Asymmetric Synthetic Approaches to the Batzelladine Alkaloids

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Abstract

This thesis describes stereoselective synthetic approaches to the bicyclic and tricyclic guanidine cores of batzelladines A and C.

Chapter 1 introduces the batzelladine alkaloids, discussing important biological properties, literature syntheses and previous synthetic studies within the Elliott group.

Chapter 2 describes our key synthetic step, a modified version of the Kishi three-component coupling in detail. In addition to studies to determine the stereochemistry of this reaction, experimental evidence has been gathered to ascertain the reaction mechanism.

Chapter 3 discusses a diastereoselective synthetic route to the western half of batzelladine A. The three-component coupling proceeds with total diastereocontrol, enabling the bicyclic pyrrolo[1,2-*c*]pyrimidine core of the left-hand side of the natural product to be constructed in an efficient manner. The stereoselectivity of this central synthetic step also offers further evidence towards the proposed reaction mechanism.

Chapter 4 describes a first-generation synthetic approach towards batzelladine C, utilising a novel stereoselective reaction of a chiral *N*-acyliminium ion and allenylsilane as a key step.

In Chapter 5, the second-generation synthetic route to Batzelladine C is discussed. With no requirement for protecting groups, a tricyclic guanidine core corresponding to batzelladine C is synthesised diastereoselectively. It is anticipated that only a few more steps will be required to achieve the total synthesis of the natural product.

Acknowledgements

There are number of people who I would like to thank for putting up with me during the course of my PhD. A postgraduate chemist is a strange beast indeed.

First of all, on the Chemistry side, a great appreciation goes out to my supervisor Mark, for without his dedication, patience and hard-work, I would have struggled manfully, particularly during my final year. I'd also like to thank Chris Davies at AstraZeneca for his input into the PhD, not to mention a great taste in restaurants/wine! Rob Jenkins and Robin Hicks, the technical wizards at Cardiff, were always on hand to run that important mass spectrum or offer helpful NMR advice. I'd also like to thank Dr Colin Robson at Prudhoe, for helping to reignite my interest in Chemistry.

My family have always been on hand to offer kind words and support me all the way, for which I shall be eternally grateful. They have had the patience of a saint.

Dedication

To Hannah

Table of Contents

Detailed Table of Contents

Abbreviations

Ac	Acetyl
AIBN	2,2`-Azobisisobutyronitrile
APCI	Atmospheric Pressure Chemical Ionisation
Asp	Aspartic Acid
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOP	Bis(2-oxo-3-oxazolidinyl)phosphonic
Cbz	Benzyloxycarbonyl
CD4	Cluster of Differentiation 4
CDI	Carbonyldiimidazole
COSY	Correlation Spectroscopy
DMAP	4-Dimethylaminopyridine
DME	Ethyleneglycol dimethylether
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulphoxide
d.e	Diastereomeric Excess
d.r.	Diastereomeric Ratio
ee	Enantiomeric Excess
EI	Electron impact
ES	Electrospray
gp120	Glycoprotein 120
gp 41	Glycoprotein 41
HIV	Human Immunodeficiency Virus
IR	Infrared
LC-MS	Liquid Chromatography-Mass Spectrometry
LDA	Lithium diisopropylamine
MS	Mass Spectrometry
Ms	Methanesulphonyl
NMR	Nuclear Magnetic Resonance

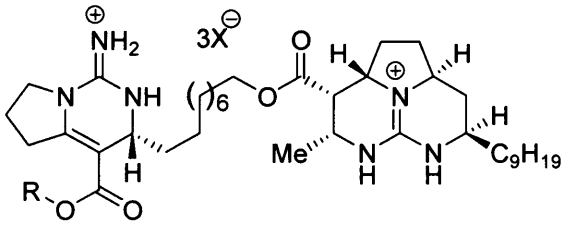
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement Spectroscopy
Nu	Nucleophile
PMB	*p*-Methoxybenzyl
RNA	Ribonucleic Acid
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	*p*-Toluenesulphonyl

Chapter 1

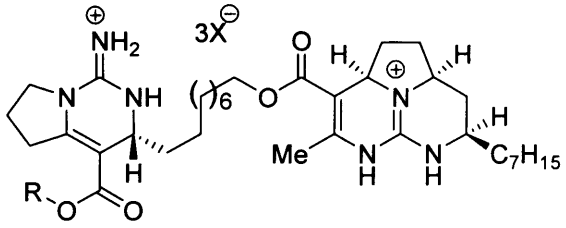
Introduction to the Batzelladine Alkaloids

1.1 The Batzelladine Alkaloids – an Introduction

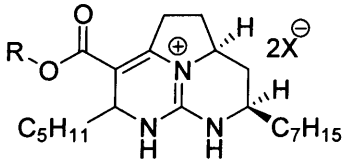
In the mid-1990's, a team from SmithKline Beecham were investigating a range of natural product extracts for their potential therapeutic use. Of these extracts, several members of a family of guanidines from the Caribbean marine sponge *Batzella sp.* were found to possess a range of interesting and useful biological activity, in particular anti-HIV activity.[1] Of the 21 compounds isolated, five were found to be novel alkaloids with key structural similarities. These natural products were christened the batzelladines, and were designated by letters A-E. **Figure 1** illustrates their structures. Batzelladine C (**3**) is the only member of this initial quintet that has since not been synthesised.



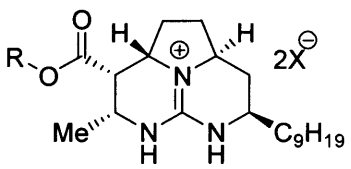
Batzelladine A (1)



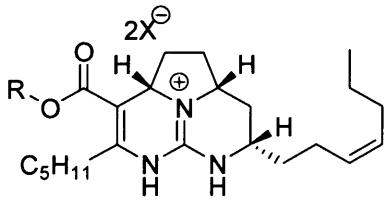
Batzelladine B (2)



Batzelladine C (3)



Batzelladine D (4)



Batzelladine E (5)

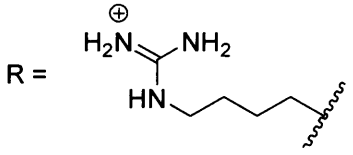


Figure 1

Two years later, a further four batzelladines were discovered.[2] Their structures are shown in **Figure 2**.

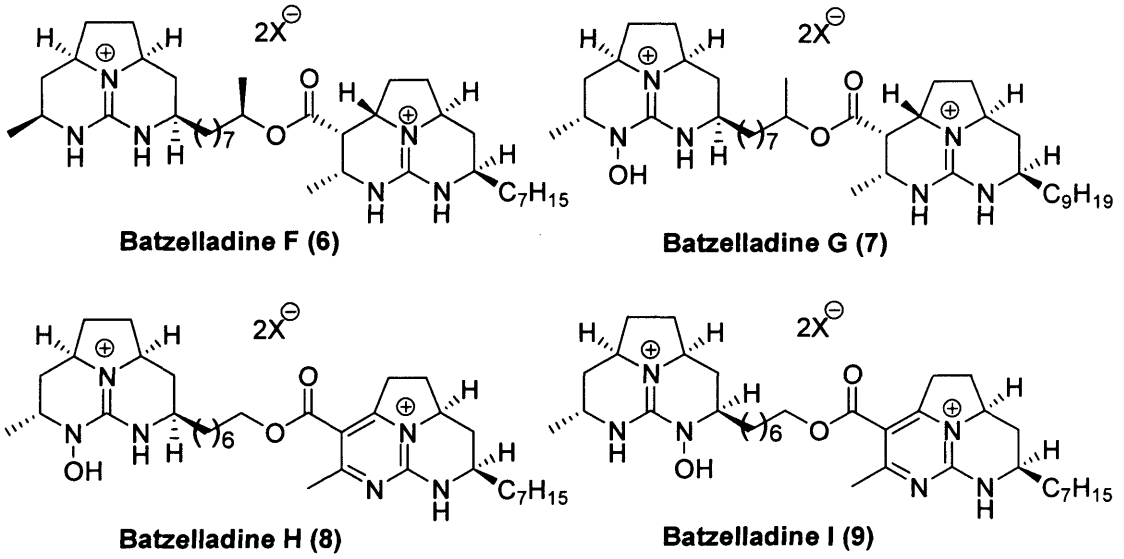


Figure 2

The tenth member of the batzelladine family, batzelladine J, was isolated from an extract of the Caribbean marine sponge *Monanchora unguifera* in 2005 **(Figure 3)**.[3]

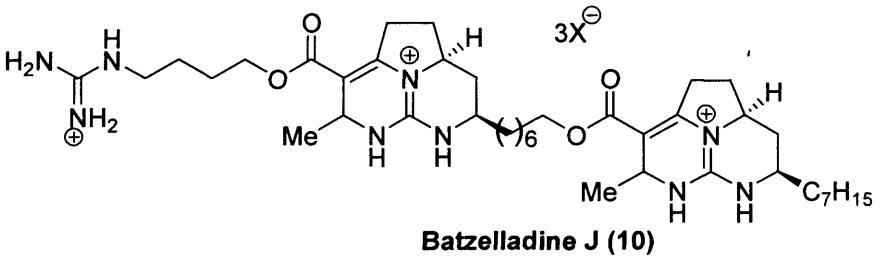


Figure 3

Finally, in 2007, batzelladines K – N and dehydrobatzelladine C were extracted from the same marine sponge, *Monanchora unguifera* (**Figure 4**).[4]

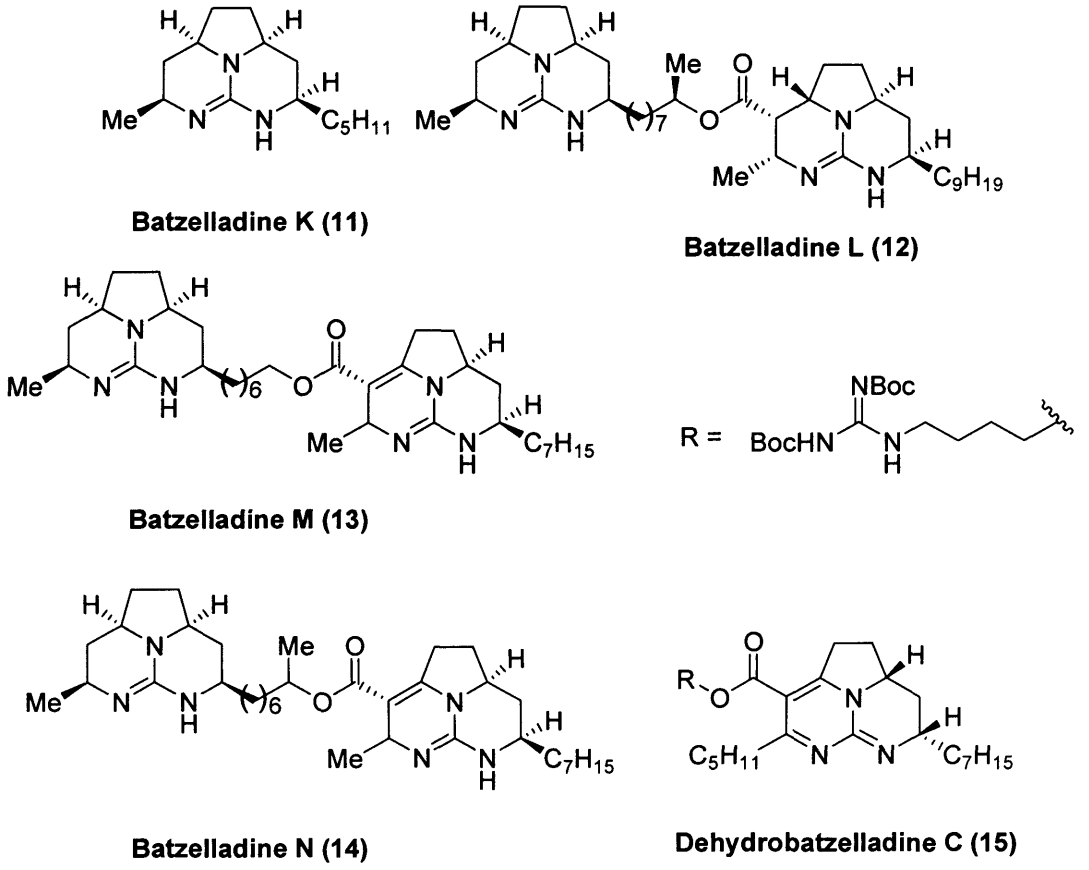


Figure 4

As previously mentioned, this family of natural products possess potentially significant biological activity; in particular, several members are known to inhibit the binding of the HIV envelope gp120 to CD4 cells. The nature of these interactions and their implications are discussed in the following section.

1.2 Biological Aspects of the Batzelladine Alkaloids

As one of the most prevalent diseases in the developing world, AIDS is now recognised as pandemic, with an estimated 0.6% of the World's population infected by the Human Immunodeficiency Virus (HIV).

The structure of HIV is represented in **Figure 5**, with the outer layer consisting of two types of glycoprotein: gp120, which is implicated in binding to the target cells, and gp41, which helps the HIV "dock" itself to the cell.[5] Inside the virus are the RNA and various enzymes, which will enter and takeover the infected cell.

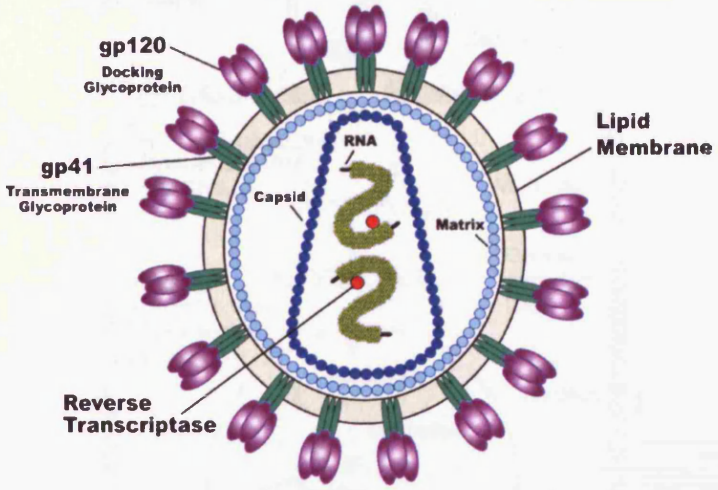


Figure 5[6]

As the name suggests, HIV primarily infects the immune system of humans, targeting vital cells such as macrophages and helper T-cells (specifically CD4 cells). HIV infection leads to low levels of CD4 cells by three main mechanisms:

- Direct killing of cells
- Increased rate of apoptosis (a programmed form of cell death)
- Killing of infected cells by lymphocytes that recognise infected cells

When $CD4^+$ cell numbers drop below a certain critical level, cell-mediated immunity is lost, meaning the body becomes highly susceptible to infections.[7]

HIV enters the host cell by docking to a surface glycoprotein, known as the CD4 receptor on the cell's surface. This interaction occurs through the gp120 protein on the surface of the virus. Upon binding, the gp120 protein undergoes a structural change, allowing the virus to bind to further receptors. HIV will then become attached to the cell membrane, allowing the HIV RNA and enzymes such as reverse transcriptase and ribonuclease to enter the cell.[8,9] **Figure 6** illustrates this principle.

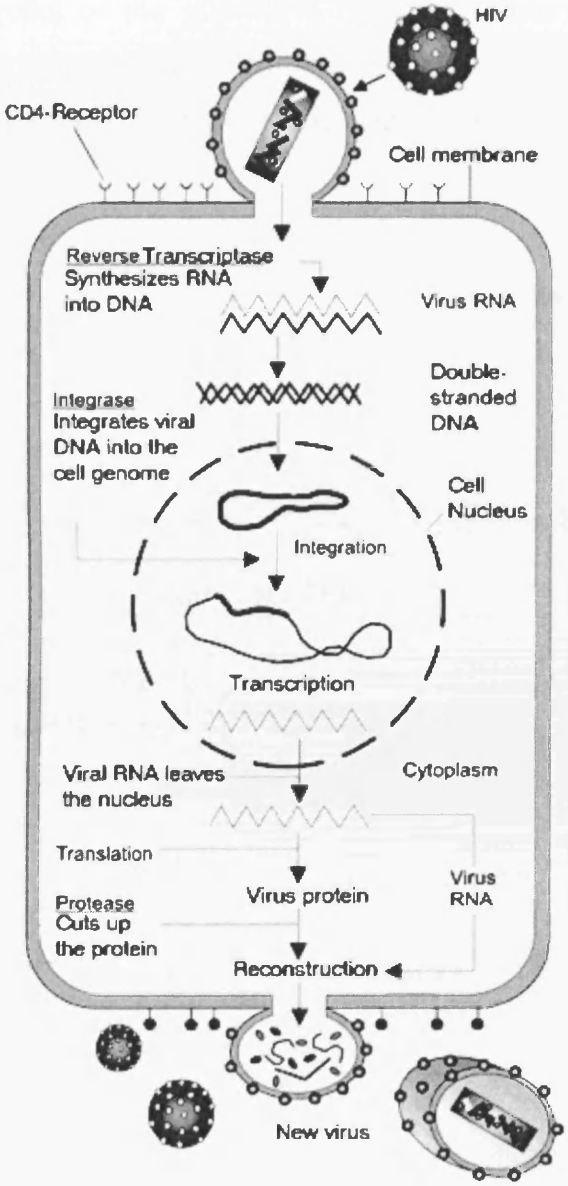
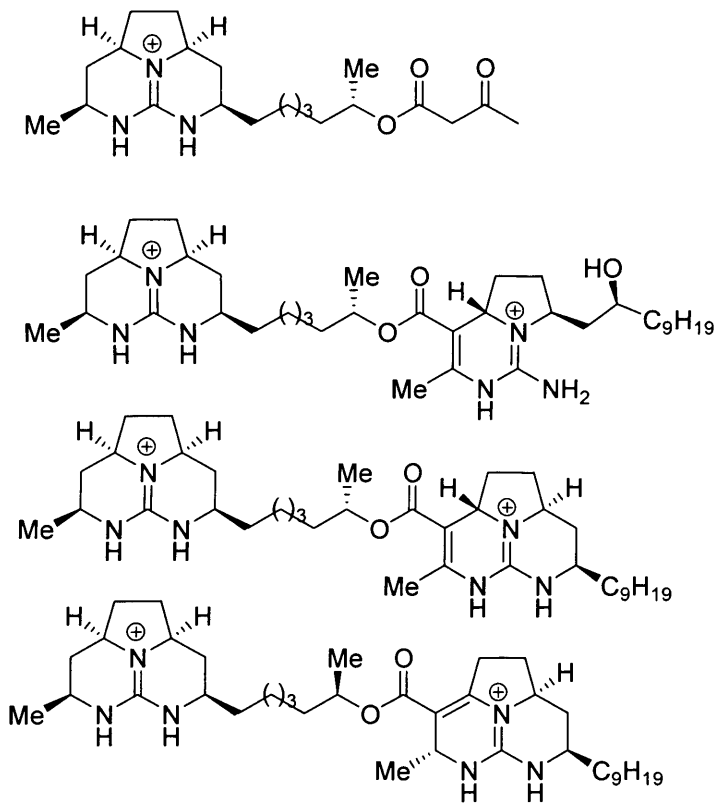


Figure 6[10]

A number of drugs are widely available which block this initial entry of the virus, known as fusion inhibitors. Two such examples are Maraviroc[11] and Enfuviritide.[12] The latter binds to the gp41 region of the virus and prevents the development of an entry pore for the cell.

The Overman group conducted a biological study of the inhibition of HIV fusion by a range of batzelladine analogues, including variation of the number and nature (bicyclic/tricyclic) of the guanidine rings, absolute configuration of the guanidine units, and number and position of substituents. **Figure 7** shows four examples (compounds **8a-d**) from the study and their IC_{50} values (in μM).[13]

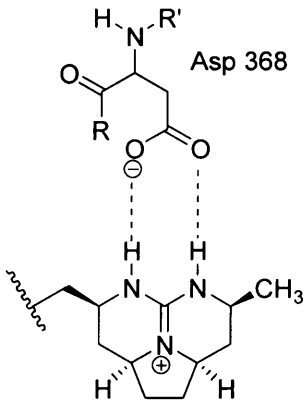


	IC_{50} (μM)
8a	17.0 ± 3.3
8b	7.7 ± 1.5
8c	1.8 ± 0.4
8d	0.8 ± 0.2

Figure 7

The most effective inhibitor, compound **8d**, exhibits very close structural similarities to batzelladine F.

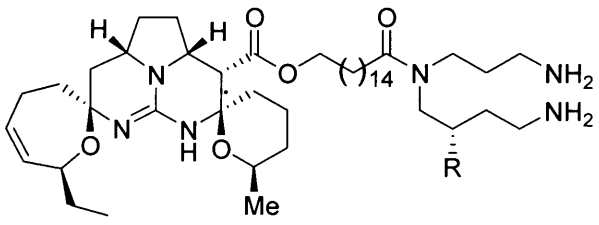
The tricyclic core of the batzelladine family was discovered to be vital in the binding of the alkaloid to the glycoprotein, with interactions of the carboxylate terminus of an aspartic acid residue to the guanidine implicated (**Figure 8**).



Tricyclic Batzelladine analogue
(similar in structure to Batzelladine F)

Figure 8

In a later biological study, five members of the batzelladine family, batzelladines K, L, M, N and dehydrobatzelladine C (see **Figure 4**) along with the structurally similar alkaloids Ptilomycalin A (**16**) and Crambescidine 300 (**17**) (**Figure 9**), were evaluated for their activity against cancer-cell lines, protozoa, HIV-1 and AIDS opportunistic infectious pathogens.[4]



Ptilomycalin A (**16**): R = H
Crambescidin 800 (**17**): R = OH

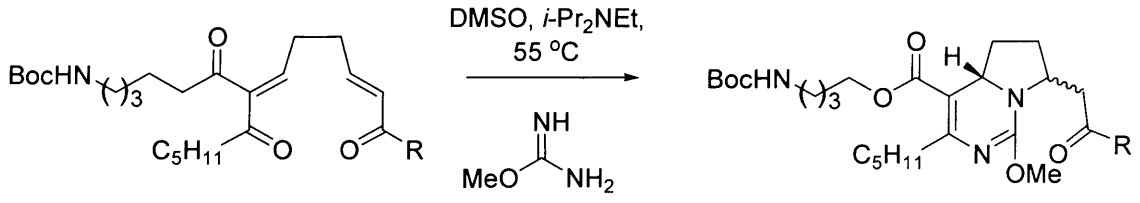
Figure 9

The evaluated batzelladines were found to be more active against *M. intracellulare* and *M. Tuberculosis* than Ptilomycalin and Crambescidine, and also more active against the malaria parasite *P. falciparum*.

1.3 Partial and Total Syntheses of the Batzelladines

Since their discovery, there has been considerable synthetic attention towards the Batzelladine alkaloids. The leading syntheses published thus far will be summarised in the next few pages.

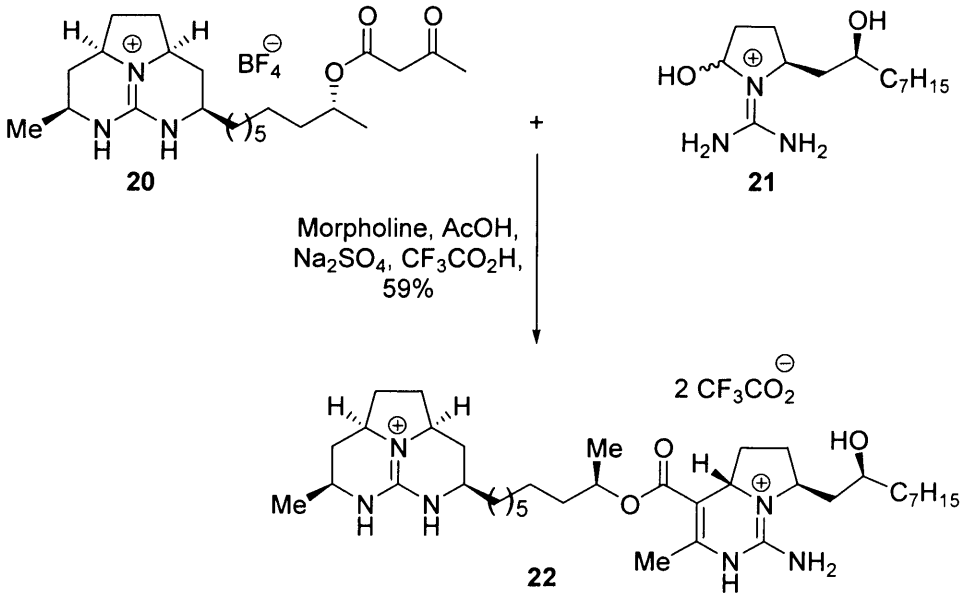
Although the synthesis of a tricyclic unit corresponding to the western half of Batzelladine F had been reported independently by Snider[14] and Murphy[15] previously, the Snider group published the very first total synthesis of a Batzelladine alkaloid.[16,17] The key step in their approach to batzelladine E involved a condensation of bis-enone **18** with *O*-methylisourea, constructing the pyrimidine core **19** (**Scheme 1**). The racemic natural product was synthesised in nine steps, with a 3% overall yield.



18 **19**

Scheme 1

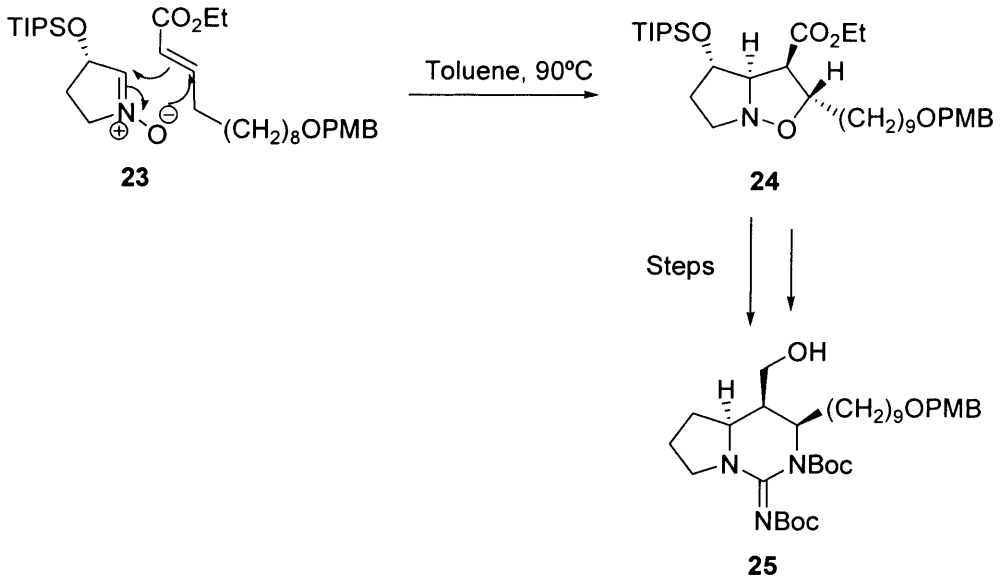
The Overman group synthesised Batzelladine F enantioselectively, leading to structural and stereochemical revision of the natural product.[18] The key step was a tethered Biginelli condensation of fragments **20** and **21** to establish the eastern core (**22**) of the natural product (**Scheme 2**). This elegant synthesis was achieved in 24 steps, and 1.4% overall yield.



Scheme 2

In addition to Batzelladine F, the Overman group used this Biginelli chemistry in the enantioselective syntheses of both Batzelladine D[19] and dehydrobatzelladine C.[20,21]

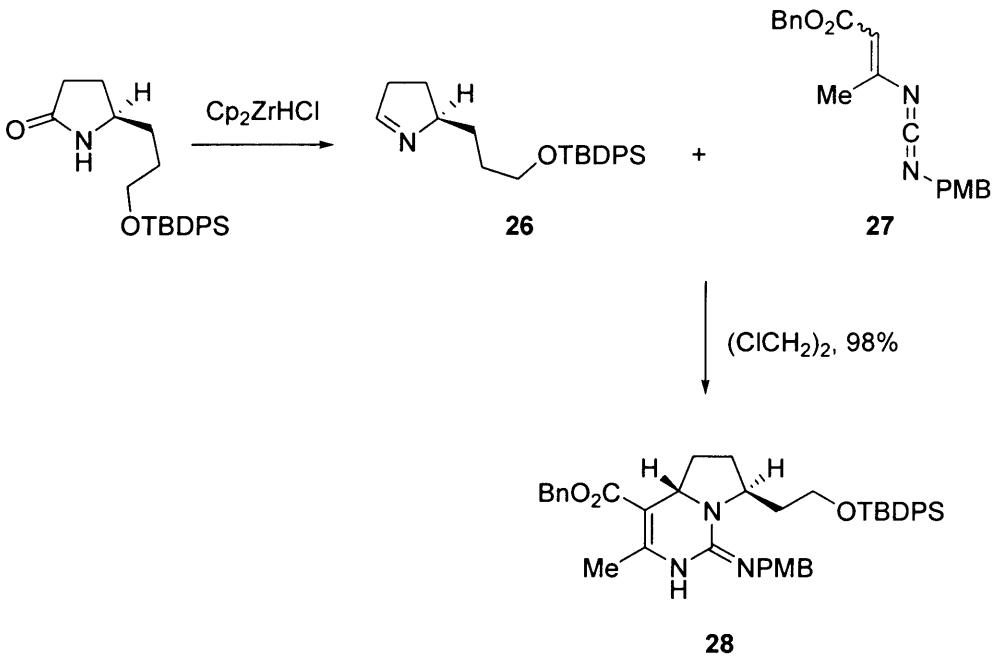
The first of two Batzelladine A total syntheses to date has been reported by the Nagasawa group.[22] Their asymmetric, thirty-step sequence (0.03% overall yield) utilised a 1,3-dipolar cycloaddition of enantiopure nitrone **23** as a key step in the synthesis of the western half of the natural product (**Scheme 3**).



Scheme 3

The Nagasawa group had also previously reported the enantioselective synthesis of batzelladine D (the eastern half of batzelladine A is identical to Batzelladine D),[23] in addition to the synthesis and confirmation of the stereochemistry of the left-hand side of batzelladine F.[24,25,26]

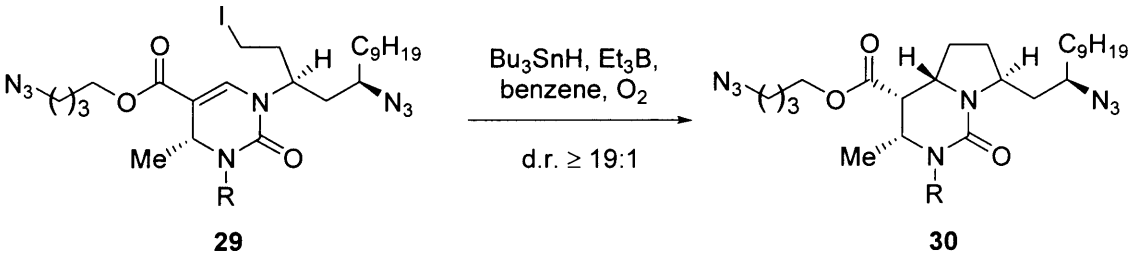
One of the more elegant syntheses to date has been published by Gin *et al.*[27] Batzelladine D was prepared enantioselectively in 14 steps, with a 5% overall yield. Their key step involves an [4+2] annulation of pyrrole **26** (prepared by Cp_2ZrHCl-mediated reduction of the corresponding lactam) and vinyl-carbodiimide **27**, establishing the bicyclic guanidine core of the natural product with the vital pyrrolidine stereogenic centres in place (**Scheme 4**).



Scheme 4

Earlier studies by the Gin group had resulted in the synthesis and stereochemical determination of the western core of batzelladine A,[28] culminating in a total synthesis of the natural product.[29]

In 2007, Evans and co-workers reported the enantioselective total synthesis of batzelladine D (**Scheme 5**).[30,31] The key step involves a stereoselective radical cyclisation of compound **29** with tributyltin hydride and triethyl borane in the presence of air.

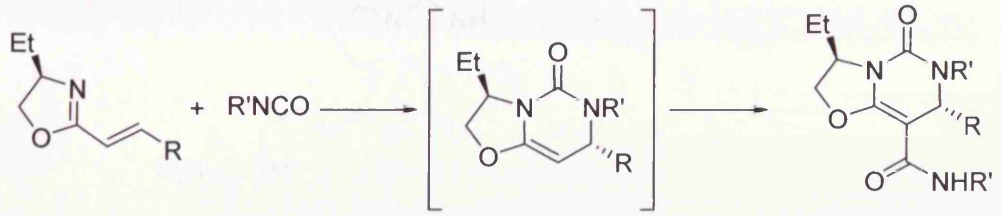


R = (1*S*)-(+)-Camphorsulphonyl

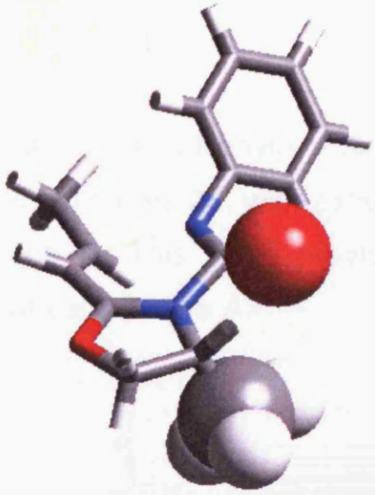
Scheme 5

1.4 The Elliott Group's Approaches Towards the Batzelladines

The group first began to explore approaches to these natural products when investigating their own diastereoselective annulations of alkenyloxazolines (**Scheme 6**).[32]



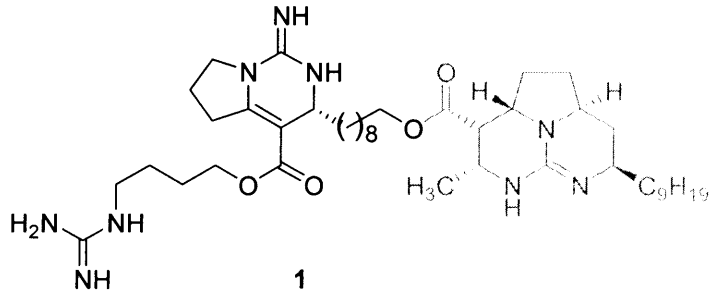
31 **32** **33**



Scheme 6

Oxazoline **31** first undergoes a stepwise, diastereoselective formal-hetero-Diels-Alder reaction to yield pyrimidine **32** (exhibiting *trans* relative stereochemistry between the substituents across the oxazolo[3,2-*c*]pyrimidine ring), with a calculated structure of the helical transitional state shown.[33] The other diastereoisomer is not formed, due to unfavourable interactions between the isocyanate oxygen and substituent on the oxazoline ring. Further acylation of the alkene moiety affords then affords compound **33**.

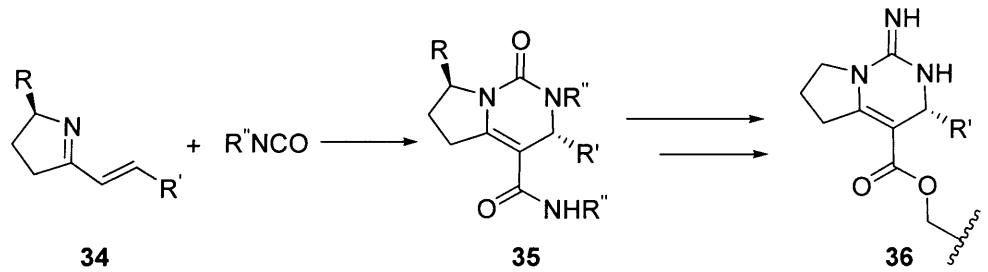
The structure of compound **33** bears obvious similarities with that of the western half of batzelladine A (**1**) (**Figure 10**), in particular sharing a fused pyrimidine core and a carbonyl group attached to the alkene.



1

Figure 10

With alteration of precursor **31** into an alkenylpyrroline **34**, one can envisage a diastereoselective entry to bicyclic urea **35**, with excellent control over structure and stereochemistry (**Scheme 7**). This could provide a very efficient way to construct the left-hand side of batzelladine A.

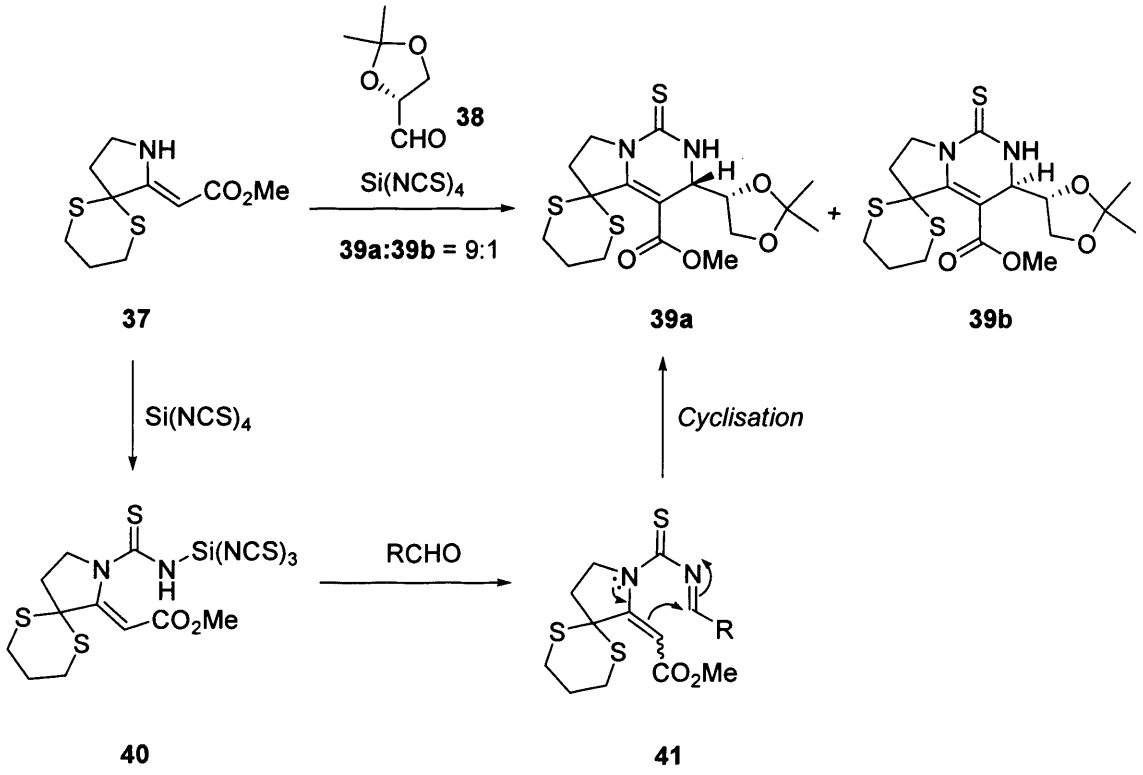


34 **35** **36**

Scheme 7

Unfortunately, this route proved not to be viable.[34] However, the three-component coupling used in Kishi's synthesis of (-)-decarbamoylsaxitoxin provides a structurally similar heterocycle.[35] This transformation is a trimolecular cyclisation of an alkylidenepyrrolidine (**37**), silicon tetraisothiocyanate, and an aldehyde.[36] With a chiral aldehyde (**38**) providing the chiral information for this

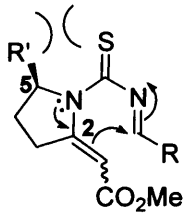
three component coupling in this instance, thiourea **39a** is formed with significant diastereoselectivity (9:1) (**Scheme 8**).



Scheme 8[35]

It was suggested that the reaction involves proceeds by way of intermediates **40** and **41** (**Scheme 8**), arising from initial acylation of the alkylidenepyrrolidine by the isothiocyanate (this mechanism will be discussed in more depth in *Chapter Two*).

Based on this mechanism, it appeared reasonable that introduction of a directing group at the 5-position of the pyrrolidine ring would provide stereocontrol due to steric interactions between this substituent and the sulphur atom in the same way as previously described (see **Scheme 6** and **Figure 11**).



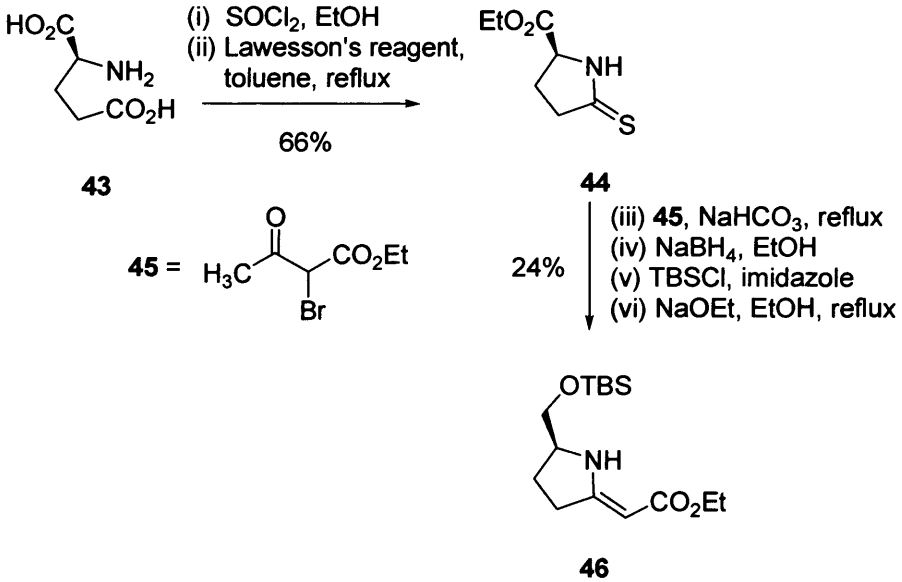
42

Figure 11

The first synthetic foray within the group was undertaken by Matthew Long towards the western half of batzelladine A, using a modified version of the Kishi annulation as a key synthetic step.[29]

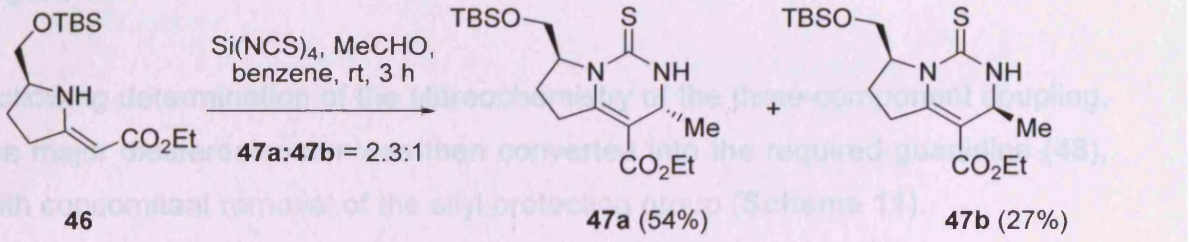
This approach constructed the pyrrolidine with a bulky silyloxy group at the 5-position of the alkylidenepyrrolidine, with steric bulk from the ring-substituent influencing the stereoselectivity of the three component coupling.

Alkylidenepyrrolidine **46** was therefore synthesised in 6 steps from glutamic acid (**43**) (**Scheme 9**).



Scheme 9

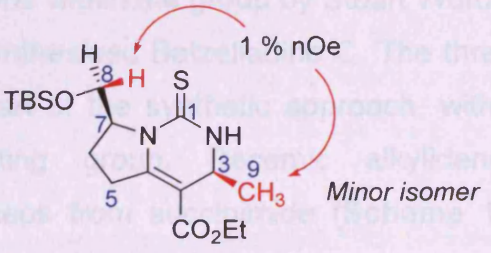
For the three-component coupling, compound **46** was treated with freshly prepared silicon tetraisothiocyanate and a simple aliphatic aldehyde, acetaldehyde. With benzene as the solvent of choice, the optimum reaction conditions were three hours at room temperature. Encouragingly, the silyloxy directing group conferred some level of stereoselectivity, with a 2.3:1 ratio of diastereoisomers **47a** and **47b** formed (**Scheme 10**).



46 **47a** (54%) **47b** (27%)

Scheme 10

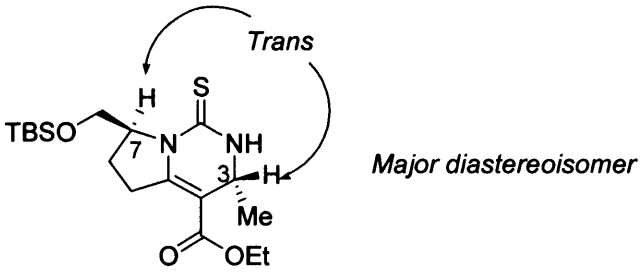
The stereoisomers were readily separated by column chromatography, and nOe NMR studies carried out in order to determine the stereochemistry of the three-component coupling. While the major diastereoisomer showed no diagnostic enhancements, a 1% nOe was discovered between the protons on the 8 and 9-positions in the minor isomer (**47b**) (**Figure 12**).



47b

Figure 12

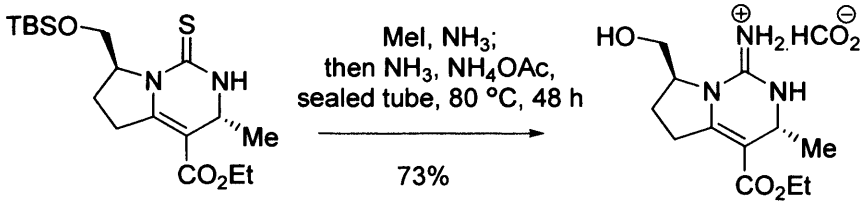
Based on this initial spectroscopic evidence, the relative stereochemistry of the protons across the pyrrolo[1,2-*c*]pyrimidine ring (positions 3 & 7) in the major diastereoisomer was assigned as *trans* (**Figure 13**).



47a

Figure 13

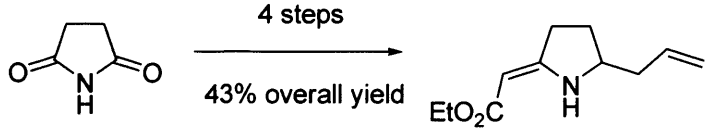
Following determination of the stereochemistry of the three-component coupling, the major diastereoisomer was then converted into the required guanidine (**48**), with concomitant removal of the silyl protecting group (**Scheme 11**).



47a **48**

Scheme 11

The next synthetic efforts within the group by Stuart Wordingham[37] concentrated on the previously unsynthesised Batzelladine C. The three-component coupling again formed a key part of the synthetic approach, with an allyl group as the stereochemical directing group. Racemic alkylidenepyrrolidine **50** was synthesised in four steps from succinimide (**Scheme 12**). This route will be discussed in more depth in *Chapter Four.*

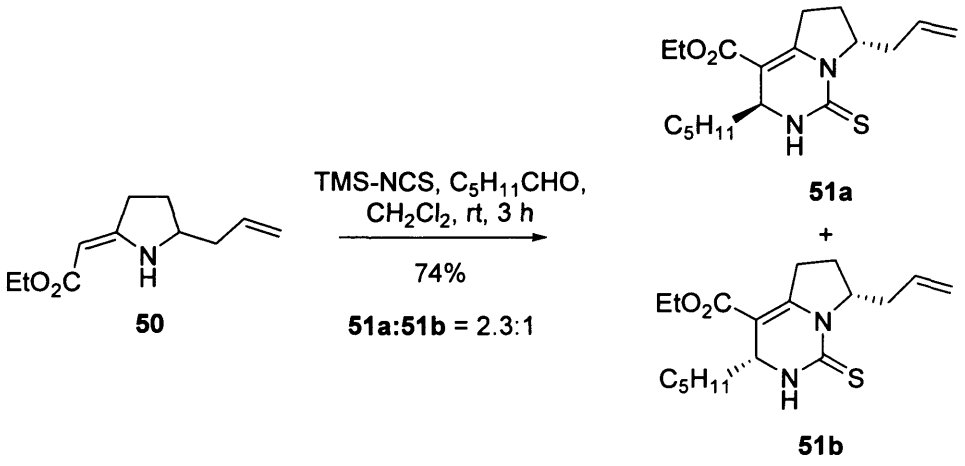


49 **50**

Scheme 12

Experimental studies at the time found that using commercially available trimethylsilylisothiocyanate in place of $Si(NCS)_4$ led to improvements in the reliability of the three-component coupling. It was also discovered that quenching the reaction with a weakly basic aqueous solution removed the silicon-oxide by-products, thus resolving previous problems encountered with chromatography.

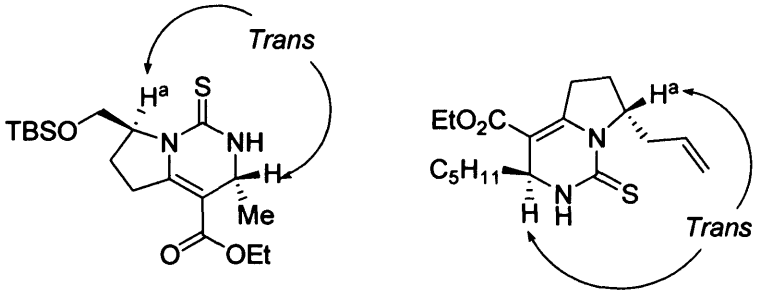
The key step was then performed with the appropriate aldehyde for the natural product (**Scheme 13**).



Scheme 13

As with Matthew Long's studies, the ratio of diastereoisomers **51a** and **51b** was determined by relative integration of two distinct signals (proton H_a on the pyrrolidine ring; **Figure 14**) in the ^1H NMR spectrum. A 2.3:1 ratio of diastereoisomers had again been formed.

In the ^1H NMR spectra of compounds **47a** and **51a**, hydrogen H^a is upfield of the corresponding hydrogen in the minor isomer. Based on this observation, it was suggested that the *trans*-stereochemistry was again observed in the major diastereoisomer (**Figure 14**).



47a

Major isomer

Matthew Long
approach (Batzelladine A)

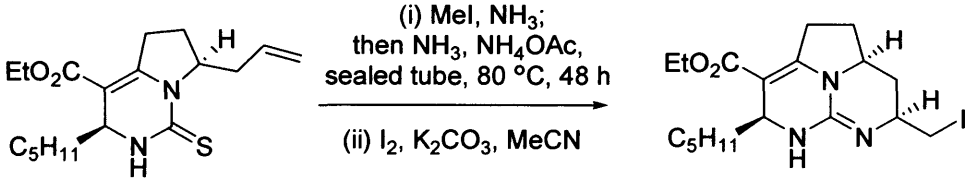
51a

Major isomer

Stuart Wordingham
approach (Batzelladine C)

Figure 14

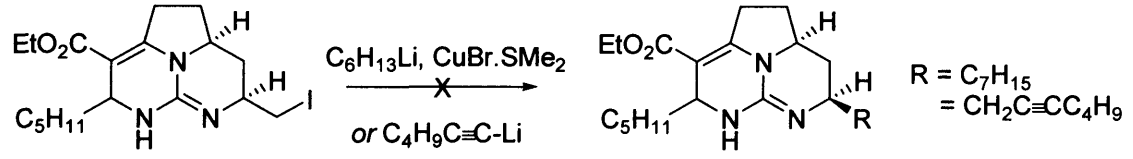
The clean mixture of stereoisomers (**51 a & b**) was first converted into the required guanidine, and then subjected to an intramolecular iodoamination to construct the tricyclic guanidine core (**Scheme 14**). A single diastereoisomer (**52**) was isolated in a 46% yield.



51 a & b **52**

Scheme 14

However, difficulties were then encountered with replacing the terminal iodide with the correct length alkyl chain for the natural product (**Scheme 15**).



52

Scheme 15

1.5 Conclusions

Although there are many efficient and stereoselective synthetic routes towards the batzelladine alkaloids, there is not yet one method which would allow entry into all of the cores of this family.

It is anticipated that with a greater understanding and control of our key step, we will be able to develop highly efficient and stereoselective routes to a number of the batzelladine family.

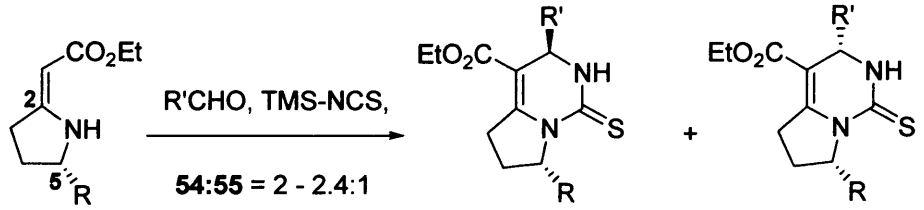
Chapter Two will discuss mechanistic and stereochemical aspects of the three-component coupling in detail, and how this may be applied to future syntheses.

Chapter 2

Mechanistic and Stereochemical Aspects of the Three-Component Coupling

2.1 Introduction

Thus far, the central step to the group's synthetic approaches has been our modification of a trimolecular cyclisation first reported by Kishi.[35] The three components employed are an alkylidenepyrrolidine (**53**), an aliphatic aldehyde and trimethylsilyl isothiocyanate. With a stereochemical directing group placed at the 5-position of the alkylidenepyrrolidine, diastereoselectivities ranging from 2 - 2.4:1 are observed (**Scheme 16**).[34,37]



53 **54** **55**

Scheme 16

Because of the relatively low diastereoselectivity of this variation of the three-component coupling, a more detailed understanding of the reaction was required.

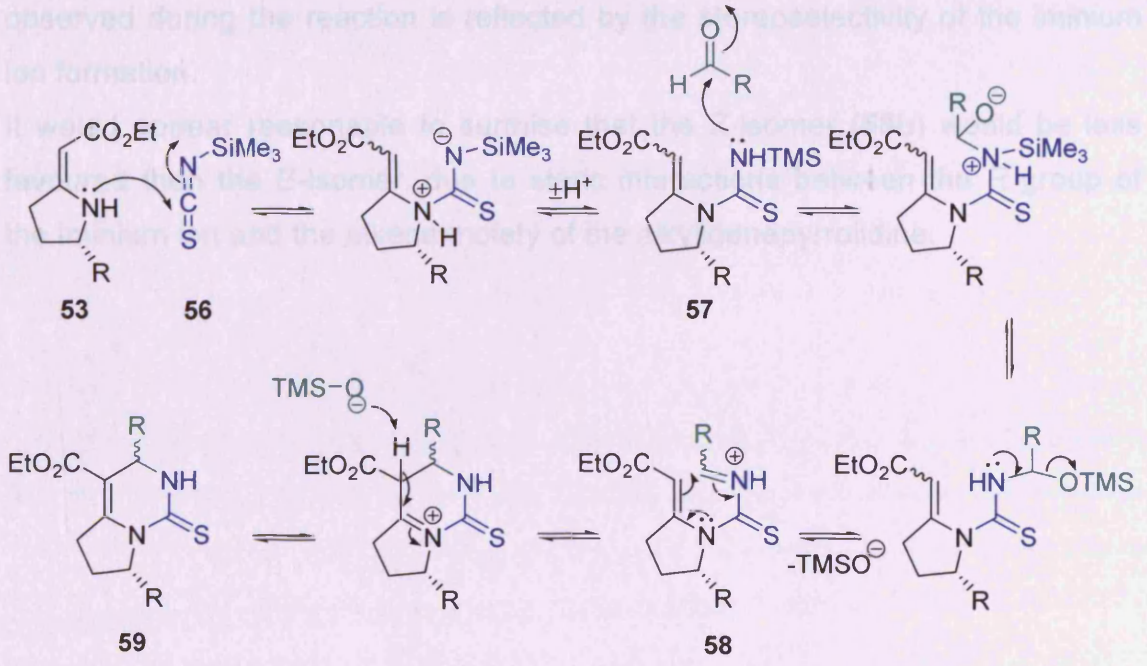
The reaction mechanism will inevitably involve initial coupling of two components to form an intermediate, followed by reaction with the third component.

2.2 Mechanistic Studies

2.2.1 The First Proposed Mechanism: Alkylidenepyrrolidine & Isothiocyanate

A mechanism for this reaction was first postulated by the group of Kishi, when investigating the stereoselectivity of their three-component coupling.

The mechanism involves initial reaction of the alkylidenepyrrolidine (**53**) and the silylisothiocyanate (**56**) (**Scheme 17**). For the required bicyclic thiourea to be formed by this pathway, acylation of the pyrrolidine at the *N*-atom has to initially occur to afford a thiourea intermediate (**57**). Thiourea **57** then reacts with the aldehyde, eliminates TMS-oxide and cyclises to yield pyrimidine **59**.



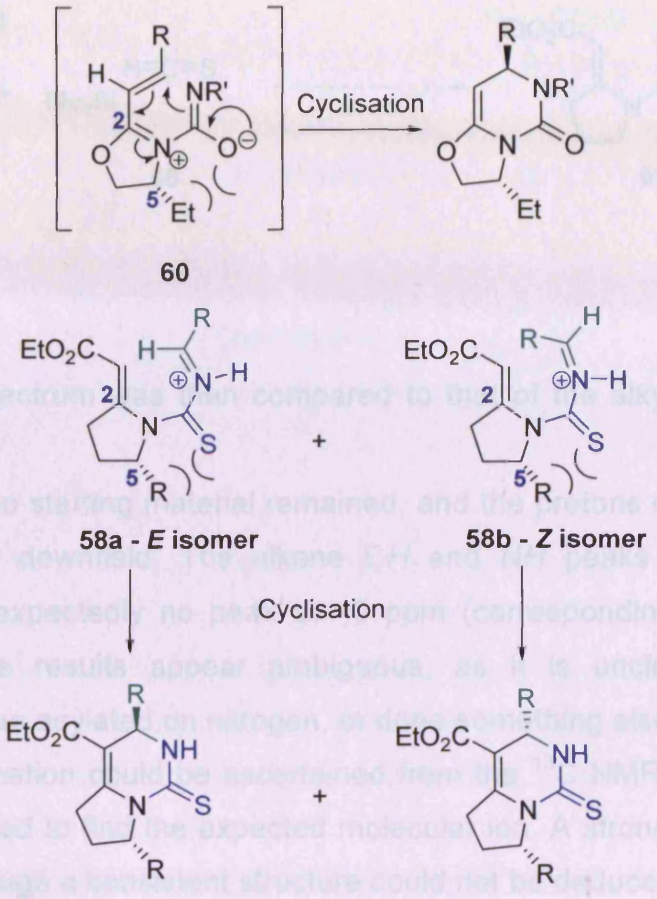
Scheme 17

The Elliott group have previously studied the asymmetric hetero-Diels-Alder reactions of dihydroalkenyloxazoles with isocyanates.[32] High diastereoselectivities are observed because of steric interactions between the isocyanate oxygen and substituent on the 5-position of the oxazoline ring in intermediate **60** (**Scheme 18**).

Regarding the Kishi three-component coupling, one can envisage the stereoinduction arising from interactions of the isothiocyanate sulphur and the substituent on the aforementioned position in a similar manner. The iminium ion (**58**) could be formed as a mixture of geometrical isomers **58a** and **58b** (**Scheme 18**). Each of these isomers would be expected to cyclise with a high level of stereocontrol.

Therefore, according to this postulated mechanism, the overall stereocontrol observed during the reaction is reflected by the stereoselectivity of the iminium ion formation.

It would appear reasonable to surmise that the *Z*-isomer (**58b**) would be less favoured then the *E*-isomer, due to steric interactions between the *R* group of the iminium ion and the alkene moiety of the alkylidenepyrrolidine.



Scheme 18

In order to provide support for the existence of this particular pathway, it was decided that experimental evidence was needed. For the three-component coupling to occur *via* this mechanism, the heterocumulene first has to acylate on the nitrogen atom of the pyrrolidine, affording silyl thiourea **61**, at an appreciable rate at room temperature.

An equimolar amount of an achiral alkylidenepyrrolidine (**62**)[38] and trimethylsilyl isothiocyanate (**56**) (**Scheme 19**) were mixed at room temperature, and ^{1}H and ^{13}C NMR spectra of the crude product recorded.

62 **56** **61**

Scheme 19

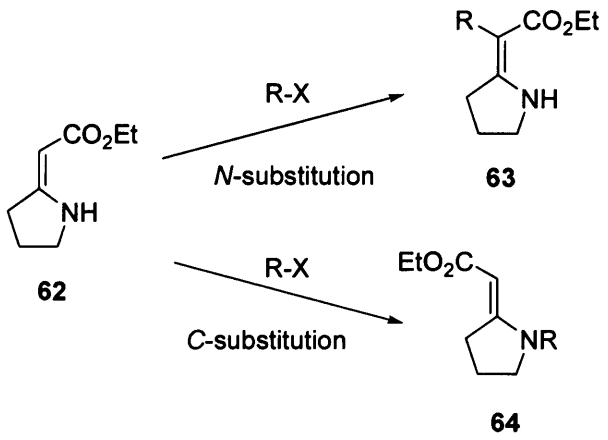
The ^{1}H NMR spectrum was then compared to that of the alkylidenepyrrolidine starting material.

Encouragingly, no starting material remained, and the protons on the pyrrolidine ring had shifted downfield. The alkene C*H* and N*H* peaks were no longer evident, and unexpectedly no peak at ~0 ppm (corresponding to Me_3Si) was observed. These results appear ambiguous, as it is unclear whether the isothiocyanate has acylated on nitrogen, or done something else entirely.

No further information could be ascertained from the ^{13}C NMR data, and mass spectrometry failed to find the expected molecular ion. A strong peak was seen at *m/z* 264, although a consistent structure could not be deduced from this.

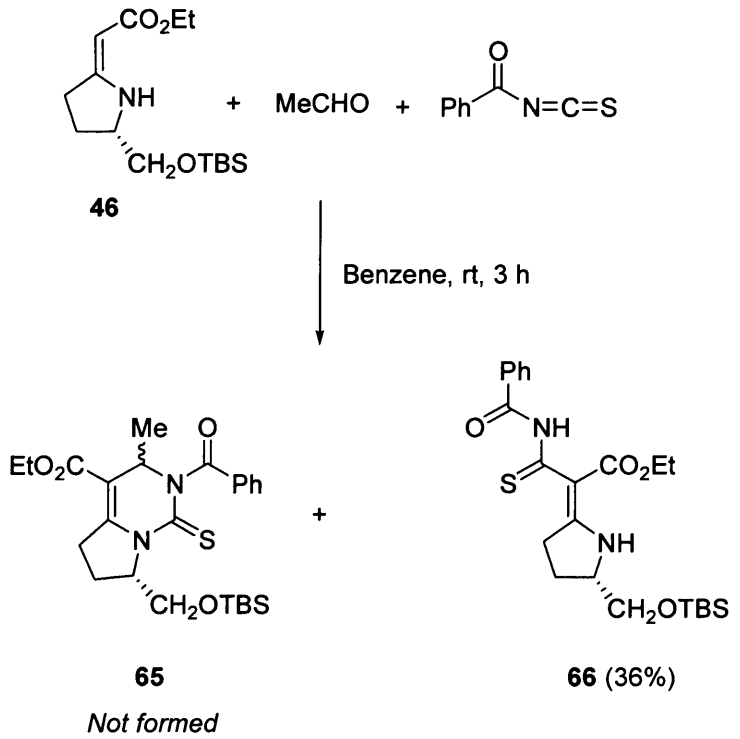
Due to the ambiguous nature of these initial experimental studies, a mechanism involving initial *N*-acylation of the alkylidenepyrrolidine could not yet be ruled out. It was beginning to become apparent that understanding of the regioselectivity of electrophilic addition to alkylidenepyrrolidines would be vital to proving or disproving the existence of this mechanism.

An alkylidenepyrrolidine is a heterocyclic enamine, with nucleophilic substitution taking place either at the alkene β-carbon, or at the nitrogen atom to afford two possible regioisomers (**63** & **64**) (**Scheme 20**).[39]



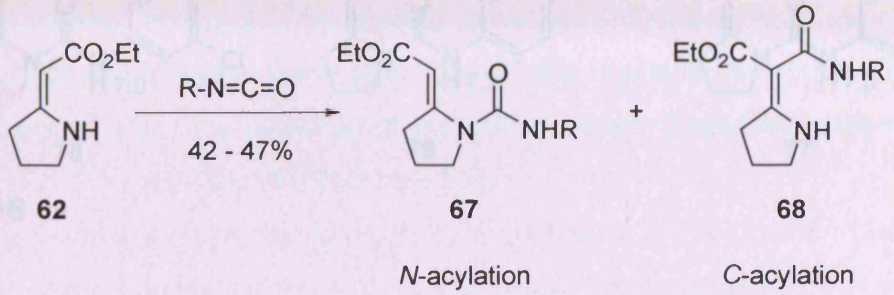
Scheme 20

One such example of the reaction of an alkylidenepyrrolidine with an isothiocyanate has been published by the Elliott group.[34] During initial studies towards the western half of Batzelladine A, the three-component coupling was attempted with benzoyl isothiocyanate (**Scheme 21**). Instead of the predicted bicyclic thiourea (**65**), the *C*-acylated regioisomer (**66**) was formed, with none of the *N*-acylated isomer observed.



Scheme 21

The sole previous literature example of acylation of alkylidenepyrrolidines with heterocumulenes (namely isocyanates) was reported by the group of Tronche.[40] **Scheme 22** illustrates the reaction of alkylidenepyrrolidine **62** with aryl and alkyl isocyanates, affording regioisomers **67** and **68**.



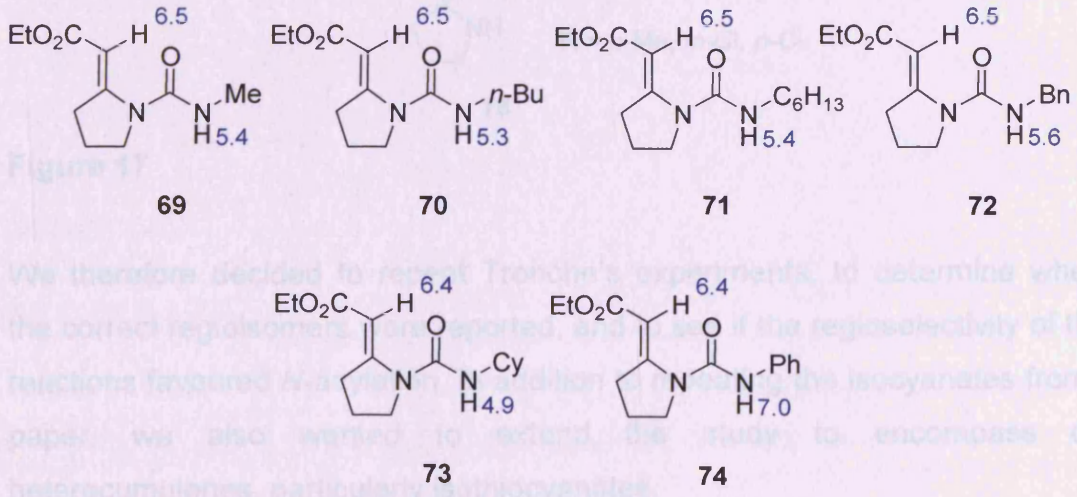
62 **67** **68**

N-acylation *C*-acylation

Scheme 22

Regardless of the nature of the *R* group used, an approximate ratio of 7:3 in favour of *N*-acylation was reported, with isolated yields between 42 and 47%.

The first six *N*-acylated regioisomers from the aforementioned paper are illustrated in **Figure 15**. The key alkene C*H* and N*H* peaks from the ^{1}H NMR data are annotated. These chemical shifts all appear reasonable.[41]

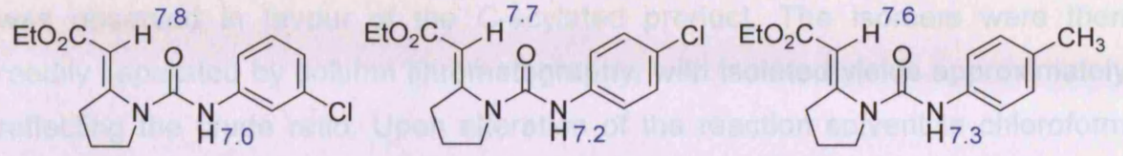


69 **70** **71** **72**

73 **74**

Figure 15

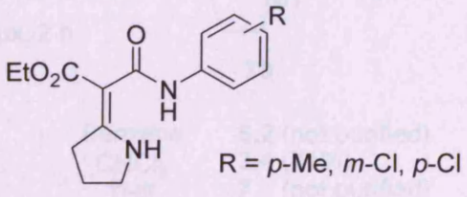
The reported chemical shifts for the same protons in the remaining three *N*-acylated isomers are significantly higher, leading us to question the structural assignments (**Figure 16**).[40]



75 **76** **77**

Figure 16

After closer interpretation of the results, it was suggested that the chemical shifts published for compounds **75-77** were in fact more consistent with structure **78**; i.e. the *C*-acylated isomer, with both signals corresponding to the two N*H* protons (**Figure 17**). The ^{13}C NMR data, which would have allowed unambiguous proof of these structures, was not presented in the paper.



78

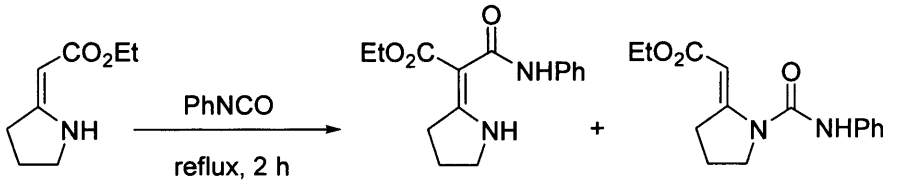
Figure 17

We therefore decided to repeat Tronche's experiments, to determine whether the correct regioisomers were reported, and to see if the regioselectivity of these reactions favoured *N*-acylation. In addition to repeating the isocyanates from the paper, we also wanted to extend the study to encompass other heterocumulenes, particularly isothiocyanates.

2.2.2 Acylation Studies[42]

Firstly, alkylidenepyrrolidine **62** was treated to the conditions described in the paper,[40] at reflux temperature in benzene. A **5.2:1** ratio of isomers **79** and **74** was observed in favour of the *C*-acylated product. The isomers were then readily separated by column chromatography, with isolated yields approximately reflecting the crude ratio. Upon alteration of the reaction solvent to chloroform and tetrahydrofuran, the regioselectivity still favoured *C*-acylation, giving a ratio of **3.4:1** and **7:1** respectively (**Scheme 23**).

The reaction was then repeated at room temperature in chloroform. Under these conditions, the *C*-acylated isomer (**A**) still predominated, affording a **2.1:1** ratio of regioisomers. The table in **Scheme 23** shows the (crude) ratio of isomers **79** and **74** for each reaction, with isolated yields in brackets.



62 **79** **74**

Benzene	**5.2** (not purified)	**1** (not purified)
$CHCl_3$	**3.4** (71%)	**1** (17%)
THF	**7** (not purified)	**1** (not purified)
$CHCl_3$ (rt, 18 h)	**2.1** (53%)	**1** (20%)

Scheme 23

The ^1H NMR and melting point data obtained for *N*-acylated isomer **74** were entirely in line with Tronche's data. Therefore, although the compound has been correctly assigned in this instance (**Figure 18**), the ratio of regioisomers clearly disagrees with the reported results.

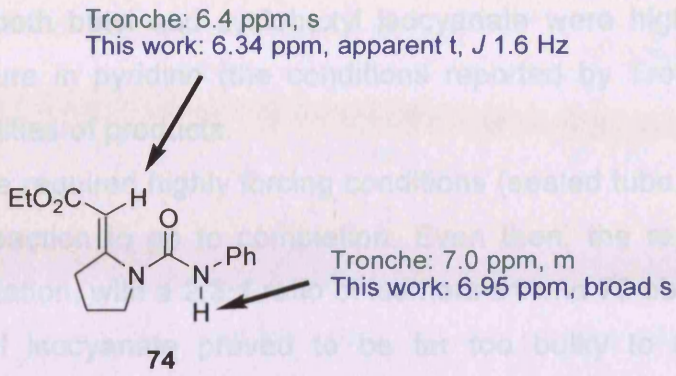
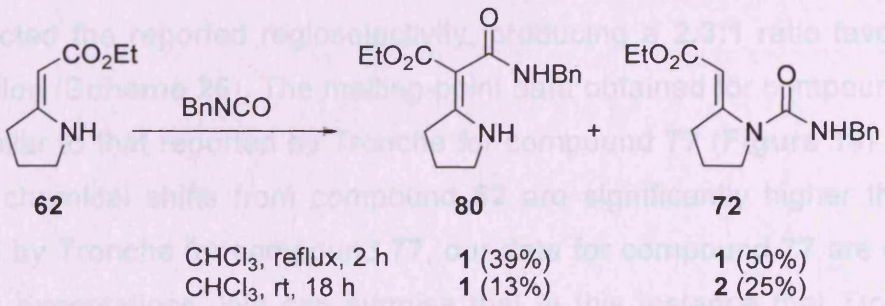


Figure 18

Our attention then turned to benzyl isocyanate. At reflux, a **1:1** mixture of isomers **80** and **72** was observed. However, upon lowering the reaction temperature to room temperature, a ratio of **2:1** favouring *N*-acylation was formed, therefore the regioselectivity is in line with Tronche's results **(Scheme 24)**. The experimental data obtained for the compound **72** also agrees with the data reported by Tronche.[40]



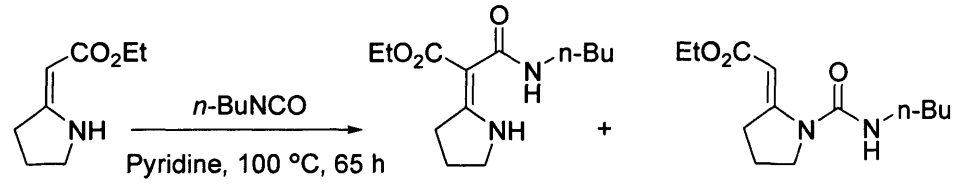
Scheme 24

At this point, we were tempted to speculate that alkyl isocyanates react predominately on nitrogen, and aryl isocyanates on carbon.

The next logical step, therefore, was to repeat the reaction of another alkyl isocyanate from the paper.

In our hands, both butyl and cyclohexyl isocyanate were highly unreactive at room temperature in pyridine (the conditions reported by Tronche), and gave negligible quantities of products.

Butyl isocyanate required highly forcing conditions (sealed tube, 100 °C, 65 h) in order for the reaction to go to completion. Even then, the regioselectivity still favoured *C*-acylation, with a **2.3:1** ratio of isomers **81** and **70** observed (**Scheme 25**). Cyclohexyl isocyanate proved to be far too bulky to react under any conditions, although a 45% yield of the *N*-acylated isomer for this reaction was reported in the original paper.

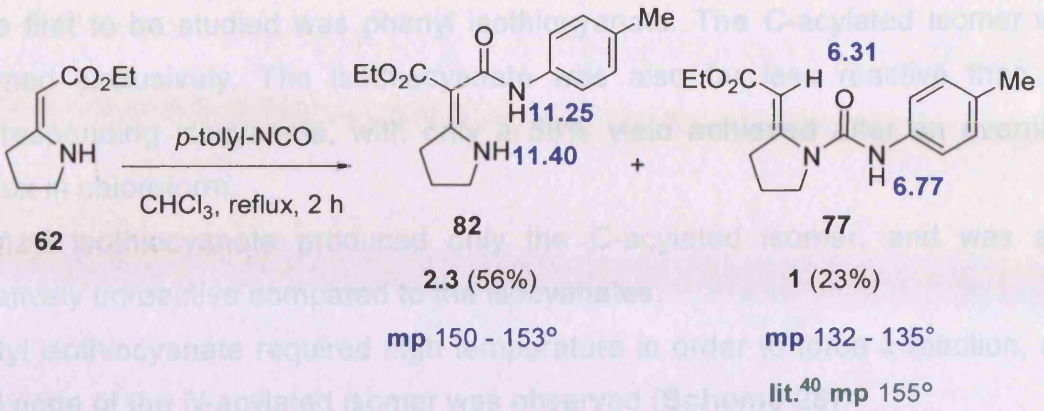


62 **81** **70**

2.3 (63%) **1** (19%)

Scheme 25

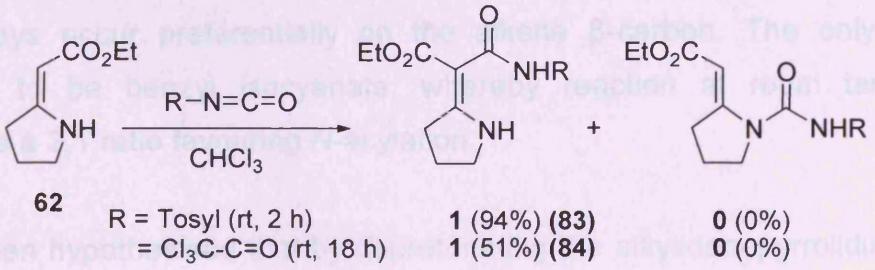
Reaction of alkylidenepyrrolidine **62** with *p*-tolyl isocyanate at reflux also contradicted the reported regioselectivity, producing a **2.3:1** ratio favouring the *C*-acylation (**Scheme 26**). The melting-point data obtained for compound **82** was very similar to that reported by Tronche for compound **77** (**Figure 16**). Although the N*H* chemical shifts from compound **82** are significantly higher than those reported by Tronche for compound **77**, our data for compound **77** are entirely in line with expectations. We can surmise that in this instance that Tronche has obtained the *C*-acylated isomer as the major product.



Scheme 26

These initial acylation results are highly perplexing. Whilst benzyl isocyanate corroborates Tronche's findings, predominantly acylating on nitrogen, the other three isocyanates preferentially acylate on carbon.
Both of the alkyl isocyanates appear far less reactive than reported, requiring elevated temperatures and extended reaction times.

In an attempt to alter the regioselectivity of the reaction in favour of *N*-acylation, we used two more reactive isocyanates; tosyl and trichloroacetyl isocyanate. Both reacted exclusively on carbon, the former requiring just two hours at room temperature to go to completion in virtually quantitative yield (**Scheme 27**).



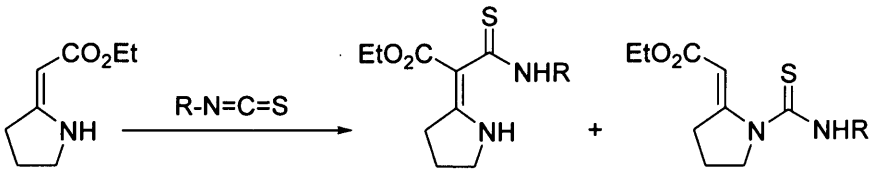
Scheme 27

Following on from the acylation studies with isocyanates, we decided to investigate the regioselectivity with isothiocyanates.

The first to be studied was phenyl isothiocyanate. The *C*-acylated isomer was formed exclusively. The isothiocyanate was also far less reactive than the corresponding isocyanate, with only a 58% yield achieved after an overnight reflux in chloroform.

Benzyl isothiocyanate produced only the *C*-acylated isomer, and was also relatively unreactive compared to the isocyanates.

Butyl isothiocyanate required high temperature in order to force a reaction, and still none of the *N*-acylated isomer was observed (**Scheme 28**).



62

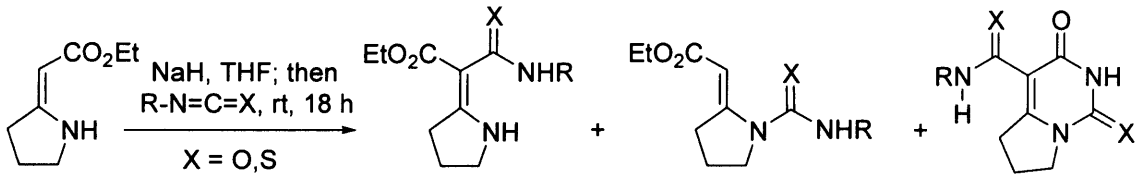
R = Ph ($CHCl_3$, reflux, 18 h)	**1** (58%) **(85)**	**0** (0%)
= Bn ($CHCl_3$, reflux, 18 h)	**1** (51%) **(86)**	**0** (0%)
= *n*-Bu (pyridine, 100 °C, 48 h, sealed tube)	**1** (89%) **(87)**	**0** (0%)

Scheme 29

These further reactions (summarised in **Tables 1** & **2**) corroborated what was now becoming the established trend for acylation of alkylidenepyrrolidines with heterocumulenes; regardless of temperature, solvent or reaction time, acylation will always occur preferentially on the alkene β-carbon. The only anomaly appears to be benzyl isocyanate, whereby reaction at room temperature produces a 2:1 ratio favouring *N*-acylation.

It was then hypothesised that by deprotonating the alkylidenepyrrolidine prior to addition of heterocumulene, we could make the nitrogen more nucleophilic, therefore more susceptible to acylation at that site.

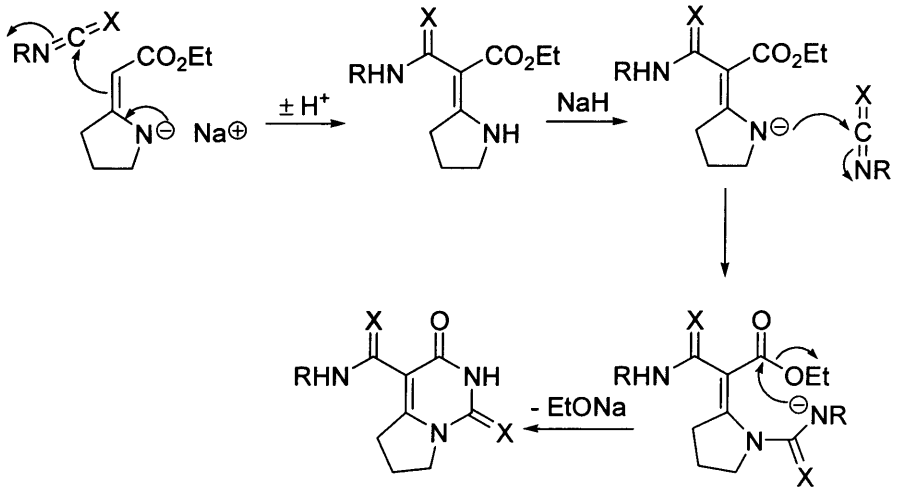
Pyrrolidine **62** was therefore stirred with 1 equivalent of sodium hydride, followed by addition of 1 equiv. of heterocumulene (PhNCO, BnNCO or PhNCS). The results were highly surprising. Along with an increased proportion of *C*-isomer, a novel pyrrolo[1,2-*c*]pyrimidine was synthesised (**Scheme 30**).



PhNCO	**79** ; (31%)	**74** ; (0%)	**88** ; (13%)
BnNCO	**80** ; (35%)	**72**; (0%)	**89** ; (9%)
BnNCS	**86** ; (38%)	Not formed	**90** ; (25%)

Scheme 30

The mechanism of formation of the pyrrolo[1,2-*c*]pyrimidine is believed to occur *via* initial acylation on carbon, followed by further acylation on nitrogen. The subsequent anion intermediate then cyclises onto the ester moiety, forming the pyrimidine ring (**Scheme 31**).

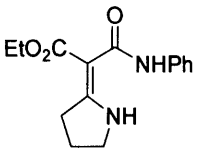


Scheme 31

The acylation studies are summarised in **Tables 1** and **2**.

Heterocumulene	Conditions	Ratio *C*:*N* Acylation	Products (% isolated yields)
PhNCO	Benzene, reflux, 2 h	5.2:1	**Not purified**
	$CHCl_3$, reflux, 2 h	3.4:1	**79** (71%); **74** (17%)
	THF, reflux, 2 h	7:1	Not purified
	$CHCl_3$, 25 °C, 18 h	2.1:1	**79** (53%); **74** (20%)
	NaH, THF, 18 h	1:0	**79** (31%); **74** (0%); **88** (13%)
BnNCO	$CHCl_3$, 25 °C, 18 h	1:2	**80** (13%); **72** (25%)
	$CHCl_3$, reflux, 20 h	1:1	**80** (39%); **72** (50%)
	NaH, THF, 18 h	1:0	**80** (39%); **72** (0%); **89** (9%)
***n*-BuNCO**	Pyridine, 100 °C, 65 h, sealed tube	2.3:1	**81** (65%); **70** (19%)
4-MeC_6H_4NCO	$CHCl_3$, reflux, 2 h	2.3:1	**82** (56%); **77** (23%)

Table 1



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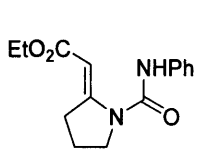

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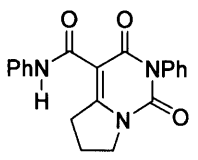

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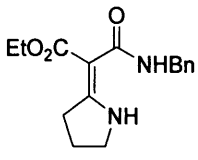

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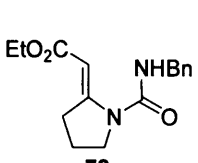

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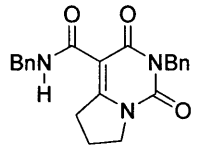

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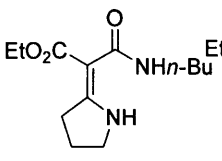

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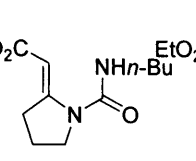

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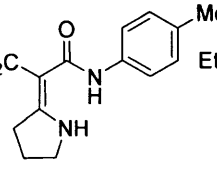

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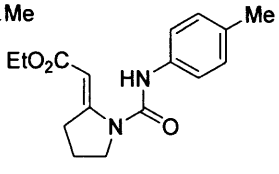
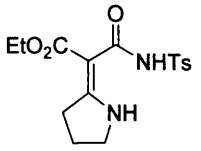


77

Heterocumulene	Conditions	Ratio *C*:*N* Acylation	Products (% isolated yields)
TsNCO	$CHCl_3$, 25 °C, 2 h	1:0	**83** (94%)
$Cl_3CCONCO$	$CHCl_3$, 25 °C, 18 h	1:0	**84** (51%)
PhNCS	$CHCl_3$, reflux, 18 h	1:0	**85** (58%)
BnNCS	$CHCl_3$, reflux, 18 h	1:0	**86** (66%)
	NaH, THF, 18 h	1:0	**86** (38%); **90** (25%)
***n*-BuNCS**	Pyridine, 100 °C, 46 h, sealed tube	1:0	**87** (89%)

Table 2



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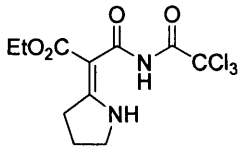

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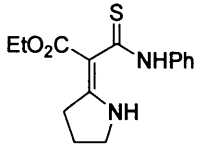

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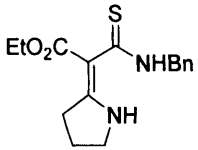

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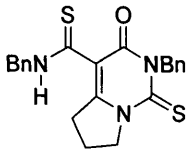

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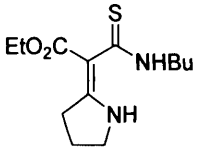


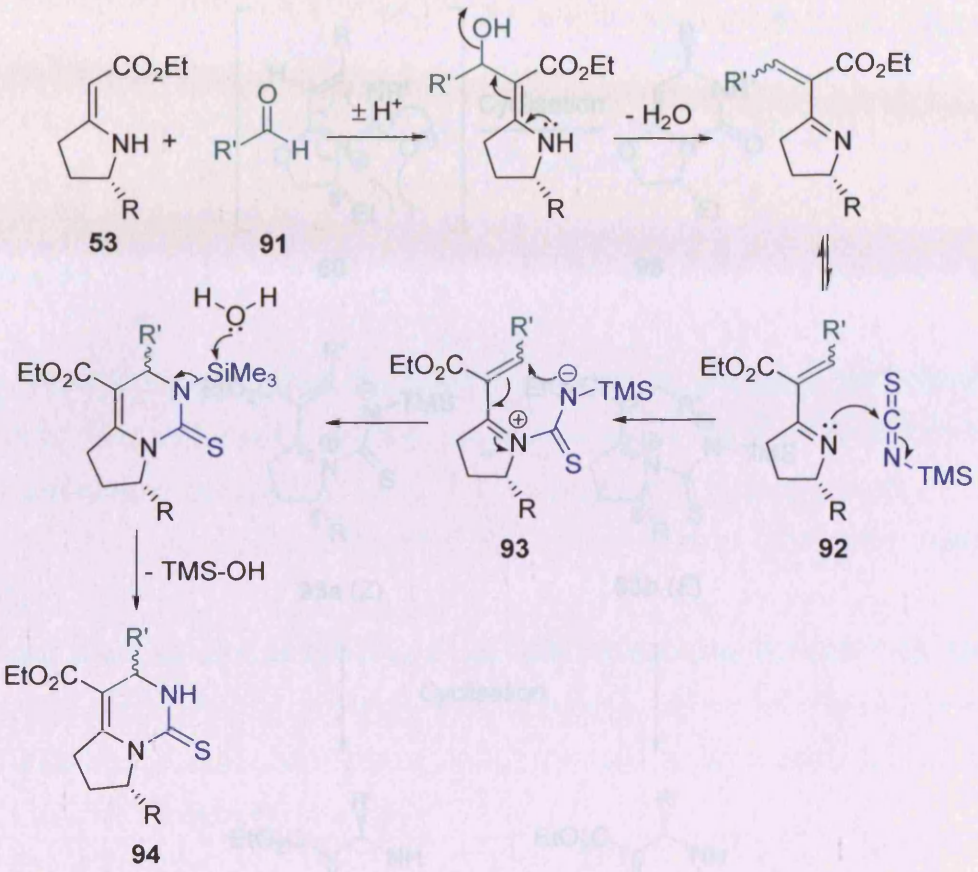
87

The proposed mechanism of the Kishi three-component coupling requires a reaction pathway whereby initial acylation of the alkylidenepyrrolidine with trimethylsilyl isothiocyanate takes place on nitrogen. It now seems highly unlikely that this could be taking place, given the regioselectivity trends for acylation of these alkylidenepyrrolidines. The three-component coupling reaction is also considerably faster than the vast majority of these acylation reactions, particularly with isothiocyanates.

