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 illustrate 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-1*H*-pyrrolo[1,2-*a*]azepine-9-carboxylate **144** and (*E*)-ethyl 2,3,5,6,7,8-hexahydro-1*H*-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-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **222**, ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **223** and ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-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-benzoyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione **233** and 1-(4-methoxybenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione **235** in a double acylation reaction between N*H* 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(6*H*)-one **337**, 3-methyl-1-(4-nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-4(6*H*)-one **338** and 1-(4-methoxybenzoyl)-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-4(6*H*)-one **339**.

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I would like to express gratitude to the National Research Foundation, the University of the Witwatersrand, the School of Chemistry and J. P. Michael for generous funding support for this project.

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.[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.

1 **2** **3** **4**

Figure 1: Pyrrolizidine 1, indolizidine 2, quinolizidine 3 and pyrrolo[1,2-*a*]azepine 4

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).[7] In virtually all of our work, the nitrogen is part of a heterocyclic ring and the alkene part is exocyclic to the ring.

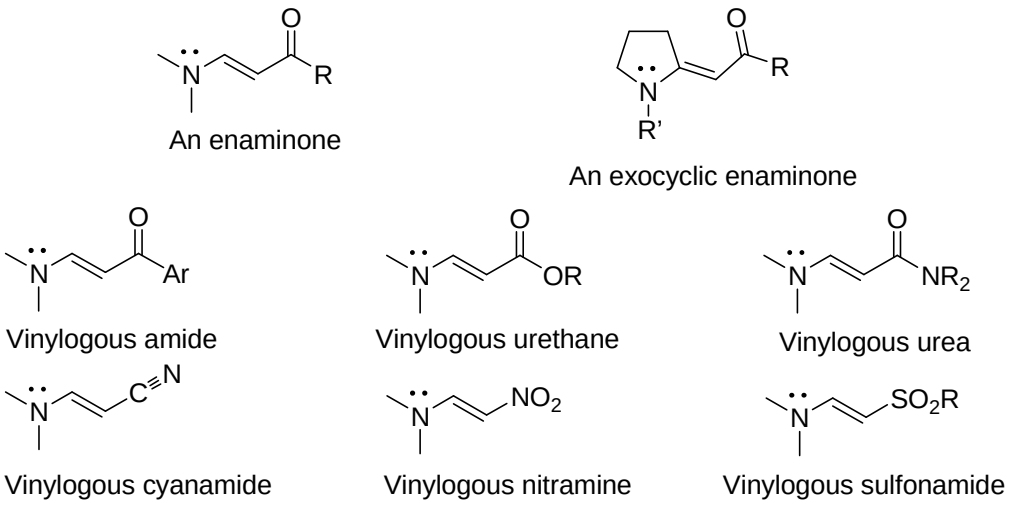
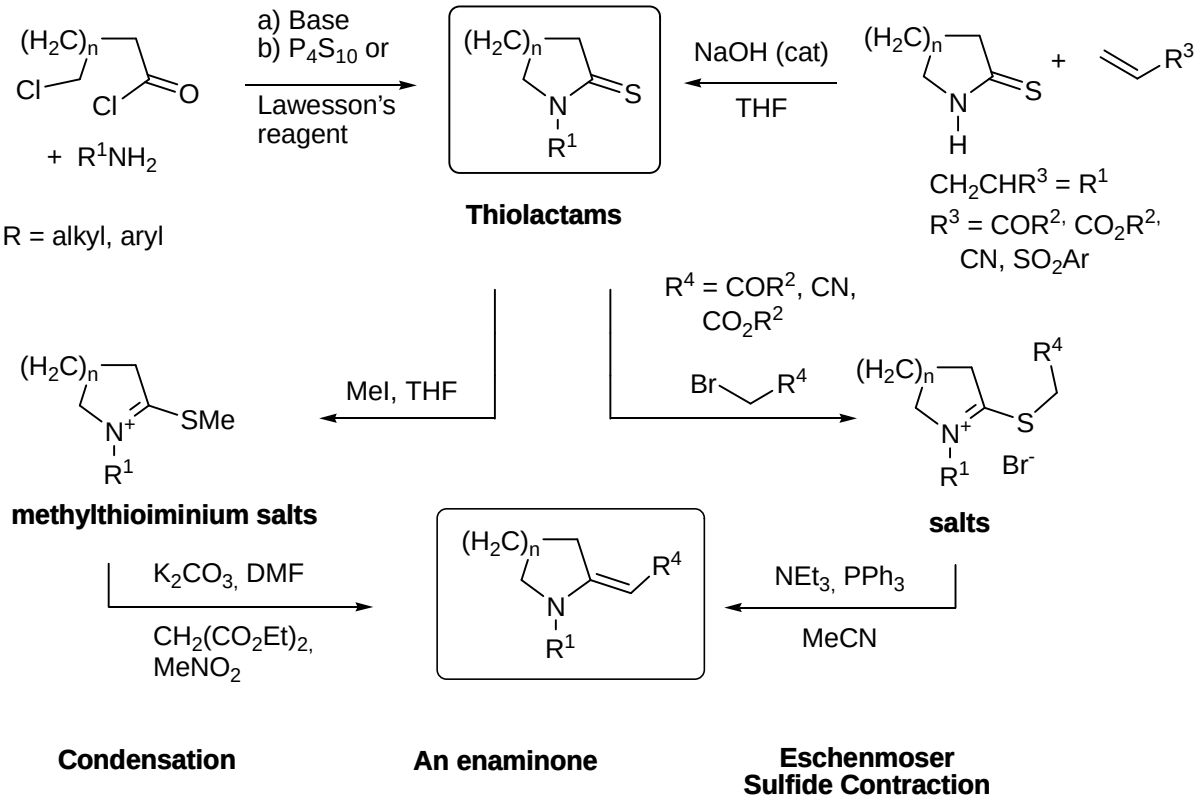


Figure 2: Examples of enaminones and related systems.[7]

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

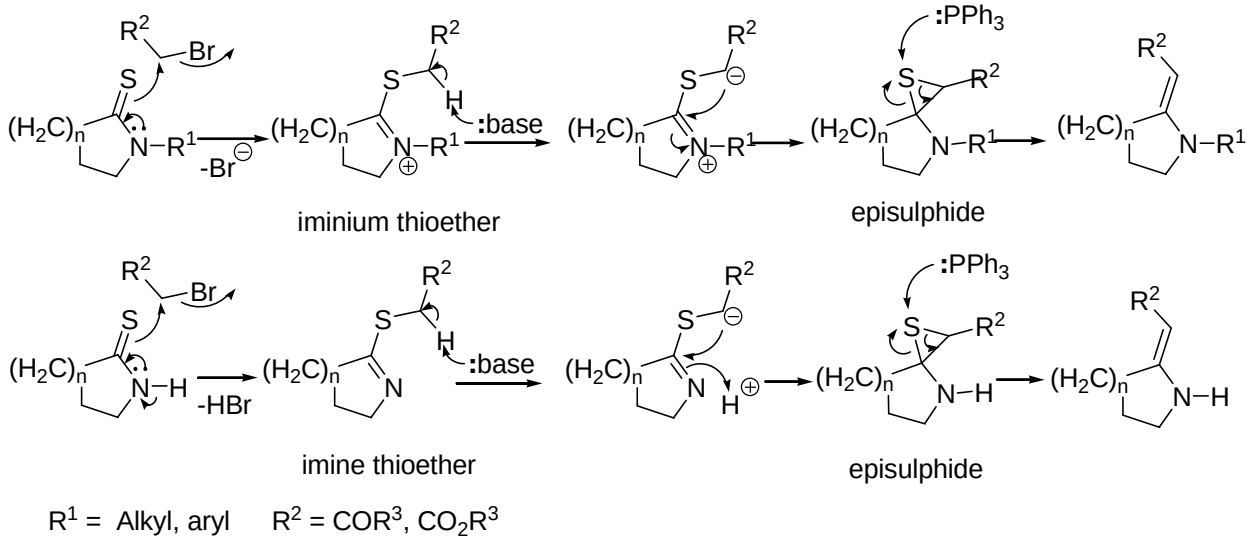
made from primary amine and bifunctional reagents (e.g. 4-chlorobutanoyl chloride) or by a Michael addition reaction of secondary thiolactams (e.g. pyrrolidine-2-thione) to α, β-unsaturated acceptors (e.g. acrylate esters). The alkylidene substituent is either introduced in a Knoevenagel like condensation 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**).[7]



Scheme 1: General approach to enaminones.[7]

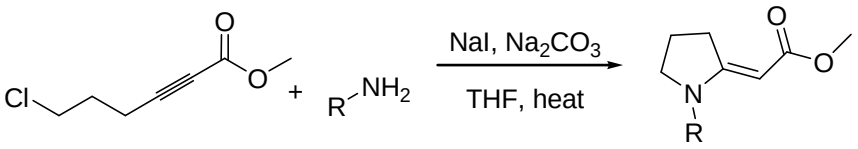
The Eschenmoser sulphide contraction reaction *via* alkylative precoupling is central to our reaction strategy achieving enaminones. Eschenmoser *et al.* elucidated the reaction mechanism, which involves the formation of the iminium or imine thioether, as a result of the nucleophilic attack of the thioamide on the alkyl halide, eliminating halide as leaving group. The base deprotonates the α-proton on the electron withdrawing group (R^4) resulting in formation of the episulphide. A thiophile then

scavenges the sulphur atom, collapsing the episulphide to an enaminone **Scheme 2**.[8, 11]



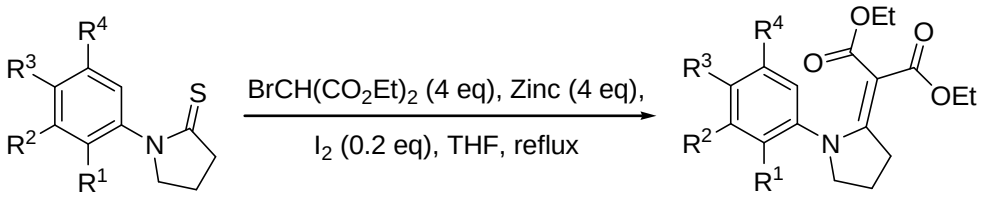
Scheme 2: Eschenmoser sulphide contraction reaction mechanism *via* alkylative precoupling.

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.



Scheme 3: Michael addition-alkylation reaction.

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]



Scheme 4: Reformatsky type reaction to enaminones.

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.[7]

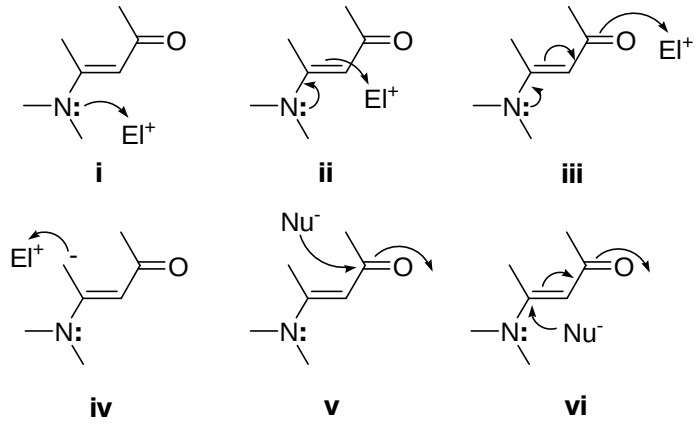


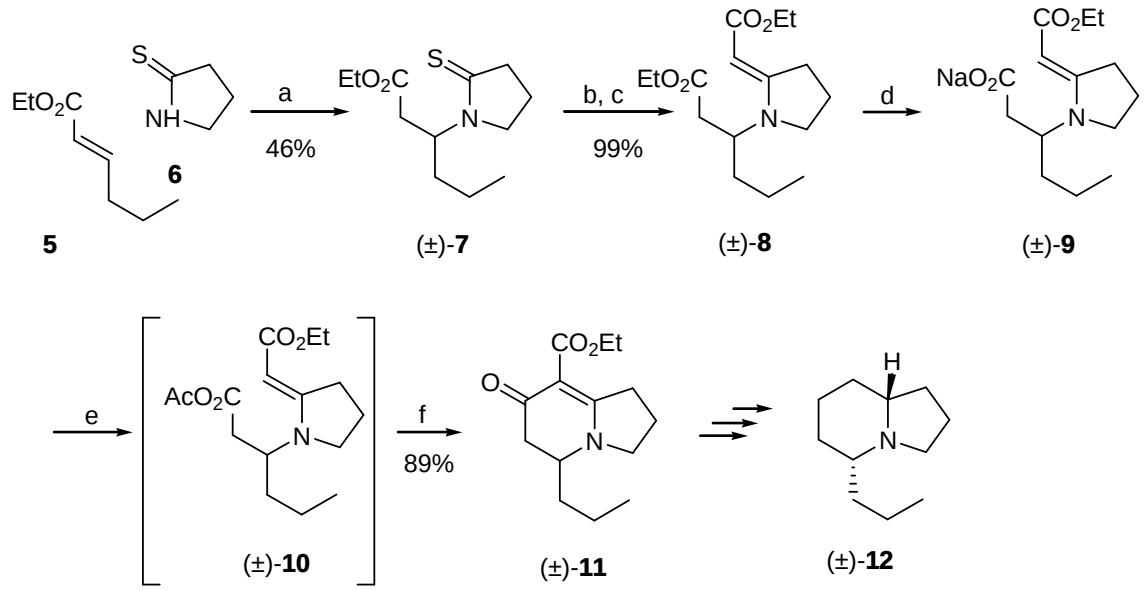
Figure 3. Enaminone reactivity.[7]

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: *Reagents and conditions:* (*a*) NaOH (cat.), THF, reflux; (*b*) $BrCH_2CO_2Et$, MeCN,rt; (*c*) PPh_3, NEt_3, MeCN, rt; (*d*) NaOH, H_2O, reflux; (*e*) Ac_2O, 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 (±)-

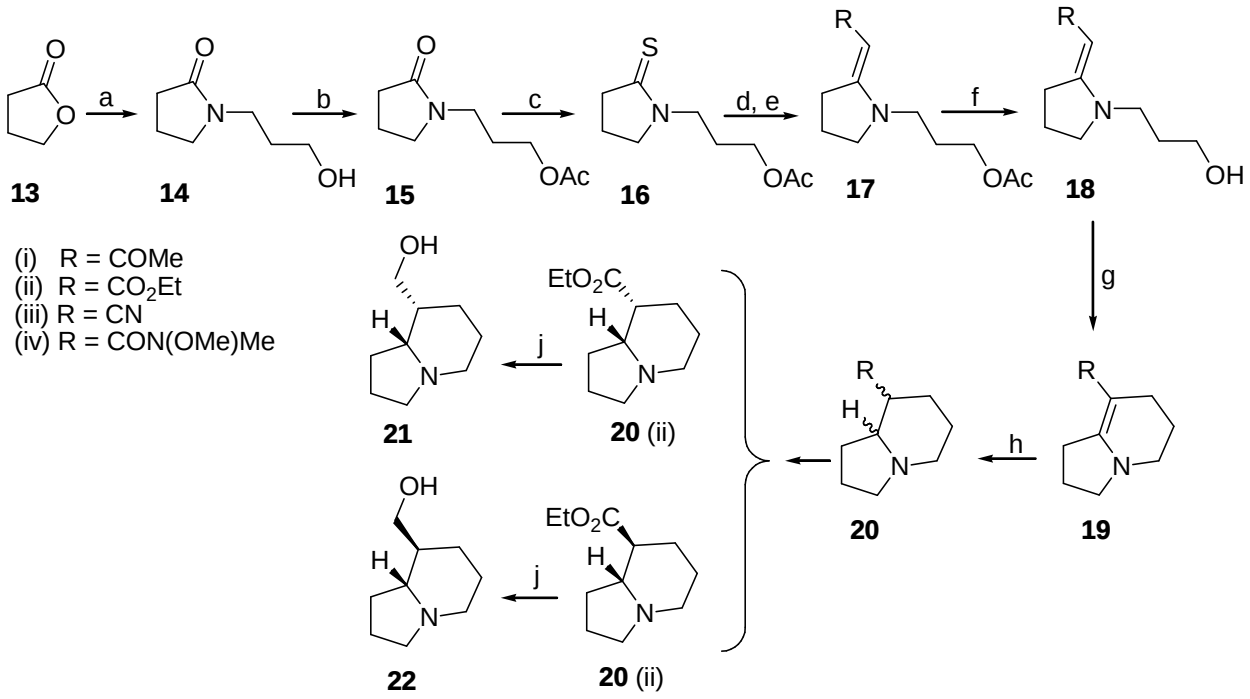
10 owing to inefficiency of the saturated ester as an acylating agent. This they did through a chemoselective hydrolysis of compound (±)-**8** heating with sodium hydroxide under reflux in water. They then followed with the reaction of the resulting salt sodium (*E*)-3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)hexanoate (±)-**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 alkylative 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 enaminones **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 enaminones with potassium carbonate in methanol, achieving **18** (i – iv) in good yields between 82 – 89% (**Scheme 6**, f). The liberated enaminones 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.



Scheme 6: Reagents and conditions:(a) $NH_2(CH_2)_3OH$, 250 °C (sealed tube), 18 h, 81%; (b) Ac_2O, pyridine, 0 °C, 10 min, then r.t., 18 h, 87%; (c) Na_2CO_3, P_2S_5, THF, 5 h, 90%; (d) $BrCH_2R$, CH_3CN, r.t., 24 h; (e) PPh_3, NEt_3, CH_3CN, 5 h, (i) 95%, (ii) 90%, (iii) 44%, (iv) 85; (f) K_2CO_3, MeOH, r.t., 3 h, (i) 82%, (ii) 85%, (iii) 89%, (vi) 83%; (g) Imidazole, PPh_3, I_2, CH_3CN-$PhCH_3$, reflux, 1 h; (i) 27%, (ii), 59%, (iii) 72%, (iv) 64%; (h) H_2 (1 atm), Adams catalyst, AcOH, r.t., 24 h, (ii) 72% (dr 85:15), (iii) 85% (dr 92:8), (iv) 25% (dr 95:5);(j) $LiAlH_4$,EtO_2, 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 diasteomeric 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).[12]

1.3.2 Alkaloids containing the quinolizidine 3 core

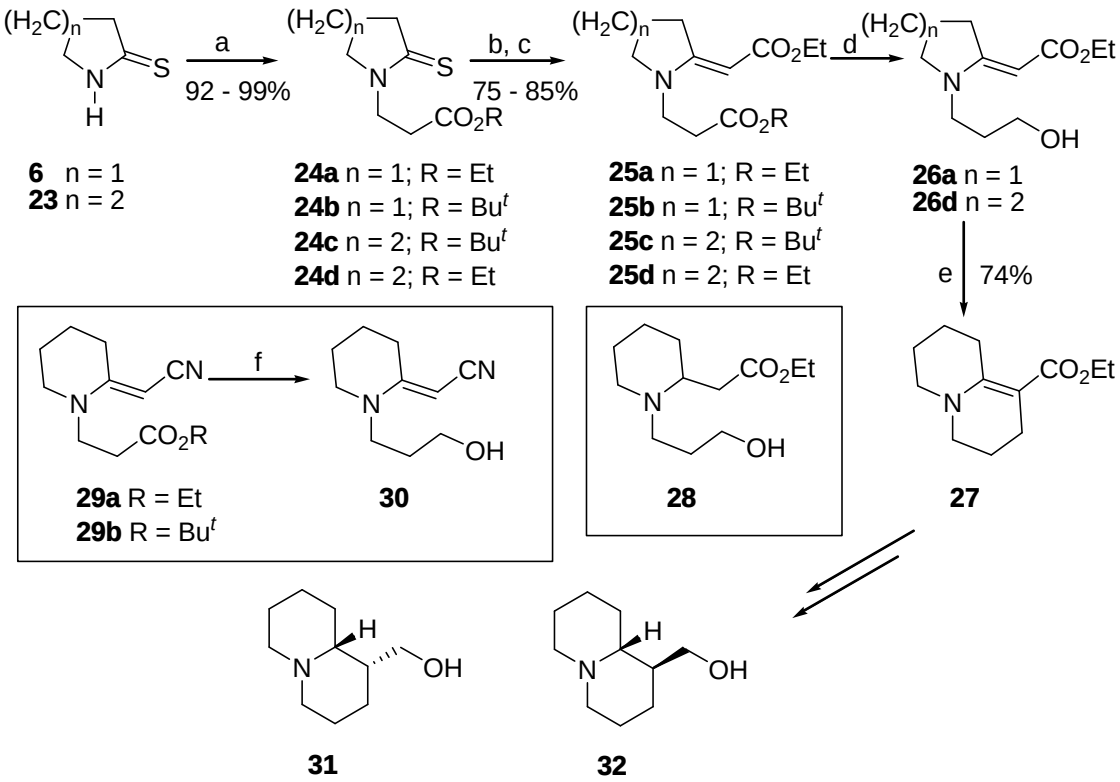
1.3.2.1 Alkylation as key ring closing step

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).[4] 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*")[5,6] about the stability and reactivity of double bonds that are exocyclic or endocyclic to rings of varying size applied to their vinylogous urethanes.[4] 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 piperidinylidene 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-2*H*-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.[4]

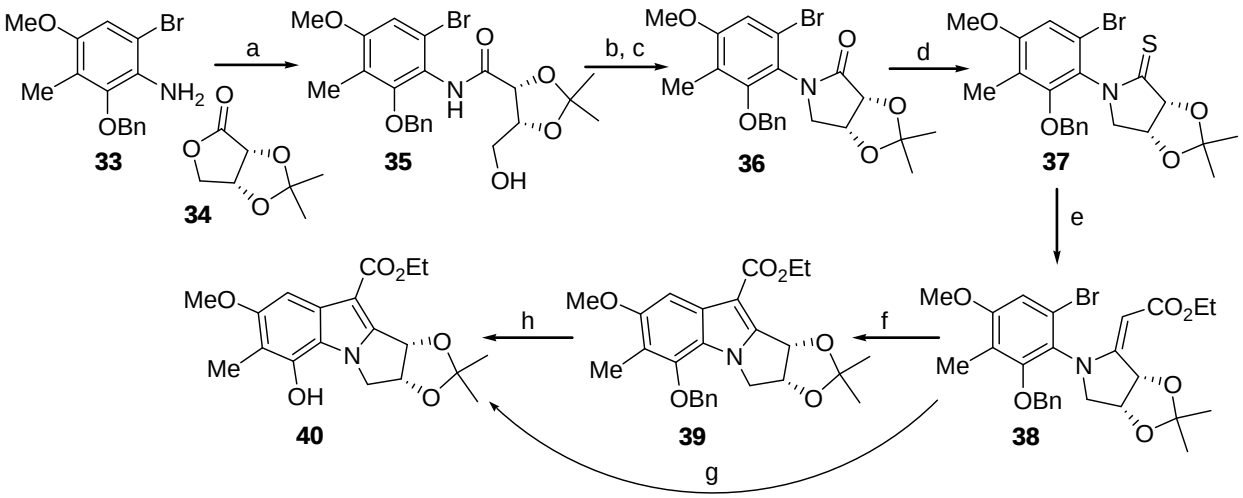


Scheme 7: *Reagents and conditions*: (a) CH_2CHCO_2R, NaOH or NaH, THF, 40 °C, 16 h; (b) $BrCH_2CO_2Et$, MeCN, rt, 16 h; (c) Ph_3P, NEt_3, MeCN, rt, 16 h; (d) $LiAlH_4$, THF, rt, 2 h; (e) Ph_3P, imizadole, I_2, toluene,120 °C, 80 min; (f) $LiAlH_4$, THF, rt, 48 h.[4]

1.3.3 Alkaloids containing the pyrrolizidine 1 core

1.3.3.1 Arylation as key ring closing step

Michael *et al*.[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 °C to deprotonate the amine followed by addition of the lactone (3a*R*,6a*R*)-2,2-dimethyl-dihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-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*-tolylphosphine, triethylamine in a 5:5:1 solvent solution of *N*,*N*-dimethylformamide, acetonitrile and water to yield **39** in 82% yield (**Scheme 8**, f).



Scheme 8: *Reagents and conditions*: (a) EtMgCl, THF, –50 °C, 50 min, then **34**, –50 °C to r.t., 22 h; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 7 d; (c) NaH, THF-DMF, r.t., 20 h, 90% from **33**; (d) Lawesson's reagent, toluene, reflux, 2.5 h, 73%; (e) $BrZnCH_2CO_2Et$ (from $BrCH_2CO_2Et$, Zn, I_2, THF, ultrasound), THF, reflux, 120 h, 87%; (f) $Pd(OAc)_2$ (0.3 eq), P(*o*-Tol)$_3$, Et_3N, H_2O, reflux, 4 h, 82%; (g) $Pd(OAc)_2$ (1.6 eq), P(*o*-Tol)$_3$, EtN, DMF, MeCN, H_2O, reflux, 4 h, 90%; (h) 10% Pd/C, H_2, EtOH, HCl (1 drop), r.t., 2 h, 92%.

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 enaminones into the 5,5-azabicyclics.[79]

1.4 A short survey of alkaloids containing the pyrrolo[1,2-a]azepine 4

1.4.1 Lehmizidines

Lehmizidine alkaloids originate from a group of Colombian dendrobatid frogs, principally *Dendrobates lehmanni*.[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, (3*R*)-3-pentyl-octahydro-1*H*-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).[7]

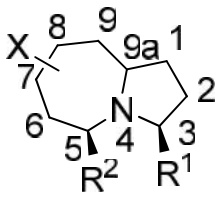


Table 1: Lehmizidines[7,14]

Lehmizidines	**R^1**	**R^2**	**X**
41	$(CH_2)_7C{\equiv}CH$	CH_3	H
42	$(CH_2)_5CH{=}CHCH{=}CH_2$	CH_3	H
43	$(CH_2)_7CH{=}CH_2$	CH_3	H
44	$C_9H_{13}O$ (=O, $C{\equiv}CH$)	CH_3	H
45	$(CH_2)_5CH{=}CHC{\equiv}CH$	CH_3	OH
46	$C_9H_{15}O$	CH_3	H
47	$(CH_2)_7C{\equiv}CH$	CH_3	OH
48	$C_9H_{17}O$ (=O)	CH_3	H
49	$(CH_2)_7CH{=}CH_2$	CH_3	OH
50	$(CH_2)_3CH_3$	H	–

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 $C_6H_{12}(C{=}O)C{\equiv}CH$, [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.[15] 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**).[15]

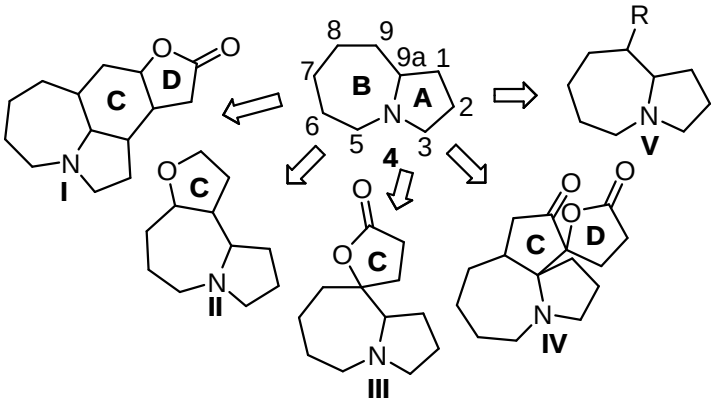


Figure 4:. Main classes of *Stemona* alkaloids.[15]

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**).

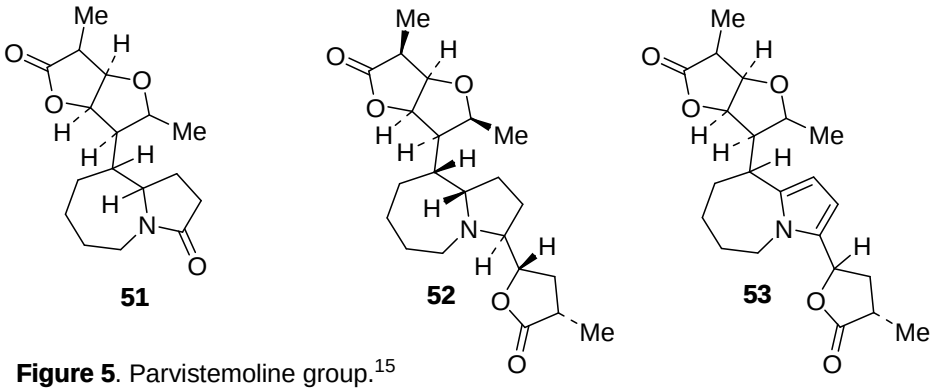
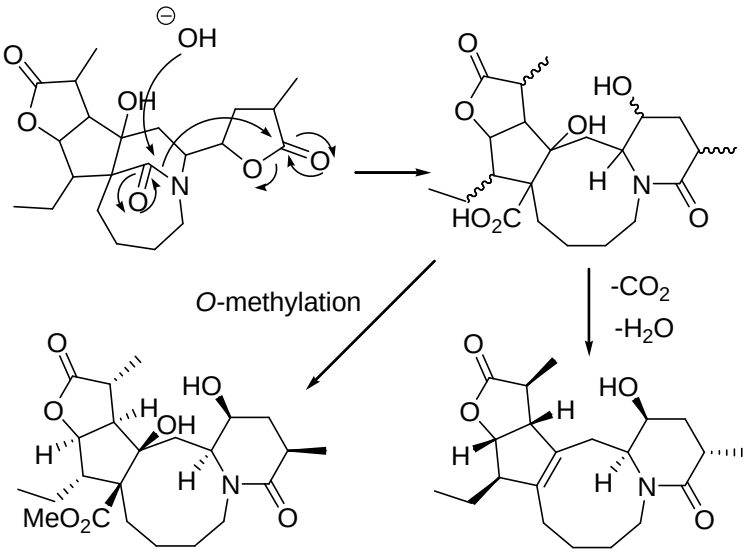


Figure 5. Parvistemoline group.[15]

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 **V** 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.[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 (**Scheme 9**).[18]



Sessilifoliamide **K** (**54**) Sessilifoliamide **L** (**55**)

Scheme 9: A possible biogenesis of Sessilifoliamide **K** **54** and **L 55** from tuberostemoninol-type alkaloids.[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 mycloid 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**).[19]

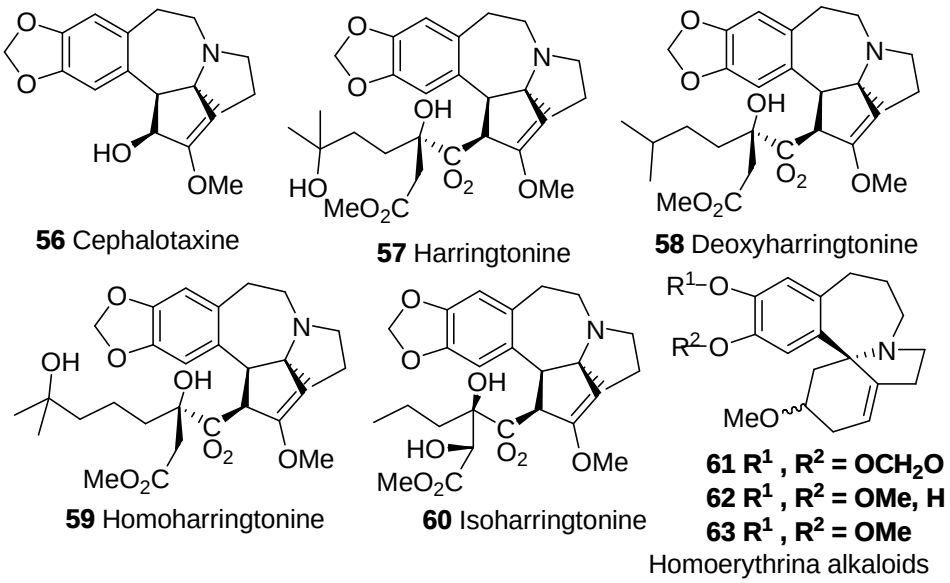
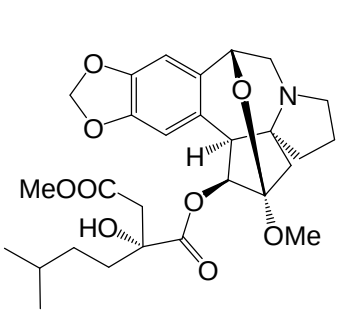


Figure 6: *Cephalotaxus* alkaloids esters and homoerythrina alkaloids.[19,20]

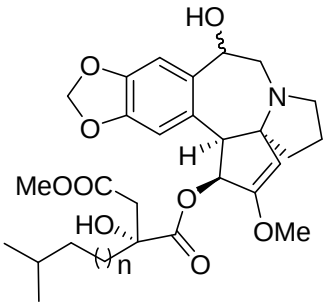
Minor homoerythrina alkaloids **61** – **63** were isolated with cephalotaxine alkaloids. Their structure is tetracyclic in nature and they gave insight to the biosynthesis of *Cephalotaxus* alkaloids (**Figure 6**).[20]

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**, 11α-hydroxyhomodeoxyharringtonine **65**, 11β-hydroxyhomodeoxyharringtonine **66**, and 11β-hydroxydeoxyharringtonine **67**, from *C. harringtonia* var. *Drupacea* (**Figure 7**). These compounds showed activity against P-388 leukaemia cells.[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.[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.* h*arringtonia* var. d*rupacea* characterised by the presence of a phenyl or benzyl groups were also found to be active against P-388 cells.[23] Kobayashi and co-workers reported more

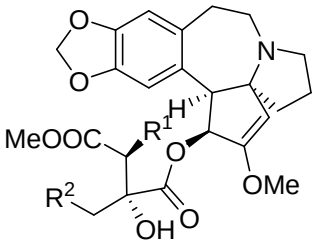
new oxygenated alkaloids which were biologically active against human epidermoid carcinoma KB cells. Of interest was the first example of a *Cephalotaxus* glycoside, cephalezomine **J 72** with a β-D-glucopyranose sugar moiety.[24,25] They also reported five new heterodimers named bis-cephalezomines from *C. harringtonia var. nana* **73 – 78** (**Figure 7**). The cytotoxicity of these dimers was relatively weaker as compared to their monomeric forms.



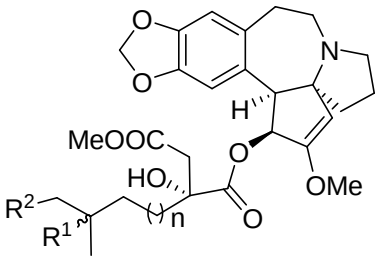
64 IC_{50} = 7.5 ng.mL^{-1}



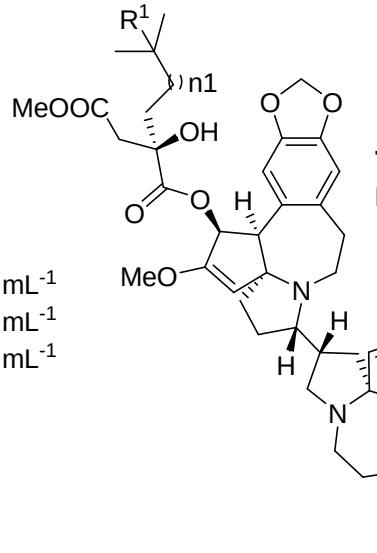
65 n = 2, α-OH, IC_{50} = 380 ng.mL^{-1}
66 n = 2, β-OH, IC_{50} = 330 ng.mL^{-1}
67 n = 1, β-OH, IC_{50} = 170 ng.mL^{-1}



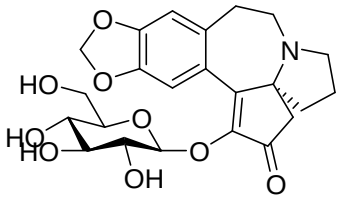
68 R^1 = H, R^2 = Ph
IC_{50} = 12 ng.mL^{-1}



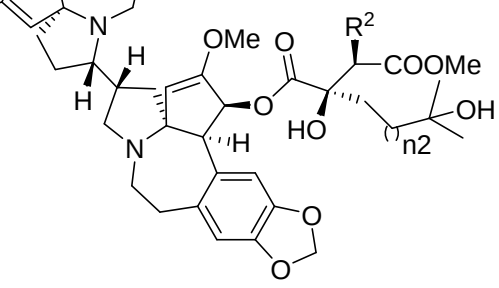
69 n = 0, R^1 = R^2 = H, IC_{50} = 27 ng.mL^{-1}
70 n = 2, R^1 = R^2 = H, IC_{50} = 56 ng.mL^{-1}
71 n = 3, R^1 = R^2 = H, IC_{50} = 24 ng.mL^{-1}



73 n1 = n2 = 2, R^1 = OH, R^2 = H
IC_{50} = 1800 ng.mL^{-1}



72 IC_{50} = 5600 ng.mL^{-1}



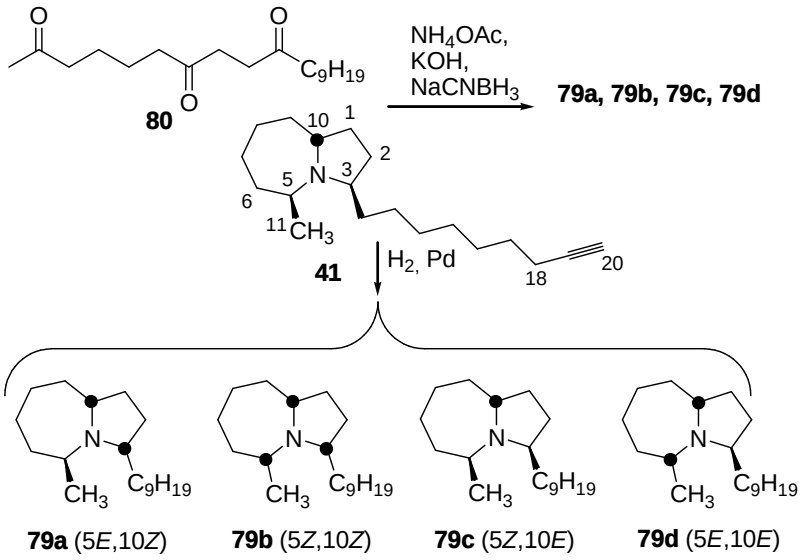
74 n1 = 2, n2 = 1, R^1 = OH, R^2 = H
75 n1 = 1, n2 = 2, R^1 = OH, R^2 = H
76 n1 = n2 = 1, R^1 = OH, R^2 = H
77 n1 = 2, n2 = 1, R^1 = OH, R^2 = OH
78 n1 = 1, n2 = 2, R^1 = H, R^2 = H
IC_{50} = 1900 - 3700 ng.mL^{-1}

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

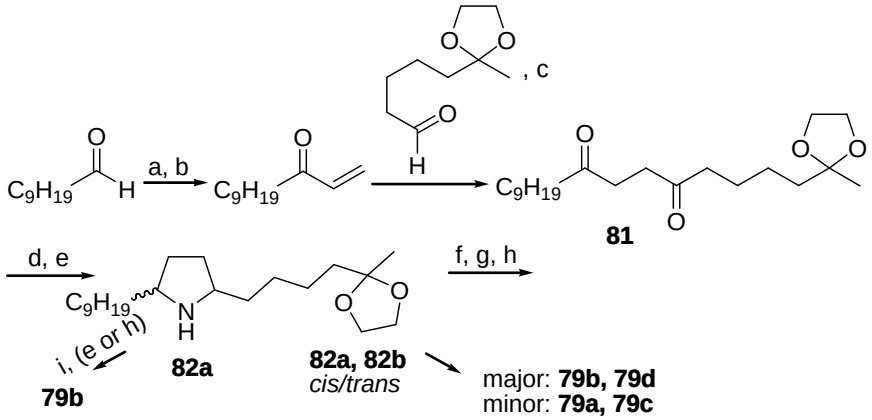
Garraffo and co-workers have synthesised four diastereomers **79a** – **79d** from reductive amination of triketone **79** in a bid to determine the stereochemistry of alkaloid **275A** (**41**) (**Scheme 10**). The central azabicyclic core was constructed in a single operation by a triple reductive amination of the triketone **80** with ammonium acetate and sodium cyanoborohydride.[27]



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.**[27] *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 (NH_3)-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

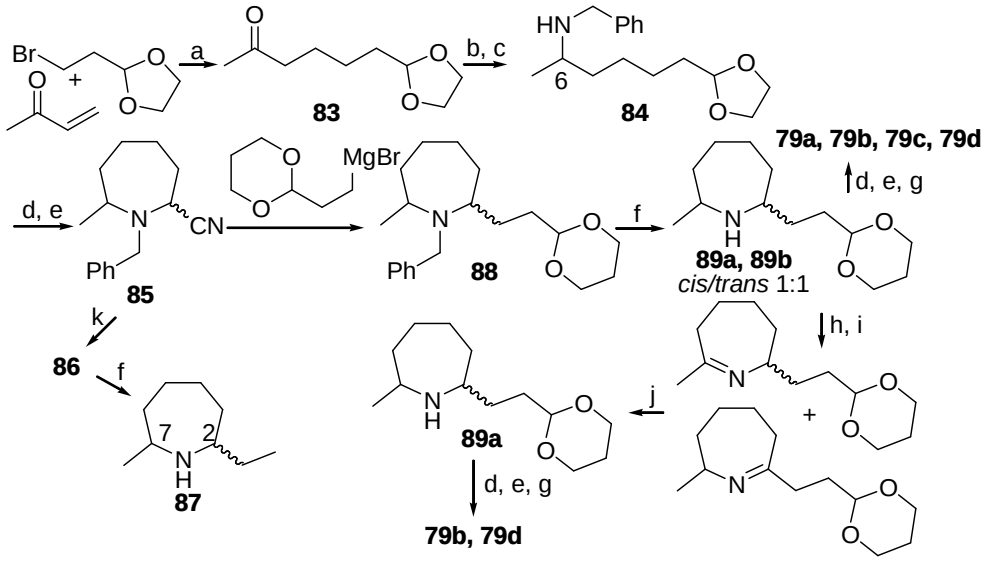
assembling the pyrrolo[1,2-*a*]azepine **4** core in a more controlled third reductive amination. This is a similar approach to the work they previously did to determine the stereochemistry of (6*Z*,10*E*)-4-methyl-6-*n*-propyl quinolizidine, which was detected in a Madagascan frog and also a Brazilian ant.[28] 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**.



Scheme 11: *Reagents and conditions*: Lehmizidines from 2,5-disubstituted pyrrolidines. (a) CH_2=CHMgBr, (b) PCC, (c) thiazolium salt, Et_3N, (d) NH_4OAc, (e) $NaCNBH_3$, (f) *N*-chlorosuccinimide, (g) KOH, (h) H_2, Rh/Al_2O_3 and (i) H^+.[27]

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 Ni^0-mediated conjugate addition.[29] The reductive amination of **83** in the presence of titanium isopropoxide resulted in aminoacetal **84**.[30] 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 5*Z*,10*E* relative stereochemistry.



