (ESI): m/z [M+H]^+ found 228.1390, calcd for C\textsubscript{16}H\textsubscript{18}NO^+ 228.1383.

**Synthesis of (E)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-nitrophenyl)ethanone**

2-Bromo-1-(4-nitrophenyl)ethanone (1.90 g, 7.79 mmol, 1.1 eq) was added to a solution of 1-allylpyrrolidine-2-thione 260 (1.00 g, 7.08 mmol, 1 eq) in dry MeCN (3.00 mL). The resulting solution was stirred at room temperature for 2 h, after which the S-alkylation was complete as shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (1.33 mL, 7.99 mmol, 1.1 eq) and triethylamine (1.09 mL, 7.79 mmol, 1.1 eq) in MeCN (80 ml) and left stirring at room temperature overnight to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was dissolved in EtOAc and saturated NaHCO\textsubscript{3} solution. The resulting mixture was then extracted with EtOAc (3 x 30 ml) and the resulting organic layer washed with brine. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10, 20, 30, 40% EtOAc: Hex to yield (E)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-nitrophenyl)ethanone 268 (1.5121 g, 78%) as a solid; melting point = 129 – 130 °C; R\textsubscript{f} 0.29 (EtOAc: Hex, 1:1); \(\nu_{\text{max}}\)/cm\(^{-1}\) 2995 (w, C-H), 1745 (s, C=O), 1585 (m, aromatic, C=C), 1402 (m, C=C), 1122 (s, C-O) and 1055 (s, C-N); \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.23 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 7.97 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 5.92 – 5.72 (m, 1H), 5.69 (s, 1H), 5.37 – 5.14 (m, 2H), 3.97 (d, J = 5.4 Hz, 2H), 3.53 (t, J = 7.4 Hz, 2H), 3.45 (t, J = 7.8 Hz, 2H), 2.20 – 1.99 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 185.1, 168.5, 148.7, 147.7, 130.1, 128.1, 123.4, 118.2, 86.8, 53.0, 49.2, 34.2, 20.8; HRMS (ESI): m/z [M+H]^+ found 273.1241, calcd for C\textsubscript{16}H\textsubscript{17}N\textsubscript{2}O\textsubscript{3}^+ 273.1234.
Synthesis of (E)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-methoxyphenyl)ethanone 269

2-Bromo-1-(4-methoxyphenyl)ethanone (1.78 g, 7.79 mmol, 1.1 eq) was added to a solution of 1-allylpyrrolidine-2-thione 260 (1.00 g, 7.08 mmol, 1 eq) in dry MeCN (3.00 mL). The resulting solution was stirred at room temperature for 1.5 h, after which the S-alkylation was complete as shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethylphosphite (1.33 mL, 7.99 mmol, 1.1 eq) and triethylamine (1.09 mL, 7.79 mmol, 1.1 eq) in MeCN (80 mL) and left stirring at room temperature overnight to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was dissolved in EtOAc and saturated NaHCO₃ solution. The resulting mixture was then extracted with ethyl acetate (3 × 30 mL) and the resulting organic layer washed with brine. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10, 20, 30, 40% EtOAc: Hex to yield (E)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-methoxyphenyl)ethanone 269 (1.6877 g, 93%) as an oil; Rf 0.28 (EtOAc: Hex, 1:1); ν<sub>max</sub> /cm⁻¹ 2999 (w, C-H), 1743 (s, C=O), 1571 (m, aromatic, C=C), 1423 (m, C=C), 1112 (s, C-O) and 1063 (s, C-N); ¹H NMR (300 MHz, CDCl₃) δ 7.86 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 6.88 (d, J = 8.9 Hz, with unresolved fine coupling, 2H), 5.87 – 5.75 (m, 1H), 5.73 (s, 1H), 5.31 – 5.12 (m, 2H), 3.91 (d, J = 5.4 Hz, 2H), 3.82 (s, 3H), 3.42 (dd, J = 14.5, 7.2 Hz, 4H), 2.09 – 1.94 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 186.8, 166.6, 161.5, 134.6, 130.7 (d, J = 8.5 Hz), 129.4 – 128.3 (m), 117.6 (t, J = 4.0 Hz), 113.4 – 112.7 (m), 86.3, 55.4 – 55.2 (m), 52.5, 49.0, 33.7, 21.0; HRMS (ESI): m/z [M+H]⁺ found 258.199, calcd for C₁₆H₂₀NO₂⁺ 258.1489.
Synthesis of 4-iodobutyl benzoate \(^{277}\)

![Chemical structure of 4-iodobutyl benzoate](image)

To a solution of sodium iodide in THF (30 mL, 370 mmol, 1.21 eq) and MeCN (15 mL), with external cooling, benzoyl chloride \(^{276}\) (42.83 g, 305 mmol, 1eq) was added all at once. The reaction mixture was stirred in the absence of light under nitrogen atmosphere at room temperature overnight. The reaction mixture was diluted with water (100 mL) and diethyl ether (100 mL). The organic layer was separated and the aqueous later was washed with diethyl ether (3 × 30 mL). The combined organic extracts were washed with saturated Na\(_2\)SO\(_3\), saturated Na\(_2\)CO\(_3\) and dried over Mg\(_2\)SO\(_4\). The solvent was evaporated in vacuo to yield 4-iodobutyl benzoate \(^{277}\) (92.8 g, 66%) as a colourless oil; \(\nu_{\text{max}}/\text{cm}^{-1}\) 2940 (w, C-H), 1721 (s, C=O), 1495 (s, C=C, aromatic) and 1130 (s, C-O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.13 – 7.98 (m, 2H), 7.63 – 7.49 (m, 1H), 7.42 (m, 2H), 4.32 (t, \(J = 6.1\) Hz, 2H), 3.23 (t, \(J = 6.7\) Hz, 2H), 2.06 – 1.78 (m, 4H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 166.5, 133.0, 130.1, 129.6, 128.4, 63.9, 30.1, 29.7, 6.3.

Synthesis of 4-(2-oxopyrrolidin-1-yl)butyl benzoate \(^{278}\)

![Chemical structure of 4-(2-oxopyrrolidin-1-yl)butyl benzoate](image)

To a round bottom flask under nitrogen atmosphere containing a solution of pyrrolidin-2-one (1.00 g, 11.8 mmol, 1 eq) in THF (50 mL) at 0 °C was added potassium bis(trimethylsilyl) amide (28.2 mL, 14.10 mmol, 1.2 eq) all at once. The solution went milky and was stirred at room temperature for 15 min, after which 4-iodobutyl benzoate \(^{277}\) (4.288 g, 14.10 mmol, 1.2 eq) was added all at once and the reaction mixture was stirred at room temperature overnight. The salt that formed was filtered and the organic layer was reduced in vacuo. The resulting yellow residue was purified by silica gel column chromatography eluting with 20% EtOAc: Hex to yield 4-(2-oxopyrrolidin-1-yl)butyl benzoate \(^{278}\) (2.333 g, 76%) as an oil; \(R_f\) 0.52 (EtOAc: Hex, 1:0); \(\nu_{\text{max}}/\text{cm}^{-1}\) 2918 (w, C-H), 1698 (s, C=O), 1505 (s, C=C, aromatic), 1232 (s, C-O) and 1211 (s, C-N); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.92
(d, J = 7.2 Hz, 2H), 7.43 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.6 Hz, 2H), 4.22 (t, J = 6.2 Hz, 2H), 3.26 – 3.20 (m, 4H), 2.23 (t, J = 8.1 Hz, 2H), 1.94 – 1.79 (m, 2H), 1.72 – 1.48 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.3, 164.8, 131.4, 128.8, 128.0, 126.9, 62.9, 45.5, 40.5, 29.5, 24.6, 22.4, 16.4.

**Synthesis of 4-(2-thioxopyrrolidin-1-yl)butyl benzoate 279**

![Chemical Structure](image)

4-(2-Oxopyrrolidin-1-yl)butyl benzoate **278** (1.250 g, 4.784 mmol, 1 eq) and Lawesson reagent (1.934 g, 4.784 mmol, 1 eq) were reacted in DCM (50 mL) at room temperature for 32 h. The reaction mixture was filtered on celite and the volatiles evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 40% EtOAc: Hex solution to yield 4-(2-thioxopyrrolidin-1-yl)butyl benzoate **279** (1.327 g, 90%) as an oil; R$_f$ 0.72 (EtOAc: Hex, 1:1); $v_{max}$/cm$^{-1}$ 2892 (w, C-H), 1722 (s, C=O), 1488 (m, C=C, aromatic), 1125 (m, C-N) and 1054 (m, C-O); $^1$H NMR (300 MHz, CDCl$_3$) δ 8.04 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 4.38 – 4.34 (m, 2H), 3.80 – 3.88 (m, 2H), 3.73 (t, J = 6.8 Hz, 2H), 3.03 (t, J = 7.9 Hz, 2H), 2.12 – 1.96 (m, 2H), 1.91 – 1.75 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 201.0, 166.6, 133.0, 130.1, 129.5, 128.4, 64.4, 54.7, 47.5, 45.0, 26.1, 23.0, 19.6.

**Synthesis of (E)-4-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butyl benzoate 280**$^{151,161}$

![Chemical Structure](image)

Ethyl 2-bromoacetate (0.55 mL, 2.42 mmol, 1 eq) was added to a solution of 4-(2-thioxopyrrolidin-1-yl)butyl benzoate **279** (0.670 g, 2.42 mmol, 1 eq) in dry MeCN (3.00 mL). The resulting solution was stirred at room temperature overnight under nitrogen atmosphere, after which the S-alkylation was complete shown by the baseline spot on the TLC plate. This was followed by the
addition of triethylphosphite (0.64 mL, 2.90 mmol, 1.2 eq) and triethylamine (0.15 mL, 2.90 mmol, 1.2 eq) in MeCN (30 mL) and left stirring at room temperature for overnight to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 50% EtOAc: Hex to yield (E)-4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butyl benzoate 280 (0.381 g, 48%) as an oil; Rf 0.53 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 2913 (w, C-H), 1728 (s, C=O), 1567 (m, C=C, aromatic), 1243 (s, C-O) and 1034 (m, C-N); ¹H NMR (300 MHz, CDCl₃) δ 8.09 – 7.97 (m, 2H), 7.55 (dd, J = 10.5, 4.2 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 4.55 (s, 1H), 4.34 (t, J = 6.0 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.38 (t, J = 7.1 Hz, 2H), 3.23 (t, J = 6.8 Hz, 2H), 3.16 (t, J = 7.8 Hz, 2H), 1.93 (p, J = 7.4 Hz, 2H), 1.75 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H).

Synthesis of (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281

(i) To a 100 ml two neck round bottom flask equipped with a condenser under nitrogen atmosphere was added 4-amino-1-butanol (0.600 g, 6.73 mmol, 1eq), ethyl 6-chlorohex-2-ynoate 285 (1.175 g, 6.73 mmol, 1 eq), K₂CO₃ (1.860 g, 13.46 mmol, 2 eq), NaI (2.018 g, 13.46 mmol, 2 eq) and 4Å molecular sieves in MeCN (50 mL). The resulting reaction mixture was heated under reflux for 48 h. The reaction mixture was cooled to room temperature and poured into brine in a separating funnel. The organic layer was extracted with diethyl ether (3 × 30 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 50% EtOAc: Hex to yield (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281 (1.530 g, 70%) as an oil; Rf 0.10 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 3401 (s, br, O-H), 2937 (s, C-H), 1657 (m, C=O), 1577 (s, C=C), 1133 (s, C-O) and 1054 (s, C-N); ¹H NMR (500 MHz, CDCl₃) δ 4.52 (s, 1H), 4.09 (q, J = 7.1, 2H), 3.67 (t, J = 6.3, 2H), 3.37 (t, J = 7.1, 2H), 3.17 (m, 4H), 1.99 – 1.88 (m, 2H), 1.73 – 1.51 (m, 4H), 1.29 – 1.20 (m, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 169.6, 165.0, 77.5, 62.4, 58.3, 52.6, 46.2, 32.8,
HRMS (ESI): m/z [M+H]^+ found 228.1606, calcd for C_{12}H_{22}NO_3^+ 228.1594.

