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**Studies Towards the Synthesis of the
Batzelladine Alkaloids**

Stuart V. Wordingham

**A Thesis Submitted for the Degree of
Doctor of Philosophy**

at

Cardiff University

September 2006

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Abstract

This thesis describes studies into the synthesis of the batzelladine alkaloids including a detailed study into the synthesis of alkylidenepyrrolidines.

Chapter 1 is a brief introduction to the batzelladine alkaloids highlighting all significant work carried out since their isolation in the mid 1990's.

Chapter 2 looks at the viability of Lewis acid promoted Friedel-Crafts reactions for the formation of quinolones, and the usefulness of this reaction to the synthesis of batzelladine alkaloids.

Chapter 3 includes a detailed methodology study into the formation of alkylidenepyrrolidines, and the reasons why a new synthesis is required.

Chapter 4 investigates the Kishi three-component coupling reaction, including a mechanistic study and a synthetic study.

Chapter 5 describes our work into the synthesis of batzelladine C and incorporates the work carried out and detailed in Chapters 2 and 3.

Acknowledgements

Many people have been involved over the course of this PhD and my journey to this point, not all of which can be mentioned in this brief acknowledgement.

Thanks must be mentioned to: Mark, without whose constant patience and help this thesis would probably never have been completed; Rob Jenkins and Robin Hicks for the tireless support in all things to do with spectrometers right up to the final hour; and to all members of the labs 1.107 and 1.119.

I would also like to thank Dr. A. Prescott. Without her encouragement during my early time in chemistry I would never have made it this far.

And finally to my family, who have supported the eternal student throughout-probably in the hope that one day he might actually go out and get a job.

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Abbreviations

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
AIDS	Acquired Immune Deficiency Syndrome
All	Allyl
APCI	Atmospheric Pressure Chemical Ionisation
Bn	Benzyl
Boc	<i>t</i> -Butoxycarbonyl
Cbz	Benzyloxycarbonyl
CDI	Carbonyldiimidazole
COSY	Correlation spectroscopy
DCM	Dichloromethane
de	Diastereomeric excess
DIOP	4,5-bis(diphenylphosphino-methyl)-2,2-dimethyl-dioxolane
DMAP	4-Dimethylaminopyridine
DME	Ethyleneglycol dimethylether
DMF	<i>N,N</i> -Dimethylformamide
DMP	Dess-Martin periodate
DMSO	Dimethylsulphoxide
ee	Enantiomeric excess
Et	ethyl
g-NOSEY	gradient Nuclear Overhauser Enhancement Spectroscopy
HIV	Human Immunodeficiency Virus
HMPA	Hexamethylphosphoramide
IPA	Isopropyl alcohol
IR	Infra Red
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
<i>m</i>-CPBA	<i>meta</i> Chloroperbenzoic acid
Me	methyl

MEM	2-Methoxyethoxymethyl
MPM	<i>para</i> -methoxybenzyl
Moc	Methoxycarbonyl
Ms	Methanesulphonyl
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement Spectroscopy
Nu	Nucleophile
Ph	Phenyl
PPA	polyphosphoric acid
psi	pounds per square inch
p-Tol	<i>para</i> -Tolyl
PTSA	<i>para</i> -Toluenesulphonic acid
RT	Room Temperature
SET	Single Electron Transfer
TBAF	Tetrabutylammonium fluoride
TBS	<i>t</i> -Butyldimethylsilyl
Tf	Trifluoromethanesulphonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
Ts	4-Toluenesulphonyl

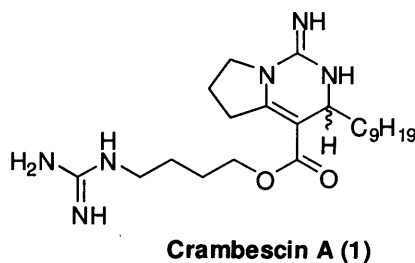
Chapter 1

Introduction to the Batzelladine Alkaloids

Introduction to the Batzelladine alkaloids

During the 1990's scientists at SmithKline Beecham were investigating potential new treatments for HIV. Specifically, they had been investigating the binding of the gp120 glycoprotein to the CD4 receptor of the human T-lymphocyte cells. This binding is vital to the replication of the virus as it controls the entry of the virus into the human cells. Without access to the biochemical environment within the cell the virus is unable to replicate. Any compound capable of interrupting or inhibiting this interaction would potentially be a treatment for HIV. Over 5000 biologically active natural product extracts were tested for their ability to disrupt the gp120-CD4 binding. Of all the extracts tested, only one displayed activity in the absence of light, the methanolic extract of the bright red Caribbean Sponge *Batzella sp.* Bioassay-directed fractionation, followed by chromatography led to the isolation of 21 compounds, of which five were novel alkaloids of similar nature named collectively as the Batzelladines, and subcategorised by letters. The initially proposed structures of batzelladine A – E are shown in **Figure 1**, although some of these structures have been revised (*vide infra*).

The structures of these compounds were elucidated using an array of NMR techniques combined with mass spectrometric information and degradation products. Results from some showed similarities to the compound crambescin A (**1**). Unfortunately they were unable to acquire X-ray data so that the absolute configuration of the stereogenic centres could not be fully determined.¹



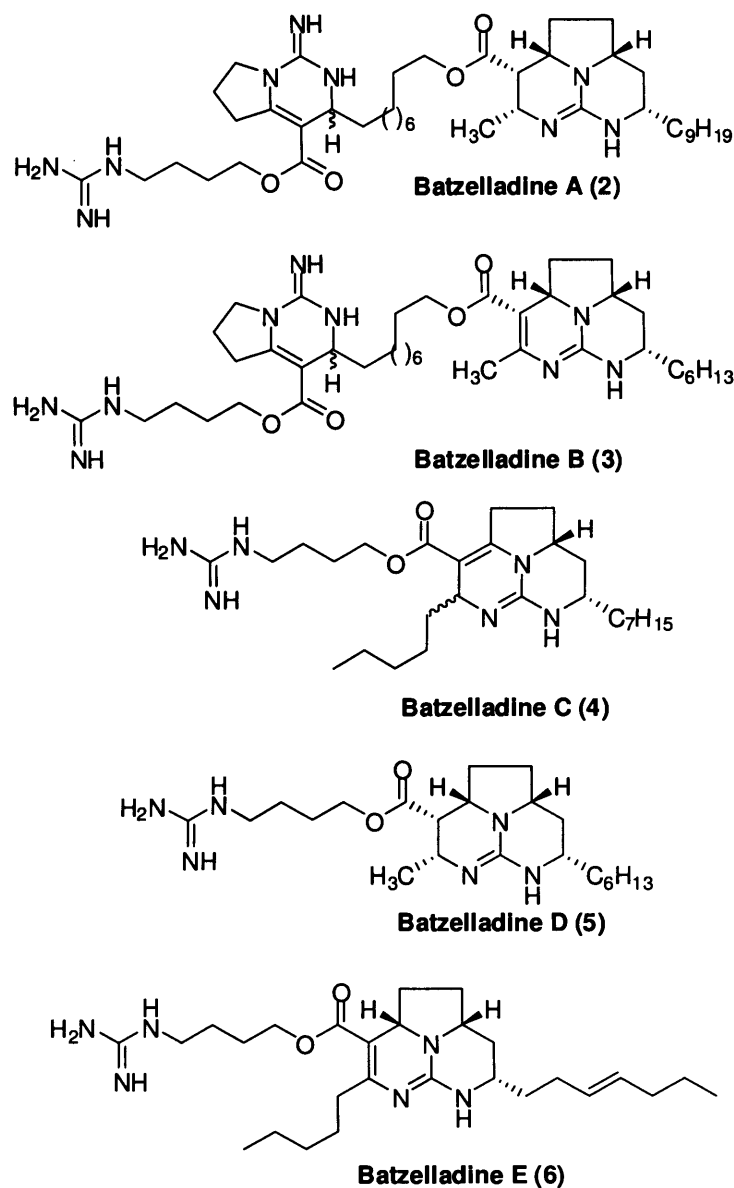


Figure 1 Initially proposed structures of batzelladines A – E

Two years later, the same group isolated four more batzelladine alkaloids (**Figure 2**). These compounds were shown to be active in the dissociation of protein tyrosine kinase from the CD4 receptor on T-lymphocyte cells. It is believed that this binding is critical in the initiation of antigenic responses. If this was the case these compounds could

provide treatment for autoimmune disorders like murine lupus and allergic encephalomyelitis.²

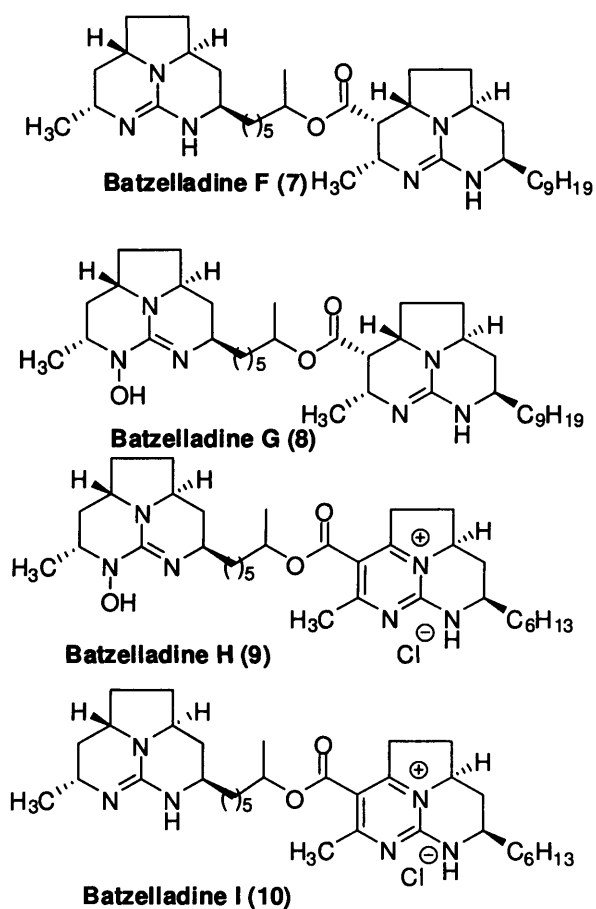
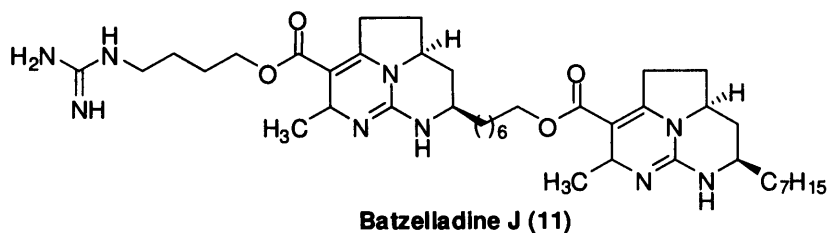


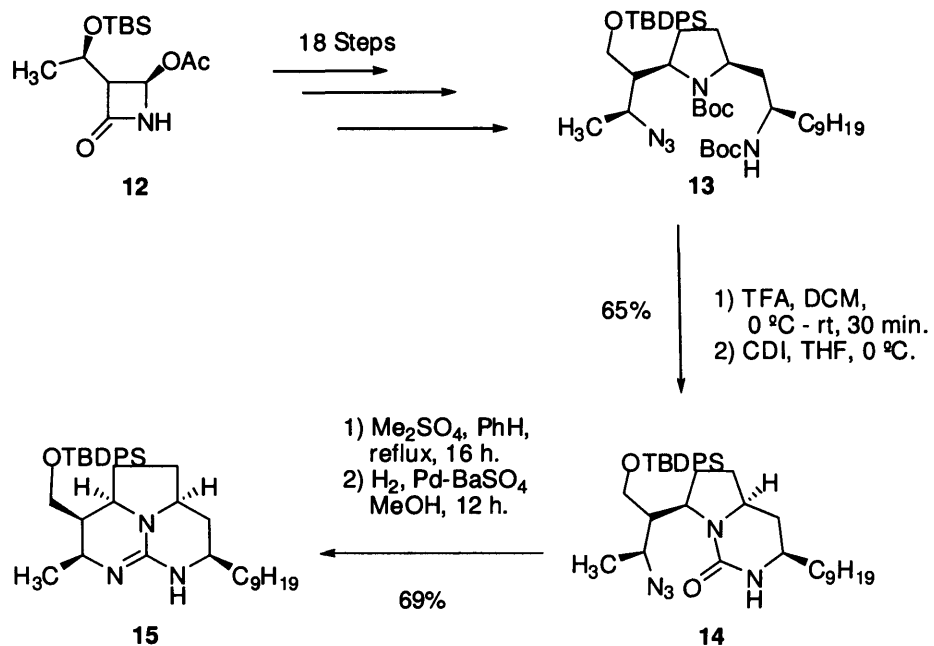
Figure 2 Initially proposed structures of batzelladines F - I

In early 2005 Gallimore *et al.* were investigating new lead compounds and extracted the Caribbean Sponge *Monanchora unguifera*. Among already known guanidine compounds was the new alkaloid batzelladine J (11).³



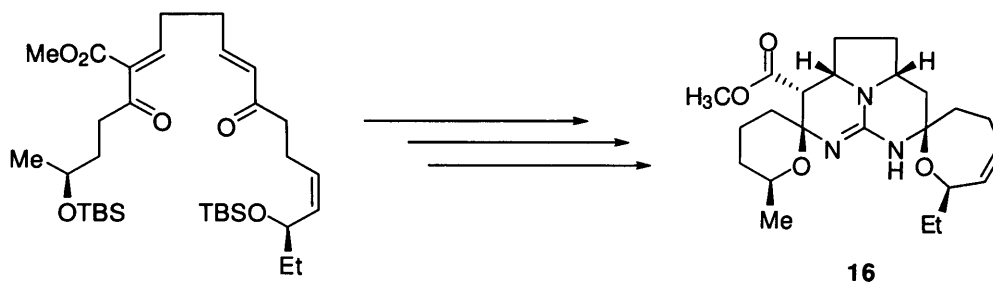
Since 1995 the batzelladine alkaloids have been the subject of a great deal of research by groups across the world. However, to date there have been relatively few enantioselective total syntheses published and a number of the alkaloids are still to be synthesised.

The earliest reported investigations into the batzelladine alkaloids is by Rao *et al.* in 1995 when they reported the synthesis of the tricyclic guanidine core of batzelladine A (**Scheme 1**).⁴ Their synthesis is based around the pyrrole intermediate **13**, which, in turn, was synthesised from the commercially available azetidinone **12** in 18 steps. This has all the necessary stereogenic centres in place for the final guanidine. Deprotection and reaction with carbonyl diimidazole yielded the urea **14**, which was *O*-methylated, and, following reduction of the azide, cyclised to the tricyclic guanidine **15**.



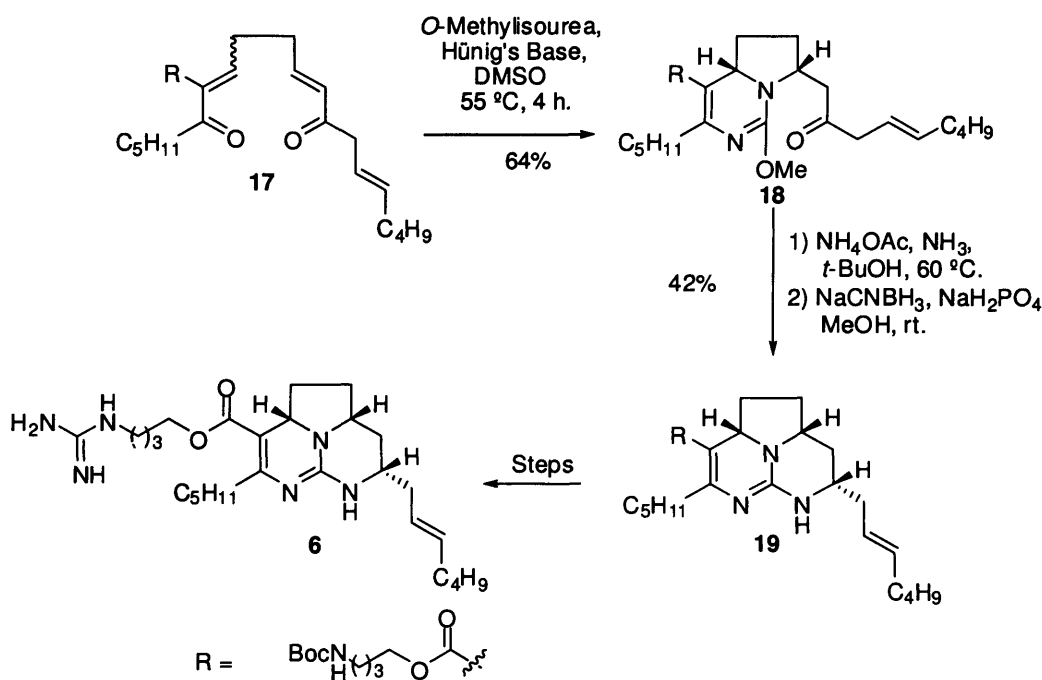
Scheme 1

During the early 1990's, Snider and co-workers had been studying the marine natural product ptilomycalin A, which contains a similar tricyclic guanidine **16** to that found in the batzelladine alkaloid family. Already they had a synthesis in place for the formation of the tricyclic core of ptilomycalin A (**Scheme 2**) that with slight modification could be used for the formation of the batzelladine alkaloids.⁵



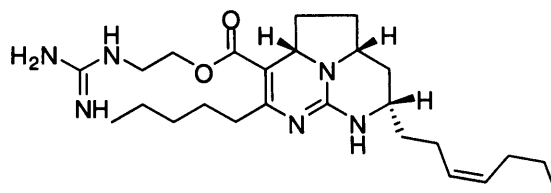
Scheme 2

Over a period of two years Snider and his group synthesised the tricyclic cores of batzelladines A, B and D⁶ and achieved the total synthesis of batzelladine E by using modifications of their original synthesis. **Scheme 3** shows their key precursor **17** for the formation of batzelladine E. Notably this was a simpler intermediate to make than for previous substrates and contained all the desired side chains for the final compound. A double conjugate addition reaction with *O*-methylisourea gave compound **18** as the major isomer, which underwent amination and further cyclisation to give compound **19**. This was then converted into structure **6**, the proposed structure of batzelladine E.⁷



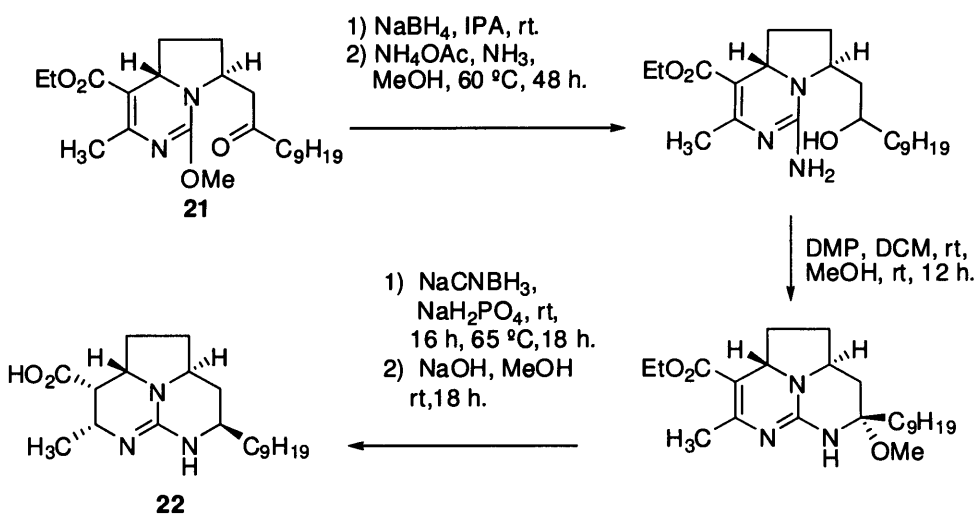
Scheme 3

On comparison of the ¹H NMR spectrum of this compound with that of natural batzelladine E, Snider observed differences. This prompted the synthesis of the *cis*-double bond isomer **18** using an identical process for the cyclisation reaction to that previously shown. The spectroscopic data obtained for this compound were identical to those of the natural product, resulting in the revision of the structure of batzelladine E to compound **20**.



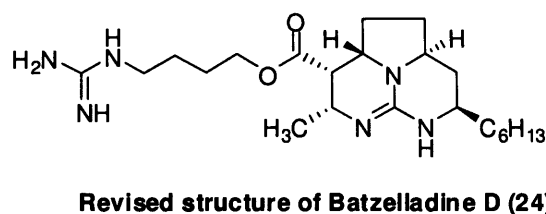
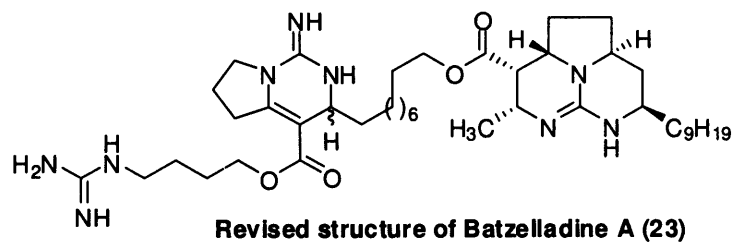
Revised structure of Batzelladine E (20)

In related work,⁶ the original stereochemistry of the tricyclic portions of batzelladine A and D were shown to be incorrect. Compound **22** was prepared from the minor *trans* isomer **21** (Scheme 4) isolated from a similar reaction to that shown in Scheme 3.

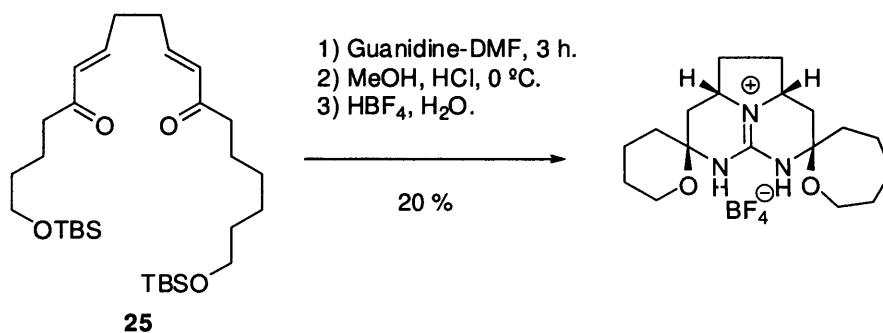


Scheme 4

The data for the acid **22** was identical to that derived from the degradation of batzelladine A. From this work, Snider was able to revise the structures of batzelladines A (**23**) and D (**24**).

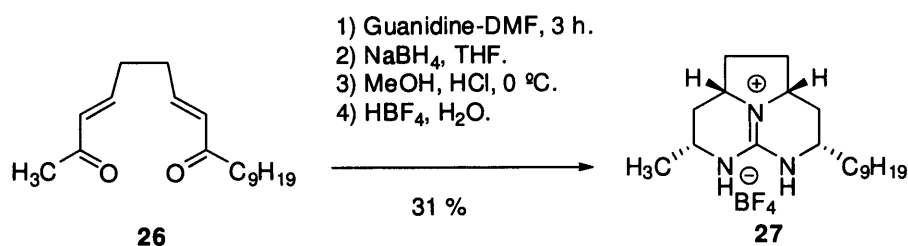


During this time, Murphy *et al.* were also working on the ptilomycalin A systems, and had developed a similar bis-enone double Michael acceptor **25**. The key difference was the use of guanidine itself as the nucleophile followed by cyclisation of the spirocyclic units (**Scheme 5**).⁸



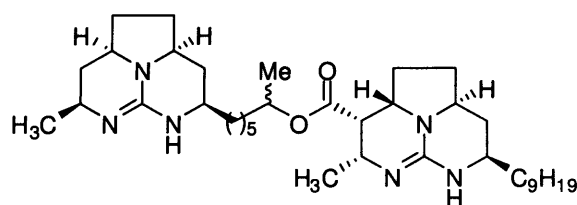
Scheme 5

Again, transfer of this system to that required for the batzelladine alkaloids involved a significantly less complex intermediate **26**. With an added reduction step, the tricyclic guanidine **27** was produced as a single diastereoisomer (**Scheme 6**).⁹



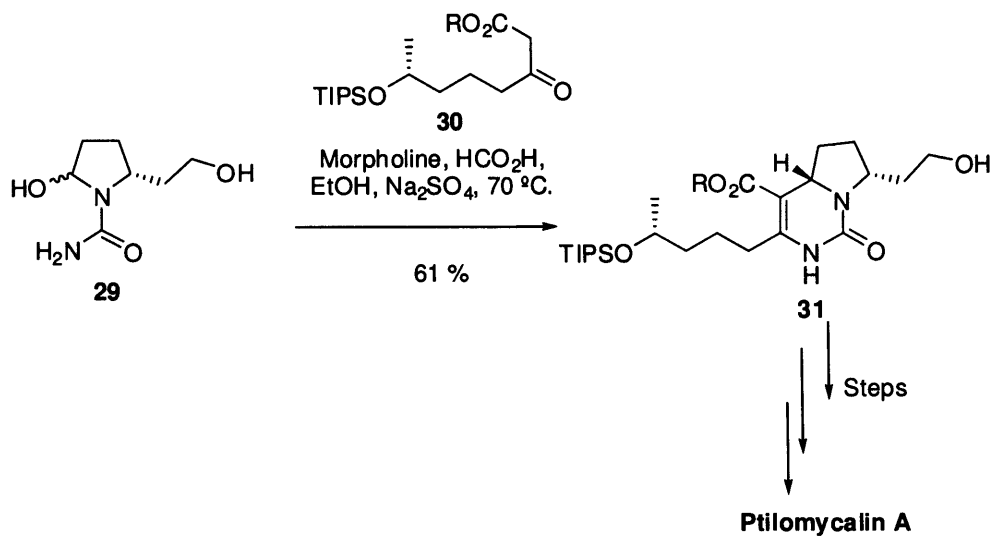
Scheme 6

This system produced only the *cis* isomer, the incorrect isomer for tricyclic portions of batzelladine A and D from Snider's revised models. However, on comparison with the left-hand tricyclic portion of batzelladine F, similarities were observed. Independent work by Murphy and Snider led to the revised structure of batzelladine F (28).¹⁰



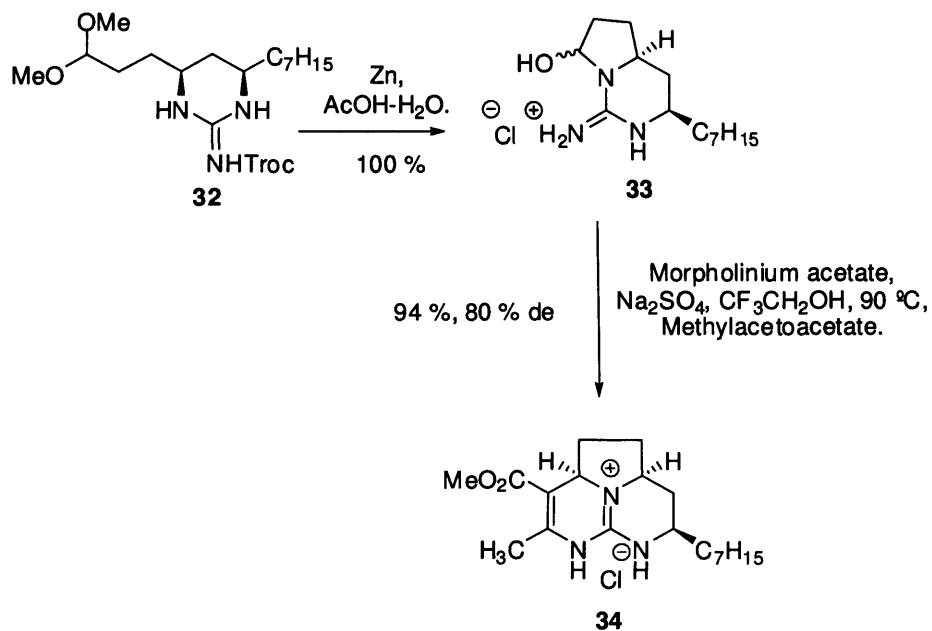
Revised structure of Batzelladine F (28)

In the early 1990's Overman's group had been developing a tethered Biginelli condensation directed towards the total synthesis of ptilomycalin A. Condensation of urea **29** with β -ketoester **30** formed the bicyclic urea **31** with good stereocontrol (Scheme 7).¹¹ As this method uses chiral non-racemic starting materials, the formation of a single enantiomer of the target compound is possible.



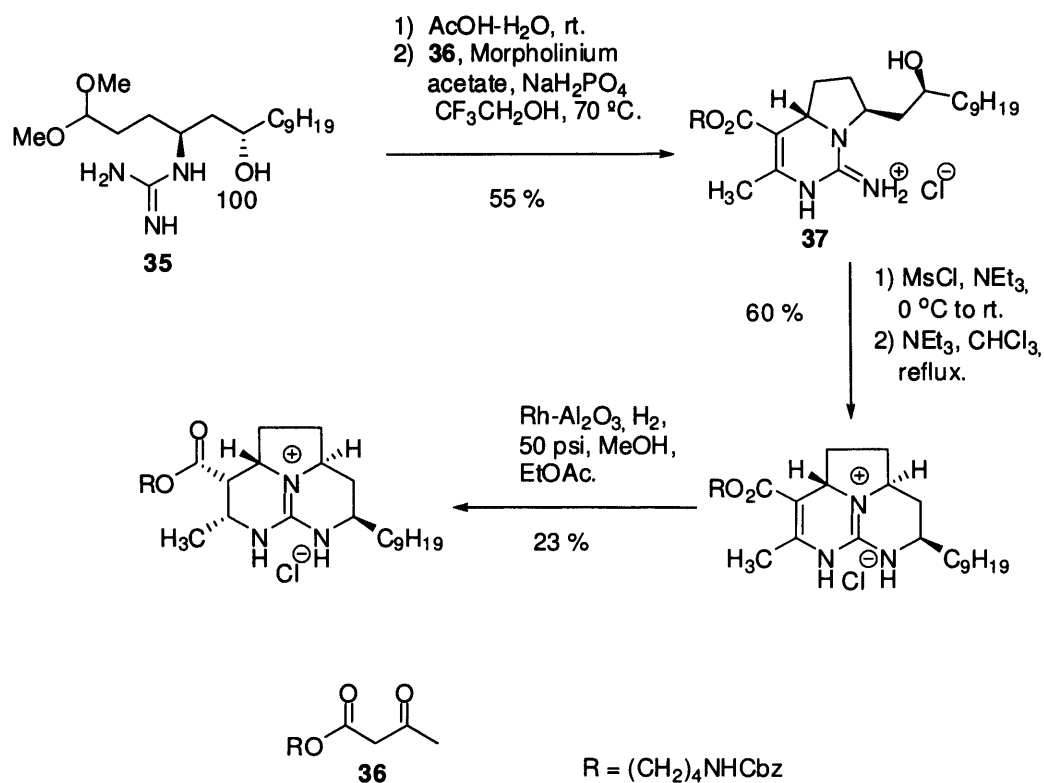
Scheme 7

A similar approach was then applied to the batzelladine alkaloids;¹² the logical starting point was batzelladine B, which requires a *cis* relationship of protons straddling the pyrrolidine nitrogen. To keep conditions of the tethered Biginelli consistent with those previously used, the cyclic guanidine **32** was synthesised. Upon hydrolysis of the acetal, spontaneous cyclisation was observed to give the bicyclic guanidine **33**, which could then be condensed under normal conditions to give the tricyclic guanidine **34** in a high yield and good stereoselectivity (90 %, 80 % de) (Scheme 8).¹³



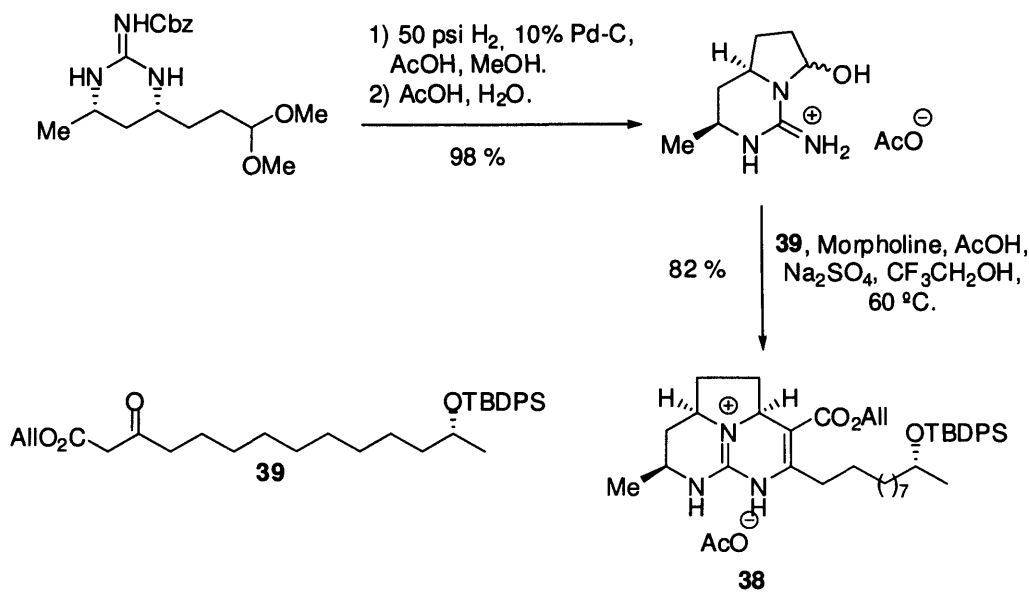
Scheme 8

Attention turned then to batzelladine D. The significant difference here is that a *trans* arrangement of protons is seen around the pyrrolidine nitrogen. To achieve this Overman used the acyclic guanidine **35** instead of the cyclic guanidine **32** shown above as the Biginelli precursor. This allowed good control (6.1 : 1) over the stereochemical outcome of the reaction, after hydrolysis and Biginelli reactions the bicyclic guanidine **37** was obtained with *trans* stereochemistry. Formation of the tricyclic system was achieved by activation of the hydroxyl group and displacement by the guanidine NH₂. The only significant downside to this route was the hydrogenation of the double bond, which proceeded with a yield of only 23 %, with the majority of the product being an undesired diastereoisomer (Scheme 9).¹⁴



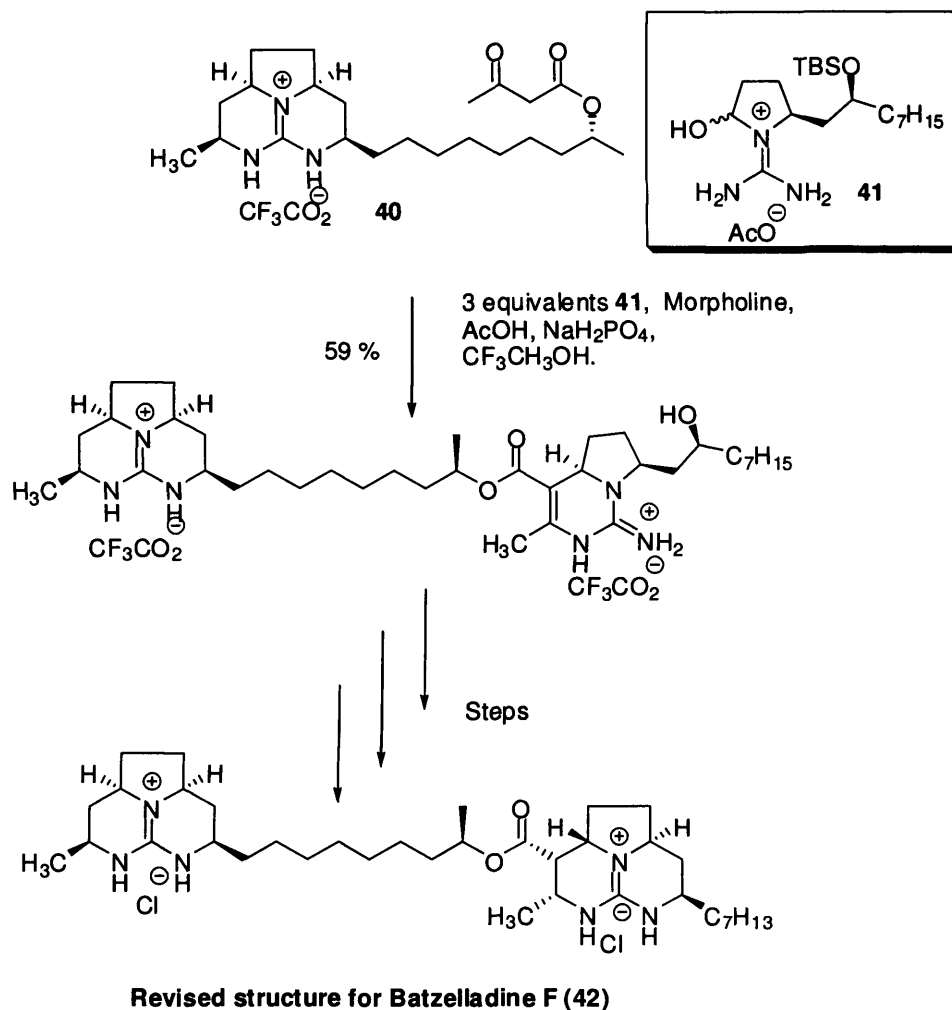
Scheme 9

Overman's most impressive achievement in the batzelladine campaign was the total synthesis of batzelladine F.¹⁵ Within this synthesis a linear approach was utilised which saw the Biginelli reaction developed for batzelladine B used to form the left-hand tricyclic core **38** (Scheme 10).



Scheme 10

The protecting group was removed and the side chain manipulated to generate the β -ketoester **40** necessary for the second tethered Biginelli reaction. This was carried out using the methodology developed for batzelladine D, and with a further hydrogenation completed the enantioselective total synthesis of batzelladine F (**42**) (Scheme 11).

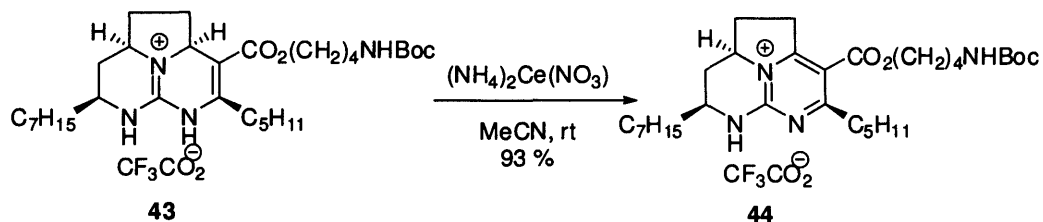


Scheme 11

It is important to note that this structure differs from that originally proposed by Patil. The revision of the structure of batzelladine F was made on the basis of the synthesis of this compound and various stereoisomers, along with the synthesis of stereoisomers of the originally proposed structure. Using this same method a number of batzelladine F analogues were synthesised and tested for biological activity.¹⁶

Having completed the total synthesis of batzelladines D and F, attention was turned to dehydrobatzelladine C. The major difference between the tricyclic moieties is in the

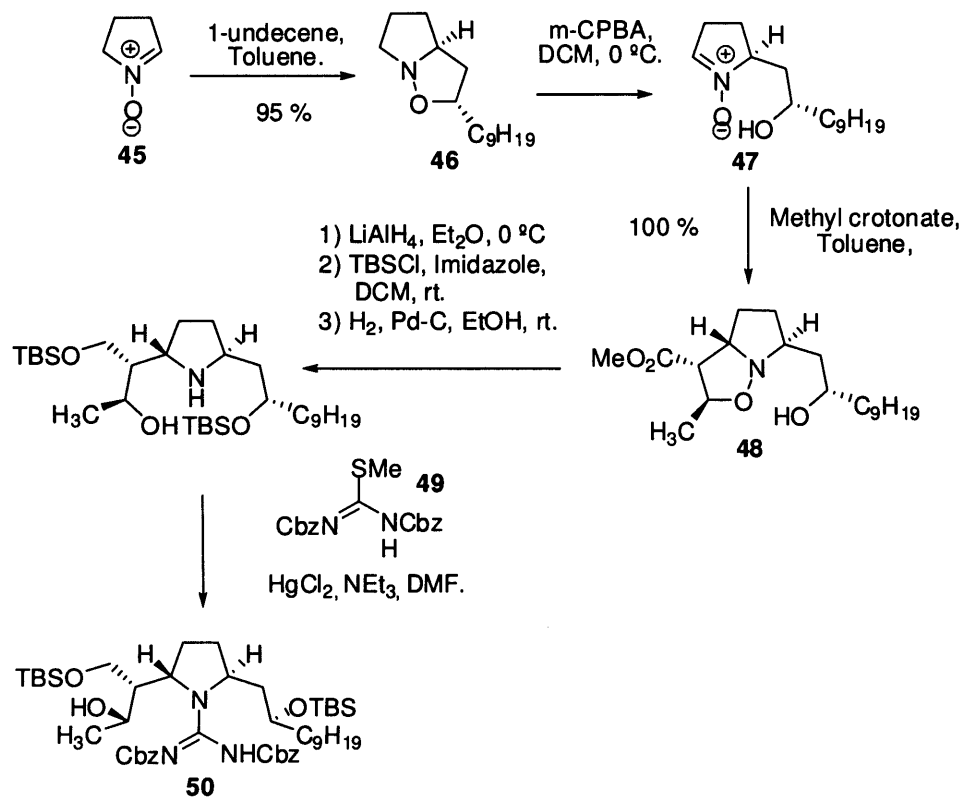
oxidation state with dehydrobatzelladine C containing a tetrahydro-5,6,6a-triazaacenaphthalene ring system. The tricyclic compound **43** was synthesised using the method described previously, and was then oxidised using ceric ammonium nitrate to the necessary oxidation state **44** (Scheme 12).¹⁷



Scheme 12

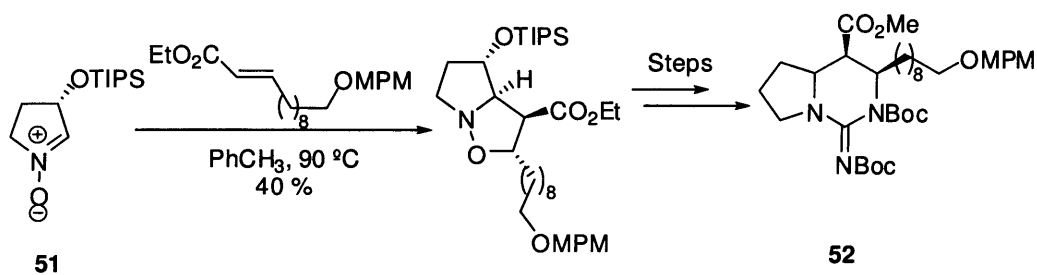
In the late 1990's Nagasawa *et al.* were investigating ways of controlling protein-protein interactions with small molecules; their chosen target was batzelladine D (**22**).

In their approach the key transformations are two 1,3-dipolar cycloadditions. The first is between the nitrene **45** and 1-undecene to give isoxazolidine **46**, which is then oxidatively cleaved to regenerate the nitrene functionality. The second cycloaddition is between this newly regenerated nitrene **47** and methyl crotonate, which gives compound **48** with the desired *trans* configuration of protons around the pyrrolidine nitrogen required for batzelladine D. The guanidine moiety is added in a single step from addition of the activated thiourea **49** to the pyrrolidine nitrogen to give the guanidine **50**, which is set up for two Mitsunobu reactions to complete the tricyclic system (Scheme 13).¹⁸ A similar approach was used to confirm the stereochemistry of the left-hand tricyclic portion of batzelladine F.¹⁹



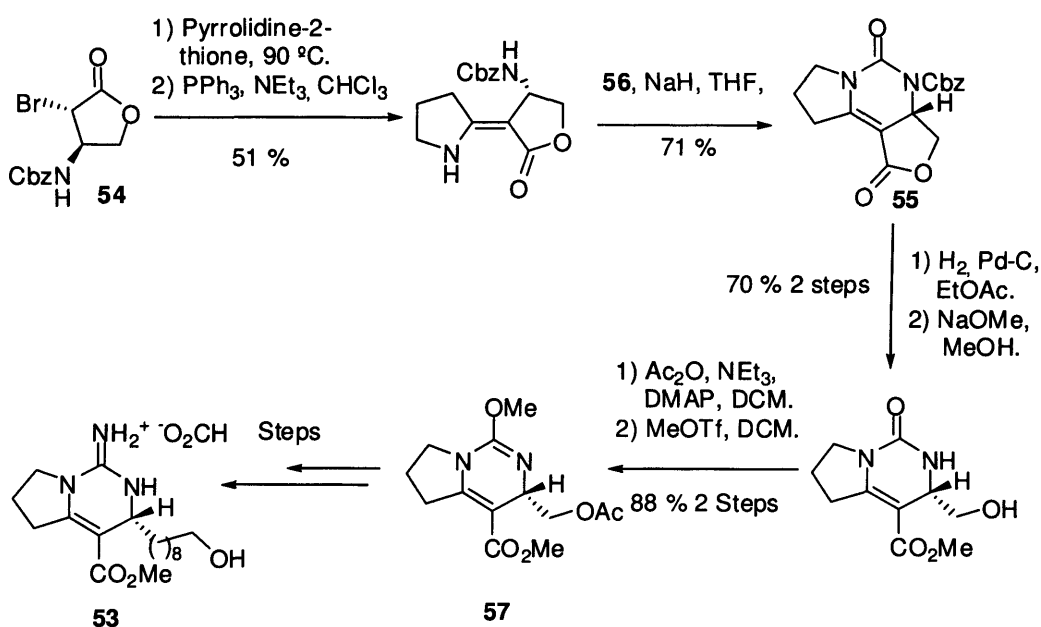
Scheme 13

Modifications to the synthesis allowed the use of a chiral nitron (**51**) as the starting material, opening up an enantioselective route; this method was then used to form compound **52** corresponding to the bicyclic portion of batzelladine A (**Scheme 14**).²⁰



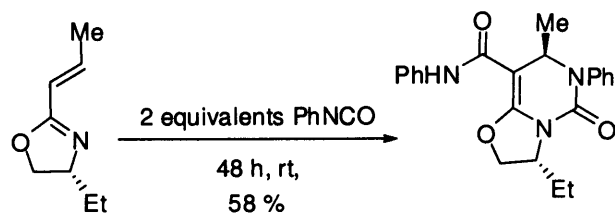
Scheme 14

Chronologically, the first to turn their attention to the bicyclic portions of batzelladines A and B were the Gin group who developed a stepwise synthesis of the bicyclic guanidine **53** from the bromolactone **54**, which gave the urea **55** after an Eschenmoser sulphide contraction and condensation with bis(4-nitrophenyl)carbonate **56**. Methanolysis of the urea **55** followed by *O*-methylation of the urea gave the robust isourea **57**, which with further manipulation was converted into the hydrolysis product of batzelladine A **53** (Scheme 15).²¹



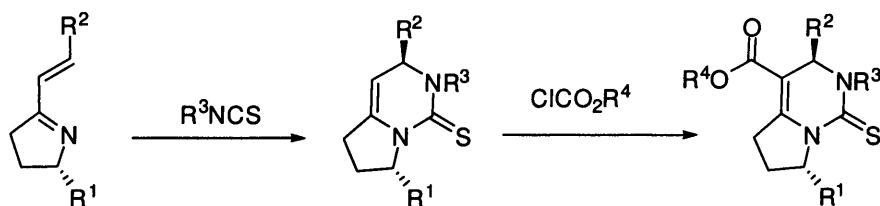
Scheme 15

During this time the Elliott group had been investigating the synthesis of the bicyclic and tricyclic cores needed for batzelladine A. The strategy employed differed from other groups, by utilising the same reaction pathways for both cyclic guanidines. Initial work was based on their annulation of azolines (Scheme 16).²²



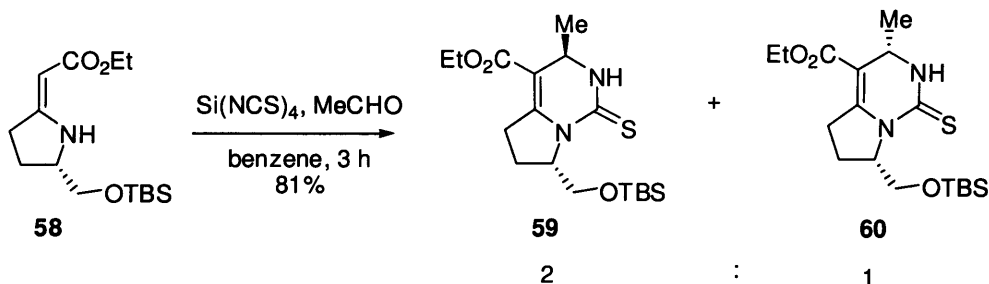
Scheme 16

It is clear to see the similarities between these products and the cyclic cores of the batzelladine alkaloids. Conceptually, the bicyclic core of batzelladines A and B could be prepared by reaction of an alkenylpyrrolidine with an isothiocyanate followed by acylation with a chloroformate (**Scheme 17**).²³



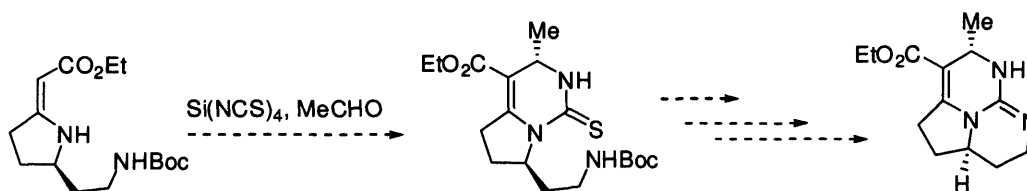
Scheme 17

Unfortunately, this sequence of steps proved not to be viable, and a modified route was devised. This utilised a three-component coupling reaction of alkyldenepyrrolidine **58**, an aldehyde and silicon tetraisothiocyanate (**Scheme 18**).



Scheme 18

With variation of the side chain in the 5-position this route could also be applied to the tricyclic cores of the batzelladine alkaloids as shown in **Scheme 19**.²⁴



Scheme 19

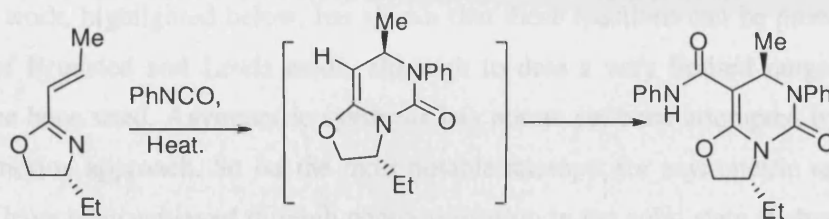
To date there has been extensive work carried out on the total synthesis of the batzelladine alkaloids, although there have been relatively few enantioselective routes reported. A number of the family are still to be synthesised.

Chapter 2

Synthesis of Quinolin-2-ones

2.1 Introduction

Early investigations, by the Elliott group, into the annulation reactions of alkenyloxazolines (**Scheme 20**) had identified a well-defined transition state in which the stereogenic centre induces a helical twist. Therefore, only one face of the alkene is available for ring-closure (**Figure 3**).²⁵



Scheme 20

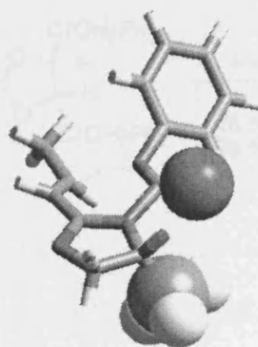


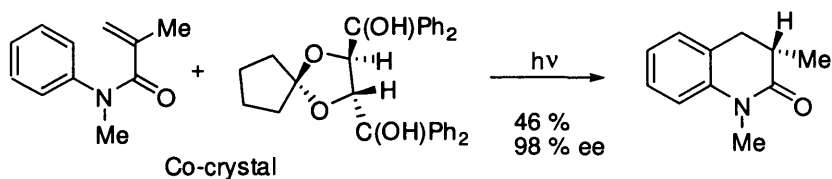
Figure 3 3 dimensional representation of the oxazoline

Following on from these interesting reactions it was postulated that if an acyclic system was used, it should be possible to influence the conformation with a Lewis acid (**Scheme 21**).



Scheme 21

Previous work, highlighted below, has shown that these reactions can be promoted with the use of Bronsted and Lewis acids, although to date a very limited range of Lewis acids have been used. Asymmetric synthesis has not as yet been attempted by using an acid promotion approach. So far the most notable attempts for asymmetric reactions of this type have been achieved through photocyclisation in the solid state (**Scheme 22**). In this case exactly the type of ‘chiral twist’ proposed above was observed in the solid state leading to high asymmetric induction.²⁶

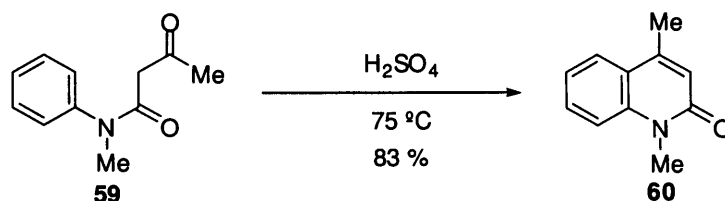


Scheme 22

2.2 – Background to Quinolin-2-one Synthesis

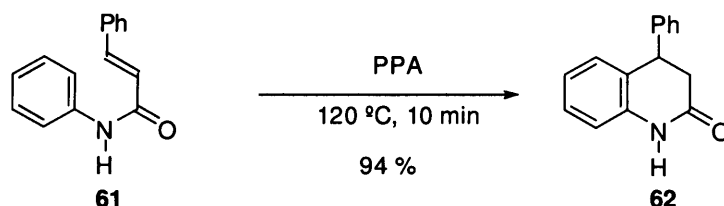
Quinolin-2-ones have found many applications in synthetic and medicinal chemistry; these include non-steroidal hormone interactions for the treatment of breast cancers and potential contraceptive properties.²⁷ They have also been shown to be good platelet aggregation inhibitors.²⁸

Early synthetic methods utilised a strong acid to cyclise aromatic amides. In 1945, Kaslow *et al.* reported the amide cyclisation with sulphuric acid to give the corresponding quinoline (**Scheme 23**).²⁹



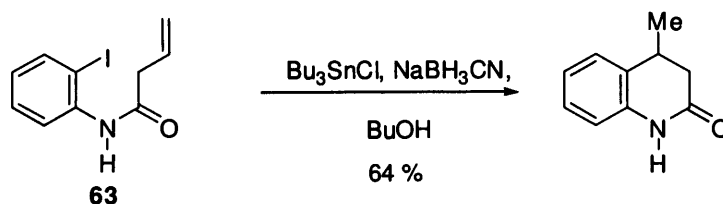
Scheme 23

A similar cyclisation used polyphosphoric acid at 120 °C to cyclise amide **61** (**Scheme 24**).³⁰



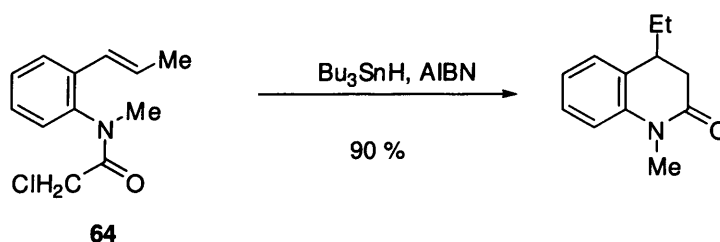
Scheme 24

Over the years free-radical chemistry has been shown to be a versatile way of constructing carbon-carbon bonds; this system is no exception lending itself to a number of different radical cyclisations. Jones *et al.* were investigating 6 *exo-trig* radical cyclisation reactions using the unsaturated aromatic amide **63**, where the aryl radical generated then cyclises onto the double bond (**Scheme 25**).³¹



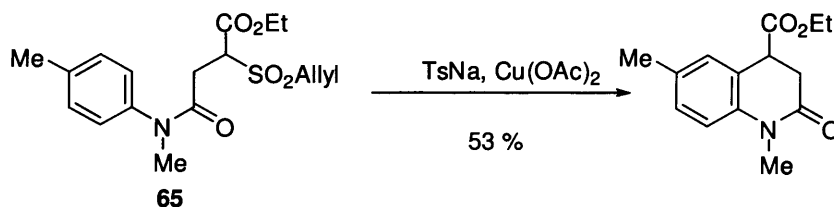
Scheme 25

As a nice modification to the reaction, both the initial radical and the radical acceptor can be on the aromatic side chains. This led to a greater regioselectivity of the 6-*exo* reactions and a higher yielding reaction. Ikeda *et al.* achieved yields in the region of 90 % using a chloroamide **64** and tributyltin hydride (**Scheme 26**).³²



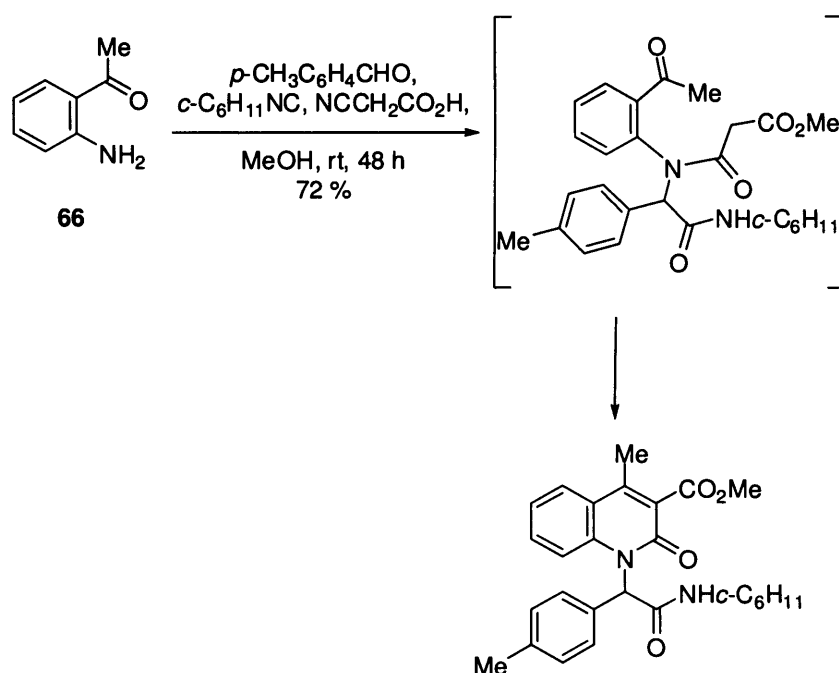
Scheme 26

Alternatively the radical can be generated to react with the aromatic ring system. **Scheme 27** shows the aromatic amide with a sulphonyl group on the side chain **65**, this sulphonyl group can be removed to generate the radical to form exclusively the six-membered product. In this example the tosyl radical is used as the radical source.³³



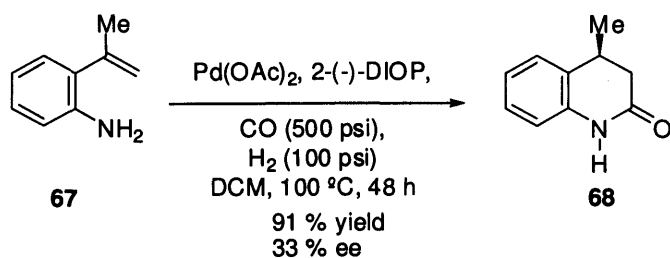
Scheme 27

An interesting way of synthesising a highly substituted quinoline was reported by Torroba *et al.* in which they used an Ugi four-component coupling reaction where amine **66** is treated with an isocyanide, aldehyde, and a carboxylic acid. This product is then nicely set up for an intramolecular Knoevenagel reaction. This method allowed the addition of considerable functionality in a single step (**Scheme 28**).³⁴



Scheme 28

To date only a small amount of the literature has referred to the asymmetric synthesis of quinolin-2-ones and those there have been have only achieved moderate yields. Alper *et al.* reported the homogeneous palladium-catalysed cyclisation of amine **67** in a high pressure atmosphere of carbon monoxide with the chiral ligand 2-(-)-DIOP to give the quinoline **68** in good yield and a 33 % ee (**Scheme 29**).³⁵

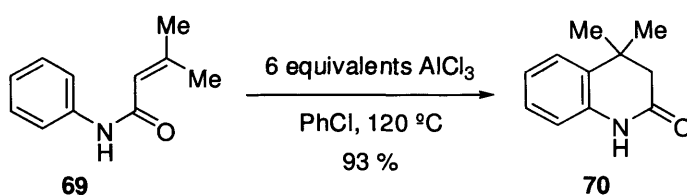


Scheme 29

2.3 New Synthetic Methods

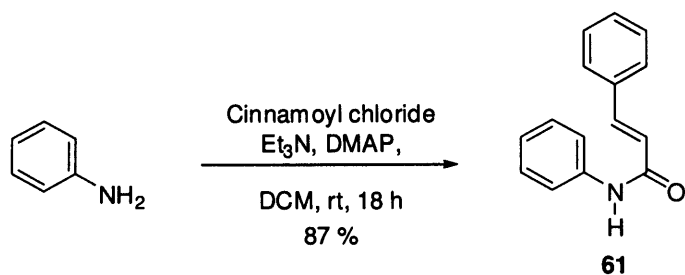
As mentioned at the start of this chapter, it was hoped that the conformation of the aromatic amide could be controlled by the use of a Lewis acid. If this was successful, the use of a chiral Lewis acid may be able to influence the stereochemical outcome of the reaction.

The use of a Lewis acid to promote this reaction had been previously reported, where the amide **69** and 6 equivalents of aluminium chloride had been reported to give the desired transformation to the quinoline **70** (Scheme 30).³⁶



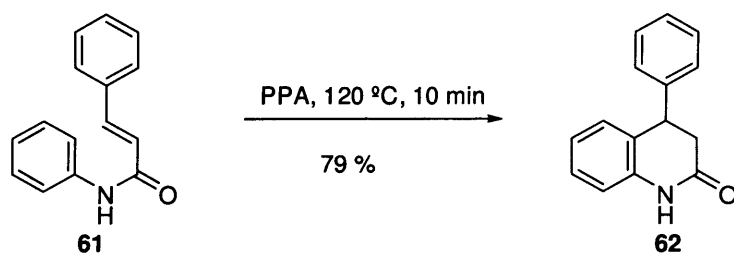
Scheme 30

Our initial studies were carried out on the similar amide **61** synthesised from aniline and cinnamoyl chloride (Scheme 31).



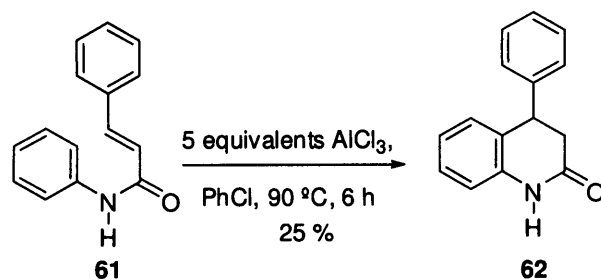
Scheme 31

Initially the cyclisation reaction of compound **61** was carried out using polyphosphoric acid. This gave compound **62** cleanly and in good yield (Scheme 32).



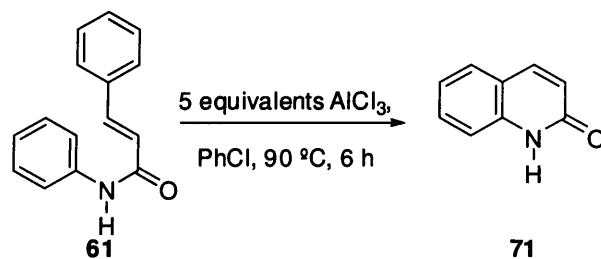
Scheme 32

The cyclisation was repeated using amide **61** and a similar method to that reported by Tzeng *et al.* (Scheme 33). Slight variations included the use of 5 equivalents of Lewis acid and the temperature was reduced to 90 °C. Although the expected product was isolated in 25 % yield, it was clear from the ^1H NMR spectrum of the crude reaction mixture that a number of side reactions had taken place. It was also noted that the aluminium chloride used for this reaction was quite old, and possibly not of good quality.



Scheme 33

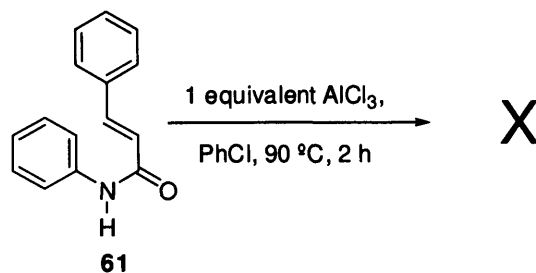
The reaction was repeated using fresh aluminium chloride (**Scheme 34**). On this occasion a single product was produced in good yield, however, it was not the desired quinoline **62**; instead it was the dearylated compound **71**.