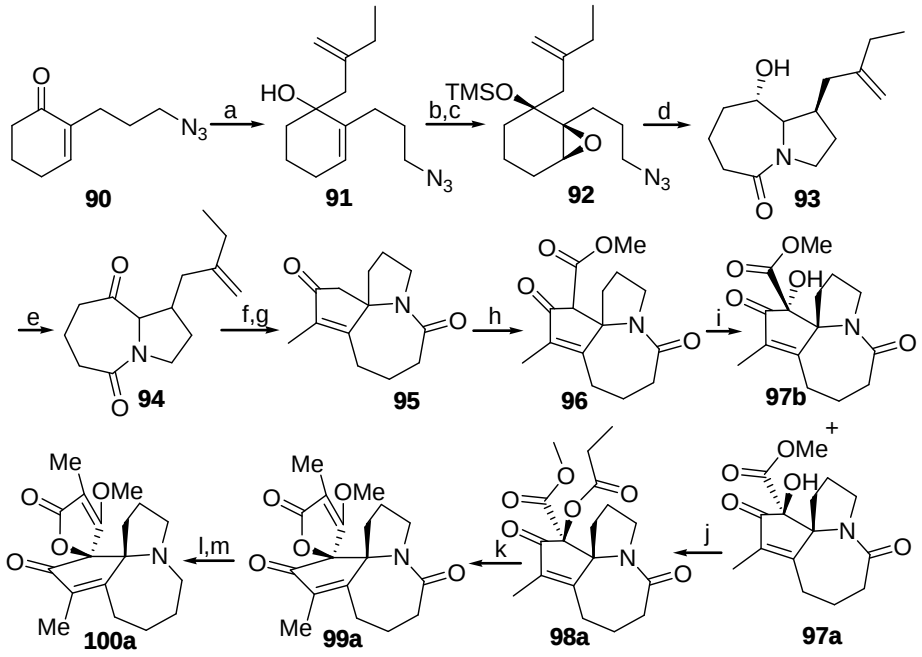
Scheme 12: *Reagents and conditions*: Lehmizidines from 2,7-disubstituted azepines. (a) Ni^0, Py, (b) $Ti(OPr)_4/PhCH_2NH_2$, (c) $NaCNBH_3$, (d) H^+, (e) KCN, (f) NH_4CO_2H/Pd/C, (g) BrMg-*n*-C_9H_{19}, (h) *N*-chlorosuccinimide, (i) KOH, (j) $H_2/Rh/Al_2O_3$, (k) BrMg-C_2H_5.[27]

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[42] to 2-(3-azidopropyl)cyclohex-2-enone **90** [44,43] 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 ($NCCO_2Me$)[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).



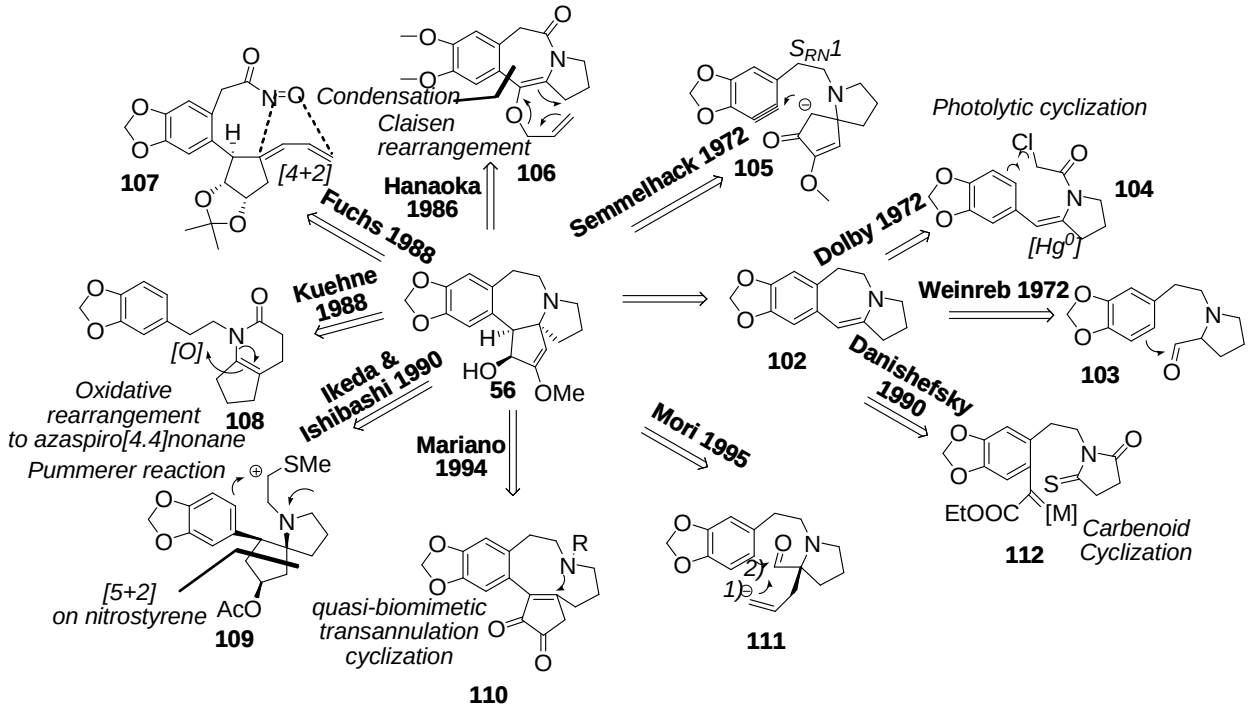
Scheme 13: *Reagents and conditions*: (a) $CH_3CH_2C(CH_2)CH_2MgBr$, THF, 76%; (b) ^tBuOOH, $VO(acac)_2$, (c) TMSCl Imid., DMF, 66%; (d) $TiCl_3$, -78 °C to 0°C, 68%; (e) PCC, CH_2Cl_2, r.t., 85%; (f) O_3, CH_2Cl_2; (g) KO^tBu, ^tBuOH, 77%; (h) LHMDS, -78 °C, then HMPA, $NCCO_2Me$, 95%; (i) $CeCl_3 \cdot 7H_2O$, O_2, ^iPrOH, r.t., 92%; (j) Et_3N, DMAP (cat.), Propionic anhydride, CH_2Cl_2, r.t., 95%; (k) KO^tBu, PhH, 18-crown-6, then Et_3N, Me_2SO_4, CH_2Cl_2, 44%; (l) Lawesson's reagent, CH_2Cl_2; (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**, l, 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 from[82] 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**.



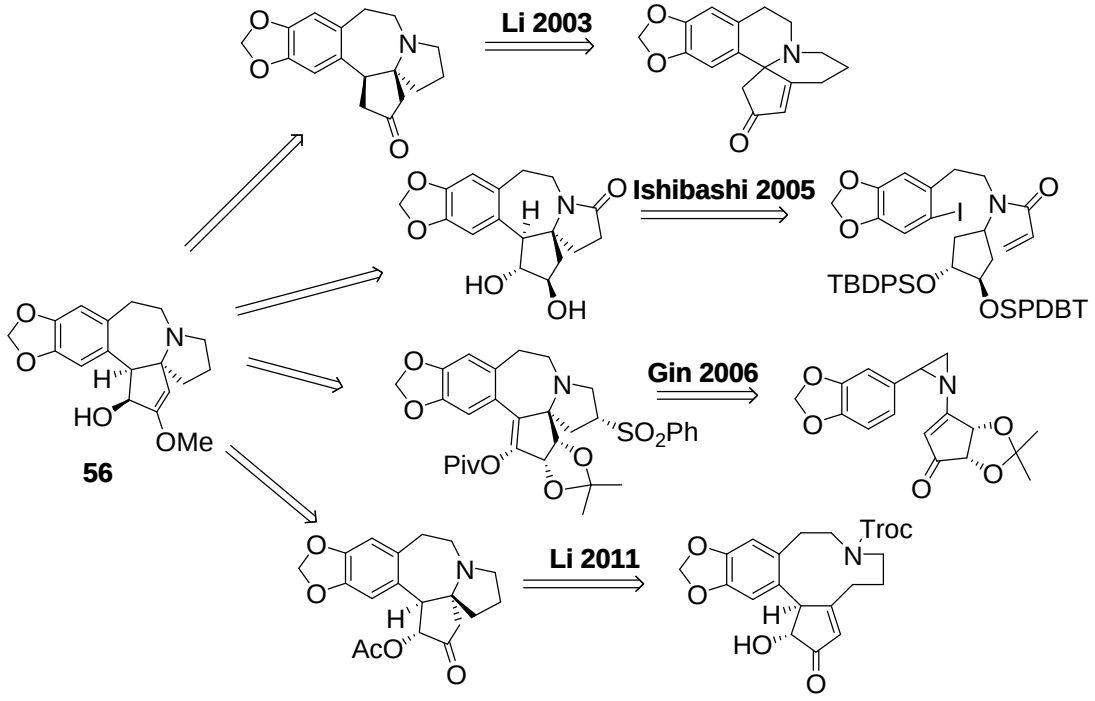
Scheme 14: Key disconnections to make the pyrrolo[1,2-*a*]azepine nucleus.[66]

Table 2: Two decades on construction of five-membered core of *Cephalotaxus* alkaloids

Author(s)	Year	Synthesis determining steps
Weinreb	1972	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]
Dolby		
Semmelhack		Used 1-azaspiro[4.4]nonane **105** intermediate in intramolecular $S_{RN}1$ substitution of a benzyne ring.[51,52,53,49]
Hanaoka	1986	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]
Fuchs	1988	Use [4+2] cycloaddition of a nitroso and a diene on intermediate **107** to introduce a quaternary nitrogen centre.[55,56]
Kuehne		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]
Ikeda & Ishibashi	1990	Used intermediate **109** in the Pummerer reaction.[58,59,60,61,62]
Danishefsky		Used intramolecular carbenoid cyclisation on intermediate **112** to achieve Weinreb-Dolby enamine.[63]
Mariano	1994	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]

Mori	1995	Constructed 1-azaspiro[4.4]nonane through intramolecular cyclisation of an alkenyl anion on intermediate **111**, followed by acid-catalysed eletrophilic cyclisation of benzazepine ring.[66]

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.[49]

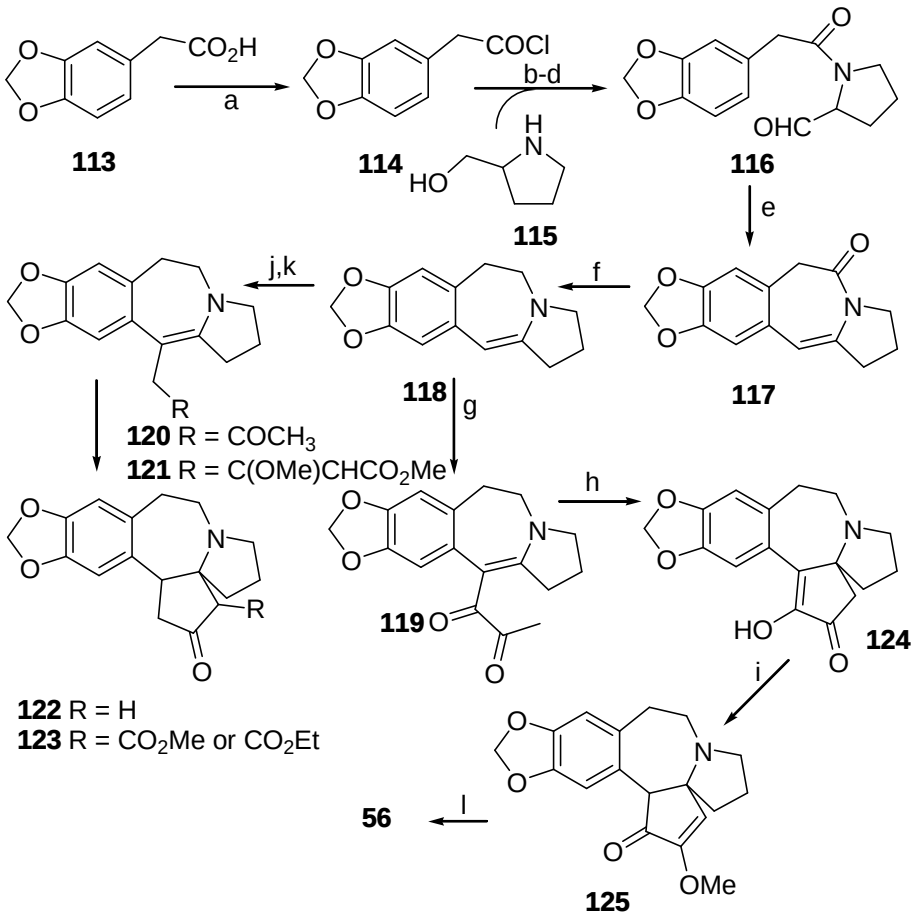
Table 3: Recent developments on construction of five-membered core of *Cephalotaxus* alkaloids

Author(s)	Year	Synthesis determining steps
Li	2003	Facile reductive rearrangement upon exposure of ketone to zinc dust in hot glacial acetic acid.[67,68,69,70,71]
Ishibashi	2005	Cascade radical cyclisation in the presence of Bu_3SnH and 1,10-azobiscyclohexanecarbonitrile (ACN) in boiling chlorobenzene.[72,73,74]
Gin	2006	Rearrangement of compound heating in 1,2-dioxane, Cs_2CO_3 followed by the [3 + 2] cycloaddition with phenyl vinyl sulfone after formation of a transient non stabilized azomethine ylide.[75]
Li	2011	Spontaneous cyclisation of compound after zinc cleavage of *N*-Troc group.[78]

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.[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) $SOCl_2$; (b) CH_3CN, -20 °C, K_2CO_3; (c) K_2CO_3 (aq.), 82%; (d) DMSO, DCC, Cl_2CHCO_2H, 67%; (e) BF_3, $CHCl_3$, r.t.; (f) $LiAlH_4$, THF; (g) $CH_3COCO_2CO_2Et$; (h) $Mg(OMe)_2$, MeOH; (i) $(MeO)_2C(CH_3)_2$, *p*-TsOH; (j) propargyl bromide or methyl 4-bromo-3-methoxycrotonate; (k) Hg^{2+}, H_3O^+, (l) Sodium borohydride.[40,41]

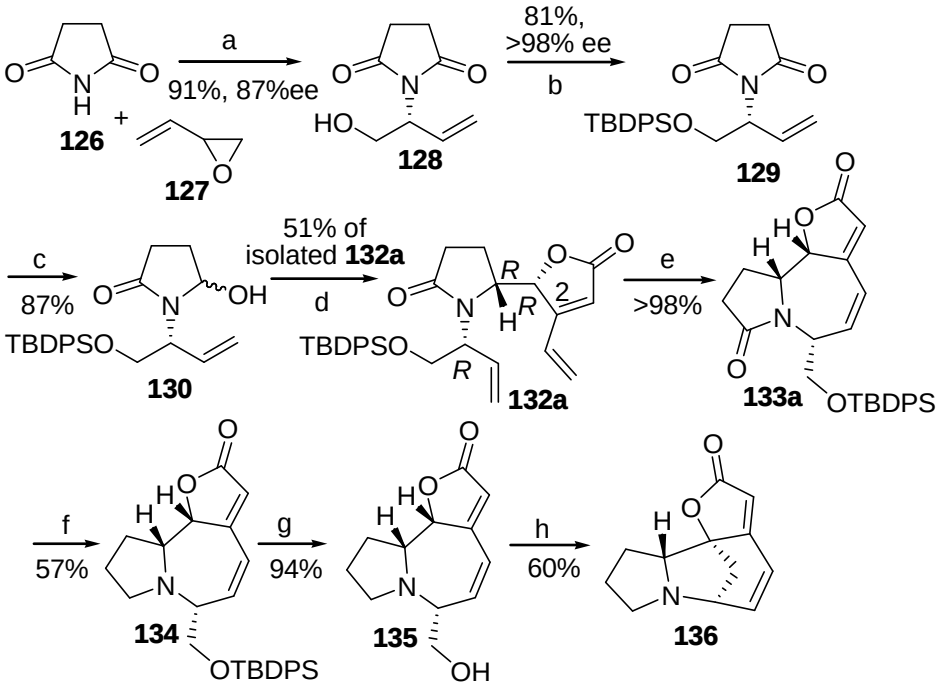
1.5.4 Miscellaneous alkaloids

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 antitumoragents.[35,34] There are a few examples on the construction of the concealed pyrrolo[1,2*a*]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*-butyldiphenylsilyl (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 epimericaminals **130** in 87% yield (**Scheme 17**, c). Triisopropylsilyloxyfuran **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% $[h^3\text{-}C_3H_5PdCl]_2$, $NaHCO_3$, CH_2Cl_2, r.t.; (b) (i) TBDPSCl, imidazole, CH_2Cl_2 (ii) crystallization in 2-propanol; (c) $LiBEt_3H$, THF, -78 °C; (d) **131**, $BF_3.Et_2O$, Et_2O, 0 °C; (e) 10% Grubbs II cat, CH_2Cl_2, r.t.; (f) 0.5 M AlH_3, THF, 0 °C, 5 min; (g) $Et_3.HF$, THF, r.t.; (h) see ref. 39

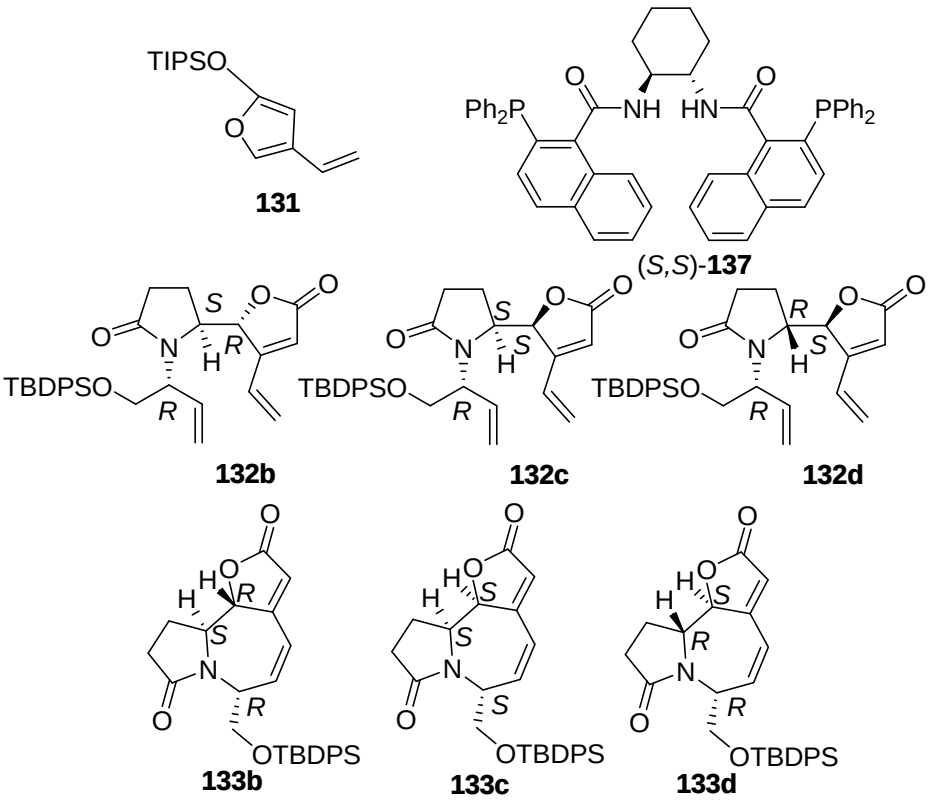


Figure 8: Isomers from ring closing metathesis reaction.

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.

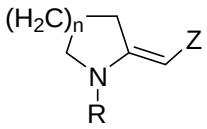
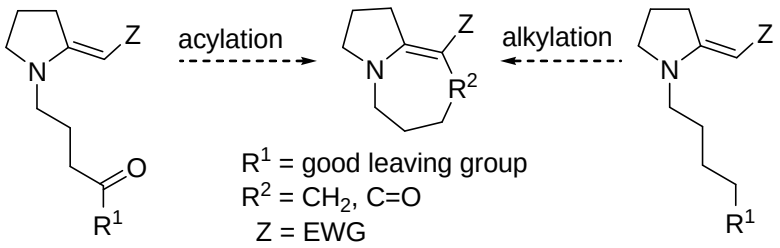


Figure 9: Enaminones

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.

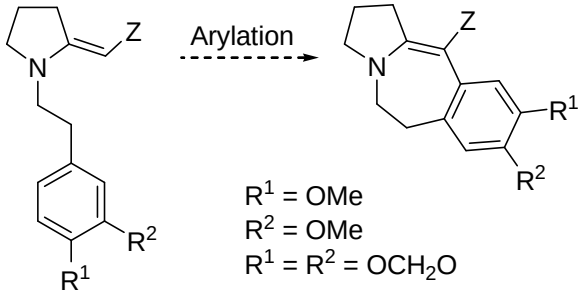
Enaminone chemistry would then take centre stage in construction of the five-membered ring by an intramolecular alkylation and intramolecular acylation of an enaminone (**Scheme 18)**.



Scheme 18: Enaminone reactivity in alkylation and acylation reactions.

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.[79,80,81] The enaminone 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.

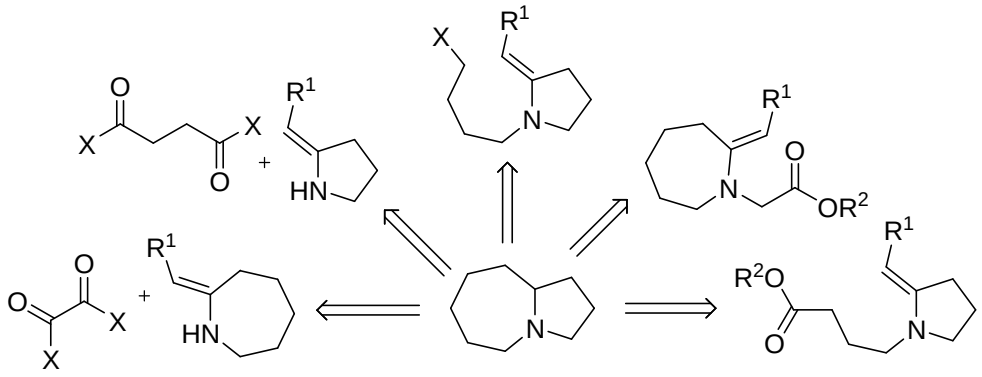


Scheme 19: Enaminone reactivity in arylation reactions.

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.

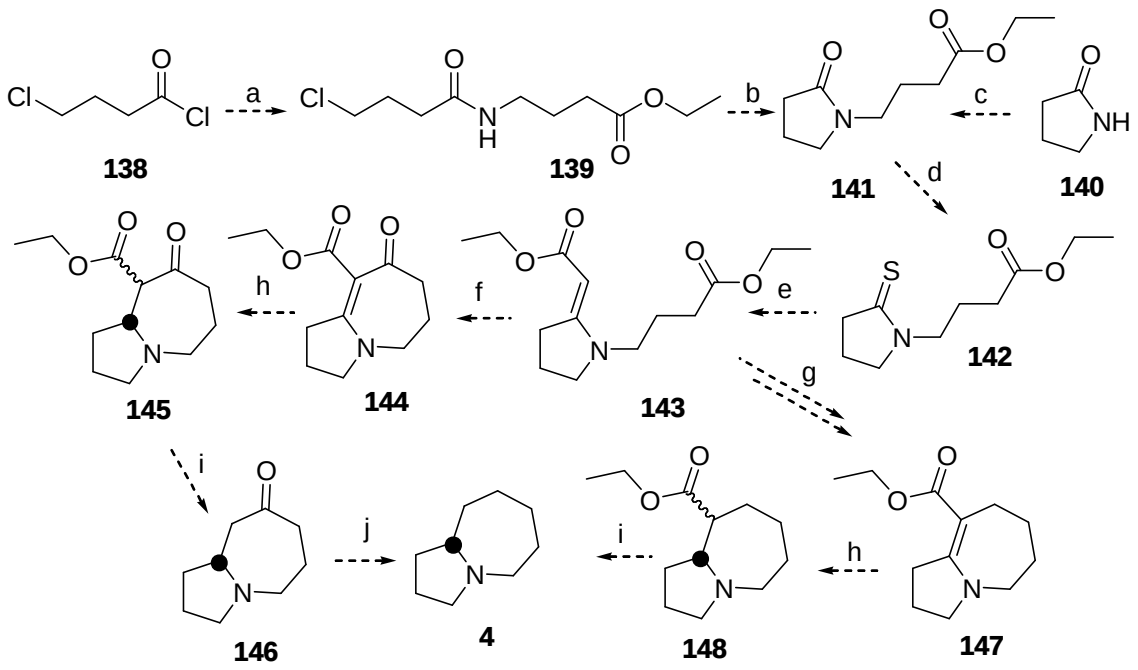


R^1 = EWG, R^2 = alkyl, X = Br, Cl or H

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

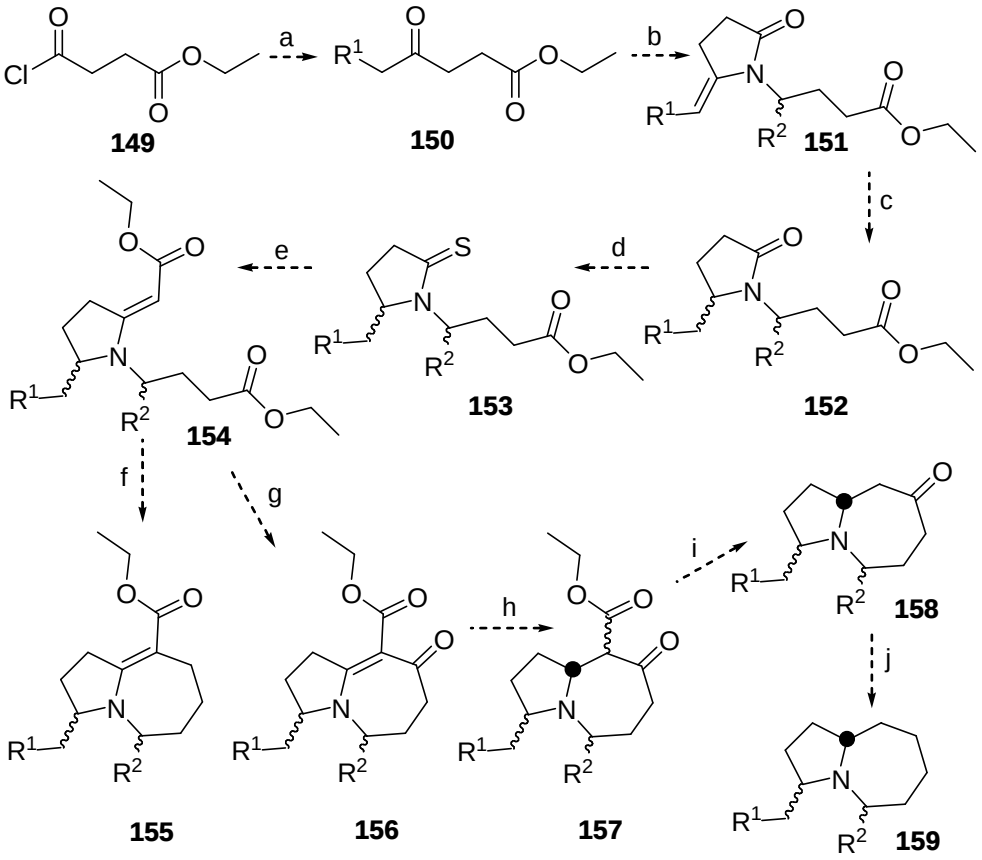
1.6.2.2 Strategy

The first strategy is an attempt on making the pyrrolo[1,2*a*]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 P_2S_5 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**.



Scheme 21: Synthetic strategy towards the 1-azabicyclo[5.3.0]decane core **4**: (a) Acylation; (b) Intramolecular *N*-alkylation; (c) Intermolecular *N*-alkylation; (d) Thionation; (e) Eschenmoser sulphide contraction; (f) Acylative ring closure; (g) Alkylative ring closure; (h) Hydgrogenation; (i) Decarboxylation; (j) Reduction.

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 R^1CH_2 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.

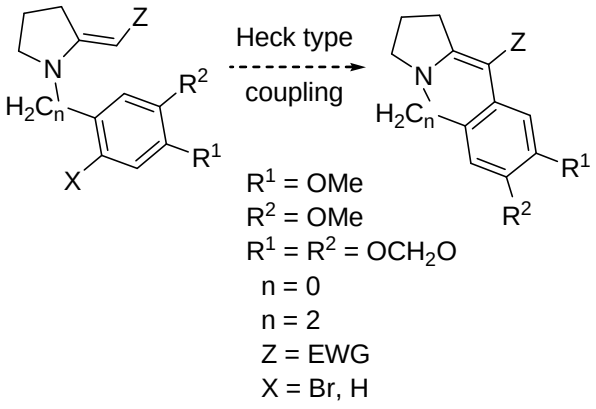


R^1CH_2 = $(CH_2)CH_3$ or $(CH_2)_5CCH$ or $(CH_2)_3CH{=}CHCH{=}CH_2$ or $(CH_2)_5CH{=}CH_2$
R^2 = CH_3 or H

Scheme 22: Synthetic strategy towards the Lehmizidine Alkaloids: (a) Substitution; (b) Tandem Alkylative/Acylative ring closure; (c) Hydrogenation.

1.6.2.3 *Cephalotaxus* alkaloids

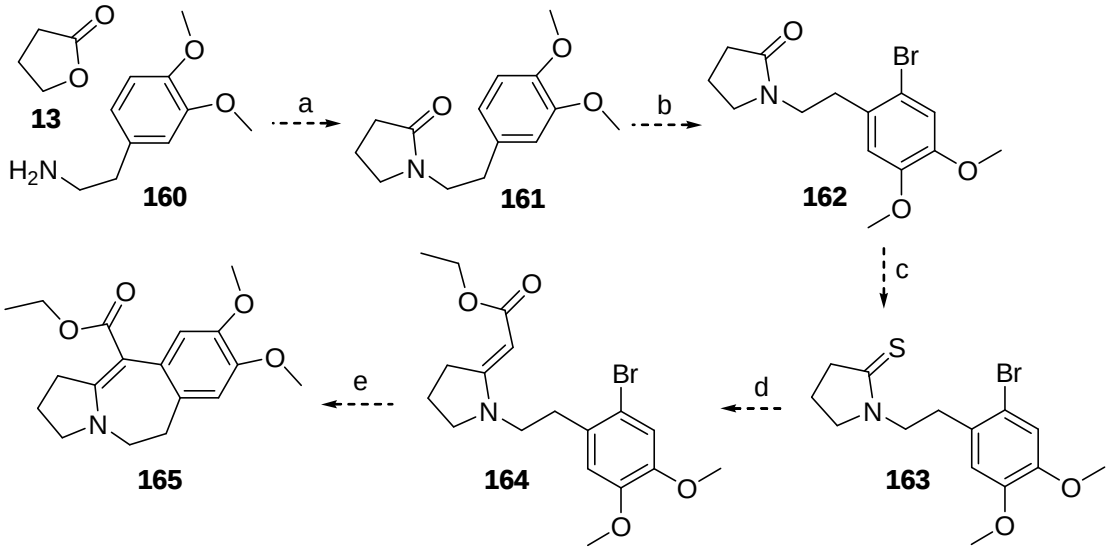
The second aim of this project is to synthesise models for cephalotaxine **56**. This will employ a recently developed methodology within the Organic Chemistry group of the University of the Witwatersrand, in creating azabicyclic alkaloid systems *via* a Heck-type coupling, linking an enaminone with a brominated aryl group. This intramolecular link has assisted in forming a five-membered ring (n = 0) in these alkaloids (**Scheme 23**).[79,80,81] 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.

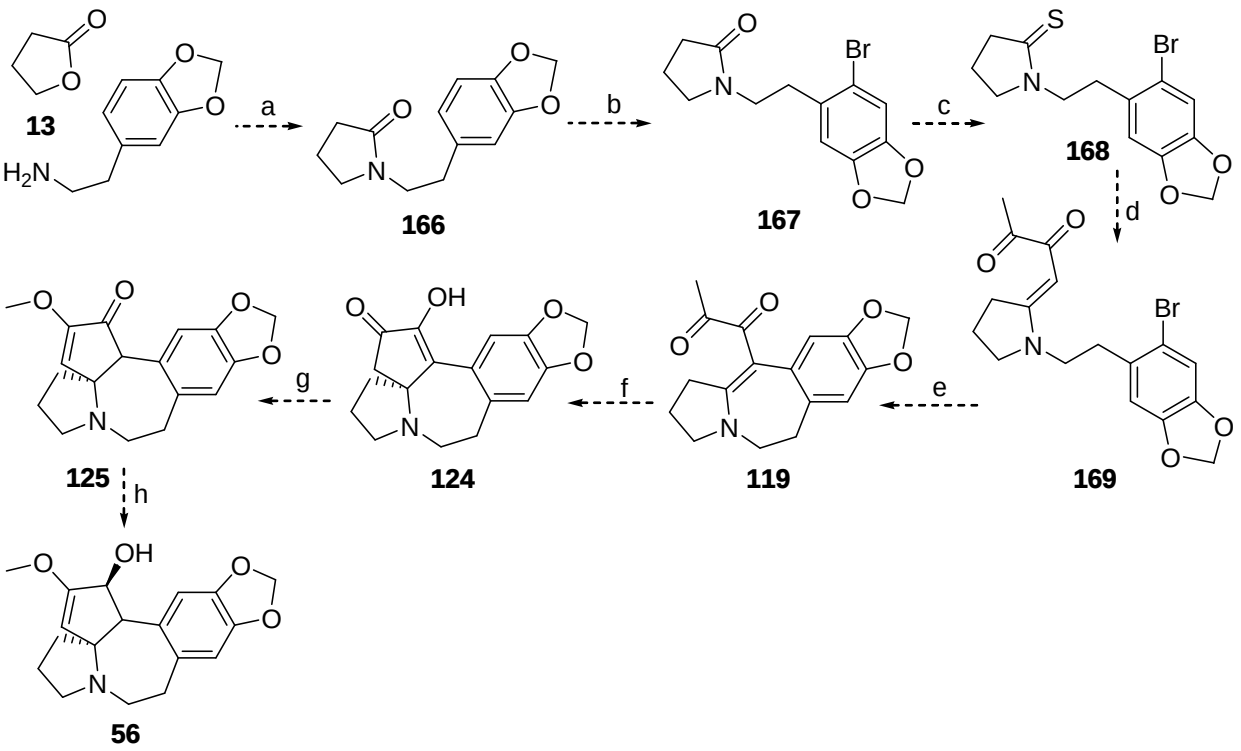
1.6.2.4 Strategy

γ-Butyrolactone **13** will be reacted with homoveratrylamine **160** in an oven using a sealed tube reactor to yield lactam1-(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 ofthiolactam1-(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.



Scheme 24: Synthetic strategy towards Cephalotaxus core.

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**.[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

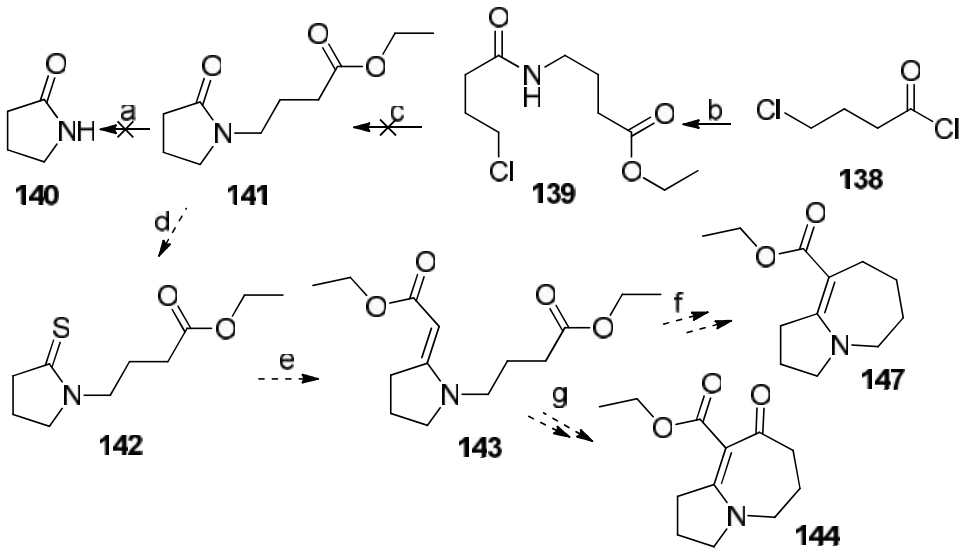
(*E*)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate **143** had to be synthesised before the strategies shown in the previous chapter could be carried out. Synthetic routes taken to achieve enaminone **143** are presented, followed by subsequent reactions towards the pyrrolo[1,2-*a*]azepine 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-1*H*-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-1*H*-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.



Scheme 26: *Reagents and conditions*: (a) Table 4; (b) Ethyl 4-aminobutyrate.HCl (1 eq), $NaHCO_3$ (2 eq), DCM, 17 h at r.t. and then 1 h at reflux, **139** = 99%; (c) *t*-BuOK (1 eq), *t*-buOH, 72 h at 35 °C, **141** = 0%.

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 ^{1}H 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_N2 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 **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 **140** indicated by ^{1}H NMR spectroscopy, revealing the chemical shift of triplet at δ 3.53 ppm to triplet at δ 2.91 ppm indicating the transformation from ClC*H*$_2$ to IC*H*$_2$ (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 **170** and **172** under *N*-alkylation reaction conditions, pyrrolidin-2-one **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 N*H* 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 **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.[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 4: Intermolecular *N*-alkylation reaction of 2-pyrrolidinone

No.	Reactants	Conditions	Solvents	Results
1	(i) NaH (1.2 eq), (ii) Ethyl 4-bromobutyrate (1.2 eq)	(i) 0.5 h at 0 °C, (ii) 26 hours at room temperature and 20 h at 90 °C	DMF	**141** = 0%; **140** = 54%
2	(i) NaH (1.1 eq), (ii) Ethyl 4-bromobutyrate(1.1 eq)	(i) 0.5 h at 0 °C, (ii) 20 hours at room temperature	DMF	**141** = 0%
3	Ethyl -4-bromobutyrate (1.1 eq), K_2CO_3 (1.1 eq), KI (1.1 eq),	5 h, heating under reflux	Acetone	**141** = 0%
4	(i) NaH (1.22 eq), (ii) Ethyl 4-iodobutyrate (1.17 eq)	(i) 10 min at 0 °C, (ii) 20 hours at room temperature	DMF	**141** = 0%
5	Ethyl -4-bromobutyrate (1 eq), *t*-BuOK (1 eq)	20 hours at 35 °C	BuOH	**141** = 0%
6	(i) NaH (1.1 eq), (ii) Ethyl 4-bromobutyrate(1.1 eq)	(i) 0.5 h at room temperature, (ii) 24 hours at room temperature	THF	**141** = 0%; **140** = 45%

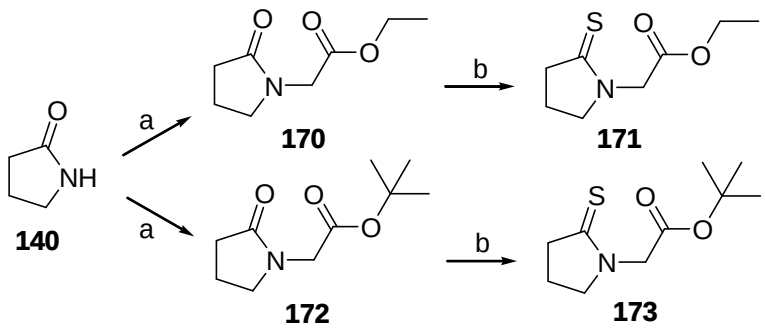
A different approach towards the synthesis of ethyl 4-(2-oxopyrrolidin-1-yl)butanoate **141** was taken involving a *C*-acylation reaction and a ring closing intramolecular *N*-alkylation reaction. The intramolecular *N*-alkylation reaction of compound **139** was expected to be more efficient as compared 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-aminobutyrate hydrochloride, 4-chlorobutyryl 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 ν_{max} = 3304 cm^{-1} for the amide proton and ν_{max} = 1730, 1644 cm^{-1} for the amide and the carboxylic ester carbonyl groups. The ^{1}H NMR spectrum showed unresolved amide N*H* peak at δ 6.19 ppm and the *N*-alkyl protons at 3.58 – 3.54 ppm, confirming the amide bond formation. The ^{13}C NMR spectrum presented with the amide and ester carbonyl carbon peaks at δ 173.0 and 171.8 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.



Scheme 27: *Reagents and conditions*: (a) (i) NaH (1 eq), THF, 0.5 h at r.t., (ii) ethyl 2-bromoacetate*/ tert*-butyl 2-bromoacetate (1 eq), 24 h at r.t.; **170** = 90%, **172** = 91%; (b) P_2S_5 (0.5 eq), DCM, 24 h at r.t., **171** = 97%, **173** = 89%.

The IR spectrum of ethyl 2-(2-oxopyrrolidin-1-yl)acetate **170** revealed a peak at ν_{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 δ 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 δ 3.87 ppm and δ 0.96 ppm, respectively. The remaining pyrrolidinone ring α, β, γ-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 δ 2.09, 1.77 and 3.19 ppm respectively. The ^{13}C NMR spectrum had peaks at δ 175.3 and 168.4 ppm for the amide and ethyl ester carbonyl carbons, respectively. The ethyl ester carbon peaks were at δ 60.9, and 13.8 ppm, while the methylene group carbon peak appeared at δ 47.4. The remaining peaks at δ 30.0, 17.7 and 43.7 ppm were for the pyrrolidinone ring α, β, γ-carbons to the amide.