(ii) To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added 4-amino-1-butanol (0.120 g, 1.35 mmol, 1 eq), ethyl 6-iodohex-2-ynoate 287 (0.431 g, 1.62 mmol, 1.2 eq), CsCO_3 (0.521 g, 2.7 mmol, 2 eq) and 4Å molecular sieves in MeCN (50 mL). The resulting reaction mixture was heated under reflux for 22 h. The reaction mixture was cooled to room temperature and poured onto brine in a separating funnel and the organic was extracted with diethyl ether (3 x 30 mL). The resulting organic layer was dried over MgSO_4 and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 50% EtOAc: Hex to yield (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281 (0.178 g, 58%) as oil. The analytical data is as above.

(iii) (E)-4-(2-(2-Ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butyl benzoate 280 (0.200 g, 0.603 mmol, 1 eq) was reacted with KOH (0.037 g, 0.663 mmol, 1.1 eq) in a 20:1 solution of MeOH and water at room temperature for 1.5 h. The resulting reaction mixture was acidified to pH~7 and the reaction mixture extracted with EtOAc (3 x 20 mL). The resulting organic layer was dried over MgSO_4 and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 50% EtOAc: Hex solution to yield (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 281 (0.115 g, 89%) as oil; ^1H NMR (300 MHz, CDCl_3) δ 4.47 (s, 1H), 4.26 (s, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.61 (t, J = 6.1 Hz, 2H), 3.33 (t, J = 7.1 Hz, 2H), 3.18 – 3.03 (m, 4H), 1.88 (p, J = 7.4 Hz, 2H), 1.68 – 1.45 (m, 4H), 1.20 (t, J = 7.1 Hz, 3H); ^13C NMR (75 MHz, CDCl_3) δ 169.8, 165.1, 77.3, 62.0, 58.3, 52.5, 46.2, 32.7, 30.0, 22.7, 20.9, 14.7.

**Synthesis of ethyl 6-chlorohex-2-ynoate 285^{155,156}**

To a solution of 5-chloro-1-pentyne 282 (4.00 g, 39 mmol, 1 eq) in THF (75 ml), in a two necked round bottom flask at –78 °C under nitrogen
atmosphere, was added n-butyllithium (24.40 ml, 39 mmol, 1 eq) solution in THF. The reaction mixture was left to warm to –20°C in about 35 min. Ethyl chloroformate in THF (75 mL) was then added and the reaction mixture was left to warm to room temperature and stirred for 20 h. A saturated solution of NaHCO₃ was poured into the reaction mixture and the organic layer was extracted with diethyl ether (3 × 50 ml). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield ethyl 6-chlorohex-2-ynoate 285 (6.811 g, 99%) as an oil; Rᵣ 0.25 (EtOAc: Hex, 1:4); νᵢₑₐ₉/cm⁻¹ 2935 (w, C-H), 2238 (w, C=\(\equiv\)C), 1714 (s, C=O) and 1200 (s, C-O); \(^{1}H\) NMR (300 MHz, CDCl₃) δ 4.22 (q, J = 7.1, 2H), 3.66 (t, J = 6.2, 2H), 2.55 (t, J = 6.9, 2H), 2.10 – 1.99 (m, 2H), 1.31 (t, J = 7.1, 3H); \(^{13}C\) NMR (75 MHz, CDCl₃) δ 153.5, 87.0, 73.9, 61.9, 43.2, 30.3, 16.1, 14.0.

**Synthesis of 6-chloro-1-phenylhex-2-yn-1-one 283**

To a solution of 5-chloro-1-pentyne 282 (4.000 g, 39 mmol, 1 eq) in THF (50 mL), in a two necked round bottom flask under nitrogen atmosphere at –78 °C, was added n-butyllithium (24.40 mL, 39 mmol, 1 eq) solution in THF. The reaction mixture was left to warm to –20 °C in about 35 min. Benzoyl chloride in THF (50 mL) was then added and the reaction mixture was left to warm to room temperature and stirred for 20 h. A saturated solution of NaHCO₃ was poured into the reaction mixture and the organic layer was extracted with diethyl ether (3 × 50 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield 6-chloro-1-phenylhex-2-yn-1-one 283 (5.124 g, 64%) as an oil; Rᵣ 0.46 (EtOAc: Hex, 1:4); νᵢₑ₉/cm⁻¹ 2962 (w, C-H), 2202 (w, C=\(\equiv\)C), 1640 (s, C=O), 1597, 1579 (m, C=C) and 1263 (s, C=O); \(^{1}H\) NMR (300 MHz, CDCl₃) δ 8.20 – 8.10 (m, 2H), 7.72 – 7.44 (m, 3H), 3.72 (t, J = 6.2, 2H), 2.73 (t, J = 6.9, 2H), 2.20 – 2.07 (m, 2H); \(^{13}C\) NMR (75 MHz, CDCl₃) δ 178.0, 136.8, 134.1, 129.6, 128.6, 94.1, 80.3, 43.4, 30.5, 16.7.
Synthesis of 6-chloro-1-cyclopropylhex-2-yn-1-one 286\textsuperscript{155,156}

To a solution of 5-chloro-1-pentyne 282 (4.00 g, 39 mmol, 1 eq) in THF (50 mL), in a two necked round bottom flask under nitrogen atmosphere at −78 °C was added 1.6 M n-butyllithium (24.40 mL, 39 mmol, 1 eq) solution in THF. The reaction mixture was left to warm to −20 °C in about 35 min. Cyclopropanecarbonyl chloride in THF (50 mL) was then added and the reaction mixture was left to warm to room temperature and stirred for 20 h. A saturated solution of NaHCO\textsubscript{3} was poured into the reaction mixture and the organic layer was extracted with diethyl ether (3 × 50 mL). The resulting organic layer was dried over MgSO\textsubscript{4} and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield 6-chloro-1-cyclopropylhex-2-yn-1-one 286 (4.498 g, 68%) as an oil; R\textsubscript{f} 0.37 (EtOAc: Hex, 1:4); \( \nu_{\text{max}}/\text{cm}^{-1} \) 2963 (w, C-H), 2218 (w, CΞC), 1651 (s, C=O) and 1261, 1173 (m, C-O); \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 3.65 (t, \( J = 6.2 \), 2H), 2.57 (t, \( J = 6.9 \), 2H), 2.11 − 1.96 (m, 3H), 1.29 − 1.15 (m, 2H), 1.10 − 0.98 (m, 2H); \(^13\)C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 188.3, 91.4, 79.6, 43.3, 30.4, 24.4, 16.3, 10.9.

Synthesis of ethyl 9-chloro-4-oxonon-5-ynoate 284\textsuperscript{155,156}

To a solution of 5-chloro-1-pentyne 282 (2.00 g, 19.5 mmol, 1 eq) in THF (50 mL), in a two necked round bottom flask under nitrogen atmosphere at −78 °C was added 1.6 M n-butyllithium (12.19 ml, 19.5 mmol, 1 eq) solution in THF. The reaction mixture was left to warm to −20 °C in about 1.5 h. Ethyl 4-chloro-4-oxobutanoate in THF (50 mL) was then added and the reaction mixture was left to warm to room temperature and stirred for 24 h. A saturated solution of NaHCO\textsubscript{3} was poured into the reaction mixture and the organic layer was extracted with diethyl ether (3 × 50 mL). The resulting organic layer was dried over MgSO\textsubscript{4} and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield ethyl 9-chloro-4-oxonon-5-
ynoate 284 (1.260 g, 28%) as an oil; Rf 0.25 (EtOAc: Hex, 1:4); v_max/cm⁻¹ 2940 (w, C-H), 2239 (w, C≡C), 1723 (s, C=O) and 1211 (s, C-O); ¹H NMR (300 MHz, CDCl₃) δ 4.15 (q, J = 7.1 Hz, 2H), 3.65 (t, J = 6.2 Hz, 2H), 2.89 (t, J = 6.7 Hz, 2H), 2.63 (t, J = 6.6 Hz, 2H), 2.59 (t, J = 6.9 Hz, 2H), 2.05 (p, J = 6.7 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H).

Synthesis of ethyl 6-iodohex-2-ynoate 287

To a solution of 6-chlorohex-2-ynoate 285 (2.510 g, 14.37 mmol, 1 eq) in dry acetone in a one necked round bottom flask equipped with a condenser was added NaI (10.770 g, 71.85 mmol, 5 eq) and the reaction mixture was heated under reflux overnight. Water was poured onto the reaction mixture and the organic layer was extracted with diethyl ether (3 × 20 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield ethyl 6-iodohex-2-ynoate 287 (2.953 g, 77%) as an oil; Rf 0.48 (EtOAc: Hex, 1:4); v_max/cm⁻¹ 2983 (w, C-H), 2238 (w, C≡C), 1708 (s, C=O) and 1248 (s, C-O); ¹H NMR (300 MHz, CDCl₃) δ 4.22 (q, J = 7.1 Hz, 2H), 3.66 (t, J = 6.2 Hz, 1H), 3.29 (t, J = 6.7 Hz, 1H), 2.55 (t, J = 7.0 Hz, 1H), 2.51 (t, J = 6.9 Hz, 1H), 2.14 – 1.98 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 153.5, 87.0, 86.7, 61.9, 31.0, 19.7, 14.0, 4.4.

Synthesis of (E)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate 288\textsuperscript{153,154}

To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added 3-amino-1-propanol (0.129 g, 1.72 mmol, 1 eq), ethyl 6-chlorohex-2-ynoate 285 (0.300 g, 1.72 mmol, 1 eq), K₂CO₃ (0.475 g, 3.44 mmol, 2 eq), NaI (0.516 g, 3.44 mmol, 2 eq) and 4Å molecular sieves in MeCN (30 mL). The resulting reaction mixture was heated under reflux for 24h.
The reaction mixture was cooled to room temperature and poured into brine in a separating funnel and the organic layer was extracted with diethyl ether (3 × 10 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 70% EtOAc: Hex to yield (E)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate 288 (0.367 g, 81%) as oil; Rᵣ 0.45 (EtOAc: Hex, 1:0); νₑᵣₛ/cm⁻¹ 3420 (m, br, O-H), 2938 (s, C-H), 1726, 1658 (m, C=O), 1577 (s, C=C), 1133 (s, C-O) and 1054 (s, C-N);¹H NMR (300 MHz, CDCl₃) δ 4.55 (s, 1H), 4.08 (q, J = 7.1, 2H), 3.67 (t, J = 6.0, 2H), 3.40 (t, J = 7.1, 2H), 3.31 (t, J = 7.2, 2H), 3.15 (t, J = 7.4, 2H), 3.23 (t, J = 7.2, 2H), 3.31 (t, J = 7.2, 2H), 3.15 (t, J = 7.4, 2H), 2.32 (s, 1H), 2.03 – 1.88 (m, 2H), 1.88 – 1.76 (m, 2H), 1.25 (t, J = 7.1, 3H);¹³C NMR (75 MHz, CDCl₃) δ 169.7, 165.1, 77.4, 60.0, 58.3, 52.8, 43.1, 32.7, 29.0, 21.1, 14.7. The data agree with those reported previously for the compound.¹⁵⁷

Synthesis of (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143¹⁵³,¹⁵⁴

(i) To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added ethyl-4-aminobutyrate hydrochloride (0.961g, 5.73mmol, 1 eq), ethyl 6-chlorohex-2-ynoate 285 (1.000g, 5.73 mmol, 1 eq), K₂CO₃ (2.376 g, 17.19 mmol, 3 eq), NaI (1.718 g, 11.46 mmol, 2 eq) and 4Å molecular sieves in MeCN (50 mL). The resulting reaction mixture was heated under reflux for 18 h. The reaction mixture was cooled to room temperature and poured into brine in a separating funnel and the organic layer was extracted with diethyl ether (3 × 30 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10% EtOAc: Hex to yield (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 (1.544 g, 74%) as an oil; Rᵣ 0.62 (EtOAc: Hex, 2:3); νₑᵣₛ/cm⁻¹ 2980 (w, C-H), 1729 (s, C=O), 1587 (s, C=C)and 1133 (s, C-O);¹H NMR (300 MHz, CDCl₃) δ 4.53 (s, 1H), 4.11 (dq, J = 18.3, 7.1 Hz, 4H), 3.38 (t, J = 7.1, 2H), 3.23 – 3.13 (m, 4H), 2.32 (t, J =7.3, 2H), 1.92 (m, 4H), 1.26 (m, 6H);¹³C NMR (75 MHz, CDCl₃) δ 172.8, 169.5, 165.0, 77.3, 60.6, 58.2, 52.6, 45.4,
32.6, 31.4, 21.5, 21.1, 14.7, 14.2; HRMS (ESI): m/z [M+H]+ found 270.1707, calcd for C_{14}H_{24}NO_{4}^+ 270.1700.