Scheme 34

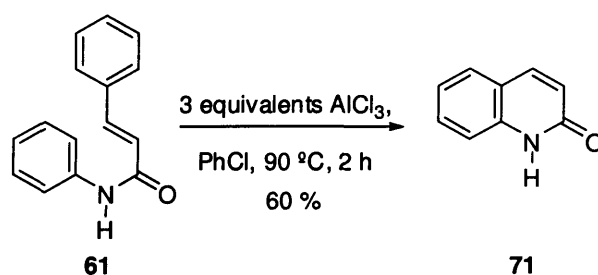
It was concluded that the original supply of aluminium chloride used was of poor quality and the actual amount of Lewis acid added for the first iteration of the reaction was unknown. To investigate the effect of variation in concentration of the Lewis acid, a range of concentrations were evaluated.

When one equivalent was used (**Scheme 35**) no reaction was observed and starting material was recovered.



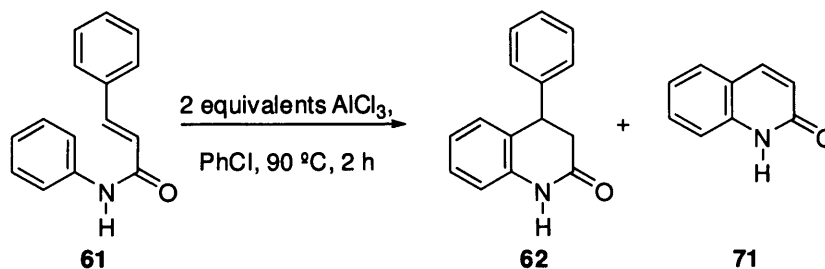
Scheme 35

However when three or more equivalents of aluminium chloride were used the dearylated compound **71** was predominant in good yield (**Scheme 36**).



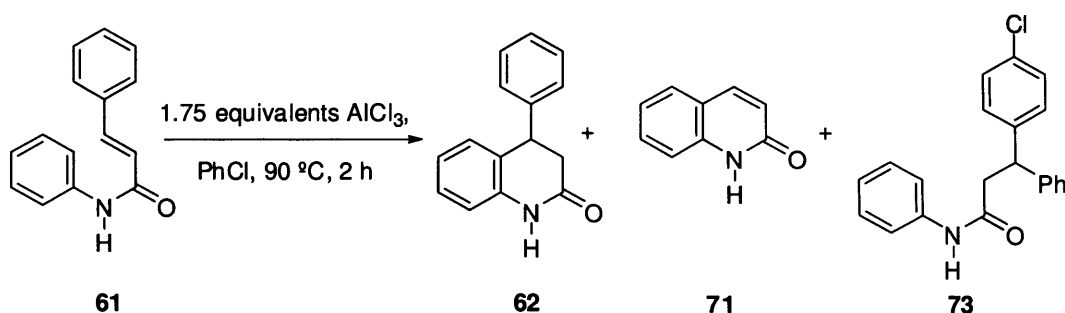
Scheme 36

When two equivalents were used, a range of products were obtained, the majority of which was the dearylated quinoline **71** with small amounts of the desired product **62** and trace amounts of as yet unidentified side products (**Scheme 37**).



Scheme 37

Two further reactions were carried out using either one and a half or one and three-quarter equivalents. When one and a half equivalents were used, only starting materials were recovered. However, when one and three-quarters were used the reaction proceeded to give a range of products some of which on comparison with the ^1H NMR of the products from 2 equivalents showed similar coupling and chemical shifts. These included the desired quinoline **62**. It was also clear that only a very small amount of the dearylated product **71** was produced (Scheme 38).

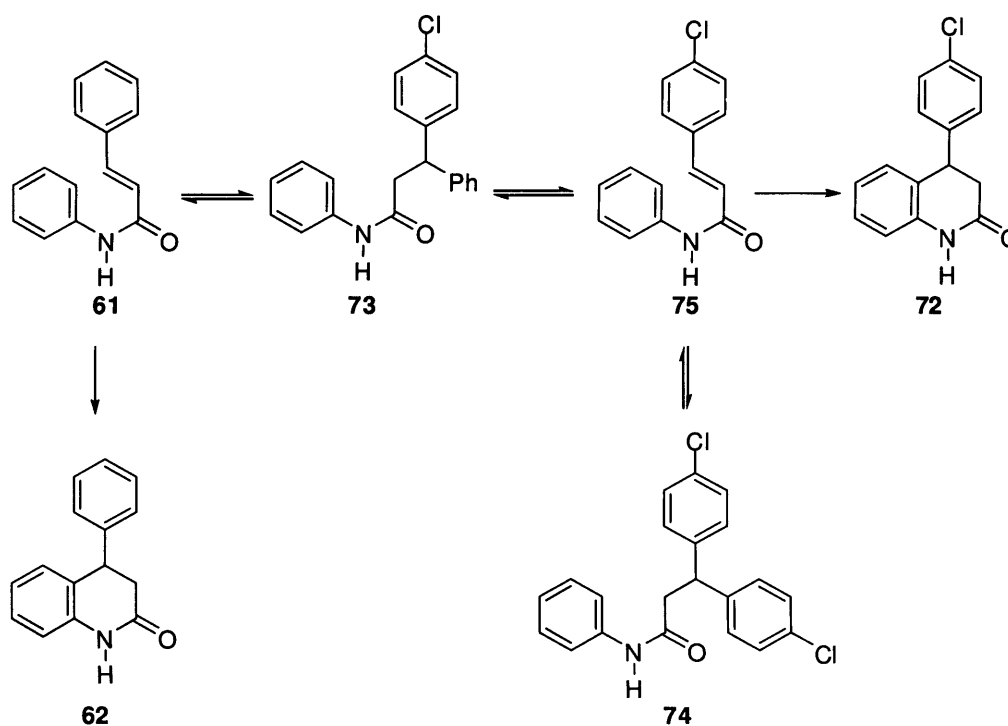


Scheme 38

It was pleasing to see that only a small amount of dearylation had occurred giving credence to the method as a way of making the desired compounds. The range of other compounds produced was surprising. Tzeng *et al.* had reported that when benzene was used as a solvent, conjugate addition of the solvent was the major product, but when chlorobenzene was used no solvent inclusion was observed.³⁷

As solvent incorporation had been previously reported, compound **73** was not wholly unexpected.

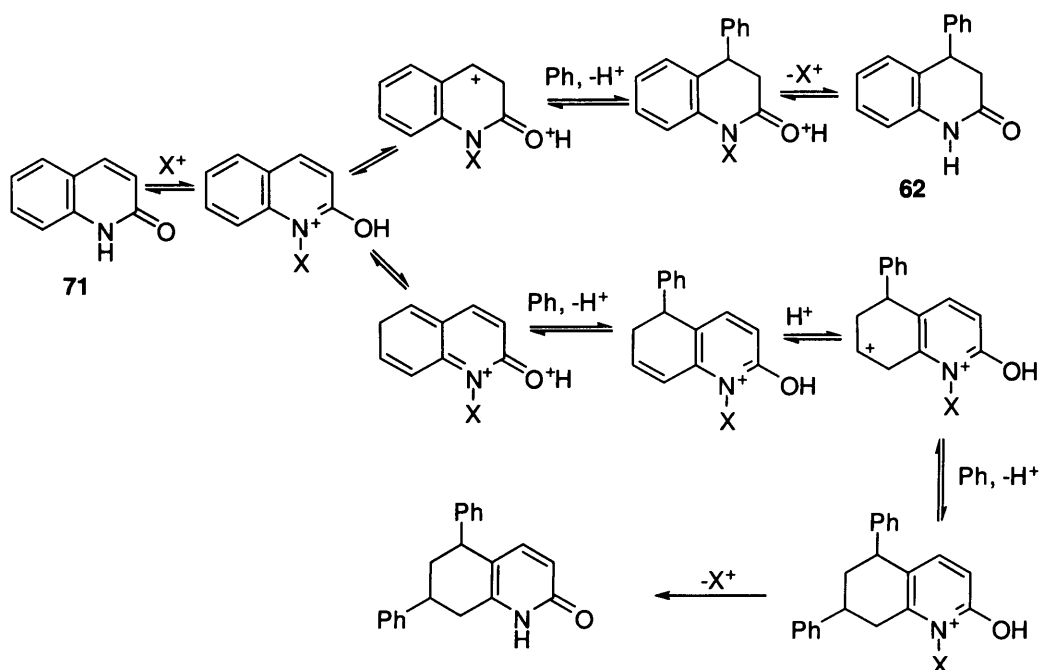
On a separate occasion it was also noted that two other compounds were formed during the reaction. These compounds **72** and **74** (identified by isotopic ratio patterns in the mass spectra) seem to suggest that a degree of reversibility within the reaction must be present (**Scheme 39**). Unfortunately separation of individual compounds was not achieved, so full characterisation was not possible.



Scheme 39

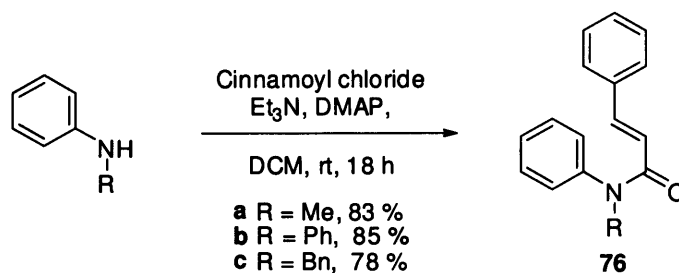
Further evidence for reversibility in this type of reaction was published by Olah *et al.*,³⁸ in which he observed a range of products during the superacid-mediated addition of benzene to compound **71**, and reasoned that the reaction pathway must involve an

number of steps in equilibrium as shown in **Scheme 40**. In particular, the loss of benzene from compound **62** was demonstrated.



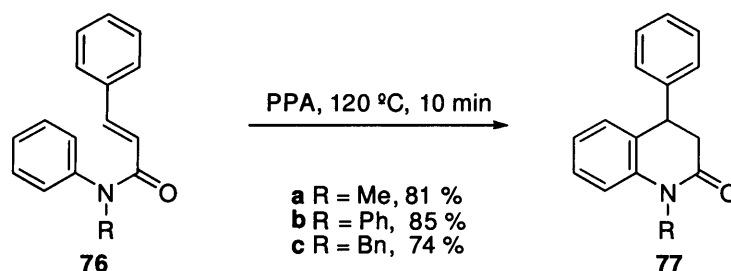
Scheme 40

Tzeng *et al.* had reported significant differences in the reaction products when substituted aromatic rings were used. They did not, however, investigate substitution on the nitrogen. We were keen to investigate the scope of the reaction and to see if substitution on the nitrogen would affect the reaction in any way. Three other amides were synthesised from their respective *N*-substituted anilines and cinnamoyl chloride (**Scheme 41**).



Scheme 41

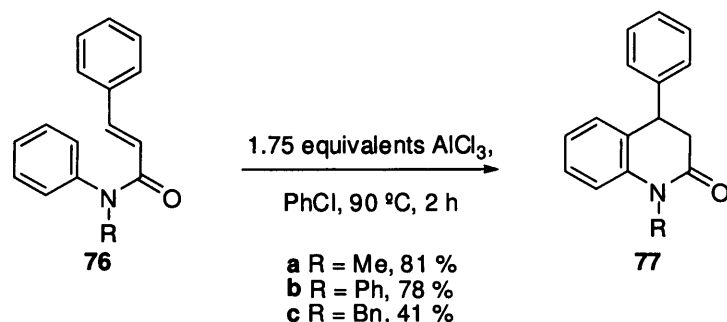
It was decided initially to try the cyclisation reactions using polyphosphoric acid to ascertain whether all the substrates behaved in a similar way to amide **61**. This was really only a concern for the benzyl derivative **76c** where there was a small chance of cyclisation through the benzyl group (**Scheme 42**).



Scheme 42

It was pleasing to see that all the chosen amides cyclised to give the desired products in good yields.

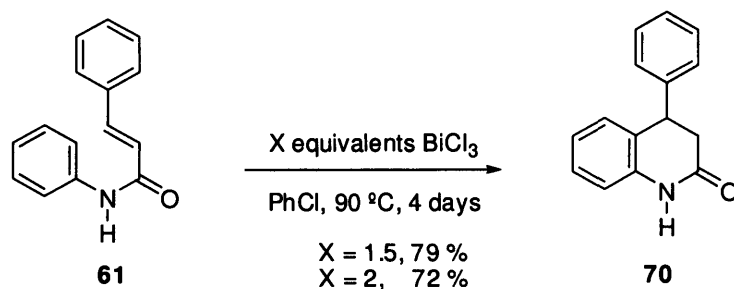
For the cyclisations using aluminium chloride, one and three-quarter equivalents were used, as it had given the best results to date; the solvent temperature and length of reaction were kept in line with those used before (**Scheme 43**).



Scheme 43

It was immediately clear that these substrates were behaving differently to amide **61**. The most notable difference was the amount of solvent incorporation. A slight trace of solvent incorporation was detected on the 1H NMR spectrum of the crude reaction mixture when amide **76a** was cyclised. For the others, no solvent incorporation was detected. The reaction of **76c** was clean with no obviously identifiable side products; however, the isolated yield was low.

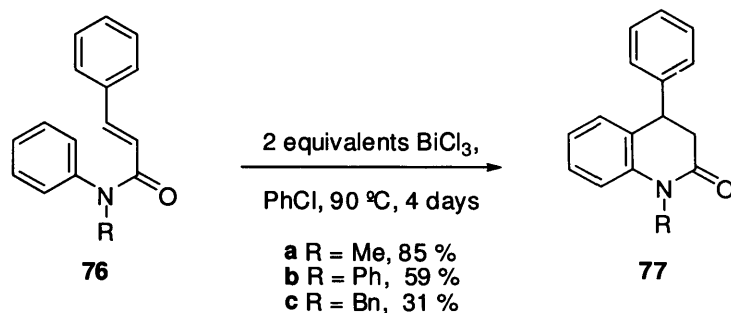
The use of acids has so far been limited to very strong acids like triflic acid, polyphosphoric acid and the Lewis acids aluminium chloride and aluminium bromide. We were interested to see whether these reactions could be promoted using a weaker Lewis acid. To this end bismuth chloride was examined as a potential alternative. It was decided to test just one and a half and two equivalents, as this would provide the necessary information to determine whether the two Lewis acids were performing in the same manner (Scheme 44).



Scheme 44

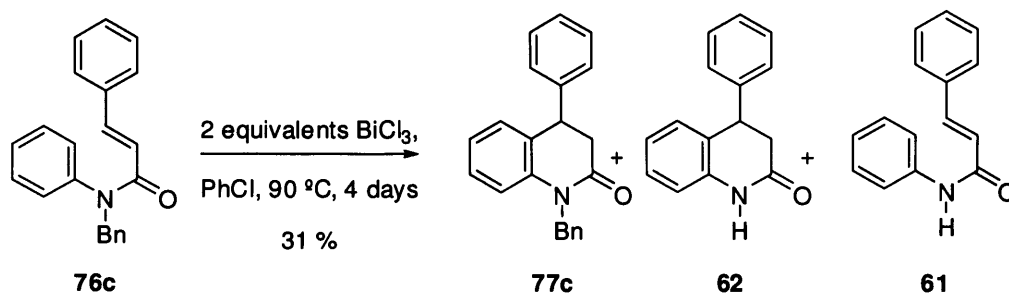
It was evidently clear that the Lewis acids were performing differently. When the reaction was evaluated after two hours, no reaction had taken place, and it took four days for the reaction to reach completion. The pleasing result was that only the desired compound had been formed and neither solvent incorporation nor dearylation was observed. It is plausible that the softer nature of the cation formed with bismuth chloride may reduce the likelihood of reaction with chlorobenzene.

Cyclisation reactions were carried out on the amides **76a**, **76b** and **76c**. In these cases two equivalents of Lewis acid were used (Scheme 45).



Scheme 45

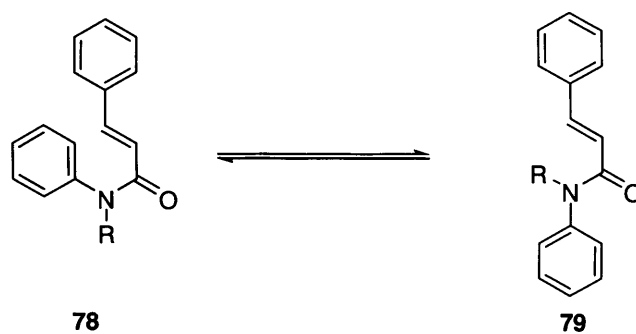
Reactions proceeded well with no incorporation of solvent. However, for R = Bn the yield was again low. On this occasion it was possible to identify some of the side products (Scheme 46).



Scheme 46

The loss of the benzyl could occur directly, or the reaction could proceed by loss of phenyl followed by hydrolysis of the resulting iminium ion.

Our original intention had been to investigate conformational control of the Friedel-Craft acylation with the catalytic use of a chiral Lewis acid, although this now looked implausible due to the amount of Lewis acid required for the reaction. Conformation of the amide may still be playing a role on the outcome of the reaction. The favourable conformation for the reaction would be **78** and could easily switch if R = a small group *e.g.* 'H' to the less favourable conformation **79**. When R = a bulky group *e.g.* Bn or Ph then the most favourable conformation would be the desired **78** (**Scheme 47**).



Scheme 47

If this was the only effect then the rates of reaction should be R = Ph being the fastest as only one conformation is available, followed by R = Bn, R = Me and finally R = H. However, this is not what was observed in the reactions when bismuth chloride was used, they followed the pattern R = Me then R = Ph, R = H and finally R = Bn. One possible explanation for this is the accessibility of the carbonyl oxygen, for complexation with the Lewis acid. When R = a bulky group the oxygen is being sterically hindered, only when R = Me is there a chance of a favourable conformation that allows free access to the carbonyl oxygen. A three-dimensional representation of the amides (76a) and (76b) (Figure 4) shows the most likely conformations. It can clearly be seen that for amide (76a) that the oxygen is less hindered.

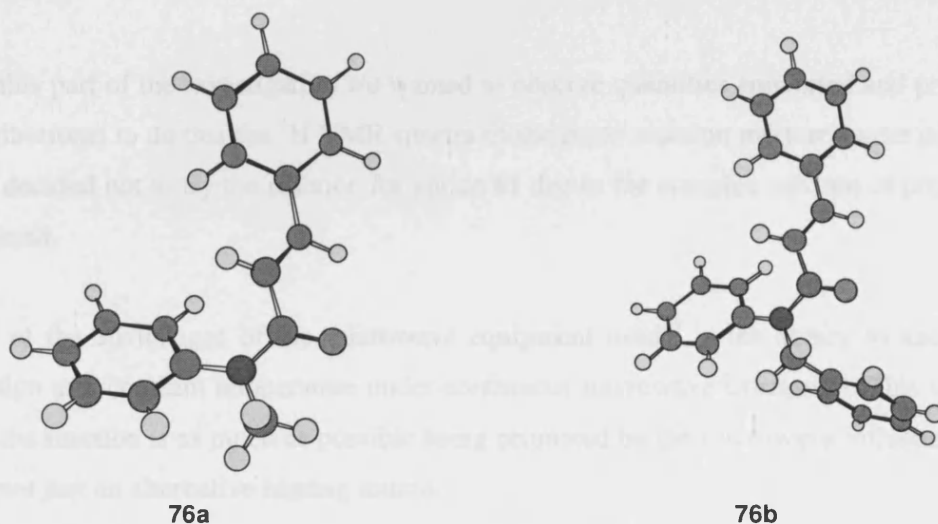
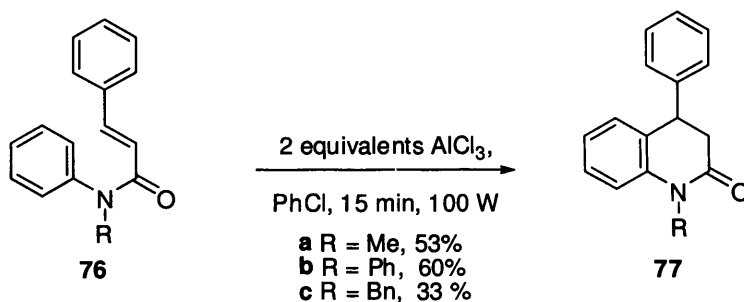


Figure 4 3 dimensional representation of compounds 76a and 76b (MM2 energy minimised).

The use of microwave radiation to initiate reactions as an alternative to conventional heating has recently received a lot of attention. It was decided to see if this reaction could be improved, with the shortening of reaction times and reduction of side reactions by the use of microwave radiation.

Due to solubility and safety issues only aluminium chloride in chlorobenzene was investigated. The conditions used were 15 minutes at 100 watts (**Scheme 48**).



Scheme 48

For this part of the investigation we wanted to observe quantities converted and product distributions; to do this the ¹H NMR spectra of the crude reaction mixtures were used. It was decided not to try the reaction for amide **61** due to the complex mixture of products obtained.

One of the advantages of the microwave equipment used³⁹ is the ability to keep the reaction at a constant temperature under continuous microwave irradiation. This means that the reaction is as much as possible being promoted by the microwave influence and it is not just an alternative heating source.

Rates of conversion were R = Ph ≈ R = Me > R = Bn. One possible reason for the similar rates of reaction of R = Ph and R = Me could be that the microwave radiation is speeding up interconversion of the two conformations effectively reducing the steric hindrance observed under conventional methods. When R = Bn there is still a high level of steric hindrance which would still produce a relatively slower reaction time.

The use of microwave radiation did indeed reduce the reaction time, though not by as much as had been hoped for. Products from the reactions were almost identical to those observed when conventional heating was employed.

In conclusion to this work, it is our belief that the use of bismuth chloride is the best for this kind of reaction, although reaction times are a lot longer the reactions are cleaner and less sensitive to small variations in the concentration of Lewis acid used.

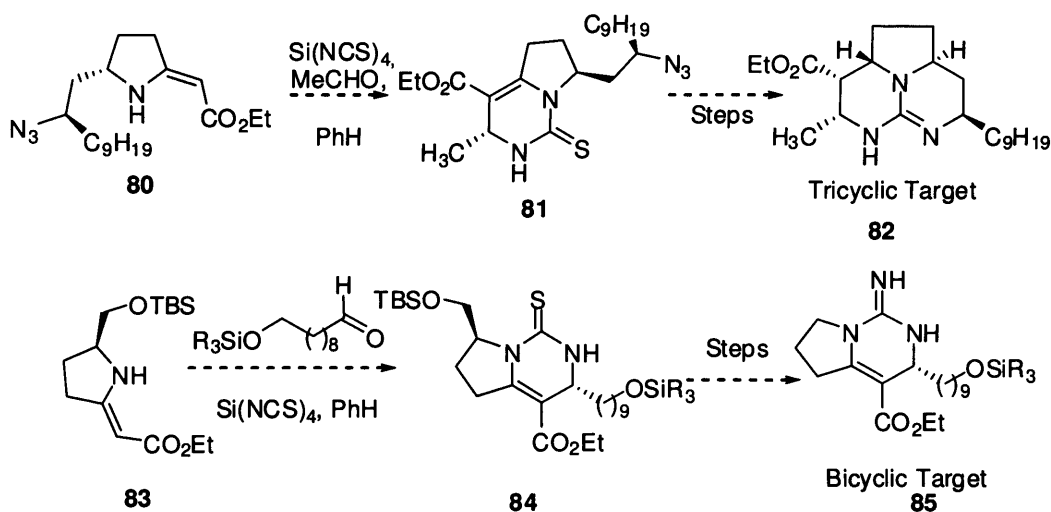
Although this work is not directly relevant to the synthesis of the Batzelladine alkaloids, and the ultimate goal of achieving an asymmetric synthesis of 3,4-dihydroquinolin-2-ones was not explored, it has provided an insight into the mechanism of the cyclisation of cinnamamides under various conditions, leading to an improved synthesis of 3,4-dihydroquinolin-2-ones.

Chapter 3

Synthesis of Alkylidenepyrrolidines

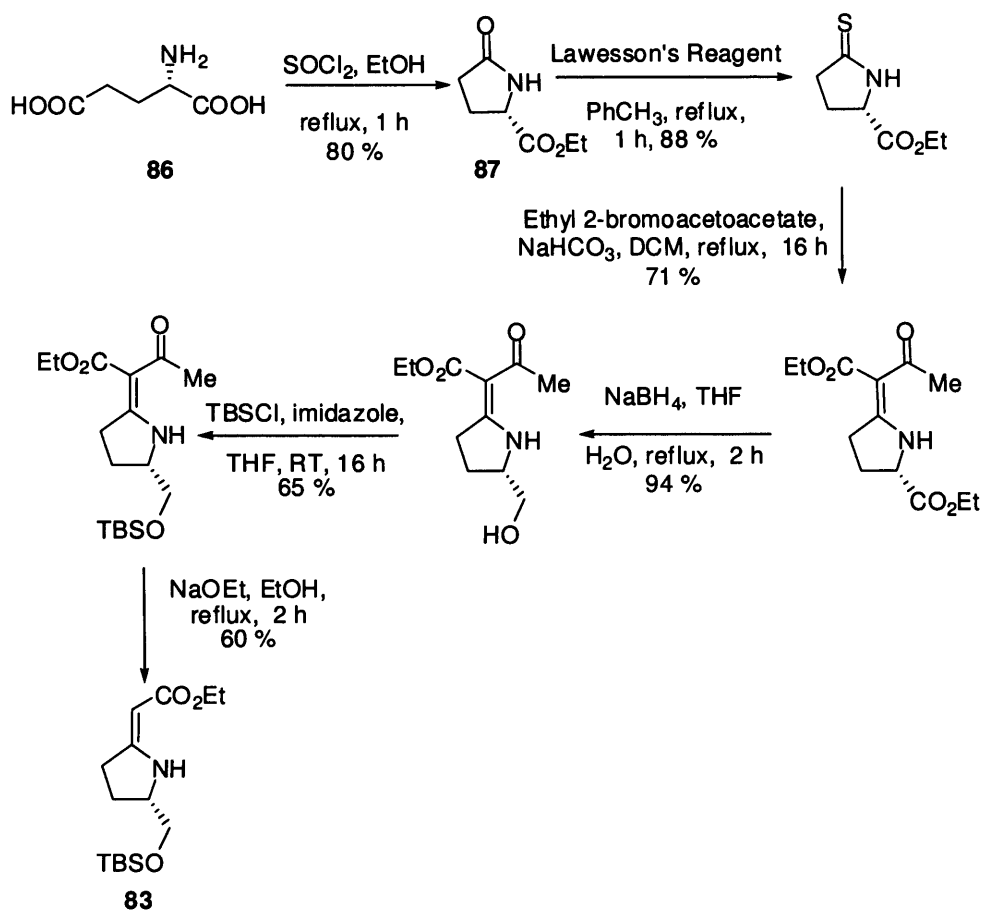
3.1 Introduction

The previous approach used by the Elliott group for the synthesis of the batzelladine alkaloids utilises an alkyldenepyrrolidine as the key starting material.²⁴ This can be transformed into the cyclic guanidine seen in all known batzelladine alkaloids (Scheme 49). For example, compound **80** would undergo three-component coupling to give compound **81**, which would then be transformed into the tricyclic target **82**. Compound **83** would give compound **84**, which would require removal of the hydroxymethyl group to give the bicyclic target **85**.



Scheme 49

The synthesis of the alkyldenepyrrolidines is key, both to the overall yield and versatility of this approach. Scheme 50 highlights the synthesis of the alkyldenepyrrolidine **83**, from glutamic acid **86**, required for the bicyclic guanidine found in batzelladine A. Six steps are required, with an overall yield of 18%.



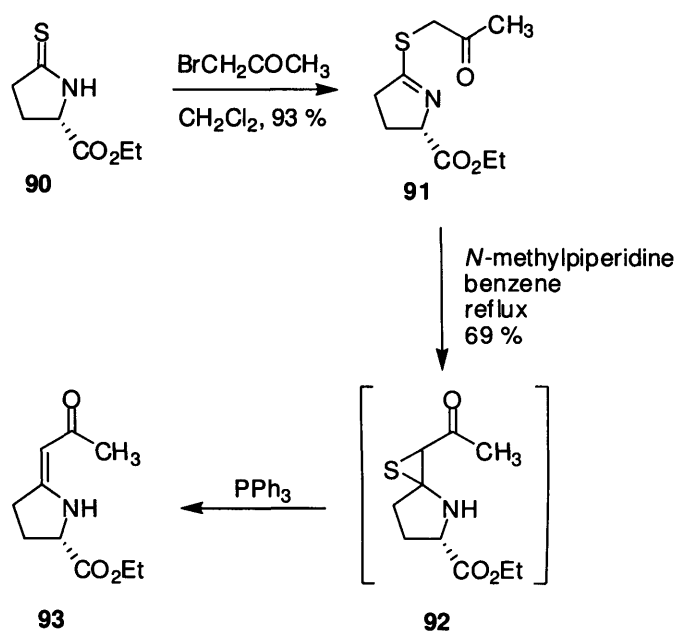
Scheme 50

A partial synthesis of a precursor to the tricyclic guanidine core of the natural products was also achieved.²⁴ An 11 step synthesis was required to reach compound **88**, while modifications would be required to form the desired target **89** (Scheme 51).

Both of the syntheses detailed above are long with low overall yields, which would result in slow progress to the desired targets. A significantly improved approach to both sides of Batzelladine A was required, and it was decided to develop an improved synthesis of alkylidenepyrrolidines.

3.2 Background to Alkylidenepyrrolidine Synthesis

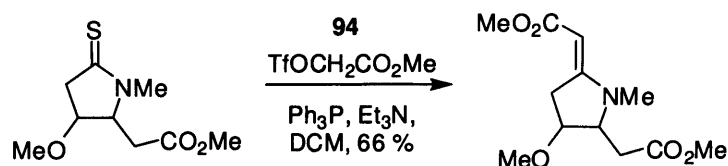
Alkylidenepyrrolidines have been shown to be useful and versatile building blocks for heterocyclic and natural product chemistry. Over the years a varied range of syntheses and use of these compounds has been documented. The most widely used synthesis to date is the Eschenmoser sulphide contraction.⁴⁰ Knott first reported the reaction in 1955.⁴¹ However, it was not until it was used in the synthesis of Vitamin B₁₂ that the true potential was realised.⁴²



Scheme 52

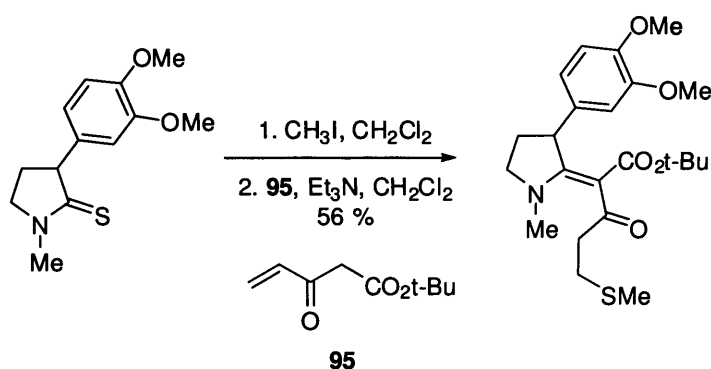
The general reaction shown above (**Scheme 52**) indicates the chemical pathway that is followed for this reaction. It starts with the alkylation of the thiolactam **90** with a α -halocarbonyl. This intermediate **91**, in the presence of a base such as *N*-methylpiperidine forms the thiirane **92**, which, in the presence of a thiophile, typically triphenylphosphine, gives the alkylidenepyrrolidine **93**.

The α -halocarbonyl compounds are most commonly used as the alkylating agent in these types of reactions. However, other leaving groups have been used. In the synthesis of carbapenems, Koskinen *et al.* utilised the triflate leaving group **94** (**Scheme 53**).⁴³



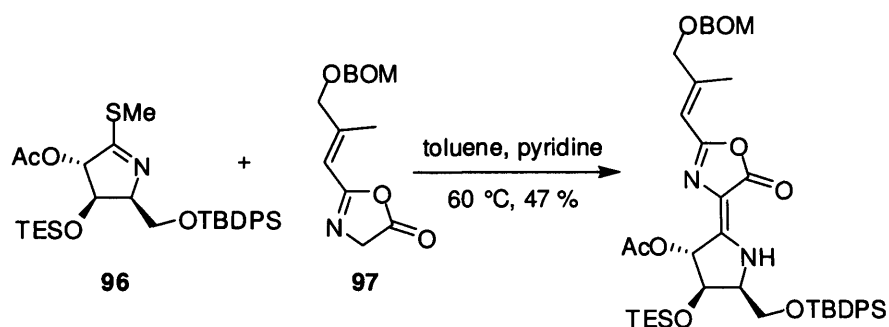
Scheme 53

A further modification to the reaction by Michael *et al.* showed that the alkylating agent does not need a leaving group adjacent to the carbonyl. In this example the methanethiolate is displaced in a Knoevenagel-type reaction (**Scheme 54**).⁴⁴



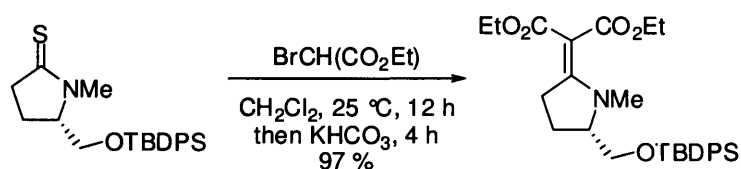
Scheme 54

This method was also used in the synthesis of the azinomycin natural products, in which the complex thiolactam **96** was reacted with an azalactone **97** (Scheme 55).⁴⁵



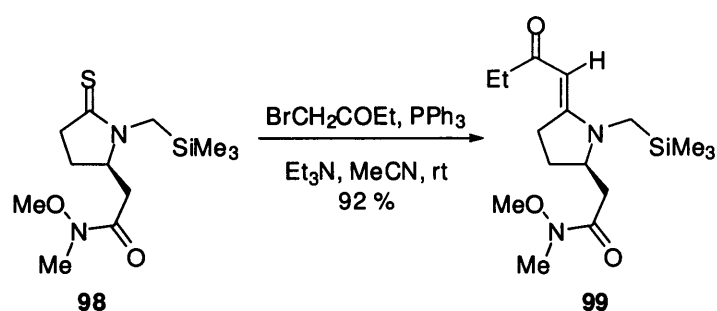
Scheme 55

Throughout all the examples illustrated above, a thiophile has been used either within the compound or a phosphorus reagent like triphenylphosphine has been added. It has been shown that in certain cases the reaction can progress in good yield without a thiophile of any sort (Scheme 56).⁴⁶



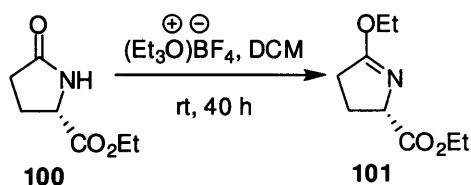
Scheme 56

In all of the Eschenmoser sulphide contractions shown, the double bond geometry is controlled by the substituents on nitrogen. If unsubstituted, the (*Z*) isomer is generally formed, while any other substituent will favour the (*E*) isomer. For example, the thiolactam **98** gives exclusively the (*E*) isomer **99** (Scheme 57).⁴⁷



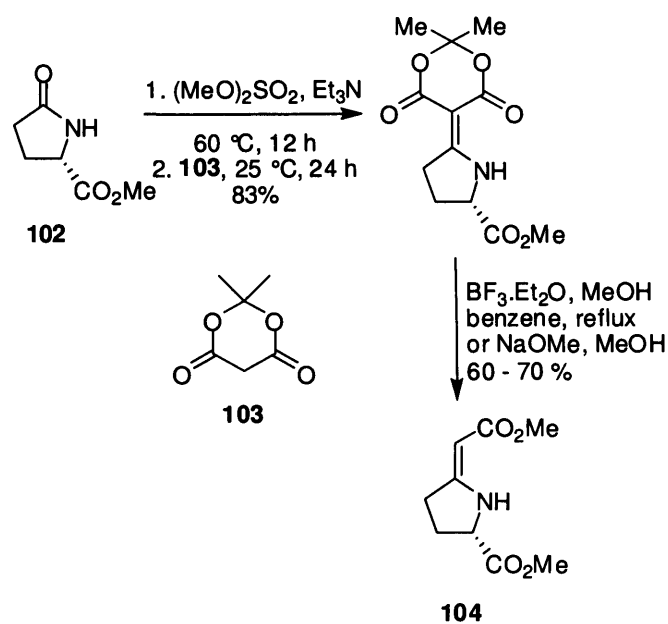
Scheme 57

Useful starting materials for these types of reactions are the pyrrolidone derivatives.⁴⁸ They provide a ready source of chiral starting materials, in which the chiral ester group is not particularly prone to racemisation under either acid or basic conditions. Although the carbonyl is relatively unreactive, it can be made more reactive in a number of ways. The use of Lawesson's reagent to convert it into the thiolactam set the stage for the examples shown above. An alternative method is to make an iminoether such as the conversion of lactam **100** to **101** as shown in **Scheme 58**.⁴⁹



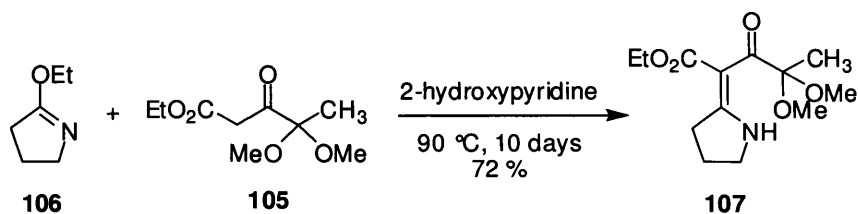
Scheme 58

The amidoester **102** can then be reacted with a 1,3-dicarbonyl nucleophile *e.g.* Meldrum's acid **103** with further elaboration to the alkylidenepyrrolidine **104** (**Scheme 59**).⁵⁰



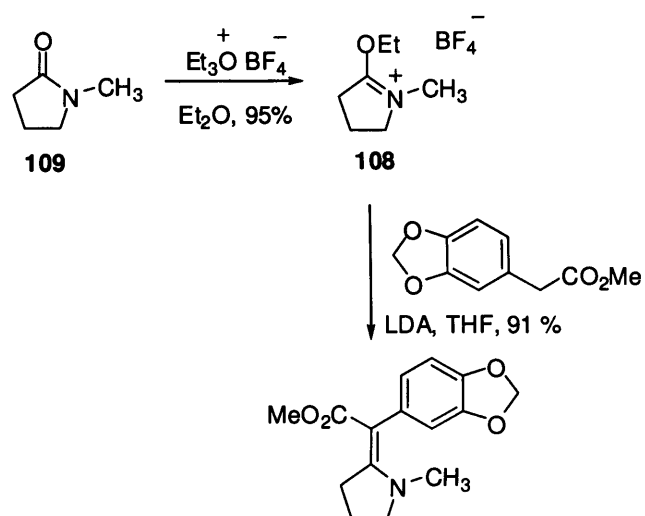
Scheme 59

The range of conditions available for this type of reaction makes it compatible with sensitive functional groups. **Scheme 60** shows the reaction of an acid sensitive ketal **105** with the iminoether **106** to the corresponding alkylidenepyrrolidine **107** in good yield.⁵¹



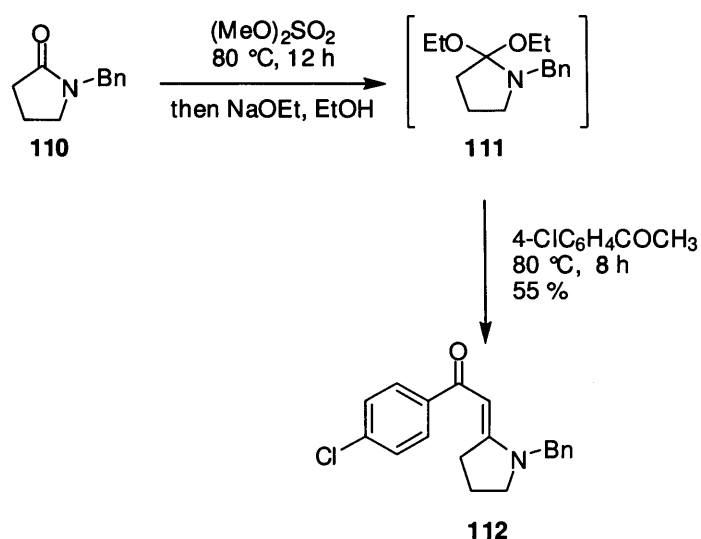
Scheme 60

Modifications to this process have allowed the reaction to progress with substitution on the nitrogen atom. It is possible to make the iminium ion **108** from the lactam **109**. This undergoes reaction with enolates as above (**Scheme 61**).⁵²



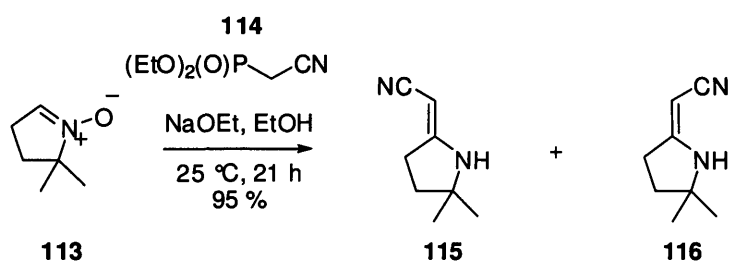
Scheme 61

The final method in this category is to make a diether derivative. This is formed by reaction of the lactam **110** with dimethyl sulphate, followed by a sodium ethoxide work up to give the intermediate **111**. This is then heated in 4-chloroacetophenone over 8 hours to give alkydenepyrrolidine **112** (Scheme 62).⁵³



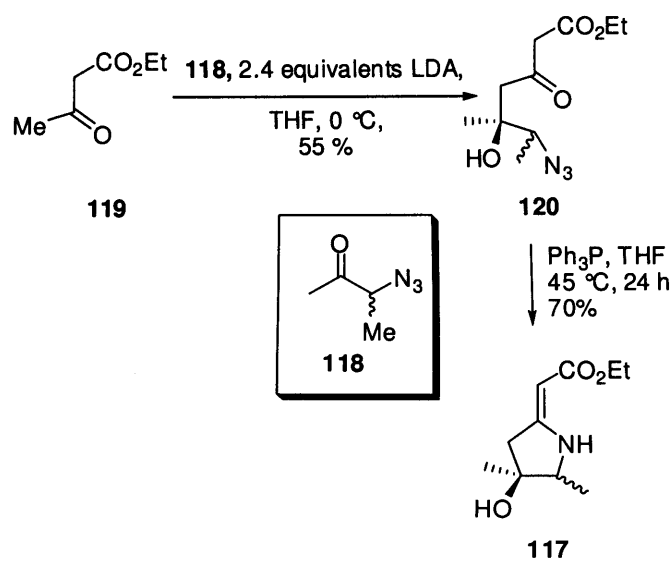
Scheme 62

An alternative electrophilic source of the pyrrolidine ring is to use a nitron. This was demonstrated well with the reaction of nitron **113** with phosphonate **114** to give the alkylidenepyrrolidine as a 1:1 mixture of double bond isomers **115** and **116** (Scheme 63).⁵⁴ This reaction proved to be a good way of producing nitrile derivatives in good yield. However, limitations include side-reactions when esters are used.



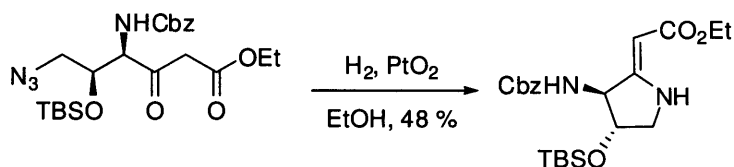
Scheme 63

All of the above methods started from similar pyrrole derivatives. An alternative is to form the ring system during the reaction. A good example is the formation of the alkylidenepyrrolidine **117**, where the azide **118** through an aldol condensation with the β -keto ester **119** to form the intermediate **120**. This intermediate **120** then undergoes a tandem Staudinger-aza-Wittig reaction to give the alkylidenepyrrolidine **117** (Scheme 64).⁵⁵



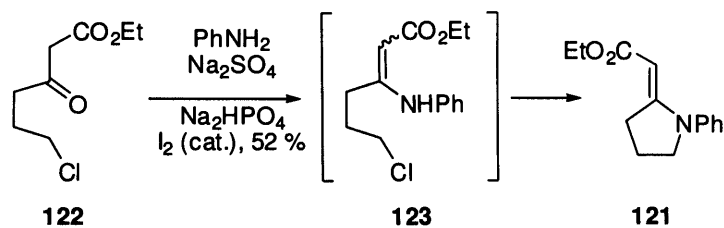
Scheme 64

Alternatively, similar reactions have been carried out under hydrogenation conditions although the overall yield is slightly lower (**Scheme 65**).⁵⁶



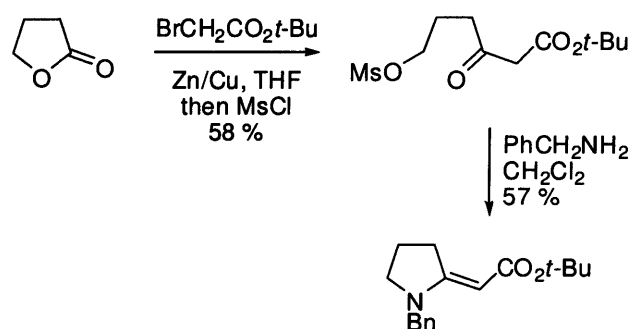
Scheme 65

The nitrogen source can simply be a substituted amine. In the formation of alkylidenepyrrolidine **121**, aniline is used as the nitrogen source, which reacts with the ketone carbonyl of the β -keto ester **122** to give the enamine intermediate **123**, which can then cyclise to give compound **121** (**Scheme 66**).⁵⁷



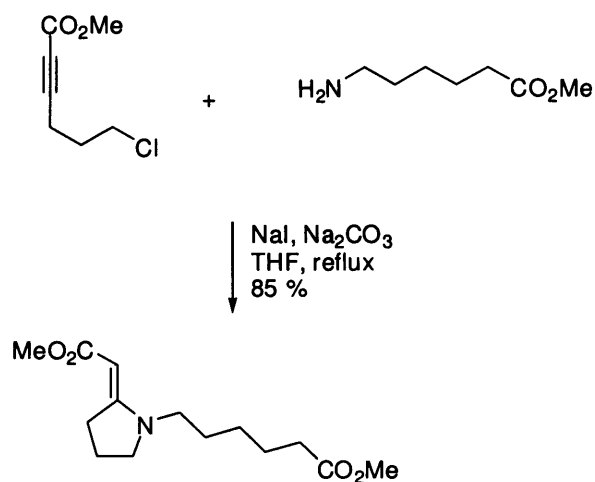
Scheme 66

This method is convenient due to the availability of starting materials which can be synthesised from commercially available lactones by a Reformatsky reaction (**Scheme 67**).⁵⁸



Scheme 67

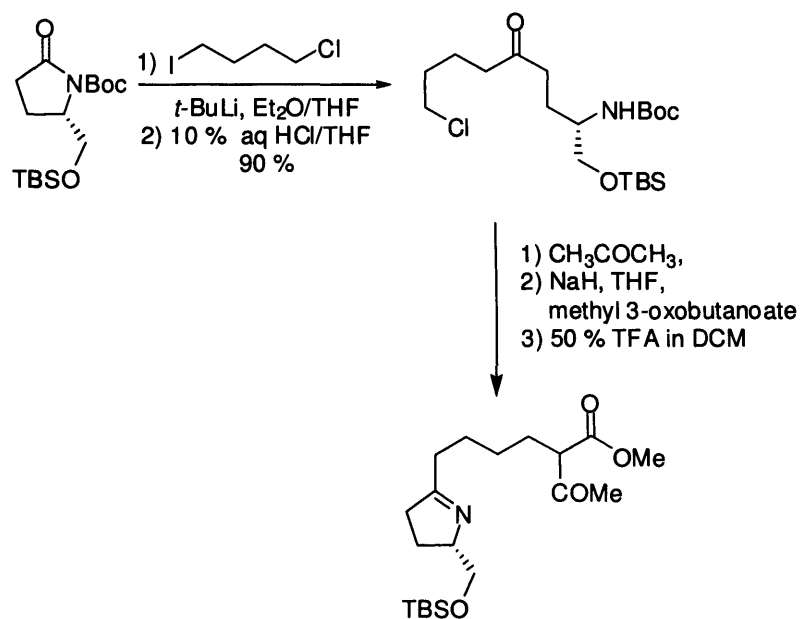
Propionic esters provide alternative electrophilic species for the formation of alkylidenepyrrolidines. An addition of an amine nucleophile will give rise to an enamine, which can then cyclise as in the example below (**Scheme 68**).⁵⁹



Scheme 68

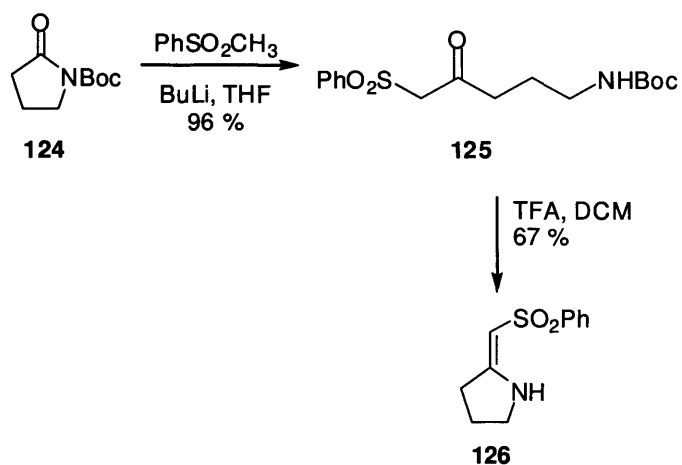
3.3 New Studies in Alkydenepyrrolidine Synthesis

It is well known that carbamates derived from lactams can be selectively attacked at the lactam carbonyl by a range of nucleophiles. These have included Grignard,⁶⁰ and other organometallic reagents.⁶¹ As well as these, hetero-nucleophiles⁶² and stabilised anions have also been extensively reported.⁶³⁻⁶⁴ In a number of instances these products have been cyclised to form pyrrolines and pyrrolidines (**Scheme 69**).⁶⁵⁻⁶⁶



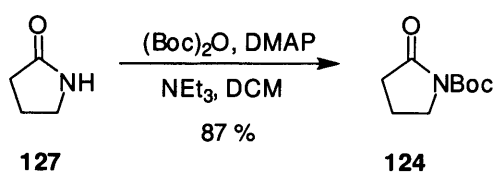
Scheme 69

However to date there has been only one such example for the formation of an alkydenepyrrolidine by this method (**Scheme 70**).⁶⁷

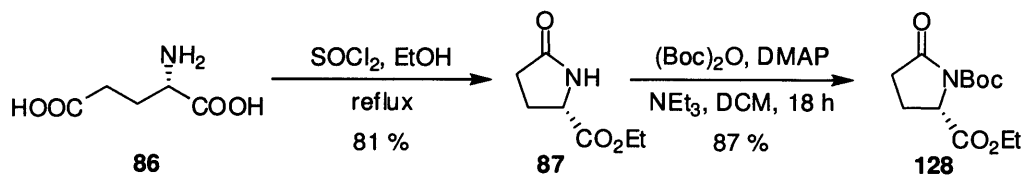


Scheme 70

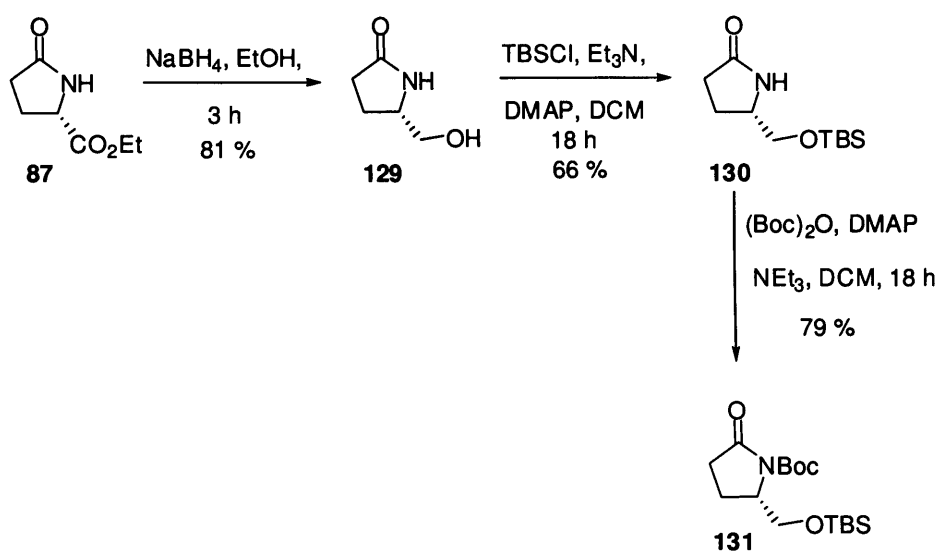
This type of approach would provide an extremely convenient synthesis of alkylidenepyrrolidines, using simple reactions, and only three steps from the lactam. We have therefore conducted a study into the scope and usefulness of this simple transformation for the formation of alkylidenepyrrolidines. Lactams **127**, **87** and **129** were chosen for the study. It was essential that any methods used can be scaled up to multi-gram quantities (**Schemes 71**, **72** and **73**). These reactions have been carried out on a 5 g scale with no significant drop in yields.



Scheme 71

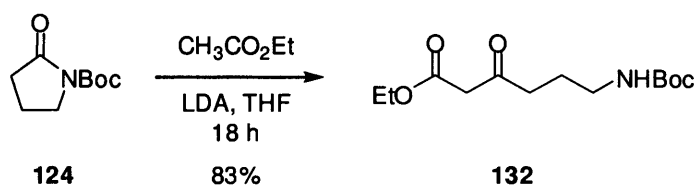


Scheme 72



Scheme 73

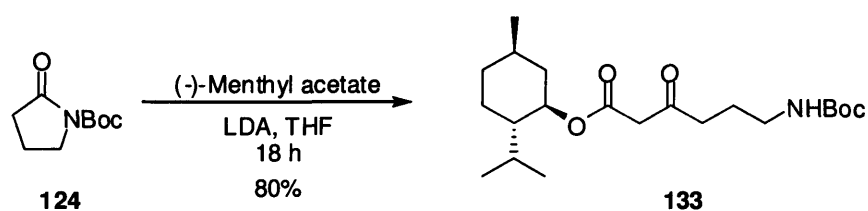
Initial studies into the viability of the reaction were carried out on the achiral lactam **124**. For the purposes of the synthesis of the batzelladine alkaloids, an ester was required as the electron withdrawing group, so ethyl acetate was chosen for optimisation of the reaction (**Scheme 74**).



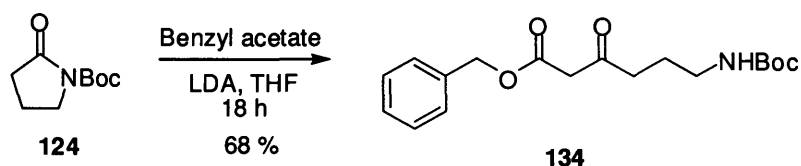
Scheme 74

Initial results from this stage were promising, with good yields achieved with little or no purification required. Early reactions were carried out using a 10% excess of lithium diisopropylamide. When this was reduced to a stoichiometric amount there was no noticeable drop in yield. However, the crude product was then essentially pure (as determined by ^1H and ^{13}C NMR spectroscopy).

Two more acetates were chosen to test the concept. These were the synthetically useful menthyl acetate and benzyl acetate. Both acetates have been shown to have potentially useful properties for the synthesis of the batzelladine alkaloids. Menthyl acetate could be used as a directing group for asymmetric induction during the three-component coupling reaction, which is described in detail in Chapter 4 (**Scheme 75**). The ease with which the benzyl group can be removed through hydrogenation makes it a useful functional group (**Scheme 76**). In both cases the same conditions were used. Although, purification was a necessity in both cases, good yields were obtained.

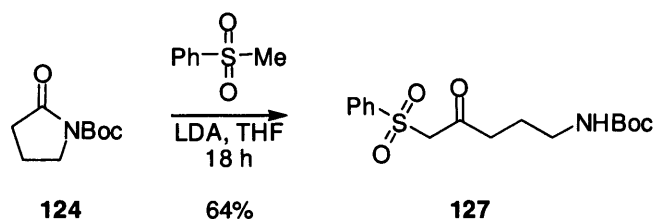


Scheme 75



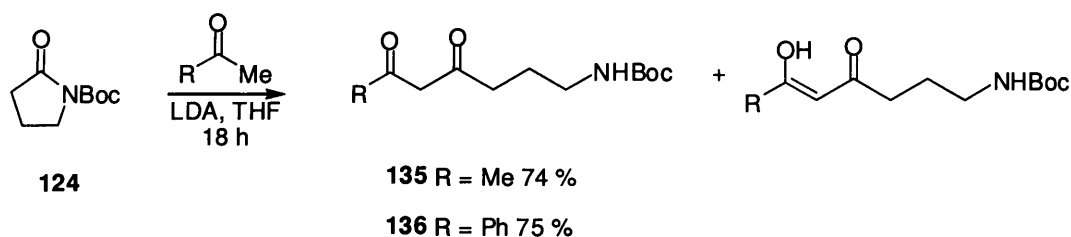
Scheme 76

The scope of the reaction was widened to incorporate other nucleophiles. As mentioned above, sulphones had already been used. These reactions were repeated, with the yields obtained in line with those reported in the literature (**Scheme 77**).



Scheme 77

Next, ketones were used as the source of the nucleophile. Two were chosen: acetone and acetophenone. From the outset these reactions proved to be inferior to those of the esters. When carried out under the same conditions as the esters, crude yields were found to be lower and the reaction produced both the enol and keto tautomers (**Scheme 78**).

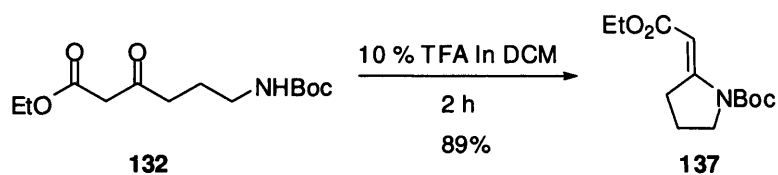


Scheme 78

After purification by flash chromatography R = Ph gave exclusively the enol tautomer, when R = Me a 5 : 1 ratio in favour of the enol tautomer was observed.

With any asymmetric synthesis it is important to reduce the chances of racemisation. One potential problem can be the use of a strong acid during the ring-closing step. The original synthesis of the sulphonyl alkylidenepyrrolidine **126** used a large excess of trifluoroacetic acid. It was not known whether this would cause racemisation of pyroglutamic ester derivatives, but it was considered prudent to investigate whether milder conditions could be utilised.

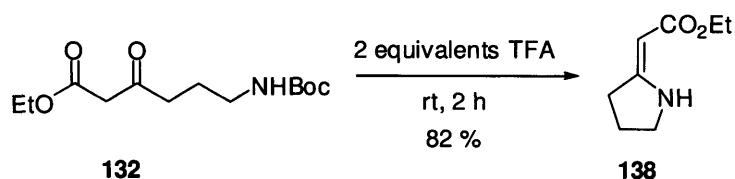
First attempts to cyclise the β -ketoester **132** to the corresponding alkylidenepyrrrolidine were successful using either a 10% solution of trifluoroacetic acid or *p*-toluenesulphonic acid in dichloromethane (**Scheme 79**). No significant difference in the yield was observed between either acid



Scheme 79

The obvious drawback to this result is that the Boc protecting group had not been removed as was hoped. In fact compound **132** undergoes the same cyclisation reaction in chloroform with no added acid, over a period of three days.

However, it was necessary for the protecting group to be removed; of the acids used above trifluoroacetic acid was chosen as any excess could be removed *in vacuo* instead of by aqueous work-up. The reaction was repeated using different amounts of acid. Less than two equivalents gave the protected product, whereas two or more equivalents gave the deprotected alkylidenepyrrrolidine **138** (**Scheme 80**).

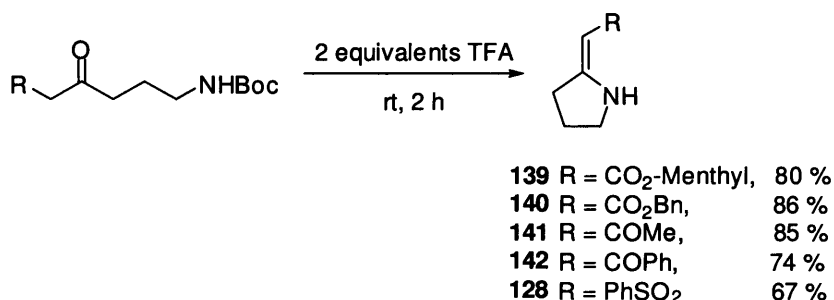


Scheme 80

Although this was a larger excess than hoped for, it had the added advantage that solvent could be omitted when the reaction was carried out on a large scale (>1 g). Due to the

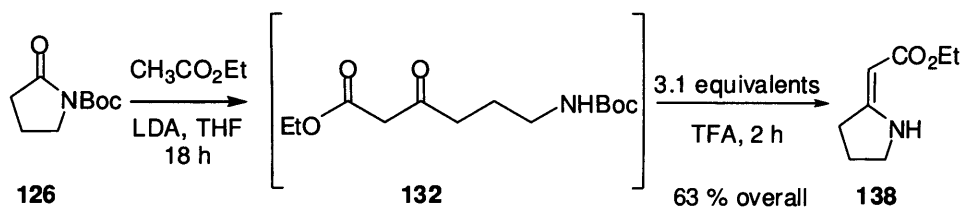
trifluoroacetic acid being removed *in vacuo*, the amount of water used in the work-up was reduced giving very high yields in the region of 85 % with excellent purity.

This same method was used on the other purified ring-opened compounds **133**, **134**, **135** and **136** (Scheme 81) and although yields were not as high as for compound **142**, they were still good with excellent purity.



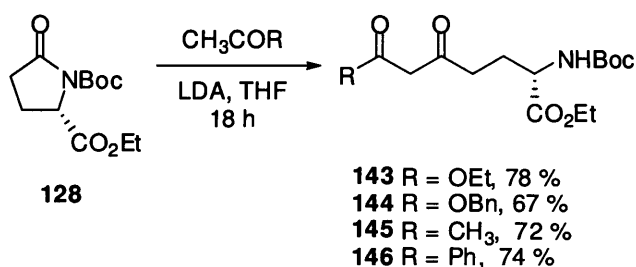
Scheme 81

Due to the simplicity of the cyclisation step, it was decided to try the reaction as a ‘one pot’ method, where the acid is added directly to the reaction mixture after the ring opening. Enough acid was added to quench the reaction plus two equivalents. The reaction was successful (Scheme 82). However, although the yield was close to that observed when the reaction was carried out over two steps, it was necessary to purify the compound by flash chromatography.



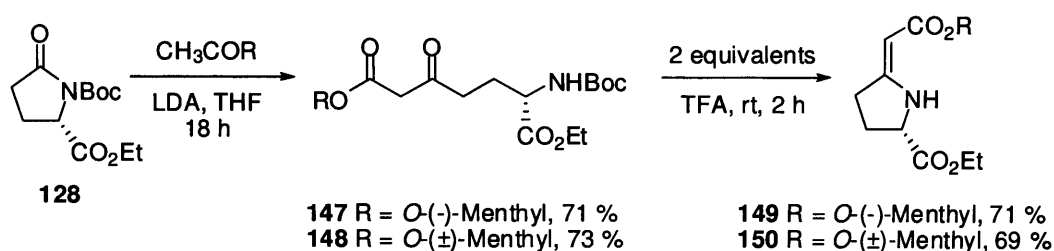
Scheme 82

Once the method had been confirmed the lactam was changed to the chiral pyrroglutamate derivative **128**. The reactions were carried out using the above methods. In general yields were similar to those for lactam **126**. When ethyl acetate was used as the source of the nucleophile, the reactions were consistently high in purity with higher yields than any other nucleophilic source tested. In both examples using ketones, only the enol tautomer was isolated after flash chromatography (**Scheme 83**).