The IR spectrum of *tert*-butyl 2-(2-oxopyrrolidin-1-yl)acetate **172** had a peak at ν_{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 δ 3.96 ppm for the methylene group, while the singlet for the *tert*-butyl protons was δ 1.47 ppm. The pyrrolidine ring α, β, γ-protons triplet with *J* = 8.1 Hz, multiplet and triplet with *J* = 7.0 Hz were at δ 2.42, 2.15 – 2.00 and 3.49 ppm, respectively. The ^{13}C NMR spectrum showed peaks at δ 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 δ 47.6 and 27.9 ppm. The remaining peaks at δ 30.3, 17.9 and 44.6 ppm were for α, β, γ-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 ν_{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**

	NCH_2CO_2	CH_2CH_3	NCH_2CH_2	$COCH_2CH_2$	NCH_2CH_2	CH_2CH_3
170 / ppm	3.74	3.87	3.19	2.09	1.77	0.96
171 / ppm	4.56	4.22	3.85	3.06 ($CSCH_2$)	2.22 – 2.05	1.30

The ^{13}C NMR spectrum of thiolactam **171** showed the absence of the amide carbonyl carbon peak, previously at δ 175.3 ppm and the presence of the thioamide carbonyl carbon peak at δ 203.5 ppm. The ethyl ester carbonyl peak was present at δ 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**

	NCH_2CO_2	NCH_2CH_2	$COCH_2CH_2$	NCH_2CH_2
170 / ppm	47.4	44.7	30.0	17.7
171 / ppm	55.5	49.0	44.3 ($CSCH_2$)	19.7

The IR spectrum of *tert*-butyl 2-(2-thioxopyrrolidin-1-yl)acetate **173** had a peak at ν_{max} = 1747 cm^{-1} for the *tert*-butyl ester carbonyl group. The ^1H 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 ^1H NMR spectroscopic signals of compounds **172** and **173**

	NCH_2CO_2	NCH_2CH_2	$COCH_2CH_2$
172 / ppm	3.96	3.49	2.42
173 / ppm	4.44	3.83	3.05 ($CSCH_2$)

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

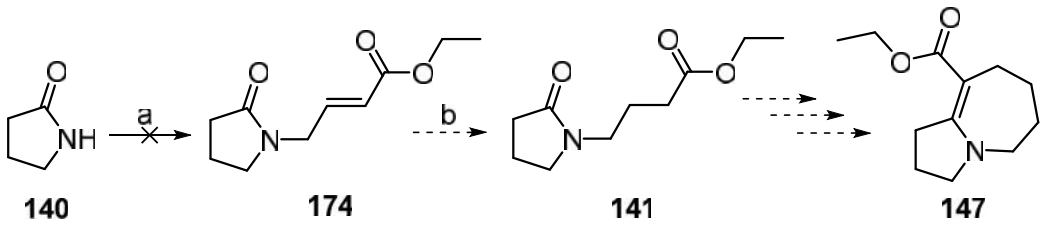
Table 8: Selected ^{13}C NMR spectroscopic signals of compounds **172** and **173**

	NCH_2CO_2	NCH_2CH_2	$COCH_2CH_2$
172 / ppm	47.6	44.6	30.3
173 / ppm	55.5	49.7	44.3 ($CSCH_2$)

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 °C 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_N2 substitution reaction as will be seen in Section 2.19.



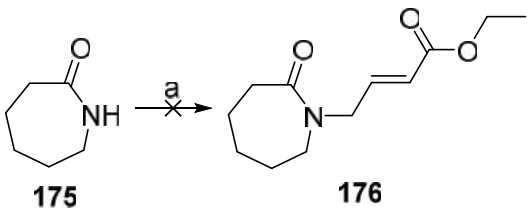
140 **174** **141** **147**

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

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

No.	Reactants	Conditions	Solvent	Results
1	(i) NaH (1.2 eq), (ii) ethyl 4-bromocrotonate (1 eq)	(i) 40 minutes at 0 °C (ii) then 80 hours at room temperature	DMF	**174** = 0%
2	(i) NaH (1.2 eq), (ii) ethyl 4-bromocrotonate (1 eq)	(i) 30 minutes at 0 °C (ii) then 22 hours heating under reflux	DMF	**174** = 0%
3	(i) NaH (1.2 eq), (ii) ethyl 4-bromocrotonate (1 eq)	(i) 30 minutes at room temperature (ii) then 26 hours at room temperature	THF	**174** = 0%
4	(i) NaH (1.2 eq), (ii) ethyl 4-bromocrotonate (1 eq)	(i) 30 minutes at room temperature (ii) then 20 hours heating under reflux.	THF	**174** = 0%

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.



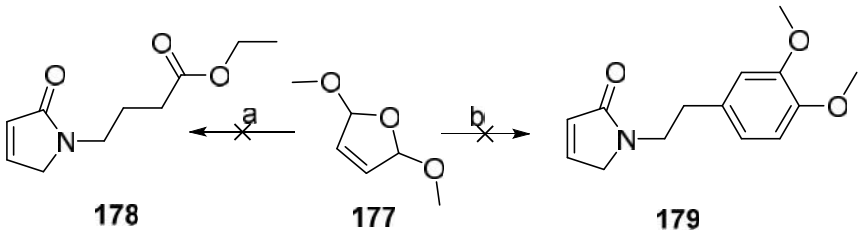
175 **176**

Scheme 29: (a) (i) NaH (1.4 eq), THF, 2 h at r.t., (ii) Ethyl 4-bromocrotonate (1.2 eq), THF, overnight at r.t.

2.5 Attempted synthesis of ethyl 4-(2-oxo-2H-pyrrol-1(5*H*)-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-2*H*-pyrrol-1(5*H*)-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)-1*H*-pyrrol-2(5*H*)-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.

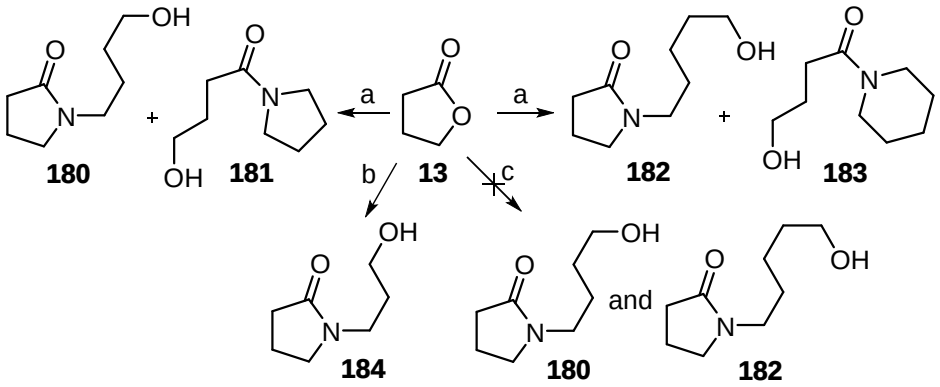


Scheme 30: *Reagents and Conditions*: (a) Ethyl 4-aminobutyrate.HCl (1 eq) or (b) homoveratrylamine (1 eq), 1M HCl, 3 - 6 h at r.t.

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(3*H*)-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]BF_4 (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 ^{1}H 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 C*H*$_2$OH and NC*H*$_2$CH$_2$CH$_2$CH$_2$OH 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 ^{13}C 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 *C*H$_2$OH and NCH$_2$CH$_2$CH$_2$CH$_2$OH 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 ^{1}H and ^{13}C 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]

^{1}H NMR ppm	^{1}H NMR (Lit.) ppm	^{13}C NMR ppm	^{13}C NMR (Lit.) ppm
3.81 (s)	3.90 (s, O*H*)	175.2	175 (*C*ON)
3.63 (t, *J* = 5.9 Hz)	3.42 (t, *J* = 6.0 Hz, C*H*$_2$OH)	61.7	61.5 (*C*H$_2$OH)
3.41 (t, 7.1 Hz)	3.22 (t, *J* = 8.0 Hz, NC*H*$_2$CH$_2$CH$_2$CO)	47.1	47.0 (N*C*H$_2$CH$_2$CH$_2$CO)
3.30 (t, 7.0 Hz)	3.11 (t, *J* = 7.0 Hz, NC*H*$_2$CH$_2$CH$_2$CH$_2$OH)	42.2	42.1 (N*C*H$_2$CH$_2$CH$_2$CH$_2$OH)
2.39 (t, 8.2 Hz)	2.19 (t, *J* = 8.0 Hz, NCH$_2$CH$_2$C*H*$_2$CO)	31.1	30.9 (NCH$_2$CH$_2$*C*H$_2$CH$_2$OH)
2.11 – 1.77 (m)	1.84 (qi, *J* = 8.0 Hz, NCH$_2$CH$_2$C*H*$_2$CO)	29.6	29.5 (NCH$_2$CH$_2$*C*H$_2$CO)
1.71 – 1.47 (m)	1.47 (m, NCH$_2$C*H*$_2$C*H*$_2$CH$_2$OH)	23.6	23.6 (NCH$_2$*C*H$_2$CH$_2$CH$_2$OH)
		17.8	17.7 (NCH$_2$*C*H$_2$CH$_2$CO)

The IR spectrum of 4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one **181** had peaks at ν_{max} = 3420 and 1667 cm^{-1} for the alcohol OH and amide carbonyl groups respectively. The ^{1}H NMR spectrum had no observable O*H* peak owing to proton exchange with the solvent MeOD. The pyrrolidinyl ring protons were shown by a triplet with *J* = 6.4 Hz at δ 3.46 for the four protons of NC*H*$_2$ and a multiplet at δ 1.45 ppm for the four protons of NCH$_2$C*H*$_2$. The butanone side chain protons were shown by the presence of a triplet with *J* = 6.5 Hz at δ 3.09 ppm for the γ-protons of the amide and by a triplet with *J* = 7.6 Hz at δ 2.16 ppm for the α-protons of the amide. The ^{13}C NMR spectrum revealed the amide carbonyl carbon peak at δ 175.9 ppm while the butanone side chain major carbon peaks were at δ 40.2 and 33.7 ppm for the *C*H$_2$OH and CO*C*H$_2$ protons correspondingly. The pyrrolidinyl ring peaks were at δ 62.6 and 62.3 ppm for the for two N*C*H$_2$ carbons, while the remaining peaks were at δ 29.9 and 26.9 ppm for two NCH$_2$*C*H$_2$ 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 $CDCl_3$ for compound **181** and Maulide *et al*. data respectively (Table 11).

Table 11: Comparison of ^{1}H and ^{13}C NMR spectroscopic data of lactam **181** to those of Maulide *et al* data[174]

^{1}H NMR (300MHz) ppm	^{1}H NMR (500 MHz) (Lit.) ppm	^{13}C NMR ppm	^{13}C NMR (Lit.) ppm
3.09 (t, *J* = 6.5 Hz)	3.70 (t, *J* = 6.0 Hz, $CH_2CH_2CH_2OH$)	175.9	172.3 (*C*=O)
	3.57 (bs, O*H*)	40.2	62.9(CH_2OH)
3.46 (t, *J* = 6.4 Hz)	3.40 – 3.50 (m, CH_2NCH_2)	62.6	46.8 (NCH_2)
2.16 (t, 7.6 Hz)	2.46 (t, *J* = 6.5 Hz, CH_2CO)	62.3	45.9(NCH_2)
1.77 – 1.62 (m)	1.97 (tt, *J* = 6.5, 6.0 Hz, $CH_2CH_2CH_2OH$)	33.7	32.8 ($COCH_2$)
1.45 (m)	1.83 – 2.00 (m, $CH_2CH_2NCH_2CH_2$)	31.0	27.2 (CH_2CH_2OH)
		29.9	26.1 (NCH_2CH_2)
		26.9	24.4 (NCH_2CH_2)

This result (**Scheme 31**, a) prompted a probe into this phenomenon. Dihydrofuran-2(3*H*)-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 ^{1}H 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 O*H* proton, a triplet with *J* = 6.5 Hz at δ 3.59 ppm for the C*H*$_2$OH protons and a triplet with *J* = 7.2 Hz at δ 3.27 ppm for the NC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH protons. The ^{13}C 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 *C*H$_2$OH and NC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH carbons respectively. The ^{1}H and ^{13}C NMR spectra were comparable with the literature values from the article by Belanger *et al.* (Table 12).[100]

Table 12: Comparison of ^{1}H and ^{13}C NMR spectroscopic data of lactam **182** to those of Belanger *et al.* [100]

^{1}H NMR ppm	^{1}H NMR (Lit.) ppm	^{13}C NMR ppm	^{13}C NMR (Lit.) ppm
3.75 (s, O*H*)		175.1	175.0 (*C*ON)
3.59 (t, *J* = 6.5 Hz)	3.64 (t, *J* = 6.5 Hz, C*H*$_2$OH)	61.9	61.6 (*C*H$_2$OH)
3.40 (t, *J* = 7.1 Hz)	3.37 (t, *J* = 7.0 Hz, NC*H*$_2$CH$_2$CH$_2$CO)	47.1	47.0 (NC*H*$_2$CH$_2$CH$_2$CO)
3.27 (t, *J* = 7.2 Hz)	3.29 (t, *J* = 7.0 Hz, NC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH)	42.3	42.2 (NC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH)
2.38 (t, *J* = 8.1 Hz)	2.39 (t, *J* = 7.0 Hz, COC*H*$_2$)	32.1	32.0 (NCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH)
2.10 – 1.95 (m)	2.01 (qi, *J* = 7.0 Hz, NCH$_2$C*H*$_2$CH$_2$CO)	31.0	30.9 (CO*C*H$_2$)
1.64 – 1.47 (m)	1.65 – 1.50 (m, NCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$OH)	26.9	26.7 (NCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH)
1.40 – 1.32 (m)	1.42 – 1.34 (m, NCH$_2$CH$_2$C*H*$_2$CH$_2$CH$_2$OH)	22.9	22.8 (NCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH)
		17.7	17.6 (NCH$_2$*C*H$_2$CH$_2$CO)

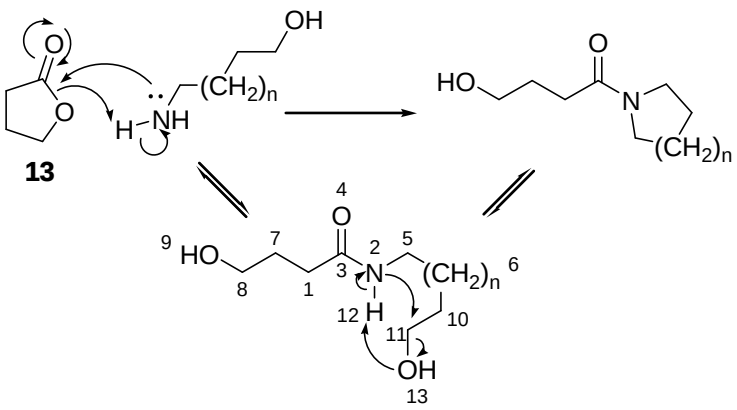
The IR spectrum of 4-hydroxy-1-(piperidin-1-yl)butan-1-ones **183** had peaks at ν_{max} = 3513 and 1697 cm^{-1} for the alcohol OH and amide carbonyl groups respectively. The

^{1}H NMR spectrum showed the piperidinyl ring's presence by a triplet of doublets with *J* = 6.4 Hz at δ 3.57 ppm for the four NC*H*$_2$ protons and a multiplet at δ 1.64 – 1.46 ppm for the four NCH$_2$C*H*$_2$ protons. The butanone chain on nitrogen was shown by a triplet with *J* = 6.9 Hz at δ 3.18 ppm for γ-protons of the amide and a triplet with *J* = 7.5 Hz at δ 2.27 ppm for the α-protons of the amide. The ^{13}C NMR spectrum showed the amide carbonyl carbon peak at δ 175.8 ppm while the butanone's major peaks were at δ 40.5 and 33.9 ppm for the γ and α carbons of the amide respectively. The piperidinyl ring carbon peaks were at δ 62.9 and 62.4 ppm for the two N*C*H$_2$ carbons and peaks at δ 30.4 and 30.3 ppm for NCH$_2$*C*H$_2$ and NCH$_2$*C*H$_2$ 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]

^{1}H NMR ppm	^{1}H NMR (Lit.) ppm	^{13}C NMR ppm	^{13}C NMR (Lit.) ppm
	3.69 (br s, 2H)	175.8 (*C*O)	171.8
3.57 (td, *J* = 6.4 Hz, C*H*$_2$NC*H*$_2$)	3.58 – 3.54 (m, 2H)	62.9 (N*C*H$_2$)	62.9
3.18 (t, *J* = 6.9 Hz, C*H*$_2$OH)	3.43 – 3.40 (m, 2H)	62.4 (N*C*H$_2$)	46.8
2.27 (t, *J* = 7.5 Hz, COC*H*$_2$)	2.51 (t, *J* = 6.5 Hz, 2H)	40.5 (*C*H$_2$OH)	42.9
1.90 – 1.75 (m, C*H*$_2$CH$_2$OH)	1.96 – 1.83 (m, 2H)	33.9 (NCH$_2$*C*H$_2$)	31.1
1.64 – 1.46 (m, C*H*$_2$CH$_2$NCH$_2$C*H*$_2$)	1.66 – 1.42 (m, 8H)	33.4 (NCH$_2$*C*H$_2$)	27.6
1.46 – 1.32 (m, C*H*$_2$CH$_2$CH$_2$N)		30.3 (CO*C*H$_2$)	26.6
		30.0 (*C*H$_2$CH$_2$OH)	26.5
		24.4 (NCH$_2$CH$_2$*C*H$_2$)	24.5

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.

It was of interest as to how 3-amino-1-propanol would react with dihydrofuran-2(3*H*)-one **13** based on previous observations (**Scheme 31**, a). Dihydrofuran-2(3*H*)-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.

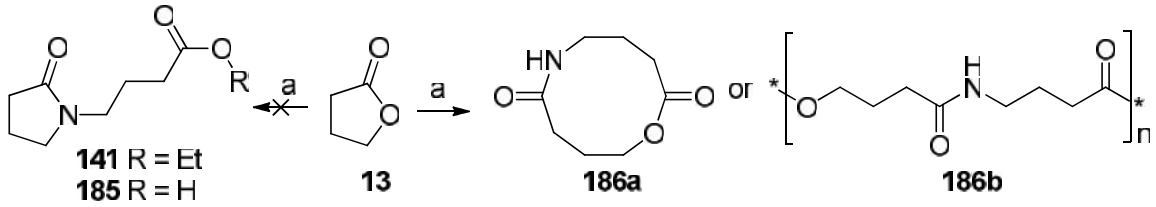
The IR spectrum of 1-(3-Hydroxypropyl)pyrrolidin-2-one **184** revealed peaks at ν_{max} = 3449 and 1632 cm^{-1} for the alcohol OH and the amide carbonyl groups in that order. The ^{1}H NMR spectrum showed a multiplet at δ 4.23 ppm for the OH proton and a multiplet at δ 3.24 – 2.90 ppm for the NC$H_2$$CH_2CH_2$OH protons of the propyl side chain. The pyrrolidinone ring protons were represented by a multiplet at δ 3.24 – 2.90 ppm for the γ-protons of the amide and a multiplet at δ 2.00 ppm for the α-protons of the amide. The ^{13}C NMR spectrum showed the lactam carbonyl peak at δ 175.2 ppm while the pyrrolidinone ring carbons were at δ 47.1 and 29.6 ppm for the γ-carbon and α-carbon of the lactam. The propyl side chain carbon peaks were at δ 61.2 and 42.2 ppm for the *C*H_2OH and N*C*$H_2$$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(3*H*)-one **13** and 5-amino-1-pentanol in [bmim]BF_4 fewer than 35 minutes of microwave irradiation at 220 °C. Dihydrofuran-2(3*H*)-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(3*H*)-one **13** quantitatively.[102]

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

The condensation reactions of γ-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 γ-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**.



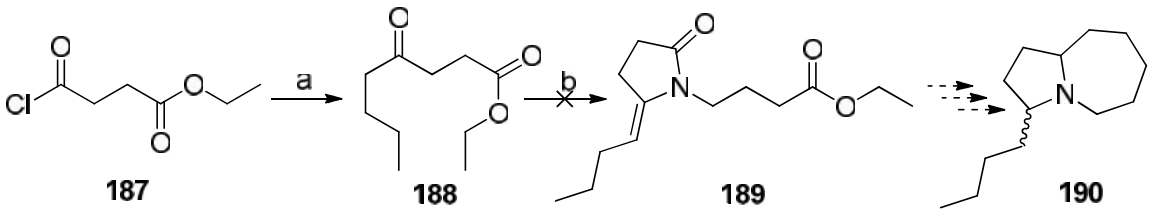
Scheme 33: *Reagents and Condition*: (a) Ethy 4-aminobutyrate.HCl or 4-aminobutyric acid, 150 W, 220 °C, 10 -20 min, **141** = 0%, **185** = 0%, **186a/186b** = 45%.

The IR spectrum of 1,6-oxazecane-2,7-dione **186a** or polymer **186b** showed peaks at ν_{max} 3400 – 3200 and 1687 cm^{-1} for the amide N*H* and the amide and ester carbonyl groups respectively. The ^{1}H NMR spectrum revealed a triplet with *J* = 7.1 Hz at δ 4.08 ppm for the γ-protons of the amide group, a triplet with *J* = 6.9 Hz at δ 3.12 ppm for the γ-protons of the ester group and a broad singlet at δ 7.22 ppm for the amide N*H* 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 δ 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-butylidene-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: *Reagents and conditions*: (a) (i) Butylmagnesium chloride (1 eq), $Fe(acac)_3$ (0.1 eq), THF, 9 min at -29 °C, **188** = 89%; (ii) Butylmagnesium chloride (1 eq), $Fe(acac)_3$ (0.1 eq), THF, 10 min at -78 °C, **188** 59%; (b) Table 14.

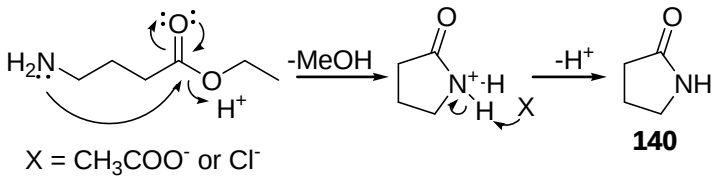
The IR spectrum of ethyl 4-oxooctanoate **188** indicated the presence of the ester and ketone carbonyl of the groups with a peak at ν_{max} = 1754 cm^{-1}. The ^1H NMR spectrum confirmed the exclusive C–C coupling between the acyl chloride and the Grignard reagent. A triplet with *J* = 7.4 hz at δ 2.17 ppm corresponded to the α-protons for the ketone on the butyl side chain while another triplet with *J* = 7.4 Hz at δ 0.61 ppm represented methyl protons on the butyl side chain. The triplet and quartet both with *J* = 7.2 Hz at δ 3.81 and 0.94 ppm respectively, maintained the

presence of the ester group. The ^{13}C NMR further corroborated this with peaks at δ 207.9 and 171.9 ppm for the ketone and ester groups, respectively.

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**.

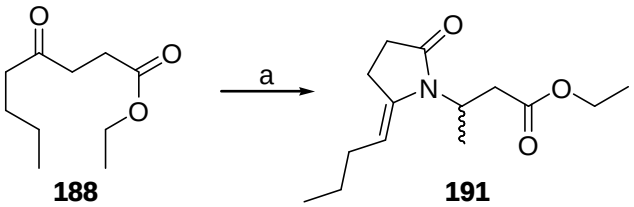


Scheme 35: Proposed mechanism for pyrrolidin-2-one formation.

Table 14: Attempted condensation of ethyl 4-oxooctanoate **188** with ethyl 4-aminobutyrate

No.	Reagents	Conditions	Solvents	Results
1	Ethyl 4-aminobutyrate·HCl (1 eq), 4Å molecular sieves	21 hours heating under reflux	Toluene	**189** = 0%; **188** = 88%
2	Ethyl 4-aminobutyrate·HCl (1 eq), $NaHCO_3$ (1 eq), acetic acid (5 eq)	64 hours heating under reflux	Toluene	**189** = 0%; **188** = 78%
3	Ethyl 4-aminobutyrate (1 eq), acetic acid (5 eq)	21–41 hours heating under reflux	Toluene,	**189** = 0%; **188** = 61 – 65%
4	Ethyl 4-aminobutyrate·HCl (1 eq), $NaHCO_3$ (1 eq), H_2O (1 eq), acetic acid (5 eq)	45 hours heating under reflux	Toluene	**189** = 0%; **188** = 21%
5	Ethyl 4-aminobutyrate·HCl (1 eq), acetic acid (5 eq)	24 hours heating under reflux	Methanol	**189** = 0%; **188** = 95%

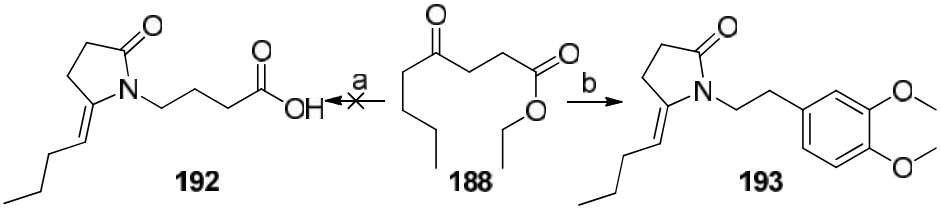
This is contrary to the PhD work of Susan Winks, who was successful in synthesising (*E*)-ethyl 2-(2-butylidene-5-oxopyrrolidin-1-yl)hexanoate **191** in 87% yield from heating ethyl 4-oxooctanoate, ethyl 3-aminobutyrate and excess acetic acid under reflux in toluene for a minimum of 72 hours (**Scheme 36**, a).[90] 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).



188 **191**

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

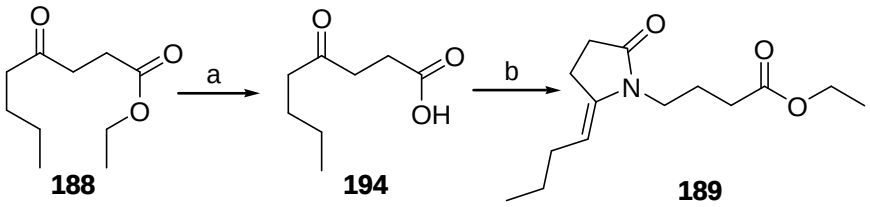
Ethyl 4-aminobutyrate was replaced with 4-aminobutyric acid in a condensation reactions with ethyl 4-oxooctanoate to avoid the possibility of competing intramolecular condensation of ethyl 4-aminobutyrate since the conditions are not conducive in the case of 4-aminobutyric acid. 4-Aminobutyric acid was 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-butylidenepyrrolidin-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.



Scheme 37: *Reagents and conditions*: (a) 4-aminobutyric acid (1.1 eq), acetic acid (5 eq), toluene 50 h at reflux, **192** = 0% (b) Homoveratrylamine (1.1 eq), acetic acid (3 eq), toluene, 22 h at reflux, **193** = 67%.

The IR spectrum of (*E*)-1-(3,4-dimethoxyphenethyl)-5-butylidenepyrrolidin-2-one **193** revealed peaks at ν_{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 δ 4.70 ppm for the alkene proton, a doublet of doublets with *J* = 8.9, 6.9 Hz at δ 2.78 ppm for β-protons to the amide and a doublet of triplets with *J* = 11.8, 5.8 Hz at δ 2.00 ppm for the C=CHCH_2 protons. Also present were the methoxy groups' singlets at δ 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-yl)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 δ 11.12 ppm. The ^{13}C NMR spectrum presented with a carboxylic acid carbonyl peak at δ 178.7 ppm which is more deshielded when compared with the peak of ester group at δ 171.9 ppm. The ketone carbonyl carbon peak was unaffected at δ 209.3 ppm.

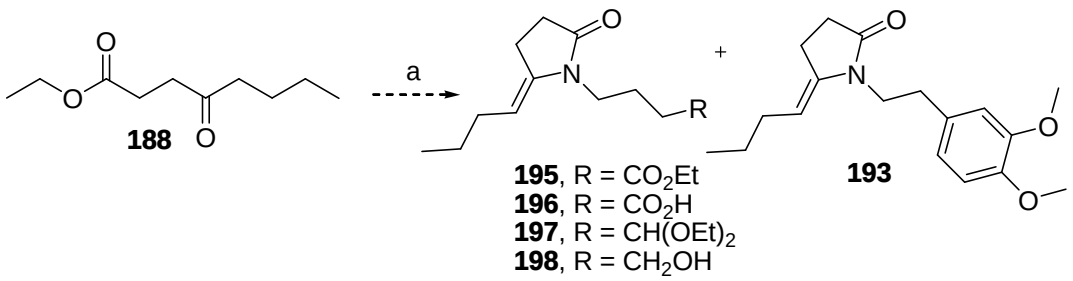


Scheme 38: *Reagents and conditions*: (a) KOH (1 eq), H_2O, 2 h at r.t., **194** = 94%; (b) (i) $SOCl_2$ (1 eq), toluene, 2 h at reflux; (ii) Ethyl 4-aminobutyrate·HCl (1.2 eq), acetic acid (3 eq), toluene, 42 h at reflux, **189** = 36%.

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 δ 4.75 ppm for the alkene proton, a triplet with J = 7.1 Hz at δ 3.51 ppm for the γ-protons to the ester carbonyl group and a triplet with J = 7.1 Hz at δ 0.96 ppm for the methyl of the butylidene chain. The ethyl ester group was still intact as shown by a quartert with J = 7.1 Hz at δ 4.14 ppm and a triplet with J = 7.1 Hz at δ 1.28 ppm. The ^{13}C NMR spectrum supported the structure with the peaks at δ 175.6 and 172.9 ppm for the amide and ester carbonyl carbons respectively, while the alkene peaks were at δ 138.9 and 100.7 ppm.

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-butylidenepyrrolidin-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

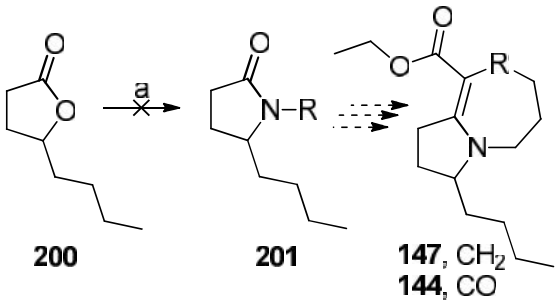
Entry	Reagents	Conditions	Results
1	Ethyl 4-aminobutyrate·HCl (1 eq)	50 W, 150 °C, 80 min	**195** = 0%
2	4-Aminobutyraldehyde diethyl acetal (1 eq)	(i) 60 W, 148 °C, 10 min, (ii) 70 W, 181 °C, 20 min, (iii) 150 W, 215 °C, 20 min	**197** = 0%
3	Homoveratrylamine (1 eq)	150 W, 220 °C, 35 min	**193** = 0%
4	4-Aminobutyric acid (1 eq)	150 W, 220 °C, 40 min	**196** = 0%
5	Ethyl 4-aminobutyrate·HCl (1 eq), acetic acid (5 eq)	(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	**195** = 0% **195** = 0%
6	4-Aminobutyraldehyde diethyl acetal (1 eq), acetic acid (5 eq)	(i) Same as in entry 5 (ii) Same as in entry 5	**197** = 0% **197** = 0%
7	4-Amino-1-butanol (1 eq), acetic acid (5 eq)	(i) Same as in entry 5, 0% (ii) Same as in entry 5, 24%	**198** = 0% **198** = 24%

(*E*)-5-Butylidene-1-(4-hydroxybutyl)pyrrolidin-2-one's **198** IR spectrum had peaks at ν_{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 δ 4.08 ppm for the (OCH_2) protons and a triplet with *J* = 6.6 Hz at δ 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 δ 4.65 ppm for the vinyl proton and a triplet with *J*

= 7.3 Hz δ 0.92 ppm for methyl protons. The pyrrolidinone ring was shown by a doublet of triplets with *J* = 7.2, 2.7 Hz at δ 2.48 ppm for the α-protons of the amide and a doublet of doublets with *J* = 14.1, 6.0 Hz at δ 2.61 ppm for the β-protons of the amide. The ^{13}C NMR spectrum showed peaks at δ 175.5, 139.1 and 100.6 ppm for the amide carbonyl, alkene quaternary and vinyl carbons respectively. The peaks at δ 64.0 and 13.7 ppm were for (*C*H_2OH) and methyl carbons.

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

Commercially available 5-butyl-dihydrofuran-2(3*H*)-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(3*H*)-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(3*H*)-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(3*H*)-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(3*H*)-one **200** reacts differently as compared to dihydrofuran-2(3*H*)-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).



Scheme 40: *Reagents and conditions*: (a) Amine, microwave conditions, Table 16.

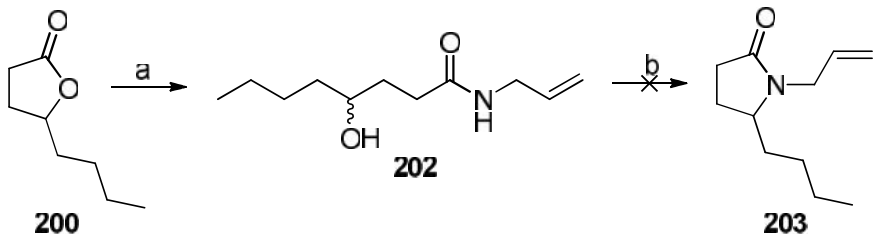
Table 16: Microwave reactions of 5-butyl-dihydrofuran-2(3*H*)-one **200** with various amines [114]

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

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-Butyldihydrofuran-2(3*H*)-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-butylpyrrolidin-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-butyldihydrofuran-2(3*H*)-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 S_N1 reaction between the secondary amide and the secondary alcohol. Thus silica was used as an acid catalyst to promote ring cyclisation by reacting 5-butyldihydrofuran-2(3*H*)-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 N*H* 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*: (a) (i) Allyl amine (1 eq),1 drop HCl, neat, (100 W, 60 min at 60 °C) and (150 W, 30 min at 100 °C), **202** = 69%; (ii) Allyl amine (1 eq), neat, over weekend at 220 °C in an oven, **202** = 88%; (iii) Allyl amine (1 eq), silica, neat, 25 h at 220 °C in an oven, **202** = 100%; (b) (i) TsCl (1 eq), pyridine, 24 h at r.t., **203** = 0%; (ii) NaH (1 eq), THF, r.t., overnight, **203** = 0%; (iii) Methane sulphonyl chloride(1 eq), TEA (1 eq), DCM, r.t., 4 days, **203** = 0%; (iv) Methane sulphonyl chloride(1 eq), TEA (1 eq), toluene, reflux, overnight, **203** = 0%.

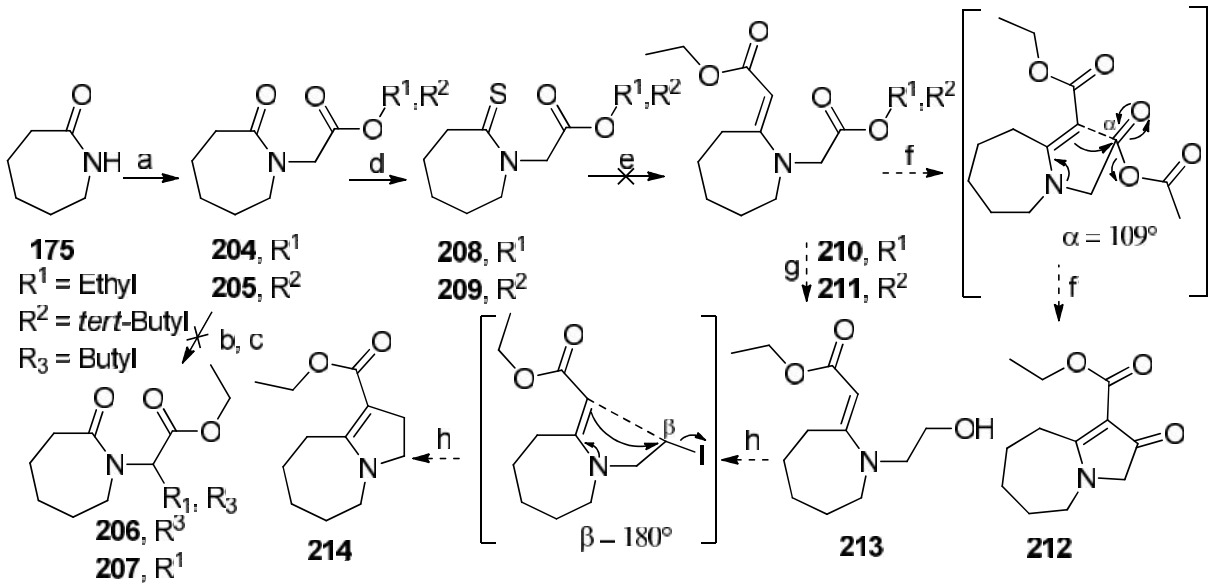
The IR spectrum of *N*-allyl-4-hydroxyoctanamide **202** had peaks at ν_{max} = 3540, 3420, 1734 and 1643 cm^{-1} for the alcohol, amide N*H*, amide carbonyl and alkene groups in that order. The ^{1}H NMR spectrum revealed a broad singlet at δ 6.96 and a singlet at δ 4.06 ppm for the amide N*H* and the alcohol OH. The OH proton is deshielded owing to hydrogen bonding. The allyl group proton peaks were at δ 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 δ 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 NC*H*$_2$ protons. The structure of the molecule was confirmed by a multiplet at δ 3.52 ppm for the γ-proton of the amide, the triplet with *J* = 7.0 Hz at δ 2.32 ppm for the α-protons of the amide, and a triplet with *J* =7.0 Hz at δ 0.83 ppm for the methyl protons. The ^{13}C NMR spectrum revealed carbon peaks at δ 174.1, 134.2, 116.0 and 41.9 ppm for the amide carbonyl and the allyl groups correspondingly. The peak at δ 71.0 ppm was for the γ-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 α-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**, h.[92,93]

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 vinylogous 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 vinylogogus 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 vinylogous urethane.



Scheme 42: *Reagents and conditions*: (a) (i) NaH (1 eq), THF, 10 - 15 min at r.t., (ii) Ethyl bromoacetate or *tert*-Butyl bromoacetate (1 eq), THF, 20 - 22 h at r.t., **204** = 95%; **205** = 97%; (b) (i) LDA (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) LDA (1.2 eq), **204**, THF, 30 min at r.t., (ii) Iodoethane, THF, r.t. for 22 h, **207** = 0%; (d) (i) P_2S_5 (0.5 eq), DCM, 5 days at r.t., **208** = 28%; **209** = 35%; (ii) P_2S_5 (0.5 eq), DCM, 20 h at r.t., **208** = 93%; **209** = 97%; (e) (i) Ethyl bromoacetate (1 eq), MeCN, 19 h at r.t., (ii) TEA (1 eq), TPP (1 eq), MeCN, 24 h at r.t.; (f) Acylative ring closure; (g) Reduction with hydrides; (h) Alkyative 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 ν_{max} = 1721 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 δ 4.18 ppm for the α-protons to the ester carbonyl and methylene of the ester ethyl group and a triplet at δ 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 δ 176.2 and 169.7 ppm, respectively. The newly formed N-CH_2 substituent was shown by the peak at δ 51.2 ppm and the ester group carbons were at δ 61.0 and 14.1 ppm.

The IR spectrum of *tert*-butyl 2-(2-oxoazepan-1-yl)acetate **205** showed peaks at ν_{max} = 1732 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 δ 4.05 ppm for the newly formed N-CH_2 bond. The tertiary butyl ester group was shown by a singlet at δ 1.47 ppm. The ^{13}C NMR presented with the carbonyl carbons of the lactam, and ester groups peaks at δ 176.1 and 168.8 ppm respectively and a *tert* butyl quartenary carbon peak at δ 81.5 ppm. The newly formed N-CH_2 bond was shown by the peak at δ 51.1 ppm and the tertiary butyl ester group methyl carbons were at δ 28.0 ppm.

The butyl substituent needed to be added at α-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 °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 42**, c). Marcin *et al*.[176] performed a similar reaction using allyl bromide as the alkylation agent and ethyl 2-(-2oxoazepan-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-(2-ethoxy-2-oxoethylidene)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 ν_{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 δ 4.61 ppm for the α-protons to the ester carbonyl group of the ester, a quartet and a triplet with *J* = 7.1 Hz at δ 4.07 and 1.14 ppm for the ethyl ester moiety. The multiplet peak for the α-protons of the thiocarbonyl was at δ 3.03 ppm, demonstrating the molecule is intact. The ^{13}C NMR spectrum revealed the absence of the lactam carbonyl peak at δ 176.2 ppm and the presence of the thiocarbonyl peak at δ 208.0 ppm. The ester carbonyl carbon peak shifted upfield to δ 167.7 ppm from δ 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 $C_{10}H_{18}NO_2S^+$ 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 δ 4.63 and 1.48 ppm for the α-protons to the ester carbonyl group of the ester and methyl protons of the *tert*-butyl ester moiety. The singlet for the α-protons of the ester carbonyl was at δ 4.63 ppm and the multiplet for the α-protons of the thiocarbonyl was at δ 3.17 ppm, demonstrating the molecule is intact. The ^{13}C NMR spectrum revealed the absence of the lactam carbonyl carbon peak at δ 176.1 ppm and the presence of the thiocarbonyl carbon peak at δ 207.9 ppm. The ester carbonyl carbon peak shifted upfield to δ 166.6 ppm from δ 168.8 ppm of the lactams ester carbonyl carbon and the quaternary carbon of the tertiary butyl ester shifted downfield to δ 82.0 ppm from δ 81.5 ppm of the lactam's tertiary butyl ester quaternary carbon.

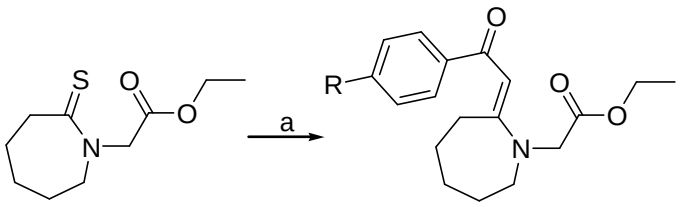
The Eschenmoser sulphide contraction reactions using ethyl bromoacetate became a crucial step in making the key enaminones in this sequence of reactions. Ethyl 2-(2-thioxoazepan-1-yl)acetate **208** or *tert*-butyl 2-(2-thioxoazepan-1-yl)acetate **209** was reacted with ethyl bromoacetate in acetonitrile 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.[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-thioxoazepan-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 compare 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-thioxoazepan-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.



208

215, R = H
216, R = NO_2
217, R = OMe

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 ν_{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 δ 7.81 ppm for the two aromatic protons closer to the carbonyl group, a multiplet at δ 7.37 ppm for the remaining three aromatic protons and a singlet at δ 5.47 ppm for the vinyl proton, confirming the newly formed double bond. The singlet for the α-protons to the ester carbonyl group was at δ 4.07 ppm which is shielded as compared to the α-protons of the ester carbonyl group in thioamide **208** at δ = 4.61 ppm. The multiplet at δ 3.50 ppm was for the (CH_2C=CH) protons, which is a slight chemical shift from a multiplet at δ 3.03 ppm for the α-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 δ 208.0 ppm for the thioamide **208** and presence of peaks at δ 188.4, 169.2 and 92.7 ppm for the ketone carbonyl, quaternary alkene and vinyl carbons respectively. The ester α-carbon peak was at δ 55.6 ppm, upfield from δ 58.6 ppm of ester α-carbon peak of thiolactam **208**. The aromatic carbon peaks were at δ 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 δ 3.5 ppm. The same hydrogens in enaminones with the *Z* configuration have signals around δ 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 ν_{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 δ 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 δ 7.91 ppm for the two aromatic protons closer to the carbonyl group and a singlet at δ 5.40 ppm for the vinyl proton. The singlet for the α-protons to the ester carbonyl group was at δ 4.11 ppm which is slightly shielded as compared to the α-protons of the ester carbonyl group in thioamide **208** at δ 4.61 ppm. The multiplet at δ 3.53 ppm was for the (CH_2C=CH) protons, which is a slight chemical shift from a multiplet at δ 3.03 ppm for the α-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 δ 208.0 ppm for the thioamide **208** and presence of peaks at δ 185.8, 171.0 and 92.4 ppm for the ketone carbonyl, quaternary alkene and vinyl carbons respectively. The ester α-carbon peak was at δ 55.7 ppm, upfield from δ 58.6 ppm of ester α-carbon peak of thiolactam **208**. The

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 $C_{18}H_{23}N_2O_5^+$ with an exact calculated mass of 347.1601.