(ii) To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added ethyl-4-aminobutyrate hydrochloride (0.107 g, 0.64 mmol, 1 eq), ethyl 6-iodohex-2-ynoate 287 (0.500 g, 1.88 mmol, 2.94 eq), CsCO_{3} (0.247 g, 1.28 mmol, 2 eq) and 4Å molecular sieves in MeCN (50 mL). The resulting reaction mixture was heated under reflux for 22 h. The reaction mixture was cooled to room temperature and poured into brine in a separating funnel and the organic layer was extracted with diethyl ether (3 × 30 mL). The resulting organic layer was dried over MgSO_{4} and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10% EtOAc: Hex to yield (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 (0.102 g, 59%) as oil. The analytical date is shown above.

**Synthesis of (E)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 144**

\[\text{(E)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143} \ (0.300 \text{ g}, 1.11 \text{ mmol}, 1 \text{ eq}) \text{ was heated under reflux in a methanolic KOH (1M, 20 mL) solution for 0.5 h. The resulting reaction mixture was acidified by addition of HCl to pH~5 followed by the extraction of the organic layer into dichloromethane (3 × 20 mL). The organic layer was dried over MgSO}_{4} \text{ and evaporated in vacuo. The resulting acid residue was dissolved in MeCN (40 mL), followed by the addition of K}_{2}\text{CO}_{3} \ (0.307 \text{ g}, 2.22 \text{ mmol}, 2 \text{ eq}) \text{ and acetic anhydride (0.113 g, 1.11 mmol, 1 eq). The resulting reaction mixture was heated under reflux for 18 h. The cooled reaction mixture was poured into water in a separation funnel and extracted with dichloromethane (3 × 20 mL). The resulting organic layer was dried over MgSO}_{4} \text{ and then evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20% EtOAc: Hex to yield (E)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 144 (0.012 g, 5%) as oil; R}_{f} \ 0.57.\]
(EtOAc: Hex, 1:1); $\nu_{\text{max/cm}^{-1}}$ 2934 (w, C-H), 1738 (m, C=O), 1622 (s, C=C), 1130 (s, C-O) and 1055 (s, C-N); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.22 (q, $J = 7.1$ Hz, 2H), 3.65 (t, $J = 7.1$ Hz, 2H), 3.50 – 3.39 (m, 2H), 3.02 (t, $J = 7.8$ Hz, 2H), 2.74 – 2.62 (m, 2H), 2.19 (dt, $J = 12.9$, 6.5 Hz, 2H), 2.13 – 1.98 (m, 2H), 1.30 (t, $J = 7.1$ Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 196.2, 168.9, 168.9, 103.0, 60.3, 57.3, 50.9, 42.7, 35.5, 26.5, 21.1, 14.3.

**Synthesis of (E)-4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoic acid 289**

![Chemical Structure](image)

KOH (0.605 g, 10.8 mmol, 1.2 eq) was added to a round bottom flask containing a solution of (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 (2.419 g, 8.98 mmol, 1 eq) in THF (30 mL) and water (20 mL). The reaction mixture was left to stir overnight in an open vessel. Acetic acid was added adjusting the pH of the solution to pH~6. The resulting solution then extracted with EtOAc (3 $\times$ 100 mL). The resulting extracts were dried over MgSO$_4$ and evaporated in vacuo. (E)-4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoic acid 289 (2.165 g, 100%) resulted as a white solid; melting point = 90 – 91 °C; $R_f$ 0.32 (EtOAc: Hex, 2:1); $\nu_{\text{max/cm}^{-1}}$ 3600 – 3200 (m, br, O-H), 2996 (w, C-H), 1695 (m, C=O), 1588 (m, C=C) and 1120 (m, C-O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.06 (s, 1H), 4.54 (s, 1H), 4.09 (q, $J = 7.1$ Hz, 2H), 3.38 (t, $J = 7.1$ Hz, 2H), 3.27 – 3.19 (m, 2H), 3.15 (t, $J = 7.8$ Hz, 2H), 2.38 (t, $J = 7.3$ Hz, 2H), 2.01 – 1.83 (m, 4H), 1.25 (t, $J = 7.1$ Hz, 3H).
Synthesis of (E)-methyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 290 and 4-((E)-2-(1-ethoxy-6-((E)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)-1,3-dioxohexan-2-ylidene)pyrrolidin-1-yl)butanoic acid 291

(i) (E)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 (0.400 g, 1.48 mmol, 1 eq) and KOH (0.415 g, 7.40 mmol, 5 eq) was heated under reflux in a MeOH (10 mL) solution for 1 h. The resulting reaction mixture was neutralised by addition of HCl to pH~7 followed by the extraction of the organic layer into DCM (3 × 20 mL). The organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting acid residue was dissolved in MeCN (40 mL) followed by the addition of K₂CO₃ (0.409 g, 2.96 mmol, 2 eq) and acetic anhydride (0.151 g, 1.48 mmol, 1 eq). The resulting reaction mixture was heated under reflux for 25.5 h. The cooled reaction mixture was poured into water, in a separation funnel and extracted with dichloromethane (3 × 20 ml). The resulting organic layer was dried over MgSO₄ and then evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 50 – 80% EtOAc: Hex to yield (E)-methyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 290 (0.018 g, 5%) as oil; Rf 0.65 (EtOAc: Hex, 2:3); νmax/cm⁻¹ 2924 (w, C=H), 1732 (s, C=O), 1660 (m, C=C), 1175 (m, C-O) and 1095 (w, C-N); ¹H NMR (300 MHz, CDCl₃) δ 4.52 (s, 1H), 4.09 (q, J = 7.1, 2H), 3.69 (s, 3H), 3.37 (t, J = 7.1, 2H), 3.24 – 3.12 (m, 4H), 2.33 (t, J = 7.3, 2H), 2.01 – 1.84 (m, 4H), 1.25 (t, J = 7.1, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.3, 171.7, 165.0, 78.0, 58.2, 52.6, 51.7, 45.5, 32.7, 31.2, 21.5, 21.1, 14.7.

(ii) After further elution with 40% MeOH: EtOAc, 4-((E)-2-(1-ethoxy-6-((E)-2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)-1,3-dioxohexan-2-ylidene)pyrrolidin-1-yl)butanoic acid 291
ylidene)pyrrolidin-1-yl)butanoic acid 291 (0.029 g, 4%) was obtained as an oil; \( R_f \) 0.33 (EtOAc: MeOH, 4:1); \( \nu_{\text{max/cm}^{-1}} \) 3340 (w, b, O-H), (2979 (w, C-H), 1711 (m, C=O), 1582 (s, C=C), 1132 (s, C-O) and 1054 (s, C-N); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.43 (s, 1H), 4.53 (s, 1H), 4.21 (q, \( J = 7.0 \) Hz, 2H), 4.08 (q, \( J = 7.1 \) Hz, 2H), 3.68 (t, \( J = 7.1 \) Hz, 2H), 3.52 – 3.43 (m, 2H), 3.38 (t, \( J = 7.0 \) Hz, 2H), 3.26 – 3.18 (m, 2H), 3.14 (t, \( J = 7.7 \) Hz, 2H), 2.68 (t, \( J = 6.7 \) Hz, 2H), 2.33 (t, \( J = 7.2 \) Hz, 2H), 2.20 (dt, \( J = 12.9, 6.6 \) Hz, 2H), 2.13 – 2.01 (m, 2H), 2.00 – 1.83 (m, 4H), 1.27 (dt, \( J = 14.5, 7.1 \) Hz, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 196.5, 169.7, 169.7, 168.8, 165.1, 165.1, 102.7, 77.8, 60.3, 58.4, 57.4, 52.7, 50.9, 45.6, 42.4, 35.7, 32.7, 31.7, 26.8, 21.6, 21.1, 14.8, 14.3.

**Synthesis of (E)-ethyl 2-(1-(4-iodobutyl)pyrrolidin-2-ylidene)acetate 292**

To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added to (E)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate 278 (0.200 g, 0.880 mmol, 1 eq), imidazole (0.180 g, 2.649 mmol, 3 eq), iodine (0.688 g, 2.649 mmol, 3 eq) and triphenylphosphine (0.695 g, 2.649 mmol, 3 eq) in toluene (50 mL). The resulting reaction mixture was heated under reflux for 3.75 h. The reaction mixture was cooled to room temperature and poured into a saturated NaHCO\(_3\) solution in a separating funnel and the organic layer was extracted with diethyl ether (3 × 10 mL). The resulting organic layer was dried over MgSO\(_4\) and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5 – 40% EtOAc: Hex to yield (E)-ethyl 2-(1-(4-iodobutyl)pyrrolidin-2-ylidene)acetate 292 (0.253 g, 85%) as an oil; \( R_f \) 0.21 (EtOAc: Hex, 1:4); \( \nu_{\text{max/cm}^{-1}} \) 2929 (w, C-H), 1736 (s, C=O), 1631 (s, C=C), 1178 (s, C-O) and 1036 (s, C-N); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 4.51 (s, 1H), 4.09 (q, \( J = 7.1 \) Hz, 2H), 3.38 (t, \( J = 7.1 \) Hz, 2H), 3.22 – 3.13(m, 6H), 2.02 – 1.88 (m, 2H), 1.89 – 1.77 (m, 2H), 1.76 – 1.62 (m, 2H), 1.24 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 169.5, 164.9, 77.7, 58.3, 52.5, 45.3, 32.7, 30.8, 27.3, 21.1, 14.8, 5.9.
Synthesis of ethyl 2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147\textsuperscript{151,122}

\[
\text{To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added (E)-ethyl 2-(1-(4-iodobutyl)pyrrolidin-2-ylidene)acetate 278 (0.091 g, 0.270 mmol, 1 eq) and Na}_2\text{HPO}_4 (0.057 g, 0.405 mmol, 1.5 eq) in DMF (50 mL). The resulting reaction mixture was heated under reflux for 3 h. The reaction mixture was cooled to room temperature and poured into distilled water in a separating funnel and the organic layer was extracted with diethyl ether (3 \times 10 mL). The resulting organic layer was dried over MgSO}_4 and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20\% EtOAc: Hex to yield ethyl 2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine-9-carboxylate 147 (0.056 g, 25\%) as an oil; R\textsubscript{f} 0.49 (EtOAc: Hex, 2:3); \textit{v}_{\text{max}}/\text{cm}^{-1} \ 2932 \text{ (w, C-H), } 1714 \text{ (s, C=O), } 1543 \text{ (m, C=C), } 1233 \text{ (s, C-O) and } 1024 \text{ (s, C-N)}; ^1\text{H NMR (500 MHz, CDCl}_3) \delta \ 4.10 \text{ (q, J = 7.1, 2H), } 3.28 \text{ (m, 4H), } 2.99 \text{ (t, J = 7.6, 2H), } 2.61 - 2.57 \text{ (m, 2H), } 1.86 \text{ (m, 2H), } 1.83 - 1.76 \text{ (m, 2H), } 1.73 \text{ (m, 2H), } 1.26 \text{ (t, J = 7.1, 3H)}; ^{13}\text{C NMR (126 MHz, CDCl}_3) \delta \ 170.2, 165.7, 94.5, 58.9, 56.2, 49.9, 35.2, 27.6, 26.0, 25.9, 22.3, 14.7.}
\]

Synthesis of ethyl 1,2,3,5,6,7-hexahydropyrazilizine-8-carboxylate 293\textsuperscript{151,122}

\[
\text{To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added (E)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidine-2-ylidene)acetate 288 (0.120 g, 0.542 mmol, 1 eq), imidazole (0.111 g, 1.63 mmol, 3 eq) iodine (0.281 g, 1.08 mmol, 2 eq), triphenylphosphine (0.428 g, 1.63 mmol, 3 eq) in toluene (40 mL). The resulting reaction mixture was heated under reflux for 18 h. The reaction mixture was cooled to room temperature and poured into a saturated NaHCO}_3 solution in a separating}
\]
funnel and the organic layer was extracted with diethyl ether (3 × 10 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield ethyl 1,2,3,5,6,7-hexahydroindolizine-8-carboxylate 293 (0.110 g, 57%) as an oil; Rₓ 0.23 (EtOAc: Hex, 1:4); νmax/cm⁻¹ 2950 (w, C-H), 1666 (m, C=O), 1586 (s, C=C), 1258 (s, C-O), and 1105 (s, C-N); 1H NMR (500 MHz, CDCl₃) δ 4.11 (q, J = 7.1, 2H), 3.28 (t, J = 7.0, 2H), 3.17 – 3.12 (m, 2H), 3.05 (t, J = 7.8, 2H), 2.35 (t, J = 6.3, 2H), 1.96 – 1.87 (m, 2H), 1.87 – 1.79 (m, 2H), 1.25 (t, J = 7.1, 3H); 13C NMR (126 MHz, CDCl₃) δ 168.9, 159.2, 87.5, 58.4, 53.0, 45.0, 32.7, 21.6, 21.4, 21.0, 14.8.