Scheme 83

Although every effort had been made to find mild conditions for the ring-closing step, racemisation was still a potential concern. In order to establish whether any racemisation was occurring the lactam **128** was subjected to the ring-opening/ring-closing protocol with optically pure *O*-(-)-menthyl acetate and with racemic menthyl acetate (**Scheme 84**).

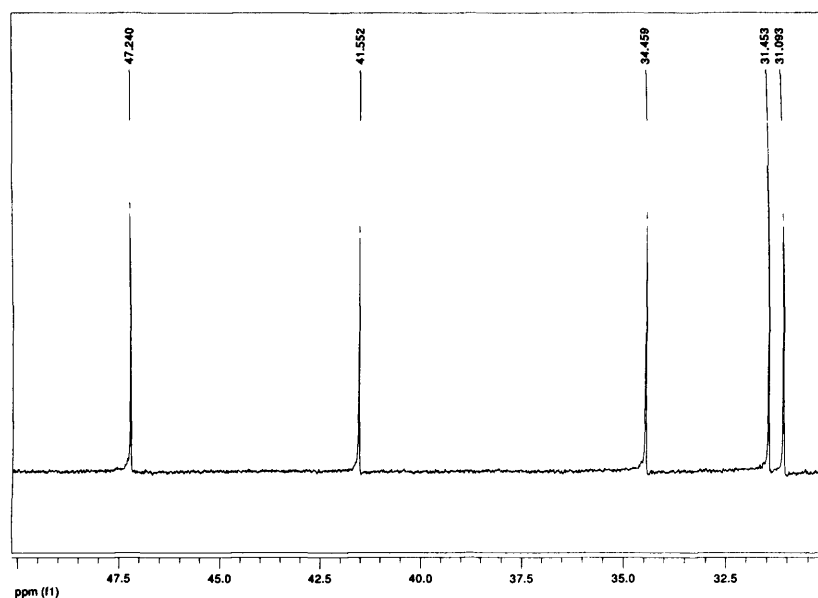


Scheme 84

The ^{13}C NMR spectrum from the ring-closure reaction derived from racemic menthyl acetate showed clear doubling of peaks. **Figure 5** shows the region from 50 ppm – 30 ppm of the ^{13}C NMR spectra of products **149** and **150**. It can clearly be seen from the

peaks at 47.2, 41.5 and 31.4 that for compound **149** no epimerisation has occurred, as the same peaks for compound **150** are doubled. There is no reason why compound **147** should behave differently to the other alkylidenepyrrolidines synthesised, so we are confident that no racemisation is occurring with any of the compounds synthesised.

*Expanded portion of the ^{13}C NMR spectrum for compound **149**.*



*Expanded portion of the ^{13}C NMR spectrum for compound **150**.*

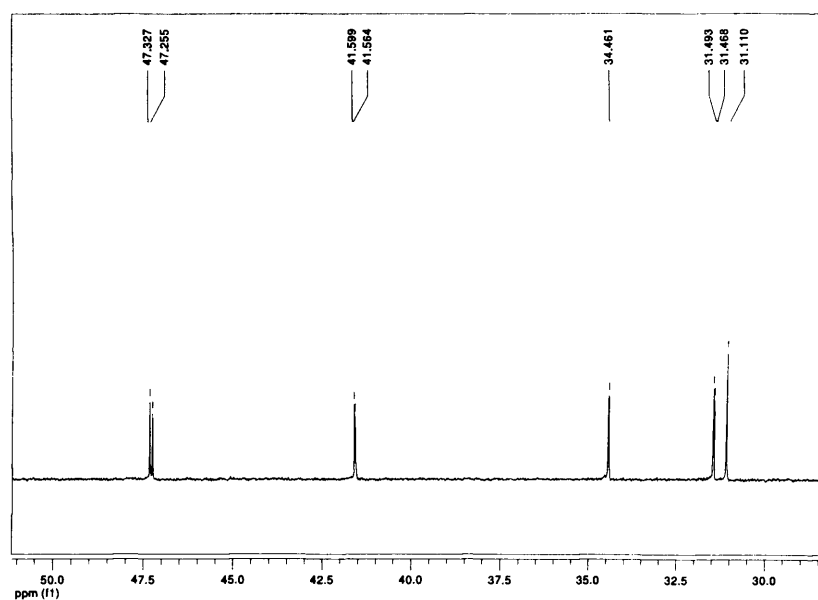
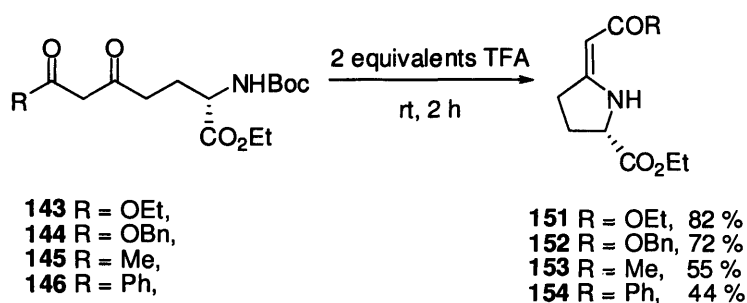


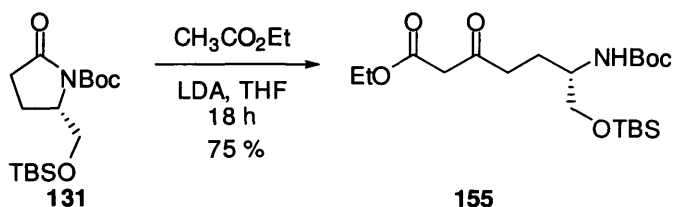
Figure 5

Using the same conditions all other products from the ring-opening step **143**, **144**, **145** and **146** were cyclised using 2 equivalents of trifluoroacetic acid. Both other acetates proceeded with yields and purity in line with that previously observed. Unfortunately cyclisation of compounds **145** and **146** proceeded with lower yields than expected, although the purity was as high as previously seen (Scheme 85).



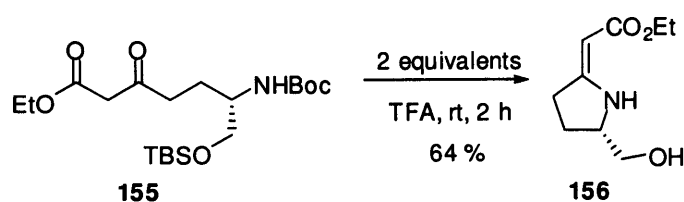
Scheme 85

The final series of reactions investigated used the TBS protected lactam **131**. As results had been consistent throughout all examples, ethyl acetate was again chosen for the first reaction (Scheme 86). As shown below this reaction progressed as expected, although the yields were slightly lower than compared to previous reactions.



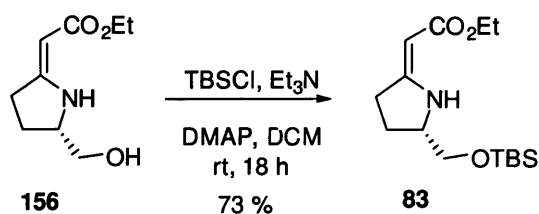
Scheme 86

When compound **155** was reacted under the same cyclisation conditions as above, both the Boc and the TBS groups were removed to give the deprotected alkylidenepyrrolidine **156** (Scheme 87).



Scheme 87

It was then possible to reprotect the hydroxyl group to give the alkylidenepyrrolidine **83** (Scheme 88), that had previously been synthesised through the alternative Eschenmoser sulphide contraction method (Scheme 50).



Scheme 88

Over the course of the investigation there were instances in which the ring-opening step failed to produce products of sufficient purity or yields to make them a viable substrate. These included the highly stabilised anions derived from nitromethane and methyldiphenylphosphine oxide.

As described in the introduction to this chapter, when a substituent is present on nitrogen, the (*E*) isomer will generally be formed for steric reasons. However, if there is no substitution on the nitrogen, the (*Z*) isomer is favoured, as in this configuration hydrogen bonding can take place between the carbonyl and the NH. This trend was supported by spectroscopic information gained during the course of these investigations. The NH peak in the ¹H NMR spectra of alkylidenepyrrolidines is broad and in the region of 8 ppm, both of which are indicative of hydrogen bonding. Also the IR spectra show a broad peak around 3370 cm⁻¹, again indicating hydrogen bonding of the NH.

Unfortunately it is not possible to determine the double-bond geometry using nOe studies, since a mutual enhancement of the alkene *CH* and the *NH* peaks can be attributed to exchange of these protons. It is expected that the *N*-protected compound **137** was isolated as the (*E*) isomer and upon deprotection isomerised to the (*Z*) isomer.

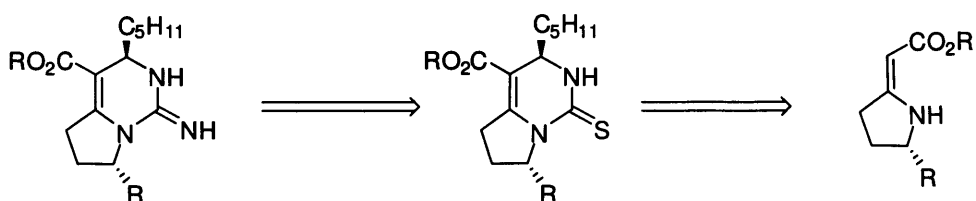
With all these factors taken into account, the method provides a useful synthesis of chiral alkylidenepyrrolidines, in overall yields of around 50 % compared with the previously reported yields in the range of 20 %, from commercially available starting materials, successfully carried out on scales of up to 5 g with little or no need for chromatography.

Chapter 4

Investigations into the Three-Component Coupling Reaction

4.1 Introduction

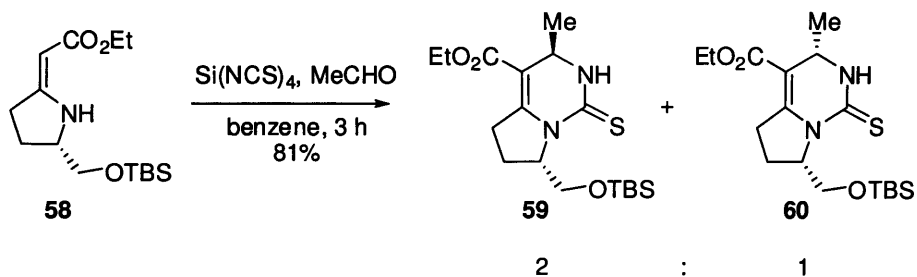
The retrosynthetic **Scheme 89** below shows a convenient short way of converting an alkylidenepyrrrolidine into a bicyclic guanidine.



Scheme 89

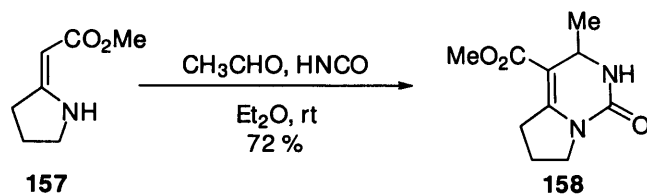
This method would allow access to both the left and right-hand sides of batzelladine A, and with small adjustments it is easy to envisage being able to form all of the bicyclic and tricyclic guanidines from the batzelladine alkaloid family.

Previous studies within the group were directed to the formation of the left-hand side of batzelladine A (**23**). Shown in **Scheme 90** is the formation of the guanidine precursors **59** and **60** from alkylidenepyrrrolidine **58**. It is important to note that the reaction proceeded cleanly and the diastereoisomers were easily separated; however, at this point there was still some uncertainty about the relative stereochemistry of the products.



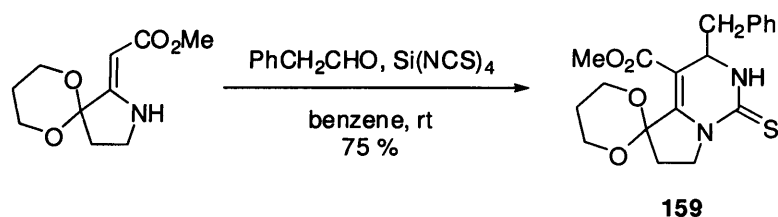
Scheme 90

Kishi *et al.* first reported this type of three-component coupling in 1977 during their synthesis of Saxitoxin. In this transformation, alkyldenepyrrolidine **157** was converted into the bicyclic urea **158** by reaction with isocyanic acid and acetaldehyde (**Scheme 91**).⁶⁸



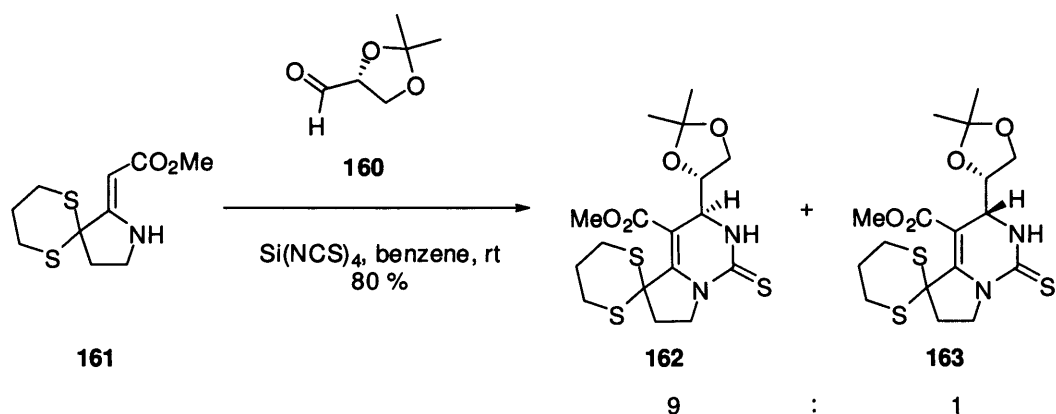
Scheme 91

This was later modified to use silicon tetrakisothiocyanate to produce the thiourea **159** as shown in **Scheme 92**.⁶⁹



Scheme 92

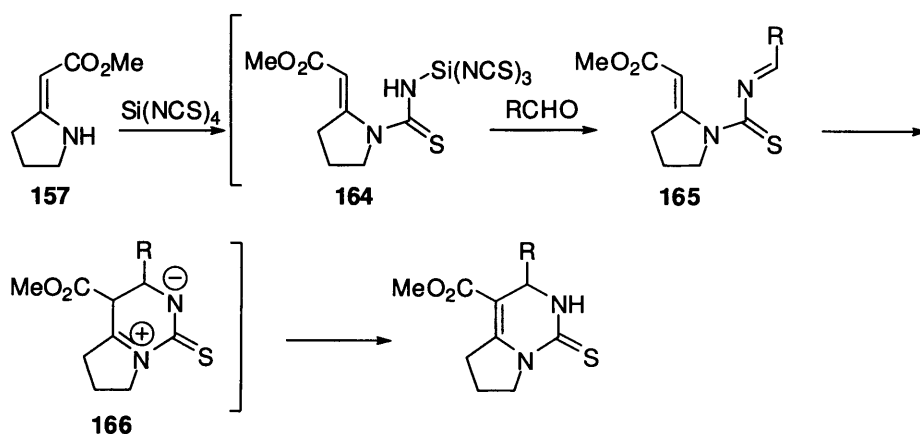
In his final modification to the reaction, the chiral aldehyde **160** was used to influence the stereoselectivity of the reaction of alkyldenepyrrolidine **161** to the thiourea **162** and its diastereoisomer **163**. The selectivity achieved was 9:1 in favour of the opposite stereochemistry to the natural product. Using the other enantiomer of the aldehyde would produce the correct natural product stereochemistry (**Scheme 93**).⁷⁰



Scheme 93

For the purposes of our batzelladine alkaloid synthesis the diastereoselectivity of this three component coupling is disappointing. A detailed understanding of the reaction mechanism would be useful in guiding further studies

To date, two mechanisms have been postulated for the formation of the bicyclic thiourea. The first was proposed by Kishi *et al.* The first step of the reaction would be an *N*-acylation with the isothiocyanate to give the thiourea **164**. This thiourea would then condense with the aldehyde to form the imine **165**. The imine could then cyclise with the enamine to form the cyclic thiourea **166** (**Scheme 94**).



Scheme 94

If a chiral aldehyde is used then stereocontrol of the cyclisation of **165** to **166** would be expected. This is best rationalised by the Felkin-Anh model,^{70b} using a Newman projection for the intermediate **165** it can clearly be seen that one conformation allows for an unhindered approach along the Burgi-Dunitz angle.

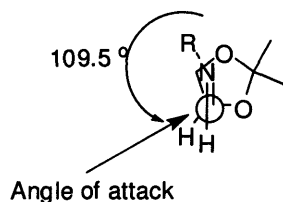
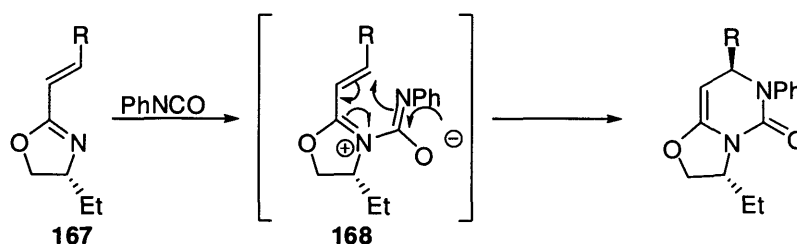


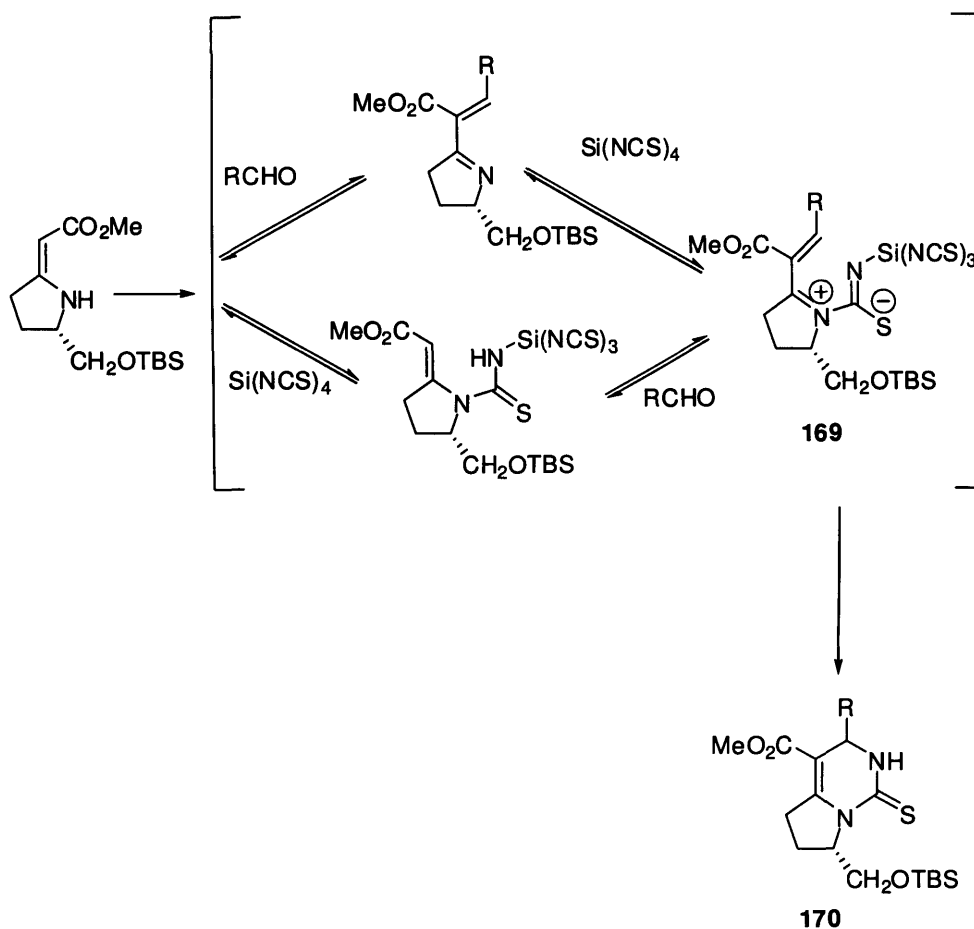
Figure 6 Felkin-Anh model of compound **165** showing the Burgi-Dunitz angle.

A related reaction shows an alternative mechanism, suggested by the Elliott group²² showed a similar reaction pathway to the formal *aza*-Diels-Alder reaction observed when an oxazoline **167** is reacted with an isocyanate (**Scheme 95**).²⁵ In examples of this type, total stereocontrol is achieved.



Scheme 95

For the case of the three component coupling, there are two possible pathways to form the intermediate **169** which is similar to the intermediate **168** shown in **Scheme 95**. Ring closure could then proceed via the same mechanism giving the desired thiourea **170** (**Scheme 96**).



Scheme 96

Based on previous results, we would expect the cyclisation of intermediate **169** to form **170** to proceed with complete stereocontrol. As the stereoselectivity is only moderate, this mechanism would appear unlikely, although if both double bond isomers of **169** were formed, selectivity of the product would be affected and potentially lowered.

Unfortunately neither of these proposed mechanisms has been backed up by any rigorous experimental data. It is our hope that the mechanism of the reaction can be fully determined and the stereochemical outcome controlled.

First of all we need to consider the reactivity of alkylidenepyrrrolidines on carbon or nitrogen and which the most likely site for reaction is.

4.2 Alkylations and Acylations of Alkylidenepyrrrolidines

Over the years, alkylidenepyrrrolidines have been finding more and more applications in synthetic chemistry. A great deal of work with alkylidenepyrrrolidines centres on their ambident nucleophilicity and which site is the more reactive under certain conditions. **Figure 7** shows the two nucleophilic sites on the simple alkylidenepyrrrolidine **157**. From here, reactions at either site will be referred to as either reaction on *nitrogen* or *carbon*.

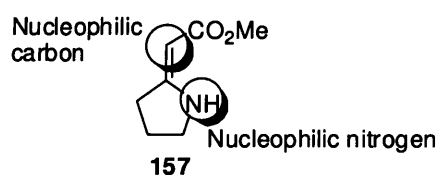
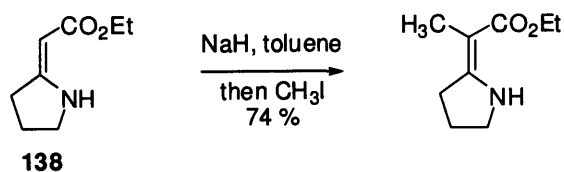


Figure 7

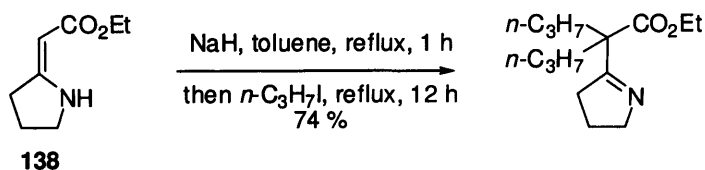
There are thought to be three main factors that dictate the regioselectivity of electrophilic attack: first, the nature of the electrophile, how reactive it is and how stable the products are; second are the conditions of the reaction, *i.e.* whether a base is used and how strong that base is also at what temperature the reaction is carried out at; third is the double bond geometry of the alkylidenepyrrrolidine, although there is not enough published material to make any firm conclusions about this particular point.

The simplest of these reactions is shown in **Scheme 97** where an alkylidenepyrrrolidine **138** containing a single electron-withdrawing group is alkylated with iodomethane.⁷¹ Under these conditions, reaction takes place on carbon.



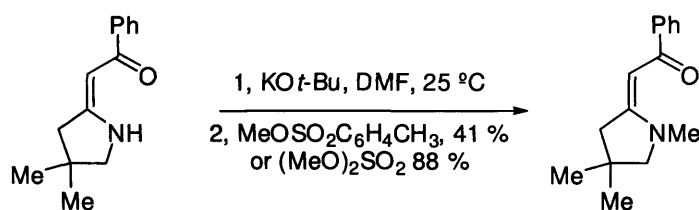
Scheme 97

It is possible to get a second alkylation on the same position by heating the sodium salt of the alkyldenepyrrolidine with an alkyl halide at high temperatures (**Scheme 98**).⁷²



Scheme 98

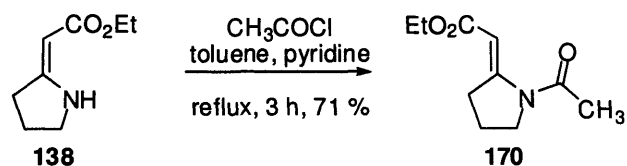
For alkylation on nitrogen, it is necessary to change the electrophile; in this case the electrophiles of choice are sulphates and sulphonates which give good yields of the *N*-alkylated compound (**Scheme 99**).⁷³



Scheme 99

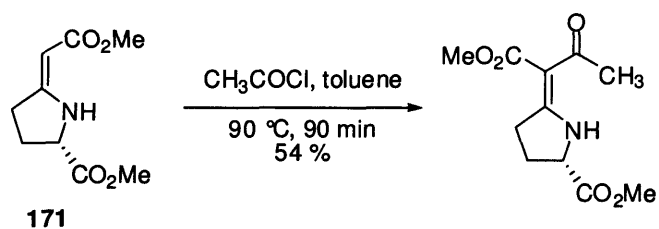
Acylation of alkyldenepyrrolidines is more sensitive to reaction conditions and steric effects than alkylations. An example of this is the reaction of alkyldenepyrrolidine **138**

with acetyl chloride where the reaction takes place on *nitrogen* to produce a good yield of compound **170** (Scheme 100).⁷⁴



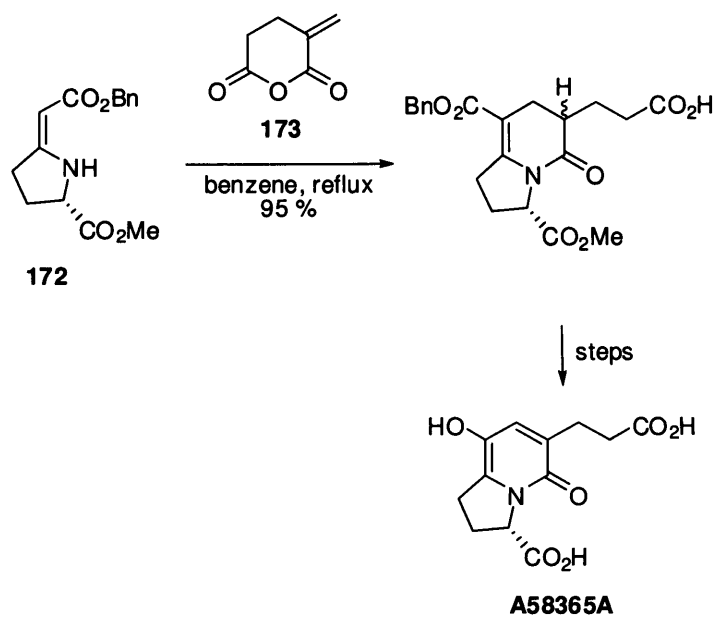
Scheme 100

When the similar reaction was carried out on the slightly more hindered alkylidenepyrrolidine **171** the reaction was solely on *carbon* (Scheme 101).⁷⁵



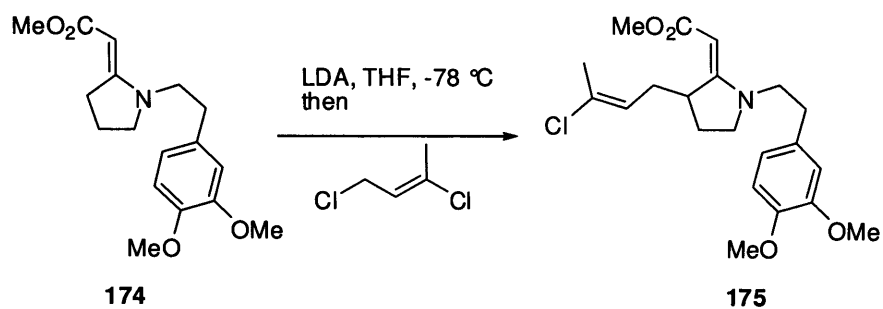
Scheme 101

Using these basic principles, a range of additional functionalities can be added to the initial alkylidenepyrrolidine to produce both structurally interesting compounds and natural products. Scheme 102 shows reaction of alkylidenepyrrolidine **172** with the anhydride **173** in the preparation of angiotensin-converting enzyme inhibitor A58365A.⁷⁶



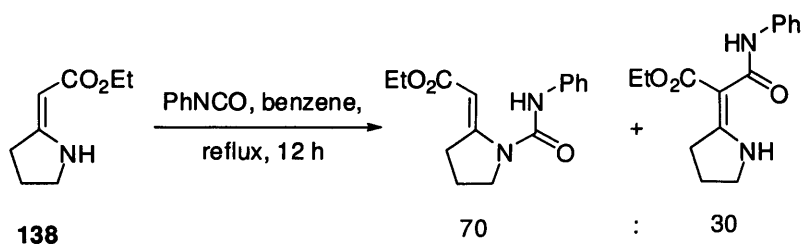
Scheme 102

It is also possible to get reaction to occur at the 3-position of the pyrrolidine ring, although this is not generally observed for *N*-unsubstituted alkylidenepyrrrolidines. Alkylidenepyrrrolidine **174** in the presence of a strong base, *e.g.* lithium diisopropylamide, and a good electrophile underwent reaction to form the new alkylidenepyrrrolidine **175** (**Scheme 103**).⁷⁷



Scheme 103

The three-component coupling reaction used for the batzelladine synthesis features an acylation-type reaction using an isothiocyanate. If we assume that the initial reaction is between the alkylidenepyrrolidine and the isothiocyanate, then this must be an *N*-acylation. This seemed likely according to the work of Tronche. In their, work a range of isocyanates were reported to react predominantly on *nitrogen* (70 : 30 regioselectivity) (Scheme 104).⁷⁸



Scheme 104

However when this was repeated within the group, the results differed significantly with those reported. Results showed the majority of isocyanates reacting preferentially on *carbon* in all but two instances (Table 1 entries 5 and 6) where a 1 : 1 and 1 : 2 ratio of products was formed, Table 1 shows a summary of results obtained from these studies.⁷⁹

Entry	Heterocumulene	Conditions	Ratio C:N acylation
1	PhNCO	CHCl ₃ , 25 °C, 18 h	2.1:1
2	PhNCO	CHCl ₃ , reflux, 2 h	3.4:1
3	PhNCO	benzene, reflux, 2 h	5.2:1
4	PhNCO	THF, reflux, 2 h	7:1
5	BnNCO	CHCl ₃ , 25 °C, 18 h	1:2
6	BnNCO	CHCl ₃ , reflux, 20 h	1:1
7	<i>n</i> -BuNCO	Pyridine, 100 °C, 65 h	2.3:1
8	4-MeC ₆ H ₄ NCO	CHCl ₃ , reflux, 2 h	2.3:1
9	TsNCO	CHCl ₃ , 25 °C, 2 h	1:0
10	Cl ₃ CCONCO	CHCl ₃ , 25 °C, 18 h	1:0
11	PhNCS	CHCl ₃ , reflux, 18 h	1:0
12	PHNCS	CHCl ₃ , 25 °C, 48 h.	0:0
13	BnNCS	CHCl ₃ , reflux, 18 h	1:0
14	<i>n</i> -BuNCS	Pyridine, 100 °C, 46 h	1:0

Table 1

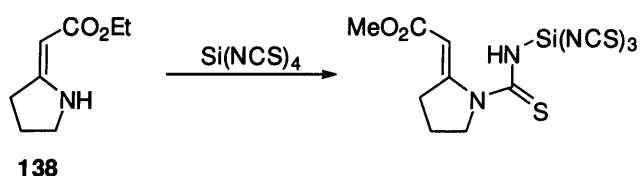
For the purpose of our investigations the important results shown are those of the isothiocyanates (**Table 1** entries 11 – 14). In none of these cases was evidence of reaction on *nitrogen* observed. It is unlikely that either C or N acylation is occurring in the much milder conditions used for the three-component coupling reaction.

4.3 The Three-Component Coupling Reaction

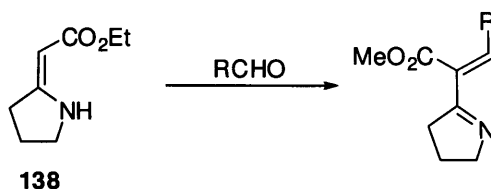
4.3.1 Mechanistic Studies on the Three-Component Coupling Reaction

Based on the results described above, it seemed likely that annulation occurs by initial attack on *carbon*. This would suggest that both mechanisms described at the start of the chapter are in fact incorrect, and a better understanding of the reaction is needed.

In the mechanisms described above, an intermediate is formed either by reaction of the isothiocyanate and the lactam (Scheme 105), or from the lactam and the aldehyde (Scheme 106).



Scheme 105

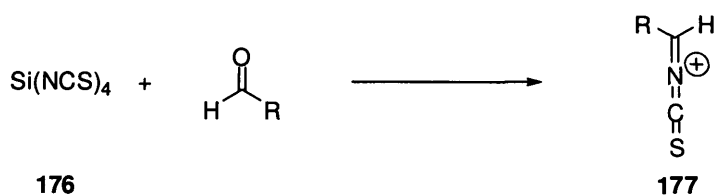


Scheme 106

It was hoped that if either of these reactions occurs, we would be able to monitor their progress by carrying out the reactions in an NMR tube and recording spectra at regular intervals.

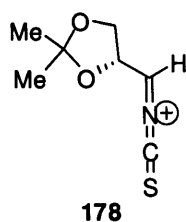
As already mentioned it was thought the most likely site for initial reaction would be on *carbon*. ^1H and ^{13}C NMR spectra were obtained every ten minutes; however, no changes were observed when either silicon tetrakisothiocyanate or the aldehyde was mixed with the lactam. If the third reactant was added to either of the mixtures, reaction proceeded to the bicyclic product within the time taken to acquire the spectrum.

Under reaction conditions reported by Kishi, the isothiocyanate is stirred with the aldehyde for a period of 30 minutes. It is possible that this produces a reactive intermediate (**Scheme 109**). This reaction was repeated in an NMR tube using benzaldehyde and silicon tetrakisothiocyanate **176** in deuterated benzene. ^1H and ^{13}C NMR spectra were obtained every 10 minutes for 1 hour. Over this time a broadening of the aldehyde *CH* peak was observed in the ^1H NMR spectrum but no change was observed in the ^{13}C NMR spectrum. When the experiment was repeated using deuterated chloroform as the solvent, no changes were observed in any of the spectra obtained. Unfortunately the isothiocyanate *C* was not observable on the spectrum.

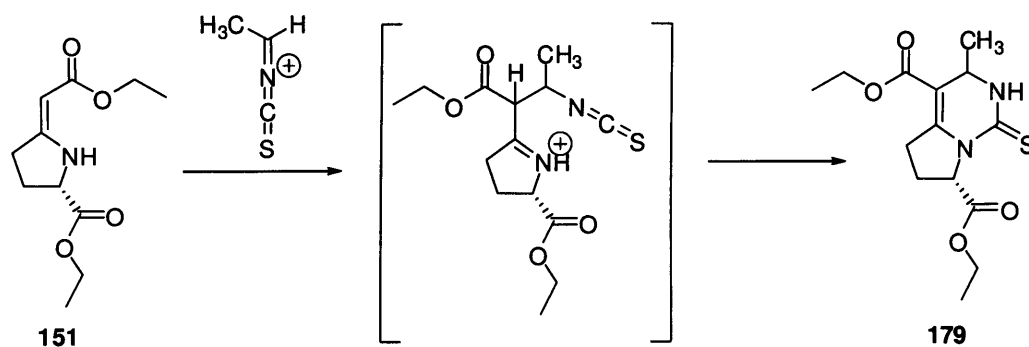


Scheme 107

Although these results proved inconclusive, the mechanism shown in **Scheme 107** still appeared to be the most likely. The product **177** would be a good electrophile and should be able to react with the alkylidenepyrrrolidine, presumably on the *carbon*. This mechanism would still be consistent with the results reported by Kishi using the chiral aldehyde **158**. Since addition of the alkylidenepyrrrolidine to the chiral intermediate **178** would give the same stereochemistry as that reported by way of the same Felkin-Anh transition state.



We therefore feel that the most likely pathway for the three-component coupling reaction is shown in **Scheme 108**. This would explain why when a chiral aldehyde is used the selectivity would be higher than when the chirality is induced from the chiral side chain shown on the alkylidenepyrrrolidine **151**.



Scheme 108

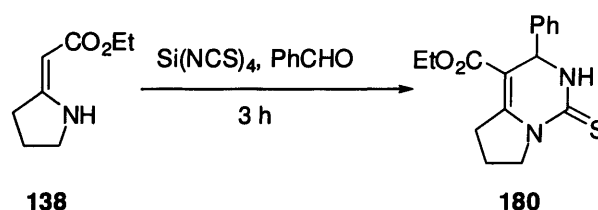
4.3.2 Synthetic Studies on the Three-Component Coupling Reaction

Although the three-component coupling reaction is reliable, purification is not straightforward. The low levels of diastereocontrol are also far from ideal. Finally, while benzene had been shown to be a good solvent for the reaction, its toxicity and hygroscopy are undesirable.

We therefore sought to optimise the reaction conditions and purification method initially, with the intention of optimising the levels of stereocontrol by investigation of a range of alkylidenepyrrrolidine substrates as prepared in Chapter 3.

When flash chromatography was carried out on crude reaction mixtures, yields were irreproducible from one reaction to the next. It was also noted that a dark purple band formed on the silica gel during chromatography, indicating that a reaction was occurring. When this band was isolated it showed some peaks from the ^1H NMR spectrum consistent with the desired product but was not the desired bicyclic thiourea.

Therefore, initial optimisation reactions were carried out by assessment of the crude reaction mixtures. At this point the achiral substrate **138** was used to optimise the conditions. A number of solvents were evaluated, in the hope that benzene could be replaced in this reaction (**Scheme 109**).



Solvent	Crude Yield of compound 180
Benzene	78 %
Toluene	76 %
THF	100 %
Dichloromethane	79 %
Chloroform	76 %

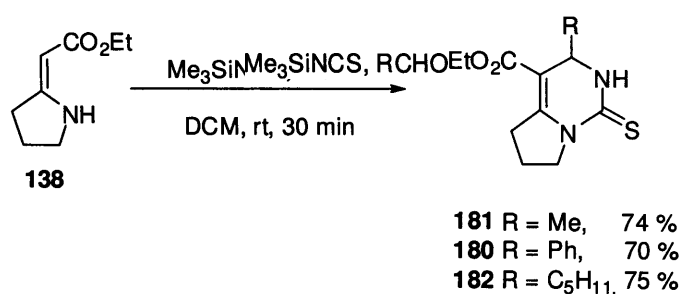
Scheme 109

Various common solvents were used for the evaluation. These included toluene, tetrahydrofuran, chloroform and dichloromethane. In general there was little or no change with the varying solvents that could not be attributed to experimental error. Only with tetrahydrofuran was the purity of the crude product significantly lower. Overall the solvent of choice is dichloromethane, due to its low toxicity, low boiling point, and ease of drying and low freezing point.

When the reaction is carried out, a silicon by-product is formed that is insoluble in all of the tested solvents listed above. It was postulated that some product might be lost by the formation of this unknown product. It was known that silicon tetraisothiocyanate degrades on contact with moisture; this degradation product is also insoluble in water. However when mixed with a dilute aqueous base, it degrades to water-soluble compounds. A simple test showed that the bicyclic urea was unaffected by washing with a 0.5 M sodium hydroxide solution.

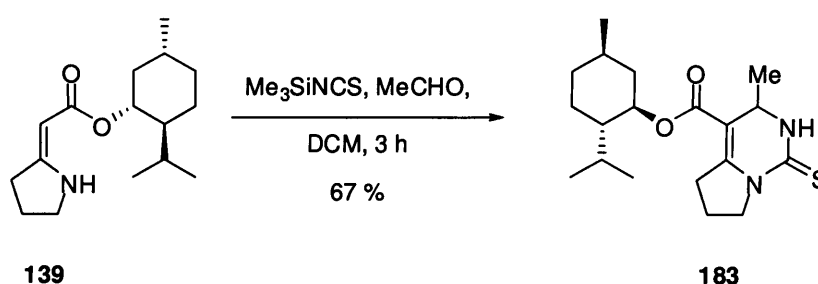
As a pleasing side-effect, after the crude product was washed with sodium hydroxide the brightly coloured band was not observed when flash chromatography on silica gel was carried out. At this point, the isolated purified yields were reproducible.

Silicon tetraisothiocyanate is only sparingly soluble in dichloromethane. We therefore considered alternative reagents, the most obvious of which is trimethylsilyl isothiocyanate. The use of this reagent would allow us to determine whether more than one isothiocyanate is required for the reaction. The first reaction was carried out using a one-to-one molar ratio of all reactants. It was pleasing to see that the yield and purity of the reaction was as good as any achieved using silicon tetraisothiocyanate. From a mechanistic point this shows that only one isothiocyanate group is required. Two other aldehydes were tested using this method to assess the versatility of the reaction (**Scheme 110**). Trimethylsilyl isothiocyanate has the additional advantage of being commercially available.



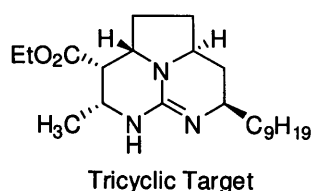
Scheme 110

To date, all diastereoselective coupling reactions carried out within our group had the directing group on the 5-position of the pyrrolidine ring. If a chiral alkylidenepyrrrolidine such as **139** where the chiral group distant from the ring was used, it might be able to influence the stereocontrol of the new stereogenic centre formed in the trimolecular annulation (**Scheme 111**). However, it was clear from the ^{13}C NMR spectrum of the crude reaction mixture, which showed equal intensity of the doubled peaks, that little or no stereoselectivity had been achieved. As the yield of the reaction is still high, it could still be a viable way of making the left-hand side bicyclic portions, as with work the diastereoisomers could be separated.



Scheme 111

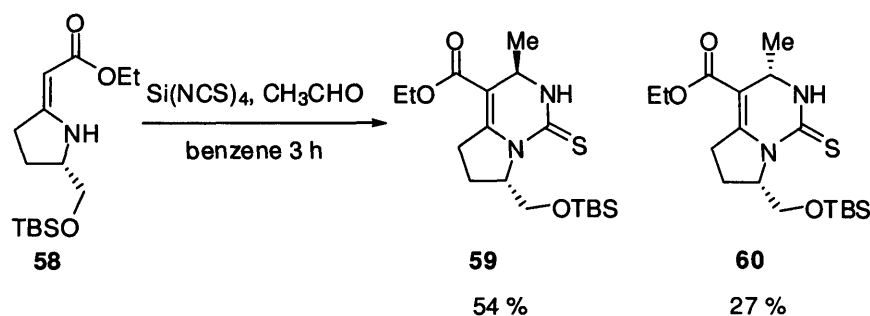
As mentioned earlier, it is necessary to have a chiral side chain on the alkylidenepyrrrolidine for the formation of the tricyclic portions of the batzelladine alkaloids (**Figure 8**). The most accessible chiral alkylidenepyrrrolidine synthesised (**151**) was used to investigate further alterations to the annulation.



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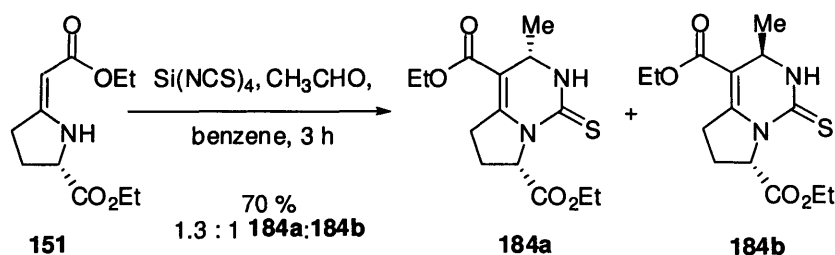
Figure 8

It was already known that some selectivity was observed in the trimolecular annulation using the similar alkylidenepyrrrolidine **58** (Scheme 114).



Scheme 112

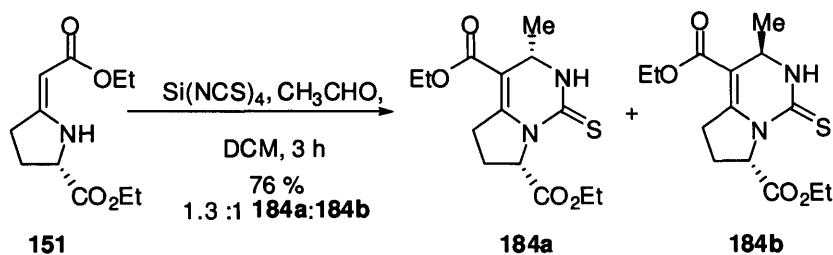
This reaction was repeated changing only the alkylidenepyrrrolidine to **151** (Scheme 113). The stereochemistry shown is based on assignments as discussed in section 5.4.



Scheme 113

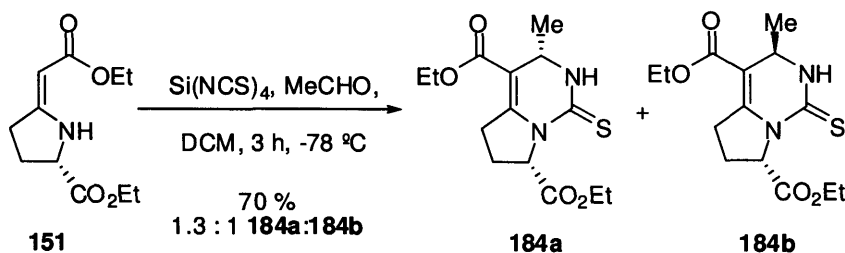
Two important things were concluded from this reaction. The first was that the stereoselectivity was slightly lower than seen in **Scheme 114**. Again this was determined from ^1H and ^{13}C NMR spectra of the crude reaction mixtures. Secondly, the diastereoisomers formed could not be easily separated by flash chromatography on silica gel. However, this substrate was used for further studies, as any change in stereoselectivity would still be identifiable.

The first change was to switch the solvent to dichloromethane, (**Scheme 114**). The reaction proceeded as expected with a very similar diastereoselectivity and yield to that when benzene was used.



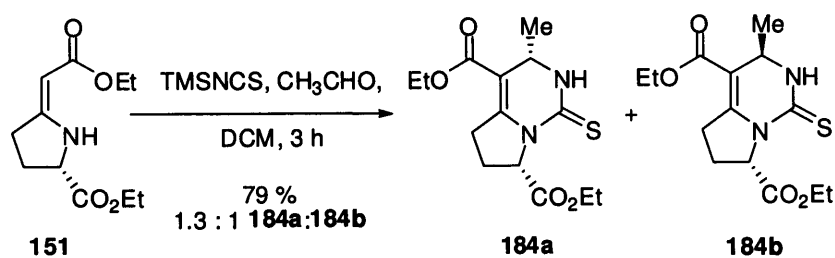
Scheme 114

As the reaction was being carried out over 3 hours it was hoped that by cooling the reaction, the stereoselectivity could be improved. By using dichloromethane as the solvent it was possible to cool the reaction to $-78\text{ }^\circ\text{C}$ (**Scheme 115**). This was done for the entire duration of the reaction including the aqueous quench. However, once again no difference was observed from the standard. This did indicate that the reaction was most probably occurring a lot quicker than the 3 hours originally used.



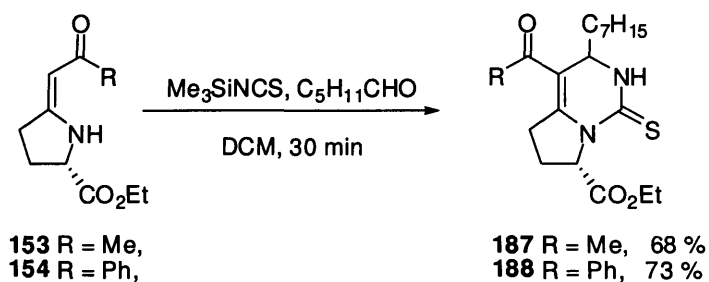
Scheme 115

Thirdly the switch to the alternative isothiocyanate, trimethylsilyl isothiocyanate was made (**Scheme 116**). Again yields and stereoselectivity were within experimental errors of previous reactions.



Scheme 116

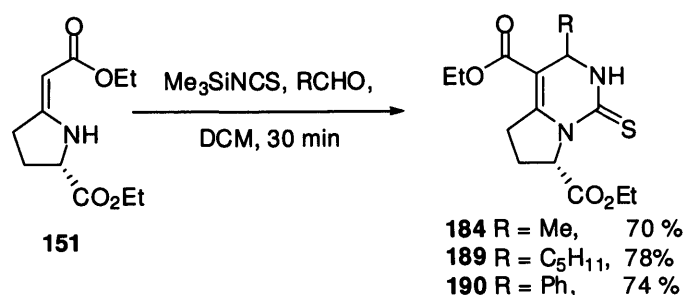
Now that an improved synthetic method had been finalised, the versatility of the reaction was investigated. To date, all three-component coupling reactions had been carried out with an ester group as the electron-withdrawing group on the alkylidenepyrrrolidine. As alkylidenepyrrrolidines **153** and **154** had already been synthesised, they became obvious candidates for the three-component coupling reaction (**Scheme 117**).



Scheme 117

The yields were again in line with previous experiments and as expected the stereoselectivity was unaffected.

As well as the different alkylidenepyrrrolidines a number of aldehydes had been used and no difference had been seen in the selectivity though yields were all consistent (**Scheme 118**).



Scheme 118

The reaction with acetaldehyde proceeded in line as that for hexanal. When benzaldehyde was used differences in the ¹H NMR spectra were observed. When the alkyl aldehydes were used the peak (identified as a double doublet) corresponding to the proton on the 5-position of the major isomer was consistently downfield of the minor isomer (identified as a doublet). In the case of benzaldehyde the peak for the major isomer (identified as a doublet) was upfield of the minor (identified as a double doublet). It is uncertain whether this is due to a switch in selectivity or just an effect of the aryl group. It is possible that the aryl group could be interacting during the initial annulation reaction, but no evidence is available at present to support or disprove this theory. Until a method to determine the absolute stereochemistry of the products becomes available it is impossible to tell which isomer is indeed being favoured from these reactions.

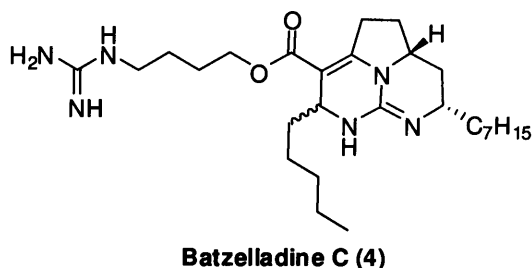
Although this work has not led to a full understanding of the mechanism of the trimolecular annulation reaction, it has shown a versatile and useful way of forming bicyclic thioureas, from a range of chiral and non-chiral alkyldenepyrrolidines without racemisation and with a good degree of stereocontrol.

Chapter 5

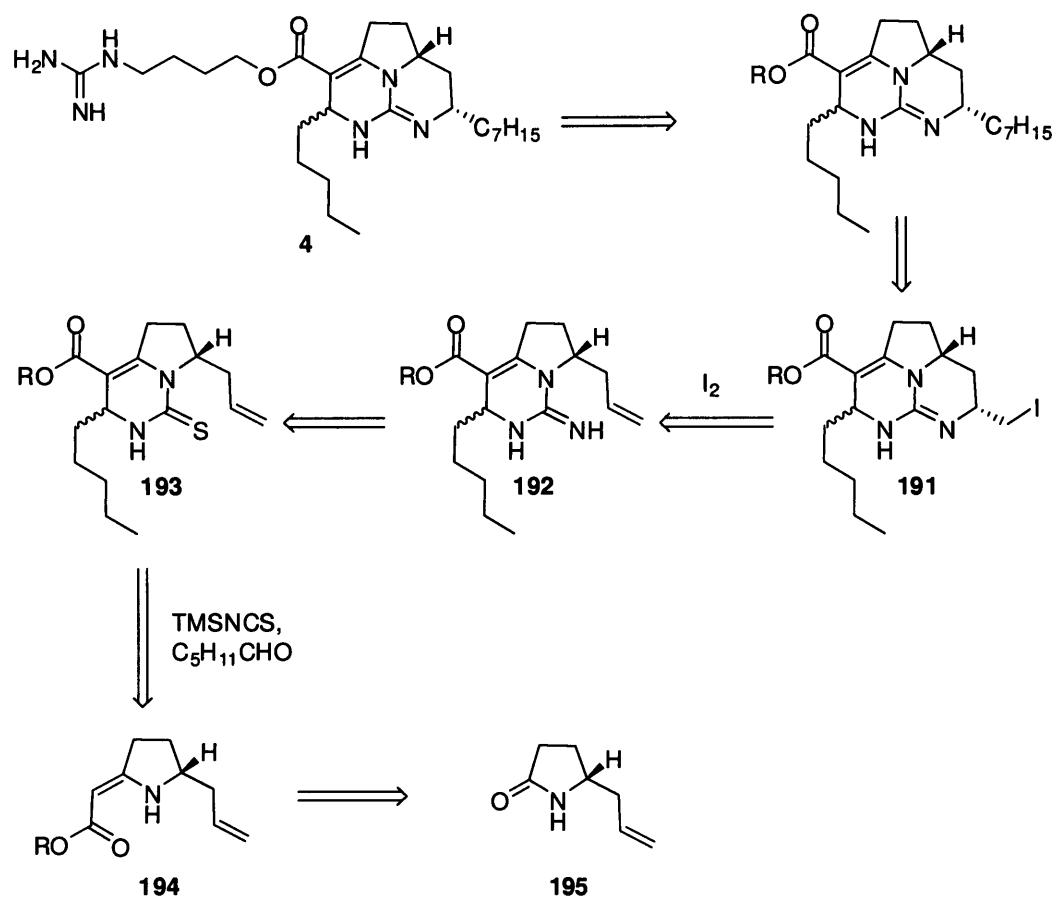
Synthesis of the Tricyclic Guanidine core of Batzelladine C

5.1 Introduction

As mentioned in Chapter 1, the batzelladine alkaloids have proven challenging targets for the past decade and to date a number are still to be synthesised. batzelladine C (**4**) is one of the family that has to date not been synthesised. It contains a single tricyclic guanidine unit with three side chains. In the original isolation and structural elucidation the stereochemistry of the heptyl carbon chain was confirmed but the authors were not able to identify the relative configuration of the pentyl chain. Total synthesis is essential to finally determine the relative and absolute stereochemistry of this alkaloid. This chapter details our investigations into the total synthesis of batzelladine C.



By utilising the methodology detailed in chapters 3 and 4 it was hoped that a short asymmetric synthesis of this challenging natural product could be accomplished. **Scheme 119** shows a retrosynthetic pathway from the natural product to a simple alkylidenepyrrolidine.



Scheme 119

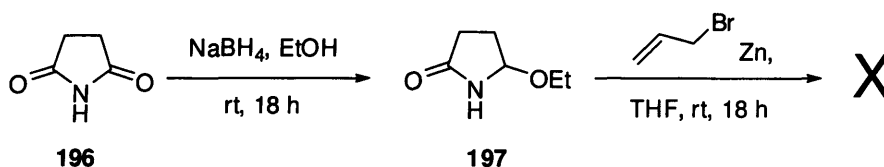
There are two key steps to this reaction sequence where the new stereogenic centres are formed. The first is the trimolecular annulation reaction to form **193**, which has been covered in the previous chapter. The second is the iodocyclisation step from the bicyclic guanidine **192** to the bicyclic guanidine **191**.

5.2 New Synthetic Strategies

From the methodology already carried out on alkylidenepyrrolidines and the trimolecular annulation, it was known that we could make the central aspect of the guanidine core, and that this could be achieved from a range of pyrrolidinones.

The obvious starting material for this sequence would be 5-allylpyrrolidin-2-one **195**. Two literature methods for the formation of this compound were evaluated. Both methods start from the inexpensive and commercially-available succinimide **196**.

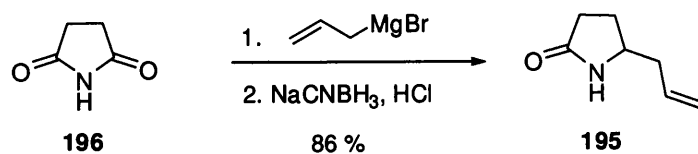
The first method by Speckamp *et al.*⁸⁰ starts with the reduction of succinimide to lactam **197**, which is then coupled with an organozinc reagent to give the desired product **195** (Scheme 120).⁸¹



Scheme 120

The first step of the reaction proceeded according to the literature; however, in our hands the organozinc coupling step was unsuccessful.

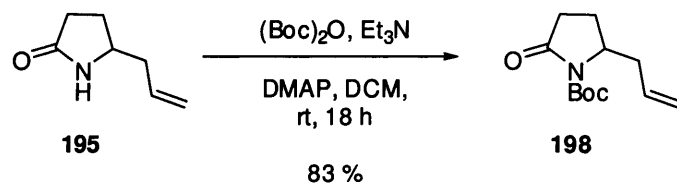
The second method, by Hiemstra's group, again starts with succinimide **196**. Addition of a Grignard reagent was immediately followed by reduction to give lactam **195** (Scheme 121).⁸²



Scheme 121

This reaction worked well, and provided the desired compound **195** in excellent yield in multi-gram quantities (up to 9 g).

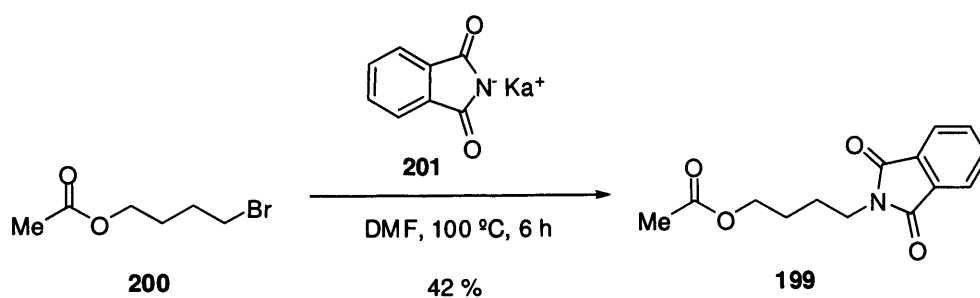
Using the methodology developed in Chapter 3, the lactam **195** was *N*-protected as the Boc carbamate providing the activated lactam **198** ready for alkylidenepyrrrolidine synthesis (**Scheme 122**).



Scheme 122

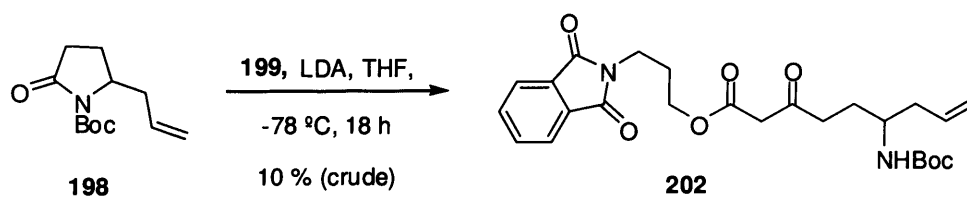
Again it was pleasing to see that this reaction could be carried out on a large scale (up to 5 g).

A number of different acetates could have been used for the formation of the alkylidenepyrrrolidine. Potentially the most useful for the synthetic target is the phthalimide protected acetate **199**, synthesised from 4-bromobutyl acetate **200** and potassium phthalimide **201** (**Scheme 123**).



Scheme 123

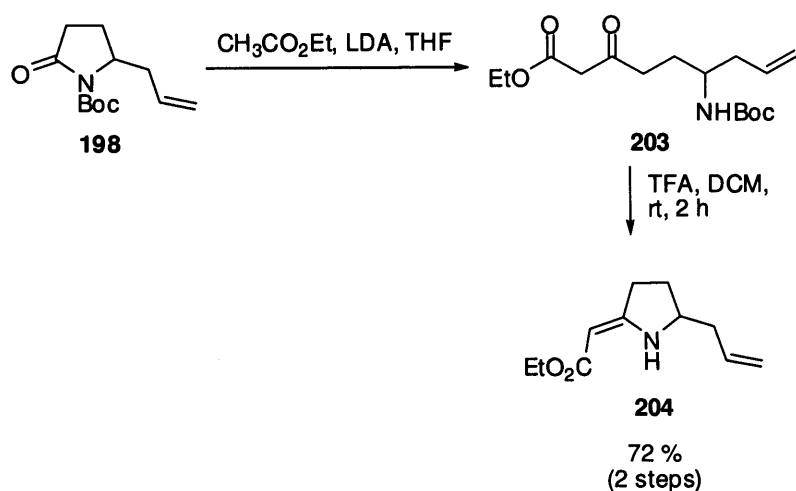
The acetate **199** was reacted under the standard conditions detailed in Chapter 3 for the ring-opening step (Scheme 124).



Scheme 124

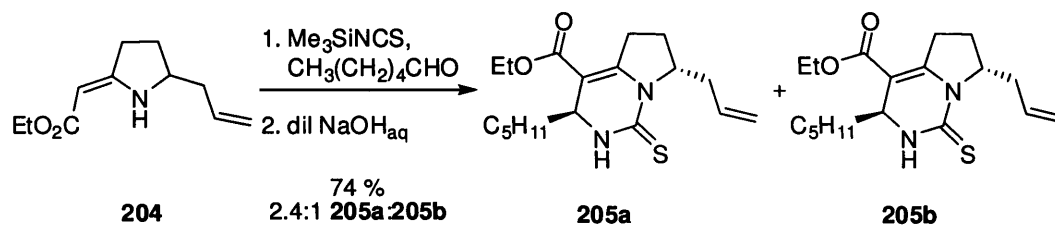
Unfortunately, yields for this step were very low, and combined with the yields for the formation of the acetate it was decided that this method was not feasible to produce the required amounts of starting alkylidenepyrrolidine required for this investigation.

The highest yielding acetate used to date was ethyl acetate, although this would require further manipulation later on in the synthesis it was considered to be a viable alternative. Using the standard method the alkylidenepyrrolidine **204** was synthesised in good yield (Scheme 125).



Scheme 125

The three-component coupling reaction, to form the bicyclic thioureas **205a** and **205b**, was carried out using the revised method of trimethylsilyl isothiocyanate and hexanal for a period of 30 minutes, then quenched with aqueous dilute sodium hydroxide, followed by a flush through a plug of silica gel (Scheme 126).



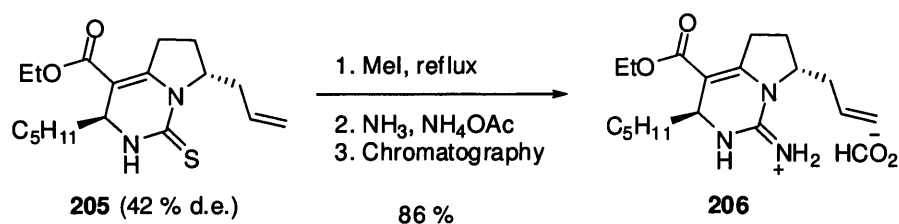
Scheme 126

Again the reaction proceeded with a good yield and purity. It was also pleasing to see that the diastereomeric ratio was in the region of 2.4 : 1. The assignment of the relative stereochemistry of these compounds is discussed in section 5.4. It was decided at this point to carry the mixture of diastereoisomers through the rest of the sequence. This was



primarily due to problems encountered with flash chromatography on previous thioureas.

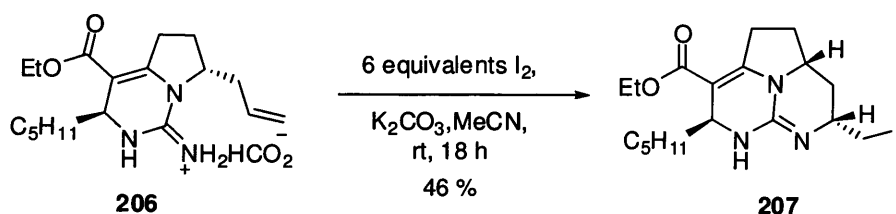
The bicyclic guanidine **206** was then formed with the conditions used previously within the Elliott group. This method does not involve isolating the *S*-methylated compound produced by the reaction of methyl iodide and the thiourea (**Scheme 127**).



Scheme 127

The reaction proceeded as expected with a high yield obtained. Purification of compound **206** was achieved by flash chromatography using a mobile phase of dichloromethane / methanol / water / formic acid. This results in isolation of the formate salt of the guanidine. However, there was no separation of diastereoisomers by chromatography. Due to this, full characterisation was not obtained on this compound.

The iodocyclisation to form the tricyclic guanidine **207** was carried out using a large excess of iodine in the presence of potassium carbonate for a period of 18 hours, (**Scheme 128**).