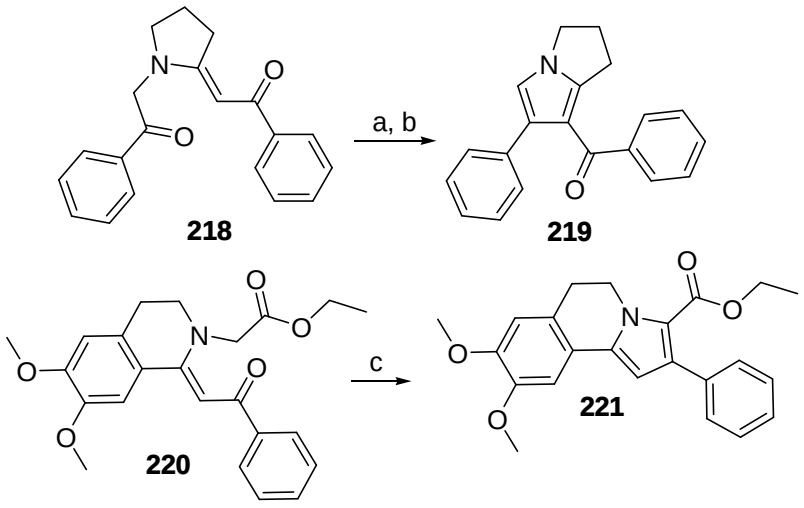
The IR spectrum of (*E*)-ethyl 2-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)azepan-1-yl)acetate **217** had peaks at ν_{max} = 1756, 1520 and 1468 cm^{-1} for the ester and ketone carbonyl and alkene groups in that order. The ^1H NMR revealed a doublet with *J* = 8.9 Hz at δ 7.81 ppm for the two aromatic 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 α-protons to the ester carbonyl group was at δ 4.07 ppm which is slightly shielded as compared to the α-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 (C*H*$_2$C=CH) protons, which is a slight chemical shift from a multiplet at δ 3.03 ppm for the α-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 ^{13}C 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 α-carbon peak was at δ 55.7 ppm upfield from δ 58.6 ppm of ester α-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 $[M+H_2O+H]^+$ equal to 350.1969 for a monohydrate molecule of molecular formula $C_{19}H_{28}NO_5^+$ 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*-

NO_2, which may lead to more pronounced second order effects on *p*-OMe as compared to the *p*-NO_2. The *p*-NO_2 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.

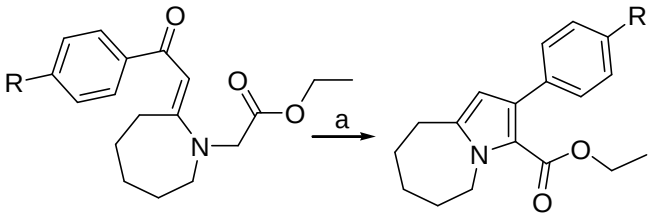
2.13 Pyrrolo[1,2-*a*]azepine nucleus from Knoevenagel condensation reactions of *N*-alkyl vinylogous amides

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: *Reagents and conditions*: (a) EtOAc, 40 °C, 24 h, **219** = 59%; (b) SiO_2, 90 °C, 2 h, **219** = 72%; (c) SiO_2, 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-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **222**, ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **223** and ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-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.



215, R = H
216, R = NO_2
217, R = OMe

222, R = H
223, R = NO_2
224, R = OMe

Scheme 45: *Reagents and conditions*: (a) (i) DMA, (i) Stage 1: 150 W, 150 °C, 10 min, (ii) Stage 2: 150 W, 165 °C, 10 min, (iii) Stage 3: 150 W, 180 °C, 10 - 40 min, **222** = 27 - 51%, **223** = 62 - 90%, **224** = 1.58%.

The IR spectrum of ethyl 2-phenyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **222** had peaks at ν_{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 δ 7.44 – 7.17 ppm and a downfield shift of the vinyl proton singlet from δ 5.47 ppm to δ 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 δ 4.07 and 1.00 ppm, revealing the absence of α-protons to the ester carbonyl at δ 4.07 ppm of the vinylogous amide **215**. The ^{13}C NMR spectrum revealed the absence of the ketone carbonyl and ester α-carbon peaks at δ 188.4 and 55.6 ppm respectively from vinylogous amide **215** and the presence of pyrrole quaternary carbon peaks at δ 118.3 ppm (CH_2C=CH*C*) and 137.3 ppm (*C*CO_2) respectively. The vinyl carbon peak which was at δ 92.7 ppm for vinylogous amide **215** shifted downfield to δ 109 ppm for the pyrrole carbon peak (CH_2C=*C*H). The alkene quaternary carbon which was at δ 169.2 ppm for vinylogous amide **215** shifted upfield to δ 142.3 ppm for the pyrrole quaternary carbon. The aromatic carbon peaks were at δ 132.69, 129.53, 127.35 and 126.25 ppm, while the ethyl carboxylate side chain peaks were at δ 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.

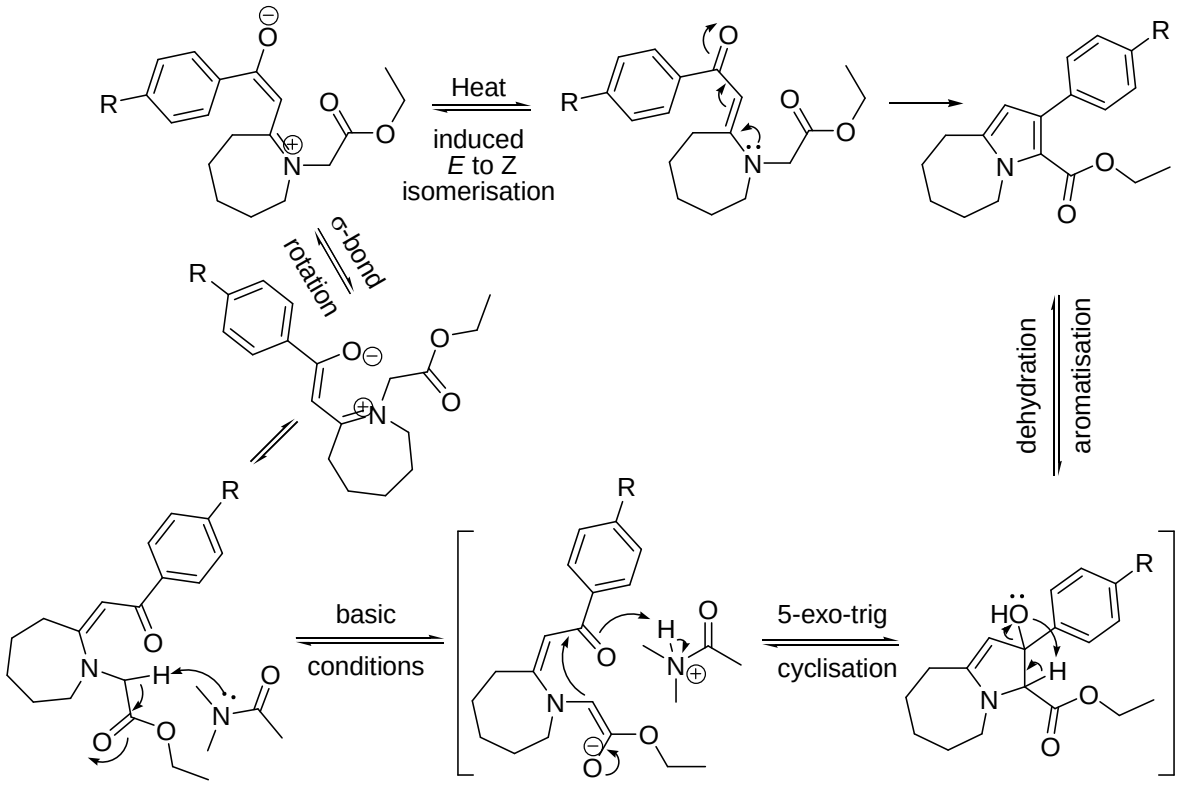
The IR spectrum of ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **223** had peaks at ν_{max} = 1692, 1598 and 1517 cm^{-1} for the ester carbonyl and alkene groups respectively. The ^{1}H NMR spectrum revealed two

doublet both with *J* = 8.8 Hz at δ 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 δ 5.96 ppm which a slight chemical field downshift from δ 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 δ 4.12 and 1.05 ppm, revealing the absence of α-protons to the ester carbonyl at δ 4.11 ppm of the vinylogous amide **216**. The ^{13}C NMR spectrum revealed the absence of the ketone carbonyl and ester α-carbon peaks at δ 185.8 and 55.7 ppm respectively from vinylogous amide **216** and the presence of pyrrole quaternary carbon peaks at δ 130.0 ppm (CH_2C=C*H*C) and 118.7 ppm (CCO_2) respectively. The vinyl carbon peak which was at δ 92.4 ppm for vinylogous amide **216** shifted downfield to δ 109.4 ppm for the pyrrole carbon peak (CH_2C=C*H*). The alkene quaternary carbon which was at δ 171.0 ppm for vinylogous amide **216** shifted upfield to δ 142.8 ppm for the pyrrole quaternary carbon. The aromatic carbon peaks were at δ 146.3, 144.5, 130.2, and 122.7 ppm, while the ethyl carboxylate side chain peaks were at δ 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 $C_{18}H_{21}N_2O_4^+$ with an exact calculated mass of 329.1496.

The IR spectrum of ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **224** had peaks at ν_{max} = 1774, 1580, 1469 cm^{-1} for the ester carbonyl and alkene groups respectively. The ^1H NMR spectrum revealed two doublets with unresolved fine coupling, both with *J* = 8.6 Hz at δ 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 δ 3.83 ppm. The new pyrrole ring proton singlet was at δ 5.90 ppm which is a slight chemical field downshift from δ 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 δ 4.10 and 1.06 ppm, revealing the absence of α-protons to the ester carbonyl at δ 4.11 ppm of the vinylogous amide **217**. The ^{13}C NMR spectrum revealed the absence of the ketone carbonyl and ester α-carbon peaks at δ 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_2C=CH*C*) and 129.8 ppm (*C*CO_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_2C=*C*H). 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 enaminones 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.[94,95]

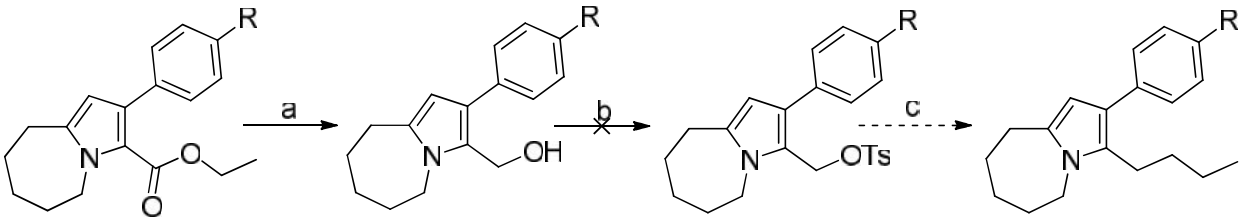


Scheme 46: Proposed mechanism for ring formation.

2.14 $LiAlH_4$ reduction of ethyl 2-(aryl)-6,7,8,9-tetrahydro-5*H*-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-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **222** or ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5*H*-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-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)methanol **225** and (2-(4-aminophenyl)-6,7,8,9-tetrahydro-5*H*-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-5*H*-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).



222, R = H
223, R = NO_2
225, R = H
226, R = NH_2
227
228

Scheme 47: *Reagents and conditions*: (a) $LiAlH_4$ (1 eq), THF, 6 - 12 h at 0 °C to r.t., **225** = 94%, **226 =** 68% R = NO_2; (b) TsCl (1.2 eq), DMAP (0.01 eq), Et_3N, CH_2Cl_2, 48 h at r.t.; (c) Grignard reaction.

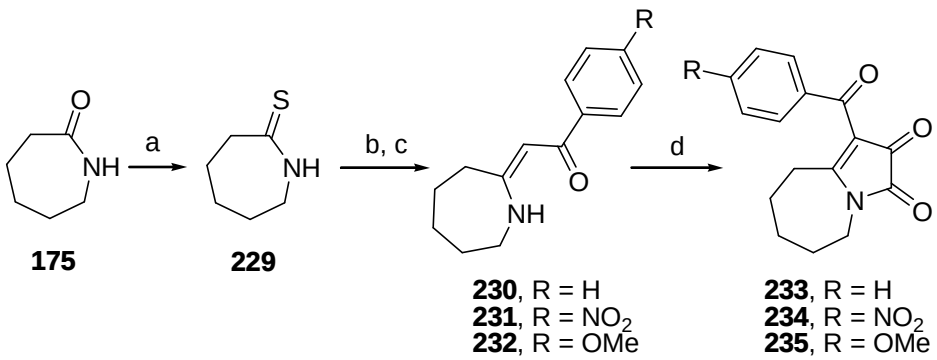
The IR spectrum of (2-phenyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)methanol **225** had peaks at ν_{max} = 3340 and 1443 cm^{-1} for the alcohol OH and alkene groups respectively. The ^1H NMR spectrum revealed the absence of the ethyl carboxylate peaks which were at δ 4.07 and 1.00 ppm and the presence of a singlet at δ 4.62 ppm for the methanol side chain's (CH_2) protons and a doublet at δ 3.50 ppm with *J* = 4.9 Hz for the OH proton. The aromatic multiplet was at δ 7.43 – 7.15 ppm, while the pyrrole proton singlet was at δ 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-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)methanol **226** had peaks at ν_{max} = 3450 and 1484 cm^{-1} for the alcohol OH and the alkene groups respectively. The ^1H NMR spectrum revealed the absence of ethyl carboxylate side chain proton peaks at δ 4.12 and 1.05 ppm and the presence of a triplet with *J* = 4.6 Hz at δ 5.14 ppm for the alcohol proton and a doublet with *J* = 3.9 Hz at δ 4.48 ppm for the methanol CH_2 protons. The spectrum showed two doublets with *J* = 8.4 and 8.3 Hz respectively at δ 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 δ 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-5*H*-pyrrolo[1,2-*a*]azepine-2,3-diones containing the pyrrolo[1,2-*a*]azepine nucleus

N*H* 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 N*H*-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 N*H*-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**.



Scheme 48: *Reagents and conditions*: (a) P_2S_5 (0.5 eq), HMDS (1.5 eq), CH_2Cl_2, overnight at r.t., **229** = 89 - 95%; (b) (i) Phenacyl bromide/ para-nitrophenacyl bromide/ para-methoxyphenacyl bromide (1.1 eq), MeCN, 5 min at r.t., (ii) TEA (1.1 eq), TPP (1.1 eq), MeCN, 24 h at r.t., **230** = 93%, **231** = 86%, **232** = 83 - 95%; (c) (i) Phenacyl bromide/ para-nitrophenacyl bromide/ para-methoxyphenacyl bromide (1.2 eq), MeCN, 5 min at r.t., (ii) TEA (1.2 eq), TEP (1.2 eq), MeCN, 24 h at r.t., **230** = 100%, **231** = 89%, **232** = 46%; (d) Oxalyl chloride (1 eq), THF, (7 h, 22 h and 18 h) respectively at reflux, **233** = 16%, **234** = 0%, **235** = 58%.

The melting point of azepane-2-thione **229** was 103 – 104 °C. The IR spectrum indicated the presence of the N*H* by an absorbance peak at ν_{max} = 3426 cm^{-1}. The ^{1}H NMR spectrum had a singlet at δ 9.56 ppm for the thioamide's N*H* proton. A doublet of doublets with *J* = 10.1, 5.9 Hz was observed at δ 3.88 ppm for the ε-protons to the thiocarbonyl group, while a multiplet at δ 3.04 – 2.90 ppm represented α-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 δ 209.4 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 ν_{max} = 3400 – 3200, 1740, 1586 and 1546 – 1436 cm^{-1} for the N*H* of the secondary enamine, carbonyl of the ketone, alkene and phenyl, respectively. The ^{1}H NMR spectrum revealed two singlets at δ 11.55 and 5.67 ppm for the secondary enamine and the vinyl proton correspondingly. The secondary enamine proton peak was greatly deshielded as compare to the thioamide's N*H* proton which was at δ 8.84 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 N*H* proton, thus strongly deshielding the

N-*H* proton. The chemical shift of the CH_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}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 $[M+H]^+$ 216.1393 matching molecular formula $C_{14}H_{18}NO^+$ with an exact calculated mass 216.1383. The spectra were comparable to those reported by Petterson *etal*.[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_{max} = 3400 – 3200, 1736, 1589 and 1474 cm^{-1} suggestive for the secondary amine N-H, carbonyl of the ketone, alkene and aromatic alkene respectively. The ^1H 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}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 $[M+H]^+$ 261.1240 which is representative of $C_{14}H_{17}N_2O_3^+$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_{max} = 3400 – 3200, 1744, 1577 and 1444 cm^{-1} for the presence of the secondary amine N*H*, carbonyl of the ketone, alkene and phenyl, respectively. The ^1H 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 δ 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 δ 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 δ 186.9, 161.2, 133.0, 128.3, and 113.0 ppm, while the methoxy carbon peak was at δ 54.9 ppm. The HRMS established $[M+H]^+$ 246.1506 equivalent to molecular formula $C_{15}H_{20}NO_2^+$ with exact calculated mass of 246.1489.

N*H* 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 N*H* 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-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione **233** in a poor 16% yield and 1-(4-methoxybenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione **235** in a good 58% yield respectively (**Scheme 48**, d). The reaction of N*H* 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 N*H* 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 α-carbon slightly nucleophilic when compared to the α-carbon of

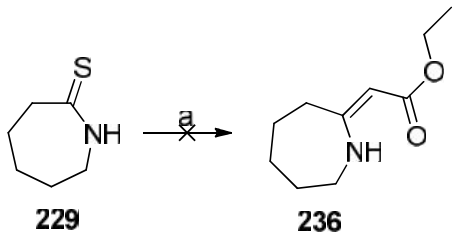
ketone in vinylogous amide **230**, which has a proton *para* to the ketone. The *para*-nitro group's ability to withdraw electrons renders the α-carbon of vinylogous amides **215** less nucleophilic, hence no desired product was observed in its case.

The IR spectrum of 1-benzoyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione **233** had major peaks at ν_{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-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione **235** had major peaks at ν_{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 N*H* 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.



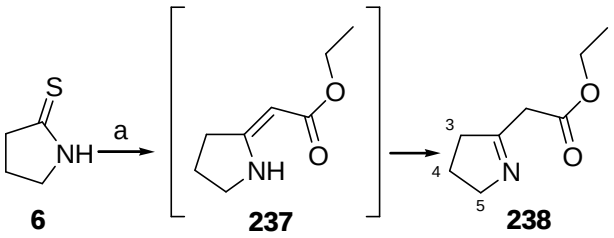
229 **236**

Scheme 49: (a) Table 17.

Table 17: Eschenmoser sulphide contraction reactions of thiolactam **229** with ethyl bromoacetate

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

On the contrary, the attempted synthesis of N*H* 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 N*H* hydride migration, resulting in an imine.



Scheme 50: *Reagents and conditions*: (a)(i) Ethyl bromoacetate (1.2 eq), MeCN, r.t., 21h, (ii) TEA (1.1 eq), TPP (1.1 eq), MeCN, r.t., over night, **238** = 78%.

The IR spectrum of ethyl 2-(4,5-dihydro-3*H*-pyrrol-2-yl)acetate **238** showed peaks at ν_{max} = 1721, 1422 cm^{-1} for the ester carbonyl and alkene groups in that order. The ^{1}H NMR spectrum revealed a singlet at δ 3.86 ppm, a quartert peak with *J* = 7.1 Hz at δ 4.01 ppm and a triplet with *J* = 7.1Hz at δ 1.09 ppm for the α-protons of the ethyl ester and ethyl protons of the ester. The pyrrolyl ring had a triplet with *J* = 7.2 Hz at δ 3.63 ppm, a triplet with *J* = 8.2 Hz at δ 2.44 ppm and a multiplet at δ 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 δ 168.9 ppm and ester α-carbon peak at δ 61.4 ppm confirming the newly formed C-C and imine bond. The ethyl ester carbon peaks were at δ 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.

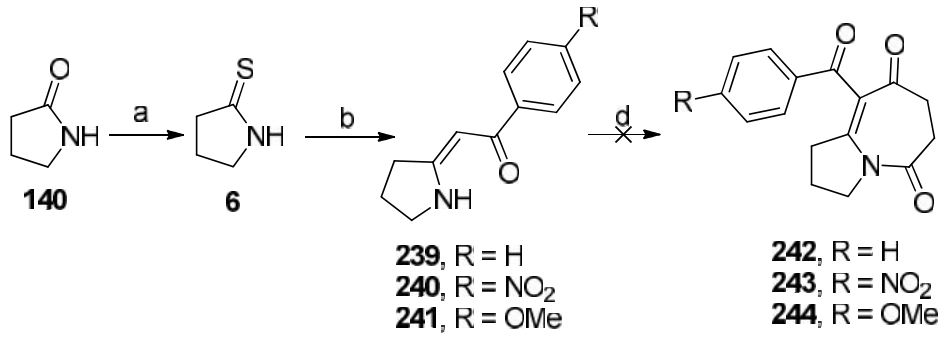
This finding is very strange indeed since there is no literature report of this transformation. It is worth noting the difference between the spectra of ethyl 2-(4,5-dihydro-3*H*-pyrrol-2-yl)acetate **238** and (*Z*)-ethyl 2-(pyrrolidin-2-ylidene)acetate **237** where the latter had peaks at 7.93, 4.52 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 α-protons next to the ester compared to one vinyl proton in N*H* vinylogous urethane **237**. In addition, carbon peak at position C-5 is less deshielded on imine **238** as compared to its counterpart on N*H* vinylogous urethane **237**, Table 18.

Table 18: Comparison of the ^{1}H and ^{13}C NMR spectra of compounds **238** and **237**

238 ^{1}H NMR (300 MHz)/ ppm	**237** ^{1}H NMR (250 MHz)/ ppm[15]	**237** ^{1}H NMR (500 MHz)/ ppm[14]
	7.93 (br, s, 1H)	7.90 (br, s, 1H, N*H*)
3.68 (s, 2H,CH_2CO_2)	4.52 (s, 1H)	4.52 (s, 1H, C=C*H*)
4.01 (q, *J* = 7.1 Hz, 2H, CH_2CH_3)	4.12 (q, *J* = 7.1 Hz, 2H)	4.09 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3)
3.63 (t, *J* = 7.2 Hz, 2H, NCH_2)	3.52 (t, *J* = 6.9 Hz, 2H)	3.50 (t, *J* = 6.9 Hz, 2H, NCH_2)
2.44 (t, *J* = 8.2 Hz, 2H, C=CCH_2)	2.58 (t, *J* = 7.7 Hz, 2H)	2.57 (t, *J* = 7.7 Hz, 2H, CH_2C=CH)
1.91 – 1.76 (m, 2H, NHCH$_2$CH_2)	1.97 (tt, *J* = 7.3, 7.3 Hz, 2H)	1.96 (tt, *J* = 7.3, 7.3 Hz, 2H, NCH$_2$CH_2)
1.09 (t, *J* = 7.1 Hz, 3H, O CH$_2$CH_3)	1.24 (t, *J* = 7.1 Hz, 3H)	1.24 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3)
238 ^{13}C NMR (75 MHz)/ ppm	**237** ^{13}C NMR (63 MHz)/ ppm	**237** ^{13}C NMR (125 MHz)/ ppm
170.1 (*C*=O)	170.3	170.8 (*C*=O)
168.9 (N=*C)*	166.1	166.4 (*C*=CH)
61.4 (*C*H$_2$CO$_2$)	76.2	76.6 (C=*C*H)
60.5 (O*C*H$_2$CH$_3$)	58.0	58.4 (O*C*H$_2$CH$_3$)
37.9 (N*C*H$_2$)	46.7	47.0 (N*C*H$_2$)
32.8 (N=C*C*H$_2$CH$_2$)	31.9	32.2 (*C*H$_2$C=CH)
23.7 (NCH$_2$*C*H$_2$)	21.7	22.0 (NCH$_2$*C*H$_2$)
14.0 (OCH$_2$*C*H$_3$)	14.4	14.7 (OCH$_2$*C*H$_3$)

2.17 Attempted synthesis of *para*-substituted (*E*)-9-benzoyl-2,3,6,7-tetrahydro-1*H*-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.



Scheme 51: *Reagents and Conditions*: (a) P_2S_5 (0.5 eq), HMDS (1.5 eq), CH_2Cl_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 (1.1 eq), TPP (1.1 eq), MeCN, 24 h at r.t., **239** = 47%, **240** = 95%, **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%; (d) Succinyl chloride (1 eq), THF, 22 h at reflux, **242** = 0%, **243** = 0%, **244** = 0%.

The melting point of pyrrolidin-2-thione **6** was 103 – 105 °C. The IR spectrum indicated the presence of the N*H* by an absorbance peak at ν_{max} = 3134 cm^{-1}. The ^{1}H NMR spectrum had a singlet at δ 8.59 ppm for the thioamides N*H* proton. A triplet peak with *J* = 7.2 Hz was observed at δ 3.67 ppm for the ε-protons to the thiocarbonyl group, while a triplet peak with *J* = 7.9 Hz was at δ 2.92 ppm represented α-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 δ 206.0 ppm with the remaining three carbon peaks also well represented. The spectra matched to those reported.[97]

The melting point of (*Z*)-1-phenyl-2-(pyrrolidin-2-ylidene)ethanone **239** was105 – 106 °C. The IR spectrum revealed peaks for the amine N*H*, carbonyl, alkene and aromatic groups at ν_{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 δ 10.28 and 5.81 ppm for the secondary enamine and the vinyl protons in that order. The aromatic multiplets were at δ 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 δ 2.75 ppm was for the γ-protons of the enaminone unit. Their chemical position suggests the *Z* isomer for vinylogous amide **239** since they are not deshielded through space by the ketone. The remainder of the peaks confirmed the

structure. The ^{13}C NMR spectrum revealed the absence of thiocarbonyl carbon peak at δ 206.0 ppm for thioamide **6** and presence of quaternary alkene carbon peak at δ 158.4 ppm. The ketone carbonyl carbon came in at δ188.14 ppm while the vinyl carbon was at δ 86.53 ppm. The aromatic group carbon peaks were at δ 149.0, 130.4, 128.2 and 127.0 ppm, while the pyrrolidinylidene ring carbon peaks were at δ 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*.[96]

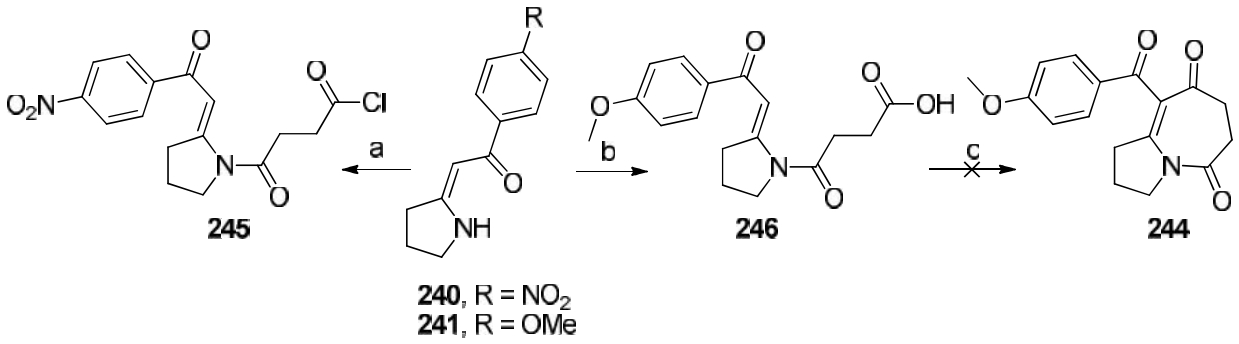
The melting point of (*Z*)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone **240** was 174 – 175 °C. The IR spectrum had peaks at ν_{max} = 3279, 1737, 1599, 1538 and 1476 cm^{-1} revealing the presence of the amine N*H*, carbonyl of ketone, alkene and aromatic nitro groups in that order. The ^1H NMR spectrum's significant two singlet peaks were at δ 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 δ 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 δ 4.11 ppm for the α-protons of the enaminone unit, a triplet with *J* = 7.1 Hz at δ 3.72 ppm for the γ-protons of the enaminone unit and a doublet of doublet with *J* = 14.8, 7.5 Hz at δ 2.11 ppm for the β-protons of the enaminone unit which confirmed the structure of the molecule. The pyrrolidinylidene ring α and γ-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 α-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 γ-protons to the enaminone unit if vinylogous amide **240** was an *E* isomer to which was not the case. The ^{13}C NMR revealed the newly formed quaternary alkene carbon at δ 170.6 ppm, replacing thioamide carbonyl carbon which was at δ 206.0 ppm for thioamide **6**. The ketone and vinyl carbon peaks were at δ 190.2 and δ 87.0 ppm correspondingly confirming the formation of the enaminone unit. The nitro aromatic carbon peaks were at δ 150.9, 148.6, 127.9 and 123.5 ppm, while the pyrrolidinylidene ring carbon peaks were at δ 48.0, 33.1 and 30.9 ppm. The HRMS established $[M+H]^+$ 233.0928

indicative for a molecule with molecular formula $C_{12}H_{13}N_2O_3^+$ 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 ν_{max} = 3400 – 3200, 1734,1576 and 1434 cm^{-1} representative of the amine N*H*, ketone carbonyl, alkene and aromatic alkene groups respectively. The ^{1}H NMR spectrum revealed at δ 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 δ 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 δ 3.84 ppm. The triplet with *J* = 7.8 Hz at δ 2.73 ppm was for the γ-protons of the enaminone unit suggestive of the *Z* isomer. The ^{13}C NMR spectrum had peaks at δ 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 δ 192.4 ppm and aromatic carbons were at δ 163.8, 130.9, 128.7 and 113.8 ppm, while the methoxy carbon peak was at δ 60.6 ppm. The remaining peaks at δ 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 $C_{13}H_{16}NO_2^+$ 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-(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.



Scheme 52: *Reagents and Conditions*: (a) Succinyl chloride (1.2 eq), THF, 2 h at reflux, overnight at r.t., **245** 25%; (b) Succinyl chloride (1.28 eq), THF, 24 h at r.t., **246** = 40%; (c) K_2CO_3 (2 eq), acetic anhydride (1.1 eq), THF, 24 h at reflux, **244** = 0%.

The IR spectrum of (*E*)-4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoyl chloride **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 ^{1}H 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 ^{13}C NMR spectrum revealed peaks at δ

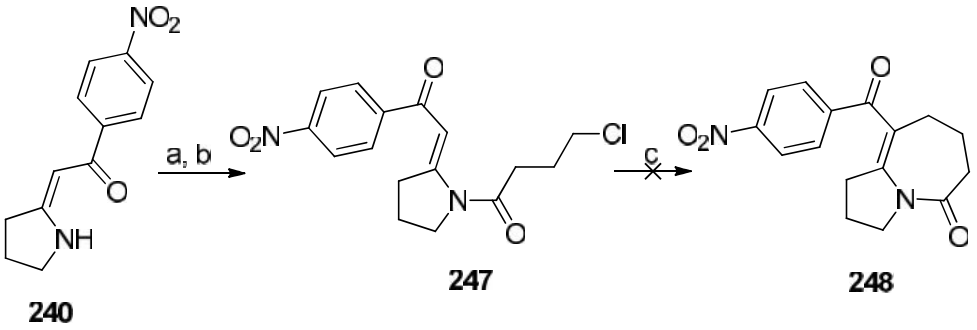
178.3, 177.2, 37.1 and 28.2 ppm for the amide carbonyl carbon, the acid chloride carbonyl carbon and the β and α carbons of the amide in that order. The ketone carbonyl, the quaternary alkene carbon and vinyl carbon peaks were at δ 198.8, 177.2 and 97.6 ppm respectively. The remaining pyrrolidinyl ring 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_{max} = 3401, 1696, 1622, 1443 cm^{-1} representing the carboxylic acid OH, carbonyl groups, alkene and aromatic groups in that order. The ^{1}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 ^{13}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.



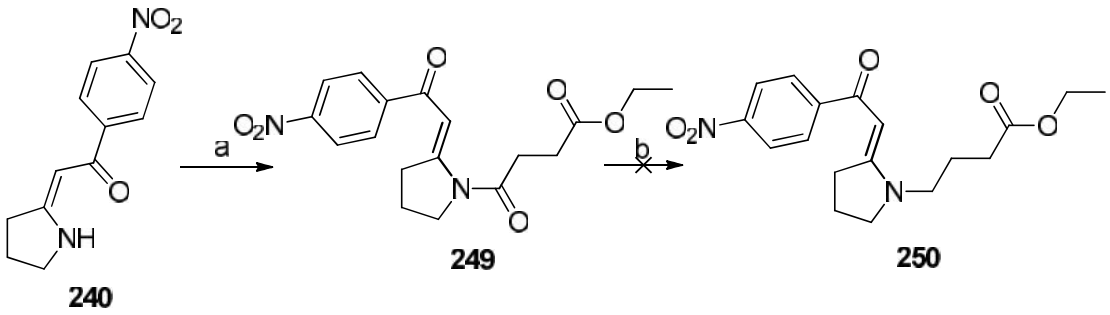
Scheme 53: *Reagents and Conditions*: (a) 4-Chlorobutanoyl chloride (1.22 eq), THF, 20 h at reflux, **247** = 74%; (a) 4-Chlorobutanoyl chloride (1.1 eq), THF, 19 h at reflux; (c) NaI (1.2 eq), MeCN, 24.5 h at reflux, **248** = 0%.

The IR spectrum of (*E*)-4-chloro-1-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)butan-1-one **247** had peaks at ν_{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 δ 10.45 ppm for vinylogous amide **240** and the presence of triplet peak with *J* = 6.0 Hz at δ 3.71 ppm and a triplet peak with *J* = 6.8 Hz at δ 2.73 ppm for the γ and α-protons of the amide respectively. The vinyl singlet was more deshielded at δ 8.23 ppm as compared to that of vinylogous amide **240** which was at δ 5.80 ppm owing to the enaminone-amide system. The molecule had an *entgegen* geometry as shown by a through space interaction between γ-protons of the ketone (a triplet of doublets with *J* = 7.8, 1.6 H at δ 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 δ 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 δ 172.7, 44.3 and 34.1 ppm for the amide carbonyl, the γ and β-carbons of the amide respectively. The vinyl carbon peak was at δ 103.0 ppm while the ketone carbonyl carbon was at δ189.6 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).

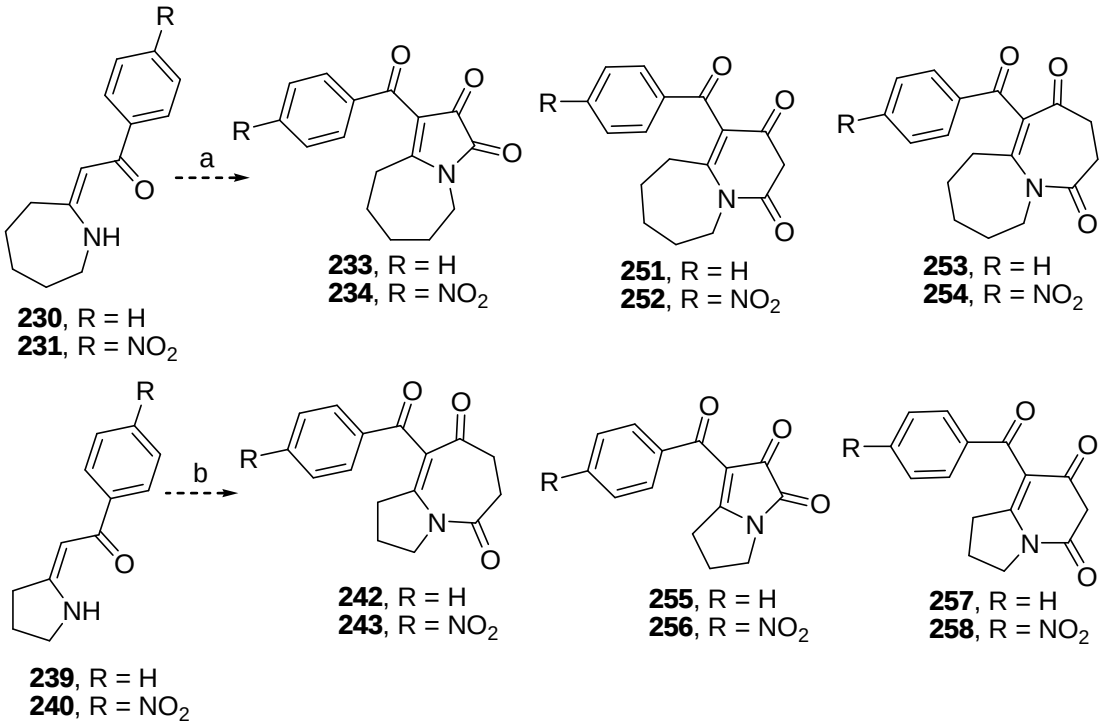


Scheme 54: *Reagents and Conditions*: (a) 4-Chloro-4-oxobutanoate (1.1 eq), THF, 18 h at reflux, **249** = 90%; (b) BH_3.THF(1M), THF, overnight at r.t., **250** = 0%.

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 ν_{max} = 1745 and 1532 cm^{-1} 1745 and 1532 for the amide, ester, ketone carbonyl and alkene groups. The ^{1}H NMR spectrum revealed the absence of the N*H* 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 ^{13}C 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 13 C 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 $[M+ H_2O+H]^+$ 379.1510 for a monohydrated molecule of molecular formula $C_{18}H_{23}N_2O_7^+$ 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.



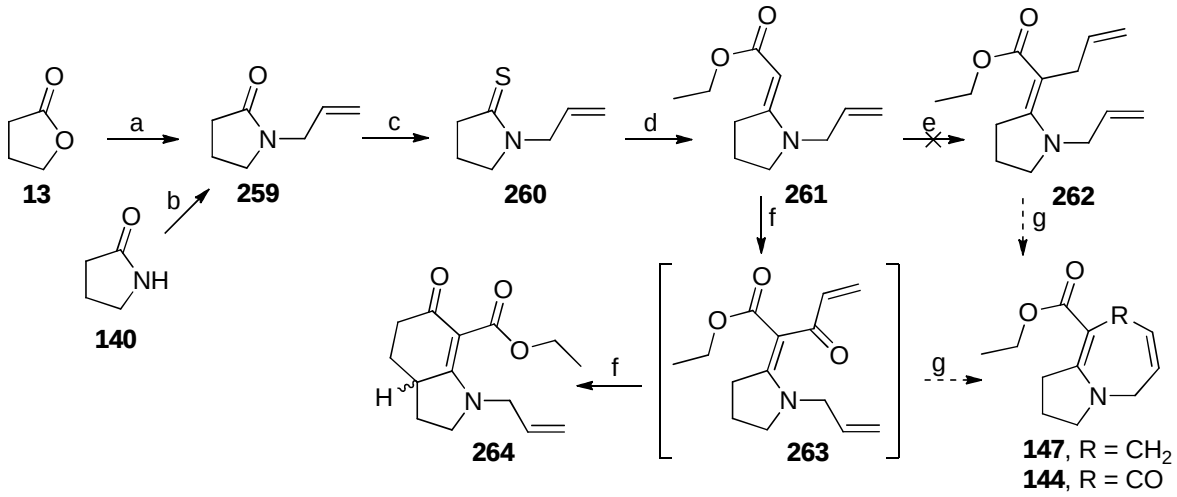
Scheme 55: *Reagents and Conditions*: (a) (i) Oxalyl chloride (1 eq)/ (ii) malonyl chloride (1 eq)/ succinyl chloride (1eq), THF, 18 h at r.t., 23 h at reflux, **233** = 16%, **234** = 0%, **251** = 0%, **252** = 0%, **253** = 0%, **254** = 0%; (b) (i) Oxalyl chloride (1 eq)/ (ii) malonyl chloride (1 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-1*H*-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.*[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.[178]



Scheme 56: *Reagents and Conditions*: (a) (i) Allyl amine (1 eq), neat, 150 W, 30 min at 220 ▪C, **259** = 79%; (ii) Allyl amine (1 eq), neat, overnight at 220 ▪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_2S_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 ν_{max} = 1691 and 1640 cm^{-1}, representative of the amide carbonyl and the alkene groups. The ^{1}H NMR spectrum confirmed the formation of a tertiary amide by a doublet with *J* = 6.0 Hz at δ 3.50 ppm for the (NC*H*$_2$CH) protons, a double of doublet of triplets with *J* = 17.0, 9.9, 6.0 Hz at δ 5.35 ppm for the (NCH$_2$C*H*) protons and a doublet of doublets with *J* = 11.1, 6.2 Hz at δ 4.81 ppm for the (CH=C*H*$_2$) protons of the allyl side chain, which did not give the expected doublet of doublet of doublets system due to poor resolution. The pyrrolidinone ring protons were represented by a triplet with *J* = 7.1 Hz at δ 2.99 ppm for the γ-protons of the amide and a triplet with *J* = 8.1 Hz at δ 2.00 ppm for the α-protons of the amide. The ^{13}C NMR spectrum showed the amide carbon peak at δ 174.3 ppm and the alkene carbon peaks at δ 132.2 and δ 117.2 ppm for (*C*H=CH$_2$) and (CH=*C*H$_2$) respectively. The ^{1}H NMR of lactam **259** obtained from a 300 MHz NMR in $CDCl_3$ was similar to literature values reported by Tokunaga *et al*. obtained from a 400 MHz NMR in $CDCl_3$ with a difference of δ 0.39 ppm in chemical shift of signals (Table 19).