5.3 Experimental Section for Chapter 3

Synthesis of 1-(3,4-dimethoxyphenethyl)pyrrolidin-2-one 161

Homoveratrylamine 160 (3.055 g, 16.86 mmol, 1 eq) and dihydrofuran-2(3H)-one 13 (1.489 g, 17.29 mmol, 1.03 eq) were irradiated in a microwave reactor under these conditions (150 W, 220 °C, 3 h). The resulting reaction mixture was then cooled, dissolved in water and extracted with ethyl acetate (3 × 50 mL). The resulting organic layer was dried over MgSO₄ and then evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with 50% EtOAc: Hex to yield 1-(3,4-dimethoxyphenethyl)pyrrolidin-2-one 161 (4.204 g, 71%) as a solid; melting point = 58 – 59 °C; Rₓ 0.17 (EtOAc: Hex, 1:0); νmax/cm⁻¹ 2989 (w, C-H), 1689 (m, C=O), 1451 (m, aromatic, C=C) and 1125 (m, C-O); 1H NMR (300 MHz, CDCl₃) δ 6.84 – 6.72 (m, 3H), 3.87 (2 x s, 6H), 3.56 – 3.47 (m, 2H), 3.27 (t, J = 7.0 Hz, 2H), 2.84 – 2.75 (m, 2H), 2.36 (t, J = 8.1 Hz, 2H), 2.02 – 1.88 (m, 2H); 13C NMR (75 MHz, CDCl₃) δ 175.0, 148.9, 147.6, 131.3, 120.6, 111.9, 111.3, 55.9, 47.7, 44.1, 33.3, 31.0, 18.0.
Synthesis of 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-one 162

![Chemical Structure](image)

To a two neck round bottom flask equipped with a dropping funnel was added 1-(3,4-dimethoxyphenethyl)pyrrolidin-2-one 161 (1.717 g, 6.89 mmol, 1 eq) and sodium acetate (1.698 g, 20.7 mmol, 3 eq) in acetic acid (10 mL). Bromine (0.34 mL, 6.89 mmol, 1 eq) in acetic acid (10 mL) was added drop wise to the above reaction mixture and left to stir at room temperature for 2.5 h. Aqueous NH$_3$ was added to the resulting reaction mixture adjust pH to pH~8. The resulting solution was extracted with DCM (3×30 mL), the organic layer dried over MgSO$_4$ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 25% MeOH: EtOAc to yield 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-one 162 (2.167 g, 96%) as an oil; R$_f$ 0.21 (MeOH: EtOAc, 1:3); $\nu_{\text{max}}$ /cm$^{-1}$ 2990 (w, C-H), 1689 (s, C=O), 1586 (m, C=C), 1112 (m, C-N) and 1056 (s, C-O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.00 (s, 1H), 6.79 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.51 (t, $J$ = 7.4 Hz, 2H), 3.31 (t, $J$ = 7.1 Hz, 2H), 2.88 (t, $J$ = 6.9 Hz, 2H), 2.36 (t, $J$ = 8.1 Hz, 2H), 1.97 (p, $J$ = 7.6 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.9, 148.5, 148.3, 130, 115.5, 114.0, 113.2, 56.1, 47.7, 42.4, 33.4, 31.0, 18.0.

Synthesis of 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidine-2-thione 163

![Chemical Structure](image)

1-(3,4-Dimethoxyphenethyl)pyrrolidin-2-one 162 (1.486 g, 4.53 mmol, 1) and P$_2$S$_5$ (0.502 g, 2.26 mmol, 0.5 eq) were reacted in DCM (100 mL) in a two neck round bottom flask under nitrogen atmosphere at room temperature for 24 h. The resulting solution was filtered on celite and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 70% EtOAc: Hex to yield 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidine-2-thione 163 (1.292 g, 83%) as a white crystals; R$_f$ 0.65 (EtOAc: Hex, 7:3); $\nu_{\text{max}}$ /cm$^{-1}$ 2972 (w, C-H), 1591
(m, C=C), 1123 (m, C-N) and 1068 (s, C-O); $^1$H NMR (300 MHz, CDCl$_3$) δ7.00 (s, 1H), 6.80 (s, 1H), 3.95 (t, $J$ = 7.4 Hz, 2H), 3.84 (s, 6H), 3.54 (t, $J$ = 7.2 Hz, 2H), 3.08 (t, $J$ = 7.2 Hz, 2H), 3.00 (t, $J$ = 8.0 Hz, 2H), 1.98 (p, $J$ = 7.6 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 201.0, 148.5, 148.4, 129.5, 116.0, 114.0, 113.4, 56.2, 55.7, 47.6, 44.9, 31.8, 19.8.

2-(3,4-Dimethoxyphenyl)ethanamine 160 (1.048 g, 5.783 mmol, 1 eq) and dihydrofuran-2(3H)-one 13 (0.498 g, 5.783 mmol, 1 eq) were reacted neat in a sealed tube reactor under microwave conditions: 150 W, 220 °C, 1 h. The resulting crude 1-(3,4-dimethoxyphenethyl)pyrrolidin-2-one was dissolved in acetic acid (50 mL) followed by the addition of NaOAc (1.423 g, 17.349 mmol, 3 eq) and bromine (0.18 ml, 5.783 mmol, 1 eq) and the resulting solution was stirred at room temperature for 17 h. Acetic acid was evaporated in vacuo and the resulting residue was neutralized with a concentrated NaHCO$_3$ solution. The resulting crude 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-one was dissolved in DCM (150 mL) in a round bottom flask followed by addition of P$_2$S$_5$ (0.643 g, 2.892 mmol, 0.5 eq) and the reaction mixture was left to stir at room temperature for 23 h. The solvent was removed in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidine-2-thione 163 (1.502 g, 75%) as oil. The analytical data is as above.

**Synthesis of (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 164**

(i) To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added 2-(2-bromo-4,5-dimethoxyphenyl)ethanamine hydrochloride 319 (1.770 g, 5.19 mmol, 1 eq), ethyl 6-chlorohex-2-ynoate 285 (1.000 g, 5.19 mmol, 1 eq), K$_2$CO$_3$ (2.376 g, 17.19 mmol, 3 eq), NaI (1.718 g, 11.46 mmol, 2 eq) and 4Å molecular sieves in MeCN (60 mL). The resulting reaction mixture was heated under reflux for 17.5 h. The reaction mixture
was cooled to room temperature and poured into brine in a separating funnel and the organic layer was extracted with diethyl ether (3 × 30 ml). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20 – 40% EtOAc: Hex to yield (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 164 (1.812 g, 88%) as an oil; R₇ 0.24 (EtOAc: Hex, 1:2); νmax/cm⁻¹ 2936 (w, C-H), 1678 (m, C=O), 1585 (s, C=C), 1127 (s, C-O) and 1029 (s, C-N); ¹H NMR (300 MHz, CDCl₃) δ 7.01 (s, 1H), 6.68 (s, 1H), 4.65 (s, 1H), 4.12 (q, J = 7.1, 3H), 3.86 (2 × s, 6H), 3.42 (t, J = 7.2, 2H), 3.17 (m, 4H), 2.93 (t, J = 7.2, 2H), 1.86 (m, 2H), 1.27 (t, J = 7.1, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.5, 164.6, 148.5, 148.4, 130.0, 115.6, 114.0, 113.4, 77.8, 58.3, 56.2, 56.2, 56.1, 53.3, 46.1, 32.4, 21.1, 14.8; HRMS (ESI): m/z [M+H]⁺ found 398.0964, calcd for C₁₈H₂₅BrNO₄⁺ 398.0961.

Ethyl bromoacetate (0.07 mL, 0.587 mmol, 1.1 eq) was added to a solution of 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidine-2-thione 163 (0.184 g, 0.534 mmol, 1 eq) in dry MeCN (1.00 mL). The resulting solution was stirred at room temperature for 24 h under nitrogen atmosphere, after which the S-alkylation was complete shown by the base line spot on TLC analysis of the thioiminium salt. This was followed by the addition of triphenylphosphine (0.154 g, 0.587 mmol, 1.1 eq) and triethylamine (0.08 mL, 0.587 mmol, 1.1 eq) in MeCN (25 mL) to induce sulphur extrusion and stirred at room temperature for 20 h. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield to (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 164 (0.171 g, 80%) as an oil. The analytical data is as above.
Synthesis of (E)-ethyl 3-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)-2-oxopropanoate 299

Ethyl bromopyruvate (0.10 mL, 0.744 mmol, 1 eq) was added to a solution of 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidine-2-thione 163 (0.256 g, 0.744 mmol, 1 eq) in dry MeCN (6.00 mL). The resulting solution was stirred at room temperature for 3 h under nitrogen atmosphere, after which the S-alkylation was complete shown by precipitation of the thioiminium salt (with deduction of the solvent under high vacuum). This was followed by the addition of triphenylphosphine (0.195 g, 0.744 mmol, 1 eq) and triethylamine (0.10 mL, 0.744 mmol, 1.0 eq) in MeCN (25.40 mL) to induce sulphur extrusion and stirred at room temperature for 20 h. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield to (E)-ethyl 3-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)-2-oxopropanoate 299 (0.265 g, 84%) as an oil; Rf 0.35 (EtOAc: Hex, 3:7); $\nu_{\text{max}}$/cm$^{-1}$ 2997 (w, C-H), 1702 (m, C=O), 1556 (s, C=C), 1135 (s, C-O) and 1042 (s, C-N); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.00 (s, 1H), 6.80 (s, 1H), 5.94 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.63 (t, J = 7.3 Hz, 2H), 3.56 – 3.47 (m, 2H), 3.29 (t, J = 7.8 Hz, 2H), 3.02 (t, J = 7.3 Hz, 2H), 2.06 – 1.92 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.8, 171.0, 165.9, 148.8, 129.1, 115.7, 114.0, 113.6, 86.3, 61.9, 56.3, 56.2, 54.4, 47.0, 34.7, 32.6, 20.5, 14.1.