Scheme 128

After chromatography on silica gel, a single diastereoisomer was obtained in 46 % yield. No other product was isolated with sufficient purity for identification. In view of the yield, it is safe to conclude that this product is derived from the major isomer of the three-component coupling reaction which had a selectivity of 2.4 : 1. A series of NMR experiments were carried out to determine the structure and stereochemistry of the product. These included standard ^1H and ^{13}C NMR spectra, and gradient NOESY and gradient $^1\text{H} - ^1\text{H}$ COSY 2-dimensional spectra.

Initial structural determination was carried out by comparison of ^1H NMR spectrum of **207** with that of batzelladine C.¹ These spectra are shown in **Figure 9** with proton assignments according to the natural product numbering. The methine proton H11, is not distinct in compound **207** since it overlaps with the CH_2O of the ethyl ester; similarly H9 β overlaps with the protons of the CH_2I functionality. These protons appear as a pair of doubled doublets at around 3.40 ppm. The assignment of these protons is supported by the correlation data.

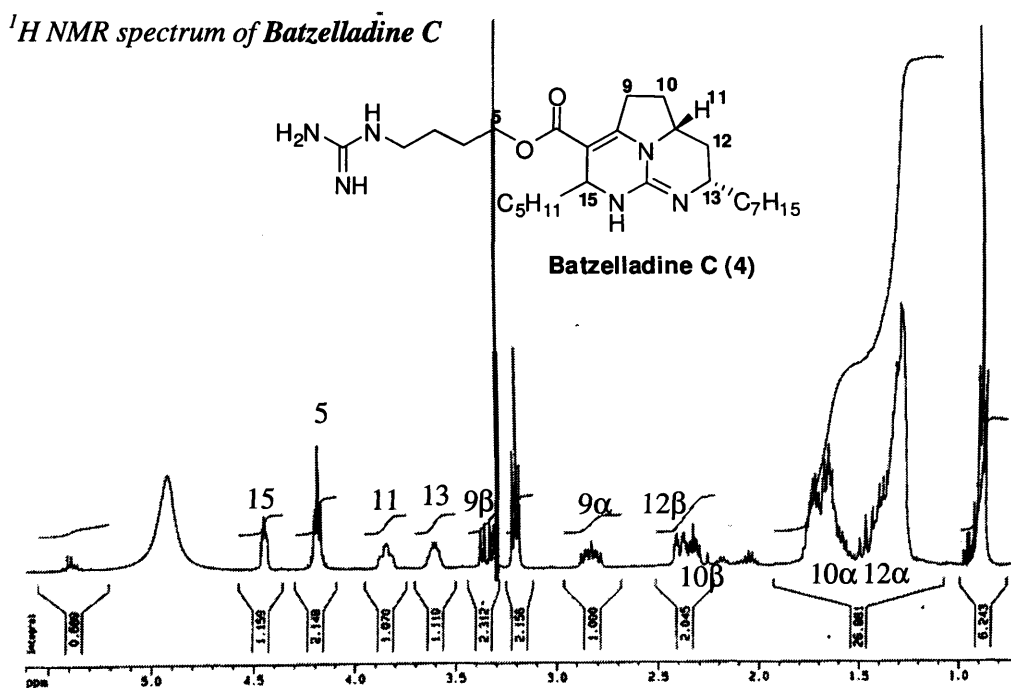


Figure 9a

¹H NMR spectrum of compound 207

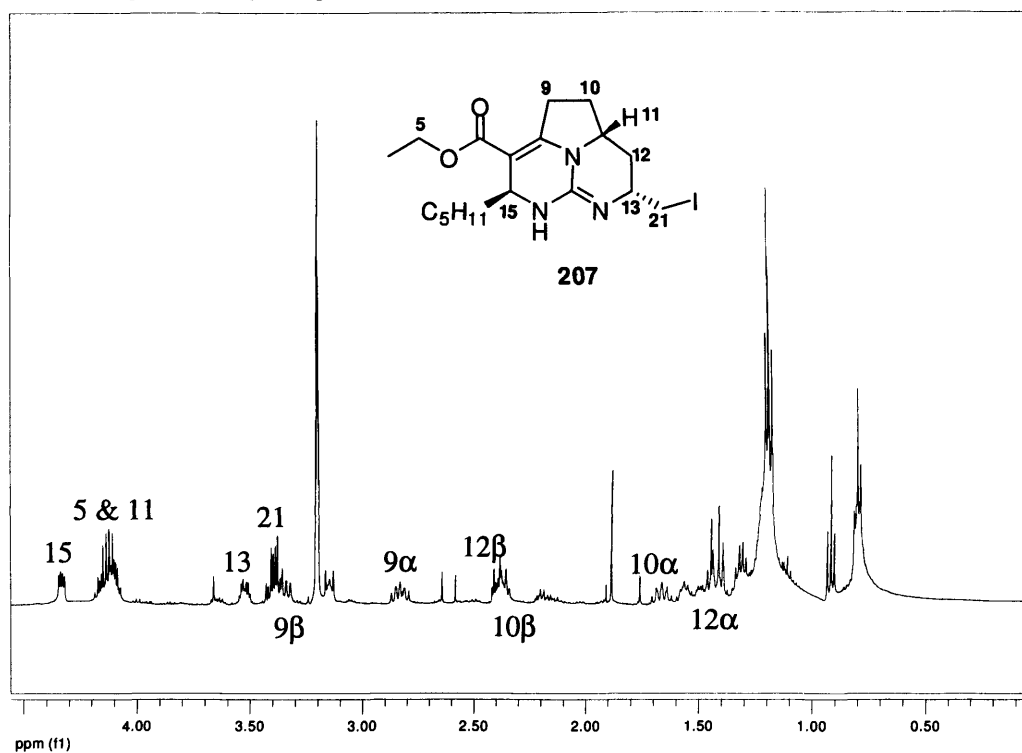


Figure 9b

¹H-¹H COSY NMR spectra of 207 and of batzelladine C are shown in **Figure 10**. Assignments of cross-peaks are shown on the spectra.

^1H - ^1H COSY NMR spectrum of Batzelladine C

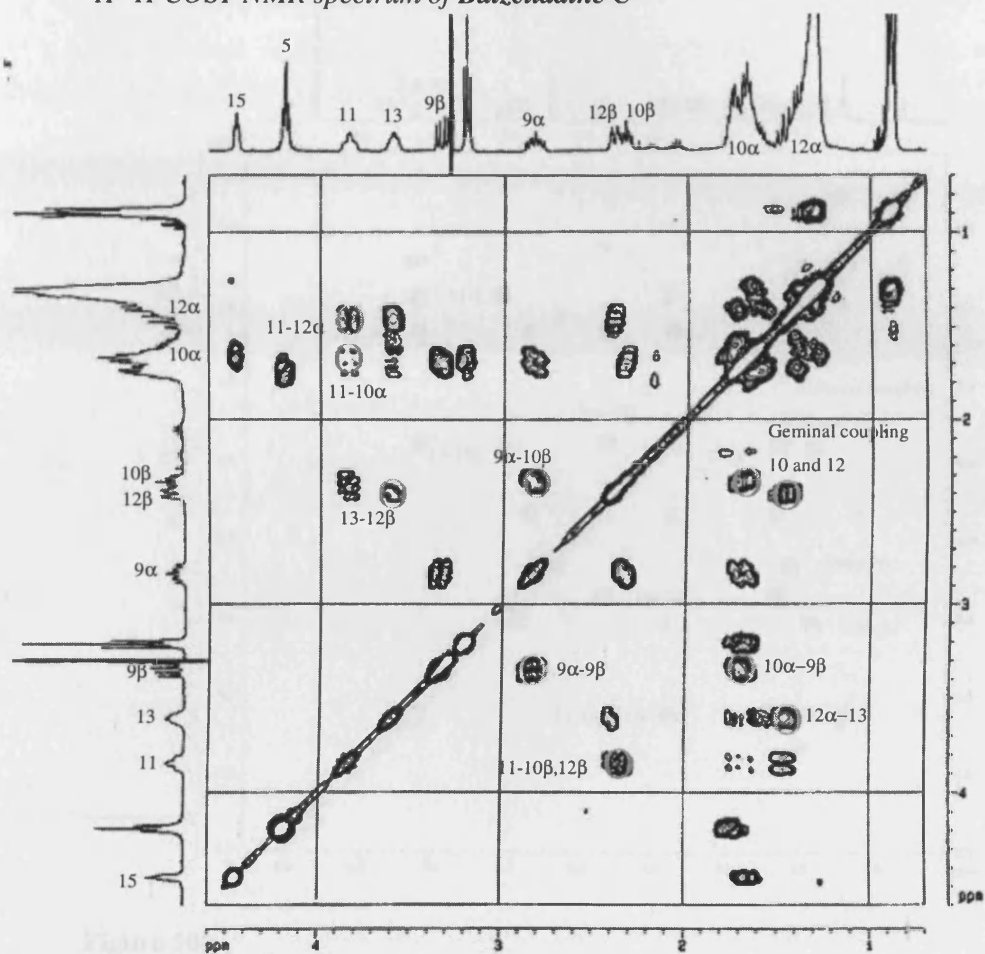


Figure 10a

The assignment of the spin-based structure to the natural product was done as shown in the original report. However, the use of the structure was not confirmed. With the data obtained between the 11-10 β data for compound 20 β and the natural product, the assignment of 20 β data was done according to 2004 β which is an isomer that assigned 20 β for structural assignment to the natural product. We could assign the relative configuration using NMR methods.

The 2D COSY NMR spectrum of compound 20 β is shown in Figure 11. The 1D ^1H NMR shows a doublet peak at 4.12 δ (through 4.12 δ and 4.12 δ) and a multiplet at 4.12 δ (through 4.12 δ and 4.12 δ). The assignment of 20 β data was done according to 2004 β which is an isomer that assigned 20 β for structural assignment to the natural product. We could assign the relative configuration using NMR methods.

^1H - ^1H COSY NMR spectrum of Compound 207

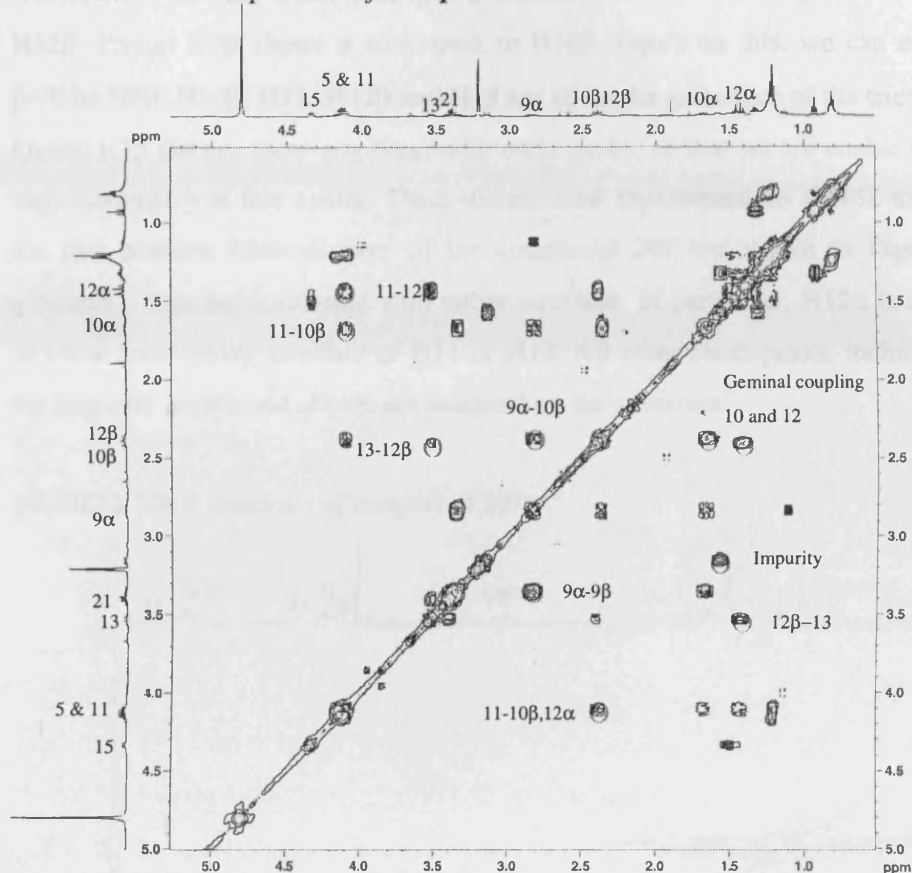


Figure 10b

The stereochemistry of the right-hand pyrimidine ring in the natural product was drawn as shown in the original report. However, the basis for this assignment was not discussed. While the close similarity between the ^1H NMR data for compound **207** and the natural product (in particular, H9 β does not show coupling to H10 β) would lead us to suggest that compound **207** has identical stereochemistry to the natural product, we sought verification of the relative configuration using NMR methods.

The g-NOESY NMR spectrum of compound **207** is shown in **Figure 11**. Proton H13 shows a distinct cross-peak to H12 β (although H10 β and H12 β are overlapping, a correlation between H13 and H10 β is extremely unlikely irrespective of the

stereochemistry) and to the CH₂I group. Proton H11 shows cross-peaks to H10 β and/or H12 β . Proton H9 β shows a cross-peak to H10 β . Based on this, we can conclude that protons H9 β , H10 β , H11, H12 β and H13 are all on the same face of the tricyclic system. Proton H15 did not show any diagnostic cross-peaks, so that we are unable to assign the stereochemistry at this centre. Three-dimensional representations (MM2 minimised) of the two possible stereoisomers of the compound **207** are shown in **Figure 12**. The *g*-NOESY data are consistent with either structure. In particular, H12 α is not expected to show cross-peaks to either of H11 or H13. All other cross-peaks, including those of the impurity mentioned above, are assigned on the spectrum.

g-NOESY NMR spectrum of compound **207**

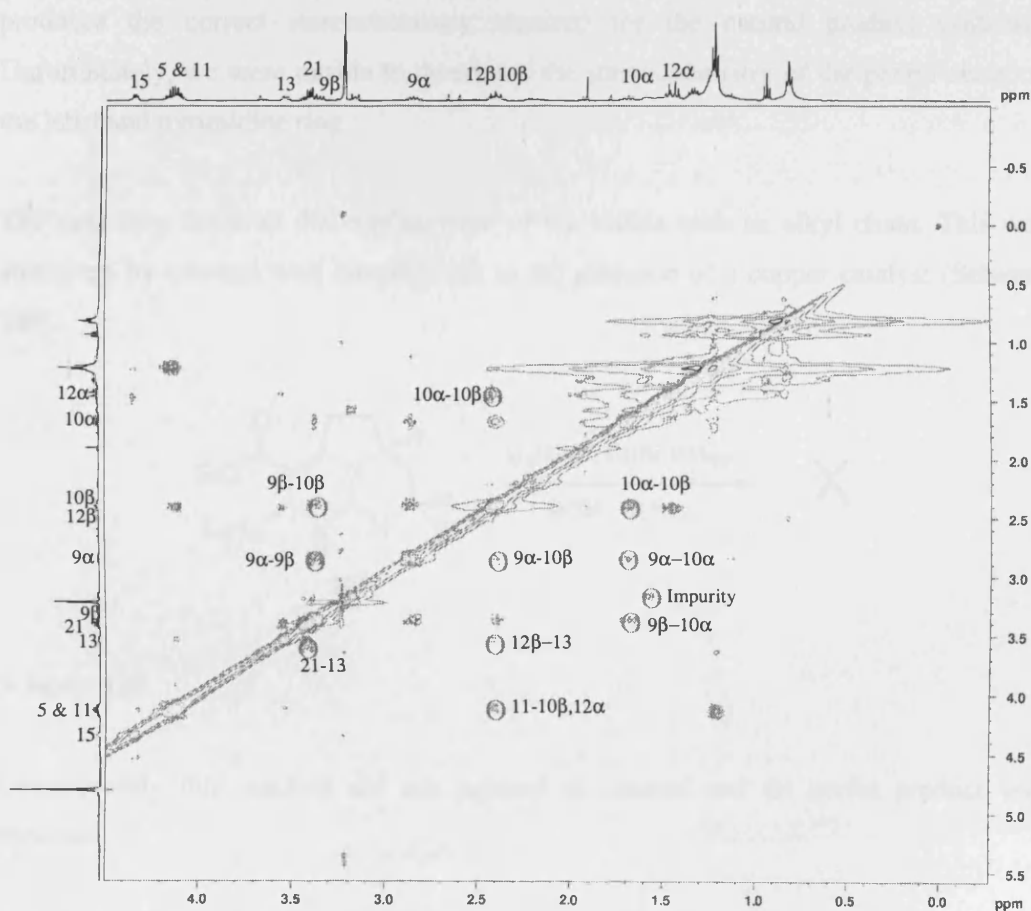


Figure 11

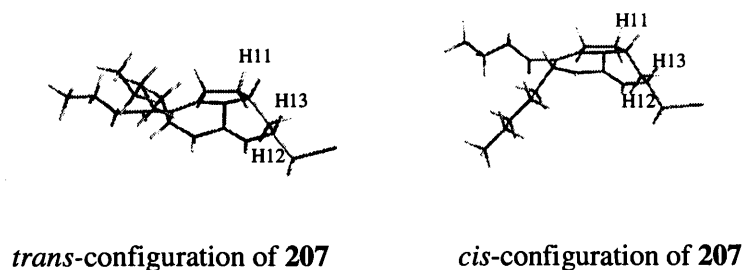
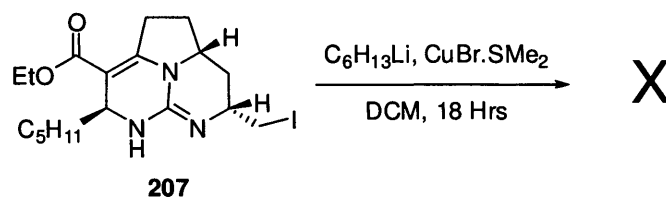


Figure 12

These results confirm the stereochemistry of the right-hand pyrimidine ring, which is the same as that found in the natural product. Therefore, the iodocyclisation reaction produces the correct stereochemistry required for the natural product synthesis. Unfortunately, we were unable to determine the stereochemistry of the pentyl chain on the left-hand pyrimidine ring.

The next step involved the displacement of the iodine with an alkyl chain. This was attempted by reaction with hexyllithium in the presence of a copper catalyst (**Scheme 129**).



Scheme 129

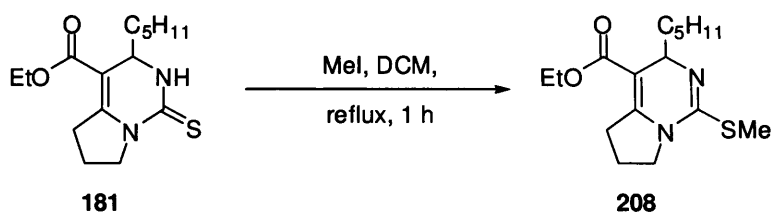
Unfortunately this reaction did not proceed as desired and no useful product was obtained.

At this point we had achieved what had originally been highlighted as the key steps for the synthesis. However, there were still a number of areas to be investigated.

5.3 Further Investigations

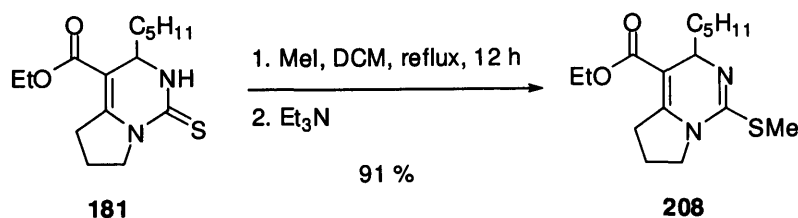
Although the key steps had been addressed and achieved, there were still areas that needed to be investigated and areas where improvements could be made. It was decided to carry out this next section of our research using model compounds that were more accessible than the intermediates for the synthetic route toward the natural product resulting from the multi-step synthesis described above.

Our attention had been drawn to the stereochemical outcome of the trimolecular annulation of the alkylidenepyrrolidine **204**; to date this had produced the highest level of selectivity seen within the Elliott group. Separation of diastereoisomers was still not possible due to degradation during chromatography, although the reasons for the degradation were not apparent. It was decided to make the *S*-methylated isothioureia and test that compound to exposure to silica gel. Initially these investigation were carried out on the achiral thiourea **181**. The method used previously involved a 1 hour reflux with methyl iodide, a quench with triethylamine, and a flush through silica gel was added to isolate the isothioureia **208** (Scheme 130).



Scheme 130

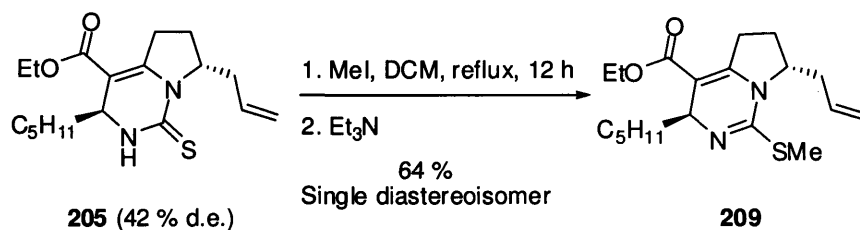
The results from this were unexpected; it transpired that in the 1 hour reflux, very little of the desired methylated compound is formed. It does in-fact complete within 12 hours at reflux in dichloromethane (Scheme 131).



Scheme 131

The bicyclic methylated compound **208** was then purified by flash chromatography on silica gel. It was pleasing to see that the yields obtained on multiple repeats of the reaction were consistent, and that when the same compound was purified repeatedly no significant loss of yield was noted.

This method was then repeated with the synthetic intermediate bicyclic thiourea **205** (Scheme 132).

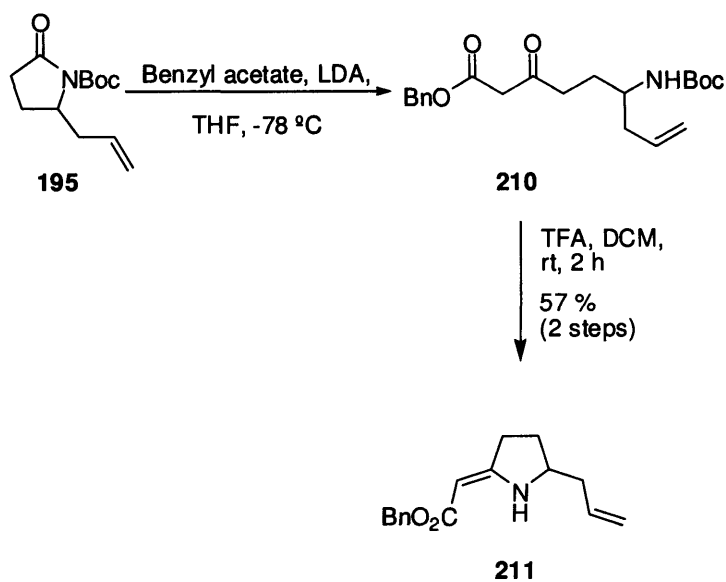


Scheme 132

This produced a high yield of the mixture of diastereoisomers, from which the major isomer **209** was easily isolated; however, the minor isomer was never isolated pure enough for characterisation purposes.

An alternative ester to ethyl acetate for the formation of the alkylidenepyrrolidine would be benzyl acetate. The benzyl ester has the major advantage over ethyl acetate, in that it can be cleaved under mild hydrogenation conditions.

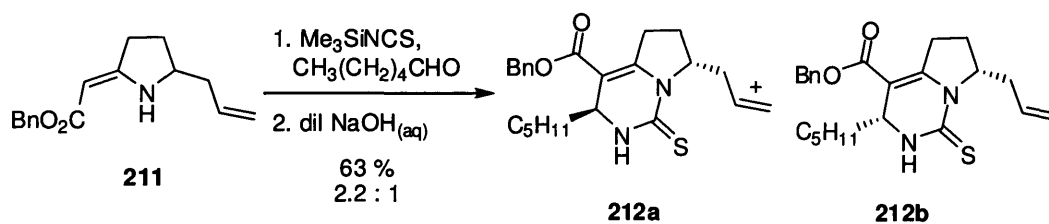
The formation of the alkyldenepyrrolidine **211** was carried out under identical conditions to those used previously (**Scheme 133**).



Scheme 133

The yields were slightly lower than those that we had come to expect from ethyl acetate but were in line with those observed when benzyl acetate had been used before (see Chapter 3).

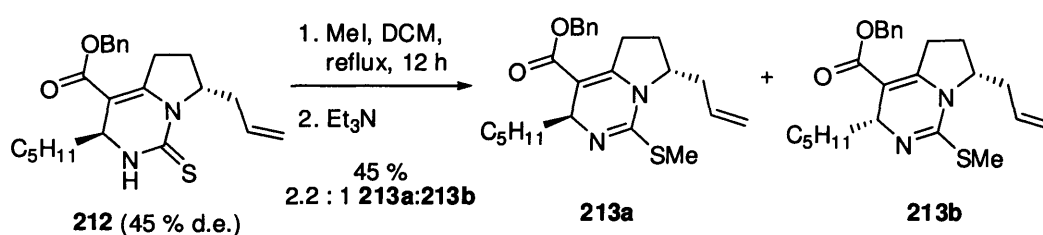
The three-component coupling reaction was carried out to form the bicyclic thiourea **212** using the standard conditions and produced good crude yields with high degree of purity (**Scheme 134**).



Scheme 134

Although the overall yields were lower than had been seen for the ethyl acetate derivative it was possible to separate out the diastereoisomers of compound **213** at this stage. Both the major and the minor isomers were separated and fully characterised.

The bicyclic thiourea **212** as a mixture of its diastereoisomers was *S*-methylated by a 12 hour reflux in methyl iodide and dichloromethane (**Scheme 135**).

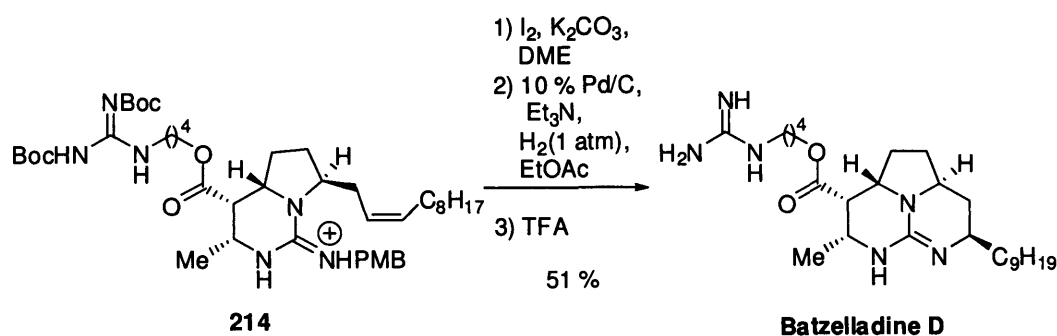


Scheme 135

Again it was possible to separate out the major diastereoisomer and obtain full characterisation, although the minor isomer was not isolated in sufficient purity for characterisation purposes.

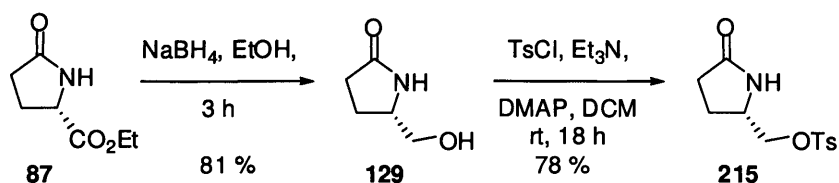
We now had two possible routes to the bicyclic urea which, depending on the final route chosen for the synthesis, could be used.

Around this time Gin, and co-workers published their work on the synthesis of Batzelladine D. In this synthesis, a similar iodocyclisation was used to form the tricyclic guanidine (**Scheme 136**).⁸³ This was carried out using a *cis* double bond on the precursor **214**. In light of this it was decided to investigate the viability of adding a *cis*-double bond in our side chain.



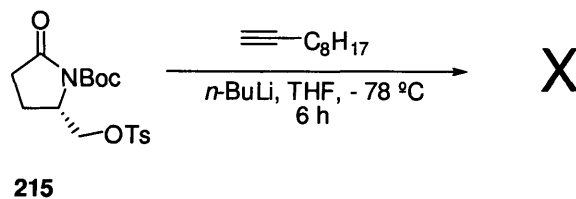
Scheme 136

A good starting point for this investigation were the chiral glutamic ester derivatives. We had previously reduced the pyroglutamate ester **87** to the alcohol **129**. This was then tosylated (**Scheme 137**).



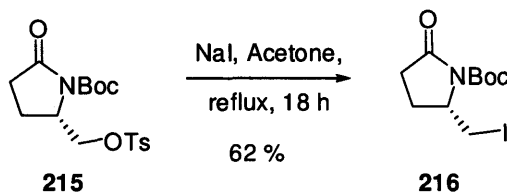
Scheme 137

The simplest way of adding the required functionality at this stage would be to displace the tosylate with an alkyne (**Scheme 138**), this could then be reduced to the alkene using Lindlar reduction which would give us the desired *cis* double-bond isomer.



Scheme 138

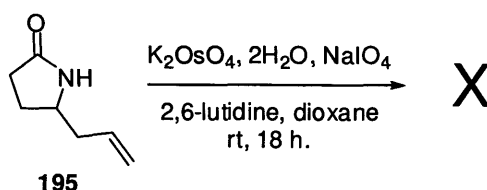
Unfortunately only starting materials were recovered. One possible modification was to replace the tosyl group with a halogen. This was done by stirring the lactam **215** in acetone with NaI under reflux, which gave a clean yield of the halogenated analogue **216** (Scheme 139).



Scheme 139

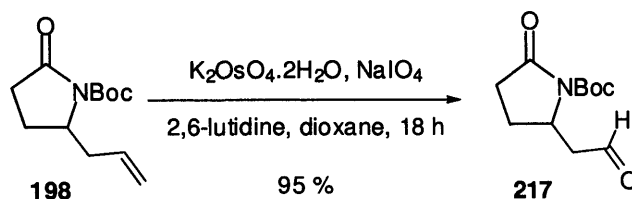
Displacement of the iodine with an acetylide was attempted under the same conditions as for the tosylate. However, again no successful reaction was achieved, although most of the starting material was recovered.

An alternative way of adding a *cis* double bond would be through a Wittig reaction using an unstabilised ylid. Using the oxidative cleavage reaction developed in the early 1950's by Johnson *et al.*⁸⁴ and later modified by Jin *et al.*⁸⁵ on the allyl lactam **195** could produce the desired aldehyde for the Wittig reaction (Scheme 140). Unfortunately this reaction was unsuccessful and no identifiable products were recovered.



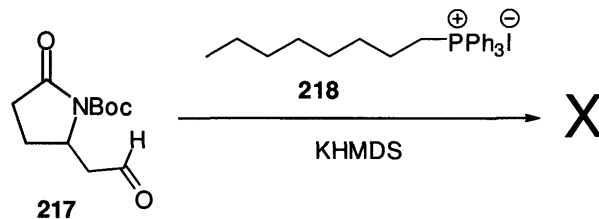
Scheme 140

When carried out on the protected lactam **198** the reaction gave a good yield with excellent purity of the aldehyde **217** (**Scheme 141**).



Scheme 141

It was hoped that a Wittig reaction could be carried out with an unstabilised ylid to give the cis double bond. The phosphonium salt **218** was prepared by literature methods,⁸⁶ and reacted under standard conditions with aldehyde **198** (**Scheme 142**). Once again, the reaction did not proceed as expected and no recoverable products were isolated.

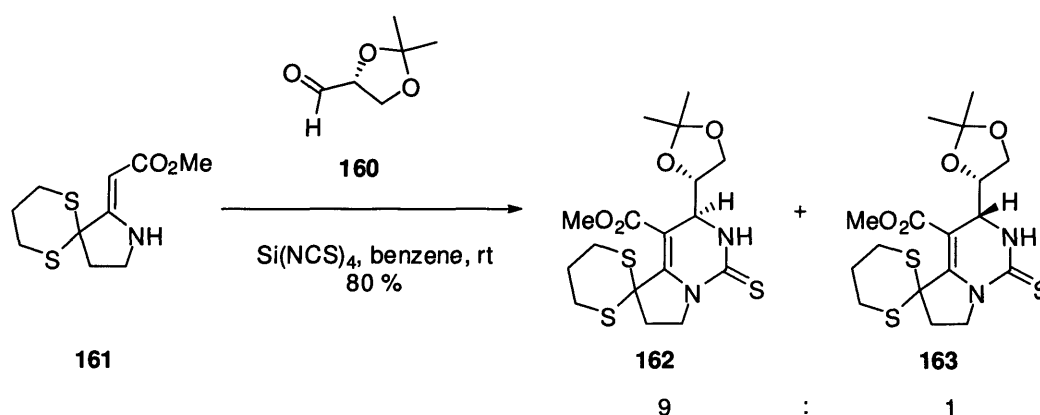


Scheme 142

One possible reason for the reactions not producing the desired products could be from the activating effect of the Boc carbamate. If this is the case the lactam carbonyl would become a viable position for reaction. A further possibility would come from steric hindrance of the aldehyde side chain from the Boc group which would further reduce the chances of reaction occurring at the desired site.

5.4 Determination of the Relative Stereochemical Outcome of the Three-Component Coupling Reaction

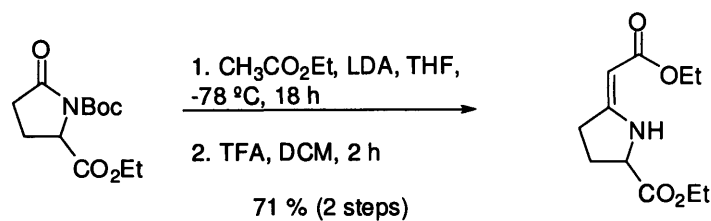
The final area of research carried out was to determine the relative stereochemistry of the three-component coupling reactions. To do this a combination of Kishi's chiral aldehyde method was combined with our own version using a chiral alkylidenepyrrrolidine. In Kishi's enantioselective total synthesis of (-)-decarbamoylsaxitoxin, a modified three-component coupling reaction was reported using the (*R*)-aldehyde **160** to give the (*S*)-configuration at the new stereogenic centre (**Scheme 143**).



Scheme 143

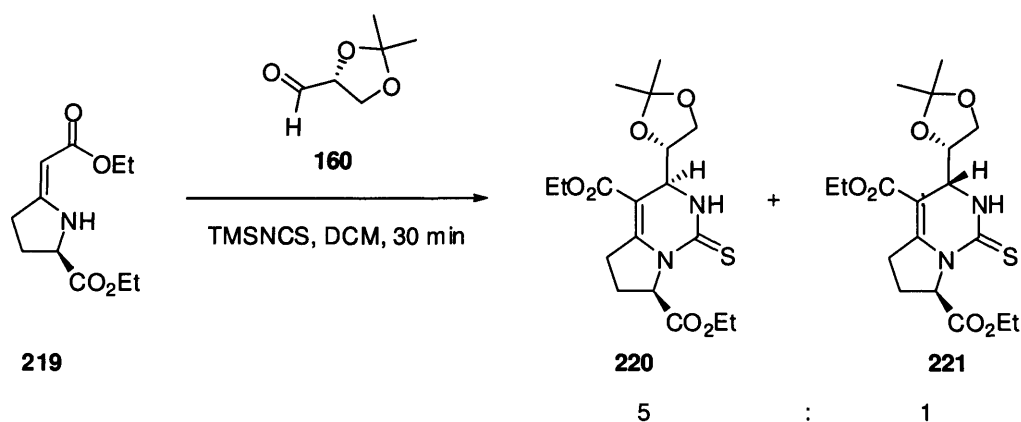
Since the chiral influence of the aldehyde is greater than that of the ester group in our alkylidenepyrrrolidine **151** then the major product from the reaction with the aldehyde **160** will also have the same (*S*) configuration at the new stereogenic centre. If we then use both enantiomers of the alkylidenepyrrrolidine **151** we will be able to determine the relative relationship between the two chiral centres.

Alkylidenepyrrrolidine **219**, the enantiomer of compound **151**, was synthesised from the corresponding amino acid (**Scheme 144**).



Scheme 144

The three-component coupling reaction was carried out using the single enantiomer alkylidenepyrrrolidine **219**, the aldehyde **160** and trimethylsilyl isothiocyanate in dichloromethane for 30 minutes (**Scheme 145**).



Scheme 145

Figure 13 shows the region of the ^1H NMR spectrum that corresponds to the proton at the pyrrolidine 5-position. It can clearly be seen that the peak corresponding to the major isomer is a doubled doublet, whereas the peak corresponding to the minor isomer is upfield and is a doublet.

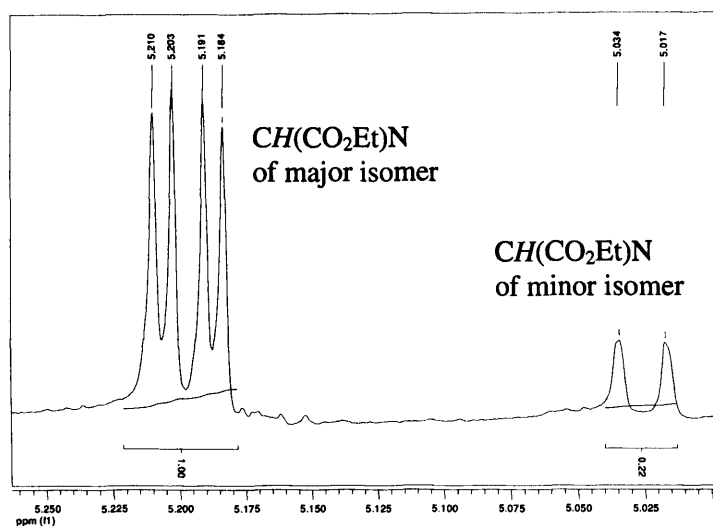
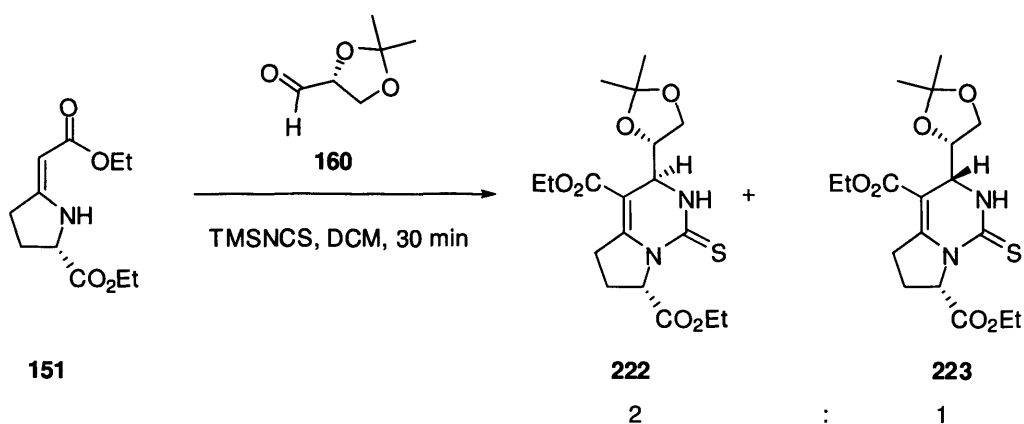


Figure 13

The reaction of the alkylidenepyrrolidine **151** was carried out under identical conditions to those above (**Scheme 146**).



Scheme 146

The 1H NMR spectrum shown in **Figure 14** clearly shows the same arrangement of peaks this time the doublet is the major isomer and the minor isomer is observed as a double doublet.

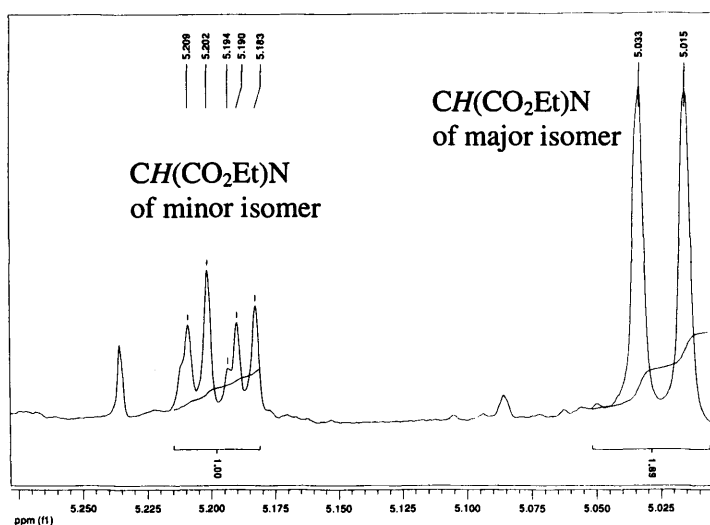


Figure 14

In neither of the reactions was the selectivity as high as reported originally by Kishi, it is assumed that the presence of the dithiane group on the alkylidenepyrrolidine **161** is enhancing the selectivity observed but that it does not affect the configuration of the major product.

With this taken into account we can assume, based on the levels of stereoselectivity observed, that when the alkylidenepyrrolidine **219** (with *R* configuration) is used the stereoselectivity is reinforced, as a higher selectivity is observed than when its enantiomer **151** is used.

If we assume that the major product in both the above cases has (*S*) stereochemistry at the new stereogenic centre then the major compound from the reaction of the (*S*) alkylidenepyrrolidine **151** will give a *trans* configuration between the new dioxolanyl group and the ester group on the 5-position. When the (*R*) alkylidenepyrrolidine **219** is used the major isomer configuration is *cis*.

This would indicate based on the relative positions of the peaks in the ¹H NMR that the major isomer observed in all cases when the alkylidenepyrrolidine **151** has been used is

the *cis* isomer. **Figure 15** shows the region in question from the ^1H NMR spectrum of the products from the reaction of alkylidenepyrrolidine **151** and hexanal.

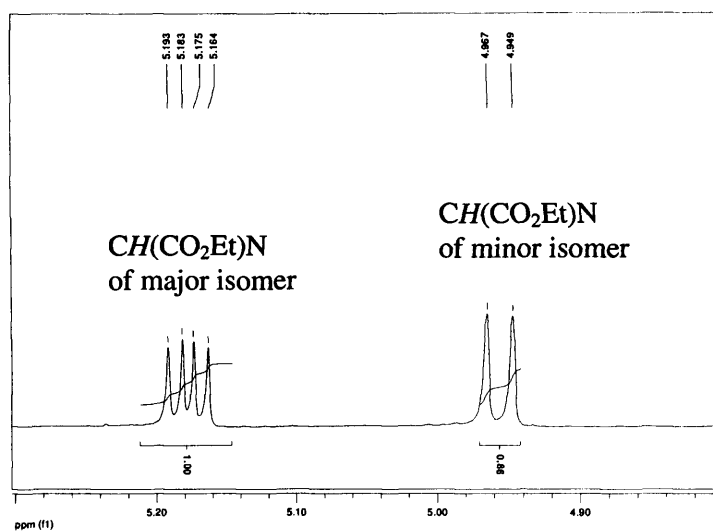
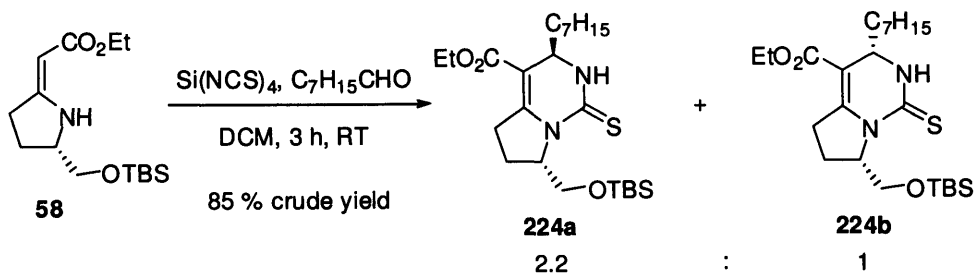


Figure 15

It can be seen that the coupling patterns are repeated in this example where a double doublet assigned to the *cis* configuration is downfield of the doublet assigned to the *trans* configuration.

The original three-component coupling reaction carried out within the Elliott group using alkylidenepyrrolidine **58** appeared to produce the opposite major isomer. The reaction was repeated using the same alkylidenepyrrolidine but with octanal as the aldehyde (**Scheme 147**).



Scheme 147

The results confirmed the originally reported data; **Figure 16** shows the ^1H NMR data from the reaction showing the same protons as those in **Figure 13**.

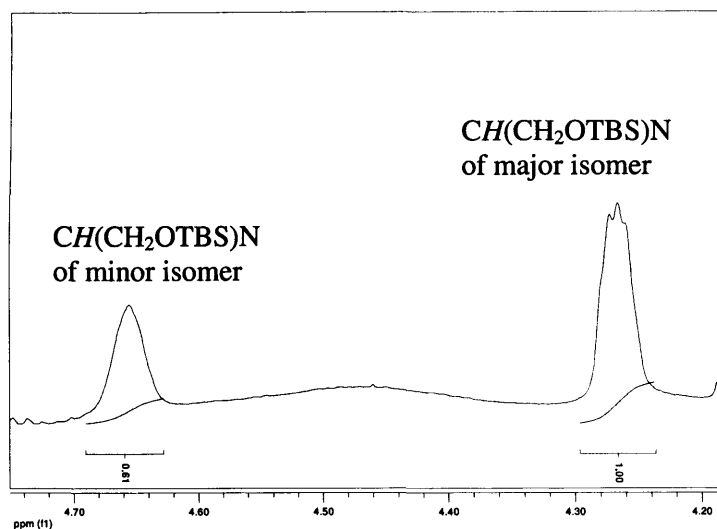


Figure 16

Although the multiplicity within this example is not as clear as those of the previous example, the relative positions of the peaks would indicate that the major product formed from this reaction has a *trans* configuration.

Recently a mixture of isomers of the thiourea **189** has been reduced using sodium borohydride.⁸⁷ The results from this work showed that only the major diastereoisomer

(assigned to be *cis* as described above) was reduced, and that the new position of the proton of the 5-position of the pyrrolidine ring was coincidental with the minor isomer from the reaction using alkylidenepyrrolidine **58** as shown in **Figure 16**. Therefore, it is clear that these two different directing groups do produce opposite stereochemical outcomes.

When the allyl alkylidenepyrrolidine **204** is used the relative positions of the peaks of the thiourea match with those from the reaction of alkylidenepyrrolidine **58**. This would indicate that the major product most likely has the *trans* configuration.

From this information we can assign the structure shown in **Figure 17** to our tricyclic guanidine **207**.

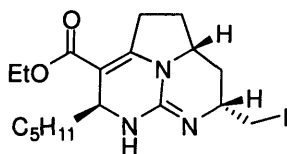
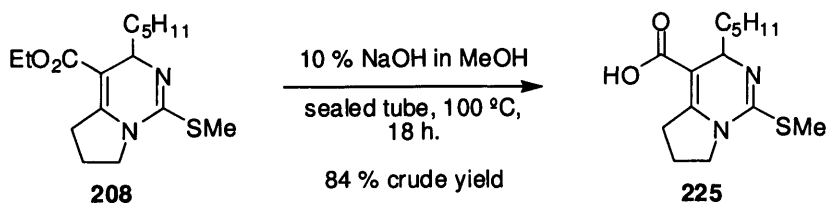


Figure 17

Although batzelladine C was never fully synthesised during the time of this project each of the key steps were successfully investigated, resulting in an excellent synthesis of bicyclic thioureas and guanidines, and tricyclic guanidines.

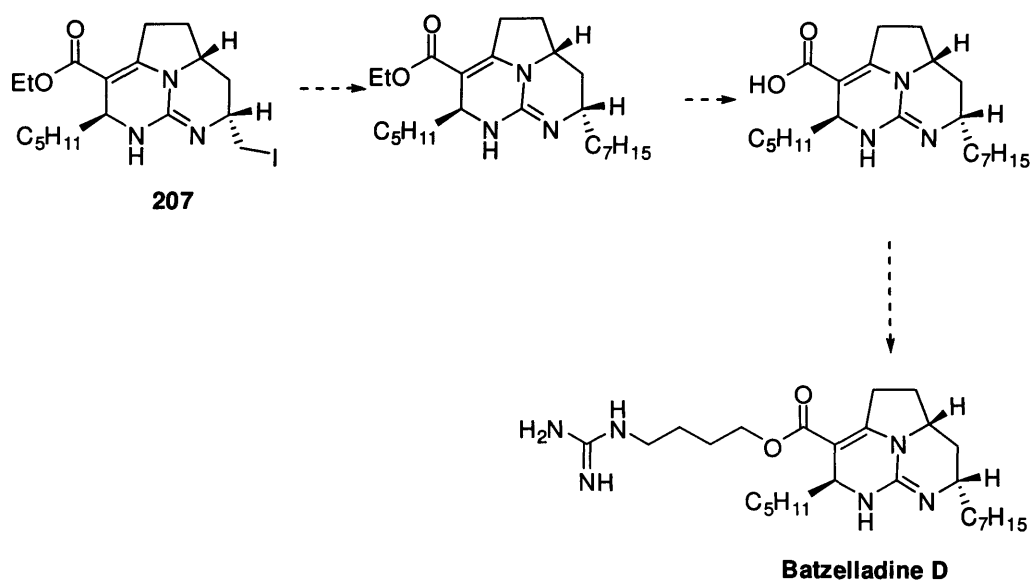
5.5 Future Work

With time for the project running out, the final piece of work to be investigated was the hydrolysis of the ester. Primarily it was important to discover how stable the resulting carboxylic acid was. To this end the achiral isothiurea **208** was hydrolysed using sodium hydroxide in methanol (**Scheme 148**).



Scheme 148

With evidence that the carboxylic acid **225** is stable the final few steps to add the second guanidine moiety can be carried out according to literature procedures, which will only leave the addition of the alkyl side chain to be investigated (**Scheme 149**).



Scheme 149

Chapter 6

Experimental Section

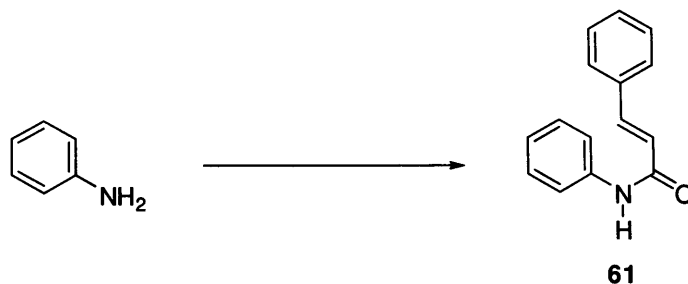
6.1. General Experimental Points

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 ^1H and at 100 MHz for ^{13}C at 25 °C, or on a Bruker Avance 500 spectrometer operating at 500 MHz for ^1H 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 ^1H NMR is reported as singlet (s), doublet (d), double doublet (dd), double double doublet (ddd), double double double doublet (dddd), double triplet (dt), double quartet (dq), 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.

Compounds **195**, **197** and **215** were kindly made by M. Loveday.

6.2 Experimental Data for Chapter 2

(*E*)-*N*-Phenylcinnamamide (61).⁸⁸



Cinnamoyl chloride (3.33 g, 20 mmol) was added to a solution of aniline (3.64 mL 40 mmol), and DMAP (10 mg) in dichloromethane 60 mL and the solution stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over magnesium sulphate and the solvent was removed *in vacuo* to give a crystalline solid which was recrystallised from diethyl ether / hexane to give the *title compound* (3.77 g, 84 %) as a white crystalline solid.

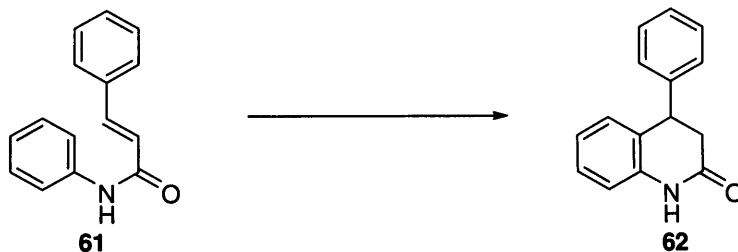
Mp: 152 – 152.5 °C (lit: 152 – 153 °C).

¹H NMR (400 MHz; CDCl₃): δ = 7.71 (d, *J* = 15.5, 1 H, alkene CH), 7.57 (broad d, *J* = 7.0, 2 H, 2 x aromatic CH), 7.49 – 7.45 (m, 2 H, 2 x aromatic CH), 7.35 – 7.28 (m, 5 H, 5 x aromatic CH), 7.07 (t, *J* = 7.2, 1 H, aromatic CH), 6.49 (d, *J* = 15.5, 1 H, alkene CH).

¹³C NMR (100 MHz; CDCl₃): δ = 142.5 (alkene CH), 138.0 (aromatic C), 134.6 (aromatic C), 130.0 (aromatic CH), 129.1 (aromatic CH), 128.9 (aromatic CH), 127.9 (aromatic CH), 119.9 (CH=CH).

3,4-Dihydro-4-phenylquinolin-2(1H)-one (62).²⁹

Reaction of 61 with polyphosphoric acid.



(*E*)-*N*-Phenylcinnamamide (1.00 g, 4.5 mmol) was added to polyphosphoric acid (10 g). The resulting mixture was stirred at 120 °C for 10 minutes. The reaction mixture was poured into cold water (250 mL) and extracted with ether (2 x 100 mL). The combined ether extracts were concentrated *in vacuo* to give a yellow crystalline solid which was recrystallised from ethanol to give the *title compound* (710 mg, 72 %) as a white crystalline solid.

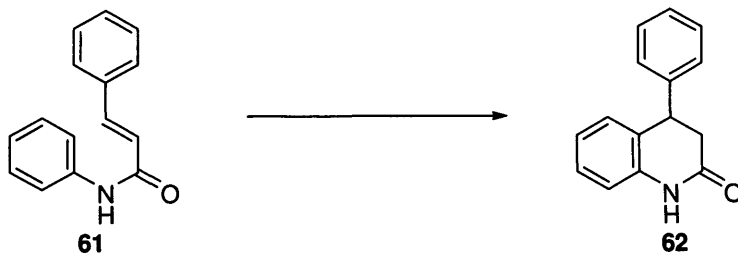
Mp: 176 – 177.5 °C (lit: 177 – 178 °C).

¹H NMR (400 MHz; CDCl₃): δ 7.26 – 6.96 (m 10 H, 9 x aromatic CH and NH), 4.51 (t, *J* = 7.7, 1 H, CH), 2.98 (dd, *J* = 17.8 and 7.7, 1 H, one of CH₂), 2.94 (dd, *J* = 17.8 and 7.7, 1 H, one of CH₂).

¹³C NMR (100 MHz; CDCl₃): δ = 171.2 (C=O), 143.5 (aromatic C), 137.1 (aromatic C), 128.9 (aromatic CH), 128.4 (aromatic CH), 127.9 (aromatic CH), 127.3 (aromatic CH), 126.7 (aromatic C), 123.4 (aromatic CH), 115.8 (aromatic CH), 42.0 (CHCH₂), 38.4 (CHCH₂).

3,4-Dihydro-4-phenylquinolin-2(1H)-one (62)

Reaction of compound 61 with 5 equivalents of poor quality aluminium chloride

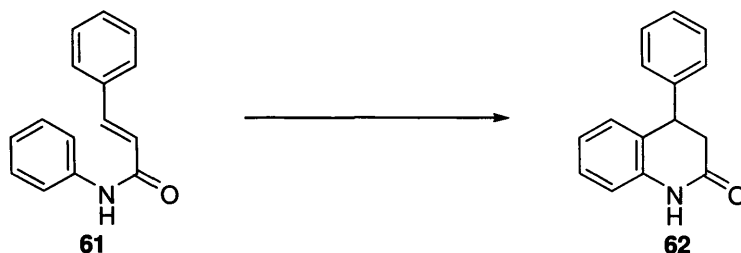


(*E*)-*N*-Phenylcinnamamide (120 mg, 0.5 mmol) was added to a solution of aluminium chloride (333 mg, 2.5 mmol) in chlorobenzene (15 mL) and the solution was stirred at 90 °C for 2 hours. The resulting mixture was quenched with hydrochloric acid (2 M, 100 mL) and extracted into diethyl ether (2 x 50 mL). The combined ether extracts were concentrated *in vacuo* to give an oily solid which was recrystallised from methanol : diethyl ether to give the *title compound* (32 mg, 28 %).

Data as previously reported.

3,4-Dihydro-4-phenylquinolin-2(1H)-one (62)

Reaction of compound 61 with 1.5 equivalents of bismuth chloride.



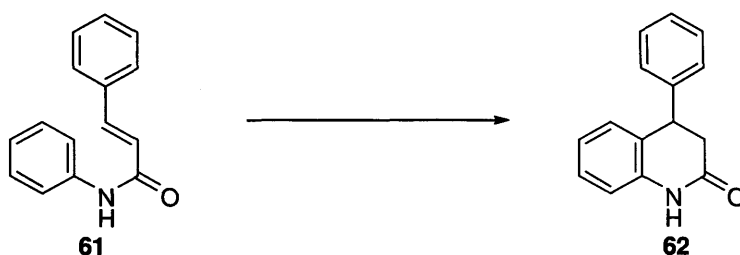
(*E*)-*N*-Phenylcinnamamide (60 mg, 0.25 mmol) was added to a solution of bismuth chloride (118 mg 0.38 mmol) in chlorobenzene (10 mL) and the resulting solution stirred at 90 °C for 4 days. The reaction mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The combined ether layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to

give an oily solid which was recrystallised from methanol to give the *title compound* (47 mg, 79%) as a white crystalline solid.

Data as previously reported.

3,4-Dihydro-4-phenylquinolin-2(1H)-one (62).

Reaction of compound 61 with 2 equivalents of bismuth chloride.

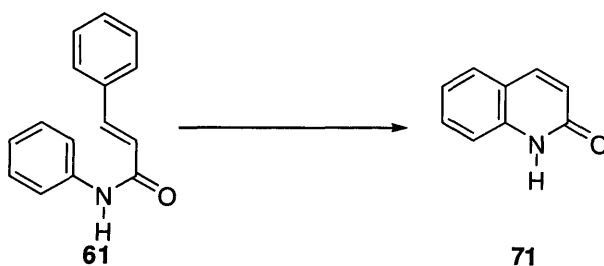


(*E*)-*N*-Phenylcinnamamide (60 mg, 0.25 mmol) was added to a solution of bismuth chloride (158 mg 0.5 mmol) in chlorobenzene (10 mL) and the resulting solution stirred at 90 °C for 4 days. The reaction mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The combined ether layers were dried over magnesium sulphate. The solvent was removed *in vacuo* to give a oily solid which was recrystallised from methanol to give *title compound* (43 mg, 72%) as a white crystalline solid.

Data as previously reported.

Quinolin-2(1H)-one (71).⁸⁹

Reaction of compound 61 with 5 equivalents of good quality aluminium chloride.



(*E*)-*N*-Phenylcinnamamide (120 mg, 0.5 mmol) was added to a solution of aluminium chloride (333 mg, 2.5 mmol) in chlorobenzene (15 mL) and the solution

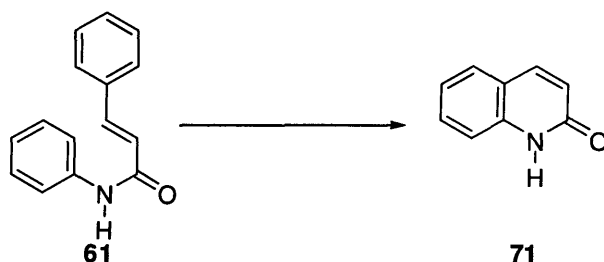
stirred at 90 °C for 2 hours. The resulting mixture was quenched with hydrochloric acid (2 M, 100 mL) and extracted with diethyl ether (2 x 50 mL). The combined ether layers were concentrated *in vacuo* to give an oily solid which was recrystallised from methanol to give the title compound (75 mg, 66 %) as a white crystalline solid. Mp. 199 – 199.5 °C (lit: 196 – 197 °C).

¹H NMR (400 MHz; CDCl₃): δ = 7.74 (d, *J* = 9.5, alkene CH), 7.52 – 6.99 (m, 5H, aromatic-CH and NH), 6.63 (d, *J* = 9.5, alkene CH).

¹³C NMR (100 MHz; CDCl₃): δ = 174.5 (C=O), 141.6 (CH), 137.3 (aromatic C) 129.1 (aromatic CH), 129.0 (aromatic CH) 128.0 (aromatic C), 120.1 (CH)

Quinolin-2(1H)-one (71).

Reaction of compound 61 with 3 equivalents of aluminium chloride.

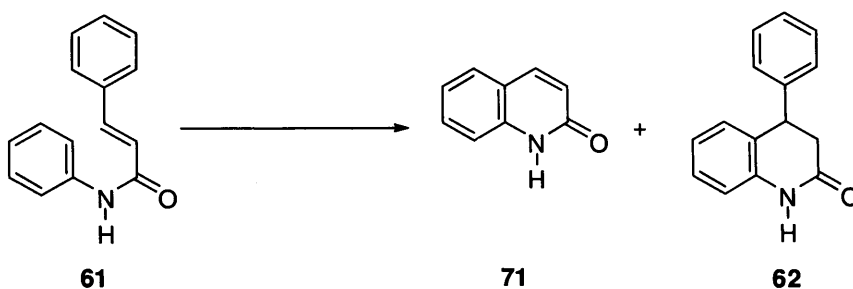


(*E*)-*N*-Phenylcinnamamide (60 mg, 0.25 mmol) was added to a solution of aluminium chloride (99 mg, 0.75 mmol) in chlorobenzene (10 mL) and the solution stirred at 90 °C for 2 hours. The resulting mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted into diethyl ether (2 x 25 mL). The combined ether layers were concentrated *in vacuo* to give an oily solid which was recrystallised from methanol to give the title compound (30 mg, 50 %) as a white crystalline solid.

Data as previously reported.

Quinolin-2(1H)-one (71).

Reaction of compound 61 with 2 equivalents aluminium chloride.

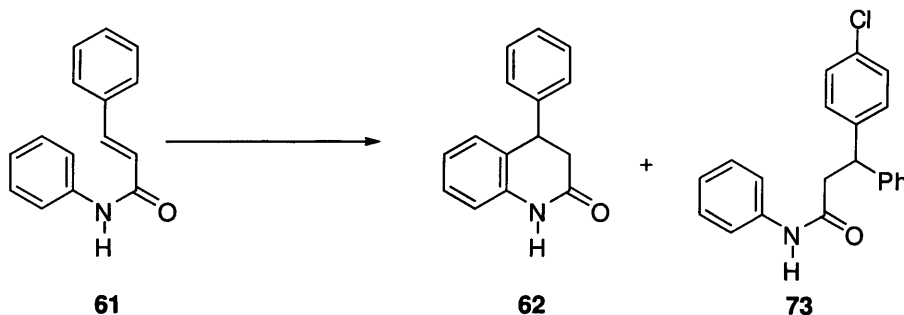


(*E*)-*N*-Phenylcinnamamide (60 mg, 0.25 mmol) was added to a solution of aluminium chloride (66 mg, 0.5 mmol) in chlorobenzene (10 mL) and the solution stirred at 90 °C for 2 hours. The resulting mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted into diethyl ether (2 x 25 mL). The combined ether layers were concentrated *in vacuo* to give an off white solid which was recrystallised from methanol to give a mixture of compounds predominantly the *title compound*, (40 mg, 72 %) contaminated with traces of 3,4-dihydro-4-phenylquinolin-2(1H)-one (62) as an off-white crystalline solid.

Data as previously reported.

3,4-Dihydro-4-phenylquinolin-2(1H)-one (62) and 3-(4-chlorophenyl)-*N*,3-diphenylpropanamide (73).

Reaction of compound 61 with 1.75 equivalents of aluminium chloride.

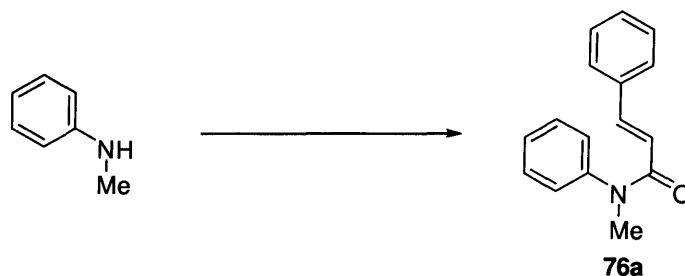


(*E*)-*N*-Phenylcinnamamide (60 mg, 0.25) was added to a solution of aluminium chloride (57 mg, 43 mmol) in chlorobenzene (10 mL) and the resulting solution stirred at 90 °C for 2 hours. The resulting solution was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The solvent was removed *in vacuo* to give a crystalline solid recrystallised from methanol to give the *title compounds* (1:1 mixture, 55 mg) as a white crystalline solid.