Table 19: ^{1}H NMR spectroscopic data for **259** compared with literature ^{1}H NMR spectroscopic data[178]

^{1}H NMR **259**/ ppm	^{1}H NMR **259**/ ppm (Lit.)
5.35 (ddt, *J* = 17.0, 9.9, 6.0 Hz)	5.69 – 5.78 (ddt, *J* = 17.2, 10.0, 6.0 Hz, C*H*=CH_2)
4.81 (dd, *J* = 11.1, 6.2 Hz)	5.19 – 5.21 (m, CH=C*H*H); 5.15 – 5.18 (m, CH=CH*H*)
3.50 (d, *J* = 6.0 Hz)	3.89 (d, *J* = 8.0 Hz, NC*H*$_2$CH=CH_2)
2.99 (t, *J* = 7.1 Hz)	3.35 (t, *J* = 7.2 Hz, NC*H*$_2$$CH_2$)
2.00 (t, *J* = 8.1 Hz)	2.41 (t, *J* = 8.0 Hz, COC*H*$_2$)
1.73 – 1.56 (m)	1.98 – 2.07 (m, NCH_2C*H*$_2$)

Lactam **259** was reacted with phosphorus pentasulphide in dichloromethane at room temperature for 24 hours, achieving 1-allylpyrrolidine-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-allylpyrrolidine-2-thione **260** revealed the absence of the amide carbonyl peak while maintaining a peak at ν_{max} = 1624 cm^{-1} for the alkene group. The ^{1}H NMR spectrum showed a downfield shift of the allyl side chain proton peaks to δ 4.39, 5.81 and 5.33 – 5.20 ppm when compared to those from lactam **259** at δ 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 δ 3.78 – 3.67 and 3.02 ppm as compared to those from lactam **259** at δ 2.99 and 2.00 ppm respectively. The ^{13}C NMR spectrum revealed the absence of the amide carbonyl carbon peak at δ 174.3 ppm and the presence of the thioamide carbonyl carbon peak at δ 201.1 ppm. The HRMS found $[M+H]^+$ 142.0693 representative of a molecular formula $C_7H_{12}NS^+$ 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-

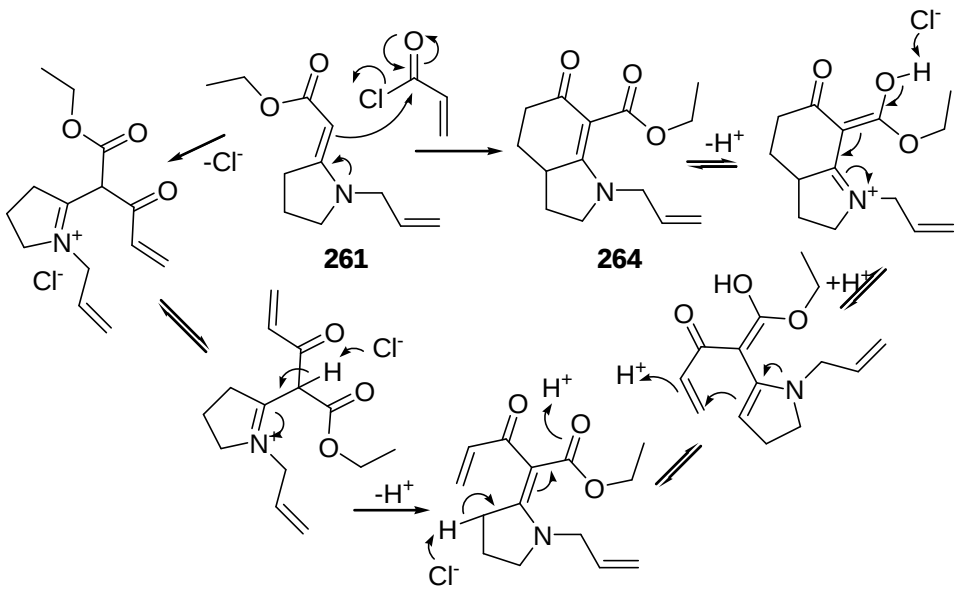
(1-allylpyrrolidin-2-ylidene)acetate **261** in good yields between 70 – 83% (**Scheme 55**, d).

The IR spectrum of (*E*)-ethyl 2-(1-allylpyrrolidin-2-ylidene)acetate **261** revealed peaks at ν_{max} = 1666 and 1514 cm^{-1} for the ester carbonyl and the alkene groups respectively. The ^{1}H NMR spectrum showed a singlet at δ 4.52 ppm for the vinyl proton, a quartet and triplet both with *J* = 7.1 Hz at δ 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 δ 201.1 and the presence of the quaternary alkene carbon peak at δ 164.4 ppm. The unsaturated ethyl ester carbon peaks were at δ 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 $[M+H]^+$ 196.1341 for molecular formula $C_{11}H_{18}NO_2^+$ 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 (6*Z*,9*E*)-ethyl 2,3,5,8-tetrahydro-1*H*-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-1*H*-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*)-ethyl 2-(1-allylpyrrolidin-2-ylidene)-3-oxopent-4-enoate **263** which would have been used in a ring closing metathesis reaction to form (6*Z*,9*E*)-ethyl 8-oxo-2,3,5,8-tetrahydro-1*H*-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**.

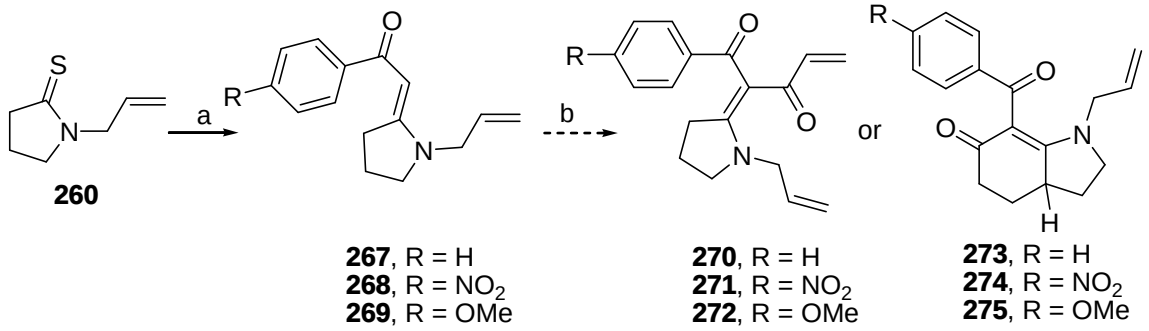


Scheme 57: Proposed cyclisation mechanism.

The IR spectrum of 1-allyl-6-oxo-2,3,3a,4,5,6-hexahydro-1*H*-indole-7-carboxylate **264** showed peaks at ν_{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 δ 3.58 ppm for the ε-protons of the ketone group, a multiplet at δ 3.47 ppm for the γ-protons of the ketone, a multiplet at δ 2.90 – 2.69 ppm for the δ-protons of the ketone and two multiplets at δ 2.57 – 2.36 and 2.32 – 2.02 ppm for the α and β-protons of the ketone. The doublet of doublet of doubles with *J* = 22.4, 10.8, 5.6 Hz at δ 5.78 ppm, and the two multiplets at δ 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 δ 4.27 – 4.15 ppm and a

triplet with J = 7.1 Hz at δ 1.29 ppm. The ^{13}C NMR revealed carbon peaks at δ 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 δ 32.9, 26.3, 38.6, 24.0 and 51.4 ppm were for α, β, γ, δ and ε-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-methoxyphenacyl 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.

The IR spectrum of (*E*)-2-(1-allylpyrrolidin-2-ylidene)-1-phenylethanone **267** had peaks at ν_{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 δ 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 ν_{max} = 1745, 1585 and 1402 cm^{-1} for the ketone and alkene groups in that order. The ^1H 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 $C_{15}H_{17}N_2O_3^+$ 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 ν_{max} = 1743, 1571 and 1423 cm^{-1} for the ketone carbonyl and alkene groups respectively. The ^1H 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

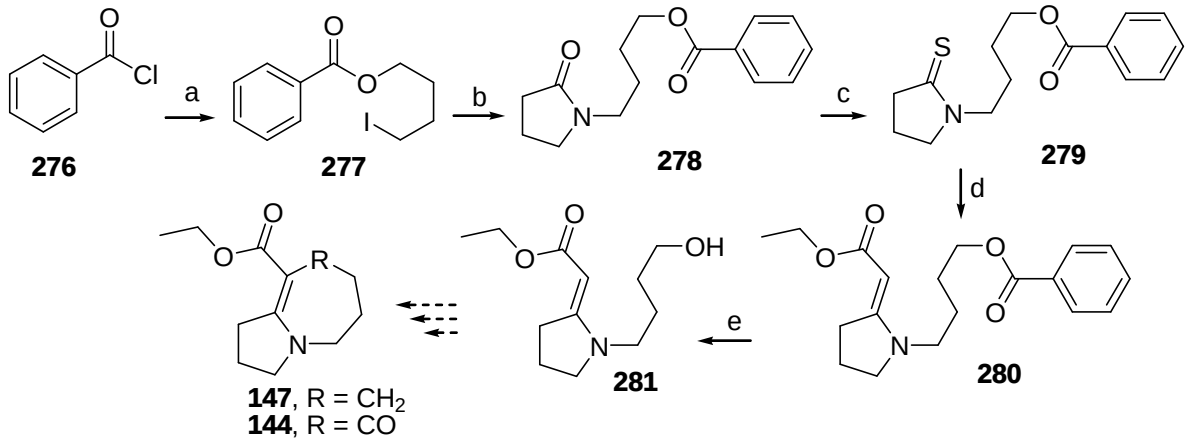
methoxy singlets were at δ 5.73 and 3.82 ppm, confirming the formation of the vinylogous amide. The allyl group and pyrrolidine ring peaks were observed demonstrating the molecule is intact. The ^{13}C NMR spectrum showed the absence of the thioamide carbonyl carbon peak at δ 201.1 ppm and the presence 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 specta 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-iodobutan-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-pyrrolidinone **140** and 4-Iodobutyl benzoate **277** followed by saponification of the benzoyl ester.[100] 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-1*H*-pyrrolo[1,2-*a*]azepine-9-carboxylate **147**.



Scheme 59: *Reagents and Conditions*: (a) Tetrahydrofuran (1 eq), NaI (1 eq), MeCN, r.t., overnight, **277** = 66%; (b) 2-pyrrolidinone **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 bromacetate (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/H_2O (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-1*H*-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 ν_{max} = 1721 and 1495 cm^{-1} for the ester carbonyl and benzyl aromatic groups. The ^{1}H NMR spectrum revealed three multiplets at δ 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 δ 4.32 ppm for the OCH_2 protons and a triplet with *J* = 6.7 Hz at δ 3.23 ppm for the ICH_2 protons. The ^{13}C NMR revealed carbon peaks at δ 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 δ 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 20: Literature comparison of ^{1}H and ^{13}C NMR spectra of 4-iodobutyl benzoate **277**

^{1}H NMR/ ppm	^{1}H NMR (Lit.)/ ppm[100,101]	^{13}C NMR/ ppm	^{13}C NMR (Lit.)/ ppm[100,101]
8.13 – 7.42 (m)	8.05 – 7.40 (m, aromatic)	166.5	166.4 (CO_2)
4.32 (t, *J* = 6.1 Hz)	4.33 (t, *J* = 6.0 Hz, OCH_2)	133.0	132.8 *para*-carbon
3.23 (t, *J* = 6.7 Hz)	3.24 (t, *J* = 6.0 Hz, ICH_2)	130.1	130.0 (CHC(CO_2)CH)
2.06 – 1.78 (m)	1.99 – 1.85 (m, $ICH_2CH_2CH_2$)	129.6	129.4 *ortho*-carbons
		128.4	128.2 *meta*-carbons
		63.9	63.6 (OCH_2)
		30.1	29.9 (ICH_2CH_2)
		29.7	29.5 (OCH_2CH_2)
		6.3	6.0 (ICH_2)

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 ν_{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 oxopyrrolidinyl ring multiplet at δ 3.26 – 3.20 ppm for the γ-protons of the lactam and a triplet with *J* = 8.1 Hz at δ 2.23 ppm for the α-protons of the lactam. The benzoate ester was represented by a doublet with *J* = 7.2 Hz at δ 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 δ 4.22 ppm for CO_2CH_2 protons and a multiplet at δ 3.26 – 3.20 ppm for the $NCH_2CH_2CH_2CH_2$ protons. The ^{13}C NMR spectrum revealed peaks at δ 173.3 and 164.8 ppm for the amide and the ester carbonyl carbons. The aromatic carbon peaks were at δ 131.4, 128.8, 128.0 and 126.9 ppm. The significant butyl chain peaks were at δ 62.9 and 40.5 ppm for CO_2CH_2 and $NCH_2CH_2CH_2CH_2$ carbons. The oxopyrrolidinyl ring's significant peaks were at δ 45.5 and, 29.5 ppm for the γ-carbon and α-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 ν_{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 δ 173.3 ppm and presence of thioamide carbonyl carbon peak at δ 201.0 ppm.

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

278 ^{1}H NMR/ ppm	**279** ^{1}H NMR/ ppm	**278** ^{13}C NMR/ ppm	**279** ^{13}C NMR/ ppm
7.92 (d, *J* = 7.2 Hz)	8.04 (d, *J* = 7.4 Hz, C*H*C(CO_2)C*H*)	173.3 (NCO)	201.0 (NCS)
7.43 (t, *J* = 7.3 Hz)	7.56 (t, *J* = 7.4 Hz, CHC*H*CH)	164.8	166.6 (*C*O_2)
7.32 (t, *J* = 7.6 Hz)	7.44 (t, *J* = 7.6 Hz, C*H*CHC*H*)	131.4	133.0 (CH*C*HCH)
4.22 (t, *J* = 6.2 Hz)	4.38 – 4.34 (m, OCH_2)	128.8	130.1 (CH*C*(CO_2)CH)
3.26 – 3.20 (m)	3.80 – 3.88 (m, NC$H_2$$CH_2$$CH_2$$CH_2$O)	128.0	129.5 (*C*HC(CO_2)*C*H)
3.26 – 3.20 (m)	3.73 (t, *J* = 6.8 Hz, NC$H_2$$CH_2$$CH_2$CS)	126.9	128.4 (*C*HCH*C*H)
2.23 (t, *J* = 8.2 Hz)	3.03 (t, *J* = 7.9 Hz, CSCH_2)	62.9	64.4 (CO_2*C*H_2)
		45.5	54.7 (N*C*$H_2$$CH_2$$CH_2$CS)
		40.5	47.5 (N*C*$H_2$$CH_2$$CH_2$$CH_2$O)
		29.5	45.0 (CS*C*H_2)

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 ν_{max} = 1728, 1567 and 1514 cm^{-1} for the ester carbonyl, alkene and aromatic groups. The ^{1}H NMR spectrum revealed a singlet at δ 4.55 ppm for the vinyl proton and a quartet and a triplet, both with *J* = 7.1 Hz at δ 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.

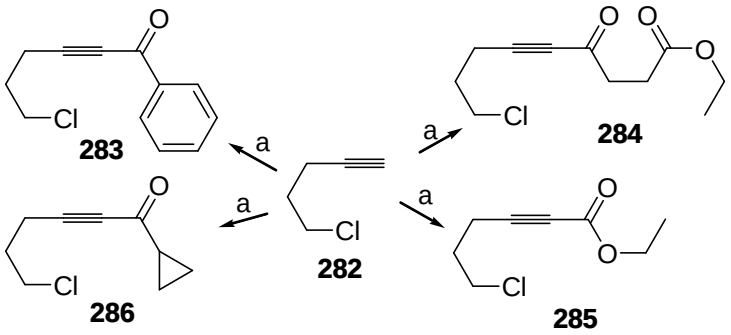
(*E*)-4-(2-(2-Ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butyl benzoate **280** was subjected to saponification reaction using potassium hydroxide in a 20:1 solution of methanol and water at room temperature for 1.5 hours to achieve (*E*)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate **281** in 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 ν_{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 δ 4.26 ppm for the alcohol proton,

while the triplet with *J* = 6.1 Hz at δ 3.61 ppm was for the C*H*$_2$OH protons. The unsaturated ester's presence was shown by a singlet at δ 4.47 ppm for the vinyl proton and a quartet and triplet, both with *J* = 7.1 Hz at δ 4.03 and 1.20 ppm for the ethyl ester side chain, showing the chemoselectivity of the reaction. The ^{13}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 δ169.8, 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 δ 62.0 ppm for the *C*H$_2$OH carbon.

2.21 Synthesis of chloroalkyne esters and amides

A new strategy involving a S_N2/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 ω-halo-α,β-alkynoates and amines, resulting in formation of desired enaminones in a single operation. A variety of ω-chloro-α,β-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-yne with butyllithium in tetrahydrofuran at –78 °C to –20 °C for 20 minutes followed by addition of benzoyl chloride, ethyl 4-chloro-4-oxobutanoate (1 eq), ethyl chloroformate or cyclopropanecarbonyl chloride at –20 °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.



Scheme 60: *Reagents and Condition*: (a) (i) BuLi (1 eq), -78 °C to -20 °C at 35 min; (ii) Benzoyl chloride (1 eq)/ ethyl 4-chloro-4-oxobutanoate (1 eq)/ ethyl carbonochloridate/ cyclopropanecarbonyl chloride (1 eq), -20 °C to r.t. for 20 h, **283** = 64%, **284** = 28%, **285** = 99% and **286** = 68%.

The IR spectrum of ethyl 6-chlorohex-2-ynoate **285** had peaks at ν_{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 δ 4.22 and 1.31 ppm. The chlorohexyne chain's major peaks were a triplet with *J* = 6.2 Hz at δ 3.66 ppm for the ε-protons of the ester, and a triplet with *J* = 6.9 Hz at δ 2.55 ppm for the γ-protons of the ester. The ^{13}C NMR spectrum showed peaks at δ 153.5, 87.0 and 73.9 ppm for the ester carbonyl and the β and α 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 ν_{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 δ 8.20 – 8.10 ppm for the *ortho*-protons and a multiplet at δ 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 δ 3.72 ppm for the ε-protons of the ketone and a triplet with *J* = 6.9 Hz at δ 2.73 ppm for the δ-protons of the ketone. The ^{13}C NMR spectrum revealed the phenyl carbon peaks at δ 136.8, 134.1, 129.6, 128.6 ppm, while the ketone peak at δ 178.0 ppm. The alkyne carbon peaks were at δ 94.1 and 80.3 ppm for the β and α alkyne quaternary carbons of the ketone respectively, while the haloalkane carbon peak was at δ 43.4 ppm illuminated the structure. The NMR spectra agreed with the literature values from Wang *et al*. (Table 22)[108]

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

^{1}H NMR/ ppm	^{1}H NMR (Lit.)/ ppm[108]	^{13}C NMR/ ppm	^{13}C NMR (Lit.)/ ppm[108]
8.20 – 8.10 (m)	8.12 (m, C*H*C(CO)C*H*)	177.98	178.1 (*C*O)
7.72 – 7.44 (m)	7.60 - 7.48 (m, C*H*C*H*C*H*)	136.76	136.8 (CH*C*(CO)CH)
3.72 (t, *J* = 6.2 Hz)	3.71 (t, *J* = 6.2 Hz, CH_2Cl)	134.07	134.2 (CH*C*HCH)
2.73 (t, *J* = 6.9 Hz)	2.72 (t, *J* = 6.9 Hz, CH_2CH_2Cl)	129.57	129.7 (*C*HCH*C*H)
2.20 – 2.07 (m)	2.13 (m, CH_2CΞC)	128.58	128.7 (*C*HC(CO)*C*H)
		94.14	94.3 (CH$_2$*C*ΞC)
		80.25	80.3 (CH$_2$CΞ*C*)
		43.37	43.5 (*C*H$_2$Cl)
		30.50	30.6 (*C*H$_2$CH$_2$Cl)
		16.65	16.7 (*C*H$_2$CΞC)

The IR spectrum of 6-chloro-1-cyclopropylhex-2-yn-1-one **286** revealed ν_{max} = 2218 and 1651 cm^{-1} for alkyne and ketone carbonyl groups. The ^{1}H 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 ^{13}C 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).[108]

Table 23: ^{1}H and ^{13}C literature NMR spectroscopic data comparison for 6-chloro-1-cyclopropylhex-2-yn-1-one **286**

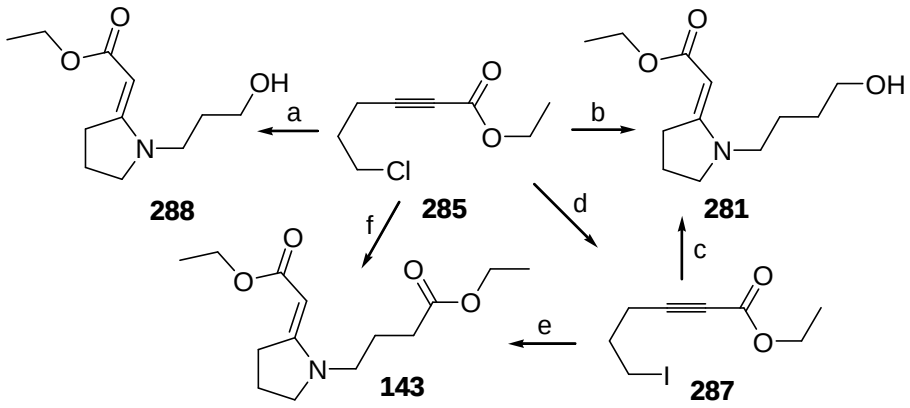
^{1}H NMR/ ppm	^{1}H NMR (Lit.)/ ppm	^{13}C NMR/ ppm	^{13}C NMR (Lit.)/ ppm
3.65 (t, *J* = 6.2 Hz)	3.62 (t, *J* = 6.2 Hz, C*H*$_2$Cl)	188.3	188.4 (*C*O)
2.57 (t, *J* 6.9 Hz)	2.54 (t, *J* = 6.9 Hz, C*H*$_2$CH$_2$Cl)	91.4	91.4 (CH$_2$*C*ΞC)
2.11 – 1.96 (m)	2.00 (m, C*H*$_2$CΞC, COC*H*)	79.6	79.6 (CH$_2$CΞ*C*)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

The IR spectrum of ethyl 9-chloro-4-oxonon-5-ynoate **284** had peaks at ν_{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 δ 4.15 and 1.26 ppm for the ethyl side chain, while a triplet with *J* = 6.7 Hz at δ 2.89 ppm for the β-protons of the ester and a triplet peak with *J* = 6.6 Hz at δ 2.63 ppm for the α-protons of the ester. The chloropropyl side chain major peaks were a triplet with *J* = 6.2 Hz at δ 3.65 ppm for the ε-protons of the ketone and triplet with *J* = 6.9 Hz at δ 2.59 ppm for the γ-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 iodode 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 iodode, 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: *Reagents and Conditions*: (a) 3-Amino-1-propanol (1 eq), K_2CO_3 (2 eq), NaI (2 eq), 4Å molecular sieves, MeCN, 24 h at reflux, **288** = 81%; (b) 4-Amino-1-butanol (1 eq), K_2CO_3 (2 eq), NaI (2 eq), 4Å molecular sieves, MeCN, 48 h at reflux, **281** = 70%; (c) 4-Amino-1-butanol (0.83 eq), Cs_2CO_3 (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), Cs_2CO_3 (2 eq), NaI (2 eq), 4Å molecular sieves, MeCN, 22 h at reflux, **143** = 59%; (f) ethyl-4-aminobutyrate hydrochloride (1 eq), K_2CO_3 (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 δ 4.22 and 1.31 ppm respectively. The iodohexyne side chain was shown by two triplets with J = 6.2 and 6.7 Hz at δ 3.66 and 3.29 ppm respectively for the ε-protons of the ester and two triplets with J = 7.0 and 6.9 Hz at δ 2.55 and 2.51 ppm for the γ-protons of the ester. The ^{13}C NMR spectrum showed peaks at δ 153.5, 87.0, and 86.7 ppm for the ethyl ester carbonyl carbon and β and α-carbons of the ethyl ester respectively, while the haloalkane carbon peak was at δ 4.35 ppm. The ^{1}H NMR spectrum was similar to literature reported values by Pier *et al*. (Table 24).[109]

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

^{1}H NMR/ ppm	^{1}H NMR (Lit.)/ ppm
4.22 (q, J = 7.1 Hz)	4.17 (q, J = 8 Hz, CH_2CH$_3$)
3.66, 3.29 (t, J = 6.2 Hz); (t, J = 6.7 Hz)	3.24 (t, J = 8 Hz, CH_2I)
2.55, 2.51 (t, J = 7.0 Hz); (t, J = 6.9 Hz)	2.45 (t, J = 8 Hz, CH_2CΞC)
2.14 – 1.98 (m)	2.02 (m, CH_2CH$_2$I)
1.31 (t, J = 7.1 Hz)	1.26 (t, J = 8 Hz, CH$_2$CH_3)

The IR spectrum of (*E*)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate **288** had peaks ν_{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 δ 4.55 ppm for the vinyl proton, a quartet and a triplet, both with J = 7.1 Hz at δ 4.08 and 1.25 ppm respectively for the ethyl side chain protons. The propanol side chain presented with a singlet at δ 2.32 ppm for the OH proton, a triplet with J = 6.0 Hz at δ 3.67 ppm for CH_2OH protons and a triplet with J = 7.1 Hz for NCH_2CH$_2$CH$_2$OH protons. The pyrrolidinyl ring was shown by a triplet with J = 7.2 Hz at δ 3.31 ppm for the γ-protons of the enaminone and a triplet with J = 7.4 Hz at δ 3.15 ppm for the α-protons of the enaminone. The ^{13}C NMR spectrum showed peaks at δ 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 δ 77.4 ppm. The propanol side chain carbon peaks were at δ 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 δ 165.1 ppm for the alkene

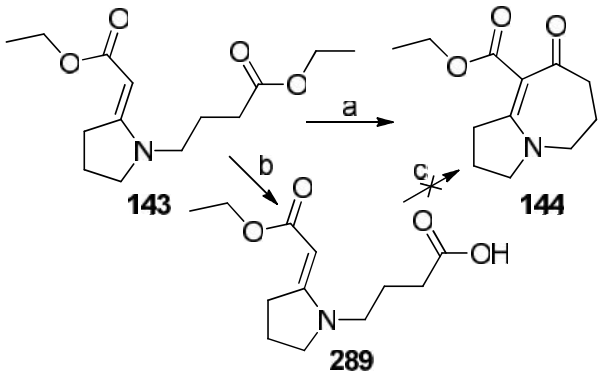
quaternary, at δ 43.1 and 29.0 ppm for the γ and α- carbons of the enaminone respectively.

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.



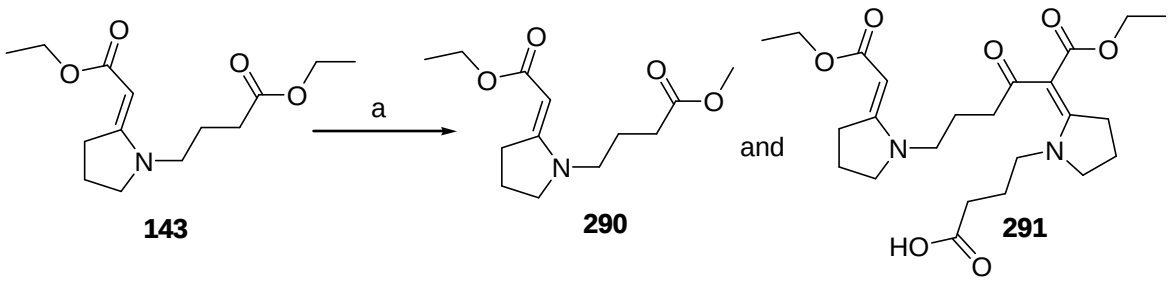
Scheme 62: *Reagents and Conditions*: (a)(i) 1M KOH (18 eq), MeOH, 30 min at reflux, (ii) K_2CO_3 (2 eq), acetic anhydride (1 eq), MeCN, 18 h at reflux, **144** = 5% (b) KOH (1.2 eq), THF: H_2O (3:2), overnight at r.t., **289** = 100%; (c) K_2CO_3 (2 eq), acetic anhydride (1 eq), MeCN, 41 h at reflux, **144** = 0%.

The IR spectrum of (*E*)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-9-carboxylate **144** IR spectrum had peaks at ν_{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 δ 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 δ 3.50 – 3.39 and 2.74 – 2.62 ppm for the γ and α-protons of the enaminone. The triplets with *J* = 7.1 Hz and *J* = 7.8 Hz at δ 3.65 and 3.02 ppm respectively were for the γ and α-protons of the ketone finally elucidating the molecular structure. The ^{13}C NMR showed the quaternary peaks at δ 196.2, 168.9, 168.9 and 103.0 ppm for the ketone carbonyl, ester carbonyl, and alkene β and α-carbons respectively. This revealed the loss of the saturated ester carbonyl and vinyl carbons. The pyrrolidinyl ring carbon peaks were at δ 50.9 and 35.5 ppm for the γ and α-carbons of the enaminone, while the ethyl side chain carbons were at δ 60.3 and 14.3 ppm. The remaining peaks at δ 57.3 and 42.7 ppm for the γ and α of the ketone confirmed structure of the molecule.

The IR spectrum of (*E*)-4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoic acid **289** had peaks at ν_{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 δ 4.54 ppm for the vinyl proton, a quartet and triplet, both with *J* = 7.1 Hz at δ 4.09 and 1.25 ppm for the unsaturated esters ethyl side chain, while the pyrrolidinyl ring presented with a multiplet at δ 3.27 – 3.19 and a triplet with *J* = 7.8 Hz at δ 3.15 ppm for the γ and α-protons of the enaminone. The singlet peak at δ 6.06 ppm was for the carboxylic acid O*H* proton, while the triplet with *J* =7.1 Hz at δ 3.38 ppm and the triplet with *J* = 7.3 Hz at δ 2.38 ppm were for the γ and α-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 **143** 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**.



Scheme 63: *Reagents and Conditions*: (a) 0.3M KOH (5 eq), MeOH, 1 h, (ii) K_2CO_3 (2 eq), acetic anhydride (1 eq), MeCN, 25.5 h heating under reflux, **290** = 5%, **291** = 4%

The IR spectrum of (*E*)-methyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoates **290** had peaks at ν_{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 δ 3.69 ppm for the methyl protons, a triplet with *J* = 7.1 Hz at δ 3.37 ppm for the γ-protons of the methyl ester and a triplet *J* = 7.3 Hz at δ 2.33 ppm for the α-protons of the methyl ester. The pyrrolidinyl ring proton peaks were shown by a multiplet at δ 3.24 – 3.12 ppm for the γ-protons of the enaminone and a multiplet at δ 2.01 – 1.84 ppm for the α-protons of the enaminone. The unsaturated ethyl ester side chain presence was shown by a singlet at δ 4.52 ppm for the vinyl proton, a quartet and triplet both with *J* = 7.1 Hz at δ 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 δ 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 δ 165.0, 45.5 and 32.7 ppm for the alkene quaternary carbon, γ-carbon of the enaminone and α-carbon of the enaminone. The methyl butanoate side chain peaks were at δ 173.3, 52.6, 51.7 and 31.2 ppm for the

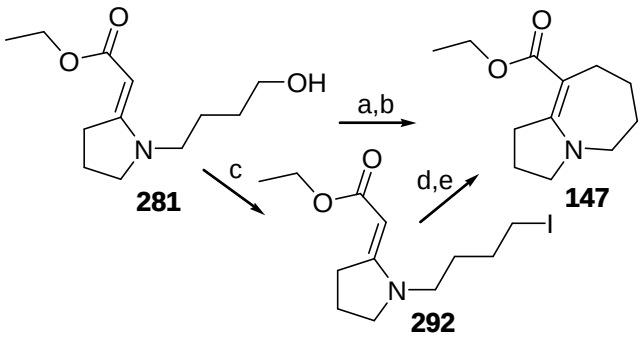
saturated ester carbonyl, the γ-carbon of the methyl ester, methyl group and α-carbon of the methyl ester.

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 **291** had peaks at ν_{max} = 3340, 1711, 1582 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 δ 8.43 and 4.53 for the CO_2H and vinyl protons in that order. The quartet with *J* = 7.0 Hz at δ 4.21 ppm and a triplet with *J* = 7.1 Hz at δ 1.27 ppm were for the $C=C(CO)CO_2CH_2CH_3$ and $C=C(CO)CO_2CH_2CH_3$ respectively of the ester, while the quartet with *J* = 7.1 Hz at 4.08 ppm and a triplet with *J* = 7.1 Hz at δ 1.27 ppm were for the $C=HCCO_2CH_2CH_3$ and $C=HCCO_2CH_2CH_3$ protons of the ester. The triplet with *J* = 7.0 Hz at δ 3.38 ppm and the triplet with *J* = 7.7 Hz at δ 3.14 ppm were for the $CH=CCH_2CH_2CH_2$ and $CH=CCH_2CH_2CH_2$ protons of the pyrrolidinyl ring, while the multiplet at δ 3.26 – 3.18 ppm and a triplet with *J* = 7.8 Hz at δ 3.03 ppm were for the $C=CCH_2CH_2CH_2$ and $C=CCH_2CH_2CH_2$ protons of the pyrrolidinyl ring. The triplet with *J* = 7.1 Hz at δ 3.68 ppm and a triplet with *J* = 6.7 Hz at δ 2.68 ppm were for the $NCH_2CH_2CH_2COC=C$ and $NCH_2CH_2CH_2COC=C$ protons of the butanoyl link. The multiplet at δ 3.52 – 3.43 ppm and triplet with *J* = 7.2 Hz at δ 2.33 ppm were for the $NCH_2CH_2CH_2CO_2H$ and $NCH_2CH_2CH_2CO_2H$ of the butanoyl chain. The ^{13}C NMR spectrum showed peaks at δ 196.5, 169.7, 168.8, 165.1, 102.7 and 77.8 ppm for the ketone, ester $CO_2CH=C$, $CO_2C=C$ and carboxylic acid CO_2OH carbonyl carbons, alkene quaternary $CO_2CH=C$, $CO_2C=C$, $CO_2C=C$ and vinyl $CO_2CH=C$ carbons respectively. The remaining peaks at δ 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 and 14.3 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 **281** 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 S_N2 alkylation with haloalkane, cyclising to form (*E*)-ethyl 2,3,5,6,7,8-hexahydro-1*H*-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-1*H*-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_2HPO_4 in *N,N*-dimethylformamide for 3 hours affording (*E*)-ethyl 2,3,5,6,7,8-hexahydro-1*H*-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_2HPO_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).



Scheme 64: *Reagents and Conditions*: (a) Imidazole (5 eq), iodine (3 eq), TPP (3 eq), toluene, reflux for 2 h, **147** = 9%; (b) Table 25; (c) Imidazole (3 eq), iodine (3 eq), TPP (3 eq), toluene, reflux for 3.75 h, **292** = 85%; (d) Na_2HPO_4 (1.5 eq), DMF, reflux for 3 h, **147** = 25%; (e) DBU (2 eq), MeCN, refluxed for 14 h, **147** = 0%.

Table 25: Alkylation reactions of vinylogous urethane **281**

Entry	Reagents	Conditions	Solvent	Results
1	Imidazole (5 eq), iodine (2 eq), TPP (3 eq)	Reflux,18 hours	MeCN	**147** = 0%
2	Imidazole (3 eq), iodine (2 eq), TPP (3 eq)	Reflux, 44 hours	Toluene	**147** = 0%
3	Imidazole (3 eq), iodine (2 eq), TPP (3 eq)	Reflux, 4 days	Toluene	**147** = 0%
4	Imidazole (5 eq), iodine (2 eq), tri-*o*-tolylphosphine (1.42 eq)	Reflux, overnight	MeCN	**147** = 0%
5	Na_2HPO_4 (3 eq), iodine (2 eq), TPP (3 eq),	Reflux, 3 hours	DMF	**147** = 0%

The IR spectrum of (*E*)-ethyl 2-(1-(4-iodobutyl)pyrrolidin-2-ylidene)acetate **292** had peaks at ν_{max} = 1736 and 1631 cm^{-1} for the ester carbonyl and alkene groups respectively. The ^1H NMR spectrum revealed a singlet at δ 4.51 ppm for the vinyl proton, a quartet and a triplet, both with *J* = 7.1 Hz at δ 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 δ 3.38 ppm for $NCH_2CH_2CH_2CH_2I$ protons and a multiplet at δ 3.22 – 3.13 ppm for CH_2I protons, where a noticeable upfield chemical shift in conversion of δ 3.61 CH_2OH ppm to CH_2I. The pyrrolidinyl ring was

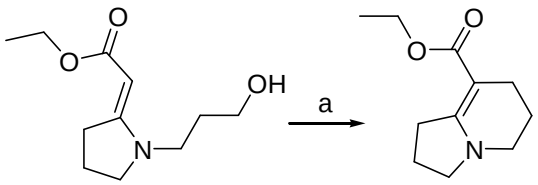
represented by a multiplet at δ 3.22 – 3.13 ppm for the γ and α-protons of the enaminone. The ^{13}C NMR spectrum showed peaks at δ 169.5 and 77.7 ppm for the ester carbonyl and vinyl carbons. The pyrrolidinyl ring carbon peaks were at δ 164.9, 52.5 and 32.7 ppm for the quaternary alkene carbon, the γ and α-carbons of the enaminone. The iodobutyl side chain peaks were at δ 45.2 for the N*C*H$_2$CH$_2$CH$_2$CH$_2$I carbon and at δ 5.9 ppm for *C*H$_2$I carbon, which is a sizeable upfield chemical shift from δ 62.0 ppm of *C*H$_2$OH carbon.

The IR spectrum of (*E*)-ethyl 2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-9-carboxylate **147** had peaks at ν_{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 C*H*$_2$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=*C*H and *C*H$_2$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 quartenary 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.*[111]

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

In contrast, (*E*)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate **288** was reacted with imidazole, triphenylphosphine 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, triphenylphosphine 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.[12,113]



288 **293**

Scheme 65: *Reagents and Condition*: (a) Imidazole (3 eq), iodine (2 eq), TPP (3 eq), toluene, reflux for 18 h, **293** = 57%.

The IR spectrum of (*E*)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate **293** had peaks at ν_{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 δ 4.55, 3.67 and 2.32 ppm for the vinyl, CH_2OH and alcohol protons. The ethyl ester side chain was shown by a quartet and a triplet both with *J* = 7.1 Hz at δ 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 δ 3.28 and a triplet with *J* = 7.8 Hz at δ 3.05 ppm for the 3-H and 1-H protons. The piperidinyl ring presented with a multiplet at δ 3.17 – 3.12 and a triplet with *J* = 6.3 Hz at δ 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 δ 159.2, 45.0 and 32.7 ppm were for the C-8a, C-3 and C-1 carbons. The piperidinyl ring peaks at δ 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.*[111]

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

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

281*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(3*H*)-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**.

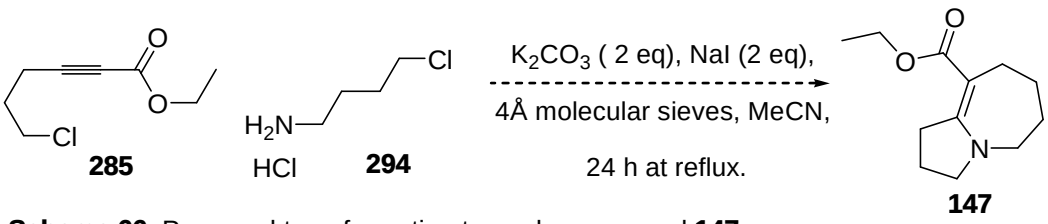
Synthesis of the vinylogous urethanes (*E*)-ethyl 2-(2-(2-ethoxy-2-oxoethylidene)azepan-1-yl)acetate **210** and (*E*)-*tert*-butyl 2-(2-(2-ethoxy-2-oxoethylidene)azepan-1-yl)acetate **211** was unsuccessful from thiolactams ethyl 2-(2-thioxoazepan-1-yl)acetate **208** and *tert*-butyl 2-(2-thioxoazepan-1-yl)acetate **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-oxoethylidene)azepan-1-yl)acetate **216** and (*E*)-ethyl 2-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)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-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **222**, ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **223** and ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **224**, which contained the pyrrolo[1,2-*a*]azepine nuclei.

N*H* 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 N*H* vinylogous amides with oxalyl chloride, leading to 1-benzoyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione **233** and 1-(4-methoxybenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione **235**, but failed to make 1-(4-nitrobenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione **234**. Similarly, the N*H* 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-1*H*-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_N2/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-1*H*-pyrrolo[1,2-*a*]azepine-9-carboxylate **147** and (*E*)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-9-carboxylate **144** in poor yields respectively. More research is recommended to find the suitable alkylating 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**

CHAPTER 3: APPROACHES TOWARDS *CEPHALOTAXUS* NUCLEUS

3.1 *Cephalotaxus* core

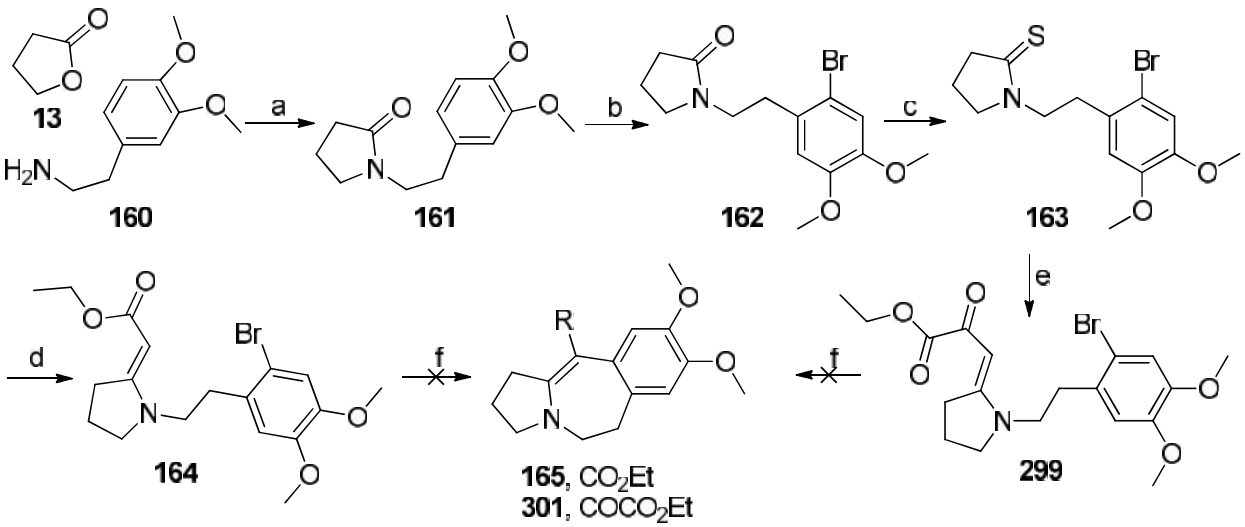
Studies towards *Cephalotaxus* alkaloids core required a synthesis of its derivatives in order to assess reaction reactivity along the route's pipe line. It was essential to initially use homoveratrylamine instead of homopiperonylamine owing to their great price difference. In addition, good reactivity has been observed in similar systems owing to the electron donating effects of the methoxy groups when the starting materials were 3,4-dimethoxyaniline **312** and 3,4-dimethoxybenzylamine **313**.[81] 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.[117,118] 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 67**).[12,119,120] Lactam **161** could then be brominated with bromine in the presence of acetic acid giving brominated lactam **162**.[141] Brominated lactam **162** could be thionated with phosphorus pentasulphide leading to the thiolactam **163**.[142] 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.[12] 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-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepine-11-carboxylate **165** and ethyl 2-(8,9-dimethoxy-

2,3,5,6-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-11-yl)-2-oxoacetate **301**.[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, making1-(3,4-dimethoxyphenethyl)pyrrolidin-2-one **161** in excellent 90% yield (**Scheme 67**, a). The resulting lactam **161** was brominated exclusively at C-4 by liquid bromine in acetic acid for 1 hour at room temperature, achieving1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-one **162** in an excellent 96% yield (**Scheme 67**, b). The brominated lactam **162** was reacted with P_2S_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 **163** in excellent 98% yield (**Scheme 67**, c). The brominated thiolactam **163** was then transformed to enaminone (*E*)-ethyl 2-(1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate **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 (**Scheme 67**, d).