Synthesis of 1-(3,4-dimethoxyphenethyl)pyrrolidine-2-thione 302

1-(3,4-Dimethoxyphenethyl)pyrrolidin-2-one 161 (4.276 g, 17.15 mmol, 1 eq), P$_2$S$_5$ (1.906 g, 8.575 mmol, 0.5 eq) were stirred in DCM (400 mL) at room temperature for 24 h. A saturated solution of NaHCO$_3$ was poured into the
reaction mixture and the organic layer was extracted with DCM (3 x 80 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 50% EtOAc: Hex to yield 1-(3,4-dimethoxyphenethyl)pyrrolidine-2-thione 302 (3.095 g, 68%) as an oil; Rf 0.31 (EtOAc: Hex, 1:1); ν\textsubscript{max}/cm\textsuperscript{-1} 2964 (w, C-H), 1456 (s, C=C, aromatic), and 1120 (s, C-N); \textsuperscript{1}H NMR (300 MHz, CDCl₃) δ 6.89 – 6.72 (m, 3H), 3.95 (t, J = 7.4 Hz, 2H), 3.86 (2 x s, 6H), 3.52 (t, J = 7.3 Hz, 2H), 3.05 – 2.87 (m, 4H), 2.05 – 1.85 (m, 2H); \textsuperscript{13}C NMR (75 MHz, CDCl₃) δ 200.6, 148.9, 147.7, 130.7, 120.6, 111.9, 111.4, 55.9, 55.9, 55.6, 49.4, 44.9, 31.7, 19.7.

**Synthesis of (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303**\textsuperscript{153,154}

To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added homoveratrylamine (0.312 g, 1.72 mmol, 1 eq), ethyl 6-chlorohex-2-ynoate (0.300 g, 1.72 mmol, 1 eq), K\textsubscript{2}CO\textsubscript{3} (0.475 g, 3.44 mmol, 2 eq), NaI (0.516 g, 3.44 mmol, 2 eq) and 4Å molecular sieves in MeCN (30 mL). The resulting reaction mixture was heated under reflux for 24h. The reaction mixture was cooled to room temperature and poured into brine in a separating funnel and the organic layer was extracted with diethyl ether (3 x 10 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 40% EtOAc: Hex to yield (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 (0.367 g, 62%) as a solid; melting point = 108 – 109 °C; Rf 0.66 (EtOAc: Hex, 1:0); ν\textsubscript{max}/cm\textsuperscript{-1} 2978 (w, C-H), 1668 (s, C=O), 1585 (s, C=C), 1130 (s, C-O) and 1018 (s, C-N); \textsuperscript{1}H NMR (300 MHz, CDCl₃) δ 6.81 (d, J = 8.1, 1H), 6.76 – 6.71 (m, 1H), 6.69 (d, J = 1.6, 1H), 4.61 (s, 1H), 4.11 (q, J = 7.1, 2H), 3.87 (2 x s, 6H), 3.39 (t, J = 7.3, 2H), 3.16 (m, 4H), 2.80 (t, J = 7.3, 2H), 1.85 (m, 2H), 1.27 (t, J = 7.1, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl₃) δ 169.5, 164.5, 149.0, 147.7, 131.4, 120.7 111.9, 111.4, 77.6, 58.2, 55.9, 53.2, 48.1, 32.7, 31.7, 21.1, 14.8; HRMS (ESI): m/z [M+H]\textsuperscript{+} found 320.1853, calcd for C\textsubscript{18}H\textsubscript{26}NO\textsubscript{4}+ 320.1856.
Ethyl 2-bromoacetate (0.41 mL, 3.31 mmol, 1.1 eq) was added to a solution of 1-(3,4-dimethoxyphenethyl)pyrrolidine-2-thione 302 (0.800 g, 3.01 mmol, 1 eq) in dry MeCN (2.00 mL). The resulting solution was stirred at room temperature for 4 h under nitrogen atmosphere, after which the S-alkylation was complete shown by the precipitation of the thioiminium salt. This was then followed by the addition of triphenylphosphine (0.868 g, 3.31 mmol, 1.1 eq) and triethylamine (0.45 mL, 3.31 mmol, 1.1 eq) in MeCN (30 mL) and left stirring at room temperature for 22 h to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 (0.341 g, 35%) as a solid; The spectra is as above.\textsuperscript{151,161}

\textbf{Synthesis of ethyl 2-(1-(3,4-dimethoxyphenyl)-1H-pyrrol-2-yl)acetate 305}\textsuperscript{158}

\chemimage{O} \text{C} \text{N} \text{O} \text{C} \text{C} \text{O} \text{C}

(E)-Ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 304 (0.130 g, 0.446 mmol, 1 eq) and palladium acetate (0.010 g, 0.045 mmol, 0.1 eq) in acetic acid (20 mL) were heated to 80 °C in a two necked round bottom flask for 1 h, while bubbling oxygen gas for the duration. After cooling to room temperature the reaction mixture was reduced in vacuo. The organic residue was then treated with saturated NaHCO\textsubscript{3} solution to pH~8 and then extracted with dichloromethane (3 × 10 mL). The resulting organic layer was dried over MgSO\textsubscript{4} and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20 – 40% EtOAc: Hex to yield ethyl 2-(1-(3,4-dimethoxyphenyl)-1H-pyrrol-2-yl)acetate 305 (0.018 g, 14%) as an oil; R\textsubscript{f} 0.53 (EtOAc: Hex, 2:3); \nu\textsubscript{max}/\text{cm}^{-1} 2953 (w, C-H), 1730 (s, C=O), 1435 (m, aromatic, C=C), 1198 (s, C-O) and 1158 (s, C-N); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 6.88 (m, 3H), 6.80 - 6.75 (m, 1H), 6.31 - 6.14 (m, 2H), 4.08 (q, J =7.1, 2H), 3.90 (m, 6H), 3.56 (s, 2H), 1.20 (t, J =7.1, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta 171.0, 149.0, 148.5, 132.9, 125.8, 122.7, 118.5, 110.9, 110.4, 109.3, 108.1, 60.9, 56.1, 32.7, 14.1; HRMS (ESI): m/z [M+H]\textsuperscript{+} found 290.1319, calcd for C\textsubscript{16}H\textsubscript{20}NO\textsubscript{4}\textsuperscript{+} 290.1387.
Synthesis of ethyl 6,7-dimethoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate 306

(E)-Ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 304 (0.070 g, 0.240 mmol, 1 eq) and palladium acetate (5.4 mg, 0.024 mmol, 0.1 eq) in acetic acid (10 mL) were heated to 55 °C in a two necked round bottom flask for 1 h, while bubbling oxygen gas for the duration. After cooling to room temperature the reaction mixture was evaporated in vacuo. The organic residue was then treated with saturated NaHCO₃ solution to pH~8 and then extracted with DCM (3 × 10 mL). The resulting organic layer was dried over MgSO₄ and then evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20 – 40% EtOAc: Hex to yield ethyl 6,7-dimethoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate 306 (0.010 g, 14%) as a solid; Rf 0.48 (EtOAc: Hex, 2:3); v_{max}/cm⁻¹ 2937 (w, C-H), 1678 (s, C=O), 1579 – 1427 (s, C=C, aromatic), 1248 (s, C-O) and 1095 (s, C-N); ¹H NMR (500 MHz, CDCl₃) δ 7.63 (s, 1H), 6.75 (s, 1H), 4.35 (q, J = 7.1, 2H), 4.07 (t, J = 7.1, 2H), 3.96 (s, 3H), 3.26 (t, J = 7.1, 2H), 2.68 – 2.61 (m, 2H), 1.40 (t, J = 7.1, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 165.6, 150.7, 146.4, 146.2, 126.8, 124.1, 103.4, 99.0, 93.5, 59.2, 56.3, 56.2, 44.6, 26.8, 26.3, 14.7; HRMS (ESI): m/z [M+H]⁺ found 290.1389, calcd for C₁₆H₂₀NO₄⁺ 290.1387.

Synthesis of 1-(3,4-dimethoxyphenyl)pyrrolidine-2-thione 309

3,4-Dimethoxyaniline (2.262 g, 14.764 mmol, 1 eq) and dihydrofurane-2(3H)-one 13 (1.398 g, 16.242 mmol, 1.1 eq) were reacted neat in a sealed tube reactor under microwave conditions: 150 W, 250 °C, 2 h. The resulting crude 1-(3,4-dimethoxyphenyl)pyrrolidin-2-one was dissolved in DCM (150 mL) in a round bottom flask followed by addition of P₂S₅ (1.004 g, 7.382 mmol, 0.5 eq) and the reaction mixture was left to stir at room temperature for 18 h. The solvent was removed in vacuo. The resulting residue was purified by silica gel column...
chromatography eluting with 30% EtOAc: Hex to yield 1-(3,4-dimethoxyphenyl)pyrrolidine-2-thione 309 (3.196 g, 91%) as an oil; Rf 0.44 (EtOAc: Hex, 3:2); \( \nu_{\text{max}}/\text{cm}^{-1} \) 2937 (w, C-H), 1509 (s, aromatic, C=C), 1144 (s, C-O) and 1031 (s, C-N); \(^1\text{H} \text{NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta 7.18 (d, J = 2.2 \text{ Hz}, 1\text{H}), 6.97 (dd, J = 8.6, 2.2 \text{ Hz}, 1\text{H}), 6.92 (d, J = 8.6 \text{ Hz}, 1\text{H}), 4.12 (t, J = 7.2 \text{ Hz}, 2\text{H}), 3.91 (2 \times s, 6\text{H}), 3.25 (t, J = 7.9 \text{ Hz}, 2\text{H}), 2.25 (m, 2\text{H}); \(^{13}\text{C} \text{NMR} (75 \text{ MHz}, \text{CDCl}_3) \delta 202.5, 149.0, 148.3, 133.6, 116.9, 111.0, 108.9, 59.1, 56.1, 56.0, 46.3, 20.6.

**Synthesis of 1-(3,4-dimethoxybenzyl)pyrrolidine-2-thione 310**

(3,4-Dimethoxyphenyl)methanamine (1.130 g, 6.758 mmol, 1 eq) and dihydrofuran-2(3H)-one 13 (0.640 g, 7.433 mmol, 1.1 eq) were reacted neat in a sealed tube reactor under microwave conditions: 150 W, 250 \( ^\circ \text{C} \), 3 h. The resulting crude 1-(3,4-dimethoxybenzyl)pyrrolidin-2-one was dissolved in dichloromethane (150 mL) in a round bottom flask followed by addition of \( \text{P}_2\text{S}_5 \) (0.751 g, 3.38 mmol, 0.5 eq) and the reaction mixture was left to stir at room temperature for 20 h. The solvent was removed in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc: Hex to yield 1-(3,4-dimethoxybenzyl)pyrrolidine-2-thione 310 (1.390 g, 77%) as an oil; Rf 0.52 (EtOAc: Hex, 3:2); \( \nu_{\text{max}}/\text{cm}^{-1} \) 2939 (w, C-H), 1514 (s, aromatic, C=C), 1136 (s, C-O) and 1022 (s, C-N); \(^1\text{H} \text{NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta 6.95 (d, J = 1.7 \text{ Hz}, 1\text{H}), 6.87 (dd, J = 8.2, 1.7 \text{ Hz}, 1\text{H}), 6.82 (d, J = 8.1 \text{ Hz}, 1\text{H}), 4.92 (s, 2\text{H}), 3.88 (s, 3\text{H}), 3.87 (s, 3\text{H}), 3.59 (t, J = 7.2 \text{ Hz}, 2\text{H}), 3.09 (t, J = 7.9 \text{ Hz}, 2\text{H}), 2.08 – 1.95 (m, 2\text{H}); \(^{13}\text{C} \text{NMR} (75 \text{ MHz}, \text{CDCl}_3) \delta 201.3, 149.2, 148.9, 127.8, 120.9, 111.6, 111.0, 56.0, 55.9, 53.9, 51.4, 45.0, 19.4.
To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added 3,4-dimethoxyaniline (0.438 g, 2.86 mmol, 1 eq), ethyl 6-chlorohex-2-ynoate 285 (0.500 g, 2.86 mmol, 1 eq), K$_2$CO$_3$ (1.186 g, 0.858 mmol, 3 eq), NaI (0.857 g, 5.72 mmol, 2 eq) and 4Å molecular sieves in MeCN (40 mL). The resulting reaction mixture was heated under reflux for 43 h. The reaction mixture was cooled to room temperature and poured into brine in a separating funnel and the organic layer was extracted with diethyl ether (3 × 30 mL). The resulting organic layer was dried over MgSO$_4$ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10–50% EtOAc: Hex to yield (E)-ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 304 (0.833 g, 73%) as a solid; melting point = 130–131 °C; R$_f$ 0.60 (EtOAc: Hex, 4:1); $\nu_{max}$/cm$^{-1}$ 2933 (w, C-H), 1674 (m, C=O), 1560 (s, C=C, aromatic) and 1140 (s, C-O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.88 (d, $J$ = 8.4, 1H), 6.82 – 6.74 (m, 2H), 4.73 (s, 1H), 4.06 (q, $J$ = 7.1, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.76 – 3.62 (t, $J$ = 7.0, 2H), 3.30 (t, $J$ = 7.6, 2H), 2.11 (t, $J$ = 7.1, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.5, 164.8, 149.5, 147.5, 134.4, 117.5, 111.6, 109.0, 80.7, 58.3, 56.0, 56.0, 55.1, 32.4, 21.6, 14.6; HRMS (ESI): m/z [M+H]$^+$ found 292.1552, calcd for C$_{16}$H$_{22}$NO$_4$ $^+$ 292.1543.