¹H NMR (400 MHz; CDCl₃): δ = 7.26 – 6.96 (m 10 H, 9 x aromatic CH and NH), 4.51 (t, *J* = 7.7, 1 H, CH), 3.04 – 2.90 (m, 2 H, CH₂CO)

MS-ES: *m/z* (%) 106 (100) 336 (90) 252 (30), 338 (30).

(*E*)-*N*-Methyl-*N*-phenylcinnamamide (76a).⁹⁰



Cinnamoyl chloride (6.22 g, 37 mmol) was added to a solution of *N*-methylaniline (4.04 mL, 37 mmol), triethylamine (5 mL) and DMAP in dichloromethane (60 mL) and the solution stirred at room temperature for 18 hours. The reaction was quenched ammonium chloride (100 mL) and extracted into dichloromethane (3 x 100 mL). The combined dichloromethane layers were washed with brine (2 x 100 mL), dried over magnesium sulphate and the solvent removed *in vacuo* to give a crystalline solid recrystallised from diethyl ether / hexane to give the *title compound* (7.34 g, 83 %) as a white crystalline solid.

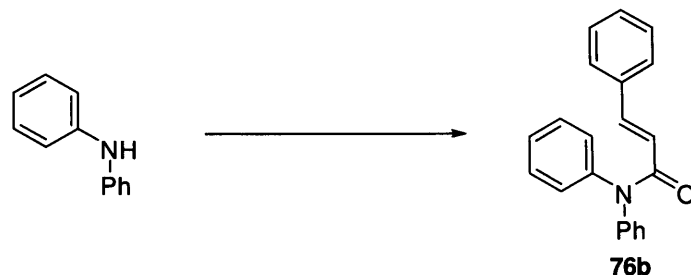
Mp: 61 – 61.5 °C (lit: 62 – 63 °C).

¹H NMR (500 MHz; CDCl₃): δ = 7.59 (d, *J* = 15.5, 1 H, alkene CH), 7.36 (apparent t, *J* = 7.6, 2 H, aromatic CH), 7.28 (t, *J* = 7.4, 1 H, aromatic CH), 7.25 – 7.15 (m, 5 H, aromatic CH), 7.14 (d, *J* = 7.3, 2 H, aromatic CH), 6.29 (d, *J* = 15.5, 1 H, alkene CH) 3.33 (s, 3 H, NCH₃).

¹³C NMR (125 MHz; CDCl₃): δ = 166.2 (C=O), 143.7 (aromatic C), 141.7 (alkene CH), 135.2 (aromatic C), 129.7 (2 x aromatic CH), 129.5 (2 x aromatic CH), 128.7

(aromatic CH), 127.9 (aromatic CH), 127.6 (2 x aromatic CH), 127.4 (2 x aromatic CH), 118.8 (alkene CH), 37.6 (CH₃).

(E)-N,N-Diphenylcinnamamide (76b).⁹¹



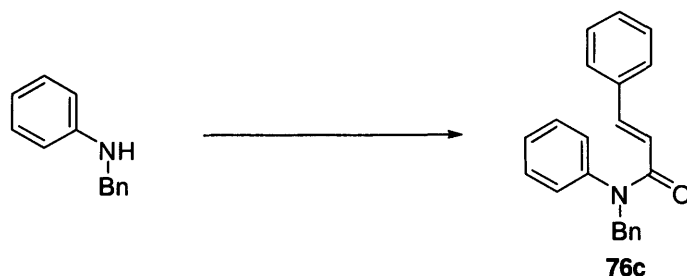
Cinnamoyl chloride (4.92 g, 30 mmol) was added to a solution of N,N-diphenylamine (5.00 g, 30 mmol), triethylamine (3 mL) and DMAP (10 mg) in dichloromethane (60 mL) and the resulting solution stirred at room temperature for 18 hours. The reaction was quenched with saturated aqueous ammonium chloride (100 mL) and extracted into dichloromethane (3 x 100 mL). The combined dichloromethane layers were washed with brine (2 x 100 mL), and dried over magnesium sulphate. The solvent was removed *in vacuo* to give a crystalline solid which was recrystallised from methanol to give the *title compound* (7.62 g, 85 %) as an off-white crystalline solid.

Mp: 101 – 101.5 °C (lit: 102 – 102.5 °C).

¹H NMR (500 MHz; CDCl₃): δ = 7.70 (d, *J* = 15.5, 1 H, alkene CH), 7.36 – 7.16 (m, 15 H, aromatic CH), 6.41 (d, *J* = 15.5, 1 H, alkene CH).

¹³C NMR (125 MHz; CDCl₃): δ = 166.2 (C=O), 142.8 (aromatic C), 142.7 (alkene CH), 135.1 (aromatic C), 129.8 (aromatic CH), 128.8 (aromatic CH), 128.0 (aromatic CH).

(E)-N-Benzyl-N-phenylcinnamamide (76c).



Cinnamoyl chloride (5.6 g, 33 mmol) was added to a solution of *N*-benzylaniline (6.2 g, 33 mmol), triethylamine (3.1 mL) and DMAP in dichloromethane (60 mL) and the resulting solution stirred at room temperature for 18 hours. The resulting solution was quenched with saturated aqueous ammonium chloride (100 mL) and extracted into dichloromethane (3 x 100 mL). The combined dichloromethane layers were washed with brine (2 x 100 mL), dried over magnesium sulphate and the solvent removed *in vacuo* to give a crystalline solid which was recrystallised from methanol to give the *title compound* (8.06 g, 78 %) as a light brown crystalline solid.

Mp: 88 – 89 °C.

¹H NMR (500 MHz; CDCl₃): δ = 7.68 (d, *J* = 15.5, 1 H, alkene CH), 7.32 – 7.14 (m, 13 H, aromatic CH), 7.00 (d, *J* = 8.0, 2 H, aromatic CH), 6.30 (d, *J* = 15.5, 1 H, alkene CH) 4.93 (s, 2 H, CH₂).

¹³C NMR (125 MHz; CDCl₃): δ = 166.0 (C=O), 142.3 (alkene CH), 142.0 (aromatic C), 137.5 (aromatic C), 135.2 (aromatic C), 129.6 (aromatic CH), 129.5 (aromatic CH), 128.7 (aromatic CH), 128.4 (aromatic CH), 128.4 (aromatic CH), 127.9 (aromatic CH), 127.8 (aromatic CH), 127.4 (aromatic CH), 118.8 (alkene CH), 53.2 (CH₂).

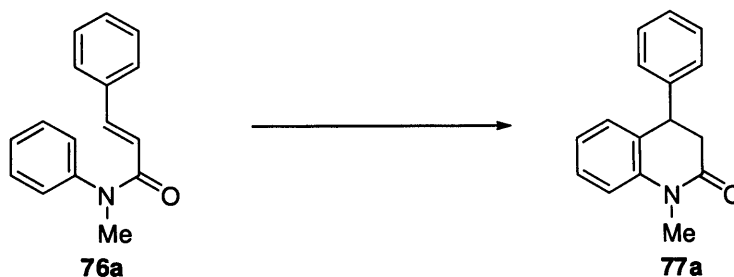
IR (Thin film): 3028, 2927, 1654, 1617, 1384, 699 cm⁻¹.

MS-ES: *m/z* (%) 314 (MH⁺, 100)

HRMS-ES: *m/z* [M + K]⁺ calcd for C₂₂H₁₉NOK: 352.1104; found: 352.1102.

3,4-Dihydro-1-methyl-4-phenylquinolin-2(1H)-one

Reaction of compound **76a** with polyphosphoric acid.



(*E*)-*N*-Methyl-*N*-phenylcinnamamide (500 mg, 2.1 mmol) was added to polyphosphoric acid (5 g) and the resulting solution stirred at 120 °C for 10 minutes. The reaction mixture was poured into cold water (125 mL) and extracted with dichloromethane (2 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a yellow crystalline solid which was recrystallised from ethanol to give the *title compound* (710 mg, 72 %) as an off-white crystalline solid.

Mp: 122 – 122.5 °C

IR (DCM): 3434, 1672, 1598, 754, 700 cm⁻¹.

¹H NMR (500 MHz; CDCl₃): δ = 7.25 (apparent t, *J* = 7.6, 2 H, aromatic CH), 7.19 (apparent q, *J* = 7.6, 2 H, aromatic CH), 7.08 (d, *J* = 7.3, 2 H, aromatic CH), 6.98 (d, *J* = 8.1, 1 H, aromatic CH), 6.91 (t, *J* = 7.5, 1 H, aromatic CH), 6.84 (d, *J* = 7.4, 1 H, aromatic CH), 4.15 (apparent t, *J* = 7.4, 1 H, CH), 3.31 (s 3 H CH₃), 2.91 (dd, *J* = 15.8 and 8.5, 1 H, one of CH₂), 2.86 (dd, *J* = 15.8 and 6.4, 1 H, one of CH₂).

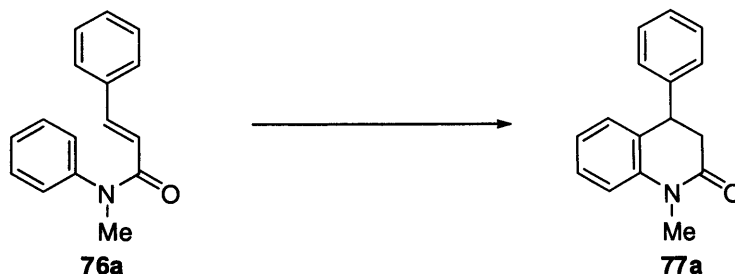
¹³C NMR (125 MHz; CDCl₃): δ = 169.4 (C=O), 141.1 (aromatic C), 140.4 (aromatic C), 129.2 (aromatic C), 128.9 (aromatic CH), 128.1 (aromatic CH), 127.9 (aromatic CH), 127.8 (aromatic CH), 127.2 (aromatic CH), 123.1 (aromatic CH), 114.9 (aromatic CH), 41.5 (CH), 38.9 (CH₂), 29.6 (CH₃).

MS-ES: *m/z* (%) 238 (MH⁺, 100).

HRMS-ES: *m/z* [M + Na]⁺ calcd for C₁₆H₁₅NONa: 260.1051; found: 260.1049.

3,4-Dihydro-1-methyl-4-phenylquinolin-2(1H)-one (77a)

Reaction of compound 76a with 1.75 equivalents of aluminium chloride.

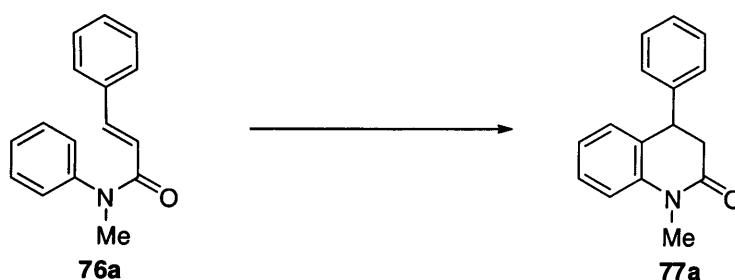


(*E*)-*N*-Methyl-*N*-phenylcinnamamide (130 mg, 0.55 mmol) was added to a solution of aluminium chloride (128 mg, 0.96 mmol) in chlorobenzene (10 mL) and the resulting solution stirred at 90 °C for 2 hours. The reaction mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The combined ether layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a oily solid. Purification by flash column chromatography (eluent; dichloromethane : methanol 100:1) gave the *title compound* (121 mg, 81%) as an off-white crystalline solid.

Data as previously reported

3,4-Dihydro-1-methyl-4-phenylquinolin-2(1H)-one (77a)

Reaction of compound 76a with 2 equivalents of bismuth chloride.



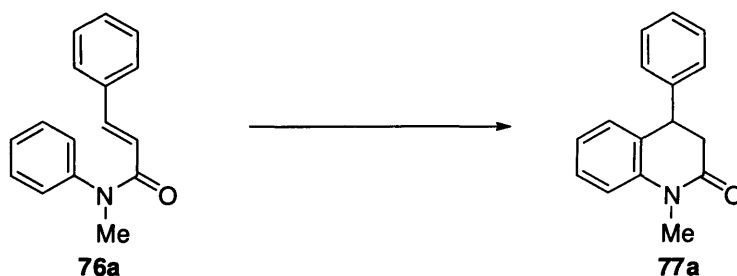
(*E*)-*N*-Methyl-*N*-phenylcinnamamide (360 mg, 1.5 mmol) was added to a solution of bismuth chloride (956 mg 3.0 mmol) in chlorobenzene (10 mL) and the resulting solution stirred at 90 °C for 4 days. The resulting solution was quenched with

hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The solvent was removed *in vacuo* to give a oily solid. Purification by flash column chromatography (eluent; dichloromethane : methanol 100:1) gave the *title compound* (306 mg, 85 %) as a off-white crystalline solid.

Data as previously reported.

3,4-Dihydro-1-methyl-4-phenylquinolin-2(1H)-one (77a)

Reaction of compound 76a with 2 equivalents of aluminium chloride under microwave conditions.

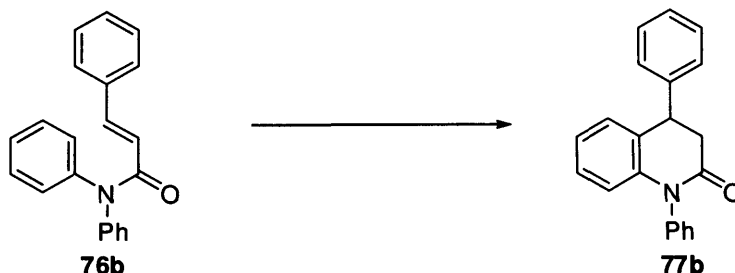


(*E*)-*N*-Methyl-*N*-phenylcinnamamide (119 mg, 0.5 mmol) was added to a solution of aluminium chloride (133 mg, 1.0 mmol) in chlorobenzene (5 mL) and the resulting solution stirred under microwave conditions 100 W at 90 °C with cooling for 15 minutes. The resulting mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The combined ether layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a oily solid identified as the *title compound* and starting material (53 % conversion from starting material).

Data as previously reported.

3,4-Dihydro-1,4-diphenylquinolin-2(1H)-one (77b)

Reaction of compound 76b with polyphosphoric acid.



(*E*)-*N,N*-Diphenylcinnamamide (250 mg, 0.8 mmol) was added to polyphosphoric acid (5 g) and the resulting solution stirred at 120 °C for 10 minutes. The reaction mixture was poured into cold water (125 mL) and extracted with dichloromethane (2 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a yellow crystalline solid which was recrystallised from ethanol to give the *title compound* (212 mg, 85 %) as an off-white crystalline solid.

Mp: 110 – 111 °C.

IR (DCM): 3061, 1685, 1599, 753, 735, 696 cm⁻¹.

¹H NMR (500 MHz; CDCl₃): δ = 7.44 (apparent t, *J* = 7.7, 2 H, 2 x aromatic CH), 7.36 (d, *J* = 7.5, 1 H, aromatic CH), 7.30 (apparent t, *J* = 7.4, 2 H, 2 x aromatic CH), 7.25 – 7.12 (m, 6 H, 6 x aromatic CH), 7.04 – 6.98 (m, 1 H, aromatic CH), 6.37 (d, *J* = 8.1, 1 H, aromatic CH), 4.33 (apparent t, *J* = 6.9, 1 H, CH), 3.10 – 3.02 (m, 2 H, CH₂).

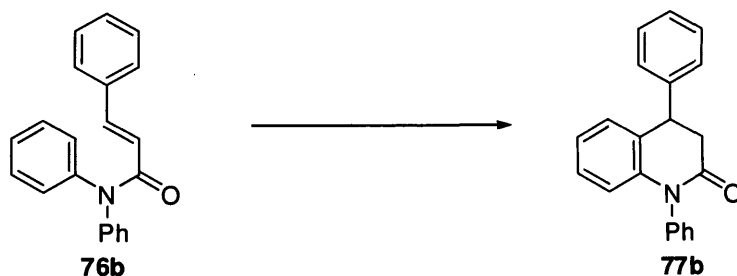
¹³C NMR (125 MHz; CDCl₃): δ = 169.1 (C=O), 141.4 (aromatic C), 141.1 (aromatic C), 138.3 (aromatic C), 129.9 (aromatic CH), 129.4 (aromatic CH), 129.0 (aromatic CH), 128.9 (aromatic CH), 128.6 (aromatic C), 128.3 (aromatic CH), 128.2 (aromatic CH), 127.8 (aromatic CH), 127.6 (aromatic CH), 127.3 (aromatic CH), 123.3 (aromatic CH), 117.8 (aromatic CH), 117.4 (aromatic CH), 41.7 (CH), 39.4 (CH₂).

MS-ES: *m/z* (%) 338 (MH⁺, 100).

HRMS-ES: *m/z* [M + K]⁺ calcd for C₂₁H₁₇K: 338.0944; found: 338.0944.

3,4-Dihydro-1,4-diphenylquinolin-2(1H)-one (76b)

Reaction of compound **76b** with 1.75 equivalents of aluminium chloride.

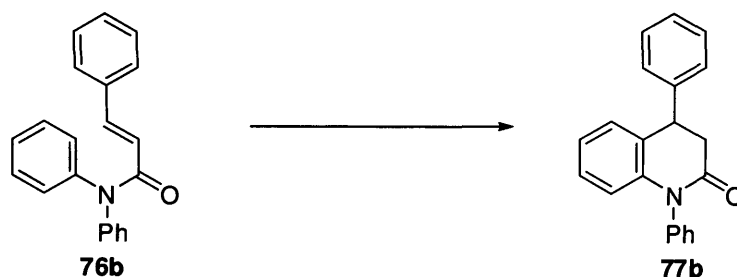


(*E*)-*N,N*-Diphenylcinnamamide (150 mg, 0.5 mmol) was added to a solution of aluminium chloride (116 mg, 0.88 mmol) in chlorobenzene (10 mL) and the resulting solution stirred at 90 °C for 2 hours. The reaction mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The combined ether layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a oily solid. Purification by flash column chromatography (eluent 100 : 1 dichloromethane : methanol) gave the *title compound* (117 mg, 78%) as an off-white crystalline solid.

Data as previously reported.

3,4-Dihydro-1,4-diphenylquinolin-2(1H)-one (76b)

Reaction of compound **76b** with 2 equivalents of bismuth chloride.

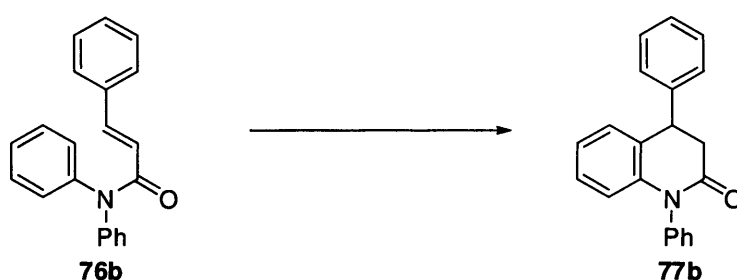


(*E*)-*N,N*-Diphenylcinnamamide (400 mg, 1.3 mmol) was added to a solution of bismuth chloride (836 mg 2.6 mmol) in chlorobenzene (10 mL) and the resulting solution stirred at 90 °C for 4 days. The reaction mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The

combined ether layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a oily solid. Purification by flash column chromatography (eluent 100 : 1 dichloromethane : methanol) gave the *title compound* (236 mg, 59 %) as an off-white crystalline solid.

3,4-Dihydro-1,4-diphenylquinolin-2(1H)-one (76b)

Reaction of compound 76b with 2 equivalents of aluminium chloride under microwave conditions.

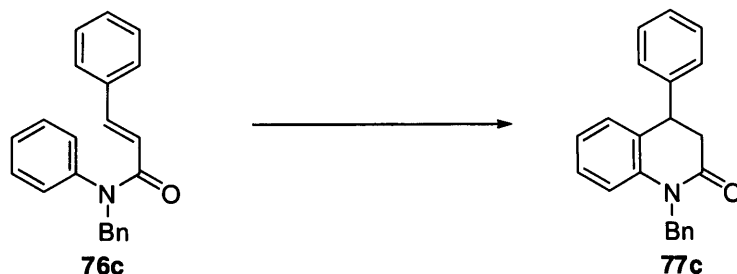


(*E*)-*N,N*-Phenylcinnamamide (150 mg, 0.5 mmol) was added to a solution of aluminium chloride (133 mg 1.0 mmol) in chlorobenzene (5 mL) and the resulting solution stirred under microwave conditions 100 W at 90 °C with cooling for 15 minutes. The resulting mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The combined ether layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a oily solid identified as the *title compound* and starting material (60 % conversion from starting material).

Data as previously reported.

1-Benzyl-3,4-dihydro-4-phenylquinolin-2(1H)-one (77c)

Reaction of compound 76c with polyphosphoric acid.



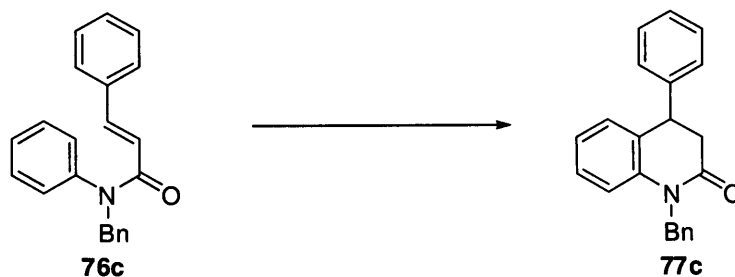
(*E*)-*N*-Benzyl-*N*-phenylcinnamamide (250 mg, 0.8 mmol) was added to polyphosphoric acid (5 g) and the resulting solution stirred at 120 °C for 10 minutes. The reaction mixture was poured onto cold water (125 mL) and extracted with dichloromethane (2 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a brown oil. Purification by flash column chromatography (eluent 100 : 1 dichloromethane : methanol) gave the *title compound* (170 mg, 68 %) as a light brown oil.

¹H NMR (400 MHz; CDCl₃): δ = 7.32 – 7.11 (m, 11 H, aromatic CH), 7.08 – 6.85 (m, 3 H, aromatic CH), 5.23 (d, *J* = 16.1, 1 H, one of benzyl CH₂), 4.99 (d, *J* = 16.1, 1 H, one of benzyl CH₂), 4.26 (apparent t, *J* = 6.9, 1 H, CH), 3.65 (dd, *J* = 15.8 and 7.9, 1 H, one of CH₂), 3.02 (dd, *J* = 15.8 and 6.0, 1 H, one of CH₂).

¹³C NMR (100 MHz; CDCl₃): δ = 170.7 (C=O), 140.9 (aromatic C), 139.9 (aromatic C), 136.8 (aromatic C), 128.8 (aromatic CH), 128.7 (aromatic CH), 128.3 (aromatic CH), 127.9 (aromatic CH), 127.8 (aromatic CH), 127.1 (aromatic CH), 126.7 (aromatic C), 126.6 (aromatic CH), 123.2 (aromatic CH), 115.6 (aromatic CH), 45.9 (benzyl CH₂), 42.0 (CH), 38.4 (CH₂).

1-Benzyl-3,4-dihydro-4-phenylquinolin-2(1H)-one (77c)

Reaction of compound 76c with 1.75 equivalents of aluminium chloride.

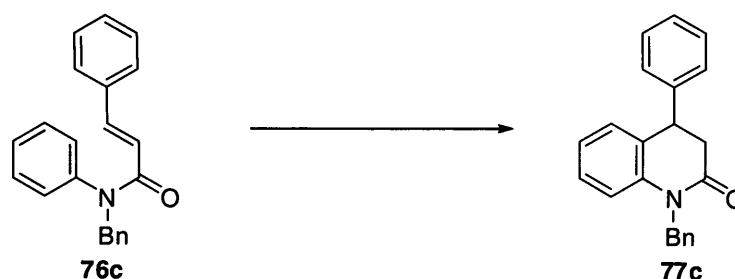


(*E*)-*N*-Benzyl-*N*-phenylcinnamamide (150 mg, 0.47 mmol) was added to a solution of aluminium chloride (112 mg, 0.83 mmol) in chlorobenzene (10 mL) and the resulting solution stirred at 90 °C for 2 hours. The combined ether The resulting solution was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The combined ether layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a brown. Purification by flash column chromatography (eluent; dichloromethane : methanol 100 : 1) gave the *title compound* (62 mg, 41%) as a light brown oil.

Data as previously reported.

1-Benzyl-3,4-dihydro-4-phenylquinolin-2(1H)-one (77c)

Reaction of compound 76c with 2 equivalents of bismuth chloride.



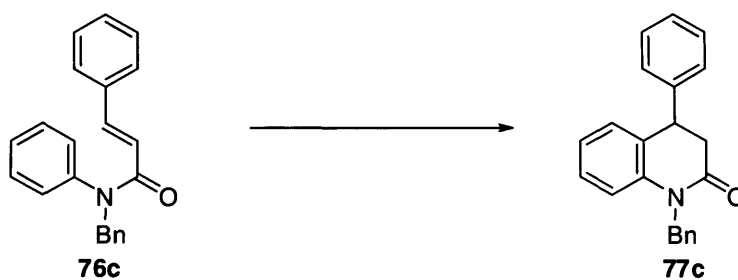
(*E*)-*N*-Benzyl-*N*-phenylcinnamamide (312 mg, 1.0 mmol) was added to a solution of bismuth chloride (630 mg 2.0 mmol) in chlorobenzene (5 mL) and the resulting solution stirred at 90 °C for 4 days. The reaction mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The

combined ether layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a oily solid. Purification by flash column chromatography (eluent 100 : 1 dichloromethane : methanol) gave the *title compound* (96 mg, 32 %) as a light brown oil.

Data as previously reported.

1-Benzyl-3,4-dihydro-4-phenylquinolin-2(1H)-one (77c)

Reaction of compound 76c with 2 equivalents of aluminium chloride under microwave conditions.

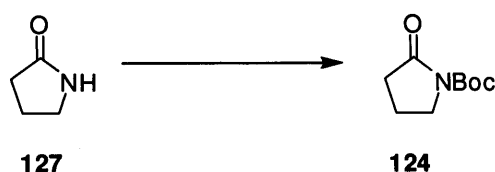


(*E*)-*N*-Benzyl-*N*-diphenylcinnamamide (78 mg, 0.25 mmol) was added to a solution of aluminium chloride (64 mg, 0.5 mmol) in chlorobenzene (5 mL) and the resulting solution stirred under microwave conditions 100 W at 90 °C with cooling for 15 minutes. The resulting mixture was quenched with hydrochloric acid (2 M, 50 mL) and extracted with diethyl ether (2 x 25 mL). The combined ether layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a oily solid identified as the *title compound* and starting material (47 % conversion from starting material).

Data as previously reported.

6.3 Experimental Data for Chapter 3

tert-Butyl 2-oxopyrrolidine-1-carboxylate (**124**).⁹²

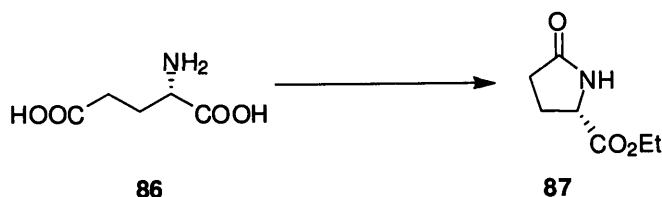


To a solution of pyrrolidinone (4.0 g, 47 mmol), DMAP (10 mg) and triethylamine (5 mL) in dichloromethane (100 mL) was added di-*tert*-butyl dicarbonate (10.25 g, 47 mmol) in dichloromethane (25 mL) over 10 minutes at 0 °C. The resulting solution was warmed to 25 °C and stirred for 18 hours. The reaction was quenched with saturated aqueous ammonium chloride solution (100 mL) and extracted into dichloromethane (3 x 100 mL). The combined dichloromethane layers were washed with brine (2 x 150 mL) and dried over magnesium sulphate. The solvent was removed *in vacuo*, to give a dark brown oil. Purification by flash column chromatography on silica gel (eluent hexane:ethyl acetate 4:1) gave the *title compound* (7.58 g, 87 %) as a pale yellow oil.

¹H NMR (400 MHz; CDCl₃): δ = 3.65 (t, *J* = 7.2, 2 H, CH₂N), 2.42 (t, *J* = 8.1, 2 H, CH₂CO), 1.90 (apparent quintet, *J* = 7.6, 2 H, CH₂CH₂), 1.43 (s, 9 H, (CH₃)₃C).

¹³C NMR (125 MHz; CDCl₃): δ = 174.4 (ester C=O), 150.3 (carbamate C=O), 82.8 ((CH₃)₃CO), 46.5 (CH₂N), 33.0 (CH₂CO), 28.1 ((CH₃)₃C), 17.4 (CH₂CH₂).

(S)-Ethyl 5-oxopyrrolidine-2-carboxylate (87).⁹³



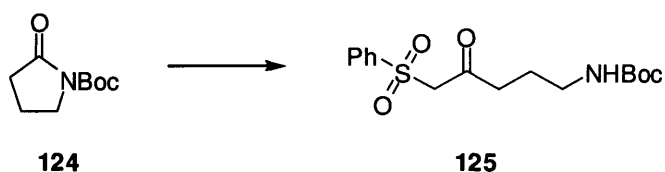
Thionyl chloride (64.6 g, 0.54 mol) was added to a suspension of *L*-glutamic acid (40.0 g, 0.27 mol) in ethanol (250 mL) dropwise at 0 °C. The resulting solution was slowly brought to reflux for 1 hour. The solvent was removed *in vacuo* to give off-white crystals which, after heating at 145 °C at 1 mm Hg for 8 hours gave the *title compound* (34.4 g, 81 %) as a waxy solid.

Mp: 49 – 50 °C (lit: 50 – 51 °C).

¹H NMR (400 MHz; CDCl₃): δ = 7.12 (s, 1 H, NH), 4.20 (dd, *J* = 8.2 and 5.1, 1 H, CHN), 4.15 (q, *J* = 7.1, 2 H, CH₂CH₃), 2.45 – 2.25 (m, 3 H, CH₂O and one of CH₂CH₂), 2.18 – 2.09 (m, 1 H, one of CH₂CH₂), 1.22 (t, *J* = 7.1, 3 H, CH₃).

¹³C NMR (125 MHz; CDCl₃): δ = 178.2 (ester C=O), 172.1 (amide C=O), 61.6 (CH₂O), 55.5 (CHN), 29.3(CH₂CO), 24.8 (CH₂CH₂), 14.1 (CH₃).

***tert*-Butyl 4-oxo-5-(phenylsulphonyl)pentylcarbamate (125).**⁶⁷



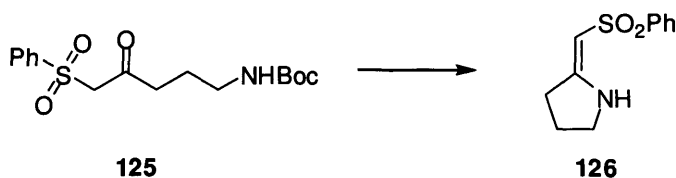
A solution of *n*-butyllithium (2 mL, 2.5 M in hexanes, 5 mmol) in THF (10 mL) was cooled to -78 °C. Methyl phenyl sulphone (0.77 g, 5 mmol) in THF (3 mL) was added over 30 minutes, after which the solution was stirred for a further 30 minutes at -78 °C. *N*-*t*-Butoxycarbonylpyrrolidine-2-one (**124**) (0.92 g, 5 mmol) in THF (5 mL) was added over 30 minutes at -78 °C, and the solution warmed to 25 °C and left

to stir for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over magnesium sulphate and the solvent removed *in vacuo* to give the *title compound* (1.8 g, 96 %) as an orange oil which solidified upon standing to give a waxy solid.

^1H NMR (400 MHz; CDCl_3): δ = 7.82 (d, J = 7.4, 2 H, aromatic CH), 7.62 (t, J = 7.5, 1 H, aromatic CH), 7.52 (apparent t, J = 7.7, aromatic CH), 4.62 (broad s, 1 H, NH), 4.15 (s, 2 H, OCCH_2CO), 3.03 (apparent q, J = 6.4, 2 H, CH_2NH), 2.70 (t, J = 6.8, 2 H, COCH_2), 1.69 (apparent quintet, J = 6.8, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.36 (s, 9 H, $\text{C}(\text{CH}_3)_3$).

^{13}C NMR (100 MHz; CDCl_3): δ = 197.8 (CH_2COCH_2), 156.1 (OCON), 138.7 (aromatic C), 134.4 (aromatic CH), 129.4 (aromatic CH), 128.3 (aromatic CH), 79.3 (OCCMe_3), 67.0 (CH_2O), 41.4 (CH_2N), 39.3 (COCH_2CO), 28.4 ($\text{C}(\text{CH}_3)_3$), 23.7 ($\text{CH}_2\text{CH}_2\text{N}$).

2-Phenylsulphonylmethyl-(Z)-ylidenepyrrolidine (126).⁶⁷



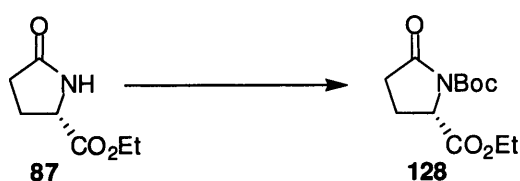
N-*t*-Butoxycarbonyl-4-oxo-5-phenylsulphonylpentylamine (**125**) (1.4 g, 4.1 mmol) was dissolved in dichloromethane (5 mL). TFA (3.48 mL, 45 mmol) was added and the solution stirred for 18 hours at 25 °C. The volatiles were removed *in vacuo* and the resulting oil was dissolved in dichloromethane (5 mL). Saturated aqueous sodium bicarbonate was added until neutral to pH paper, and the organic material was extracted into dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The residual yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (620 mg, 67 %) as a yellow oil.

^1H NMR (400MHz; CDCl_3): δ = 7.78 (d, J = 6.7, 2 H, aromatic CH), 7.43 – 7.34 (m, 3 H, aromatic CH), 7.05 (broad s, 1 H, NH), 4.58 (s, 1 H, CCH), 3.38 (t, J = 6.9, 2 H,

CH₂N), 2.48 (t, *J* = 7.8, 2 H, CH₂CO), 1.86 (apparent quintet, *J* = 7.3, 2 H, CH₂CH₂CH₂).

¹³C NMR (100MHz; CDCl₃): δ = 161.9 (alkene C), 145.4 (aromatic C), 131.8 (aromatic CH), 128.1 (aromatic CH), 125.6 (aromatic CH), 80.8 (alkene CH), 47.5 (CH₂N), 33.2 (CH₂C=C), 21.7 (CH₂CH₂N).

(S)-1-tert-Butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate (128).⁹⁴

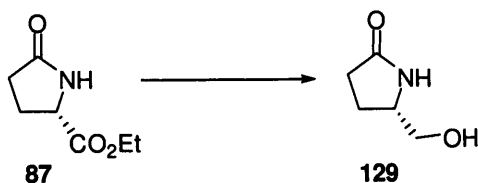


Di-*tert*-butyl dicarbonate (10.6 g, 48.4 mmol) in dichloromethane (25 mL) was added to a solution of (*S*)-ethyl 5-oxopyrrolidine-2-carboxylate (**87**) (7.6 g, 48.4 mmol), DMAP (10 mg) and triethylamine (5 mL) in dichloromethane (100 mL) over 10 minutes at 0 °C. The solution was warmed to 25 °C and stirred for 18 hours. The resulting mixture was quenched with aqueous saturated ammonium chloride solution (100 mL) extracted into dichloromethane (3 x 100 mL). The combined dichloromethane layers were washed with brine (2 x 150 mL) and dried over magnesium sulphate. The solvent was removed *in vacuo* to give a dark oil which upon purification by flash column chromatography (eluent; hexane:ethyl acetate 4:1) gave the *title compound* (10.5 g, 84 %) as a pale yellow oil.

¹H NMR (400 MHz; CDCl₃): δ = 4.50 (dd, *J* = 9.5 and 2.9, 1 H, CHN), 4.15 (q, *J* = 7.1, 2 H, CH₂O), 2.56 (apparent dt, *J* = 17.5 and 9.5, 1 H, one of CH₂CO), 2.41 (ddd, *J* = 17.5, 9.5 and 3.5, 1 H, one of CH₂CO), 2.25 (ddd, *J* = 19.5, 13.3 and 3.8, one of CH₂CH₂), 1.96 (ddt, *J* = 13.3, 9.6 and 3.3, 1 H, one of CH₂CO), 1.39 (s, 9 H, (CH₃)₃), 1.25 (t, *J* = 7.1, 3 H, CH₃).

¹³C NMR (63 MHz; CDCl₃): δ = 173.4 (ester C=O), 171.3 (amide C=O), 149.3 (carbamate C=O), 83.5 (OC(CH₃)₃), 61.7 (CHN), 58.9 (CH₂O), 27.4 (CH₂CH₂), 21.5 ((CH₃)₃), 14.2 (CH₃).

(S)-5-(Hydroxymethyl)pyrrolidin-2-one (129).⁹⁵

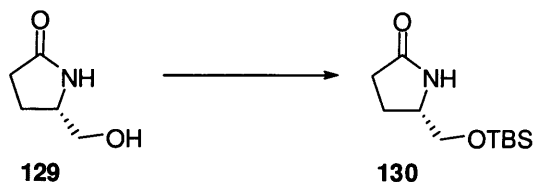


Sodium borohydride (2.53 g, 66.8 mmol) was added to a solution of (*S*)-ethyl 5-oxopyrrolidine-2-carboxylate (**87**) (10.5 g, 66.8 mmol) in ethanol (150 mL) portion wise over 30 minutes at 0 °C. The resulting solution was warmed to 25 °C and stirred for 4 hours. The resulting mixture was acidified with concentrated hydrochloric acid and the solvent removed *in vacuo*. The resulting oily solid was dissolved in chloroform / methanol (10:1) and filtered through celite. The solvent was removed *in vacuo* to give the *title compound* (6.2 g, 81 %) as a waxy solid.

¹H NMR (400 MHz; CDCl₃): δ = 8.67 (s, 1 H, NH), 5.54 (broad s, 1 H, OH), 3.88 (m, 1 H, CHN), 3.69 (dd, *J* = 11.8 and 3.1, 1 H, one of CH₂O), 3.45 (dd, *J* = 11.8 and 6.1, 1 H, one of CH₂O), 2.50 (m, 2 H, CH₂CO), 2.17 (m, 1 H, one of CH₂CH₂) 1.87 (m, 1 H, one of CH₂CH₂).

¹³C NMR (62.5 MHz; CDCl₃): δ = 180.3 (C=O), 64.9 (CHN), 57.9 (CH₂O), 30.5 (CH₂CO), 22.4 (CH₂CH₂).

(S)-tert-Butyl 2-((tert-butyldimethylsilyloxy)methyl)-5-oxopyrrolidine-1-carboxylate (130).⁹⁶



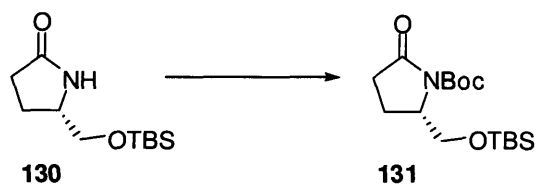
tert-Butyldimethylsilyl chloride (7.46 g, 49.5 mmol) was added to a solution of (*S*)-5-(hydroxymethyl)pyrrolidin-2-one (**129**) (4.0 g, 34.7 mmol), imidazole (2.35 g,

35.0 mmol) and DMAP (10 mg) in dry dimethylformamide (100 mL). The resulting solution was stirred at 25 °C for 18 hours. Excess solvent was removed *in vacuo*, and the resulting oily solid was dissolved in dichloromethane and washed with saturated aqueous ammonium chloride solution (2 x 50 mL) and saturated brine (3x 50 mL). The dichloromethane layer was concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography on silica gel (eluent hexane:ethyl acetate 1:1) gave the *title compound* (5.26 g, 66 %) as a pale yellow oil.

¹H NMR (250 MHz; CDCl₃): δ = 6.2 (s, 1 H, NH), 3.75 – 3.64 (m, 1 H, CHN), 3.55 (dd, *J* = 10.1 and 4.1, 1 H, one of CH₂OTBS), 3.40 (dd, *J* = 10.1 and 7.3, 1 H, one of CH₂OTBS), 2.33 – 2.23 (m, 2 H, CH₂CO), 2.18 – 2.02 (m, 1 H, one of CH₂CH₂), 1.71 (dddd, *J* = 18.1, 9.1, 7.0 and 5.3, 1 H, one of CH₂CH₂), 0.82 (s, 9 H (CH₃)₃), 0.0 (s, 6 H, 2 x CH₃).

¹³C NMR (62.5 MHz; CDCl₃): δ = 178.2 (C=O), 66.8 (CH₂O), 55.8 (CHN), 29.9 (CH₂CO), 25.8 ((CH₃)₃), 22.8 (CH₂CH₂), 18.2 (C(CH₃)₃), -5.4 (2 x CH₃).

(*S*)-*tert*-Butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-5-oxopyrrolidine-1-carboxylate (131).⁹⁷



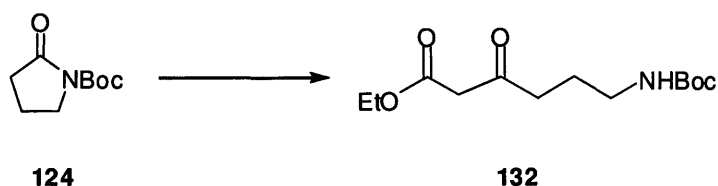
di-*tert*-Butyl dicarbonate (1.20 g, 5.5 mmol) in dichloromethane (5 mL) was added to a solution of (*S*)-*tert*-butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-5-oxopyrrolidine-1-carboxylate (**130**) (1.25 g, 5.5 mmol), triethylamine (1.5 mL) and DMAP (10 mg) in dichloromethane (50 mL) over 5 minutes at 0 °C. The resulting solution was warmed to 25 °C and stirred for 18 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (50 mL) and extracted with dichloromethane (2 x 100 mL). The combined dichloromethane layers were washed with brine (2 x 100 mL) and dried over magnesium sulphate. Excess solvent was removed *in vacuo* to give a light brown oil. Purification by flash column

chromatography on silica gel (eluent hexane:ethyl acetate 4:1) gave the *title compound* (1.43 g, 79 %) as a colourless oil.

^1H NMR (250 MHz; CDCl_3): δ = 4.14 (ddt, J = 5.0, 4.2 and 2.1, 1 H, CHN), 3.89 (dd, J = 10.4 and 3.8, 1 H, one of CH_2O), 3.65 (dd, J = 10.4 and 3.8, 1 H, one of CH_2O), 2.68 (dt, J = 17.4 and 10.4, 1 H, one of CH_2CO), 2.34 (ddd, J = 17.5, 9.3 and 2.6, 1 H, one of CH_2CO), 2.17 – 1.91 (m, 2 H, CH_2CH_2), 1.49 (s, 9 H, $\text{OC}(\text{CH}_3)_3$), 0.82 (s, 9 H, $\text{SiC}(\text{CH}_3)_3$), 0.0 (s, 6 H, 2 x CH_3).

^{13}C NMR (62.5 MHz; CDCl_3): δ = 174.9 (amide $\text{C}=\text{O}$), 150.0 (carbamates $\text{C}=\text{O}$), 82.6 (OC), 64.3 (OCH_2), 58.9 (CHN), 32.3 (CH_2CO), 28.1 ($\text{OC}(\text{CH}_3)_3$), 25.8 ($\text{SiC}(\text{CH}_3)_3$), 21.1 (CH_2CH_2), 18.1 (SiC), -5.6 (CH_3), -5.6 (CH_3).

Ethyl 6-*t*-butoxycarbonylamino-3-oxohexanoate (132).



A solution of lithium diisopropylamide (13.5 mL, 2 M in heptane, 27 mmol) in THF (100 mL) was cooled to -78 °C. Ethyl acetate (2.58 mL, 27 mmol) in THF (3 mL) was added dropwise over 30 minutes, and the solution allowed to stir for a further 30 minutes. *N-t*-Butoxycarbonylpyrrolidine-2-one (**124**) (5.0 g, 27 mmol) in THF (5 mL) was added over 30 minutes at -78 °C, and the solution warmed to 25 °C and left to stir for 18 hours. Saturated aqueous ammonium chloride solution (100 mL) was added and the organic material extracted with into dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over magnesium sulphate and the solvent removed *in vacuo*. Purification by flash column chromatography (eluent 2:1 hexane:ethyl acetate) gave the *title compound* (6.46 g, 88 %) as a pale yellow oil.

IR (neat): 3380, 2977, 2925, 1739, 1709, 1521 cm^{-1} .

^1H NMR (400 MHz; CDCl_3): δ = 4.60 (broad s, 1 H, NH), 4.12 (q, J = 7.1, 2 H, CH_2O), 3.41 (s, 2 H, COCH_2CO), 3.06 (apparent q, J = 6.5, 2 H, CH_2NHBoc), 2.53

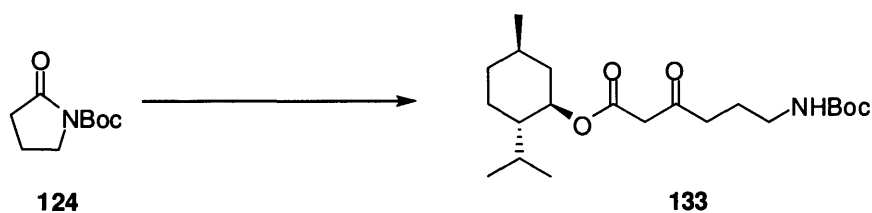
(t, $J = 7.1$, 2 H, COCH₂), 1.72 (apparent quintet, $J = 6.9$, 2 H, CH₂CH₂CH₂), 1.37 (s, 9 H, *t*-Bu), 1.21 (t, $J = 7.1$, 3 H, CH₃CH₂O).

¹³C NMR (100 MHz; CDCl₃): $\delta = 203.7$ (C=O), 168.3 (C=O), 157.0 (C=O), 79.7 (OC(CH₃)₃), 61.8 (OCH₂), 49.6 (NCH₂), 40.2 (COCH₂CO), 39.9 (COCH₂CH₂), 28.6 ((CH₃)₃), 24.0 (CH₂CH₂N), 14.2 (OCH₂CH₃).

MS-ES: m/z (%) = 296 (M + Na, 83), 240 (7), 156 (100), 128 (16).

HRMS-ES: m/z [M + Na]⁺ calcd for C₁₃H₂₃NO₅Na: 296.1474; found: 296.1473.

(-)-Menthyl 6-*t*-butoxycarbonylamino-3-oxohexanoate (133).



A solution of lithium diisopropylamide (1.5 mL, 2 M in heptane, 3 mmol) in THF (10 mL) was cooled to -78 °C. (-)-Menthyl acetate (595 mg, 3 mmol) in THF (3 mL) was added over 30 minutes. After stirring for 30 minutes at -78 °C, *N-t*-butoxycarbonylpyrrolidine-2-one (**124**) (555 mg, 3 mmol) in THF (5 mL) was added over 30 minutes at -78 °C, and the solution warmed to 25 °C and left to stir for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over magnesium sulphate and the solvent removed *in vacuo* to give a yellow crystalline solid which was recrystallised from hexane/diethyl ether to give the *title compound* (965 mg, 84 %) as an off-white crystalline solid.

Mp. 88 – 89 °C.

IR (CHCl₃): 3398, 2958, 1735, 1715, 1170 cm⁻¹.

¹H NMR (500 MHz; CDCl₃): $\delta = 4.65$ (apparent dt, $J = 4.4, 10.9$, 1 H, menthyl 1-H), 4.59 – 4.52 (broad s, 1 H, NH), 3.37 and 3.35 (AB quartet, $J = 15.5$, 2 H, COCH₂CO), 3.05 (apparent q, $J = 6.3$, 2 H, CH₂N), 2.52 (t, $J = 7.1$, 2 H, CH₂CO),

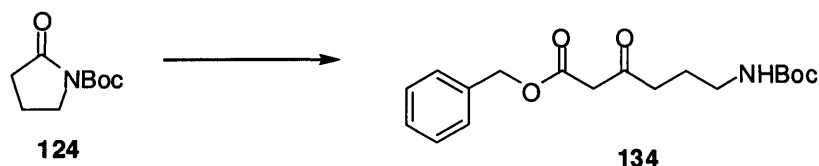
1.98 – 1.92 (m, 1 H, menthyl 6- H_{eq}), 1.82 – 1.75 (apparent doubled septet, $J = 2.7$, 7.0, 1 H, $CH(CH_3)_2$), 1.72 (apparent quintet, $J = 6.9$, 2 H, $CH_2CH_2CH_2$), 1.64 – 1.58 (m, 2 H, menthyl 3- H_{eq} and 4- H_{eq}), 1.48 – 1.40 (m, 1 H, menthyl 5- H_{ax}), 1.37 (s, 9 H, $(CH_3)_3C$), 1.35 – 1.27 (m, 1 H, menthyl 2- H_{ax}), 1.03 – 0.96 (m, 1 H, menthyl 3- H_{ax}), 0.92 (apparent q, $J = 11.7$, 1 H, menthyl 4- H_{ax}), 0.84 (d, $J = 6.6$, 3 H, CH_3), 0.82 (d, $J = 7.1$, 3 H, CH_3), 0.82 – 0.77 (m, 1 H, menthyl 4- H_{ax}), 0.70 (d, $J = 7.0$, 3 H, CH_3).

^{13}C NMR (125 MHz; $CDCl_3$): $\delta = 202.5$ (ketone C=O), 166.9 (ester C=O), 156.1 (carbamate C=O), 79.2 (C-O), 75.5 (menthyl 1-CH), 49.6 ($COCH_2CO$), 46.8 (menthyl 2-CH), 40.7 (menthyl 6- CH_2), 40.0 (CH_2), 39.7 (CH_2), 34.1 (menthyl 4- CH_2), 31.4 (menthyl 5-CH), 28.4 ($(CH_3)_3CO$), 26.1 (CH), 23.8 (menthyl 3- CH_2), 23.2 (CH_2), 22.0 (CH_3), 20.7 (CH_3), 16.1 (CH_3).

MS-ES: m/z (%) = 406 (M + Na, 100), 266 (73), 128 (32).

HRMS-ES: m/z [M + Na] $^+$ calcd for $C_{21}H_{37}NO_5Na$: 406.2569; found: 406.2585.

Benzyl 6-*t*-butoxycarbonylamino-3-oxohexanoate (134).



A solution of lithium diisopropylamide (2.7 mL, 2 M in heptane, 5.4 mmol) in THF (40 mL) was cooled to -78 °C. Benzyl acetate (810 mg, 5.4 mmol) in THF (3 mL) was added over 30 minutes. After stirring for 30 minutes at -78 °C, *N-t*-butoxycarbonylpyrrolidine-2-one (**124**) (1.0 g, 5.4 mmol) in THF (8 mL) was added over 30 minutes at -78 °C, and the solution allowed to warm to 25 °C and the resulting solution stirred for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the organic material extracted into dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over magnesium sulphate and the solvent removed *in vacuo* to give a yellow oil. Purification by flash column chromatography (eluent 5:1 hexane:ethyl acetate) gave the *title compound* (1.2 g, 68 %) as a colourless oil.

IR (neat): 3402, 2976, 2925, 1739, 1714, 1519, 1167, 751, 698 cm^{-1} .

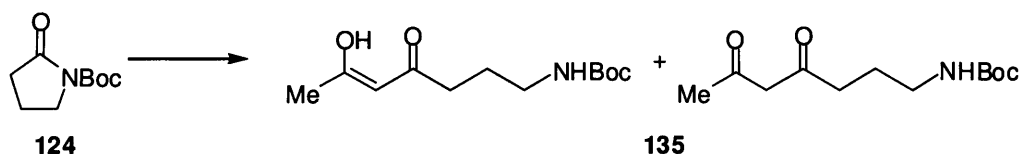
^1H NMR (400 MHz; CDCl_3): δ = 7.36 - 7.26 (m, 5 H, aromatic CH), 5.10 (s, 2 H, OCH_2), 4.50 (broad s, 1 H, NH), 3.42 (s, 2 H, COCH_2CO), 3.01 (apparent q, J = 6.4 CH_2N), 2.50 (t, J = 7.1, 2 H, CH_2CO), 1.68 (apparent quintet, J = 6.8, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.37 (s, 9H, $\text{C}(\text{CH}_3)_3$).

^{13}C NMR (125 MHz; CDCl_3): δ = 202.7 (ketone $\text{C}=\text{O}$), 167.1 (ester $\text{C}=\text{O}$), 156.1 (carbamate $\text{C}=\text{O}$), 135.2 (aromatic C), 128.7 (aromatic CH), 128.6 (aromatic CH), 128.5 (aromatic CH), 79.3 ($(\text{CH}_3)_3\text{CO}$), 67.2 (CH_2O), 49.2 (CH_2N), 45.0 (COCH_2CO), 39.6 (COCH_2), 28.4 ($(\text{CH}_3)_3\text{C}$), 23.8 ($\text{CH}_2\text{CH}_2\text{N}$).

MS-ES: m/z (%) = 358 (M + Na, 62), 218 (100).

HRMS-ES: m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_5\text{Na}$: 358.1630; found: 358.1623.

N-*t*-Butoxycarbonyl-4,6-dioxoheptylamine (135).



A solution of lithium diisopropylamide (1.5 mL, 2 M in heptane, 3 mmol) in THF (10 mL) was cooled to -78 $^{\circ}\text{C}$. Acetone (174 mg, 3 mmol) in THF (3 mL) was added over 30 minutes. After stirring for 30 minutes at -78 $^{\circ}\text{C}$, *N*-*t*-butoxycarbonylpyrrolidine-2-one (**124**) (555 mg, 3 mmol) in THF (5 mL) was added over 30 minutes at -78 $^{\circ}\text{C}$, and the solution warmed to 25 $^{\circ}\text{C}$ and left to stir for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (535 mg, 74 %) as a colourless oil (5:1 mixture of enol and keto tautomers).

IR (CH_2Cl_2): 3357, 2976, 1703, 1619, 1170 cm^{-1} .

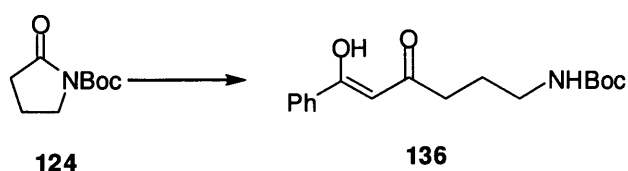
^1H NMR (500 MHz; CDCl_3): (enol tautomer) δ = 5.44 (s, 1 H, enol CH), 4.58 (broad s, 1 H, NH), 3.09 (apparent q, J = 6.5, 2 H, CH_2N), 2.25 (t, J = 7.3, COCH_2), 1.98 (s, 3 H, CH_3), 1.73 (apparent quintet, J = 7.5, 2 H, CH_2), 1.37 (s, 9 H, $(\text{CH}_3)_3$).

^{13}C NMR (125 MHz; CDCl_3): (enol tautomer) δ = 194.0 (C=O), 190.7 (enol C-O), 156.0 (C=O), 100.0 (enol CH), 79.3 (C-O), 40.0 (CN_2N), 35.7 (CH_2), 28.4 ($(\text{CH}_3)_3\text{C}$), 25.9 (CH_2), 24.8 (CH_3).

MS-ES: m/z (%) = 266 (M + Na, 100), 127 (28).

HRMS-ES: m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_4\text{Na}$: 266.1368; found: 266.1355.

***N*-*t*-Butoxycarbonyl-4,6-dioxo-6-phenylhexylamine (136).**



A solution of lithium diisopropylamide (2.8 mL, 2 M solution in heptane, 5.6 mmol) in THF (10 mL) was cooled to -78 °C. Acetophenone (0.67 mL, 5.6 mmol) in THF (2 mL) was added over 20 minutes. After stirring for 25 minutes at -78 °C, *N*-*t*-butoxycarbonylpyrrolidine-2-one (**124**) (1.0 g, 5.4 mmol) in THF (5 mL) was added over 30 minutes at -78 °C and the solution warmed to 25 °C and left to stir for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over magnesium sulphate and the solvent removed *in vacuo* to give an oily solid which was recrystallised from ethyl acetate/hexane to give the *title compound* (1.23 g, 75 %), as a off-white crystalline solid existing exclusively as the *enol* tautomer.

Mp. $72 - 73$ °C.

IR (CHCl_3): 3360, 2975, 2929, 1702, 1601, 1169 cm^{-1} .

^1H NMR (400 MHz; CDCl_3): δ = 7.81 (d, J = 7.3, 2 H, aromatic CH), 7.43 (t, J = 7.3, 1 H, aromatic CH), 7.34 (apparent t, J = 7.4, 2 H, aromatic CH), 6.12 (s, 1 H, enol

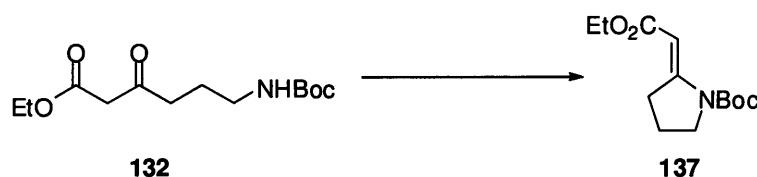
CH), 4.60 (broad s, 1 H, NH), 3.11 (apparent q, $J = 6.5$, 2 H, CH_2N), 2.40 (t, $J = 7.4$, 2 H, CH_2CO), 1.81 (apparent quintet, $J = 7.2$, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.35 (s, 9 H, $(\text{CH}_3)_3$).

^{13}C NMR (125 MHz; CDCl_3): $\delta = 196.5$ (ketone C), 182.9 (enol C), 156.0 (carbamate C), 134.8 (aromatic C), 132.3 (aromatic CH), 128.6 (aromatic CH), 127.0 (aromatic CH), 96.2 (enol CH), 78.9 ($(\text{CH}_3)_3\text{CO}$), 40.1 (CH_2N), 36.6 (CH_2), 28.4 ($(\text{CH}_3)_3\text{C}$), 26.0 (CH_2).

MS-ES: m/z (%) = 328 (M + Na, 89), 188 (100).

HRMS-ES: m/z [M + Na] $^+$ calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_4\text{Na}$: 328.1525; found: 328.1499.

(E)-tert-Butyl 2-(2-ethoxy-2-oxoethylidene)pyrrolidine-1-carboxylate ester (137).⁹⁸



To a solution of trifluoroacetic acid (1 mL) in dichloromethane (10 mL) was added Ethyl 6-*t*-butoxycarbonylamino-3-oxohexanoate (132) (1.0 g, 3.6 mmol) and the resulting solution stirred for 2 hours. The reaction was quenched with aqueous sodium bicarbonate and extracted into dichloromethane (3 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent removed *in vacuo* to give a dark oil. Purification by flash chromatography on silica gel (eluent ethyl acetate:hexane 1:4) gave the *title compound* (0.82 g, 89%) as a white crystalline solid.

Mp: 70 – 70.5 °C.

IR (DCM): 2979, 2936, 1718, 1617, 736 cm^{-1} .

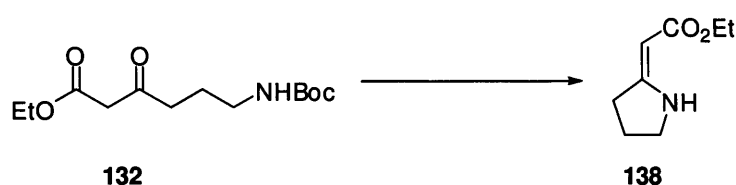
^1H NMR (500 MHz; CDCl_3): $\delta = 4.49$ (q, $J = 7.1$, 2 H, CH_2O), 3.60 (apparent t, $J = 7.2$, 2 H, $J = 7.2$, 2 H, CH_2N), 3.10 (apparent dt, $J = 1.8$ and 7.7, 2 H, $\text{CH}_2\text{C}=\text{CH}$), 1.81 (apparent quintet, $J = 7.5$, 2 H, CH_2CH_2), 1.45 (s, 9 H, $(\text{CH}_3)_3$), 1.18 (t, $J = 7.1$, CH_3).

^{13}C NMR (125 MHz; CDCl_3): δ = 169.0 (ester C=O), 157.4 (carbamate C=O), 152.0 (NC=CH), 96.1 (NC=CH), 82.0 ($\text{OC}(\text{CH}_3)_3$), 59.1 (CH_2O), 49.7 (CH_2N), 31.8 ($\text{CH}_2\text{C}=\text{CH}$), 28.2 ($(\text{CH}_3)_3$), 21.0 (CH_2CH_2), 14.4 (CH_3).

MS-ES: m/z (%) = 110 (100), 256 (M + H, 30).

HRMS-ES: m/z [M + H] $^+$ calcd for $\text{C}_{13}\text{H}_{22}\text{NO}_4$: 256.1549; found: 256.1560.

Pyrrolidin-(2Z)-ylidene-acetic acid ethyl ester (138).⁹⁹



Ethyl 6-*t*-butoxycarbonylamino-3-oxohexanoate (132) (0.5 g, 1.8 mmol) was dissolved in TFA (0.3 mL, 3.6 mmol) and the resulting solution stirred for 3 hours at 25 °C. Saturated aqueous sodium bicarbonate was added until neutral to pH paper, and the organic materials extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow solid was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (0.22 g, 78 %) as a yellow / orange crystalline solid.

Mp. 62 - 62.5 °C (Lit. 60 – 62 °C).

IR (CH_2Cl_2): 3360, 2983, 1652, 1590, 1143 cm^{-1} .

^1H NMR (400MHz; CDCl_3): δ = 7.85 (broad s, 1 H, NH), 4.49 (broad s, 1 H, alkene CH), 4.05 (q, $J = J$ 7.1, 2 H, CH_2O), 3.45 (t, $J = 6.9$, 2 H, CH_2N), 2.51 (t, $J = 7.8$, 2 H, CH_2CO), 1.91 (apparent quintet, J 7.3, 2 H $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.19 (q, $J = 7.1$, 3 H, CH_3CH_2).

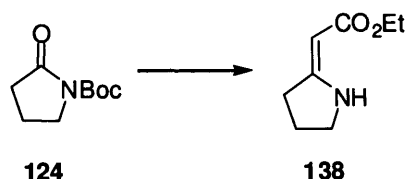
^{13}C NMR (125 MHz; CDCl_3): δ = 170.8 (C=O), 166.6 (alkene C), 76.5 (alkene CH), 58.4 (CH_2O), 47.1 (CH_2N), 32.2 (CH_2), 22.0 (CH_2), 14.7 (CH_3).

MS-ES: m/z (%) = 156 (MH^+ , 100), 128 (37).

HRMS-ES: m/z [M + Na] $^+$ calcd for $\text{C}_8\text{H}_{14}\text{NO}_2\text{Na}$: 156.1025; found: 156.1015.

Pyrrolidin-(2Z)-ylidene-acetic acid ethyl ester (138).

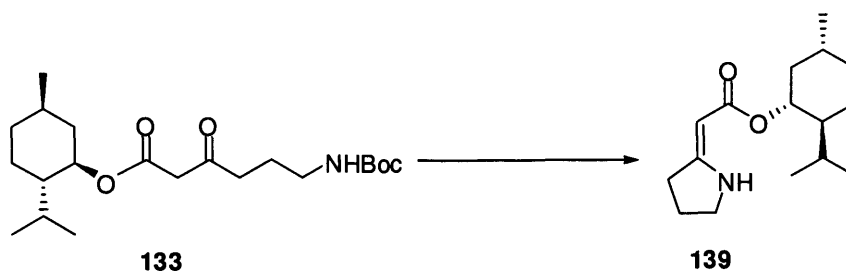
One-pot reaction from compound 124 to 138.



A solution of lithium diisopropylamide (13.5 mL, 2 M in heptane, 27 mmol) in THF (100 mL) was cooled to $-78\text{ }^{\circ}\text{C}$. Ethyl acetate (0.26 mL, 2.7 mmol) in THF (3 mL) was added dropwise over 30 minutes, and the solution allowed to stir for a further 30 minutes. *N*-*t*-Butoxycarbonylpyrrolidine-2-one (**124**) (0.50 g, 2.7 mmol) in THF (5 mL) was added over 30 minutes at $-78\text{ }^{\circ}\text{C}$, and the solution warmed to $25\text{ }^{\circ}\text{C}$ and left to stir for 18 hours. TFA (0.65 mL, 8.37 mmol) was added and the solution stirred for 2 hours at $25\text{ }^{\circ}\text{C}$. The volatiles were removed *in vacuo* and the resulting oil was dissolved in dichloromethane (5 mL). Saturated aqueous sodium bicarbonate was added until neutral to pH paper, and the organic material was extracted into dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The residual yellow oil was purified by flash column chromatography on silica gel (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (275 mg, 63 %) as a crystalline solid.