Although no evidence could be ascertained from the reaction of trimethylsilyl isothiocyanate and alkylidenepyrrolidine **62**, the general acylation trends appear to point away from the existence of this reaction pathway.

2.2.3 The Second Postulated Mechanism: Alkylidenepyrrolidine & Aldehyde

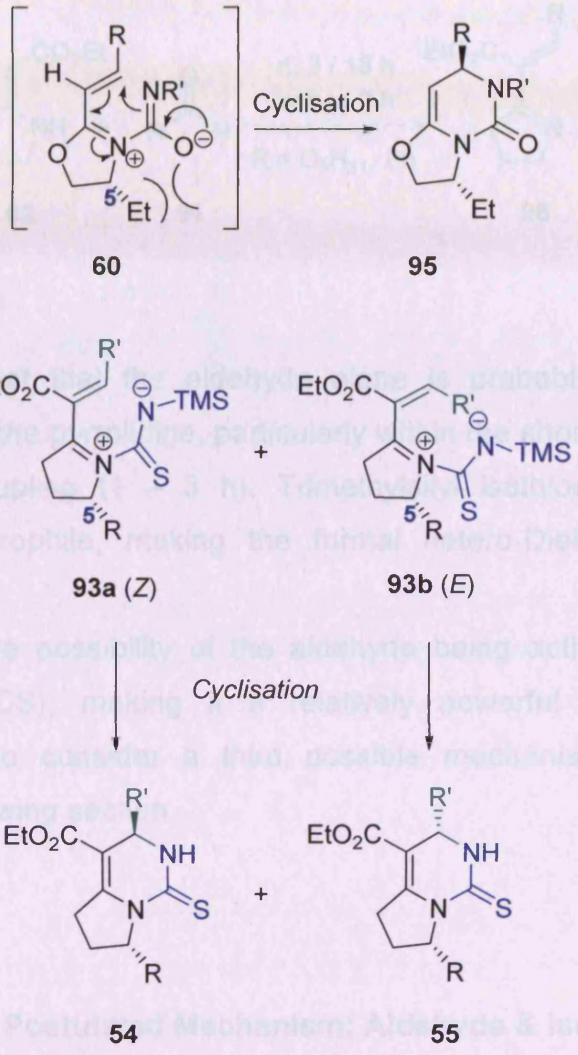
The second possible mechanism involves the initial reaction of alkylidenepyrrolidine (**53**) and aldehyde (**91**) to produce an aza-diene intermediate (**92**). Based on the group's studies of annulation reactions of alkenyloxazoline with heterocumulenes, the heterocumulene would be expected to react with the aza-diene in a stepwise, formal hetero-Diels-Alder pathway *via* intermediate **93**, affording pyrimidine **94** (**Scheme 32**).[32] Cyclisation onto the sulphur of the thiourea would be disfavoured, owing to the steric bulk of the sulphur atom.



Scheme 32

It is known from previous studies[32] that intermediate **60** will cyclise stereospecifically to give the corresponding *trans*-isomer (**95**) (**Scheme 33**). To compare this to the three-component coupling, one can envisage the corresponding *trans*-isomer **54** resulting from double-bond isomer **93a**, with the *cis*-isomer **55** resulting from double-bond isomer **93b**.

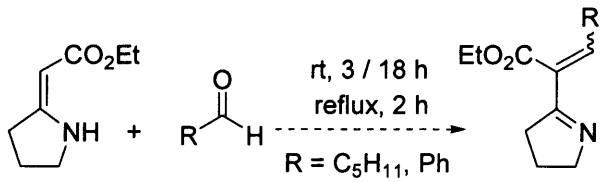
Therefore, formation of an approximate 2:1 mixture of double-bond isomers **93a** and **93b** could explain the overall stereochemical outcome of the reaction.



Scheme 33

Again, in order to prove, or indeed disprove the mechanism, experimental evidence would be required.

Equimolar amounts of alkylidenepyrrolidine **62** and aldehyde **91** were therefore mixed together (**Scheme 34**). On a laboratory scale, and in an NMR tube, no reaction was observed.



62 91 96

Scheme 34

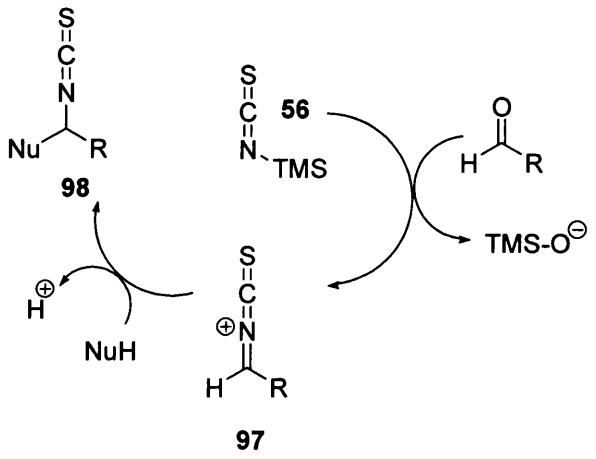
These results suggest that the aldehyde alone is probably not electrophilic enough to react with the pyrrolidine, particularly within the short time-frame of the three-component coupling (1 – 3 h). Trimethylsilyl isothiocyanate is also a relatively poor electrophile, making the formal hetero-Diels-Alder step also unlikely.

However, there is the possibility of the aldehyde being activated by the third component (TMS-NCS), making it a relatively powerful electrophile. This hypothesis led us to consider a third possible mechanism, which will be discussed in the following section.

2.2.4 The Third Postulated Mechanism: Aldehyde & Isothiocyanate

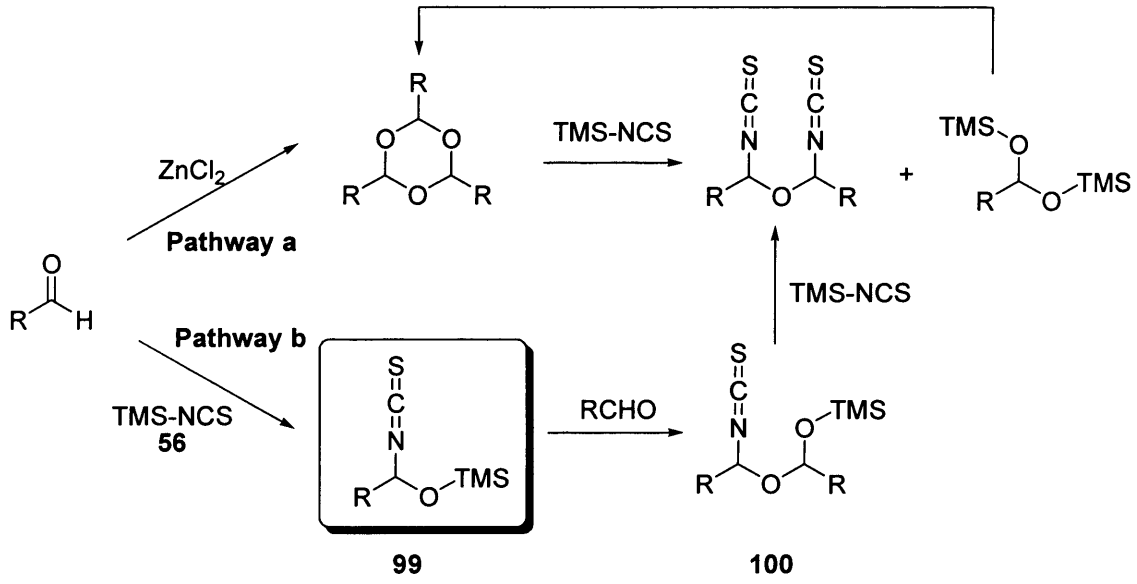
Thus far, the proposed reaction pathways for our key step have involved initial coupling of two of the components, followed by reaction with the third. As previously discussed, the aldehyde appears to be unreactive towards nucleophilic attack by the alkylidenepyrrolidine. However, if the aldehyde is activated beforehand by the isothiocyanate component, an electrophilic iminium ion species may be formed.

Scheme 35 illustrates this principle, whereby nucleophilic attack of the isothiocyanate nitrogen onto the aldehyde initially takes place to form compound **97**, an 'extended heterocumulene'. This species then reacts with a nucleophile at the position shown.



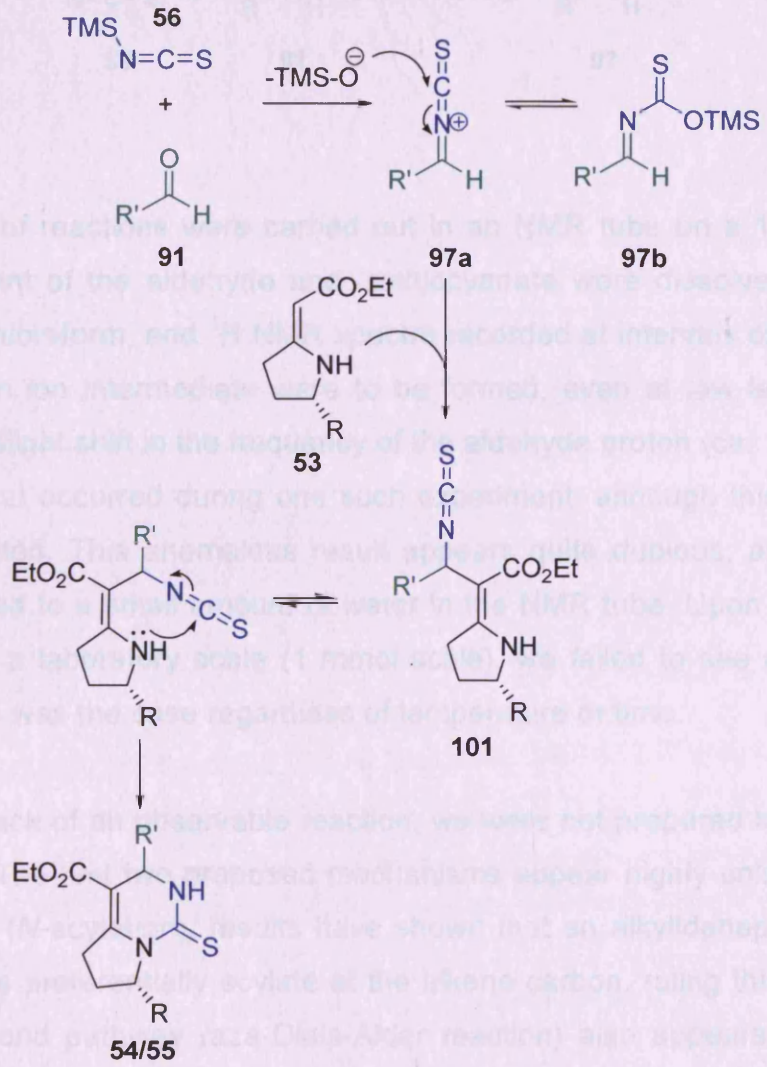
Scheme 35

Nishiyama and co-workers reported the zinc chloride-catalysed reaction of trimethylsilyl isothiocyanate and a range of aliphatic aldehydes (**Scheme 36**).[43] Two reaction pathways were proposed, with pathway b resulting from formation of an α-siloxy isothiocyanate intermediate (**99**) which arose through electrophilic addition of the aldehyde to the nitrogen of compound **56**.



Scheme 36

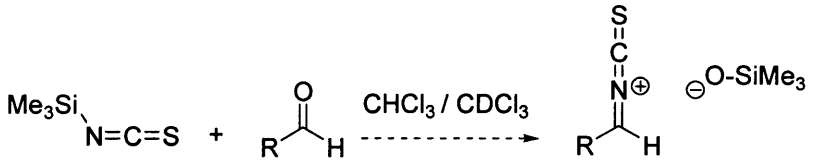
With intermediate **99** in mind, a full mechanistic pathway for the three-component coupling was proposed (**Scheme 37**). Beginning with reaction of TMS-NCS and aldehyde, intermediate **97** could either exist as an 'extended heterocumulene' **97a**, or as *N*-thiocarbamoyl imine **97a**. As both **97a** and **97b** will lead to the same eventual product, only one pathway has been described to simplify matters. Electrophilic addition of the iminium ion to alkylidenepyrrolidine **53** takes place on the alkene carbon, creating a new stereogenic centre. The alkene double bond of compound **101** then isomerises, allowing cyclisation onto the isothiocyanate moiety to occur, affording pyrimidine **54/55**.



Scheme 37

The experimental procedure for the three-component coupling consists of mixing the aldehyde and isothiocyanate, stirring the reaction for half an hour, and then adding the alkylidenepyrrolidine. We have attempted to mix all three components simultaneously, and although we have observed some signs of the product, although the reaction is not as clean as with the former method.

In the same manner as the first two mechanisms, equimolar quantities of the two components were mixed together together (**Scheme 38**).



56 **91** **97**

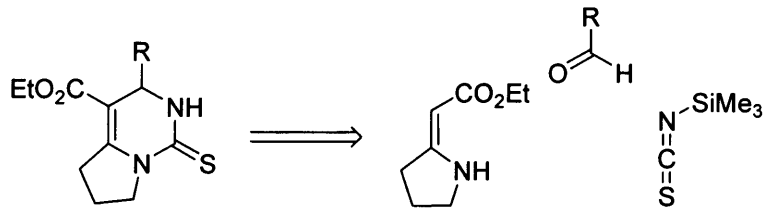
Scheme 38

The first set of reactions were carried out in an NMR tube on a 1 mmol scale. One equivalent of the aldehyde and isothiocyanate were dissolved in 1 mL of deuterated chloroform, and ^{1}H NMR spectra recorded at intervals of ten minutes. If the iminium ion intermediate were to be formed, even at low levels, it could appear as a slight shift in the frequency of the aldehyde proton (ca. 10 ppm). This is exactly what occurred during one such experiment, although this result could not be repeated. This anomalous result appears quite dubious, and may have been attributed to a small amount of water in the NMR tube. Upon changing the conditions to a laboratory scale (1 mmol scale), we failed to see any sign of a reaction. This was the case regardless of temperature or time.

Despite the lack of an observable reaction, we were not prepared to dismiss this mechanism. The first two proposed mechanisms appear highly unlikely; with the first pathway (*N*-acylation), results have shown that an alkylidenepyrrolidine will almost always preferentially acylate at the alkene carbon, ruling this mechanism out. The second pathway (aza-Diels-Alder reaction) also appears disfavoured, given the relatively low reactivity of both the isothiocyanate, and the short timeframe (1 – 3 h) required for the three-component coupling.

2.2.5 Tentative Support for the 'Extended Heterocumulene' Mechanism

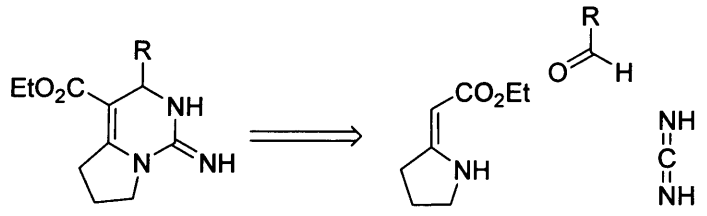
As previously discussed, the three-component coupling is a convenient and reliable method to construct the required bicyclic thiourea core(s) of the Batzelladine alkaloids (**102**) (**Scheme 39**).



102 **62** **56**

Scheme 39

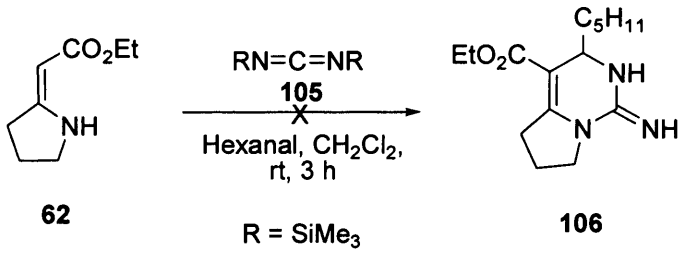
The thiourea can then be converted into the required guanidine (**103**).[28] If, however, the guanidine can be installed directly from the alkylidenepyrrolidine, then the synthetic advantages would be significant. If the same retrosynthetic analysis is applied to guanidine **103** (**Scheme 40**), one can envisage replacing the isothiocyanate with a directly analogous heterocumulene. An apposite reagent might be a carbodiimide equivalent (**104**).



103 **62** **104**

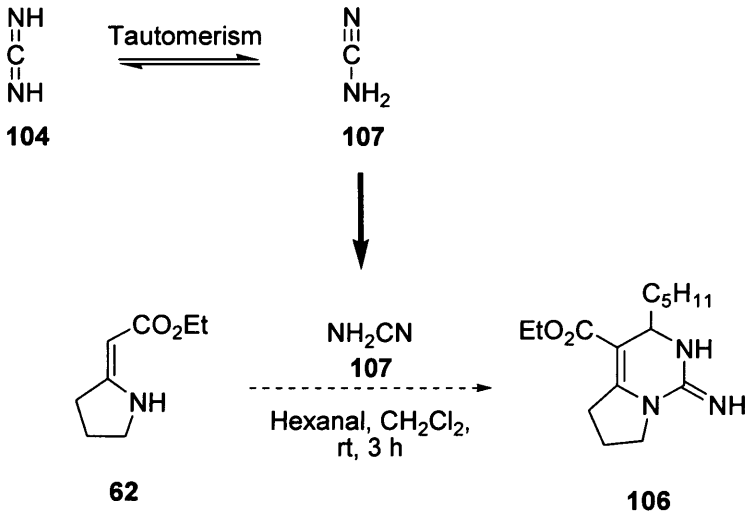
Scheme 40

The standard conditions of the three-component coupling were repeated within the group, replacing trimethylsilyl isothiocyanate with a nitrogen equivalent, bis-trimethylsilylcarbodiimide (**105**) (**Scheme 41**).[44] Unfortunately, no reaction was observed.



Scheme 41

Compound **104** can exist either as its carbodiimide (**104**) or cyanamide tautomer (**107**) (**Scheme 42**). Therefore, the next logical step was to repeat the three-component coupling, replacing bis-trimethylsilylcarbodiimide with cyanamide.



Scheme 42

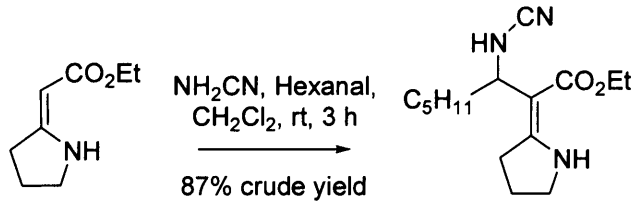
The initial results were promising, producing very clean ^{1}H NMR spectra. There was no discernible trace of alkylidenepyrrolidine, and the coupling patterns indicated the presence of diastereotopic hydrogen atoms on the pyrrolidine ring, implying the formation of a stereogenic centre during the reaction.

However, this compound was found to be clearly different from guanidine **106** (as the acetate salt) prepared by an independent route (see *Experimental, Section 6.2*).

The ^{13}C NMR spectrum corroborated this, with a clear signal corresponding to the C≡N peak still present.

However, the synthetic material proved unexpectedly unstable to column chromatography or a mild aqueous wash.

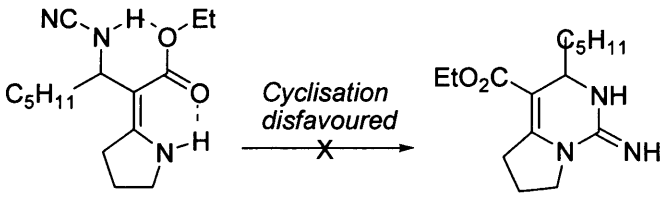
Compound **108** was then proposed according to the combined spectroscopic evidence (**Scheme 43**).



62 **108**

Scheme 43

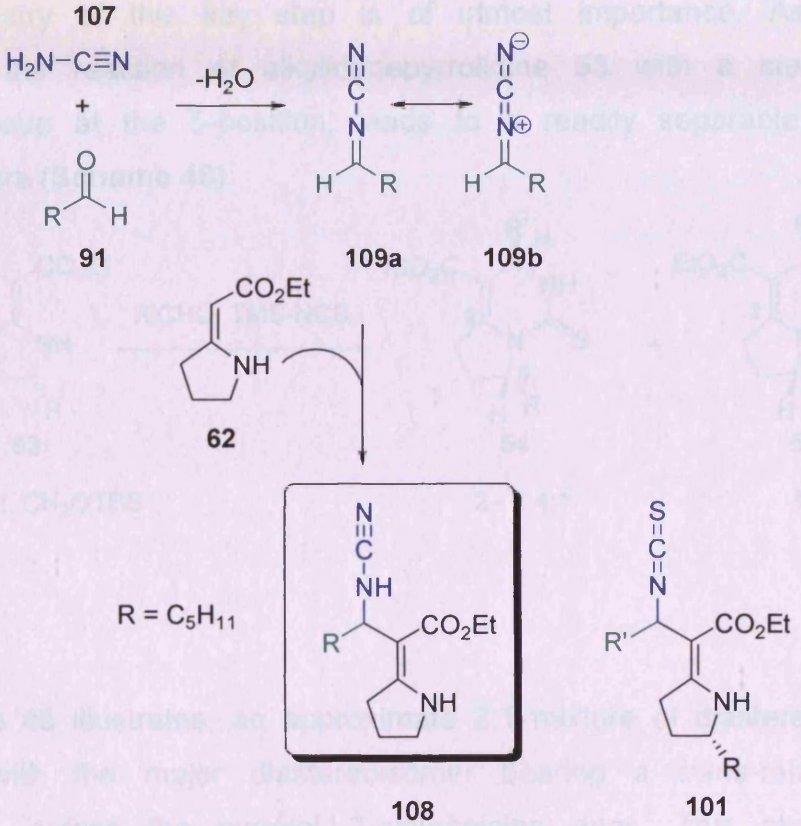
It is known that intramolecular hydrogen bonding exists between the NH and the ester carbonyl; intermediate **108** almost certainly has further hydrogen bonding between the cyanamide unit and the ether oxygen of the ester. This extra bonding would lead to a more stable structure, resulting in cyclisation becoming less favoured (**Scheme 44**).



108 **106**

Scheme 44

A mechanism analogous to that proposed for the three-component coupling can be envisaged (**Scheme 45**).

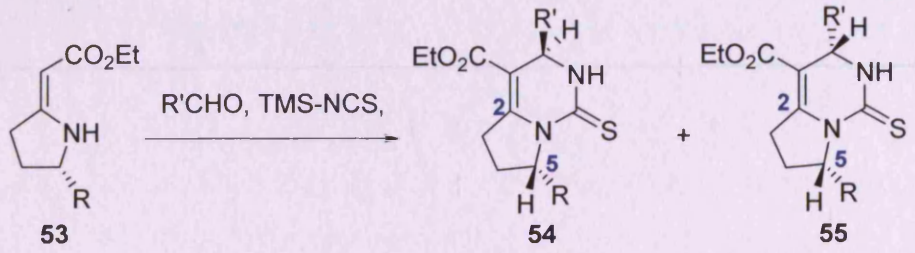


Scheme 45

Compound **108** is analogous to intermediate **101** proposed for the three-component coupling. The isolation of this compound therefore provides support for the proposed mechanism.

2.3 Stereochemical Aspects of the Three-Component Coupling

Particularly with a view to future synthetic approaches, understanding the stereochemistry of this key step is of utmost importance. As previously discussed, the reaction of alkylidenepyrrolidine **53** with a stereochemical directing group at the 5-position, leads to a readily separable mixture of diastereomers (**Scheme 46**).



53 **54** **55**

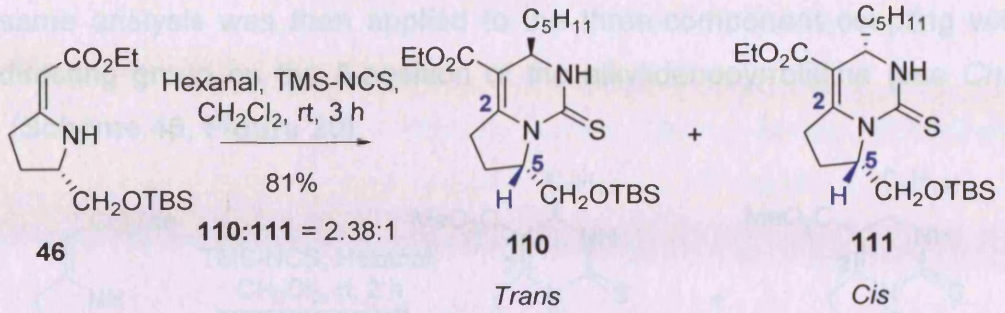
R = allyl, CH_2OTBS 2 - 2.4:1 1

Scheme 46

As **Scheme 46** illustrates, an approximate 2:1 mixture of diastereoisomers is obtained, with the major diastereoisomer bearing a *trans*-relationship of substituents across the pyrrolo[1,2-*c*]pyrimidine rings. This stereochemical assignment is based on initial nOe evidence.[34]

Upon interpretation of the ^{1}H NMR spectra of these three-component couplings, it was found that the diastereomeric ratio could be determined from the relative integrations of the proton on the 5-position of the pyrrolidine rings (**54** & **55**).

The ^{1}H NMR spectrum of isomers **110** and **111** (**Scheme 47**, **Figure 19**) was the first three-component coupling to be analysed in this manner.



46 **110** *Trans* **111** *Cis*

Scheme 47

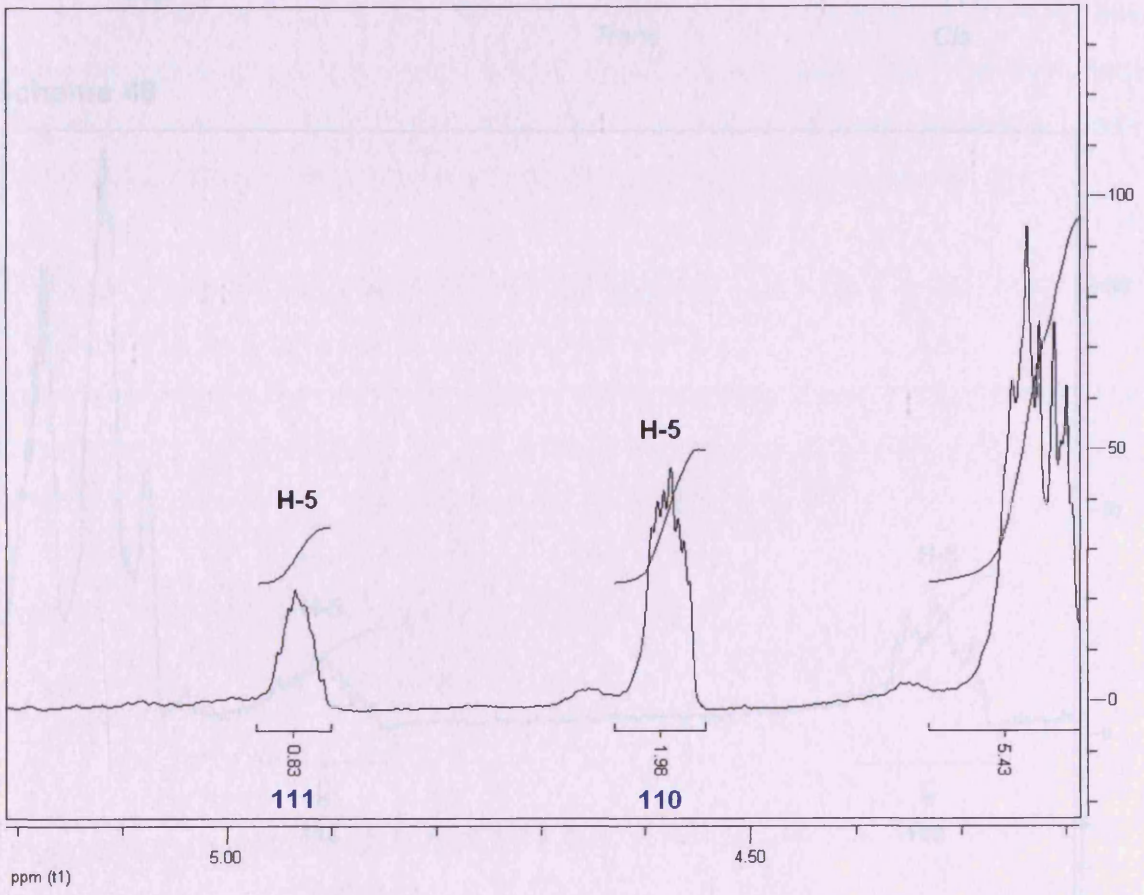
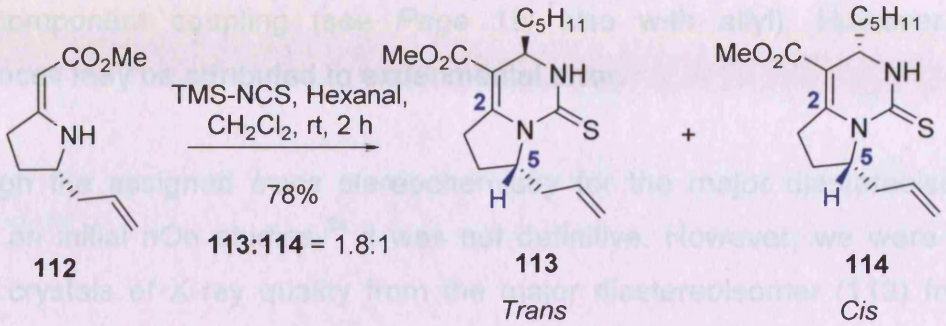


Figure 19

Figure 19 shows the region of the ^{1}H NMR spectrum from 4.3 - 5.2 ppm, with an approximate 2.38:1 ratio of diastereoisomers measured. The proton on the 5-position of the major (*trans*) isomer is upfield that in of the minor isomer.

The same analysis was then applied to the three-component coupling with an allyl directing group on the 5-position of the alkylidenepyrrolidine (see *Chapter Five*) (**Scheme 48**, **Figure 20**).



112 **113** *Trans* **114** *Cis*

Scheme 48

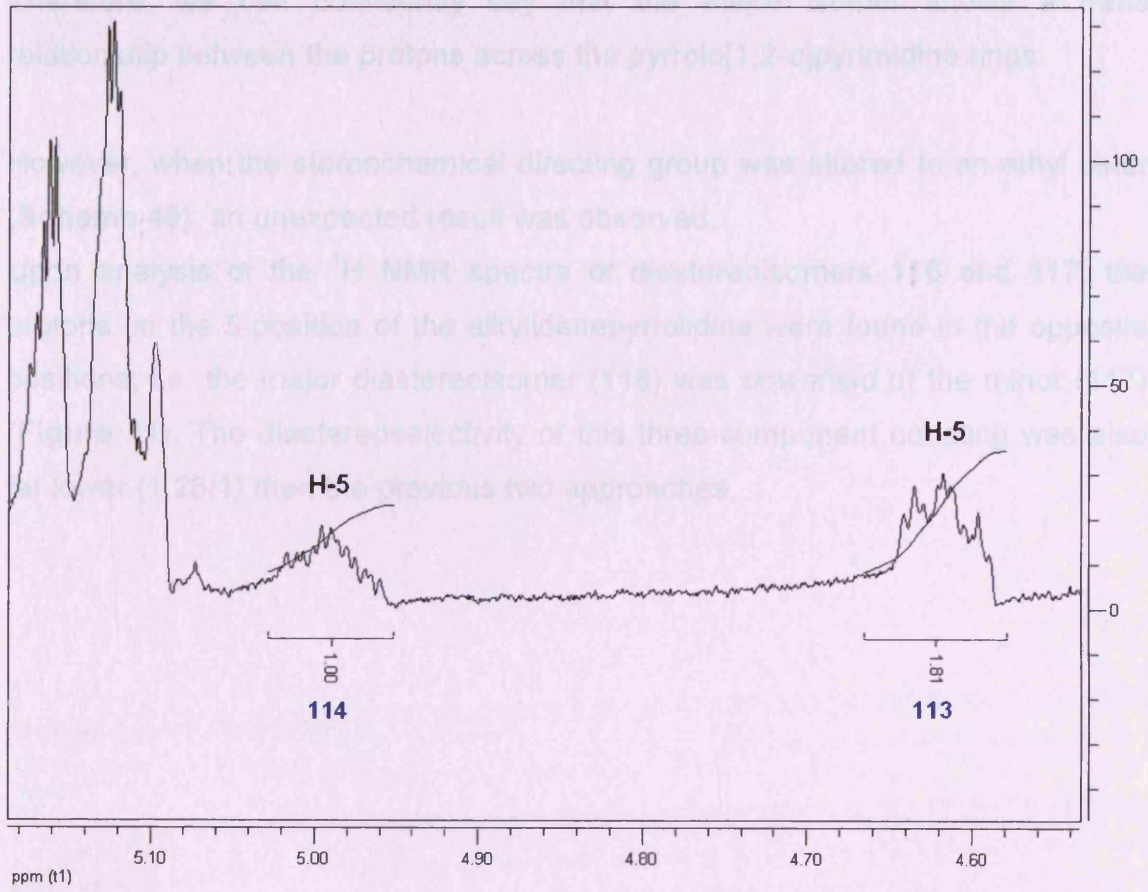


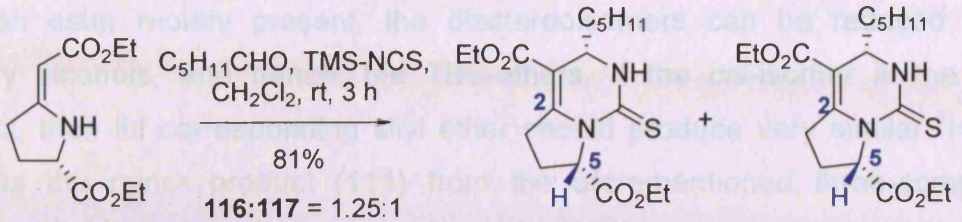
Figure 20

The equivalent region of the ^{1}H NMR of diastereoisomers **113** and **114** is shown in **Figure 20**. As with the aforementioned three-component coupling, the 5-H in

the major isomer is upfield of the minor, with an approximate d.r. of 1.8:1 calculated.
The diastereoselectivity is slightly lower than Stuart Wordingham's three-component coupling (see *Page* 19; also with allyl). However, these differences may be attributed to experimental error.

Although the assigned *trans* stereochemistry for the major diastereoisomer is based on initial nOe studies,[34] it was not definitive. However, we were able to obtain crystals of X-ray quality from the major diastereoisomer (**113**) from this three-component coupling (see *Chapter Five*), corroborating the nOe evidence. Therefore, we can confidently say that the major isomer shows a *trans* relationship between the protons across the pyrrolo[1,2-*c*]pyrimidine rings.

However, when the stereochemical directing group was altered to an ethyl ester (**Scheme 49**), an unexpected result was observed.
Upon analysis of the ^{1}H NMR spectra of diastereoisomers **116** and **117**, the protons on the 5-position of the alkylidenepyrrolidine were found in the opposite positions; i.e. the major diastereoisomer (**116**) was *downfield* of the minor (**117**) (**Figure 21**). The diastereoselectivity of this three-component coupling was also far lower (1.25:1) than the previous two approaches.



115 **116** **117**

Cis *Trans*

Scheme 49

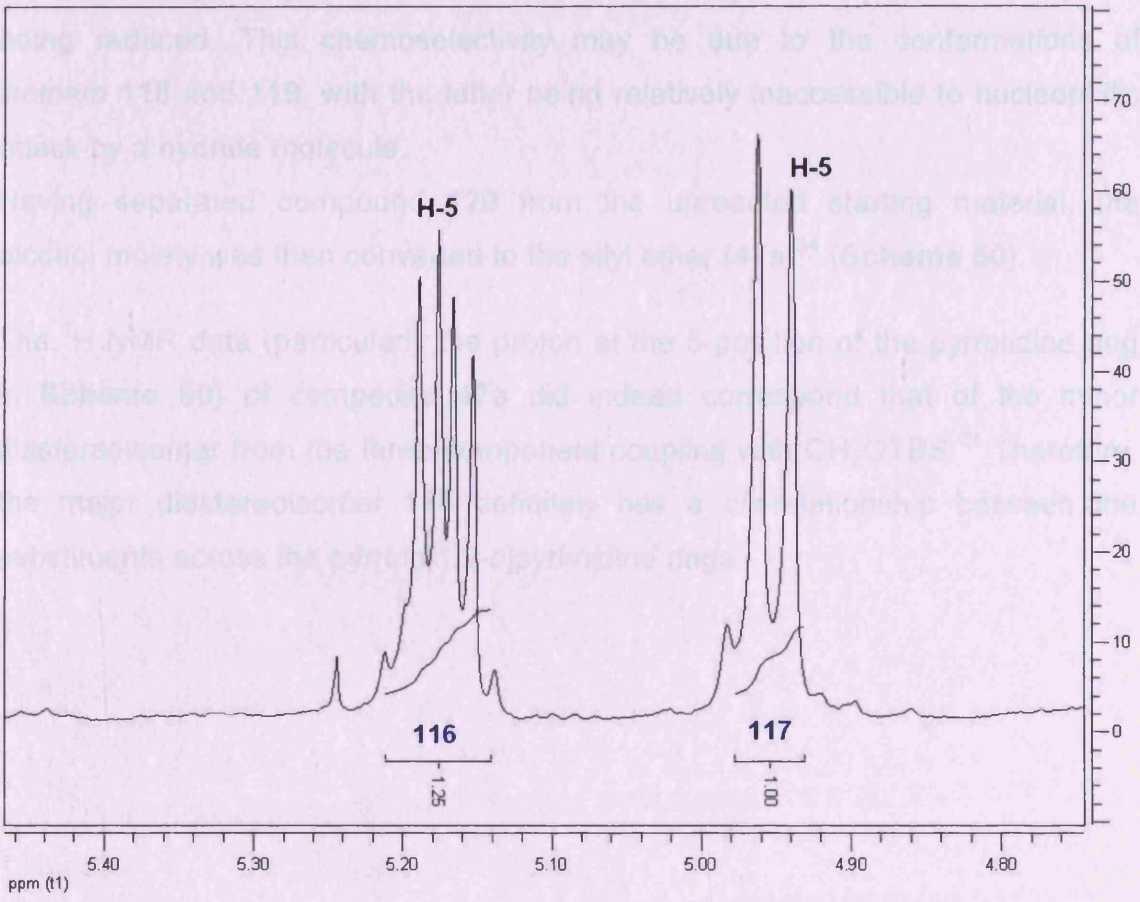


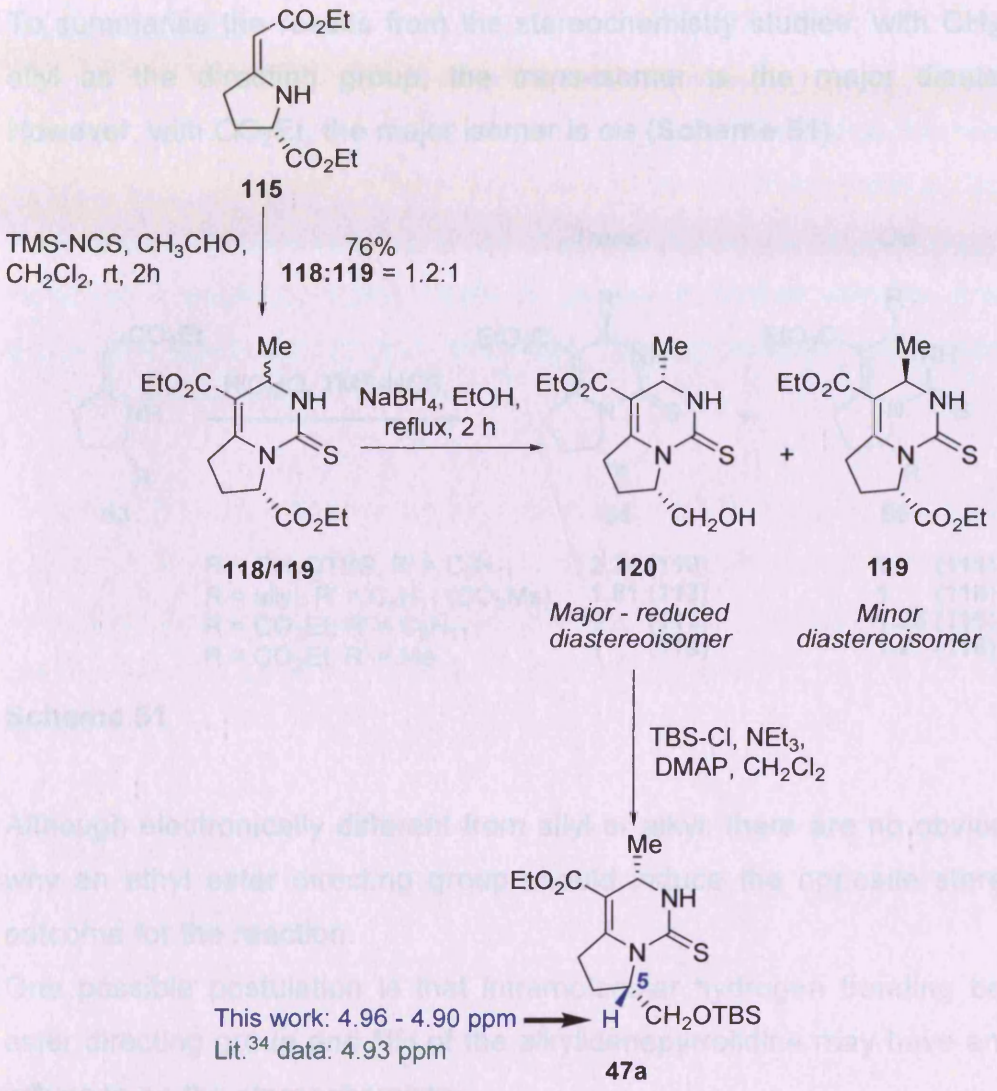
Figure 21

One possible explanation for this result is that CO_2Et might be producing the opposite stereochemical outcome; i.e. the major isomer has a *cis*-relationship between the protons across the pyrrolo[1,2-*c*]pyrimidine rings.

With an ester moiety present, the diastereoisomers can be reduced to the primary alcohols, and hence, the TBS-ethers. If the *cis*-isomer is the major product, then its corresponding silyl ether should produce very similar ^{1}H NMR data as the minor product (**111**) from the aforementioned three-component coupling (**Scheme 47**).

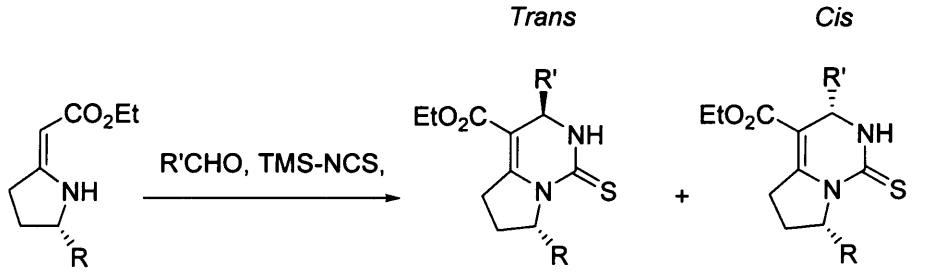
Diastereoisomers **118** and **119**, from a similar three-component coupling (with acetaldehyde rather than hexanal), were treated initially with sodium borohydride to afford the primary alcohol, with surprisingly only the major diastereoisomer being reduced. This chemoselectivity may be due to the conformations of isomers **118** and **119**, with the latter being relatively inaccessible to nucleophilic attack by a hydride molecule.
Having separated compound **120** from the unreacted starting material, the alcohol moiety was then converted to the silyl ether (**47a**)[34] (**Scheme 50**).

The ^{1}H NMR data (particularly the proton at the 5-position of the pyrrolidine ring in **Scheme 50**) of compound **47a** did indeed correspond that of the minor diastereoisomer from the three-component coupling with CH_2OTBS.[34] Therefore, the major diastereoisomer **118** definitely has a *cis*-relationship between the substituents across the pyrrolo[1,2-*c*]pyrimidine rings.


CO2Et
NH
CO2Et
115
TMS-NCS, CH3CHO,
CH2Cl2, rt, 2h
76%
118:119 = 1.2:1
Me
EtO2C
NH
N
S
CO2Et
118/119
NaBH4, EtOH,
reflux, 2 h
CH2OH
120
Major - reduced
diastereoisomer
+
119
Minor
diastereoisomer
TBS-Cl, NEt3,
DMAP, CH2Cl2
5
H
CH2OTBS
This work: 4.96 - 4.90 ppm
Lit.[34] data: 4.93 ppm
47a

Scheme 50

To summarise the results from the stereochemistry studies: with CH_2OTBS and allyl as the directing group, the *trans*-isomer is the major diastereoisomer. However, with CO_2Et, the major isomer is *cis* (**Scheme 51**).



53 **54** **55**

R = CH_2OTBS; R' = C_5H_{11}	**2.38 (110)**	**1 (111)**
R = allyl; R' = C_5H_{11} (CO_2Me)	**1.81 (113)**	**1 (114)**
R = CO_2Et; R' = C_5H_{11}	**1 (117)**	**1.25 (116)**
R = CO_2Et; R' = Me	**1 (119)**	**1.2 (118)**

Scheme 51

Although electronically different from allyl or alkyl, there are no obvious reasons why an ethyl ester directing group should induce the opposite stereochemical outcome for the reaction.

One possible postulation is that intramolecular hydrogen bonding between the ester directing group and N*H* of the alkylidenepyrrolidine may have an additional influence on the stereochemistry.

2.4 Conclusions

Through experimental evidence, we now strongly believe that the mechanism of our key step proceeds by initial activation of the isothiocyanate by the aldehyde to produce a reactive species, which then reacts with the alkylidenepyrrolidine. However, it would be highly useful to be able to further validate, and ultimately prove the existence of the 'extended heterocumulene' mechanism through synthetic methodology.

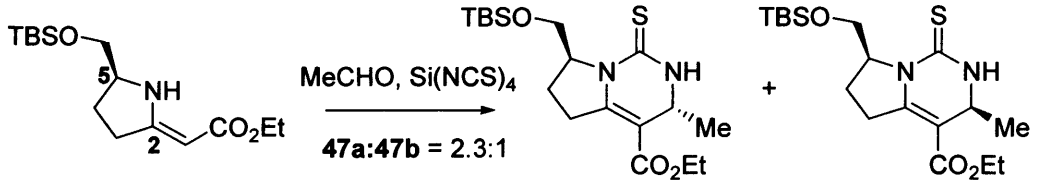
Chapter Three will discuss an asymmetric synthetic route to the western half of batzelladine A, with the three-component coupling employed as the key synthetic step. The stereochemical directing group of the alkylidenepyrrolidine component will be located adjacent to the double bond, close to the proposed reaction centre.

Chapter 3

A Highly Diastereoselective Approach to the Western Half of Batzelladine A

3.1 Introduction

The group's previous synthetic studies towards the western half of Batzelladine A (**Scheme 51**) utilised this three–component coupling as a central step.[34] With a stereochemical directing group at the 5-position of alkylidenepyrrolidine **46**, a diastereomeric ratio of 2.3:1 of **47a:47b** was obtained.

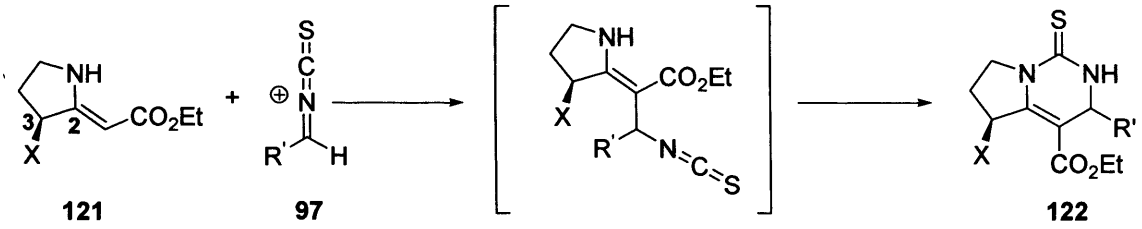


46 **47a** (54%) **47b** (27%)

Scheme 51

This synthetic approach (along with other three-component couplings; see *Chapter Two*) used a stereochemical directing group remote from what we now believe is the site of reaction. If a directing group can be placed at a closer position to the reaction centre, then the stereoselectivity of the reaction should be influenced to a far greater degree.

Scheme 52 illustrates this hypothesis, whereby a bulky directing group (X) is situated at the 3-position of alkylidenepyrrolidine (**d**), reacting with the 'extended heterocumulene' (**97**) at the alkene carbon.



121 **97** **122**

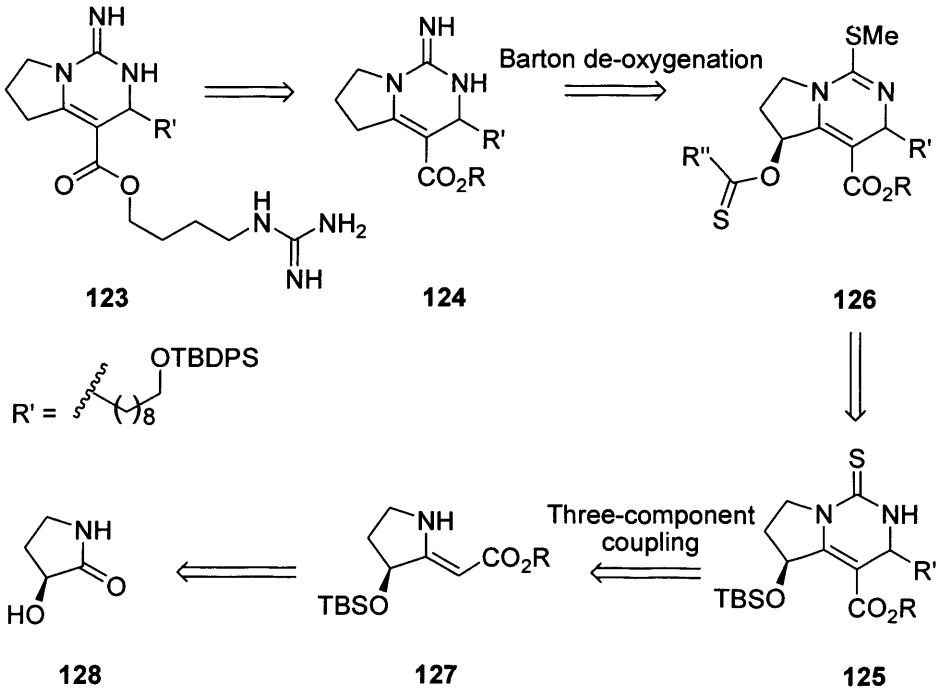
Scheme 52

If a high diastereoselectivity arises from this three-component coupling, then this would offer further supporting evidence for the postulated reaction mechanism.

3.2 Retrosynthetic approach to Batzelladine A

Scheme 53 shows the planned approach to the western half of Batzelladine A. The natural product (**123**) should be formed *via* a transesterification of compound **124** and the appropriate guanidine alcohol. It is anticipated that thiourea **125** can be protected as the *S*-methyl isothiourea, and converted to the thioacyl derivative (**126**). An oxygen-containing directing group alpha to the double-bond would be an ideal choice, as a Barton deoxygenation can be used to remove this group in the presence of an *S*-methyl isothiourea,[45] forming guanidine **124** as a single enantiomer.

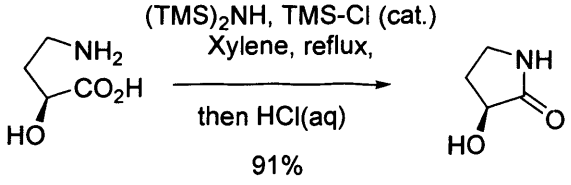
The three-component coupling of enantiopure alkylidenepyrrolidine **127**, aldehyde and isothiocyanate will be the key step in the synthesis, establishing the bicyclic core with the appropriate length alkyl-chain for the left-hand side. Compound **127** will in turn be synthesised from hydroxy lactam **128**.



Scheme 53

3.3 Synthetic Strategies Towards the Natural Product

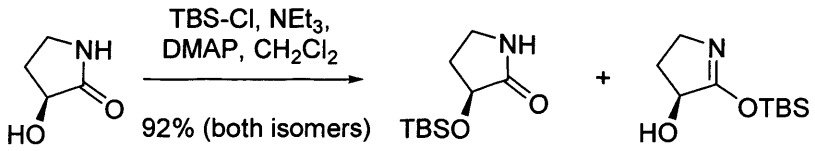
As we were aiming towards an asymmetric total synthesis, the commercially-available (*S*)-enantiomer of amino acid **129** was chosen as the building block (**Scheme 54**).



129 **128**

Scheme 54

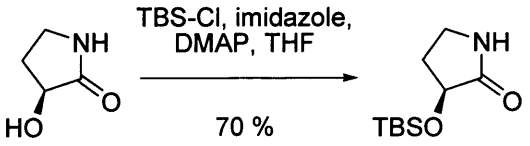
Ring-closing *via* the trimethylsilyl ester afforded the lactam, protected as the trimethylsilyl-ether.[46] Straightforward silyl-deprotection with aqueous HCl then yielded lactam **128** in very high purity. The next synthetic step was protection of the hydroxy group as the *tert*-butyldimethylsilyl ether. Under standard protecting conditions,[47] a 1:1 mixture of desired lactam **130** and undesired imino-ether **131** was produced (**Scheme 55**).



128 **130** **131**

Scheme 55

However, by alteration of the reaction solvent and base, the regioselectivity was enhanced in favour of the desired isomer (**130**) (**Scheme 56**).



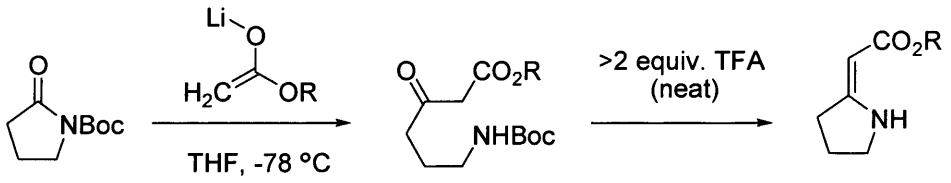
128 **130**

Scheme 56

Pleasingly, the first two steps could be carried out on a 5 - 15 g scale, with no requirement for chromatography.

3.4 Approaches Towards Alkylidenepyrrolidine Formation (I)

The Elliott group have devised a novel method for alkylidenepyrrolidine formation, involving the use of ester-enolate chemistry.[38] The general protocol begins with Boc-protected lactam (**132**), which is treated with the appropriate enolate, opening-up the five-membered ring to afford **133**. With an excess of trifluoroacetic acid, ring-closing is promoted, followed by dehydration and Boc-deprotection to afford pyrrolidine **134** (**Scheme 57**).



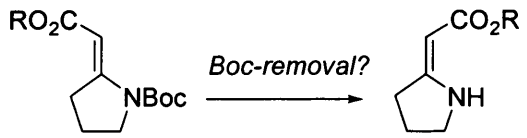
132 **133** **134**

Scheme 57

However, it is expected that the *tert*-butyldimethylsilyl protecting group may not survive the acid-mediated ring-closing step.

It is known that carbamate **133** will spontaneously ring-close and dehydrate if left on the bench for a substantial length of time. If Boc-protected

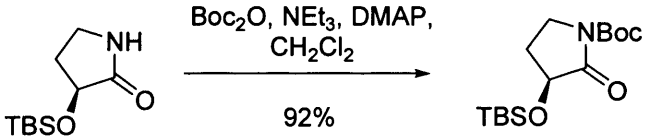
alkylidenepyrrolidine **135** can be isolated, milder methods of Boc-removal could be investigated (**Scheme 58**).



135 **134**

Scheme 58

Lactam **130** was treated with di-*tert*-butyl dicarbonate in order to prepare the *tert*-butyl carbamate precursor for alkylidenepyrrolidine formation (**Scheme 59**).

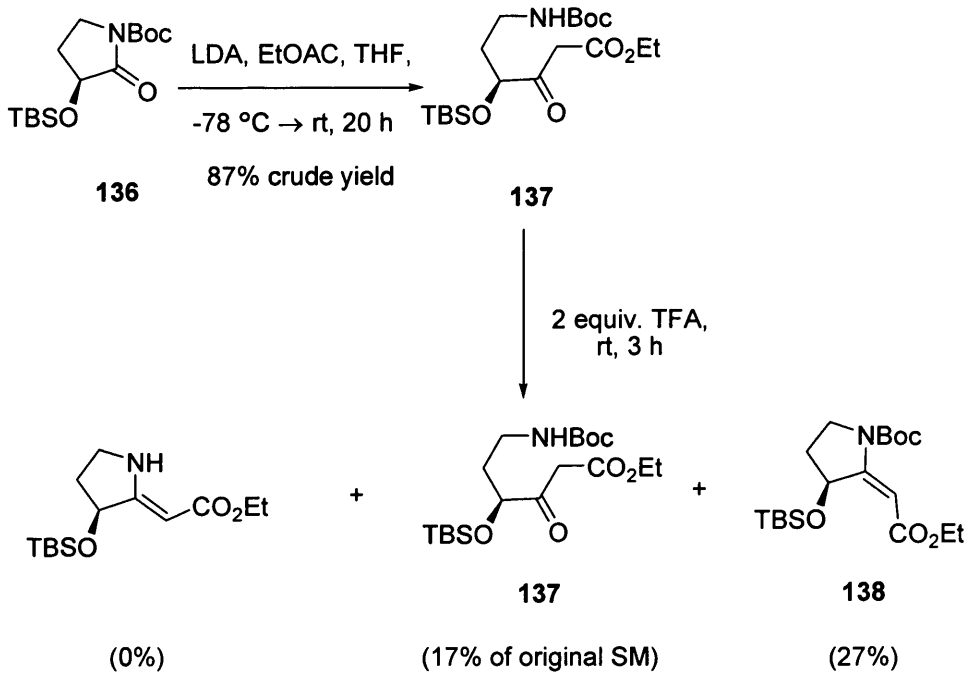


130 **136**

Scheme 59

Compound **136** was then reacted with the enolate derived from ethyl acetate, affording the ring-opened carbamate (**137**).

To test the efficacy of the ring-closing reaction, compound **137** was treated with 1 equivalent of TFA (neat; the standard conditions[38] employ 2 equivalents of acid), and stirred at room temperature for 3 h (**Scheme 60**).



Scheme 60

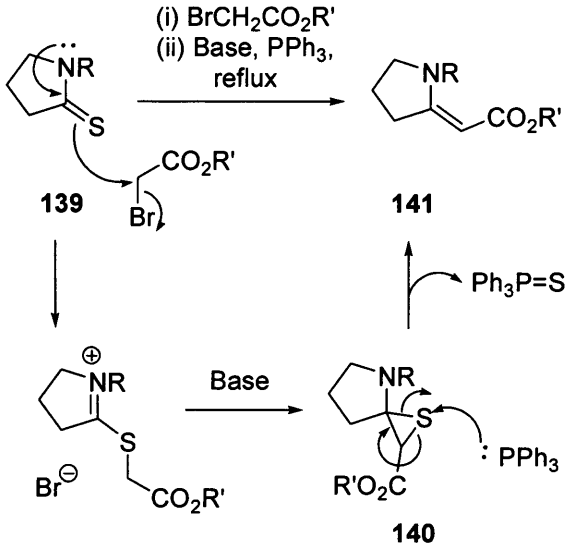
Upon purification of the crude reaction mixture, several products were isolated: Boc-protected alkylidenepyrrolidine **138**, some unreacted starting material and indeterminable impurities. However, none of the desired alkylidenepyrrolidine was isolated.

With Boc-protected alkylidenepyrrolidine (**138**) isolated, efforts were then made to de-protect the Boc group. Several acids, including TFA and *p*-TsOH were employed, but unfortunately, less than 10% of the required product was synthesised on any occasion.
The ring-closing step was then re-attempted with the aforementioned acids, with still none of the desired alkylidenepyrrolidine formed.

As a result of these studies, we elected to employ an alternative method to synthesise our key alkylidenepyrrolidine, particularly one which avoided the use of an acid source.

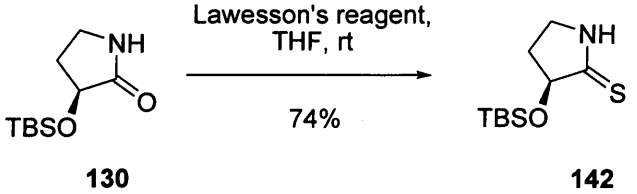
3.5 Approaches Towards Alkylidenepyrrolidine Formation (II)

Of the main methods for synthesising alkylidenepyrrolidines,[39] the Eschenmoser sulphide contraction[48,49] was chosen as the most suitable reaction for our synthesis, most notably for the lack of acid required (**Scheme 61**). The reaction mechanism of the sulphide contraction is believed to involve initial alkylation of thiolactam **139** with an α-bromocarbonyl compound. Subsequent deprotonation with a weak base affords thiirane intermediate **140**, with sulphur extrusion then occurring to give alkylidenepyrrolidine **141**.



Scheme 61

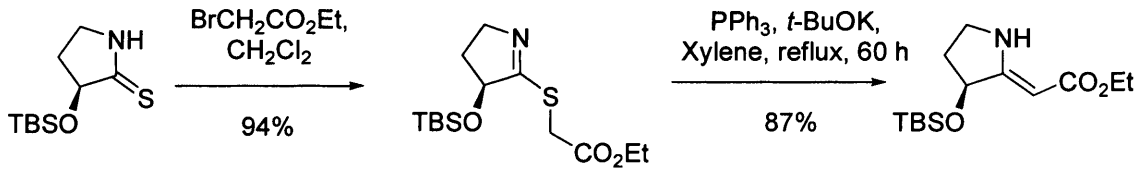
Thiolactam **142** was first prepared, by reacting lactam **130** with Lawesson's reagent (**Scheme 62**).[50]



Scheme 62

Alkylation of compound **142** then afforded imino thioether **143** in highly pure form, which could be isolated[51] and stored in the freezer for several weeks (**Scheme 63**).

Although the sulphide contraction step of the reaction required long, forcing conditions to go to completion,[48] a straightforward flash silica gel column was required to purify alkylidenepyrrolidine **144**, with the silyl protecting group pleasingly remaining intact.



142 **143** **144**

Scheme 63

On a small scale (100 - 600 mg of thioether **143**; 0.32 – 1.9 mmol), the sulphide contraction proceeded in high yield. However, upon scaling up the reaction, the yields dropped quite drastically (**Table 3**).

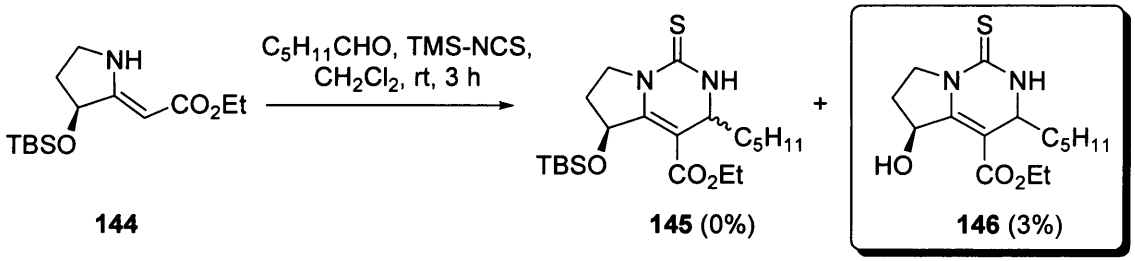
Quantity of **143**	Moles of **143**	Yield of compound **144** (**143** → **144**)
108 mg	0.34 mmol	79%
576 mg	1.82 mmol	87%
1.03 g	3.25 mmol	19%
5.24 g	16.53 mmol	8%

Table 3

Despite the scale-up difficulties, we were still able to synthesise a substantial amount of the alkylidenepyrrolidine to use in the three-component coupling.

3.6 A Highly Diastereoselective Three-Component Coupling

With a quantity of the alkylidenepyrrolidine **144** prepared, the group's standard three-component coupling conditions (see *Chapters 1 & 2*) were employed (**Scheme 64**), with hexanal as a 'test' aldehyde. Surprisingly, instead of the expected thiourea **145** formed as a mixture of diastereoisomers, a very small amount of de-silylated thiourea **146** was isolated as a single diastereoisomer. Aside from compound **146**, no other determinable products could be recovered. The ^{1}H NMR spectrum of the crude reaction mixture had also confirmed that the starting materials had been consumed.



144 **145** (0%) **146** (3%)

Scheme 64

The key diagnostic region (1 - 5 ppm) of the ^{1}H NMR spectrum of thiourea **146** is shown in **Figure 22**. All peaks clearly show the existence of only one diastereoisomer. This is also corroborated by the ^{13}C NMR spectrum.

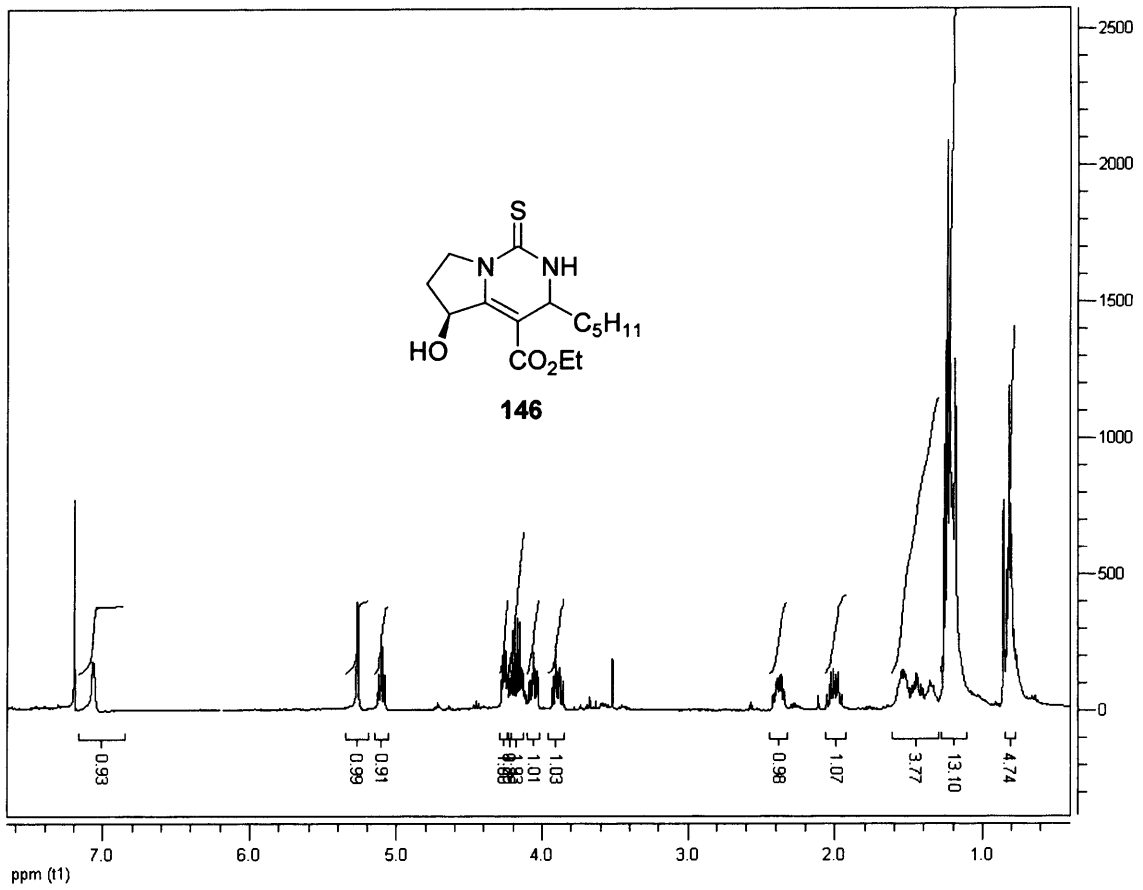
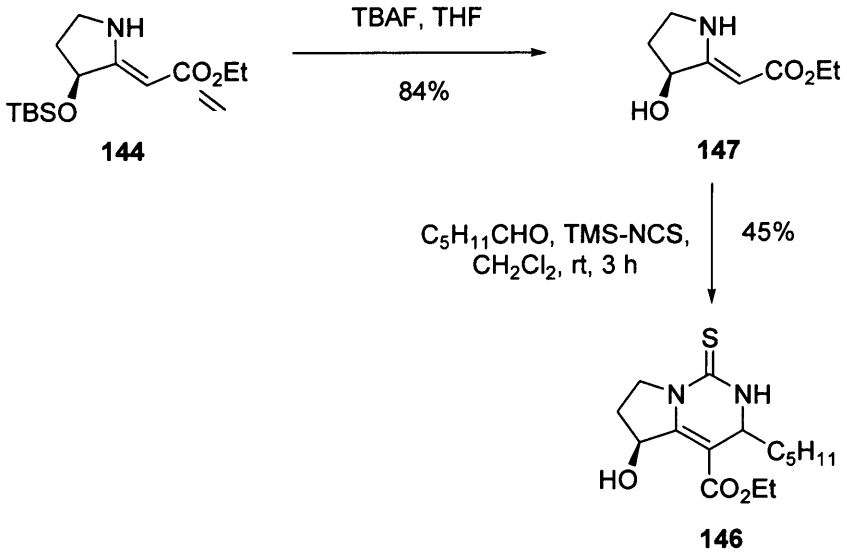


Figure 22 – ^1H NMR spectrum of Compound **146** (400 MHz; $CDCl_3$)

There were various explanations postulated for this perplexing result. One such explanation was that thiourea **146** may have arisen from a small proportion of de-silylated alkylidenepyrrolidine in the starting material.
Alkylidenepyrrolidine **144** was therefore treated with tetra-butylammonium fluoride[52] to remove the silyl protecting group.

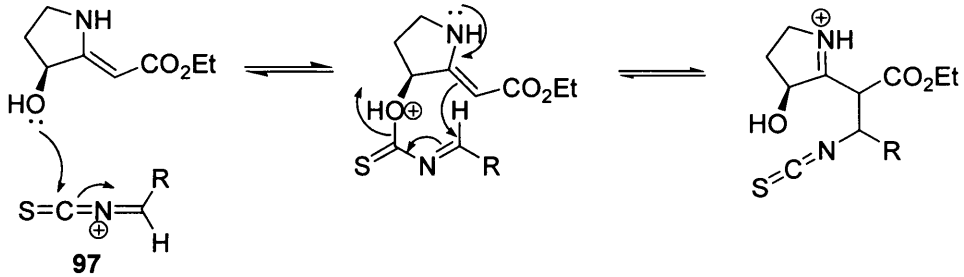
Under identical three-component coupling conditions, de-silylated thiourea **145** was again formed as a single diastereoisomer (**Scheme 65**).



Scheme 65

According to our proposed mechanism, the bulky silicon protecting group is expected to block one face of the alkylidenepyrrolidine towards electrophilic attack. However, the TBS group appears to hinder the reaction altogether.

Because a single diastereoisomer is formed in the three-component coupling, the iminium ion **97** may be approaching in one orientation only. If the hydroxy group reacts with the iminium ion first, then this could perhaps explain the high observed levels of diastereocontrol (**Scheme 66**).
It would be interesting to see whether the same high levels of diastereoselectivity are observed with a relatively bulky methyl ester as the directing group.

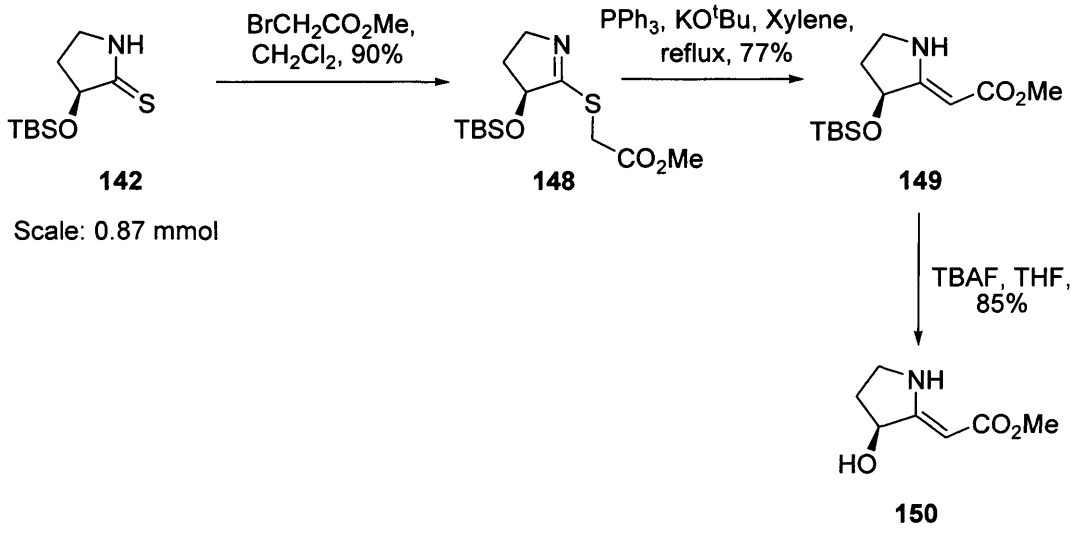


Scheme 66

We have so far been unable to determine the configuration of the new stereogenic centre, as no diagnostic nOe signals are observed.

With a completely diastereoselective synthetic route to the western half of Batzelladine A developed, it was now left to repeat the three-component coupling with the correct alkyl linkage for the natural product. The ester moiety was also altered from ethyl to methyl, for comparison with literature syntheses.[22,28,29]

The Eschenmoser sulphide contraction of thiolactam **142** was therefore performed with methyl bromoacetate, with the sulphur extrusion step proceeding as before (**Scheme 67**). De-silylation with TBAF then afforded alkylidenepyrrolidine **150**.

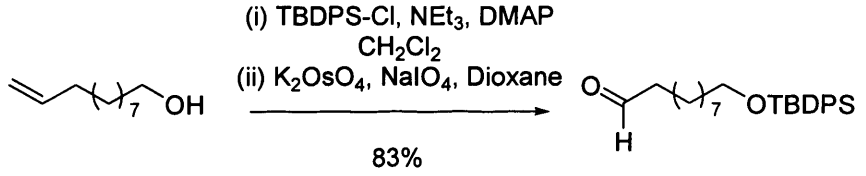


Scheme 67

Note: imino-thioether **148** was isolated and fully-characterised (see *Experimental*).

The requisite aldehyde for the three-component coupling was synthesised in two steps. Beginning with undec-10-en-1-ol, TBDPS-protection and oxidative

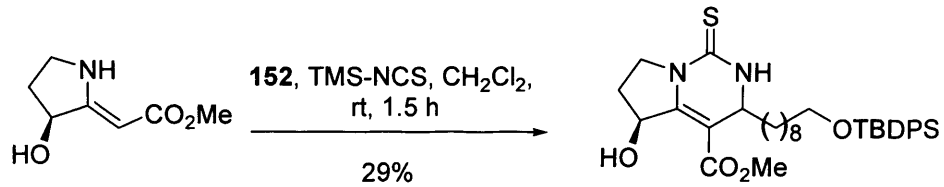
cleavage under Lemieux-Johnson conditions[53] yielded aldehyde **152**[54] (**Scheme 68**).



151 **152**

Scheme 68

Because of excess osmium impurities, which were difficult to completely remove by column chromatography, we were slightly concerned that the aldehyde might be unstable. Therefore, the three-component coupling was carried out immediately. Although producing a slightly lower yield than with hexanal, bicyclic thiourea **153** was still obtained as a single diastereoisomer (**Scheme 69**).

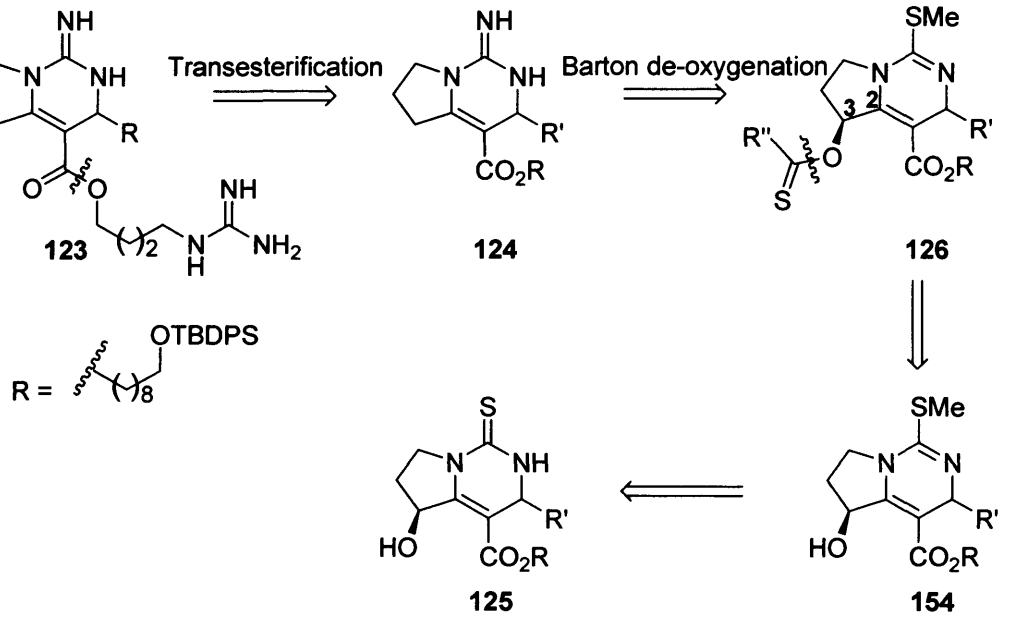


150 **153**

Scheme 69

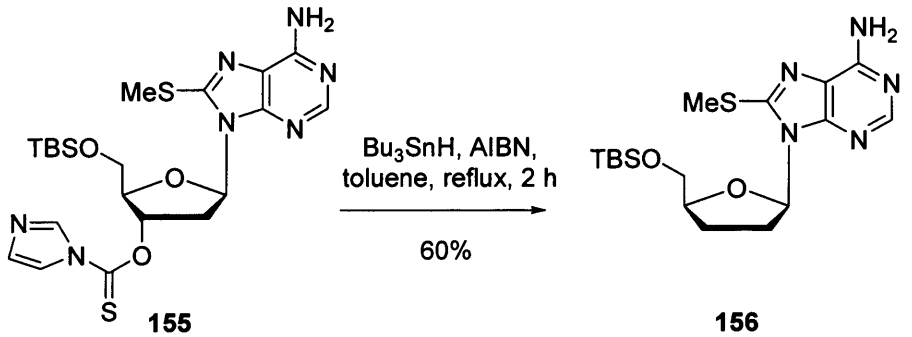
3.7 Further Elaboration of the Natural Product Core

As discussed in *Section 3.2*, further functional group manipulation of the bicyclic thiourea would be required to synthesis the western half of the natural product. **Scheme 70** shows the amended retrosynthetic pathway.



Scheme 70

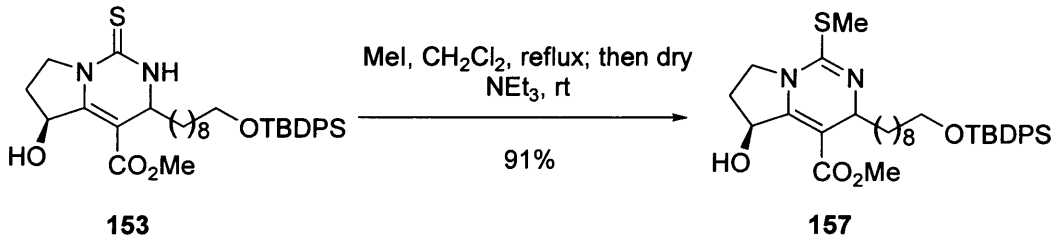
The thioacyl group on the 3-position of the pyrrolidine, which is not present in the natural product, will be removed by Barton deoxygenation. There is literature precedent for the selective removal of an oxygen-containing group in the presence of an S-methyl isothiourea (**Scheme 71**).[45]



Scheme 71

Once the oxygen directing has been removed, the *S*-methyl isothiourea moiety can then be converted into the guanidine.[28]

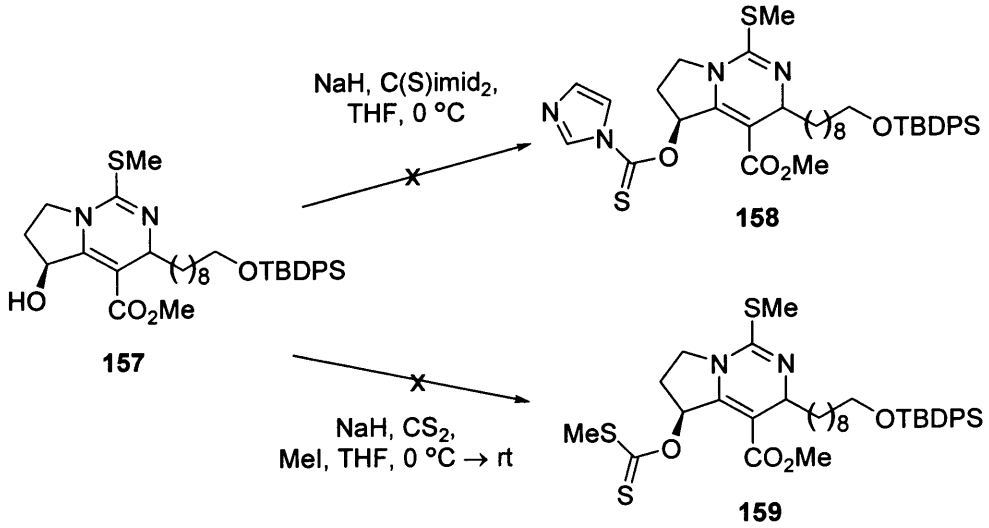
The manipulation of the bicyclic core began with protection of the thiourea unit. Thiourea **153** was alkylated with a large excess (up to 20 equivalents) of iodomethane, with forcing conditions required for the reaction to go to completion (**Scheme 72**). Following an unusual work-up (washing with dry triethylamine!),[37] isothiourea **157** was obtained following flash column chromatography.



Scheme 72

Several methods of forming thioacyl derivatives were then investigated (**Scheme 73**).

Unfortunately, *S*-methyl isothiourea **157** failed to react with either carbonylthioimidazole[55] or carbon disulphide/methyl iodide,[56] even following initial deprotonation (although the starting material was recovered in each case).

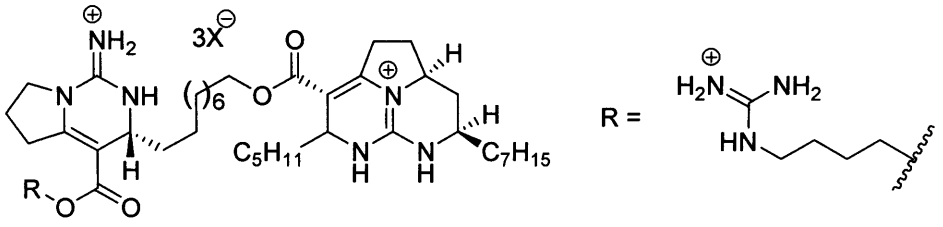

NaH, C(S)imid2,
THF, 0 °C
SMe
N
N
HO
(CH2)8
OTBDPS
CO2Me
157
158
NaH, CS2,
MeI, THF, 0 °C → rt
MeS
O
S
159

Scheme 73

3.8 Conclusions & Future Work

To summarise, we have developed a highly diastereoselective, efficient synthetic route to the core of the western portion of batzelladine A. The three-component coupling, with a hydroxy directing group adjacent to the double-bond of the alkylidenepyrrolidine, proceeds with total diastereocontrol.
With further elaboration, including conversion to the guanidine and removal of the oxygen-containing directing group, the total synthesis of the left-hand side of the natural product will be achieved.

It is also anticipated that once the western half of the natural product is synthesised, it may be coupled to a tricyclic guanidine, either to complete the total synthesis of batzelladine A, or to construct a batzelladine A analogue, with the batzelladine C core as the eastern half (**1a**) (**Figure 24**).



Batzelladine A analgoue (1a)

Figure 24

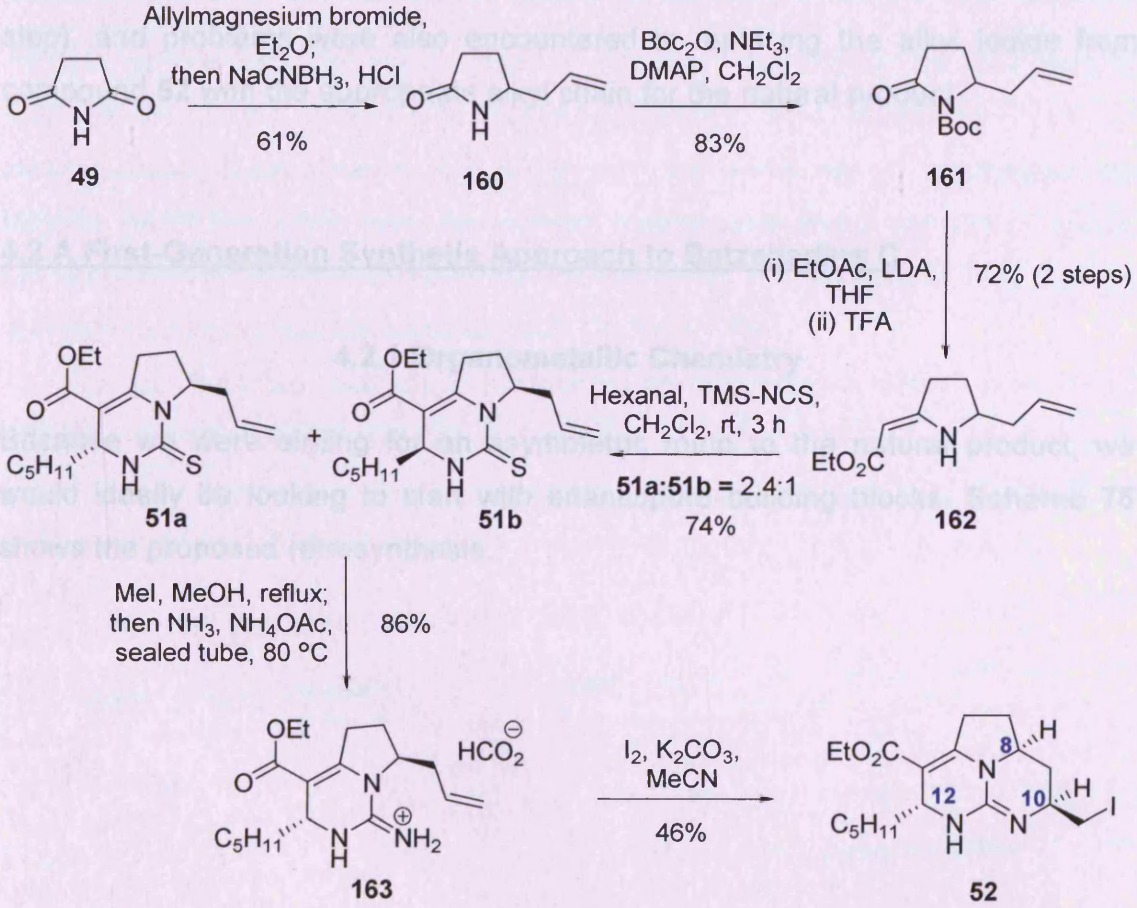
Chapter 4

Batzelladine C: A First-Generation Approach

4.1 Introduction

Having already developed a highly diastereoselective synthetic route to the western half of Batzelladine A, we then investigated approaches to other members of the Batzelladine family.

Our attention turned to the previously unsynthesised Batzelladine C, which we envisaged our own alkylidenepyrrolidine methodology and three-component coupling would be key steps in the synthesis. An approach to the tricyclic core of this natural product has previously been developed in the group by Stuart Wordingham.[37] The synthetic pathway is outlined in **Scheme 74**.