Ethyl 2-bromoacetate (0.17 mL, 1.48 mmol, 1 eq) was added to a solution of 1-(3,4-dimethoxyphenyl)pyrrolidine-2-thione 309 (0.352 g, 1.48 mmol, 1 eq) in dry MeCN (2.50 mL). The resulting solution was stirred at room temperature for 3.5 h under nitrogen atmosphere, after which the S-alkylation was complete shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethyl phosphite (0.35 mL, 1.63 mmol, 1.1 eq) and triethylamine (0.18 mL, 1.63 mmol, 1.1 eq) in MeCN (30 mL) and left stirring at room temperature for 20 h to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography gel eluting with 5
Synthesis of (E)-ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307153,154

To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added (3,4-dimethoxyphenyl)methanamine (0.478 g, 2.86 mmol, 1 eq), ethyl 6-chlorohex-2-ynoate 285 (0.500 g, 2.86 mmol, 1 eq), K$_2$CO$_3$ (0.791 g, 5.72 mmol, 2 eq), NaI (0.857 g, 5.72 mmol, 2 eq) and 4Å molecular sieves in MeCN (40 mL). The resulting reaction mixture was heated under reflux for 21 h. The reaction mixture was cooled to room temperature and poured into brine in a separating funnel and the organic layer was extracted with diethyl ether (3 × 30 mL). The resulting organic layer was dried over MgSO$_4$ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 10 – 50% EtOAc : Hex to yield (E)-ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307 (0.751 g, 86%) as an oil; R$_f$ 0.79 (EtOAc: Hex, 4:1); $\nu_{\text{max}}$/cm$^{-1}$ 2936 (w, C-H), 1678 (m, C=O), 1581 (s, C=C, aromatic) and 1127 (s, C-O); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.82 (d, $J$ = 8.1, 1H), 6.77 – 6.71 (m, 1H), 6.70 (d, $J$ = 1.7, 1H), 4.72 (s, 1H), 4.30 (s, 2H), 4.09 (q, $J$ = 7.1, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.32 (t, $J$ = 7.1, 2H), 3.23 (t, $J$ = 7.4, 2H), 2.02 – 1.87 (m, 2H), 1.25 (t, $J$ = 7.1, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.6, 165.3, 149.2, 148.5, 128.5, 119.6, 111.2, 110.6, 78.3, 58.3, 55.9, 52.2, 49.8, 32.7, 21.1, 14.7; HRMS (ESI): m/z [M+H]$^+$ found 306.1698, calcd for C$_{17}$H$_{24}$NO$_4$ $^+$ 306.17.

Ethyl 2-bromoacetate (0.17 mL, 1.38 mmol, 1 eq) was added to a solution of 1-(3,4-dimethoxybenzyl)pyrrolidine-2-thione 310 (0.354 g, 1.38 mmol, 1 eq) in dry MeCN (2.00 mL). The resulting solution was stirred at room temperature for 3.5 h under nitrogen atmosphere, after which the S-alkylation was complete shown by the precipitation of the thioiminium salt. This was then followed by the addition of triethyl
phosphite (0.33 mL, 1.52 mmol, 1.1 eq) and triethylamine (0.17 mL, 1.52 mmol, 1.1 eq) in MeCN (30 mL) and left stirring at room temperature for 19 h to induce sulphur extrusion. The resulting organic layer was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5 – 10% EtOAc:Hex to yield (E)-ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307 (0.400 g, 95%) as an oil.\textsuperscript{151,161} The spectra are as above.

**Synthesis of (E)-(2-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)ethyl)-4,5-dimethoxyphenyl)(oxo)vanadium(V) fluoride 311**

\[
\begin{align*}
\text{(E)-ethyl} & & 2-(1-(3,4\text{-dimethoxyphenethyl})\text{pyrrolidin-2-ylidene})\text{acetate 303 (0.300 g, 0.939 mmol, 1 eq) in DCM (19 mL) was added all at once into a solution of VOF}_3 (0.352 g, 2.82 mmol, 2 eq) and trifluoroacetic anhydride (0.4 mL) in a 2:1 solvent mixture of DCM and trifluoroacetic acid in a round bottom flask at \(-15\) °C and stirred for 2.5 h. The reaction mixture was evaporated in vacuo and the resulting residue was purified by silica gel chromatography eluting with 100 EtOAc to yield (E)-(2-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)ethyl)-4,5-dimethoxyphenyl)(oxo)vanadium(V) fluoride 311 (0.168 g, 42%) as an oil; \nu_{\text{max}}/\text{cm}^{-1} 2992 (w, C-H), 1702 (s, C=O), 1590 (s, C=C), 1112 (s, C-O) and 1073 (s, C-N); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 6.78 (s, 1H), 6.69 (s, 1H), 4.38 (s, 1H), 4.08 (q, \textit{J} = 7.1 Hz, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 3.17 (t, \textit{J} = 7.7 Hz, 2H), 3.06 (ddd, \textit{J} = 15.8, 8.4, 2.4 Hz, 4H), 2.59 (dtd, \textit{J} = 20.9, 13.5, 7.7 Hz, 2H), 1.83 (p, \textit{J} = 7.5 Hz, 2H), 1.25 (t, \textit{J} = 7.1 Hz, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta 169.4, 164.3, 148.4, 147.4, 132.6, 128.8, 113.4, 112.5, 77.7, 58.2, 56.0, 56.0, 52.7, 52.6, 47.3, 32.6, 20.9, 14.7.\end{align*}
\]
Synthesis of (E)-(1-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)-2-ethoxy-2-oxoethyl)(oxo)vanadium(V) fluoride 312

\[
\text{F} \quad \text{C} \quad \text{O} \quad \text{C} \quad \text{C} \quad \text{C} \\
\text{N} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \\
\text{F} \quad \text{F}
\]

A solution of (E)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303 (0.250 g, 0.783 mmol, 1 eq) and TFAA (0.08 mL, 0.576 mmol, 1.3 eq) in DCM (2.38 mL) was added drop wise to a solution of vanadium(v) oxytrifluoride (0.196 g, 1.58 mmol, 2.02 eq) and TFA (0.16 mL, 2.09 mmol, 2.6 eq) in DCM (2.38 mL) and EtOAc (0.19 mL) over 3 min at –5 °C. The reaction mixture was left to react overnight with temperature gradually rising to room temperature. The reaction mixture was poured onto ice and extracted with DCM (3×15 mL). The resulting organic layer was washed with brine, dried over MgSO₄ and volatiles evaporated in vacuo. The resulting residue was purified by silica gel chromatography eluting with 50% EtOAc: Hex to yield (Z)-(1-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)-2-ethoxy-2-oxoethyl)(oxo)vanadium(V) fluoride 312 (0.0422 g, 13%) as an oil; ν\text{max}/\text{cm}⁻¹ 2942 (w, C-H), 1735 (s, C=O), 1588 (s, C=C), 1205 (s, C-O) and 1084 (s, C-N); ¹H NMR (300 MHz, CDCl₃) δ 6.81 (d, J = 7.9 Hz, 1H), 6.74 – 6.65 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.52 (dt, J = 14.6, 7.2 Hz, 4H), 3.14 (t, J = 7.8 Hz, 2H), 2.79 (t, J = 7.3 Hz, 2H), 2.00 – 1.86 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.0, 167.5, 149.2, 148.0, 129.9, 120.7, 111.9, 111.5, 95.0, 60.9, 57.9, 55.9, 55.9, 52.3, 37.1, 30.6, 20.3, 13.9.

Synthesis of (2-bromo-4,5-dimethoxyphenyl)methanamine hydrobromide 118₁⁵⁹,₁⁶⁰

\[
\text{BrHH}_2\text{N} \quad \text{O} \\
\text{O} \quad \text{O}
\]

A bromine solution (1.23 ml, 23.92 mmol, 1 eq) in acetic acid (20 mL) was added drop-wise to a solution of (3,4-dimethoxyphenyl)methanamine 114 (4.000 g, 23.92 mmol, 1 eq) in acetic acid (80 mL). The solution was left stirring
at room temperature for 2 h. The precipitated (2-bromo-4,5-
dimethoxyphenyl)methanamine hydrobromide was filtered and washed with DCM (3 × 30 mL) followed by Hex (3 × 30 mL). The resulting solid was dried in vacuo. The resulting organic layer was dried over MgSO₄ and then evaporated in vacuo to achieve a combined yield (2-bromo-4,5-dimethoxyphenyl)methanamine hydrobromide 118 (6.942 g, 88%) as a solid; v_max/cm⁻¹ 3111 (m, br, N-H), 2911 (m, C-H), 1478 (s, C=C, aromatic), 1232 (s, C-O) and 1044 (s, C-N); ¹H NMR (300 MHz, D₂O) δ 7.06 (s, 1H), 6.92 (s, 1H), 4.08 (s, 2H), 3.69 (2 × s, 6H).

**Synthesis of 2-(2-bromo-4,5-dimethoxyphenyl)ethanamine hydrobromide 119**¹⁵⁹,¹⁶⁰

A bromine solution (1.15 mL, 22.32 mmol, 1 eq) in acetic acid (20 mL) was added drop-wise to a solution of 2-(3,4-
dimethoxyphenyl)ethanamine 160 (4.00 g, 22.32 mmol, 1 eq) in acetic acid (80 mL). The solution was left stirring at room temperature for 2 h. The precipitated 2-(2-bromo-4,5-dimethoxyphenyl)ethanamine hydrobromide was filtered and washed with DCM (3 × 30 mL) followed by Hex (3 × 30 mL). The resulting solid was dried in vacuo. The resulting organic layer was dried over MgSO₄ and then evaporated in vacuo to achieve a combined yield of 2-(2-bromo-4,5-dimethoxyphenyl)ethanamine hydrobromide 119 (5.387 g, 93%) as a solid; v_max/cm⁻¹ 3114 (m, br, N-H), 2901 (m, C-H), 1509 –1439 (s, C=C, aromatic), 1265 – 1167 (s, C-O) and 1021 (s, C-N); ¹H NMR (300 MHz, CDCl₃) δ 7.00 (s, 1H), 6.82 (s, 1H), 3.86 (s, 6H), 3.09 (t, J = 7.7 Hz, 2H), 3.01 (t, J = 7.7 Hz, 2H), 1.37 (s, 2H).