Data as previously reported.

Pyrrolidin-(2Z)-ylidene-acetic acid (-)-menthyl ester (139).



(-)-Menthyl 6-*t*-butoxycarbonylamino-3-oxohexanoate (**133**) (900 mg, 2.3 mmol) was dissolved in TFA (0.35 mL, 4.6 mmol) and the resulting solution stirred for 3 hours at 25 °C. Saturated aqueous sodium bicarbonate was added until neutral to pH paper, and the organic material was extracted into dichlorormethane (3 x 20 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow solid was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (485 mg, 80 %) as a yellow oil.

IR (CHCl₃): 3365, 2951, 2868, 1651, 1603, 1236 cm⁻¹.

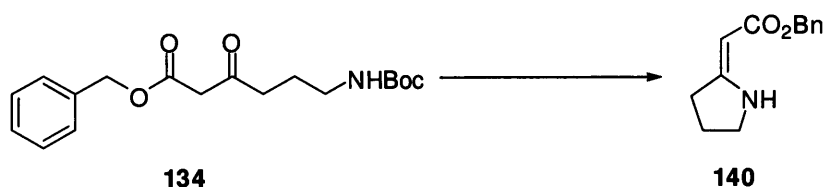
¹H NMR (500 MHz; CDCl₃): δ = 7.82 (broad s, 1 H, NH), 4.58 (apparent dt, *J* = 4.2, 10.8, 1 H, menthyl 1-H), 4.50 – 4.35 (broad s, 1 H, alkene CH), 3.43 (t, *J* = 6.8, 2 H, CH₂N), 2.50 (t, *J* = 7.6, 2 H, CH₂C=C), 1.97 – 1.82 (m, 4 H, CH₂CH₂CH₂ + menthyl 6-H_{eq} + CH(CH₃)₂), 1.63 – 1.55 (m, 2 H, menthyl 3-H_{eq} + 4-H_{eq}), 1.47 – 1.36 (m, 1 H, menthyl 5-H_{ax}), 1.27 (apparent broad t, *J* = 11.5, 1 H, menthyl 2-H_{ax}), 0.99 (apparent dq, *J* = 2.7, 12.7, 1 H, menthyl 3-H_{ax}), 0.88 (apparent q, *J* = 11.7, 1 H, menthyl 6-H_{ax}), 0.87 – 0.76 (m, 1 H, menthyl 4-H_{ax}), 0.81 (d, *J* = 6.5, 3 H, CH₃), 0.80 (d, *J* = 7.0, 3 H, CH₃), 0.70 (d, *J* = 7.0, 3 H, CH₃).

¹³C NMR (125 MHz; CDCl₃): δ = 170.5 (C=O), 166.4 (C-N), 76.8 (alkene CH), 71.7 (CH-O), 47.3 (CH), 47.1 (CH₂N), 41.6 (CH₂), 34.5 (CH₂), 32.2 (CH₂), 31.5 (CH), 26.3 (CH), 23.7 (CH₂), 22.1 (CH₃), 22.0 (CH₂), 20.8 (CH₃), 16.6 (CH₃).

MS-ES: *m/z* (%) = 266 (MH⁺, 100), 128 (39).

HRMS-ES: *m/z* [M + H]⁺ calcd for C₁₆H₂₈NO₂: 266.2120; found: 266.2139.

Pyrrolidin-(2Z)-ylidene-acetic acid benzyl ester (140).¹⁰⁰



Benzyl 6-*t*-butoxycarbonylamino-3-oxohexanoate (**134**) (2.0 g, 7.42 mmol) was dissolved in TFA (5.11 g, 44.5 mmol) and the resulting solution stirred for 3 hours at 25 °C. Saturated aqueous sodium bicarbonate was added until neutral to pH paper, and the organic material extracted into dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (1.5 g, 86 %) as a waxy solid.

Mp. 57 – 58 °C (Lit. 75 – 76 °C).

IR (neat): 3372, 2946, 1651, 1600, 1495, 1454, 1235, 1141, 740, 697 cm⁻¹.

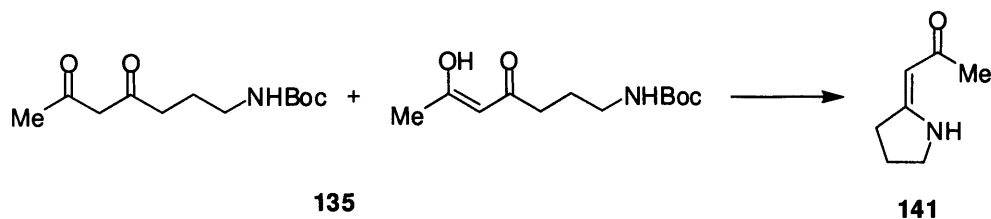
¹H NMR (500MHz; CDCl₃): δ = 7.85 (broad s, 1 H, NH), 5.04 (s, 2 H, CH₂O), 4.54 (broad s, 1 H, alkene CH), 3.45 (t, *J* = 6.9, 2 H, CH₂N), 2.52 (t, *J* = 7.8, 2 H, CH₂CO), 1.90 (apparent quintet, *J* 7.3, 2 H CH₂CH₂CH₂).

¹³C NMR (125 MHz; CDCl₃): δ = 170.4 (C=O), 167.0 (alkene C), 137.7 (aromatic C), 128.4 (aromatic CH), 127.8 (aromatic CH), 127.6 (aromatic CH), 76.3 (alkene CH), 64.4 (CH₂O), 47.1 (CH₂N), 32.3 (CH₂), 22.0 (CH₂).

MS-ES: *m/z* (%) = 218 (MH⁺, 100), 91 (36).

HRMS-ES: *m/z* [M + H]⁺ calcd for C₁₃H₁₅NO₂Na: 240.1000; found: 240.0995.

1-Pyrrolidin-(2Z)-ylidene-propan-2-one (141).¹⁰¹



N-*t*-Butoxycarbonyl-4,6-dioxoheptylamine (**135**) (530 mg, 2.2 mmol) was dissolved in TFA (0.34 mL, 4.4 mmol) and the resulting solution stirred for 3 hours at 25 °C. Saturated aqueous sodium bicarbonate was added until neutral to pH paper, and the organic material extracted into dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow solid was purified by recrystallisation from hexane/diethyl ether to give the *title compound* (233 mg, 85 %) as a yellow crystalline solid.

Mp. 52 – 52.5 °C.

IR (CHCl₃): 3272, 1618, 1556, 1505, 1258 cm⁻¹.

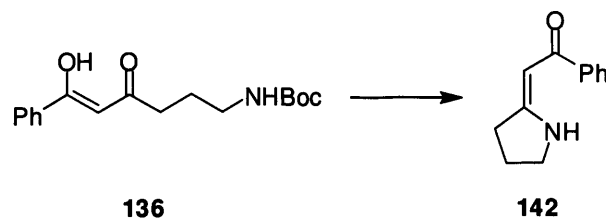
¹H NMR (500 MHz; CDCl₃): δ = 9.72 (broad s, 1 H, NH), 5.04 (s, 1 H, alkene CH), 3.50 (t, *J* = 7.0, CH₂N), 2.52 (t, *J* = 7.8, CH₂), 1.96 (s, 3 H, CH₃CO), 1.91 (apparent quintet, *J* = 7.4, CH₂).

¹³C NMR (125 MHz; CDCl₃): δ = 195.0 (C=O), 167.4 (C-N), 89.8 (alkene CH), 47.5 (CH₂N), 32.3 (CH₂), 28.7 (CH₃), 21.4 (CH₂).

MS-ES: *m/z* (%) = 126 (MH⁺, 100).

HRMS-ES: *m/z* [M + H]⁺ calcd for C₇H₁₂NO: 126.0919; found: 126.0917.

1-Phenyl-2-pyrrolidin-(2Z)-ylidene-ethanone (142).¹⁰²



N-*t*-Butoxycarbonyl-4,6-dioxo-6-phenylhexylamine (**136**) (200 mg, 0.65 mmol) was dissolved in dichloromethane (5 mL). TFA (0.10 mL, 1.3 mmol) was added and the resulting solution stirred for 3 hours at 25 °C. The volatiles were removed *in vacuo* and the resulting oil dissolved in dichloromethane (2 mL). Saturated aqueous sodium carbonate was added until neutral to pH paper, and the organic material extracted into dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. Purification by flash column chromatography (eluent 5:1 hexane:ethyl acetate) gave the *title compound* (90 mg, 74 %) as a yellow solid.

Mp. 108 – 109 °C (Lit. 108 – 109 °C).

IR (CHCl₃): 3278, 2956, 1700, 1610, 1521, 1260 cm⁻¹.

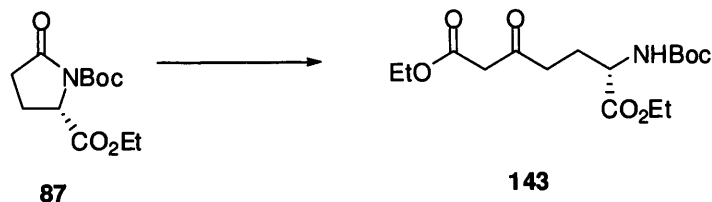
¹H NMR (400MHz; CDCl₃): δ = 10.23 (broad s, 1 H, NH), 7.80 (dd, *J* = 7.6, 1.9, aromatic CH), 7.35 – 7.29 (m, 3 H, aromatic CH), 5.70 (s, 1 H, alkene CH), 3.56 (t, *J* = 7.0, 2 H, CH₂NH), 2.65 (t, *J* = 7.9, 2 H, CH₂CCH), 1.95 (apparent quintet, *J* = 7.5, 2 H, CH₂CH₂CH₂).

¹³C NMR (125 MHz; CDCl₃): δ = 188.1 (C=O), 169.4 (C-N), 140.3 (aromatic C), 130.5 (aromatic CH), 128.2 (aromatic CH), 127.0 (aromatic CH), 86.6 (alkene CH), 47.8 (CH₂N), 33.0 (CH₂), 21.4 (CH₂).

MS-ES: *m/z* (%) = 188 (MH⁺, 100).

HRMS-ES: *m/z* [M + H]⁺ calcd for C₁₂H₁₄NO: 188.1075; found: 188.1062.

(2S)-2-*t*-Butoxycarbonylamino-5-oxoheptanedioic acid diethyl ester (143).^{64a}



A solution of lithium diisopropylamide (3.9 mL, 2 M solution in heptane, 7.8 mmol) in THF (15 mL) was cooled to $-78\text{ }^{\circ}\text{C}$. Ethyl acetate (0.76 mL, 7.8 mmol) in THF (4 mL) was added over 25 minutes. After stirring for 20 minutes at $-78\text{ }^{\circ}\text{C}$, ethyl (*S*)-1-*tert*-butoxycarbonyl-5-oxopyrrolidine-2-carboxylate (**87**) (2.0 g, 7.8 mmol) in THF (5 mL) was added over 30 minutes at $-78\text{ }^{\circ}\text{C}$. The solution was then allowed to warm to $25\text{ }^{\circ}\text{C}$ and left to stir for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over magnesium sulphate and the solvent removed *in vacuo*. Filtration through a short plug of silica, eluting with ethyl acetate, gave the *title compound* (2.1 g, 78 %), as a yellow oil.

IR (neat): 3368, 2979, 2934, 1741, 1713, 1512 cm^{-1} .

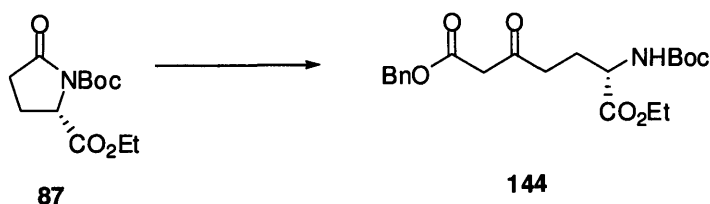
^1H NMR (400 MHz; CDCl_3): δ = 5.07 (broad d, J = 7.6, 1 H, NH), 4.23 – 4.05 (m, 1 H, CHNH), 4.12 (apparent q, J = 7.2, 4 H, CH_2O), 3.39 (s, 2 H, COCH_2CO), 2.70 – 2.50 (m, 2 H, m, CH_2CO), 2.16 – 2.05 (m, 1 H, one of CH_2CHN), 1.89 – 1.76 (m, 1 H, one of CH_2CHN), 1.39 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.21 (apparent t, J = 7.2, 6 H, CH_2CH_3).

^{13}C NMR (100 MHz; CDCl_3): δ = 201.7 (ketone $\text{C}=\text{O}$), 172.2 (ester $\text{C}=\text{O}$), 167.1 (ester $\text{C}=\text{O}$), 155.5 (carbamate $\text{C}=\text{O}$), 80.0 ($\text{OC}(\text{CH}_3)_3$), 61.6 (OCH_2), 61.5 (OCH_2), 52.7 (CHNH), 49.3 (CH_2NH), 38.8 (CH_2CO), 28.3 ($\text{C}(\text{CH}_3)_3$), 26.5 (CH_2), 14.2 (CH_2CH_3), 14.1 (CH_2CH_3).

MS-ES: m/z (%) = 384 (M + K, 34), 368 (M + Na, 100), 328 (17).

HRMS-ES: m/z [$\text{M} + \text{Na}$]⁺ calcd for $\text{C}_{16}\text{H}_{27}\text{NO}_7\text{Na}$: 368.1685; found: 368.1659.

(2S)-2-*t*-Butoxycarbonylamino-5-oxoheptanedioic acid 1-ethyl ester 7-benzyl ester (144).



A solution of lithium diisopropylamide (5.93 mL, 2 M in heptane, 11.87 mmol) in THF (60 mL) was cooled to -78°C . Benzyl acetate (1.78 g, 11.87 mmol) in THF (10 mL) was added over 30 minutes. After stirring for 30 minutes at -78°C , ethyl (*S*)-1-*tert*-butoxycarbonyl-5-oxopyrrolidine-2-carboxylate (**87**) (3.05 g, 11.87 mmol) in THF (10 mL) was added over 30 minutes at -78°C . The solution was allowed to warm to 25°C and the resulting solution stirred for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the organic material extracted into dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over magnesium sulphate, and the solvent removed *in vacuo* to give a yellow oil. Purification by flash column chromatography (eluent 6:1 hexane:ethyl acetate) gave the *title compound* (3.1 g, 67 %) as a pale oil.

IR (neat): 3384, 2977, 1740, 1710, 1368 cm^{-1} .

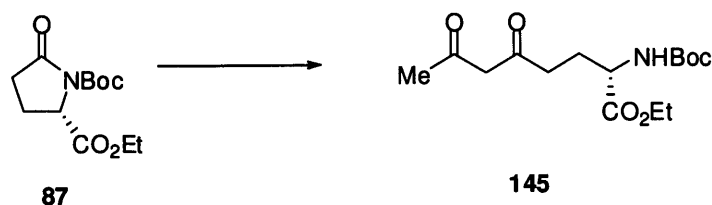
^1H NMR (500 MHz; CDCl_3): δ = 7.36 – 7.27 (m, 5 H, aromatic CH), 5.12 (s, 2 H, OCH_2), 5.05 (broad d, J = 6.5, 1 H, NH), 4.22 – 4.09 (m, 3 H, CHNH and CH_2O), 3.45 (s, 2 H, COCH_2CO), 2.67 – 2.50 (m, 2 H, CH_2CO), 2.18 – 2.06 (m, 1 H, one of CH_2CHN), 1.90 – 1.78 (m, 1 H, one of CH_2CHN), 1.39 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.22 (t, J = 7.1, 3 H, CH_2CH_3).

^{13}C NMR (125 MHz; CDCl_3): δ = 201.4 (ketone $\text{C}=\text{O}$), 172.2 (ester $\text{C}=\text{O}$), 166.9 (ester $\text{C}=\text{O}$), 155.5 (carbamate $\text{C}=\text{O}$), 135.3 (aromatic C), 128.7 (aromatic CH), 128.5 (aromatic CH), 128.4 (aromatic CH), 80.0 ($\text{OC}(\text{CH}_3)_3$), 67.2 (OCH_2), 61.6 (OCH_2), 52.7 (CHNH), 49.2 (CH_2NH), 38.9 (CH_2CO), 28.3 ($\text{C}(\text{CH}_3)_3$), 26.5 (CH_2), 14.2 (CH_2CH_3).

MS-ES: m/z (%) = 430 (M + Na, 18), 352 (40), 290 (100).

HRMS-ES: m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_7\text{Na}$: 430.1842; found: 430.1842.

Ethyl (2*S*)-2-*t*-butoxycarbonylamino-5,7-dioxooctanoate (145).



A solution of lithium diisopropylamide (2.5 mL, 2 M solution in heptane, 5 mmol) in THF (10 mL) was cooled to $-78\text{ }^{\circ}\text{C}$. Acetone (0.31 mL, 4.3 mmol) in THF (2 mL) was added over 20 minutes. After stirring, for 25 minutes at $-78\text{ }^{\circ}\text{C}$, ethyl (*S*)-1-*tert*-butoxycarbonyl-5-oxopyrrolidine-2-carboxylate (**87**) (1.0 g, 3.9 mmol) in THF (5 mL) was added over 30 minutes at $-78\text{ }^{\circ}\text{C}$. The solution was then allowed to warm to $25\text{ }^{\circ}\text{C}$ and the resulting solution stirred for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over magnesium sulphate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (eluent 4:1 hexane:diethyl ether) to give the *title compound* (900 mg, 72%) as a yellow oil, existing as the enol tautomer.

IR (CHCl_3): 3372, 2979, 1712 (v. broad), 1164 cm^{-1} .

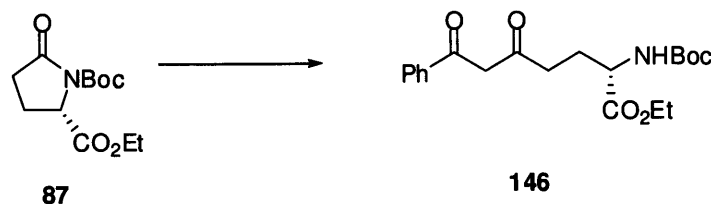
^1H NMR (400 MHz; CDCl_3): δ = 5.41 (s, 1 H, enol CH), 5.04 (broad d, J = 7.3, 1 H, NH), 4.23 (m, 1 H, CHNH), 4.13 (q, J = 7.1, 2 H, CH_2O), 2.35 – 2.29 (m, 2 H, CH_2CH_2), 2.15 – 2.05 (m, 1 H, one of CH_2CHN), 1.97 (s, 3 H, CH_3CO), 1.93 – 1.83 (m, 1 H, one of CH_2CHN), 1.37 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.21 (t, J = 7.1, 3 H, CH_2CH_3).

^{13}C NMR (125 MHz; CDCl_3): δ = 194.0 (C=O), 189.7 (enol C-O), 172.3 (C=O), 155.4 (C=O), 100.0 (enol C-H), 79.9 (C-O), 61.5 (CH_2O), 53.1 (CH-N), 34.5 (CH_2), 28.3 ($(\text{CH}_3)_3\text{C}$), 28.0 (CH_2), 24.4 (CH_3), 14.1 (CH_3).

MS-ES: m/z (%) = 354 (M + K, 62), 338 (100), 282 (21).

HRMS-ES: m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_6\text{Na}$: 338.1580; found: 338.1569.

Ethyl (2*S*)-2-*t*-butoxycarbonylamino-5,7-dioxo-7-phenylheptanoate (**146**).¹⁰³



A solution of lithium diisopropylamide (2.5 mL, 2 M solution in heptane, 5 mmol) in THF (10 mL) was cooled to $-78\text{ }^{\circ}\text{C}$. Acetophenone (0.53 mL, 4.3 mmol) in THF (2 mL) was added over 20 minutes. After stirring for 25 minutes at $-78\text{ }^{\circ}\text{C}$, ethyl (*S*)-1-*tert*-butoxycarbonyl-5-oxopyrrolidine-2-carboxylate (**87**) (1.0 g, 3.9 mmol) in THF (5 mL) was added over 30 minutes at $-78\text{ }^{\circ}\text{C}$. The solution was then allowed to warm to $25\text{ }^{\circ}\text{C}$ and left to stir for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over magnesium sulphate and the solvent removed *in vacuo* to give a orange oil which was purified by flash column chromatography (eluent 10:3 hexane:diethyl ether) to give the *title compound* (1.1 g, 74 %) as a yellow crystalline solid.

Mp. $63 - 64\text{ }^{\circ}\text{C}$.

IR (CHCl_3): 3367, 2979, 1715 (v. broad), 1606, 1164 cm^{-1} .

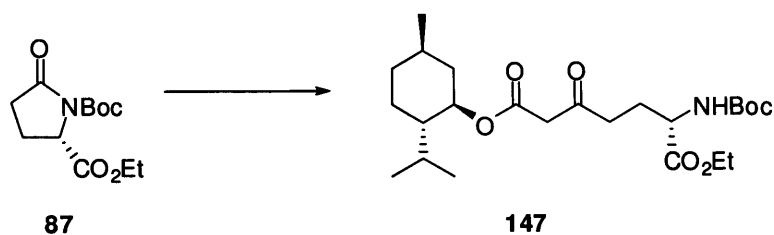
^1H NMR (500 MHz; CDCl_3): $\delta = 7.79$ (apparent d, $J = 7.2$, 2 H, aromatic CH), 7.40 (apparent tt, $J = 7.4$, 1.2, 1 H, aromatic CH), 7.32 (apparent t, $J = 7.6$, 2 H, aromatic CH), 6.10 (s, 1 H, $\text{CH}=\text{CCOH}$), 5.11 (broad d, $J = 8.3$, 1 H, NH), 4.28 – 4.22 (m, 1 H, CHNH), 4.09 (q, $J = 7.2$, 2 H, CH_2O), 2.52 – 2.41 (m, 2 H, CH_2CH_2), 2.19 – 2.10 (m, 1 H, one of CH_2CHN), 1.99 – 1.90 (m, 1 H, one of CH_2CHN), 1.35 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.21 (t, $J = 7.2$, 3 H, CH_2CH_3).

^{13}C NMR (125 MHz; CDCl_3): $\delta = 196.4$ (PhCOCH_2), 182.0 (enol ether C), 172.3 (ester $\text{C}=\text{O}$), 155.5 (carbamate $\text{C}=\text{O}$), 134.4 (aromatic C), 132.5 (aromatic CH), 128.6 (aromatic CH), 126.9 (aromatic CH), 79.7 (Me_3CO), 61.4 (OCH_2), 53.1 (NCH), 35.4 (CH_2COH), 28.2 ($(\text{CH}_3)_3$), 28.0 (CH_2CHN), 14.1 (CH_3).

MS-ES: m/z (%) = 416 (M + K, 75), 400 (M + Na, 100), 378 (M^+ , 24).

HRMS-ES: m/z $[M + Na]^+$ calcd for $C_{20}H_{27}NO_6Na$: 400.1736; found: 400.1729.

(2S)-2-*t*-Butoxycarbonylamino-5-oxoheptanedioic acid 1-ethyl ester 7-(-)-menthyl ester (147).



A solution of lithium diisopropylamide (3.1 mL, 2 M in heptane, 6.2 mmol) in THF (10 mL) was cooled to -78 °C. (-)-Menthyl acetate (1.23 g, 6.2 mmol) in THF (3 mL) was added over 30 minutes. After stirring for 30 minutes at -78 °C, ethyl (*S*)-1-*tert*-butoxycarbonyl-5-oxopyrrolidine-2-carboxylate (**87**) (1.6 g, 6.2 mmol) in THF (5 mL) was added over 30 minutes at -78 °C, and the solution warmed to 25 °C and allowed to stir for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (2.0 g, 71 %) as an off-white solid.

Mp. $82 - 82.5$ °C.

IR ($CHCl_3$): 3367, 2957, 1717 (v. broad), 1168 cm^{-1} .

1H NMR (500 MHz; $CDCl_3$): δ = 5.03 (broad d, J = 6.3, 1 H, NH), 4.65 (apparent dt, J = 4.4, 10.9, 1 H, menthyl 1-H), 4.22 – 4.14 (m, 1 H, CH-N), 4.11 (q, J = 7.1, 2 H, CH_2O), 3.38 and 3.35 (AB quartet, J = 15.5, 2 H, $COCH_2CO$), 2.65 – 2.50 (m, 2 H, CH_2CO), 1.98 – 1.92 (m, 1 H, menthyl 6- H_{eq}), 1.87 – 1.75 (m, 3 H, CH_2CH_2CO and $CH(CH_3)_2$), 1.64 – 1.58 (m, 2 H, menthyl 3- H_{eq} and 4- H_{eq}), 1.47 – 1.39 (m, 1 H, menthyl 5- H_{ax}), 1.37 (s, 9 H, $C(CH_3)_3$), 1.34 – 1.26 (m, 1 H, menthyl 2- H_{ax}), 1.21 (t, J = 7.1, 3 H, CH_3CH_2), 1.03 – 0.93 (m, 1 H, menthyl 3- H_{ax}), 0.92 (apparent q, J =

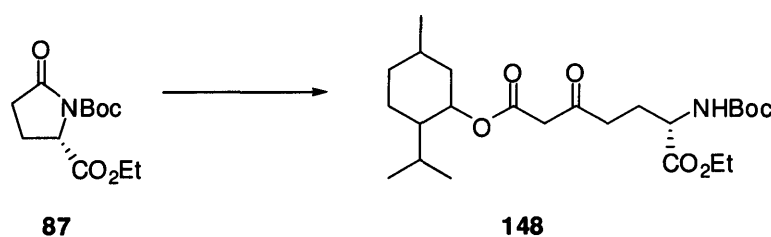
11.8, 1 H, menthyl 6- H_{ax}), 0.84 (d, $J = 6.6$, 3 H, CH_3), 0.82 (d, $J = 7.0$, 3 H, CH_3), 0.81 – 0.76 (m, 1 H, menthyl 4- H_{ax}), 0.69 (d, $J = 7.0$, 3 H, CH_3).

^{13}C NMR (125 MHz; $CDCl_3$): $\delta = 201.7$ (ketone C=O), 172.2 (ester C=O), 166.7 (ester C=O), 155.5 (carbamate C=O), 80.0 ($(CH_3)_3CO$), 75.6 (menthyl 1-CH), 61.2 (CH_2O), 52.8 (CHN), 49.6 (CH_2), 46.9 (menthyl 2-CH), 40.7 (menthyl 6- CH_2), 38.8 (CH_2), 34.2 (menthyl 4- CH_2), 31.4 (menthyl 5-CH), 28.3 ($(CH_3)_3C$), 26.6 (CH_2), 26.2 (CH), 23.3 (menthyl 3- CH_2), 22.0 (CH_3), 20.7 (CH_3), 16.2 (CH_3), 14.2 (CH_3).

MS-ES: m/z (%) = 494 (M + K, 13), 478 (M + Na, 24), 338 (100).

HRMS: m/z [M + Na] $^+$ calcd for $C_{24}H_{41}NO_7Na$: 478.2781; found: 478.2795.

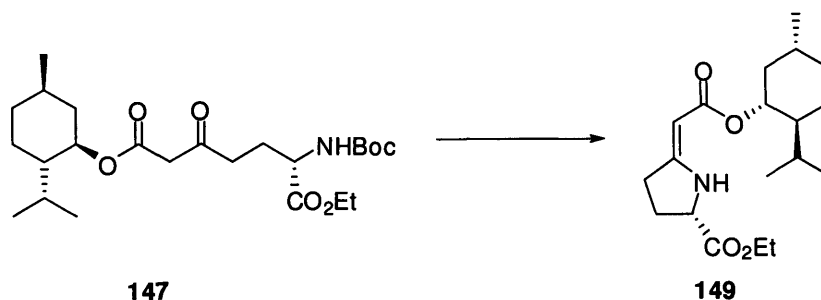
(2S)-2-*t*-Butoxycarbonylamino-5-oxoheptanedioic acid 1-ethyl ester 7-(\pm)-menthyl ester (148).



A solution of lithium diisopropylamide (1.15 mL, 2 M in heptane, 2.3 mmol) in THF (10 mL) was cooled to -78 °C. Menthyl acetate (0.46 g, 2.3 mmol) in THF (3 mL) was added over 30 minutes. After stirring for 30 minutes at -78 °C, ethyl (*S*)-1-*tert*-butoxycarbonyl-5-oxopyrrolidine-2-carboxylate (**87**) (0.6 g, 2.3 mmol) in THF (5 mL) was added over 30 minutes at -78 °C, and the solution warmed to 25 °C and allowed to stir for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (764 mg, 73 %) as an off-white solid.

¹H NMR and ¹³C NMR data are in line with compound **147**; additional peaks are observed due to the existence of diastereoisomers in a 1:1 ratio.

(2S)-5-[1-(-)-Menthylloxycarbonyl-meth-(Z)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (149**).**



TFA (0.23 mL, 3 mol) was added to a solution of (2S)-2-*t*-Butoxycarbonylamino-5-oxoheptanedioic acid 1-ethyl ester 7-(-)-menthyl ester (**147**) (696 mg, 1.53 mmol) in dichloromethane (10 mL). After stirring for 3 hours at 25 °C, the solution was neutralized with saturated aqueous sodium carbonate and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 10:1 dichloromethane:methanol) to give the *title compound* (387 mg, 75 %) as a white crystalline solid.

Mp. 72.0 – 72.5 °C.

IR (nujol): 3370, 1738, 1661, 1605, 1200 cm⁻¹.

¹H NMR (500 MHz; CDCl₃): δ = 8.05 (broad s, 1 H, NH), 4.58 (apparent dt, *J* = 4.3, 10.8, 1 H, menthyl 1-H_{ax}), 4.52 (s, 1 H, alkene CH), 4.28 (dd, *J* = 8.3, 5.4, 1 H, CHN), 4.17 – 4.09 (m, 2 H, OCH₂), 2.63 (dddd, *J* = 16.6, 8.9, 6.8, 0.7, 1 H, one of CH₂CO), 2.52 (dddd, *J* = 16.6, 8.9, 6.3, 0.7, 1 H, one of CH₂CO), 2.22 (apparent ddt, *J* = 12.8, 6.9, 8.6, 1 H, one of CH₂CH₂CO), 2.09 – 2.01 (m, 1 H, one of CH₂CH₂CO), 1.98 – 1.92 (m, 1 H, menthyl 6-H_{eq}), 1.87 (apparent doubled septet, *J* = 2.6, 7.0, 1 H, CH(CH₃)₂), 1.63 – 1.56 (m, 2 H, menthyl 3-H_{eq} + 4-H_{eq}), 1.47 – 1.39 (m, 1 H, menthyl 5-H_{ax}), 1.32 – 1.25 (m, 1 H, menthyl 2-H_{ax}), 1.21 (t, *J* = 7.1, 3 H, CH₃CH₂), 1.00 (apparent dq, *J* = 3.5, 13.0, 1 H, menthyl 3-H_{ax}), 0.89 (apparent q, *J* = 11.7, 1 H,

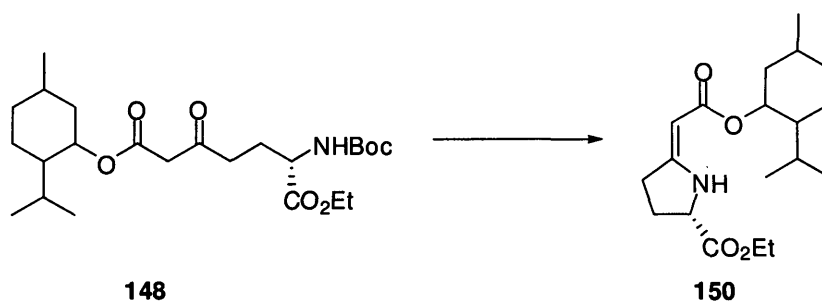
menthyl 6-H_{ax}), 0.82 (d, *J* = 6.5, 3 H, CH₃), 0.81 (d, *J* = 7.0, 3 H, CH₃), 0.80 – 0.75 (m, 1 H, menthyl 4-H_{ax}), 0.70 (d, *J* = 7.0, 3 H, CH₃).

¹³C NMR (125 MHz; CDCl₃): δ = 172.0 (ester C=O), 170.0 (ester C=O), 164.7 (C=CH), 79.2 (C=CH), 72.1 (menthyl 1-CH), 61.5 (CH₂O), 60.4 (CH-N), 47.2 (menthyl 2-CH), 41.5 (menthyl 6-CH), 34.4 (menthyl 4-CH₂), 31.4 (menthyl 5-CH₂), 31.1 (CH₂C=C), 26.2 (CH(CH₃)₂), 26.1 (CH₂CH₂CH-N), 23.6 (menthyl 3-CH₂), 22.1 (CH₃), 20.8 (CH₃), 16.5 (CH₃), 14.2 (CH₃).

MS-ES: *m/z* (%) = 360 ([M+Na]⁺, 12), 339 (22), 338 (100).

HRMS-ES: *m/z* [M + Na]⁺ calcd for C₁₉H₃₁NO₄Na: 360.2151; found: 360.2155.

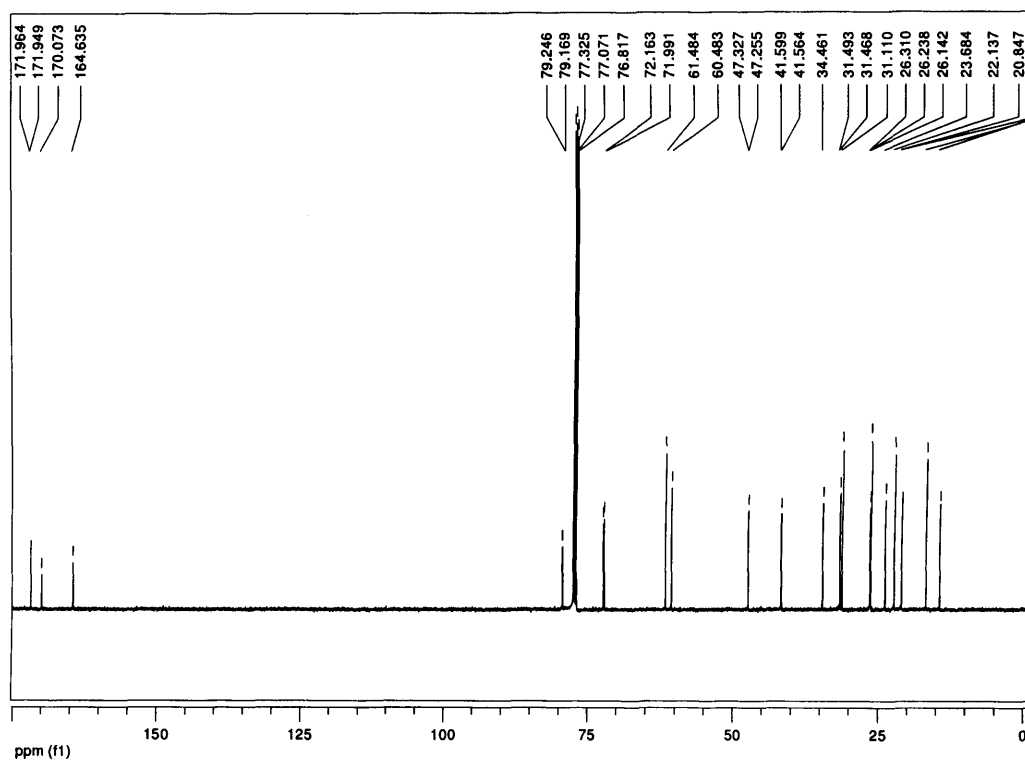
(2S)-5-[1-(±)-Menthylloxycarbonyl-meth-(Z)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (150)



TFA (0.17 mL, 2.2 mmol) was added to a solution of (2S)-2-*t*-Butoxycarbonylamino-5-oxoheptanedioic acid 1-ethyl ester 7-(±)-menthyl ester (148) (500 mg, 1.1 mmol) in dichloromethane (10 mL). After stirring for 3 hours at 25 °C, the solution was neutralized with saturated aqueous sodium carbonate and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 10:1 dichloromethane:methanol) to give the *title compound* (256 mg, 69 %) as a pale yellow oil.

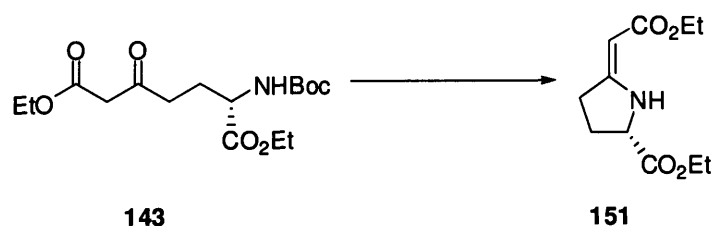
^1H NMR and ^{13}C NMR data are in line with compound **149**; additional peaks are observed due to the existence of diastereoisomers in a 1:1 ratio.

^{13}C NMR spectrum for compound **150**



Selected peaks: $\delta = 172.0$ and 171.9 (ester C=O), 170.1 (ester C=O), 164.6 (NC=C), 79.2 and 79.1 (NC=C), 72.1 and 71.9 (CHO), 61.4 (CH_2O), 60.4 (CHN), 47.3 and 47.2 (menthyl 2-CH), 41.6 (menthyl 6-CH), 34.5 (menthyl 4- CH_2), 31.5 and 31.4 (menthyl 5- CH_2), 31.1 ($\text{CH}_2\text{C}=\text{C}$), 26.3 and 26.2 ($\text{CH}(\text{CH}_3)_2$), 26.1 (CH_2CH_2 pyrrolidine), 23.6 (menthyl 3- CH_2), 22.1 (CH_3), 20.9 and 20.8 (CH_3), 16.6 (CH_3), 14.2 and 14.1 (ester CH_3).

(2S)-5-[1-Ethoxycarbonyl-meth-(Z)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (151).



(2S)-2-*t*-Butoxycarbonylamino-5-oxoheptanedioic acid diethyl ester (**143**) (4.9 g, 14.2 mmol) was dissolved in TFA (2.1 mL, 28 mmol) and the solution stirred for 3 hours at 25 °C. Excess TFA was removed *in vacuo* and the resulting, oil dissolved in dichloromethane (5 mL). Saturated aqueous sodium carbonate was added until neutral to pH paper, and the organic material extracted into dichloromethane (3 x 150 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (2.6 g, 82 %) as a pale yellow oil.

IR (CHCl₃): 3372, 2980, 1738, 1664, 1604, 1196 cm⁻¹.

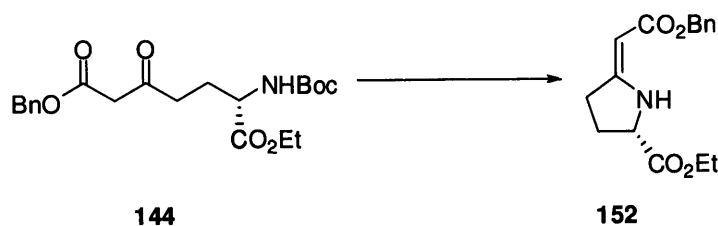
¹H NMR (500 MHz; CDCl₃): δ = 8.05 (broad s, 1 H, NH), 4.53 (broad s, 1 H, alkene CH), 4.29 (dd, *J* = 8.3, 5.2, *CH*-N), 4.16 – 4.11 (m, 2 H, CH₂O), 4.03 (q, *J* = 7.1, CH₂O), 2.63 (ddd, *J* = 16.7, 8.1, 7.0, 1 H, one of CH₂C=C), 2.57 – 2.50 (m, 1 H, one of CH₂C=C), 2.23 (apparent ddt, *J* = 12.9, 7.1, 8.6, 1 H, one of CH₂), 2.05 (apparent ddt, *J* = 12.9, 9.0, 5.6, 1 H, one of CH₂), 1.21 (t, *J* = 7.1, 3 H, CH₃), 1.19 (t, *J* = 7.1, 3 H, CH₃).

¹³C NMR (125 MHz; CDCl₃): δ = 171.9 (C=O), 170.4 (C=O), 164.9 (C-N), 78.8 (alkene CH), 61.5 (OCH₂), 60.5 (*CH*-N), 58.7 (OCH₂), 31.1 (CH₂), 26.2 (CH₂), 14.6 (CH₃), 14.2 (CH₃).

MS-ES: *m/z* (%) = 250 (M + Na, 34), 228 (MH⁺, 100), 182 (13).

HRMS-ES: *m/z* [M + H]⁺ calcd for C₁₁H₁₈NO₂: 228.1236; found: 228.1239.

(2S)-5-[1-(-)-Benzyloxycarbonyl-meth-(Z)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (152)



(2S)-2-*t*-Butoxycarbonylamino-5-oxoheptanedioic acid 1-ethyl ester 7-benzyl ester (**144**) (2.45 g, 6.01 mmol) was dissolved in TFA (4.11 g, 36 mmol) and the resulting solution stirred for 3 hours at 25°C. Saturated aqueous sodium bicarbonate was added until neutral to pH paper, and the organic material extracted into dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (1.26 g, 72 %) as a yellow oil.

IR (neat): 3366, 2979, 2905, 1738, 1665, 1602, 1454, 1373, 1198, 1144, 1023, 739, 698 cm⁻¹.

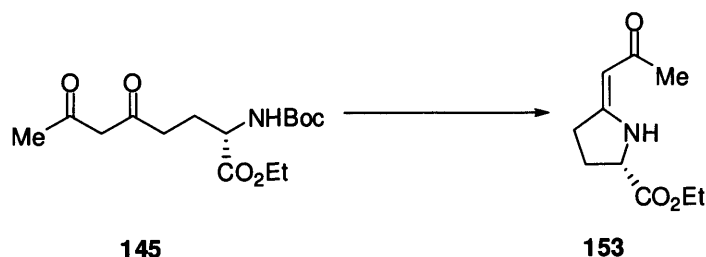
¹H NMR (400 MHz; CDCl₃): δ = 8.08 (broad s, 1 H, NH), 7.32 – 7.16 (m, 5 H, aromatic CH), 5.07 and 5.02 (AB quartet, *J* = 12.6, 2 H, PhCH₂O), 4.28 (dd, *J* = 8.3, 5.2, CHN), 4.16 – 4.09 (m, 2 H, CH₂O), 2.68 – 2.45 (m, 2 H, CH₂C=C), 2.28 – 2.16 (m, 1 H, one of CH₂), 2.10 – 1.97 (m, 1 H, one of CH₂), 1.21 (3 H, t, *J* = 7.1, CH₃).

¹³C NMR (100 MHz; CDCl₃): δ = 171.9 (C=O), 170.0 (C=O), 165.4 (C=CH), 135.2 (aromatic C), 128.5 (aromatic CH), 127.9 (aromatic CH), 127.7 (aromatic CH), 78.5 (alkene CH), 64.6 (OCH₂Ph), 61.5 (OCH₂), 60.5 (CHN), 31.2 (CH₂), 26.1 (CH₂), 14.2 (CH₃).

MS-ES: *m/z* (%) = 290 (MH⁺, 100%).

HRMS-ES: *m/z* [M + H]⁺ calcd for C₁₆H₂₀NO₄: 290.1392; found: 290.1382.

(2S)-5-[2-Oxo-prop-(Z)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (153).¹⁰³



Ethyl (2S)-2-*t*-butoxycarbonylamino-5,7-dioxooctanoate (**145**) (400 mg, 1.27 mmol) was dissolved in dichloromethane (3 mL) and TFA (0.16 mL, 2.4 mmol) and the resulting solution stirred for 3 hours at 25 °C. After removal of the volatiles *in vacuo*, the resulting, oil was dissolved in dichloromethane (5 mL) and saturated aqueous sodium carbonate was added until neutral to pH paper. The organic material was extracted into dichloromethane (3 x 50 mL), the combined organic layers dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (138 mg, 55 %) as a pale yellow oil.

IR (neat): 3297, 2982, 1740, 1628, 1555, 1202 cm⁻¹.

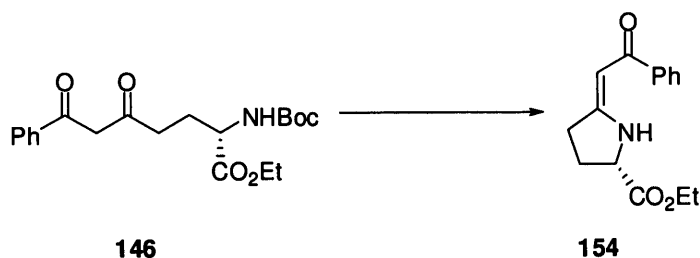
¹H NMR (500 MHz; CDCl₃): δ = 9.80 (broad s, 1 H, NH) 5.10 (broad s, 1 H, alkene CH), 4.35 (dd, *J* = 8.5, 5.1, CHN), 4.18 – 4.10 (m, 2 H, OCH₂), 2.65 (ddd, *J* = 16.9, 8.9, 7.3, one of CH₂C=C), 2.54 (ddd, *J* = 16.9, 9.1, 5.9, one of CH₂C=C), 2.27 – 2.19 (m, 1 H, one of CH₂), 2.10 – 2.02 (m, 1 H, one of CH₂), 1.98 (s, 3 H, CH₃), 1.22 (t, *J* = 7.1, CH₃CH₂).

¹³C NMR (125 MHz; CDCl₃): δ = 196.0 (ketone C=O), 171.6 (ester C=O), 165.8 (alkene C), 91.0 (alkene CH), 61.6 (OCH₂), 61.0 (CH), 31.3 (CH₂), 28.9 (CH₃), 25.6 (CH₂) and 14.1 (CH₃).

MS-ES: *m/z* (%) = 198 (MH⁺, 100).

HRMS-ES: *m/z* [M + H]⁺ calcd for C₁₀H₁₆NO₃: 198.1130; found: 198.1131.

(2S)-5-[2-Oxo-2-phenyl-eth-(Z)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (154).



Ethyl (2S)-2-*t*-butoxycarbonylamino-5,7-dioxo-7-phenylheptanoate (**146**) (377 mg, 1.0 mmol) was dissolved in dichloromethane (5 mL) and TFA (0.13 mL, 2 mmol) and the resulting solution stirred for 3 hours at 25 °C. After removal of the volatiles *in vacuo*, the resulting, oil was dissolved in dichloromethane (5 mL) and saturated aqueous sodium carbonate was added until neutral to pH paper. The organic material was extracted into dichloromethane (3 x 50 mL), the combined organic layers dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 7:1 hexane:ethyl acetate) to give the *title compound* (114 mg, 44 %) as a pale yellow crystalline solid.

Mp. 64 – 64.5 °C.

IR (CHCl₃): 3288, 2981, 1740 (v. broad), 1615, 1522, 1210 cm⁻¹.

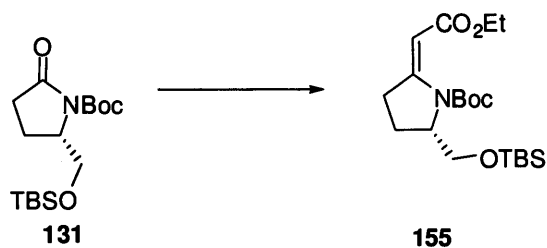
¹H NMR (500 MHz; CDCl₃): δ = 10.32 (broad s, 1 H, NH), 7.87 – 7.84 (m, 2 H, aromatic CH), 7.42 – 7.35 (m, 3 H, aromatic CH), 5.84 (s, 1 H, alkene CH), 4.47 (dd, *J* = 8.6, 5.4, 1 H, CH-N), 4.24 – 4.16 (m, 2 H, OCH₂), 2.84 (ddd, *J* = 17.1, 9.1, 7.0, 1 H, one of CH₂C=C), 2.73 (ddd, *J* = 17.1, 8.9, 5.8, 1 H, one of CH₂C=C), 2.34 (dddd, *J* = 13.0, 8.9, 8.6, 7.0, 1 H, one of CH₂), 2.18 (dddd, *J* = 13.0, 9.1, 5.8, 5.4, 1 H, one of CH₂), 1.27 (t, *J* = 7.1, 3 H, CH₃).

¹³C NMR (125 MHz; CDCl₃): δ = 188.8 (ketone C=O), 171.4 (ester C=O), 167.7 (alkene C), 139.9 (aromatic C), 130.8 (aromatic CH), 128.2 (aromatic CH), 127.2 (aromatic CH), 87.5 (alkene CH), 61.7 (OCH₂), 61.3 (CH), 31.9 (CH₂), 25.6 (CH₂), 14.2 (CH₃).

MS-ES: *m/z* (%) = 260 (MH⁺, 100).

HRMS-ES: m/z $[M + H]^+$ calcd for $C_{15}H_{18}NO_3$: 260.1287; found: 260.1271.

(2S)-2-(*t*-Butyldimethylsilyloxymethyl)-5-[1-ethoxycarbonyl-meth-(*E*)-ylidene]-pyrrolidine-1-carboxylic acid *t*-butyl ester (155**).¹⁰⁴**



A solution of lithium diisopropylamide (0.25 mL, 2 M in heptane, 0.5 mmol) in THF (5 mL) was cooled to -78 °C. Ethyl acetate (43 mg, 0.5 mmol) in THF (3 mL) was added over 20 minutes. After stirring for 25 minutes at -78 °C, (2S)-2-(*t*-butyldimethylsilyloxymethyl)-5-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**131**) (164 mg, 0.5 mmol) in THF (2 mL) was added over 20 minutes at -78 °C. The solution was allowed to warm to 25 °C and left to stir for 18 hours. Saturated aqueous ammonium chloride (20 mL) was added and the solution extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (123 mg, 63 %), as a yellow oil.

IR (neat): 3368, 2955, 2857, 1739, 1709, 1501, 1471 cm^{-1} .

1H NMR (500 MHz; $CDCl_3$): δ = 6.42 (broad s, 1 H, alkene CH), 4.19 – 4.15 (m, 1 H, CH-N), 4.08 (q, J = 7.1, 2 H, CH_2O), 3.68 – 3.62 (m, 2 H, CH_2OSi), 3.36 (apparent ddt, J = 18.4, 9.5, 1.5, 1 H, one of $CH_2C=C$), 2.96 (dddd, J = 18.4, 11.3, 9.1, 2.3, 1 H, one of $CH_2C=C$), 2.03 – 1.85 (m, 2 H, CH_2), 1.50 (s, 9 H, $(CH_3)_3CO$), 1.21 (t, J = 7.1, 3 H, CH_3CH_2), 0.83 (s, 9 H, $(CH_3)_3Si$), 0.00 (s, 3 H, one of CH_3Si), -0.02 (s, 3 H, one of CH_3Si).

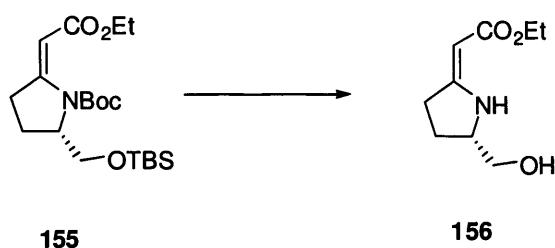
^{13}C NMR (125 MHz; $CDCl_3$): δ = 169.0 (ester C=O), 158.4 (carbamate C=O), 151.6 (alkene C), 96.1 (alkene CH), 82.1 ($(CH_3)_3CO$), 63.7 (CH_2OSi), 62.2 (CH-N), 59.1

(CH₂O), 31.0 (CH₂), 28.3 ((CH₃)₃CO), 25.8 ((CH₃)₃CSi), 23.8 (CH₂), 18.2 (C-Si), 14.5 (CH₃CH₂), -5.4 (one of CH₃Si), -5.5 (one of CH₃Si).

MS-ES: m/z (%) = 400 (MH⁺, 9), 300 (100).

HRMS-ES: m/z [M + H]⁺ calcd for C₂₀H₃₈NO₅Si: 400.2519; found: 400.2510

(2S)-2-(Hydroxymethyl)-5-[1-ethoxycarbonyl-meth-(Z)-ylidene]-pyrrolidine (156).



Pyrrolidine-1-carboxylic acid *t*-butyl ester (**155**) (200 mg, 0.50 mmol) was dissolved in dichloromethane (3 mL). TFA (115 mg, 1.0 mmol) was added and the solution stirred for 3 hours at 25 °C. Saturated aqueous sodium carbonate was added until neutral to pH paper, and the organic material extracted into dichloromethane (3 x 20 mL). The organic layer was dried over magnesium sulphate and the solvent removed *in vacuo* to give a yellow oil which was purified by flash column chromatography (eluent 5:1 hexane:ethyl acetate) to give the *title compound* (81 mg, 87 %) as a colourless oil.

IR (neat): 3402, 2955, 1714, 1689, 1171 cm⁻¹.

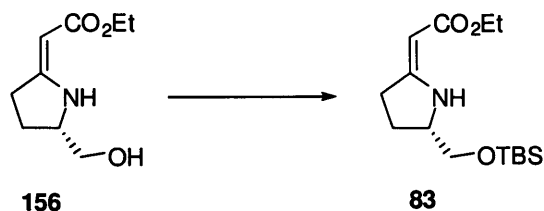
¹H NMR (400 MHz; CDCl₃): δ = 8.00 (broad s, 1 H, NH), 4.46 (s, 1 H, alkene CH), 4.01 (q, *J* = 7.1, 2 H, CH₂CH₃), 3.87 (apparent quintet, *J* = 5.6, 1 H, CHNH), 3.62 (dd, *J* = 11.2, 3.9, 1 H, one of CH₂OH), 3.45 (dd, *J* = 11.2, 6.3, 1 H, one of CH₂OH), 2.53 (m, 2 H, CH₂C=C), 1.99 (m, 1 H, one of CH₂CHN), 1.69 (m, 1 H, one of CH₂CHN), 1.19 (t, *J* 7.1, 3 H, CH₂CH₃).

¹³C NMR (100MHz; CDCl₃): δ = 171.9 (C=O), 167.3 (alkene CH), 77.7 (alkene C), 65.9 (CH₂O), 61.4 (CH), 59.0 (CH), 32.0 (CH₂CO), 24.0 (CH₂), 14.8 (CH₃).

MS-ES: m/z (%) = 186 (MH⁺, 100).

HRMS-ES: m/z $[M + H]^+$ calcd for $C_9H_{16}NO_3$: 186.1130; found: 186.1125.

(*S,Z*)-ethyl 2-(5-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidin-2-ylidene)acetate (83).^{24a}



(2*S*)-2-(Hydroxymethyl)-5-[1-ethoxycarbonyl-meth-(*Z*)-ylidene]-pyrrolidine (**156**) (600 mg, 3.2 mmol) in dimethyl formamide (3 mL), was added to a solution of *tert*-butyldimethylsilyl chloride (530 mg, 3.5 mmol), imidazole (238 mg, 3.5 mmol) and DMAP (20 mg) in dimethyl formamide (10 mL). The resulting solution was stirred at 25 °C for 18 hours. The reaction was quenched with saturated aqueous ammonium chloride (100 mL) and extracted into dichloromethane (2 x 100 mL). The combined dichloromethane layers were washed with water (3 x 100 mL), brine (2 x 100 mL) and dried over magnesium sulphate. Solvent was removed *in vacuo* to give a yellow oil which was purified by flash column chromatography on silica gel (eluent 3:1 hexane:ethyl acetate) to give the *title compound* (721 mg, 78 %) as a colourless oil which solidified on standing.

Mp: 50 – 51 °C (lit 49 – 50 °C).

¹H NMR (500 MHz; CDCl₃): δ = 7.91 s, 1 H, NH), 4.42 (s, 1 H, C=CH), 4.05 (q, J = 7.1, 2 H, CH₂O), 3.84 – 3.78 (m, 1 H, CHN), 3.53 (dd, J = 10.1 and 4.6, one of CH₂OTBS), 3.45 (dd, J = 10.1 and 6.5, 1 H, one of CH₂OTBS), 2.62 – 2.46 (m, 2 H, CH₂C=CH), 2.01 – 1.92 (m, 1 H, one of CH₂CH₂), 1.66 – 1.58 (m, 1 H, one of CH₂CH₂), 1.19 (t, J = 7.1, 3 H, CH₃CH₂), 0.83 (2, 9 H, (CH₃)C), 0.00 (s, 3 H, one of CH₃Si), -0.01 (s, 3 H, one of CH₃Si).

6.4 Experimental Data for Chapter 4

Silicon tetrakisothiocyanate (176).¹⁰⁵



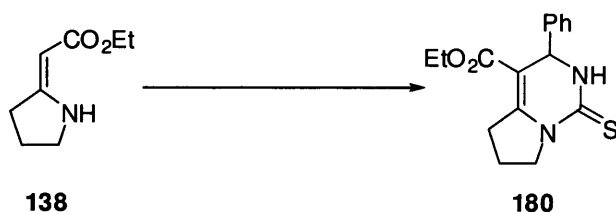
Note: All reagents glassware and solvents were dried prior to use and at all times an atmosphere of nitrogen was employed.

Ammonium thiocyanate (19 g, 0.25 mol) was suspended in dry benzene (80 mL) and silicon tetrachloride (5.74 mL, 0.05 mol) added over 10 minutes. The resulting suspension was refluxed for 3 hours, cooled to 70 °C and filtered through a glass sinter. 75 % of the solvent was removed by distillation at atmospheric pressure, with the remaining being cooled to 25 °C and left to stand for 18 hours. The resulting suspension was filtered and the solids washed with cold benzene. Excess benzene was removed from the crystals to give the *title compound* (10.5 g, 81 %) as a pale yellow crystalline solid.

Mp: 143 – 143.5 °C (lit 143.5 – 144 °C).

Ethyl 3-phenyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (180).

Reaction of compound 138 with benzaldehyde and silicon tetrakisothiocyanate.



Benzaldehyde (0.55 mL, 0.5 mmol) was added to a suspension of silicon tetrakisothiocyanate (130 mg, 0.5 mmol) in dry benzene (10 mL). The mixture was stirred for 20 minutes at 25 °C under a nitrogen atmosphere. Pyrrolidin-(2Z)-ylideneacetic acid ethyl ester (**138**) (78 mg, 0.5 mmol) in dry benzene (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 3 hours. The

solvent was removed *in vacuo*. The resulting residue was dissolved in chloroform and filtered through celite. The solvent was removed *in vacuo* to give a yellow oil purified by flash chromatography on silica gel (eluent hexane:ethylacetate 4:1) to give the *title compound* (117 mg, 78 %) as a pale oil.

IR (Neat): 3300, 3243, 2979, 2919, 1689, 1650, 1454, 1373, 698 cm^{-1} .

^1H NMR (500 MHz; CDCl_3): δ = 7.44 (s, 1 H, NH), 7.26 – 7.19 (m, 5 H, aromatic CH), 5.29 (d, J = 3.1, 1 H, CH), 4.29 – 3.94 (m, 4 H, CH_2O and CH_2N), 3.27 (ddd, J = 18.3, 8.5 and 4.3, 1 H, one of $\text{CH}_2\text{C}=\text{C}$), 3.01, (apparent dt, J = 18.2 and 9.0, 1 H, one of $\text{CH}_2\text{C}=\text{C}$), 2.04 – 1.89 (m, 2 H, pyrrolidine CH_2CH_2), 1.11 (t, J = 7.1, 3 H, CH_3).

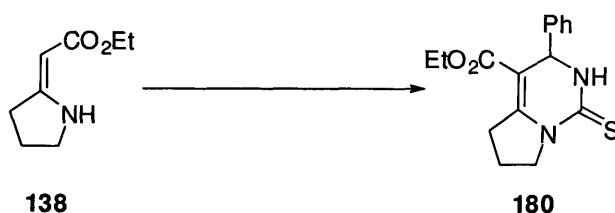
^{13}C NMR (125 MHz; CDCl_3): δ = 175.2 (C=S), 165.4 (C=O), 149.5 (C=CN), 142.9 (aromatic C), 128.7 (2 x aromatic CH), 128.1 (aromatic CH), 126.7 (2 x aromatic CH), 100.7 (C=CN), 60.3 (CH_2O), 55.5 (CHN), 52.1 (CH_2N), 32.2 ($\text{CH}_2\text{C}=\text{C}$), 21.1 (CH_2CH_2), 14.2 (CH_3).

MS-ES: m/z (%) = 303 (MH^+ , 100).

HRMS-ES: m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$: 303.1167; found: 303.1165.

Ethyl 3-phenyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (180).

Reaction of compound 138 with benzaldehyde and trimethylsilyl isothiocyanate.

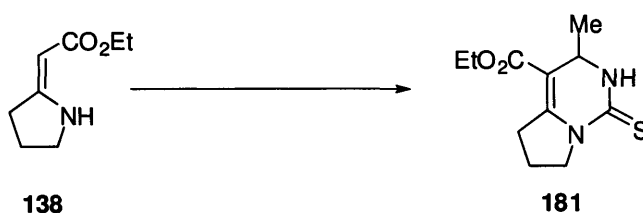


Trimethylsilyl isothiocyanate (131 mg, 1.0 mmol) was added to a solution of benzaldehyde (106 mg, 1.0 mmol) in dichloromethane (5 mL) and the resulting solution stirred for 30 minutes at 25 °C under a nitrogen atmosphere. Pyrrolidin-(2Z)-ylidene-acetic acid ethyl ester (**138**) (157 mg, 1.0 mmol) in dichloromethane (2.5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 30 minutes. Dilute sodium hydroxide (50 mL) was added and the resulting solution extracted with dichloromethane (3 x 50 mL). The combined

dichloromethane layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting residue was dissolved in ethyl acetate:hexane (1:4) and flushed through a plug of silica gel. The solvent was removed *in vacuo* to give the *title compound* (210 mg, 70 %) as a pale oil.

Data as previously reported.

Ethyl 3-methyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (181).



Trimethylsilyl isothiocyanate (1.25 g, 9.5 mmol) was added to a solution of acetaldehyde (421 mg, 9.5 mmol) in dichloromethane (10 mL) and the resulting solution stirred for 30 minutes at 25 °C under a nitrogen atmosphere. Pyrrolidin-(2*Z*)-ylidene-acetic acid ethyl ester (**138**) (1.5 g, 9.5 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 30 minutes. Dilute sodium hydroxide (50 mL) was added and the resulting solution extracted with dichloromethane (3 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting residue was dissolved in ethyl acetate:hexane (1:4) and flushed through a plug of silica gel. The solvent was removed *in vacuo* to give the *title compound* (1.7 g, 74 %) as a pale yellow oil.

IR (Neat): 3208, 2977, 2922, 1690, 1649, 1512, 1376 cm⁻¹.

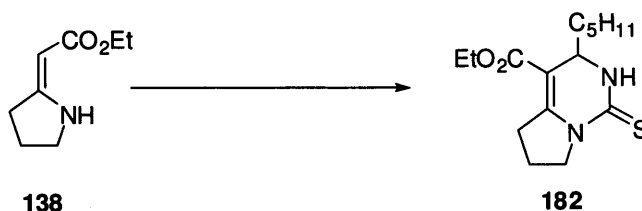
¹H NMR (500 MHz; CDCl₃): δ = 6.90 (s, 1 H, NH), 4.30 (dq, *J* = 3.5 and 6.3, 1 H CHN), 4.18 – 4.08 (m, 2 H, CH₂N), 4.01 – 3.90 (m, 2 H, CH₂O), 3.23 (ddd, *J* = 18.3, 12.0 and 8.5, 1 H, one of CH₂C=C), 2.94 (apparent dt, *J* = 18.3 and 9.1, 1 H, one of CH₂C=C), 2.04 – 1.95 (m, 1 H, one of CH₂CH₂), 1.90 (ddd, *J* = 18.1, 9.1 and 3.8, 1 H, one of CH₂CH₂), 1.24 – 1.20 (m, 6 H, ester CH₃ and CH₃CH).

^{13}C NMR (125 MHz; CDCl_3): δ = 179.9 (C=S), 165.4 (C=O), 149.87 (C=CN), 101.8 (C=CN), 60.3 (CH_2O), 51.9 (CH_2N), 47.8 (CHN), 32.0 ($\text{CH}_2\text{C}=\text{C}$), 23.6 (CH_3CH), 21.2 ($\text{CH}_2=\text{CH}_2$), 14.4 (ester CH_3).

MS-ES: m/z (%) = 241 (MH^+ , 100).

HRMS-ES: m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{11}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$: 241.1011; found: 241.1003.

Ethyl 3-pentyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (182).