Scheme 74

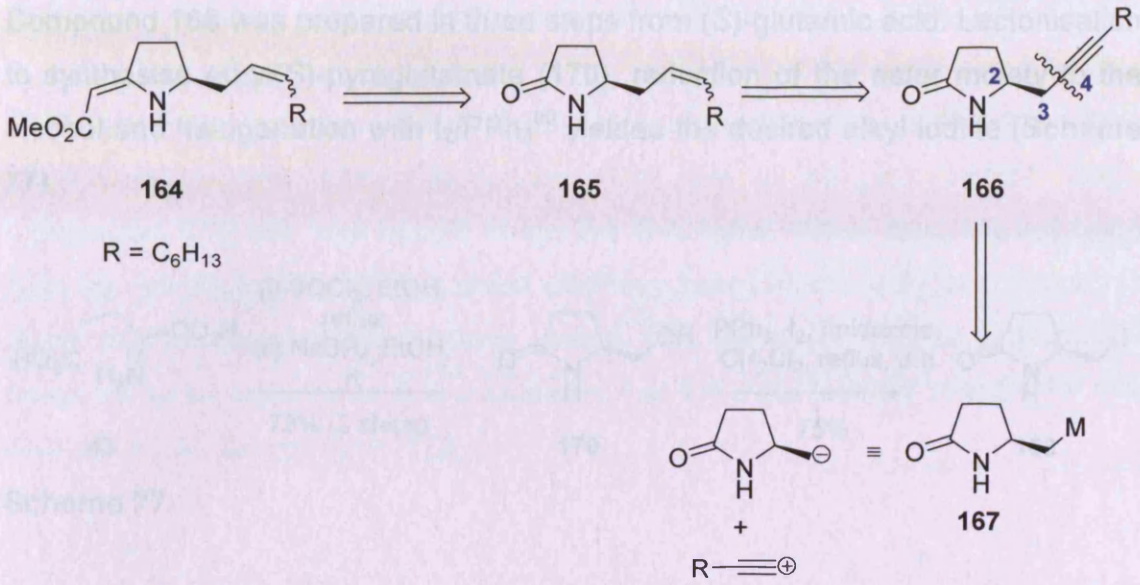
Beginning with an allylation reaction under reductive conditions,[57] allyl lactam **157** was formed from succinimide. Subsequent Boc-protection, and then reaction under the group's conditions afforded alkylidenepyrrolidine **162**.[37] Compound **162** was then treated with hexanal and trimethylsilyl isothiocyanate to form thioureas **51a** and **51b**. Subsequent reaction with ammonia and ammonium acetate converted the thiourea moiety to a guanidine, followed by base-mediated iodocylisation to form the tricyclic guanidine (**52**). Spectroscopic data obtained from this guanidine was in close agreement with the corresponding data from the natural product paper,[1] therefore the stereochemistry of the protons at positions 8, 10 and 12 was tentatively assigned as shown in **Scheme 74**.

However, there were several disadvantages with this synthetic route, namely the approach being inherently racemic (there is no stereocontrol in the allylation step), and problems were also encountered in replacing the alkyl iodide from compound **52** with the appropriate alkyl chain for the natural product.

4.2 A First-Generation Synthetic Approach to Batzelladine C

4.2.1 Organometallic Chemistry

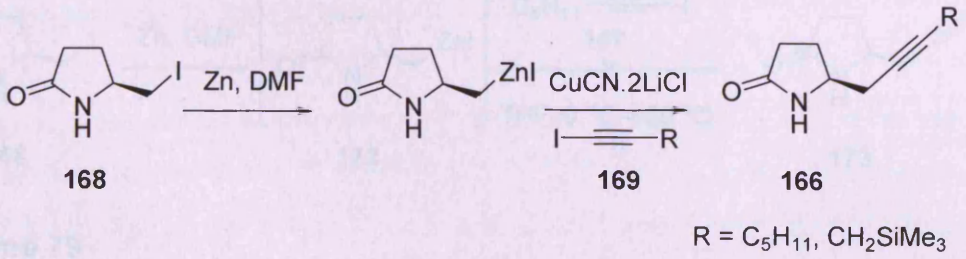
Because we were aiming for an asymmetric route to the natural product, we would ideally be looking to start with enantiopure building blocks. **Scheme 75** shows the proposed retrosynthesis.



Scheme 75

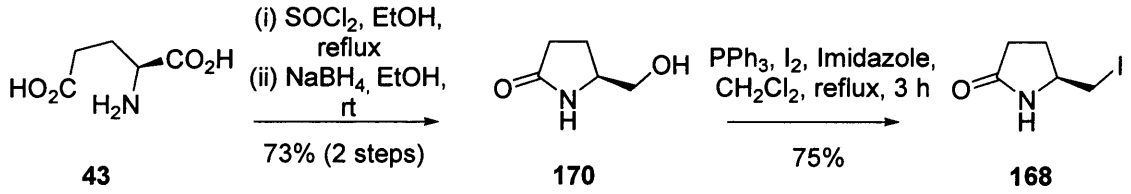
Alkylidenepyrrolidine **164** will be used to construct the bicyclic thiourea core of Batzelladine C *via* a three-component coupling. It is anticipated that an intramolecular iodoamination will be in turn be employed to synthesise the tricyclic guanidine core, with the correct carbon side-chain already in place. Compound **166**,[58] disconnected at the 3-4 C-C bond, can be synthesised from an appropriate organometallic species (**167**) (**Scheme 75**).

An apposite literature reaction to synthesise an enantiopure lactam of structure **167** was reported by the Hiemstra group.[59] Iodo-lactam **168** is first treated with zinc metal to form the organozinc species, and then reacted with CuCN.2LiCl and iodo-acetylide **169**, affording the progargylic lactam (**166**) (**Scheme 76**).



Scheme 76

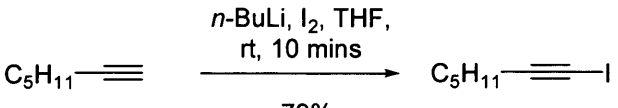
Compound **168** was prepared in three steps from (*S*)-glutamic acid. Lactonisation to synthesise ethyl(*S*)-pyroglutamate (**170**), reduction of the ester moiety to the alcohol and halogenation with I_2/PPh_3[60] yielded the desired alkyl iodide (**Scheme 77**).



43 **170** **168**

Scheme 77

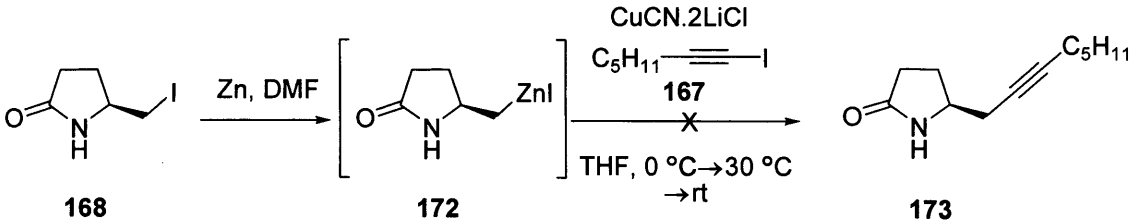
Iodo-acetylide **171** was synthesised by reaction of 1-octyne, *n*-butyl lithium and iodine (**Scheme 78**).[61]



171

Scheme 78

The zinc-iodide species was then formed according to literature procedure.[62] For the zinc-copper coupling, lactam **172** was kept in solution in DMF, and added to the reaction vessel *via* cannulation (**Scheme 79**).



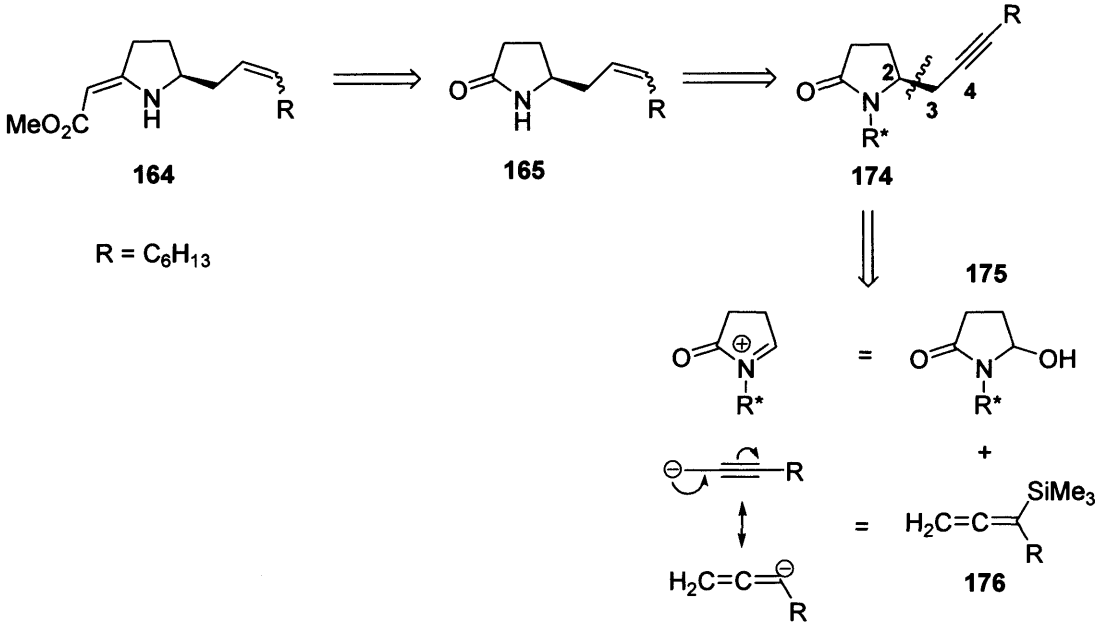
168 **172** **173**

Scheme 79

Although the ^1H and ^{13}C NMR spectra of the crude reaction mixture showed that the starting materials had been consumed, the expected lactam was not formed.

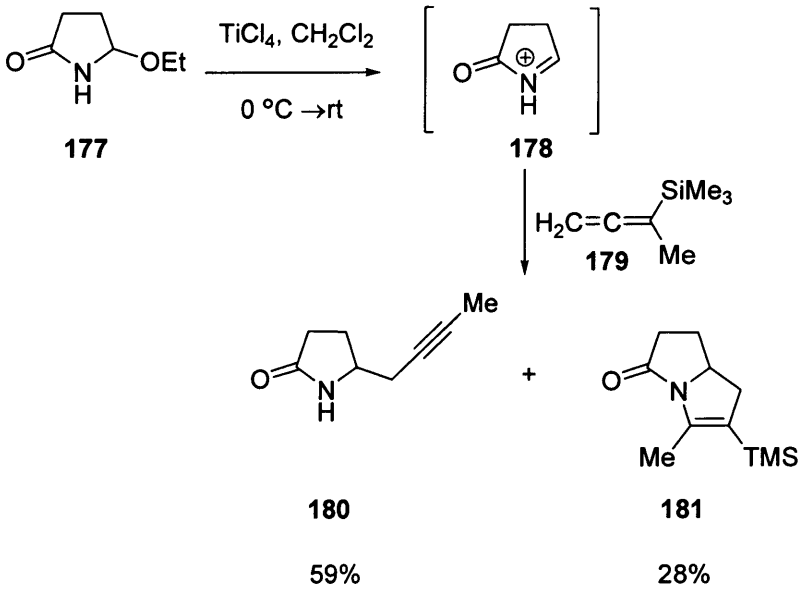
4.2.2 *N*-Acyliminium Ion Chemistry

Scheme 80 shows an amended retrosynthetic pathway from alkylidenepyrrolidine **164**. Disconnection at the propargylic lactam stage (compound **174**) this time occurs at the 2-3 C-C bond, rather than the 3-4 bond from the previous route. With a chiral directing group attached to the nitrogen to direct the stereochemistry, hydroxy lactam **175** will react with an appropriate propargyl anion equivalent. It is anticipated that the most suitable reagent for this step will be an allenylsilane (**176**).[63,64]



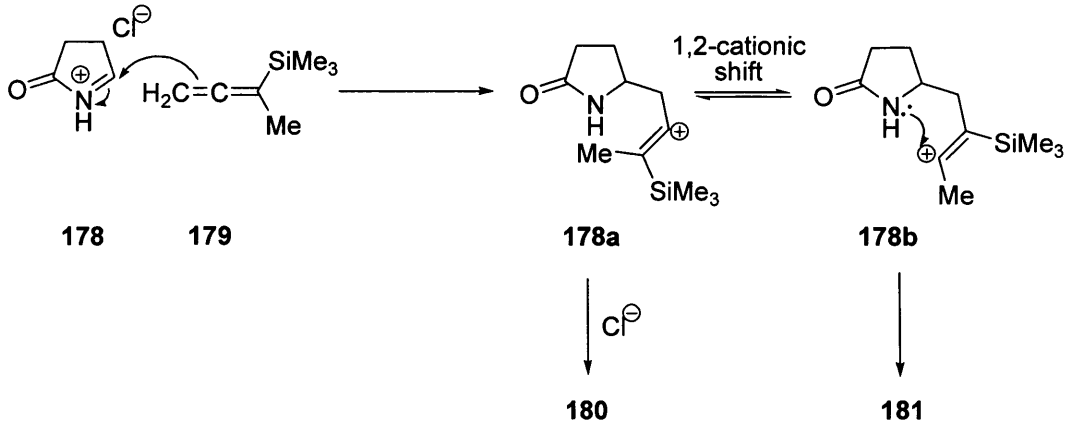
Scheme 80

There is one literature example of addition of an allenylsilane to an *N*-acyl iminium ion (**Scheme 81**).[65] Mixing lactam **177** and titanium(IV) chloride creates the *N*-acyliminium ion (**178**),[66] which is then treated with allenylsilane **179** to afford an approximate 2:1 mixture of propargyl lactam **180** and pyrrolidinone **181**.



Scheme 81

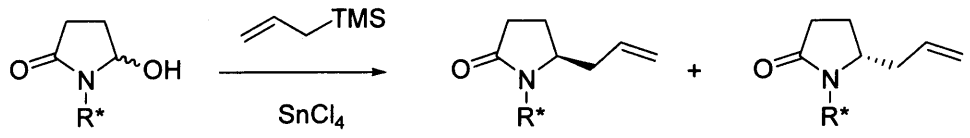
The initial reaction pathway for compound **181** is initially identical to **180**, producing vinyl cation intemediate **178a** (stabilised by hyperconjugation with the C-Si bond). A 1,2-cationic shift of the trimethylsilyl group produces isomeric vinyl cation **178b**, which is in turn trapped by the lactam nitrogen to form heterocycle **181** (**Scheme 82**).



Scheme 82

Although there is no precedent for the chiral addition of an allenylsilane to lactams in this manner, the Polniaszek group reported the related reaction of

allyltrimethylsilane and a series of chiral hydroxy lactams (**Scheme 83**; explained in more detail in *Chapter Five*).[67]



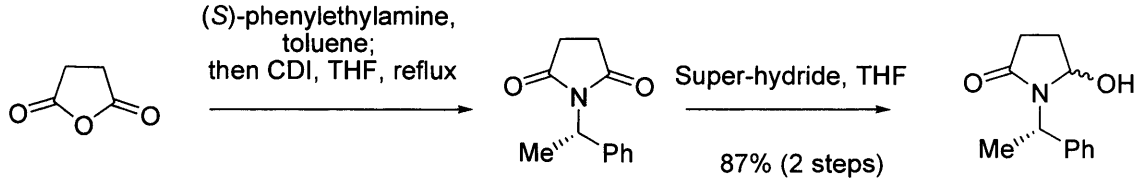
175 **182:183** > 5:1 **182** **183**

R* = CH(Me)Ar

Scheme 83

It was then hypothesised that due to the structural similarity of an allenylsilane and allyltrimethylsilane, if we attach a chiral directing group to the central nitrogen atom, the addition of an allenylsilane to the corresponding *N*-acyliminium ion should proceed with some level of stereocontrol.

Our synthesis therefore began with condensation of commercially available succinic anhydride (**184**), available inexpensively and in multigram quantities. For introduction of the stereochemical directing group, (*S*)-phenylethylamine was reacted with succinimide to form the chiral imide, followed by a chemoselective reduction to afford hydroxy lactam **186** (**Scheme 84**).

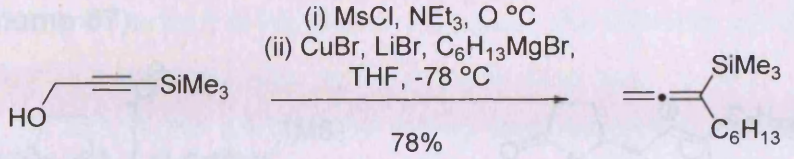


184 **185** **186**

Scheme 84

Both reactions were very clean and high-yielding, with little or no purification required.

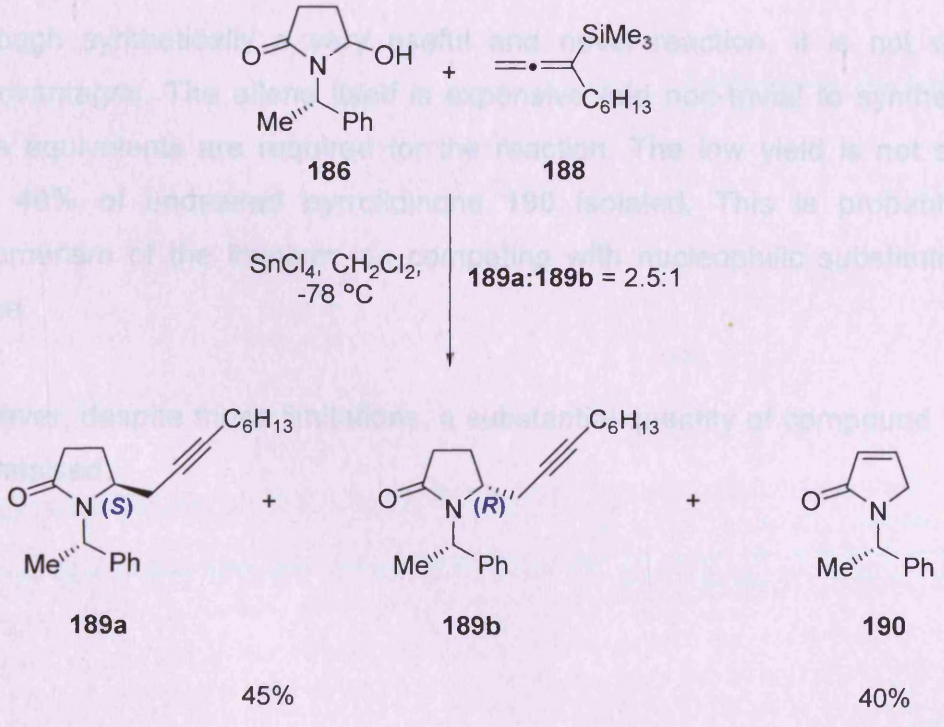
The allenylsilane (**188**) was then prepared in accordance with a literature procedure (**Scheme 85**).[68]



187 **188**

Scheme 85

Chiral hydroxy lactam **186** was then treated with tin(IV) chloride and allenylsilane **188** to yield diastereoisomers **189a** and **189b**, with a diastereomeric ratio of 2.5:1 measured from integration traces of the ^{1}H NMR spectrum (**Scheme 86**). By analogy with the work by Polniaszek *et. al.*,[67] the required (*S*)-stereochemistry for the natural product should be present at the newly-formed stereogenic centre of the major diastereoisomer (**189a**).



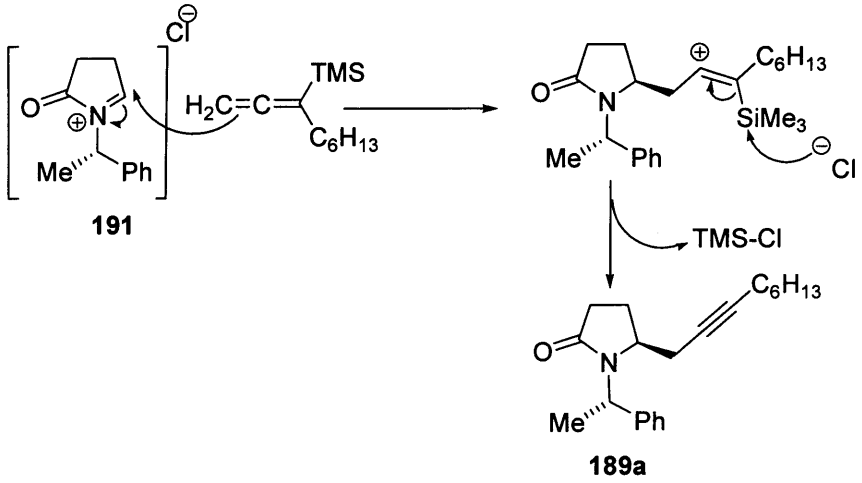
186 **188**

189a **189b** **190**

45% 40%

Scheme 86

The mechanism is believed to involve initial nucleophilic addition of the allenylsilane, followed by elimination of chlorotrimethylsilane to afford the desired product (**Scheme 87**).



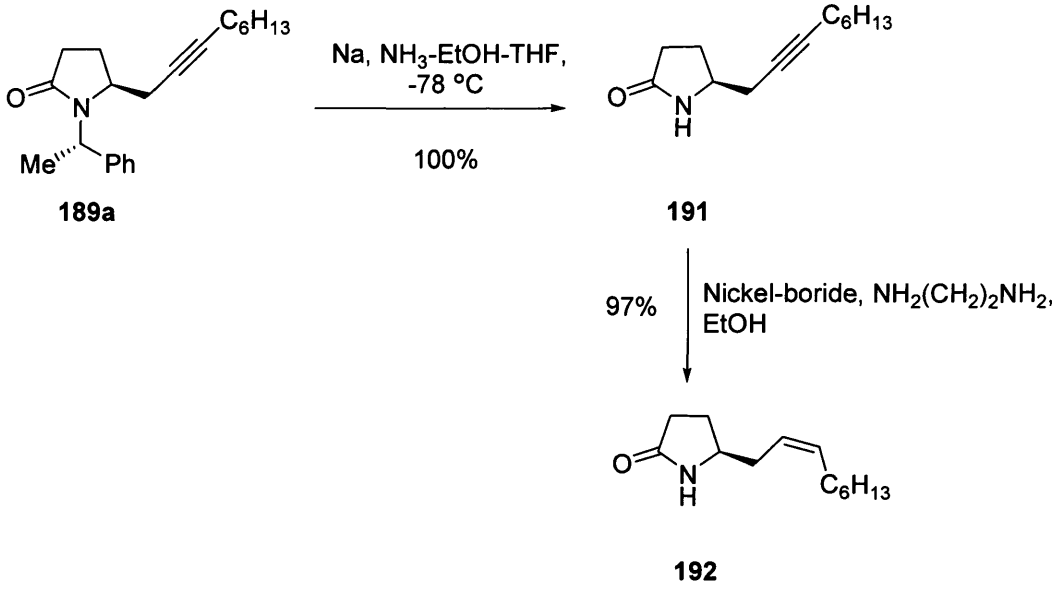
Scheme 87

Although synthetically a very useful and novel reaction, it is not without its disadvantages. The allene itself is expensive and non-trivial to synthesise, and three equivalents are required for the reaction. The low yield is not surprising, with 40% of undesired pyrrolidinone **190** isolated. This is probably due to tautomerism of the iminium ion competing with nucleophilic substitution of the allene.

However, despite these limitations, a substantial quantity of compound **189a** was synthesised.

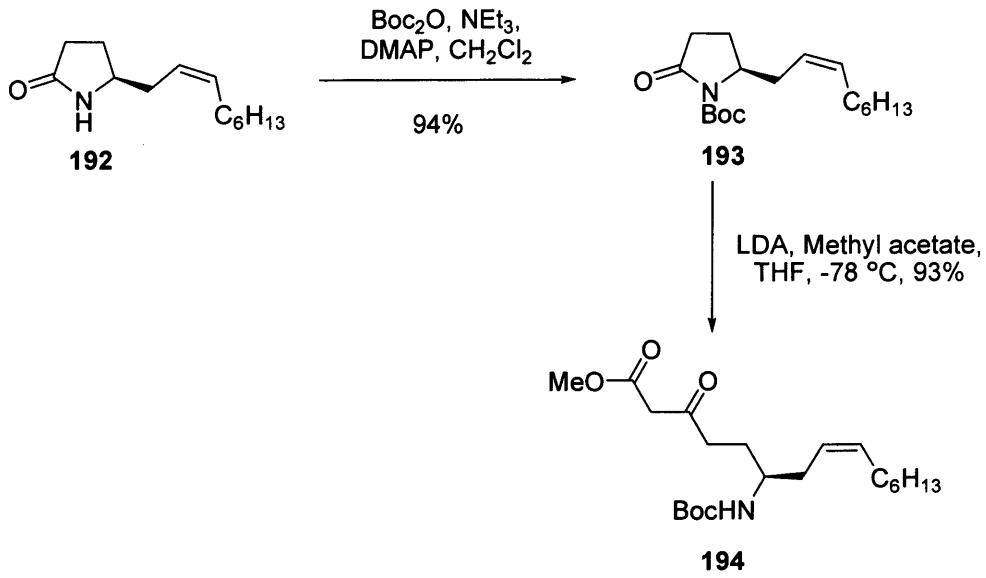
4.3. Synthesis of the Bicyclic Guanidine Core of Batzelladine C

With the propargylic lactam in hand (unfortunately, the isomers were inseparable by column chromatography), the next synthetic step was removal of the chiral directing group. While the phenylethyl group was removed, the alkyne moiety was surprisingly left untouched by the reductive conditions.[69] Further reduction of the alkyne moiety to the *Z*-alkene with nickel-boride[70] then afforded alkenyl lactam **192** (**Scheme 88**). Both steps proceeded in very high yield, with no requirement for purification.



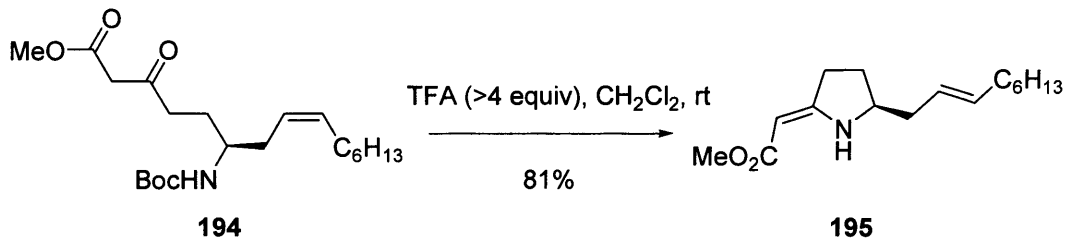
Scheme 88

Lactam **192** was first protected as the *tert*-butyl carbamate derivative, and then reacted under the group's novel conditions for alkylidenepyrrolidine formation[38] (**Scheme 89**).



Scheme 89

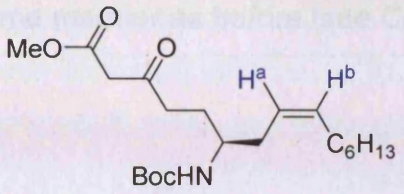
Conversion to alkylidenepyrrolidine **195** was then achieved by treating ring-opened carbamate **194** with an excess of trifluoroacetic acid (**Scheme 90**).



Scheme 90

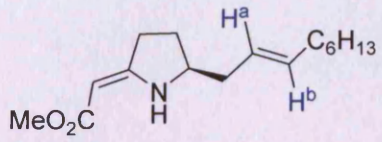
Upon analysis of the NMR data, it was found that alkylidenepyrrolidine **195** had isomerised to afford a mixture of *E/Z* geometrical isomers. By measurement of the alkene C*H* peaks from the ^{13}C NMR of alkylidenepyrrolidine **195,** the *E/Z* ratio was estimated to be at least 3:1.

Analysis of the coupling constants from the ^{1}H NMR spectrum of the alkene C*H* peaks confirmed that the *E*-alkene was present. The alkene coupling constant for compound **194** was 10.8 Hz, while the corresponding coupling constant for compound **195** was 15.2 Hz (a *trans* alkene would be expected to have coupling constants in the range of 12 - 18 Hz) (**Figure 24**).



194

H^a: 5.46 (1H, apparent dt, J 10.9 & 7.3)
H^b: 5.27 (1H, m, apparent dt, J 10.9 & 7.5)



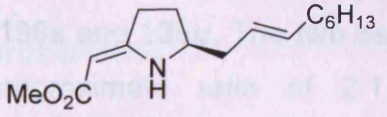
195

H^a: 5.49 (1H, apparent dt, J 15.2 & 6.7)
H^b: 5.28 (1H, apparent dt, J 15.2 & 7.1)

Figure 24

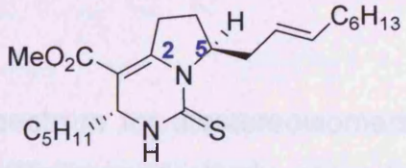
Nevertheless, we saw no reason why the outcome of the subsequent iodocyclisation reaction would depend on the double-bond geometry, and continued with the synthesis.

The three-component coupling was then employed to construct the bicyclic pyrimidine core of Batzelladine C, with the correct length side-chain (pentyl) for the natural product (**Scheme 91**).



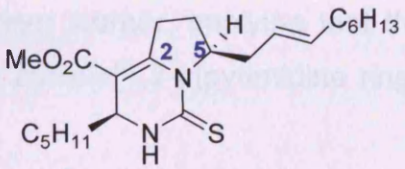
195

TMS-NCS, $C_5H_{11}CHO$
CH_2Cl_2, rt, 3 h
82%
196a:196b = 2:1



196a (58%)

+



196b (24%)

Scheme 91

The ^{1}H NMR spectrum of the three-component coupling reaction was analysed in the same manner as before (see *Chapter Two*) (**Figure 25**)

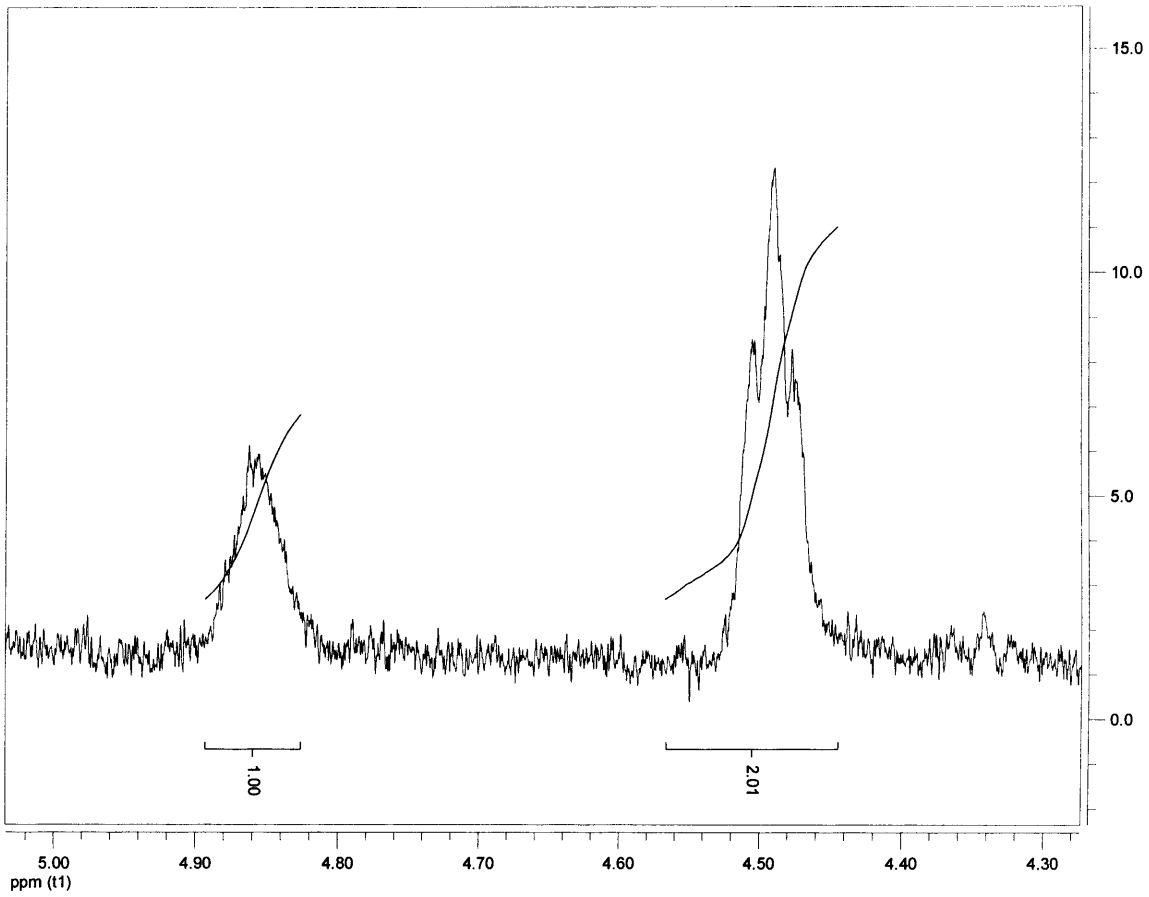
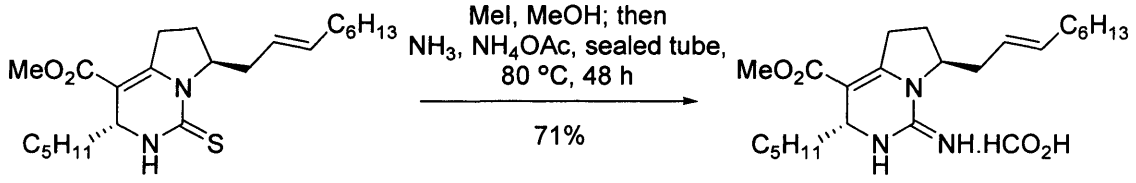


Figure 25

Figure 25 shows an expansion of the ^{1}H NMR spectrum for diastereoisomers **196a** and **196b**. The two key signals, at 4.82 and 4.49ppm respectively, show an approximate ratio of 2:1. The chemical shift of the 5-H in the major diastereoisomer (**196a**) is *upfield* of that of the minor isomer, implying that the relative stereochemistry of the protons across the pyrrolo[1,2-*c*]pyrimidine rings once again is *trans*.

Following column chromatography, the two diastereoisomers were isolated in approximately the same ratio.

With the major isomer isolated, the required guanidine was then formed. The thiourea was first heated under reflux with iodomethane, and then treated with ammonia and ammonium acetate, before being heated in a sealed tube.[34] Following purification on a silica gel column with a small amount of formic acid in the eluent, guanidine **197** was isolated as the formate salt (**Scheme 92**).

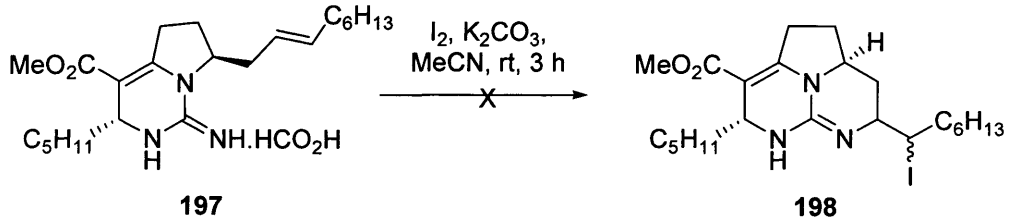


196a **197**

Scheme 92

The guanidine (predominately as the *E*-isomer) was reacted then under iodocyclisation conditions previously used within the group (see *Chapter One, Page 20*).[37]

Disappointingly, guanidine **197** failed to cyclise (**Scheme 93**).



197 **198**

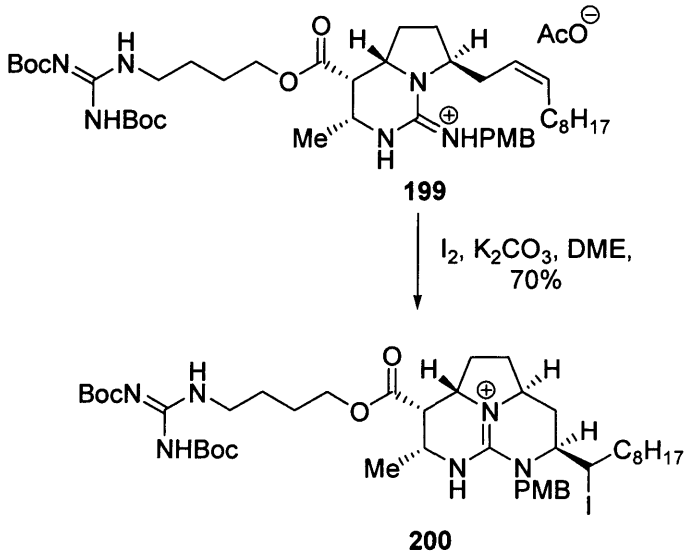
Scheme 93

While there is no literature precedent for this type of intramolecular iodoamination with a *trans*-alkene, we see no discernible reasons why cyclisation should be disfavoured.

We have attempted to suppress the proportion of *E*-isomer at the alkylidenepyrrolidine formation stage; however, reducing the equivalents or using

alternative acids failed to hinder isomerism, and also led to greatly reduced yields.

While the iodocyclisation was being developed within the group,[37] the Gin group published their synthesis of batzelladine D, employing a similar intramolecular iodoamination of a *cis*-alkene (**Scheme 94**).[27]



Scheme 94

It is unclear whether the *cis*-alkene is a requirement for iodocyclisation in this instance, as reaction of the *trans*-alkene isn't reported.

4.4 Conclusions

To summarise, we have developed an efficient, diastereoselective route to the bicyclic core of batzelladine C, with a novel addition of an allenylsilane to a chiral *N*-acyliminium ion, and a modified version of the Kishi three-component coupling used as key synthetic steps.

However, this approach suffers from a number of shortcomings. The allenylsilane (**188**) is expensive to prepare, and is used in excess. More importantly, the *E*-double bond in the pyrrolidine side-chain fails to undergo the required iodocyclisation, whereas literature precedent[27] suggests that the corresponding *Z*-isomer will permit formation of the tricyclic guanidine core.

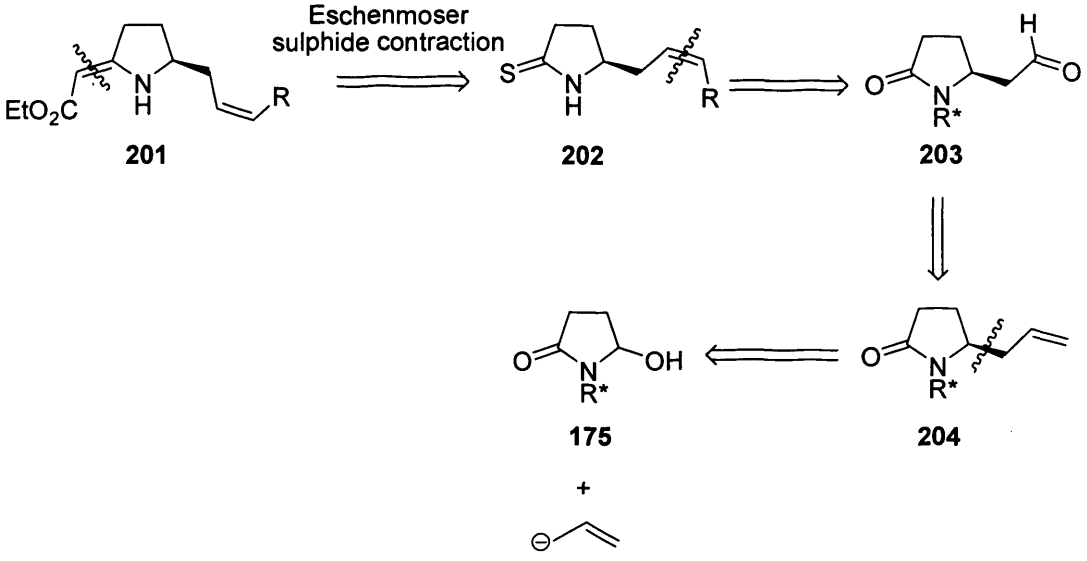
Chapter Five will discuss a second-generation synthetic route towards batzelladine C, where problems encountered with the present route were tackled and solved.

Chapter Five

A Diastereoselective Synthesis of Batzelladine C Ethyl Ester

5.1 Introduction

In light of the problems encountered with the previous route to batzelladine C, in particular the failure of the intramolecular iodoamination with an *E*-alkene and number of equivalents required for the allenylsilane reaction, a second-generation synthesis was devised. The retrosynthetic approach is illustrated in **Scheme 95**.



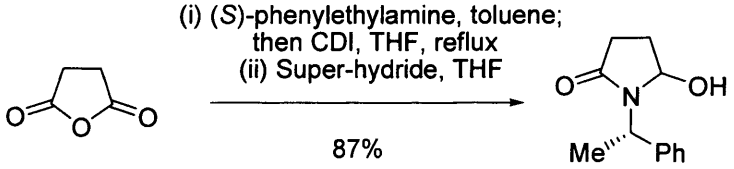
Scheme 95

Following the first-generation approach (see *Chapter Four*), it is now known that a *Z*-alkene is mandatory for the intramolecular iodocyclisation. Our common synthetic intermediate, the alkylidenepyrrolidine (**201**), will be synthesised *via* an Eschenmoser sulphide contraction,[49] negating any problems associated with double-bond isomerism. Thiolactam **202** can be disconnected further to allyl lactam **204**, with a chiral directing group employed to influence the stereochemistry.

As with the first-generation synthesis (see *Chapter Four*), succinic anhydride was used as the building block.

5.2 A Second-Generation Synthetic Approach to Batzelladine C

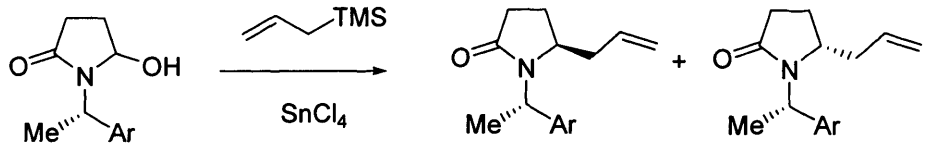
The first synthetic steps proceeded as before, with condensation of commercially available succinic anhydride with (*S*)-phenylethylamine, followed by a chemoselective reduction of the imide carbonyl to produce compound **186** (**Scheme 96**).



184 **186**

Scheme 96

As previously mentioned, the Polniaszek group have described the diastereoselective addition of π-nucleophiles to chiral *N*-acyliminium ions (**Scheme 97**).[67] Chlorination of the aromatic moiety was found to drastically affect the stereochemical outcome of the reaction. Various experimental and theoretical studies ascertained that the stereoselectivity of the coupling was influenced by subtle electronic interactions of the nucleophile with the aromatic system, rather than solely by steric factors.



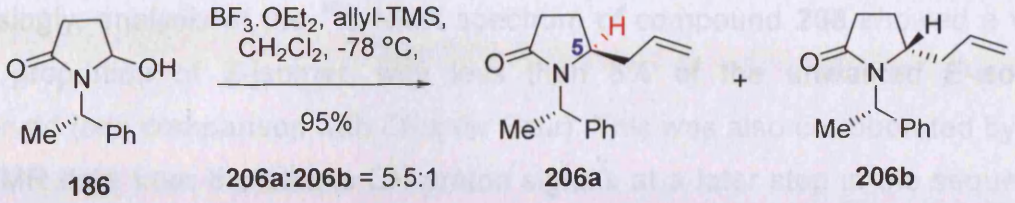
186 **205a** **205b**

Ar	Yield	Ratio of diastereoisomers 205a:205b
Ph	90%	82:18
2-ClC_6H_4	90%	71:29
2,6-ClC_6H_3	91%	9:91
$Cl_5C_6Cl_5$	91%	3:97

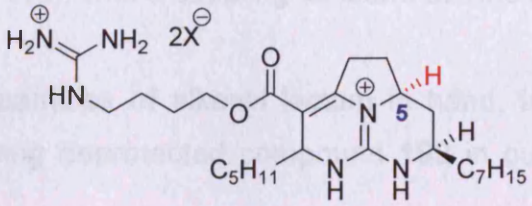
Scheme 97

With the prospect of a much improved diastereomeric ratio and yield, as well as replacing expensive allenylsilane **188** with commercially available allyltrimethylsilane, we were soon in a position to synthesise multigram quantities of material. With phenyl as the stereochemical directing group, major isomer **206a** possesses the correct stereochemistry for the natural product core (**Scheme 98**, Compounds **3** and **206a**).

In our hands, both boron trifluoride and tin(IV) chloride resulted in very similar stereoselectivities and yields, but boron trifluoride was preferred for its low toxicity. Although the diastereoisomers were inseparable by column chromatography, the peaks for the major diastereoisomer from the ^1H NMR of the crude reaction mixture was in line with the literature data for compound **206a**,[67,71] confirming that the major isomer had the required (*S*)-stereochemistry at position 5 (**Scheme 98**).



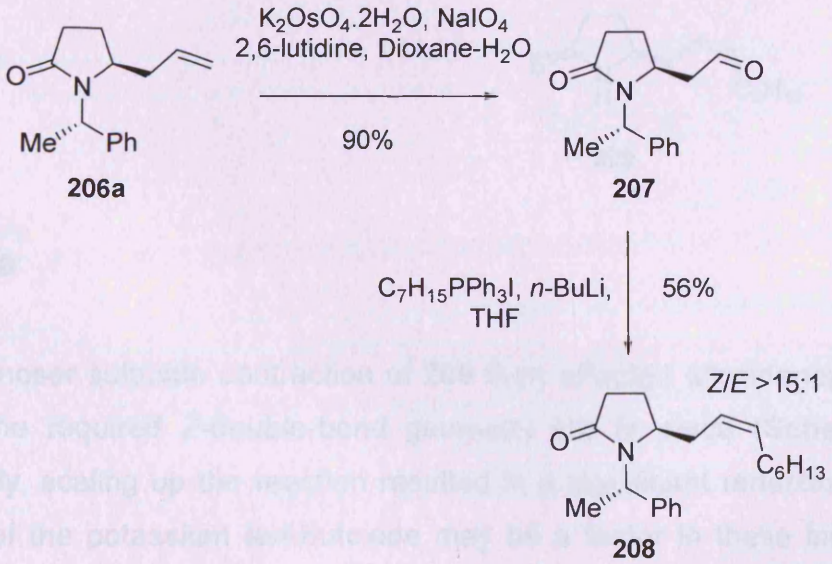
186 **206a:206b** = 5.5:1 **206a** **206b**



Batzelladine C (3)

Scheme 98

To introduce the required alkyl chain for the natural product, the terminal alkene was first oxidatively cleaved with OsO_4-$NaIO_4$,[53] affording aldehyde **207**. A Wittig reaction then proceeded smoothly to give alkenyl lactam **208** (**Scheme 99**), with no chromatography problems encountered regarding removal of excess phosphonium salts. The Wittig reaction could be used on scales up to 5g of aldehyde.



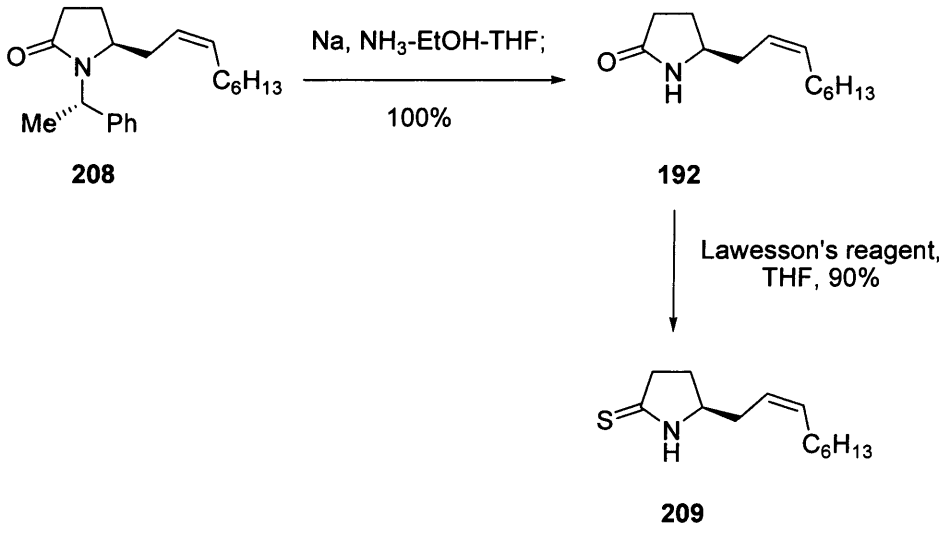
206a **207** **208**

Scheme 99

Pleasingly, analysis of the ^{13}C NMR spectrum of compound **208** showed a very high proportion of *Z*-isomer, with less than 5% of the unwanted *E*-isomer observed (see comparison with *Chapter Four*). This was also corroborated by the ^{1}H NMR data from the alkene C*H* proton signals at a later step in the sequence (see Compound **211a**), with a coupling constant of 10.8 Hz measured.

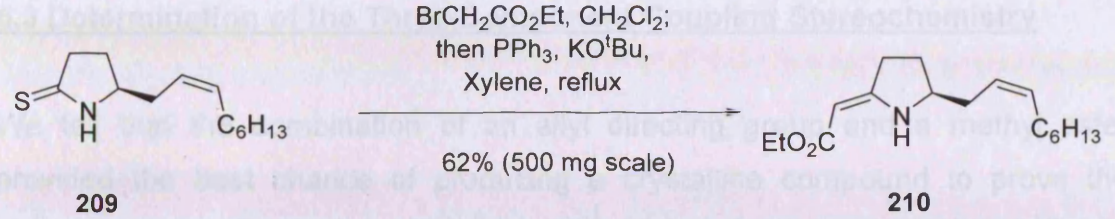
With multigram quantities of alkenyl lactam in hand, the chiral directing group was removed, giving deprotected compound **192** in quantitative yield and very high purity.

Thiolactam **209**, the starting material for the Eschenmoser sulphide contraction[72] was then prepared from by reaction with Lawesson's reagent (**Scheme 100**).



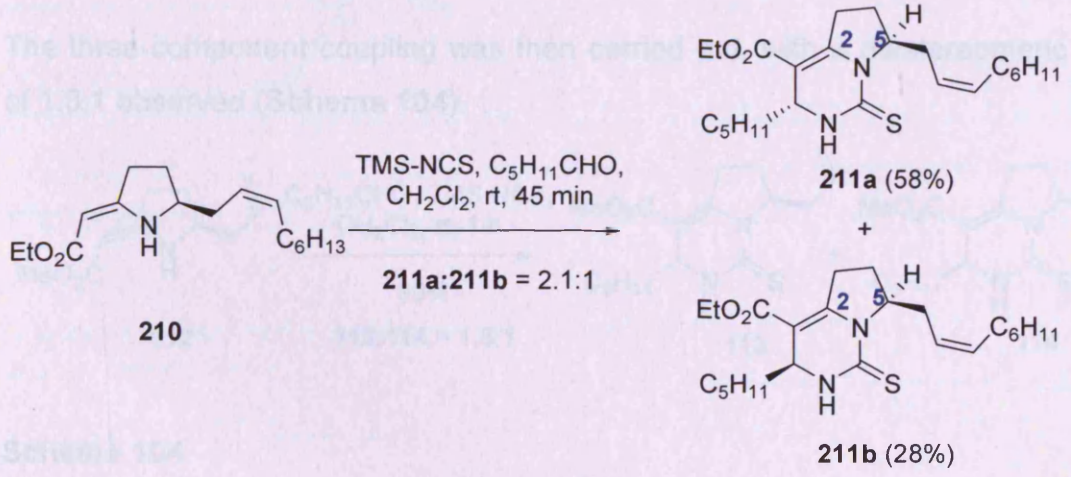
Scheme 100

An Eschenmoser sulphide contraction of **209** then afforded alkylidenepyrrolidine **210**, with the required *Z*-double-bond geometry still in place (**Scheme 101**). Unfortunately, scaling up the reaction resulted in a significant reduction in yield. The purity of the potassium *tert*-butoxide may be a factor in these inconsistent yields. We were still able to synthesise sufficient quantities (>2 grams) of alkylidenepyrrolidine with which to continue the synthesis.



Scheme 101

The alkylidenepyrrolidine was then treated to the standard three-component coupling conditions, yielding diastereoisomers **211a** and **211b** in a 2.1:1 ratio (**Scheme 102**). The chemical shifts of 5-H in the major and minor isomers are in line with those previously observed with CH_2OTBS and allyl directing groups, so that we once again assign the relative *trans* stereochemistry for the major isomer.

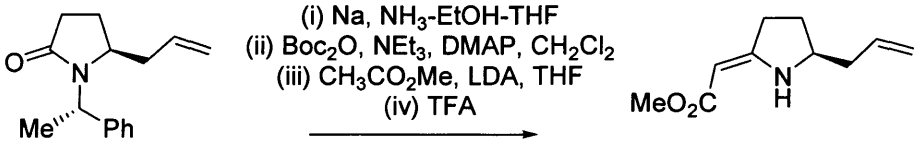


Scheme 102

However, all of these stereochemical assignments stem from observation of a very weak nOe in the initial synthetic studies.[34] We therefore sought conclusive evidence.

5.3 Determination of the Three-Component Coupling Stereochemistry

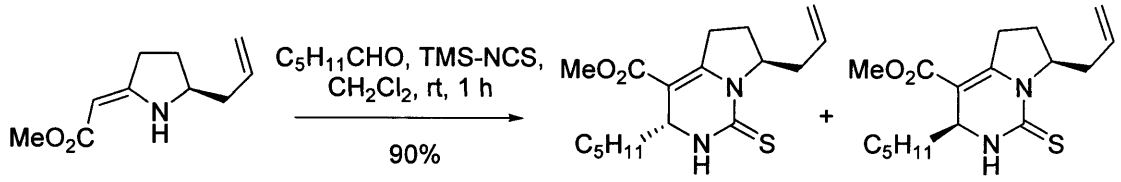
We felt that the combination of an allyl directing group and a methyl ester provided the best chance of producing a crystalline compound to prove the stereochemistry. Beginning with allyl lactam **206a**, alkylidenepyrrolidine **112** was formed in 4 steps (**Scheme 103**) using the Elliott group's methodology.[38]



206a **112**

Scheme 103

The three-component coupling was then carried out, with a diastereomeric ratio of 1.8:1 observed (**Scheme 104**).



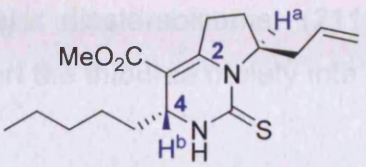
112 **113** **114**

Scheme 104

Compounds **113** and **114** were readily separated by column chromatography, with both isomers pleasingly in solid form.

Various methods were then employed to attempt recrystallisation of the major isomer, including mixed and single solvent methods. As with the acylation studies (see *Chapter Two*), the trusty ethanol-water combination produced high quality crystals of the major diastereoisomer. The crystal structure gave us the result we

were expecting; the relationship between protons H^a & H^b (compound **113**) (**Figure 26**) was indeed *trans*.



113

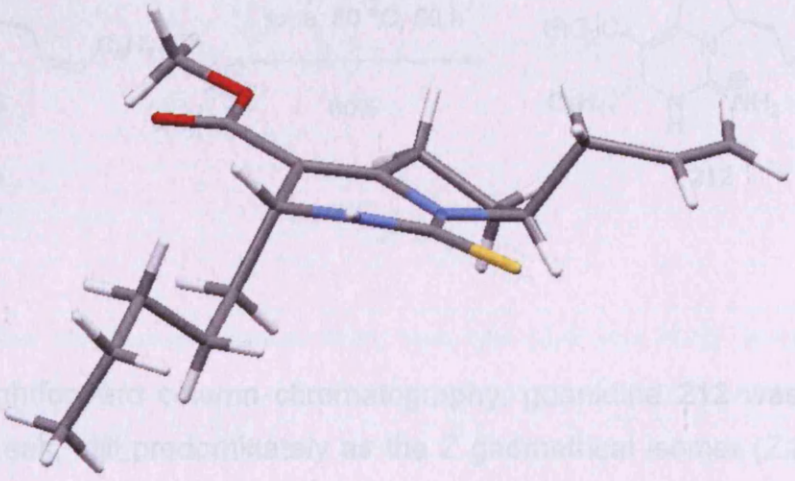
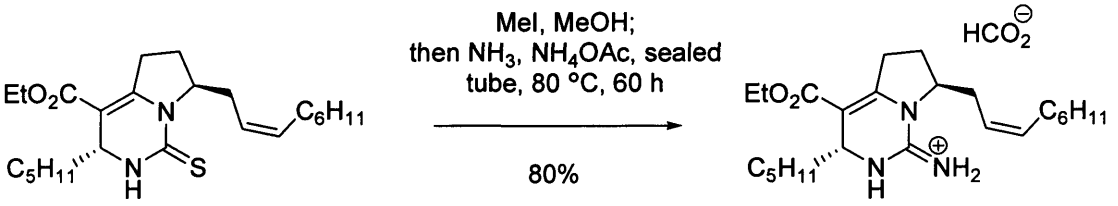


Figure 26

5.4 Construction of the Tricyclic Core of the Natural Product

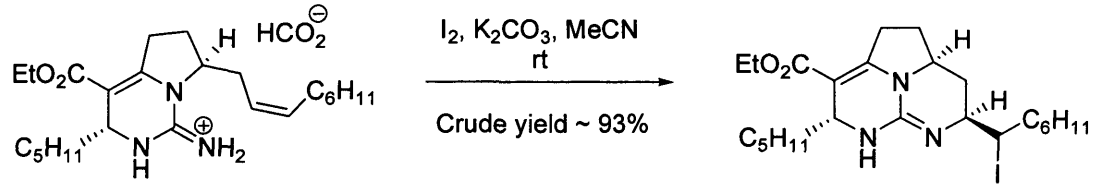
Having carried out the three-component coupling with the alkenyl directing group (see *Section 5.2*), the major diastereoisomer (**211a**) was isolated. The next synthetic goal was to convert the thiourea moiety into a guanidine (**Scheme 105**).



211a **212**

Scheme 105

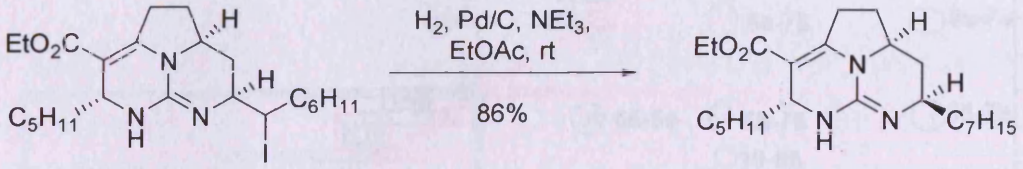
Following straightforward column chromatography, guanidine **212** was isolated as the formate salt, still predominately as the *Z* geometrical isomer (*Z*:*E* >18:1). The guanidine was then treated under iodocyclisation (see *Chapter Four, Page 88*) conditions. Very encouragingly, the intramolecular iodoamination proceeded efficiently, affording tricyclic guanidine **213** in excellent yield (**Scheme 106**). A simple flash silica gel column provided very clean material, with the ^{1}H NMR spectrum clearly showing the presence of a single diastereoisomer (see **Figure 34**). There is literature precedent for this type of intramolecular iodoamination proceeding with complete diastereocontrol.[27]



212 **213**

Scheme 106

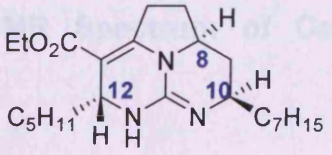
Because of the potentially unstable nature of tricyclic iodo-guanidine **213**, the iodine was immediately removed by palladium in the presence of a hydrogen atmosphere.[73] A swift filtration through Celite®, followed by a flash silica gel column afforded the de-iodinated guanidine **213a** in high purity and good yield (**Scheme 107**).



213 **213a**

Scheme 107

We know that the relative stereochemistry between H-8 and H-12 in compound **213a** is *anti*. This is by analogy with the crystal structure data from compound **113** (*see Section 5.3*) (**Figure 27**).



213a

Figure 27

To determine the relative stereochemistry of protons H-8 and H-10, NOESY spectroscopy was employed. **Figure 28** shows the g-NOESY spectrum of compound **213a**.

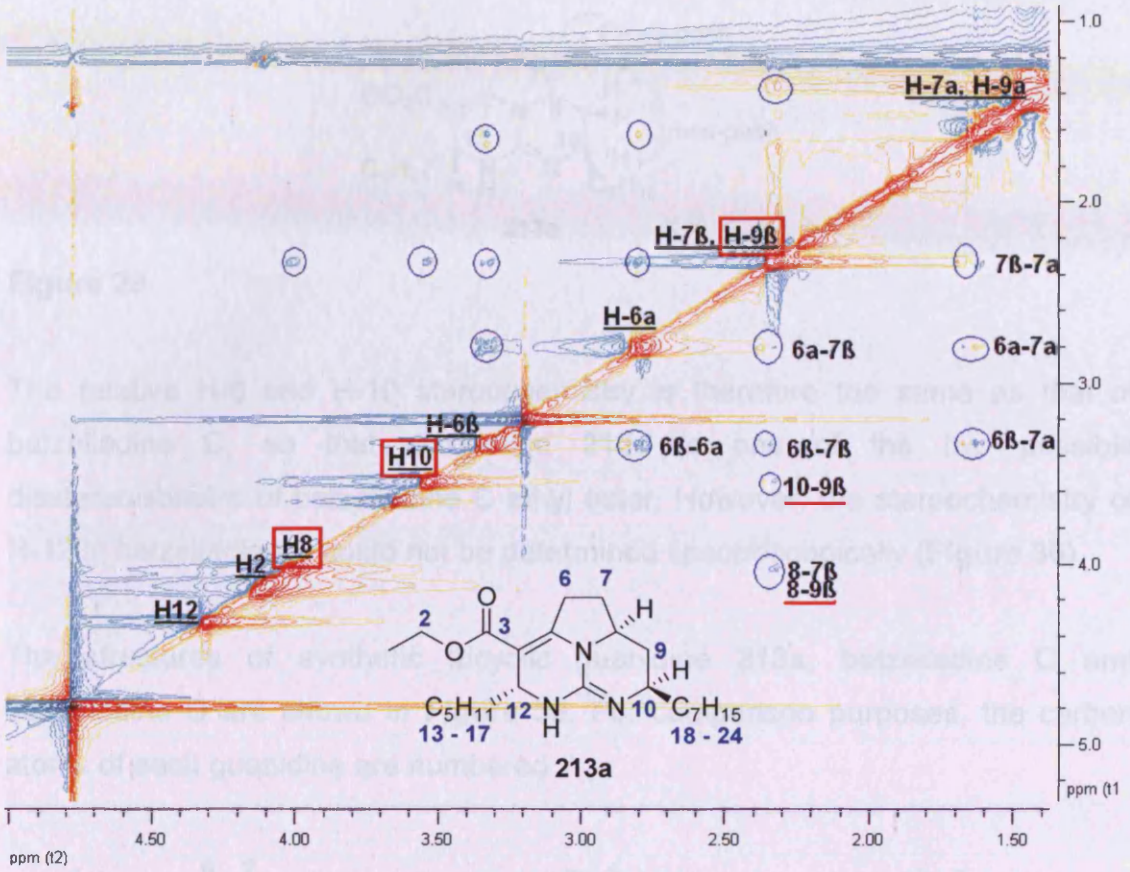


Figure 28 - g-NOESY NMR Spectrum of Compound 213a (500 MHz; MeOH-d_4)

Figure 28 highlights the key area of the ^{1}H NMR from 1.5 - 5 ppm, with the relevant peaks labelled. The key diagnostic cross-peaks (**H8**, **H9α/β** & **H10**) are marked in red, with all other cross-peaks assigned on the spectrum.

H8 shows a cross-peak to **H9β**, but not to **H9α**. **H9β** in turn shows a cross-peak to **H10**, therefore protons **H8**, **H9β** and **H10** are on the same face of the tricyclic system.

The stereochemistry of compound **213a** is therefore assigned as follows (**Figure 29**).

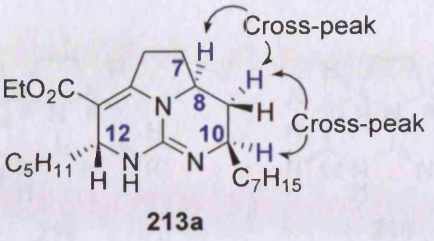
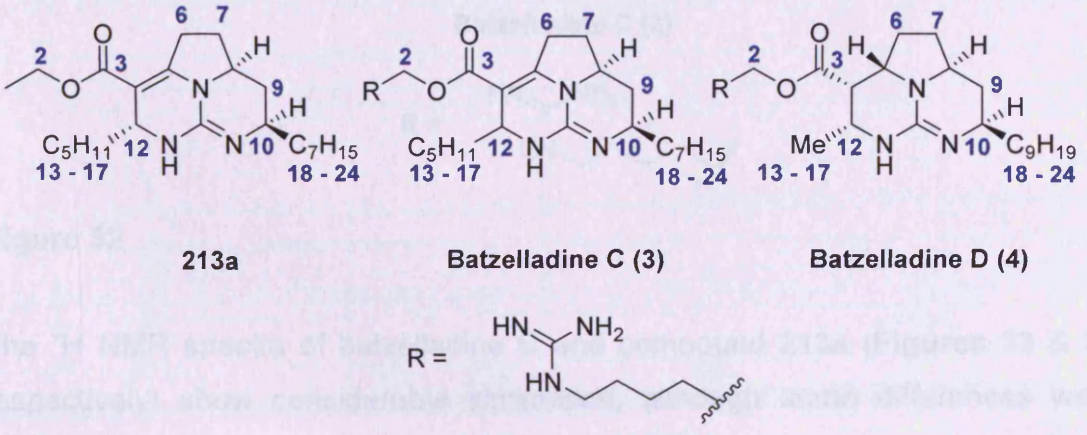


Figure 29

The relative H-8 and H-10 stereochemistry is therefore the same as that of batzelladine C, so that compound **213a** is one of the two possible diastereoisomers of batzelladine C ethyl ester. However, the stereochemistry of H-12 in batzelladine C could not be determined spectroscopically (**Figure 30**).

The structures of synthetic tricyclic guanidine **213a**, batzelladine C and batzelladine D are shown in **Figure 30**. For comparison purposes, the carbon atoms of each guanidine are numbered.



213a **Batzelladine C (3)** **Batzelladine D (4)**

Figure 30

With the tricyclic guanidine cores of batzelladines A, D, F – I and K - M, there is a common trend in the relative stereochemistry of H-8 and H-12 (**Figure 31**). When there is an ester group at the 4-position (compound **214**), H-8 and H-12 are *anti* to each other. When there is no group on the 4-position (compound **215**), the two protons are *syn* to each other.

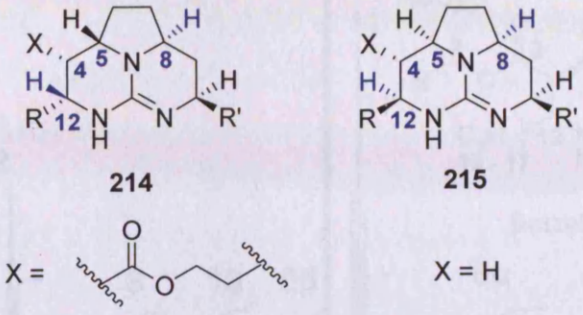


Figure 31

Therefore, according to this precedent, H-12 will most likely be *anti* to H-8 in batzelladine C (**Figure 32**).

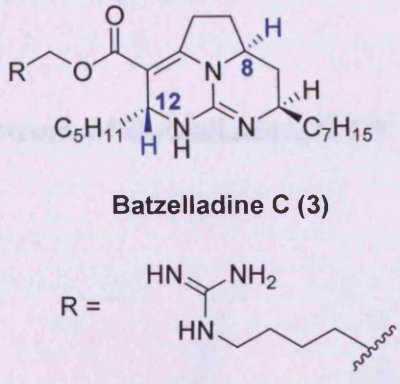


Figure 32

The ^{1}H NMR spectra of batzelladine C and compound **213a** (**Figures 33** & **34** respectively) show considerable similarities, although some differences were observed.

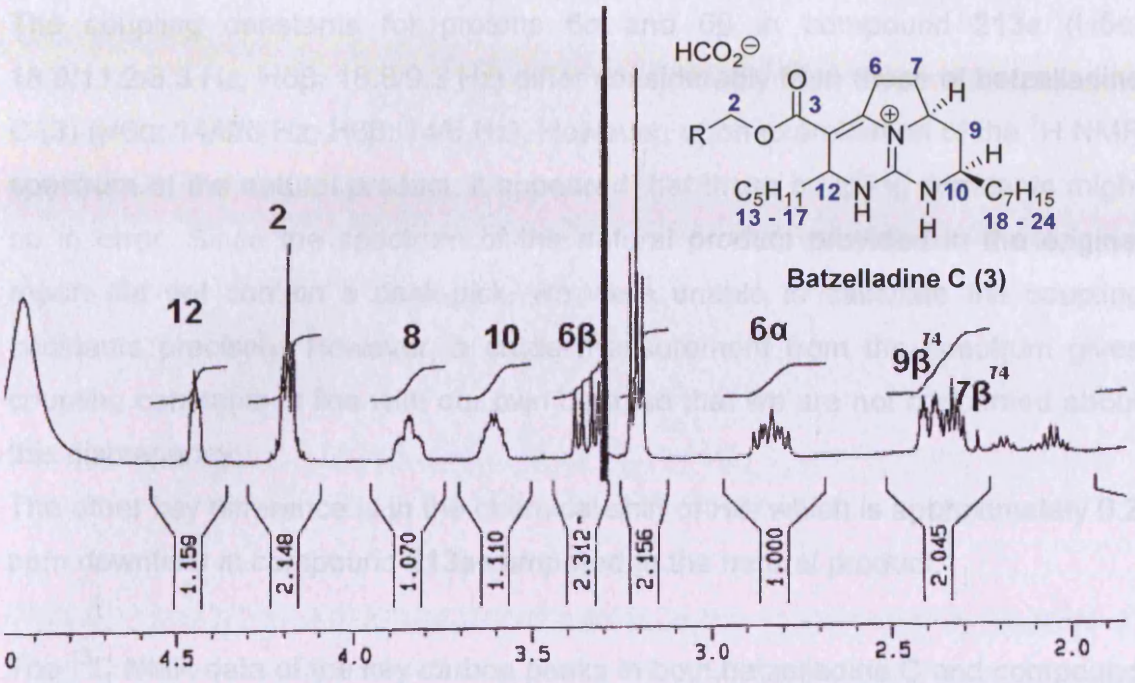


Figure 33 – ^{1}H NMR Spectrum of Batzelladine C (3)[1,74] (400 MHz; MeOH-d_4)

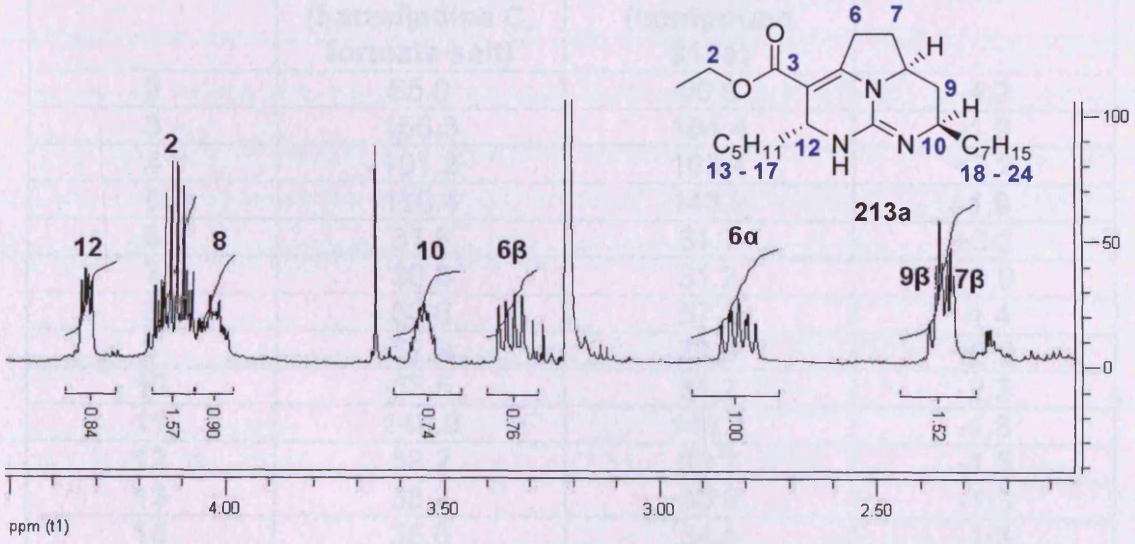


Figure 34 – ^{1}H NMR Spectrum of Compound 213a (500 MHz; MeOH-d_4)

The coupling constants for protons 6α and 6β in compound **213a** (H6α: 18.8/11.2/8.3 Hz, H6β: 18.8/9.3 Hz) differ considerably from those of batzelladine C (**3**) (H6α: 14/8/6 Hz; H6β: 14/6 Hz). However, upon examination of the ^{1}H NMR spectrum of the natural product, it appeared that these coupling constants might be in error. Since the spectrum of the natural product provided in the original report did not contain a peak-pick, we were unable to calculate the coupling constants precisely. However, a crude measurement from the spectrum gives coupling constants in line with our own data, so that we are not concerned about this discrepancy.

The other key difference is in the chemical shift of H8, which is approximately 0.2 ppm downfield in compound **213a** compared to the natural product.

The ^{13}C NMR data of the key carbon peaks in both batzelladine C and compound **213a** are shown in **Table 4**, with the differences between the two values as a point of comparison.

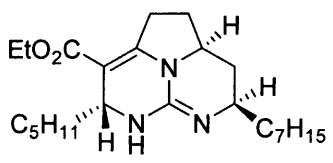
	δ_C (batzelladine C, formate salt)	**δ_C (compound 213a)**	**$\Delta\delta_C$**
2	65.0	60.8	-4.2
3	166.3	164.4	-1.9
4	101.2	103.4	+2.2
5	150.4	148.9	-1.9
6	31.5	31.7	+0.2
7	30.3	31.2	+0.9
8	58.6	57.2	-1.4
9	32.9	33.8	+0.9
10	53.5	51.2	-2.3
11	149.9	148.1	-1.8
12	52.2	50.7	-1.5
13	38.2	36.9	-1.3
18	35.8	34.5	-1.3

Table 4

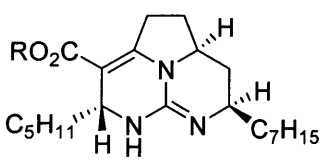
Although there are differences between the chemical shifts of compound **213a** and batzelladine C, the $\Delta\delta_c$ are generally similar (typically -1.5 to -2.5 ppm, with the exception of the few anomalies highlighted in blue).
However, the natural product has been isolated as the formate salt (clearly indicated by a broad singlet at *ca.* 8 ppm in the ^{1}H NMR spectrum), whereas **213a** is isolated as the free guanidine. Therefore, any chemical shift differences from the ^{1}H and ^{13}C NMR spectra may be because of this fact.

The optical rotation of **213a** has the same sign as the natural product data ($[\alpha]_D$: -150° (*c* = 0.2, CH_2Cl_2), $[\alpha]_D$: -30° (*c* 0.2, MeOH); lit.[1]: *batzelladine C*: $[\alpha]_D$: -3.7° (*c* 2.4, MeOH), *batzelladine C methyl ester*: $[\alpha]_D$: -4.2° (*c* 0.93, MeOH).
Others[30] have noted significant discrepancies in the specific optical rotations of natural and synthetic batzelladine D, which have subsequently been attributed to purity.

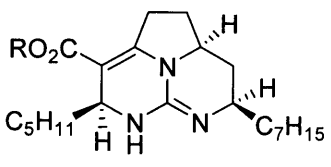
Figure 35 compares compound **213a** to the two possible diastereoisomers of batzelladine C, compounds **216** and **217**.
Because our data is very similar, but not quite identical to that of the natural product, we cannot be 100% certain that **213a** corresponds to the natural product stereochemistry (**Figure 35**). We still feel that according to the general stereochemical trends for the tricyclic cores of the batzelladines (see **Figure 31**), diastereoisomer **216** has the most likely stereochemistry for batzelladine C.



213a



Batzelladine C - *diastereoisomer 1* (216)

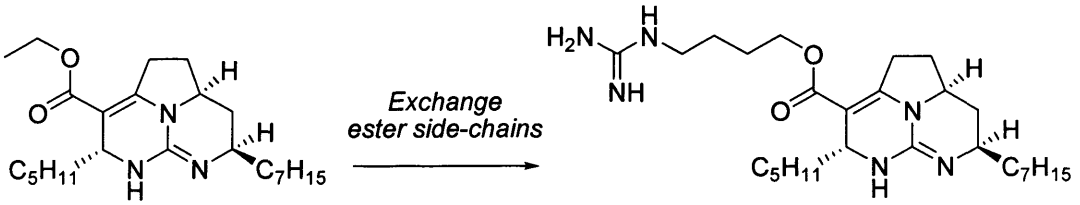


Batzelladine C - *diastereosiomer 2* (217)

Figure 35

5.5 Further Manipulation of the Tricyclic Guanidine Core

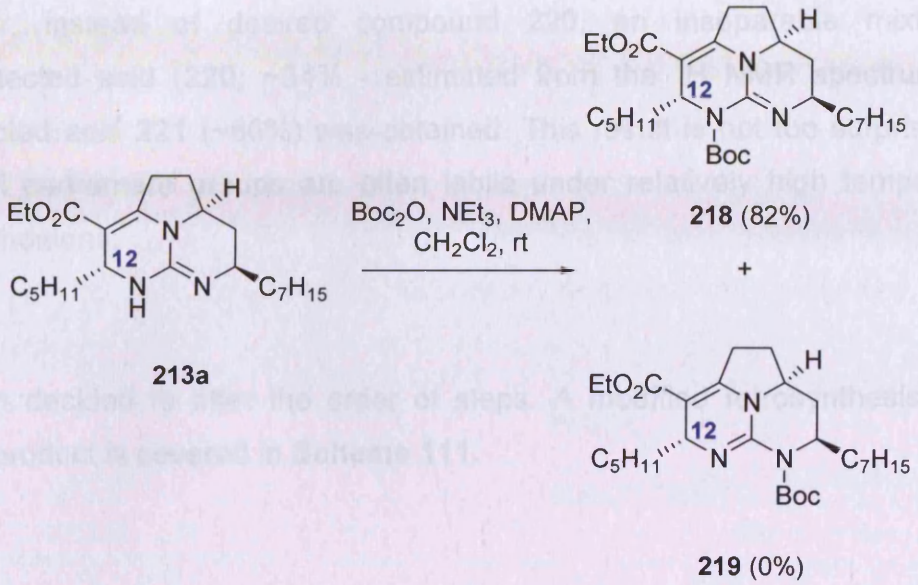
In order to achieve our original goals, that being the synthesis of Batzelladine C, a few functional group modifications were required. Firstly, the ethyl ester has to be exchanged with the required alkyl guanidine side-chain (**Scheme 108**).



213a **Batzelladine C (3)**

Scheme 108

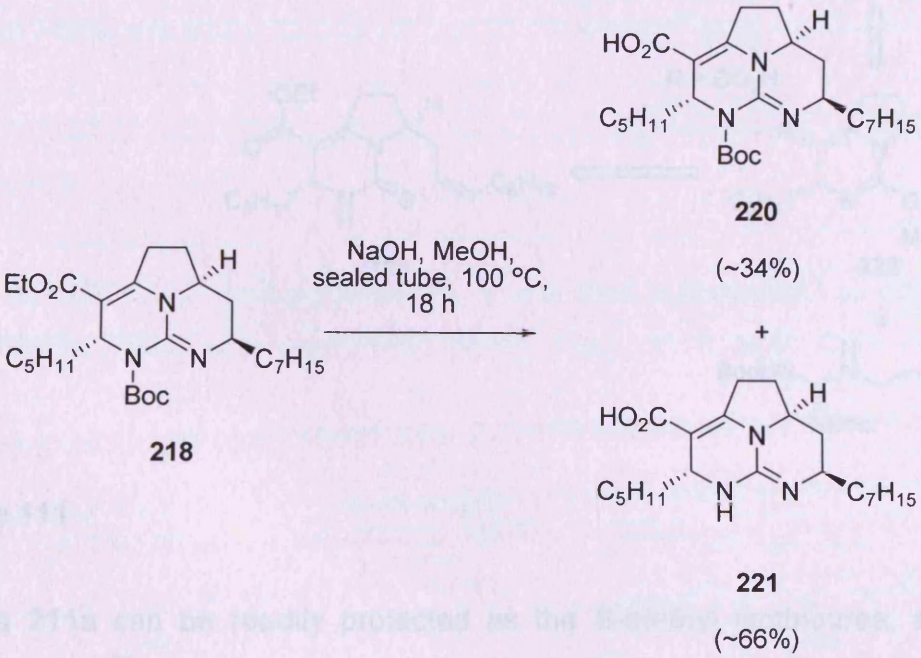
Because of its nucleophilic nature, the guanidine unit was first protected. The *tert*-butyl carbamate was found to be the most apposite choice, as it should be robust enough to survive the ensuing steps, and labile enough to be deprotected in the final step. Free guanidine **213a** was therefore treated to the standard Boc-protection conditions to afford compound **218** (**Scheme 109**). The structure of **219** was confirmed by comparison with the chemical shift of H-12 from the starting material. The regioselectivity of this step is surprising, since the two nucleophilic guanidine nitrogen atoms are in extremely similar environments.



213a

Scheme 109

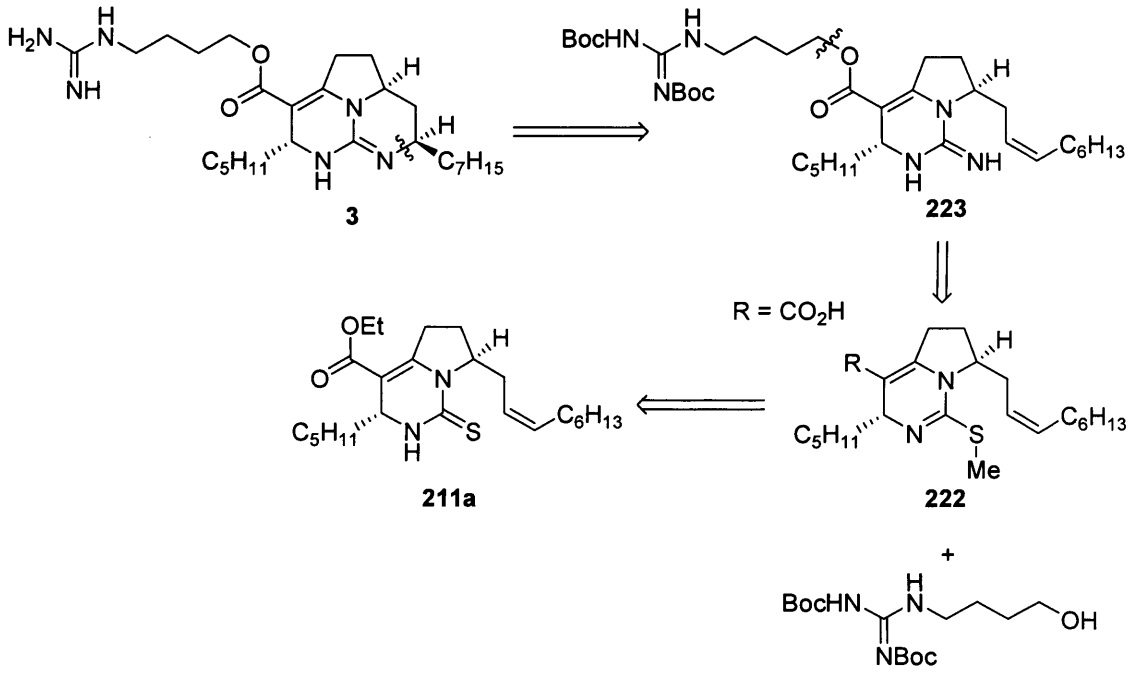
Boc-protected guanidine **218** was then hydrolysed with a concentrated sodium hydroxide solution in methanol (**Scheme 110**).[75]



Scheme 110

However, instead of desired compound **220**, an inseparable mixture of Boc-protected acid (**220**; ~34% - estimated from the ^{1}H NMR spectrum) and deprotected acid **221** (~66%) was obtained. This result is not too surprising, as *tert*-butyl carbamate groups are often labile under relatively high temperature, basic conditions.

We then decided to alter the order of steps. A modified retrosynthesis to the natural product is covered in **Scheme 111**.

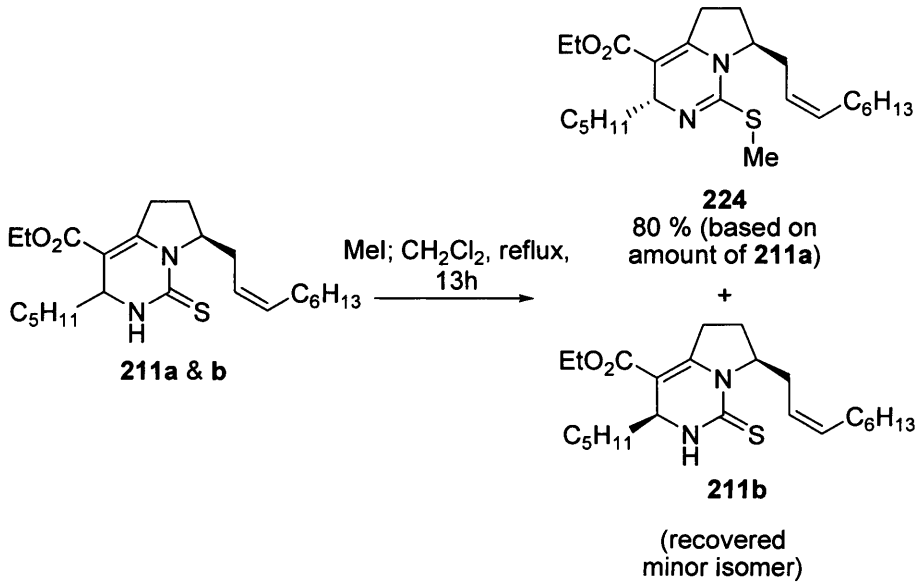


Scheme 111

Thiourea **211a** can be readily protected as the *S*-methyl isothiourea, allowing ester hydrolysis[76] to be carried out to produce carboxylic acid **222**. Acid-alcohol coupling[77,78] then installs the alkyl guanidine side-chain, followed by functional group interconversion to the guanidine (**223**).[28] It is then expected that formation

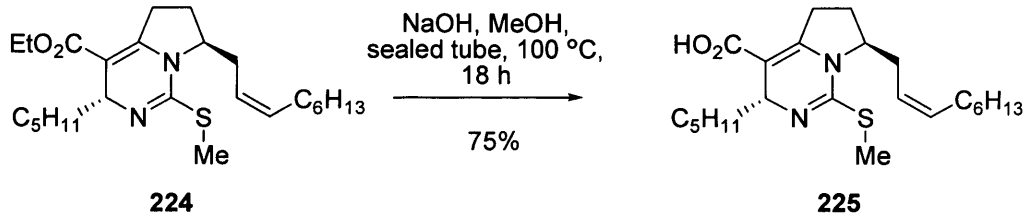
of the tricyclic core will be accomplished by the previously employed iodocyclisation conditions.

This approach began with protection of compounds **211a/b** with iodomethane, yielding *S*-methyl isothiourea **224**. It was discovered that this step is chemoselective, with only the major diastereoisomer becoming alkylated (**Scheme 112**). This negated the need to separate the stereoisomers prior to *S*-methylation.



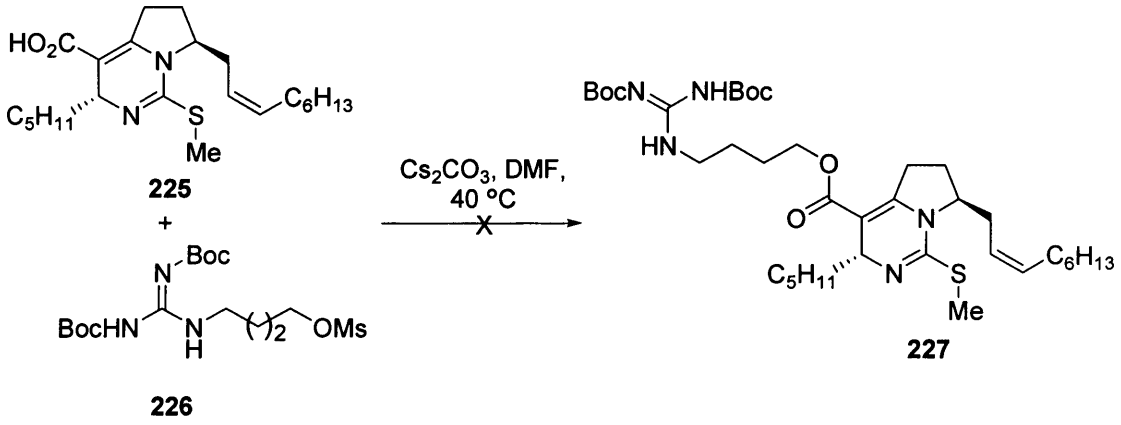
Scheme 112

Having isolated the *S*-methylisothiourea, it was then hydrolysed[76] to afford acid **225** (**Scheme 113**), with purification taking place on a swift flash silica gel column.