**Synthesis of (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 320**¹⁵³,¹⁵⁴
To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added (2-bromo-4,5-dimethoxyphenyl)methanamine hydrochloride 118 (0.500 g, 2.86 mmol, 1 eq), ethyl 6-chlorohex-2-ynoate 285 (0.935 g, 2.86 mmol, 1 eq), K$_2$CO$_3$ (1.186 g, 8.58 mmol, 3 eq), NaI (0.857 g, 5.72 mmol, 2 eq) and 4Å molecular sieves in MeCN (40 mL). The resulting reaction mixture was heated under reflux for 23 h. The reaction mixture was cooled to room temperature and poured into brine in a separating funnel and the organic layer was extracted with diethyl ether (3 × 30 mL). The resulting organic layer was dried over MgSO$_4$ and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20 – 40% EtOAc: Hex to yield (E)-ethyl 2-(1-(2-bromo-4,5-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 320 (0.907 g, 83%) as a solid; melting point = 108 – 109 °C; R$_f$ 0.27 (EtOAc: Hex, 1:2); $\nu_{\text{max}}$/cm$^{-1}$ 2971 (w, C-H), 1683 (m, C=O), 1589 (s, C=C), 1131 (s, C-O) and 1060, 1029 (m, C-N); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.03 (s, 1H), 6.60 (s, 1H), 4.63 (s, 1H), 4.34 (s, 2H), 4.09 (q, J = 7.1, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.33 (t, J = 7.0, 2H), 3.25 (t, J = 7.4, 2H), 2.08 – 1.91 (m, 2H), 1.24 (t, J = 7.1, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.5, 165.1, 149.1, 148.8, 126.8, 115.8, 113.4, 111.3, 79.0, 58.4, 56.3, 56.2, 52.3, 50.1, 32.5, 21.3, 14.7; HRMS (ESI): m/z [M+H]$^+$ found 384.0811, calcd for C$_{17}$H$_{23}$BrNO$_4$ $^+$ 384.0805.

**Synthesis of (E)-ethyl 4-(2-(2-ethoxy-2-oxo-1-phenylethylidene)pyrrolidin-1-yl)butanoate 327**

(E)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate 143 (0.120 g, 0.445 mmol, 1 eq), 2-
(trimethylsilyl)phenyltrifluoromethanesulfonate **326** (0.166 g, 0.557 mmol, 1.25 eq) and cesium fluoride (0.226 g, 1.484 mmol, 3.34 eq) were stirred at room temperature in MeCN (3.71 mL) under nitrogen atmosphere for 74 h. Water was added followed by extraction with DCM (3 × 20 mL). The organic extracts were dried over MgSO₄, and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5 – 40% EtOAc: Hex mixture to yield (E)-ethyl 4-(2-(2-ethoxy-2-oxo-1-phenylethylidene)pyrrolidin-1-yl)butanoate **327** (0.059 g, 39%) as an oil; Rf 0.63 (EtOAc: Hex, 1:1); v\(\text{max}/\text{cm}^{-1}\) 2982 (w, C-H), 1734 (m, C=O), 1567 (m, C=C), 1454 (m, aromatic, C=C) and 1110 (m, C-O); \(^1\text{H NMR (300 MHz, CDCl}_3\) δ 7.35 – 7.12 (m, 6H), 4.05 (p, \(J = 7.2\) Hz, 4H), 3.32 (t, \(J = 6.9\) Hz, 2H), 3.25 (t, \(J = 7.7\) Hz, 2H), 2.60 – 2.46 (m, 2H), 2.01 – 1.87 (m, 2H), 1.70 (t, \(J = 7.6\) Hz, 2H), 1.52 (dt, \(J = 18.1, 7.4\) Hz, 2H), 1.22 (t, \(J = 7.1\) Hz, 3H), 1.11 (t, \(J = 7.1\) Hz, 3H); \(^{13}\text{C NMR (75 MHz, CDCl}_3\) δ 172.9, 169.6, 162.1, 139.1, 132.0, 127.7, 126.0, 96.1, 60.4, 58.9, 54.2, 47.6, 35.8, 31.1, 21.7, 21.6, 14.6, 14.2.

(ii) TBAF (0.155 g, 0.594 mmol, 2.0 eq) was added drop-wise for 30 min through a syringe into a solution of (E)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate **143** (0.080 g, 0.297 mmol, 1 eq), and 2-(trimethylsilyl)phenyltrifluoromethanesulfonate **326** (0.133 g, 0.445 mmol, 1.5 eq), heated under reflux in THF (3.50 mL) under nitrogen atmosphere. The reaction was left heating under reflux over 20 h. Water was added followed by an extraction with DCM (3 × 10 mL). The organic extracts were dried over MgSO₄, and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 5, 10, 20 30, 40% EtOAc: Hex mixture to yield (E)-ethyl 4-(2-(2-ethoxy-2-oxo-1-phenylethylidene)pyrrolidin-1-yl)butanoate **327** (0.028 g, 27%) as an oil; The analytical data is as above.
Synthesis of (Z)-1-(4-nitrophenyl)-2-phenyl-2-(pyrrolidin-2-ylidene)ethanone 328

2-(Trimethylsilyl)phenyltrifluoromethanesulfonate 326 (0.125 g, 0.420 mmol, 1.5 eq) was added drop-wise for 5 min through a syringe into solution of (Z)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone 240 (0.065 g, 0.280 mmol, 1 eq), and cesium fluoride (0.085 g, 0.560 mmol, 2 eq) in MeCN (3.50 mL) at 60 °C under nitrogen atmosphere. The temperature was raised to heat under reflux and the reaction was over 23 h. Water was added followed by an extraction with DCM (3 × 10 mL). The organic extracts were dried over MgSO₄, and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography eluting with 20, 30, 40% EtOAc: Hex mixture to yield (Z)-1-(4-nitrophenyl)-2-phenyl-2-(pyrrolidin-2-ylidene)ethanone 328 (0.063 g, 79%) as an oil; Rf 0.32 (EtOAc: Hex, 1:1); νmax/cm⁻¹ 3400 – 3200 (m, br, N-H), 2943 (w, C-H), 1742 (s, C=O), 1567 (m, C=C), 1541 (m, aromatic, N-O), 1480 (m, aromatic, C=C), and 1326 (s, aromatic, C-N); ¹H NMR (300 MHz, CDCl₃) δ 11.19 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.16 (m, 3H), 7.02 (m, 2H), 3.79 (t, J = 7.1 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H), 2.13 – 1.88 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 187.9, 170.9, 148.4, 147.3, 139.0, 132.1, 129.1, 128.3, 126.4, 122.6, 105.4, 48.5, 33.5, 21.3.

5.4 Experimental Section for Chapter 4

Synthesis of azonan-2-one 332

Sodium azide (3.79 g, 61.0 mmol, 1.54 eq) was added portion wise into a 150 mL round bottom flask containing a solution of conc HCl (30.00 mL) and cyclooctanone 331 (5.00 g, 39.6 mmol, 1 eq) placed in an ice-bath. The reaction
mixture was stirred for 4 h allowing the temperature to rise to room temperature. Sodium carbonate was added until the mixture was slightly alkaline. Distilled water was added to dissolve the inorganic salts, and the oil which had separated was extracted with DCM (3 × 30 mL). The organic extracts were dried over anhydrous magnesium sulphate and the solvent was removed in vacuo. The crystals which were formed on cooling were purified by re-crystallisation from an EtOAc: Hex solvent mixture to give azonan-2-one 332 (5.50 g, 98%) as colourless crystals; melting point = 75 – 76 °C; Lit. m.p. 74 – 76 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3301 (s, br, N-H), 2930 (s, C-H) and 1651 (s, C=O); \(^1\)H NMR (300 MHz; CDCl\(_3\)) \( \delta \) 6.36 (s, 1H), 3.36 (m, 2H), 2.43 (t, \( J = 6.35, 2\)H), 1.81 (m, 2H) and 1.62 – 1.40 (m, 8H) ppm; \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \( \delta \) 178.1, 43.4, 33.1, 30.1, 27.9, 25.5, 24.6, 23.2 ppm. The spectra are similar to that reported previously.\(^{171}\)

**Synthesis of azonane-2-thione 333\(^{171}\)**

A mixture of azonan-2-one 332 (5.50 g, 38.9 mmol, 1 eq) P\(_2\)S\(_5\) (4.33 g, 19.5 mmol, 0.5 eq) and hexamethyldisiloxane (12.41 mL, 58.4 mmol, 1.5 eq) in dry DCM (150 mL) in a 250 mL round bottom flask under nitrogen atmosphere was stirred at room temperature under nitrogen atmosphere for 20 h. Saturated aqueous K\(_2\)CO\(_3\) was carefully added to the reaction mixture which was stirred for another 5 min before being transferred to a separating funnel. The organic layer was extracted repeatedly with DCM (5 × 50 mL). The organic extracts were dried over anhydrous magnesium sulphate and the solvent was evaporated in vacuo. The crude product was purified by column chromatography on silica gel using 5, 10, 20 and 30% EtOAc: Hex solvent mixture as eluent and then recrystallised from an EtOAc: Hex solvent mixture to give azocane-2-thione 333 (4.96 g, 81%) as colourless crystals; melting point = 72 – 75 °C; Lit. m.p. 84 – 87 °C;\(^{173}\) R\(_f\) 0.77 (EtOAc: Hex, 4:1); \( \nu_{\text{max}}/\text{cm}^{-1} \) 3407 (m, br, N-H); \(^1\)H NMR (300 MHz; CDCl\(_3\)) \( \delta \) 8.30 (s, 1H), 3.51 (m, 2H), 2.92 (m, 2H), 1.95 (m, 2H), 1.68 (m, 2H) and 1.57 (m, 6H); \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \( \delta \) 209.5, 47.9, 41.3, 29.1, 28.3, 27.6, 24.6, 24.0 ppm; The spectra are similar to those reported previously.\(^{171}\)
Preparation of NH vinylogous amides from thiolactams

In separate reactions; phenacyl bromide, para-nitrophenacyl bromide or para-methoxyphenacyl bromide were added to a stirred solution of thiolactams in dry acetonitrile. The resulting solution was stirred at room temperature for 30 min, 2 min and 5 sec respectively, after which the S-alkylation was complete. This was then followed by the addition of triethylphosphite and triethylamine to induce sulphur extrusion. The resulting solution was left to stir at ambient temperature for 2 days. Distilled water was added and the resulting solution was extracted with dichloromethane (3 × 30 mL). The organic extracts were dried over anhydrous sodium sulphate, filtered and evaporated in vacuo. The crude product was purified by column chromatography on silica gel using 5, 10, 20% EtOAc: Hex solvent mixture as eluent. The following compounds were prepared by this method.

Synthesis of (Z)-2-(azonan-2-ylidene)-1-phenylethanone 334

Azonane-2-thione 333 (1.300 g, 8.264 mmol, 1 eq) and phenacyl bromide (1.974 g, 9.917 mmol, 1.2 eq) in dry MeCN (20.00 mL) were reacted as described above, followed by the addition of triethylphosphite (1.648 g, 9.917 mmol, 1.2 eq) and triethylamine (1.003 g, 9.917 mmol, 1.2 eq) to give (Z)-2-(azonan-2-ylidene)-1-phenylethanone 334 (1.400 g, 70%) as an oil; R\textsubscript{f} 0.72 (EtOAc: Hex, 1:1); ν\textsubscript{max} /cm\textsuperscript{-1} above 3000 (m, br, N-H), 2927 (m, CH), 1739 (w, C=O), 1586 (m, C=C) and 1474 (m, aromatic, C=C); \textsuperscript{1}H NMR (300 MHz; CDCl\textsubscript{3}) δ 11.77 (s, 1H), 7.88 (m, 2H), 7.38 (m, 3H), 5.63 (s, 1H), 3.50 (m, 2H), 2.43 (m, 2H), 1.80 (m, 2H), 1.69 (m, 2H), 1.65 – 1.45 (m, 6H); \textsuperscript{13}C NMR (75 MHz; CDCl\textsubscript{3}) δ 187.4, 171.3, 171.3, 140.6, 130.3, 128.1, 126.8, 91.0, 43.8, 32.8, 30.2, 28.5, 27.2, 25.3, 22.5; HRMS (ESI) Found: [M+H]\textsuperscript{+}, 244.1711, C\textsubscript{18}H\textsubscript{22}NO\textsuperscript{+} exact calculated mass: 244.1696.
Synthesis of (Z)-2-(azonan-2-ylidene)-1-(4-nitrophenyl)ethanone 335

Azonane-2-thione 333 (1.300 g, 8.264 mmol, 1 eq) and p-nitrophenacyl bromide (2.420 g, 9.917 mmol, 1.2 eq) in dry MeCN (20.00 mL) were reacted as described above, followed by the addition of triethylphosphite (1.648 g, 9.917 mmol, 1.2 eq) and triethylamine (1.003 g, 9.917 mmol, 1.2 eq) to give (Z)-2-(azonan-2-ylidene)-1-(4-nitrophenyl)ethanone 335 (2.011 g, 100%) as yellow crystals; melting point = 121 – 122 °C; Rf 0.67 (EtOAc: Hex, 1:1); \( \nu_{\text{max}}/\text{cm}^{-1} \) above 3000 (v br, N-H), 2927 (m, CH), 1739 (w, C=O), 1586 (m, C=C), 1555 (s, aromatic, N-O), 1474 (m, aromatic, C=C) and 1338 (s, aromatic, N-O); \( ^1H \) NMR (300 MHz; CDCl\(_3\)) \( \delta \) 12.02 (s, 1H), 8.26 (d, \( J = 8.25 \), 2H), 8.03 (d, \( J = 8.02 \), 2H), 6.18 – 4.65 (s, 1H), 3.58 (dd, \( J = 3.58 \), 2H), 2.51 (m, 2H), 1.85 (m, 2H), 1.78 (m, 2H) and 1.70 – 1.50 (m, 6H) ppm; \( ^{13}C \) NMR (75 MHz; CDCl\(_3\)) \( \delta \) 184.3, 172.9, 148.8, 146.1, 127.8, 123.4, 90.9, 44.1, 32.8, 29.8, 28.2, 26.9, 25.2, 22.5 ppm; HRMS (ESI) Found: [M+1]\(^+\), 289.1556, \( C_{16}H_{21}N_2O_3 \) exact calculated mass: 289.1547.