Trimethylsilyl isothiocyanate (805 mg, 6.1 mmol) was added to a solution of hexanal (610 mg, 6.1 mmol) in dichloromethane (15 mL) and the resulting solution stirred for 30 minutes at 25 °C under a nitrogen atmosphere. Pyrrolidin-(2*Z*)-ylidene-acetic acid ethyl ester (**138**) (1.2 g, 6.1 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 30 minutes. Dilute sodium hydroxide (50 mL) was added and the resulting solution extracted with dichloromethane (3 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent was removed *in vacuo*. The resulting residue was dissolved in ethyl acetate:hexane (1:4) and flushed through a plug of silica gel. Solvent was removed *in vacuo* to give the *title compound* (1.5 g, 74 %) as a pale oil.

IR (Neat): 3424, 2930, 1689, 1647, 1377 cm^{-1} .

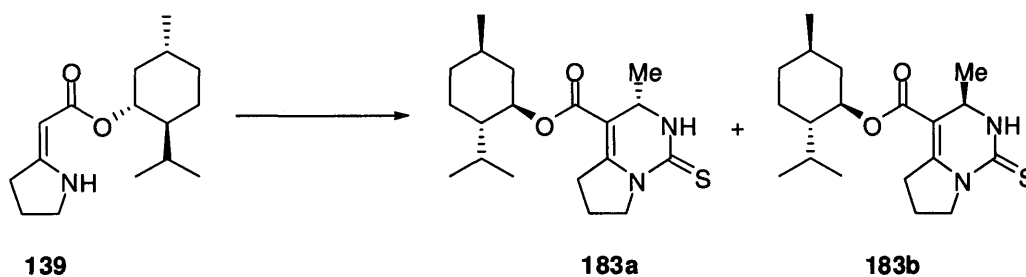
^1H NMR (500 MHz; CDCl_3): δ = 7.12 (broad d, J = 2.42, 1 H, NH), 4.23 (dt, J = 7.6 and 3.8, 1 H, CH), 4.17 – 4.08 (m, 2 H, CH_2N), 3.97 – 3.92 (m, 2 H, CH_2O), 3.24 (ddd, J = 18.1, 8.5 and 3.6, 1 H, one of $\text{CH}_2\text{C}=\text{C}$), 2.92 (apparent dt, J = 18.1 and 9.2, 1 H, one of $\text{CH}_2\text{C}=\text{C}$), 2.04 – 1.95 (m, 1 H, one of pyrrolidine CH_2CH_2), 1.92 – 1.83 (m, 1 H, one of pyrrolidine CH_2CH_2), 1.54 – 1.48 (m, 1 H, one of NCHCH_2), 1.48 – 1.40 (m, 1 H, one of NCHCH_2), 1.26 – 1.25 (m, 9 H, 3 x pentyl CH_2 and ester CH_3), 0.81 (t, J = 6.9, 3 H, pentyl CH_3).

^{13}C NMR (125 MHz; CDCl_3): δ = 176.2 (C=S), 165.5 (C=O), 150.2 (C=CN), 100.7 (C=CN), 60.2 (CH_2O), 51.9 (CH_2N), 51.8 (CHN), 36.9 ($\text{CH}_2\text{C}=\text{C}$), 31.9 (pyrrolidine CH_2CH_2), 31.4 (pentyl CH_2CH), 23.8 (pentyl CH_2), 22.5 (pentyl CH_2), 21.1 (pentyl CH_2), 14.3 (ester CH_3), 14.0 (pentyl CH_3).

MS-ES: m/z (%) = 297 (MH^+ , 100).

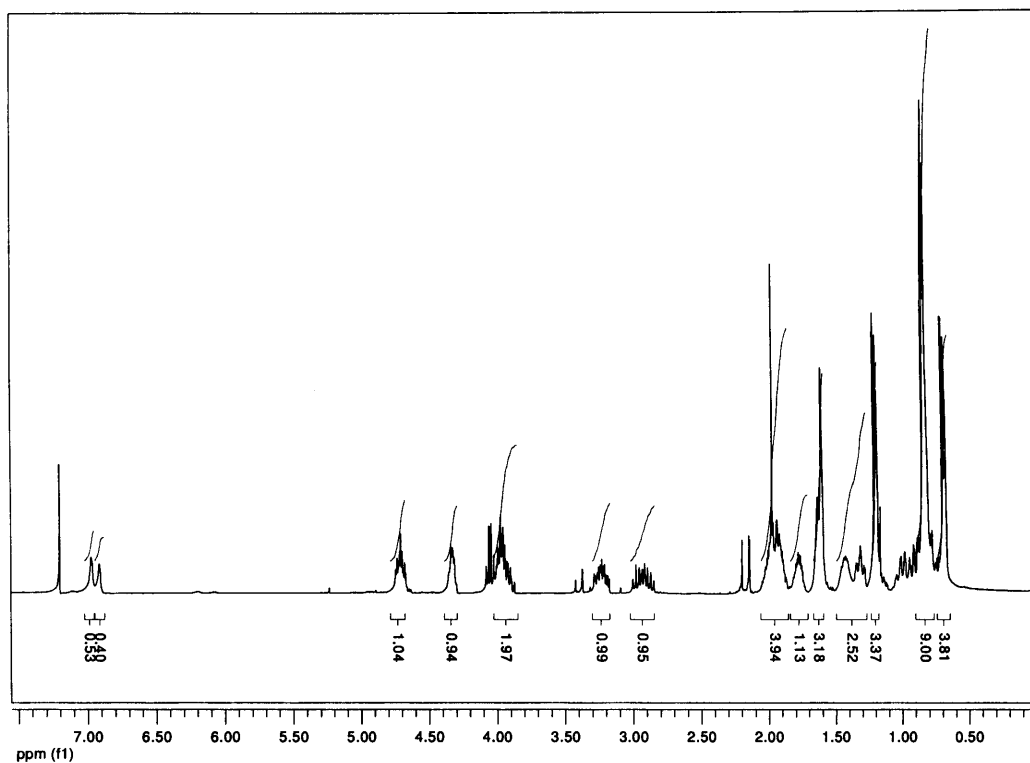
HRMS-ES: m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_2\text{S}$: 297.1637; found: 297.1628.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 3-methyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (183a) and (183b).



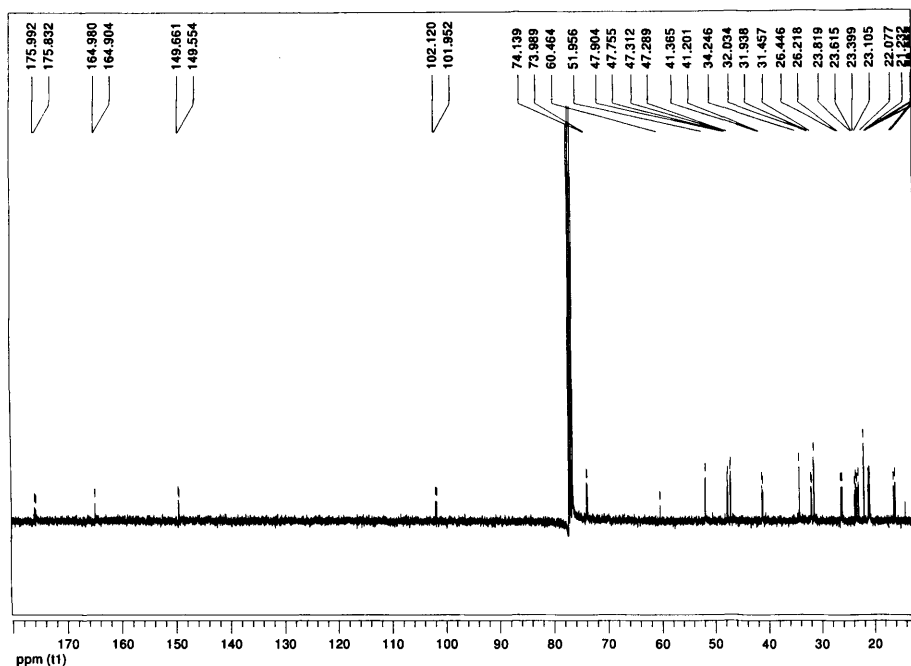
Acetaldehyde (0.06 mL, 1 mmol) was added to a suspension of silicon tetraisothiocyanate (260 mg, 1 mmol) in dry benzene (15 mL). The resulting solution was then stirred for 30 minutes at 25 °C under a nitrogen atmosphere. Pyrrolidin-(2*Z*)-ylidene-acetic acid (-)-menthyl ester (**139**) (338 mg, 1 mmol) in dry benzene (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 3 hours. Dilute sodium hydroxide (50 mL) was added and the resulting solution extracted with dichloromethane (3 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent removed *in vacuo* to give the *title compounds* as a 1:1 mixture of diastereoisomers (234 mg, 67 %) as a pale yellow oil.

¹H NMR spectrum, (400 MHz; CDCl₃) for compounds 183a and 183b



Selected peaks: $\delta = 6.98$ (s, 1 H, NH), 6.93 (s, 1 H, NH), 4.76 – 4.66 (m, 2 H, CHO major and minor), 4.38 – 4.29 (m, 2 H, CHNH major and minor), 4.02 – 3.87 (m, 4 H, CH₂N major and minor), 3.30 – 3.18 (m, 2 H, one of CH₂C=C major and minor), 3.02 – 2.84 (m, 2 H, one of CH₂N major and minor).

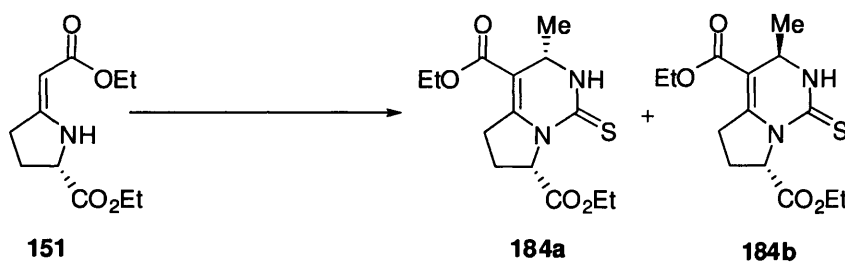
¹³C NMR spectrum (125MHz; CDCl₃) for compound **183a** and **183b**



Selected peaks: $\delta = 175.9$ and 175.8 (C=S), 164.9 and 164.9 (C=O), 149.6 and 149.5 (NC=C), 102.1 and 101.9 (NC=C), 74.1 and 73.9 (CHO), 60.5 (CH₂N), 51.9 (CHNH).

(7*S*)-Diethyl 3-methyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4,7-dicarboxylate (**184a**) and (**184b**).

Reaction of compound **151** with silicon tetrathiocyanate and acetaldehyde at 25 °C in benzene.



Acetaldehyde (0.06 mL, 1 mmol) was added to a suspension of silicon tetrathiocyanate (260 mg, 1 mmol) in dry benzene (15 mL). The resulting mixture was stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (2*S*)-5-[1-Ethoxycarbonyl-meth-(*Z*)-ylidene]-pyrrolidine-2-carboxylic acid ethyl

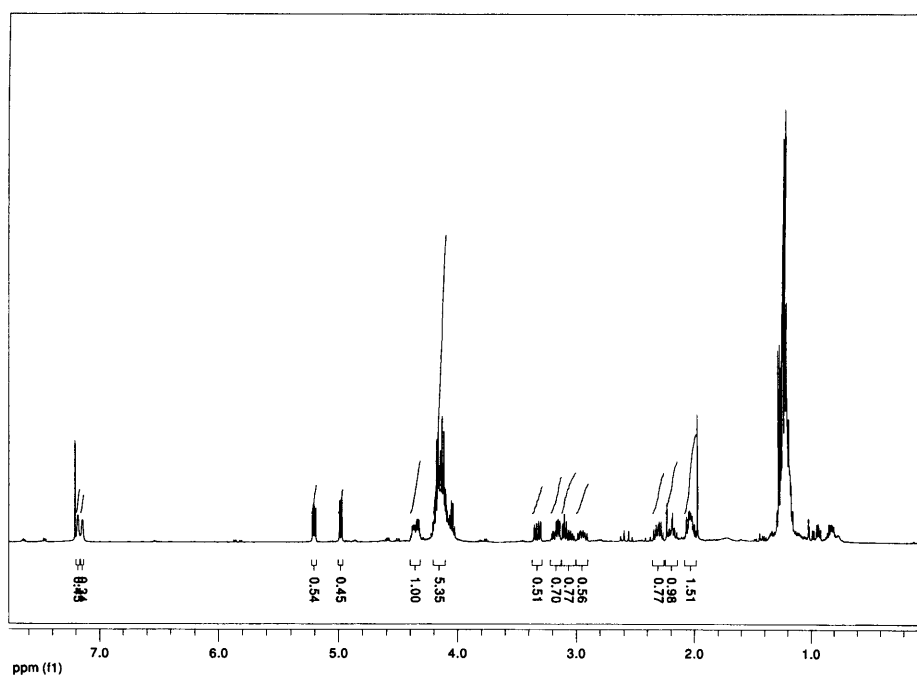
ester (**151**) (227 mg, 1 mmol) in dry benzene (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 3 hours. Solvent was removed *in vacuo*. The residue was redissolved in chloroform and filtered through celite. The solvent was removed *in vacuo* to give the *title compound* as a mixture of diastereoisomers (1.3:1) (243 mg, 78 %) as a pale yellow oil.

IR (Neat): 3329, 2979, 1740, 1692, 1656, 1447, 1377 cm^{-1} .

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

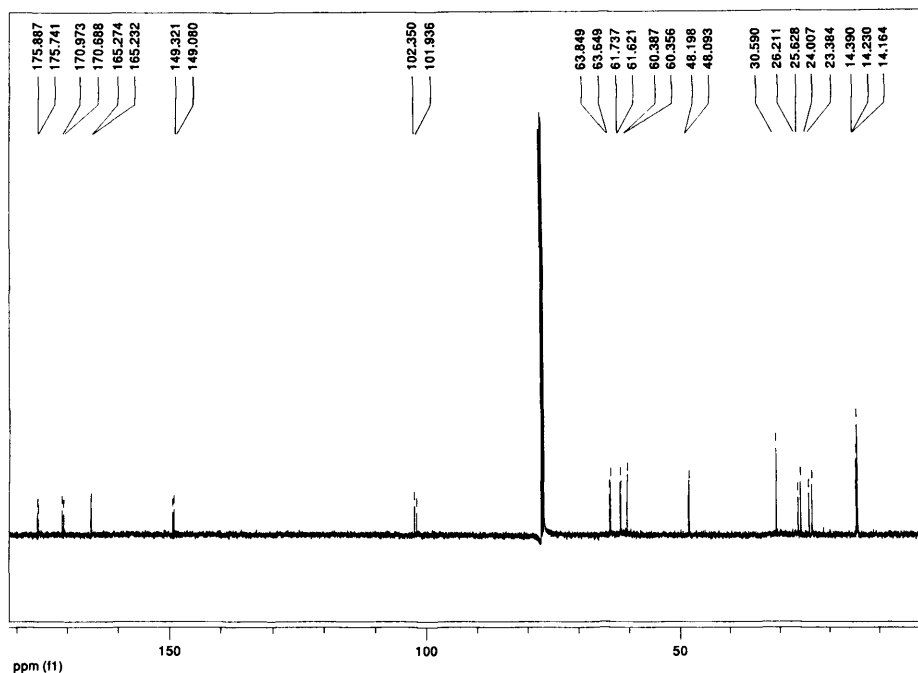
HRMS-ES: m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_4\text{SNa}$: 335.1041; found: 335.1051.

^1H NMR spectrum (500 MHz; CDCl_3) for compounds **184a** and **184b**



Selected peaks: 7.18 (broad d, $J = 2.4$, NH major), 7.15 (broad d, $J = 1.6$, NH minor), 5.21 (dd, $J = 9.2, 4.8$, CHN major), 4.98 (d, $J = 9.0$, CHN minor).

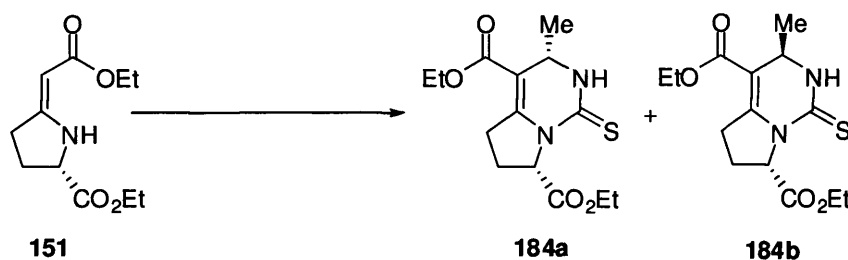
¹³C NMR spectrum (125MHz; CDCl₃) for compound 184a and 184b



Selected peaks: 175.9 and 175.7 (C=S), 171.0 and 170.7 (C=O), 165.3 and 165.2 (C=O), 149.3 and 149.1 (NC=C), 102.4 and 101.9 (NC=C), 63.8 and 63.7 (CHN), 61.7 and 61.6 (CH₂O), 60.4 and 60.4 (CH₂O), 48.2 and 48.1 (CHNH).

(7S)-Diethyl 3-methyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4,7-dicarboxylate (184a) and (184b).

Reaction of compound 151 with silicon tetrathiocyanate and acetaldehyde at 25 °C in dichloromethane.



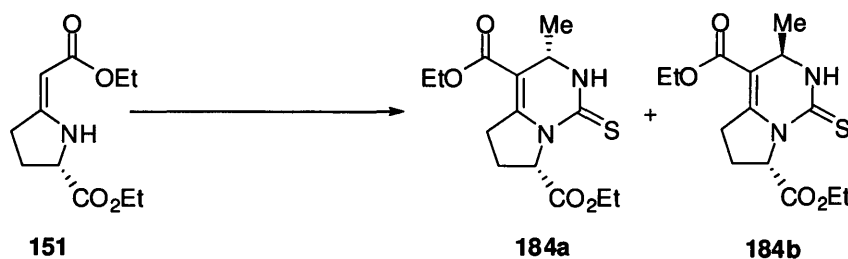
Acetaldehyde (0.06 mL, 1 mmol) was added to a suspension of silicon tetrathiocyanate (260 mg, 1 mmol) in dichloromethane (15 mL). The resulting mixture was stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (2S)-5-[1-Ethoxycarbonyl-meth-(Z)-ylidene]-pyrrolidine-2-carboxylic acid ethyl

ester (**151**) (227 mg, 1 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 3 hours. The solvent was removed *in vacuo* and the residue was redissolved in chloroform and filtered through celite. The solvent was removed *in vacuo* to give the *title compound* as a mixture of diastereoisomers (1.3:1) (231 mg, 74 %) as a pale yellow oil.

Data as previously reported.

(7S)-Diethyl 3-methyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4,7-dicarboxylate (184a**) and (**184b**).**

Reaction of compound 151 with silicon tetrathioisocyanate and acetaldehyde at -78 °C in dichloromethane.

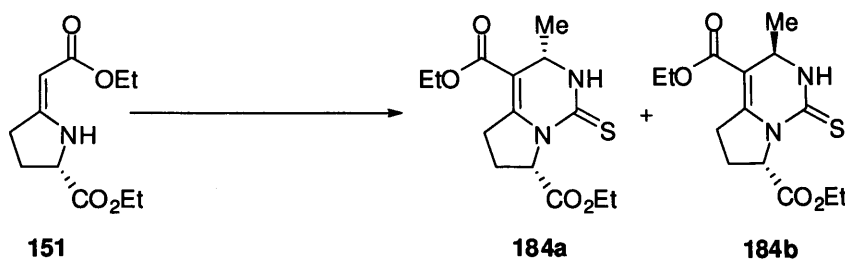


Acetaldehyde (0.06 mL, 1 mmol) was added to a suspension of silicon tetrathioisocyanate (260 mg, 1 mmol) in dichloromethane (15 mL). The resulting mixture was stirred for 30min at -78 °C under a nitrogen atmosphere. (2S)-5-[1-Ethoxycarbonyl-meth-(Z)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (**151**) (227 mg, 1 mmol) in dichloromethane (5 mL) was added and the mixture stirred at -78 °C under a nitrogen atmosphere for a further 3 hours. Excess solvent was removed *in vacuo* and the residue was dissolved in chloroform and filtered through celite. The solvent was removed *in vacuo* to give the *title compound* as a mixture of diastereoisomers (1.3:1) (218 mg, 70 %) as a pale yellow oil.

Data as previously reported.

(7*S*)-Diethyl 3-methyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4,7-dicarboxylate (184a) and (184b).

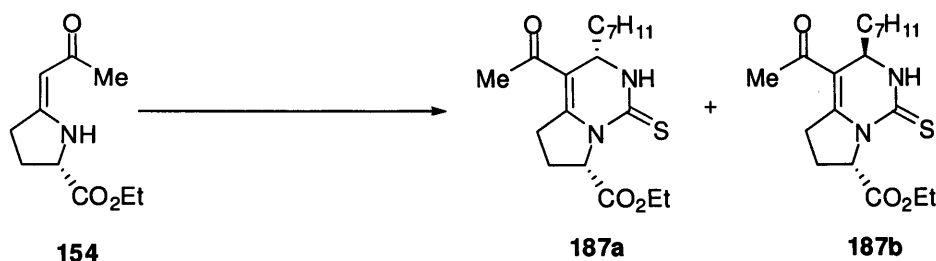
Reaction of compound 151 with trimethylsilyl isothiocyanate and acetaldehyde at 25 °C in dichloromethane.



Acetaldehyde (0.06 mL, 1 mmol) was added to a solution of trimethylsilyl isothiocyanate (260 mg, 1 mmol) in dichloromethane (15 mL). The resulting mixture was stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (2*S*)-5-[1-Ethoxycarbonyl-meth-(*Z*)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (**151**) (227 mg, 1 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 3 hours. Solvent was removed *in vacuo* and the residue was redissolved in chloroform and filtered through celite. The solvent was removed *in vacuo* to give the *title compound* as a mixture of diastereoisomers (1.3:1) (218 mg, 70 %) as a pale yellow oil.

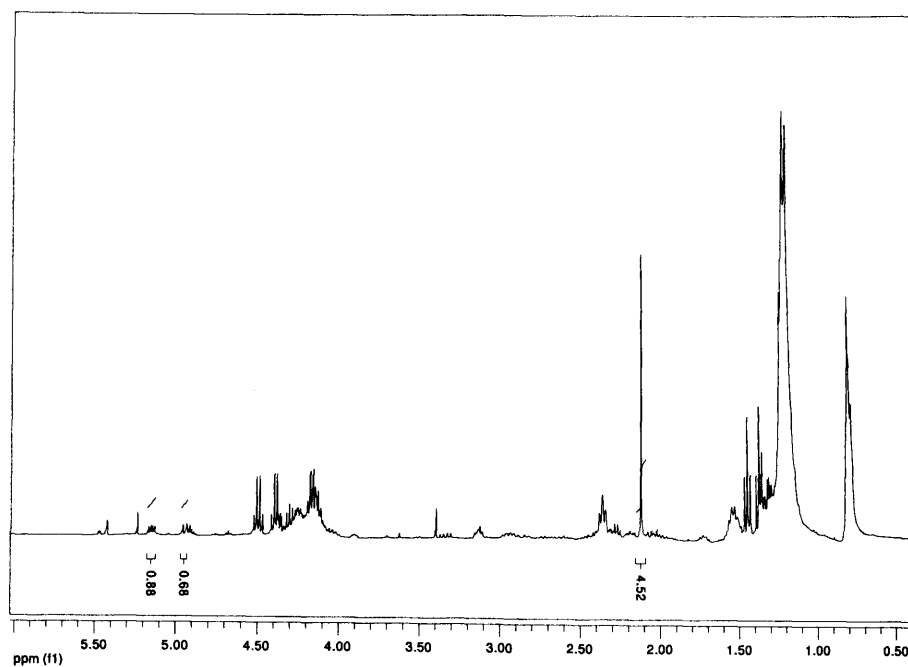
Data as previously reported.

(7*S*)-Ethyl 4-acetyl-3-heptyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-7-carboxylate (**187a**) and (**187b**).



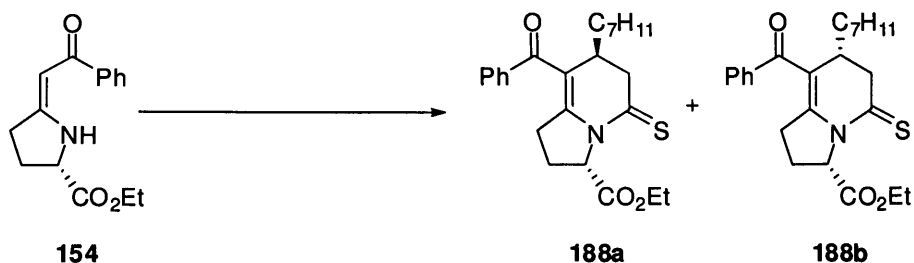
Octanal (143 mg, 1.1 mmol) was added to a suspension of silicon tetrathioisocyanate (290 mg, 1.1 mmol) in dichloromethane (15 mL). The resulting mixture was stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (2*S*)-5-[2-Oxo-prop-(*Z*)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (**153**) (113 mg, 0.5 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 3 hours. Solvent was removed *in vacuo* and residue was dissolved in chloroform and filtered through celite. The solvent was removed *in vacuo* to give the crude *title compound* as a mixture of diastereoisomers (1.3:1) (274 mg, 68 %) as a pale yellow oil.

¹H NMR spectrum for the crude reaction products 187



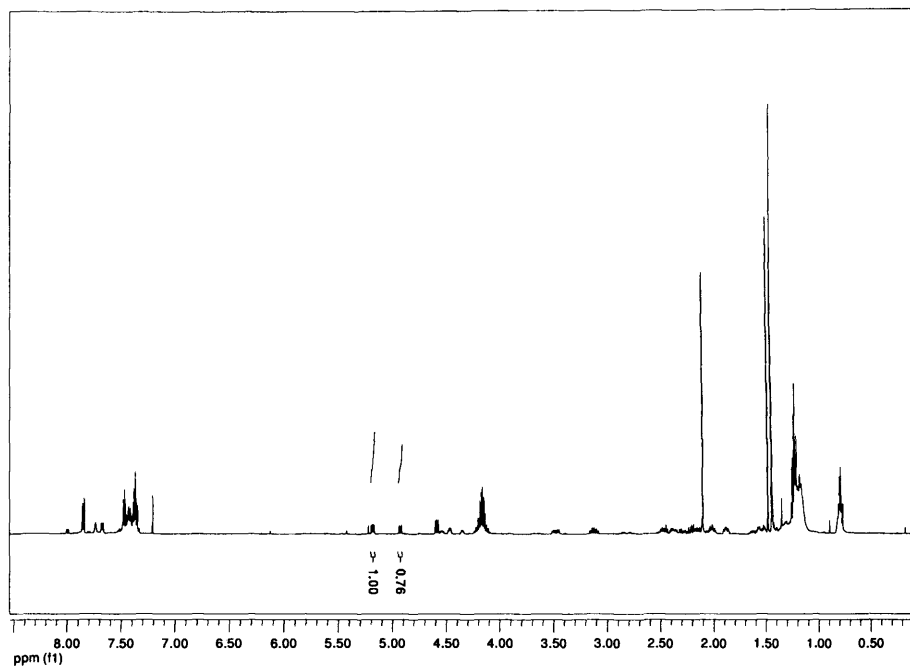
Selected peaks: $\delta = 5.15$ (dd, $J = 9.1$ and 5.3 , 1 H, CHN **187a**), 4.95 (d, $J = 8.6$, 1 H, CHN **187b**).

(7*S*)-Ethyl 4-benzyl-3-heptyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-7-carboxylate (188a) and (188b).



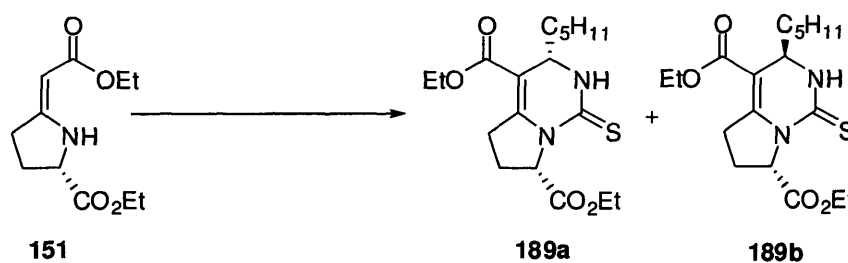
Octanal (143 mg, 1.1 mmol) was added to a suspension of silicon tetraisothiocyanate (290 mg, 1.1 mmol) in dichloromethane (15 mL). The resulting mixture was stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (2*S*)-5-[2-Oxo-2-phenyl-eth-(*Z*)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (154) (113 mg, 0.5 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 3 hours. Solvent was removed *in vacuo* and residue was dissolved in chloroform and filtered through celite. The solvent was removed *in vacuo* to give the crude *title compound* as a mixture of diastereoisomers (1.3:1) (274 mg, 68 %) as a pale yellow oil.

¹H NMR spectrum for the crude reaction products 188



Selected peaks: $\delta = 5.18$ (dd, $J = 8.8$ and 4.7 , 1 H, CHN **188a**), 4.93 (d, $J = 8.5$, CHN **188b**).

(7*S*)-Diethyl 3-heptyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4,7-dicarboxylate (**189a**) and (**189b**).



Hexanal (100 mg, 1 mmol) was added to a solution of trimethylsilyl isothiocyanate (131 mg, 1 mmol) in dichloromethane (15 mL). The resulting solution stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (2*S*)-5-[1-Ethoxycarbonyl-meth-(*Z*)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (227 mg, 1 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen

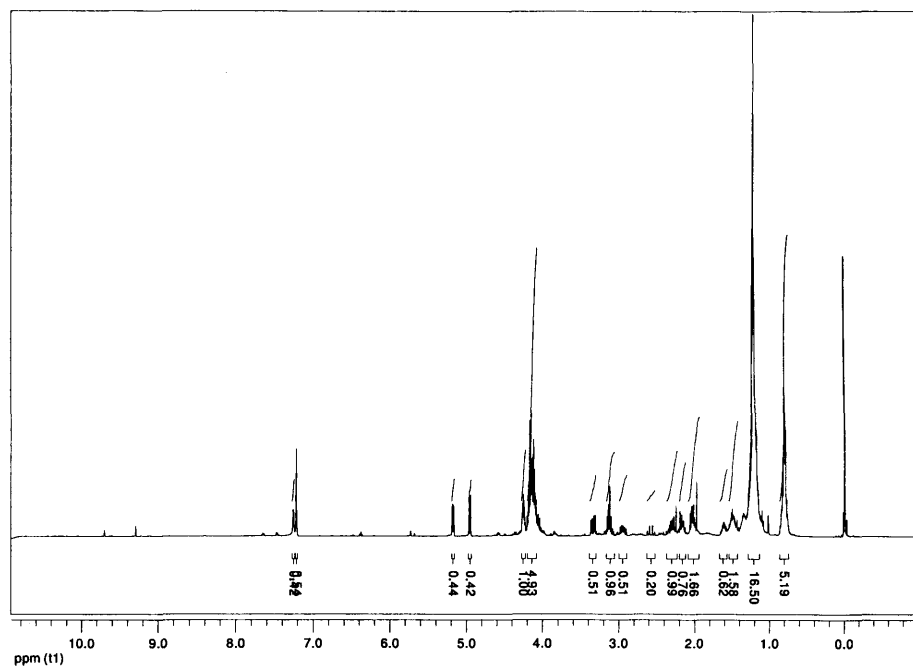
atmosphere for a further 3 hours. The reaction was quenched with sodium hydroxide (0.5 M, 25 mL) and extracted with dichloromethane (3 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent was removed *in vacuo*. The resulting residue was dissolved in ethyl acetate:hexane (1:4) and flushed through a plug of silica gel. The solvent was removed *in vacuo* to give the *title compound* as a mixture of diastereoisomers (287 mg, 78 %) as a pale yellow oil.

IR (Neat): 3395, 2931, 2853, 1738, 1709, 1655, 1377 cm^{-1} .

MS-ES: m/z (%) = 369 (MH^+ , 100).

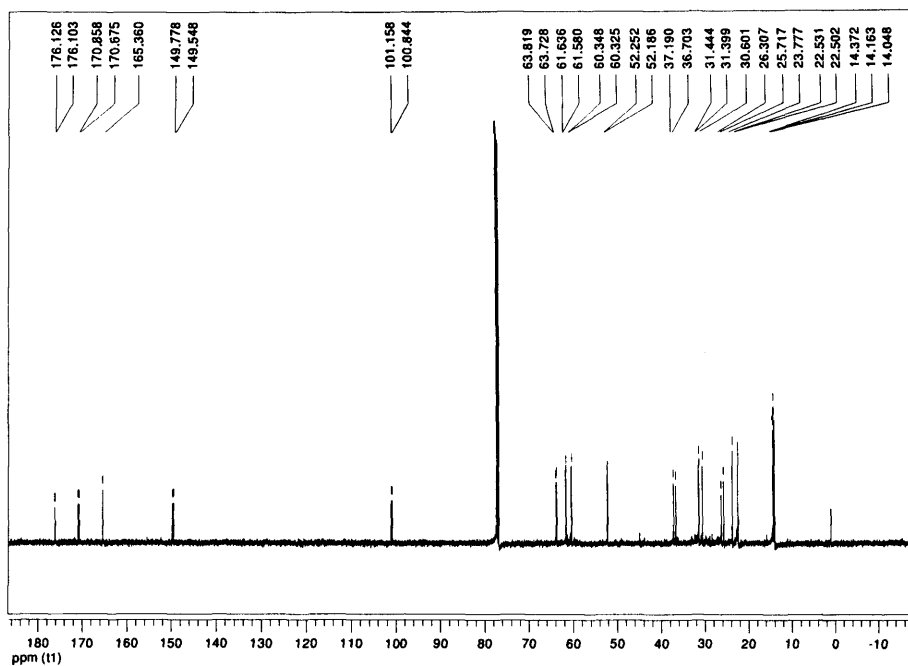
HRMS-ES: m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_4\text{SNa}$: 391.1667; found: 391.1677.

^1H NMR spectrum (500 MHz; CDCl_3) for compounds **189a** and **189b**.



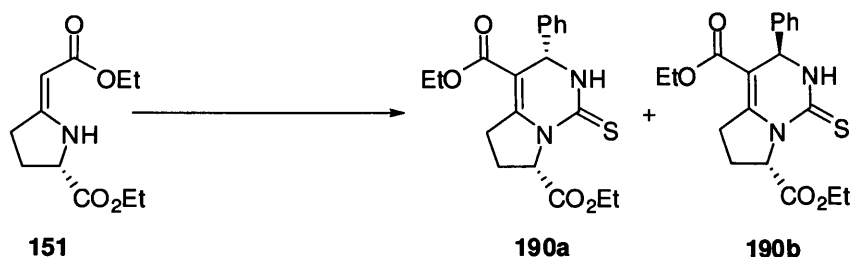
Selected peaks: δ = 7.25 (d, J = 3.14, 1 H, NH **189b**), 7.21 (broad s, NH **189a**), 5.18 (dd, J = 9.2 and 5.1, 1 H, CHN **189a**), 4.96 (d, J = 8.9, 1 H, CHN **189b**), 3.34 (dd, J = 18.0 and 8.16, 1 H, one of $\text{CH}_2\text{C}=\text{C}$ **189a**), 3.20 – 3.06 (m, 2 H, $\text{CH}_2\text{C}=\text{C}$ **189b**), 2.95 (ddd, J = 18.0, 12.1 and 8.9, 1 H, one of $\text{CH}_2\text{C}=\text{C}$ **189a**).

¹³C NMR spectrum (125 MHz; CDCl₃) for compounds **189a** and **189b**.



Selected peaks: $\delta = 176.1$ and 176.1 (C=S), 170.9 and 170.7 (C=O), 165.4 (C=O) 149.8 and 149.5 (NC=C), 101.2 and 100.8 (NC=C), 63.8 and 63.7 (CHN), 61.6 and 61.6 (CH₂O), 60.3 and 60.3 (CH₂O), 52.3 and 52.2 (CHNH), 37.2 and 36.9 (CH₂C=C), 31.4 and 31.4 (pyrrolidine CH₂CH₂), 30.6 (pentyl CH₂CH), 26.3 and 25.7 (pentyl CH₂), 23.8 (pentyl CH₂), 22.5 and 22.5 (pentyl CH₂), 14.8 and 14.2 (CH₃).

(7S)-Diethyl 3-phenyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4,7-dicarboxylate (190a) and (190b).



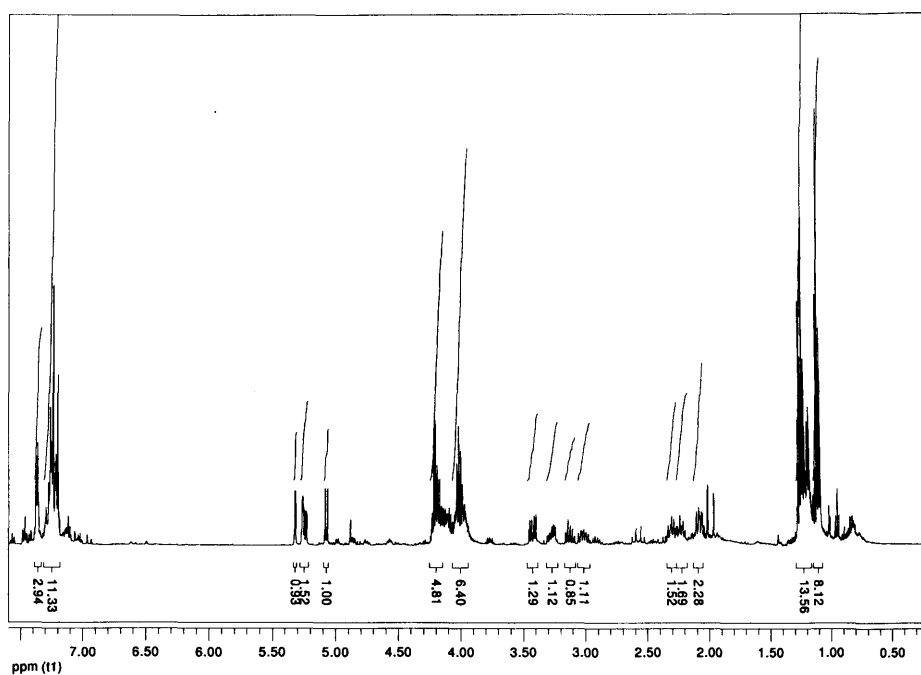
Benzaldehyde (0.053 mL, 0.5 mmol) was added to a suspension of silicon tetraisothiocyanate (130 mg, 0.5 mmol) in dichloromethane (15 mL). The resulting mixture was stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (2S)-5-[1-Ethoxycarbonyl-meth-(Z)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (**151**) (113 mg, 0.5 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 3 hours. Solvent was removed *in vacuo* and the residue was dissolved in chloroform and filtered through celite. The solvent was removed *in vacuo* to give the *title compound* as a mixture of diastereoisomers (139 mg, 74 %) as a pale yellow oil.

IR (Neat): 3300, 2980, 2922, 1739, 1692, 1657, 1455, 1375, 700 cm^{-1} .

MS-ES: m/z (%) = 375 (MH^+ , 30), 316 (100).

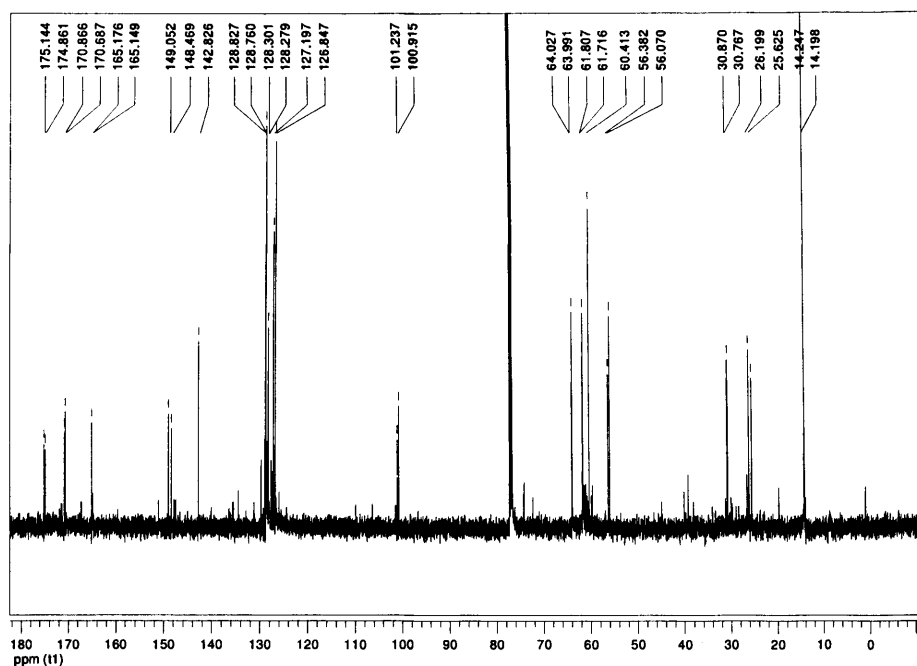
HRMS-ES: m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4\text{SNa}$: 397.1198; found: 397.1202.

¹H NMR spectrum (500 MHz; CDCl₃) for compounds **190a** and **190b**.



Selected peaks: $\delta = 5.32$ (d, $J = 2.7$, CHPh **190a**) 5.27 (d, $J = 2.9$, 1 H, CHPh **190b**), 5.24 (dd, $J = 9.4$ and 4.1 , 1 H, CHN **190b**), 5.07 (d, $J = 8.8$, 1 H, CHN **190a**).

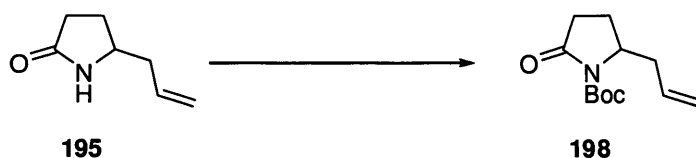
¹³C NMR spectrum (125 MHz; CDCl₃) for compounds **190a** and **190b**



Selected peaks: $\delta = 175.1$ and 174.9 (C=S), 170.9 and 170.7 (C=O), 165.2 and 165.1 (C=O), 149.1 and 148.5 (NC=C), 142.8 (aromatic C), 128.8 and 128.7 (aromatic CH), 128.3 and 128.3 (aromatic CH), 127.2 and 126.8 (aromatic CH), 101.2 and 100.9 (NC=C), 64.0 and 64.0 (CHN), 61.8 and 61.7 (CH₂O), 60.4 (CH₂O), 56.4 and 56.1 (CHNH), 30.9 and 30.8 (CH₂C=C), 26.2 and 25.6 (CH₂CH₂), 14.2 and 14.2 (CH₃).

6.5 Experimental Data for Chapter 5

tert-Butyl 2-allyl-5-oxopyrrolidine-1-carboxylate (**198**).



di-*tert*-Butyl dicarbonate (2.7 g, 12.3 mmol) in dichloromethane (10 mL) was added to a solution of 5-allylpyrrolidin-2-one (**195**) (1.6 g, 12.3 mmol), triethylamine (2.0 mL, 20 mmol) and DMAP (10 mg) in dichloromethane (75 mL) over 15 minutes. The resulting solution was stirred at 25 °C for 18 hours. The reaction was quenched with saturated ammonium chloride (150 mL) and extracted into dichloromethane (3 x 100 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography on silica gel (eluent; ethyl acetate:hexane 1:4) to give the *title compound* (2.3 g, 83 %) as a pale oil.

IR (neat): 2978, 1936, 1785, 1750, 1714, 1156, 850, 780 cm⁻¹.

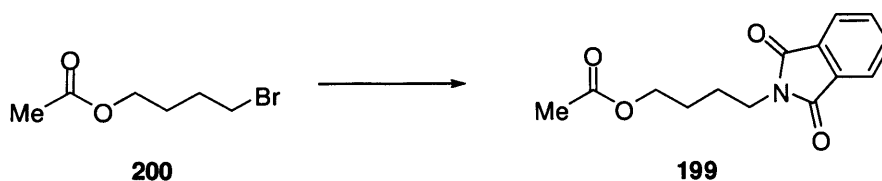
¹H NMR: δ = 5.61 – 5.51 (m, 1 H, CH=CH₂), 4.89 – 4.87 (m, 1 H, one of CH=CH₂), 4.86 – 4.85 (m, 1 H, one of CH=CH₂), 3.99 (tdd, J = 8.6, 5.3 and 3.5, 1 H, CHN), 2.38 (ddd, J = 17.8, 11.0 and 9.3, 1 H, one of CH₂CO), 2.35 – 2.28 (m, 1 H, 1 H, one of CH₂CH₂), 2.22 (ddd, J = 17.8, 12.2 and 9.6, 1 H, 1 H, one of CH₂CO), 2.15 – 2.08 (m, 1 H, 1 H, one of CH₂CH₂).

¹³C NMR: δ = 174.4 (ester C=O), 149.9 (carbamate C=O), 133.6 (CH=CH₂), 118.5 (CH=CH₂), 82.9 (C=O), 53.7 (CHN), 38.1 (CH₂CH=CH₂), 31.4 (CH₂CO), 28.1 ((CH₃)C), 21.9 (CH₂CH₂).

MS-ES: m/z (%) = 84 (100), 184 (MH⁺, 10)

HRMS-ES: m/z [M + H]⁺ calcd for C₉H₁₄NO₃ 184.0974; found: 192.0972.

4-(1,3-Dioxoisindolin-2-yl)butyl acetate (199).



4-Bromobutyl acetate (**200**) (1.30 g, 6.6 mmol) was added to a suspension of potassium phthalimide (1.23 g, 6.6 mmol) in dimethylformamide (10 mL) and the resulting mixture stirred at 100 °C for 6 hours. The resulting mixture was added to diethyl ether (150 mL) and washed with water (5 x 200 mL). The combined ether layers were dried over magnesium sulphate and the solvent was removed *in vacuo*. The resulting off-white crystalline solid was recrystallised from ether:hexane to give the *title compound* (800 mg, 45 %) a white crystalline solid.

Mp: 57 – 57.5 °C.

IR (DCM): 2949, 1771, 1712, 1437, 1395, 720 cm⁻¹.

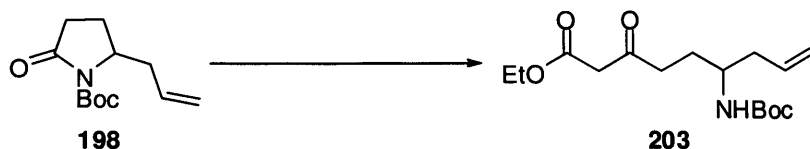
¹H NMR: δ = (500 MHz; CDCl₃): δ = 7.75 (apparent dd, J = 5.4 and 3.1, 2 H, 2 x aromatic CH), 7.65 (apparent dd, J = 5.4 and 3.0, 2 H, 2 x aromatic CH), 4.02 (t, J = 6.3, 2 H, OCH₂), 3.65 (t, J = 6.9, 2 H, CH₂N), 1.89 (s, 3 H, CH₃), 1.74 – 1.57 (m, 4 H, CH₂CH₂).

¹³C NMR: δ = 171.1 (ester C=O), 168.4 (imide C=O), 133.9 (aromatic CH), 132.1 (aromatic C), 123.3 (aromatic CH), 63.8 (CH₂O), 37.6 (CH₂N), 26.1 (CH₂), 25.3 (CH₂), 21.0 (CH₃).

MS-ES: m/z (%) = 262 (MH⁺, 100).

HRMS-ES: m/z [M + H]⁺ calcd for C₁₄H₁₆NO₄: 262.1079; found: 262.1078.

***tert*-Butyl 8-(ethoxycarbonyl)-7-oxooct-1-en-4-ylcarbamate (203).**

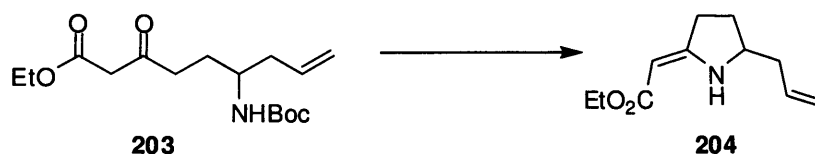


Ethyl acetate (0.64 mL, 6.6 mmol) in THF (4 mL) was added to a solution of lithium diisopropylamide (3.3 mL, 2 M solution in heptane, 6.6 mmol) in THF (15 mL) at $-78\text{ }^{\circ}\text{C}$ over 25 minutes. After stirring for 20 minutes at $-78\text{ }^{\circ}\text{C}$, *tert*-butyl 2-allyl-5-oxopyrrolidine-1-carboxylate (**198**) (1.5 g, 6.6 mmol) in THF (5 mL) was added over 30 minutes at $-78\text{ }^{\circ}\text{C}$. The solution was warmed to $25\text{ }^{\circ}\text{C}$ and stirred for 18 hours. The reaction was quenched with saturated aqueous ammonium chloride (100 mL) and extracted into dichloromethane (3 x 100 mL). The combined dichloromethane layers were washed with brine (2 x 150 mL) and dried over magnesium sulphate. The solvent was removed *in vacuo* to give the crude *title compound* (1.7 g, 81 %) as a pale oil.

^1H NMR (500 MHz; CDCl_3): δ = 5.74 – 5.64 (m, 1 H, $\text{CH}=\text{CH}_2$), 5.02 (apparent broad d, J = 12.9, 2 H, $\text{CH}=\text{CH}_2$), 4.26 (broad d, J = 8.2, 1 H, NH), 4.12 (q, J = 7.1, 2 H, CH_2O), 3.59 – 3.49 (m, 1 H, CHN), 3.38 (s, 2 H, COCH_2CO), 2.59 – 2.52 (m, 2 H, COCH_2CH_2), 2.21 – 2.08 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.82 – 1.74 (m, 1 H, one of CH_2CHN), 1.58 – 1.42 (m, 1 H, one of CH_2CHN), 1.36 (s, 9 H, $(\text{CH}_3)_3$), 1.21 (t, J = 7.1, 3 H, CH_3CH_2).

^{13}C NMR (125 MHz; CDCl_3): δ = 155.7 (carbamate C=O), 134.0 ($\text{CH}=\text{CH}_2$), 118.2 ($\text{CH}=\text{CH}_2$), 90.1 ($\text{OC}(\text{CH}_3)_3$), 61.4 (OCH_2), 49.6 (CHN), 49.5 (COCH_2CO), 40.1 (COCH_2), 39.8 ($\text{CH}_2\text{CH}=\text{CH}_2$), 28.4 (CH_2CH_2), 28.4 ($\text{C}(\text{CH}_3)_3$), 14.2 (CH_3). Ketone and ester carbonyl peaks not observed.

(Z)-Ethyl 2-(5-allylpyrrolidin-2-ylidene)acetate (204).



tert-Butyl 8-(ethoxycarbonyl)-7-oxooct-1-en-4-ylcarbamate (**203**) (1.7 g, 5.4 mmol) was dissolved in TFA (0.84 mL, 11.0 mmol) and the solution stirred for 3 hours at 25 °C. Excess TFA was removed *in vacuo* and the resulting oil dissolved in dichloromethane (5 mL). Saturated aqueous sodium carbonate was added until neutral to pH paper, and the organic material extracted into dichloromethane (3 x 150 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (4.8 g, 89 %) as a pale yellow oil.

IR (neat): 3364, 2976, 1661, 1598, 1049, 781 cm⁻¹.

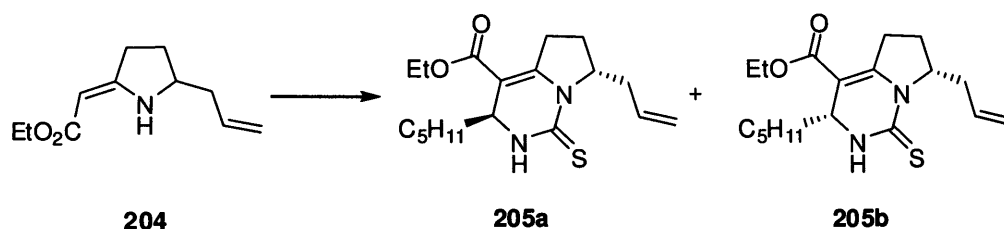
¹H NMR (500 MHz; CDCl₃): δ = 7.91 (s, 1 H, NH), 5.71 (dddd, *J* = 17.2, 10.2, 7.6 and 6.4, 1 H, CH=CH₂), 4.42 (s, 1 H, CH=C), 5.10 – 5.04 (m, 2 H, CH=CH₂), 4.07 – 4.00 (m, 2 H, CH₃CH₂), 3.76 (apparent dt, *J* = 13.4 and 6.8, 1 H CHN), 2.59 – 2.47 (m, 2 H, one of CH₂CH₂CH and one of CH₂CH=CH₂), 2.26 – 2.12 (m, 2 H, one of CH₂CH₂CH and one of CH₂CH=CH₂), 2.02 (dddd, *J* = 12.6, 8.4, 6.9 and 5.2, 1 H, one of CH₂CH₂CH₂), 1.53 (apparent dtd, *J* = 12.6, 8.7 and 6.8, 1 H, one of CH₂CH₂CH₂), 1.18 (t, *J* = 7.1, 3 H, CH₃).

¹³C NMR (125 MHz; CDCl₃): δ = 134.2 (CH=CH₂), 118.0 (CH=CH₂), 76.6 (CH=C), 58.9 (CH₂O), 58.5 (CHN), 40.5 (CH₂CH=CH₂), 31.9 (CH₂C=CH), 27.7 (CH₂CH₂), 14.8 (CH₃). Quaternary peaks not observed.

MS-ES: *m/z* (%) = 108 (100), 195 (MH⁺, 20).

HRMS-ES: *m/z* [M + H]⁺ calcd for C₁₁H₁₇NO₂: 195.1258; found: 195.1258.

(3*SR*,7*RS*)-Ethyl 7-allyl-3-pentyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**205a**) and (3*RS*,7*SR*)-ethyl 7-allyl-3-pentyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**205b**).



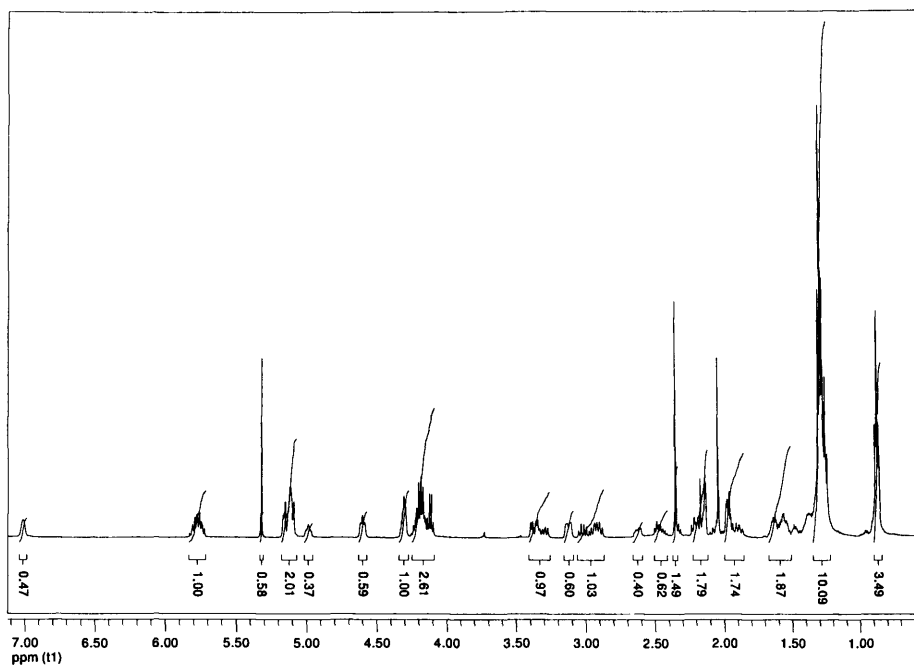
Hexanal (205 mg, 2.0 mmol) was added to a solution of trimethylsilyl isothiocyanate (262 mg, 2.0 mmol) in dichloromethane (15 mL). The resulting solution was stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (*Z*)-Ethyl 2-(5-allylpyrrolidin-2-ylidene)acetate (**204**) (400 mg, 2.0 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 30 minutes. The reaction was quenched with sodium hydroxide (2 M, 50 mL) and extracted into dichloromethane (3 x 50 mL). The dichloromethane layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting residue was dissolved in ethyl acetate:hexane (1:4) and flushed through a plug of silica gel. The solvent was removed *in vacuo* to give the *title compound* (522 mg, 74 %) as a pale oil.

IR (neat): 3148, 2929, 2858, 1693, 1649, 1380 cm^{-1} .

MS-ES: m/z (%) = 337 (MH^+ , 100).

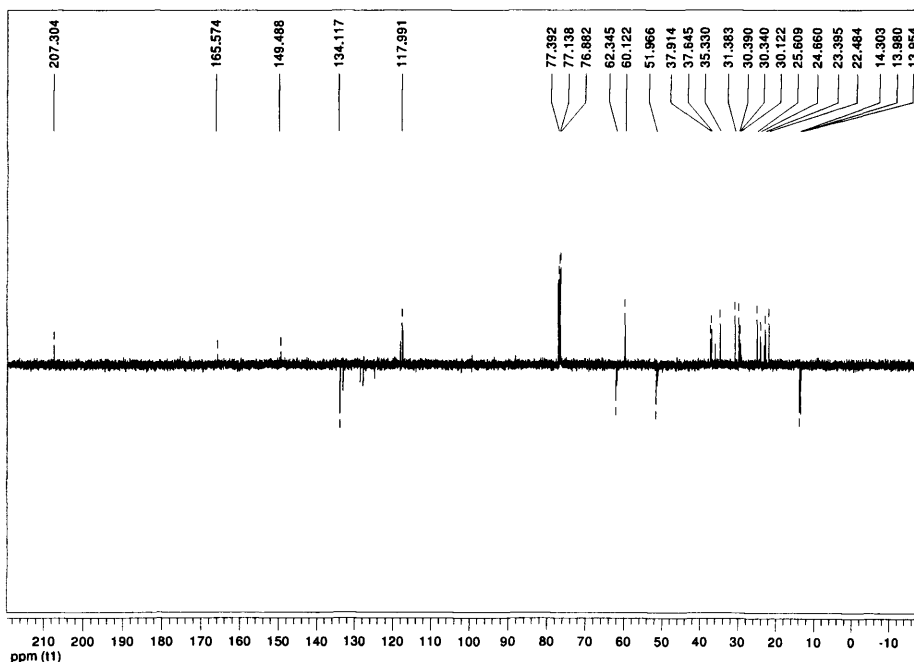
HRMS-ES: m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}_4\text{S}$: 337.1950; found: 337.1937.

¹H NMR spectrum for compounds **205a** and **205b**



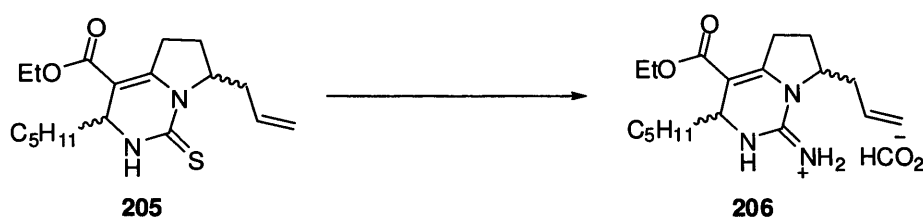
Selected peaks: $\delta = 7.01$ (broad s, 2 H, NH, **205a** and **205b**), 5.84 – 5.72 (m, 2 H, CH=CH₂, **205a** and **205b**), 5.19 – 5.08 (m, 4 H, CH=CH₂, **205a** and **205b**), 5.02 – 4.96 (m, 1 H, CH-allyl **205b**), 4.63 – 4.57 (m, 1 H, CH-allyl, **205a**), 4.34 – 4.29 (m, 2 H, CH-pentyl, **205a** and **205b**).

¹³C NMR(APT) spectrum for compounds **205a** and **205b**



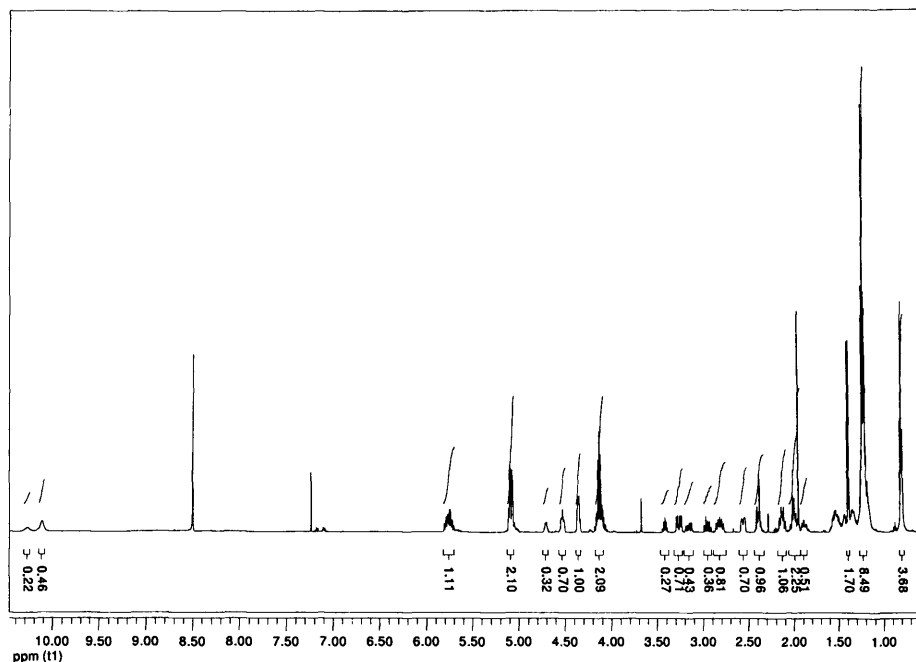
Selected peaks: δ = 207.3 (C=S) 165.6 (C=O), 149.5 (NC=C), 134.1 and 133.6 (CH=CH₂), 118.5 and 118 (CH=CH₂), 100.0 (NC=C), 62.3 (CH-allyl), 60.1 and 60.1 (CH₂O), 51.9 and 51.6 (CH-pentyl).

7-Allyl-4-(ethoxycarbonyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-c]pyrimidin-1(5H)-iminium formate (206).



Iodomethane (156 mg 1.1 mmol) was added to a solution of ethyl 7-allyl-1,2,3,5,6,7-hexahydro-3-pentyl-1-thioxopyrrolo[1,2-c]pyrimidine-4-carboxylate (**205**) (400 mg, 1.1 mmol) in methanol (10 mL) and refluxed for 1 hour. The solvent was removed *in vacuo* to give a yellow gum, taken up into methanol (5 mL) and added to a solution of ammonium acetate (420 mg, 5.5 mmol) in methanol (6 mL). Ammonia was bubbled through the resulting solution for 10 minutes. The resulting mixture was heated in a sealed tube for 48 hours at 80 °C. The resulting solution was loaded directly onto a silica gel column and eluted with (dichloromethane:methanol:formic acid:water, 85:14:0.5:0.5) yielding the *title compound* (360 mg, 86 %) as a white solid.

¹H NMR spectrum for compound 206.



Selected peaks: $\delta = 5.82 - 5.70$ (m, 2 H, $\text{CH}=\text{CH}_2$ major and minor), $5.12 - 5.03$ (m, 4 H, $\text{CH}=\text{CH}_2$ major and minor), $4.74 - 4.68$ (m, 1 H, CHN minor), $4.55 - 4.50$ (m, 1 H, CHN major), $4.38 - 4.33$ (m, 2 H, CHNH major and minor), $4.17 - 4.09$ (m, 4 H, CH_2O major and minor), 3.27 (dd, $J = 18.5$ and 7.5 , 1 H, one of $\text{CH}_2\text{C}=\text{C}$ major), 3.14 (ddd, $J = 19.1$, 10.0 and 3.7 , 1 H, one of $\text{CH}_2\text{C}=\text{C}$ minor), 2.95 (apparent dt, $J = 19.1$ and 9.1 , 1 H, one of $\text{CH}_2\text{C}=\text{C}$ minor), $2.87 - 2.75$ (m, 1 H, one of $\text{CH}_2\text{C}=\text{C}$ major).

(4*S*,7*R*,8*aR*)-Ethyl-7-iodomethyl-4-pentyl-2,4,5,7,8,8*a*-hexahydro-1*H*-5,6,8*b*-triazacyclopentapyridine-3-carboxylate (207).