Scheme 113

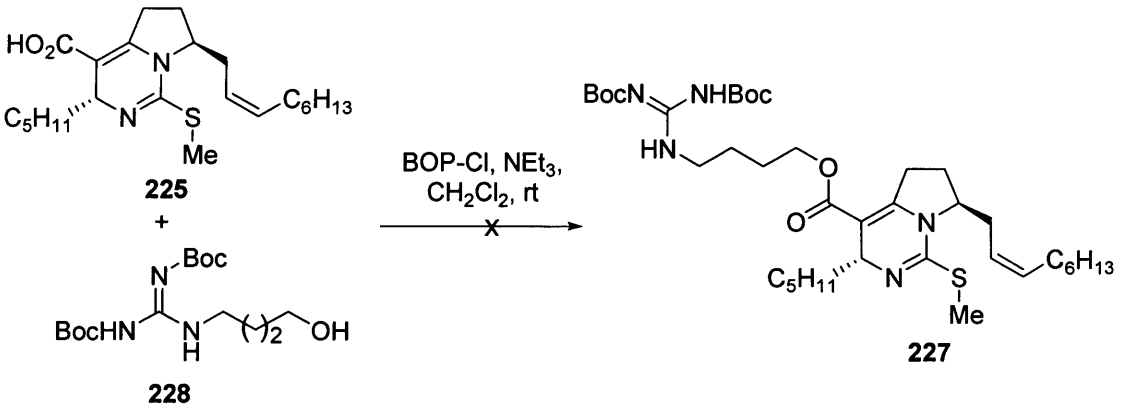
With carboxylic acid **225** in hand, a coupling with the requisite alkyl guanidine was attempted. Mesylate **226** (prepared in 3 steps from thiourea),[79] caesium carbonate and the carboxylic acid were reacted together (**Scheme 114**).



Scheme 114

Unfortunately, ^{1}H NMR, ^{13}C NMR and mass spectrometry confirmed that only starting material was present, with no sign of the coupled product (**227**).

Guanidine ester formation was also attempted with the reaction of carboxylic acid **225**, alcohol guanidine **228** and a coupling reagent; BOP-Cl (**Scheme 115**).



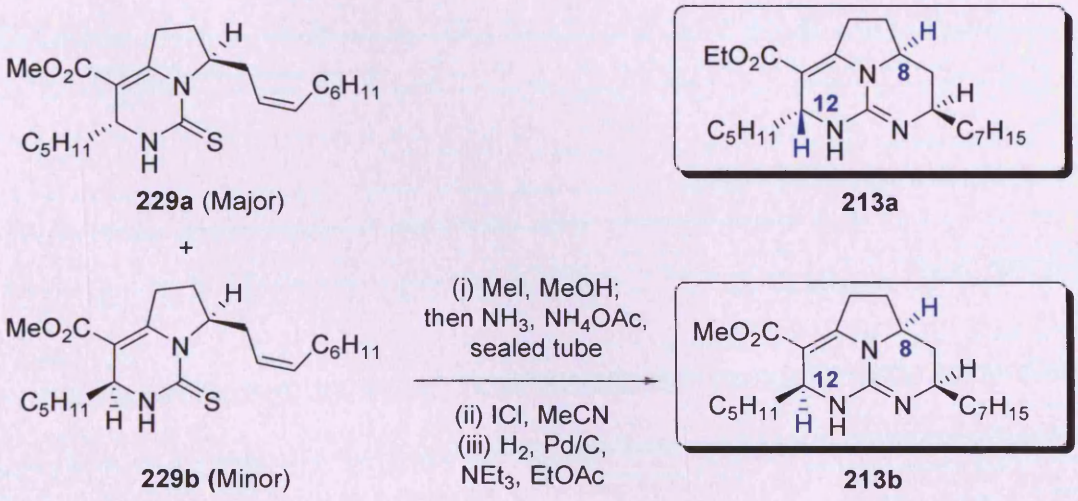
Scheme 115

However, this reaction was also unsuccessful.

5.6 Conclusions & Future Work

In summary, we have developed a diastereoselective, efficient synthetic route to the tricyclic guanidine core of batzelladine C, with no requirement for protecting groups. The spectroscopic data recorded for compound **213a** does have a few discrepancies with the natural product data,[1] therefore the stereochemistry of batzelladine C either corresponds to that of compound **213a**, or its epimer, compound **213b**.

Recently, **213b** has been prepared within the group.[80] Beginning at the bicyclic thiourea stage, minor diastereoisomer **229b** was first converted to the guanidine, and then iodocyclised with iodine monochloride to again form the tricyclic guanidine core. Compound **213b** (with protons H-8 and H-12 *syn* to each other) was isolated in highly pure form following a reductive de-iodination (**Scheme 116**).



Scheme 116

The ^{1}H NMR spectrum of compound **213b** is virtually identical to that of the natural product, in particular the relative position of proton H-8 (which was *ca.* 0.2

ppm downfield in the ^{1}H NMR spectrum of compound **213a**; see **Figures 33** & **34**). The coupling patterns, particularly protons 6β and 6α, are also extremely similar.

We therefore have conclusive evidence of the stereochemistry of batzelladine C.

With compound **213b** in hand, only three steps (including transesterification and reduction of the subsequent alkyl azide) will be required to complete the first synthesis of batzelladine C.

Chapter 6

Experimental Section

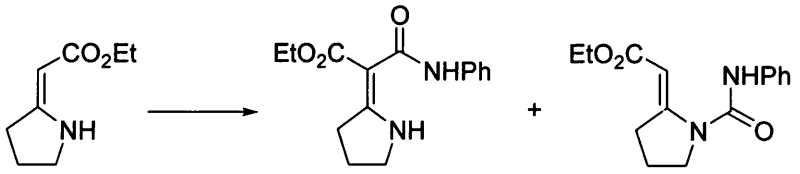
6.1. General Experimental Points

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were recorded on a Fisons VG Platform II spectrometer, a Micromass Q-TOF Micro spectrometer. A Waters 2795 Alliance HT Separation Module, a Micromass ZMD and a Waters Photodiode Array Detector along with a Phenomenex Gemini 5 micron C18 110A 50 x 2mm Column were used for LC-MS. NMR spectra were recorded on a Bruker DPX 400 spectrometer or Bruker Avance 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C, or on a Bruker Avance 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H NMR is reported as singlet (s), doublet (d), double doublet (dd), double double doublet (ddd), double double double doublet (dddd), double double triplet (ddt) double triplet (dt), double quartet (dq), triplet (t), triple triplet (tt), quartet (q) and multiplet (m). Multiplicity in the ^{13}C NMR was obtained using the DEPT pulse sequence. Column chromatography was obtained using Matrex silica 60 35-70 micron, and Silicycle Silicaflash Prepacked Silica Cartridges.

Compound **230** was kindly prepared by Stuart Wordingham.

6.2. Experimental Data for Chapter 2

N-Phenyl-2-pyrrolidin-(2*E*)-ylidene-malonamic acid ethyl ester (79) and (1-Phenylcarbamoyl-pyrrolidin-(2*E*)-ylidene)-acetic acid ethyl ester (74)



62 **79** **74**

(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester was prepared according to ref. 38.

Phenyl isocyanate (89 µL, 0.8 mmol) was added to a solution of *(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester*[38] (106 mg, 0.7 mmol) in dry $CHCl_3$ (6 mL), and the reaction stirred at rt for 18 h under N_2. The solvent was then removed *in vacuo*, and the resulting orange oil (**79:74=2.1:1**) purified by column chromatography (eluting with EtOAc-Hexane, 4.5:7) to afford *title compounds* **79** (R_f 0.8; yellow solid) and **74** (R_f 0.37; colourless solid).

N-Phenyl-2-pyrrolidin-(2E)-ylidene-malonamic acid ethyl ester (**79;** 99 mg, 53%):
Mp: 76 – 78 °C.
δ_H (400 MHz; $CDCl_3$): 11.44 (1H, broad s, CH_2NH), 11.29 (1H, broad s, PhN*H*), 7.50 (2H, d, *J* 7.6, aromatic C*H*), 7.21 (2H, apparent t, *J* 7.9, aromatic C*H*), 6.95 (1H, t, *J* 7.4, aromatic C*H*), 4.14 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.52 (2H, t, *J* 7.7, CH_2NH), 3.11 (2H, t, *J* 7.9, $CH_2C{=}C$), 1.91 (2H, m, CH_2CH_2NH) and 1.25 (3H, t, *J* 7.1, $CO_2CH_2CH_3$).
δ_C (100 MHz; $CDCl_3$): 174.9 (*C*=C-CO_2Et), 169.9 (*C*=O), 168.9 (*C*=O), 139.2 (aromatic *C*), 128.7 (aromatic *C*H), 123.0 (aromatic *C*H), 120.6 (aromatic *C*H),

87.0 (C=*C*-CO_2Et), 59.9 (CO_2*C*$H_2$$CH_3$), 47.7 (*C*$H_2$NH), 36.5 (*C*$H_2$C=C), 21.3 (*C*$H_2$$CH_2$NH) and 14.6 ($CO_2$$CH_2$*C*$H_3$).

IR (solution in CH_2Cl_2): 3236, 1650 and 1614 cm^{-1}.

MS-ES: *m/z* (%): 297 (MNa^+, 7); 275 (MH^+, 2); 182 (100).

HRMS-ES: *m/z* $[MH]^+$: found: 275.1373; $C_{15}H_{19}N_2O_3$ requires 275.1396.

(1-Phenylcarbamoyl-pyrrolidin-(2E)-ylidene)-acetic acid ethyl ester (**74**; 38 mg, 20%):

Mp: 127 – 129 °C (lit.[40] m.p. 128 °C).

δ_H (400 MHz; $CDCl_3$): 7.31 (2H, d, *J* 7.7, aromatic C*H*), 7.22 (2H, apparent t, *J* 7.9, aromatic C*H*), 7.01 (1H, t, *J* 7.4, aromatic C*H*), 6.95 (1H, broad s, N*H*Ph), 6.34 (1H, apparent t, *J* 1.6, C*H*=C), 4.03 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.64 (2H, t, *J* 7.1, CH_2NCO), 3.12 (2H, apparent dt, *J* 1.6 & 7.8, CH_2C=C), 1.87 (2H, apparent quintet, *J* 7.4, CH_2CH_2NCO) and 1.16 (3H, t, *J* 7.1, $CO_2CH_2CH_3$).

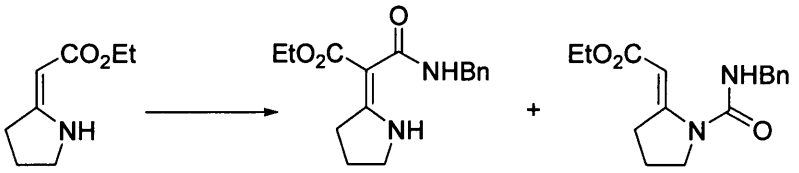
δ_C (100 MHz; $CDCl_3$): 168.9 (ester *C*=O), 158.2 (*C*=CH-CO_2Et), 152.1 (urea *C*=O), 137.5 (aromatic *C*), 129.0 (aromatic *C*H), 124.3 (aromatic *C*H), 120.7 (aromatic *C*H), 95.6 (*C*=CH-CO_2Et), 59.4 (CO_2CH_2), 49.4 (CH_2NCO), 31.9 (CH_2C=C), 21.1 (CH_2CH_2NCO) and 14.5 (CH_3CH_2OCO).

IR (solution in CH_2Cl_2): 3377, 1689, 1660 and 1594 cm^{-1}.

MS-ES: *m/z* (%): 275 (MH^+, 55); 156 (100).

HRMS-ES: *m/z* $[MH]^+$: found: 275.1397; $C_{15}H_{19}N_2O_3$ requires 275.1396.

_N_-Benzyl-2-pyrrolidin-(2_E_)-ylidene-malonamic acid ethyl ester (80) and (1-Benzylcarbamoyl-pyrrolidin-(2_E_)-ylidene)-acetic acid ethyl ester (72)



62 **80** **72**

Benzyl isocyanate (80 µL, 0.7 mmol) was added to a solution of *(2Z)-Pyrrolidin-2-ylidene acetic acid ethyl ester* (103 mg, 0.7 mmol) in dry $CHCl_3$ (6 mL), and the reaction stirred at rt for 18 h under N_2. The solvent was then removed *in vacuo* and the resulting orange oil (**80:72=1:2**) purified by column chromatography (eluting with EtOAc-Hexane, 3:7) yielding, in order of elution, *title compounds* **D** (R_f = 0.41; yellow solid) and **E** (R_f = 0.18; off-white solid).

N-Benzyl-2-pyrrolidin-(2E)-ylidene-malonamic acid ethyl ester (**D**; 25 mg, 13%):

Mp: 95 – 98 °C.

δ_H (400 MHz; $CDCl_3$): 11.40 (1H, s, CH_2NH), 9.51 (1H, m, $PhCH_2NH$), 7.27 7.18 (5H, m, aromatic C*H*), 4.43 (2H, d, *J* 5.7, $PhCH_2NH$), 4.09 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.50 (2H, t, *J* 7.4, CH_2NH), 3.09 (2H, t, *J* 7.9, $CH_2C{=}C$), 1.92 (2H, apparent quintet, *J* 7.7, CH_2CH_2NH) and 1.22 (3H, t, *J* 7.1, $CO_2CH_2CH_3$).

δ_C (100 MHz; $CDCl_3$): 174.4 (*C*=C-CO_2Et), 170.5 (*C*=O), 169.7 (*C*=O), 139.6 (aromatic *C*), 128.5 (aromatic *C*H), 127.3 (aromatic *C*H), 126.8 (aromatic *C*H), 86.6 (C=*C*-CO_2Et), 59.5 ($CO_2CH_2CH_3$), 47.5 ($PhCH_2NH$), 43.0 (CH_2NH), 36.2 ($CH_2C{=}C$), 21.4 (CH_2CH_2NH) and 14.6 ($CO_2CH_2CH_3$).

IR (solution in CH_2Cl_2): 3408, 1639 and 1594 cm^{-1}.

MS-ES: *m/z* (%): 289 (MH^+, 10); 182 (100).

HRMS-ES: *m/z* $[MH]^+$: found: 289.1548; $C_{16}H_{22}N_2O_3$ requires 289.1552.

(1-Benzylcarbamoyl-pyrrolidin-(2E)-ylidene)-acetic acid ethyl ester (**E**; 48 mg, 25%):

Mp: 88 – 92 °C (lit.[40] mp 86 °C).

δ_H (400 MHz; $CDCl_3$): 7.28 – 7.14 (5H, m, aromatic C*H*), 6.41 (1H, apparent t, *J* 1.7, C*H*=C), 5.32 (1H, broad s, N*H*CH_2Ph), 4.38 (2H, d, *J* 5.6, NHC*H*$_2$Ph), 4.02 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.54 (2H, t, *J* 7.1, C*H*$_2$NCO), 3.11 (2H, apparent dt, *J* 1.7 & 7.8, C*H*$_2$-C=C), 1.87 (2H, apparent quintet, *J* 7.5, C*H*$_2$$CH_2$NCO) and 1.16 (3H, t, *J* 7.1, $CO_2CH_2CH_3$).

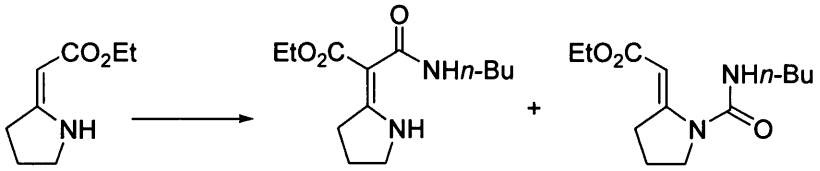
δ_C (100 MHz; $CDCl_3$): 169.1 (ester *C*=O), 158.3 (*C*=C-CO_2Et), 154.5 (urea *C*=O), 158.5 (aromatic *C*), 128.7 (aromatic *C*H), 127.7 (aromatic *C*H), 127.5 (aromatic *C*H), 95.0 (*C*=C-CO_2Et), 59.2 ($CO_2CH_2CH_3$), 49.1 (NHCH_2Ph), 44.5 (*C*H_2NCO), 31.8 (CH_2C=C), 21.1 (*C*$H_2$$CH_2$NCO) and 14.5 ($CO_2CH_2CH_3$).

IR (nujol): 3357, 1669 and 1604 cm^{-1}.

MS-ES: *m/z* (%): 329 (M+Na+H_2O, 65); 156 (100).

HRMS-ES: *m/z* $[MH]^+$: found: 289.1548; $C_{16}H_{22}N_2O_3$ requires 289.1552.

_N_-Butyl-2-pyrrolidin-(2_E_)-ylidene-malonamic acid ethyl ester (81) and [1-_n_-Butyl carbamoyl-pyrrolidin-(2_E_)-ylidene]-acetic acid ethyl ester (70)



62 **81** **70**

(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester (147 mg, 0.9 mmol) was dissolved in pyridine (0.5 mL), and butyl isocyanate (128 µL, 1.1 mmol) added. The solution was stirred at 100 °C in a sealed tube for 65 h, after which time the solvent was removed under reduced pressure. The resultant dark brown oil (**81:70=2.3:1**) was purified by column chromatography (eluting with EtOAc-Hexane, 4:7), yielding *title compounds* **81** (R_f = 0.33; yellow oil) and **70** (R_f = 0.11; pale yellow oil) in order of elution.

N-Butyl-2-pyrrolidin-(2E)-ylidene-malonamic acid ethyl ester (**81**; 156 mg, 65%):

δ_H (400 MHz; $CDCl_3$): 11.45 (1H, broad s, CH_2NH), 9.10 (1H, broad s, CH_2NHCO), 4.10 (2H, q, *J* 7.1, CO_2CH_2), 3.51 (2H, t, *J* 7.4, CH_2NH), 3.21 (2H, apparent q, *J* 6.5, CH_2NHCO), 3.08 (2H, t, *J* 7.9, $CH_2C{=}C$), 1.93 (2H, apparent quintet, *J* 7.7, CH_2CH_2NH), 1.46 (2H, apparent quintet, *J* 7.3, $CH_3CH_2CH_2$), 1.31 (2H, sextet, *J* 7.4, $CH_3CH_2CH_2$), 1.23 (3H, t, *J* 7.1, $CO_2CH_2CH_3$) and 0.85 (3H, t, *J* 7.3, $CH_3CH_2CH_2$).

δ_C (100 MHz; $CDCl_3$): 174.1 ($C{=}C\text{-}CO_2Et$), 170.3 ($C{=}O$), 169.6 ($C{=}O$), 86.5 ($C{=}C\text{-}CO_2Et$), 59.3 (CO_2CH_2), 47.3 (CH_2NH), 38.6 (CH_2NHCO), 36.0 ($CH_2C{=}C$), 31.8 ($CH_3CH_2CH_2$), 21.3 (CH_2CH_2NH), 20.3 ($CH_3CH_2CH_2$), 14.4 ($CO_2CH_2CH_3$) and 13.8 ($CH_3CH_2CH_2$).

IR (solution in CH_2Cl_2): 3314, 1654 and 1598 cm^{-1}.

MS-APCI: *m/z* (%): 255 (MH^+, 24); 182 (100).

HRMS-ES: *m/z* $[MH]^+$: found: 255.1704; $C_{13}H_{23}N_2O_3$ requires 255.1709.

[1-n-Butyl carbamoyl-pyrrolidin-(2E)-ylidene]-acetic acid ethyl ester (**70**; 45 mg, 19%):

δ_H (400 MHz; $CDCl_3$): 6.28 (1H, broad s, alkene C*H*), 4.97 (1H, broad s, N*H*-Bu), 4.04 (2H, q, *J* 7.1, CO_2CH_2), 3.56 (2H, t, *J* 7.1, CH_2NCO), 3.21 (2H, apparent q, *J* 6.6, CH_2NHCO), 3.13 (2H, t, *J* 7.7, $CH_2C{=}C$), 1.89 (2H, apparent quintet, *J* 7.4, CH_2CH_2NCO), 1.47 (2H, quintet, *J* 7.4, $CH_3CH_2CH_2$), 1.29 (2H, sextet, *J* 7.4, $CH_3CH_2CH_2$), 1.18 (3H, t, *J* 7.1, $CO_2CH_2CH_3$) and 0.87 (3H, t, *J* 7.3, $CH_3CH_2CH_2$).

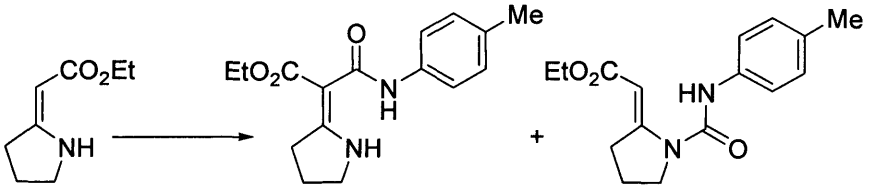
δ_C (100 MHz; $CDCl_3$): 169.0 (ester *C*=O), 158.4 (*C*=C-CO_2Et), 154.4 (urea *C*=O), 94.3 (C=*C*-CO_2Et), 59.2 (CO_2CH_2), 49.2 (CH_2NCO), 40.4 (CH_2NHCO), 32.0 ($CH_2C{=}C$), 31.9 ($CH_3CH_2CH_2$), 21.1 (CH_2CH_2NH), 20.9 ($CH_3CH_2CH_2$), 14.5 ($CO_2CH_2CH_3$) and 13.8 ($CH_3CH_2CH_2$).

IR (solution in CH_2Cl_2): 3348, 1646 and 1565 cm^{-1}.

MS-APCI: *m/z* (%): 273 ($M+H_3O^+$, 42); 255 (MH^+, 19); 156 (100).

HRMS-ES: *m/z* $[MH]^+$: found: 255.1704; $C_{13}H_{23}N_2O_3$ requires 255.1709.

2-Pyrrolidin-(2*E*)-ylidene-*N*-*p*-tolyl-malonamic acid ethyl ester (82) and (1-*p*-tolyl carbamoyl-pyrrolidin-(2*E*)-ylidene)-acetic acid ethyl ester (77)



62 **82** **77**

p-Tolyl isocyanate (130 µL, 1 mmol) was added to a solution of *(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester* (161 mg, 1 mmol) in dry $CHCl_3$ (6 mL), and the reaction stirred under reflux for 2 h under N_2. The solvent was removed *in vacuo*

to produce a yellow oil, which solidified on standing. The resulting yellow solid (**82:77=2.3:1**) was purified by column chromatography (eluting with EtOAc-Hexane, 4.5:7) giving, in order of elution, *title compounds* **82** (R_f = 0.76; pale yellow solid) and **77** (R_f = 0.29; colourless solid).

2-Pyrrolidin-(2E)-ylidene-N-p-tolyl-malonamic acid ethyl ester (**82**; 168 mg, 56%):
Mp: 150 – 153 °C.
δ_H (400 MHz; $CDCl_3$): 11.40 (1H, broad s, CH_2NH), 11.25 (1H, broad s, ArNH), 7.37 (2H, apparent d, *J* 7.4, aromatic CH), 7.01 (2H, apparent d, *J* 7.4, aromatic CH), 4.12 (2H, q, *J* 7.1, CO_2CH_2), 3.49 (2H, t, *J* 7.4, CH_2NH), 3.08 (2H, t, *J* 7.9, $CH_2C{=}C$), 2.20 (3H, s, CH_3Ar), 1.88 (2H, apparent quintet, *J* 7.7, CH_2CH_2NH) and 1.23 (3H, t, *J* 7.1, $CO_2CH_2CH_3$).
δ_C (100 MHz; $CDCl_3$): 174.8 (*C*=C-CO_2Et), 169.9 (*C*=O), 168.8 (*C*=O), 136.5 (aromatic *C*), 132.5 (aromatic *C*), 129.3 (aromatic *C*H), 120.4 (aromatic *C*H), 87.0 (C=*C*-CO_2Et), 59.8 (CO_2CH_2), 47.6 (CH_2NH), 36.5 ($CH_2C{=}C$), 21.3 (CH_2CH_2NH), 20.9 (CH_3Ar) and 14.6 ($CO_2CH_2CH_3$).
IR (solution in CH_2Cl_2): 3216, 1649 and 1619 cm^{-1}.
MS-ES: *m/z* (%): 311 (MNa^+, 30); 289 (MH^+, 30); 182 (100).
HRMS-ES: *m/z* $[MH]^+$: found 289.1537; $C_{16}H_{22}N_2O_3$ requires 289.1552.

(1-p-tolyl carbamoyl-pyrrolidin-(2E)-ylidene)-acetic acid ethyl ester (**77**; 69 mg, 23%):
Mp: 132 – 135 °C (lit.[40] m.p. 155 °C).
δ_H (400 MHz; $CDCl_3$): 7.25 (2H, d, *J* 8.3, aromatic CH), 7.04 (2H, d, *J* 8.3, aromatic CH), 6.77 (1H, s, NHAr), 6.31 (1H, apparent t, *J* 1.7, CH=C), 4.04 (2H, q, *J* 7.1, CO_2CH_2), 3.66 (2H, t, *J* 7.1, CH_2NCO), 3.15 (2H, apparent dt, *J* 1.7 & 7.8, $CH_2C{=}C$), 2.24 (3H, s, CH_3Ar), 1.90 (2H, apparent quintet, *J* 7.4, CH_2CH_2NCO) and 1.17 (3H, t, *J* 7.1, $CO_2CH_2CH_3$).
δ_C (100 MHz; $CDCl_3$): 168.8 (ester *C*=O), 158.1 (*C*=CH-CO_2Et), 152.1 (urea *C*=O), 134.8 (aromatic *C*), 134.0 (aromatic *C*), 129.5 (aromatic *C*H), 120.7

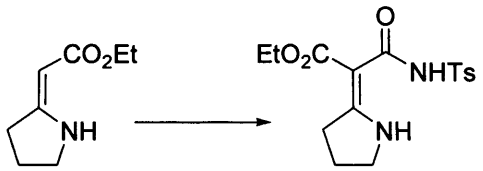
(aromatic *C*H), 95.4 (C=*C*H-CO_2Et), 59.3 (CO_2CH_2), 49.4 (CH_2NCO), 32.0 (CH_2C=C), 21.1 (CH_2CH_2NCO), 20.8 (CH_3Ar) and 14.5 ($CO_2CH_2CH_3$).

IR (solution in CH_2Cl_2): 3448, 1694 and 1609 cm^{-1}.

MS-ES: *m/z* (%): 311 (MNa^+, 22); 289 (MH^+, 8); 156 (100).

HRMS-ES: *m/z* $[MNa]^+$: found: 311.1356; $C_{16}H_{20}N_2O_3Na$ requires 311.1372.

3-Oxo-2-pyrrolidin-(2*E*)-ylidene-3-(toluene-4-sulfonylamino)-propionic acid ethyl ester (83)



62 **83**

(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester (102 mg, 0.7 mmol) was dissolved in dry $CHCl_3$ (6 mL), and *p*-tosyl isocyanate (100 µL, 0.7 mmol) added. The reaction mixture was then stirred at reflux for 2 h under N_2. The solvent was removed *in vacuo* to yield the *title compound* (220 mg, 94%) as a white crystalline solid.

Mp: 154 – 158 °C.

δ_H (400 MHz; $CDCl_3$): 12.20 (1H, s, CH_2NH), 11.30 (1H, s, SO_2NHCO), 7.83 (2H, d, *J* 8.3, aromatic C*H*), 7.18 (2H, d, *J* 8.3, aromatic C*H*), 4.09 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.46 (2H, t, *J* 7.5, CH_2NH), 3.05 (2H, t, *J* 7.9, CH_2C=C), 2.29 (3H, s, CH_3Ar), 1.89 (2H, apparent quintet, *J* 7.7, CH_2CH_2NH) and 1.20 (3H, t, *J* 7.1, $CO_2CH_2CH_3$).

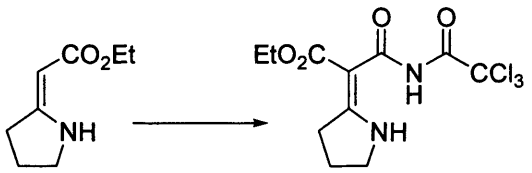
δ_C (100 MHz; $CDCl_3$): 175.9 (*C*=C-CO_2Et), 169.5 (*C*=O), 167.7 (*C*=O), 143.9 (aromatic *C*), 137.4 (aromatic *C*), 129.3 (aromatic *C*H), 128.1 (aromatic *C*H), 86.5 (C=*C*-CO_2Et), 60.5 ($CO_2CH_2CH_3$), 48.1 (CH_2NH), 36.6 (CH_2C=C), 21.6 (CH_3Ar), 20.8 (CH_2CH_2NH) and 14.4 ($CO_2CH_2CH_3$).

IR (nujol): 3447, 1644 and 1594 cm^{-1}.

MS-ES: *m/z* (%): 353 (MH^+, 34); 182 (100).

HRMS-ES: *m/z* $[MH]^+$: found: 353.1166; $C_{16}H_{21}N_2O_5S$ requires 353.1171.

3-Oxo-2-pyrrolidin-(2*E*)-ylidene-3-(2,2,2-trichloro-acetylamino)-propionic acid ethyl ester (84)



62 **84**

Trichloroacetyl isocyanate (48 µL, 0.4 mmol) was added to a stirred solution of *(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester* (63 mg, 0.4 mmol) in dry $CHCl_3$ (3 mL) under N_2, and the resultant mixture stirred for 18 h at rt. The solvent was then removed *in vacuo*. The resulting yellow oil was purified by column chromatography (eluting with EtOAc-Hexane, 4:7), early fractions (R_f = 0.25) yielding the *title compound* (72 mg, 51%) as an off-white solid.

Mp: 110 – 112 °C.

δ_H (400 MHz; $CDCl_3$): 13.38 (1H, broad s, Cl_3CCO-N*H*-CO), 11.31 (1H, broad s, CH_2NH), 4.20 (2H, q, *J* 7.1, CO_2CH_2), 3.66 (2H, t, *J* 7.5, CH_2NH), 3.20 (2H, t, *J* 7.9, CH_2C=C), 2.04 (2H, apparent quintet, *J* 7.8, CH_2CH_2NH) and 1.28 (3H, t, *J* 7.1, $CO_2CH_2CH_3$).

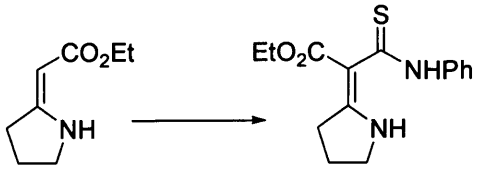
δ_C (100 MHz; $CDCl_3$): 176.6 (Cl_3CCONH), 174.9 (*C*=C-CO_2Et), 169.8 (ester *C*=O), 167.8 (NH-*C*O-C=C), 93.2 (Cl_3C), 87.8 (C=*C*-CO_2Et), 60.8 (CO_2CH_2), 48.4 (CH_2NH), 36.9 (CH_2C=C), 20.9 (CH_2CH_2NH) and 14.4 ($CO_2CH_2CH_3$).

IR (solution in CH_2Cl_2): 3197, 1750, 1664 and 1614 cm^{-1}.

MS-ES: *m/z* (%): 343 (MH^+, 18) (+ consistent isotope peaks); 182 (100).

HRMS-ES: *m/z* $[MH]^+$: found: 343.0015; $C_{11}H_{14}N_2O_4{}^{35}Cl_3$ requires 343.0019.

Phenylthiocarbamoyl-(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester (85)



62 **85**

Phenyl isothiocyanate (46 µL, 0.4 mmol) was added to a solution of *(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester* (60 mg, 0.4 mmol) in dry $CHCl_3$ (6 mL), and the reaction stirred under N_2 for 20 h at reflux. The solvent was removed *in vacuo* and the resulting brown solid recrystallised from aqueous ethanol to yield the *title compound* (65 mg, 58%) as colourless needles.

Mp: 118 – 120 °C.

δ_H (400 MHz; $CDCl_3$): 13.28 (1H, broad s, CH_2NH), 12.47 (1H, broad s, PhN*H*), 7.38 (2H, d, *J* 7.6, aromatic C*H*), 7.31 (2H, apparent t, *J* 7.9, aromatic C*H*), 7.16 (1H, t, *J* 7.4, aromatic C*H*), 4.18 (2H, q, *J* 7.2, CO_2CH_2), 3.64 (2H, t, *J* 7.4, CH_2NH), 3.15 (2H, t, *J* 7.8, $CH_2C{=}C$), 1.98 (2H, apparent quintet, *J* 7.6, CH_2CH_2NH) and 1.28 (3H, t, *J* 7.2, $CO_2CH_2CH_3$).

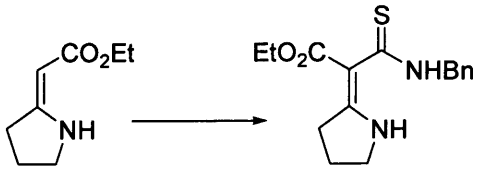
δ_C (100 MHz; $CDCl_3$): 190.2 (thioamide *C*=S), 174.1 (*C*=C-CO_2Et), 170.2 (ester *C*=O), 139.7 (aromatic *C*), 128.6 (aromatic *C*H), 126.3 (aromatic *C*H), 126.2 (aromatic *C*H), 95.0 (C=*C*-CO_2Et), 60.4 (CO_2CH_2), 48.0 (CH_2NH), 37.8 ($CH_2C{=}C$), 21.9 (CH_2CH_2NH) and 14.4 ($CO_2CH_2CH_3$).

IR (solution in CH_2Cl_2): 3176, 1649 and 1248 cm^{-1}.

MS-ES: *m/z* (%):291 (MH^+, 29); 198 (100).

HRMS-ES: *m/z* $[MH]^+$: found: 291.1172; $C_{15}H_{19}N_2O_2S$ requires 291.1167.

Benzylthiocarbamoyl-(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester (86)



62 **86**

(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester (155 mg, 1 mmol) was dissolved in dry $CHCl_3$ (6 mL), and benzyl isothiocyanate (160 µL, 1.2 mmol) added. The reaction was then stirred at reflux under N_2 for 23 h. The mixture was allowed to cool and the solvent removed *in vacuo*. The resulting dark orange oil was then purified by column chromatography (eluting with EtOAc-Hexane, 1:4), mid-fractions (R_f = 0.41) affording the *title compound* (204 mg, 66%) as buff waxy solid.

Mp: 83 – 87 °C.

δ_H (400 MHz; $CDCl_3$): 13.05 (1H, broad s, CH_2NH), 12.22 (1H, broad s, $PhCH_2NH$), 7.18 – 7.11 (5H, m, aromatic C*H*), 4.79 (2H, apparent d, *J* 4.9, $PhCH_2NH$), 4.08 (2H, q, *J* 7.2, CO_2CH_2), 3.59 (2H, t, *J* 7.3, CH_2NH), 3.09 (2H, t, *J* 7.8, $CH_2C{=}C$), 1.93 (2H, apparent quintet, *J* 7.6, CH_2CH_2NH) and 1.20 (3H, t, *J* 7.2, $CO_2CH_2CH_3$).

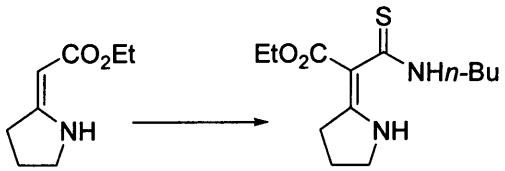
δ_C (100 MHz; $CDCl_3$): 190.0 (thioamide *C*=S), 173.4 (*C*=C-CO_2Et), 169.9 (ester *C*=O), 137.7 (aromatic *C*), 128.7 (aromatic *C*H), 127.9 (aromatic *C*H), 127.3 (aromatic *C*H), 94.3 (C=*C*-CO_2Et), 60.1 (CO_2CH_2), 49.1 ($PhCH_2NH$), 47.8 (CH_2NH), 37.5 ($CH_2C{=}C$), 21.9 (CH_2CH_2NH) and 14.4 ($CO_2CH_2CH_3$).

IR (solution in CH_2Cl_2): 3197, 1639 and 1268 cm^{-1}.

MS-ES: *m/z* (%): 305 (MH^+, 100); 259 (24); 198 (78).

HRMS-ES: *m/z* $[MH]^+$: found: 305.1300; $C_{16}H_{21}N_2O_2S$ requires 305.1324.

_n_-Butylthiocarbamoyl-(2_Z_)-pyrrolidin-2-ylidene acetic acid ethyl ester (87)



62 **87**

(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester (160 mg, 1.0 mmol) was dissolved in pyridine (0.5 mL), and *n*-butyl isothiocyanate (149 µL, 1.2 mmol) added. The reaction was stirred at 100 °C in a sealed tube for 46 h, after which time the solvent was removed under reduced pressure. The resulting dark orange solid was recrystallised from aqueous ethanol to give the *title compound* (240 mg, 89%) as an orange solid.

Mp: 53 – 56 °C.

δ_H (400 MHz; $CDCl_3$): 13.05 (1H, broad s, pyrrolidine CH_2NH), 10.92 (1H, broad s, CH_2NH-C=S), 4.13 (2H, q, *J* 7.2, CO_2CH_2), 3.59 (2H, apparent q, *J* 7.3, CH_2NH-C=S), 3.58 (2H, t, *J* 7.3, CH_2NH), 3.08 (2H, t, *J* 7.8, CH_2C=C), 1.94 (2H, apparent quintet, *J* 7.6, CH_2CH_2NH), 1.58 (2H, apparent quintet, *J* 7.3, $CH_3CH_2CH_2$), 1.36 (2H, sextet, *J* 7.4, $CH_3CH_2CH_2$), 1.24 (3H, t, *J* 7.2, $CO_2CH_2CH_3$) and 0.88 (3H, t, *J* 7.3, CH_3CH_2-alkyl).

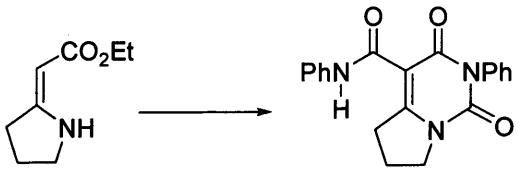
δ_C (100 MHz; $CDCl_3$): 189.5 (*C*=S), 173.1 (*C*=C-CO_2Et), 169.9 (ester *C*=O), 94.0 (C=*C*-CO_2Et), 60.0 (CO_2CH_2), 47.6 (CH_2NH), 44.7 (CH_2NH-C=S), 37.4 (CH_2C=C), 30.3 ($CH_3CH_2CH_2$), 21.8 (CH_2CH_2NH), 20.4 ($CH_3CH_2CH_2$), 14.3 ($CO_2CH_2CH_3$) and 13.8 (CH_3CH_2-alkyl).

IR (solution in CH_2Cl_2): 3176, 1633 and 1257 cm^{-1}.

MS-APCI: *m/z* (%): 271 (MH^+, 74).

HRMS-ES: *m/z* $[MH]^+$: found: 271.1476; $C_{13}H_{23}N_2O_2S$ requires 271.1480.

1,3-Dioxo-2-phenyl-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid phenylamide (88)



62 **88**

A solution of *(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester* (207 mg, 1.3 mmol) in dry THF (5 mL) at 0 °C under N_2 was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil, 35 mg, 1.5 mmol) in THF (15 mL). The mixture was stirred for 2 h at rt, phenyl isocyanate (159 mg, 1.3 mmol) added and the mixture stirred for 18 h at rt. The reaction mixture was then quenched with sat. aqueous NH_4Cl solution (30 mL), the organic layer extracted and the aqueous layer washed with CH_2Cl_2 (3 x 30 mL). The combined organic washings were washed with brine (2 x 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo.* The resulting residue was recrystallised from ethanol to give the *title compound* (60 mg, 13%) as a pale yellow solid.

Mp: 253 – 255 °C.

δ_H (400 MHz; $CDCl_3$): 11.12 (1H, broad s, PhN*H*CO), 7.60 – 7.35 (5H, m, aromatic C*H*), 7.30 – 7.15 (4H, m, aromatic C*H*), 7.00 (1H, t, *J* 7.3, aromatic C*H*), 4.00 (2H, t, *J* 7.5, CH_2NCO), 3.77 (2H, t, *J* 7.9, CH_2C=C) and 2.17 (2H, apparent quintet, *J* 7.7, CH_2CH_2NCO).

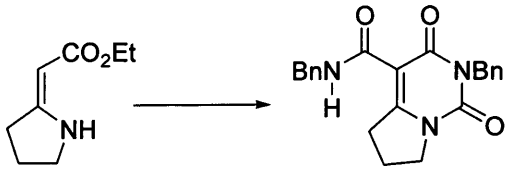
δ_C (100 MHz; $CDCl_3$): 164.9 (*C*=O), 163.5 (*C*=O), 160.6 (*C*=O), 147.8 (*C*=C-C(O)NHPh), 137.2 (aromatic *C*), 133.4 (aromatic *C*), 128.7 (aromatic *C*H), 128.3 (aromatic *C*H), 127.9 (aromatic *C*H), 127.1 (aromatic *C*H), 123.0 (aromatic *C*H), 119.3 (aromatic *C*H), 100.3 (C=*C*-C(O)NHPh), 48.2 (*C*H_2NCO), 33.4 (*C*H_2C=C) and 19.4 (*C*H_2CH_2NCO).

IR (solution in CH_2Cl_2): 3239, 1705, 1682, 1591 and 1437 cm^{-1}.

MS-ES: *m/z* (%): 370 (MNa^+, 92); 348 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 348.1343; $C_{20}H_{18}N_3O_3$ requires 348.1348.

1,3-Dioxo-2-benzyl-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzylamide (89)



62 **89**

A solution of *(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester* (159 mg, 1.0 mmol) in dry THF (5 mL) at 0 °C under N_2 was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil, 45 mg, 1.1 mmol) in THF (15 mL). The mixture was then stirred for 2 h at rt. Benzyl isocyanate (0.13 mL, 1.0 mmol) was added, and the mixture stirred for 18 h at rt. The reaction mixture was quenched with sat. aqueous NH_4Cl solution (30 mL), the organic layer was separated and the aqueous layer washed with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo.* The resulting orange solid was purified by column chromatography (eluting with EtOAc-Hexane, 3:7), early fractions (R_f 0.41) affording the *title compound* (103 mg, 35 %) as a yellow solid.

Mp: 117 – 120 °C.

δ_H (400 MHz; $CDCl_3$): 11.10 (1H, broad s, CH_2NHCO), 7.31 (4H, apparent t, *J* 7.6, aromatic C*H*), 7.26 – 7.12 (6H, m, aromatic C*H*), 5.04 (4H, s, 2 x PhCH_2N), 3.64 (2H, t, *J* 7.6, CH_2NCO), 3.39 (2H, t, *J* 8.0, $CH_2C{=}C$) and 2.06 (2H, apparent quintet, *J* 7.8, CH_2CH_2NCO).

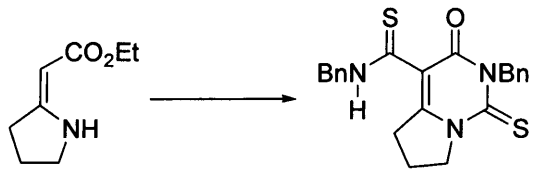
δ_C (100 MHz; $CDCl_3$): 165.2 (*C*=O), 162.4 (*C*=O), 160.9 (*C*=O), 151.6 (*C*=C-C(O)NHBn), 137.6 (aromatic *C*), 137.6 (aromatic *C*), 128.5 (aromatic *C*H), 128.4 (aromatic *C*H), 128.2 (aromatic *C*H), 127.4 (aromatic *C*H), 127.3 (aromatic *C*H), 88.5 (C=*C*-C(O)NHBn), 48.2 (CH_2NCO), 44.19 (PhCH_2N), 44.16 (PhCH_2N), 35.3 ($CH_2C{=}C$) and 20.8 (CH_2CH_2NCO).

IR (solution in CH_2Cl_2): 3248, 1705, 1646, 1623, 1545 and 1442 cm^{-1}.

MS-ES: *m/z* (%): 376 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 376.1657; $C_{22}H_{22}N_3O_3$ requires 376.1661.

2-Benzyl-3-oxo-1-thioxo-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carbothioic acid benzylamide (90)



62 **90**

A solution of *(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester* (62 mg, 0.4 mmol) in dry THF (2 mL) under N_2 was cooled to 0 °C, and added dropwise to a suspension of sodium hydride (60% dispersion in oil, 18 mg, 0.44 mmol) in THF (5 mL). The resultant orange suspension was stirred for 2 h at rt, benzyl isothiocyanate (53 µL, 1.0 mmol) added and the mixture stirred for 18 h. The reaction mixture was then quenched with sat. aqueous NH_4Cl solution (30 mL), the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over $MgSO_4$, and the solvent removed *in vacuo.* The resulting dark orange solid was purified by column chromatography (eluting with EtOAc-Hexane, 3:7), early fractions (R_f = 0.45) yielding the *title compound* (42 mg, 25%) as a pale solid.

Mp: 130 – 132 °C.

δ_H (400 MHz; $CDCl_3$): 14.0 (1H, broad s, N*H*-C=S), 7.45 – 7.05 (10H, m, aromatic C*H*), 6.45 (2H, s, one of PhCH_2N), 5.73 (2H, s, one of PhCH_2N), 3.74 (2H, t, *J* 7.4, CH_2N-C=S), 3.55 (2H, t, *J* 7.9, CH_2C=C) and 2.17 (2H, apparent quintet, *J* 7.7, CH_2CH_2N-C=S).

δ_C (100 MHz; $CDCl_3$): 191.0 (*C*=S), 183.4 (*C*=S), 176.6 (*C*=O), 157.8 (BnNH-C(S)-C=*C*), 135.6 (aromatic *C*), 135.5 (aromatic *C*H), 127.3 (aromatic *C*H), 127.2 (aromatic *C*H), 126.5 (aromatic *C*H), 126.1 (aromatic *C*H), 125.6

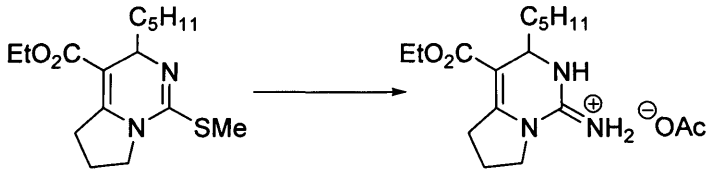
(aromatic *C*H), 125.6 (aromatic *C*H), 102.8 (BnNH-C(S)-*C*=C), 56.0 (*C*H_2NH), 50.5 (*C*H_2NH), 47.9 (*C*H_2N-C=S), 37.1 (*C*H_2C=C) and 20.1 (*C*H_2CH_2N-C=S).

IR (solution in CH_2Cl_2): 3337, 1664 and 1288 cm^{-1}.

MS-ES: *m/z* (%): 408 (MH^+, 100); 182 (58).

HRMS-ES: *m/z* $[MH]^+$: found: 408.1208; $C_{22}H_{22}N_3OS_2$ requires 408.1204.

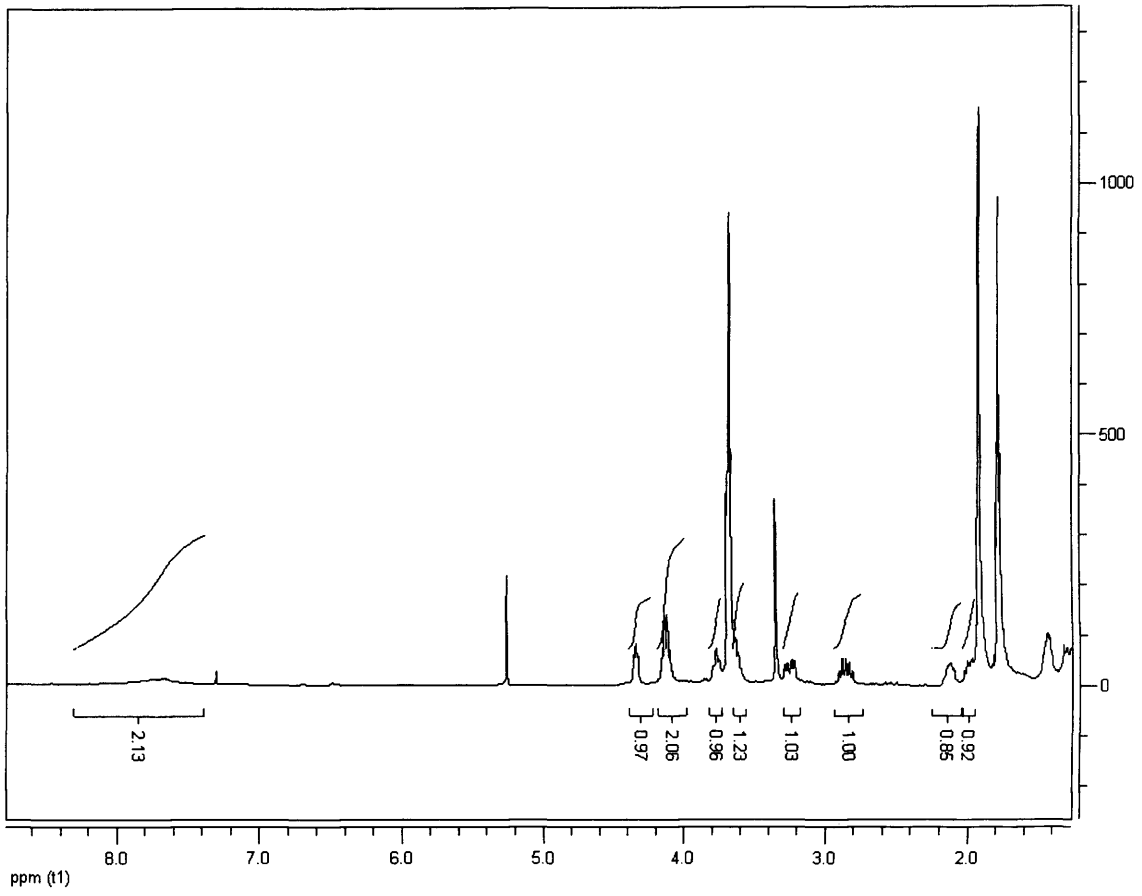
4-(Ethoxycarbonyl)-3-pentyl-2,3,5,6,7-pentahydropyrrolo[1,2-*c*]pyrimidine-1-iminium acetate (106)



230 **106**

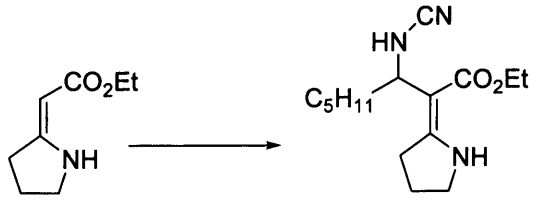
To a solution of *ethyl 3,5,6,7-tetrahydro-1-(methylthio)-3-pentylpyrrolo[1,2-f]pyrimidine-4-carboxylate* (**230**)[38] (100 mg, 0.32 mmol) in dry MeOH (4 mL) was added ammonium acetate, and gaseous ammonia bubbled through the solution for 10 min. The solution was then heated at 80 °C for 48 h in a sealed tube. The reaction was allowed to cool and the volatiles removed *in vacuo* to afford the *title compound* (90 mg, 84% crude yield) as a yellow gum.

^{1}H NMR Spectrum of Compound **106** (400 MHz; $CDCl_3$)



Selected peaks: 7.74 (2H, broad s, $(NH_2)^+$), 4.33 (1H, apparent dd, *J* 6.8 & 4.4, C*H*-pentyl), 3.78 – 3.74 (1H, m, one of CH_2-N-C=N), 3.68 – 3.59 (1H, m, one of CH_2-N-C=N), 3.24 (1H, ddd, *J* 18.3, 8.3 & 2.3, one of CH_2C=C), 2.86 (1H, apparent dt, *J* 18.3 & 9.3, one of CH_2C=C).

(2Z)-Ethyl 3-(cyanoamino)-2-(pyrrolidin-2-ylidene)octanoate (108)



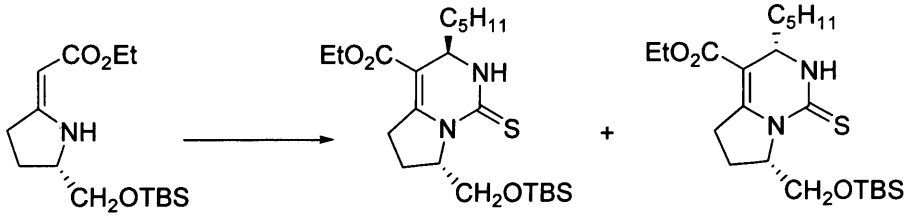
62 **108**

Cyanamide (16 mg, 0.4 mmol) was added to a solution of hexanal (48 µL, 0.4 mmol) in dry CH_2Cl_2 (4 mL) under N_2, and the resulting suspension stirred at rt for 30 mins. A solution of *(2Z)-Pyrrolidin-2-ylidene-acetic acid ethyl ester* (60 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) was added, and the resulting mixture stirred at rt for 3 h. The solvent was then removed *in vacuo* (temperature of the water bath ≤ 30 °C) to afford the *title compound* as a pale yellow gum (94 mg, 87% crude yield).

δ_H (500 MHz; $CDCl_3$): 8.26 (1H, broad s, N*H*), 4.37 (1H, broad s, N*H*-CN), 4.18 – 4.0 (2H, m, CO_2CH_2), 3.75 (1H, apparent q, *J* 7.4, C*H*-NHCN), 3.50 (2H, apparent t, *J* 7.0, CH_2NH), 2.78 (1H, ddd, *J* 16.1, 9.1 & 7.0, one of CH_2C=C), 2.58 (1H, ddd, *J* 16.1, 9.2 & 6.9, one of CH_2C=C), 2.03 – 1.89 (2H, m, pyrrolidine CH_2CH_2NH), 1.85 – 1.64 (2H, m, CH_2CH-NHCN), 1.26 – 1.14 (9H, m, 3 x alkyl CH_2 protons & $CO_2CH_2CH_3$) and 0.81 (3H, t, *J* 6.9, CH_3CH_2-alkyl).

δ_C (125 MHz; $CDCl_3$): 169.0 (ester *C*=O), 166.0 (*C*=C-CO_2Et), 117.3 (NH-*C*≡N), 88.3 (C=*C*-CO_2Et), 59.0 (CO_2CH_2), 47.3 (*C*H-NHCN), 35.2 (CH_2NH), 31.55 (CH_2C=C), 31.5 (CH_2CH-NHCN), 26.6 (pyrrolidine CH_2CH_2NH), 22.5 (CH_2), 22.4 (CH_2), 21.6 (CH_3CH_2-alkyl), 14.6 ($CO_2CH_2CH_3$) and 13.9 (CH_3CH_2-alkyl).

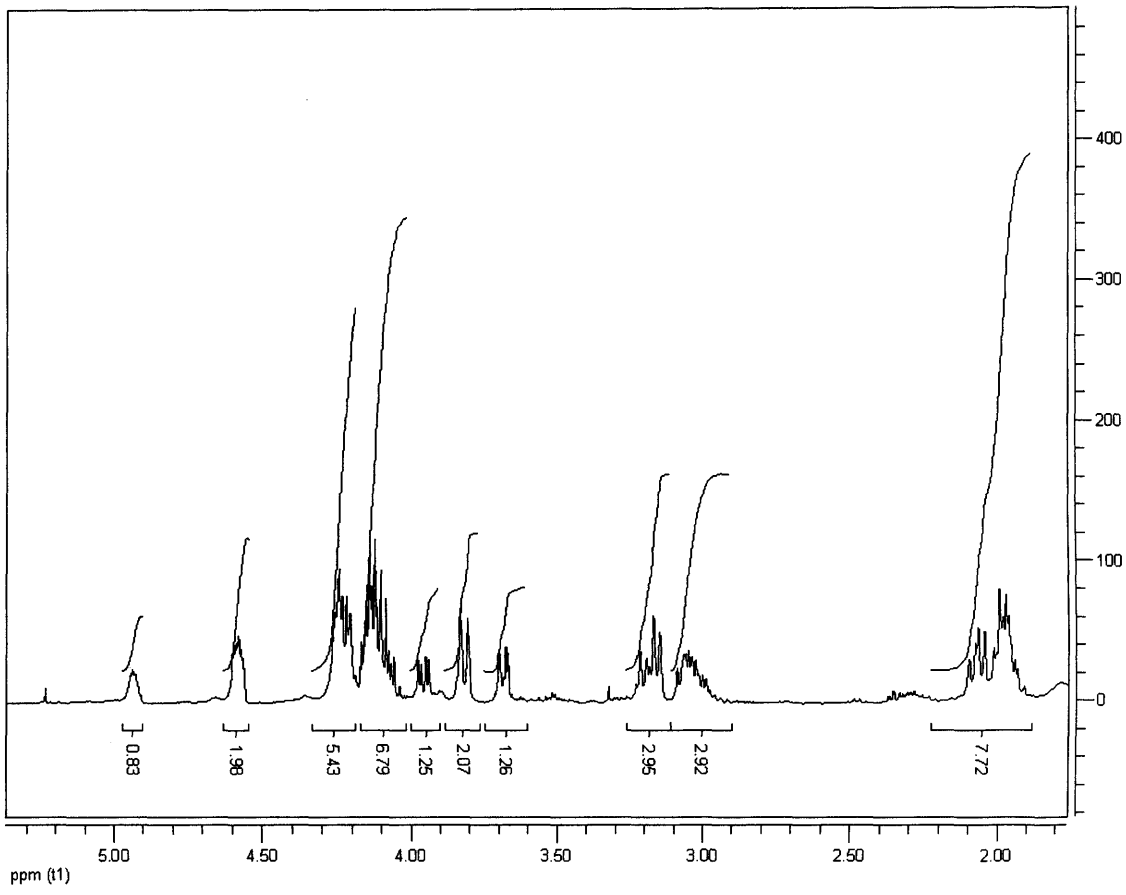
(3*R*,7*S*)-Ethyl 1,2,3,5,6,7-hexahydro-7-((*tert* butyl dimethyl silyl)oxy methyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (110) and (3*S*,7*S*)-Ethyl 1,2,3,5,6,7-hexahydro-7-((*tert* butyl dimethyl silyl)oxy methyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (111)



46 **110** **111**

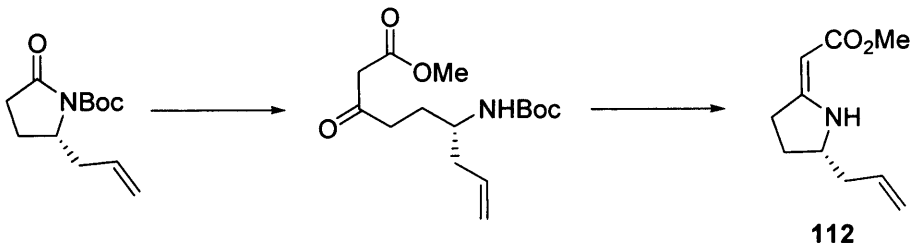
A mixture of hexanal (22 µL, 0.18 mmol) and trimethylsilyl isothiocyanate (25 µL, 0.18 mmol) in dry CH_2Cl_2 (3 mL) was stirred at rt under N_2 for 30 mins. A solution of *(2Z)-Ethyl-2-[(S)-5-(tertbutyldimethylsilyl)oxymethyl)pyrrolidin-2-ylidene)acetate*[29] (**46**) (54 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was added, and the resulting pale solution stirred at rt for 3 h. The reaction was then quenched with the addition of 0.1 M aqueous NaOH solution (30 mL), the layers separated and the aqueous layer washed with CH_2Cl_2 (3 x 25 mL). The combined organic washings were dried over Na_2SO_4 and the solvent removed *in vacuo*. The resultant orange oil was purified by flash column chromatography (CH_2Cl_2 → EtOAc) to afford the *title compounds* (64 mg, 81%) as a viscous orange oil (**110:111**=2.38:1).

^{1}H NMR spectrum (400 MHz; $CDCl_3$) of compounds **110** and **111.**



Selected peaks: 4.97 – 4.90 (**111**; 1H, m, C*H*N-C=S), 4.61 – 4.55 (**110**; 1H, m, C*H*N-C=S) and 4.28 – 4.19 (**110** & **111**; 1H, m, C*H*-pentyl).

(*Z*)-Methyl 2-((5*S*)-5-allylpyrrolidin-2-ylidene)acetate (112)



112

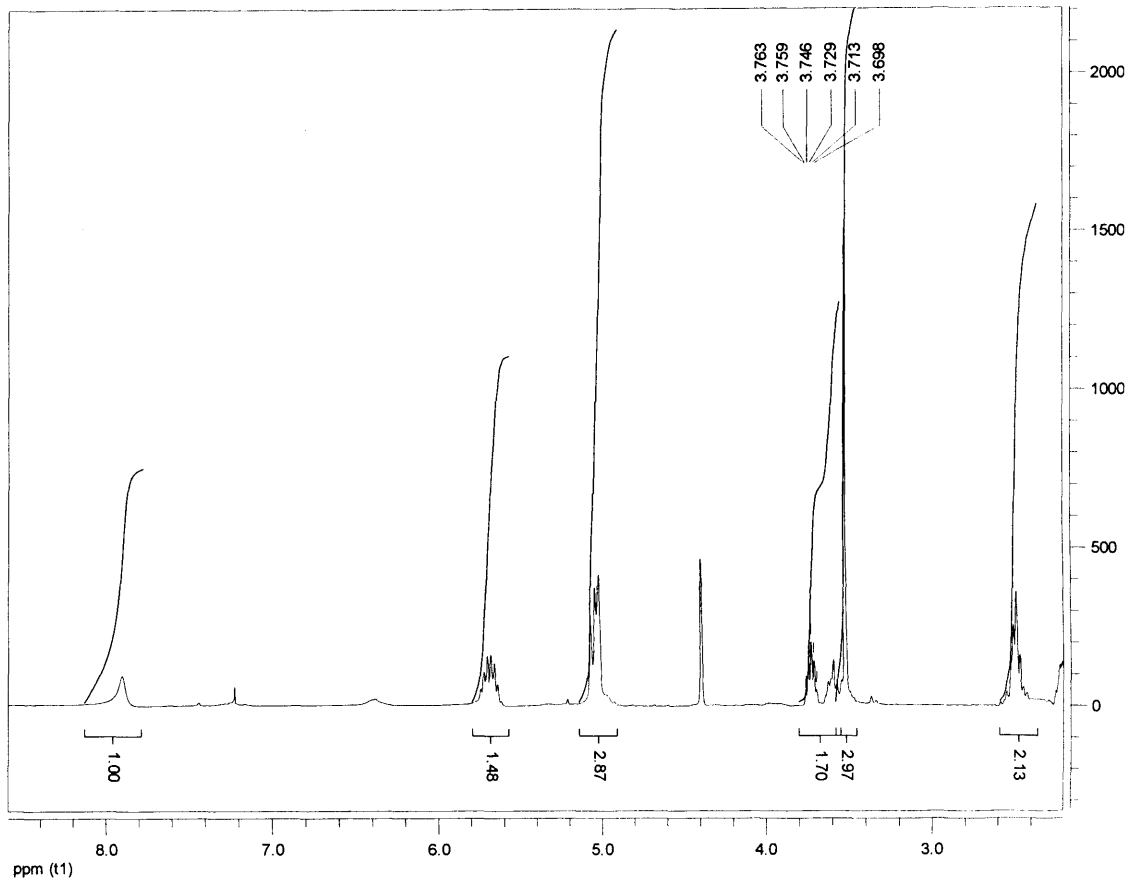
Ring-opening step:

Diisopropylamine (0.35 mL, 2.49 mmol) was added dropwise to *n*-butyl lithium (2.5 M solution in hexanes; 1.0 mL, 2.49 mmol) at 0 °C under N_2, and the resulting gel stirred for 10 min. Dry THF (10 mL) was added, and the yellow solution stirred for a further 20 min. The reaction was then cooled to –78 °C, and dry methyl acetate (0.20 mL, 2.49 mmol) added dropwise. After 30 min, a solution of *(S)-tert-butyl 2-allyl-5-oxopyrrolidine-1-carboxylate* (640 mg, 2.49 mmol) in THF (3 mL) was added dropwise, and the resultant orange solution allowed to warm to rt over 20 h. The reaction mixture was quenched with sat. NH_4Cl solution (30 mL), the layers separated and the aqueous layer washed with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. *tert-Butyl (S)-8-(methoxycarbonyl)-7-oxooct-1-en-4-ylcarbamate* was obtained in sufficient purity, and used immediately in the ring-closing step.

Ring-closing step:

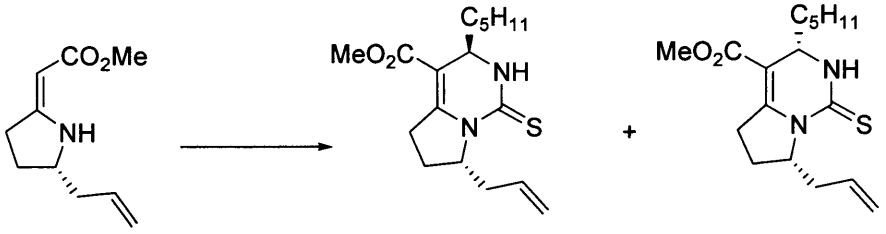
Trifluoroacetic acid (0.32 mL, 4.14 mmol) was added to *tert-butyl (S)-8-(methoxycarbonyl)-7-oxooct-1-en-4-ylcarbamate* (589 mg, 1.97 mmol), and the resulting dark orange residue stirred for 3 h at rt. The reaction was then neutralized to pH 7 with $NaHCO_3$ solution, and the residue washed with CH_2Cl_2 (3 x 30 mL). The comined organic washings were then dried over Na_2SO_4, and the solvent removed *in vacuo*. The resulting oil was purified by column chromatography (eluting with EtOAc-Hexane, 1:4), early fractions (R_f 0.42) affording the *title compound* (307 mg, 68%) as a viscous orange oil.

^{1}H NMR spectrum (400 MHz; $CDCl_3$) of compound **112**



Selected peaks: 7.88 (1H, broad s, N*H*), 5.75 – 5.59 (1H, m, C*H*=CH_2), 5.08 – 4.99 (2H, m, CH=CH_2), 4.39 (1H, broad s, C=C*H*-CO_2Me), 3.76 (1H, apparent quintet, *J* 6.7, C*H*-NH), 3.51 (3H, s, CO_2CH_3) and 2.58 – 2.42 (2H, m, one of pyrrolidine CH_2C=C & one of CH_2CH=CH_2).

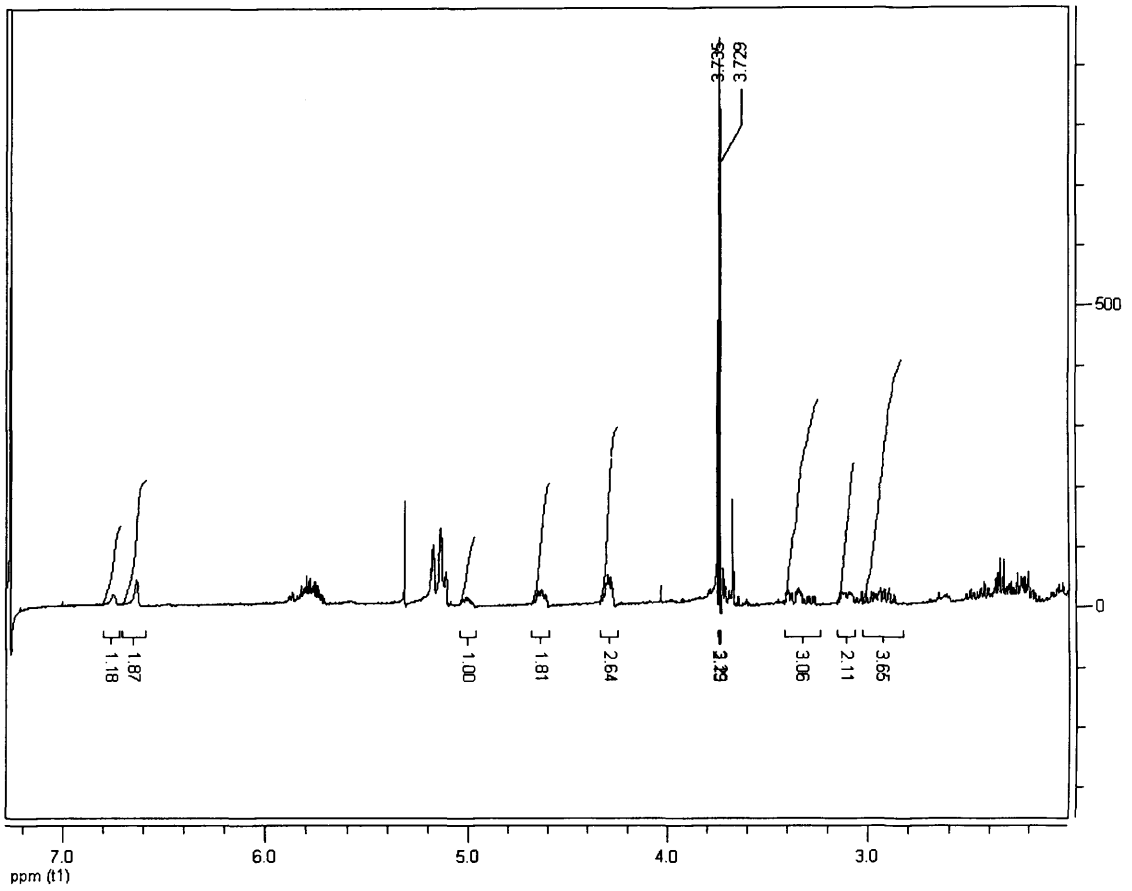
(3*R*,7*S*)-Methyl 7-allyl-1,2,3,5,6-hexahydro-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (113) and (3*S*,7*S*)-Methyl 7-allyl-1,2,3,5,6-hexahydro-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (114)



112 **113** **114**

Trimethylsilyl isothiocyanate (0.22 mL, 1.58 mmol) was added to a solution of hexanal (0.19 mL, 1.58 mmol) in dry CH_2Cl_2 (15 mL) under N_2, and the resulting yellow solution stirred for 30 min at rt. A solution of *(2Z)-methyl 2-((allylpyrrolidin-2-ylidene)acetate* (**112**) (287 mg, 1.58 mmol) in CH_2Cl_2 (3 mL) was then added, and the mixture stirred for a further 2 h at rt. The reaction was then quenched with ~0.1 M aqueous NaOH solution (40 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 35 mL). The combined organic washings were then dried over Na_2SO_4, and the solvent removed *in vacuo* to afford the *title compounds* (399 mg, 78%) as a yellow gum (**113:114**=1.81:1).

^{1}H NMR spectrum (400 MHz; $CDCl_3$) of compounds **113** and **114.**



Selected peaks: 6.74 (**114**; broad s, N*H*), 6.61 (**113**; 1H, broad s, N*H*), 5.01 – 4.95 (**114**; 1H, m, C*H*-allyl), 4.64 – 4.59 (**113**; 1H, m, C*H*-allyl), 4.30 – 4.26 (**113** & **114**; 1H, m, C*H*-pentyl) and 3.74 (**114**; 3H, s, CO_2CH_3) and 3.74 (**113**; 3H, s, CO_2CH_3).

Diastereoisomers **113** and **114** were then purified by column chromatography (eluting with EtOAc-Hexane, 1:6), mid-fractions (R_f 0.45) affording the *major diastereoisomer* (**113**) (276 mg, 54%) as a yellow solid. Subsequent recrystallisation from aqueous ethanol produced crystals suitable for X-ray analysis.

(3R,7S)-Methyl 7-allyl-1,2,3,5,6-hexahydro-3-pentyl-1-thioxopyrrolo[1,2-c]pyrimidine-4-carboxylate (**113**):

Mp: 120 – 124 °C.

δ_H (400 MHz; $CDCl_3$): 6.94 (1H, broad s, N*H*), 5.73 – 5.67 (1H, m, C*H*=CH_2), 5.09 – 5.03 (2H, m, CH=C*H*$_2$), 4.56 – 4.52 (1H, C*H*-allyl), 4.23 – 4.21 (1H, m, C*H*-pentyl), 3.65 (3H, s, CO_2CH_3), 3.32 – 3.26 (1H, m, one of pyrrolidine C*H*$_2$C=C), 3.04 (1H, apparent dd, *J* 13.3 & 4.5, one of pyrrolidine C*H*$_2$C=C), 2.90 – 2.80 (1H, m, one of C*H*$_2$CH=CH_2), 2.15 (1H, apparent dt, *J* 13.5 & 9.0, one of C*H*$_2$CH=CH_2), 1.94 – 1.83 (2H, m, pyrrolidine C*H*$_2$CH-N), 1.61 – 1.44 (2H, m, C*H*$_2$CH-NH), 1.48 – 1.12 (6H, m, 3 x alkyl C*H*$_2$ protons) and 0.81 (3H, t, *J* 6.8, C*H*$_3$CH$_2$-alkyl).

δ_C (125 MHz; $CDCl_3$): 175.2 (thiourea *C*=S), 166.1 (ester *C*=O), 149.8 (MeO_2C-C=*C*), 134.1 (*C*H=CH_2), 118.1 (CH=*C*H$_2$), 99.8 (MeO_2C-*C*=C), 62.5 (*C*H-allyl), 52.1 (CO_2CH_3), 51.3 (*C*H-pentyl), 37.7 (*C*H$_2$CH=CH_2), 35.4 (pyrrolidine *C*H$_2$C=C), 31.4 (*C*H$_2$), 30.4 (*C*H$_2$), 25.7 (pyrrolidine *C*H$_2$CH-allyl), 23.5 (*C*H$_2$), 22.5 (CH$_3$*C*H$_2$-alkyl) and 14.0 (*C*H$_3$CH$_2$-alkyl).

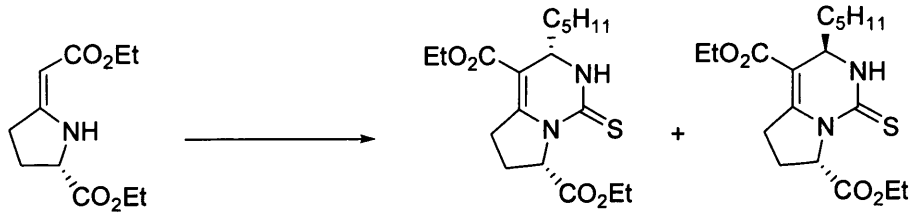
$[\alpha]_D$: +20° (c=0.5, CH_2Cl_2).

IR (CH_2Cl_2): 3265, 3212, 2834, 1690, 1647, 1527, 1354 and 1221 cm^{-1}.

MS-ES: *m/z* (%) = 323 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 323.1792; $C_{17}H_{27}N_2O_2S$ requires 323.1793.

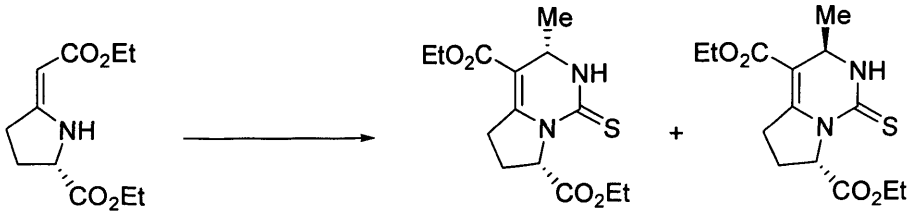
(3*S*,7*S*)-Diethyl 1,2,3,5,6,7-hexahydro-3-pentyl-1-thioxopyrrolo[1,2-*f*]pyrimidine-4,7-dicarboxylate (116) and (3*R*,7*S*)-diethyl 1,2,3,5,6,7-hexahydro-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4,7-dicarboxylate (117)[37]



115 **116** **117**

A mixture of hexanal (0.11 mL, 0.9 mmol) and trimethylsilyl isothiocyanate (0.12 mL, 0.9 mmol) in dry CH_2Cl_2 (5 mL) was stirred at rt under N_2 for 30 min. A solution of *(S,Z)-Ethyl 5-((ethoxycarbonyl)methylene)pyrrolidine-2-carboxylate* (**115**) (200 mg, 0.9 mmol) in CH_2Cl_2 (2 mL) was added, and the resulting pale yellow solution stirred at rt for 3 h. The reaction was then quenched with the addition of ~0.1 M aqueous NaOH solution (30 mL), the layers separated and the aqueous layer washed with CH_2Cl_2 (3 x 25 mL). The combined organic washings were dried over Na_2SO_4 and the solvent removed *in vacuo*. The resultant orange oil was purified by flash column chromatography ($CH_2Cl_2 \rightarrow$ EtOAc) to afford the *title compounds* (263 mg, 81%) as a viscous orange gum (**116:117**=1.25:1).

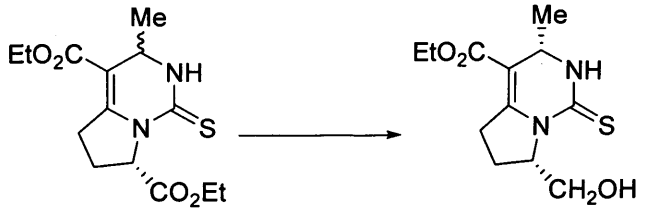
(3*S*,7*S*)-diethyl 1,2,3,5,6,7-hexahydro-3-methyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4,7-dicarboxylate (118) and (3*R*,7*S*)-diethyl 1,2,3,5,6,7-hexahydro-3-methyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4,7-dicarboxylate (119)[37]



115 **118** **119**

A mixture of acetaldehyde (0.15 mL, 2.62 mmol) and trimethylsilyl isothiocyanate (0.37 mL, 2.62 mmol) in dry CH_2Cl_2 (5 mL) was stirred at rt under N_2 for 30 min. A solution of *(S,Z)-Ethyl 5-(ethoxycarbonyl)methylene)pyrrolidine-2-carboxylate* (**115**) (297 mg, 1.31 mmol) in CH_2Cl_2 was then added, and the resulting yellow solution stirred for rt for 2h. The reaction was then quenched with the addition of ~0.1 M aqueous NaOH solution (40 mL), the layers separated and the aqueous layer washed with CH_2Cl_2 (3 x 30 mL). The combined organic washings were dried over Na_2SO_4 and the solvent removed *in vacuo*. The resultant orange oil was purified by flash column chromatography ($CH_2Cl_2 \rightarrow$ EtOAc) to afford the *title compounds* (310 mg, 76%) as a viscous orange gum (**118:119** = 1.2:1).

(3*S*,7*S*)-Ethyl 1,2,3,5,6,7-hexahydro-7-(hydroxymethyl)-3-methyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (120)



118/119 **120**

(2S)-diethyl 1,2,3,5,6,7-hexahydro-3-methyl-1-thioxopyrrolo[1,2-c]pyrimidine-4,7-dicarboxylate (**118/119**) (160 mg, 0.51 mmol) was dissolved in absolute EtOH (8 mL), and sodium borohydride (492 mg, 10.3 mmol) added portion-wise. The resulting suspension was stirred at reflux for 2½ h under N_2. The mixture was then quenched by dropwise addition of sat. aqueous NH_4Cl solution (20 mL), the reaction diluted with EtOAc (30 mL) and the layers separated. The aqueous layer was washed with further portions of EtOAc (3 x 15 ml). The organic layers were combined, washed with brine (40 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The resultant oil was purified by column chromatography (eluting with EtOAc-Hexane, 1:2), mid-fractions (R_f CH_2Cl_2: 0.29) affording the *title compound* (46 mg, 60 % – based on theoretical amount of sm (**118**)) as a clear gum.

δ_H (400 MHz; $CDCl_3$): 7.06 (1H, broad s, N*H*), 5.03 – 4.98 (1H, m, C*H*-CH_2OH), 4.34 (1H, apparent dq, *J* 2.5 & 6.2, C*H*-Me), 4.15 (2H, q, *J* 7.2, CO_2CH_2), 3.92 (1H, dd, *J* 11.2 & 4.3, one of CH_2OH), 3.71 (1H, dd, *J* 11.2 & 5.5, one of CH_2OH), 3.24 (1H, ddd, *J* 18.9, 10.0 & 3.2, one of CH_2C=C), 3.06 – 2.97 (1H, m, one of CH_2C=C), 2.57 (1H, broad s, CH_2OH), 2.07 (1H, apparent dq, 12.9 & 9.5, pyrrolidine CH_2CH-NCS), 1.89 (1H, apparent ddt, *J* 12.9, 9.5 & 2.9, pyrrolidine CH_2CH-NCS) and 1.24 – 1.17 (6H, m, CH_3-CH & $CO_2CH_2CH_3$).

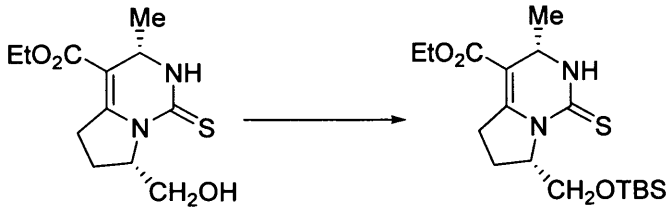
δ_C (500 MHz; $CDCl_3$): 176.2 (thiourea *C*=S), 165.3 (ester *C*=O), 150.1 (CO_2Et-C=*C*), 102.2 (CO_2Et-*C*=C), 65.0 (CO_2CH_2), 64.0 (CH_2OH), 60.4 (*C*H-NCS), 47.8 (*C*H-Me), 30.7 (pyrrolidine CH_2C=C), 23.9 (CH_3-CH), 23.1 (pyrrolidine CH_2CH-NCS) and 14.4 (CH_3CH_2OCO).

IR (solution in CH_2Cl_2): 3085 – 3647 (broad OH stretch), 1693, 1647, 1515, 1377 and 1262 cm^{-1}.

MS-APCI: *m/z* (%): 271 (MH^+, 100).

HRMS-APCI: *m/z* $[MH]^+$: found: 271.1105; $C_{12}H_{18}N_2O_3S$ requires 271.1116.

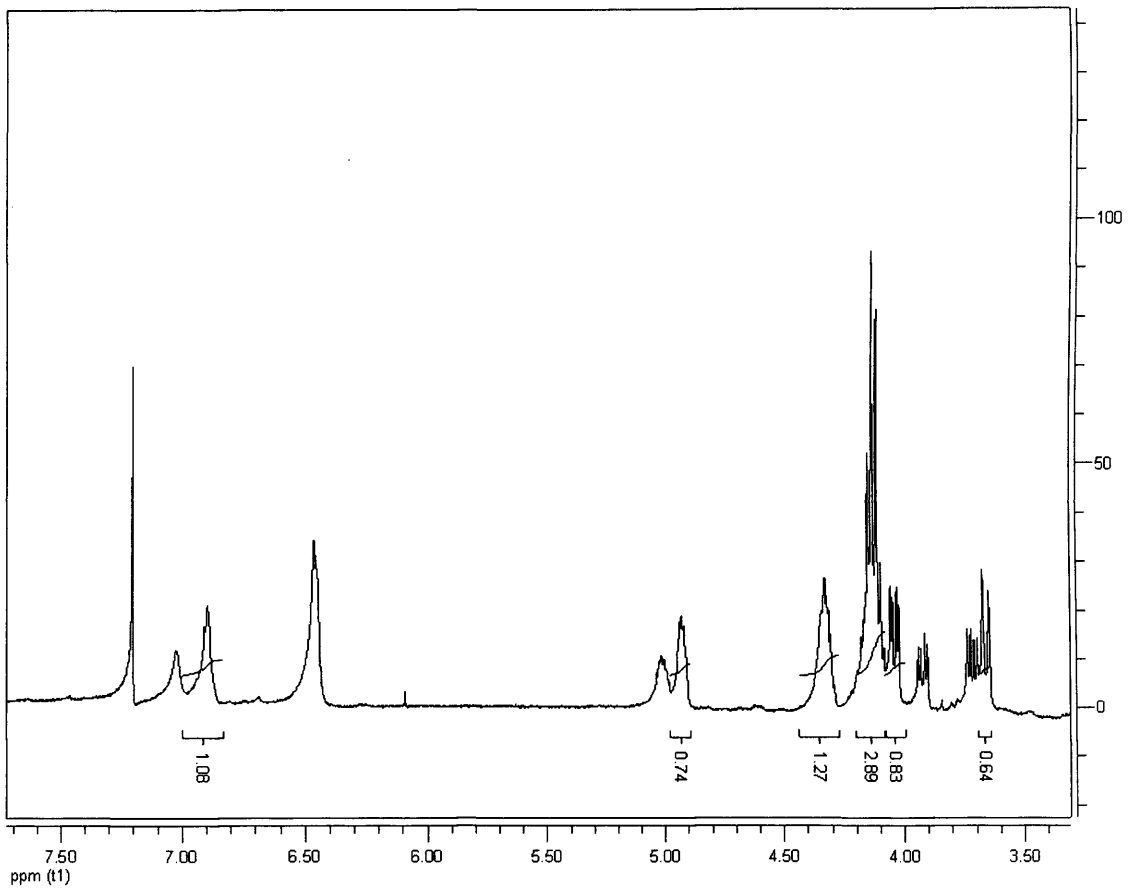
(3*S*,7*S*)-Ethyl 1,2,3,5,6,7-hexahydro-7-((*tert* butyl dimethyl silyl)oxy methyl)-3-methyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (47a)[34]



120 **47a**

Triethylamine (15 µL, 0.11 mmol), *tert*-butyl dimethyl silyl chloride (11 mg, 0.08 mmol) and DMAP (0.5 mg, *catalytic*) were added to a solution of *(3S,7S)-Ethyl 1,2,3,5,6,7-hexahydro-7-(hydroxymethyl)-3-methyl-1-thioxopyrrolo[1,2-f]pyrimidine-4-carboxylate* (19 mg, 0.07 mmol) in CH_2Cl_2 (2 mL). The resulting suspension was stirred at rt under N_2 for 17 h. The reaction was then quenched with sat. aqueous $NaHCO_3$ solution (15 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer washed with further portions of CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 to afford the crude *title compound* as a pale yellow solid.

^{1}H NMR spectrum (400 MHz; $CDCl_3$) of crude compound **47a.**



Selected peaks:

My data:

4.96 – 4.90 (1H, m, C*H*-CH_2OTBS), 4.39 – 4.29 (1H, m, C*H*-Me), 4.04 (1H, dd, *J* 10.4 & 3.7, one of CH_2OTBS) and 3.66 (1H, dd, *J* 10.4 & 2.2, one of CH_2OTBS).

Lit. data:[34]

4.93 (1H, m, C*H*-CH_2OTBS), 4.35 (1H, m, C*H*-Me), 4.06 (1H, dd, *J* 10.4 & 3.6, one of CH_2OTBS) and 3.67 (1H, dd, *J* 10.4 & 2.3, one of CH_2OTBS).

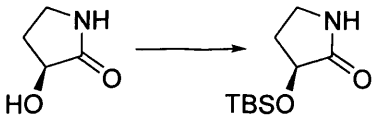
6.3. Experimental Data for Chapter 3

(*S*)-3-hydroxy-pyrrolidin-2-one[46] (128)

128

1,1,1,3,3,3-hexamethyl disilazane (12.48 mL, 58.8 mmol) was added to a suspension of (*S*)-4-amino-2-hydroxy butyric acid (1 g, 8.39 mmol) in dry xylene (200 mL), and a few drops of chlorotrimethylsilane added. The mixture was stirred at reflux for 16 h under N_2, and the xylene removed under reduced pressure. The residue was re-dissolved in THF/H_2O (9:1), a few drops of 12M HCl added and the solution stirred for 10 min at rt. The solvent was then removed *in vacuo*. The resulting pale yellow oil was purified by column chromatography (eluting with $CHCl_3$-MeOH, 7:1), late fractions yielding the *title compound* as a white solid (775 mg, 91%).

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-pyrrolidin-2-one[81] (130)



128 **130**

(S)-3-hydroxypyrrolidin-2-one (**128**) (429 mg, 4.25 mmol) was dissolved in dry THF (40 mL), and *tert*-butyldimethylsilyl chloride (703 mg, 4.67 mmol), imidazole (578 mg, 8.5 mmol) and a catalytic amount of DMAP added. The resulting mixture was stirred under N_2 at rt for 18 h. The mixture was then washed with sat. aqueous $NaHCO_3$ solution (40 mL), the organic layer separated and the aqueous layer washed with CH_2Cl_2 (3 x 50 mL). The combined organic washings

were washed with brine (2 x 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*, yielding the *title compound* as a pale yellow solid (639 mg, 70%).

δ_H (400 MHz; $CDCl_3$): 7.87 (1H, broad s, N*H*), 4.13 (1H, apparent t, *J* 7.8, C*H*-OTBS), 3.23 (1H, ddd, *J* 10.0, 9.4 & 2.8, one of CH_2NH), 3.10 (1H, apparent dt, *J* 10.0 & 7.6, one of CH_2NH), 2.21 (1H, dddd, *J* 12.6, 7.8, 7.3 & 2.8, one of CH_2CH_2NH), 1.85 (1H, apparent dq, *J* 12.6 & 8.2, one of CH_2CH_2NH), 0.78 (9H, s, $((CH_3)_3C)$, 0.01 (3H, s, one of CH_3Si) and 0.00 (3H, s, one of CH_3Si).

δ_C (125 MHz; $CDCl_3$): 177.3 (lactam *C*=O), 70.5 (*C*H-OTBS), 38.5 (CH_2NH), 31.4 (CH_2CH-OTBS), 25.7 ($(CH_3)_3C$), 18.2 ($(CH_3)_3C$), -4.6 (One of CH_3Si) and -5.2 (One of CH_3Si).