Synthesis of (Z)-2-(azonan-2-ylidene)-1-(4-methoxyphenyl)ethanone 336 (546)

Azonane-2-thione 333 (1.00 g, 6.36 mmol, 1 eq) and 2-bromo-1-(4-methoxyphenyl)ethanone (1.60 g, 6.99 mmol, 1.1 eq) in dry MeCN (10.00 mL) were reacted as described above, followed by the addition of triethylphosphite (1.16 g, 6.99 mmol, 1.1 eq) and triethylamine (0.707 g, 6.99 mmol, 1.1 eq) to give (Z)-2-(azonan-2-ylidene)-1-(4-methoxyphenyl)ethanone 336 (1.59 g, 91%) as a solid; Rf 0.66 (EtOAc: Hex, 1:1); \( \nu_{\text{max}}/\text{cm}^{-1} \) above 3000 (m, br, N-H), 2929 (m, CH), 1742 (w, C=O), 1577 (m, C=C), 1484 (m, aromatic, C=C) and 1244 (m, C=O); \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 11.67 (s, 1H), 7.86 (d, \( J = 8.9 \) Hz, 2H), 6.90 (d, \( J = 8.9 \) Hz, 2H), 5.60 (s, 1H), 3.84 (s, 3H), 3.49 (td, \( J = 7.2, 5.8 \) Hz, 2H), 2.50 – 2.33 (m, 2H), 1.90 – 1.37 (m, 10H) ppm; \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 184.3, 172.9, 148.8, 146.1, 127.8, 123.4, 90.9, 44.1, 32.8, 29.8, 28.2, 26.9, 25.2, 22.5 ppm; HRMS (ESI) Found: [M+H]\(^+\), 274.1807, \( C_{17}H_{24}NO_2 \) exact calculated mass: 274.1802.
Reactions of NH vinylogous amides with methacrylic anhydride

Methacrylic anhydride and the NH vinylogous amide were placed in a microwave tube. The sealed tube with its contents was subjected to 150W, 150 °C in a microwave reactor for 60 minutes. The crude products were purified by column chromatography over silica gel eluting with 10%, 20% and 30% EtOAc: Hex mixture. The following compounds were prepared by this procedure.

Synthesis of 1-benzoyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 337

(Z)-2-(Azonan-2-ylidene)-1-phenylethenone 334 (471 mg, 1.94 mmol) and methacrylic anhydride (597 mg, 3.87 mmol, 2.0 eq) were heated in a microwave reactor as described above to give 1-benzoyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 337 (604 mg, 94%) as an oil; Rf 0.55 (EtOAc: Hex, 3:7); νmax /cm⁻¹ 2928 (m, C-H), 1701 (m, C=O), 1575, 1465 (s, C=C), and 1228 (s, C-O) ¹H NMR (300 MHz; CDCl₃) δ 7.67 (d, J = 6.0, 2H), 7.49 (m, 1H), 7.40 (m, 2H), 4.20 – 3.30 (m, 2H), 3.00 – 2.50 (m, 2H), 2.50 (m, 1H), 2.32 (m, 2H), 2.10 – 1.30 (m, 10H) 1.15 (d, J = 6.0, 3H) ppm; ¹³C NMR (75 MHz; CDCl₃) δ 196.7, 173.5, 154.5, 138.8, 132.3, 128.5, 128.5, 116.6, 44.4, 35.8,32.2, 29.7, 29.4, 29.1, 27.8, 23.9, 23.9,14.8 ppm; HRMS (ESI) Found: [M+H]⁺, 312.1970, C₂₀H₂₆NO₂⁺ exact calculated mass: 312.1958.
Synthesis of 3-methyl-1-(4-nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 338

(Z)-2-(Azonan-2-ylidene)-1-(4-nitrophenyl)ethanone 335
(200 mg, 0.694 mmol, 1 eq) and methacrylic anhydride (180 mg, 1.17 mmol, 1.7 eq) were heated in a microwave reactor as described above to give 3-methyl-1-(4-nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 338 (222 mg, 90%) as yellow crystals; melting point = 104 – 105 °C; Rf 0.50 (EtOAc: Hex, 3:7); νmax /cm⁻¹ 2912 (m, C-H), 1670 (m, C=O), 1598, 1452 (s, C=C), 1510 (s, N-O) and 1312 (s, N-O); ¹H NMR (300 MHz; CDCl₃) δ 8.30 (d, J = 9.0, 2H), 7.79 (d, J = 6.0, 2H), 4.30 – 3.40 (m, 2H), 3.20 – 2.60 (m, 2H), 2.51 (m, 1H) 2.31 (d, J = 9.0, 2H), 2.20 – 1.40 (m, 10H) 1.19 (d, J = 6.0, 3H) ppm; ¹³C NMR (75 MHz; CDCl₃) δ 194.1, 173.3, 154.7, 149.4, 144.9, 129.0, 123.8, 114.8, 44.8, 35.8,32.0, 29.7, 29.5, 29.2, 27.6, 24.0, 23.7, 14.8 ppm; HRMS (ESI) Found: [M+H]^⁺, 357.1814, C₂₀H₂₅N₂O₄⁺ exact calculated mass: 357.1809.

Synthesis of 1-(4-methoxybenzoyl)-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 339

(Z)-2-(Azonan-2-ylidene)-1-(4-methoxyphenyl)ethanone 336
(500 mg, 1.83 mmol, 1 eq) and methacrylic anhydride (282 mg, 1.83 mmol, 1 eq) were heated in a microwave reactor as described above to give 1-(4-methoxybenzoyl)-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 339 (542 mg, 87%) as an oil; Rf 0.52 (EtOAc: Hex, 3:7); νmax /cm⁻¹ 2990 (m, C-H), 1720 (m, C=O), 1548 (s, C=C) and 1169 (s, C-O); ¹H NMR (300 MHz, CDCl₃) δ 7.81 – 7.67 (m, 2H), 7.00 – 6.86 (m, 2H), 3.91 (m, 4H), 3.63 (s, 1H), 2.73 (s, 1H), 2.71 – 2.50 (m, 4H), 1.19 (d, J = 6.0, 3H) ppm.
2.61 – 2.45 (m, 2H), 2.45 – 2.25 (m, 2H), 2.07 – 1.81 (m, 2H), 1.80 – 1.34 (m, 10H), 1.21 (d, J = 6.7 Hz, 3H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ 195.9, 173.5, 148.2, 131.1, 131.0, 117.2, 113.8, 55.5, 44.4, 35.9, 32.3, 29.7, 29.4, 29.1, 27.9, 23.5, 23.2, 14.9 ppm; HRMS (ESI) Found: [M+H]\(^+\), 342.2072, C\(_{21}\)H\(_{28}\)NO\(_3\)\(^+\) exact calculated mass: 342.2064.

**Synthesis of 1-benzyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 340**

A mixture of 1-benzoyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 337 (327 mg, 1.05 mmol, 1 eq), Pd/C (5.3 mg, 0.05 mmol, 0.05 eq) in methanol (50 mL) was stirred at room temperature under hydrogen atmosphere (balloon) for 20 h. The reaction mixture was filtered over celite and evaporated in vacuo. The residue was then columned over silica gel eluting with 30% EtOAc: Hex solvent mixture to give 1-benzyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 340 (0.298 mg, 30%) as an oil; R\(_t\) 0.60 (EtOAc: Hex, 3:7); \(\nu_{\text{max}} /\text{cm}^{-1}\) 2890 (m, C-H), 1648 (m, C=O), 1520, 1450 (s, C=C) and 1150 (w, C-O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 7.22 (t, J = 7.1 Hz, 2H), 7.12 (dd, J = 14.4, 7.0 Hz, 3H), 3.69 (d, J = 34.4 Hz, 2H), 3.50 – 3.27 (m, 2H), 2.57 (dd, J = 12.8, 9.8 Hz, 1H), 2.49 – 2.20 (m, 2H), 1.99 – 1.69 (m, 4H), 1.67 – 1.38 (m, 8H), 1.02 (d, J = 6.9 Hz, 3H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ 173.1, 139.7, 137.9, 128.5, 128.4, 126.2, 114.9, 43.7, 38.0, 35.7, 32.6, 30.3, 29.1, 28.5, 28.2, 24.7, 23.4, 15.2 ppm.
Synthesis of 3-methyl-1-(4-nitrobenzoyl)-decahydropyrido[1,2-a]azonin-4(1H)-one 341

A mixture of 3-methyl-1-(4-nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one 338 (0.093 g, 0.261 mmol, 1 eq), triphenylsilane (0.217 g, 0.835 mmol, 3.2 eq) and trifluoroacetic acid (0.068 g, 0.600 mmol, 2.3 eq) was heated under reflux in 1,2 dichloroethane (20 mL) for 23 h under nitrogen atmosphere. A solution of sodium carbonate was added to the reaction mixture followed by extraction with dichloromethane (3 × 10 mL). The resulting organic layer was dried over MgSO₄ and evaporated in vacuo. The resulting residue was columned on silica gel eluting with 5, 10, 20, 30% EtOAc: Hex to yield 3-methyl-1-(4-nitrobenzoyl)-decahydropyrido[1,2-a]azonin-4(1H)-one 341 (0.038g, 40%) as an oil; Rf (EtOAc: Hex, 3:7); νmax /cm⁻¹ 2939 (m, C-H), 1710 (m, C=O), 1518 (s, N-O), 1480 (s, C=C), 1330 (s, N-O) and 1240 (s, C-O); ¹H NMR (300 MHz, CDCl₃) δ 8.37 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.8 Hz, 2H), 4.20 – 4.08 (m, 1H), 4.08 – 3.99 (m, 1H), 2.80 – 2.66 (m, 1H), 2.63 – 2.46 (m, 1H), 2.17 (dt, J = 12.7, 5.4 Hz, 1H), 2.11 – 1.92 (m, 2H), 1.84 – 1.38 (m, 11H), 1.23 (d, J = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 198.6, 173.3, 150.6, 140.4, 129.3, 124.2, 60.3, 49.1, 45.9, 35.6, 32.5, 29.7, 26.8, 26.5, 25.1, 24.9, 22.7, 16.4.
CHAPTER 6: REFERENCES


144. S. T. Mthembu, MSc dissertation, University of the Witwatersrand, 2008.
171. Siyanda T. Mthembu, MSc dissertation, University of the Witwatersrand, 2008.