Scheme 67: *Reagents and conditions*: (a) Dihydrofuran-2(3*H*)-one (1.1 eq) and 2-(3,4-dimethoxyphenyl)ethanamine (1 eq), neat, 150 W, 220 °C, 60 - 80 min, **161** = 90%; (b) Br_2 (1 eq), NaOAc (3 eq), Acetic acid, 1.5 h at r.t., **162** = 96%; (c) P_2S_5 (0.5 eq), DCM, r.t. for 17 h, **163** = 98%; (d) (**i**) Ethyl bromoacetate (1.1 eq), MeCN, r.t. for 24 h, (**ii**) TEA (1.1 eq), TTP (1.1 eq), MeCN, r.t. for 20 h, **164** = 80%; (e) (**i**) Ethyl bromopyruvate (1.1 eq), MeCN, r.t. 3 h, (**ii**) TEA (1.1 eq), TTP (1.1 eq), MeCN, r.t., 20 h, **299** = 84%; (f) $Pd(OAc)_2$ (0.3 eq), Tri(o-tolyl)phosphine (1.6 eq), TEA (10 eq), DMF/ MeCN/ H_2O (5:5:1), **165** = 0%, **301** = 0%.

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 ν_{max} = 1689 and 1451 cm^{-1} for the amide carbonyl and aromatic functional groups. The ^1H NMR spectrum showed multiplets at δ 6.84 – 6.72 ppm for the aromatic protons, a singlet at δ 3.87 ppm for the two methoxy groups protons and two multiplets at δ 3.56 – 3.47 and 2.84 – 2.75 ppm for the NC*H*$_2$CH$_2$-Ar and NCH$_2$C*H*$_2$-Ar protons of the 3,4-dimethoxyphenethyl side chain. The pyrrolidinone ring was shown by a triplet peak with *J* = 7.0 Hz at δ 3.27 ppm for the γ-protons of the lactam and a triplet with *J* =8.1 Hz at 2.36 ppm for α-protons of the lactam protons. The ^{13}C NMR spectrum revealed peaks at δ 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 δ 55.9 ppm and the ethyl side chain peaks were at δ 47.7 and 33.3 ppm for the NC*H*$_2$CH$_2$-Ar and NCH$_2$C*H*$_2$-Ar

carbons. 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 ν_{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 ν_{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_2CH_2-Ar and a triplet with *J* = 7.2 Hz at δ 3.08 ppm for NCH_2CH_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 201.0ppm for the thioacarbonyl carbon, revealing the absence of lactam carbonyl peak at δ 174.9 ppm in the spectrum of **162**. The pyrrodinethione 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 ν_{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 ^{1}H 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 ^{13}C 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 precendent 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.

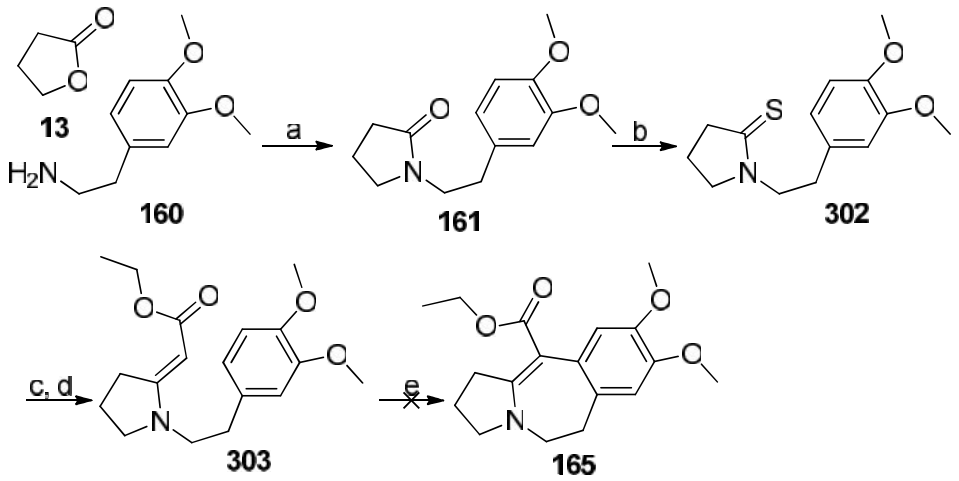
3.3 Alternative attempts to synthesise compound 165

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 N*H* 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) Dihydrofuran-2(3*H*)-one (1 eq) and 2-(3,4-dimethoxyphenyl)ethanamine (1 eq), neat, 150 W, (Run 1:180 °C, 40 min, Run 2: 200 °C, 10 min, Run 3: 222 °C, 10 min), **160** = 64%, (ii) Dihydrofuran-2(3*H*)-one (1.2 eq) and 2-(3,4-dimethoxyphenyl)ethanamine (1 eq), neat, (Run: 150 W, 220 °C, 1 h), **161** = 87%; (b) P_2S_5 (0.5 eq), DCM, overnight, **302** = 51, 68 - 77%; (c) (i) Ethyl bromoacetate (1.4 eq), MeCN, r.t., 4 h, (ii) TEA (1.4 eq), TTP (1.4 eq), MeCN, r.t., 22 h, **303** = 35%; (d) (i) Ethyl bromoacetate (1.1 eq), MeCN, r.t., overnight, (ii) TEA (1.1 eq), TTP (1.1 eq), MeCN, r.t., overnight, **303** = 60%; (e) Table 28.

Table 28: Various coupling reactions of compound **303**

No.	Reagents	Conditions	Solvents	Results
1.	(0.1 eq) $Pd(OAc)_2$, (3 eq) $Cu(OAc)_2$, (3 eq) K_2CO_3	140 °C, 18 h	DMF	**165** = 0%; **303** = 86%
2.	(0.1 eq) $Pd(OAc)_2$, bubbling O_2 gas	Reflux, 1 h	Acetic acid	**165** = 0%; **303** = 86%
3.	(0.1 eq) $Pd(OAc)_2$, bubbling O_2 gas	100 °C, 1 h	DMF	**165** = 0%; **303** = 86%
4.	(0.4 eq) $Pd(OAc)_2$, (1.6 eq) P(*o*-tolyl)$_3$, (10.6 eq) TEA	55 °C, 22 h	DMF, MeCN, H_2O	**165** = 0%; **303** = 79%
5.	(10 eq) $FeCl_3$	r.t.	DCM	**165** = 0%; **303** = 93%

Changing the solvent from acetic acid to *N,N*-dimethylformamide had no benefit for the reaction. (*E*)-Ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)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 ν_{max} = 1456 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 δ 175.0 ppm and the presence of the thiocarbonyl carbon peak at δ 200.6 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**

161 ^{1}H NMR /ppm	**302** ^{1}H NMR /ppm	**161** ^{13}C NMR /ppm	**302** ^{13}C NMR /ppm
3.56 – 3.47 (m)	3.95 (t, *J* = 7.4 Hz, NC*H*$_2$CH$_2$Ar)	47.7	55.6 (NC*H*$_2$CH$_2$Ar)
3.27 (t, *J* = 7.0 Hz)	3.52 (t, *J* = 7.3 Hz, γ-protons)	44.1	49.4 (γ-carbon)
2.36 (t, *J* = 8.1 Hz)	3.05 – 2.87 (m, α-protons)	33.3	44.9 (NCH$_2$*C*H$_2$Ar)
2.84 – 2.75 (m)	3.05 – 2.87 (m, NCH$_2$C*H*$_2$Ar)	31.0	31.7 (α-carbon)

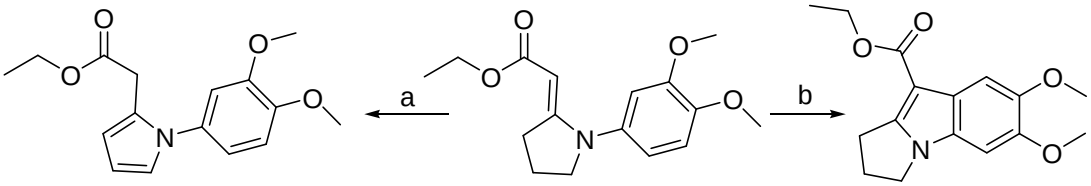
The melting point of (*E*)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate **303** was 108 – 109 °C. The IR spectrum revealed peaks at ν_{max} = 1668 and 1585 cm^{-1} for the ester carbonyl and the vinyl groups. The ^{1}H NMR spectrum revealed new peaks, a singlet at δ 4.61 ppm for the vinyl peak and a triplet and a quartet, both with *J* = 7.1 Hz at δ 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**

302 ^{1}H NMR /ppm	**303** ^{1}H NMR /ppm
3.92	3.39 (t, *J* = 7.3 Hz, NC*H*$_2$CH$_2$Ar)
3.52	3.16 (m, ε-protons)
3.05 – 2.87	2.80 (t, *J* = 7.3 Hz, γ-protons)
3.05 – 2.87	3.16 (m, NCH$_2$C*H*$_2$Ar)

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_2CH_2Ar 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)-1*H*-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-1*H*-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.



305 **304** **306**

Scheme 69: *Reagents and Conditions*: (a) $Pd(OAc)_2$ (0.1 eq), O_2 balloon, acetic acid, 1 h at relfux (80°C), **305** = 14%; (b) $Pd(OAc)_2$ (0.1 eq), O_2 balloon, acetic acid, 1 h at 55 °C, **305** = 14%.

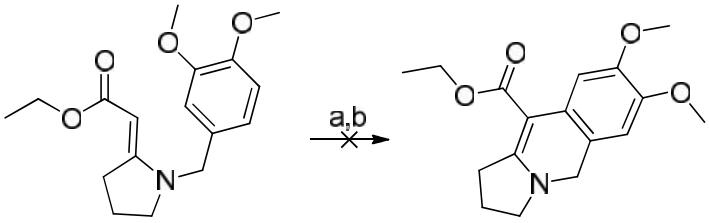
The IR spectrum of ethyl 2-(1-(3,4-dimethoxyphenyl)-1*H*-pyrrol-2-yl)acetate **305** had peaks at ν_{max} = 1730 and 1435 cm^{-1} for the ester carbonyl and aromatic groups. The

^{1}H NMR spectrum revealed the absence of the vinyl peak which was at δ 4.65 ppm in **306**'s ^{1}H NMR spectrum and the presence of a singlet at δ 3.56 ppm for α-protons of the ethyl ester. The pyrrole ring was represented by a multiplet at δ 6.80 – 6.75 ppm for the ε-proton and a multiplet at δ 6.31 – 6.14 ppm for the γ and δ-protons of the ethyl ester revealing the absence of the pyrrolidinyl ring proton peaks which were at δ 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 δ 80.7 and 164.8 ppm in **304**'s ^{1}H NMR spectrum and the presence of pyrrol peaks at δ 125.8, 122.7, 110.4 and 109.3 ppm for the β, ε, γ and δ carbons of the ethyl ester respectively. The α-carbon peak to the ester group registered at δ 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-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate **306** showed peaks at ν_{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 δ 4.65 ppm in **304**'s ^{1}H NMR spectrum. The aromatic peaks resolved to two singlets at δ 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 δ 80.7 ppm in **306**'s ^{1}H NMR spectrum and the presence of a quaternary alkene carbon peak at δ 99.0 ppm for C-6. The newly formed quaternary aromatic carbon peak C-9 was at δ 124.1 ppm, a downfield shift from δ 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 δ 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 δ-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).



307 **308**

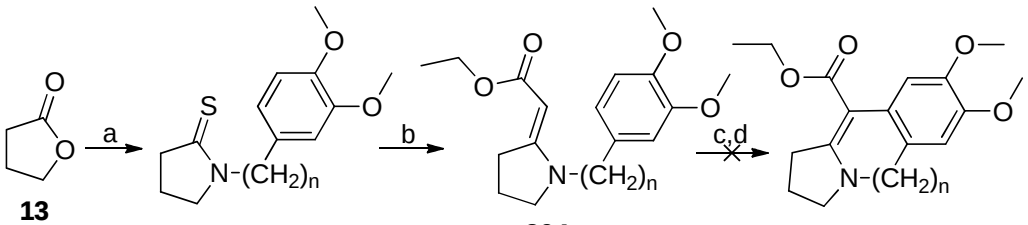
Scheme 70: *Reagents and Conditions*: (a) $Pd(OAc)_2$ (0.1 eq), O_2 balloon, acetic acid, 1 - 24 h at reflux, **308** = 0%; (b) $Pd(OAc)_2$ (0.1 eq), O_2 ballon, acetic acid, 4 h at 50 °C, **308** = 0%.

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 CH_2 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-dimethoxyaniline, 3,4-dimethoxybenzylamine or homoveratrylamine neat in a microwave reactor at 150 W, 220 °C 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]).



13

309, n = 0 **310**, n = 1 **302**, n = 2

304, n = 0 **307**, n = 1 **303**, n = 2

306, n = 0 **308**, n = 1 **165**, n = 2

Scheme 71: *Reagents and Condition*: (a) (i) 3,4-dimethoxybenzenamine (1 eq)/ (3,4-dimethoxyphenyl)methanamine (1 eq)/ 2-(3,4-dimethoxyphenyl)ethanamine (1 eq), 150 W, 1 h at 220 ▪C, (ii) P_2S_5 (0.5 eq), DCM, 18 h at r.t., **309** = 88%, **310** = 77%, **302** = 86%; (b) (i) Ethyl bromoacetate (1 eq), MeCN, 3 h at r.t., (ii) TEA (1 eq), TEP (1 eq), MeCN, 20 h at r.t., **304** = 87%, **307** = 84%, **303** = 60%; (c) $Pd(OAc)_2$ (0.15 eq), $Cu(OAc)_2{\cdot}H_2O$ (0.40 eq), EtOH, O_2, 10 min at r.t., 28 - 42 h at reflux, **306** = 0%, **308** = 0%, **165** = 0%; (d) $Pd(OAc)_2$ (0.10 eq), 3 $Cu(OAc)_2$ (3 eq), K_2CO_3, DMF, 18 h at 140 ▪C, **306** = 0%, **308** = 0%, **165** = 0%.

The IR spectrum of **309** had peaks at ν_{max}= 1509 cm^{-1} for the aromatic ring. The ^1H 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 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 ν_{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 ν_{max} = 1671, 1577, 1505 and 1450 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 δ 4.72 ppm for the vinyl proton and a quatert and a triplet both with *J* = 7.1 Hz at δ 4.06 and 1.21 ppm respectively for the ethyl side chain. The pyrrolidinylidene ring was shown by a triplet with *J* = 7.0 Hz at δ 3.69 ppm for ε-protons and a triplet with *J* = 7.8 Hz at δ 3.31 ppm for the γ-protons of the unsaturated ethyl ester. The chemical shift of γ-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 δ 202.5 ppm of **309**'s ^{13}C NMR spectrum and the presence of the ester carbonyl carbon peak at δ 169.5 ppm, the quaternary alkene carbon peak at δ 164.9 ppm and the vinyl carbon peak at δ 80.7 ppm. The pyrrolidinylidene ring carbon peaks shifted up field to δ 55.1 and 32.5 ppm for ε and γ-carbons of the unsaturated ethyl ester respectively, from δ 56.1 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 ν_{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 Hz at δ 4.07 and 1.22 ppm respectively for the ethyl side chain protons and a singlet at δ 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 γ-protons of the unsaturated ethyl ester at δ 3.21 ppm with *J* = 7.8 Hz by the ester carbonyl oxygen atom through space. The ^{13}C NMR spectrum revealed the absence of the thiolactam carbonyl carbon peak at δ 201.3 ppm on **310**'s ^{13}C NMR spectrum and the presence of the alkene quaternary carbon peak at δ 165.2 ppm confirming the thioamide to alkene transformation. The ester carbonyl and vinyl carbon peaks at δ 169.6 and 78.2 ppm respectively confirmed the presence of the unsaturated ester. The γ-carbon became more shielded with the introduction of the unsaturated ester group appearing at δ 32.7 ppm from δ 45.0 ppm on the **310**'s ^{13}C NMR spectrum.

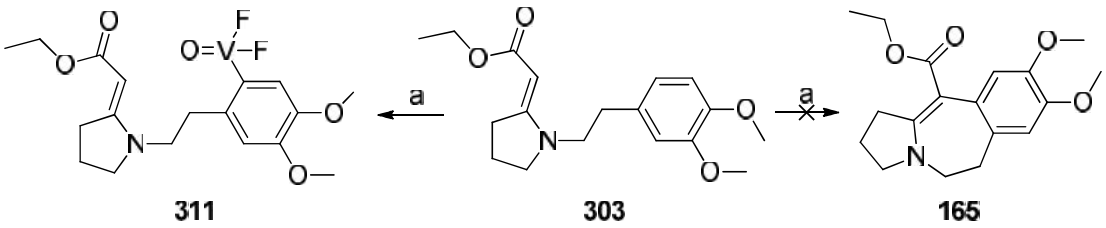
The vinylogous urethanes were then subjected to palladium-catalyzed oxidative coupling reactions. A mixture of **303**, palladium(II) acetate, copper(II) acetate monohydrate was reacted in ethanol for 10 minutes at room temperature. It was then heated under reflux under oxygen atmosphere in a balloon 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.*[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.[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 °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 °C and left to react for 2.5 hours, giving what appeared to be (*E*)-(2-(2-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)ethyl)-4,5-dimethoxyphenyl)(oxo)vanadium(V) fluoride **311** in 42% yield (**Scheme 72**, a).



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 ν_{max} = 1702 and 1590 cm^{-1} for the ester carbonyl and aromatic alkene groups. The ^1H NMR spectrum showed two singlets at δ 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 γ-protons of the unsaturated ethyl ester in **311** as compared to the same protons in **303** may indicate split attention from the olefinic =CH hydrogen bonding with the vanadium group (Table 31).

Table 31: Comparison of ^{1}H NMR spectra of compounds **311** and **303**

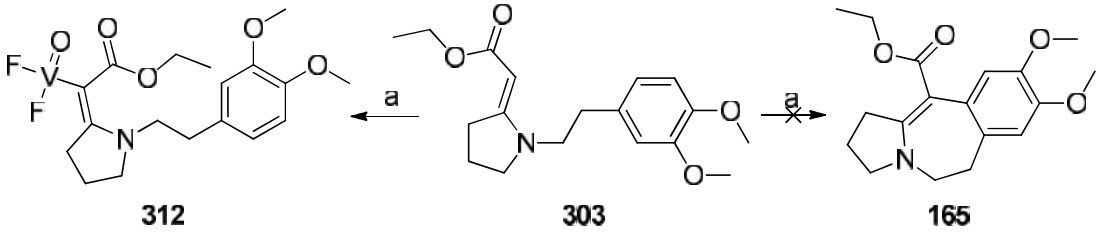
311 ^{1}H NMR /ppm	**303** ^{1}H NMR /ppm
4.38 (s, vinyl proton)	4.61 (s)
4.08 (q, *J* = 7.1 Hz, C*H*$_2$CH$_3$)	4.11 (q, *J* = 7.1 Hz)
3.94, 3.87 (2×s, methoxy protons)	3.87 (s)
3.17 (t, *J* = 7.7 Hz, NC*H*$_2$CH$_2$-Ar)	3.39 (t, *J* = 7.3 Hz)
3.06 (ddd, *J* = 15.8, 8.4, 2.4 Hz, ε-protons, NCH$_2$C*H*$_2$-Ar)	3.16 (m)
2.59 (dtd, *J* = 20.9, 13.5, 7.7 Hz, γ-protons)	2.80 (t, *J* = 7.3 Hz)
1.83 (p, *J* = 7.5 Hz, δ-protons)	1.83 (m)
1.25 (t, *J* = 7.1 Hz, CH$_2$C*H*$_3$)	1.27 (t, *J* = 7.1 Hz)

The ^{13}C NMR spectrum contained a deshielded chemical shift of carbon atom C-2 from δ 120.7 ppm in compound **303** to δ 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 N*C*H$_2$CH$_2$-Ar and NCH$_2$*C*H$_2$-Ar carbons, since their chemical environments shifted downfield to δ 52.1 and 47.3 ppm from δ 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**

311 ^{13}C NMR /ppm	**303** ^{13}C NMR /ppm	**311** ^{13}C NMR /ppm	**303** ^{13}C NMR /ppm
148.4 (Ar C-5)	149.0	77.7 (α-carbon)	77.6
147.4 (Ar C-4)	147.7	52.7 (ε-carbon)	48.1
132.6 (Ar C-1)	131.4	52.6 (N*C*H$_2$CH$_2$-Ar)	53.2
128.8 (Ar C-2)	120.7	47.3 (NCH$_2$*C*H$_2$-Ar)	32.7
113.4 (Ar C-3)	111.9	32.6 (γ-carbon)	31.7
112.5 (Ar C-6)	111.4	20.9 (δ-carbon)	21.1

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).



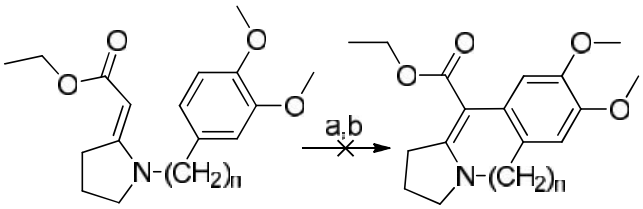
Scheme 73: *Reagents and Conditions*: (a) VOF_3 (2 eq), TFAA (1.3 eq), TFA (2.6 eq), DCM: EtOAc (4:1), overnight at -5 °C to r.t., **312** = 13%, **303** = 2.7%.

The IR spectrum of vanadium(V) intermediate **312** had peaks at ν_{max} = 1735 and 1588 cm^{-1} for the ester carbonyl and aromatic groups respectively. The ^{1}H NMR revealed that compound **312** had no vinyl peak present which would have been at δ 4.61 ppm in **303**'s ^{1}H NMR spectrum and maintained the presence of the three aromatic peaks, a doublet with *J* = 7.9 Hz at δ 6.81 ppm for 5-H and a multiplet at δ 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}H NMR spectrum. The ^{13}C NMR revealed that α-carbon of the unsaturated ethyl ester was at δ 95.0 ppm which is significantly downfield from δ 77.6 ppm in **303**'s ^{13}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}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-dimethoxyphenyl)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**.



304, n = 0
307, n = 1

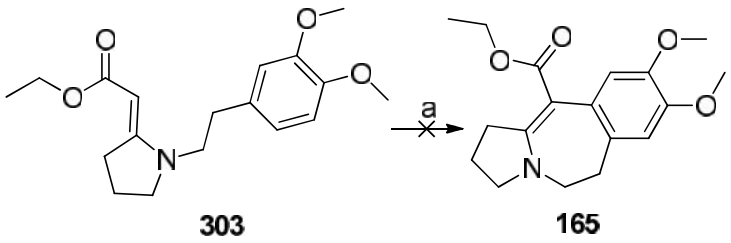
306, n = 0
308, n = 1

Scheme 74: *Reagents and Conditions*: (a) VOF_3 (3 eq), TFA: DCM (2:1), TFAA, 2.5 h at -15 °C, **306** = 0%, **308** = 0%; (b) VOF_3 (2 eq), TFAA (1.3 eq), TFA (2.6 eq), DCM: EtOAc (4:1), overnight at -5 °C to r.t., **306** = 0%, **308** = 0%.

3.6 Ultraviolet radical coupling reactions of compound 303

(*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]).



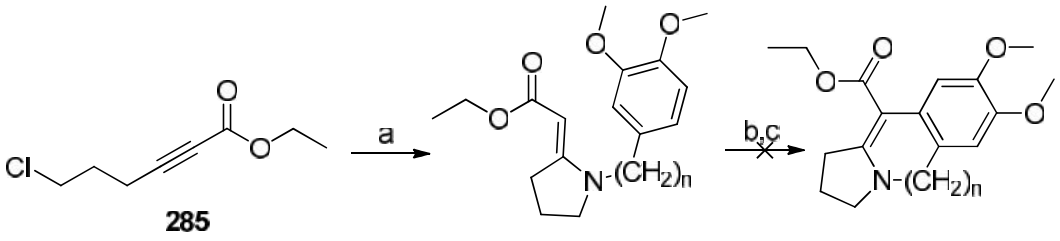
303 **165**

Scheme 75: *Reagents and Conditions*: (a)(i) UV lamp (256 nm), DCM, 16 h, **165** = 0%; (ii) UV lamp (650 W, 120 V), MeCN, 20 h, **165** = 0%.

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).

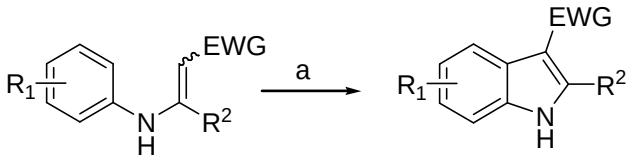


304, n = 0
307, n = 1
303, n = 2

306, n = 0
308, n = 1
165, n = 2

Scheme 76: *Reagents and Conditions*: (a) 3,4-Dimethoxyaniline **313** (1 eq), 3,4-dimethoxybenzylamine **314** (1 eq) or homoveratrylamine **294** (1 eq), NaI (2 eq), K_2CO_3 (2 eq), 4Å molecular sieve, MeCN, 21 - 43 h at reflux, **304** = 43 - 73%, **307** = 62 - 86%, **303** = 78 - 89%; (b) PIDA (1.3 eq), DCE, 3 h at 60 °C, **306** = 0%, **308** = 0%, **165** = 0%; (c) PIFA (1.3 eq), DCM , 22 h at r.t., **306** = 0%, **308** = 0%, **165** = 0%.

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-phenyl-aminoacrylonitrile derivatives in dichloroethane and reacting at 60 °C for 2 hours were optimal conditions for indole synthesis (**Scheme 77**).[127,128,129]



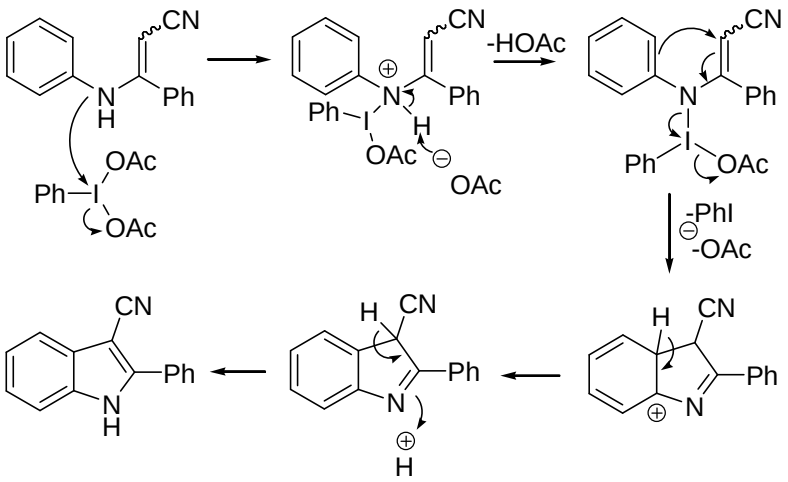
R_1 = Me, OMe, F, Br R^2 = alkyl, aryl

Scheme 77: (a) PIDA (1.3 eq), DCE, 2 h at 60 °C, 33 - 91%

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.

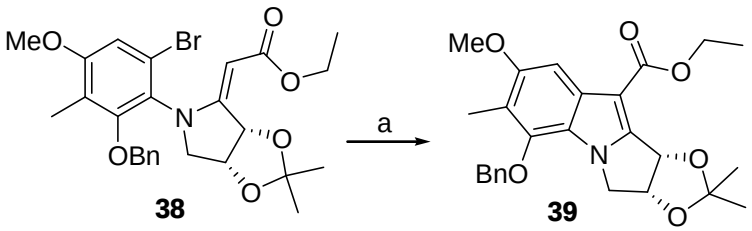
The absence of a N*H* proton on enaminones could have led to the reaction's failure, since the proton plays an important role on the elimination of first acetic acid molecule. A complex salt could have formed in the case of enaminones which could not react any further and be lost during reaction work up (**Scheme 78**).



Scheme 78: Intramolecular S_N2-type cyclisation mechanism for the PIDA-mediated construction of indoles.

3.8 Attempted synthesis of compounds 165, 308, 321 and 322 via Heck-type, Herrmann-Beller catalyst and Bu_3SnH 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-((3a*S*,6a*R*)-5-(2-(benzyloxy)-6-bromo-4-methoxy-3-methylphenyl)-2,2-dimethyl-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-4(5*H*)-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(3a*R*,10b*S*)-6-benzyloxy-8-methoxy-2,2,7-trimethyl-3a,10b-dihydro-4*H*-[1,3]dioxolo-[4',5':3,4]pyrrolo[1,2-*a*]indole-10-carboxylate **39** in 82% yield (**Scheme 79**, a).



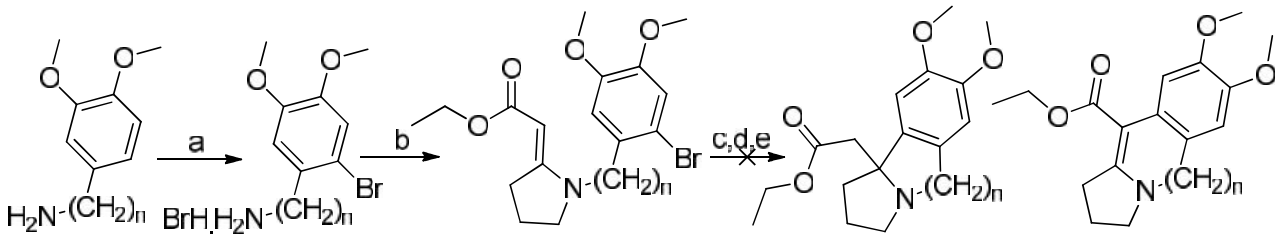
Scheme 79: *Reagents and Conditions*: (a) $Pd(OAc)_2$ (0.3 eq), P(*o*-tolyl)$_3$ (1.6 eq), TEA (10 eq), $CH_3CN/DMF/H_2O$ (1:1:0.21), 4 h at reflux, **39** = 82%.

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 ν_{max} = 3111 and 1478 cm^{-1} respectively. The ^1H NMR spectrum had two single peaks at δ 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 ν_{max} = 3114 and 1509 – 1439 cm^{-1} for the amine and aromatic groups respectively. The ^1H NMR spectrum revealed two singlet peaks at δ 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 enaminones. 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).



313, n = 0 **314**, n = 1 **160**, n = 2 | **317**, n = 0 **318**, n = 1 **319**, n = 2 | **320**, n = 1 **164**, n = 2 | **321**, n = 1 **322**, n = 2 | **308**, n = 1 **165**, n = 2

Scheme 80: *Reagents and Conditions*: (a) Br_2 (1 eq), 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_2CO_3 (3 eq), 4Å molecular sieves, MeCN, reflux over night, **320** = 83%, **164** = 88%; (c) $Pd(OAc)_2$ (0.4 eq), P(*o*-tolyl)$_3$ (1.6 eq), TEA (10.6 eq), DMF:MeCN:H_2O (5:5:1), 22 h at reflux, **308** = 0%, **165** = 0%; (d) Herrman-Beller catalyst (0.01 eq), NaOAc, DMA, 17 h at 130 °C, **308** = 0%, **165** = 0%; (e) Bu_3SnH (2 eq), AIBN (1.5 eq), benzene, 5 h at reflux, **321** = 0%, **322** = 0%.

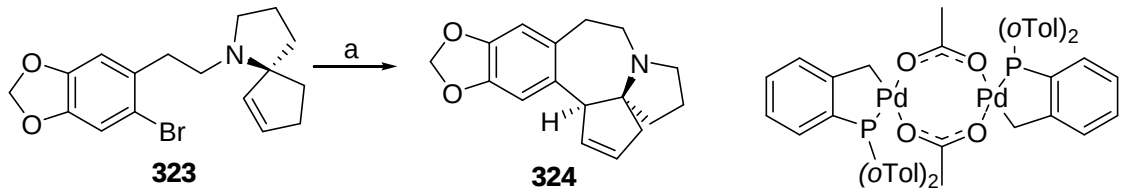
The melting point of **320** was 108 – 109 °C. The IR spectrum had peaks at ν_{max} = 1683 and 1589 cm^{-1} for the ester carbonyl, alkene and aromatic groups in that order. The ^1H NMR spectrum revealed presence of the vinyl proton by a singlet at δ 4.63 ppm indicative of the formation of the carbon-carbon double bond from the Michael addition reaction and a triplet with *J* = 7.0 Hz at δ 3.33 ppm for the ε-protons confirming the alkylative reaction. The remainder of the molecule was confirmed by quartet and a triplet both with *J* = 7.1 Hz at δ 4.09 and 1.24 ppm respectively for the ethyl chain of the ester and the two singlets at δ 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 δ 165.1 and 79.0 ppm respectively. The ester carbonyl carbon was at δ 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-4*H*-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*-butylammonium acetate and the above two reagents was stirred for 7 hours at 120 °C (**Scheme 81**, a).[131]



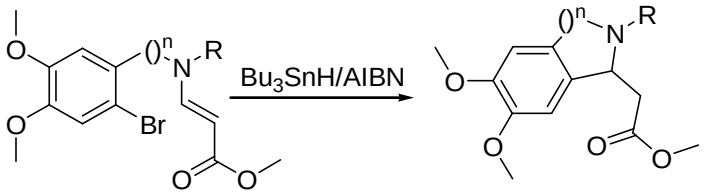
323 **324** **325**

Scheme 81: *Reagents and Conditions*: (a) **325** (0.04 eq), nBu_4NOAc (2 eq), $CH_3CN/DMF/H_2O$ (5:5:1), 7 h at 110 -120 °C, **324** = 81%.

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 enamonines 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**).[130]

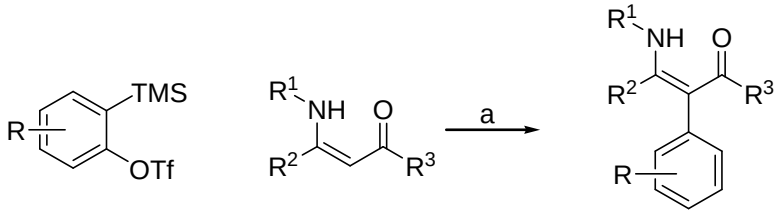


Scheme 82: Aryl radical cyclisation in enaminone esters.

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-1*H*-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.

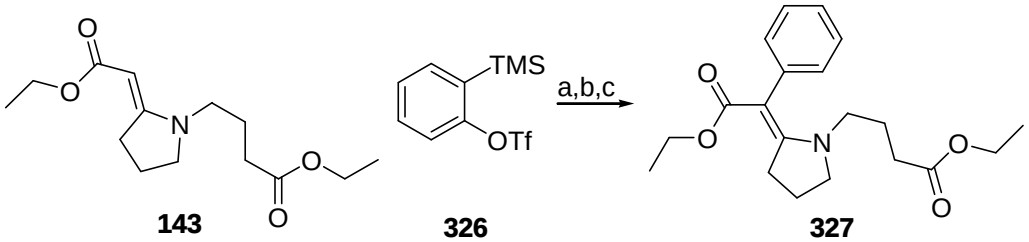
3.10 Reactions of vinylogous urethanes and amides with benzyne

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]



Scheme 83: *Reagents and Conditions*: (a) CsF (2.5 eq), MeCN, 4 - 8 h at r.t, 50 - 93%.

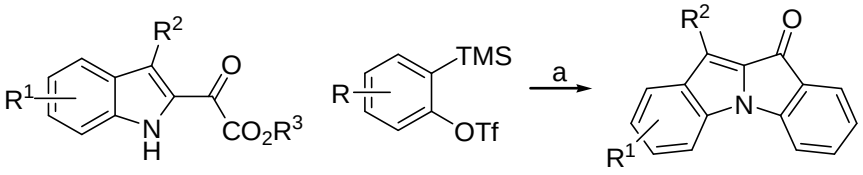
As a trial experiment to see which kinds of enaminones would react with arynes, (*E*)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate **143** was treated with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **326** and cesium fluoride in acetonitrile at 25 °C for 50 hours. (*E*)-Ethyl 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.



Scheme 84: *Reagents and Conditions*: (a) **326** (1.25 eq), CsF (1.67 eq), MeCN, 50 h at 25 °C, **327** = 39%; (b) **326** (1.5 eq), CsF (2 eq), MeCN, 18 h at reflux, **327** = 31%; (c) **326** (1.5 eq), TBAF (2 eq), THF, 20 h at 65 °C, **327** = 27%.

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"[137] where the indoles, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **326** and anhydrous tetramethylammonium fluoride (TMAF) were reacted at room temperature for 1 – 2 hours, yielding desired products in good yields (**Scheme 85**).

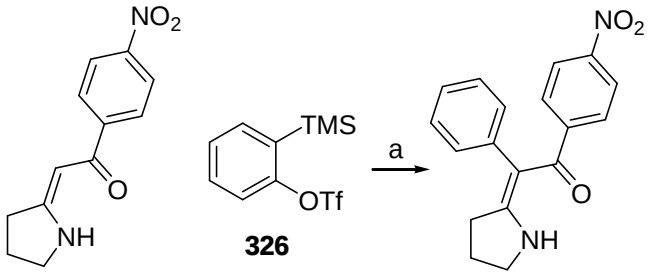


Scheme 85: *Reagents and Conditions*: (a) TMAF (2.27 eq), THF, 1 - 2 h at r.t, 53 - 90%.[25]

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 **326** 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 ν_{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 δ 4.53 ppm in **143**'s ^{1}H NMR spectrum and the presence of a multiplet at δ 7.35 – 7.12 ppm for the aromatic group. The ^{13}C NMR spectrum revealed the absence of the vinyl carbon peak at δ 77.3 ppm in **143**'s ^{13}C NMR spectrum and the presence of quaternary carbon peak at δ 96.1 ppm for the α-carbon of the unsaturated ester. The aromatic carbon peaks appeared at δ 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 enaminones.



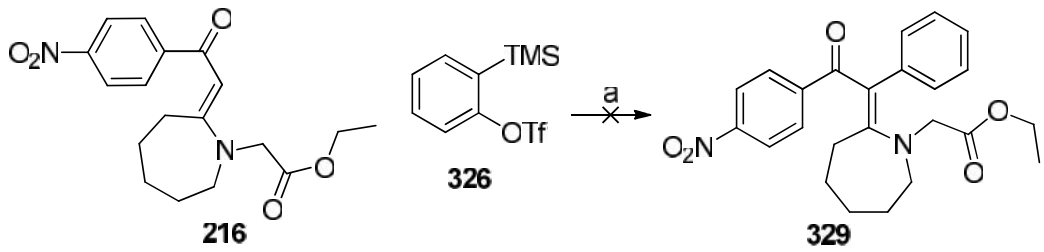
240 **326** **328**

Scheme 86: *Reagents and Conditions*: (a) CsF (2 eq), MeCN, 23 h at 60 °C - reflux, 79%.

The IR spectrum of **328** had peaks at ν_{max} = 3400 – 3200, 1742, 1567, 1541 and 1480 cm^{-1} for the amine N*H*, alkene and aromatic groups respectively. The ^{1}H NMR spectrum revealed the absence of the vinyl singlet at δ 5.80 ppm in compounds **240**'s ^{1}H NMR spectrum and revealed the presence of the phenyl ring with multiplets at δ 7.16 and 7.02 ppm for (*ortho* and *para* protons) and *meta* protons. The N*H* singlet appeared at δ 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 δ 87.0 ppm in **240**'s spectrum and the emergence of a quaternary alkene carbon peak (α-carbon of the ketone) at δ 105.4 ppm. There were eight aromatic carbon peaks representative of the structure.

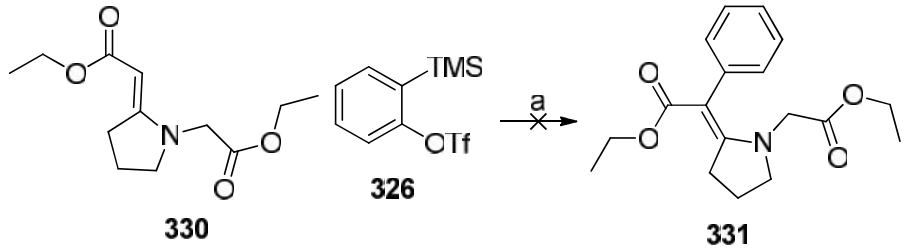
Compound **326** was added drop wise into a solution of (*E*)-ethyl 2-(2-(2-(4-nitrophenyl)-2-oxoethylidene)azepan-1-yl)acetate **216** and cesium fluoride in

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, 18 h at 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, 6 h at 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.

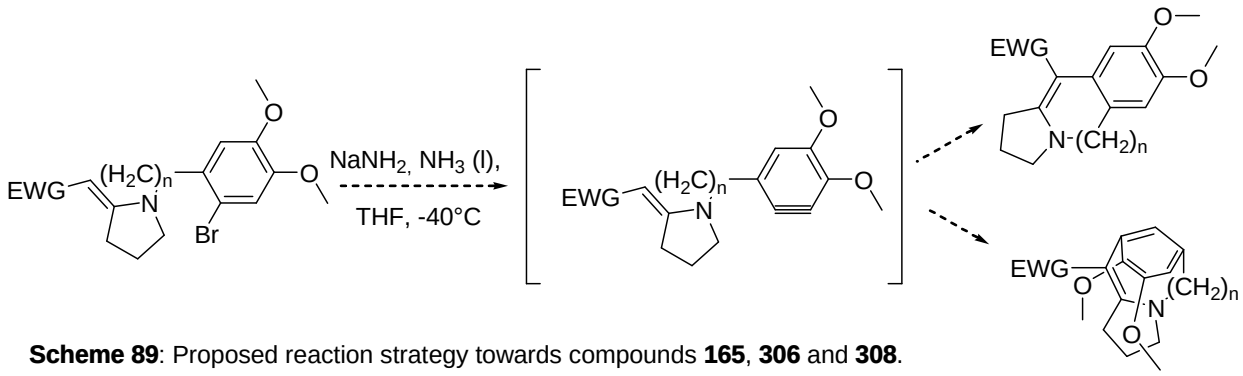
The enaminones were subjected to a number of oxidative olefin/aryl coupling reaction but to no avail, except when compounds **305** and **306** were formed by palladium(II) acetate coupling reaction in acetic acid at moderate temperatures. Other interesting results were formation of the vanadium intermediates **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 derivetives 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**.