(*S*)-*tert*-Butyl 3-((*tert*-butylsilyldimethyl)oxy)-2-oxopyrrolidine-1-carboxylate[81] (136)

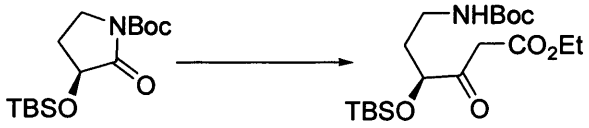
130 **136**

Triethylamine (1.66 mL, 12.0 mmol) and a few crystals of DMAP were added to a solution of *(S)-3-((tert-butyldimethylsilyl)oxy)-pyrrolidin-2-one* (**130**) (1.7131 g, 8.0 mmol) in dry CH_2Cl_2 (25 mL) under N_2. A solution of di-*tert*-butyl dicarbonate (1.9107 g, 8.76 mmol) in CH_2Cl_2 (10 mL) was then added, and the resulting orange mixture stirred at rt for 18 h. The reaction was then quenched with sat. aqueous $NaHCO_3$ solution (35 mL), the layers separated and the aqueous layer washed with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the *title compound* (2.310 g, 92%) as an orange oil.

δ_H (400 MHz; $CDCl_3$): 4.20 (1H, apparent dd, *J* 9.6 & 8.0, C*H*-OTBS), 3.65 (1H, apparent ddd, *J* 13.6, 10.9 & 8.9, one of CH_2N-Boc), 3.35 (1H, apparent ddd, *J* 13.6, 10.0 & 6.7, one of CH_2N-Boc), 2.22 – 2.15 (1H, m, one of CH_2CH-OTBS),

1.78 (1H, apparent dq, *J* 12.5 & 9.4, one of C*H*$_2$CH-OTBS), 1.39 (9H, s, ((C*H*$_3$)$_3$C-OCO), 0.77 (9H, s, ((C*H*$_3$)$_3$C-Si), 0.04 (3H, s, one of *C*H$_3$Si) and 0.00 (3H, s, one of *C*H$_3$Si).

tert-Butyl-(_S_)-5-(ethoxycarbonyl)-3-((_tert_-butyldimethylsilyl)oxy)-4-oxopentylcarbamate (137)



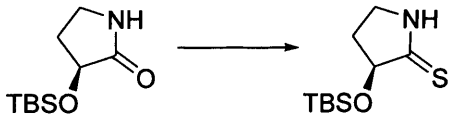
136 **137**

n-BuLi (2.5M solution in hexanes; 0.94 mL, 2.36 mmol) was added dropwise to a solution of diisopropylamine (0.33 mL, 2.36 mmol) in dry THF (8 mL) at 0 °C under N_2, and the resulting pale yellow mixture stirred for 30 mins. The reaction was then cooled to -78 °C, and a solution of dry ethyl acetate (0.23 mL, 2.36 mmol) in THF (2 mL) added dropwise. The reaction was stirred for a further 30 min, and a solution of *(S)-tert-butyl 3-((tert-butylsilyldimethyl)oxy)-2-oxopyrrolidine-1-carboxylate* (**136**) (744 mg, 2.36 mmol) in THF (2 mL) added dropwise. The resultant pale orange solution was allowed to warm slowly to rt (gradual darkening in colour) over 17 h. The reaction was then quenched with sat. aqueous NH_4Cl solution (20 mL), and the layers separated. The aqueous layer was washed with CH_2Cl_2 (3 x 30 mL), and the organic washings were combined, washed with brine (40 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford the *title compound* as a viscous orange oil (828 mg, 87% crude yield).

δ_H (400 MHz; $CDCl_3$): 4.97 (1H, m, N*H*), 4.13 – 4.11 (1H, m, C*H*-OTBS), 4.07 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 3.51 (1H, d, *J* 16.2, one of C(O)-C*H*$_2$-CO_2Et), 3.45 (1H, d, *J* 16.2, one of C(O)-C*H*$_2$-CO_2Et), 3.16 – 3.04 (2H, m, C*H*$_2$NH-Boc), 1.92 – 1.80 (2H, m, C*H*$_2$CH-OTBS), 1.32 (9H, m, ((C*H*$_3$)C)-OCO), 1.16 (3H, t, *J* 7.1,

$CO_2CH_2CH_3$), 0.83 (9H, s, $((CH_3)_3C)$-Si), 0.00 (3H, s, one of CH_3-Si) and -0.01 (3H, s, one of CH_3-Si).

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-pyrrolidine-2-thione (142)



130 **142**

Lawesson's reagent (382 mg, 0.94 mmol) was added to a solution of *(S)-3-((tert-butyldimethylsilyl)oxy)-pyrrolidin-2-one* (**130**) (339 mg, 1.57 mmol) in dry toluene (20 mL), and the reaction stirred at reflux under N_2 for 1½ h. The solvent was removed *in vacuo*, and the resulting dark orange oil purified by column chromatography (eluting with CH_2Cl_2-EtOAc, 9:1), mid-fractions (R_f 0.62) yielding the *title compound* (270 mg, 74%) as a pale yellow crystalline solid.

Mp: 65 – 68 °C.

δ_H (400 MHz; $CDCl_3$): 9.44 (1H, broad s, N*H*), 4.34 (1H, apparent t, *J* 7.2, C*H*-OTBS), 3.44 – 3.40 (1H, m, one of CH_2NH), 3.30 (1H, apparent dt, *J* 11.2 & 7.4, one of CH_2NH), 2.28 – 2.22 (1H, m, one of CH_2CH_2NH), 1.85 (1H, apparent dq, *J* 12.6 & 8.1, one of CH_2CH_2NH), 0.74 (9H, s, $((CH_3)_3C)$, 0.02 (3H, s, one of CH_3Si) and 0.00 (3H, s, one of CH_3Si).

δ_C (125 MHz; $CDCl_3$): 205.5 (thiolactam *C*=S), 79.6 (*C*H-OTBS), 45.6 (CH_2NH), 32.8 (CH_2CH-OTBS), 25.8 ($(CH_3)_3C$), 18.3 ($(CH_3)_3C$), -4.2 (One of CH_3Si) and -4.9 (One of CH_3Si).

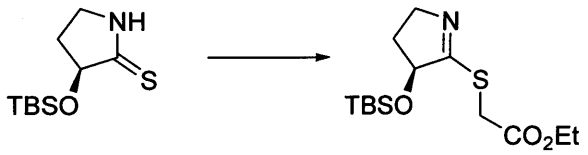
IR (solution in CH_2Cl_2): 3236, 2951, 1523, 1452 and 1264 cm^{-1}.

$[\alpha]_D$: -60.0° (*c* = 1, CH_2Cl_2).

MS-ES: *m/z* (%): 232.2 (MH^+, 84 %); 216.1 ($MH^+ - CH_3$, 100).

HRMS-ES: *m/z* $[MH]^+$: found 232.1181; $C_{10}H_{22}NOSSi$ requires 232.1191.

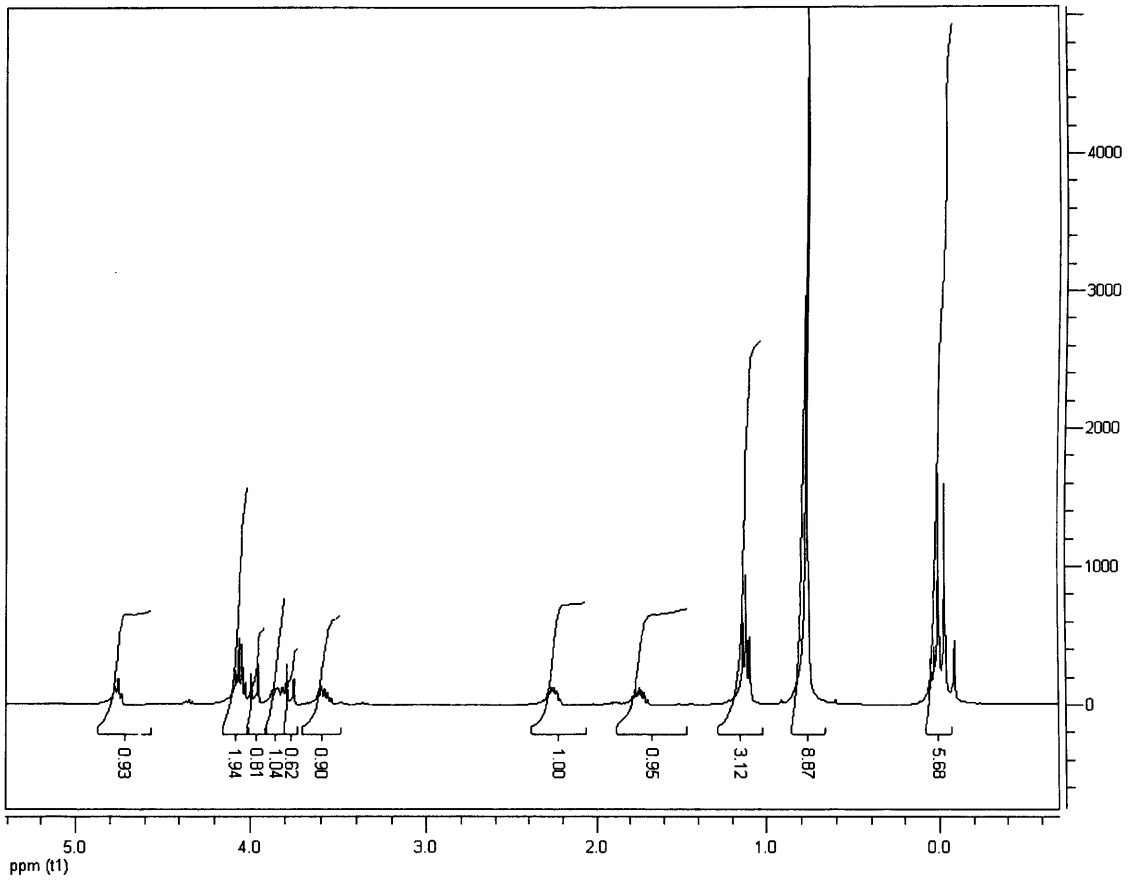
Ethyl 2-[(*S*)-4,5-dihydro-3-((*tert*-butyldimethylsilyl)oxy-3*H*-pyrrol-2-ylthio]acetate (143)



142 **143**

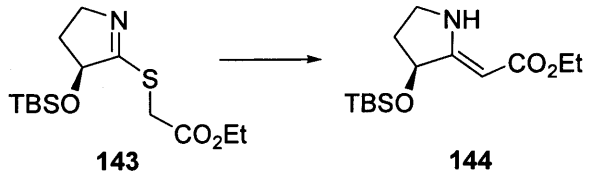
Ethyl bromoacetate (0.23 mL, 2.06 mmol) was added to a solution of *(S)-3-((tert-butyldimethylsilyl)oxy)-pyrrolidine-2-thione* (**142**) (461 mg, 2.0 mmol) in dry CH_2Cl_2 (30 mL), and the reaction stirred for 3 h at rt under N_2. The mixture was then washed with sat. aqueous $NaHCO_3$ solution (40 mL), the layers separated and the aqueous layer washed with CH_2Cl_2 (3 x 50 mL). The combined organic washings were dried over Na_2SO_4, and the solvent removed *in vacuo* to yield an orange oil (595 mg, 94%), which was used immediately in the Eschenmoser sulphide contraction.

^{1}H NMR (400 MHz; $CDCl_3$) spectrum of compound **143**.



δ_H (400 MHz; $CDCl_3$): 4.75 (1H, apparent t, *J* 7.6, C*H*-OTBS), 4.04 (2H, q, *J* 7.1, CO_2CH_2), 3.96 (1H, d, *J* 16.2, one of CH_2S), 3.84 (1H, apparent dd, *J* 14.4 & 8.6, one of CH_2N), 3.76 (1H, d, *J* 16.2, one of CH_2S), 3.58 (1H, apparent dt, *J* 14.4 & 7.4, one of CH_2N), 2.29 – 2.22 (1H, m, one of CH_2CH-OTBS), 1.74 (1H, apparent dq, *J* 12.4 & 8.2, one of CH_2CH-OTBS), 1.12 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 0.76 (9H, s, $((CH_3)_3C)$, 0.00 (3H, s, one of CH_3Si) and -0.04 (3H, s, one of CH_3Si).

(*Z*)-Ethyl 2-[(*S*)-3-((*tert*-butyldimethylsilyl)oxy)]pyrrolidin-2-ylidene]acetate (144)



143 **144**

Ethyl 2-[(S)-4,5-dihydro-3-((tert-butyldimethylsilyl)oxy-3H-pyrrol-2-ylthio]acetate (**143**) (576 mg, 1.82 mmol) was dissolved in dry xylene (20 mL), and potassium *tert*-butoxide (31 mg, 0.27 mmol) added. The resultant mixture was stirred at rt for 15 min under N_2, and triphenylphosphine (1.9 g, 7.27 mmol) added. The reaction was then stirred at reflux for 48 h under N_2. The mixture was washed with sat. aqueous $NaHCO_3$ solution (25 mL), and the organic layer separated. The aqueous layer was washed with CH_2Cl_2 (3 x 30 mL), the organic layers combined, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting solid was purified by flash column chromatography (CH_2Cl_2 → EtOAc), affording the *title compound* (450 mg, 87%) as a pale yellow solid.

Mp: 60 – 64°.

δ_H (400 MHz; $CDCl_3$): 7.57 (1H, broad s, N*H*), 4.56 (1H, apparent t, *J* 7.6, C*H*-OTBS), 4.50 (1H, broad s, C*H*=C), 3.98 (2H, q, *J* 7.1, CH_2OCO), 3.46 – 3.40 (1H, m, one of CH_2NH), 3.29 – 3.23 (1H, m, one of CH_2NH), 2.13 – 2.06 (1H, m, one of CH_2CH-OTBS), 1.76 (1H, apparent dq, *J* 12.3 & 8.3, CH_2CH-OTBS), 1.13 (3H, t, *J* 7.1, CH_3CH_2OCO), 0.80 (9H, s, $((CH_3)_3C)$, 0.02 (3H, s, one of CH_3Si) and 0.00 (3H, s, one of CH_3Si).

δ_C (125 MHz; $CDCl_3$): 171.0 (CH=*C*), 165.6 (ester *C*=O), 77.0 (*C*H=C), 74.2 (C*H*-OTBS), 58.7 (CO_2CH_2), 43.9 (CH_2NH), 33.0 (CH_2CH-OTBS), 25.8 ($(CH_3)_3C$), 18.1 ($(CH_3)_3C$), 14.7 ($CO_2CH_2CH_3$), -4.7 (CH_3-Si) and -4.7 (CH_3-Si).

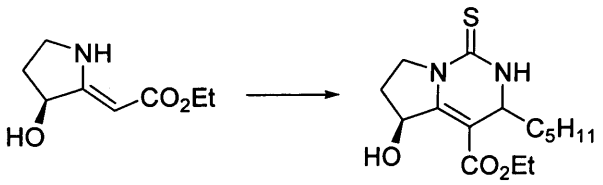
$[\alpha]_D$: -8° (c=1, CH_2Cl_2).

IR (solution in CH_2Cl_2): 3362, 2935, 2842, 1665, 1613, 1464, 1365 and 1239 cm^{-1}.

MS-ES: *m/z* (%): 286 (MH^+, 100).

HRMS-MS: *m/z* $[MH]^+$: found: 286.1838; $C_{14}H_{28}NO_3Si$ requires 286.1838.

(5*S*)-Ethyl 1,2,3,5,6,7-hexahydro-5-hydroxy-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (146)



147 **146**

Hexanal (35 µL, 0.3 mmol) was added to a mixture of trimethylsilyl isothiocyanate (26 µL, 0.3 mmol) in dry CH_2Cl_2 (3 mL), and the resulting pale yellow solution stirred for 30 min at rt under N_2. *(Z)-Ethyl 2-((S)-3-hydroxypyrrolidin-2-ylidene)acetate* (**147**) (49 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was added, and the reaction stirred for 3 h. The reaction was then quenched with ~0.1 M aqueous NaOH solution (20 mL) and the layers separated. The aqueous layer was washed with CH_2Cl_2 (3 x 25 mL), the combined organic layers dried with Na_2SO_4 and the solvent removed *in vacuo*. The resulting orange gum was purified by column chromatography (eluting with EtOAc-Hexane, 1:3), early fractions (R_f 0.42) affording the *title compound* (40 mg, 41%) as a yellow gum (*single diastereoisomer*).

δ_H (400 MHz; $CDCl_3$): 7.05 (1H, broad s, N*H*), 5.27 (1H, apparent d, *J* 1.4, O*H*), 5.11 (1H, apparent t, *J* 8.0, C*H*-OH), 4.26 (1H, apparent dt, *J* 7.8 & 3.9, C*H*-pentyl), 4.20 (2H, q, *J* 7.1, CO_2CH_2), 4.06 (1H, ddd, *J* 11.8, 9.0 & 3.4, one of CH_2N-CS), 3.89 (1H, ddd, *J* 11.8, 9.3 & 7.7, one of CH_2N-CS), 2.42 – 2.34 (1H, m, one of CH_2CH-OH), 2.05 – 1.95 (1H, m, one of CH_2CH-OH), 1.58 – 1.31 (4H, m, 2 x alkyl CH_2 protons), 1.26 – 1.18 (7H, m, CH_3CH_2OCO & 2 x alkyl CH_2 protons) and 0.82 (3H, t, *J* 6.7, CH_3CH_2-alkyl).

δ_C (100 MHz; $CDCl_3$): 176.3 (thiourea *C*=S), 166.8 (ester *C*=O), 154.0 (*C*=C-CO_2Et), 100.9 (C=*C*-CO_2Et), 72.2 (*C*H-OH), 61.3 (CO_2CH_2), 51.8 (*C*H-pentyl), 49.7 (pyrrolidine CH_2N), 37.0 (pyrrolidine CH_2CH-OH), 31.3 (CH_2CH-NH), 29.2 (CH_2CH_2CH-NH), 23.7 ($CH_3CH_2CH_2$), 22.5 ($CH_3CH_2CH_2$), 14.2 ($CO_2CH_2CH_3$) and 14.0 (CH_3CH_2-alkyl).

$[\alpha]_D$: -26° (*c* = 1, CH_2Cl_2).

IR (solution in CH_2Cl_2): 3425, 2941, 1671, 1632, 1444, 1408, 1323 and 1251 cm^{-1}.

MS-AP: *m/z* (%): 313 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 313.1577; $C_{15}H_{25}N_2O_3S$ requires 313.1586.

(*Z*)-Ethyl 2-((*S*)-3-hydroxypyrrolidin-2-ylidene)acetate (147)

(Z)-Ethyl 2-[(S)-3-((tert-butyldimethylsilyl)oxy)]pyrrolidin-2-ylidene]acetate (**144**) (233 mg, 0.30 mmol) was dissolved in THF (20 mL), and TBAF (1 M solution in THF; 1.72 mL) added. The reaction mixture stirred at rt for 40 min, after which time the excess solvent was removed *in vacuo*. The resulting orange gum was purified by column chromatography (eluting with EtOAc-Hexane, 1:1), early fractions (R_f 0.40) affording the *title compound* as a pale yellow crystalline solid (117 mg, 84%).

Mp: 40 – 44 °C.

δ_H (400 MHz, $CDCl_3$): 7.53 (1H, broad s, N*H*), 4.65 (1H, broad s, C*H*=C), 4.60 (1H, apparent t, *J* 6.7, C*H*-OH), 4.04 (2H, q, *J* 7.2, CH_2OCO), 3.57 – 3.51 (1H, m, one of CH_2NH), (1H, apparent dt, *J* 9.9 & 7.0, one of CH_2NH), 2.89 (1H, broad s, O*H*), 2.25 – 2.17 (1H, m, one of CH_2CHOH), 1.85 (1H, apparent dq, *J* 14.1 & 6.5, one of CH_2CH-OH) and 1.19 (3H, t, *J* 7.2, CH_3CH_2OCO).

δ_C (125 MHz, $CDCl_3$): 171.1 (CH=*C*), 165.6 (ester *C*=O), 77.0 (*C*H=C), 73.7 (*C*H-OH), 58.8 (CO_2CH_2), 44.5 (CH_2NH), 32.0 (CH_2CH-OH) and 14.6 ($CO_2CH_2CH_3$).

$[\alpha]_D$: -22° (c=1, CH_2Cl_2).

IR (solution in CH_2Cl_2): 3581, 3385, 3154, 2981, 2865, 1648, 1602, 1492, 1331 and 1239 cm^{-1}.

MS-ES: *m/z* (%): 172 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 172.0966; $C_8H_{13}NO_3$ requires 172.0974.

Methyl 2-[(*S*)-4,5-dihydro-3-((*tert*-butyldimethylsilyl)oxy)-3*H*-pyrrol-2-ylthio]acetate (148)

142 **148**

Methyl bromoacetate (98 µL, 1.04 mmol) was added to a solution of *(S)-3-[(tert-butyldimethylsilyl)oxy]-pyrrolidine-2-thione* (**142**) (200 mg, 0.87 mmol) in dry CH_2Cl_2 (10 mL), and the reaction stirred for 3 h at rt under N_2. The mixture was then washed with sat. aqueous $NaHCO_3$ solution (40 mL), the organic layer separated and the aqueous layer washed with CH_2Cl_2 (3 x 20 mL). The combined organic washings were dried over Na_2SO_4, and the solvent removed *in vacuo* to yield the *title compound* as an orange oil (236 mg, 90%).

δ_H (400 MHz; $CDCl_3$): 4.71 (1H, apparent t, *J* 7.6, C*H*-OTBS), 3.90 (1H, d, *J* 16.0, one of CH_2S), 3.88 – 3.82 (1H, m, one of CH_2N), 3.68 (1H, d, *J* 16.0, one of CH_2S), 3.62 (3H, s, CO_2CH_3), 3.55 (1H, apparent dt, *J* 14.7 & 7.2, one of CH_2N), 2.24 (1H, dddd, *J* 12.7, 7.6, 7.4 & 2.5, one of CH_2CH-OTBS), 1.74 (1H, apparent dq, *J* 12.7 & 8.1, one of CH_2CH-OTBS), 0.80 (9H, s, (CH_3)$_3$C), 0.04 (3H, s, CH_3-Si) and 0.00 (3H, s, CH_3-Si).

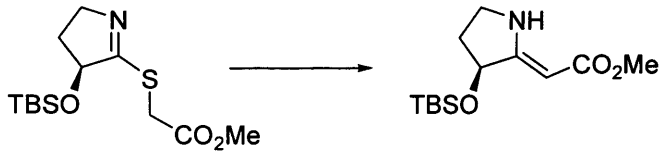
δ_C (125 MHz; $CDCl_3$): 175.9 (imine *C*=N), 169.4 (ester *C*=O), 79.6 (*C*H-OTBS), 57.5 (*C*H_2S), 52.7 (CO_2CH_3), 34.6 (*C*H_2N=C), 32.8 (*C*H_2CH-OTBS), 25.7 ((*C*H_3)$_3$C), 18.1 ((CH$_3$)$_3$*C*), -4.7 (*C*H_3Si) and -5.0 (*C*H_3Si).

IR (neat): 2953, 2858, 1744, 1598, 1471, 1436, 1362, 1300 and 1255 cm^{-1}.

MS-AP: *m/z* (%): 304 (MH^+, 100).

HRMS-AP: *m/z* $[MH]^+$: found: 304.1389; $C_{13}H_{26}NO_3SiS$ requires 304.1403.

(*Z*)-Methyl 2-[(*S*)-3-((*tert*-butyldimethylsilyl)oxy)pyrrolidin-2-ylidene]acetate (149)



148 **149**

Methyl 2-[(S)-4,5-dihydro-3-((tert-butyldimethylsilyl)oxy)-3H-pyrrol-2-ylthio]acetate (**148**) (220 mg, 0.73 mmol) was dissolved in dry xylene (15 mL), potassium *tert*-butoxide (12 mg, 0.11 mmol) added and the resulting suspension stirred at rt for 15 min under N_2. Triphenylphosphine (761 mg, 2.90 mmol) was then added, and the mixture stirred at reflux for 48 h. The mixture was quenched with sat. aqueous $NaHCO_3$ solution (20 mL) and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (3 x 20 mL), the organic layers combined, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting solid was purified by flash column chromatography (CH_2Cl_2 → EtOAc), affording the *title compound* (152 mg, 77%) as an orange crystalline solid.

Mp: 60 – 64 °C.

δ_H (400 MHz; $CDCl_3$): 7.54 (1H, broad s, N*H*), 4.55 (1H, apparent t, *J* 7.6, C*H*-OTBS), 4.51 (1H, broad s, C*H*=C), 3.51 (3H, s, CO_2CH_3), 3.43 (1H, m, one of CH_2NH), 3.26 (1H, m, one of CH_2NH), 2.09 (1H, m, one of CH_2CH_2NH), 1.75 (1H, m, one of CH_2CH_2NH), 0.70 (9H, s, $(CH_3)_3C$), 0.00 (3H, s, one of CH_3Si) and -0.02 (3H, s, one of CH_3Si).

δ_C (125 MHz; $CDCl_3$): 171.2 (CH=*C*), 166.7 (ester *C*=O), 76.6 (*C*H=C), 74.1 (*C*H-OTBS), 50.1 (CO_2CH_3), 44.0 (CH_2NH), 32.8 (CH_2CH-OTBS), 25.8 ($(CH_3)_3C$), 18.1 ($(CH_3)_3C$), -4.7 (One of CH_3Si) and -4.8 (One of CH_3Si).

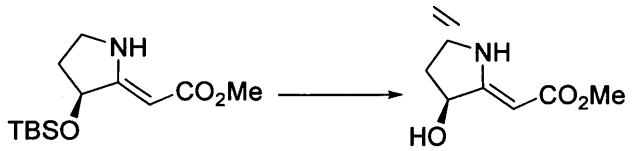
IR (solution in CH_2Cl_2): 3362, 1665, 1464 and 1365 cm^{-1}.

$[\alpha]_D$: -6° (*c* = 1, CH_2Cl_2).

MS-ES: *m/z* (%): 272 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 272.1671; $C_{13}H_{26}NO_3Si$ requires 272.1676.

(*Z*)-Methyl 2-((*S*)-3-hydroxypyrrolidin-2-ylidene)acetate (150)



149 **150**

TBAF (1 M solution in THF; 1.18 mL) was added to a solution of *(Z)-Methyl 2-[(S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-2-ylidene]acetate* (**149**) (152 mg, 0.56 mmol) in THF (8 mL), and the reaction stirred at rt for 40 min. The excess solvent was removed *in vacuo*, and the resulting orange gum purified by column chromatography (eluting with EtOAc-Hexane, 1:1), early fractions (R_f 0.32) affording the *title compound* as a pale yellow solid (75 mg, 85%).

Mp: 37 – 39 °C.

δ_H (400 MHz; $CDCl_3$): 7.53 (1H, broad s, N*H*), 4.65 (1H, broad s, C*H*=C), 4.61 (1H, apparent t, *J* 6.7, C*H*-OH), 3.58 (3H, s, CO_2CH_3), 3.54 (1H, one of CH_2NH), 3.37 (1H, apparent dt, *J* 10.0 & 6.9, one of CH_2NH), 2.73 (1H, broad s, O*H*), 2.21 (1H, m, one of CH_2CH_2NH) and 1.86 (1H, m, one of CH_2CH_2NH).

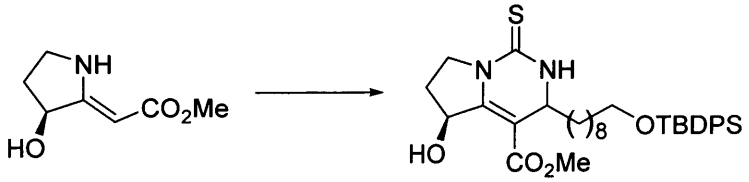
δ_C (125 MHz; $CDCl_3$): 170.4 (CH=*C*), 165.54 (ester *C*=O), 75.7 (*C*H-OH), 72.9 (*C*H=C), 49.4 (CO_2CH_3), 43.5 (CH_2NH) and 31.1 (CH_2CH_2NH).

$[\alpha]_D$: -22° (*c* = 1, CH_2Cl_2).

MS-ES: *m/z* (%): 158 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 158.0810; $C_7H_{12}NO_3$ requires 158.0812.

(5*S*)-Methyl 1,2,3,5,6,7-hexahydro-5-hydroxy-3-(9-*tert*-butyldiphenylsilyloxynonyl)-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (153)



150 **153**

Trimethylsilyl isothiocyanate (62 µL, 0.45 mmol) was added to a solution of *10-((tert-butyldiphenylsilyl)oxy decanal* (**152**) (183 mg, 0.45 mmol) in dry CH_2Cl_2 (3 mL) under N_2, and the resulting brown solution stirred for 30 min at rt. A solution of *(Z)-Methyl 2-((S)-3-hydroxypyrrolidin-2-ylidene)acetate* (**150**) (70 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) was then added, and the reaction stirred for 3 h. The reaction was quenched with ~0.1 M aqueous NaOH solution (20 mL) and the layers separated. The aqueous layer was washed with CH_2Cl_2 (3 x 25 mL), the combined organic layers dried with Na_2SO_4 and the solvent removed *in vacuo*. The resulting orange gum was purified by column chromatography (eluting with EtOAc-Hexane, 1:2.5) mid-fractions (R_f 0.55) affording the *title compound* (79 mg, 29%) as a yellow gum (*single diastereoisomer*).

δ_H (500 MHz; $CDCl_3$): 7.70 – 7.55 (4H, m, aromatic C*H*), 7.41 – 7.28 (6H, m, aromatic C*H*), 6.99 (1H, broad s, N*H*), 5.20 (1H, broad s, O*H*), 5.10 (1H, apparent t, *J* 8.0, C*H*-OH), 4.24 (1H, apparent dt, *J* 7.8 & 3.8, C*H*-NH), 4.06 (1H, ddd, *J* 11.6, 8.8 & 3.3, one of CH_2N-CS), 3.89 (1H, ddd, *J* 11.6, 9.0 & 8.0, one of CH_2N-CS), 3.65 (3H, s, CO_2CH_3), 3.58 (2H, t, *J* 6.5, CH_2OTBDPS), 2.40 – 2.33 (1H, m, one of CH_2CH-OH), 2.0 – 1.95 (1H, m, one of CH_2CH-OH), 1.54 – 1.40 (6H, m, 3 x alkyl CH_2 protons) and 1.36 – 1.10 (19H, m, 5 x alkyl CH_2 protons & ((CH_3)$_3$C).

δ_C (125 MHz; $CDCl_3$): 175.3 (thiourea *C*=S), 166.2 (ester *C*=O), 153.2 (*C*=C-CO_2Me), 139.8 (aromatic *C*), 134.6 (aromatic *C*H), 128.5 (aromatic *C*H), 126.6 (aromatic *C*H), 99.6 (C=*C*-CO_2Me), 71.2 (*C*H-OH), 63.0 (*C*H_2OTBDPS), 51.15 (CO_2CH_3), 50.9 (*C*H-NH), 48.7 (*C*H_2N-C=S), 36.1 (pyrrolidine *C*H_2CH-OH),

31.6 (CH_2CH-NH), 28.8 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 25.9 ((CH_3)$_3C$), 24.8 (CH_2), 23.0 (CH_2) and 18.2 ((CH_3)$_3C$).

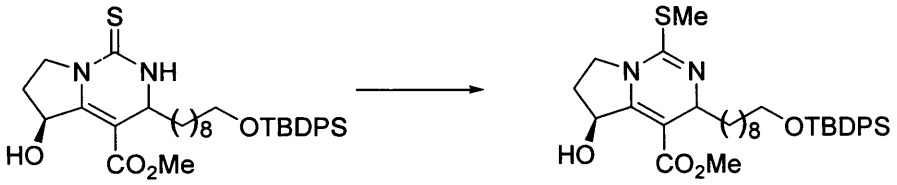
IR (solution in CH_2Cl_2): 3401, 3205, 2883, 1675, 1629, 1531, 1462, 1416, 1324 and 1255 cm^{-1}.

$[\alpha]_D$: -16° (*c* = 1, CH_2Cl_2).

MS-ES: *m/z* (%): 609 (MH^+, 25), 279 (100).

HRMS-ES: *m/z* $[MH]^+$: found: 609.3196; $C_{34}H_{49}N_2O_4SiS$ requires 609.3182.

(5*S*)-Methyl 3-(9-*tert*-butyldiphenylsilyloxynonyl)-3,5,6,7-tetrahydro-5-hydroxy-1-(methlthio)pyrrolo[1,2-*c*]pyrimidine-4-carboxylate (157)



153 **157**

(5S)-Methyl 1,2,3,5,6,7-hexahydro-5-hydroxy-3-(9-tert-butyldiphenylsilyloxynonyl)-1-thioxopyrrolo[1,2-c]pyrimidine-4-carboxylate (**153**) (21 mg, 0.035 mmol) was dissolved in dry CH_2Cl_2 (10 mL), methyl iodide (43 µL, 0.69 mmol) added and the resultant orange solution stirred at reflux under N_2 for 16 h. The reaction was allowed to cool to rt, dry triethylamine (96 µL, 0.69 mmol) added and the reaction stirred for 30 min. The volatiles were then removed *in vacuo*, and the subsequent solid was washed with hexane (30 mL) and removed *via* gravity filtration. The filtrate was concentrated *in vacuo* to produce an orange oil, which was purified by flash column chromatography (eluting with EtOAc-Hexane, 1:1.5; R_f 0.95), affording the title compound as an orange gum (19.6 mg, 91%).

δ_H (500 MHz; $CDCl_3$): 7.70 – 7.55 (4H, m, aromatic C*H*), 7.41 – 7.28 (6H, m, aromatic C*H*), 5.73 (1H, broad s, O*H*), 5.10 (1H, apparent t, *J* 8.4, C*H*-OH), 4.66 – 4.54 (1H, m, C*H*-N=C), 3.81 – 3.72 (1H, m, one of pyrrolidine CH_2N-C=N), 3.66

(3H, s, CO_2CH_3), 3.58 (2H, t, *J* 6.2, CH_2OTBDPS), 3.40 – 3.30 (1H, m, one of pyrrolidine CH_2N-C=N), 2.46 – 2.21 (4H, m, one of pyrrolidine CH_2CH-OH & S-CH_3), 2.03 – 1.87 (1H, m, one of pyrrolidine CH_2CH-OH), 1.55 – 1.42 (6H, m, 3 x alkyl CH_2 protons) and 1.32 – 1.04 (19H, m, 5 x alkyl CH_2 protons & $(CH_3)_3C$).

δ_C (125 MHz; $CDCl_3$): 168.1 (ester *C*=O), 155.1 (*C*=C-CO_2Me), 145.5 (MeS-*C*=N), 139.1 (aromatic *C*), 134.6 (aromatic *C*H), 128.5 (aromatic *C*H), 126.5 (aromatic *C*H), 95.9 (C=*C*-CO_2Me), 70.4 (*C*H-OH), 63.0 (CH_2OTBDPS), 54.9 (*C*H-N=C), 50.6 (CO_2CH_3), 45.3 (pyrrolidine CH_2N-C=N), 36.3 (pyrrolidine CH_2CH-OH), 31.6 (CH_2CH-N=C), 28.9 (CH_2), 28.72 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 25.9 ($(CH_3)_3C$), 24.8 (CH_2), 23.6 (CH_2), 21.7 (CH_2), 19.0 ($(CH_3)_3C$) and 13.1 (S-CH_3).

IR (solution in CH_2Cl_2): 2850, 1673, 1628, 1544, 1466 and 1420 cm^{-1}.

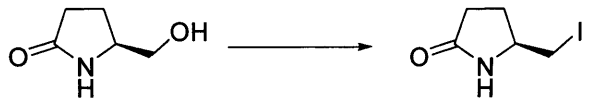
$[\alpha]_D$: -8° (*c* = 0.5, CH_2Cl_2).

MS-AP: *m/z* (%): 623 (MH^+, 100).

HRMS-AP: *m/z* $[MH]^+$: found: 623.3315; $C_{35}H_{51}N_2O_4SiS$ requires 623.3339.

6.4. Experimental Data for Chapter 4

(5*S*)-5-(Iodomethyl)pyrrolidin-2-one[82] (168)

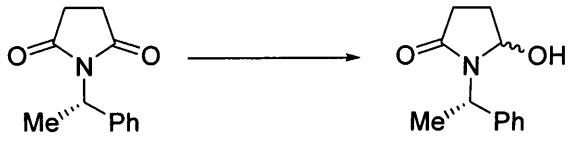


168

Iodine (1.347 g, 5.31 mmol) was added to a solution of triphenylphosphine (1.390g, 5.31 mmol) in dry CH_2Cl_2 (10 mL), and the reaction stirred at rt for 15 min under N_2. Imidazole (0.410 g, 6.03 mmol) and a solution of *(S)-5-(hydroxymethyl)pyrrolidin-2-one* (0.275 g, 2.41 mmol) in CH_2Cl_2 (5 mL) were added, and the reaction stirred at reflux for 3 h. The reaction was then quenched with sat. aqueous sodium thiosulphate solution (20 mL) and the layers separated. The aqueous phase was washed with EtOAc (3 x 40 mL), and the organic layers were combined and dried with $MgSO_4$. The solvent was removed *in vacuo* to give a yellow oil, which was purified by column chromatography (eluting with EtOAc – 1% triethylamine-EtOAc), late fractions (R_f 0.21) affording the *title compound* (373 mg, 69%) as a colourless oil which crystallised on standing.

δ_H (500 MHz; $CDCl_3$): 3.77 (1H, apparent quintet, *J* 5.9, C*H*-NH), 3.18 (2H, d, *J* 6.1, CH_2I), 2.43 – 2.36 (1H, m, one of CH_2C=O), 2.32 – 2.23 (2H, m, one of CH_2C=O & one of CH_2CH-NH) and 1.80 – 1.73 (1H, m, one of CH_2CH-NH).

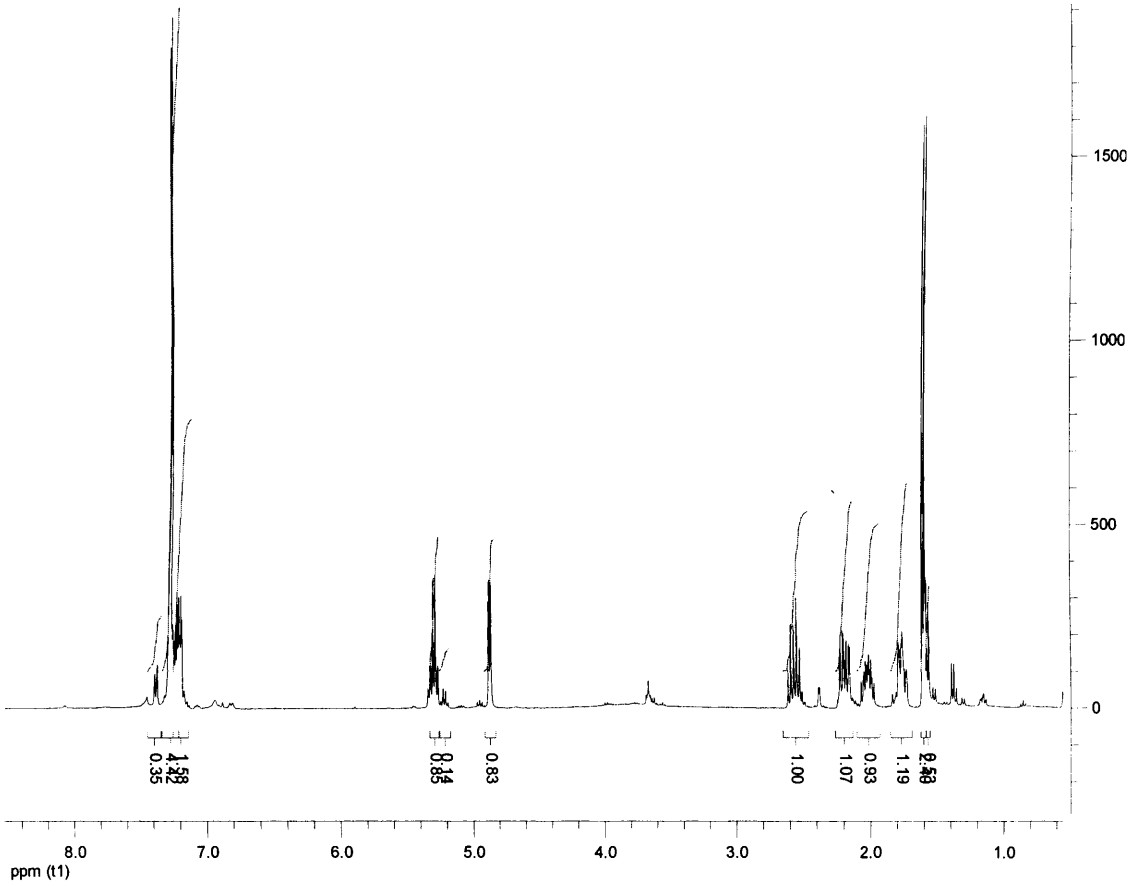
5-Hydroxy-2-((*S*)-1-phenylethyl)pyrrolidin-2-one[83] (186)



185 **186**

$LiEt_3BH$ (1.0 M sol. in THF; 68.2 mL, 68.2 mmol) was added dropwise to a solution of *1-((S)-1-phenylethyl)pyrrolidine-2,5-dione* (**185**) (8.94 g, 48 mmol) in dry THF (80 mL) at -78 °C under N_2, and the resultant mixture stirred for 40 min. The excess THF was then removed *in vacuo*, and the residue cooled to 0 °C. The reaction was quenched by the dropwise addition of sat. aqueous $NaHCO_3$ solution (70 mL). CH_2Cl_2 (50 mL) was added, the layers separated, and the aqueous layer washed with further portions of CH_2Cl_2 (3 x 40 mL). The combined organic layers were treated with a few drops of hydrogen peroxide solution (30%), washed with brine (50 mL) and dried over Na_2SO_4. The volatiles were then removed *in vacuo* to yield the *title compound* (**d.r.** ~6:1; 8.486 g, 94%) as a pale yellow solid.

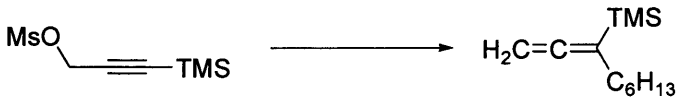
^{1}H NMR spectrum of compound **186** (400 MHz; $CDCl_3$).



δ_H (400 MHz; $CDCl_3$): 7.39 – 7.19 (5H, m, aromatic C*H*), 5.28 (1H, q, *J* 7.3, C*H*-Me *major diastereoisomer*), 5.23 (1H, q, *J* 7.2, C*H*-Me *minor*), 4.86 (1H, apparent dd, *J* 6.3 & 1.2, C*H*-OH), 2.57 (1H, apparent dt, *J* 17.2 & 8.7, one of CH_2C=O), 2.19 (1H, ddd, *J* 17.2, 9.8 & 2.8, one of CH_2C=O), 2.07 – 1.97 (1H, m, one of CH_2CH-OH), 1.82 – 1.73 (1H, m, one of CH_2CH-OH) and 1.60 (3H, d, *J* 7.2, CH_3-CH).

$[\alpha]_D$: -96° (*c* = 1, EtOH). *Lit.*[83] *data* ((*R*)-hydroxy lactam): +112.46° (*c* = 1, EtOH).

Trimethyl(nona-1,2-dien-3-yl)silane (188)



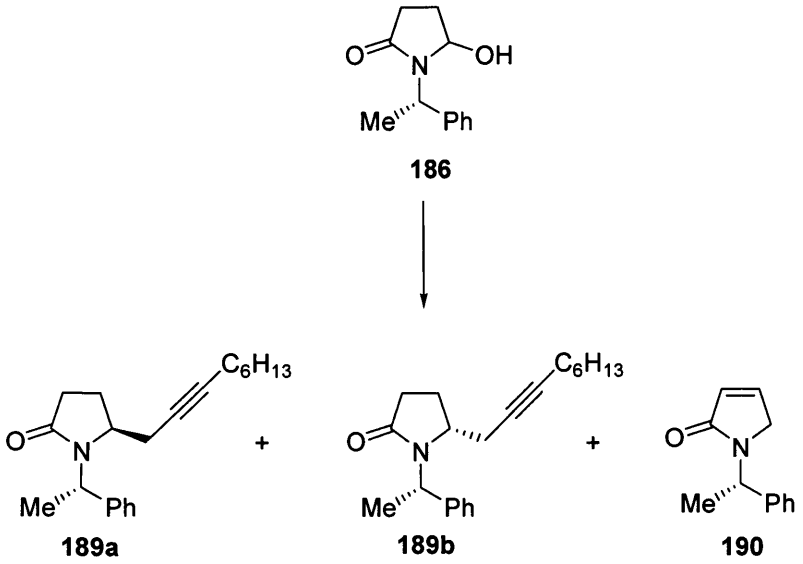
188

Lithium bromide (601mg, 6.92 mmol) was added to a suspension of copper(I) bromide (993 mg, 6.92 mmol) in dry THF (20 mL) under N_2, and the mixture stirred until a green colour was obtained. The reaction was cooled to -78 °C, and hexylmagnesiumbromide (2.0 M sol. in Et_2O; 3.46 mL, 6.92 mmol) added dropwise. The resulting dark yellow solution was stirred for 2 h, and a solution of *3-(trimethylsilyl)prop-2-ynyl methanesulphonate* (1.299 g, 6.30 mmol) in THF (3 mL) added dropwise. The subsequent brown mixture was allowed to warm to rt overnight. The reaction was then quenched with sat. aqueous NH_4Cl solution (25 mL), the layers separated and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic washings were dried over Na_2SO_4, and the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (eluting with Hexane; R_f 0.98), producing the *title compound* as a colourless oil (803 mg, 65%).

δ_H (400 MHz; $CDCl_3$): 4.22 (2H, t, *J* 3.3, H_2C=C=C-TMS), 1.84 (2H, apparent tt, *J* 6.7 & 3.3, H_2C=C=C-CH_2CH_2), 1.36 (2H, qnt, *J* 7.3, H_2C=C=C-CH_2CH_2), 1.24 – 1.18 (6H, m, 3 x alkyl CH_2 protons), 0.79 (3H, t, *J* 6.8, CH_3CH_2-alkyl) and 0.00 (9H, s, ((CH_3)$_3$Si).

δ_c (125 MHz; $CDCl_3$): 219.0 (H_2C=*C*=C), 96.3 (H_2C=C=*C*), 70.3 (H_2*C*=C=C), 33.4 (CH_2CH_2-C=C=CH_2), 32.3 (*C*H_2), 31.4 (*C*H_2), 30.8 (*C*H_2), 24.4 (CH_3CH_2-alkyl), 15.8 (*C*H_3CH_2-alkyl) and 0.00 ((*C*H_3)$_3$Si).

(5*S*)-5-(Non-2-ynl)-1-((*S*)-1-phenylethyl)pyrrolidin-2-one (189a), (5*R*)-5-(non-2-ynl)-1-((*S*)-1-phenylethyl)pyrrolidin-2-one (189b) and 1-((*S*)-1-phenylethyl)-1*H*-pyrrol-2(5*H*)-one (190)



5-hydroxy-2-((S)-1-phenylethyl)pyrrolidin-2-one (**186**) (824 mg, 4.02 mmol) was dissolved in dry CH_2Cl_2 (45 mL) at -78 °C under N_2. Tin(IV) chloride (1.11 mL, 6.02 mmol) and a solution of *trimethyl(nona-1,2-dien-3-yl)silane* (2.366g, 12.05 mmol) in CH_2Cl_2 (4 mL) were then added. The resulting yellow suspension was allowed to warm slowly to rt, and stirred at that temperature for 18 h. The reaction mixture was then quenched with dropwise addition of sat. aqueous $NaHCO_3$ solution (40 mL), the organic layer separated and the aqueous layer washed with CH_2Cl_2 (3 x 35 mL). The combined organic layers were dried over $MgSO_4$, and the solvent removed *in vacuo*. The subsequent dark orange oil (**189a:189b**=2.5:1) was purified by column chromatography (eluting with EtOAc-Hexane, 1:4), affording, in order of elution, *title compounds* **189a/189b** and **190**.

(5*S*)-5-(Non-2-ynl)-1-((*S*)-1-phenylethyl)pyrrolidin-2-one (189a) and (5*R*)-5-(non-2-ynl)-1-((*S*)-1-phenylethyl)pyrrolidin-2-one (189b) (pale yellow oil): (563 mg, 45%; R_f 0.26):

δ_H (400 MHz; $CDCl_3$): 7.39 – 7.24 (5H, m, aromatic C*H*), 5.44 (**189b**; 0.44 H, q, *J* 7.1, C*H*-Me), 5.36 (**189a**; 1H, q, *J* 7.7, C*H*-Me), 3.74 – 3.69 (**189b**; 1H, m, C*H*-N), 3.29 – 3.24 (**189a**; 0.44 H, m, C*H*-N *minor*), 2.62 – 2.45 (1H, m, one of CH_2C=O), 2.40 – 2.23 (1H, m, one of CH_2C=O), 2.12 – 1.95 (2H, m, CH_2C≡C), 1.89 – 1.81 (1H, m, one of CH_2C≡C), 1.62 (1H, apparent dd, *J* 13.3 & 5.9, one of CH_2C≡C), 1.56 (3H, d, *J* 7.2, CH_3-CH), 1.43 – 1.38 (1H, m, one of CH_2CH_2C=O), 1.37 – 1.31 (1H, m, one of CH_2CH_2C=O), 1.28 – 1.12 (8H, m, 4 x alkyl CH_2 protons) and 0.81 (3H, t, *J* 6.9, CH_3CH_2-alkyl).

δ_C (125 MHz; $CDCl_3$): 175.4 (lactam *C*=O), 141.5 (aromatic *C*), 128.7 (aromatic *C*H), 127.6 (aromatic *C*H), 127.4 (aromatic *C*H), 77.4 (*C*≡C), 75.6 (C≡*C*), 55.8 (pyrrolidine *C*H-N), 49.3 (*C*H-Ph), 31.3 (CH_2C=O), 31.0 (CH_2*C*≡C), 30.8 (CH_2*C*≡C), 28.8 (CH_2), 28.6 (CH_2), 25.1 (pyrrolidine CH_2CH-N), 24.6 (CH_2), 22.6 (CH_3CH_2-alkyl), 18.7 (CH_3-CH) and 14.1 (CH_3CH_2-alkyl).

IR (neat): 2930, 1687, 1496, 1413 and 1278 cm^{-1}.

$[\alpha]_D$: -12° (*c* = 1, CH_2Cl_2).

MS-ES: *m/z* (%): 312 (MH^+, 92); 623 ($2M+H^+$, 100).

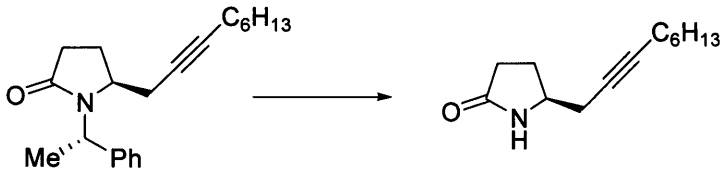
HRMS-ES: *m/z* $[MH]^+$: found: 312.2317; $C_{21}H_{30}NO$ requires 312.2327.

1-((*S*)-1-phenylethyl)-1*H*-pyrrol-2(5*H*)-one (190; dark orange oil): (391 mg, 52%):

δ_H (400 MHz; $CDCl_3$): 7.36 – 7.24 (5H, m, aromatic C*H*), 6.94 (1H, apparent d, *J* 5.9, CO-C*H*=CH), 6.07 (1H, apparent d, *J* 5.9, CO-CH=C*H*), 5.47 (1H, q, *J* 7.1, C*H*-Me), 3.87 (1H, apparent d, *J* 20.4, one of CH_2N), 3.54 (1H, apparent d, *J* 20.4, one of CH_2N) and 1.61 (3H, d, *J* 7.2, C*H*-Me).

δ_C (100 MHz; $CDCl_3$): 171.0 (*C*=O), 142.8 (CO-*C*H=CH), 141.0 (aromatic *C*), 128.7 (aromatic *C*H), 128.0 (CO-CH=*C*H), 127.5 (aromatic *C*H), 127.0 (aromatic *C*H), 48.9 (CH_2N), 48.6 (*C*H-Me) and 17.8 (CH_3-CH).

(5*S*)-5-(Non-2-ynl)pyrrolidin-2-one (191)



189a **191**

Note: only the major diastereoisomer is reported.

(5S)-5-(non-2-ynl)-1-((S)-1-phenylethyl)pyrrolidin-2-one (**189a**) (1.13g, 3.63 mmol) was dissolved in liquid ammonia-THF-absolute EtOH (4:1:1; 90 mL), and the resulting yellow solution cooled to -78 °C. Sodium chunks (836 mg, 36.3 mmol) were then added portion-wise, until the blue colour had persisted for longer than 3 min. The reaction was then allowed to warm to rt for 30 min (until the mixture had turned colourless), and solid NH_4Cl (763 mg, 14.5 mmol) added. The ammonia was allowed to evaporate, water (20 mL) and EtOAc (30 mL) added, and the layers separated. The aqueous layer was then washed with EtOAc (3 x 30 mL), the combined organic layers dried over Na_2SO_4 and the excess solvent removed *in vacuo*. The *title compound* was afforded (751 mg, 100%) as a pale yellow oil.

δ_H ($CDCl_3$; 400 MHz): 6.70 (1H, broad s, N*H*), 3.69 (1H, apparent quintet, *J* 6.2, C*H*-NH), 2.32 – 2.19 (4H, m, CH_2C=O & CH_2C≡C), 2.08 – 2.03 (2H, m, CH_2C≡C), 1.81 – 1.72 (1H, m, one of pyrrolidine CH_2CH-NH), 1.55 – 1.52 (1H, m, one of pyrrolidine CH_2CHNH), 1.40 (2H, quintet, *J* 7.3, C≡C-$CH_2CH_2CH_2$), 1.30 – 1.15 (6H, m, 3 x alkyl CH_2) and 0.82 (3H, t, *J* 6.9, CH_3CH_2-alkyl).

δ_C ($CDCl_3$; 125 MHz): 176.9 (lactam *C*=O), 82.0 (*C*≡C), 74.4 (C≡*C*), 52.6 (*C*H-NH), 30.3 (CH_2C=O), 29.3 (CH_2C≡C), 27.9 (CH_2C≡C), 27.6 (CH_2), 25.7 (CH_2), 25.3 (pyrrolidine CH_2CH-NH), 21.6 (CH_2), 17.8 (CH_3CH_2-alkyl) and 13.0 (CH_3CH_2-alkyl).

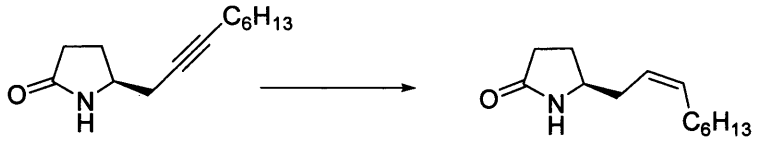
IR (neat): 3240, 2956, 2928, 1699, 1462, 1424, 1379, 1346 and 1302 cm^{-1}.

$[\alpha]_D$: -4° (*c* = 0.5, CH_2Cl_2).

MS-ES: *m/z* (%): 208 (MH^+, 68); 249 (M+MeCN, 100).

HRMS-EI: *m/z* $[M]^+$: found: 207.1625; $C_{13}H_{21}NO$ requires 207.1623.

(5*S*)-5-((*Z*)-Non-2-enyl)pyrrolidin-2-one (192)



191 **192**

Sodium borohydride (51 mg, 1.35 mmol) was added to a solution of $Ni(OAc)_2$ (291 mg, 1.2 mmol) in abs. EtOH (20 mL), and the resulting solution stirred for 15 min at rt under N_2. $NH_2(CH_2)_2NH_2$ (60 µL, 0.8 mmol) was added, the mixture stirred for 5 min and a solution of *(5S)-5-(non-2-ynl)pyrrolidin-2-one* (**191**) (185 mg, 0.8 mmol) in abs. EtOH (3 mL) added. The atmosphere in the flask was then evacuated and purged with H_2. The reaction was then stirred under a hydrogen atmosphere for 16 h. The resulting purple suspension was quenched with sat. aqueous $NaHCO_3$ solution (15 mL) and EtOAc (20 mL). The organic layer was separated, and the aqueous layer washed with EtOAc (3 x 20 mL). The combined organic washings were then dried over Na_2SO_4 and the excess solvent removed *in vacuo*. The *title compound* was afforded (181 mg, 97%) as a yellow oil.

δ_H (400 MHz; $CDCl_3$): 5.55 (1H, broad s, N*H*), 5.58 – 5.37 (1H, m, one of C*H*=CH), 5.19 – 5.13 (1H, m, one of CH=C*H*), 3.51 (1H, apparent quintet, *J* 6.7, C*H*-NH), 2.24 – 2.10 (4H, m, CH_2C=O & CH_2C=C), 1.90 – 1.83 (3H, m, CH_2C=C & one of pyrrolidine CH_2CHNH), 1.64 – 1.57 (1H, m, one of pyrrolidine CH_2CHNH), 1.22 – 1.07 (8H, m, 4 x CH_2 protons) and 0.73 (3H, t, *J* 6.9, CH_3CH_2-alkyl).

δ_C (125 MHz; $CDCl_3$): 178.5 (lactam *C*=O), 133.5 (*C*H=CH), 123.7 (CH=*C*H), 54.5 (*C*H-NH), 34.2 (CH_2C=O), 31.7 (CH_2C=C), 30.363 (CH_2C=C), 29.5 (CH_2), 28.9 (CH_2), 27.4 (CH_2), 26.5 (pyrrolidine CH_2CH_2C=O), 22.6 (CH_3CH_2-alkyl) and 14.1 (CH_3CH_2-alkyl).

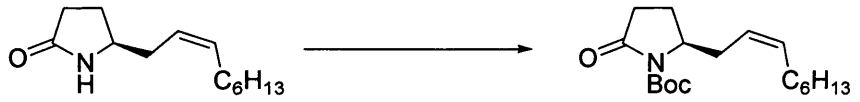
IR (neat): 3221, 2854, 1687, 1624 and 1456 cm^{-1}.

$[\alpha]_D$: -14°(*c* = 1, CH_2Cl_2).

MS-ES: *m/z* (%) = 210 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 210.1849; $C_{13}H_{24}NO$ requires 210.1858.

(5*S*)-*tert*-Butyl 2-((*Z*)-non-2-enyl)-5-oxopyrrolidine-1-carboxylate (193)



192 **193**

Triethylamine (0.12 mL, 0.87 mmol) and DMAP (*catalytic*, 5 mg) were added to a solution of *(5S)-5-((Z)-non-2-enyl)pyrrolidin-2-one* (**192**) (120 mg, 0.58 mmol) in dry CH_2Cl_2 (15 mL) under N_2. A solution of di-*tert*-butyl dicarbonate (138 mg, 0.63 mmol) in CH_2Cl_2 (6 mL) was added dropwise, and the resulting dark orange solution stirred for 17 h. The reaction was then quenched with sat. aqueous $NaHCO_3$ solution (35 mL), the layers separated and the aqueous layer washed with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting orange solid was purified by flash column chromatography (EtOAc; R_f 0.95), affording the *title compound* (167 mg, 94%) as an orange oil.

δ_H (400 MHz; $CDCl_3$): 5.46 – 5.41 (1H, m, one of C*H*=CH), 5.29 – 5.24 (1H, m, one of CH=C*H*), 4.13 – 4.05 (1H, m, C*H*-NBoc), 2.53 – 2.44 (1H, m, one of CH_2C=O), 2.38 – 2.24 (2H, m, one of CH_2C=O & one of CH_2C=C), 2.19 (1H, apparent dt, *J* 14.0 & 7.9, one of CH_2C=C), 2.06 – 1.96 (1H, m, one of pyrrolidine CH_2CH-NBoc), 1.93 (2H, apparent q, *J* 7.1, CH_2C=C), 1.78 – 1.72 (1H, m, one of pyrrolidine CH_2CH-NBoc), 1.46 (9H, s, $((CH_3)_3C)$, 1.28 – 1.07 (8H, m, 4 x alkyl CH_2 protons) and 0.81 (3H, t, *J* 6.9, CH_3CH_2-alkyl).

δ_C (100 MHz; $CDCl_3$): 173.4 (lactam *C*=O), 148.9 (carbamate *C*=O), 134.3 (*C*H=CH), 123.1 (CH=*C*H), 81.6 ($(CH_3)_3C$), 56.8 (*C*H-NBoc), 35.9 (CH_2C=O), 31.7 (CH_2C=C), 30.7 (CH_2C=C), 28.4 (CH_2), 27.9 (CH_2), 27.1 ($(CH_3)_3C$), 26.5

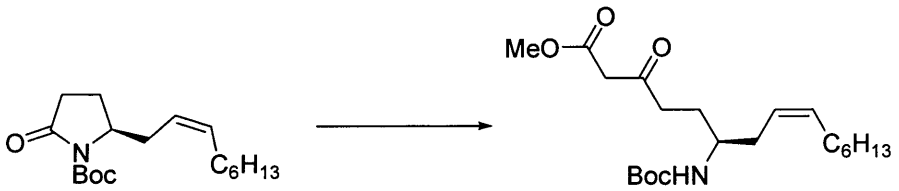
(CH_2), 21.7 (pyrrolidine CH_2CHN-Boc), 20.6 (CH_3CH_2-alkyl) and 13.1 (CH_3CH_2-alkyl).

$[\alpha]_D$: -6° (*c* = 1, CH_2Cl_2).

IR (neat): 2931, 2872, 1784, 1749, 1708, 1461, 1361 and 1296 cm^{-1}.

HRMS-AP: *m/z* $[2MH + NH_4]^+$: found: 636.4944; $C_{36}H_{66}N_3O_6$ requires 636.4952.

tert-Butyl (*S*,*Z*)-1-(methoxycarbonyl)-2-oxotetradec-7-en-5-ylcarbamate (194)



193 **194**

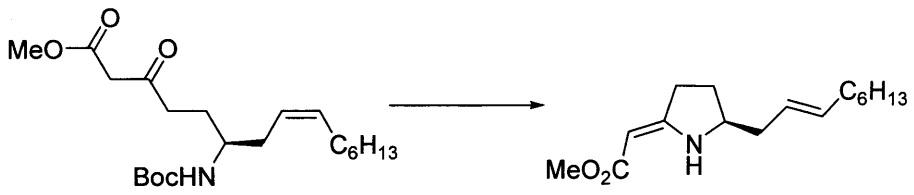
n-Butyl lithium (2.5M solution in hexanes; 0.86 mL, 2.14 mmol) was added to a solution of diisopropylamine (0.3 mL, 2.14 mmol) in dry THF (5 mL) at 0 °C, and the resulting pale yellow mixture stirred for 30 min under N_2. The reaction was then cooled to -78 °C, and a solution of dry methyl acetate (0.17 mL, 2.14 mmol) in THF (1 mL) added dropwise. The reaction was stirred for a further 30 min, and a solution of *(5S)-tert-butyl 2-((Z)-non-2-enyl)-5-oxopyrrolidine-1-carboxylate* (**193**) (130 mg, 0.43 mmol) in THF (3 mL) added dropwise. The resultant pale orange solution was then allowed to warm slowly to rt (gradual darkening in colour) over 17 h. The reaction was quenched with sat. aqueous NH_4Cl solution (20 mL), and the layers separated. The aqueous layer was washed with CH_2Cl_2 (3 x 30 mL), and the organic washings combined, washed with brine (40 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford a viscous orange oil (150 mg, 93% crude yield).

δ_H (500 MHz; $CDCl_3$): 5.44 (1H, apparent dt, *J* 10.9 & 7.3, one of C*H*=CH), 5.27 (1H, apparent dt, *J* 10.9 & 7.5, one of CH=C*H*), 4.35 (1H, apparent d, *J* 8.5, N*H*-Boc), 3.66 (3H, s, CO_2CH_3), 3.54 – 3.47 (1H, m, C*H*-NHBoc), 3.39 (2H, s,

CO-CH_2-CO), 2.57 – 2.52 (2H, m, CO-CH_2CH_2), 2.23 – 2.15 (1H, m, one of CH_2C=C), 2.11 – 2.04 (1H, m, one of CH_2C=C), 1.94 (2H, apparent q, *J* 7.1, CH_2C=C), 1.80 – 1.72 (1H, m, one of CH_2CH$_2$CO), 1.58 – 1.52 (1H, m, one of CH_2CH$_2$CO), 1.36 (9H, s, ((CH_3)$_3$COCO), 1.30 – 1.15 (8H, m, 4 x alkyl CH_2 protons) and 0.80 (3H, t, *J* 6.9, CH_3CH$_2$-alkyl).

δ_C (100 MHz; CDCl$_3$): 201.5 (ketone *C*=O), 166.6 (ester *C*=O), 154.8 (carbamate *C*=O), 132.3 (*C*H=CH), 123.3 (CH=*C*H), 78.0 ((CH$_3$)$_3$*C*), 51.3 (CO$_2$*C*H$_3$), 49.2 (*C*H-NHBoc), 48.1 (CO-*C*H$_2$-CO), 38.9 (CH$_2$*C*H$_2$CO), 38.8 (*C*H$_2$C=C), 35.0 (*C*H$_2$C=C), 28.7 (*C*H$_2$CH-NH), 28.6 (*C*H$_2$), 28.0 (*C*H$_2$), 27.4 ((*C*H$_3$)$_3$C), 26.4 (*C*H$_2$), 21.6 (CH$_3$*C*H$_2$-alkyl) and 13.1 (*C*H$_3$CH$_2$-alkyl).

(2*Z*)-Methyl 2-((*S*)-5-(non-2-enyl)pyrrolidin-2-ylidene)acetate (195)



194 **195**

tert-Butyl (S,Z)-1-(methoxycarbonyl)-2-oxotetradec-7-en-5-ylcarbamate (**194**) (160 mg, 0.42 mmol) was dissolved in CH_2Cl_2 (1 mL), and triflouroacetic acid (0.13 mL, 1.7 mmol) added. The resultant dark orange oil was stirred at rt for 3 h. The reaction was then quenched with sat. aqueous $NaHCO_3$ solution until pH 7 was reached, and diluted with CH_2Cl_2 (30 mL). The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed in vacuo. The resulting oil was then purified by column chromatography (eluting with EtOAc-Hexane, 1:9), early fractions (R_f 0.51) giving the title compound (140 mg, 81%) as an orange oil (***E*/*Z*** estimated to be 3:1).

δ_H (500 MHz; $CDCl_3$): 7.90 (1H, broad s, N*H*), 5.49 (1H, apparent dt, *J* 15.2 & 6.7, one of C*H*=CH), 5.28 (1H, apparent dt, *J* 15.2 & 7.1, one of CH=C*H*), 4.41 (1H, broad s, C*H*=C-NH), 3.71 (1H, apparent quintet, *J* 6.6, C*H*-NH), 3.57 (3H, m, CO_2CH_3), 2.60 – 2.42 (2H, m, one of pyrrolidine CH_2C=C & one of CH_2C=C), 2.26 – 2.18 (1H, m, one of CH_2C=C), 2.17 – 2.08 (1H, m, one of pyrrolidine CH_2C=C), 1.94 (2H, apparent q, *J* 7.1, CH_2C=C), 1.58 – 1.48 (2H, m, one of pyrrolidine CH_2CH-NH), 1.29 – 1.20 (8H, m, 4 x alkyl CH_2 protons) and 0.81 (3H, t, *J* 6.8, CH_3CH_2-alkyl).

δ_c (125 MHz; $CDCl_3$): 169.8 (ester *C*=O), 168.2 (*C*=CH-CO_2Me), 134.7 (one of *C*H=CH *E-isomer*), 124.7 (one of *C*H=*C*H *E-isomer*), 133.7 (one of CH=*C*H *Z-isomer*), 123.8 (one of *C*H=*C*H *Z-isomer*), 76.0 (C=*C*H-CO_2Me), 59.6 (*C*H-NH), 50.0 (CO_2CH_3), 32.6 (CH_2C=C), 31.9 (pyrrolidine CH_2C=C), 31.8 (CH_2C=C), 29.4 (pyrrolidine CH_2CH-NH), 28.9 (CH_2), 27.7 (CH_2), 27.5 (CH_2), 22.6 (CH_3CH_2-alkyl) and 14.1 (CH_3CH_2-alkyl).

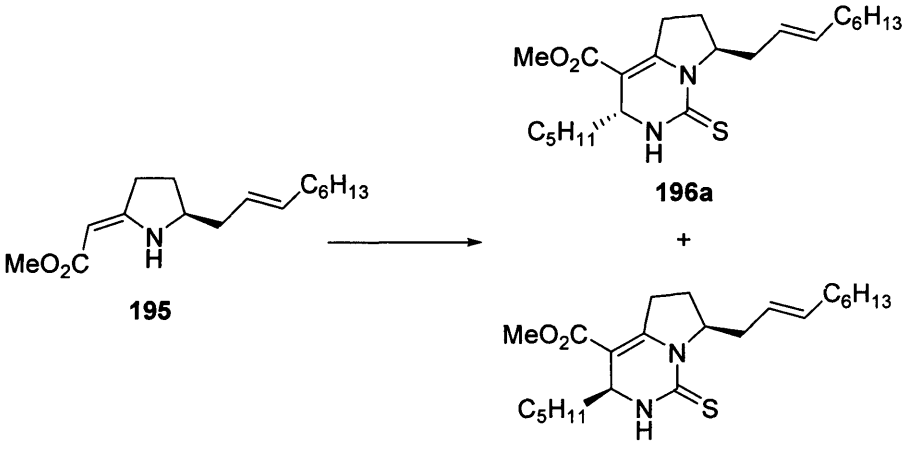
$[\alpha]_D$: -18° (*c* = 1, CH_2Cl_2).

IR (neat): 3420, 2942, 1660 and 1602 cm^{-1}.

MS-ES: *m/z* (%) = 266 (MH^+, 91).

HRMS-ES: *m/z* $[MH]^+$: found: 266.2104; $C_{16}H_{28}NO_2$ requires 266.2115.

(3*R*,7*S*)-Methyl 1,2,3,5,6,7-hexahydro-7-((*E*)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate – major diastereoisomer (196a) and (3*S*,7*S*)-Methyl 1,2,3,5,6,7-hexahydro-7-((*E*)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate – minor diastereoisomer (196b)



Hexanal (100 µL, 0.84 mmol) was added to a solution of trimethylsilyl isothiocyanate (120 µL, 0.84 mmol) in dry CH_2Cl_2 (6 mL), and the resulting orange solution stirred at rt under N_2 for 30 min. A solution of *(2Z)-Methyl 2-((S)-5-(non-2-enyl)pyrrolidin-2-ylidene)acetate* (**195**) (110 mg, 0.42 mmol) in CH_2Cl_2 (4 mL) was added, and the reaction mixture stirred at rt for 45 min. The reaction was then quenched with ~0.1 M aqueous NaOH solution (30 mL) and the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL). The organic washings were combined, dried over Na_2SO_4 and the CH_2Cl_2 removed *in vacuo*. The subsequent yellow gum (**196a:196b**=2.01:1) was purified by column chromatography (eluting with EtOAc-Hexane, 1:9), yielding the *title compound*s, in order of elution:

(3*R*,7*S*)-Methyl 1,2,3,5,6,7-hexahydro-7-((*E*)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**196a**; off-white oil): (231 mg, 58%; R_f 0.5):

δ_H (400 MHz; $CDCl_3$): 6.57 (1H, broad s, N*H*), 5.46 (apparent dt, *J* 15.0 & 6.9, one of C*H*=CH), 5.29 – 5.23 (1H, m, one of CH=C*H*), 4.52 – 4.47 (1H, m, C*H*-NCS), 4.21 – 4.18 (1H, m, C*H*-pentyl), 3.65 (3H, s, CO_2CH_3), 3.32 – 3.24 (1H, m, one of pyrrolidine CH_2C=C), 3.02 – 2.98 (1H, m, one of pyrrolidine CH_2C=C), 2.93 – 2.79 (2H, m, CH_2C=C), 2.19 – 2.07 (1H, m, one of CH_2C=C), 2.04 – 1.99 (1H, m, one of CH_2C=C), 1.94 – 1.84 (2H, m, pyrrolidine CH_2CH-N), 1.63 – 1.44 (2H, m, CH_2CHNH), 1.35 – 1.15 (17H, 7 x CH_2 alkyl protons & CH_3CH_2OCO) and 0.81 (6H, t, *J* 6.9, 2 x CH_3CH_2-alkyl).

δ_C (125 MHz; $CDCl_3$): 174.4 (*C*=S), 165.1 (ester *C*=O), 149.0 (*C*=C-CO_2Me), 133.6 (one of *C*H=CH), 124.0 (one of CH=*C*H), 98.7 (C=*C*-CO_2Me), 62.0 (*C*H-NCS), 51.2 (*C*H-pentyl), 50.2 (CO_2CH_3), 36.8 (pyrrolidine CH_2C=C), 31.7 (CH_2C=C), 30.4 (CH_2C=C), 29.5 (pyrrolidine CH_2CH-N), 28.7 (CH_2CH-NH), 28.3 (CH_2), 27.8 (CH_2), 26.7 (CH_2), 24.6 (CH_2), 22.5 (CH_2), 21.6 (pentyl CH_3CH_2), 21.5 (CH_3CH_2-alkyl), 13.1 (CH_3CH_2-alkyl) and 13.0 (CH_3CH_2-alkyl).

$[\alpha]_D$: +10° (c=1, CH_2Cl_2).

IR (neat): 3267, 2941, 2857, 1682, 1654, 1521, 1460, 1380 and 1231 cm^{-1}.

MS-ES: *m/z* (%) = 421 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 421.2892; $C_{24}H_{41}N_2O_2S$ requires 421.2889.

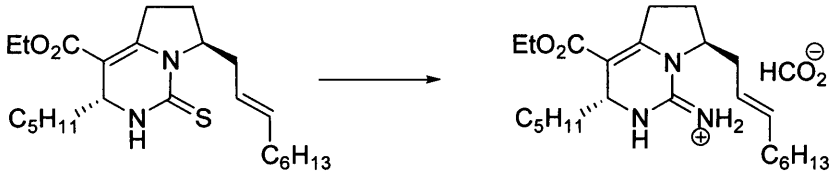
(3*S*,7*S*)-Methyl 1,2,3,5,6,7-hexahydro-7-((*E*)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**196b;** yellow gum): (96 mg, 24%; R_f 0.26):

δ_H (250 MHz; $CDCl_3$): 7.06 (1H, broad s, N*H*), 5.53 – 5.41 (1H, m, one of C*H*=CH), 5.34 – 5.18 (1H, m, one of CH=C*H*), 4.90 – 4.77 (1H, m, C*H*-NCS), 4.26 – 4.20 (1H, m, C*H*-pentyl), 3.66 (3H, s, CO_2CH_3), 3.30 – 3.16 (1H, m, one of pyrrolidine CH_2C=C), 3.02 – 2.87 (1H, apparent dt, *J* 19.2 & 9.5, one of CH_2C=C), 2.78 – 2.53 (1H, m, one of pyrrolidine CH_2C=C), 2.39 – 2.25 (1H, m, one of CH_2C=C), 2.07 – 1.89 (3H, m, CH_2C=C & one of pyrrolidine CH_2CH-N), 1.83 – 1.73 (1H, m, one of pyrrolidine CH_2CH-N), 1.55 – 1.39 (2H, m, CH_2CH-NH), 1.36 – 1.16 (14H, m, 7 x alkyl CH_2 protons) and 0.87 – 0.74 (6H, m, 2 x CH_3CH_2-alkyl).

δ_C (62.5 MHz; $CDCl_3$): 174.8 (*C*=S), 165.0 (ester *C*=O), 149.5 (MeO_2C-C=*C*), 133.0 (*C*H=CH), 122.6 (CH=*C*H), 99.3 (MeO_2C-*C*=C), 62.1 (*C*H-NCS), 50.7 (*C*H-pentyl), 50.3 (CO_2CH_3), 35.8 (pyrrolidine CH_2C=C), 33.4 (CH_2C=C), 32.5 (CH_2C=C), 30.8 (pyrrolidine CH_2CH-N), 30.5 (CH_2CH-NH), 29.4 (CH_2), 28.7 (CH_2), 26.6 (CH_2), 24.2 (CH_2), 22.7 (CH_2), 21.7 (CH_3CH_2-alkyl), 21.6 (CH_3CH_2-alkyl), 13.1 (CH_3CH_2-alkyl) and 13.0 (CH_3CH_2-alkyl).

$[\alpha]_D$: -14° (c=1, CH_2Cl_2).

(3*R*,7*S*)- 7-((*E*)-Non-2-enyl)-4-(methoxycarbonyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidine-1(5*H*)-iminium formate (197)



196a **197**

Iodomethane (31 µL, 0.51 mmol) was added to a solution of *(3R,7S)-Methyl 1,2,3,5,6,7-hexahydro-7-((E)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-c]pyrimidine-4-carboxylate* (**196a**) (205 mg, 0.51 mmol) in dry MeOH (2 mL), and the reaction mixture heated at reflux under N_2 for 1 h. The volatiles were removed *in vacuo*, and the resulting pale gum re-dissolved in dry MeOH (3 mL). This solution was then transferred to a mixture of NH_4OAc (193 mg, 2.54 mmol) in dry MeOH (2 mL), and liquid ammonia bubbled through the reaction for 10 min. The yellow mixture was heated at in a sealed tube at 80 °C for 48 h. The subsequent dark orange mixture was loaded directly onto a silica column (eluting with CH_2Cl_2-MeOH-HCOOH-H_2O, 84:14:0.5:0.5), early fractions (R_f 0.99) producing a viscous gum, which was further purified by flash column chromatography (eluting with CH_2Cl_2 → EtOAc), late fractions afforded the *title compound* (156 mg, 71%) as an off-brown oil.

δ_H (500 MHz; $CDCl_3$): 8.23 (2H, broad s, $(NH_2)^+$), 5.48 (apparent dt, *J* 14.9 & 6.6, one of C*H*=CH), 5.38 – 5.35 (1H, m, one of CH=C*H*), 4.64 – 4.60 (1H, m, C*H*-NC=N), 4.39 – 4.35 (1H, m, C*H*-NH), 3.66 (3H, s, CO_2CH_3), 3.30 – 3.23 (1H, m, one of pyrrolidine CH_2C=C), 2.98 – 2.78 (1H, m, one of pyrrolidine CH_2C=C), 2.51 – 2.39 (2H, m, CH_2C=C), 2.11 – 2.02 (1H, m, one of CH_2C=C), 1.96 – 1.91 (1H, m, one of CH_2C=C), 1.87 – 1.82 (2H, m, pyrrolidine CH_2CH-N), 1.61 – 1.42 (2H, m, CH_2CHNH), 1.35 – 1.20 (14H, 7 x CH_2 alkyl protons) and 0.77 (6H, t, *J* 6.7, 2 x CH_3CH_2-alkyl).

δ_C (125 MHz; $CDCl_3$): 165.2 (ester *C*=O), 151.2 (guanidine *C*=N), 150.2 (*C*=C-CO_2Me), 133.9 (one of *C*H=CH), 124.2 (one of *C*H=*C*H), 101.1 (C=*C*-CO_2Me), 59.8 (*C*H-NC=N), 50.3 (*C*H-NH), 50.7 (CO_2CH_3), 37.4 (pyrrolidine CH_2C=C), 32.7 (CH_2C=C), 32.9 (CH_2C=C), 29.4 (pyrrolidine CH_2CH-N), 28.7 (CH_2CH-NH), 28.1 (CH_2), 27.6 (CH_2), 26.7 (CH_2), 24.5 (CH_2), 22.1 (CH_2), 21.5 (pentyl CH_3CH_2), 21.3 (CH_3CH_2-alkyl), 13.1 (CH_3CH_2-alkyl) and 13.1 (CH_3CH_2-alkyl).

$[\alpha]_D$: +18° (c=1, CH_2Cl_2).

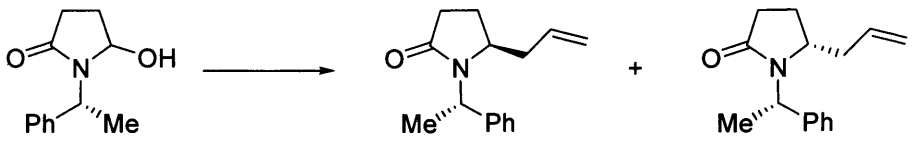
IR (neat): 3284, 2932, 1665, 1541, 1486, 1384 and 1235 cm^{-1}.

MS-ES: *m/z* (%) = 404 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 404.3281; $C_{24}H_{42}N_3O_2$ requires 404.3277.

6.5 Experimental Data for Chapter 5

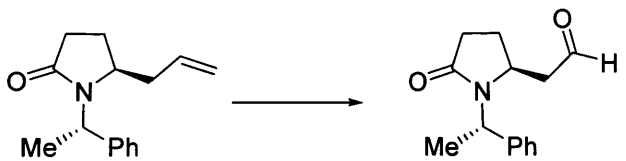
(5*S*)-Allyl-((*S*)-1-phenylethyl)pyrrolidin-2-one (206a) and (5*R*)-Allyl-((*S*)-1-phenylethyl)pyrrolidin-2-one (206b)[71]



186 **206a** **206b**

Boron trifluoride-diethyl etherate (4.67 mL, 38 mmol) was added dropwise to a solution of *5-hydroxy-1-((S)-1-phenylethyl)pyrrolidin-2-one* (**186**) (5.2 g, 25.3 mmol) in dry CH_2Cl_2 (30 mL) at -78 °C under N_2. Allyltrimethylsilane (12.05 mL, 76 mmol) was then added dropwise, and the reaction allowed to warm to room temperature over 16 h. The reaction was quenched with sat. aqueous $NaHCO_3$ solution (careful addition; 25 mL), and the layers separated. The aqueous layer was then washed with CH_2Cl_2 (3 x 20 mL), and the organic washings combined and dried with Na_2SO_4. The solvent was removed *in vacuo* to afford the *title compounds* (**206a:206b** = 5.26:1) as a pure viscous orange oil (5.518 g, 95%), which crystallised on standing to afford an orange solid.

((2*S*)-5-Oxo-1-((*S*)-1-phenylethyl)pyrrolidin-2-yl)acetaldehyde (207)



206a **207**

Potassium osmate dihydrate (23 mg, 0.063 mmol), sodium periodate (10.491 g, 49.05 mmol) and 2,6-lutidine (2.86 mL, 24.52 mmol) were added to a solution of *(5S)-Allyl-((S)-1-phenylethyl)pyrrolidin-2-one* (**206a**) (2.810g, 12.26 mmol; **d.e.** *ca.* 85%) in dioxane-H_2O (3:1, 260 mL) and the resulting white suspension stirred

at rt under nitrogen for 18 h. The reaction mixture was then quenched with water (100 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The organic extracts were combined, washed with brine (100 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting dark brown oil was purified by flash column chromatography (eluting with EtOAc-Me_2CO, 1:2), affording the *title compound* as a viscous brown oil (2.549 g, 90%).

Note: the d.e. has been enhanced to 87%. From this step onwards, only the data for the major diastereoisomer will be reported.

δ_H (400 MHz; $CDCl_3$): 9.19 (1H, broad s, C*H*O), 7.26 – 7.12 (5H, m, aromatic C*H*), 5.37 (1H, q, *J* 7.3, C*H*-Me), 4.08 (1H, apparent ddt, *J* 11.8, 7.9 & 3.7, pyrrolidine C*H*-N), 2.42 – 2.35 (2H, m, CH_2CHO), 2.26 – 2.19 (1H, m, one of pyrrolidine CH_2C=O), 2.17 – 2.11 (1H, m, one of pyrrolidine CH_2C=O), 2.05 – 2.01 (1H, m, one of pyrrolidine CH_2CHN), 1.54 – 1.51 (1H, m, one of pyrrolidine CH_2CHN) and 1.47 (3H, d, *J* 7.1, CH_3-CHPh).

δ_C (125 MHz; $CDCl_3$): 199.4 (*C*HO), 174.8 (lactam *C*=O), 141.1 (aromatic *C*), 128.4 (aromatic *C*H), 127.3 (aromatic *C*H), 126.9 (aromatic *C*H), 50.8 (*C*HMe), 48.7 (pyrrolidine *C*HN), 47.9 (*C*H_2CHO), 29.7 (pyrrolidine *C*H_2C=O), 25.3 (pyrrolidine *C*H_2CHN), 15.5 (*C*H_3-CHPh).

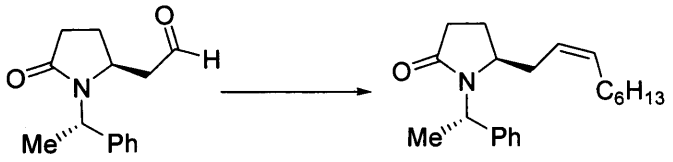
IR (neat): 2974, 1718, 1667, 1528 and 1492 cm^{-1}.

$[\alpha]_D$: -128° (*c* = 1, CH_2Cl_2).

MS-EI: *m/z* (%) = 231 (M^+, 22); 105 (100).

HRMS-ES: *m/z* [M^+]: found: 231.1265; $C_{14}H_{14}NO_2$ requires 231.1259.

(5*S*)-[(*Z*)-Non-2-enyl)-1-((*S*)-1-phenylethyl]pyrrolidin-2-one (208)



207 **208**

n-Butyl lithium (2.5 M solution in hexanes; 8.52 mL, 21.30 mmol) was added dropwise to a vigorously stirred solution of heptyltriphenylphosphonium iodide (10.394 g, 21.30 mmol) in dry THF (75 mL) at 0 °C under N_2. After stirring for 2 h at that temperature, the resultant deep red mixture was cooled to -78 °C and a solution of *((2S)-5-oxo-1-((S)-1-phenylethyl)pyrrolidin-2-yl)acetaldehyde* (**207**) (2.460 g, 10.64 mmo) in THF (8 mL) added dropwise. The resulting brown solution was allowed to warm to rt and stirred for 16 h. The reaction was quenched with saturated $NaHCO_3$ solution (50 mL), and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with brine (40 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting brown gum was purified by column chromatography (eluting with EtOAc-Hexane, 1:2), early fractions (R_f 0.6) affording the *title compound* (1.85 g, 56%; *Z/E*>15:1) as a thick orange oil.

δ_H (400 MHz; $CDCl_3$): 7.31 (2H, d, *J* 7.2, 2 x aromatic C*H*), 7.24 (2H, t, *J* 7.5, 2 x aromatic C*H*), 7.18 (1H, d, *J* 7.4, 1 x aromatic *C*H), 5.42 – 5.28 (2H, m, one of C*H*=CH & C*H*Me), 5.02 – 4.97 (1H, m, one of CH=C*H*), 3.65 – 3.60 (1H, m, C*H*-N), 2.43 (1H, ddd, *J* 17.2, 9.3 & 8.1, one of CH_2C=O), 2.26 (1H, apparent ddd, *J* 14.7, 9.8 & 4.9, one of CH_2C=C), 2.02 – 1.94 (1H, m, one of CH_2C=C), 1.88 – 1.80 (1H, m, one of CH_2C=O), 1.75 (2H, apparent q, *J* 6.6, CH_2C=C), 1.65 – 1.61 (1H, m, one of pyrrolidine CH_2CH-N), 1.58 (3H, d, *J* 7.2, CH_3CH), 1.54 – 1.51 (1H, m, one of pyrrolidine CH_2CH-N), 1.23 – 1.14 (8H, m, 4 x alkyl CH_2 protons) and 0.81 (3H, t, *J* 7.1, CH_3CH$_2$-alkyl).

δ_C (125 MHz; $CDCl_3$): 175.3 (lactam *C*=O), 142.0 (aromatic *C*), 133.11 (one of *C*H=CH), 128.3 (aromatic *C*H), 127.3 (aromatic *C*H), 127.2 (aromatic *C*H), 123.9 (one of CH=*C*H), 56.1 (*C*HMe), 49.5 (*C*HN), 32.1 (*C*H$_2$C=C), 31.7 (*C*H$_2$C=O),

30.3 (CH_2C=C), 29.4 (CH_2), 28.9 (CH_2), 27.5 (CH_2), 24.2 (pyrrolidine CH_2CHN), 22.6 (CH_3CH_2-alkyl), 16.3 (CH_3CHPh) and 14.1 (CH_3CH_2-alkyl).

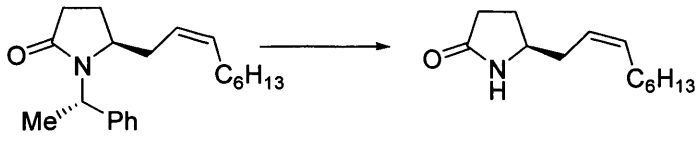
$[\alpha]_D$: -138° (*c* = 1, CH_2Cl_2).

IR (neat): 2930, 2860, 1680, 1493, 1453 and 1406 cm^{-1}.