Iodine (700 mg, 2.7 mmol) was added to a solution of 7-allyl-4-(ethoxycarbonyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidin-1(5*H*)-iminium formate (**206**) (180 mg, 0.47 mmol) and potassium carbonate (194 mg, 1.4 mmol) in acetonitrile (5 mL)

and the resulting solution stirred for 18 hours at 25 °C. The resulting solution was loaded directly onto a silica column and eluted with ethyl acetate:hexane (1:20) to give a single diastereoisomer of the *title compound* (100 mg, 46 %) as a light brown oil.

IR (DCM): 3428, 2961, 2922, 2858, 1718, 1676, 1457, 1101, 1021 cm^{-1} .

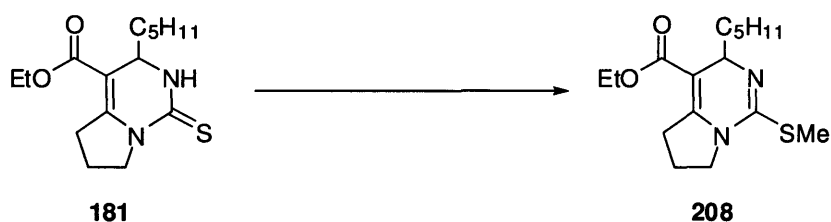
^1H NMR (500 MHz; CD_3OD): δ = 4.33 (dd, J = 8.1 and 4.0, 1 H, H15), 4.16 – 4.08 (m, 3 H, H5 and H11), 3.56 – 3.50 (m, 1 H, H13), 3.44 – 3.32 (m, 3 H, H21 and 9 β), 2.88 – 2.79 (m, 1 H, 9 α), 2.43 – 2.32 (m, 2 H, 10 β and 12 β), 1.73 – 1.62 (m, 1 H, 10 α), 1.60 – 1.39 (m, 3 H, 12 α and 16) 1.39 – 1.1 (m, 6 H, 3 x pentyl CH_2) 1.21 (t, J = 7.1, 3 H, ester CH_3), 0.81 (t, J = 6.9, 3 H, $\text{C}_4\text{H}_8\text{CH}_3$).

^{13}C NMR (125 MHz; CDCl_3): δ = 164.4 (C=O), 148.6 (C=N) 147.9 (NC=C), 103.5 (C=CN), 60.8 (CH_2O), 56.4 (CHN), 50.8 (CHN=C), 50.7 (CHNH), 36.9 ($\text{CH}_2\text{C}=\text{C}$), 34.8 (CH CH_2CH), 31.2 (pyrrolidine CH_2CH_2), 29.7 ($\text{C}_4\text{H}_9\text{CH}_2$), 29.5 ($\text{C}_3\text{H}_7\text{CH}_2$), 24.0 ($\text{C}_2\text{H}_5\text{CH}_2$), 22.4 ($\text{CH}_3\text{CH}_2\text{C}_3\text{H}_6$), 14.3 (ester CH_3), 14.1 ($\text{CH}_3\text{C}_4\text{H}_8$).

MS-ES: m/z (%) = 446 (MH^+ , 100).

HRMS-ES: m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{18}\text{H}_{29}\text{N}_3\text{O}_2$: 446.1304; found: 445.1336.

Ethyl 1-(methylthio)-3-pentyl-3,5,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**208**).



Iodomethane (2.0 g, 14.1 mmol) was added to a solution of ethyl 3-methyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**181**) (1.05 g, 3.5 mmol) in dichloromethane (50 mL) and stirred at reflux for 18 hours. The resulting reaction mixture was quenched with dry triethylamine (1.43 mL, 14.1 mmol). Solvent was removed *in vacuo* to give a dark yellow oil. Purification by flash chromatography on silica gel (eluent ethyl acetate:hexane 1:6) gave the *title compound* (1.0 g, 91 %) as a clear oil.

IR (neat): 2928, 2356, 1693, 1650, 1596, 1443, 1380 cm^{-1} .

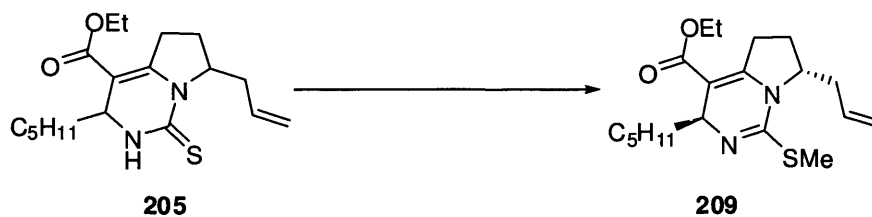
^1H NMR (500 MHz; CDCl_3): δ = 4.57 (t, J = 6.2, 1 H, CH-pentyl), 4.08 (dq, J = 1.5 and 7.1, 2 H, CH_2O), 3.64 (dt, J = 2.5 and 9.3, 1 H, one of CH_2CN), 3.44 (dt, J = 7.1 and 9.3, 1 H, one of CH_2CN), 3.15 (ddd, J = 18.1, 8.4 and 2.6, 1 H, one of $\text{CH}_2\text{C}=\text{C}$), 2.79 (apparent dt, J = 18.1 and 9.0, 1 H, one of $\text{CH}_2\text{C}=\text{C}$), 2.34 (s, 3 H, SCH_3), 2.05 – 1.80 (m, 2 H, CH_2CH_2 pyrrolidine), 1.40 – 1.30 (m, 2 H, CH_2CH), 1.30 – 1.15 (m, 6 H, 3 x pentyl CH_2), 1.19 (t, J = 7.1, 3 H, $\text{CH}_3\text{CH}_2\text{O}$), 0.81 (t, J = 6.8, 3 H, pentyl CH_3).

^{13}C NMR (125 MHz; CDCl_3): δ = 167.0 (C=O), 152.7 (C=CN), 97.4 (C=CN), 59.4 (CH_2O), 56.1 (CHN), 48.2 (CH_2N), 37.2 ($\text{CH}_2\text{C}=\text{C}$), 31.9 (CH_2CH_2 pyrrolidine), 30.9 (pentyl CH_2CH), 24.5 (pentyl CH_2), 22.7 (pentyl CH_2), 22.1 (pentyl CH_2), 14.5 (ester CH_3), 14.1 (pentyl CH_3), 13.8 (SCH_3). CSMe peak not observed though all other quaternary carbon peaks were of a high intensity.

MS-ES: m/z (%) = 311 (MH^+ , 100).

HRMS-ES: m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_2\text{S}$: 311.1788; found: 311.1788.

(3*SR*,7*RS*)-Ethyl 7-allyl-1-(methylthio)-3-pentyl-3,5,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (209).



Iodomethane (2.48 g, 17.6 mmol) was added to a solution of ethyl 7-allyl-1,2,3,5,6,7-hexahydro-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**205**) (2.2:1 mixture of diastereoisomers 1.5 g, 4.4 mmol) in dichloromethane (4 mL) and refluxed for 18 hours. The resulting solution was cooled to 25 °C and dry triethylamine (1.8 mL, 17.6 mmol), added. The resulting solution was stirred for 30 minutes at 25 °C. Solvent was removed *in vacuo* to give a yellow oil purified by flash column chromatography (eluent 12:1 hexane:ethyl acetate) to give the *title compound* as a single diastereoisomer (1.0 g, 64 %) as a pale yellow oil.

IR (neat): 3394, 2928, 2856, 1686, 1652, 1443, 1380 cm^{-1} .

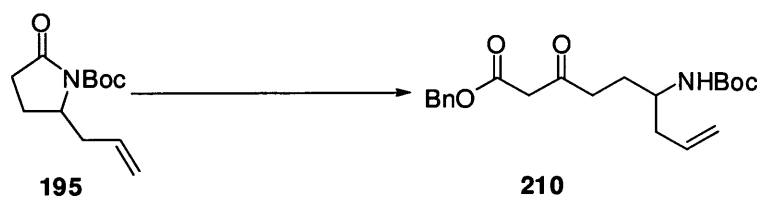
^1H NMR (500 MHz; CDCl_3): δ = 5.65 (dddd, J = 16.9, 10.2, 7.9 and 6.3, 1 H, $\text{CH}=\text{CH}_2$), 5.07 (broad apparent d, J = 16.9, 1 H, one of $\text{CH}=\text{CH}_2$), 5.03 (broad apparent d, J = 9.9, 1 H, one of $\text{CH}=\text{CH}_2$), 4.53 (dd, J = 7.0 and 3.6, 1 H, pentyl CHN), 4.12 – 4.02 (m, 2 H, ester CH_2), 3.98 – 3.92 (m, 1 H, CH allyl), 3.14 (ddd, J = 18.3, 5.0 and 4.2, 1 H, one of $\text{CH}_2\text{C}=\text{C}$), 2.77 (apparent dt, J = 18.3 and 9.7, 1 H, one of $\text{CH}_2\text{C}=\text{C}$), 2.65 (dd, J = 13.9 and 5.8, 1 H, one of $\text{CH}_2\text{CH}=\text{CH}_2$), 2.33 (s, 3 H, SCH_3), 2.06 (apparent dt, J = 13.9 and 9.1, 1 H, one of $\text{CH}_2\text{CH}=\text{CH}_2$), 1.87 – 1.81 (m, 2 H, pyrrolidine CH_2CH_2), 1.55 – 1.45 (m, 1 H, one of pentyl $\text{CH}_2\text{CH}_2\text{CH}$), 1.43 – 1.33 (m, 1 H, one of pentyl $\text{CH}_2\text{CH}_2\text{CH}$), 1.29 – 1.16 (m, 6 H, 3 x pentyl CH_2), 1.19 (t, J = 7.1, 3 H, ester CH_3), 0.80 (t, J = 6.8, pentyl CH_3).

^{13}C NMR (125 MHz; CDCl_3): δ = 167.3 (C=O), 151.9 (C=CN), 148.8 (C-SCH₃), 133.8 (CH=CH₂), 118.3 (CH=CH₂), 96.5 (C=CN), 59.65 (CH-allyl), 59.3 (ester CH₂), 56.1 (CH-pentyl), 38.9 (CH₂CH=CH₂), 36.9 (CH₂C=C), 31.8 (pyrrolidine CH₂CH₂), 29.2 (pentyl CH₂CH), 26.4 (pentyl CH₂), 24.1 (pentyl CH₂), 22.7 (pentyl CH₂), 14.5 (ester CH₃), 14.1 (pentyl CH₃), 13.8 (SCH₃).

MS-ES: m/z (%) = 351 (MH^+ , 100).

HRMS-ES: m/z [$\text{M} + \text{H}$]⁺ calcd for $\text{C}_{19}\text{H}_{31}\text{N}_2\text{O}_2\text{S}$: 351.2106; found: 351.2094.

***tert*-Butyl 8-((benzyloxy)carbonyl)-7-oxooct-1-en-4-ylcarbamate (**210**).**



Ethyl acetate (584 mg, 3.9 mmol) in THF (4 mL) was added to a solution of lithium diisopropylamide (1.95 mL, 2 M solution in heptane, 3.9 mmol) in THF (15 mL) at -78 °C. over 25 minutes. After stirring for 20 minutes at -78 °C, *tert*-butyl 2-allyl-5-oxopyrrolidine-1-carboxylate (**195**) (1.0 g, 3.9 mmol) in THF (5 mL) was added over 30 minutes at -78 °C. The solution was warmed to 25 °C and the resulting mixture stirred for 18 hours. The reaction was quenched with saturated aqueous ammonium chloride (100 mL) and extracted into dichloromethane (3 x 100 mL). The dichloromethane layers were washed with brine (2 x 150 mL) and dried over

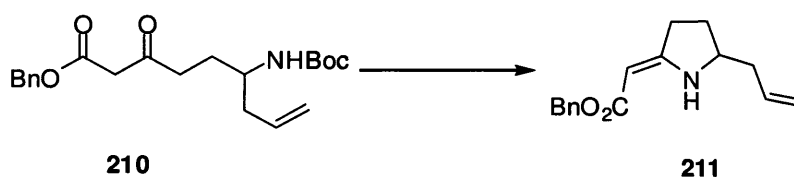
magnesium sulphate. The solvent was removed *in vacuo*, to give the crude *title compound* (1.05 g, 72 %) as a yellow oil.

IR (Neat): 3365, 2976, 2932, 1739, 1713, 1514 cm^{-1} .

^1H NMR (500 MHz; CDCl_3): δ = 7.33 – 7.23 (m, 5 H, aromatic CH), 5.72 – 5.62 (m, 1 H, $\text{CH}=\text{CH}_2$), 5.09 (s, 2 H, CH_2O), 5.02 – 4.97 (m, 2 H, $\text{CH}=\text{CH}_2$), 4.28 (broad d, J = 8.7, 1 H, NH), 3.61 – 3.50 (m, 1 H, CHN), 3.43 (s, 2 H, COCH_2CO), 2.55 – 2.49 (m, 2 H, COCH_2), 2.17 – 2.05 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.80 – 1.65 (m, 1 H, one of CH_2CHN), 1.52 – 1.38 (m, 1 H, one of CH_2CHN), 1.35 (s, 9 H, $(\text{CH}_3)_3$).

^{13}C NMR (125 MHz; CDCl_3): δ = 202.3 (ketone $\text{C}=\text{O}$), 167.0 (ester $\text{C}=\text{O}$), 155.7 (carbamate $\text{C}=\text{O}$), 135.3 (aromatic C), 134.0 ($\text{CH}=\text{CH}_2$), 128.6 (2 x aromatic CH), 128.5 (aromatic CH), 128.4 (2 x aromatic CH), 118.0 ($\text{CH}=\text{CH}_2$), 79.9 ($\text{OC}(\text{CH}_3)_3$), 67.1 (OCH_2), 49.6 (CHN), 49.3 (COCH_2CO), 39.9 (COCH_2), 39.8 ($\text{CH}_2\text{CH}=\text{CH}_2$), 28.4 ($(\text{CH}_3)_3$), 28.4 (CH_2CH_2).

(Z)-Benzyl 2-(5-allylpyrrolidin-2-ylidene)acetate (211).



Crude *tert*-butyl 8-((benzyloxy)carbonyl)-7-oxooct-1-en-4-ylcarbamate (**210**) (1.1 g, 2.9 mmol) was dissolved in TFA (0.465 mL, 6.0 mmol) and the solution stirred for 3 hours at 25 °C. Excess TFA was removed *in vacuo* and the resulting oil dissolved in dichloromethane (5 mL). Saturated aqueous sodium carbonate was added until neutral to pH paper, and the organic material extracted into dichloromethane (3 x 150 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent was removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (600 mg, 79 %) as a pale oil.

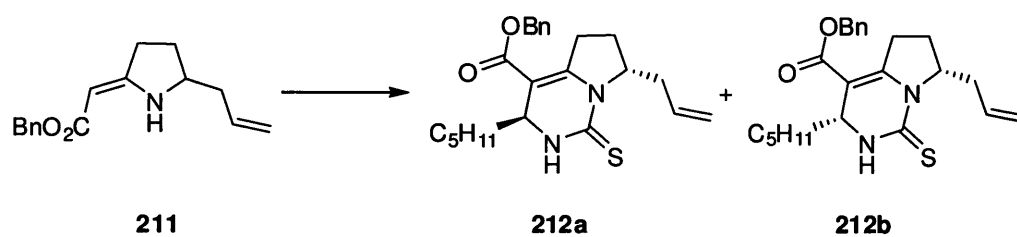
IR (Neat): 3414, 2978, 2935, 1719, 1614, 1383, 1317, 1244, 740, 698 cm^{-1} .

^1H NMR (500 MHz; CDCl_3): δ = 7.80 (broad s, 1 H, NH), 7.19 – 7.06 (m, 5 H, aromatic CH), 5.58 (dddd, J = 17.0, 10.2, 7.4 and 6.5, 1 H, $\text{CH}=\text{CH}_2$), 4.99 – 4.88 (m, 4 H, $\text{CH}=\text{CH}_2$ and CH_2O), 4.38 (s, 1 H, $\text{CH}=\text{C}$), 3.64 (apparent quintet, J = 6.7, 1

H, CHN), 2.47 – 2.34 (m, 2 H, one of CH₂C=CH and one of CH₂CH=CH₂), 2.13 – 2.01 (m, 2 H, one of CH₂C=CH and one of CH₂CH=CH₂), 1.95 – 1.84 (m, 1 H, one of CH₂CH₂CH), 1.48 – 1.38 (m, 1 H, one of CH₂CH₂CH).

¹³C NMR (125 MHz; CDCl₃): δ = 170.3 (C=O), 166.1 (C=CH), 137.6 (aromatic C), 134.1 (CH=CH₂), 128.4 (2 x aromatic CH), 127.8 (aromatic CH), 127.7 (2 x aromatic CH), 118.1 (CH=CH₂), 76.4 (CH=C), 64.4 (CH₂O), 58.9 (CHN), 43.7 (CH₂CH=CH₂), 31.9 (CH₂C=CH), 27.7 (CH₂CH₂CH).

(3SR,7RS)-Benzyl 7-allyl-3-pentyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (212a) and **(3RS,7SR)-Benzyl 7-allyl-3-pentyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (212b)**.



Hexanal (84 mg, 0.84 mmol) was added to a solution of trimethylsilyl isothiocyanate (110 mg, 0.84 mmol) in dichloromethane (15 mL). The resulting solution was stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (*Z*)-Butyl 2-(5-allylpyrrolidin-2-ylidene)acetate (**211**) (200 mg, 0.84 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 30 minutes. The reaction was quenched with sodium hydroxide (0.5 M, 50 mL) and extracted into dichloromethane (3 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (eluent: ethyl acetate:hexane 3:10) to give the *title compounds* as a pale oil.

Major isomer (212a) (143 mg, 44 %).

IR Neat: 3203, 2954, 2857, 1690, 1648, 1388, 748, 697 cm⁻¹.

¹H NMR (500 MHz; CDCl₃): δ = 7.31 – 7.25 (m, 5 H, aromatic CH), 6.84 (broad d, *J* = 1.9, 1 H NH), 5.68 (dddd, *J* = 17.1, 10.2, 8.2 and 5.9, 1 H, CH=CH₂), 5.14 and 5.07 (AB quartet, *J* = 12.3, 2 H PhCH₂), 5.08 – 5.01 (m, 2 H, CH=CH₂), 4.56 – 4.51 (m, 1 H, CH-allyl), 4.25 – 4.20 (m, 1 H, C₅H₁₁CHN), 3.32 – 3.26 (m, 1 H, one of

CH₂C=C), 3.07 – 3.01 (m, 1 H, one of CH₂C=C), 2.88 – 2.78 (m, 1 H, one of CH₂CH=CH₂), 2.15 – 2.07 (m, 1 H one of CH₂CH=CH₂), 1.90 – 1.83 (m, 2 H, pyrimidine CH₂CH₂), 1.58 – 1.47 (m, 2 H, C₄H₉CH₂CH), 1.34 – 1.10 (m, 6 H, 3 x pentyl CH₂), 0.78 (t, *J* = 7.0, 3 H, CH₃).

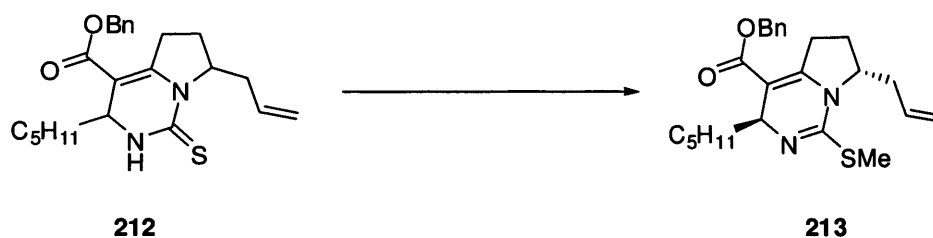
¹³C NMR (125 MHz; CDCl₃): δ = 175.2 (C=S), 165.4 (C=O), 150.1 (C=CN), 136.0 (aromatic C), 134.1 (CH=CH₂), 128.6 (2 x aromatic CH), 128.3 (aromatic CH), 128.2 (2 x aromatic CH), 118.1 (CH=CH₂), 99.7 (C=CN), 66.1 (CH₂O), 62.5 (CH-allyl), 52.1 (CH-pentyl), 37.8 (CH₂CH=CH₂), 35.4 (CH₂C=C), 31.4 (pyrrolidine CH₂CH₂), 30.5 (pentyl CH₂CH), 25.7 (pentyl CH₂), 23.5 (pentyl CH₂), 22.5 (pentyl CH₂), 14.1 (pentyl CH₃).

Minor isomer (212b) (60 mg, 23 %).

¹H NMR (500 MHz; CDCl₃): δ = 7.31 – 7.25 (m, 5 H, aromatic CH), 6.84 (broad d, *J* = 3.2, 1 H NH), 5.70 (dddd, *J* = 17.0, 10.1, 7.6 and 6.8, 1 H, CH=CH₂), 5.15 and 5.07 (AB quartet, *J* = 12.4, 2 H PhCH₂), 5.10 – 5.03 (m, 2 H, CH=CH₂) 4.91 (tdd, *J* = 8.4, 3.8 and 2.3 1 H, CH-allyl), 4.24 (dt, *J* = 7.5 and 3.8, 1 H, C₅H₁₁CHN), 3.23 (ddd, *J* = 19.1, 9.9 and 2.8, 1 H, one of CH₂C=C), 2.93 (apparent dt, *J* = 19.1 and 9.4, 1 H, one of CH₂C=C), 2.58 – 2.52 (m, 1 H, one of CH₂CH=CH₂), 2.39 (apparent dt, *J* = 14.7 and 7.8, 1 H one of CH₂CH=CH₂), 1.98 (ddd, *J* = 18.6, 12.9 and 9.9 1 H, one of pyrrolidine CH₂CH₂), 1.80 (apparent ddt, *J* = 12.9, 9.1 and 2.8, 1 H, one of pyrrolidine CH₂CH₂), 1.50 – 1.43 (m, 1 H, one of C₄H₉CH₂CH), 1.43 – 1.35 (m, 1 H, one of C₄H₉CH₂CH), 1.30 – 1.11 (m, 6 H, 3 x pentyl CH₂), 0.79 (t, *J* = 6.9, 3 H, CH₃).

¹³C NMR (125 MHz; CDCl₃): δ = 175.9 (C=S), 165.3 (C=O), 150.8 (C=CN), 136.0 (aromatic C), 133.3 (CH=CH₂), 128.6 (2 x aromatic CH), 128.3 (aromatic CH), 128.2 (2 x aromatic CH), 118.7 (CH=CH₂), 100.3 (C=CN), 66.2 (CH₂O), 62.4 (CH-allyl), 51.2 (CH-pentyl), 37.9 (CH₂CH=CH₂), 36.8 (CH₂C=C), 31.4 (pyrrolidine CH₂CH₂), 30.6 (C₄H₉CH₂), 24.7 (pentyl CH₂), 23.8 (pentyl CH₂), 22.5 (pentyl CH₂), 14.0 (CH₃C₄H₈).

(3*SR*,7*RS*)-Benzyl 7-allyl-1-(methylthio)-3-pentyl-3,5,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (213).



Iodomethane (2.82 g, 20 mmol) was added to a solution of a diastereomeric mixture of isomers of benzyl 7-allyl-3-pentyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**212**) (2.2:1 mixture of diastereoisomers 2.0 g, 5.2 mmol) in dichloromethane (4 mL) and refluxed for 18 hours. The resulting solution was cooled to 25 °C and dry triethylamine (2.1 mL, 20 mmol), added. The resulting solution stirred for 30 minutes at 25 °C. Solvent was removed *in vacuo* to give a yellow oil purified by flash column chromatography (eluent 12:1 hexane:ethyl acetate) to give the *title compound* as a single diastereoisomer (980 mg, 46 %) as a pale oil.

IR (Neat): 2927, 2855, 2686, 2650, 2594, 1455, 1384, 734, 697 cm⁻¹.

¹H NMR (500 MHz; CDCl₃): δ = 7.32 – 7.20 (m, 5 H, aromatic CH), 5.65 (dddd, *J* = 17.2, 10.1, 7.8 and 6.2, 1 H, CH=CH₂), 5.08 (apparent bs, 2 H, CH₂O) 5.06 (dd, *J* = 17.2 and 1.2, 2 H, one of CH=CH₂), 5.04 (dd, *J* = 10.1 and 1.2, 1 H one of CH=CH₂) 4.58 (dd, *J* = 7.2 and 3.6, 1 H, pentyl CHN), 3.98 – 3.91 (m, 1 H, CH allyl), 3.13 (ddd, *J* = 18.2, 5.5 and 3.8, 1 H, one of CH₂C=C), 2.76 (apparent dt, *J* = 18.2 and 10.3, 1 H, one of CH₂C=C), 2.65 (apparent broad dd, *J* = 13.7 and 5.6, 1 H, one of CH₂CH=CH₂), 2.32 (s, 3 H, SCH₃), 2.10 – 2.02 (m, 1 H, one of CH₂CH=CH₂), 1.85 – 1.78 (m, 2 H, pyrrolidine CH₂CH₂), 1.57 – 1.47 (m, 1 H, one of C₄H₉CH₂CH), 1.46 – 1.31 (m, 1 H, one of pentyl CH₂CH₂CH), 1.30 – 1.11 (m, 6 H, 3 x pentyl CH₂), 0.78 (t, *J* = 6.9, pentyl CH₃). Assignments confirmed by ¹H-¹H COSY NMR spectroscopy.

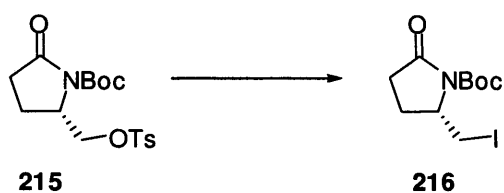
¹³C NMR (125 MHz; CDCl₃): δ = 166.9 (C=O), 152.6 (C=CN), 148.8 (C-SCH₃), 136.9 (aromatic C), 133.7 (CH=CH₂), 128.5 (3 x aromatic CH), 127.8 (2 x aromatic CH), 118.3 (CH=CH₂), 96.1 (C=CN), 65.3 (CH₂O), 59.6 (CH-allyl), 56.2 (C₅H₁₁CH), 39.1 (CH₂CH=CH₂), 36.9 (CH₂C=C), 31.9 (pyrrole CH₂CH₂), 29.3

(C₄H₉CH₂CH), 26.4 (pentyl CH₂), 24.1 (pentyl CH₂), 22.7 (pentyl CH₂), 14.1 (CH₃C₄H₈), 13.8 (SCH₃).

MS-ES: m/z (%) = 413 (MH⁺, 100).

HRMS-ES: m/z [M + H]⁺ calcd for C₂₄H₃₃N₂O₂S: 413.2263; found: 413.2263.

(S)-tert-Butyl 2-(iodomethyl)-5-oxopyrrolidine-1-carboxylate (216).¹⁰⁶

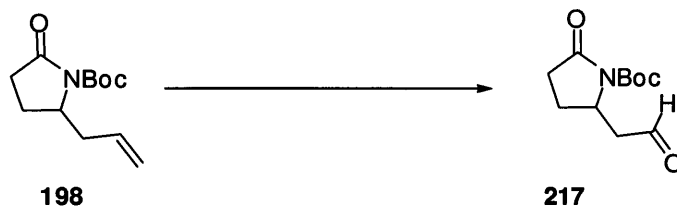


Sodium iodide (13.6 g, 90 mmol) was added to a solution of (*S*)-tert-butyl 2-oxo-5-(tosyloxymethyl)pyrrolidine-1-carboxylate (**215**) (1.76 g, 6.6 mmol) in acetonitrile and refluxed for 4 hours. The resulting suspension was filtered and the solvent removed *in vacuo*. The resulting solid was recrystallised from ethanol to give the *title compound* (1.33 g, 62 %) as a white crystalline solid.

¹H NMR (500 MHz; CDCl₃): δ = 3.78 (dt, *J* = 11.5 and 5.8, 1 H, CHN), 3.17 (d, *J* = 5.8, 2 H, CH₂I), 2.43 – 2.35 (m, 1 H, one of CH₂CO), 2.30 – 2.20 (m, 1 H, one of CH₂CO and one of CH₂CH₂), 1.80 – 1.72 (m, 1 H, one of CH₂CH₂).

¹³C NMR (125 MHz; CDCl₃): δ = 178.5 (C=O), 55.2 (CHN), 30.4 (CH₂CO), 27.4 (CH₂CH), 11.8 (CH₂I).

tert-Butyl 2-(formylmethyl)-5-oxopyrrolidine-1-carboxylate (217).



tert-Butyl 2-allyl-5-oxopyrrolidine-1-carboxylate (**198**) (100 mg, 0.4 mmol) was added to a solution of potassium osmate (5 mg) 2,6-lutidine (43 mg 0.4 mmol) and sodium metaperiodate (340 mg, 1.6 mmol) in dioxane:water (3:1) and the resulting

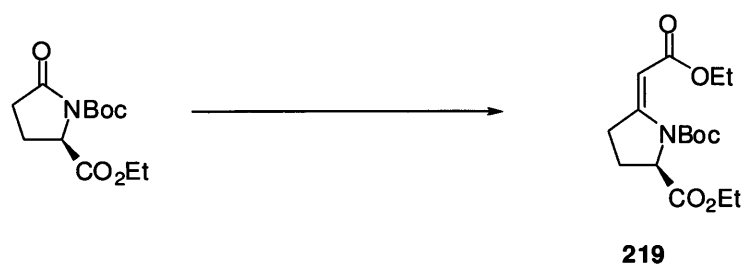
solution stirred for 18 hours at 25 °C. The resulting solution was diluted with water (100 mL) and extracted with dichloromethane (3 x 75 mL). The dichloromethane layers were dried over magnesium sulphate and the solvent was removed *in vacuo* to give a dark brown oil. The residual brown oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (86 mg, 93 %) as a clear gum.

IR (neat): 2978, 2925, 1784, 1752, 1715, 1458, 1311, 1152 cm⁻¹.

¹H NMR (500 MHz; CDCl₃): δ = 9.73 (t, *J* = 1.2, 1 H, CHO), 4.58 (tdd, *J* = 8.8, 3.8 and 2.3, 1 H, CHN), 2.95 (broad apparent dd, *J* = 17.4 and 3.8, 1 H, one of CH₂CHO), 2.65 (ddd, *J* = 17.4, 8.8 and 1.2, one of CH₂CHO), 2.52 (ddd, *J* = 17.8, 10.8 and 9.1, 1 H, one of CH₂CO), 2.41 (ddd, *J* = 17.8, 9.5 and 3.1, 1 H, one of CH₂CO), 2.23 (m, 1 H, one of CH₂CH₂), 1.68 (apparent ddt, *J* = 13.2, 9.1 and 2.6, 1 H, one of CH₂CH₂).

¹³C NMR (125 MHz; CDCl₃): δ = 199.1 (aldehyde C=O), 173.6 (amide C=O), 149.9 (carbamate C=O), 83.7 (OC), 52.9 (CHN), 48.1 (CH₂CHO), 31.2 (CH₂CO), 28.1 ((CH₃)₃), 23.6 (CH₂CH₂).

(2*R*)-5-[1-Ethoxycarbonyl-meth-(*Z*)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (151).

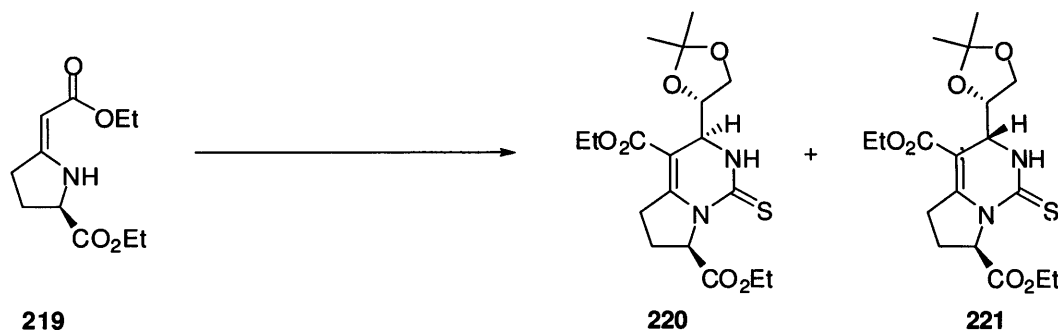


A solution of lithium diisopropylamide (4.0 mL, 2 M solution in heptane, 8.0 mmol) in THF (15 mL) was cooled to -78 °C. Ethyl acetate (0.78 mL, 8.0 mmol) in THF (4 mL) was added over 25 minutes. After stirring for 20 minutes at -78 °C, ethyl (*R*)-*tert*-butoxycarbonyl-5-oxopyrrolidine-2-carboxylate (2.1 g, 7.8 mmol) in THF (5 mL) was added over 30 minutes at -78 °C. The solution was then allowed to warm to 25 °C and left to stir for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution extracted with dichloromethane (3 x 100 mL). The

combined organic layers were washed with brine (2 x 150 mL), dried over magnesium sulphate and the solvent removed *in vacuo* to give a yellow oil (2.48 g, 7.2 mmol) which was dissolved in TFA (1.1 mL, 14.5 mmol). The resulting solution was stirred for 3 hours at 25 °C. Excess TFA was removed *in vacuo* and the resulting, oil dissolved in dichloromethane (5 mL). Saturated aqueous sodium carbonate was added until neutral to pH paper, and the organic material extracted into dichloromethane (3 x 100 mL). The combined organic layers were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (eluent 4:1 hexane:ethyl acetate) to give the *title compound* (1.3 g, 71 %) as a pale yellow oil.

Data identical to compound 151.

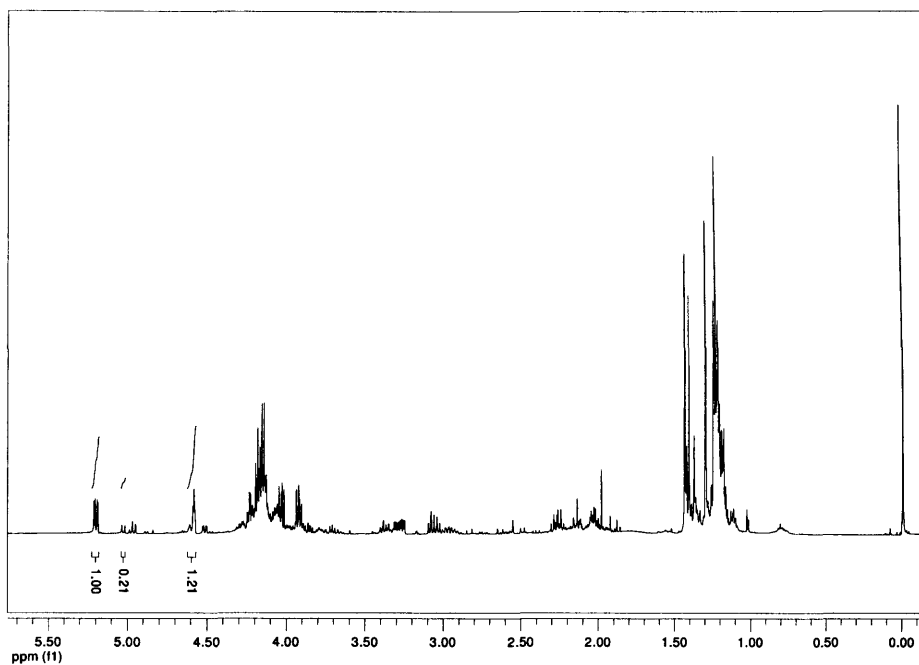
(3*S*,7*R*)-diethyl 3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4,7-dicarboxylate (220) and (3*R*,7*R*)-diethyl 3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-thioxo-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4,7-dicarboxylate (221).



(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (260 mg, 2 mmol) in dichloromethane (5 mL) was added to a solution of trimethylsilyl isothiocyanate (260 mg, 2 mmol) in dichloromethane (10 mL). The resulting solution was stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (*2R*)-5-[1-Ethoxycarbonyl-meth-(*Z*)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (**219**) (455 mg, 2 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 30 minutes. The reaction was quenched with sodium hydroxide (0.5 M, 50 mL) and the mixture extracted with dichloromethane (3 x 50

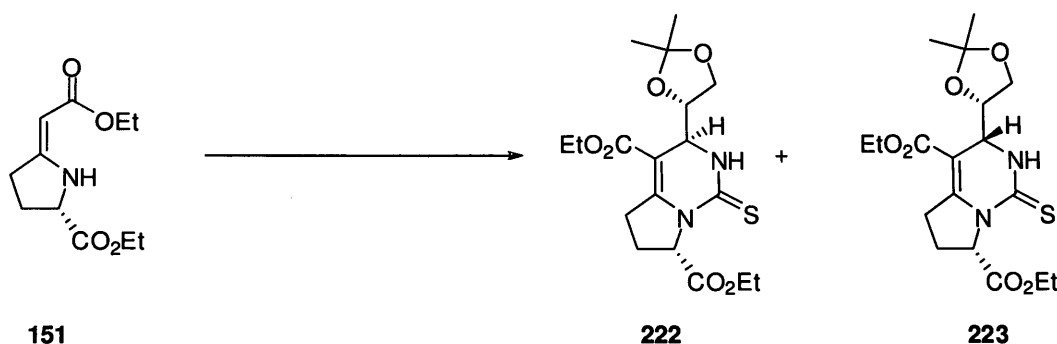
mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent removed *in vacuo* to give the crude *title compound* as a yellow oil.

¹H NMR spectrum (500 MHz; CDCl₃) for crude compounds (220) and (221).



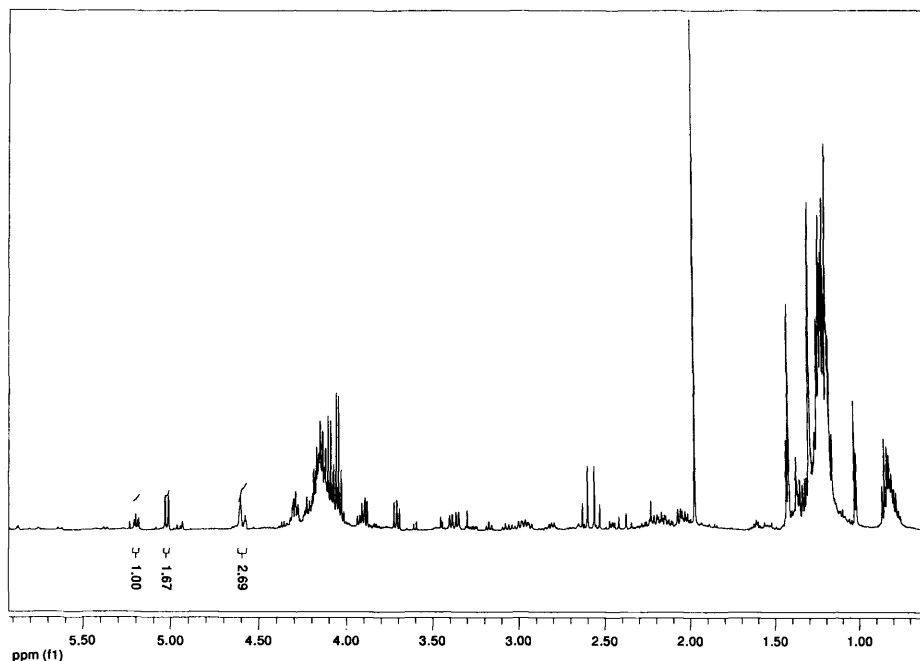
Selected peaks: $\delta = 5.20$ (dd, $J = 9.5$ and 3.7 , 1 H, CHN **220**), 5.03 (d, $J = 8.7$, 1 H, CHN **221**), $4.62 - 4.57$ (m, 2 H, CHNH both **220** and **221**).

(3*S*,7*S*)-diethyl 3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4,7-dicarboxylate (222) and (3*R*,7*S*)-diethyl 3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4,7-dicarboxylate (223).



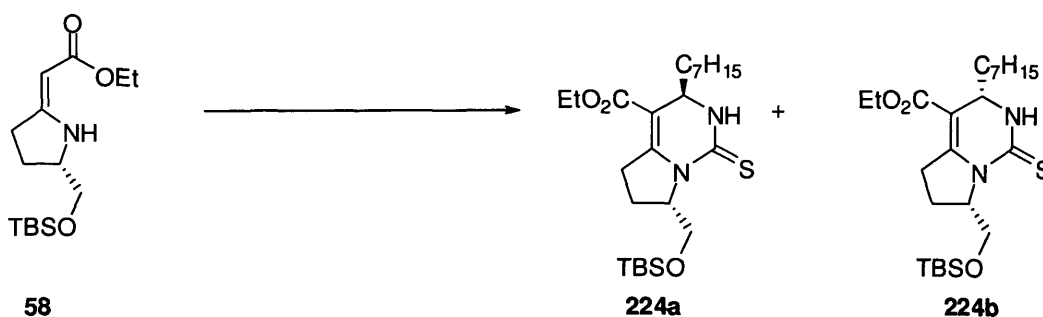
(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (260 mg, 2 mmol) in dichloromethane (5 mL) was added to a solution of trimethylsilyl isothiocyanate (260 mg, 2 mmol) in dichloromethane (10 mL). The resulting solution was stirred for 30 minutes at 25 °C under a nitrogen atmosphere. (2*S*)-5-[1-Ethoxycarbonyl-meth-(*Z*)-ylidene]-pyrrolidine-2-carboxylic acid ethyl ester (**151**) (455 mg, 2 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 30 minutes. The reaction was quenched with sodium hydroxide (0.5 M, 50 mL) and extracted into dichloromethane (3 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent removed *in vacuo* to give the crude *title compound* as a yellow oil.

¹H NMR spectrum (500 MHz; CDCl₃) for crude compounds (222) and (223).



Selected peaks: $\delta = 5.20$ (dd, $J = 9.5$ and 3.7 , 1 H, CHN **222**), 5.02 (d, $J = 8.9$, 1 H, CHN **223**), $4.62 - 4.57$ (m, 2 H, CHNH both **222** and **223**).

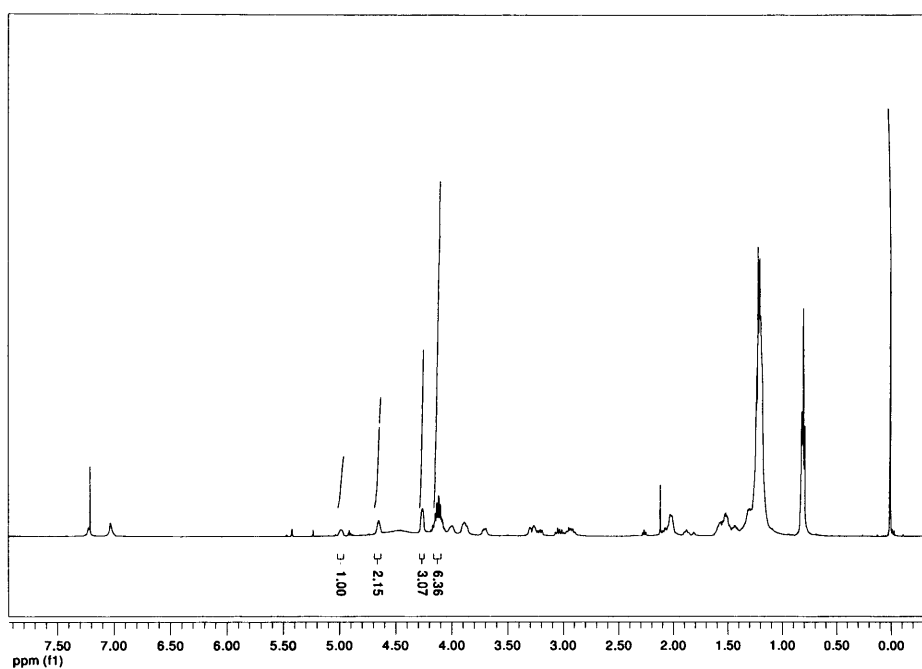
(3R,7S)-ethyl 7-((tert-butyldimethylsilyloxy)methyl)-3-heptyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (224a) and (3S,7S)-ethyl 7-((tert-butyldimethylsilyloxy)methyl)-3-heptyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (224b).



Silicon tetrathioisocyanate (91 mg, 0.35 mmol) was added to a solution of octanal (45 mg, 0.35 mmol) in dichloromethane (15 mL) and the resulting solution stirred for 30min at 25 °C under a nitrogen atmosphere. Ethyl 2-[(5R)-5-((tert-

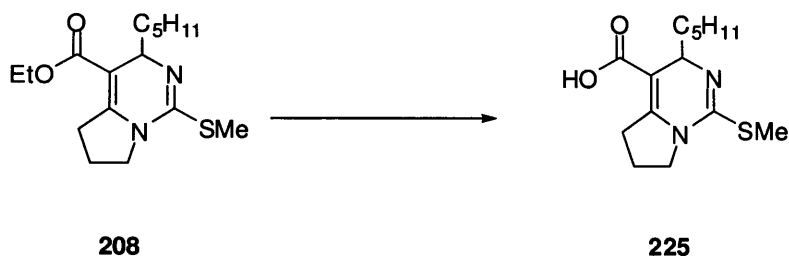
butyl(dimethyl)silyloxy)methyl)pyrrolidinylidene] ethyl ester (**58**) (100 mg, 0.35 mmol) in dichloromethane (5 mL) was added and the mixture stirred at 25 °C under a nitrogen atmosphere for a further 3 hours. Excess solvent was removed *in vacuo*. The residue was redissolved in chloroform and filtered through celite and the solvent removed *in vacuo* to give the crude *title compound* as a mixture of diastereoisomers (140 mg, 85 %) as a pale yellow oil.

¹H NMR spectrum (500 MHz; CDCl₃) for crude compounds (**224a**) and (**224b**).



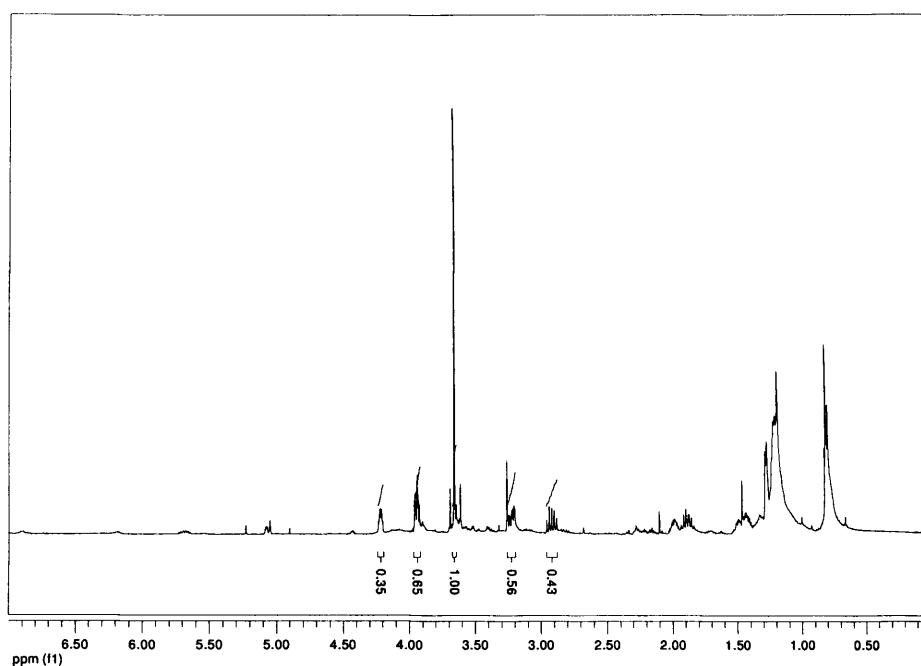
Selected peaks: $\delta = 5.02 - 4.95$ (m, 1 H, CHN **224a**), $4.69 - 4.63$ (m, 1 H, CHN **224b**), $4.29 - 4.24$ (m, 2 H, CHNH both **224a** and **224b**).

3-Pentyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]pyrimidine-4-carboxylic acid (225)



Ethyl 1-(methylthio)-3-pentyl-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (**208**) (500 mg, 1.6 mmol) in methanol (3 mL) was added to a solution of sodium hydroxide in methanol (10 %, 15 mL) and heated in a sealed tube at 100 °C for 18 hours. The reaction was quenched with saturated ammonium chloride and extracted into dichloromethane (2 x 50 mL). The combined dichloromethane layers were dried over magnesium sulphate and the solvent removed *in vacuo* to give the crude *title compound* (380 mg, 84 %) as a pale yellow oil.

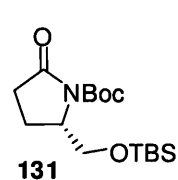
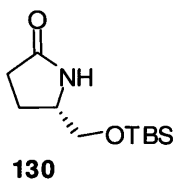
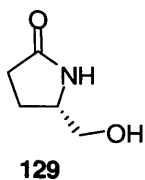
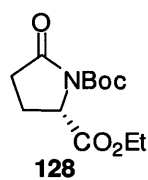
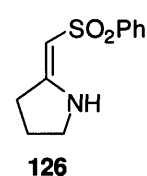
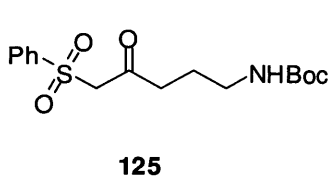
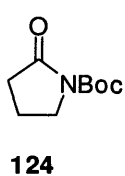
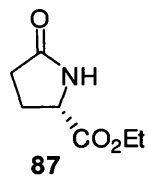
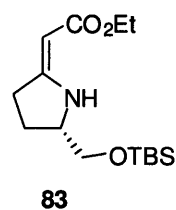
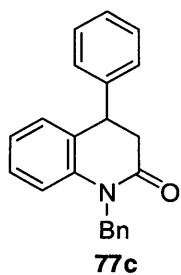
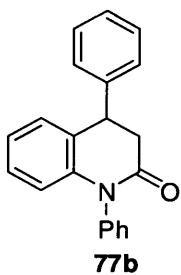
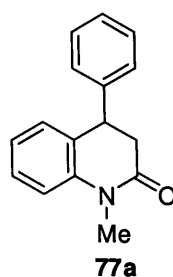
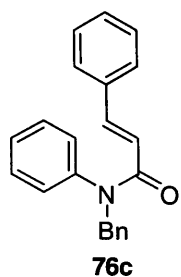
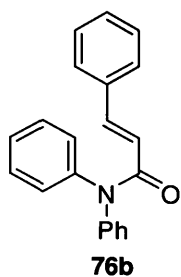
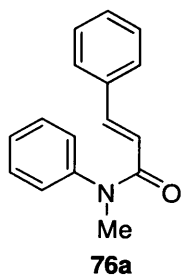
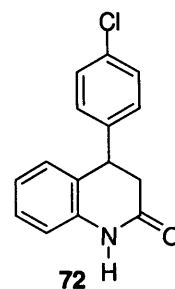
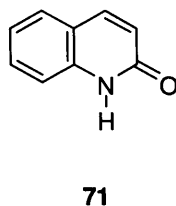
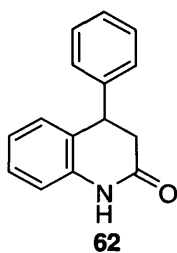
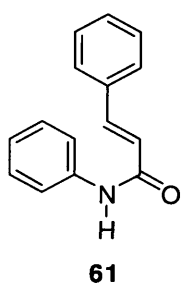
¹H NMR (500 MHz, CDCl₃) spectrum for compound 225.

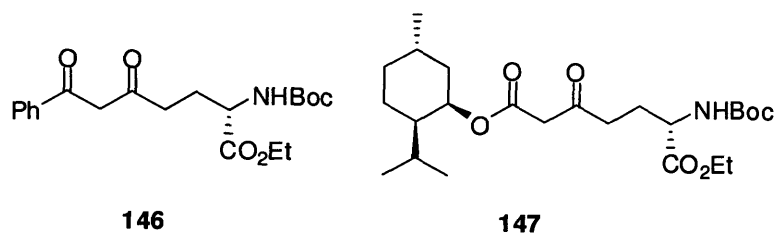
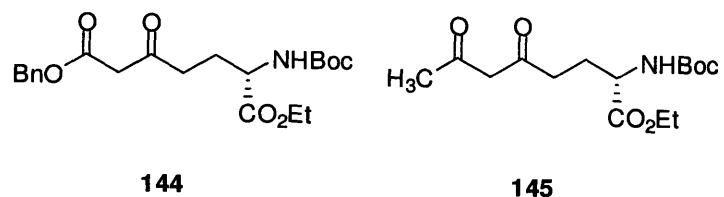
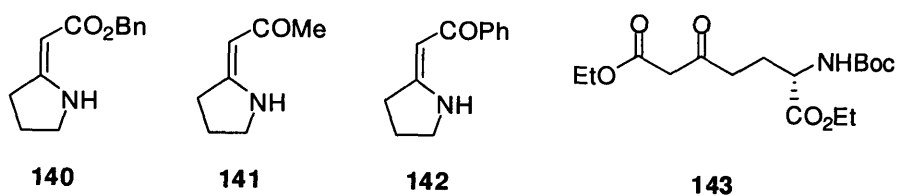
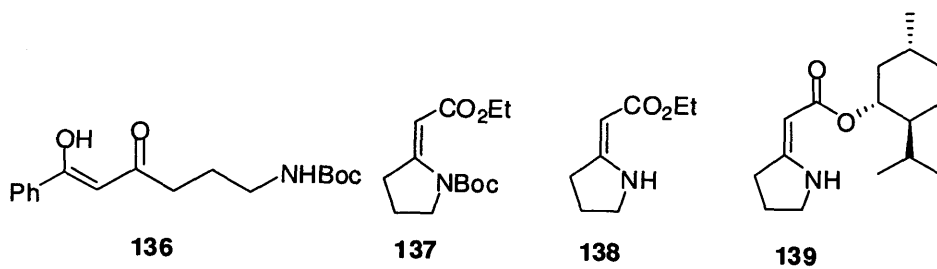
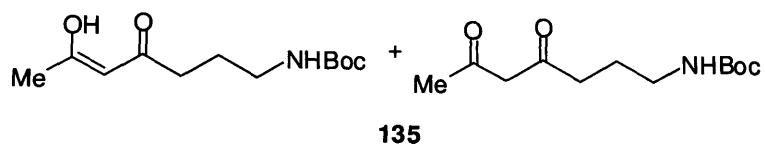
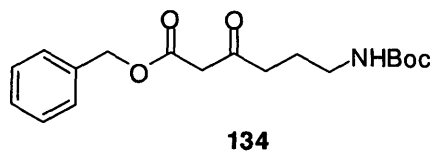
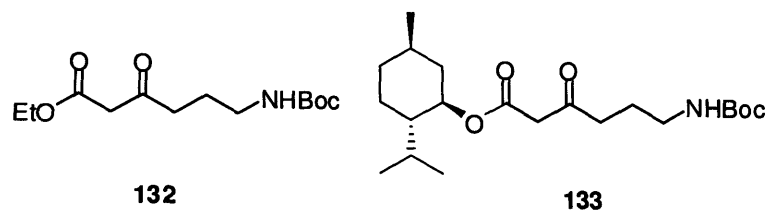


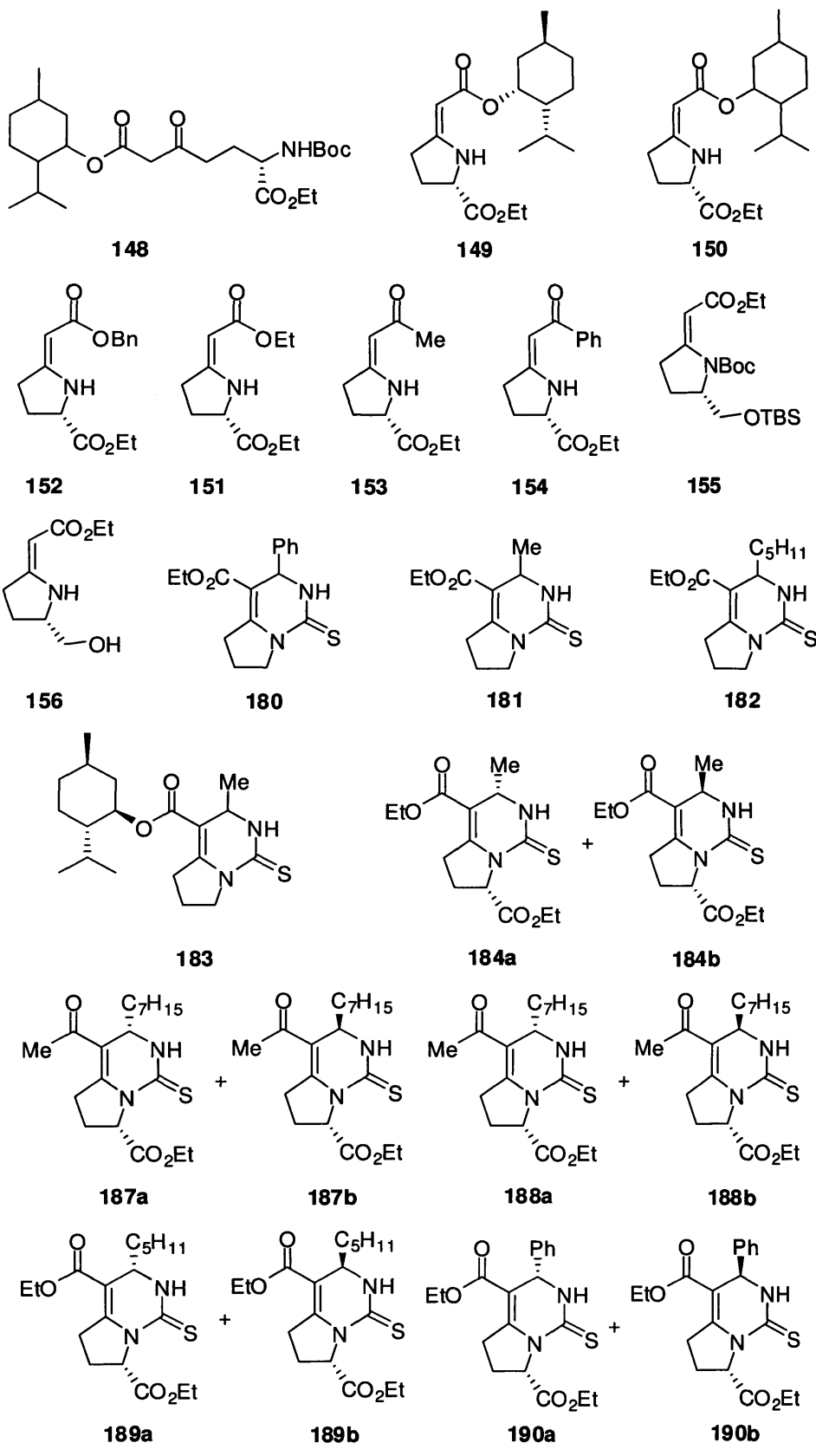
Selected peaks: $\delta = 4.24 - 4.20$ (m, 1 H, CHN), 3.97 – 3.93 (m, 2 H, CH₂N), 3.66 (s, 3 H, CH₃), 3.24 (ddd, $J = 18.4, 8.5$ and 3.6 , 1 H, one of CH₂C=C), 2.93 (dt, $J = 18.4$ and 9.3 , 1 H, one of CH₂C=C), 2.50 – 1.85 (m, 2 H, CH₂CH₂ pyrrolidine), 1.55 – 1.36 (m, 2 H, pentyl-CH₂CH), 1.30 – 1.15 (m, 6 H, 3 x pentyl CH₂), 0.8 (t, $J = 6.6$, 3 H, CH₃).

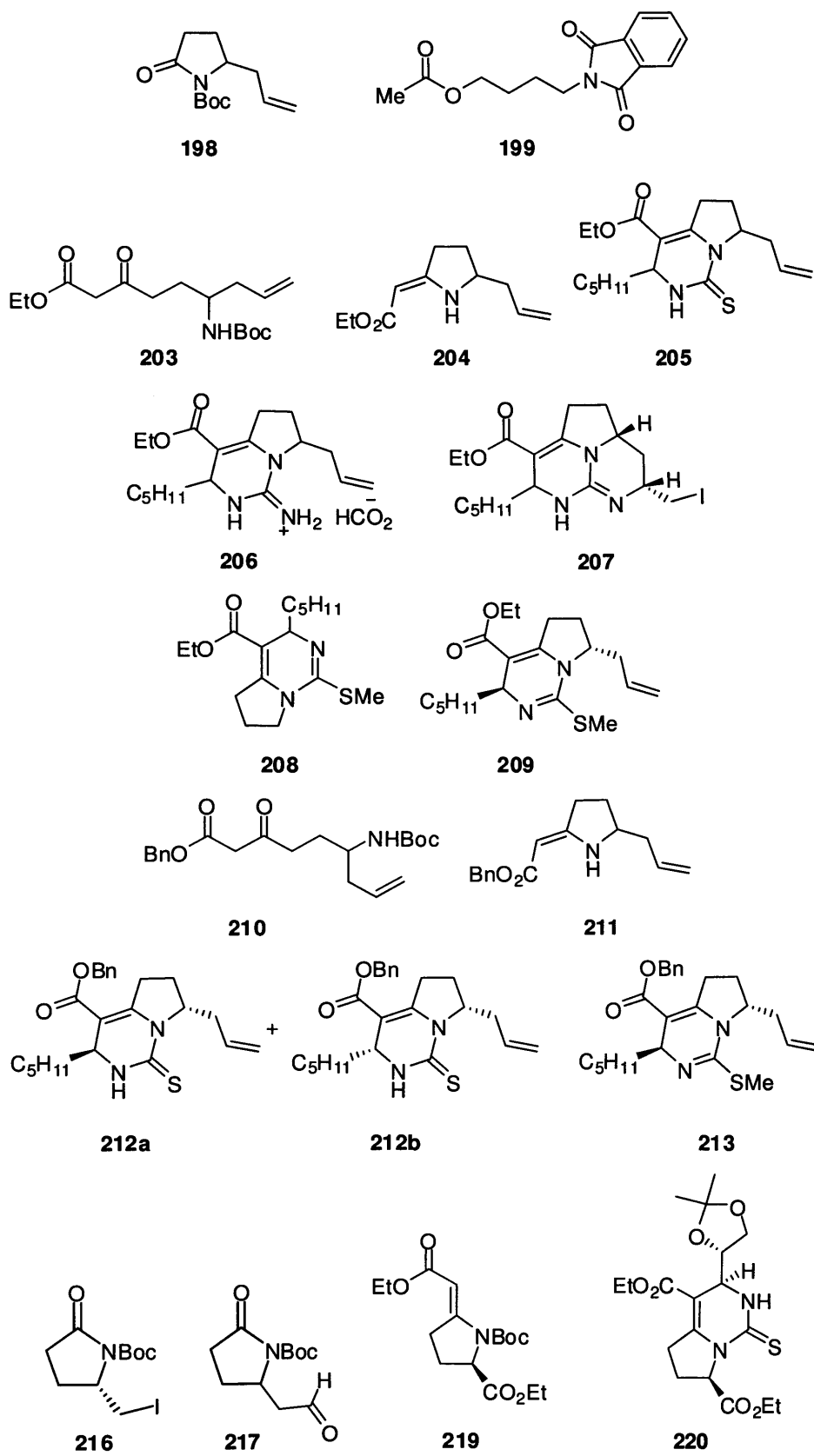
Appendix A

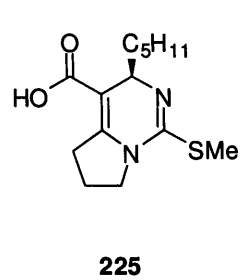
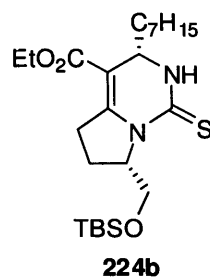
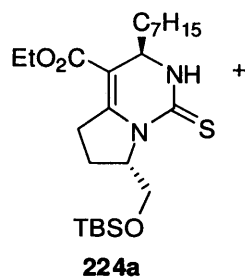
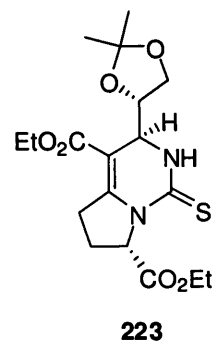
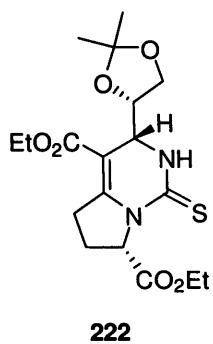
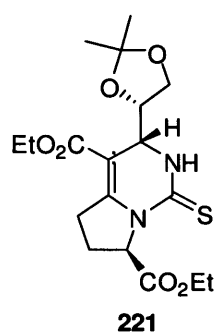
Compound List











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