CHAPTER 4: APPROACHES TOWARDS SESSILIFOLIAMIDE NUCLEUS

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

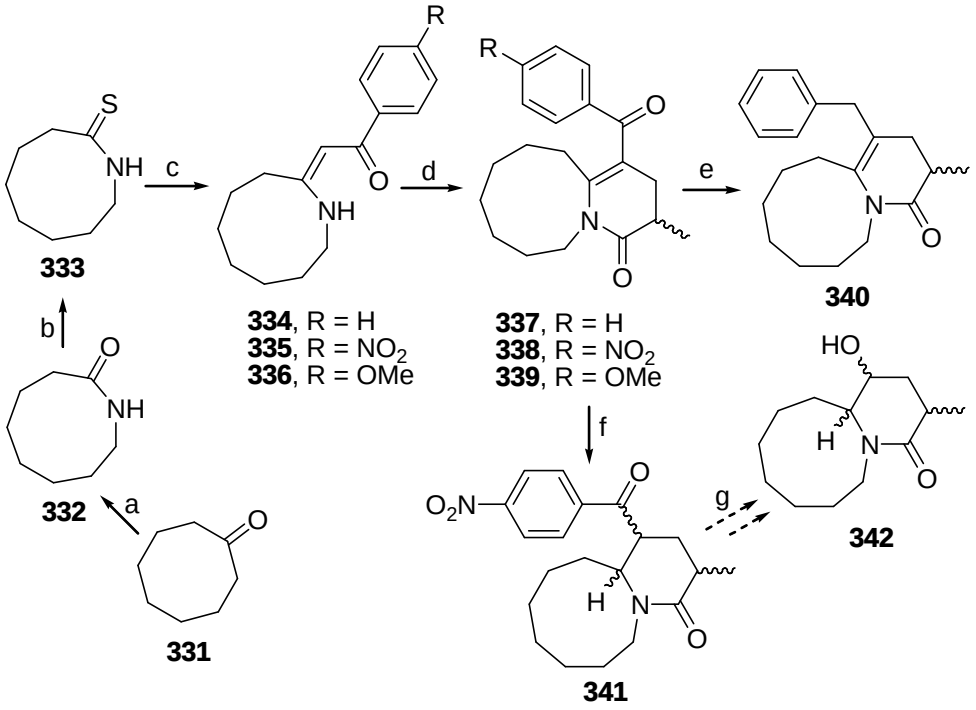
An opportunity of making the pyrido[1,2-*a*]azonine nucleus based on work previously done in our laboratories[144] presented itself as a side issue in this project. The pyrido[1,2-*a*]azonine nucleus contains a nine-membered and six-membered fused units system that can be used a scaffold in creating 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.[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 ν_{max} = 3301 and 1651 cm^{-1} for the lactam N*H* and the amide's carbonyl group respectively. The ^{1}H NMR spectrum showed a singlet at δ 6.36 ppm for the N*H* proton, while a multiplet at δ 3.36 ppm and a triplet with *J* = 6.35 Hz at δ 2.43 ppm represented the α and η-protons of the lactam respectively. The ^{13}C NMR spectrum revealed the presence of the lactam's carbonyl carbon at δ 178.1 ppm.

Forming the six-membered ring onto the nine-membered ring required a combination of a tandem Michael addition/acylation reactions between N*H* vinylogous amides and methacrylic anhydride. The N*H* vinylogous amides had to be synthesised from thiolactam **333** in an Eschenmoser sulphide contraction[122] reaction. Thiolactam **333** was made from lactam **332** in a thionation reaction.[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 N*H* proton at ν_{max} = 3407 cm^{-1}. The ^{1}H NMR spectrum

revealed a downfield chemical shift of N*H* 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 ^{13}C 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: *Reagents and Conditions*: (a) Sodium azide (1.54 eq), HCl (conc), 4 h at 0 - r.t., **332** = 98%; (b) P_2S_5 (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) H_2 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 N*H* 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 α-protons of the ketone in the sulphur extrusion stage.

The IR spectrum of (*Z*)-2-(azonan-2-ylidene)-1-phenylethanone **334** had peaks at ν_{max} = above 3000, 1739, 1586 and 1474 cm^{-1} for the enaminone N*H*, ketone carbonyl, vinyl and aromatic groups respectively. The ^{1}H NMR spectrum showed two singlets at δ 11.77 and 5.63 ppm for the enaminone N*H* and vinyl protons, indicating that the Eschenmoser sulphide contraction reaction was a success. The much deshielded N*H* signal strongly suggests intramolecular hydrogen bonding to the carbonyl group, implying that the compound has *Z* geometry. The two multiplets at δ 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 δ 2.43 ppm for the γ-protons of the ketone, showing the lack of space deshielding from the oxygen atom. The ^{13}C NMR spectrum showed peaks δ 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 δ 140.6, 130.3, 128.1, 126.8 ppm. The HRMS found $[M+H]^+$ equal to 244.1711 for molecular formula $C_{16}H_{22}NO^+$ 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 ν_{max} = above 3000, 1739, 1586, 1555 and 1474 cm^{-1} for the enaminone N*H*, ketone carbonyl, vinyl and aromatic groups respectively. The ^{1}H NMR spectrum showed two singlets at δ 12.02 and 6.18 – 4.65 ppm for the enaminone's N*H* 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 δ 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 δ 2.51 ppm for the γ-protons of the ketone, and the highly deshielded N*H* signal. The ^{13}C NMR spectrum showed peaks at δ 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 $C_{16}H_{21}N_2O_3^+$ 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 N*H*, 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 N*H* 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 ^{13}C 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 N*H* vinylogous amides.[148] 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(6*H*)-one **337**, 3-methyl-1-(4-nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-4(6*H*)-one **338** and 1-(4-methoxybenzoyl)-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-4(6*H*)-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 N*H* 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 ^{13}C NMR spectrum revealed the absence of the vinyl carbon peak at δ 91.0 ppm of **334**'s

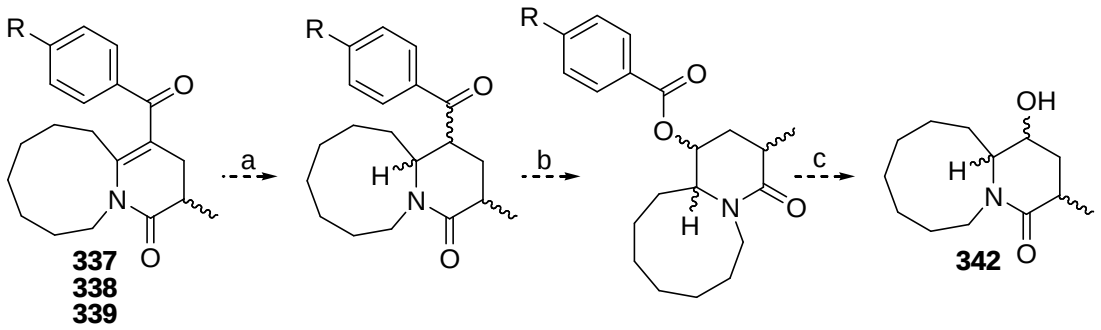
spectrum and the presence of quaternary alkene carbon peak at δ 116.6 ppm for the α-carbon of the ketone. The amide carbonyl carbon peak was δ 173.5 ppm confirming that the isomer that had formed only contained one ketone group. The HRMS found $[M+H]^+$ equal to 312.1970 for a molecular formula $C_{20}H_{26}NO_2^+$ with exact calculated mass of 312.1958.

The melting point of **338** was 104 – 105 °C. The IR spectrum had peaks at ν_{max} = 1670, 1598 and 1452 cm^{-1} for the ketone and amide carbonyl, alkene and aromatic groups. The ^1H NMR spectrum revealed the absence of enaminone N*H* 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 $C_{20}H_{25}N_2O_4^+$ with exact calculated mass of 357.1809.

The IR spectrum of **339** had peaks at ν_{max} = 1720 and 1548 cm^{-1} for the ketone and amide carbonyl, alkene and aromatic groups. The ^1H NMR spectrum revealed the absence of enaminone N*H* 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(1*H*)-one **342** (**Scheme 91**).

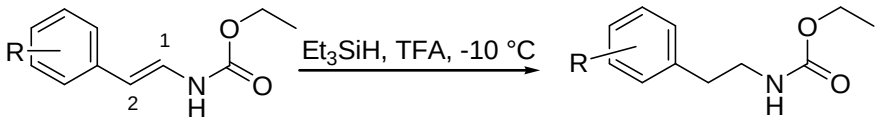


Scheme 91: *Proposed synthetic path towards* **342**: (a) Hydrogenation; (b) Baeyer Villiger Oxidation; (c) Hydrolysis.

A reaction mixture containing **337** and palladium on carbon in methanol was stirred under hydrogen atmosphere (balloon) at room temperature for 20 hours.[149] This resulted in 31% yield of 1-benzyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-4(6*H*)-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*.[145]

The IR spectrum of **340** had peaks at ν_{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 δ 3.69 ppm for the benzylic protons. The ^{13}C NMR spectrum showed the absence of the ketone carbonyl carbon peak at δ 196.7 ppm of **337**'s spectrum, followed by an upfield chemical shift of the δ-carbon peak to δ 137.9 ppm owing to the replacement of the ketone carbonyl carbon by CH_2. The amide carbonyl carbon peak and the γ-carbon peak of the amide were at δ 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**).[150]



Scheme 92: Et_3SiH-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(1*H*)-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 ν_{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 δ 4.08 – 3.99 ppm for the δ-proton of the amide and a doublet of doublet of doublets with *J* = 10.5, 7.6, 5.3 Hz for the α-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 δ 1.23 ppm indicating that there were diastereomers. The ^{13}C NMR spectrum revealed the absence of quaternary alkene carbon peaks at δ 154.7 and 114.8 ppm of **338**'s spectrum and the presence of peaks at δ 60.3 and 45.9 ppm for the δ-carbon of the amide and for the α-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 constrains. 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

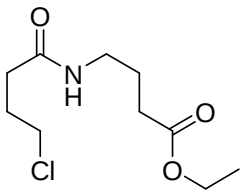
Glassware was washed and dried in an oven at 110 °C for moisture sensitive reactions. Reactions were done either under nitrogen atmosphere, in vessels open to atmospheric pressure, in sealed tubes in a microwave reactor, and oven reactor as indicated for individual experiments. Solvents used in reactions 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 (δ) are reported in parts per million (ppm) relative to TMS. The multiplicity is abbreviated as follows: d = doublet, m = multiplet, q = quartet, t = triplet ands = 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

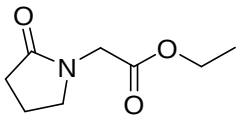
Synthesis of ethyl 4-(4-chlorobutanamido)butanoate 139



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-chlorobutryl 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 × 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_f 0.69 (EtOAc: Hex, 1:0); ν_{max}/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]

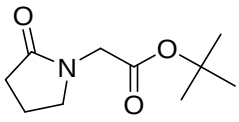


NaH 60% in oil (0.395 g, 16.45 mmol, 1.4 eq) was washed with Hex (3 × 5 mL) in a two necked round bottom flask under nitrogen atmosphere. Clean NaH was then dried under high vacuum. Pyrrolidin-2-one **140** (1.00 g, 11.8 mmol, 1 eq) in dry DCM (5 mL) was added to the two necked round bottom flask all 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; ν_{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* **170** (1.828 g, 91%) as oil; The analytical data was as shown above.

Synthesis of *tert*-butyl 2-(2-oxopyrrolidin-1-yl)acetate 172[162,163]

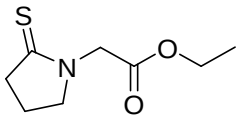


NaH 60% in oil (0.395 g, 16.45 mmol, 1.4 eq) was washed with hexane (3 × 5 m) in a two necked round bottom flask under nitrogen atmosphere. Clean NaH was then dried under high vacuum. Pyrrolidin-2-one **140** (1.00 g, 11.75 mmol, 1 eq) in dry DCM (5 mL) was added to the two necked round bottom flask 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 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 *tert-butyl 2-(2-oxopyrrolidin-1-yl)acetate* **172** (1.047 g, 48%) as a low melting solid; ν_{max}/cm^{-1} 2997 (w, C-H), 1765 (s, C=O), 1170 (s, C-O) and 1011 (s, C-N); ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 **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

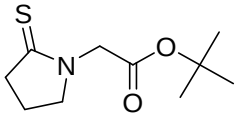
room temperature for 24 h. 1 M HCl was added to the reaction mixture adjusting the pH to pH~5 and the organic was extracted with diethyl ether (3 × 40 mL). The resulting organic layer was dried over $MgSO_4$ and evaporated in *vacuo*. The resulting residue was purified by silica gel column chromatography 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



Ethyl 2-(2-oxopyrrolidin-1-yl)acetate **170** (0.400 g, 2.34 mmol, 1 eq) and of P_2S_5 (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 K_2CO_3 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 $MgSO_4$ 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; R_f 0.29 (EtOAc: Hex, 3:7); ν_{max}/cm^{-1} 2954 (w, C-H), 1733 (s, C=O), 1131 (m, C-N) and 1034 (m, C-O); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 167.0, 61.5, 55.5, 49.0, 44.3, 19.7, 14.1.

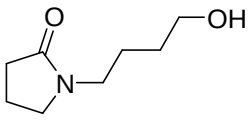
Synthesis of *tert*-butyl 2-(2-thioxopyrrolidin-1-yl)acetate 173



tert-Butyl 2-(2-oxopyrrolidin-1-yl)acetate **172** (0.400 g, 2.01 mmol, 1 eq) and of P_2S_5 (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 K_2CO_3 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 $MgSO_4$ and evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography

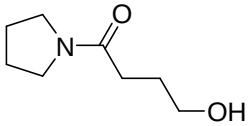
eluting with 30% EtOAc: Hex to yield *tert-butyl 2-(2-thioxopyrrolidin-1-yl)acetate* **173** (0.385 g, 89%) as an oil; R_f 0.38 (EtOAc: Hex, 3:7); ν_{max}/cm^{-1} 2998 (w, C-H), 1747 (s, C=O), 1135 (m, C-N) and 1044 (m, C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 4.44 (s, 2H), 3.83 (t, *J* = 7.3 Hz, 2H), 3.05 (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, $CDCl_3$) δ 203.27, 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 × 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.

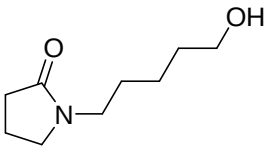
1-(4-Hydroxybutyl)pyrrolidin-2-one **180**: R_f 0.26 (MeOH: EtOAc, 1:4); ν_{max}/cm^{-1} 3441 (s, br, O-H), 2922 (w, C-H), 1669 (s, C=O), 1100 (m, C-O) and 1065 (m, C-N); ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 1H), 3.63 (t, *J* = 5.9 Hz, 2H), 3.41 (t, *J* = 7.1 Hz, 2H), 3.30 (t, *J* = 7.0 Hz, 2H), 2.39 (t, *J* = 8.2 Hz, 2H), 2.11 – 1.77 (m, 2H), 1.71 – 1.47 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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); ν_{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); ^1H NMR (300 MHz, MeOD) δ 3.46 (t, *J* = 6.4 Hz, 4H), 3.09 (t,

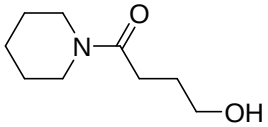
J = 6.5 Hz, 2H), 2.16 (t, *J* = 7.6 Hz, 2H), 1.77 – 1.62 (m, 2H), 1.45 (m, 4H); ^{13}C NMR (75 MHz, MeOD) δ 175.9, 62.6, 62.3, 40.2, 33.7, 31.0, 29.9, 26.9.

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



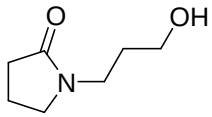
Dihydrofuran-2(3*H*)-one **13** (0.834 g, 9.69 mmol, 1 eq) and 5-aminopentan-1-ol (1.00 g, 9.96 mmol, 1 eq) was reacted neat in a sealed tube reactor under microwave conditions: 150 W, 220 °C, 20 min. The resulting reaction mixture was cooled, dissolved in water and extracted with diethyl ether (3 × 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); ν_{max}/cm^{-1} 3384 (s, br, O-H), 2929 (w, C-H), 1701 (s, C=O), 1239 (m, C-O) and 1129 (m, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.



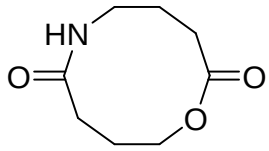
4-Hydroxy-1-(piperidin-1-yl)butan-1-one **183**: R_f 0.27 (MeOH: EtOAc, 1:4); ν_{max}/cm^{-1} 3513 (s, br, O-H), 2968 (w, C-H), 1697 (s, C=O), 1230 (m, C-O) and 1140 (m, C-N); ^{1}H NMR (300 MHz, MeOD) δ 3.57 (td, *J* = 6.4, 3.5 Hz, 4H), 3.18 (t, *J* = 6.9 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 1.90 – 1.75 (m, 2H), 1.64 – 1.46 (m, 4H), 1.46 – 1.32 (m, 2H) ppm; ^{13}C NMR (75 MHz, MeOD) δ 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 °C, 1 h, 10 min). The resulting reaction mixture was then 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 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; ν_{max}/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, $CDCl_3$) δ 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, $CDCl_3$) δ 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

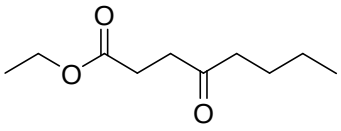


Dihydrofuran-2(3*H*)-one **13** (0.203 g, 2.40 mmol, 1.2 eq) and ethyl 4-aminobutyrate hydrochloride (0.335 g, 2.00 mmol, 1 eq) was reacted neat in a sealed tube reactor under microwave conditions: 150 W, 220 °C, 10 min. The reaction mixture was cooled down to room temperature. The residue was purified 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; ν_{max}/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, $CDCl_3$) δ 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, $CDCl_3$) δ 179.5, 177.9, 68.5, 42.3, 30.0, 27.6, 21.9, 20.5.

Dihydrofuran-2(3*H*)-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



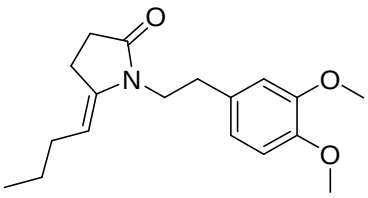
Conditions (i): Ethyl 4-chloro-4-oxobutanoate (5.00 mL, 35 mmol, 1 eq) and $Fe(acac)_3$ (0.371 g, 1.05 mmol, 0.03 eq) were added to an oven-dried two necked round bottom flask containing dry THF (50 mL) under nitrogen atmosphere, equipped with a dropping funnel containing prepared *n*-butylmagnesium 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 $NaHCO_3$ solution, distilled water and dried over $MgSO_4$. 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; R_f 0.45 (EtOAc: Hex, 1:5); ν_{max}/cm^{-1} 2991 (w, C-H), 1754 (s, C=O), 1241 (s, C-O); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

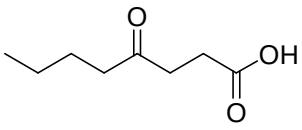
Conditions (iv): Ethyl 4-chloro-4-oxobutanoate (5.00 mL, 35 mmol, 1 eq) and $Fe(acac)_3$ (0.371 g, 1.05 mmol, 0.03 eq) were added to an oven dried two necked round bottom flask containing dried THF (50 mL), equipped with a dropping funnel containing butylmagnesium chloride (20 mL, 1.6 M, 35 mmol, 1 eq) 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



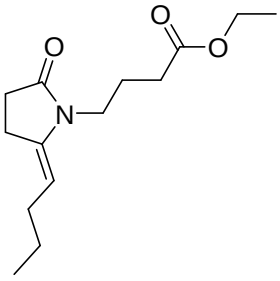
Ethyl 4-oxooctanoate **188** (0.123 g, 0.731 mmol, 1 eq), homoveratrylamine **160** (0.146 g, 0.804 mmol, 1.1 eq), acetic acid (0.220 g, 3.66 mmol, 5 eq) and 4 Å molecular sieves were heated under reflux in toluene (45 mL) under nitrogen atmosphere for 45 h. The resulting reaction mixture was evaporated *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); ν_{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, $CDCl_3$) δ 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



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 $MgSO_4$ 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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

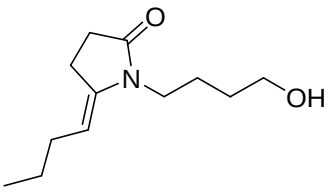


4-Oxooctanoic acid **194** (1.50 g, 9.48 mmol, 1 eq) and $SOCl_2$ (1.13 g, 9.48 mmol, 1 eq) in toluene (20 mL) was heated under reflux for 3.5 h under nitrogen atmosphere. Ethyl 4-aminobutyrate hydrochloride (2.38 g, 14.22 mmol, 1.5 eq) and K_2CO_3 (3.94 g, 28.44 mmol, 3 eq) were added to the reaction 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 $MgSO_4$, 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); ν_{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.

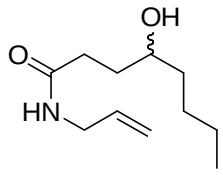
Synthesis of (*E*)-5-butylidene-1-(4-hydroxybutyl)pyrrolidin-2-one 198



Ethyl 4-oxooctanoate **188** (1.34 g, 7.21 mmol, 1 eq), 4-amino-1-butanol (0.643 g, 7.21 mmol, 1eq) 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

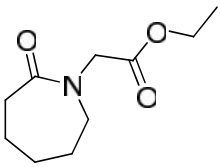
DCM (3 × 30 mL).The organic solvent was dried over $MgSO_4$ and evaporated in *vacuo.* The resulting residue was purified by silica gel column chromatography eluting with 10,20, 33, 40% EtOAc: Hex to yield *(E)-5-butylidene-1-(4-hydroxybutyl)pyrrolidin-2-one* **198** (0.3595 g, 24%) as an oil; R_f 0.41 (EtOAc: Hex, 1:3); ν_{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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 139.1, 100.6, 64.0, 39.3, 28.9, 28.8, 26.2, 23.3, 23.1, 21.4, 13.7.

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



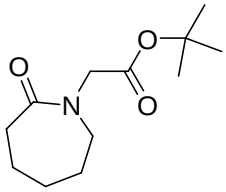
5-Butyl-dihydrofuran-2(3*H*)-one **200** (0.800 g, 5.63 mmol, 1 eq) and allylamine (0.321 g, 5.63 mmol, 1 eq) and HCl (10 drops) were irradiated neat in a microwave reactor under these conditions (Stage 1: 100 w, 60 °C, 1 h; Stage 2: 150 w, 100°C, 0.5 h). The resulting reaction mixture was cooled, dissolved in water and extracted with diethyl ether (3 × 5 mL). The resulting organic layer was dried over $MgSO_4$ 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; R_f 0.13 (EtOAc: Hex, 2:3); ν_{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); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1H), 5.75 (dtd, *J* = 15.8, 10.6, 5.5 Hz, 1H), 5.07 (ddd, *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 (dtd, *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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{11}H_{22}NO_2^+$ 200.1645.

Synthesis of ethyl 2-(2-oxoazepan-1-yl)acetate 204[162,163]



NaH 60% in oil (2.121 g, 53.01 mmol, 1 eq) was washed with Hex (3 × 10 mL) in a two necked round bottom flask under nitrogen atmosphere. Clean NaH 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 (30mL) 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 later 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 – 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_f 0.47 (EtOAc: Hex, 3:2); ν_{max}/cm^{-1} 2937 (w, C-H), 1721 (s, C=O), 1232 (s, C-O) and 1045 (s, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 169.7, 61.0, 51.2, 50.4, 36.9, 29.9, 28.0, 23.2, 14.1.

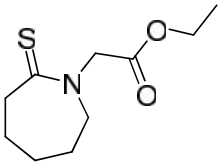
Synthesis of *tert*-butyl 2-(2-oxoazepan-1-yl)acetate 205[162,163]



NaH 60% in oil (0.254 g, 10.60 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. 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,

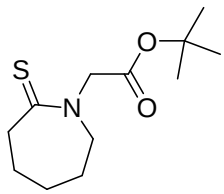
1.2 eq) in THF (20 mL) was added all at once and the reaction mixture was left to stir at room temperature for 22 h. The reaction mixture was dissolved in water in a separating funnel and the organic was extracted with diethyl ether (3 × 40 mL). The resulting organic layer was dried over $MgSO_4$ and 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; R_f 0.43 (EtOAc: Hex, 3:2); ν_{max}/cm^{-1} 2940 (w, C-H), 1732 (s, C=O), 1221 (s, C-O) and 1015 (s, C-N); ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 2H), 3.40 (m, 2H), 2.64 – 2.51 (m, 2H), 1.74 (s, 6H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 208[147]



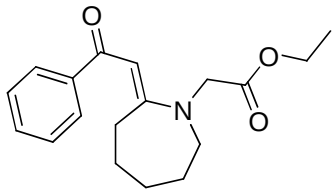
Ethyl 2-(2-oxoazepan-1-yl)acetate **204** (9.50 g, 47.7 mmol, 1 eq), P_2S_5 (5.299 g, 23.84 mmol, 0.5 eq) and hexamethyldisiloxane (11.612 g, 71.51 mmol, 1.5 eq) were stirred in DCM (500 mL) at room temperature for 24 h under nitrogen atmosphere. A saturated solution of $NaHCO_3$ was poured onto the reaction mixture and the organic layer was extracted with DCM (3 × 50 mL). The resulting organic layer was then dried over $MgSO_4$ 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; R_f 0.62 (EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 2928 (w, C-H), 1739 (s, C=O), 1185 (s, C-O) and 1118 (s, C-N); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{10}H_{18}NO_2S^+$ 216.1053.

Synthesis of *tert*-butyl 2-(2-thioxoazepan-1-yl)acetate 209



tert-Butyl 2-(2-oxoazepan-1-yl)acetate **205** (1.00 g, 4.40 mmol, 1 eq), P_2S_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_2CO_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-thioxoazepan-1-yl)acetate* **209** (0.378 g, 35%) as an oil; R_f 0.53 (EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 2995 (w, C-H), 1741(s, C=O), 1176 (s, C-O) and 1127 (s, C-N); ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 207.9, 166.6, 82.0, 59.5, 56.0, 46.7, 29.2, 28.0, 26.4, 24.5.

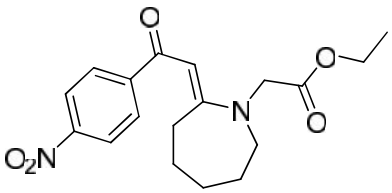
Synthesis of (*E*)-ethyl 2-(2-(2-oxo-2-phenylethylidene)azepan-1-yl)acetate 215[151,161]



Phenacyl bromide (0.490 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, 1eq) 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 to *(E)-ethyl 2-(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); ν_{max}/cm^{-1} 2932 (w, C-H),

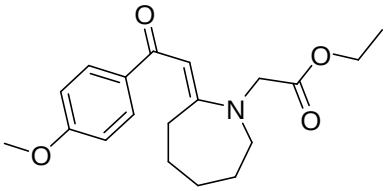
1709 (s, C=O), 1599 (s, C=C),1265 (s, C-O) and 1223 (s, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.8, 1.7, 2H), 7.37 (m, 3H), 5.47 (s, 1H), 4.23 (q, *J* = 7.1, 2H), 4.07 (s, 2H), 3.56 (m, 2H), 3.50 (m, 2H), 1.73 (m, 6H), 1.28 (t, *J* = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.4, 169.2, 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* $[M+H_2O+H]^+$ 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]



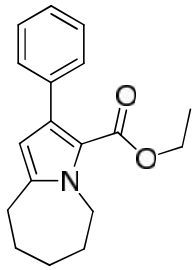
p-Nitrophenacyl bromide (0.600 g, 2.46 mmol, 1 eq) was added to a solution of ethyl 2-(2-thioxoazepan-1-yl)acetate **208** (0.500g, 2.46 mmol, 1 eq) in dry MeCN (10.00 mL). The resulting solution was stirred at room temperature for 2 h under nitrogen atmosphere, after which the *S*-alkylation was complete 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, 1eq) 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-(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); ν_{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 (w, N-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.9, 2H), 7.91 (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, $CDCl_3$) δ 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 $C_{18}H_{23}N_2O_5^+$ 347.1601.

Synthesis of (*E*)-ethyl 2-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)azepan-1-syl)acetate 217[151,161]



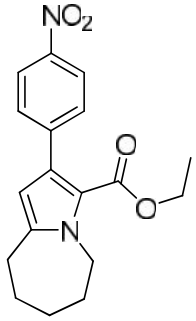
2-Bromo-1-(4-methoxyphenyl)ethanone (0.532 g, 2.32 mmol, 1 eq) was added to a solution of ethyl 2-(2-thioxoazepan-1-yl)acetate **208** (0.500 g, 2.32 mmol, 1 eq) in dry MeCN (5.00 mL). The resulting solution was stirred at room temperature for 40 min, after which the *S*-alkylation was complete as shown 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_f 0.44 (EtOAc: Hex, 1:1); ν_{max}/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, $CDCl_3$) δ 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, $CDCl_3$) δ 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* $[M+H_2O+H]^+$ found 350.1969, calcd for $C_{19}H_{28}NO_5^+$ 350.9162.

Synthesis of ethyl 2-phenyl-6,7,8,9-tetrahydro-5*H*-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 $MgSO_4$ 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; R_f 0.83 (EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 2927 (w, C-H), 1683 (s, C=O), 1471, 1434 (m, C=C), 1183 (s, C-O) and 1122 (s, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{22}NO_2^+$ 284.1645.

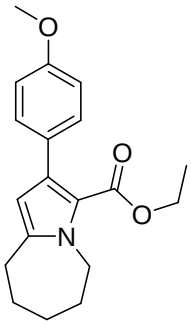
Synthesis of ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate 223



(*E*)-Ethyl 2-(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 $MgSO_4$ 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; R_f 0.81 (EtOAc: Hex, 1:1); ν_{max}/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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{21}N_2O_4^+$ 329.1496.

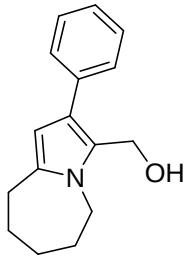
Synthesis of ethyl 2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate 224



(*E*)-Ethyl 2-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)azepan-1-yl)acetate **217** (20.1 mg, $6.67e^{-2}$ 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 $MgSO_4$ 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; R_f 0.79 (EtOAc: Hex, 1:1); ν_{max}/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, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz,

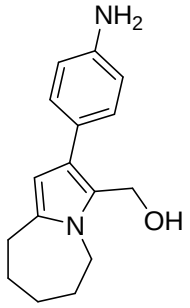
with unresolved fine coupling, 2H), 6.87 (m, d, *J* = 8.6 Hz, with unresolved fine coupling, 2H), 5.90 (s, 1H), 4.51 (s, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.77 – 2.72 (m, 2H), 1.85 – 1.75 (m, 4H), 1.69 (dt, *J* = 10.5, 5.3 Hz, 2H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{19}H_{24}NO_3^+$ 314.1751.

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



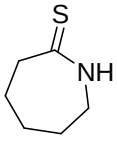
To a solution of ethyl 2-phenyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **222** (0.100 g, 0.353 mmol, 1 eq) in THF (10 mL) at 0 °C was added $LiAlH_4$ (0.013 g, 0.353 mmol, 1 eq). The reaction mixture was left to stir at room temperature for 12 h. The reaction mixture was adsorbed 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; R_f 0.59 (EtOAc: Hex, 1:1); ν_{max}/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); ^{1}H NMR (300 MHz, $CDCl_3$) 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-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)methanol 226



To a solution of ethyl 2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5*H*-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 $LiAlH_4$ (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; R_f 0.49 (EtOAc: Hex, 1:1); ν_{max}/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); ^{1}H 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); ^{13}C 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

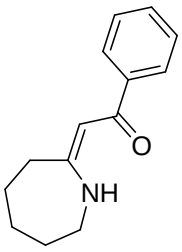


Azepan-2-one **175** (5.00 g, 44.2 mmol, 1 eq) and P_2S_5 (6.527 g, 22.09 mmol, 1 eq) were stirred in DCM (150 mL) at room temperature for 17 h under nitrogen atmosphere. A saturated solution of $NaHCO_3$ was poured into the reaction mixture and the organic layer was extracted with DCM (3 × 50 mL). The resulting organic layer was then dried over $MgSO_4$ 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; R_f 0.42 (EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 3423 (m, br, N-H), 2936 (w, C-H); ^1H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$) 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 P_2S_5 (4.517 g, 20.32 mmol, 0.46 eq), which were reacted at room temperature for 24 h. A saturated solution of $NaHCO_3$ 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 $MgSO_4$ 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.

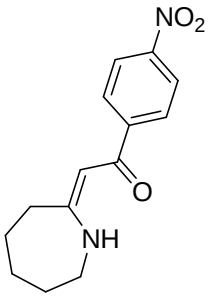
Synthesis of (Z)-2-(azepan-2-ylidene)-1-phenylethanone 230[151,161]



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; R_f 0.66 (EtOAc: Hex, 1:1); ν_{max}/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

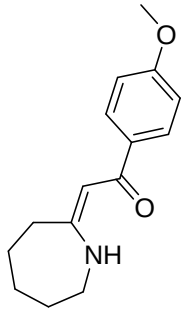
MHz, $CDCl_3$) δ 11.55 (s, 1H), 7.86 (m, 2H), 7.39 (m, 3H), 5.67 (s, 1H), 3.42 (dd, *J* = 10.0, 5.8 Hz, 2H), 2.55 – 2.37 (m, 2H), 1.91 – 1.52 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.2, 171.4, 140.7, 130.4, 128.1, 126.9, 91.0, 44.4, 35.4, 30.6, 29.3, 25.9; HRMS (ESI): *m/z* $[M+H]^+$ found 216.1393, calcd for $C_{14}H_{18}NO^+$ 216.1383.

Synthesis of (Z)-2-(azepan-2-ylidene)-1-(4-nitrophenyl)ethanone 231[151,161]



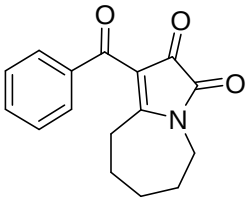
2-Bromo-1-(4-nitrophenyl)ethanone (1.36 g, 5.57 mmol, 1.2 eq) was added to a solution of azepane-2-thione **229** (0.600 g, 4.64 mmol, 1 eq) in dry MeCN (5 mL). The resulting solution was stirred at room temperature 30 seconds, after which the *S*-alkylation was complete as shown by the precipitation 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); ν_{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 $C_{14}H_{17}N_2O_3^+$ 261.1234.

Synthesis of (Z)-2-(azepan-2-ylidene)-1-(4-methoxyphenyl)ethanone 232[151,161]



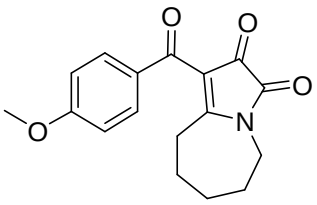
2-Bromo-1-(4-methoxyphenyl)ethanone (2.23 g, 9.75 mmol, 1.2 eq) was added to a solution of azepane-2-thione **229** (1.05 g, 8.12 mmol, 1 eq) in dry MeCN (12 mL). The resulting solution was stirred at room temperature for 2 minutes, after which the *S*-alkylation was complete shown by the precipitation 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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{15}H_{20}NO_2^+$ 246.1489.

Synthesis of 1-benzoyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione 233



(*Z*)-2-(Azepan-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 $NaHCO_3$ (5 mL) was added to the reaction mixture and extracted with DCM (35 mL). The resulting extracts were 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 *1-benzoyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2,3-dione* **233** (0.020 g, 16%) as an oil; R_f 0.28 (EtOAc: Hex, 2:3); ν_{max}/cm^{-1} 2984 (w, C-H), 1719 (m, C=O), 1544 (m, C=C) and 1460 (m, aromatic, C=C);^{1}H NMR (300 MHz, $CDCl_3$) 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).

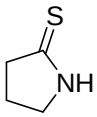
Synthesis of 1-(4-methoxybenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-2,3-dione 235



(Z)-2-(Azepan-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 $NaHCO_3$ (5 mL) was added to the residue and extracted with DCM (3 × 5 mL). The resulting extracts were 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 *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; R_f 0.28 (EtOAc: Hex, 1:1); ν_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

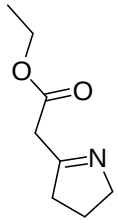
Pyrrolidine-2-thione 6



Pyrrolidin-2-one **140** (5.00 g, 58.7 mmol, 1 eq) and P_2S_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 $NaHCO_3$ 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 $MgSO_4$ 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 °C; R_f 0.33 (EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 3135 (w, br, N-H), 2947 (w, C-H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 206.0, 49.7, 43.3, 23.0.

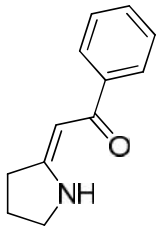
To a 250 mL two necked round bottom flask containing DCM (80 mL) equipped with a nitrogen line was added γ-butyrolactam **140** (5.00 g, 70.4 mmol, 1 eq), HMDSO (14.31 g, 88.11 mmol, 1.5 eq) and P_2S_5 (4.517 g, 20.32 mmol, 0.46 eq), which were reacted at room temperature for 7 days. A saturated solution of $NaHCO_3$ was poured onto the reaction mixture and the organic layer was extracted with DCM (3 × 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-3*H*-pyrrol-2-yl)acetate 238[122]



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 to *ethyl 2-(4,5-dihydro-3H-pyrrol-2-yl)acetate* **238** (0.653 g, 78%) as an oil; R_f 0.36 (EtOAc: Hex, 3:7); ν_{max} /cm^{-1}2898 (w, C-H), 1721 (s, C=O), 1422 (m, C=C), 1145 (m, C-N) and 1132 (s, C-O); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 168.9, 61.4, 60.5, 37.9, 32.8, 23.7, 14.0.

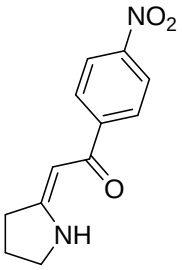
Synthesis of (Z)-1-phenyl-2-(pyrrolidin-2-ylidene)ethanone 239[151,161]



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; R_f 0.42 (EtOAc: Hex, 1:1); ν_{max}/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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

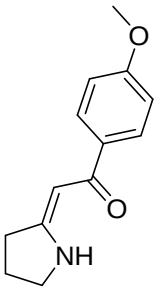
Synthesis of (*Z*)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone 240[151,161]



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; R_f 0.25 (EtOAc: Hex, 1:1); ν_{max}/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, $CDCl_3$) δ 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,

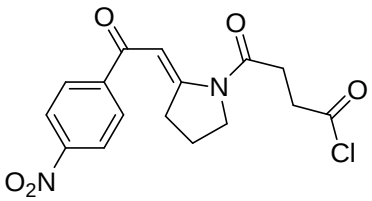
$CDCl_3$) δ 190.2, 170.6, 150.9, 148.6, 127.9, 123.5, 87.0, 48.0, 33.1, 30.9; HRMS (ESI): *m/z* $[M+H]^+$ found 233.0928, calcd for $C_{12}H_{13}N_2O_3^+$ 233.0921.

Synthesis of (Z)-1-(4-methoxyphenyl)-2-(pyrrolidin-2-ylidene)ethanone 241[151,161]



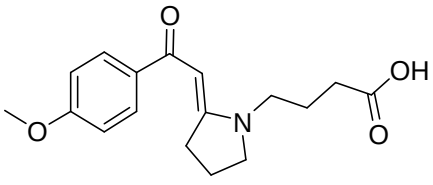
2-Bromo-1-(4-methoxyphenyl)ethanone (2.80 g, 12.2 mmol, 1.2 eq) was added to a solution of pyrrolidine-2-thione **6** (1.03 g, 10.2 mmol, 1 eq) in dry MeCN (12 mL). The resulting solution was stirred at room temperature for 2 minutes, after which the *S*-alkylation was complete shown by the precipitation 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; R_f 0.31 (EtOAc: Hex, 1:1); ν_{max}/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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{13}H_{16}NO_2^+$ 218.1176.

Synthesis of (*E*)-4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoyl chloride 245



(*Z*)-1-(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); ν_{max}/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}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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.

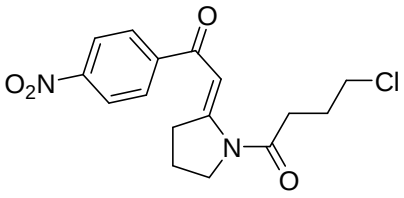
Synthesis of (*E*)-4-(2-(2-(4-methoxyphenyl)-2-oxoethylidene)pyrrolidin-1-yl)butanoic acid 246



(*Z*)-1-(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 × 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-*

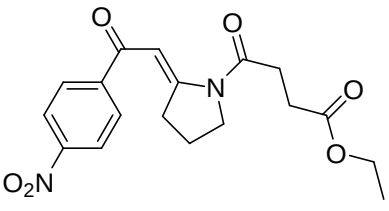
yl)butanoic acid **246** (0.349 g, 40%) as an oil; R_f 0.67 (EtOAc: Hex, 7:3); ν_{max}/cm^{-1} 3401 (m, br, O-H), 2993 (w, C-H), 1696 (s, C=O), 1622 (m, C=C), 1443 (m, C=C, aromatic), 1120 (s, C-O) and 1054 (m, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.44 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *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, $CDCl_3$) δ 187.3, 171.0, 170.8, 161.5, 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



(*Z*)-1-(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone **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); ν_{max}/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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

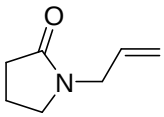
Synthesis of (*E*)-ethyl 4-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)-4-oxobutanoate 249



(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; R_f 0.24 (EtOAc: Hex, 7:3); ν_{max}/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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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* $[M+H_2O+H]^+$ found 379.1510, calcd for $C_{18}H_{23}N_2O_7^+$ 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.

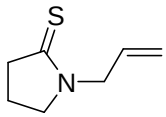
Synthesis of 1-allylpyrrolidin-2-one 259[162,163]



Dihydrofuran-2(3H)-one **13** (1.334 g, 15.49 mmol, 1eq) 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 $MgSO_4$ 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; R_f 0.43 (EtOAc: Hex, 1:0); ν_{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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 132.2, 117.2, 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 × 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 × 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 *1-allylpyrrolidin-2-one* **259** (1.471 g, 91%) as a low melting solid. The analytical data is as above.

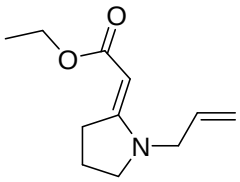
Synthesis of 1-allylpyrrolidine-2-thione 260



1-Allylpyrrolidin-2-one **259** (1.419 g, 10.05 mmol, 1 eq) and P_2S_5 (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 $NaHCO_3$ was poured into the reaction mixture and the organic layer was extracted with DCM (3 × 80 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 40% EtOAc: Hex to yield *1-allylpyrrolidine-2-thione* **260** (1.420 g, 78%) as an oil; R_f 0.50 (EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 2900 (w, C-H), 1624 (s, C=C), and 1131 (m, C-N); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_7H_{12}NS^+$ 142.0685.