MS-ES: *m/z* (%) = 314 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 314.2484; $C_{21}H_{32}NO$ requires 314.2484.

(5*S*)-5-[(*Z*)-Non-2-enyl]pyrrolidin-2-one (192)



208 **192**

A solution of *(5S)-[(Z)-non-2-enyl)-1-((S)-1-phenylethyl]pyrrolidin-2-one* (**208**) (760 mg, 2.45 mmol) in liquid NH_3-THF-absolute EtOH (8:1:1; 56 mL) under N_2 was cooled to -78 °C, and sodium chunks (279 mg, 12.14 mmol) added portion-wise. After the purple colour had persisted for longer than 3 min, the solution was warmed to rt until the reaction turned colourless. Solid NH_4Cl was then added, the ammonia allowed to evaporate and the reaction mixture washed with water (15 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL), the combined organic washings dried over Na_2SO_4, and the solvent removed *in vacuo*. The *title compound* was afforded (**e.e.** *ca.* 78%; 512 mg, 100%) as a yellow oil.

δ_H (400 MHz; $CDCl_3$): 5.55 (1H, broad s, N*H*), 5.58 – 5.37 (1H, m, one of C*H*=CH), 5.19 – 5.13 (1H, m, one of CH=C*H*), 3.51 (1H, apparent quintet, *J* 6.7, C*H*-NH), 2.24 – 2.10 (4H, m, CH_2C=O & CH_2C=C), 1.90 – 1.83 (3H, m, CH_2C=C & one of pyrrolidine CH_2CHNH), 1.64 – 1.57 (1H, m, one of pyrrolidine CH_2CHNH), 1.22 – 1.07 (8H, m, 4 x alkyl CH_2 protons) and 0.73 (3H, t, *J* 6.9, CH_3CH_2-alkyl).

δ_C (125 MHz; $CDCl_3$): 178.5 (lactam *C*=O), 133.5 (*C*H=CH), 123.7 (CH=*C*H), 54.5 (*C*H-NH), 34.2 (CH_2C=O), 31.7 (CH_2C=C), 30.4 (CH_2C=C), 29.5 (CH_2), 28.9 (CH_2), 27.4 (CH_2), 26.5 (pyrrolidine CH_2CH-NH), 22.6 (CH_3CH_2-alkyl) and 14.1 (CH_3CH_2-alkyl).

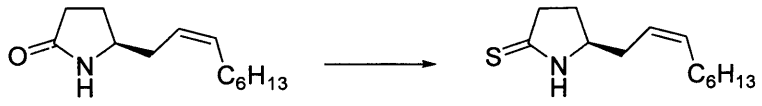
$[\alpha]_D$: -10° (*c* = 1, CH_2Cl_2).

IR (neat): 3237, 2919, 2849, 1690, 1455 and 1290 cm^{-1}.

MS-ES: *m/z* (%) = 210 (MH^+, 90); 419 ($2MH^+$, 90).

HRMS-ES: *m/z* $[MH]^+$: found: 210.1854; $C_{13}H_{24}NO$ requires 210.1858.

(5*S*)-5-((*Z*)-Non-2-enyl)pyrrolidine-2-thione (209)



192 **209**

Lawesson's reagent (553 g, 1.37 mmol) was added portion-wise to a solution of *(5S)-5-[(Z)-non-2-enyl]pyrrolidin-2-one* (**192**) (520 mg, 2.49 mmol) in dry THF (20 mL), and the resulting suspension stirred at rt under N_2 for 2 h. The THF was removed *in vacuo*, and the resultant orange gum purified by column chromatography (eluting with CH_2Cl_2-EtOAc, 2:1), early fractions (R_f 0.95) yielding the *title compound* (508 mg, 90%) as an orange oil.

δ_H (400 MHz; $CDCl_3$): 7.51 (1H, broad s, N*H*), 5.56 – 5.51 (1H, m, one of C*H*=CH), 5.27 – 5.22 (1H, m, one of CH=C*H*), 3.88 (1H, apparent quintet, *J* 6.9, C*H*-NH), 2.92 (1H, ddd, *J* 14.4, 9.4 & 5.1, one of CH_2C=S), 2.87 – 2.78 (1H, m, one of CH_2C=S), 2.32 – 2.19 (3H, m, CH_2C=C and one of pyrrolidine CH_2CH-NH), 1.97 (2H, apparent q, *J* 7.1, CH_2C=C), 1.80 (1H, dddd, *J* 12.9, 9.3, 8.0 & 6.5, one of pyrrolidine CH_2CH-NH), 1.30 – 1.17 (8H, m, 4 x alkyl CH_2 protons) and 0.82 (3H, t, *J* 6.9, CH_3CH_2-alkyl).

δ_C (100 MHz; $CDCl_3$): 206.5 (*C*=S), 134.5 (one of *C*H=CH), 123.2 (one of CH=*C*H), 62.4 (*C*H-NH), 43.1 (CH_2C=S), 33.1 (CH_2C=C), 31.7 (CH_2C=C), 29.5

(CH_2), 29.0 (CH_2), 28.9 (CH_2), 27.5 (pyrrolidine CH_2CHNH), 22.6 (CH_3CH_2-alkyl), 14.1 (CH_3CH_2-alkyl).

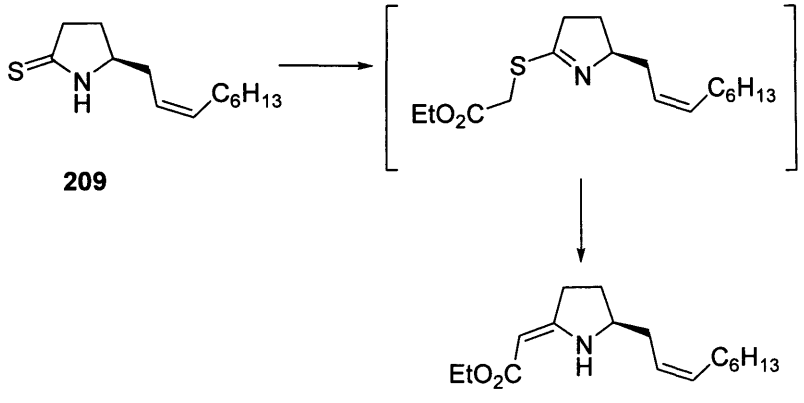
$[\alpha]_D$: -40° (*c* = 1, CH_2Cl_2).

IR (neat): 3163, 2918, 2848, 1523, 1459, 1296 and 1261 cm^{-1}.

MS-ES: *m/z* (%) = 226 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 226.1622; $C_{13}H_{24}NS$ requires 226.1624.

(2*Z*)-Ethyl 2-[(*S*)-5-(non-2-enyl)pyrrolidin-2-ylidene]acetate (210)



209 **210**

Ethyl bromo-acetate (0.29 mL, 2.59 mmol) was added to a solution of *(5S)-5-((Z)-non-2-enyl)pyrrolidine-2-thione* (**209**) (490 mg, 2.16 mmol) in dry CH_2Cl_2 (15 mL), and the resulting orange solution stirred at rt under N_2 for 3 h. The reaction mixture was washed with saturated $NaHCO_3$ solution (40 mL), and the organic layer separated. The aqueous layer was then washed with CH_2Cl_2 (3 x 40 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*.

The residue was then redissolved in dry Xylene (12 mL), and triphenylphosphine (2.3 g, 8.63 mmol) and dried potassium *tert*-butoxide (24 mg, 0.22 mmol) added. The resulting suspension was stirred for 10 min at rt, and then heated at reflux for 48 h. The volatiles were then removed *in vacuo*. The resulting dark orange solid was purified by column chromatography (eluting with EtOAc-Hexane, 1:9),

mid-fractions (R_f 0.5) affording the *title compound* (352 mg, 62%) as a pale orange oil.

δ_H (400 MHz; $CDCl_3$): 7.92 (1H, broad s, N*H*), 5.49 – 5.44 (1H, m, one of C*H*=CH), 5.31 – 5.25 (1H, m, one of CH=C*H*), 4.41 (1H, broad s, C*H*=C-NH), 4.03 (2H, q, *J* 7.1, CH_2OCO), 3.72 (1H, apparent quintet, *J* 6.6, C*H*-NH), 2.59 – 2.46 (2H, m, one of CH_2C=C & one of pyrrolidine CH_2C=C), 2.26 – 2.20 (1H, m, one of CH_2C=C), 2.17 – 2.12 (1H, m, one of pyrrolidine CH_2C=C), 2.03 – 1.98 (1H, m, one of pyrrolidine CH_2CH-NH), 1.93 (2H, apparent q, *J* 7.1, CH_2C=C), 1.53 (1H, dddd, *J* 12.5, 9.0, 8.1 & 6.3, one of pyrrolidine CH_2CH-NH), 1.27 – 1.14 (11 H, m, 4 x CH_2 alkyl protons & CH_3CH_2OCO) and 0.81 (3H, t, *J* 7.0, CH_3CH_2-alkyl).

δ_C (125 MHz; $CDCl_3$): 169.5 (ester *C*=O), 164.5 (*C*=CH-CO_2Et), 132.4 (*C*H=CH), 123.5 (CH=*C*H), 76.7 (C=*C*H-CO_2Et), 58.6 (CO_2CH_2), 57.3 (*C*H-NH), 32.0 (CH_2C=C), 30.8 (pyrrolidine *C*H_2C=C), 28.6 (CH_2C=C), 28.0 (pyrrolidine *C*H_2CHNH), 26.8 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 21.6 (CH_3CH_2-alkyl), 13.7 (CH_3CH_2OCO) and 13.1 (CH_3CH_2-alkyl).

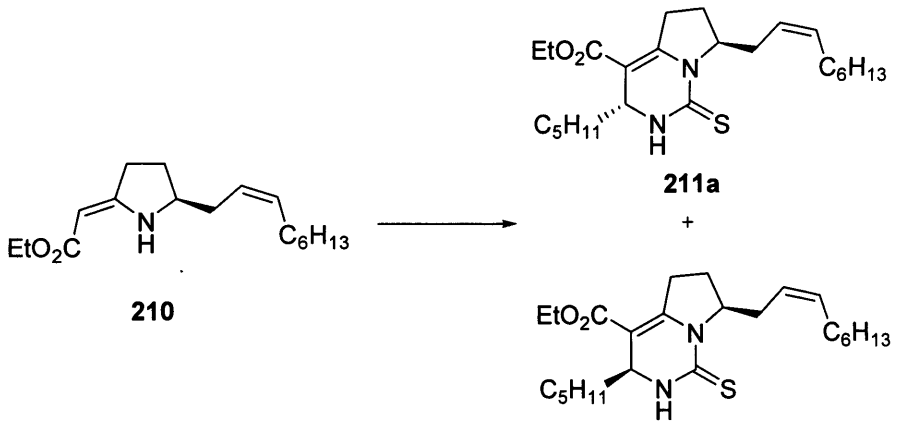
$[\alpha]_D$: -114° (*c* = 1, CH_2Cl_2).

IR (neat): 3370, 2920, 1657 and 1594 cm^{-1}.

MS-ES: *m/z* (%) = 280 (MH^+, 85).

HRMS-ES: *m/z* $[MH]^+$: found: 280.2268; $C_{17}H_{30}NO_2$ requires 280.2271.

(3*R*,7*S*)-Ethyl 1,2,3,5,6,7-hexahydro-7-((*Z*)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (major diastereoisomer; 211a) and (3*S*,7*S*)-Ethyl 1,2,3,5,6,7-hexahydro-7-((*Z*)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (minor diastereoisomer; 211b)



Trimethylsilyl isothiocyanate (280 µL, 1.98 mmol) was dissolved in dry CH_2Cl_2 (8 mL), hexanal (240 µL, 1.98 mmol) added and the resulting pale yellow solution stirred at rt under N_2 for 30 min. A solution *of (2Z)-ethyl 2-[(S)-5-(non-2-enyl)pyrrolidin-2-ylidene]acetate* (**210**) (260 mg, 0.99 mmol) in CH_2Cl_2 (4 mL) was added, and the reaction mixture stirred at rt for 45 min. The reaction was then quenched with ~0.1 M aqueous NaOH solution (30 mL) and the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL). The organic washings were combined, dried over Na_2SO_4 and the solvent removed *in vacuo*. The subsequent yellow gum (**211a:211b**=2.1:1) was purified by column chromatography (eluting with EtOAc-Hexane, 1:9), yielding the *title compounds*.

(3*R*,7*S*)-Ethyl 1,2,3,5,6,7-hexahydro-7-((*Z*)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**211a**; off-white gum): (231 mg, 58%; R_f 0.5).

δ_H (400 MHz; $CDCl_3$): 6.97 (1H, broad s, N*H*), 5.46 (1H, apparent dt, *J* 10.8 & 7.4, one of C*H*=CH), 5.27 – 5.22 (1H, m, one of CH=C*H*), 4.51 – 4.47 (1H, m,

C*H*-NCS), 4.23 – 4.20 (1H, m, C*H*-pentyl), 4.11 (2H, q, *J* 7.4, CH_2OCO), 3.30 (1H, ddd, *J* 18.1, 5.34 & 3.6, one of pyrrolidine CH_2C=C), 3.04 – 3.00 (1H, m, one of CH_2C=C), 2.85 (1H, apparent dt, *J* 18.1 & 10.4, one of pyrrolidine CH_2C=C), 2.13 (1H, apparent dt, *J* 13.6 & 9.2, one of CH_2C=C), 2.04 – 1.99 (2H, m, CH_2C=C), 1.88 – 1.84 (2H, m, pyrrolidine CH_2CH-N), 1.60 – 1.46 (2H, m, CH_2CHNH), 1.35 – 1.15 (17H, 7 x CH_2 alkyl protons and CH_3CH$_2$OCO) and 0.82 – 0.79 (6H, m, 2 x CH_3CH$_2$-alkyl).

δ_C (125 MHz; $CDCl_3$): 174.2 (*C*=S), 164.7 (ester *C*=O), 148.6 (*C*=C-CO_2Et), 132.7 (*C*H=CH), 123.3 (CH=*C*H), 99.0 (C=*C*-CO_2Et), 62.1 (*C*H-NCS), 59.2 (CO_2CH_2), 51.1 (*C*H-pentyl), 36.8 (pyrrolidine CH_2C=C), 30.8 (CH_2C=C), 30.4 (CH_2C=C), 29.5 (pyrrolidine CH_2CH-N), 28.7 (CH_2CH-NH), 28.0 (CH_2), 26.7 (CH_2), 27.7 (CH_2), 24.0 (CH_2), 22.5 (CH_2), 21.7 (pentyl CH_3CH_2), 21.5 (CH_3CH_2-alkyl), 13.4 (CH_3CH_2OCO), 13.1 (CH_3CH_2-alkyl) and 13.0 (CH_3CH_2-alkyl).

$[\alpha]_D$: +100° (c=1, CH_2Cl_2).

IR (neat): 3288, 3205, 2925, 2852, 1694, 1647, 1527, 1460, 1377 and 1226 cm^{-1}.

MS-ES: *m/z* (%) = 421 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 421.2877; $C_{24}H_{41}N_2O_2S$ requires 421.2889.

(3*S*,7*S*)-Ethyl 1,2,3,5,6,7-hexahydro-7-((*Z*)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**211b**; yellow oil)**:** (129 mg, 28%; R_f 0.38).

δ_H (400 MHz; $CDCl_3$): 6.94 (1H, broad s, N*H*), 5.52 – 4.48 (1H, m, C*H*=CH), 5.28 – 5.21 (1H, m, CH=C*H*), 4.89 – 4.80 (1H, m, C*H*-NCS), 4.30 – 4.20 (1H, m, C*H*-pentyl), 4.19 – 4.03 (2H, m, CO_2CH_2), 3.26 – 3.20 (1H, m, one of pyrrolidine CH_2C=C), 2.99 – 2.90 (1H, m, one of CH_2C=C), 2.69 – 2.55 (1H, m, one of pyrrolidine CH_2C=C), 2.38 – 2.26 (1H, m, one of CH_2C=C), 2.08 – 1.86 (3H, m, CH_2C=C & one of pyrrolidine CH_2CH-N), 1.80 – 1.72 (1H, m, one of pyrrolidine CH_2CH-N), 1.50 – 1.34 (2H, m, CH_2CH-NH), 1.35 – 1.12 (17H, m, 7 x alkyl CH_2 protons & CH_3CH$_2$OCO) and 0.84 – 0.75 (6H, m, 2 x CH_3CH$_2$-alkyl).

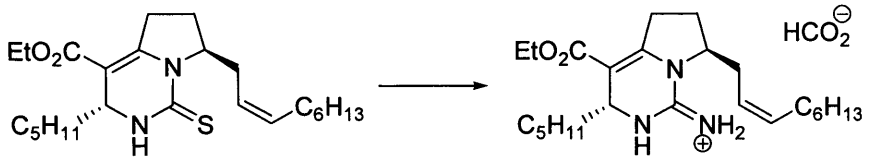
δ_C (125 MHz; $CDCl_3$): 175.1 (*C*=S), 165.6 (ester *C*=O), 150.3 (*C*=C-CO_2Et), 133.9 (*C*H=CH), 123.7 (CH=*C*H), 100.6 (C=*C*-CO_2Et), 62.8 (*C*H-NCS), 60.2 (CO_2CH_2), 51.8 (*C*H-pentyl), 36.8 (pyrrolidine CH_2C=C), 31.8 (CH_2C=C), 31.4 (CH_2C=C), 31.0 (pyrrolidine CH_2CH-N), 30.4 (CH_2CH-NH), 29.6 (CH_2), 29.0 (CH_2), 27.6 (CH_2), 24.8 (CH_2), 23.7 (CH_2), 22.6 (pentyl CH_3CH_2), 22.6 (CH_3CH_2-alkyl), 14.4 (CH_3CH_2OCO), 14.2 (CH_3CH_2-alkyl) and 14.0 (CH_3CH_2-alkyl).

$[\alpha]_D$: -116° (c=1, CH_2Cl_2).

MS-ES: *m/z* (%) = 421 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 421.2888; $C_{24}H_{41}N_2O_2S$ requires 421.2889.

(3*R*,7*S*)-7-((*Z*)-Non-2-enyl)-4-(ethoxycarbonyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidine-1(5H)-iminium formate (212)



211a **212**

Iodomethane (19 µL, 0.31 mmol) was added to a solution of *(3R,7S)-ethyl 1,2,3,5,6,7-hexahydro-7-((Z)-non-2-enyl)-3-pentyl-1-thioxopyrrolo-[1,2-c]pyrimidine-4-carboxylate* (**211a**) (125 mg, 0.31 mmol) in dry MeOH (3 mL), and the reaction mixture heated at reflux under N_2 for 1 h. The volatiles were removed *in vacuo* and the resulting pale gum re-dissolved in dry MeOH (3 mL). This solution was then transferred to a mixture of NH_4OAc (100 mg, 1.54 mmol) in MeOH (2 mL), and liquid ammonia bubbled through the reaction for 10 min. The resultant yellow suspension was heated at in a sealed tube for 48 h at 80 °C and loaded directly onto a silica gel column (eluting with CH_2Cl_2-MeOH-HCOOH-H_2O, 84:14:0.5:0.5), early fractions (R_f 0.99) affording the title compound (91 mg, 80%) as a dark orange oil.

δ_H (400 MHz; $CDCl_3$): 8.86 (1H, broad s, N*H*), 8.17 (2H, broad s, (C=NH_2)$^+$), 5.50 (1H, apparent dt, *J* 10.8 & 7.2, one of C*H*=CH), 5.44 – 5.36 (1H, m, one of CH=C*H*), 4.65 – 4.61 (1H, m, C*H*-NC=N), 4.40 – 4.37 (1H, m, C*H*-pentyl), 4.15 (2H, q, *J* 7.2, CO_2CH_2), 3.28 (1H, apparent dd, *J* 18.6 & 7.6, one of pyrrolidine CH_2C=C), 2.86 – 2.77 (1H, m, one of CH_2C=C), 2.49 – 2.40 (1H, m, one of pyrrolidine CH_2C=C), 2.28 (1H, apparent dt, *J* 14.3 & 9.2, one of CH_2C=C), 2.04 – 1.90 (4H, m, CH_2C=C & pyrrolidine CH_2CH-N), 1.62 – 1.49 (2H, m, CH_2CH-NH), 1.48 – 1.39 (1H, m, one of CH_2CH_2CH-NH), 1.30 – 1.15 (16H, m, 13 x alkyl protons & CH_3CH_2OCO) and 0.65 (6H, t, *J* 6.6, 2 x CH_3CH_2-alkyl).

δ_C (125 MHz; $CDCl_3$): 164.9 (ester *C*=O), 151.0 (guanidine *C*=N), 149.9 (EtO_2C-C=*C*), 134.2 (*C*H=CH), 123.2 (CH=*C*H), 101.4 (EtO_2C-*C*=C), 60.5 (*C*H_2OCO), 59.6 (*C*H-NC=N), 50.2 (*C*H-pentyl), 37.5 (pyrrolidine *C*H_2C=C), 31.8 (*C*H_2C=C), 31.3 (*C*H_2C=C), 29.5 (*C*H_2CH-N=C), 29.3 (pyrrolidine *C*H_2CH-N), 29.0 (*C*H_2), 28.7 (*C*H_2), 27.6 (*C*H_2), 26.4 (*C*H_2), 23.5 (*C*H_2), 22.6 (pentyl CH_3CH_2), 22.6 (CH_3CH_2-alkyl), 14.3 (*C*H_3CH_2OCO), 14.1 (*C*H_3CH_2-alkyl) and 14.1 (*C*H_3CH_2-alkyl).

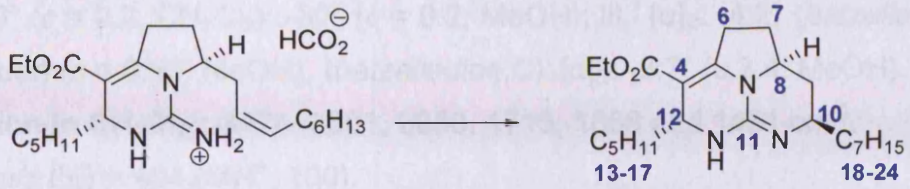
$[\alpha]_D$: +86° (c=1, CH_2Cl_2).

IR (solution in CH_2Cl_2): 3284, 3154, 2837, 1684, 1537, 1455, 1378 and 1260 cm^{-1}.

MS-ES: *m/z* (%) = 404 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 404.3270; $C_{24}H_{42}N_3O_2$ requires 404.3277.

(8*S*,10*R*,12*R*)-Ethyl-10-heptyl-6,7,8,9,10,12-hexahydro-12-pentyl-11aH-8a,10a,11a-triaza-acenapthylene-4-carboxylate (213a)



212 **213a**

(3R,7S)-7-((Z)-non-2-enyl)-4-(ethoxycarbonyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-1(5H)-iminium formate (**212**) (90 mg, 0.20 mmol) was dissolved in acetonitrile (3 mL), and iodine (305 mg, 1.21 mmol) and potassium carbonate (81 mg, 0.6 mmol) added. The resulting red-brown mixture was stirred at rt under N_2 for 3 h, and the solvent removed *in vacuo*. The subsequent red gum was purified by flash column chromatography (eluting with CH_2Cl_2 → EtOAc/Me_2CO, 1:1), late washings affording the iodinated tricyclic guanidine (**213**) (115mg, 95%) as a viscous brown oil.

The iodinated tricyclic guanidine (110mg, 0.21 mmol) was immediately re-dissolved in EtOAc (6 mL) and triethylamine (0.14 mL, 1.04 mmol), and 10% Pd/C (100 mg) added. The black suspension was de-gassed and stirred under an atmosphere of H_2 for $2^1/_2$ h. The reaction mixture was then filtered through Celite, and concentrated *in vacuo*. The subsequent oil was purified by flash column chromatography (eluting with CH_2Cl_2 → EtOAc/Me_2CO, 1:1), yielding the *title compound* (67 mg, 80%) as a yellow oil.

δ_H (500 MHz; MeOH-d_4): 4.33 (1H, apparent dd, *J* 7.7 & 4.2, H-12), 4.12 (2H, t, *J* 6.9. CO_2CH_2), 4.07 – 4.00 (1H, m, H-8), 3.58 – 3.53 (1H, m, H-10), 3.34 (1H, apparent dd, *J* 18.8 & 9.3, H-6β), 2.82 (1H, ddd, *J* 18.8, 11.2 & 8.3, H-6α), 2.38 – 2.32 (2H, m, H-7β & H-9β), 1.68 – 1.54 (2H, m, H-7α & H-9α), 1.50 – 1.40 (4H, m, H-13 & H-18), 1.35 – 1.22 (19H, m, 8 x alkyl CH_2 protons & CH_3CH_2OCO) and 0.82 – 0.80 (6H, m, 2 x CH_3CH_2-alkyl).

δ_C (62.5 MHz; $CDCl_3$): 164.4 (*C*-3), 148.9 (*C*-5), 148.1 (*C*-11), 103.4 (*C*-4), 60.8 (*C*-2), 57.2 (*C*-8), 51.2 (*C*-10), 50.7 (*C*-12), 36.9 (*C*-13), 34.5 (*C*-18), 33.8 (*C*-9),

31.7 (*C*-6), 31.2 (*C*-7), 29.9 (CH_2), 29.6 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.4 (CH_2), 24.2 (CH_2), 22.6 (*C*-16), 22.4 (*C*-23), 14.3 (*C*-1) and 14.1 (*C*-17 & *C*-24).

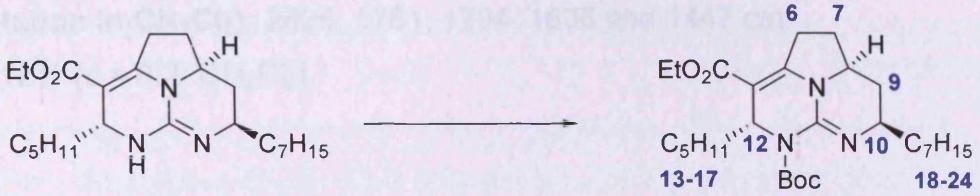
$[\alpha]_D$: -150° (*c* = 0.2, CH_2Cl_2); -30° (*c* = 0.2, MeOH); lit.[1] $[\alpha]_D$: -4.2° (*batzelladine C methyl ester*) (*c* = 0.93, MeOH), (*batzelladine C*): $[\alpha]_D$: -3.7° (*c* 2.4, MeOH).

IR (solution in CH_2Cl_2): 3274, 3201, 2850, 1715, 1658 and 1451 cm^{-1}.

MS-ES: *m/z* (%) = 404 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 404.3262; $C_{24}H_{42}N_3O_2$ requires 404.3277.

(8*S*,10*R*,12*R*)-11a-*tert*-Butyl-4-ethyl-10-heptyl-6,7,8,9,10,12- hexahydro-12-pentyl-8a,10a,11a-triaza-acenapthylene-4,11a-dicarboxylate (218)



53 **218**

Triethylamine (90 µL, 0.6 mmol) and DMAP (0 – 1 mg, *catalytic*) were added to a solution of *(8S,10R,12R)-Ethyl-10-heptyl-6,7,8,9,10,12-hexahydro-12-pentyl-11aH-8a,10a,11a-triaza-acenapthylene-4-carboxylate* (**213a**) (87 mg, 0.2 mmol) in dry CH_2Cl_2 (1 mL) under N_2. A solution of di-*tert*-butyldicarbonate (103 mg, 0.47 mmol) in CH_2Cl_2 (0.2 mL) was then added to the mixture, and the resulting pale yellow solution stirred at rt for 18 h. The reaction was quenched with sat. aqueous $NaHCO_3$ solution (10 mL) and CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer washed with CH_2Cl_2 (3 x 15 mL). The combined organic washings were then washed with brine (20 mL), the solvent evaporated to *ca.* 1 mL and the aqueous residue removed by decantation. The excess solvent was removed *in vacuo*, and the resulting oil purified by flash column chromatography (eluting with CH_2Cl_2 → EtOAc/Me_2CO, 1:1), yielding the

title compound (R_f 0.95; CH_2Cl_2-2.5% MeOH) as a viscous brown oil (89 mg, 82%).

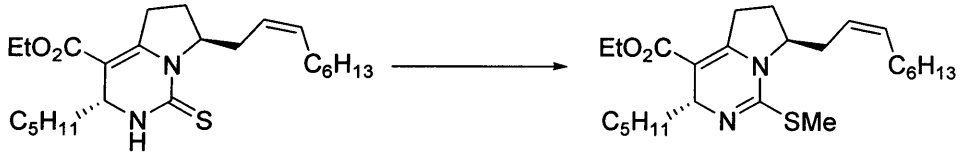
δ_H (400 MHz; $CDCl_3$): 5.28 – 5.24 (1H, m, H-12), 4.21 – 4.08 (3H, m, CO_2CH_2 & H-8), 3.48 – 3.39 (1H, m, H-10), 3.27 (1H, apparent dd, *J* 19.1 & 9.1, H-6β), 2.96 – 2.71 (1H, m, H-6α), 2.56 – 2.32 (2H, m, H-7β & H-9β), 1.98 – 1.85 (2H, m, H-7α & H-9α), 1.82 – 1.72 (1H, m, H-13β), 1.66 – 1.53 (3H, m, H-13α & H-18), 1.49 (9H, s, $((CH_3)_3C)$, 1.28 – 1.12 (19H, m, 8 x alkyl CH_2 protons & CH_3CH_2OCO) and 0.82 – 0.79 (6H, m, 2 x CH_3CH_2-alkyl).

δ_C (125 MHz; $CDCl_3$): 161.5 (*C*-3), 156.7 (carbamate *C*=O), 150.7 (*C*-11), 150.4 (C-5), 106.6 (*C*-4), 87.2 ($(C(CH_3)_3)$), 60.0 (*C*-2), 57.6 (*C*-8), 53.0 (*C*-12), 49.3 (*C*-10), 36.2 (*C*-13), 33.8 (*C*-18), 32.5 (*C*-9), 30.7 (*C*-6), 30.2 (*C*-7), 30.2 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 26.9 ($(C(CH_3)_3)$), 24.2 (CH_2), 24.2 (CH_2), 22.7 (CH_2), 21.6 (*C*-16), 21.6 (*C*-23), 13.4 (*C*-1), 13.1 (*C*-17) and 13.0 (*C*-24).

IR (solution in CH_2Cl_2): 2826, 1781, 1704, 1636 and 1447 cm^{-1}.

$[\alpha]_D$: -124° (*c* = 0.2, CH_2Cl_2).

(3*R*,7*S*)-Ethyl 3,5,6,7-tetrahydro-1-(methylthio)-7-((*Z*)-non-2-enyl)-3-pentylpyrrolo[1,2-*c*]pyrimidine-4-carboxylate (224)



211a **224**

Iodomethane (75 µL, 1.2 mmol) was added to a solution of *(3R,7S)-ethyl 1,2,3,5,6,7-hexahydro-7-((Z)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-c]pyrimidine-4-carboxylate* (**211a**) (50 mg, 0.12 mmol) in dry CH_2Cl_2 (4 mL), and the resulting orange solution stirred at reflux under N_2 for 17 h. The reaction was allowed to cool, dry triethylamine (166 µL, 1.2 mmol) added and the mixture

stirred at rt for 30 min. The solvent was then removed *in vacuo* and the resultant solid washed with hexane. The solid was removed, the filtrate concentrated to yield an orange oil and the subsequent thick oil purified by column chromatography (eluting with EtOAc-Hexane, 1:12), early fractions (R_f 0.52) affording the *title compound* (39 mg, 76%) as a dark yellow gum.

δ_H (500 MHz; $CDCl_3$): 5.46 (1H, apparent dt, *J* 10.7 & 7.4, one of C*H*=CH), 5.23 – 5.18 (1H, m, one of CH=C*H*), 4.53 (1H, apparent dd, *J* 7.0 & 3.7, C*H*-pentyl), 4.19 – 4.02 (2H, m, CO_2CH_2), 3.93 – 3.88 (1H, m, C*H*-N-C-SMe), 3.13 (1H, apparent dd, *J* 18.4 & 7.2, one of pyrrolidine CH_2C=C), 2.83 – 2.74 (1H, m, one of pyrrolidine CH_2C=C), 2.60 (1H, apparent dd, *J* 14.1 & 6.2, one of CH_2C=C), 2.33 (3H, s, S-CH_3), 2.08 (1H, apparent dt, *J* 14.1 & 9.5, one of CH_2C=C), 2.01 – 1.92 (2H, m, CH_2C=C), 1.84 – 1.76 (2H, m, pyrrolidine CH_2CH-N), 1.64 – 1.58 (2H, m, CH_2CH-N=C), 1.40 – 1.05 (17H, m, 7 x alkyl CH_2 protons & CH_3CH_2OCO) and 0.82 – 0.78 (6H, m, 2 x CH_3CH_2-alkyl).

δ_C (62.5 MHz; $CDCl_3$): 167.3 (ester *C*=O), 152.0 (*C*=C-CO_2Et), *C*=N-SMe peak *not observed*, 133.7 (*C*H=CH), 124.1 (CH=*C*H), 96.5 (C=*C*-CO_2Et), 68.2 (CO_2CH_2), 60.2 (*C*H-NC=N), 53.5 (*C*H-pentyl), 38.9 (pyrrolidine CH_2C=C), 31.9 (CH_2C=C), 31.8 (CH_2C=C), 30.4 (pyrrolidine CH_2CH-N), 29.6 (CH_2CH-N=C), 29.0 (CH_2), 27.4 (CH_2), 26.5 (CH_2), 24.2 (CH_2), 23.0 (CH_2), 22.7 (CH_3CH_2-alkyl), 22.7 (CH_3CH_2-alkyl), 14.5 (CH_3CH_2OCO), 14.1 (CH_3CH_2-alkyl) and 13.8 (S-CH_3).

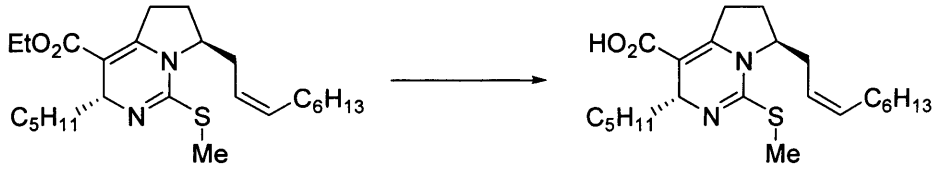
$[\alpha]_D$: +28° (*c* = 0.5, CH_2Cl_2).

IR (neat): 2931, 2861, 1690, 1649, 1596, 1455 and 1378 cm^{-1}.

MS-ES: *m/z* (%) = 435 (MH^+, 100).

HRMS-ES: *m/z* $[MH]^+$: found: 435.3059; $C_{25}H_{43}N_2O_2S$ requires 435.3045.

(3*R*,7*S*)-3,5,6,7-Tetrahydro-1-(methylthio)-7-((*Z*)-non-2-enyl)-3-pentylpyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid (225)



224 **225**

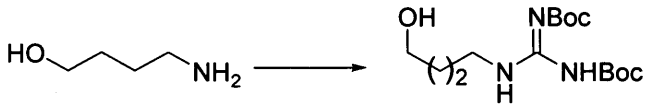
A solution of sodium hydroxide in MeOH (10% w/v; 0.8 mL) was added to a solution of *(3R,7S)-Ethyl 3,5,6,7-tetrahydro-1-(methylthio)-7-((Z)-non-2-enyl)-3-pentylpyrrolo[1,2-c]pyrimidine-4-carboxylate* (24 mg, 0.055 mmol) in MeOH (0.4 mL), and the resulting solution heated in sealed tube at 100 °C for 18 h. The reaction was then quenched with sat. aqueous NH_4Cl solution (12 mL), washed with CH_2Cl_2 (3 x 30 mL) and the organic washings combined and washed with brine (20 mL). The excess solvent was then removed *in vacuo*, the resulting organic residue decanted from the aqueous impurities. The *title compound* (crude yield *ca.* 16 mg, 71%) was afforded as an off-white gum.

δ_H (500 MHz; $CDCl_3$): 5.44 (1H, apparent dt, *J* 9.7 & 7.5, C*H*=CH), 5.27 – 5.18 (1H, m, one of CH=C*H*), 4.45 (1H, apparent dd, *J* 6.4 & 3.7, C*H*-pentyl), 3.94 – 3.89 (1H, m, C*H*-NC=N), 3.62 (3H, s, S-CH_3), 3.11 (1H, apparent dd, *J* 18.1 & 8.2, one of pyrrolidine CH_2C=C), 2.83 – 2.73 (1H, m, one of pyrrolidine CH_2C=C), 2.40 – 2.35 (1H, m, one of CH_2C=C), 2.27 – 2.22 (1H, m, one of CH_2C=C), 2.12 – 2.02 (2H, m, pyrrolidine CH_2CH-N), 1.94 (2H, apparent q, *J* 6.8, CH_2C=C), 1.96 – 1.74 (2H, m, CH_2CH-N=C), 1.41 – 1.31 (2H, m, alkyl CH_2), 1.28 – 1.14 (12 H, m, 6 x alkyl CH_2 protons) and 0.86 – 0.77 (6H, m, 3 x CH_3CH$_2$-alkyl).

δ_C (62.5 MHz; $CDCl_3$): 179.0 (carboxylic acid *C*=O), 153.0 (MeS-*C*=N), 147.9 (HO_2C-C=*C*), 132.4 (*C*H=CH), 127.7 (CH=*C*H), HO_2C-*C*=C peak *not observed*, 58.5 (*C*H-NC=N), 52.5 (*C*H-pentyl), 39.0 (pyrrolidine *C*H_2C=C), 31.0 (*C*H_2C=C), 30.8 (*C*H_2C=C), 28.80 (pyrrolidine *C*H_2CH-N), 28.78 (*C*H_2CH-N=C), 28.6 (*C*H_2), 28.4 (*C*H_2), 28.0 (*C*H_2), 26.4 (*C*H_2), 23.0 (*C*H_2), 21.7 (CH_3*C*H_2-alkyl), 21.6 (CH_3*C*H_2-alkyl), 13.1 (*C*H_3CH$_2$-alkyl) and *C*H_3S peak *not observed*.

MS-ES: *m/z* (%) = 405 (M – H^+, 100).

***N,N*-Bis(*tert*-butoxycarbonyl)-*N*''-(4'-hydroxy butyl)guanidine[79] (228)**

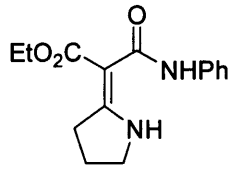


228

4-amino-butan-1-ol (129 mg, 1.45 mmol) was dissolved in THF/H_2O (14:1; 15 mL), and a solution of bis-boc thiourea (200 mg, 0.72 mmol) in THF (6 mL) added dropwise. The resulting pale green solution was stirred at 55 °C for 1 h, and then quenched with H_2O (20 mL). The layers were separated, and the aqueous layer washed with CH_2Cl_2 (3 x 10 mL). The combined organic washings were dried over Na_2SO_4 and the solvent removed *in vacuo*. The resultant crude oil was purified by flash column chromatography (eluting with CH_2Cl_2 → EtOAc), late fractions affording the *title compound* (R_f CH_2Cl_2: 0.48) as a light yellow oil (170 mg, 71%) which crystallised on standing.

Appendix A

Compound List



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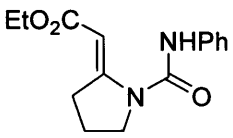

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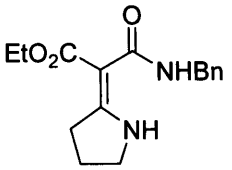

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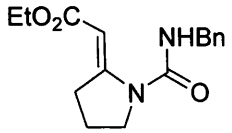

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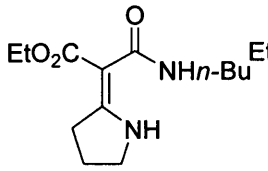

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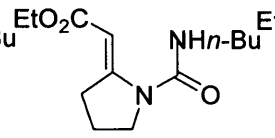

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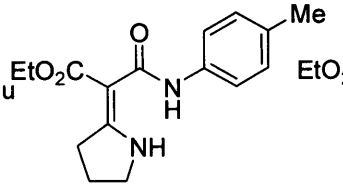

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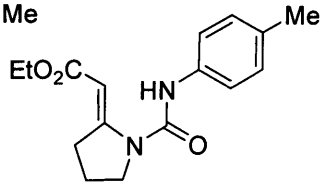

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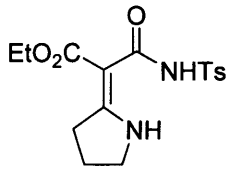

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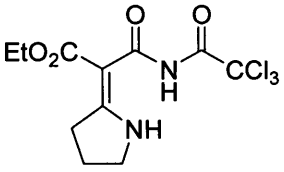

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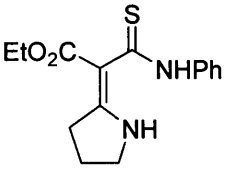

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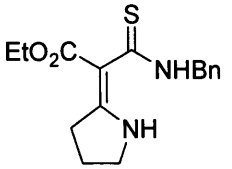

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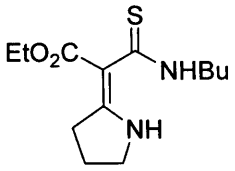

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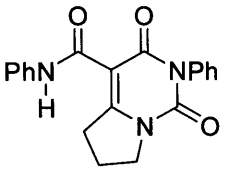

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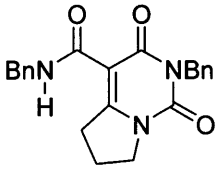

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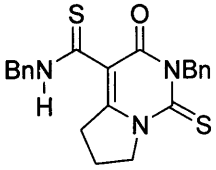

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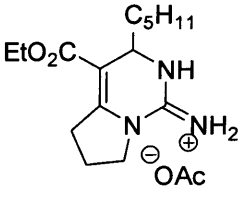

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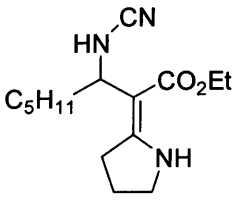

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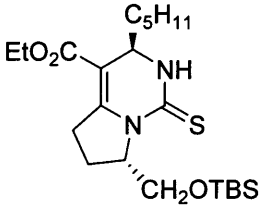

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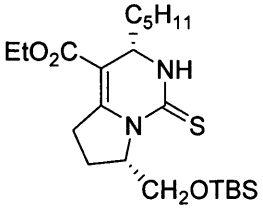

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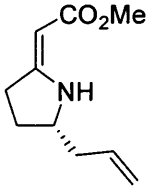

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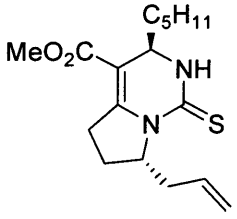

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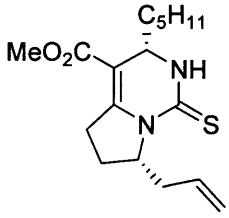

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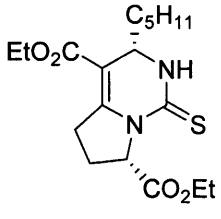

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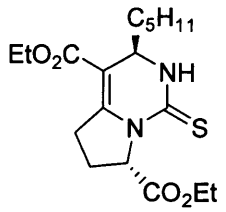

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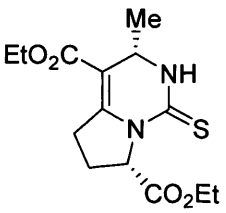

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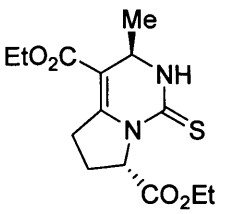

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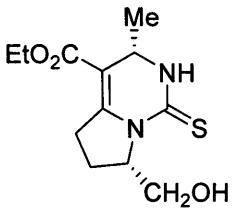

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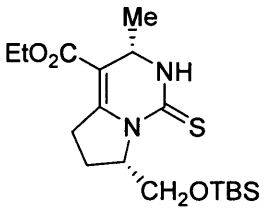

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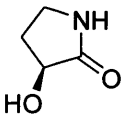

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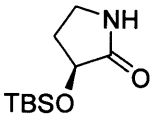

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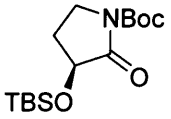

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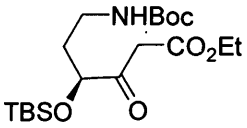

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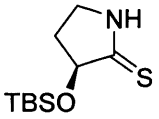

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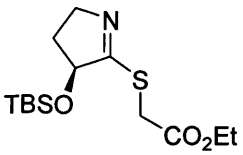

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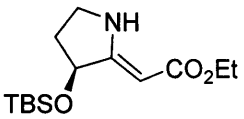

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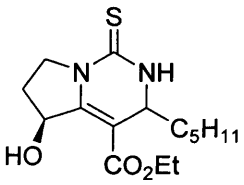

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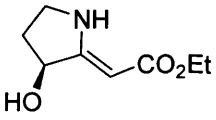

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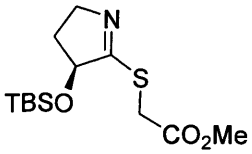

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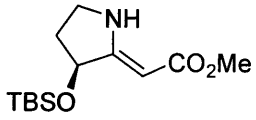

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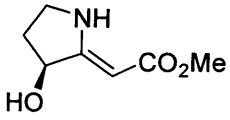

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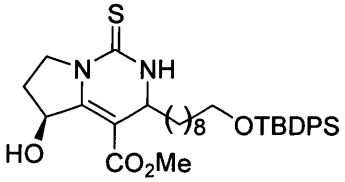

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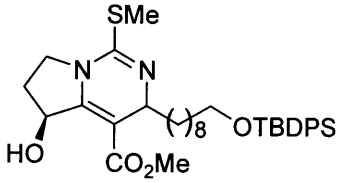

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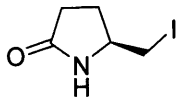

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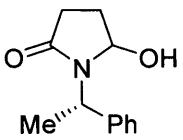

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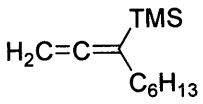

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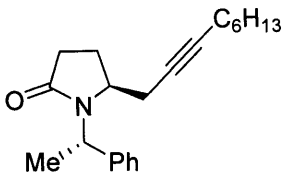

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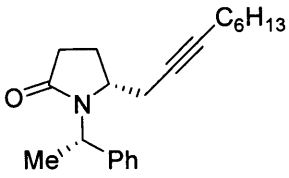

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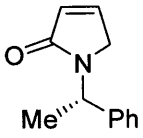

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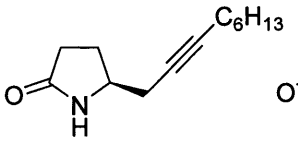

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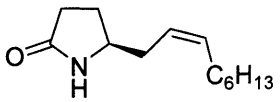

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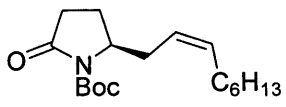

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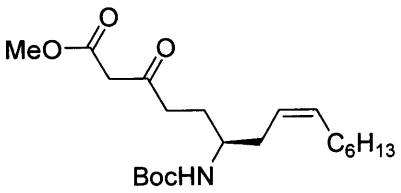

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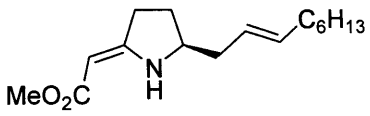

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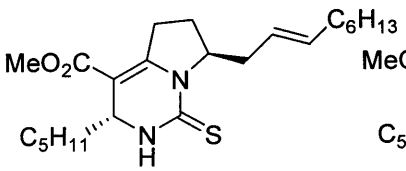

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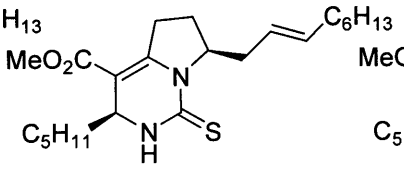

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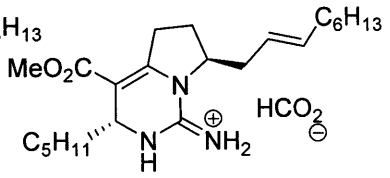

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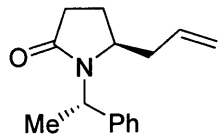

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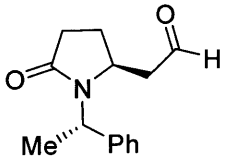

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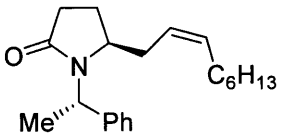

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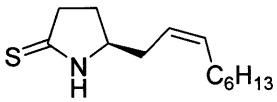

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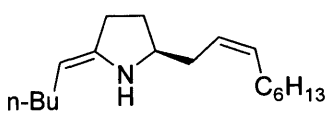

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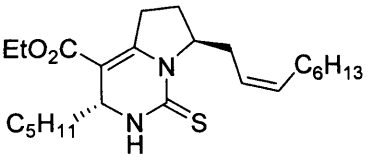

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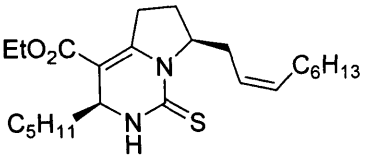

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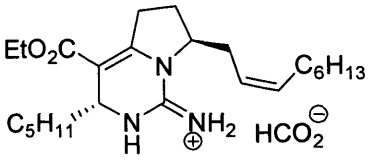

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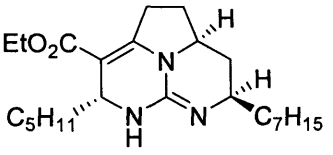

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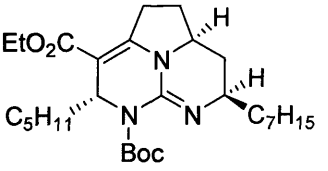

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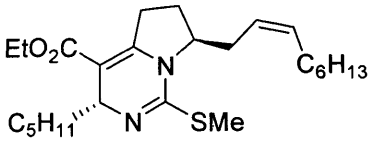

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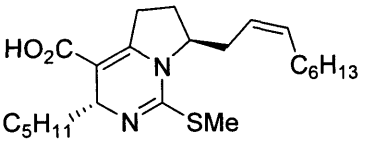

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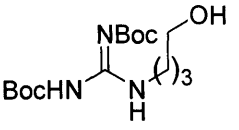
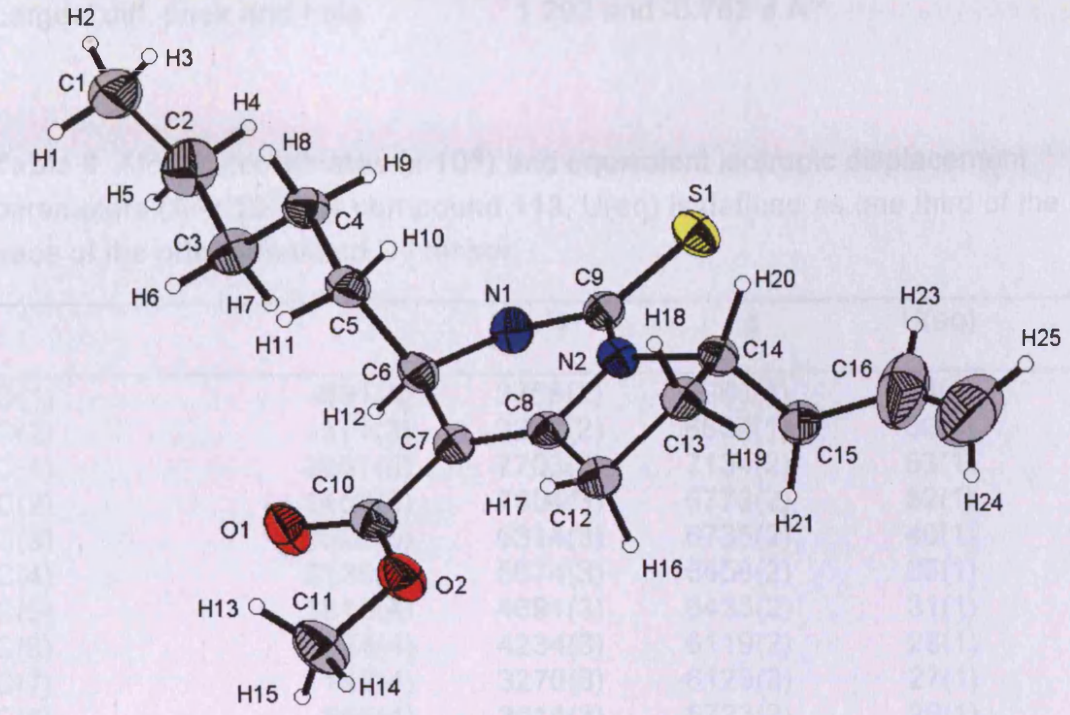


228

Appendix B

Crystallographic Data

Table 5. Crystal data and structure refinement for compound **113**.



Empirical formula	$C_{17}H_{26}N_2O_2S$
Formula weight	322.46
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 8.8940(1) Å, a = 106.777(1)°
	b = 15.5730(2) Å, b = 95.504(1)°
	c = 26.7230(4) Å, g = 92.328(1)°
Volume	3518.35(8) $Å^3$
Z, Calculated density	8, 1.218 Mg/m^3
Absorption coefficient	0.193 mm^{-1}
F(000)	1392
Crystal size	0.25 x 0.10 x 0.10 mm
Theta range for data collection	2.95 to 27.56 °
Limiting indices	-11<=h<=11, -20<=k<=20, -34<=l<=34
Reflections collected / unique	57727 / 16125 [R(int) = 0.1019]
Completeness to theta = 27.56	99.1 %
Absorption correction	None
Max. and min. transmission	0.9810 and 0.9534
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	16125 / 108 / 811
Goodness-of-fit on F^2	1.015

Final R indices [I>2s(I)]	$R_1 = 0.0959$, $wR_2 = 0.2157$
R indices (all data)	$R_1 = 0.1521$, $wR_2 = 0.2451$
Largest diff. peak and hole	1.292 and -0.762 e.Å^{-3}

Table 6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for compound **113**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-691(4)	3758(2)	6966(1)	44(1)
O(2)	-371(3)	2292(2)	6634(1)	39(1)
C(1)	2861(6)	7703(3)	7134(2)	53(1)
C(2)	1456(6)	7304(3)	6773(2)	52(1)
C(3)	1028(5)	6314(3)	6735(2)	40(1)
C(4)	2136(5)	5674(3)	6458(2)	35(1)
C(5)	1813(4)	4691(3)	6433(2)	31(1)
C(6)	324(4)	4234(3)	6119(2)	28(1)
C(7)	142(4)	3270(3)	6125(2)	27(1)
C(8)	555(4)	2614(3)	5723(2)	26(1)
C(9)	752(4)	3617(3)	5177(2)	28(1)
C(10)	-352(4)	3142(3)	6611(2)	32(1)
C(11)	-758(6)	2175(4)	7125(2)	52(1)
C(12)	708(4)	1627(3)	5640(2)	30(1)
C(13)	1762(4)	1388(3)	5207(2)	32(1)
C(14)	1340(4)	1993(3)	4869(2)	30(1)
C(15)	-32(4)	1593(3)	4454(2)	35(1)
C(16)	463(7)	1027(5)	3966(3)	87(2)
C(17)	490(8)	367(6)	3713(3)	105(2)
S(1)	1077(1)	3792(1)	4601(1)	35(1)
N(2)	971(3)	2811(2)	5273(1)	27(1)
N(1)	257(4)	4248(2)	5569(1)	30(1)

Table 7. Bond lengths [Å] and angles [°] for compound **113**.

O(1)-C(10)	1.209(5)	C(16)-C(17)	1.057(9)
O(2)-C(10)	1.342(5)	C(16)-H(23)	0.9500
O(2)-C(11)	1.448(5)	C(17)-H(24)	0.9500
C(1)-C(2)	1.496(7)	C(17)-H(25)	0.9500
C(1)-H(1)	0.9800	N(1)-H(26)	0.8800
C(1)-H(2)	0.9800		
C(1)-H(3)	0.9800	C(110)-O(12)-C(111)	114.8(3)
C(2)-C(3)	1.545(6)	C(12)-C(11)-H(1)	109.5
C(2)-H(4)	0.9900	C(12)-C(11)-H(2)	109.5
C(2)-H(5)	0.9900	H(1)-C(11)-H(2)	109.5
C(3)-C(4)	1.518(6)	C(12)-C(11)-H(3)	109.5
C(3)-H(6)	0.9900	H(1)-C(11)-H(3)	109.5
C(3)-H(7)	0.9900	H(2)-C(11)-H(3)	109.5
C(4)-C(5)	1.527(6)	C(11)-C(12)-C(13)	114.2(4)
C(4)-H(8)	0.9900	C(11)-C(12)-H(4)	108.7
C(4)-H(9)	0.9900	C(13)-C(12)-H(4)	108.7
C(5)-C(6)	1.526(5)	C(11)-C(12)-H(5)	108.7
C(5)-H(10)	0.9900	C(13)-C(12)-H(5)	108.7
C(5)-H(11)	0.9900	H(4)-C(12)-H(5)	107.6
C(6)-N(1)	1.472(5)	C(14)-C(13)-C(12)	112.8(4)
C(6)-C(7)	1.510(6)	C(14)-C(13)-H(6)	109.0
C(6)-H(12)	1.0000	C(12)-C(13)-H(6)	109.0
C(7)-C(8)	1.344(5)	C(14)-C(13)-H(7)	109.0
C(7)-C(10)	1.473(5)	C(12)-C(13)-H(7)	109.0
C(8)-N(2)	1.404(5)	H(6H7)-C(13)-H(7)	107.8
C(8)-C(12)	1.501(5)	C(13)-C(14)-C(15)	115.1(3)
C(9)-N(1)	1.337(5)	C(13)-C(14)-H(8)	108.5
C(9)-N(2)	1.369(5)	C(15)-C(14)-H(8)	108.5
C(9)-S(1)	1.688(4)	C(13)-C(14)-H(9)	108.5
C(11)-H(13)	0.9800	C(15)-C(14)-H(9)	108.5
C(11)-H(14)	0.9800	H(8)-C(14)-H(9H10)	107.5
C(11)-H(15)	0.9800	C(16)-C(15)-C(14)	115.9(3)
C(12)-C(13)	1.530(5)	C(16)-C(15)-H(10)	108.3
C(12)-H(16)	0.9900	C(14)-C(15)-H(10)	108.3
C(12)-H(17)	0.9900	C(16)-C(15)-H(11)	108.3
C(13)-C(14)	1.518(6)	C(14)-C(15)-H(11)	108.3
C(13)-H(18)	0.9900	H(10)-C(15)-H(11)	107.4
C(13)-H(19)	0.9900	N(11)-C(16)-C(17)	108.6(3)
C(14)-N(2)	1.484(5)	N(11)-C(16)-C(15)	111.1(3)
C(14)-C(15)	1.544(5)	C(17)-C(16)-C(15)	110.6(3)
C(14)-H(20)	1.0000	N(11)-C(16)-H(12)	108.8
C(15)-C(16)	1.467(7)	C(17)-C(16)-H(12)	108.8
C(15)-H(21)	0.9900	C(15)-C(16)-H(12)	108.8
C(15)-H(22)	0.9900	C(18)-C(17)-C(110)	125.1(4)

C(18)-C(17)-C(16)	119.4(3)	H(24)-C(117)-H(25)	120.0
C(110)-C(17)-C(16)	115.2(3)	C(19)-N(12)-C(18)	123.1(3)
C(17)-C(18)-N(12)	120.2(4)	C(19)-N(12)-C(114)	123.7(3)
C(17)-C(18)-C(112)	132.7(4)	C(18)-N(12)-C(114)	111.8(3)
N(12)-C(18)-C(112)	107.1(3)	C(19)-N(11)-C(16)	125.3(3)
N(11)-C(19)-N(12)	115.3(3)	C(19)-N(11)-H(26)	117.4
N(11)-C(19)-S(11)	122.7(3)	C(16)-N(11)-H(26)	117.4
N(12)-C(19)-S(11)	122.0(3)		
O(11)-C(110)-O(12)	122.6(4)		
O(11)-C(110)-C(17)	122.6(4)		
O(12)-C(110)-C(17)	114.8(4)		
O(12)-C(111)-H(13)	109.5		
O(12)-C(111)-H(14)	109.5		
H(13)-C(111)-H(14)	109.5		
O(12)-C(111)-H(15)	109.5		
H(13)-C(111)-H(15)	109.5		
H(14)-C(111)-H(15)	109.5		
C(18)-C(112)-C(113)	103.0(3)		
C(18)-C(112)-H(16)	111.2		
C(113)-C(112)-H(16)	111.2		
C(18)-C(112)-H(17)	111.2		
C(113)-C(112)-H(17)	111.2		
H(16)-C(112)-H(17)	109.1		
C(114)-C(113)-C(112)	103.9(3)		
C(114)-C(113)-H(18)	111.0		
C(112)-C(113)-H(18)	111.0		
C(114)-C(113)-H(19)	111.0		
C(112)-C(113)-H(19)	111.0		
H(18)-C(113)-H(19)	109.0		
N(12)-C(114)-C(113)	100.9(3)		
N(12)-C(114)-C(115)	111.6(3)		
C(113)-C(114)-C(115)	112.6(4)		
N(12)-C(114)-H(20)	110.5		
C(113)-C(114)-H(20)	110.5		
C(115)-C(114)-H(20)	110.5		
C(116)-C(115)-C(114)	110.7(4)		
C(116)-C(115)-H(21)	109.5		
C(114)-C(115)-H(21)	109.5		
C(116)-C(115)-H(22)	109.5		
C(114)-C(115)-H(22)	109.5		
H(21)-C(115)-H(22)	108.1		
C(117)-C(116)-C(115)	146.2(10)		
C(117)-C(116)-H(23)	106.9		
C(115)-C(116)-H(23)	106.9		
C(116)-C(117)-H(24)	120.0		
C(116)-C(117)-H(25)	120.0		

Table 8. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **113**.

	x	y	z	U(eq)
H(1)	2734	7671	7489	80
H(2)	3046	8332	7144	80
H(3)	3724	7366	7006	80
H(4)	1597	7343	6417	62
H(5)	603	7668	6895	62
H(6)	992	6260	7093	48
H(7)	4	6136	6541	48
H(8)	3166	5877	6641	41
H(9)	2132	5712	6095	41
H(10)	2652	4346	6278	37
H(11)	1818	4655	6797	37
H(12)	-533	4563	6283	33
H(13)	-40	2546	7415	77
H(14)	-712	1541	7112	77
H(15)	-1786	2358	7180	77
H(16)	-286	1282	5524	36
H(17)	1161	1511	5965	36
H(18)	2837	1512	5358	39
H(19)	1589	746	5000	39
H(20)	2229	2130	4695	36
H(21)	-724	1228	4595	42
H(22)	-595	2086	4380	42
H(23)	974	1418	3812	104
H(24)	34	-127	3798	125
H(25)	971	269	3401	125
H(26)	-142	4709	5492	36

Table 9. Torsion angles [°] for compound **113**.

C(11)-C(12)-C(13)-C(14)	-68.7(6)
C(12)-C(13)-C(14)-C(15)	177.1(4)
C(13)-C(14)-C(15)-C(16)	63.6(5)
C(14)-C(15)-C(16)-N(11)	59.3(4)
C(14)-C(15)-C(16)-C(17)	180.0(3)
N(11)-C(16)-C(17)-C(18)	26.4(5)
C(15)-C(16)-C(17)-C(18)	-95.7(4)
N(11)-C(16)-C(17)-C(110)	-159.3(3)
C(15)-C(16)-C(17)-C(110)	78.5(4)
C(110)-C(17)-C(18)-N(12)	178.4(3)
C(16)-C(17)-C(18)-N(12)	-7.9(5)
C(110)-C(17)-C(18)-C(112)	-2.6(7)
C(16)-C(17)-C(18)-C(112)	171.0(4)
C(111)-O(12)-C(110)-O(11)	-2.8(6)
C(111)-O(12)-C(110)-C(17)	176.1(4)
C(18)-C(17)-C(110)-O(11)	178.8(4)
C(16)-C(17)-C(110)-O(11)	4.9(6)
C(18)-C(17)-C(110)-O(12)	0.0(6)
C(16)-C(17)-C(110)-O(12)	-173.9(3)
C(17)-C(18)-C(112)-C(113)	-159.4(4)
N(12)-C(18)-C(112)-C(113)	19.7(4)
C(18)-C(112)-C(113)-C(114)	-34.0(4)
C(112)-C(113)-C(114)-N(12)	34.7(4)
C(112)-C(113)-C(114)-C(115)	-84.4(4)
N(12)-C(114)-C(115)-C(116)	158.2(5)
C(113)-C(114)-C(115)-C(116)	-89.1(6)
C(114)-C(115)-C(116)-C(117)	110.9(13)
N(11)-C(19)-N(12)-C(18)	6.8(5)
S(11)-C(19)-N(12)-C(18)	-172.8(3)
N(11)-C(19)-N(12)-C(114)	172.5(3)
S(11)-C(19)-N(12)-C(114)	-7.1(5)
C(17)-C(18)-N(12)-C(19)	-11.0(5)
C(112)-C(18)-N(12)-C(19)	169.8(3)
C(17)-C(18)-N(12)-C(114)	-178.2(3)
C(112)-C(18)-N(12)-C(114)	2.6(4)
C(113)-C(114)-N(12)-C(19)	169.1(3)
C(115)-C(114)-N(12)-C(19)	-71.1(5)
C(113)-C(114)-N(12)-C(18)	-23.8(4)
C(115)-C(114)-N(12)-C(18)	96.0(4)
N(12)-C(19)-N(11)-C(16)	17.2(5)
S(11)-C(19)-N(11)-C(16)	-163.2(3)
C(17)-C(16)-N(11)-C(19)	-32.7(5)
C(15)-C(16)-N(11)-C(19)	89.2(5)

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Publications

Diastereoselective Dimerisation of Alkenylthiazolines: A Combined Synthetic and Computational Study

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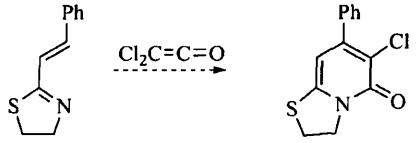
The acylative dimerisation of 2-alkenyl-1,3-thiazolines **1** gives compounds **3** and **8** upon treatment with trichloroacetyl chloride and trifluoroacetic anhydride, respectively. This reaction is completely diastereoselective, in particular giving only a single double-bond isomer. The scope of the reaction has been evaluated synthetically, while a computational study has elucidated the mechanism of the reaction and the origin of stereocontrol.

Introduction

Over the last few years we have investigated the annulation reactions for unsaturated azolines with heterocumulenes.[1] These reactions provide access to a range of novel heterocycles with excellent stereocontrol.[2]

As a continuation of this study we anticipated that reaction of a simple alkenylthiazoline– such as **1a**– with dichloroketene would be followed by loss of HCl to give compound **2a** (Scheme 1). In the event, this reaction turned out to be far from straightforward, and the results of this study are described in full herein.[3]

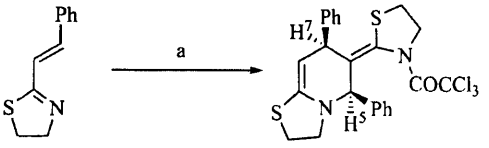


1a **2a**

Scheme 1.

Results and Discussion

When trichloroacetyl chloride was added to a solution of the alkenylthiazoline **1a** containing zinc-copper couple, the expected product **2a** was not obtained. Detailed examination of the spectroscopic data allowed us to propose structure **3** for the product, although we were unable at this stage to elucidate the double-bond geometry. When the reaction was carried out without the zinc-copper couple present, the acylated dimer was formed once again (Scheme 2). From this observation it was clear that the trichloroacetyl chloride was reacting with the thiazoline, and furthermore this acylation was so rapid that in the presence of zinc-copper couple, the ketene did not have time to form. The relatively low yield is a result of losses on chromatography, and we were able to confirm from NMR spectra of the crude reaction products that only a single stereoisomer had been formed. The *cis* relationship between the phenyl rings was initially suggested due to the presence of a 3.5-Hz W-coupling between the two benzylic protons, and was subsequently confirmed by nOe experiments. (Scheme 2).



1a **3**

10% nOe and 3.5 Hz coupling between H^5 and H^7

Scheme 2. a) Cl_3CCOCl, DME, Et_2O, 25 °C, 3 h, 29%.

There appears to be no direct precedent for this transformation, although a related dimerisation of the 2-(benzylideneamino)benzothiazoline **4** to give **5** is known (Scheme 3).[4]

Upon consideration of the possible mechanisms, the formation of a single double-bond isomer is particularly surprising. Reaction of an acylated alkenylthiazoline **6** with compound **1** will ultimately give compound **7**, either by a concerted or stepwise pathway (vide infra). Loss of a proton from this compound will then give the observed product **3**

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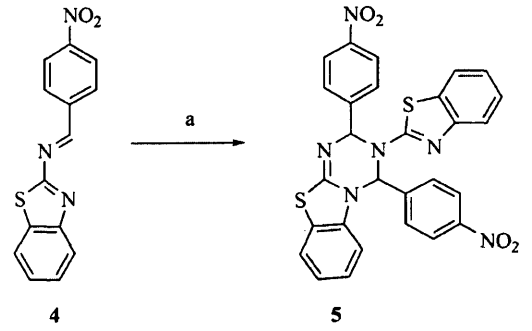
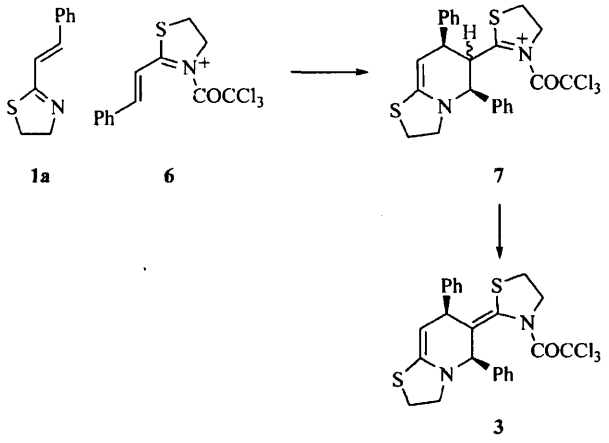


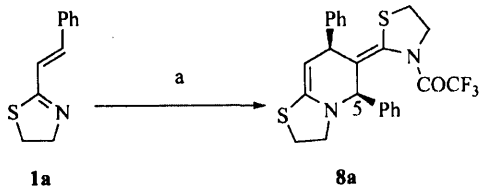
Scheme 3. a) Xylene, reflux, 60 h, 65%.

(Scheme 4). The stereoselective formation of tetrasubstituted double bonds is particularly challenging, and since the environment around the tetrasubstituted double-bond in **3** is almost symmetrical it would be optimistic to expect much stereocontrol in the deprotonation of compound **7**. Indeed, semi-empirical calculations showed that the (*E*) and (*Z*) isomers of compound **8** have negligible differences in energy. We therefore sought to confirm the double-bond geometry and probe the mechanism of this new reaction.



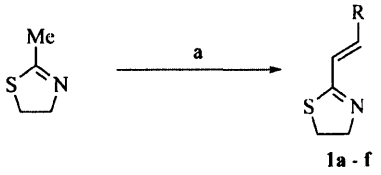
Scheme 4. The basic reaction mechanism.

Despite extensive efforts, compound **3** did not produce crystals suitable for X-ray diffraction. We therefore decided to examine the scope and limitations of the reaction in the hope of producing a crystalline analogue. A range of other acylating agents was screened for their ability to promote the dimerisation of compound **1a**. Triflic anhydride, 4-toluenesulfonyl chloride, acetyl chloride, acetic anhydride and methanesulfonyl chloride returned only starting materials under a variety of conditions. The dimerisation was smoothly induced by trifluoroacetic anhydride, acylated dimer **8a** being formed in 41% yield (Scheme 5). Compared to compound **3**, the 5-H in compound **8a** was shifted approximately 0.5 ppm upfield in the proton NMR spectrum. We tentatively ascribe this as a difference in the through-space effect between the $COCCl_3$ and $COCF_3$ groups; this supports the double-bond geometry shown, although it certainly does not constitute proof.



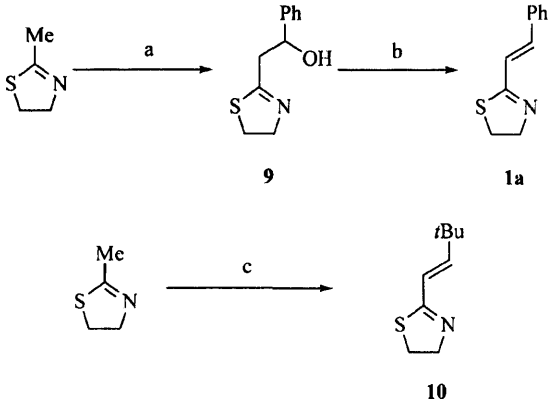
Scheme 5. a) TFAA, DME, Et_2O, 25 °C, 3 h, 41%.

The alkenylthiazolines **1a–1f** were prepared by the iodine-catalysed condensation of 2-methylthiazoline with 4-substituted benzaldehydes (Scheme 6). The yields for this reaction, although comparable to those reported in the literature, are modest.[5,6] As an alternative, compounds **1a** and the *tert*-butyl analogue **10** were prepared by a two-step method (Scheme 7).



a, R = Ph, 30%
b, R = 4-BrC_6H_4, 29%
c, R = 4-$NO_2C_6H_4$, 31%
d, R = 4-$MeOC_6H_4$, 33%
e, R = 4-PhC_6H_4, 21%
f, R = 4-MeC_6H_4, 35%

Scheme 6. a) RC_6H_4CHO, I_2, toluene, reflux, 16 h.

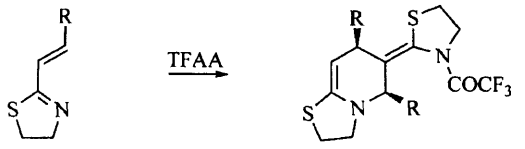


Scheme 7. a) *n*BuLi, THF,–78 °C then PhCHO, 90%; b) TFA, toluene, 4-Å molecular sieves, 1 h, 75%; c) i. *n*BuLi, THF,–78 °C then *t*BuCHO; ii. TFA, toluene, reflux, 3 h, 50% over two steps.

The reaction conditions employed to form the parent compound **8a** were suitable for the 4-methoxyphenyl analogue **8d**, while the 4-bromophenyl, 4-nitrophenyl and 4-phenylphenyl analogues **8b**, **8c** and **8e** called for a change in solvent and elevated temperature (75 °C). The 2-(4-methylphenyl)ethenyl-1,3-thiazoline (**1f**) did not react under any conditions; the *tert*-butyl substrate **10** was also unreactive (Table 1). Within this series, it is impossible to see any trend in either reactivity or yield. We tentatively attribute the lack of reactivity of compound **10** to steric effects, although the

apparent lack of reactivity of compound **1f** is bewildering. None of these compounds gave crystals suitable for X-ray diffraction. The ^{13}C NMR spectroscopic data for these compounds warrant brief comment. It is not surprising, given the anticipated low intensity of quaternary carbons, that the expected quartets for the trifluoroacetamide carbonyl peaks could not be assigned with any degree of confidence. The CF_3 carbon itself in these compounds was also of low intensity, and in the case of compound **8b** was difficult to observe. More surprisingly in all of compounds **8b**, **8c** and **8d** only two distinct aromatic CH peaks were observed in the ^{13}C NMR spectra, whereas the ^1H NMR spectra clearly showed the presence of two different, albeit similar, aromatic rings. Compound **3** also shows only three distinct aromatic CH peaks, and compound **8a** shows four. This coincidence of peaks is unexpected, but all other data (including the aromatic quaternary carbon atoms in the same ^{13}C NMR spectra) are fully consistent with the proposed structures.

Table 1. Acylative dimerisation of 2-alkenyl-1,3-thiazolines.

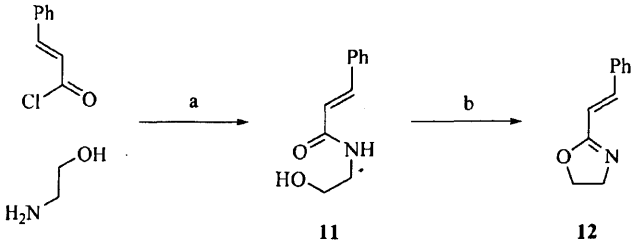


8a - e

Compound	R	Conditions	Yield%
8a	Ph	Et_2O, DME, 25 °C, 3 h	41
8b	4-BrC_6H_4	$CHCl_3$, reflux, 6 h	43
8c	4-$O_2NC_6H_4$	$CHCl_3$, reflux, 3 h	50
8d	4-$MeOC_6H_4$	Et_2O, DME, 25 °C, 3 h	31
8e	4-PhC_6H_4	$CHCl_3$, reflux, 6 h	25[a]

[a] Compound **8e** was obtained with difficulty from a complex mixture and was not obtained analytically pure.

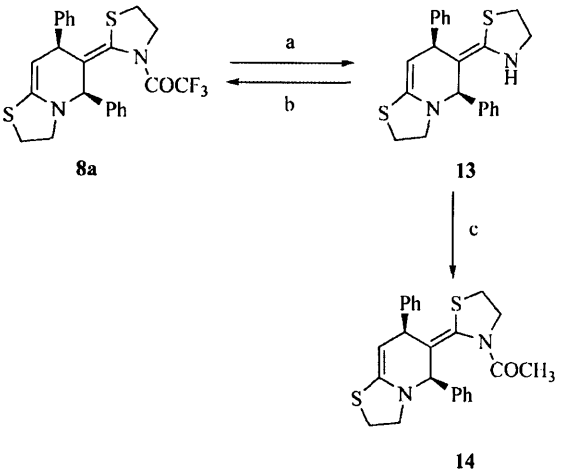
We also briefly investigated whether the reaction could be extended to alkenyloxazolines. The 2-styryl-1,3-oxazoline (**12**) was prepared in two steps from cinnamoyl chloride and ethanolamine via the amide **11** (Scheme 8). This compound failed to react with trifluoroacetic anhydride under any of the conditions used for the corresponding thiazolines.



11 **12**

Scheme 8. a) NaOH, CH_2Cl_2, H_2O, 25 °C, 24 h, 78%; b) MsCl, Et_3N, CH_2Cl_2, 25 °C, 16 h, 90%.

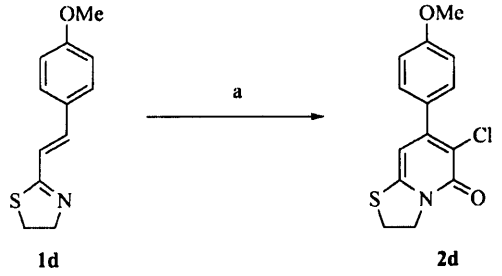
Having failed to prove the double-bond geometry crystallographically, we sought indications of the likely geometry from the NMR spectroscopic data. Apart from the difference in the 5-H between compounds **3** and **8a** mentioned above, the only hint was the upfield shift of two aromatic protons away from the body of the aryl signals, presumably due to the proximity of the trifluoroacetyl group. These were shown by nOe studies to be the *ortho* protons on the phenyl ring at the 5-position, tentatively supporting the double-bond geometry as drawn throughout. It seemed reasonable that upon replacement of the trifluoroacetyl group with an acetyl group a nOe from the acetyl CH_3 to one of the benzylic ring protons might be seen, and the double bond geometry therefore unambiguously proven. The trifluoroacetyl group was cleaved reductively using sodium borohydride, presenting the dimer as the free enamine **13.** This reaction was far from clean and the free enamine was intolerant to chromatography. Re-acylation of this compound with trifluoroacetic anhydride returned an impure sample of **8a** as the same double-bond isomer. Reaction with acetic anhydride gave a very impure sample of the desired compound **14** such that no meaningful nOe data could be obtained (Scheme 9). However, the relative stability and facile acylation of compound **13** appears to preclude an alternative mechanism for the reaction whereby compound **1a** undergoes dimerisation, this being followed by acylation.



8a **13** **14**

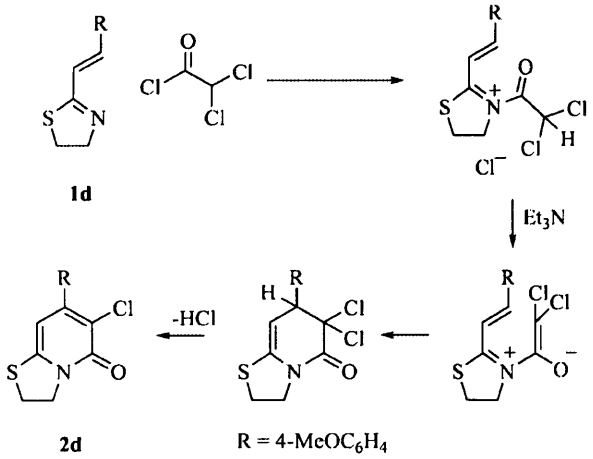
Scheme 9. a) $NaBH_4$, EtOH, 25 °C, 48 h, 80% crude; b) TFAA, Et_3N, DMAP, CH_2Cl_2; c) Ac_2O, DMAP, Et_3N, DMAP, 25 °C, 24 h, see discussion.

Returning to our original synthetic goal, the formation of compounds of general structure **2**, it was clear that while trichloroacetyl chloride is a sufficiently strong electrophile to induce dimerisation of compounds **1**, dichloroacetyl chloride is not. Since dichloroacetyl chloride can be used as a dichloroketene precursor,[7] we added triethylamine to a mixture of compound **1d** and dichloroacetyl chloride in THF. This gave the desired compound **2d** in 89% yield (Scheme 10).[8]



Scheme 10. a) $Cl_2CHCOCl$, Et_3N, THF, 25 °C, 2.5 h, 89%.

This reaction may proceed by attack of **1d** on in situ-generated dichloroketene. However, there is a distinct colour change on addition of dichloroacetyl chloride to **1d**, which leads us to favour reaction between these two species followed by deprotonation and cyclisation as the more likely course of reaction (Scheme 11). Alkenylthiazoline **1a** did not react cleanly under these conditions, possibly reflecting the lower nucleophilicity of this compound.



Scheme 11. Mechanism of formation of compound **2d**.

Computational Studies

Since we had been unable to unequivocally determine the double-bond geometry by chemical and spectroscopic methods, and were unable to rationalise the completely stereoselective formation of a tetrasubstituted double bond in an almost symmetrical local environment, we undertook a computational study of the reaction of compound **1a** with trifluoroacetic anhydride in order to attempt to answer these questions. This study was carried out using the PM3[9] Hamiltonian in the MOPAC program.[10] All calculations were performed with an SCF tolerance of 10^{-6} eV and geometry optimisations and transition state searches used a gradient cut-off of 4 kJ·mol^{-1} Å^{-1}. The potential energy surface for the reaction was searched using a series of constrained optimisations to approximately locate transition states between minima. In the following discussion the degree of freedom constrained will be identified, all other degrees of freedom were optimised at each point of a search. The approximate transition states were optimised using the eigenvector follower approach[11] without constraints and both minima and transition states were confirmed by a frequency analysis at the same level of theory, minima being recognised by a complete set of positive normal modes and transition states by a single negative (imaginary force constant) mode.

The formation of intermediate **7** could proceed via a concerted aza-Diels–Alder pathway, or a stepwise mechanism involving sequential conjugate addition reactions.[12] Proton loss from this compound then leads to the formation of compound **8a**. We initially had reservations about the ability of PM3 calculations to predict the stereochemical outcome of this proton loss. In order to allay these concerns, we elected to calculate the reaction pathway leading to compound **7**, since if we were able to distinguish between concerted and stepwise pathways and rationalise the stereochemistry of this reaction, we could be confident that this level of theory was indeed adequate.

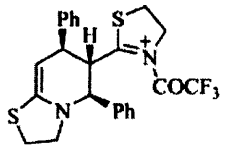
The Concerted Reaction Pathway

This pathway is more straightforward to investigate computationally, as the transition states would be relatively rigid. We investigated both the *exo* and *endo* Diels–Alder pathways for this reaction, but were unable to locate a transition state in either case. These transition states were also unsuccessfully sought using DFT calculations (B3LYP 6-31G** basis set). We were therefore satisfied that the reaction was unlikely to proceed via an initial concerted Diels–Alder pathway, and so turned our attention to the eventually more productive stepwise mechanism. This gave entirely reasonable results which explain all of the stereochemical features of the pathway, and so we are confident that the PM3 level of theory is perfectly adequate in this case.

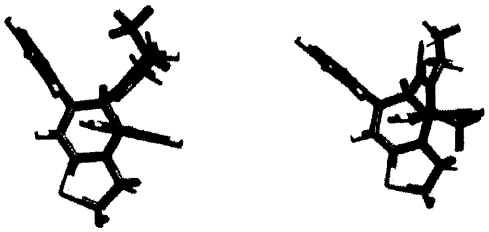
The Stepwise Reaction Pathway

Since the double-bond geometry is defined in the final abstraction of a proton from an intermediate such as **15**, we examined the barrier to rotation of the acylated thiazoline ring in this compound. The rotational profile is essentially sinusoidal with a substantial barrier to rotation (33 kJ·mol^{-1}). Both minima **15a** and **15b** have similar energies, with the acylated thiazoline ring essentially perpendicular to the bicyclic fragment of the molecule (Figure 1). Therefore, no preference for either clockwise or anticlockwise rotation to give a single product isomer is indicated.

It seemed reasonable that if intermediate **15** was formed in a given conformation, it would be deprotonated to form the final product **8a** rapidly. This would preclude rotation about the C6–C2′ bond and so give rise to a single double-bond isomer. In order to investigate this possibility, we considered all steps in the proposed reaction mechanism in order to understand the conformational bias at each stage. Since much of this study did not eventually shed light



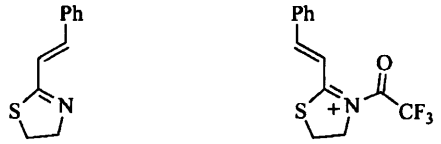
15



15a **15b**

Figure 1. Minimum conformations **15a** and **15b** of intermediate **15**.

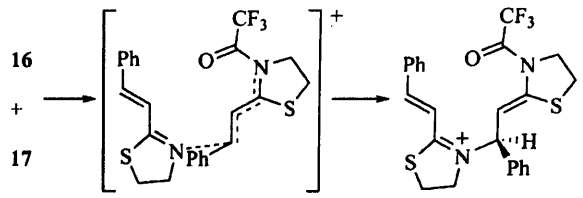
on the reason behind the formation of a single double-bond isomer, it will be presented in a condensed form. The *s-trans* conformation **16** of the free thiazoline is slightly favoured (3.5 kJ·mol^{-1}), while after acylation the *s-cis* conformation **17** is more favoured (13 kJ·mol^{-1}) (Figure 2). While these conformations do in fact give rise to the lowest energy transition states and intermediates along the reaction coordinate, the entire reaction pathway was investigated beginning with the *s-cis* and *s-trans* conformers of each.



16 **17**

Figure 2.

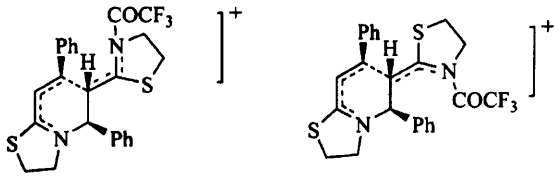
Location of the transition state **18** for nucleophilic attack of **16** onto **17** proved straightforward. In intermediate **19** the double-bond geometry for the ring closure is fixed (Scheme 12), with the transition state forming the opposite double-bond isomer being 13 kJ·mol^{-1} higher in energy.



18 **19**

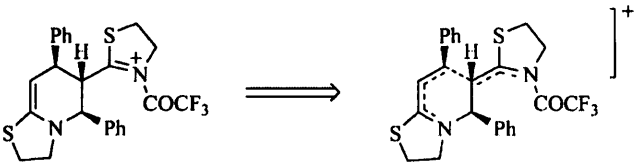
Scheme 12.

Of the four possible transition states for the actual ring-closure step, structures **20a** and **20b** are shown schematically in Figure 3. These were located by systematically increasing the corresponding carbon–carbon bond length in the intermediate **15** (Scheme 13) and its rotamer. The analogous transition states to form the 5,7-*anti* diastereomeric transition states were found to be 19 kJ·mol^{-1} and 33 kJ·mol^{-1} higher in energy than **20a** and **20b**, respectively. Therefore, irrespective of the double-bond geometry the 5,7-*syn* arrangement of the phenyl groups is overwhelmingly favoured. It is encouraging that the calculations are able to reproduce this aspect of the experimental observations.



20a, +0 kJmol^{-1} **20b**, +16 kJmol^{-1}

Figure 3.



15 **20b**

Scheme 13.

Although these calculations had established the likely conformation of the various intermediates and transition states along the reaction pathway, conformations **15a** and **15b** (of essentially identical energy) were shown to be favoured from **20a** and **20b**, respectively. We therefore still had no basis upon which to predict which double-bond isomer would be formed, or even that any selectivity would be observed. Up to this point the anion for the cationic intermediates had been omitted for simplicity, not least because its location is difficult to determine. However, for the final step of hydrogen abstraction the inclusion of a trifluoroacetate anion to receive the proton was found to be crucial. At this point the positioning of the anion is also less ambiguous since it must be placed with the carboxylate group in close proximity to C6-H. The bulk of the phenyl substituents also place additional limitations on its position. With the anion in place the calculated energy difference between the two intermediate structures **15a**·$CF_3CO_2^-$ and **15b**·$CF_3CO_2^-$ is now significant as shown in Figure 4.

The introduction of the anion causes significant conformational change of the phenyl substituents to allow its interaction with the C6 proton. This change is more notable at the 5-phenyl than the 7-phenyl which is held more rigidly in place by the C=C bond of the six membered heterocycle. However the C6-H and C–N bonds are still found to be near co-planar and so the geometry of the product double bond is still ambiguous at this stage. Transition states for the proton removal were located using two methods. Firstly a series of constrained optimisations with the C6-H bond length systematically increased was explored and secondly

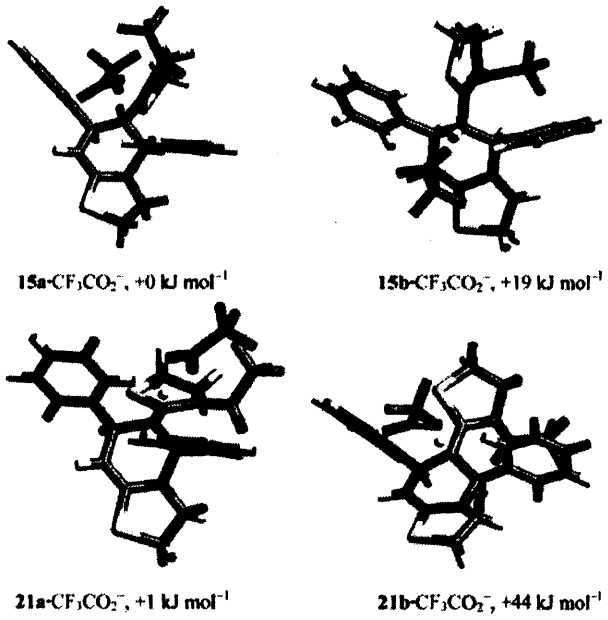


Figure 4.

by rotation of the acylated thiazoline ring from each of the intermediates **15a**·$CF_3CO_2^-$ and **15b**·$CF_3CO_2^-$ without constraining the C6-H distance. Both approaches led to the same conclusion that proton loss occurs as the five-membered ring rotates to become co-planar with the six-membered heterocycle, so that the formation of the new double bond occurs simultaneously with proton loss to form the neutral acylated dimer. From **15a**·$CF_3CO_2^-$ we obtained the preferred transition state **21a** and from **15b**·$CF_3CO_2^-$ the transition state **21b** was located. Both structures therefore lead to the same (*E*) double bond isomer. Rotational searches to find the corresponding (*Z*) isomer failed since the steric hindrance between the trifluoroacetyl group and the 7-phenyl prevented the five-membered ring rotating to become co-planar with the piperidine ring. It appears, then, that selectivity is controlled by the ease of rotation of the acylated thiazoline ring to form the new C=C bond. This is impeded by steric interactions between the trifluoroacetyl group and the phenyl substituents. In the case of the (*Z*) isomer, the 7-phenyl group has less conformational mobility so that rotation to give the (*E*) isomer is the preferred process.

Conclusions

A novel stereoselective acylative dimerisation reaction of alkenylthiazolines has been investigated experimentally and computationally. The calculations show the importance of including counterions in the structure in order to fully explain the stereoselectivity in such reactions.

Experimental Section

General Remarks: Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded with a Fisons VG Platform II spectrometer. High-resolution mass spectra were performed at the EPSRC centre for Mass Spectroscopy in Swansea. NMR spectra were recorded at 25 °C with a Bruker DPX 400 spectrometer operating at 400 MHz for ^1H and at 100 MHz for ^{13}C or with a Bruker Avance 500 spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Multiplicity in ^1H NMR is reported as singlet (s), doublet (d), double doublet (dd), triplet (t), and multiplet (m). Multiplicity in ^{13}C NMR was obtained using the DEPT pulse sequence. Flash chromatography was performed using matrex silica 60 35–70 micron.

4,5-Dihydro-2-[(*E*)-2-phenylethenyl]-1,3-thiazole (1a): 2-Methylthiazoline (5.06 g, 50 mmol), and benzaldehyde (5.36 g, 50.0 mol) were heated under reflux in toluene (50 mL) under Dean–Stark conditions. After 1 h iodine (100 mg) was added and reflux allowed to continue for 16 h. The reaction mixture was washed with saturated sodium thiosulfate solution (100 mL), dried with $MgSO_4$, and the solvent removed in vacuo. The resulting thick oil was dissolved in diethyl ether and filtered, the filtrate was concentrated in vacuo and distilled under reduced pressure (kugelrohr, oven temperature 180 °C at 0.5 Torr), to give **1a** (2.8 g, 30%) as a white crystalline solid, m.p. 103–105 °C (ref.[6] m.p. 101–102 °C). IR (CH_2Cl_2): $\tilde{\nu}$ = 1583, 1462, 1377 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.43 [dd, ^3J(H,H) = 7.9, $^4J_{H,H}$ = 1.3, 2 H, aromatic C*H*], 7.40–7.25 (m, 3 H, aromatic C*H*), 7.05 (d, $^3J_{H,H}$ = 16.2, 1 H, one of alkene C*H*), 6.95 (d, $^3J_{H,H}$ = 16.2, 1 H, one of alkene C*H*), 4.30 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2N), 3.25 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.3 (thiazoline *C*), 141.6 (alkene *C*H), 135.7 (aromatic *C*), 129.8 (aromatic *C*H) 129.3 (aromatic *C*H), 127.9 (aromatic *C*H), 123.1 (alkene *C*H), 65.1 (CH_2N), 33.4 (CH_2S) ppm. MS (APCI): *m/z* (%) = 190 (100) $[M + H]^+$.

2-[(*E*)-2-(4-Bromophenyl)ethenyl]-4,5-dihydro-1,3-thiazole (1b): 2-Methylthiazoline (2.2 g, 20 mmol) and 4-bromobenzaldehyde (3.6 g, 20 mmol), were heated under reflux in toluene (100 mL) under Dean–Stark conditions for 1 h. Iodine (100 mg) was added and the reflux continued for 16 h. The resulting reaction mixture was washed with saturated sodium thiosulfate solution (100 mL), dried with $MgSO_4$, and the solvent removed in vacuo. The dark oil resulting was dissolved in diethyl ether (40 mL) and filtered. The diethyl ether was removed in vacuo to give a brown solid which was purified by column chromatography (eluting with diethyl ether/CH_2Cl_2, 1:9), late fractions yielding **1b** (1.6 g, 30%) as a white solid; m.p. 160–163 °C. IR ($CDCl_3$): $\tilde{\nu}$ = 1634, 1574, 1489, 1007 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.39 (d, $^3J_{H,H}$ = 7.4, 2 H, aromatic C*H*), 7.29 (d, $^3J_{H,H}$ = 7.4, 2 H, aromatic C*H*), 6.95 (apparent s, 2 H, 2 × alkene C*H*), 4.30 (t, $^3J_{H,H}$ = 8.0, 2 H, CH_2N), 3.25 (t, $^3J_{H,H}$ = 8.0, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.0 (thiazoline *C*), 140.1 (alkene *C*H), 134.7 (aromatic *C*) 132.5 (aromatic *C*H), 129.3 (aromatic *C*H), 123.9 (aromatic *C*), 123.7 (alkene *C*H), 65.2 (CH_2N), 33.5 (CH_2S) ppm. MS (APCI): *m/z* (%) = 270 (100) $[M + H]^+$, 268 (100) $[M + H]^+$, 71 (58). HRMS (CI) $C_{11}H_{11}{}^{79}BrNS$ $[M + H]^+$: 267.9795; found 267.9797.

4,5-Dihydro-2-[(*E*)-2-(4-nitrophenyl)ethenyl]-1,3-thiazole (1c): 2-Methylthiazoline (2.20 g, 20 mmol) and 4-nitrobenzaldehyde (3.0 g, 22 mmol) were heated under reflux in toluene (100 mL) under Dean–Stark conditions for 1 h. Iodine (100 mg) was added and the reflux continued for 16 h. The reaction mixture was washed with sodium thiosulfate solution (100 mL), dried with $MgSO_4$ and the toluene removed in vacuo. Diethyl ether (40 mL) was added to

the resulting dark oil, and **1c** (1.45 g, 31%) isolated by filtration as a light brown solid; m.p. 213–216 °C, (ref.[6] m.p. 214–216 °C) which was used without further purification. IR (CH_2Cl_2): $\tilde{\nu}$= 1629, 1604, 1508, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.25 (d, $^3J_{H,H}$ = 8.8, 2 H, aromatic C*H*), 7.64 (d, $^3J_{H,H}$ = 8.8, 2 H, aromatic C*H*), 7.17 (d, $^3J_{H,H}$ = 16.4, 1 H, one of alkene C*H*), 7.10 (d, $^3J_{H,H}$ = 16.4, 1 H, one of alkene C*H*), 4.40 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2N), 3.35 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2S). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.6 (thiazoline *C*), 148.3 (aromatic *C*), 141.9 (aromatic *C*), 139.5 (alkene *C*H), 128.3 (aromatic *C*H), 127.1 (alkene *C*H), 124.6 (aromatic *C*H), 65.4 (CH_2N), 33.7 (CH_2S) ppm. MS (ammonia CI): *m/z* (%) = 235 (26) [M + H]$^+$, 220 (33), 205 (100). HRMS (CI) $C_{11}H_{11}N_2O_2S$ [M + H]$^+$: 235.0541; found 235.0545.

4,5-Dihydro-2-[(*E*)-2-(4-methoxyphenyl)ethenyl]-1,3-thiazole (1d): 2-Methylthiazoline (2.5 g, 25 mmol) and 4-methoxybenzaldehyde (2.8 g, 24 mmol) were heated under reflux in toluene (100 mL) under Dean–Stark conditions for 1 h. Iodine (50 mg) was added and the reflux continued for 18 h. The resulting brown solution was washed with saturated sodium thiosulfate solution (50 mL), dried with $MgSO_4$ and the solvent removed in vacuo. The brown oil remaining was dissolved in diethyl ether (30 mL), filtered and the diethyl ether was removed in vacuo, to yield a brown solid which was purified by column chromatography (eluting with diethyl ether) late fractions yielding **1d** (1.8 g, 33%,) as colourless plates, m.p. 100–102 °C (ref.[6] m.p. 99–101 °C). IR (CH_2Cl_2): $\tilde{\nu}$ = 1463, 1377 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.45 (d, $^3J_{H,H}$ = 8.7, 2 H, aromatic C*H*), 7.07 (d, $^3J_{H,H}$ = 16.1, 1 H, one of alkene C*H*), 6.93 (d, $^3J_{H,H}$ = 16.1, 1 H, one of alkene C*H*), 6.89 (d, $^3J_{H,H}$ = 8.7, 2 H, aromatic C*H*), 4.35 (t, $^3J_{H,H}$ = 8.5, 2 H, CH_2N), 3.85 (s, 3 H, OCH_3), 3.30 (t, $^3J_{H,H}$ = 8.5, 2 H, CH_2S) ppm. ^{13}C NMR (125 MHz. $CDCl_3$, 25 °C): δ = 168.5 (thiazoline *C*), 160.8 (aromatic *C*), 141.2 (alkene *C*H), 129.1 (aromatic *C*H), 128.0 (aromatic C), 120.2 (alkene *C*H), 114.3 (aromatic *C*H), 64.3 (CH_2N) 55.4 (OCH_3), 32.9 (CH_2S) ppm. MS (APCI): *m/z* (%) = 220 (100) [M + H]$^+$.

2-[(*E*)-2-(4-Phenylphenyl)ethenyl]-4,5-dihydro-1,3-thiazole (1e): 2-Methylthiazoline (1.75 g, 17 mmol) and 4-phenylbenzaldehyde (3.15 g, 17 mmol) were heated under reflux in toluene (100 mL) under Dean–Stark conditions for 1 h. Iodine (100 mg) was added and the reflux continued for 16 h. The reaction mixture was washed with saturated sodium thiosulfate solution (100 mL), dried with $MgSO_4$, and the toluene removed in vacuo. The resulting dark oil was dissolved in diethyl ether (40 mL) and filtered. The diethyl ether was removed in vacuo to give a brown solid which was purified by column chromatography (eluting with CH_2Cl_2), late fractions yielding **1e** (960 mg, 21%) as an off-white crystalline solid, m.p. 141–144 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 1633, 1582, 1488, 1177 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.74–7.56 (m, 6 H, aromatic C*H*), 7.46 (apparent t, $^3J_{H,H}$ = 7.5, 2 H, aromatic C*H*), 7.36 (t, $^3J_{H,H}$ = 7.4, 1 H, aromatic C*H*), 7.26 (d, $^3J_{H,H}$ = 16.2, 1 H, alkene C*H*), 7.08 (d, $^3J_{H,H}$ = 16.2, 1 H, alkene C*H*), 4.40 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2N), 3.36 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 168.3 (thiazoline *C*), 142.2 (aromatic *C*), 141.1 (alkene *C*H), 140.7 (aromatic *C*), 134.7 (aromatic *C*), 129.3, 128.3, 128.1, 127.9 and 127.4 (all aromatic *C*H), 123.0 (alkene *C*H), 65.2 (CH_2N), 33.5 (CH_2S) ppm. MS (APCI): *m/z* (%) = 266 (100) [M + H]$^+$. HRMS (CI) $C_{17}H_{16}NS$ [M + H]$^+$: 266.1003; found 266.0997.

2-[(*E*)-2-(4-Methylphenyl)ethenyl]-4,5-dihydro-1,3-thiazole (1f): 2-Methylthiazoline (2.5 g, 25 mmol) and 4-tolualdehyde (2.84 g, 25 mmol) were heated under reflux in toluene (100 mL) under Dean–Stark conditions for 1 h. Iodine (100 mg) was added and the reflux continued for 16 h. The reaction mixture was washed with saturated sodium sulfite solution (40 mL). The solvent was removed in vacuo to give a brown solid which was purified by column chromatography (eluting with CH_2Cl_2), late fractions affording **1e** (1.8 g, 35%) as a white solid, m.p. 148–150 °C (ref.[6] m.p. 148–150 °C). IR (CH_2Cl_2): $\tilde{\nu}$ = 1634, 1579, 1318, 1177 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31 (d, $^3J_{H,H}$ = 8.0, 2 H, aromatic C*H*), 7.11 (d, $^3J_{H,H}$ = 8.0, 2 H, aromatic C*H*), 6.99 (d, $^3J_{H,H}$ = 15.8, 1 H, one of alkene C*H*), 6.93 (d, $^3J_{H,H}$ = 15.8, 1 H, one of alkene C*H*), 4.30 (t, $^3J_{H,H}$ = 8.1, 2 H, CH_2N), 3.26 (t, $^3J_{H,H}$ = 8.1, 2 H, CH_2S), 2.30 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 168.3 (thiazoline *C*), 141.6 (alkene *C*H), 140.1 (aromatic *C*), 133.0 (aromatic *C*), 130.0 and 127.8 (aromatic *C*H), 122.1 (alkene *C*H), 65.1 (CH_2N), 33.4 (CH_2S), 21.8 (CH_3) ppm. MS (APCI): *m/z* (%) = 204 (100) [M + H]$^+$.

6-Chloro-2,3-dihydro-7-(4-methoxyphenyl)-5*H*-[1,3]thiazolo[3,2-*a*]-pyridin-5-one (2d): 4,5-Dihydro-2-[(*E*)-2-(4-methoxyphenyl)ethenyl]-1,3-thiazole (**1d**) (520 mg, 2.4 mmol) was dissolved in dry THF (8 mL). Dichloroacetyl chloride (230 µL, 2.24 mmol) was added and the resulting bright red mixture stirred at 25 °C under N_2 for 20 min. Triethylamine (340 µL, 2.4 mmol) was added and the resulting cloudy brown mixture stirred for a further 2 h. The resulting suspension was filtered and the filtrate dried with $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (eluting with diethyl ether/CH_2Cl_2, 1:5) yielded **2d** (625 mg, 89%) as a light brown solid m.p. 128–130 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1636, 1513 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33 (d, $^3J_{H,H}$ = 8.6, 2 H, aromatic C*H*), 6.87 (d, $^3J_{H,H}$ = 8.6, 2 H, aromatic C*H*), 6.15 (s, 1 H, 8-*H*), 4.52 (d, $^3J_{H,H}$ = 7.4, 2 H, CH_2N), 3.79 (s, 3 H, OCH_3), 3.41 (t, $^3J_{H,H}$ = 7.4, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 159.0 (*C*=O), 157.6 (*S*CN), 149.6 (*C*Cl), 144.4 (aromatic *C*), 128.9 (aromatic *C*H), 128.3 (aromatic *C*), 116.7 (aromatic *C*), 112.7 (aromatic *C*H), 101.4 (8-*C*), 52.3 (OCH_3), 50.8 (CH_2N), 27.9 (CH_2S) ppm. MS (APCI): *m/z* (%) = 296 (35) [M + H]$^+$, 294 (100) [M + H]$^+$. HRMS (CI) $C_{12}H_{13}NO_4S^{35}Cl$ [M + H]$^+$: 294.0355; found 294.0359.

(5*RS*,7*RS*,*E*)-6-(4,5-Dihydro-3-trichloroacetyl-1,3-thiazol-2-ylidene)-2,3,5,7-tetrahydro-5,7-diphenyl[1,3]thiazolo[3,2-*a*]pyridine (3): 4,5-Dihydro-2-[(*E*)-2-phenylethenyl]-1,3-thiazole (**1a**) (250 mg, 1.3 mmol) was dissolved in dry diethyl ether (1 mL) and dry DME (4 mL). Trichloroacetyl chloride (15 µL, 0.8 mmol) was added dropwise with stirring under N_2 at 25 °C. The reaction mixture was stirred for 3 h, washed with aqueous $NaHCO_3$ solution (10 mL) then with brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to yield a glassy orange solid, which was purified by chromatography on neutral alumina (eluting with CH_2Cl_2) late fractions yielding compound **3** as a colourless solid (98 mg, 29%), m.p. 186–188 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 2920, 1691, 1625 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.20–7.10 (m, 8 H, aromatic C*H*), 6.90 (m, 2 H, aromatic C*H*), 5.05 (d, $^4J_{H,H}$ = 3.5, 1 H, 5-*H*), 4.55 (d, $^3J_{H,H}$ = 11.8, 1 H, alkene C*H*), 3.95–3.85 (m, 2 H, CH_2NCO), 3.50–3.35 (m, 3 H, 7-*H* and CH_2N), 3.10–2.95 (m, 2 H, CH_2S), 2.90–2.80 (m, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 175.6 (*C*=O), 168.7, 167.2 (both thiazoline *C*), 139.6 and 138.7 (aromatic *C*), 128.5, 127.8, 127.2 (all aromatic *C*H), 97.5 (CCl_3), 96.7 (alkene *C*), 64.5 (CH_2NCO), 60.5 (alkene *C*H), 52.9 (CH_2N), 50.0 (5-*C*), 43.6 (7-*C*), 33.3 (CH_2S), 27.0 (CH_2S) ppm. MS (APCI): *m/z* (%) = 525 (9) [M + H]$^+$, 523 (10) [M + H]$^+$, 190 (100) [M + H]$^+$ (molecular ion shows expected isotopic distribution pattern). HRMS (CI) $C_{24}H_{22}^{35}Cl_3N_2O_2S$ [M + H]$^+$: 523.0239; found 523.0240.

(5*RS*,7*RS*,*E*)-6-(4,5-Dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)-2,3,5,7-tetrahydro-5,7-diphenyl[1,3]thiazolo[3,2-*a*]pyridine (8a): 2-[(*E*)-2-Phenylethenyl]-4,5-dihydro-1,3-thiazole (**1a**) (150 mg, 0.8 mmol) was dissolved in dry diethyl ether (1 mL) and dry DME (4 mL). Trifluoroacetic anhydride (70 μL, 0.5 mmol) was added dropwise with stirring under N_2 at 25 °C. The reaction mixture was stirred for 3 h, washed with aqueous $NaHCO_3$ solution (10 mL) then with brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to yield a glassy orange solid, which was purified by chromatography on neutral alumina (eluting with CH_2Cl_2), late fractions yielding **8a** (78 mg, 41%) as a white solid, m.p. 196–198 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1691, 1625, 1499 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.32–7.12 (m, 8 H, aromatic C*H*), 6.85 (dd, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.7, 2 H, aromatic C*H*), 4.56 (d, $^3J_{H,H}$ = 11.1, 1 H, alkene C*H*), 4.51 (d, $^4J_{H,H}$ = 4.2, 1 H, 5-*H*), 3.79 (m, 2 H, CH_2NCO), 3.41 (dd, $^3J_{H,H}$ = 11.1, $^4J_{H,H}$ = 4.2, 1 H, 7-*H*), 3.35–3.30 (m, 2 H, CH_2N), 3.00–2.80 (m, 4 H, 2×SCH_2) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 166.5 and 164.6 (both thiazoline *C*), 139.5 and 136.9 (both aromatic *C*), 127.6, 127.1, 126.9, 126.3 (all aromatic *C*H), 117.1 (q, $^1J_{C,F}$ = 290 Hz, *C*F_3), 97.9 (alkene *C*), 70.7 (NCO*C*H_2), 59.1 (alkene *C*H), 51.8 (N*C*H_2), 48.8 (5-*C*), 40.7 (7-*C*), 32.3 (*C*H_2S), 29.2 (*C*H_2S) ppm. MS (APCI): *m/z* (%) = 475 (100) [M + H]$^+$, 102.5 (29). HRMS (EI) $C_{24}H_{22}F_3N_2OS_2$ [M + H]$^+$: 475.1127; found 475.1125.

(5*RS*,7*RS*,*E*)-2,3,5,7-Tetrahydro-5,7-bis(4-bromophenyl)-6-(4,5-dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)[1,3]thiazolo[3,2-*a*]pyridine (8b): 2-[(*E*)-2-(4-Bromophenyl)ethenyl]-4,5-dihydro-1,3-thiazole (**1b**) (200 mg, 0.74 mmol), was dissolved in dry chloroform (5 mL). Trifluoroacetic anhydride (75 μL, 0.53 mmol) was added dropwise and the reaction mixture heated under reflux for 6 h. The resulting orange solution was washed with aqueous $NaHCO_3$ solution (10 mL) then brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to give a light brown solid which was purified by column chromatography on alumina (eluting with CH_2Cl_2) early fractions yielding **8b** (100 mg, 43%) as a white solid, m.p. 200–203 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 1692, 1625, 1500, 1464 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38 (d, $^3J_{H,H}$ = 8.4, 2 H, aromatic CH), 7.30 (d, $^3J_{H,H}$ = 8.4, 2 H, aromatic CH), 7.08 (d, $^3J_{H,H}$ = 8.5, 2 H, aromatic CH), 6.73 (d, $^3J_{H,H}$ = 8.5, 2 H, aromatic C*H*), 4.50 (d, $^3J_{H,H}$ = 11.1, 1 H, alkene *C*H), 4.47 (d, $^4J_{H,H}$ = 4.2, 1 H, 5-*H*), 3.80 (apparent t, $^3J_{H,H}$ = 8.3, 2 H, CH_2NCO), 3.40–3.30 (m, 3 H, 7-*H* and CH_2N), 3.11–3.03 (m, 2 H, CH_2S), 2.95–2.88 (m, 2 H, CH_2S) ppm. ^{13}C NMR (125 MHz. $CDCl_3$, 25 °C): δ = 166.5 and 165.8 (both thiazoline *C*), 138.4 and 136.0 (both aromatic *C*), 130.1, 128.6 (both aromatic *C*H), 121.7, 120.3 (both *C*–Br), 97.5 (alkene *C*), 63.2 (*C*H_2NCO), 58.5 (alkene *C*H), 51.8 (N*C*H_2), 48.4 (5-*C*), 40.0 (7-*C*), 32.4 (S*C*H_2), 26.2 (S*C*H_2) ppm. MS (APCI): *m/z* (%) = 635 (58) [M + H]$^+$, 633 (100) [M + H]$^+$, 631 (48) [M + H]$^+$. HRMS (CI) $C_{24}H_{19}{}^{79}Br_2F_3N_2OS_2$ [M + H]$^+$: 630.9336; found 630.9335.

(5*RS*,7*RS*,*E*)-6-(4,5-Dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)-2,3,5,7-tetrahydro-5,7-bis(4-nitrophenyl)[1,3]thiazolo[3,2-*a*]pyridine (8c): 4,5-Dihydro-2-[(*E*)-2-(4-nitrophenyl)ethenyl]-1,3-thiazole (**1c**) (200 mg, 0.85 mmol) was dissolved in dry chloroform (5 mL). Trifluoroacetic anhydride (83 μL, 0.6 mmol) was added dropwise and the solution heated under reflux for 3 h. The resulting orange solution was washed with aqueous $NaHCO_3$ solution (10 mL), then brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to give a yellow solid which was purified by flash chromatography on alumina (eluting with CH_2Cl_2), yielding **8c** (120 mg, 50%) as a pale yellow solid, m.p. 210–212 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 1683, 1625, 1462 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.13 (d, $^3J_{H,H}$ = 8.3, 2 H, aromatic C*H*), 8.09 (d, $^3J_{H,H}$ = 8.7, 2 H, aromatic C*H*), 7.40 (d, $^3J_{H,H}$ = 8.6, 2 H, aromatic C*H*), 7.06 (d, $^3J_{H,H}$ = 8.7, 2 H, aromatic C*H*), 4.66 (d, $^3J_{H,H}$ = 11.1, 1 H, alkene C*H*), 4.61 (d, $^4J_{H,H}$ = 4.1, 1 H, 5-*H*), 3.71–3.65 (m, 2 H, CH_2NCO), 3.49 (dd, $^3J_{H,H}$ = 11.1, $^4J_{H,H}$ = 4.1, 1 H, 7-*H*), 3.45–3.40 (m, 1 H, one of CH_2N) 3.31 (ddd, $^2J_{H,H}$ = 10.6, $^3J_{H,H}$ = 7.7, $^3J_{H,H}$ = 2.9, 1 H, one of CH_2N), 3.17–2.98 (m, 4 H, 2×CH_2S) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 168.4, 166.7 (both thiazoline *C*), 148.5, 148.1, 147.7, 145.4 (all aromatic *C*), 129.2, 123.8 (both aromatic *C*H), 118.1 (q, $^1J_{C,F}$ = 290 Hz, *C*F_3), 98.2 (alkene *C*), 64.7 (*C*H_2NCO), 59.7 (alkene *C*H), 53.3 (*C*H_2N), 49.6 (5-*C*), 41.7 (7-*C*), 33.9 (*C*H_2S), 27.7 (*C*H_2S) ppm. MS (APCI): *m/z* (%) = 565 (100) [M + H]$^+$, 65 (57). HRMS (CI) $C_{24}H_{20}N_4O_5F_3S_2$ [M + H]$^+$: 565.0828; found 565.0857.

(5*RS*,7*RS*,*E*)-2,3,5,7-Tetrahydro-5,7-bis(4-methoxyphenyl)-6-(4,5-dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)[1,3]thiazolo[3,2-*a*]pyridine (8d): 2-[(*E*)-2-(4-Methoxyphenyl)ethenyl]-4,5-dihydro-1,3-thiazole (**1d**) (200 mg, 0.93 mmol) was dissolved in dry diethyl ether (1 mL) and dry DME (4 mL). Trifluoroacetic anhydride (90 μL, 0.64 mmol) was added dropwise and the solution stirred under N_2 at 25 °C for 3 h. The orange solution resulting was washed with aqueous $NaHCO_3$ solution (10 mL), then brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to give an orange solid which was purified by flash chromatography on alumina (eluting with CH_2Cl_2) yielding **8d** (77 mg, 31%) as a pale yellow solid; m.p. 183–185 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 1683, 1624, 1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.10 (d, $^3J_{H,H}$ = 8.8, 2 H, aromatic C*H*), 6.80–6.69 (m, 6 H, aromatic C*H*), 4.52 (d, $^3J_{H,H}$ = 11.1, 1 H, alkene C*H*), 4.45 (d, $^4J_{H,H}$ = 3.9, 1 H, 5-*H*), 3.83 (m, 2 H, CH_2NCO), 3.72 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.40 (m, 3 H, CH_2N and 7-*H*), 3.05 (m, 2 H, CH_2S), 2.93 (m, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 167.9, 167.7 (both thiazoline *C*), 160.0, 158.9, 133.0, 130.2 (all aromatic *C*), 129.5 (aromatic *C*H), 118.0 (q, $^1J_{C,F}$ = 290 Hz, *C*F_3), 113.6 (aromatic *C*H), 99.7 (alkene *C*), 64.6 (*C*H_2NCO), 60.1 (alkene *C*H), 55.6 (OCH_3), 55.4 (OCH_3), 53.2 (*C*H_2N), 50.4 (5-*C*), 41.1 (7-*C*), 33.7 (*C*H_2S), 27.6 (*C*H_2S) ppm. MS (APCI): *m/z* (%) = 535 (100) [M + H]$^+$. HRMS (EI) $C_{24}H_{20}N_4O_5F_3S_2$ [M]$^+$: 534.1259; found 534.1260.

(5*RS*,7*RS*,*E*)-2,3,5,7-Tetrahydro-5,7-bis(4-phenylphenyl)-6-(4,5-dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)[1,3]thiazolo[3,2-*a*]pyridine (8e): 2-[(*E*)-2-(4-Phenylphenyl)ethenyl]-4,5-dihydro-1,3-thiazole (**1e**) (150 mg, 0.57 mmol) was dissolved in dry chloroform (5 mL). Trifluoroacetic anhydride (70 μL, 0.5 mmol) was added dropwise and the solution heated under reflux for 6 h. The resulting orange solution was washed with aqueous $NaHCO_3$ solution (10 mL), then brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to give a yellow solid which was purified twice by flash chromatography on alumina (eluting with CH_2Cl_2), yielding **8e** (45 mg, 25%) as a pale yellow solid. This compound exhibited spectroscopic data in line with compounds **8a**–**8d**, but could not be purified to allow full characterisation.

2-(4,5-Dihydro-1,3-thiazol-2-yl)-1-phenyl-1-ethanol (9):[13] 2-Methylthiazoline (2.0 g, 20 mmol) was dissolved in dry THF and cooled to–78 °C. *n*-Butyllithium (8.7 mL of a 2.5 M solution in hexanes, 22 mmol) was added and the resulting orange solution stirred at–78 °C under N_2 for 1 h. Benzaldehyde (2.1 g, 20 mmol) was added and the reaction mixture stirred for a further 2 h at–78 °C then allowed to warm to 25 °C over 1 h. Saturated ammonium chloride solution (20 mL) was added, and the products extracted with diethyl ether (3 × 30 mL), the organic portions were washed with brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo to give compound **9** (3.6 g, 90%) as an orange solid, m.p. 76–79 °C

(dec.). IR (CH_2Cl_2): $\tilde{\nu}$ = 3267, 1624, 1434, 1124 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30 (apparent t, $^3J_{H,H}$ = 7.5, 2 H, aromatic CH), 7.26 (d, $^3J_{H,H}$ = 7.6, 2 H, aromatic CH), 7.19 (t, $^3J_{H,H}$ = 6.9, 1 H, aromatic C*H*), 5.04 (apparent t, $^3J_{H,H}$ = 6.3, 1 H, C*H*OH), 4.70 (broad s, 1 H, O*H*), 4.18 (m, 2 H, CH_2N), 3.21 (apparent t, $^3J_{H,H}$ = 8.2, 2 H, CH_2S), 2.72 (m, 2 H, CH_2CHOH) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 171.0 (thiazoline *C*), 142.3 (aromatic *C*), 128.8, 128.0 and 126.2 (aromatic *C*H), 71.8 (*C*HOH), 64.6 (CH_2N), 43.1 (CH_2S), 33.8 (CH_2CHOH) ppm. MS (APCI): *m/z* (%) = 208 (40) $[M + H]^+$, 190 (100).

Alternative Preparation of 2-[(*E*)-2-Phenylethenyl]-4,5-dihydro-1,3-thiazole (1a): 2-(4,5-Dihydro-1,3-thiazol-2-yl)-1-phenyl-1-ethanol (**9**) (1.5 g, 7.2 mmol) was dissolved in toluene (15 mL). Trifluoroacetic acid (2 drops) was added followed by 4-Å molecular sieves, and the mixture heated under reflux for 1 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (50 mL), washed with water (50 mL) and brine (50 mL). The resulting solution was dried with $MgSO_4$ and the solvent removed in vacuo to give an orange solid which was purified by kugelrohr distillation (180 °C, 0.5 Torr) to give the title compound (1.03 g, 75%) as a colourless solid. Data were as previously reported.

4,5-Dihydro-2-[(*E*)-3,3-dimethyl-1-butenyl]-1,3-thiazole (10): 2-Methylthiazoline (2.5 g, 25 mmol) was dissolved in THF (15 mL) and cooled to–78 °C. *n*-Butyllithium (7.8 mL of a 2.5 M solution in hexanes, 26 mmol) was added dropwise and the resulting orange anion was stirred for 30 min. 2,2-(Dimethyl)propionaldehyde (1.86 g, 21 mmol) was then added dropwise and the clear orange solution resulting was stirred for 1 h at–78 °C then warmed to 25 °C over 2 h. Water (20 mL) was then added, and the organic layer separated, the aqueous layers was extracted with diethyl ether (3 × 20 mL). The combined organic layers were concentrated in vacuo. The resulting red solid was dissolved in toluene (40 mL), trifluoroacetic acid (30 mg) was added and the mixture heated under reflux, under Dean–Stark conditions for 1 h. The brown solution remaining was washed with saturated sodium hydroxide solution (30 mL), dried with $MgSO_4$, and the solvent removed in vacuo to yield the essentially pure **10** (2.1 g, 50%) as a yellow oil. IR (CH_2Cl_2): $\tilde{\nu}$ = 1647, 1460 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.26 (d, $^3J_{H,H}$ = 15.3, 1 H, one of alkene C*H*), 6.23 (d, $^3J_{H,H}$ = 15.3, 1 H, one of alkene C*H*), 4.24 (t, $^3J_{H,H}$ = 8.1, 2 H, CH_2N), 3.20 (t, $^3J_{H,H}$ = 8.1, 2 H, CH_2S), 1.03 (s, 9 H 3 × CH_3) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 171.7 (thiazoline *C*), 155.2 (alkene *C*H), 120.6 (alkene CH), 64.5 (CH_2N), 34.0 [$C(CH_3)_3$], 32.8 (CH_2S), 29.0 (3 × CH_3) ppm. MS (APCI): *m/z* (%) = 170 (100) $[M + H]^+$. HRMS (CI) $C_8H_{16}NS$ $[M + H]^+$: 170.1003; found 170.1000.

(*E*)-*N*-(2-Hydroxyethyl)-3-phenyl-2-propenamide (11): (*E*)-Cinnamoyl chloride (1.0 g, 6 mmol) and ethanolamine (336 mg, 6 mmol) were dissolved in CH_2Cl_2 (20 mL). A saturated solution of sodium carbonate (54 mL) was added and the mixture stirred at 25 °C for 16 h. Brine was added and the products extracted into CH_2Cl_2 (3 × 30 mL), dried with $MgSO_4$, and concentrated in vacuo to afford a white solid. Recrystallisation from ethyl acetate gave compound **11** (0.91 g, 78%) as a white crystalline solid, m.p. 67–69 °C (ref.[14] m.p. 67–68 °C). IR: ν (melt) = 3298, 1650, 1597 1556, 1456 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.60 (d, $^3J_{H,H}$ = 15.6, 1 H, alkene C*H*), 7.55 (m, 2 H, aromatic C*H*), 7.25 (m, 3 H, aromatic C*H*), 6.37 (d, $^3J_{H,H}$ = 15.6, 1 H, alkene C*H*), 6.30 (broad s, 1 H, N*H*), 3.75 (m, 2 H, CH_2O), 3.52 (m, 2 H, CH_2N), 3.00 (broad s, 1 H, O*H*) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 167.6 (amide *C*=O), 142.0 (alkene CH), 135.0 (aromatic *C*), 130.3 (aromatic *C*H), 129.3 (aromatic *C*H), 128.3 (aromatic *C*H), 120.6 (alkene *C*H), 62.7 (CH_2O), 43.1 (CH_2N) ppm. MS (APCI): *m/z* (%) = 192 (100) $[M + H]^+$.

4,5-Dihydro-2-[(*E*)-2-phenylethenyl]-1,3-oxazole (12): (*E*)-*N*-(2-Hydroxyethyl)-3-phenyl-2-propenamide (**11**) (1.1 g 5.75 mmol), was dissolved in CH_2Cl_2 (50 mL), triethylamine (580 mg, 5.75 mmol) was added and the mixture cooled to 0 °C. Methanesulfonyl chloride (665 mg, 5.75 mmol) was added and the resulting solution stirred at 25 °C for 24 h. The reaction mixture was washed with $NaHCO_3$ solution (10 mL), dried with $MgSO_4$, and concentrated in vacuo to afford a green oil which was purified by column chromatography (eluting with ethyl acetate/diethyl ether, 1:10), early fractions yielding compound **12** (895 mg, 90%) as a white solid, m.p. 51–54 °C (ref.[15] m.p. 53–55 °C). IR ($CHCl_3$): $\tilde{\nu}$ = 2924, 1651, 1450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.28 (d, $^3J_{H,H}$ = 7.6, 2 H, aromatic C*H*), 7.21–7.08 (m, 4 H, aromatic C*H* and one of alkene C*H*), 6.43 (d, $^3J_{H,H}$ = 15.1, 1 H, alkene C*H*), 4.13 (t, $^3J_{H,H}$ = 9.3, 2 H, CH_2N), 3.79 (t, $^3J_{H,H}$ = 9.3, 2 H, CH_2O) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 166.2 (oxazoline *C*), 140.2 (alkene *C*H), 135.6 (aromatic *C*), 129.8, 129.2 and 127.9 (all aromatic *C*H), 115.5 (alkene *C*H), 67.6 (CH_2O), 55.3 (CH_2N) ppm. MS (APCI): *m/z* (%) = 174 (100) $[M + H]^+$.

(5*RS*,7*RS*,*E*)-5,7-Diphenyl-6-(4,5-dihydro-1,3-thiazol-2-ylidene)-2,3,6,7-tetrahydro[1,3]thiazolo[3,2-*a*]pyridine (13): (5*RS*,7*RS*,*E*)-6-(4,5-Dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)-2,3,5,7-tetrahydro-5,7-diphenyl[1,3]thiazolo[3,2-*a*]pyridine (**8a**) (200 mg, 0.4 mmol) was dissolved in ethanol (10 mL). Sodium borohydride (30 mg, 0.8 mmol) was added and the mixture stirred at 25 °C for 24 h. Water (10 mL) and DCM (10 mL) were added and the phases separated. The organic phase was dried with $MgSO_4$, and concentrated in vacuo to give compound **13** (127 mg, 80%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.15 (m, 10 H, aromatic C*H*), 4.29 (d, $^3J_{H,H}$ = 11.3, 1 H, alkene C*H*), 4.11 (d, $^4J_{H,H}$ = 5.1, 1 H, 5-*H*), 3.60 (m, 2 H, CH_2N), 3.49 (dd, $^3J_{H,H}$ = 11.3, $^4J_{H,H}$ = 5.1, 1 H, 7-*H*), 3.21–2.99 (m, 4 H, CH_2N and CH_2S), 2.80 (t, $^3J_{H,H}$ = 8.5, 2 H, CH_2S) ppm.

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Review

Alkylidenepyrrolidines: synthesis and applications in heterocyclic chemistry

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ABSTRACT

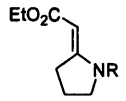
The chemistry of alkylidenepyrrolidines is reviewed, including the full range of methods for the synthesis and a discussion of their reactivity and applications in heterocyclic chemistry.

KEYWORDS: alkylidenepyyolidine, enamine, alkaloid, alkylation, acylation

1. INTRODUCTION

Alkylidenepyrrolidines are versatile intermediates for the synthesis of a range of heterocycles. As heterocyclic enamines, they can be considered to be *C, N*-dianion equivalents, and so react with a range of electrophiles. Diastereoselective reduction reactions have also been reported, giving rise to a range of (fused) pyrrolidine derivatives. This review will describe the range of methods used for alkylidenepyrrolidine formation, and describe a number of their applications in heterocyclic chemistry. While we have attempted to give examples from the range of alkylidenepyrrolidine chemistry, this review is not intended to be comprehensive.

Alkylidenepyrrolidines bearing a single electron-withdrawing group on the double-bond exist as either the (*E*) isomer **1** or the (*Z*) isomer **2**. It is generally observed that where R = H, the (*Z*) isomer is more stable as a result of hydrogen bonding, while where R is more bulky the (*E*) isomer is usually more stable. Various authors have presented evidence for the double-bond geometry based on infrared stretches of N-H bonds and chemical shifts for the N-H and 3-CH_2 protons. However, it is difficult to make direct comparisons of data, since it is extremely rare that the (*E*) and (*Z*) isomers of the same compound have been made and unambiguously characterised. We have attempted to use Nuclear Overhauser NMR studies, but since the NH and alkene CH protons are both exchangeable with deuterium (and therefore with each other) so it is common to see large cross-peaks in NOESY NMR spectra between these hydrogen atoms. These should not be used as indicators of double-bond geometry. Based on our own, albeit limited, experience we see no apparent differences in reactivity between the (*E*) and (*Z*) isomers, and are unaware of literature examples which do show such a difference.



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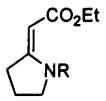

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2. Preparation of Alkylidenepyrrolidines

2. 1. Introduction

Most methods for the formation of alkylidenepyrrolidines start from the readily available pyroglutamic acid derivatives. As the γ-lactam carbonyl is relatively unreactive, various methods are used to enhance the reactivity of this key functional group. Two main methods are common: (i) conversion into the thioamide, forming the basis of the Eschenmoser sulfide contraction; (ii) conversion into a more reactive iminoether. Additionally, a number of other methods

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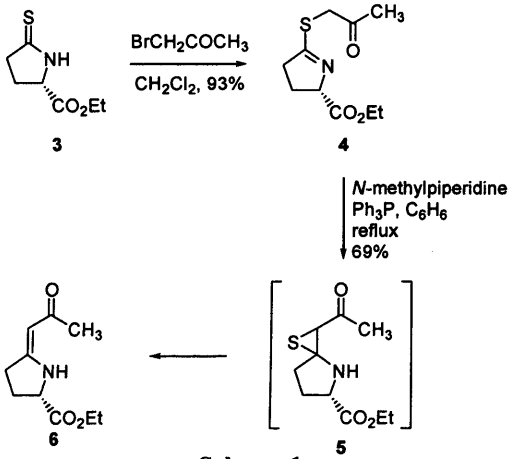
have been used. The methods for the synthesis of alkylidenepyrrolidines will be discussed within these broad classifications, with a particular emphasis on scope and limitations of each method. Their applications in synthesis will be discussed in the following sections.

2.2. Eschenmoser Sulfide Contraction

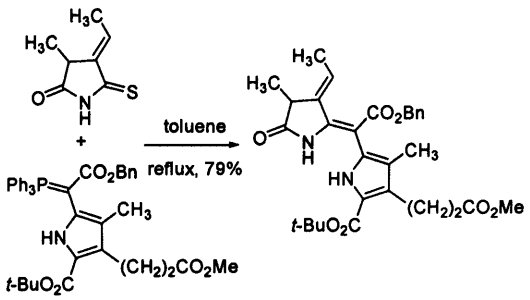
The sulfide contraction reaction which bears Eschenmoser's name was actually first reported in 1955 by Knott.[1] However, it was during the synthetic studies which culminated in the total synthesis of vitamin B12 that this reaction realised its true synthetic potential.[2] As this reaction was reviewed in 1991,[3] the present discussion will be kept brief, and will focus on the more recent modifications of reaction conditions. The general reaction in shown in **Scheme 1** for the reaction of thiolactam **3** with 2-bromoacetone. Alkylation on sulfur takes place to provide intermediate **4**, which is then deprotonated to give thiirane **5**. Reaction with a thiophile, typically triphenylphosphine, then gives the alkylidenepyrrolidine **6**.[4] The key features of this reaction are a good leaving group on a carbon atom which also contains an acidic hydrogen atom, so that the reagents (as above) are generally α-halocarbonyl compounds. Although the base is not actually necessary, lower yields are obtained in its absence.[5]



Scheme 1

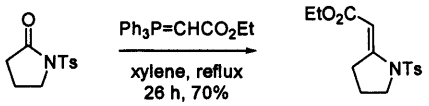
The most complex examples of the use of this reaction are still the corrins and related systems for which the reaction was originally developed.[6] A number of modifications of the Eschenmoser sulfide contraction have been developed during the course of these studies.

One of these is a Wittig-type reaction in which the thiophile has been incorporated into the carbonyl component (**Scheme 2**).[7]



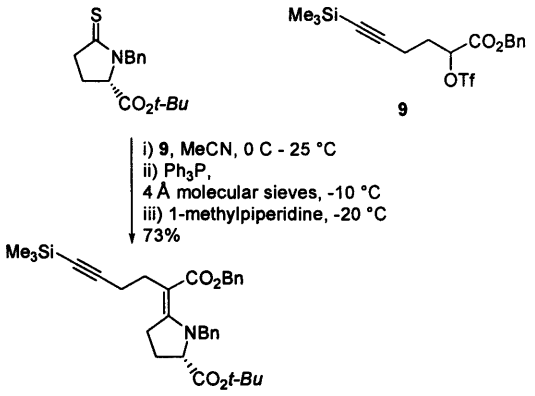
Scheme 2

These Wittig reactions can also be carried out on the lactams if a suitable electron-withdrawing group is present on nitrogen. For example, in **Scheme 3** the 4-toluenesulfonyl lactam **7** undergoes smooth reaction to give alkylidenepyrrolidine **8**.[8]



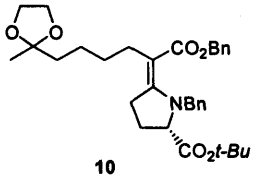
Scheme 3

Halides have been most commonly used as leaving groups in Eschenmoser sulfide contractions. However, results from the group of Rapoport show that in difficult cases, use of triflate can be advantageous. In the example shown in **Scheme 4**, the desired product was obtained in 73% yield, while a closely related iodide gave only 32% of the corresponding alkylidenepyrrolidine.[9]



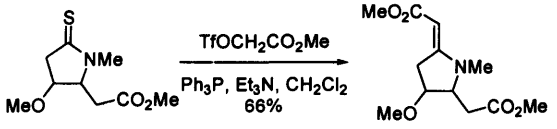
Scheme 4

These conditions give only a very small amount of racemisation when used with chiral thiolactam esters such as that shown above. In contract, use of triethylamine as base led to substantial loss of stereochemical integrity.[10] These conditions were used to prepare lactam **10**, the use of which in a synthesis of anatoxin is described in section 3.[11]



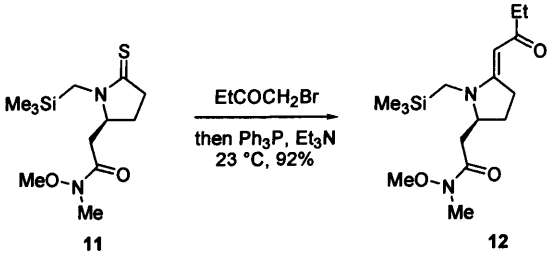
10

The same reaction conditions have been used by Koskinen and Ghiaci in a new synthesis of carbapenems,[12] while others have used triethylamine as base in conjunction with a triflate leaving group.[13] In the example shown in **Scheme 5**, the methoxy group on the pyrrolidine ring proved crucial. An acetoxy group led to extensive elimination to give the corresponding pyrrole.[14]



Scheme 5

The double-bond geometry in Eschenmoser sulfide contractions is controlled by the substituents on the nitrogen atom. If this position is unsubstituted, the (*Z*) double-bond isomer is generally formed exclusively, while almost any substituent on nitrogen favours the (*E*) double-bond isomer. For example, in a recent synthesis from Gin's group in Illinois, reaction of substrate **11** gave only alkylidenepyrrolidine isomer **12** as a single double-bond isomer (**Scheme 6**).[15]

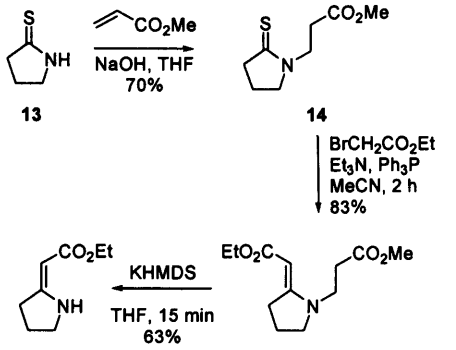


11 **12**

Scheme 6

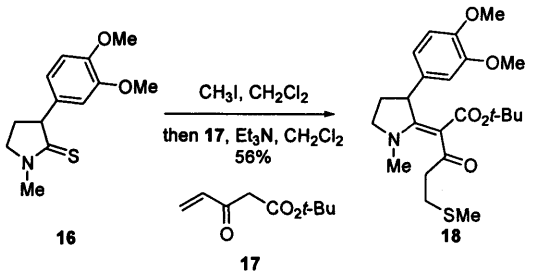
N-Unsubstituted thiolactams tend to require more forcing conditions for sulfide contraction, so that a protection-deprotection strategy has been devised. Reaction of thiolactam **13** with methyl acrylate gave the *N*-alkylated product **14**. After sulfide contraction under standard conditions, the protecting group was removed to give alkylidenepyrrolidine **15** (**Scheme 7**).[16]

A useful modification of the Eschenmoser sulfide contraction does not require the use of a halide or pseudohalide adjacent to the carbonyl. Methylation of thiolactam **16** was followed by treatment with ketoester **17** to give a Knoevenagel-type reaction in which the methanethiolate anion has then added to the enone, ultimately forming compound **18** (**Scheme 8**).[17]



13 **14** **15**

Scheme 7

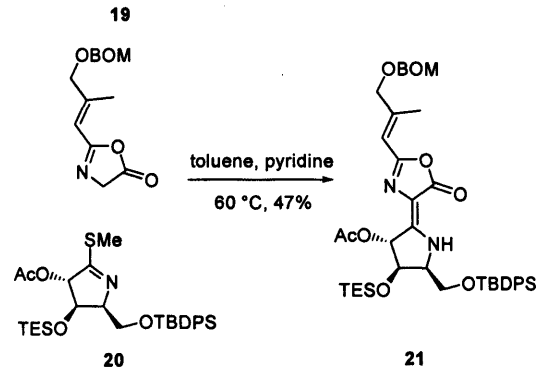


16 **17** **18**

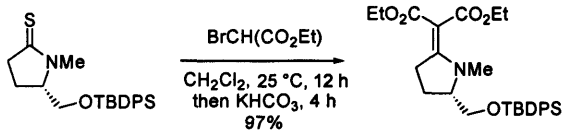
Scheme 8

The azinomycin (carzinophilin) natural products contain an alkylidenepyrrolidine at their core. A similar approach was used to prepare an advanced intermediate for use in total synthesis, with the key step (for the purpose of this review) being the coupling of compound **20** with azlactone **19** to give alkylidenepyrrolidine **21** (**Scheme 9**).[18]

Although triphenylphosphine is the most commonly used thiophile, other phosphorus reagents have been used.[19] In fact, sulfide contractions are known in which no thiophile is used (for example, **Scheme 10**).[20]

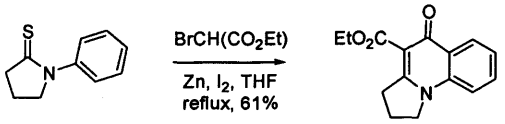


Scheme 9



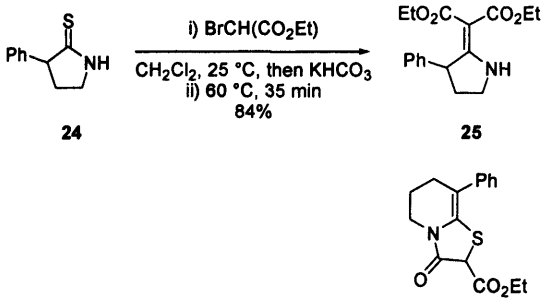
Scheme 10

One further alternative is shown by the use of Reformatsky-type reagents. For example, treatment of thiolactam **22** with diethyl 2-bromomalonate and activated zinc gave, after a further cyclisation step, tricyclic ester **23** (**Scheme 11**).[21]



22 **Scheme 11** **23**

While the Eschenmoser sulfide contraction is very effective for the elaboration of γ-thiolactams, reports concerning δ-thiolactams are sparse. A recent study by Michael and co-workers has shown that while compound **24** undergoes sulfide contraction to give alkylidenepyrrolidine **25**, the corresponding piperidinethione gives compound **26** in which the piperidine nitrogen has attacked one of the ester carbonyl groups in the alkylated intermediate (**Scheme 12**).[22]

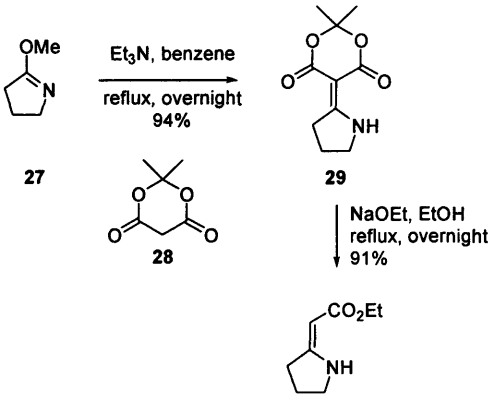


24 **25** **26**

Scheme 12

2.3. Formation and Reactions of Iminoethers

The typical reaction here is alkylation of the amide oxygen with, for example, dimethyl sulfate followed by reaction with Meldrum's acid **28**. In an early report, lactim ether **27** underwent smooth reaction in benzene in the presence of triethylamine to give alkylidenepyrrolidine **29**. Reaction with sodium ethoxide in ethanol then gave the (*Z*) isomer **15** exclusively (**Scheme 13**).[23] Alternatively, the final step in this sequence can be carried out by reaction with the alcohol under Lewis-acidic conditions, for example using boron trifluoride etherate in refluxing benzene.[24]



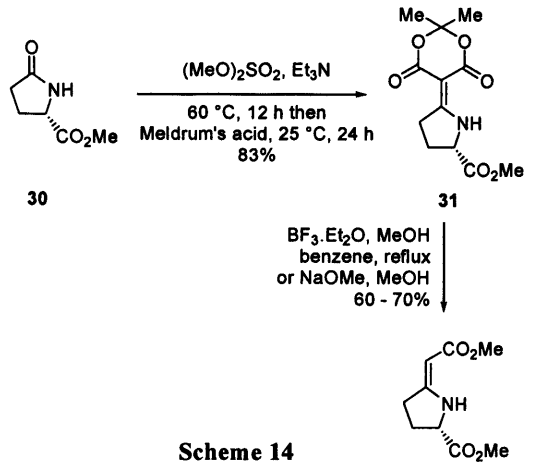
27 **28** **29** **15**

Scheme 13

More recently, the reaction with Meldrum's acid has been promoted by nickel(II) acetate.[25] This now appears to be the method of choice, and has been used

for a range of other 1,3-dicarbonyl nucleophiles in addition to Meldrum's acid.[26] Applications of the products of these reactions in alkaloid synthesis are discussed in the final section of this review.

Since pyroglutamic acid esters are not particularly prone to racemisation, this method is compatible with such compounds. For example, reaction of lactam **30** with dimethyl sulfate followed by Meldrum's acid provided compound **31** in 83% yield in a one-pot procedure (**Scheme 14**). Solvolysis/decarboxylation can be carried out under acidic or basic conditions.[27] Once again, other active methylene compounds have been used as nucleophiles in this reaction, in particular *t*-butyl cyanoacetate which allows ready decarboxylation under acidic conditions.[28]

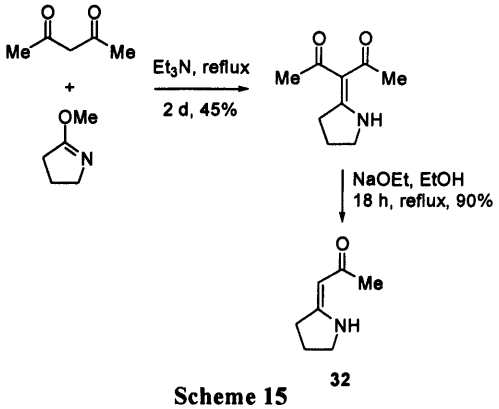


Scheme 14

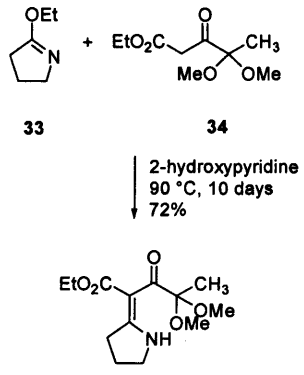
Using 1,3-diketones as nucleophiles, it is then possible to carry out a mono-deacylation to give alkylidenepyrrolidines such as **32** (**Scheme 15**).[29]

This approach to alkylidenepyrrolidines may well be the method of choice for compounds containing acid-sensitive functionality. For example, iminoether **33** underwent smooth condensation with ketal **34** to give alkylidenepyrrolidine **35** (**Scheme 16**).[30]

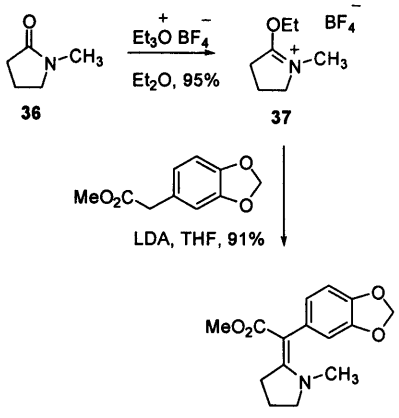
If the ring nitrogen is substituted, formation of the lactim ether is impossible. However, in this case two related approaches have been used. In the first, the iminium ion **37** can be formed from the lactam **36**. This then undergoes reaction with ester enolates as before (**Scheme 17**).[31] Alternatively, reaction of lactam **38** with dimethyl sulfate followed by addition of sodium ethoxide provided intermediate **39** which was directly allowed to react with 4-chloroacetophenone in the absence of solvent to give **40** (**Scheme 18**).[32]



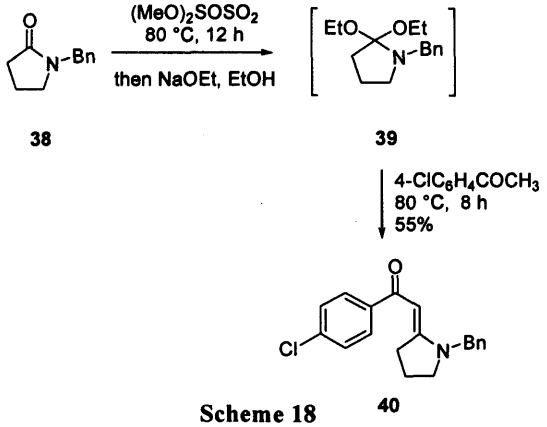
Scheme 15



Scheme 16



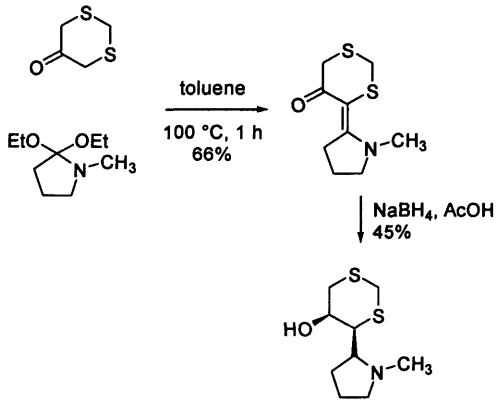
Scheme 17



38 39 40

Scheme 18

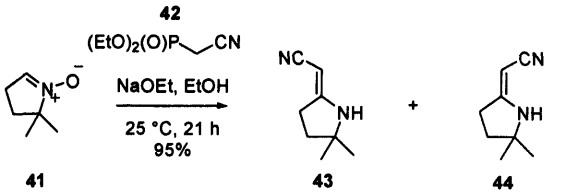
One further example of this reaction is shown in **Scheme 19**. In this case, the alkylidenepyrrolidine was then subjected to a diastereoselective reduction using sodium borohydride in acetic acid.[33]



Scheme 19

2.4. Other Methods

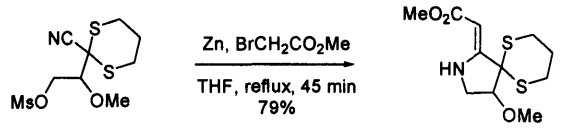
The two methods described in the preceding sections rely on the attack of a nucleophile onto a modified lactam carbonyl. A related method has been developed involving nucleophilic attack onto a nitrone. For example, reaction of nitrone **41** with diethyl cyanomethylphosphonate **42** gave a 1:1 mixture of double bond isomers **43** and **44** (**Scheme 20**). This method was less efficient for the formation of the corresponding esters, with aziridines being formed as by-products or in some cases the major product.[34]



41 43 44

Scheme 20

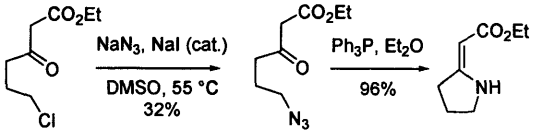
Initial nucleophilic attack onto nitrile **45** was used as the basis for the preparation of alkylidenepyrrolidine **46** by Hannick and Kishi. The anion formed by action of zinc on methyl 2-bromoacetate adds to the nitrile. This is followed by displacement of the mesylate by the resulting imine nitrogen and tautomerisation (**Scheme 21**).[35]



45 46

Scheme 21

As alkylidenepyrrolidines are enamines, various other synthetic possibilities present themselves. Azide displacement from the readily accessible ω-halo-2-ketoester **47** gave only a modest yield of substitution product **48**, with intramolecular nucleophilic attack by the ketone oxygen being a significant competing reaction. Treatment with triphenylphosphine gave an essentially quantitative yield of the alkylidenepyrrolidine **15** (**Scheme 22**). The first step in this sequence gave much higher yields when applied to homologous ω-halo-2-ketoesters, giving six-membered ring vinylogous carbamates.[36]

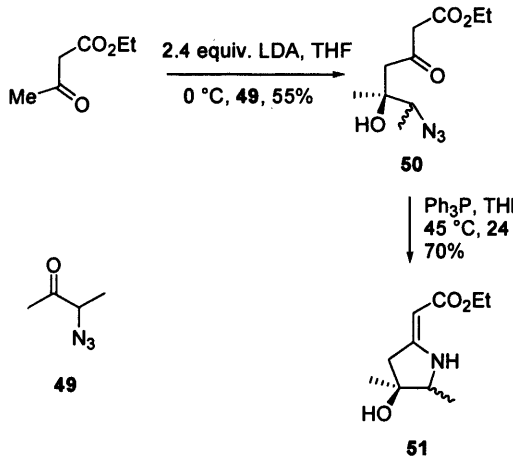


47 48 15

Scheme 22

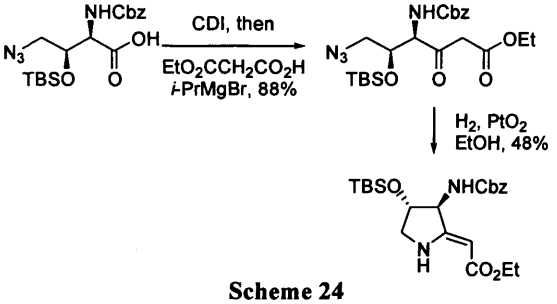
A related example introduces the azide in a dianion addition. Thus, reaction of ethyl acetoacetate with azidoketone **49** gives azide **50**, which then undergoes a tandem Staudinger-aza-Wittig reaction to

give alkylidenepyrrolidine **51** as a 3:1 mixture of diastereoisomers (**Scheme 23**).[37]



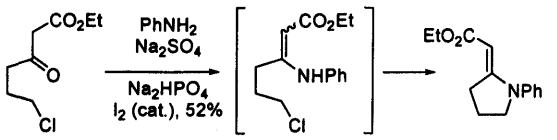
Scheme 23

Alternatively, the azide can be present from the start, while the β-ketoester is elaborated using the neutral magnesium malonate method as shown in **Scheme 24**. Some epimerisation of the stereogenic centre bearing the nitrogen substituent was observed during this sequence.[38]



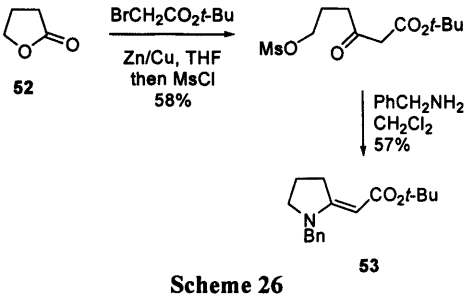
Scheme 24

A related procedure from Michael's group uses aniline nucleophiles to prepare *N*-aryl alkylidenepyrrolidines. In this case, higher yields are observed, as the aniline reacts with the carbonyl group to give the acyclic enamine, followed by cyclisation (**Scheme 25**).[39] The same method has recently been used by Lhommet's group.[40] For these particular *N*-substituted alkylidenepyrrolidines, this method gives higher yields than the sulfide contraction method.



Scheme 25

Substrates for this alkylidenepyrrolidine formation are readily available from lactones by way of a Reformatsky reaction. For example, reaction of lactone **52** with the zinc reagent formed *in situ* from *t*-butyl 2-bromoacetate gave a ε-hydroxy-β-ketoester which was directly reacted with methanesulfonyl chloride. Simply stirring this compound in dichloromethane with benzylamine gave the alkylidenepyrrolidine **53** (**Scheme 26**).[41]

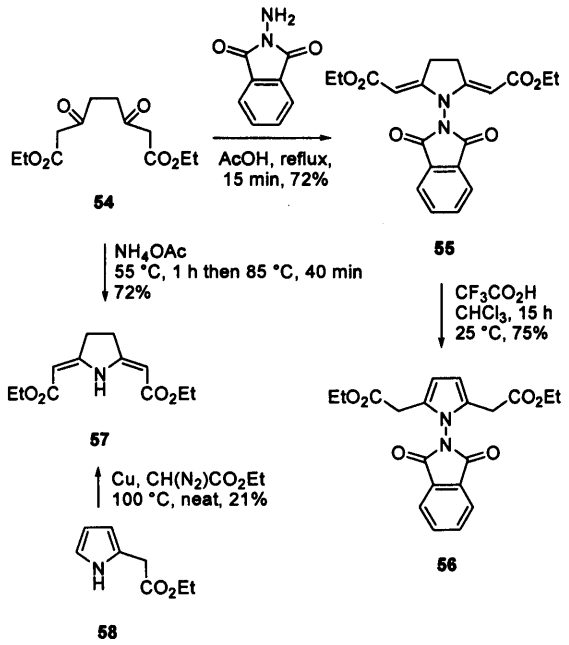


Scheme 26

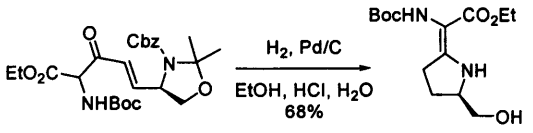
Reaction of diester **54** with *N*-aminophthalimide gave bis-alkylidenepyrrolidine **55**, which then underwent smooth isomerisation to give the pyrrole **56** (**Scheme 27**). Subsequent deprotection and a second such condensation provided access to *N,N'*-bipyrroles.[42] Using ammonium acetate in the condensation provided compound **57**, which is surprisingly tautomerically stable, by an analogous method.[43] The same compound can be accessed by copper-catalysed decomposition of ethyl diazoacetate in the presence of pyrrole **58**.[44]

One approach to the azinomycins (carzinophilins) has already been described. Hydrogenolysis of the easily accessible benzyl carbamate **59** in the presence of acid gave the key fragment **60** in good yield (**Scheme 28**).[45] Simplified analogues were produced by a related route.[46]

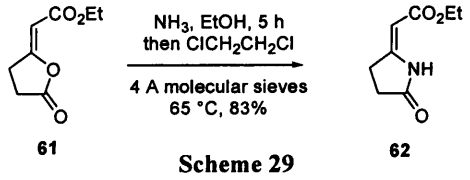
Alkylidenepyrrolidine lactams **62** are relatively straightforward to prepare from the corresponding lactones **61** by simple ammonolysis (**Scheme 29**).[47]



Scheme 27



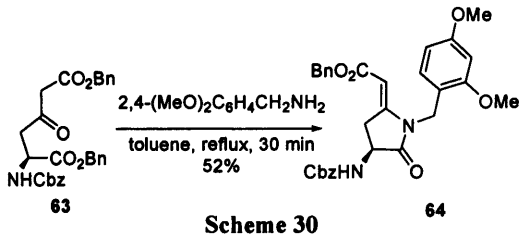
Scheme 28



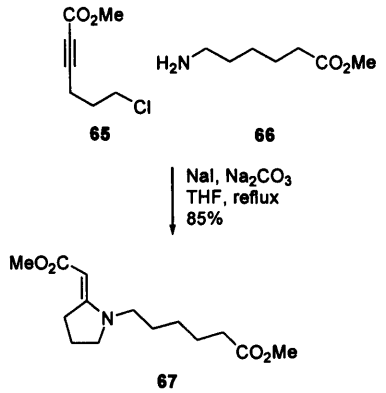
Scheme 29

This alkylidenelactone is essentially a cyclic anhydride of a ketoacid derivative such as **63**, readily accessible from aspartic acid. Treatment of this compound with 2,4-dimethoxybenzylamine in refluxing toluene gave alkylidenepyrrolidine **64** in moderate yield (**Scheme 30**).[48]

Addition of an amine nucleophile to a propiolic ester will give rise to a similar enamine, either intramolecularly to give the alkylidenepyrrolidine directly, or alternatively intermolecularly which is then followed by a cyclisation reaction. These reactions are therefore similar in many ways to those described above. For example, reaction of methyl 6-chloro-2-hexynoate **65** with aminoester **66** gave alkylidenepyrrolidine **67** in good yield (**Scheme 31**).[49]



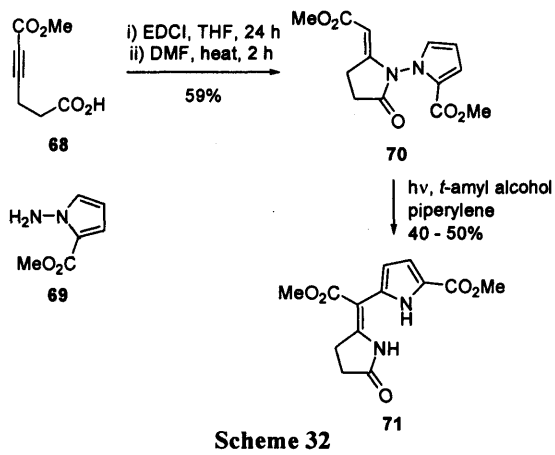
Scheme 30



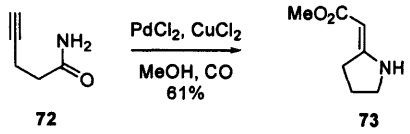
Scheme 31

A number of methods which use this general approach have been developed and used by Jacobi's group in the synthesis of corrin derivatives. One of the simpler examples from this work is shown in **Scheme 32**, where compound **68** is used as a bis-electrophile. Reaction with 1-aminopyrrole **69** gave alkylidenepyrrolidine **70**. This then underwent a photolytic rearrangement to give compound **71**.[50]

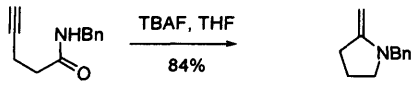
Further development of this reaction allows the use of unactivated alkynes in a palladium/copper catalysed process. For example, cyclisation of substrate **72** in methanol under an atmosphere of carbon monoxide gave alkylidenepyrrolidine **73** in moderate yield (**Scheme 33**). *N*-Substituted amides such as **74** undergo cyclisation with TBAF to give alkylidenepyrrolidines such as **75** lacking the usual electron-withdrawing group (**Scheme 34**).[51]



Scheme 32

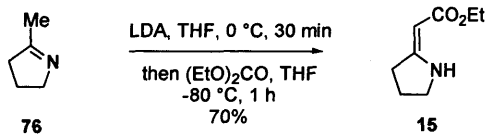


Scheme 33



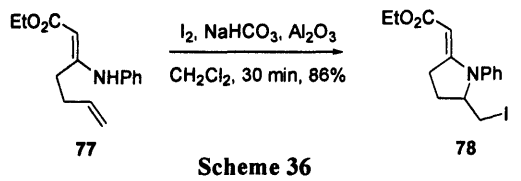
Scheme 34

The alkylidenepyrrolidine tautomer is generally favoured as a result of the electron-withdrawing group present, so that deprotonation of 2-methylpyrroline **76** and quenching with diethyl carbonate gives the alkylidenepyrrolidine **15** in good yield (**Scheme 35**). This reaction is not limited to alkylidenepyrrolidine synthesis, and works well for other ring sizes and acyclic imines.[52] Analogous reactions with ester electrophiles give alkylidenepyrrolidine ketones.[53]



Scheme 35

Iodocyclisation of an acyclic vinylogous carbamate such as **77** gives alkylidenepyrrolidine **78** in good yield (**Scheme 36**).[54] This compound was subsequently dehydroiodinated to give the corresponding pyrrole.

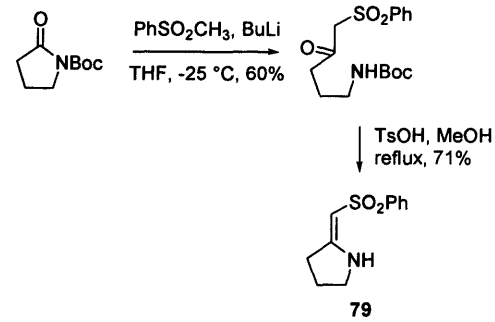


Scheme 36

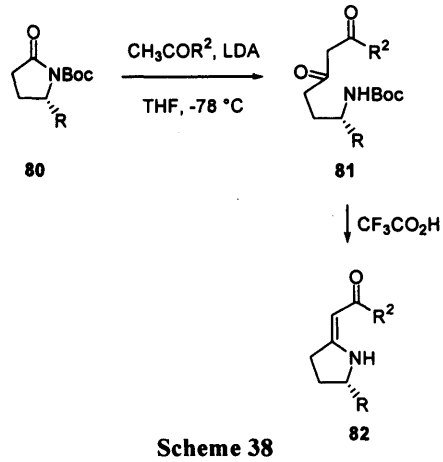
Part of the attraction of the use of the Eschenmoser sulfide contraction and iminoether methodology is their ready applicability to the preparation of (generally glutamate-derived) chiral alkylidenepyrrolidines. In our opinion, none of the methods described so far in this section have this key advantage. The following methodology appears to be reasonably general and is applicable to the formation of single-enantiomer alkylidenepyrrolidines. However, the reader is warned that these results are from the reviewer's own laboratories, and so we may be biased!

It is well known that protection of the lactam nitrogen as the carbamate renders the lactam carbonyl susceptible to attack by a range of nucleophiles. This approach was used in 2001 to prepare the sulfonyl alkylidenepyrrolidine **79** in the two-step sequence shown in **Scheme 37**. The double-bond geometry of this compound was elucidated by nuclear Overhauser enhancements in the proton NMR data.[55]

Based on this general approach, Elliott and Wordingham have devised an efficient method for the preparation of a range of chiral alkylidenepyrrolidines. Reaction of lactams of general structure **80** with various enolate anions gives the ring-opened products **81**, which then undergo cyclisation without racemisation upon treatment with trifluoroacetic acid to give alkylidenepyrrolidines **82** (**Scheme 38**).[56]



Scheme 37

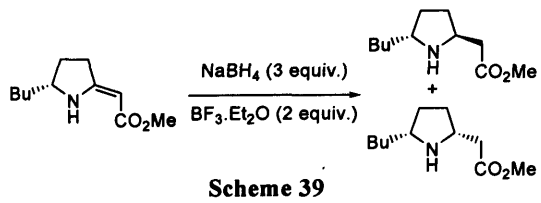


Scheme 38

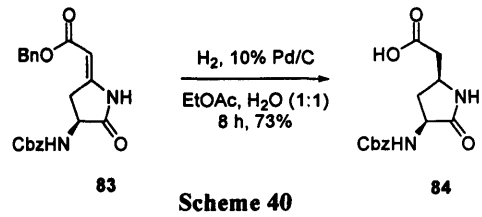
3. Use of Alkylidenepyrrolidines

One of the simpler elaborations of alkylidenepyrrolidines is reduction of the carbon-carbon double bond. This is non-trivial, and the carbon-carbon double bond of alkylidenepyrrolidine esters is particularly resistant to hydride reduction (significantly more so than the corresponding alkylidenepiperidines[57]). However, the reduction can be accomplished using a combination of sodium borohydride and boron trifluoride etherate, although no diastereoselectivity was observed in the example in **Scheme 39**.[58]

A wide range of conditions have been used for this transformation, along with a significant number of substrates. In general, catalytic hydrogenation methods generally give good selectivity for the *cis*-disubstituted pyrrolidine, while hydride reduction is far more dependant on the substrate, and can give either diastereoisomers preferentially, but usually with modest diastereoselectivity.[59] Benzyl ester **83** (or its double-bond isomer) gave a 10:1 diastereomeric mixture favouring **84** simply by stirring under an atmosphere of hydrogen in the presence of 10% palladium on carbon (**Scheme 40**).[60]

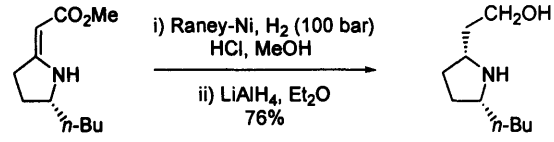


Scheme 39



Scheme 40

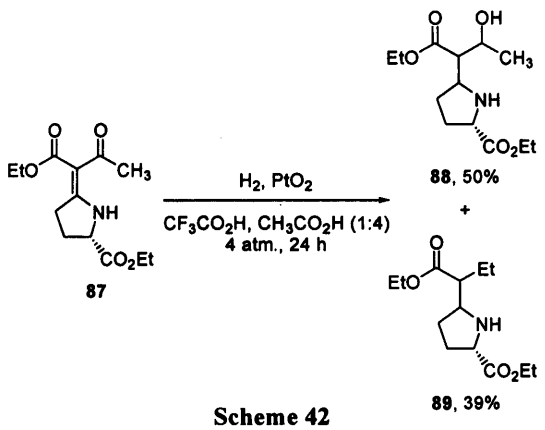
The same type of hydrogenation has also been used to prepare *cis*-2,5-disubstituted pyrrolidines. For example, the two-step reduction of alkylidenepyrrolidine **85** into **86** was accomplished by hydrogenation over Raney nickel to reduce the carbon-carbon double-bond followed by a routine ester reduction with lithium aluminium hydride (**Scheme 41**).[61]



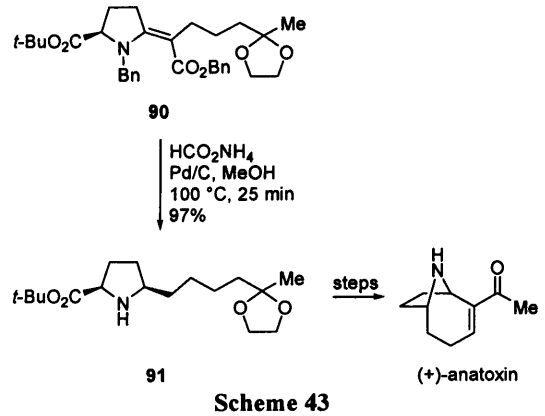
Scheme 41

Introduction of a further electron-withdrawing substituent onto the double-bond reduces the ease of reduction even more, so that compound **87** could only be reduced by hydrogenation over PtO_2 in a mixture of trifluoroacetic acid and acetic acid. This also led to partial and total reduction of the ketone group giving compounds **88** and **89**, both as a mixture of diastereoisomers (**Scheme 42**).[62] Hussaini and Moloney have investigated a range of conditions for the reduction of similar compounds, and shown that, in addition to the conditions shown in **Scheme 42**, sodium cyanoborohydride in ethanol at pH 3 – 5 is effective.[63] Petersen *et al.* have previously used these conditions to reduce alkylidenepyrrolidine esters with only a single electron-withdrawing group, and shown them to form predominantly the *cis*-2,5-disubstituted pyrrolidine, albeit with lower stereoselectivity than hydrogenation methods.[64]

Rapoport uses an elegant variation on this theme in his synthesis of anatoxin and analogues thereof. In the hydrogenation of compound **90**, both benzyl groups are removed, leading to decarboxylation. Under these conditions, only the *cis* isomer of compound **91** was produced (**Scheme 43**).[11,64,65]

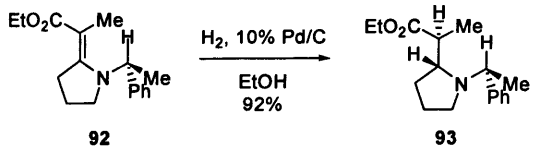


Scheme 42



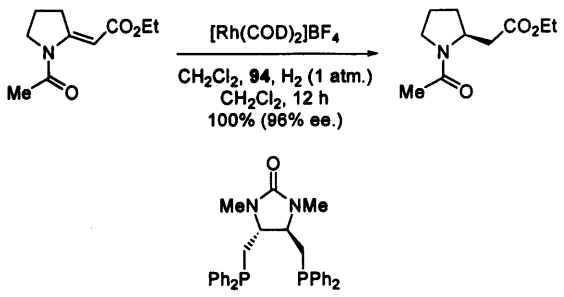
Scheme 43

The diastereoselectivity of these double-bond reductions can also be controlled by substituents on the nitrogen atom.[66] For example, hydrogenation of compound **92** (9:1 *E*:*Z* mixture) over palladium on carbon gave, surprisingly, the product of *anti* hydrogen addition **93** as the major stereoisomer (**Scheme 44**). Similar results were obtained with other catalysts, as well as with sodium triacetoxyborohydride in acetic acid.[40,67]



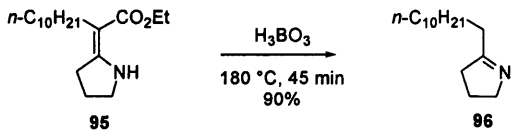
Scheme 44

This type of double-bond reduction can also be carried out using a chiral catalyst to effect enantiocontrol. For example, with ligand **94**, complete conversion to the product with 96% ee. was observed (**Scheme 45**).[68]



Scheme 45

One other very synthetically useful transformation is shown in **Scheme 46**. Alkylidenepyrrolidines such as **95** undergo an efficient decarboxylation upon heating with two equivalents of boric acid.[69] As the product pyrrolines **96** are ant venom alkaloids, this reaction has found significant use in natural product synthesis.[70]

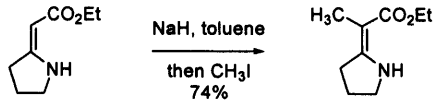


Scheme 46

Much of the chemistry of alkylidenepyrrolidines centres on their ambident nucleophilicity. The regioselectivity of electrophilic addition to alkylidenepyrrolidines is dependant on the nature of the electrophile and upon the reaction conditions. It is probably affected by the double-bond geometry of the alkylidenepyrrolidine, although there is insufficient data at present to assess this properly.