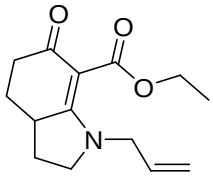
Dihydrofuran-2(3H)-one **13** (15.00 g, 174.2 mmol, 1 eq) and allylamine (10.00g, 175.1 mmol, 1.01eq) were heated at 220 °C in a sealed tube oven for 1 day. The resulting reaction mixture was dissolved in water (100 mL), adjusted to pH~ 8 using $NaHCO_3$ and extracted with EtOAc (3 × 100 mL). The resulting organic layer was dried over $MgSO_4$, evaporated *in vacuo* to yield crude *1-allylpyrrolidin-2-one* which was used in the next reaction without further purification. Crude 1-allylpyrrolidin-2-onewas dissolved in DCM (250 mL) followed by the addition of P_2S_5 (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 $NaHCO_3$ 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 $MgSO_4$ 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[151,161]



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, 1eq) 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; R_f 0.53 (EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 2935 (w, C-H), 1666 (s, C=O), 1514 (s, C=C), 1154 (s, C-O) and 1026 (s, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) 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* = 7.1 Hz, 2H), 3.15 (t, *J* = 7.6 Hz, 2H), 2.03 – 1.88 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{11}H_{18}NO_2^+$ 196.1332.

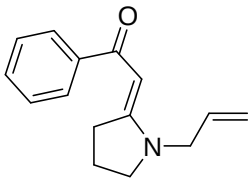
Synthesis of ethyl 1-allyl-6-oxo-2,3,3a,4,5,6-hexahydro-1*H*-indole-7-carboxylate 264



(*E*)-Ethyl 2-(1-allylpyrrolidin-2-ylidene)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 $MgSO_4$ 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; R_f 0.44 (EtOAc: Hex, 7:3); ν_{max}/cm^{-1} 2926 (w, C-H),1732 (s, C=O), 1645 (m, C=C), 1213 (s, C-O) and 1120 (m, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{14}H_{12}NO_3^+$ 250.1438.

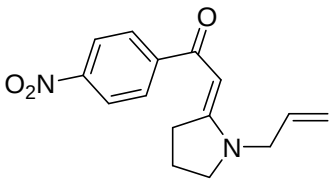
Synthesis of (*E*)-2-(1-allylpyrrolidin-2-ylidene)-1-phenylethanone 267[151,161]



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 $NaHCO_3$ 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-phenylethanone* **267** (1.7041 g, 93%) as an oil; R_f 0.30 (EtOAc: Hex, 1:1); ν_{max} /cm^{-1} 2889 (w, C-H), 1743 (s, C=O), 1582 (m, aromatic, C=C), 1432(m, C=C) and 1212 (s, C-O); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.8, 167.1, 142.0, 130.6 – 130.5 (m), 130.3, 128.0, 127.2 (t, *J* = 4.7

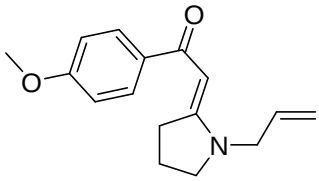
Hz), 117.7 (dd, *J* = 4.8, 2.5 Hz), 86.8, 52.6, 49.1, 33.8, 20.9; HRMS (ESI): *m/z* $[M+H]^+$ found 228.1390, calcd for $C_{15}H_{18}NO^+$ 228.1383.

Synthesis of (*E*)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-nitrophenyl)ethanone 268[151,161]



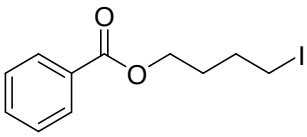
2-Bromo-1-(4-nitrophenyl)ethanone (1.90 g, 7.79 mmol, 1.1 eq) was added to a solution of 1-allylpyrrolidine-2-thione **260** (1.00 g, 7.08 mmol, 1 eq) in dry MeCN (3.00 mL). The resulting solution was stirred at room temperature for 2 h, after which the *S*-alkylation was complete as shown by the precipitation 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 $NaHCO_3$ solution. The resulting mixture was then extracted with EtOAc (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-nitrophenyl)ethanone* **268** (1.5121 g, 78%) as a solid; melting point = 129 – 130 °C; R_f 0.29 (EtOAc: Hex, 1:1); ν_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{15}H_{17}N_2O_3^+$ 273.1234.

Synthesis of (*E*)-2-(1-allylpyrrolidin-2-ylidene)-1-(4-methoxyphenyl)ethanone 269[151,161]



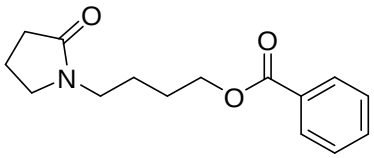
2-Bromo-1-(4-methoxyphenyl)ethanone (1.78 g, 7.79 mmol, 1.1 eq) was added to a solution of 1-allylpyrrolidine-2-thione **260** (1.00 g, 7.08 mmol, 1 eq) in dry MeCN (3.00 mL). The resulting solution was stirred at room temperature for 1.5 h, after which the *S*-alkylation was complete as shown by the 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, 1.1eq) 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 $NaHCO_3$ 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; R_f 0.28 (EtOAc: Hex, 1:1); ν_{max} /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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{16}H_{20}NO_2^+$ 258.1489.

Synthesis of 4-iodobutyl benzoate 277[152]



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_2SO_3, saturated Na_2CO_3 and dried over Mg_2SO_4. The solvent was evaporated *in vacuo* to yield *4-iodobutyl benzoate* **277** (92.8 g, 66%) as a colourless oil; ν_{max}/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, $CDCl_3$) δ 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, $CDCl_3$) δ 166.5, 133.0, 130.1, 129.6, 128.4, 63.9, 30.1, 29.7, 6.3.

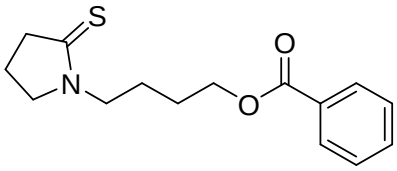
Synthesis of 4-(2-oxopyrrolidin-1-yl)butyl benzoate 278



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); ν_{max}/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, $CDCl_3$) δ 7.92

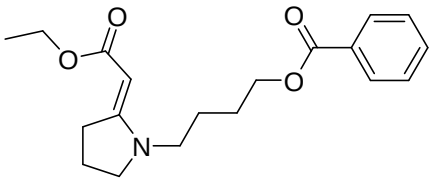
(d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 4.22 (t, *J* = 6.2 Hz, 2H), 3.26 – 3.20 (m, 4H), 2.23 (t, *J* = 8.1 Hz, 2H), 1.94 – 1.79 (m, 2H), 1.72 – 1.48 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 164.8, 131.4, 128.8, 128.0, 126.9, 62.9, 45.5, 40.5, 29.5, 24.6, 22.4, 16.4.

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



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); ν_{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.

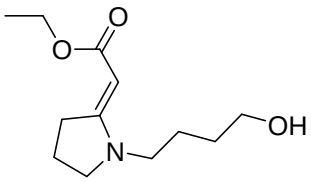
Synthesis of (*E*)-4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butyl benzoate 280[151,161]



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; R_f 0.53 (EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 2913 (w, C-H), 1728 (s, C=O), 1567 (m, C=C), 1514 (s, C=C, aromatic), 1243 (s, C-O) and 1034 (m, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) 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[153,154]



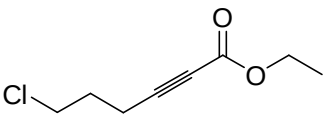
(i) To a 100 ml two neck round bottom flask equipped with a condenser under nitrogen atmosphere was added 4-amino-1-butanol (0.600 g, 6.73 mmol, 1eq), ethyl 6-chlorohex-2-ynoate **285** (1.175 g, 6.73 mmol, 1 eq), K_2CO_3 (1.860 g, 13.46mmol, 2 eq), NaI (2.018 g, 13.46 mmol, 2 eq) and 4Å molecular sieves 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 $MgSO_4$ 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** (1.530 g, 70%) as an oil; R_f 0.10 (EtOAc: Hex, 1:1); ν_{max}/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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 165.0, 77.5, 62.4, 58.3, 52.6, 46.2, 32.8,

30.1, 22.7, 21.1, 14.8; 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 × 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 × 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; ^{1}H 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); ^{13}C 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.

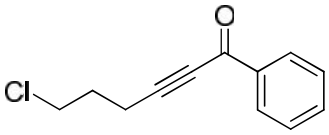
Synthesis of ethyl 6-chlorohex-2-ynoate 285[155,156]



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

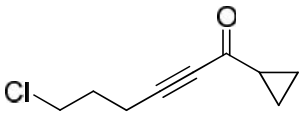
atmosphere, was added *n*-butyllithium (24.40 ml, 39 mmol, 1 eq) solution in THF. The reaction mixture was left to warm to –20°C in about 35 min. Ethyl chloroformate in THF (75 mL) was then added and the reaction mixture was left to warm to room temperature and stirred for 20 h. A saturated solution of $NaHCO_3$ 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 $MgSO_4$ 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; R_f 0.25 (EtOAc: Hex, 1:4); ν_{max}/cm^{-1} 2935 (w, C-H), 2238 (w, C≡C), 1714 (s, C=O) and 1200 (s, C-O); ^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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[155,156]



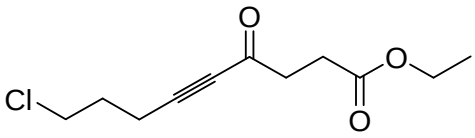
To a solution of 5-chloro-1-pentyne **282** (4.000 g, 39 mmol, 1 eq) in THF (50 mL), in a two necked round bottom flask under nitrogen atmosphere at – 78 °C, was added *n*-butyllithium (24.40 mL, 39 mmol, 1 eq) solution in THF. The reaction mixture was left to warm to –20 °C in about 35 min. Benzoyl 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 $NaHCO_3$ 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 $MgSO_4$ and evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography eluting with 5% EtOAc: Hex to yield *6-chloro-1-phenylhex-2-yn-1-one* **283** (5.124 g, 64%) as an oil; R_f 0.46 (EtOAc: Hex, 1:4); ν_{max}/cm^{-1} 2962 (w, C-H), 2202 (w, C≡C), 1640 (s, C=O), 1597, 1579 (m, C=C) and 1263 (s, C-0); ^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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[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 $NaHCO_3$ 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 $MgSO_4$ 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_f 0.37 (EtOAc: Hex, 1:4); ν_{max}/cm^{-1} 2963 (w, C-H), 2218 (w, C≡C), 1651 (s, C=O) and 1261, 1173 (m, C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 188.3, 91.4, 79.6, 43.3, 30.4, 24.4, 16.3, 10.9.

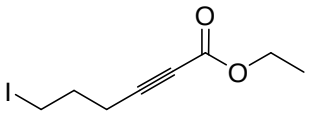
Synthesis of ethyl 9-chloro-4-oxonon-5-ynoate 284[155,156]



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 $NaHCO_3$ 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 $MgSO_4$ 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-*

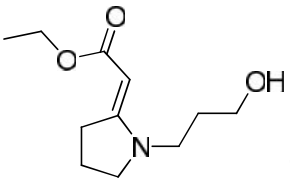
ynoate **284** (1.260 g, 28%) as an oil; R_f 0.25 (EtOAc: Hex, 1:4); ν_{max}/cm^{-1} 2940 (w, C-H), 2239 (w, C≡C), 1723 (s, C=O) and 1211 (s, C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.1 Hz, 2H), 3.65 (t, *J* = 6.2 Hz, 2H), 2.89 (t, *J* = 6.7 Hz, 2H), 2.63 (t, *J* = 6.6 Hz, 2H), 2.59 (t, *J* = 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 $MgSO_4$ 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; R_f 0.48 (EtOAc: Hex, 1:4); ν_{max}/cm^{-1} 2983 (w, C-H), 2238 (w, C≡C), 1708 (s, C=O) and 1248 (s, C-O); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 87.0, 86.7, 61.9, 31.0, 19.7, 14.0, 4.4.

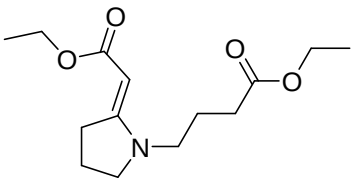
Synthesis of (*E*)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate 288[153,154]



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), K_2CO_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 × 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 70% EtOAc: Hex to yield *(E)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate* **288** (0.367 g, 81%) as oil; R_f 0.45 (EtOAc: Hex, 1:0); ν_{max}/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); ^{1}H NMR (300 MHz, $CDCl_3$) 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), 2.32 (s, 1H), 2.03 – 1.88 (m, 2H), 1.88 – 1.76 (m, 2H), 1.25 (t, *J* = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 143[153,154]

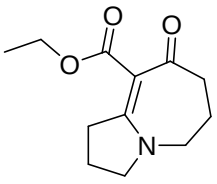


(i) To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added ethyl-4-aminobutyrate hydrochloride (0.961g, 5.73mmol, 1 eq), ethyl 6-chlorohex-2-ynoate **285** (1.000g, 5.73 mmol, 1 eq), K_2CO_3 (2.376 g, 17.19 mmol, 3 eq), NaI (1.718 g, 11.46 mmol, 2 eq) 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 $MgSO_4$ 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** (1.544 g, 74%) as an oil; R_f 0.62 (EtOAc: Hex, 2:3); ν_{max}/cm^{-1} 2980 (w, C-H), 1729 (s, C=O), 1587 (s, C=C)and 1133 (s, C-O); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

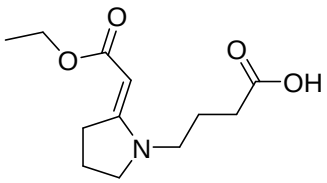
Synthesis of (*E*)-ethyl 8-oxo-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-9-carboxylate 144[122]



(*E*)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate **143** (0.300 g, 1.11 mmol, 1 eq) 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 $MgSO_4$ and evaporated *in vacuo.* The resulting acid residue was dissolved in MeCN (40 mL), followed by the addition of K_2CO_3 (0.307 g, 2.22 mmol, 2 eq) 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 $MgSO_4$ 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

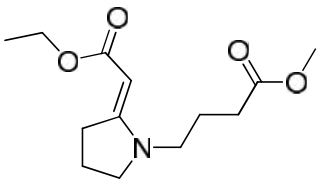
(EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 2934 (w, C-H), 1738 (m, C=O), 1622 (s, C=C), 1130 (s, C-O) and 1055 (s, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (q, *J* = 7.1 Hz, 2H), 3.65 (t, *J* = 7.1 Hz, 2H), 3.50 – 3.39 (m, 2H), 3.02 (t, *J* = 7.8 Hz, 2H), 2.74 – 2.62 (m, 2H), 2.19 (dt, *J* = 12.9, 6.5 Hz, 2H), 2.13 – 1.98 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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

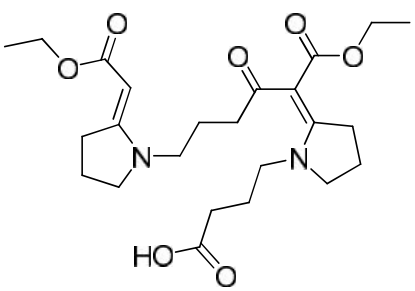


KOH (0.605 g, 10.8 mmol, 1.2 eq) was added to a round bottom flask containing a solution of (*E*)-ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate **143** (2.419 g, 8.98 mmol, 1 eq) in THF (30 mL) and water (20 mL). The reaction mixture was left to stir overnight in an open vessel. Acetic acid was added adjusting the pH of the solution to pH~6. The resulting solution then extracted with EtOAc (3 × 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); ν_{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, $CDCl_3$) δ 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



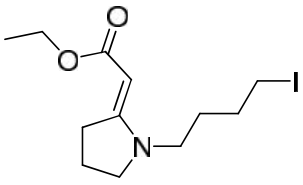
(i) (*E*)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate **143** (0.400 g, 1.48 mmol, 1 eq) and KOH (0.415 g, 7.40 mmol, 5 eq) was heated under reflux in a MeOH (10 mL) solution for 1 h. The resulting reaction mixture was neutralised by addition of HCl to pH~7 followed by the extraction of the organic layer into DCM (3 × 20 mL). The organic layer was dried over $MgSO_4$ and evaporated *in vacuo.* The resulting acid residue was dissolved in MeCN (40 mL) followed by the addition of K_2CO_3 (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 $MgSO_4$ 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; R_f 0.65 (EtOAc: Hex, 2:3); ν_{max}/cm^{-1} 2924 (w, C-H), 1732 (s, C=O), 1660 (m, C=C), 1175 (m, C-O) and 1095 (w, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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-*

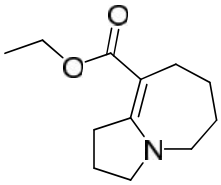
ylidene)pyrrolidin-1-yl)butanoic acid **291** (0.029 g, 4%) was obtained as an oil; R_f 0.33 (EtOAc: MeOH, 4:1); ν_{max}/cm^{-1}3340 (w, b, O-H), (2979 (w, C-H), 1711 (m, C=O), 1582 (s, C=C), 1132 (s, C-O) and 1054 (s, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 4.53 (s, 1H), 4.21 (q, *J* = 7.0 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), 3.03 (t, *J* = 7.8 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, $CDCl_3$) δ 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[122],[151,]



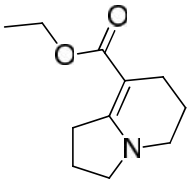
To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added to (*E*)-ethyl 2-(1-(4-hydroxybutyl)pyrrolidin-2-ylidene)acetate **278** (0.200 g, 0.880 mmol, 1 eq), imidazole (0.180 g, 2.649 mmol, 3 eq), iodine (0.688g, 2.649 mmol, 3 eq) and triphenylphosphine (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); ν_{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, $CDCl_3$) δ 4.51 (s, 1H), 4.09 (q, *J* = 7.1, 2H), 3.38 (t, *J* = 7.1, 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, $CDCl_3$) δ 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-1*H*-pyrrolo[1,2-*a*]azepine-9-carboxylate 147[151,122]



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_2HPO_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 ×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_f 0.49 (EtOAc: Hex, 2:3); ν_{max}/cm^{-1} 2932 (w, C-H), 1714 (s, C=O), 1543 (m, C=C), 1233 (s, C-O) and 1024 (s, C-N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.1, 2H), 3.28 (m, 4H), 2.99 (t, *J* = 7.6, 2H), 2.61 – 2.57 (m, 2H), 1.86 (m, 2H), 1.83 – 1.76 (m, 2H), 1.73 (m, 2H), 1.26 (t, *J* = 7.1, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 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-hexahydroindolizine-8-carboxylate 293[151,122]

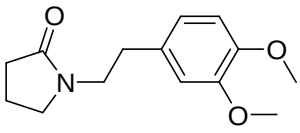


To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added (*E*)-ethyl 2-(1-(3-hydroxypropyl)pyrrolidin-2-ylidene)acetate **288** (0.120 g, 0.542 mmol, 1 eq), imidazole (0.111 g, 1.63 mmol, 3 eq) iodine (0.281 g, 1.08 mmol, 2 eq), triphenylphosphine (0.428 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 $MgSO_4$ 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; R_f 0.23 (EtOAc: Hex, 1:4); ν_{max}/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, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 159.2, 87.5, 58.4, 53.0, 45.0, 32.7, 21.6, 21.4, 21.0, 14.8.

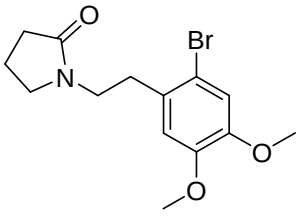
5.3 Experimental Section for Chapter 3

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



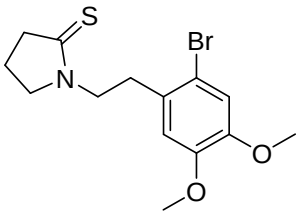
Homoveratrylamine **160** (3.055 g, 16.86 mmol, 1 eq) and dihydrofuran-2(3H)-one **13** (1.489 g, 17.29 mmol, 1.03 eq) were irradiated in a microwave reactor under these conditions (150 W, 220 °C, 3 h). The resulting reaction mixture was then cooled, dissolved in water and extracted with ethyl acetate (3 × 50 mL). The resulting organic layer was dried over $MgSO_4$ 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; meting point = 58 – 59 °C; R_f 0.17 (EtOAc: Hex, 1:0); ν_{max}/cm^{-1} 2989 (w, C-H), 1689 (m, C=O), 1451 (m, aromatic, C=C) and 1125 (m, C-O); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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



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); ν_{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, $CDCl_3$) δ7.00 (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, $CDCl_3$) δ 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

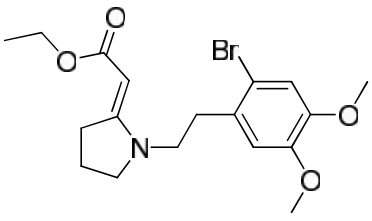


1-(3,4-Dimethoxyphenethyl)pyrrolidin-2-one **162** (1.486 g, 4.53 mmol, 1) and P_2S_5 (0.502 g, 2.26 mmol, 0.5 eq) were reacted in DCM (100 mL) in a two neck round bottom flask under nitrogen atmosphere at room temperature for 24 h. The resulting solution was filtered on celite and evaporated *in vacuo*. 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); ν_{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), 6.82 (s, 1H), 3.95 (t, *J* = 7.4 Hz, 2H), 3.85 (s, 6H), 3.57 (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(3*H*)-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 neutralised 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_2S_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[153,154]

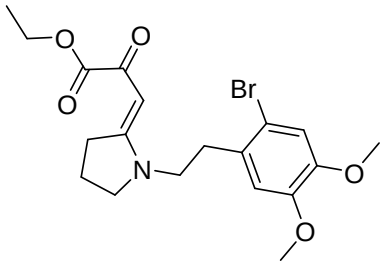


(i) To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added 2-(2-bromo-4,5-dimethoxyphenyl)ethanamine hydrochloride **319** (1.770 g, 5.19 mmol, 1 eq), ethyl 6-chlorohex-2-ynoate **285** (1.000 g, 5.19 mmol, 1 eq), K_2CO_3 (2.376 g, 17.19 mmol, 3 eq), NaI (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 $MgSO_4$ 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-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate* **164** (1.812 g, 88%) as an oil; R_f 0.24 (EtOAc: Hex, 1:2); ν_{max}/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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{25}BrNO_4^+$ 398.0961.

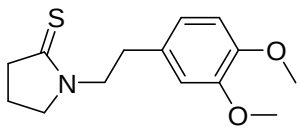
Ethyl bromoacetate (0.07 mL, 0.587 mmol, 1.1 eq) was added to a solution of 1-(2-bromo-4,5-dimethoxyphenethyl)pyrrolidine-2-thione **163** (0.184 g, 0.534 mmol, 1 eq) in dry MeCN (1.00 mL). The resulting solution was stirred at room temperature for 24 h under nitrogen atmosphere, after which the *S*-alkylation 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[151,161]



Ethyl bromopyruvate (0.10mL, 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; R_f 0.35 (EtOAc: Hex, 3:7); ν_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

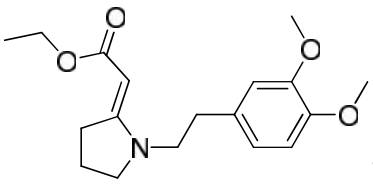
Synthesis of 1-(3,4-dimethoxyphenethyl)pyrrolidine-2-thione 302



1-(3,4-Dimethoxyphenethyl)pyrrolidin-2-one **161** (4.276 g, 17.15 mmol, 1 eq), P_2S_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 $MgSO_4$ 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; R_f 0.31 (EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 2964 (w, C-H), 1456 (s, C=C, aromatic), and 1120 (s, C-N); ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 – 6.72 (m, 3H), 3.95 (t, *J* = 7.4 Hz, 2H), 3.86 (2 × s, 6H), 3.52 (t, *J* = 7.3 Hz, 2H), 3.05 – 2.87 (m, 4H), 2.05 – 1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

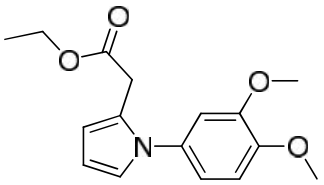
Synthesis of (*E*)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate 303[153,154]



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_2CO_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 × 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 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; R_f 0.66 (EtOAc: Hex, 1:0); ν_{max}/cm^{-1} 2978 (w, C-H), 1668 (s, C=O), 1585 (s, C=C), 1130 (s, C-O) and 1018 (s, C-N); ^1H NMR (300 MHz, $CDCl_3$) 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 × 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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* $[M+H]^+$ found 320.1853, calcd for $C_{18}H_{26}NO_4^+$ 320.1856.

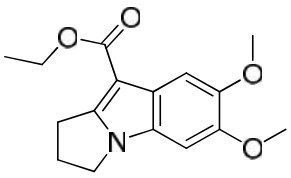
Ethyl 2-bromoacetate (0.41 mL, 3.31 mmol, 1.1 eq) was added to a solution of 1-(3,4-dimethoxyphenethyl)pyrrolidine-2-thione **302** (0.800 g, 3.01 mmol, 1 eq) in dry MeCN (2.00 mL). The resulting solution was stirred at room temperature for 4 h under nitrogen atmosphere, after which the *S*-alkylation 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.[151,161]

Synthesis of ethyl 2-(1-(3,4-dimethoxyphenyl)-1*H*-pyrrol-2-yl)acetate 305[158]



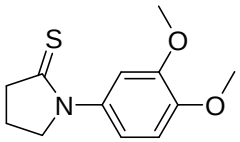
(*E*)-Ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate **304** (0.130 g, 0.446 mmol, 1 eq) and palladium acetate (0.010 g, 0.045 mmol, 0.1 eq) in acetic acid (20 mL) were heated to 80 °C in a two necked round bottom flask for 1 h, while bubbling oxygen gas for the duration. After cooling to room temperature the reaction mixture was reduced *in vacuo*. The organic residue was then treated with saturated $NaHCO_3$ solution to pH~8 and then extracted with dichloromethane (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 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_f 0.53 (EtOAc: Hex, 2:3); ν_{max}/cm^{-1} 2953 (w, C-H), 1730 (s, C=O), 1435 (m, aromatic, C=C), 1198 (s, C-O) and 1158 (s, C-N); ^1H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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* $[M+H]^+$ found 290.1319, calcd for $C_{16}H_{20}NO_4^+$ 290.1387.

Synthesis of ethyl 6,7-dimethoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate 306[158]



(*E*)-Ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate **304** (0.070 g, 0.240 mmol, 1 eq) and palladium acetate (5.4mg, 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 $NaHCO_3$ solution to pH~8 and then extracted with DCM (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 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; R_f 0.48 (EtOAc: Hex, 2:3); ν_{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, $CDCl_3$) 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), 3.93 (s, 3H), 3.26 (t, *J* = 7.5, 2H), 2.68 – 2.61 (m, 2H), 1.40 (t, *J* = 7.1, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{16}H_{20}NO_4^+$ 290.1387.

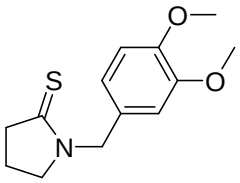
Synthesis of 1-(3,4-dimethoxyphenyl)pyrrolidine-2-thione 309



3,4-Dimethoxyaniline (2.262 g, 14.764 mmol, 1 eq) and dihydrofuran-2(3*H*)-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 P_2S_5 (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

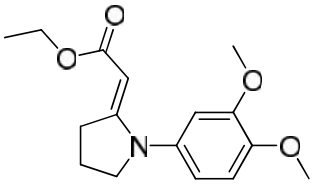
chromatography eluting with 30% EtOAc: Hex to yield *1-(3,4-dimethoxyphenyl)pyrrolidine-2-thione* **309** (3.196 g, 91%) as an oil; R_f 0.44 (EtOAc: Hex, 3:2); ν_{max}/cm^{-1} 2937 (w, C-H), 1509(s, aromatic, C=C), 1144 (s, C-O) and 1031 (s, C-N); ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 2.2 Hz, 1H), 6.97 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 4.12 (t, *J* = 7.2 Hz, 2H), 3.91 (2 × s, 6H), 3.25 (t, *J* = 7.9 Hz, 2H), 2.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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(3*H*)-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 °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 P_2S_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; R_f 0.52 (EtOAc: Hex, 3:2); ν_{max}/cm^{-1} 2939 (w, C-H), 1514 (s, aromatic, C=C), 1136 (s, C-O) and 1022 (s, C-N); ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 1.7 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 4.92 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.59 (t, *J* = 7.2 Hz, 2H), 3.09 (t, *J* = 7.9 Hz, 2H), 2.08 – 1.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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.

Synthesis of (*E*)-ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate 304[153,154]

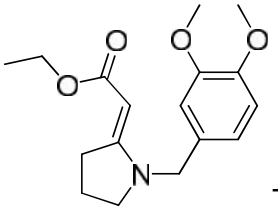


To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added 3,4-dimethoxyaniline (0.438 g, 2.86 mmol, 1 eq), ethyl 6-chlorohex-2-ynoate **285** (0.500 g, 2.86 mmol, 1 eq), K_2CO_3 (1.186 g, 0.858 mmol, 3 eq), NaI (0.857 g, 5.72 mmol, 2 eq) and 4Å molecular 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); ν_{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, $CDCl_3$) δ 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 (m, 2H), 1.21 (t, *J*= 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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, 1.1eq) 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

– 10% EtOAc: Hex to yield to *(E)-ethyl 2-(1-(3,4-dimethoxyphenyl)pyrrolidin-2-ylidene)acetate* **304** (0.432 g, 94%) as a solid. The spectra were as above.[151,161]

Synthesis of (*E*)-ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate 307[153,154]

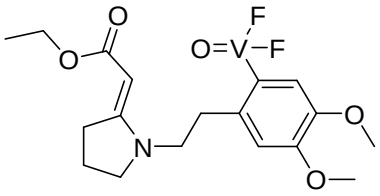


To a 100 mL two necked round bottom flask equipped with a condenser under nitrogen atmosphere was added (3,4-dimethoxyphenyl)methanamine (0.478 g, 2.86 mmol, 1 eq), ethyl 6-chlorohex-2-ynoate **285** (0.500 g, 2.86 mmol, 1 eq), K_2CO_3 (0.791 g, 5.72 mmol, 2 eq), NaI (0.857 g, 5.72 mmol, 2 eq) and 4Å 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); ν_{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

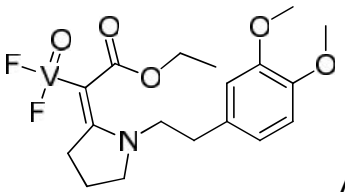
phosphite (0.33 mL, 1.52 mmol, 1.1 eq) and triethylamine (0.17 mL, 1.52 mmol, 1.1 eq) in MeCN (30 mL) and left stirring at room temperature for 19 h to induce sulphur extrusion. The resulting organic layer was evaporated in *vacuo*. The resulting residue was purified by silica gel column chromatography eluting with 5 – 10% EtOAc: Hex to yield to *(E)-ethyl 2-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-ylidene)acetate* **307** (0.400 g, 95%) as an oil.[151,161] The spectra are as above.

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



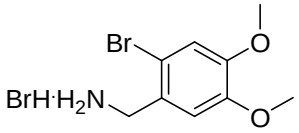
(*E*)-ethyl 2-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)acetate **303** (0.300 g, 0.939 mmol, 1 eq) in DCM (19 mL) was added all at once into a solution of VOF_3 (0.352 g, 2.82 mmol, 2 eq) and trifluoroacetic anhydride (0.4 mL) in a 2:1 solvent mixture of DCM and trifluoroacetic acid in a round 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-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)ethyl)-4,5-dimethoxyphenyl)(oxo)vanadium(V) fluoride* **311** (0.168 g, 42%) as an oil; ν_{max}/cm^{-1} 2992 (w, C-H), 1702 (s, C=O), 1590 (s, C=C), 1112 (s, C-O) and 1073 (s, C-N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.69 (s, 1H), 4.38 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 3.17 (t, *J* = 7.7 Hz, 2H), 3.06 (ddd, *J* = 15.8, 8.4, 2.4 Hz, 4H), 2.59 (dtd, *J* = 20.9, 13.5, 7.7 Hz, 2H), 1.83 (p, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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.

Synthesis of (*E*)-(1-(1-(3,4-dimethoxyphenethyl)pyrrolidin-2-ylidene)-2-ethoxy-2-oxoethyl)(oxo)vanadium(V) fluoride 312



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 $MgSO_4$ 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_{max}/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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

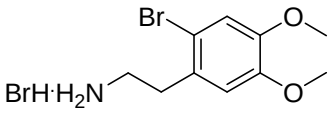
Synthesis of (2-bromo-4,5-dimethoxyphenyl)methanamine hydrobromide 118[159,160]



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

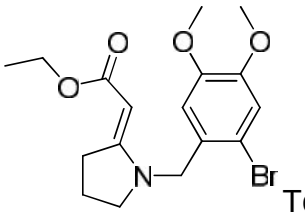
at room temperature for 2 h. The precipitated (2-bromo-4,5-dimethoxyphenyl)methanamine hydrobromide was filtered and washed with DCM (3 × 30mL) followed by Hex (3 × 30 mL). The resulting solid was dried *in vacuo.* The resulting organic layer was dried over $MgSO_4$ and then evaporated *in vacuo* to achieve a combined yield *(2-bromo-4,5-dimethoxyphenyl)methanamine hydrobromide* **118** (6.942 g, 88%) as a solid; ν_{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, D_2O) 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]



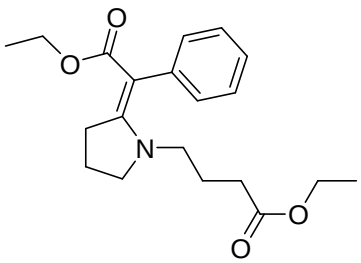
A bromine solution (1.15 mL, 22.32 mmol, 1 eq) in acetic acid (20 mL) was added drop-wise to a solution of 2-(3,4-dimethoxyphenyl)ethanamine **160** (4.00 g, 22.32 mmol, 1 eq) in acetic acid (80 mL). The solution was left stirring at room temperature for 2 h. The precipitated 2-(2-bromo-4,5-dimethoxyphenyl)ethanamine 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 $MgSO_4$ 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; ν_{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, $CDCl_3$) 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_2CO_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); ν_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 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[136]

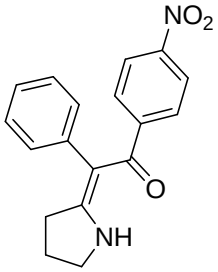


(i) (*E*)-Ethyl 4-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)butanoate **143** (0.120 g, 0.445 mmol, 1 eq), 2-

(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 $MgSO_4$, 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; R_f 0.63 (EtOAc: Hex, 1:1); ν_{max}/cm^{-1} 2982 (w, C-H), 1734 (m, C=O), 1567 (m, C=C), 1454 (m, aromatic, C=C) and 1110 (m, C-O); ^1H 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}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 $MgSO_4$, 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.

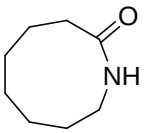
Synthesis of (*Z*)-1-(4-nitrophenyl)-2-phenyl-2-(pyrrolidin-2-ylidene)ethanone 328[136]



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 $MgSO_4$, 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; R_f 0.32 (EtOAc: Hex, 1:1); ν_{max}/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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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

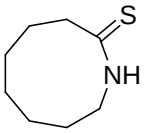
Synthesis of azonan-2-one 332[171]



Sodium azide (3.79 g, 61.0 mmol, 1.54 eq) was added potion 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;[172] ν_{max}/cm^{-1} 3301 (s, br, N-H), 2930 (s, C-H) and 1651 (s, C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.36 (s, 1H), 3.36 (m, 2H), 2.43 (t, *J* = 6.35, 2H), 1.81 (m, 2H) and 1.62 – 1.40 (m, 8H) ppm; ^{13}C NMR (75 MHz; $CDCl_3$) δ 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]

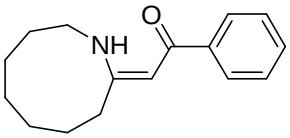


A mixture of azonan-2-one **332** (5.50 g, 38.9 mmol, 1 eq) P_2S_5 (4.33 g, 19.5 mmol, 0.5 eq) and hexamethyldisiloxane (12.41 mL, 58.4 mmol, 1.5 eq) in dry DCM (150 mL) in a 250 mL round bottom flask under nitrogen atmosphere was stirred at room temperature under nitrogen atmosphere for 20 h. Saturated aqueous K_2CO_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); ν_{max}/cm^{-1} 3407 (m, br, N-H); ^{1}H NMR (300 MHz; $CDCl_3$) δ 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; $CDCl_3$) δ 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 N*H* vinylogous amides from thiolactams

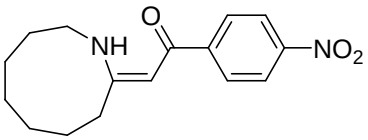
In separate reactions; phenacyl bromide, *para*-nitrophenacyl bromide or *para*-methoxyphenacyl bromide were added to a stirred solution of thiolactams in dry acetonitrile. The resulting solution was stirred at room temperature for 30 min, 2 min and 5 sec respectively, after which the *S*-alkylation 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



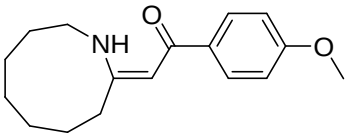
Azonane-2-thione **333** (1.300 g, 8.264 mmol, 1 eq) and phenacyl bromide (1.974 g, 9.917 mmol, 1.2 eq) in dry MeCN (20.00 mL) were reacted as described above, followed by the addition of triethylphosphite (1.648 g, 9.917 mmol, 1.2 eq) and triethylamine (1.003 g, 9.917 mmol, 1.2 eq) to give *(Z)-2-(azonan-2-ylidene)-1-phenylethanone* **334** (1.400 g, 70%) as an oil; R_f 0.72 (EtOAc: Hex, 1:1); ν_{max} /cm^{-1} above 3000 (m, br, N-H), 2927 (m, CH), 1739 (w, C=O), 1586 (m, C=C) and 1474 (m, aromatic, C=C); ^{1}H NMR (300 MHz; $CDCl_3$) 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); ^{13}C NMR (75 MHz; $CDCl_3$) δ 187.4, 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: $[M+H]^+$, 244.1711, $C_{16}H_{22}NO^+$ 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; R_f 0.67 (EtOAc: Hex, 1:1); ν_{max}/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); ^{1}H NMR (300 MHz; $CDCl_3$) δ 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; $CDCl_3$) δ 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)

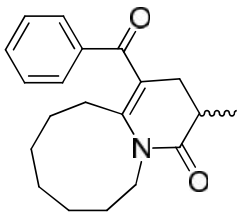


Azonane-2-thione **333** (1.00 g, 6.36 mmol, 1 eq) and 2-bromo-1-(4-methoxyphenyl)ethanone (1.60 g, 6.99 mmol, 1.1 eq) in dry MeCN (10.00 mL) were reacted as described above, followed by the addition of triethylphosphite (1.16 g, 6.99 mmol, 1.1 eq) and triethylamine (0.707 g, 6.99 mmol, 1.1 eq) to give *(Z)-2-(azonan-2-ylidene)-1-(4-methoxyphenyl)ethanone* **336** (1.59 g, 91%) as a solid; R_f 0.66 (EtOAc: Hex, 1:1); ν_{max} /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); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 186.8, 170.7, 161.5, 133.3, 128.6, 113.3, 90.5, 55.3, 43.7, 32.9, 30.3, 28.6, 27.3, 25.4, 22.5 ppm; HRMS (ESI) Found: $[M+H]^+$, 274.1807, $C_{17}H_{24}NO_2^+$ exact calculated mass: 274.1802.

Reactions of N*H* vinylogous amides with methacrylic anhydride

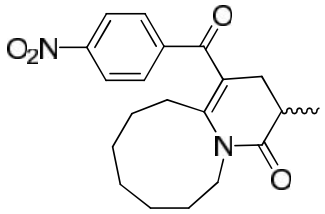
Methacrylic anhydride and the N*H* vinylogous amide were placed in a microwave tube. The sealed tube with its contents was subjected to 150W, 150 °C in a microwave reactor for 60 minutes. The crude products were purified by column chromatography over silica gel eluting with 10%, 20% and 30% EtOAc: Hex 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(6*H*)-one 337



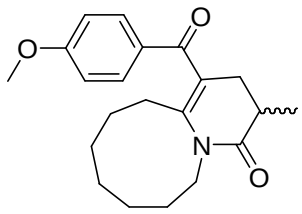
(*Z*)-2-(Azonan-2-ylidene)-1-phenylethenone **334** (471 mg, 1.94 mmol) and methacrylic anhydride (597 mg, 3.87 mmol, 2.0 eq) were heated in a microwave reactor as described above to give *1-benzoyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6H)-one* **337** (604 mg, 94%) as an oil; R_f 0.55 (EtOAc: Hex, 3:7); ν_{max} /cm^{-1} 2928 (m, C-H), 1701 (m, C=O), 1575, 1465 (s, C=C), and 1228 (s, C-O) ^{1}H NMR (300 MHz; $CDCl_3$) 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; ^{13}C NMR (75 MHz; $CDCl_3$) 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, $C_{20}H_{26}NO_2^+$ 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(6*H*)-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; R_f 0.50 (EtOAc: Hex, 3:7); ν_{max} /cm^{-1} 2912 (m, C-H), 1670 (m, C=O), 1598, 1452 (s, C=C), 1510 (s, N-O) and 1312 (s, N-O); ^{1}H NMR (300 MHz; $CDCl_3$) 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; ^{13}C NMR (75 MHz; $CDCl_3$) 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, $C_{20}H_{25}N_2O_4^+$ exact calculated mass: 357.1809.

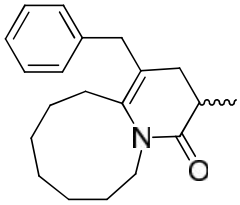
Synthesis of 1-(4-methoxybenzoyl)-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-4(6*H*)-one 339



(*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; R_f 0.52 (EtOAc: Hex, 3:7); ν_{max} /cm^{-1} 2990 (m, C-H), 1720 (m, C=O), 1548 (s, C=C) and 1169 (s, C-O); ^{1}H NMR (300 MHz, $CDCl_3$) 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),

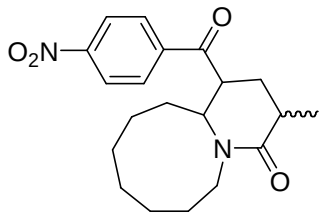
2.61 – 2.45 (m, 2H), 2.45 – 2.25 (m, 2H), 2.07 – 1.81 (m, 2H), 1.80 – 1.34 (m, 10H), 1.21 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 173.5, 148.2, 131.1, 131.0, 117.2, 113.8, 55.5, 44.4, 35.9, 32.3, 29.7, 29.4, 29.1, 27.9, 23.5, 23.2, 14.9 ppm; HRMS (ESI) Found: $[M+H]^+$, 342.2072, $C_{21}H_{28}NO_3^+$ 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(6*H*)-one 340



A mixture of 1-benzoyl-3-methyl-2,3,7,8,9,10,11,12-octahydropyrido[1,2-a]azonin-4(6*H*)-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_f 0.60 (EtOAc: Hex, 3:7); ν_{max} /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(1*H*)-one 341



A mixture of 3-methyl-1-(4-nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-4(6*H*)-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 $MgSO_4$ 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; R_f (EtOAc: Hex, 3:7); ν_{max} /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);^{1}H NMR (300 MHz, $CDCl_3$) 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), 3.88 (ddd, *J* = 10.5, 7.6, 5.3 Hz, 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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

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