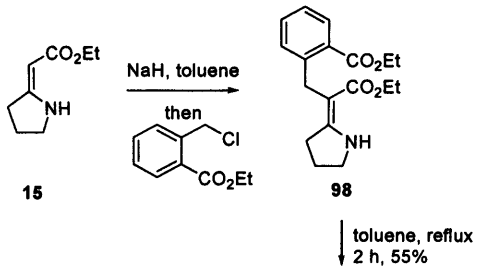
Alkylation of alkylidenepyrrolidines bearing a single electron-withdrawing group generally occurs on carbon. For example, treatment of compound **15** with iodomethane under conditions shown in **Scheme 47** gave compound **97** selectively.[71] This reaction type has been used as the basis of annulation reactions. For example, alkylation of compound **15** on carbon to give adduct **98** was followed by an intramolecular

C-acylation and subsequent decarboxylation to provide new alkylidenepyrrolidine **99** (**Scheme 48**).[72] Alkylidenepyrrolidine **100**, prepared by a similar alkylation reaction with an α-bromo Weinreb amide, undergoes attack by a range of organometallic nucleophiles followed by facile cyclisation to prepare pyrrolizidines such as **101** (**Scheme 49**).[73] A similar approach has been used to prepare saturated pyrrolizidine alkaloids.[74]



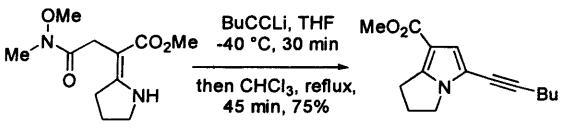
15 **97**

Scheme 47



15 **98** **99**

Scheme 48

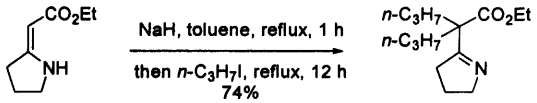


100 **101**

Scheme 49

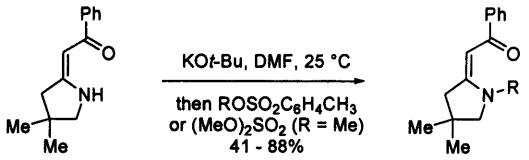
A second alkylation on carbon is possible, leading to the cyclic imine tautomers. Typically this requires heating of the sodium salt of the alkylidene-pyrrolidine with excess alkyl halide (**Scheme 50**).[75]

An almost complete change to *N*-alkylation can be accomplished by choice of electrophile, although the base and solvent also play a role. Dimethyl sulfate is the electrophile of choice for methylations, while alkyl 4-toluenesulfonates give good yields and selectivities for *N*-alkylation with other groups (**Scheme 51**).[76] Such alkylations have also been carried out under phase-transfer conditions.[77]



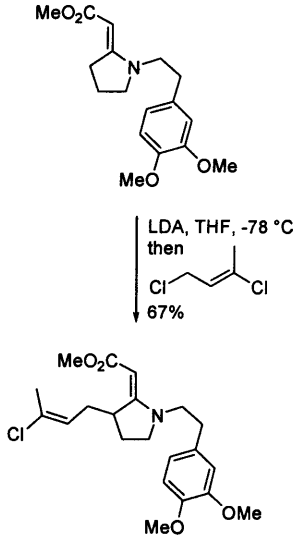
15

Scheme 50



Scheme 51

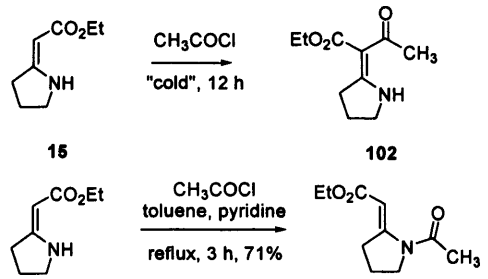
Although not generally observed for *N*-unsubstituted alkylidenepyrrolidines, alkylation at the 3-position of the pyrrolidine ring has also been observed. This γ-alkylation, an example of which is shown in **Scheme 52**, is generally observed with β-enaminoesters.[78]



Scheme 52

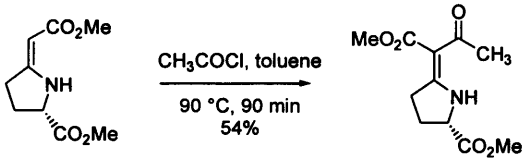
The acylation of alkylidenepyrrolidines is sensitive to reaction conditions as well as steric effects. The kinetic

product from compound **15** is compound **102**, where acylation has taken place on carbon (**Scheme 53**).[79] However, at higher temperatures, with or without the presence of pyridine as a catalyst, compound **103** is favoured.[26,80] A second acylation on carbon is straightforward with alkylidenepiperidines, but not with alkylidenepyrrolidines.[26]



Scheme 53

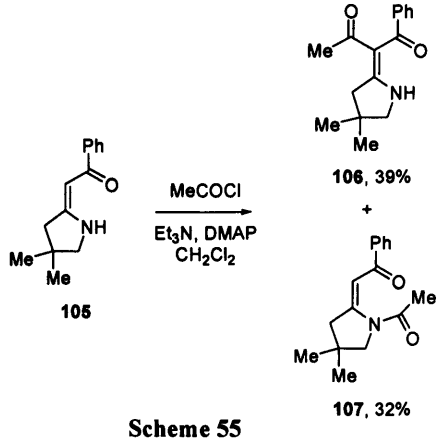
With the slightly more hindered alkylidenepyrrolidine **104**, only *C*-acylation was observed in toluene at a range of temperatures (0 °C; 20 °C; 90 °C) (**Scheme 54**).[81]



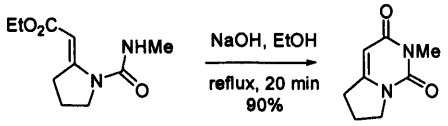
Scheme 54

In contrast, the use of strong bases (BuLi, NaH, *t*-BuOK) favours *N*-acylation of alkylidenepyrrolidine **105** with acetyl chloride, and only in dichloromethane in the presence of triethylamine and DMAP is any appreciable *C*-acylation observed (**Scheme 55**).[76,82]

Acylation of alkylidenepyrrolidines with a range of alkyl and aryl isocyanates have been reported to take place exclusively on nitrogen,[83] although it has been suggested that some of the products reported may actually be the *C*-acylated alkylidenepyrrolidines.[84] In earlier work, Micheel and Flitsch reported the reaction of an alkylidenepyrrolidine with phenyl isocyanate, but were unable to determine whether the acylation had taken place on nitrogen or on carbon.[85] It is clear that in some instances the *N*-acylated products are produced, as these undergo cyclisation as shown in **Scheme 56**.[86]

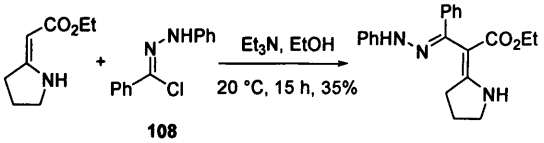


Scheme 55

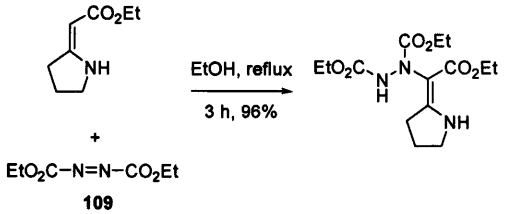


Scheme 56

A number of less common electrophiles have been used in this type of reaction, *e.g.* the nitrilimine generated *in situ* from iminoyl chloride **108** (**Scheme 57**)[87] and diethyl azodicarboxylate **109** (**Scheme 58**).[29]



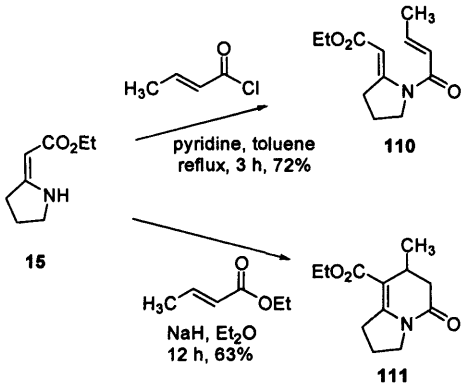
Scheme 57



Scheme 58

With ambident electrophiles, further possibilities present themselves. The reactions of alkylidenepyrrolidine

15 with crotonyl chloride and with ethyl crotonate are shown in **Scheme 59**. As above, the use of toluene and pyridine at reflux favours *N*-acylation with acid chlorides, giving compound **110**. This acylation attenuates the enamine-type reactivity so cyclisation to **111** does not occur. With ethyl crotonate, initial attack is *via* the carbon onto the β-position of the crotonate ester - this is followed by ready cyclisation giving **111**. However, ring-size is important, and with six- and seven-membered vinylogous carbamates the annulated products are obtained in both cases.[88] The reaction is clearly sensitive to steric demands, since with acryloyl chloride the annulated product (analogous to **111**) is formed under a range of conditions.[88,89]

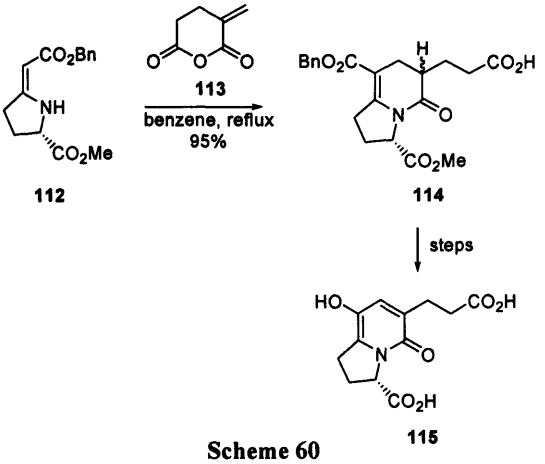


Scheme 59

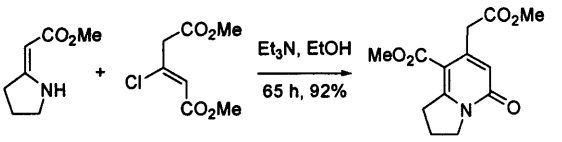
Additional functionality can be readily incorporated into the unsaturated carbonyl compound to suit target synthesis. For example, in the preparation of angiotensin-converting enzyme inhibitor A58365A (**115**), benzyl ester **112** underwent annulation with anhydride **113** to give compound **114** as a 2:1 mixture of diastereoisomers (**Scheme 60**).[24,90] Related annulation reactions have been carried out with succinic anhydride.[91]

In the previous case, oxidation to the aromatic pyridone was accomplished using DDQ, but it is also possible to incorporate a leaving group on the β-position of the unsaturated ester double bond, so that elimination follows annulation giving this oxidation state directly (**Scheme 61**).[92]

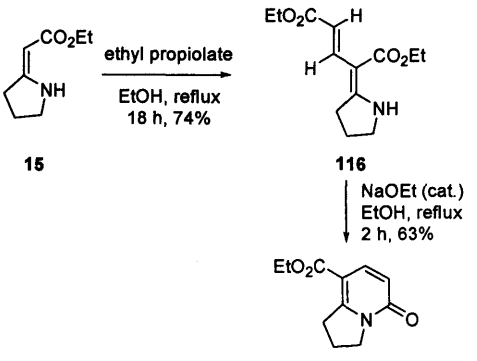
As a further alternative, propiolic acid and its derivatives can be used in annulation reactions. Although propiolic acid itself undergoes annulation in low yield by way of a DCC coupling, [5] higher yields be achieved with propiolate esters. For example, reaction of alkylidenepyrrolidine **15** with ethyl propiolate again proceeds *via* Michael addition to give **116**. This can then be followed by treatment with sodium ethoxide to give the annulated product **117** in good yield (**Scheme 62**).[93]



Scheme 60



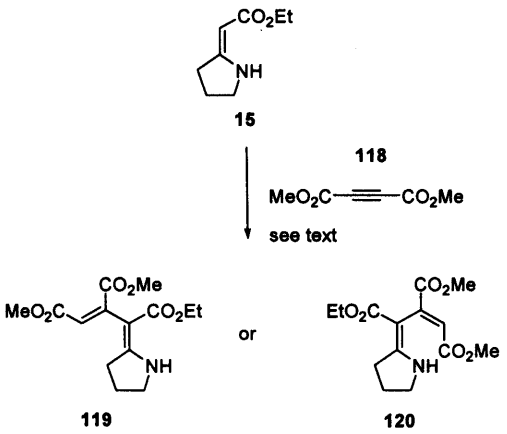
Scheme 61



Scheme 62

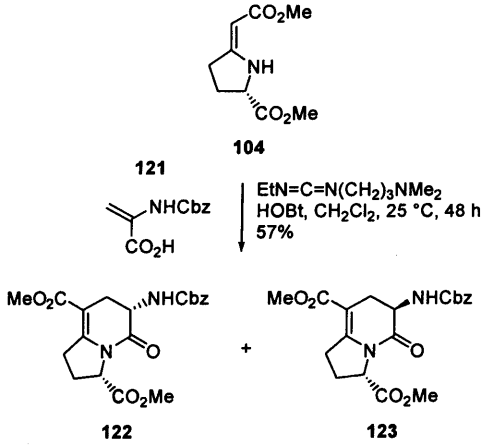
In reactions with doubly-substituted alkyne esters, the double-bond geometry formed depends upon the reaction conditions. For example, in the reaction of

alkylidenepyrrolidine **15** with diester **118** at room temperature in benzene, the (*Z,Z*) isomer **119** is formed preferentially (92% isolated yield after 24 h), while at reflux the (*E,E*) isomer **120** is the major product (72% after 2 h) (**Scheme 63**).[91]



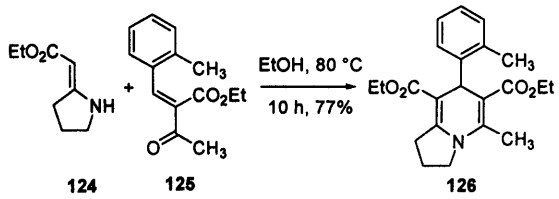
Scheme 63

With dehydro-aminoacid derivative **121** this approach forms the basis of a useful annulation reaction to give dipeptide mimetics as well as a range of neurokinin A and substance P receptor antagonists. For instance, reaction of alkylidenepyrrolidine **104** gave a 2.4:1 mixture of diastereoisomers **122** and **123** (**Scheme 64**).[94]



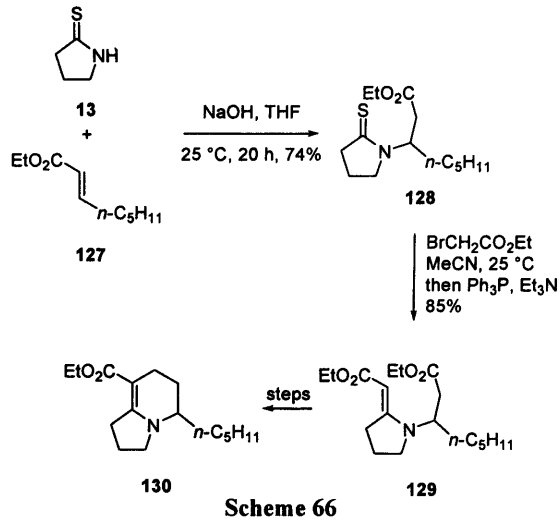
Scheme 64

A number of related annulation reactions have been reported. For example, reaction of alkylidenepyrrolidine **124** with unsaturated ketone **125** gives cycloadduct **126** in 77% yield (**Scheme 65**).[95]



Scheme 65

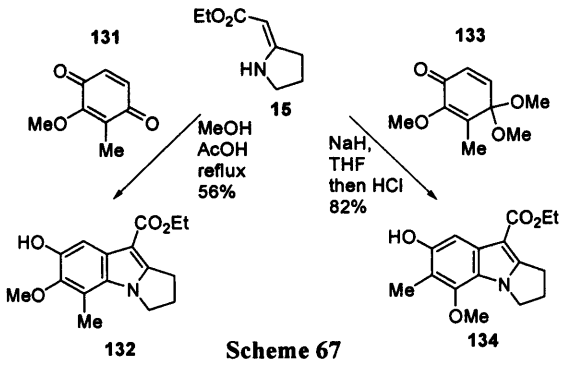
If one desires conjugate addition reactions initiated by attack of nitrogen rather than carbon, this can be achieved by a simple but effective modification of the order of steps. For example, reaction of thiolactam **13** with unsaturated ester **127** gave adduct **128**. This was then followed by Eschenmoser sulfide contraction to give the alkylidenepyrrolidine **129**. Subsequent steps converted this compound into the indolizidine **130** (**Scheme 66**).[96]



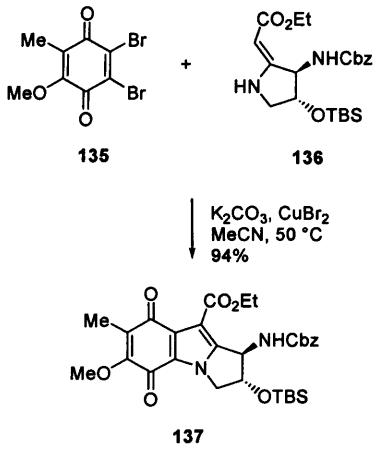
Scheme 66

Alkylidenepyrrolidines have been used in Nenitzescu-type annulation reactions[97] with 1,4-quinones. In this case, the regiochemical outcome can be controlled by use of either the quinone or the quinone ketal. For example, reaction of **15** with quinone **131** gave regioisomer **132**, while the use of ketal **133** gave compound **134** instead (**Scheme 67**).[98]

Others have used the same method, followed by oxidation to the indolequinone, for the preparation and biological evaluation of a range of mitosene analogues.[99] The quinone oxidation state is directly accessible by way of quinone **135**. In this way, indolequinone **137** was prepared by annulation of alkylidenepyrrolidine **136** (**Scheme 68**).[38]



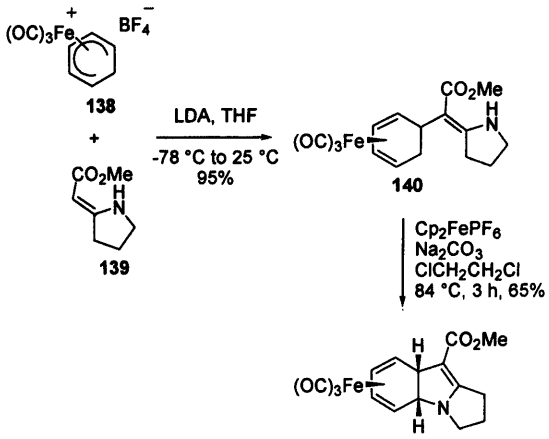
Scheme 67



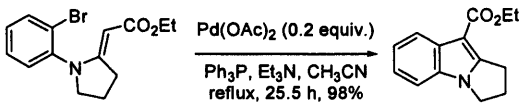
Scheme 68

The tricarbonyl[η^5-cyclohexadienylium]iron salt **138** provides a viable alternative to quinones in such indole synthesis. For example, with alkylidenepyrrolidine **139** the *C*-alkylated product **140** was formed first. This underwent oxidative cyclisation to give the indole-iron complex **141** in good yield (**Scheme 69**).[100]

Similar compounds have also been formed by intramolecular Heck reactions. For example, alkylidenepyrrolidine **142** underwent cyclisation to give indole **143** in good overall yield (**Scheme 70**).[101] It is worth noting that in most of the examples in this early report, palladium acetate was used in stoichiometric amounts.



Scheme 69

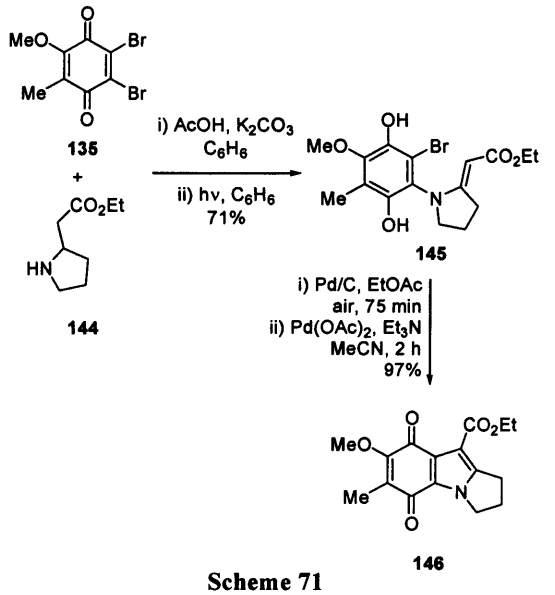


Scheme 70

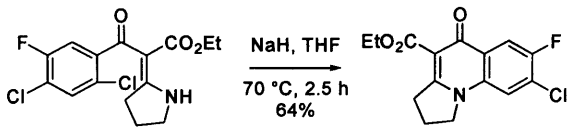
A combination of the Nenitzescu methodology with a Heck cyclisation has been used to great effect by Luly and Rapoport in their synthesis of mitosene analogues. Starting this time with the saturated pyrrolidine **144**, reaction with quinone **135** was followed by a photochemical disproportionation reaction to give alkylidenepyrrolidine **145**. This was then followed by a palladium-catalysed oxidation to regenerate the quinone followed by an intramolecular Heck reaction to furnish indolequinone **146** (**Scheme 71**).[102] Other annulation reactions have been reported where the final ring-closure is by C-N bond formation onto an aromatic ring. Compound **147** (contaminated with some of the methyl ester), prepared by condensation of a β-ketoester with an iminoether, underwent such a cyclisation to give quinolone **148** (**Scheme 72**).[103]

Reactions with *bis*-acid chlorides can be complex, and the outcome of the reaction depends on a number of factors. Ring size, in particular, is important so that

reactions of alkylidenepyrrolidines do not translate well to the piperidine and azepane analogues. Reaction of alkylidenepyrrolidine **15** with malonyl chloride gives the simple double addition product **149** (**Scheme 73**).[104] With phthaloyl chloride the reaction is more complex, as the initial adduct undergoes reaction with a second equivalent of **15** to give compound **150**, albeit in modest yield (**Scheme 73**).[105]

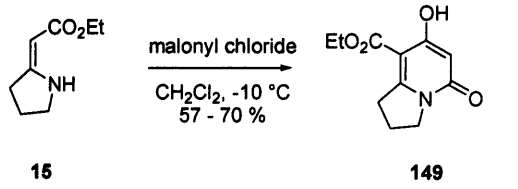


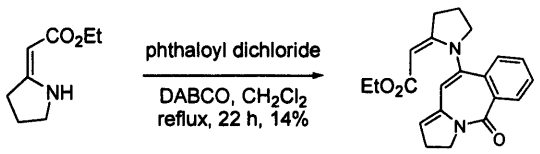
Scheme 71



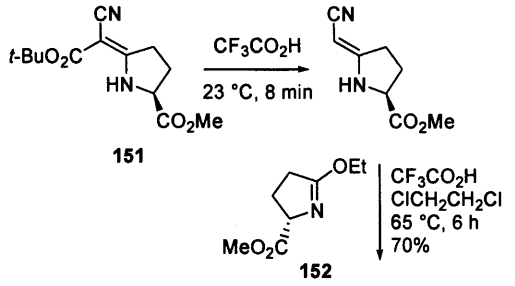
Scheme 72

One particularly important application of alkylidenepyrrolidine chemistry is in the preparation of semi-corrin ligands, pioneered by the group of Pfaltz. For example, alkylidenepyrrolidine **151**, prepared by the iminoether method, underwent smooth decarboxylation upon treatment with trifluoroacetic acid at room temperature. Further treatment with the same reagent in the presence of iminoether **152** gave semi-corrin **153** (**Scheme 74**).[106] The use of these compounds as chiral ligands, and their ultimate development towards the now ubiquitous bis-oxazolines and phosphinoaryloxazolines falls outside the scope of this review.





Scheme 73

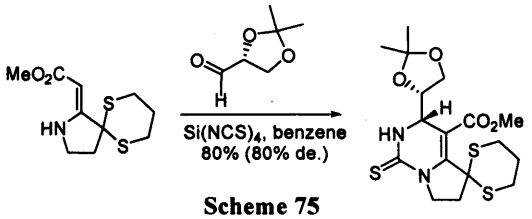


Scheme 74

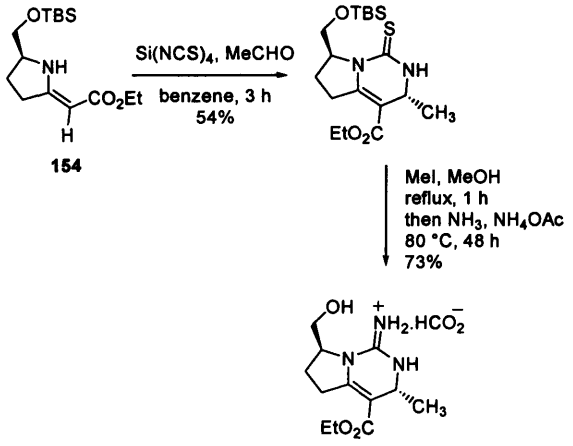
Kishi's group turned their attention to the synthesis of saxitoxin in the late 1970s. Following an initial report of a three-component coupling of an alkylidenepyrrolidine with isocyanic acid and acetaldehyde,[107] the first synthesis of the racemic natural product was reported in 1977.[108] This work was subsequently extended using the diastereoselective three-component coupling reaction shown in **Scheme 75** to provide an enantioselective synthesis of the natural product.[109]

Elliott and Long have used an analogous annulation of alkylidenepyrrolidine **154** to prepare compound **155** as

a model for the left-hand side of batzelladine A, a marine natural product with anti-HIV properties (**Scheme 76**).[84,110]

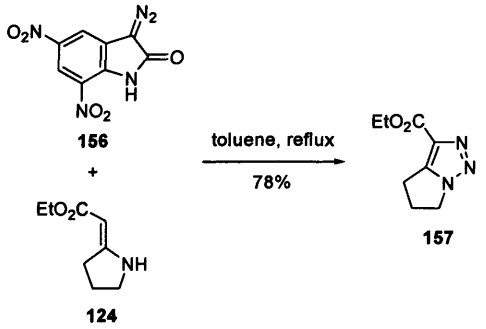


Scheme 75



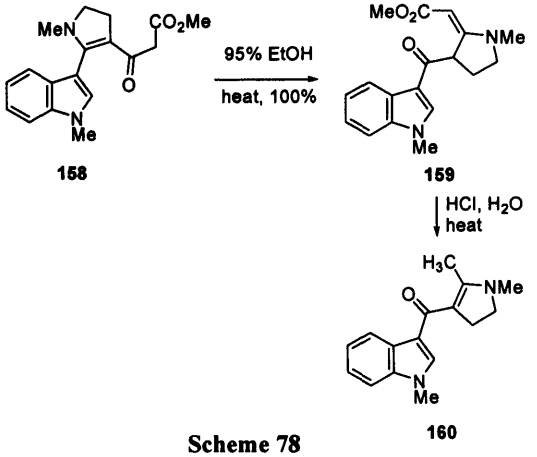
Scheme 76

A relatively unusual diazo-transfer reaction occurs between alkylidenepyrrolidine **124** and diazoindolone **156**, giving the triazole **157** (**Scheme 77**). This reaction is in fact relatively general, and works with many vinylogous carbamates and amides.[111]



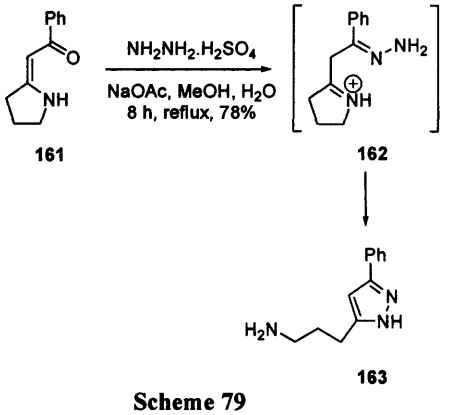
Scheme 77

There are a number of ring-transposition reactions during which the alkylidenepyrrolidine ring is either formed or lost. In the first example of these, heating compound **158** causes equilibration to form alkylidenepyrrolidine **159**. Upon treatment with aqueous acid, this compound undergoes decarboxylation to give the endocyclic enamine **160** (**Scheme 78**).[112]



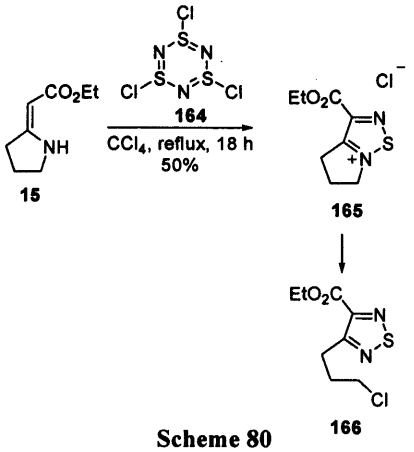
Scheme 78

Dannhardt and co-workers have used alkylidenepyrrolidine ketones to prepare a range of pyrazole and isoxazole derivatives with antibacterial activity. For example, treatment of substrate **161** with hydrazine sulfate gave pyrazole **163** *via* hydrazone **162** (**Scheme 79**).[113] Similar reactions with hydroxylamine hydrochloride give the analogous isoxazoles,[114] including *N*-alkyl and *N*-acyl derivatives.[115]



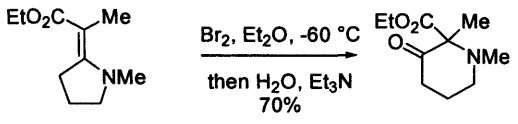
Scheme 79

One further ring-transposition reaction is shown in **Scheme 80**. Reaction of alkylidenepyrrolidine **15** with trithiazyl trichloride **164** gives thiadiazole **166** by way of the isolable intermediate **165**.[116]



Scheme 80

Alkylidenepyrrolidines such as **167** can undergo ring-expansion reactions. In this case the Wagner-Meerwein type rearrangement is initiated by bromohydrin formation (**Scheme 81**).[117]



Scheme 81

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Acylation of alkylidenepyrrolidines with heterocumulenes—a reinvestigation

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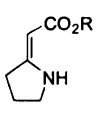
Abstract—The reactions of alkylidenepyrrolidine esters with isocyanates generally favour C-acylation, except in the case of benzyl isocyanate. Reactions with alkyl isocyanates are slow, and require forcing conditions. Reactions with isothiocyanates give exclusively the C-acylated products.

1. Introduction

Alkylidenepyrrolidines **1** are versatile heterocyclic ambident nucleophiles, which have been extensively used in organic synthesis.[1] During the course of our studies towards the synthesis of the batzelladine alkaloids,[2] we had occasion to undertake a three-component coupling reaction of an alkylidenepyrrolidine with an aldehyde and a silyl isothiocyanate.[3] Since the stereoselectivity in this reaction was modest, we sought an understanding of the mechanism in order to optimise this. For this study, we required a range of compounds of general structure **2** in order to study the stereoselectivity of their reactions with aldehydes. The N-acylation of alkylidenepyrrolidines has been reported with a range of alkyl and aryl isocyanates.[4] However, when we attempted to repeat some of the reactions in this report, we observed somewhat different results. In order to verify the trends observed during this work, a number of additional heterocumulenes were also investigated. We now report our results herein.



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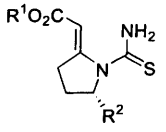
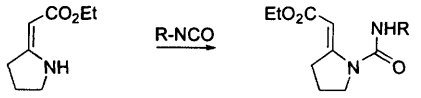


2

2. Results and discussion

The publication by Tronche[4] states that in general, all isocyanates used gave an approximately 70:30 mixture of products favouring N-acylation. With alkyl isocyanates, reactions were carried out in pyridine at room temperature for 2 h, while reactions with aryl isocyanates were undertaken in benzene at reflux (12 h). The examples reported are shown in Scheme 1.

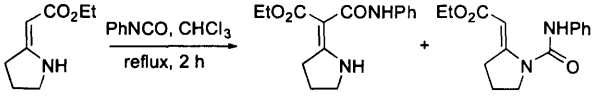


3

R = Me, *n*-Bu, *n*-C_6H_{13}, *c*-C_6H_{11}, Bn, Ph, 3-ClC_6H_4, 4-ClC_6H_4, 4-$CH_3C_6H_4$

Scheme 1.

In our hands, reaction of phenyl isocyanate with (*Z*)-alkylidenepyrrolidine **3** in chloroform under reflux gave a 3.4:1 crude mixture of C- and N-acylated products **4** and **5**. The isolated yields approximately reflect this regioselectivity (Scheme 2). At room temperature in the same solvent, a 2.1:1 mixture of the same compounds was obtained. When benzene (reflux) was used as solvent, a 5.2:1 mixture was obtained, while THF (also at reflux) gave the highest selectivity at 7:1. In all cases, the C-acylated product **4** predominated.



3 **4**, 71% **5**, 17%

Scheme 2.

All compounds in our study have been fully characterised (^{1}H NMR, ^{13}C NMR+DEPT, IR, MS, HRMS). The ^{1}H NMR

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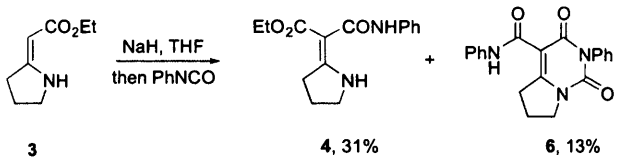
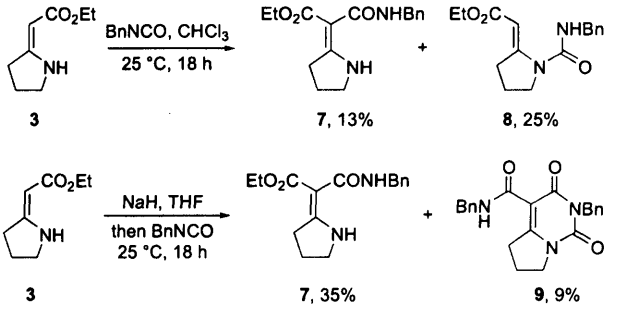
and melting point data which we have obtained for compound **5** are entirely in line with those reported by Tronche.[4] In an attempt to favour N-acylation, compound **3** was deprotonated with sodium hydride prior to reaction with phenyl isocyanate. However, this gave only a mixture of compound **4** and the novel heterocycle **6** (Scheme 3). Clearly the formation of compound **6** requires N-acylation, but this could occur after the C-acylation. In no case have we been able to obtain a mixture favouring the N-acylated product **5**.



Scheme 3.

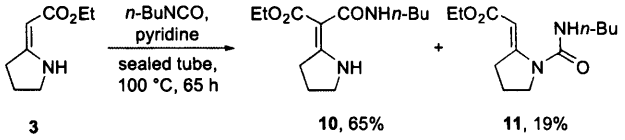
In contrast, reaction of alkylidenepyrrolidine **3** with benzyl isocyanate proceeds to give a 2:1 mixture of N-acylated compound **8** and C-acylated compound **7**, exactly as reported.[4] We chose to carry out this reaction in chloroform rather than pyridine, and obtained poor conversion (Scheme 4). Upon heating, the overall yields were dramatically improved at the expense of regioselectivity (1:1). Deprotonation of the alkylidenepyrrolidine with sodium hydride gave good selectivity for C-acylation (5.3:1). In this case, the bicyclic compound **9** was also formed (9% yield), while the low conversion meant that compound **8** was not actually isolated.

At this point we felt that we were beginning to establish a trend, and that alkyl isocyanates would give predominantly N-acyl products while aryl isocyanates would give predominantly C-acyl products. In order to verify this, reactions were carried out with cyclohexyl and butyl isocyanates. In both



Scheme 4.

cases, no reaction was observed in either chloroform or pyridine at room temperature. With butyl isocyanate, upon heating for 65 h at 100 °C, C-acylation was again found to predominate (Scheme 5).

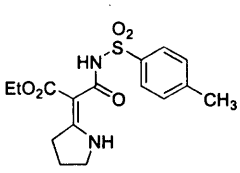


Scheme 5.

Following on from these results, a number of other isocyanates and some isothiocyanates were investigated in this reaction. The results are summarised in Table 1. Of these other compounds, only 4-methylphenyl isocyanate was found to produce any of the N-acylated product, this being the minor compound produced. As we have previously discussed,[2] we believe that the data reported by Tronche for the N-acylated

Table 1. Reactions of alkylidenepyrrolidine **3** with a range of heterocumulenes

Entry	Heterocumulene	Conditions	Ratio C:N acylation	Products (% isolated yield)
1	PhNCO	$CHCl_3$, 25 °C, 18 h	2.1:1	**4** (53%); **5** (20%)
2	PhNCO	$CHCl_3$, reflux, 2 h	3.4:1	**4** (71%); **5** (17%)
3	PhNCO	Benzene, reflux, 2 h	5.2:1	Not purified
4	PhNCO	THF, reflux, 2 h	7:1	Not purified
5	PhNCO	NaH, THF, 18 h	1:0	**4** (31%); **6** (13%)
6	BnNCO	$CHCl_3$, 25 °C, 18 h	1:2	**7** (13%); **8** (25%)
7	BnNCO	$CHCl_3$, reflux, 20 h	1:1	**7** (39%); **8** (50%)
8	BnNCO	NaH, THF, 18 h	5.3:1	**7** (35%); **9** (9%)
9	*n*-BuNCO	Pyridine, 100 °C, 65 h	2.3:1	**10** (65%); **11** (19%)
10	4-MeC_6H_4NCO	$CHCl_3$, reflux, 2 h	2.3:1	**12** (56%); **13** (23%)
11	TsNCO	$CHCl_3$, 25 °C, 2 h	1:0	**14** (94%)
12	$Cl_3CCONCO$	$CHCl_3$, 25 °C, 18 h	1:0	**15** (51%)
13	PhNCS	$CHCl_3$, reflux, 18 h	1:0	**16** (58%)
14	BnNCS	$CHCl_3$, reflux, 18 h	1:0	**17** (66%)
15	*n*-BuNCS	Pyridine, 100 °C, 46 h	1:0	**18** (89%)
16	BnNCS	NaH, THF, 18 h	1:0	**17** (38%); **19** (25%)



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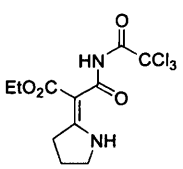

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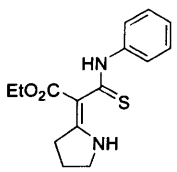

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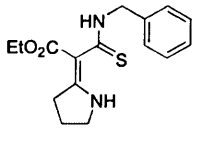

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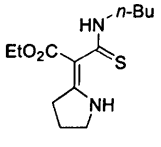

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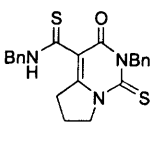
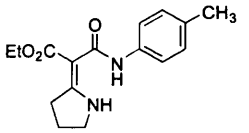


19

product **13** are actually more consistent with the C-acylated product **12**, so that our results are actually in agreement. In particular, the melting point reported for compound **13** is close to that which we have measured for compound **12**. In all other cases, the C-acylated product was formed exclusively, and in each case as a single double-bond isomer according to the spectroscopic data. The double-bond geometry is presumed to be that shown as a result of more favourable hydrogen bonding.[5]



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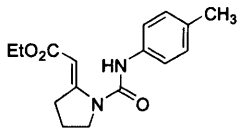
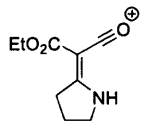


13

With the benefit of hindsight, it is straightforward to distinguish the C- and N-acyl compounds by mass spectrometry (electrospray or APCI). The former all give a strong peak at *m/z* 182 corresponding to fragment **20**, while the latter all give a peak at *m/z* 156, which presumably corresponds to **21**.



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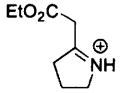
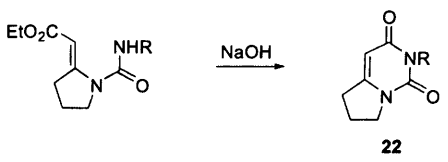


21

Tronche's group subsequently reported the formation of pyrrolo[1,2-*c*]pyrimidines **22** as shown in Scheme 6.[6] All of these compounds presented plausible NMR and analytical data, and it is difficult to see how any of these compounds could have been formed from the C-acyl isomers. We therefore have no doubt that the N-acyl compounds were indeed formed, although particularly in the case of R=*n*-Bu and *c*-C_6H_{13}, we are unable to reproduce their formation. The alkylidenepyrrolidine literature shows numerous examples of subtle reactivity,[7] so it seems possible that impurities present in either Tronche's or our own starting materials could affect the regioselectivity.



R = Me, *n*-C_4H_9, *n*-C_6H_{13}, *c*-C_6H_{11}, Bn, Ph

Scheme 6.

The other factor which could affect the regiochemical outcome is the double-bond geometry in the alkylidenepyrrolidine. Earlier reports[8] from the group of Tronche state that the (*Z*)-alkylidenepyrrolidine **3** gives exclusively the C-acylation product with methyl and phenyl isocyanates, while an unspecified mixture of (*E*) and (*Z*) isomers leads to the 70:30 mixture favouring N-acylation. In their 1988 paper,[4] Tronche and co-workers do state that a mixture of double-bond isomers was used. However, they prepared alkylidenepyrrolidine **3** by an Eschenmoser sulfide contraction, which is known to strongly favour the (*Z*)-alkylidenepyrrolidine,[1] and indeed the authors state in their experimental section that the (*Z*) isomer **3** was isolated in 46% yield, while the (*E*) isomer was unstable and was not isolated under these conditions.[4] Assuming that the (*Z*) isomer **3** and (*E*) isomer give C- and N-acylation products respectively, it is difficult to see how a mixture favouring the (*Z*) isomer could possibly give a 70:30 mixture favouring N-acylation. We are only aware of a single unequivocal example of the synthesis of the (*E*) isomer of a simple NH alkylidenepyrrolidine.[9] While many authors do draw the (*E*) isomer, it seems likely that this is for convenience, and generally no comment is made about the double-bond geometry. In the cases where the (*E*) isomer has been drawn and spectroscopic data are presented, all of these compounds appear to be the (*Z*) isomer.

Based on these observations, we can offer no conclusive explanation for the discrepancies between our own results and those of Tronche. Nevertheless, our results have proven to be reproducible and consistent over a range of heterocumulenes, and with batches of alkylidenepyrrolidine **3** prepared on a number of different occasions. We therefore feel that the results reported herein represent the norm for the acylation of alkylidenepyrroldines with heterocumulenes.

3. Experimental

3.1. General

All reactions were carried out under an atmosphere of dry nitrogen. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C. All chemical shifts are reported in parts per million downfield from TMS. Coupling constants (*J*) are reported in hertz. Multiplicity in ^{13}C NMR was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex silica 60 35–70 μm. Compound **3** was prepared according to a literature method.[10]

3.1.1. *N*-Phenyl-2-pyrrolidin-(2*E*)-ylidene-malonamic acid ethyl ester (4) and (1-phenylcarbamoyl-pyrrolidin-(2*E*)-ylidene)-acetic acid ethyl ester (5). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (106 mg, 0.7 mmol) in $CHCl_3$ (6 mL) was added phenyl isocyanate (89 μL, 0.8 mmol), and the mixture stirred at 25 °C for 18 h. The solvent was then removed in vacuo. The resulting orange oil was purified by column chromatography (eluting with ethyl acetate/hexane 4.5:7) to give compound **4** (R_f=0.8) (99 mg, 53%) and compound **5** (R_f=0.37) (38 mg, 20%).

Data for compound **4**: yellow solid, mp 76–78 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3236, 1650, 1614; δ_H (400 MHz; $CDCl_3$) 11.44 (1H, br s, CH_2NH), 11.29 (1H, br s, PhN*H*), 7.50 (2H, d, *J* 7.6, aromatic CH), 7.21 (2H, apparent t, *J* 7.9, aromatic CH), 6.95 (1H, t, *J* 7.4, aromatic CH), 4.14 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.52 (2H, t, *J* 7.7, CH_2NH), 3.11 (2H, t, *J* 7.9, $CH_2C{=}C$), 1.91 (2H, m, CH_2CH_2NH), 1.25 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 174.9 (CH_2CNH), 169.9 (*C*=O), 168.9 (*C*=O), 139.2 (aromatic C), 128.7 (aromatic CH), 123.0 (aromatic CH), 120.6 (aromatic CH), 87.0 ($COCCO_2Et$), 59.9 ($CO_2CH_2CH_3$), 47.7 (CH_2NH), 36.5 ($CH_2C{=}C$), 21.3 (CH_2CH_2NH), 14.6 ($CO_2CH_2CH_3$); *m/z* (ES$^+$) 297.2 (MNa$^+$, 7%), 275.3 (MH$^+$, 2), 183.1 (28), 182.1 (100), 154.0 (99), 138.0 (98); HRMS (ES$^+$) calcd for $C_{15}H_{19}N_2O_3$ (MH$^+$) 275.1396, found 275.1373.

Data for compound **5**: colourless solid, mp 127–129 °C (lit.[4] mp 128 °C); ν_{max} (CH_2Cl_2)/cm^{-1} 3377, 1689, 1660, 1594; δ_H (400 MHz; $CDCl_3$) 7.31 (2H, d, *J* 7.7, aromatic CH), 7.22 (2H, apparent t, *J* 7.9, aromatic CH), 7.01 (1H, t, *J* 7.4, aromatic CH), 6.95 (1H, br s, N*H*Ph), 6.34 (1H, apparent d, *J* 1.6, C*H*=C), 4.03 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.64 (2H, t, *J* 7.1, CH_2NCO), 3.12 (2H, apparent dt, *J* 1.6, 7.8, $CH_2C{=}C$), 1.87 (2H, apparent quintet, *J* 7.4, CH_2CH_2NCO), 1.16 (3H, t, *J* 7.1, $CO_2CH_2CH_3$). δ_C (100 MHz; $CDCl_3$) 168.9 (ester *C*=O), 158.2 (alkene C), 152.1 (urea *C*=O), 137.5 (aromatic C), 129.0 (aromatic CH), 124.3 (aromatic CH), 120.7 (aromatic CH), 95.6 (alkene CH), 59.4 (CO_2CH_2), 49.4 (CH_2NCO), 31.9 ($CH_2C{=}C$), 21.1 (CH_2CH_2NCO), 14.5 (CH_3CH_2OCO); *m/z* (ES$^+$) 275 (MH$^+$, 55%), 156 (100); HRMS (ES$^+$) calcd for $C_{15}H_{19}N_2O_3$ (MH$^+$) 275.1396, found 275.1397.

3.1.2. 1,3-Dioxo-2-phenyl-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid phenylamide (6). To a stirred suspension of sodium hydride (60% dispersion in oil, 35 mg, 1.5 mmol) in dry THF (15 mL), was added dropwise a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (207 mg, 1.3 mmol) in THF (5 mL) at 0 °C. The mixture was then stirred for 2 h at 25 °C. Phenyl isocyanate (159 mg, 1.3 mmol) was added, and the mixture stirred for 18 h at rt. The reaction mixture was quenched with saturated NH_4Cl solution (30 mL), the organic layer extracted, and the aqueous layer washed with DCM (3×30 mL). The combined organic washings were washed with brine (2×50 mL), dried over $MgSO_4$, and the solvent removed in vacuo. The residue was recrystallised from ethanol to give the *title compound* (60 mg, 13%) as a pale yellow solid, mp 253–255 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3239, 1705, 1682, 1591, 1437; δ_H (400 MHz; $CDCl_3$) 11.12 (1H, br s, PhN*H*CO), 7.60–7.35 (5H, m, aromatic CH), 7.30–7.15 (4H, m, aromatic CH), 7.00 (1H, t, *J* 7.3, aromatic CH), 4.00 (2H, t, *J* 7.5, CH_2NCO), 3.77 (2H, t, *J* 7.9, $CH_2C{=}C$), 2.17 (2H, apparent quintet, *J* 7.7, CH_2CH_2NCO); δ_C (100 MHz; $CDCl_3$) 164.9 (*C*=O), 163.5 (*C*=O), 160.6 (*C*=O), 147.8 (CH_2CNCO), 137.2 (aromatic C), 133.4 (aromatic C), 128.7 (aromatic CH), 128.3 (aromatic CH), 127.9 (aromatic CH), 127.1 (aromatic CH), 123.0 (aromatic CH), 119.3 (aromatic CH), 100.3 (NHCO–*C*–CO), 48.2 (CH_2NCO), 33.4 ($CH_2C{=}C$), 19.4 (CH_2CH_2NCO); *m/z* (ES$^+$) 370.3 (MNa$^+$, 92%), 348.3 (MH$^+$, 100), 273.2 (44), 255.2 (95); HRMS (ES$^+$) calcd for $C_{20}H_{18}N_3O_3$ (MH$^+$) 348.1348, found 348.1343. Purification of the filtrate by flash column chromatography gave compound **4** (113 mg, 31%) (data as above).

3.1.3. *N*-Benzyl-2-pyrrolidin-(2*E*)-ylidene-malonamic acid ethyl ester (7) and (1-benzylcarbamoyl-pyrrolidin-(2*E*)-ylidene)-acetic acid ethyl ester (8). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (103 mg, 0.7 mmol) in $CHCl_3$ (6 mL) was added benzyl isocyanate (80 μL, 0.7 mmol), and the mixture stirred at 25 °C for 18 h. The solvent was then removed in vacuo and the resulting orange oil purified by column chromatography (eluting with ethyl acetate/hexane 3:7) giving, in order of elution, compound **7** (R_f=0.41) (25 mg, 13%) and compound **8** (R_f=0.18) (48 mg, 25%).

Data for compound **7**: yellow solid, mp 95–98 °C; ν_{max} (Nujol)/cm^{-1} 3408, 1639, 1594; δ_H (400 MHz; $CDCl_3$) 11.40 (1H, s, CH_2NH), 9.51 (1H, m, $PhCH_2NH$), 7.27–7.18 (5H, m, aromatic CH), 4.43 (2H, d, *J* 5.7, $PhCH_2NH$), 4.09 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.50 (2H, t, *J* 7.4, CH_2NH), 3.09 (2H, t, *J* 7.9, $CH_2C{=}C$), 1.92 (2H, apparent quintet, *J* 7.7, CH_2CH_2NH), 1.22 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 174.4 (CH_2CNH), 170.5 (*C*=O), 169.7 (*C*=O), 139.6 (aromatic C), 128.5 (aromatic CH), 127.3 (aromatic CH), 126.8 (aromatic CH), 86.6 ($COCCO_2Et$), 59.5 ($CO_2CH_2CH_3$), 47.5 ($PhCH_2NH$), 43.0 (CH_2NH), 36.2 ($CH_2C{=}C$), 21.4 (CH_2CH_2NH), 14.6 ($CO_2CH_2CH_3$); *m/z* (ES$^+$) 311 (MNa+H_2O^+, 26%), 289 (MH$^+$, 10), 243 (5), 182 (100); HRMS (ES$^+$) calcd for $C_{16}H_{22}N_2O_3$ (MH$^+$) 289.1552, found 289.1548.

Data for compound **8**: colourless solid, mp 88–92 °C, lit.[4] mp 86 °C; ν_{max} (Nujol)/cm^{-1} 3357, 1669, 1604; δ_H (400 MHz; $CDCl_3$) 7.28–7.14 (5H, m, aromatic CH), 6.41 (1H, apparent t, *J* 1.7, C*H*=C), 5.32 (1H, br s, N*H*CH_2Ph), 4.38 (2H, d, *J* 5.6, NHCH_2Ph), 4.02 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.54 (2H, t, *J* 7.1, CH_2NCO), 3.11 (2H, apparent dt, *J* 1.7, 7.8, $CH_2C{=}CH$), 1.87 (2H, apparent quintet, *J* 7.5, CH_2CH_2NCO), 1.16 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 169.1 (ester *C*=O), 158.3 (CH_2CNCO), 154.5 (urea *C*=O), 158.5 (aromatic C), 128.7 (aromatic CH), 127.7 (aromatic CH), 127.5 (aromatic CH), 95.0 (*C*H=C), 59.2 ($CO_2CH_2CH_3$), 49.1 (NHCH_2Ph), 44.5 (CH_2NCO), 31.8 ($CH_2C{=}C$), 21.1 (CH_2CH_2NCO), 14.5 ($CO_2CH_2CH_3$); *m/z* (ES$^+$) 329 (M+Na+H_2O, 65%), 261 (38), 156 (100), 128 (97); HRMS (ES$^+$) calcd for $C_{16}H_{22}N_2O_3$ (MH$^+$) 289.1552, found 289.1548.

3.1.4. 1,3-Dioxo-2-benzyl-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzylamide (9). To a stirred suspension of sodium hydride (60% dispersion in oil, 45 mg, 1.1 mmol) in dry THF (15 mL), was added dropwise a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (159 mg, 1.0 mmol) in THF (5 mL) at 0 °C. The mixture was then stirred for 2 h at 25 °C. Benzyl isocyanate (0.13 mL, 1.0 mmol) was added, and the mixture stirred for 18 h at 25 °C. The reaction mixture was quenched with saturated NH_4Cl solution (30 mL), the organic layer was separated and the aqueous layer washed with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (2×50 mL), dried over $MgSO_4$, and the solvent

removed in vacuo. The resulting orange solid was purified by column chromatography (eluting with 3:7 ethyl acetate/hexane) giving, in order of elution, compound **9** (R_f=0.57) (36 mg, 9%) and compound **7** (R_f=0.41) (103 mg, 35%) (data as above).

Data for compound 9: yellow solid, mp 117–120 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3248, 1705, 1646, 1623, 1545, 1442; δ_H (400 MHz; $CDCl_3$) 11.10 (1H, br s, CH_2NHCO), 7.31 (4H, apparent t, *J* 7.6, aromatic CH), 7.26–7.12 (6H, m, aromatic CH), 5.04 (4H, apparent s, 2×PhCH_2N), 3.64 (2H, t, *J* 7.6, CH_2NCO), 3.39 (2H, t, *J* 8.0, CH_2C=C), 2.06 (2H, apparent quintet, *J* 7.8, CH_2CH$_2$NCO); δ_C (100 MHz; $CDCl_3$) 177.2 (Cl_3CC=O), 165.2 (*C*=O), 162.4 (*C*=O), 151.6 (CH_2CNCO), 137.6 (aromatic C), 137.6 (aromatic C), 128.5 (aromatic CH), 128.4 (aromatic CH), 128.2 (aromatic CH), 127.4 (aromatic CH), 127.3 (aromatic CH), 88.5 (NHCO–*C*–CO), 48.2 (*C*H$_2$NCO), 44.19, 44.16 (2×PhCH$_2$N), 35.3 (*C*H$_2$C=C), 20.8 (*C*H$_2$CH$_2$NCO); *m/z* (ES$^+$) 376 (MH$^+$, 100%), 310 (32), 238 (23), 123 (66); HRMS (ES$^+$) calcd for $C_{22}H_{22}N_3O_3$ (MH$^+$) 376.1661, found 376.1657.

3.1.5. *N*-Butyl-2-pyrrolidin-(2*E*)-ylidene-malonamic acid ethyl ester (10) and (1-*n*-butylcarbamoyl-pyrrolidin-(2*E*)-ylidene)-acetic acid ethyl ester (11). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (147 mg, 0.9 mmol) in pyridine (0.5 mL) was added butyl isocyanate (128 μL, 1.1 mmol). The solution was stirred at 100 °C in a sealed tube for 65 h, after which time the solvent was removed under reduced pressure. The resulting dark brown oil was purified by column chromatography (eluting with ethyl acetate/hexane 4:7), to give compound **10** (R_f=0.33) (156 mg, 65%) and compound **11** (R_f=0.11) (45 mg, 19%) both as pale yellow oils.

Data for compound 10: pale yellow oil; ν_{max} (CH_2Cl_2)/cm^{-1} 3314, 1654, 1598; δ_H (400 MHz; $CDCl_3$) 11.45 (1H, br s, CH_2NH), 9.10 (1H, br s, CH_2NHCO), 4.10 (2H, q, *J* 7.1, CO_2CH_2), 3.51 (2H, t, *J* 7.4, CH_2NH), 3.21 (2H, apparent q, *J* 6.5, CH_2NHCO), 3.08 (2H, t, *J* 7.9, CH_2C=C), 1.93 (2H, apparent quintet, *J* 7.7, CH_2CH$_2$NH), 1.46 (2H, apparent quintet, *J* 7.3, $CH_3CH_2CH_2$), 1.31 (2H, apparent sextet, *J* 7.4, $CH_3CH_2CH_2$), 1.23 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 0.85 (3H, t, *J* 7.3, $CH_3CH_2CH_2$); δ_C (100 MHz; $CDCl_3$) 174.1 (CH_2CNH), 170.3 (*C*=O), 169.6 (*C*=O), 86.5 ($COCCO_2Et$), 59.3 (CO_2CH_2), 47.3 (*C*H$_2$NH), 38.6 (CH_2NHCO), 36.0 (*C*H$_2$C=C), 31.8 ($CH_3CH_2CH_2$), 21.3 (CH_2CH_2NH), 20.3 ($CH_3CH_2CH_2$), 14.4 ($CO_2CH_2CH_3$), 13.8 ($CH_3CH_2CH_2$); *m/z* (APCI) 255 (MH$^+$, 24%), 182 (100); HRMS (ES$^+$) calcd for $C_{13}H_{23}N_2O_3$ (MH$^+$) 255.1709, found 255.1704.

Data for compound 11: pale yellow oil; ν_{max} (CH_2Cl_2)/cm^{-1} 3348, 1646, 1565; δ_H (400 MHz; $CDCl_3$) 6.28 (1H, br s, alkene C*H*), 4.97 (1H, br s, N*H*CON), 4.04 (2H, q, *J* 7.1, CO_2CH_2), 3.56 (2H, t, *J* 7.1, CH_2NCO), 3.21 (2H, apparent q, *J* 6.6, CH_2NHCO), 3.13 (2H, t, *J* 7.7, CH_2C=C), 1.89 (2H, apparent quintet, *J* 7.4, CH_2CH$_2$NCO), 1.47 (2H, apparent quintet, *J* 7.4, $CH_3CH_2CH_2$), 1.29 (2H, apparent sextet, *J* 7.4, $CH_3CH_2CH_2$), 1.18 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 0.87 (3H, t, *J* 7.3, $CH_3CH_2CH_2$); δ_C (100 MHz; $CDCl_3$) 169.0 (ester *C*=O), 158.4 (CH_2CNCO), 154.4 (urea *C*=O), 94.3 ($CHCCO_2Et$), 59.2 (CO_2CH_2), 49.2 (*C*H$_2$NCO), 40.4 (*C*H$_2$NHCO), 32.0 (*C*H$_2$C=C), 31.9 ($CH_3CH_2CH_2$), 21.1 (*C*H$_2$CH$_2$NH), 20.9 ($CH_3CH_2CH_2$), 14.5 ($CO_2CH_2CH_3$), 13.8 ($CH_3CH_2CH_2$); *m/z* (APCI) 273 (M+H$_3$O$^+$, 42%), 255 (MH$^+$, 19%), 227 (16), 156 (100); HRMS (ES$^+$) calcd for $C_{13}H_{23}N_2O_3$ (MH$^+$) 255.1709, found 255.1704.

3.1.6. 2-Pyrrolidin-(2*E*)-ylidene-*N*-*p*-tolyl-malonamic acid ethyl ester (12) and (1-*p*-tolylcarbamoyl-pyrrolidin-(2*E*)-ylidene)-acetic acid ethyl ester (13). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (161 mg, 1 mmol) in $CHCl_3$ (6 mL) was added *p*-tolyl isocyanate (130 μL, 1 mmol), and the solution stirred under reflux for 2 h. The solvent was removed in vacuo to produce a yellow oil, which solidified on standing. The yellow solid was purified by column chromatography (eluting with EtOAc/hexane 4.5:7) giving, in order of elution, compound **12** (R_f=0.76) (168 mg, 56%) and compound **13** (R_f=0.29) (69 mg, 23%).

Data for compound 12: pale yellow solid, mp 150–153 °C; ν_{max} (solution)/cm^{-1} 3216, 1649, 1619; δ_H (400 MHz; $CDCl_3$) 11.40 (1H, br s, CH_2NH), 11.25 (1H, br s, ArN*H*), 7.37 (2H, apparent d, *J* 7.4, aromatic CH), 7.01 (2H, apparent d, *J* 7.4, aromatic CH), 4.12 (2H, q, *J* 7.1, CO_2CH_2), 3.49 (2H, t, *J* 7.4, CH_2NH), 3.08 (2H, t, *J* 7.9, CH_2C=C), 2.20 (3H, s, CH_3Ar), 1.88 (2H, apparent quintet, *J* 7.7, CH_2CH$_2$NH), 1.23 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 174.8 (CH_2CNH), 169.9 (*C*=O), 168.8 (*C*=O), 136.5 (aromatic C), 132.5 (aromatic C), 129.3 (aromatic CH), 120.4 (aromatic CH), 87.0 ($COCCO_2Et$), 59.8 (CO_2CH_2), 47.6 (*C*H$_2$NH), 36.5 (*C*H$_2$C=C), 21.3 (*C*H$_2$CH$_2$NH), 20.9 (*C*H$_3$Ar), 14.6 ($CO_2CH_2CH_3$); *m/z* (ES$^+$) 311 (MNa$^+$, 30%), 289 (MH$^+$, 30), 182 (100); HRMS (ES$^+$) calcd for $C_{16}H_{22}N_2O_3$ (MH$^+$) 289.1552, found 289.1537.

Data for compound 13: colourless solid, mp 132–135 °C, lit.[4] mp 155 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3448, 1694, 1609; δ_H (400 MHz; $CDCl_3$) 7.25 (2H, apparent d, *J* 8.3, aromatic CH), 7.04 (2H, apparent d, *J* 8.3, aromatic CH), 6.77 (1H, s, N*H*Ar), 6.31 (1H, apparent t, *J* 1.6, C*H*=C), 4.04 (2H, q, *J* 7.1, CO_2CH_2), 3.66 (2H, t, *J* 7.1, CH_2NCO), 3.15 (2H, apparent dt, *J* 1.7, 7.8, CH_2C=C), 2.24 (3H, s, CH_3Ar), 1.90 (2H, apparent quintet, *J* 7.4, CH_2CH$_2$NCO), 1.17 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 168.8 (ester *C*=O), 158.1 (CH_2CNCO), 152.1 (urea *C*=O), 134.8 (aromatic C), 134.0 (aromatic CH), 129.5 (aromatic CH), 120.7 (aromatic CH), 95.4 (*C*H=C), 59.3 (CO_2CH_2), 49.4 (*C*H$_2$NCO), 32.0 (*C*H$_2$C=C), 21.1 (*C*H$_2$CH$_2$NCO), 20.8 (*C*H$_3$Ar), 14.5 ($CO_2CH_2CH_3$); *m/z* (ES$^+$) 311 (MNa$^+$, 22%), 289 (MH$^+$, 8), 156 (100), 110 (34); HRMS (ES$^+$) calcd for $C_{16}H_{20}N_2O_3Na$ (MNa$^+$) 311.1372, found 311.1356.

3.1.7. 3-Oxo-2-pyrrolidin-(2*E*)-ylidene-3-(toluene-4-sulfonylamino)-propionic acid ethyl ester (14). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (102 mg, 0.7 mmol) in $CHCl_3$ (6 mL) was added *p*-tosyl isocyanate (100 μL, 0.7 mmol) and the mixture stirred at reflux for 2 h. The solvent was removed in vacuo to yield the *title compound* (220 mg, 94%) as a white crystalline solid, without need for further purification, mp 154–158 °C; ν_{max} (Nujol)/cm^{-1} 3447, 1644, 1594; δ_H (400 MHz; $CDCl_3$) 12.20

(1H, s, CH_2NH), 11.30 (1H, s, SO_2NHCO), 7.83 (2H, apparent d, J 8.3, aromatic CH), 7.18 (2H, apparent d, J 8.3, aromatic CH), 4.09 (2H, q, J 7.1, $CO_2CH_2CH_3$), 3.46 (2H, t, J 7.5, CH_2NH), 3.05 (2H, t, J 7.9, $CH_2C{=}C$), 2.29 (3H, s, CH_3Ar), 1.89 (2H, apparent quintet, J 7.7, CH_2CH_2NH), 1.20 (3H, t, J 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 175.9 (CH_2CNH), 169.5 ($C{=}O$), 167.7 ($C{=}O$), 143.9 (aromatic C), 137.4 (aromatic C), 129.3 (aromatic CH), 128.1 (aromatic CH), 86.5 ($COCCO_2Et$), 60.5 ($CO_2CH_2CH_3$), 48.1 (CH_2NH), 36.6 ($CH_2C{=}C$), 21.6 (CH_3Ar), 20.8 (CH_2CH_2NH), 14.4 ($CO_2CH_2CH_3$); *m/z* (ES^+) 353 (MH^+, 34%), 182 (100); HRMS (ES^+) calcd for $C_{16}H_{21}N_2O_5S$ (MH^+) 353.1171, found 353.1166.

3.1.8. 3-Oxo-2-pyrrolidin-(2*E*)-ylidene-3-(2,2,2-trichloro-acetylamino)-propionic acid ethyl ester (15). To a stirred solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (63 mg, 0.4 mmol) was added trichloroacetyl isocyanate (48 μL, 0.4 mmol) and the mixture stirred for 18 h at 25 °C. The solvent was then removed in vacuo. The resulting yellow oil was purified by column chromatography (eluting with ethyl acetate/hexane 4:7) to give the *title compound* (R_f=0.25) (72 mg, 51%) as an off-white solid, mp 110–112 °C; ν_{max} (solution)/cm^{-1} 3197, 1750, 1664, 1614; δ_H (400 MHz; $CDCl_3$) 13.38 (1H, br s, Cl_3CCO–N*H*–CO), 11.31 (1H, br s, CH_2NH), 4.20 (2H, q, J 7.1, CO_2CH_2), 3.66 (2H, t, J 7.5, CH_2NH), 3.20 (2H, t, J 7.9, $CH_2C{=}C$), 2.04 (2H, apparent quintet, J 7.8, CH_2CH_2NH), 1.28 (3H, t, J 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 176.6 (Cl_3CCONH), 174.9 (CH_2CNH), 169.8 (ester $C{=}O$), 167.8 ($NHCOC{=}C$), 93.2 (Cl_3C), 87.8 ($COCCO_2Et$), 60.8 (CO_2CH_2), 48.4 (CH_2NH), 36.9 ($CH_2C{=}C$), 20.9 (CH_2CH_2NH), 14.4 ($CO_2CH_2CH_3$); *m/z* (ES^+) 343 (MH^+, 18%) (+consistent isotopomer peaks), 182 (100); HRMS (ES^+) calcd for $C_{11}H_{14}N_2O_4{}^{35}Cl_3$ (MH^+) 343.0019, found 343.0015.

3.1.9. Phenylthiocarbamoyl-(2*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester (16). To a stirred solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (60 mg, 0.4 mmol) in $CHCl_3$ (6 mL) was added phenyl isothiocyanate (46 μL, 0.4 mmol), and the mixture stirred for 20 h under reflux. The solvent was removed in vacuo and the resulting brown solid recrystallised from aqueous ethanol to yield the *title compound* (65 mg, 58%) as colourless needles, mp 118–120 °C; ν_{max} (solution)/cm^{-1} 3176, 1649, 1248; δ_H (400 MHz; $CDCl_3$) 13.28 (1H, br s, CH_2NH), 12.47 (1H, br s, PhN*H*), 7.38 (2H, d, J 7.6, aromatic CH), 7.31 (2H, apparent t, J 7.9, aromatic CH), 7.16 (1H, t, J 7.4, aromatic CH), 4.18 (2H, q, J 7.2, CO_2CH_2), 3.64 (2H, t, J 7.4, CH_2NH), 3.15 (2H, t, J 7.8, $CH_2C{=}C$), 1.98 (2H, apparent quintet, J 7.6, CH_2CH_2NH), 1.28 (3H, t, J 7.2, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 190.2 (thioamide $C{=}S$), 174.1 (CH_2CNH), 170.2 (ester $C{=}O$), 139.7 (aromatic C), 128.6 (aromatic CH), 126.3 (aromatic CH), 126.2 (aromatic CH), 95.0 ($CSCCO$), 60.4 (CO_2CH_2), 48.0 (CH_2NH), 37.8 ($CH_2C{=}C$), 21.9 (CH_2CH_2NH), 14.4 ($CO_2CH_2CH_3$); *m/z* (ES^+) 291 (MH^+, 29%), 198 (100); HRMS (ES^+) calcd for $C_{15}H_{19}N_2O_2S$ (MH^+) 291.1167, found 291.1172.

3.1.10. Benzylthiocarbamoyl-(2*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester (17). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (155 mg, 1 mmol) in $CHCl_3$ (6 mL) was added benzyl isothiocyanate (160 μL, 1.2 mmol), and the solution was stirred under reflux for 23 h. The mixture was allowed to cool, and the solvent was removed in vacuo. The resulting dark orange oil was purified by column chromatography (eluting with ethyl acetate/hexane 1:4) to give the *title compound* (R_f=0.41) (204 mg, 66%) as buff waxy solid, mp 83–87 °C; ν_{max} (solution)/cm^{-1} 3197, 1639, 1268; δ_H (400 MHz; $CDCl_3$) 13.05 (1H, br s, CH_2NH), 12.22 (1H, br s, $PhCH_2NH$), 7.18–7.11 (5H, m, aromatic CH), 4.79 (2H, apparent d, J 4.9, $PhCH_2NH$), 4.08 (2H, q, J 7.2, CO_2CH_2) 3.59 (2H, t, J 7.3, CH_2NH), 3.09 (2H, t, J 7.8, $CH_2C{=}C$), 1.93 (2H, apparent quintet, J 7.6, CH_2CH_2NH), 1.20 (3H, t, J 7.2, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 190.0 (thioamide $C{=}S$), 173.4 (CH_2CNH), 169.9 (ester $C{=}O$), 137.7 (aromatic C), 128.7 (aromatic CH), 127.9 (aromatic CH), 127.3 (aromatic CH), 94.3 ($CSCCO_2Et$), 60.1 (CO_2CH_2), 49.1 ($PhCH_2NH$), 47.8 (CH_2NH), 37.5 ($CH_2C{=}C$), 21.9 (CH_2CH_2NH), 14.4 ($CO_2CH_2CH_3$); *m/z* (ES^+) 305 (MH^+, 100%), 259 (24), 198 (78); HRMS (ES^+) calcd for $C_{16}H_{21}N_2O_2S$ (MH^+) 305.1324, found 305.1300.

3.1.11. *n*-Butylthiocarbamoyl-(2*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester (18). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (160 mg, 1.0 mmol) in pyridine (0.5 mL) was added butyl isothiocyanate (149 μL, 1.2 mmol). The solution was stirred at 100 °C in a sealed tube for 46 h, after which time the solvent was removed under reduced pressure. The resulting dark orange solid was recrystallised from aqueous ethanol to give the *title compound* (240 mg, 89%) as an orange solid, mp 53–56 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3176, 1633, 1257; δ_H (400 MHz; $CDCl_3$) 13.05 (1H, br s, CH_2NH), 10.92 (1H, br s, CH_2NHCS), 4.13 (2H, q, J 7.2, CO_2CH_2), 3.59 (2H, apparent q, J 7.3, CH_2NHCS), 3.58 (2H, t, J 7.3, CH_2NH), 3.08 (2H, t, J 7.8, $CH_2C{=}C$), 1.94 (2H, apparent quintet, J 7.6, CH_2CH_2NH), 1.58 (2H, apparent quintet, J 7.3, $CH_3CH_2CH_2$), 1.36 (2H, apparent sextet, J 7.4, $CH_3CH_2CH_2$), 1.24 (3H, t, J 7.2, $CO_2CH_2CH_3$), 0.88 (3H, t, J 7.3, $CH_3CH_2CH_2$); δ_C (100 MHz; $CDCl_3$) 189.5 (thiocarbamoyl $C{=}S$), 173.1 (CH_2CNH), 169.9 (ester $C{=}O$), 94.0 ($CSCCO_2Et$), 60.0 (CO_2CH_2), 47.6 (CH_2NH), 44.7 (CH_2NHCS), 37.4 ($CH_2C{=}C$), 30.3 ($CH_3CH_2CH_2$), 21.8 (CH_2CH_2NH), 20.4 ($CH_3CH_2CH_2$), 14.3 ($CO_2CH_2CH_3$), 13.8 ($CH_3CH_2CH_2$); *m/z* (APCI) 271 (MH^+, 74%), 225 (26), 198 (100), 156 (19); HRMS (ES^+) calcd for $C_{13}H_{23}N_2O_2S$ (MH^+) 271.1480, found 271.1476.

3.1.12. 2-Benzyl-3-oxo-1-thioxo-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carbothioic acid benzylamide (19). To a stirred suspension of sodium hydride (60% dispersion in oil, 18 mg, 0.44 mmol) in dry THF (10 mL), was added dropwise a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (62 mg, 0.4 mmol) in THF (5 mL) at 0 °C. The mixture was then stirred for 2 h at 25 °C. Benzyl isothiocyanate (53 μL, 1.0 mmol) was added, and the mixture stirred for 18 h at 25 °C. The reaction mixture was quenched with saturated NH_4Cl solution (30 mL), the organic layer separated, and the aqueous layer extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (2×50 mL), dried over $MgSO_4$, and the solvent removed in vacuo. The resulting dark orange solid was purified by column chromatography

(eluting with ethyl acetate/hexane 3:7) to give, in order of elution, compound **17** (R_f=0.68) (46 mg, 38%) (data as above) and the *title compound* (R_f=0.45) (42 mg, 25%) as a pale solid, mp 130–132 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3337, 1664, 1288; δ_H (400 MHz; $CDCl_3$) 14.0 (1H, br s, $PhCH_2NHCS$), 7.45–7.05 (10H, m, aromatic CH), 6.45 (2H, s, one of $PhCH_2N$), 5.73 (2H, s, one of $PhCH_2N$), 3.74 (2H, t, *J* 7.4, CH_2NCS), 3.55 (2H, t, *J* 7.9, $CH_2C{=}C$), 2.17 (2H, apparent quintet, *J* 7.7, CH_2CH_2NCO); δ_C (100 MHz; $CDCl_3$) 191.0 (C=S), 183.4 (C=S), 176.6 (C=O), 157.8 (alkene C), 135.6 (aromatic C), 135.5 (aromatic C), 127.3 (aromatic CH), 127.2 (aromatic CH), 126.5 (aromatic CH), 126.1 (aromatic CH), 125.6 (aromatic CH), 125.6 (aromatic CH), 102.8 (alkene C), 56.0 (CH_2N), 50.5 (CH_2N), 47.9 (CH_2N), 37.1 (CH_2), 20.1 (CH_2); *m/z* (ES^+) 408 (MH^+, 100%), 383 (28), 303 (22), 238 (29), 182 (58); HRMS (ES^+) calcd for $C_{22}H_{22}N_3OS_2$ (MH^+) 408.1204, found 408.1208.

Acknowledgements

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A Concise Diastereoselective Approach to the Left-Hand Side of Batzelladine A

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Abstract: A highly diastereoselective three-component coupling reaction has been used in a concise approach to the left-hand side of batzelladine A. The stereoselectivity of this reaction, along with related observations described herein, provides insight into the mechanism of this reaction.

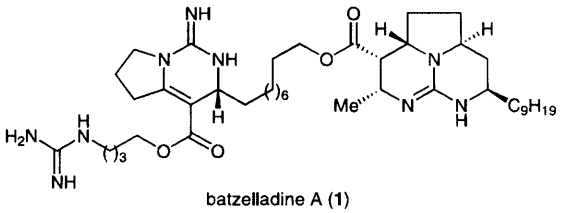
Key words: multicomponent reactions, alkaloids, imines, stereoselectivity, isothiocyanates

The batzelladine alkaloids form part of a structurally and biologically fascinating group of natural products obtained from marine sources.[1] Fifteen members of this group have now been isolated,[2] with representative structures shown in Figure 1. Batzelladines A (**1**) and B (**2**) inhibit the binding of HIV glycoprotein gp120 to the CD4 receptor, and so are of therapeutic interest for the treatment of HIV. Batzelladines C–E, of which batzelladine D (**3**) is structurally representative, are cytotoxic. Various analogues of the batzelladine alkaloids have also been shown to disrupt the gp120-CD4 interaction.[3]

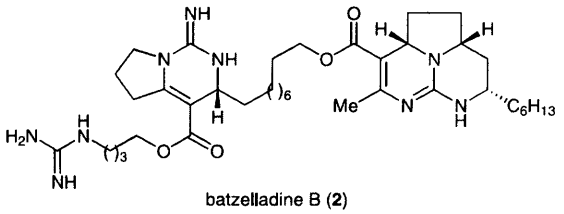
These compounds have been the subject of a number of synthetic studies, leading to the development of a wealth of new methodology. In particular, batzelladines A,[4] D,[5] E,[6] F,[7] and dehydrobatzelladine C[8] have been synthesized.[9]

Our own work in this area[10] has focused on the use of the Kishi three-component coupling[11] of an alkylidenepyrrolidine with a silyl isothiocyanate and an aldehyde to give the key pyrrolo[1,2-*c*]pyrimidine core. However, with a stereochemical directing-group at the 5-position of the pyrrolidine, as shown in Scheme 1, the stereoselectivity is typically 2:1, which falls far short of the total stereocontrol which we observed during the formation of similar compounds by annulation of alkenylazolines with isocyanates.[12]

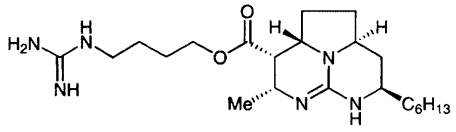
In order to improve the stereoselectivity of this reaction, we sought an understanding of the reaction mechanism. The mechanism originally proposed required initial N-acylation of the alkylidenepyrrolidine by the isothiocyanate, followed by condensation with the aldehyde and cyclisation. However, isothiocyanates only react with alkylidenepyrrolidines under relatively forcing conditions,[13] giving only the product of acylation of the enamine carbon. On this basis, we would tentatively exclude this mechanism.



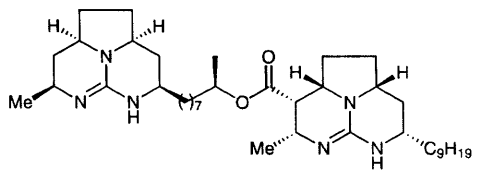
batzelladine A (**1**)



batzelladine B (**2**)



batzelladine D (**3**)



batzelladine F (**4**)

Figure 1

The reaction of trimethylsilyl isothiocyanate with aldehydes under Lewis acidic conditions is known to give compounds of general structure **8**.[14] This provides precedent for the nucleophilic addition of trimethylsilyl isothiocyanate onto aldehydes, so that generation of an intermediate of structure **9** or **10** is not unreasonable. Such species would presumably be capable of reacting with the enamine carbon of alkylidenepyrrolidine **11** to give a compound **12**, which would undergo rapid tautomerism to compound (*Z*)-**13**. Double-bond isomerisation could then provide the *E*-isomer, which would cyclise to give the final product **14** (Scheme 2).

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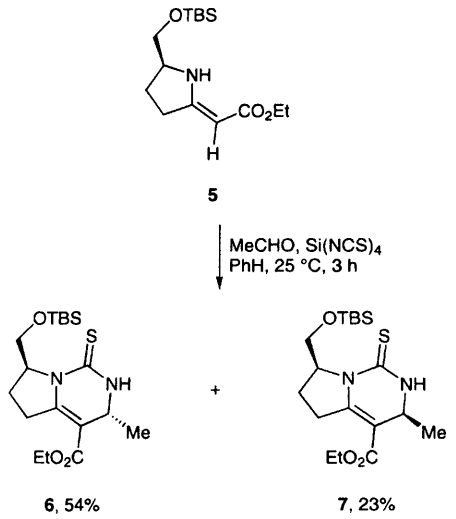
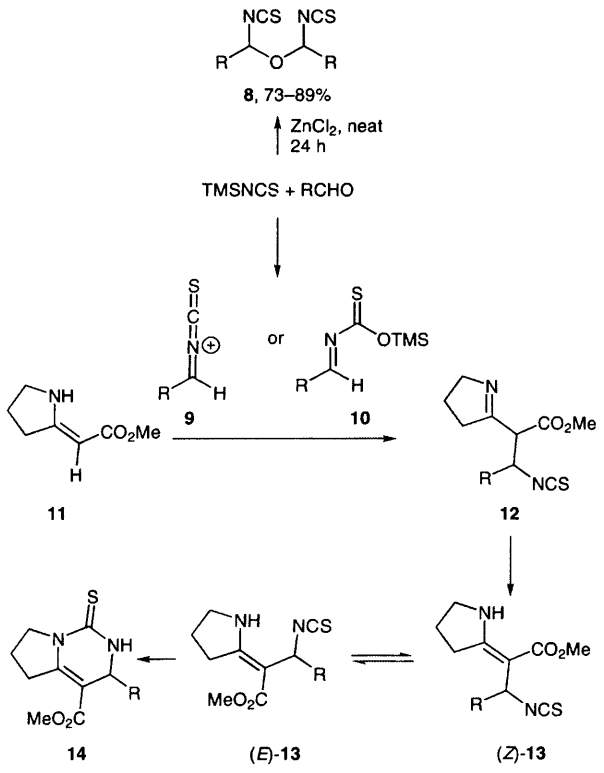
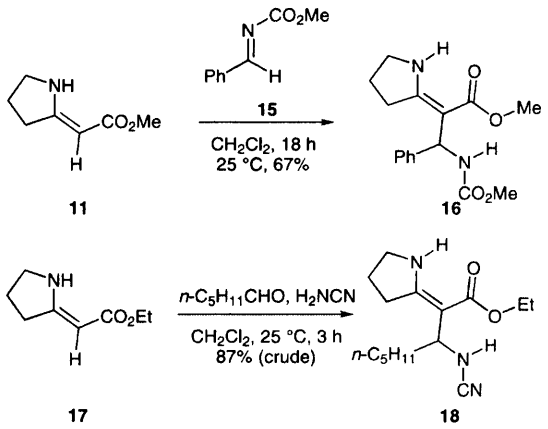


Scheme 1



Scheme 2

We felt that intermediates such as **13** could be stabilised by additional hydrogen bonding, and therefore investigated the reaction of alkylidenepyrrolidine **11** with known imine **15**, and the corresponding ethyl ester **17** with the *N*-cyanoimine formed in situ from hexanal and cyanamide. These gave compounds **16**[15] and **18**,[16] respectively (Scheme 3), thus lending support to our mechanistic hypothesis. While compound **16** was stable, compound **18** reverted to the alkylidenepyrrolidine **17** over approximately three days.

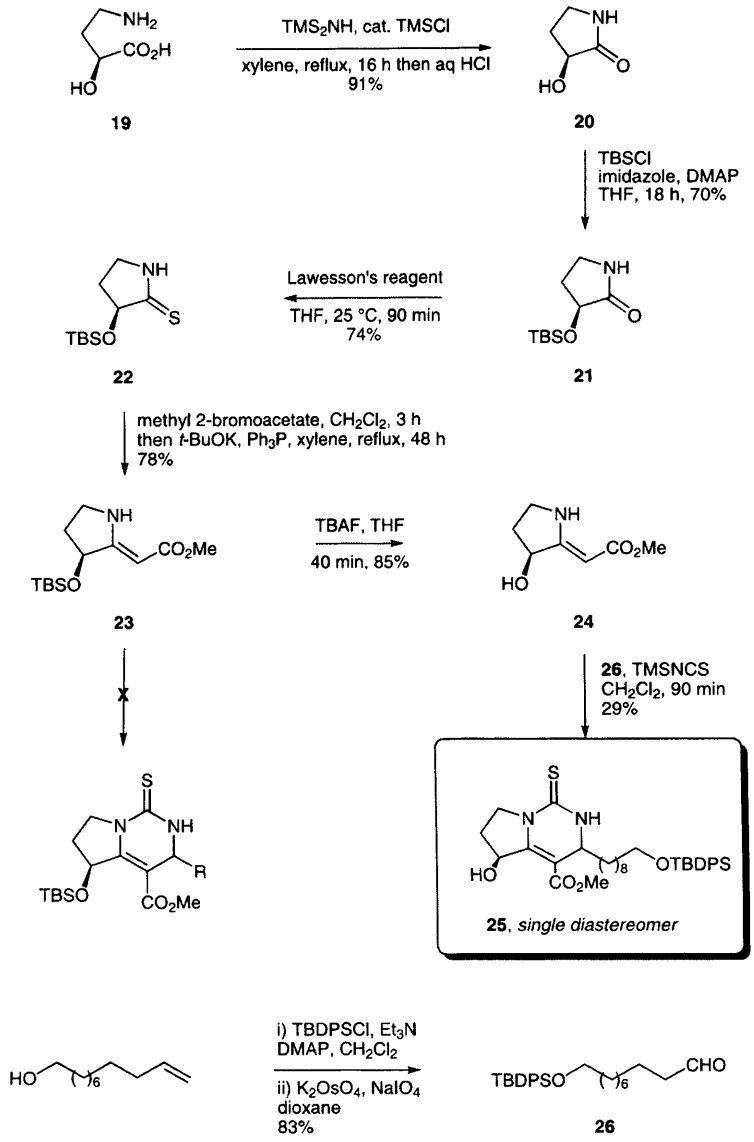


Scheme 3

If this stereogenic centre in the Kishi three-component coupling reaction is formed by attack of an electrophile at the alkene carbon adjacent to the ester, the closest site for a stereochemical directing group would be the 3-position of the pyrrolidine ring. A protected hydroxy directing group was chosen, with the eventual goal of removal by deoxygenation. Therefore, commercially available amino acid **19** was readily converted into lactam **20** (Scheme 4). The primary alcohol in this compound was silylated efficiently under the conditions shown, whereas use of TBSCl in CH_2Cl_2 with Et_3N and DMAP gave mixtures of the desired product and the silyl iminoether. Thionation of lactam **21** was followed by Eschenmoser sulfide contraction to give the alkylidenepyrrolidine **23**. This compound was smoothly deprotected to give compound **24**. To our surprise, alkylidenepyrrolidine **23** is unreactive under the conditions of the three-component coupling. However, compound **24** underwent a completely diastereoselective three-component coupling reaction with aldehyde **26** to give pyrrolo[1,2-*c*]pyrimidine **25** corresponding to the left-hand side of batzelladine A.[17]

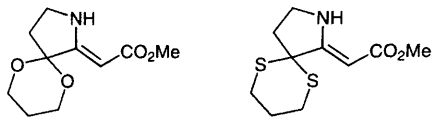
This short and efficient sequence (6 steps, 9% overall yield) compares extremely favourably with the three previously reported routes to this part of the natural product.[4,18] Compound **25** exhibited no diagnostic NOE enhancements which would permit direct assignment of the stereochemistry. However, the required stereoisomer for the natural product could be formed by appropriate choice of starting-material enantiomer followed by deoxygenation and guanidine formation from compound **25**.[19]

While we had expected the bulky silyl ether in compound **23** to block one face of the alkylidenepyrrolidine, it actually prevents reaction completely. This is particularly perplexing, since Kishi has reported successful and high yielding three-component coupling reactions with a dioxane **27** or a dithiane **28** at this position (Figure 2).[11] Although improved diastereoselectivity was anticipated in the reaction of compound **24** compared to that of compound **5**, we were particularly delighted to see the formation of only one isomer of product **25**. While the details are presently unclear, we would attribute this high level of



Scheme 4

stereocontrol to a direct interaction between the reacting electrophile and the hydroxy group.



27 28

Figure 2

In conclusion, we have completed a short synthesis of the bicyclic guanidine core present in batzelladine A, and in doing so gained insight into the mechanism of the Kishi three-component coupling reaction. Further studies are under way to delineate the mechanism of this fascinating reaction.

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(15) **(*Z*)-Methyl [3-Methoxycarbonylamino)-3-phenyl-2-pyrrolidin-2-ylidene]propionate (16)**

Methyl *N*-phenylmethylenecarbamate (**15**, 62 mg, 0.38 mmol) was added to a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid methyl ester (**11**, 54 mg, 0.38 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred at r.t. overnight, concentrated in vacuo, and purified by flash column chromatography (eluent: hexane–EtOAc, 2:1; R_f = 0.4) to give the title compound (78 mg, 67%) as a colourless oil. HRMS: *m/z* calcd for $C_{16}H_{21}N_2O_4$ [M]: 305.1501. Found: 305.1515 [MH^+]. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (1 H, br s, NH), 7.21–7.18 (4 H, m, *J* = 4.2 Hz, arom. CH), 7.14–7.08 (1 H, m, arom. CH), 5.91 (1 H, app. br d, *J* = 9.4 Hz, NH), 5.11 (1 H, d, *J* = 10.0 Hz, C*H*Ph), 3.65 (3 H, s, Me), 3.54–3.50 (2 H, m, CH_2N), 3.42 (3 H, s, Me), 3.05 (1 H, ddd, *J* = 16.8, 8.6, 6.9 Hz, one of CH_2), 2.70 (1 H, ddd, *J* = 16.8, 8.8, 7.1 Hz, one of CH_2C=C) and 2.00–1.94 (2 H, m, CH_2). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 169.7 (C=O), 166.2 (C=O), 157.1 (*C*=CCO_2Me), 143.2 (arom. C), 128.0 (arom. CH), 126.3 (arom. CH), 125.8 (arom. CH), 90.1 (C=*C*CO_2Me), 53.6 (CH), 52.0 (CH_3), 50.1 (CH_3), 47.5 (CH_2), 31.5 (CH_2), 21.7 (CH_2). MS (TOF AP$^+$): *m/z* (%) = 305 (22) [MH^+], 230 (100), 195 (43).

(16) **(*Z*)-Ethyl 3-(Cyanoamino)-2-(pyrrolidin-2-ylidene)octanoate (18)**

Cyanamide (16 mg, 0.4 mmol) was added to a solution of hexanal (48 μL, 0.4 mmol) in dry CH_2Cl_2 (4 mL) under N_2, and the resulting suspension was stirred at 25 °C for 30 min. A solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester (**17**, 60 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) was added, and the resulting mixture was stirred at 25 °C for 3 h. The solvent was then removed in vacuo to afford the title compound as a pale yellow gum (94 mg, 87% crude yield). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.26 (1 H, br s, NH), 4.37 (1 H, br s, NHCN), 4.00–4.18 (2 H, m, CO_2CH_2), 3.75 (1 H, app. q, *J* = 7.4 Hz, C*H*NHCN), 3.50 (2 H, app. t, *J* = 7.0 Hz, CH_2NH), 2.78 (1 H, ddd, *J* = 16.1, 9.1, 7.0 Hz, one of CH_2C=C), 2.58 (1 H, ddd, *J* = 16.1, 9.2, 6.9 Hz, one of CH_2C=C), 1.89–2.03 (2 H, m, pyrrolidine CH_2CH_2NH), 1.64–1.85 (2 H, m, $CH_2CHNHCN$), 1.14–1.26 [9 H, m, $(CH_2)_3$ and $CO_2CH_2CH_3$], 0.81 (3 H, t, *J* = 6.9 Hz, CH_3CH_2-alkyl). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (ester *C*=O), 166.0 (*C*=CCO_2Et), 117.3 (NHC≡N), 88.3 (C=*C*CO_2Et), 59.0 (CO_2CH_2), 47.3 (*C*HNHCN), 35.2 (CH_2NH), 31.6 (CH_2C=C), 31.5 ($CH_2CHNHCN$), 26.6 (CH_2CH_2NH), 22.5 (CH_2) 22.4 (CH_2), 21.6 (CH_3CH_2-alkyl), 14.6 ($CO_2CH_2CH_3$), 13.9 (CH_3CH_2-alkyl).

(17) **Methyl (5*S*)-1,2,3,5,6,7-Hexahydro-3-(9-*tert*-butyldiphenylsilyloxynonyl)-5-hydroxy-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (25)**

Trimethylsilyl isothiocyanate (62 μL, 0.45 mmol) was added to a solution of aldehyde **26** (183 mg, 0.45 mmol) in dry CH_2Cl_2 (3 mL) under N_2, and the resulting brown solution was stirred for 30 min at 25 °C. A solution of alkylidene-pyrrolidine **24** (70 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) was then added, and the reaction was stirred for 3 h. The reaction was quenched with ca. 0.1 M aq NaOH solution (20 ml) and the layers separated. The aqueous layer was washed with CH_2Cl_2 (3 × 25 mL), the combined organic layers dried with Na_2SO_4, and the solvent removed in vacuo. The resulting orange gum was purified by column chromatography (eluent: hexane–EtOAc, 2.5:1; R_f = 0.55) to give the title compound (79 mg, 29%) as a yellow gum. HRMS: *m/z* calcd for $C_{34}H_{49}N_2O_4SiS$ [M]: 609.3182. Found: 609.3196 [MH^+]. IR (CH_2Cl_2): ν_{max} = 3401, 3205, 2883, 1675, 1629, 1531, 1462, 1416, 1324 and 1255 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.55 (4 H, m, arom. CH), 7.41–7.28 (6 H, m, arom. CH), 6.99 (1 H, br s, NH), 5.20 (1 H, br s, OH), 5.10 (1 H, app. t, *J* = 8.0 Hz, C*H*OH), 4.24 (1 H, app. dt, *J* = 7.8, 3.8 Hz, C*H*NH), 4.06 (1 H, ddd, *J* = 11.6, 8.8, 3.3 Hz, one of CH_2NCS), 3.89 (1 H, ddd, *J* = 11.6, 9.0, 8.0 Hz, one of CH_2NCS), 3.65 (3 H, s, CO_2CH_3), 3.58 (2 H, t, *J* = 6.5 Hz, $CH_2OTBDPS$), 2.40–2.33 (1 H, m, one of CH_2CHOH), 2.00–1.95 (1 H, m, one of CH_2CHOH), 1.54–1.40 (6 H, m, 3 × CH_2) and 1.36–1.10 [19 H, m, 5 × CH_2 and $((CH_3)_3C]$. ^{13}C NMR (125 MHz, $CDCl_3$): d = 175.3 (C=S), 166.2 (C=O), 153.2 (*C*=CCO_2Me), 139.8 (arom. C), 134.6 (arom. CH), 128.5 (arom. CH), 126.6 (arom. CH), 99.6 (C=*C*CO_2Me), 71.2 (CHOH), 63.0 ($CH_2OTBDPS$), 51.2 (CO_2CH_3), 50.9 (*C*H-alkyl), 48.7 (CH_2NC=S), 36.1 (pyrrolidine CH_2CHOH), 31.6 (CH_2CH-NH), 28.8 (CH_2),

28.6 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 25.9 [(CH_3)$_3$C], 24.8 (CH_2), 23.0 (CH_2), 18.2 [(CH_3)$_3$*C*]. MS (ES^+): *m/z* (%) = 609 (25) [MH^+], 577 (32), 279 (100). $[a]_D$ –30 (*c* 1, CH_2Cl_2).

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